

ORGN

DIVISION OF ORGANIC CHEMISTRY

S. Silverman and E. McLaughlin, *Program Chairs*

SUNDAY MORNING

Section A

Pennsylvania Convention Center
116

New Reactions & Methodology

S. M. Silverman, *Organizer*

8:00 1. Copper catalyzed reductive carbonylation of alkyl iodides. **S. Zhao**, N.P. Mankad

8:20 2. Sulfenate-anion-catalyzed diastereoselective aziridination of imines. **Z. Zheng, P.J. Walsh**

8:40 3. Cyanoalkylcopper species in carbon-carbon bond forming reactions. **D.L. Silverio**

9:00 4. New reactivity enabled by cation- π interactions. **P.J. Walsh**

9:20 5. Dipolar alkynyl-prins (DAP) cyclization for the rapid construction of complex polycycles. **S. Abdul-Rashed**, G. Alachouzos, A. Frontier

9:40 6. Subphthalocyanines and perylene-diimide derivatives in organic photovoltaics. **L. Chockalingam Kasi Viswanath**

10:00 7. Silylated α -aminonitriles for late-stage functionalization. **T. Mathew**, T. Yamato, S.G. Prakash

10:20 8. Synthesis of differentially substituted diynes via tandem nucleophilic addition/fragmentation pathways. **A. Tavakoli**, G.B. Dudley

10:40 9. Analogues of Bestmann's ylide, $\text{Ph}_3\text{P}=\text{C}=\text{C}=\text{O}$: Syntheses, structures and Lewis acid catalyzed cyclizations with organic substrates. **C. Krempner**

11:00 10. Diastereoselective alkynylations of β -(Bromo)iminium ions via copper(I) catalysis. **S.O. Santana**, W. Guan, M.P. Watson

11:20 11. Modular three-component difunctionalization of aryl/cyclohexenyl triflates via arynes and cyclohexynes. **S. Cho**, Q. Wang

11:40 12. 1,2-aminocyanation of alkenes via distal migration. **Y. Kwon**, Q. Wang

Section B

Pennsylvania Convention Center
117

Heterocycles & Aromatics

S. M. Silverman, *Organizer*

8:00 13. Formal [4+2] cycloaddition between alkynes and allene-ynes to generate functionalized toluenes. **A.D. Le**, D. Lee, S. Gupta

8:20 14. Regioselective carbonylation of 2,2-disubstituted epoxides. **A.K. Hubbell**, J.R. Lamb, A.M. LaPointe, K. Klimovica, G.W. Coates

8:40 15. Cupper catalyzed N-arylation of 4-R-1,2,4-triazoles. **J.L. Bolliger**

9:00 16. Formation of tricyclic aromatic heterocycles mediated by oxidative disulfide coupling. **J.L. Bolliger**

9:20 17. New methods for aryl C-N and C-O bond formation using sequential iron and copper catalysis. **M.C. Henry**

9:40 18. Control of halogen dance and its application to the synthesis of substituted heteroaromatic compounds. **K. Okano**, S. Hirai, Y. Hayashi, K. Inoue, M. Aoki, A. Mori

10:00 19. Development of 2-pyridinyl-1,2,4-triazine alkoxy-substituted scaffolds for minor actinide separations. **M.L. Tedder**, J.D. Carrick

10:20 20. Convergent strategy for the synthesis of oxa-, thia-, and seleno[5]helicenes by acetylene-activated S_NAr reactions. **J.L. Katz**, S. Hoenig, Y. Yan, E. Dougherty, S. Petovic, C. Lee, Y. Hu, L. Gomez

10:40 21. Synthesis of polycyclic spiro lignan natural product model substrates. G. Ali, **G.D. Cuny**

11:00 22. Para- and [4+4] photocycloadditions in mixed pyridone–benzene systems. **L.M. Rossiter**, S. Fletcher, B. Garas, S.M. Sieburth

11:20 23. Cyclopentannulation and cyclodehydrogenation of isomerically pure 5,11-dibromoanthradithiophenes leading to contorted aromatics. **W.a. Hussain**

11:40 24. Diastereoselective synthesis of *N*-(hetero)aryl-piperidines. **M.A. Larsen**, A.C. Sather, M. Deem, E. Hennessy, J. Sauri, C. Lam

Section C

Pennsylvania Convention Center
120A

Flow Chemistry & Continuous Processes

S. M. Silverman, *Organizer*

9:00 25. Approaches to scaling-up linked continuous flow photo-, electro- and thermal-chemistry: New reactors and new approaches. **M.W. George**

9:30 26. "Machine-Assisted Synthesis: Programmable Precision Polymers by the Push of a Button". **T. Junkers**

10:00 27. Continuous plug flow antisolvent crystallization of active pharmaceutical ingredients. **A.H. Bond**, K. Nordquist, K. Schaab, S. Ferdous, T. Kinnibrugh, A. Thorat, G. Capellades, A.S. Myerson

10:30 28. Synthesis of substituted heteroarenes and their subsequent reduction using flow technology to produce novel heterocycles. **G.V. Sipos**, I.K. Varga, K. Bodroghy

Section D

Pennsylvania Convention Center
120B

Contributions of Synthetic Chemistry to Energy Storage

C. Sevov, S. Zhang, *Organizers, Presiding*

8:30 Introductory Remarks.

8:35 29. Synthetic control of stoichiometry, size, and defect distributions: Beneficial impact on resultant electrochemistry. **K.J. Takeuchi**, A.C. Marschilok, E.S. Takeuchi

9:05 30. Making new materials for energy storage. **C.P. Nuckolls**

9:35 31. Organic electrode material design for beyond lithium-ion batteries. **Y. Yao**

10:05 Intermission.

10:25 32. Diversity-oriented synthesis of new polymers for battery applications. **B. Helms**, M. Baran, M. Carrington, M. Baird, A.I. Baskin, D. Prendergast

10:55 33. Going a step beyond: Isolating and characterizing the charged states of active battery materials. **S.A. Odom**

11:25 34. Design strategies for organic solids and solutions in hybrid redox flow batteries. **C.S. Sevov**

11:55 Concluding Remarks.

Section E

Pennsylvania Convention Center
118A

The Power of High-Throughput Experimentation: Accelerated Synthetic Development & New Reaction Discovery

M. Jouffroy, *Organizer*

M. Emmert, *Organizer, Presiding*

M. Jouffroy, *Presiding*

9:00 Introductory Remarks.

9:05 35. Use of high-pressure and high-throughput experimentation, and theory to optimize the catalytic borylation of methane with well-defined iridium complexes. **D.J. Mindiola**

9:35 36. Utilizing high-throughput experimentation to catalyze diverse chemistry and collaborations within and outside of Merck. **D.M. Schultz**

10:05 37. Engaging esters, aldehydes, and alcohols in cross-coupling: High throughput approach to reaction discovery. **S. Newman**

10:35 38. Applications of HTE to the discovery and development of robust, scalable catalytic transformations for the synthesis of complex pharmaceutical intermediates. **E. Simmons**

11:05 39. High-throughput experimentation for the life sciences. **T. Cernak**

Pennsylvania Convention Center
Michael A Nutter Theatre

Carbon Allotropes, Materials, Devices & Switches

Cosponsored by I&EC
S. M. Silverman, *Organizer*

8:00 40. Aryl amphiphile shape-directors for the shape-controlled synthesis of organic semiconductor micro- and nano-crystals. **D. Jones**, N. Gavvalapalli

8:20 41. Light-driven chiral liquid crystal nanostructures enabled by chiral molecular switches or motors: Dynamic photonics. **Q. Li**

8:40 42. Bisphenalenyl Radical Salts and their Uniquely Open-shell Optoelectronic Properties. **C.M. Wehrmann**, M.S. Chen

9:00 43. Synthesis of [5]- and [7]-Carbohelicene through regioselective cyclodehydrogenation. **Z. Qiu**, A. Narita, K. Muellen

9:20 44. Evidence of orientational order in thiophene derived carbon nanothreads. **A. Biswas**, M. Ward, T. Wang, L. Zhu, H. Huang, J.V. Badding, V. Crespi, T.A. Strobel

9:40 45. Customizing the optoelectronic and chiroptical properties of carbon-based dots. M. Vázquez-Nakagawa, A. Ferrer-Ruiz, L. Rodríguez-Pérez, N. Martín, **M. Herranz**

10:00 46. Tubularenes: Redefining carbon-based nanotubes. **E. Castro**, S. Mirzaei, O. Abarbanel, R. Hernandez Sanchez

10:20 47. Nanocarbon morphology shapes hybrid functional matter. D. Iglesias, M. Melle-Franco, A. Beltram, S. Kralj, M. Melchionna, **S. Marchesan**

10:40 48. Tubular[n]arenes: Bottom-up approach to carbon-based nanotubes analogues. **O. Abarbanel**, E. Castro, S. Mirzaei, R. Hernandez Sanchez

11:00 49. Synthesis and polymerization of diynes containing thiocyanate and thiophene end-groups en route towards polydiacetylenes. **R. DeCicco**

11:20 50. Award Address (ACS Award for Creative Invention sponsored by the ACS Corporation Associates). Photochromism and its commercial application. **A. Kumar**

SUNDAY AFTERNOON

New Reactions & Methodology

S. M. Silverman, *Organizer*

J. Li, *Presiding*

1:00 51. Metal-free trifluoromethylation of phenols via xanthates: New synthesis of aryl and heteroaryl-trifluoromethyl ethers. **A.T. Londregan**, M. Yoritake, Y. Lian, J.F. Hartwig

1:20 52. Development of safer methods for cleavage of the Evans auxiliary. **G. Beutner**, D.D. Dixon, E. Lo, J.M. Stevens

1:40 53. New strategies toward catalytic alkene dicarbofunctionalization. **R. Giri**

2:00 54. Sequencing [4+1]-cycloaddition and aza-Michael addition reactions: Tandem cascades for the rapid and modular access of unique collections of anticancer and anti-superbugs motifs. **T.H. Altel**, S. Vunnam

2:20 55. Synthesis of 2,4'-bipyridines via a unique radical coupling of cyanopyridines and heteroaryl phosphonium salts. **J.W. Greenwood**, J.L. Koniarczyk, J.V. Alegre-Requena, R.S. Paton, A. McNally

2:40 56. Regioselective nucleophilic substitution of the Baylis-Hillman (BH) adducts: Applications to the synthesis of heterocyclic derivatives. **Z. Shafiq**, L. Liu

3:00 57. Hindered urea bond: Bilaterally responsive chemistry to hydrogen peroxide. **Y. Yang**, H. Ying, J. Cheng

3:20 58. Shedding new light on squaraines: Utilizing squaraine dyes as building blocks in organic synthesis. **E. Bacher**, B.L. Ashfeld

3:40 59. Photochemical synthesis of bicyclic amines for drug discovery. **P. Mykhailiuk**, A. Denisenko, Y. Skalenko, A. Kirichok, B. Chalyk, T. Druzhenko, D. Dibchak

4:00 60. Rapid access to functionalized trifluoromethyl-substituted aliphatic derivatives. **P. Mykhailiuk**, M. Bugera, S. Trofymchuk, K. Tarasenko, Y. Pustovit

4:20 61. Photoacid catalyzed C-C bond-formation: Synthesis of triarylmethanes and 3,3'-diarylindolin-2-ones. Z.M. Salem, J. Saway, **J.J. Badillo**

4:40 62. Direct decarboxylative functionalization of carboxylic acids via O-H hydrogen atom transfer. **C.G. Na**, E.J. Alexanian

Pennsylvania Convention Center
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Biologically-Related Molecules & Processes

S. M. Silverman, *Organizer*

1:00 63. Non-enzymatic synthesis of biologically important phosphates and polyphosphates. M. Perez-Ramirez, N. Zungpoih, **B. Otoo**

1:20 64. Chemical targeting of voltage sensitive dyes to specific cell types in the brain. **T. Fiala**, J. Wang, M. Dunn, S. Choi, P. Sebej, E.C. Nwadibia, E. Fialova, D.M. Martinez, D. Sulzer, D. Sames

1:40 65. BODIPY photocages: Structure-activity relationship in quantum yield of photorelease. **P. Shrestha**

2:00 66. Synthetic simplification of carolacton leads to identification of novel biofilm target. **A.E. Solinski**, A. Scharnow, A.J. Fraboni, E. Shaw, W.M. Wuest

2:20 67. Unusual ethyl branched chain fatty acids: Synthesis and biological evaluation. **D. Szczerbowski**, J. Caspers, M. Miyazaki, R.P. de Freitas, S. Schulz

2:40 68. Synthesis of a single chromophore for the development of photoluminescence switches: Detection of multiple analytes. **H. Saadeh**

3:00 69. Synthesis and structural studies of peptidomimetic *N*-substituted azole-rich macrocycles. **A.A. Fuller**, S. Motevalli, M. Nguyen, J. Tan

3:20 70. Water-soluble amphiphilic rosamine-based photoinduced electron transfer (PET) sensors for cell membrane potential. **M.E. EL KHATIB**, M. Thunemann, T. Zaman, A.L. Obeid, B. Salzberg, B. Prosser, E.M. Goldberg, A. Devor, S. Vinogradov

3:40 71. Bio-inspired chemistry for synthesis of a polybrominated pyrrole marine alkaloid with antibacterial properties. **T.L. Suyama**

4:00 72. Assessing the influence of $n \rightarrow \pi^*$ interactions on hydrolysis rates of *n*-acyl homoserine lactone derivatives. **M.A. Bertucci**, D. Schmucker, S.R. Dunbar, T.D. Shepherd

4:20 73. Fluorous-soluble cyanines and their photophysical characterizations in aqueous, organic, and fluorous media. **I. Lim**, E.M. Sletten

4:40 74. Discovery and synthesis of PF-06882961, a small molecule GLP-1 receptor agonist: From lead to clinical candidate. **J.M. Curto**, S.W. Bagley, E.L. Conn, G. Ingle, W. Jiao, C. Limberakis, A. Shavnya, L. Wei, D.W. Piotrowski, M. Dowling, M.E. Flanagan, D.J. Edmonds, D.A. Griffith, V. Mascitti, A. Mathiowetz

Section C

Pennsylvania Convention Center
120A

Metal-Mediated Reactions & Syntheses

S. M. Silverman, *Organizer*

1:00 75. New developments in palladium-catalyzed alkene diamination reactions of nitrogen electrophiles. **J.K. Kirsch**, J.P. Wolfe

1:20 76. Monosubstituted, anionic N-heterocyclic carbene complexes of palladium and their reactivity in cross coupling reactions. **E. Martinez**, H. Nazari, A. Larson, C. Jensen, K. Kenney, D. Michaelis

1:40 77. Nickel-catalyzed domino reactions. **K.A. Hewitt**, E.R. Jarvo

2:00 78. Evaluating activity of transition metal catalysts of the salen/an framework and mechanistic pathway of oxidative coupling utilizing high throughput experimentation. **A. Jemison**, C. Ochoa, M. Kozlowski

2:20 79. Cobalt catalyzed multicomponent cyclizations of enynes and alkenes. **J. Herbort**, T.V. RajanBabu

2:40 80. Synthesis of diisobutyl aluminum borohydride for the reduction of tertiary amides at ambient temperatures. **R. Snelling**

3:00 81. Ca-mediated SuFEx reaction toward the synthesis of sulfamides, sulfamates, and sulfonamides from S(VI) fluorides. **N.D. Ball**, S. Mahapatra, C.P. Woroch, S.C. Kwan, S.N. Carneiro, S.R. Khasnavis, J. Dutra, T.W. Butler, C. Am Ende

3:20 82. ATRP inspired modifications upon Ullmann cross coupling. **A.K. Fung**, M. Coote

3:40 83. Click chemistry assisted regioselective synthesis of new phosphorous moiety linked 1,2,3-triazoles. **J. Anireddy**

4:00 84. Stereoselective synthesis of bile acid metabolites. **M.R. Krout**

4:20 85. Cationic cobalt(I) intermediates in hydrofunctionalization reactions. **M.M. Parsutkar**, S.M. Jing, K. Duvvuri, T.V. RajanBabu

4:40 86. Metal-mediated modular synthesis of eumelanin-inspired 5,6-dimethoxyindole oligomers. **A. Aebly**, B.J. Steger, J. Levy, J.C. Quirke, J.M. Belitsky

Section D

Pennsylvania Convention Center
120B

Contributions of Synthetic Chemistry to Energy Storage

C. Sevov, S. Zhang, *Organizers, Presiding*

1:30 Introductory Remarks.

1:35 87. Redox active organic materials. **D.S. Seferos**

2:05 88. Phenazine-based covalent organic framework cathode materials with high energy and power densities. E. Vitaku, C. Gannett, K.L. Carpenter, L. Shen, H.D. Abruna, **W.R. Dichtel**

2:35 Intermission.

2:55 89. New molecules for non-aqueous organic redox flow batteries. **K. Hendriks**, N. Daub, R.A. Janssen

3:25 90. Developing electrolyte chemistry for organic redox flow batteries. **T.L. Liu**, B. Hu, J. Luo

3:55 91. Two electron storage using metal picolinamide complexes for redox flow batteries. G. Andrade, C.R. Federico, I.A. Popov, P. Yang, E.R. Batista, **B.L. Davis**

4:25 Concluding Remarks.

Section E

Pennsylvania Convention Center
118A

The Power of High-Throughput Experimentation: Accelerated Synthetic Development & New Reaction Discovery

M. Jouffroy, *Organizer*

M. Emmert, *Organizer, Presiding*

M. Jouffroy, *Presiding*

1:30 92. High throughput experimentation as a tool for catalyst discovery with earth abundant transition metals. **P.J. Chirik**

2:00 93. Democratization of high throughput experimentation for process chemistry. **K.F. VanGelder**

2:30 94. Miniaturization + automation = Acceleration. **A. Doemling**

3:00 95. High-throughput experimental approaches to mapping chemical reactivity. **D. Leitch**

3:30 96. Nanoflow-HTE: Quick decision enablement for parallel medicinal chemistry. **S. Berritt**

4:00 Intermission.

4:05 97. Lessons learned and future opportunities for HTE. **S.W. Krska, J. Tucker, M. Tudge, E. Simmons, M. Christensen**

4:50 Concluding Remarks.

Section F

Pennsylvania Convention Center

Michael A Nutter Theatre

Elias J. Corey Award for Outstanding Original Contribution in Organic Synthesis by a Young Investigator

S. M. Silverman, *Organizer*

J. Pierce, *Presiding*

1:00 Introductory Remarks.

1:05 98. Solving Ni puzzles in alkene difunctionalization reactions. **C. Nevado**

1:45 99. Strategic covalent bond transformations using mechanical force. **M.J. Robb**

2:25 100. Recent efforts in the synthesis of complex natural products: Efficient synthesis of phyllantidine and progress towards haenamindole. **J.L. Wood**

3:05 Intermission.

3:25 101. New directions in Ni-Catalyzed cross coupling. **A.G. Doyle**

4:05 Introductory Remarks.

4:10 102. Necessity is the mother of invention: Natural products and the chemistry they inspire.
S.E. Reisman

SUNDAY EVENING

Section A

Pennsylvania Convention Center
Exhibit Hall A

Asymmetric Reactions & Syntheses

E. C. McLaughlin, *Organizer*

5:30 - 7:30

103. Stereoselective cyclopropanation of amino acid-derived enones using cinchona alkaloids. **N.K. Dunlap**, H. Kerns, A. Anwar

104. Efforts towards the formal asymmetric synthesis of the Akaji Human T-cell leukemia virus (HTLV-1) protease inhibitor. **M.A. Addo**, S.R. Hitchcock

105. Oxadiazinones as chiral auxiliaries: Asymmetric conjugate addition reactions with *Ephedra* based oxadiazinones. **F.O. Obe**, S.R. Hitchcock

106. Asymmetric synthesis of stereogenic phosphorous centers using chiral nucleophilic catalysis. **A. Numan**, M. Brichacek

107. *De novo* asymmetric synthesis of purpurosamine. G.A. O'Doherty, C. Liang, A. Aljahdali, **T. Hopkins**

108. Diverse derivatization of *trans*-cyclooctenes using diastereoselective functionalization of a scalable ketone-*trans*-cyclooctene precursor. **J.E. Pigga**, J. Fox

109. Peptoid helices for the enantioselective trifluoromethylation of carbonyls. K.B. Toll, **B.C. Gorske**

110. Peptoid turns for the enantioselective trifluoromethylation of carbonyls. R.J. Londoner, **B.C. Gorske**

111. Enantioselective synthesis of phenanthridinone analogs with quaternary carbons utilizing the Birch-Heck sequence. **M. Sexton**, W.P. Malachowski

- 112.** Asymmetric cyclopropanation using chiral group 11/N-heterocyclic carbene complexes. **P.D. Kunselman**, N. Johnson, M.G. Coleman
- 113.** Light-triggered catalytic asymmetric allylic benzylation with photogenerated C-nucleophiles. **X. Companyo**, S. Paria, E. Carletti, M. Marcon, A. Cherubini-Celli, L. Dell'Amico, M. Bonchio
- 114.** Diastereomer differentiation in magnesium-oppenauer oxidation of chiral secondary alcohols. C.M. Martin, C.M. Webb, **K.J. Brown**
- 115.** Palladium-catalyzed asymmetric allylic alkylation of ortho nitro hydroxy acrylate: total synthesis of (-)-coerulescine. **M. Ali**
- 116.** Synthesis of a chiral organocatalyst via a novel asymmetric tandem conjugate addition, diazo transfer and 1,3-dipolar cycloaddition. **S.M. Severson**, D. Just, U. Jahn
- 117.** Catalytic enantioselective synthesis of chiral esters from ketenes and allyl aryl ethers. **N. Kerrigan**, A. Ibrahim
- 118.** Luminescent ionic materials toward neutron radiation sensors. **A.Q. Kane**, N. del Giudice, L. Stuttgé, L. Douce
- 119.** Enantiomerically pure *tert*-butylsulfinamide as a template for synthesizing sulfinate esters and sulfinamides not accessible through direct alkylation. **J. Shaw**
- 120.** Discovery of an annulating reagent enabling the one-step and highly stereoselective synthesis of cyclopentanes. J. McDaniel, **C. Farley**, B. Sandhu, Q. Shi, A. Han, W.P. Gallagher, J. Hynes, M. Dhar, F. Gonzalez Bobes, J.R. Coombs, D. Marcoux
- 121.** Syntheses of pharmaceutically relevant *N*-heterocycles atropisomers via nucleophilic aromatic substitution. **M.M. Cardenas**, M.A. Saputra, A.N. Sanchez, J.L. Gustafson
- 122.** Synthesis and characterization of S-camphorquinone derived quinoxalines and imines. **D. Hopkins**, N.M. Glagovich
- 123.** Lewis acid carbocation catalyzed reduction of imines. J.J. Badillo, **D. Glynn**
- 124.** Organocatalytic mannich-hemiaminalization cascade strategy for the asymmetric synthesis of spirooxindole tetrahydroisoquinoline derivatives as novel Ras-GTP inhibitors. **Q. Zhao**, X. He, B. Han, C. Peng
- 125.** Asymmetric synthesis of naturally occurring homoisoflavonoids having either 5,6,7- or 5,7,8-trisubstituted groups and their biological evaluation for antiangiogenic activity. S. Kwon, S. Lee, **S. Seo**

126. Hydrogen-bonding effect directed stereodivergent synthesis of lactams bearing vicinal tertiary and fluorine-containing quaternary stereogenic centers via sequential approach. **K. Zhang**, X. Sheng, L. Deiana, K. Inge, F. Himo, A. Cordova

Section A

Pennsylvania Convention Center
Exhibit Hall A

CH Activation

E. C. McLaughlin, *Organizer*

5:30 - 7:30

127. Towards cobalt catalyzed C-H activation with thio heterocycles. **K. Suppan**

128. Direct comparison of fluorination methods for the functionalization of biologically relevant molecules. **M.T. Morales Colon**, M.S. Sanford

129. Differential regioselectivity profiles of rhodium(III) and iridium(III) catalysts in allylic C-H amidation. **T. Kowal-Safron**, J. Park, J. Won, B. Park, J. Burman, S. Blakey, M. Baik

130. Rhodium(II)-catalyzed branch-selective C-H alkylation of benzenesulfonamide derivatives with vinylsilanes. **S. Rej**, **N. Chatani**

131. Cascade C–H arylation/lactamization of benzylamines enabled by a transient directing group strategy. **P.K. Chand Thakuri**, V.G. Landge, M. Kapoor, M.C. Young

132. Palladium–catalyzed gamma–arylation of allyl amines using dry ice. **V.G. Landge**, J.M. Maxwell, P.K. Chand Thakuri, M. Kapoor, E. Diemler, M.C. Young

133. Protocol for the *ortho*-deuteration of acidic aromatic compounds in D₂O catalyzed by cationic Rh^{III}. **A.L. Garreau**, M.C. Young

134. Exploration of new avenues for development of dirhodium catalysts for asymmetric C-H functionalization reactions. **J. Fu**, Z. Garlets, Z. Ren, H.M. Davies

135. Heterogeneous palladium-catalyzed oxidative benzylation via benzylic C(sp³)-H activation. **P. Basnet**, C.E. Hendrick, P.A. Amadeo, M. Kozlowski

136. Environmentally benign solid acid-catalyzed coupling of diazonium salts with aromatic hydrocarbons and heterocycles for the syntheses of biaryls and heterobiaryls. **G. Pandey**

Section A

Pennsylvania Convention Center
Exhibit Hall A

Cross Coupling Reactions

E. C. McLaughlin, *Organizer*

5:30 - 7:30

137. Efforts toward the total synthesis of trocheliophorolide A: Assessing a cadre of hydroboration techniques to afford a viable coupling partner. **K. Clark**, J. Dominguez, K. Houghtling, H. Simpson, J. Swartzenberg, T.G. Goudreau Collison

138. Cu₂O nanoparticles catalyzed C-N coupling of tetrazolones with boronic acids. **T. Reason**, A.K. Fionah, E.M. Zahran, S. Rayat

139. Development of titanium oxide-supported palladium catalysts and evaluation of the catalyst activities for ligand-free Suzuki–Miyaura coupling using aryl chlorides. **T. Yamada**, H. Masuda, K. Park, T. Tachikawa, N. Ito, T. Ichikawa, H. Sajiki

140. Regio- and stereoselective synthesis of functionalized dihydropyridines, pyridines, and 2*H*-pyrans: Heck coupling of monocyclopropanated heterocycles. J. Yedoyan, **N. Wurzer**, U. Klimczak, T. Ertl, O. Reiser

141. Deaminative vinylation of pyridinium ions. **W. Guan**, J. Liao, M.P. Watson

142. Deaminative cross couplings of the side chain of lysine and its derivatives to synthesize unnatural amino acids. **C. Twitty**, Y. Hong, S. Tsang, M.P. Watson

143. Deaminative reductive methylation of alkylpyridinium salts. **O. Bercher**, S.L. Plunkett

144. New methodology to controlling regioselectivity utilizing a copper-catalyzed boracarboxylation. **M.D. Hamilton**, B.V. Popp, T.M. Perrone

145. Optimization of a Negishi cross-coupling reaction for the synthesis of β,β -disubstituted ketones. **C.B. Berlin**, H.R. Rensch, M.R. Krout

146. Toward an optimized copper-catalyzed sequential addition with functionalized monoorganozinc reagents. **C.N. Pierson**, H.R. Rensch, T.J. Fulton, M.R. Krout

147. Synthesis of ammonium organotetrafluorosilicates from trialkoxysilanes. **J. Posz**, S. Harruff, R. Van Hoveln

148. Nickel-catalyzed cross-coupling of ammonium organotetrafluorosilicates. **J. Wilkinson**, R. Van Hoveln

149. Synthesis of allenes using the alkynyl-Heck reaction. **M. Cadena, E. Thomas**, C.S. Strong, C. Munteanu, D.E. Frantz

150. Iron-based catalysts for Suzuki-Miyaura cross-coupling reactions involving alkyl electrophiles. **C.C. Tyrol**

Section A

Pennsylvania Convention Center
Exhibit Hall A

Heterocycles & Aromatics

E. C. McLaughlin, *Organizer*

5:30 - 7:30

151. Synthesis of substituted 4*H*-chalcogenochromenes promoted by iron(III) and diaryl dichalcogenides. **I.M. Oliveira**, M.P. Darbem, H.A. Stefani

152. Purification of flavone derivatives: 3-Hydroxy-2-phenyl-4-chromenone via Algar-Flynn-Oyamada reaction. **D. Rainone**, Z. Poulos, C. Kelley

153. Preparation of isoxazolines via ring closure of oximes. **A. Kirsch**, M.D. Mosher

154. Synthesis, resolution, and configurational stability of 7-isopropoxy-8-(naphth-1-yl)quinoline and the influence of its absolute configuration on effectiveness of HIV-1 neutralization. **C.A. Cedeño**, R.D. Overacker, S. Loesgen, P.R. Blakemore

155. Synthesis of bridged azapolycycles from tropone. **D. Griffith**, Z.K. Phelan, Y. He, Z. Guan, P. Weiss

156. Michael additions to β -haloethyl amine derivatives. **L. Morelli**, D.A. Hunt

157. Synthesis of aromatic silyl ketones for Brook Rearrangement studies. **L. Tahir**, L.M. Bradley, D.A. Hunt

158. Intermolecular [3+3] ring expansion of bicyclic aziridines to access functionalized piperazines via aziridinium ylides. **H. Dequina**, J. Eshon, I. Fernández, J.M. Schomaker

159. Synthesis of a library of folate mimics as inhibitors of fungal methionine synthase. **Z.D. Bennett**, A. Bockman, G. Burkhart, J. Pruet

160. Synthesis of push-pull tetrazoles and investigation of their spectroscopic properties. A.R. West, J.D. Huang, **S. Rayat**

- 161.** Progress toward catalytic enantioselective Friedel-Crafts reactions for the preparation of chiral tetraarylmethanes. **A.J. Catino**, S. Whittaker, J. Selingo, B. Kilner
- 162.** Synthesis of GPCR and sigma-1 receptor ligands using allylic azides. **N. Vail**, M.R. Porter, J.J. Topczewski
- 163.** Convenient access to conformationally rigid sultams. D. Dibchak, V. Shcherbacova, A. Denisenko, **P. Mykhailiuk**
- 164.** Investigation of oxoammonium salt mediated oxidative rearrangements. **R. Meador**, J.D. Chisholm
- 165.** Efficient synthesis of heterocycle rings through a one-pot cross coupling / intramolecular ring opening of oxetanes. **C. Wang**, S.D. Kuduk
- 166.** Diastereoselective multicomponent synthesis of tetrahydro-1*H*-pyrrolopyrazino[2,1-*b*]quinazolin-11(5*H*)-ones via sequential quinazolinone rearrangement & intramolecular ring closure of (*Z*)-benzamidines. **J. Fitz-Henley**, V.A. Jaffett, M.M. Khalifa, J.E. Golden
- 167.** Cu-catalyzed heteroatom-vinylation for synthesis of 2-imidazolidinethiones, 2-imidazolidinones, and 2-iminoimidazolidines. **T.J. Eckroat**
- 168.** Functionalized heterocycles by nucleophilic substitution at olefinic groups. **D.A. Klumpp**, J.C. Hood
- 169.** Synthesis of Oxyquinoliziniporphyrin. **E. Cramer**, T.D. Lash
- 170.** New approach to carbohydrate functionalized spiro-chromanone heterocycles. **J. Lopez**, **Z.J. Witczak**, R. Bielski, D.E. Mencer
- 171.** Hetero-oxa-claisen rearrangement: New examples. R. Bielski, **Z.J. Witczak**
- 172.** Multicomponent protocol for the synthesis of novel substituted thiazoles Ayaa Shabana. **A. Shabana**
- 173.** Synthesis of novel substituted indeno pyrroles and their transformations Toka Farhat. **T. Farhat**
- 174.** Hindered, solvatochromic, fluorescent naphthalimides. **A.A. Pollock**, D.E. Lewis
- 175.** Investigations into the synthesis of benziporphyrin and pyreniporphyrin dimers. **R.A. Tomlovich**, T.D. Lash
- 176.** Novel Reagents for the Synthesis of 1-Aryl-5-trifluoromethylimidazoles. **A.S. Bunev**

- 177.** Efficient route for the synthesis of diverse heteroannelated 3-trifluoromethylpyridines. **S. Ryabukhin**, A. Mityuk, D. Volochnyuk
- 178.** Chemistry of a “bottleable” propargyl carbocation. **M. Laprade**, K. Robertson, J.A. Clyburne
- 179.** Efficient route for the synthesis of diverse heteroannelated 3-cyanopyridines. **D. Volochnyuk**, A. Mityuk, S. Ryabukhin
- 180.** 1,3-Bis(benzylidene)isobenzofuran synthesis via copper(I) catalyzed hydration of ortho-diynylarenes. **T.S. Hughes**, **L. Gaglio**, **H.E. Hagearty**, K.M. Allen
- 181.** Cyclooligo-(para, ortho)-phenylenes obtained by threefold Diels-Alder benzannulation of phenylene ethynylene macrocycles: Examination of the toposelectivity of cycloadditions to macrocycles by experiment and theory. **T.S. Hughes**, **R.H. Somwaru**, **A.R. Bevilacqua**, **J. Dunn**
- 182.** Cyclooctatetraene-based acene tetramers. **V. Brosius**, L. Ahrens, F. Rominger, J. Freudenberg, U. Bunz
- 183.** Synthesis of diverse pyridinium salts via nitrogen-ligated hypervalent iodine mediated aminolactonization. A. Tierno, J. Walters, **A. Vazquez-Lopez**, X. Xiao, S. Wengryniuk
- 184.** N-(9-Acridinyl)-O-phenylhydroxylamines. **J. Forster**, M.D. Mosher
- 185.** One-pot synthesis of fluorinated pyrazoles from fluoroalkenes. **M. Saucier**, S. Jana, S. Roy
- 186.** Formation of stable anion radical oligomers from the one electron reduction of alkyl isothiocyanates. S.J. Peters, **Z. Becerra**
- 187.** Synthetic chemistry of superelectrophilic phosphonium ions. D.A. Klumpp, **N. Scanlon**
- 188.** Computational studies of intramolecular and intermolecular Diels–Alder reactions for heterocyclic syntheses. **S. Parrinelli**, E. Heil, N.B. Sizemore
- 189.** Charged aza-crown ethers and azolium-linked macrocycles for energy applications. **C. Do-Thanh**, B. Prasad Thapaliya, I. Popovs, S.M. Mahurin, S. Dai
- 190.** Determination of reactivity and selectivity for the dearomative dehydro-Diels-Alder reaction of heteroarenes. **J.A. Winkelbauer**, A. Bober, E. Kusevska, P. Liu, K.M. Brummond
- 191.** Synthesis of 2- and 6-substituted tryptophan spectroscopic reporters. A. Pecora, M. Cardiges, T. Limone, **M.W. Fennie**
- 192.** Copper iodide catalyzed imino-alkyne hydroamination. **J. Fose**, M. Ferraro, M.W. Fennie

- 193.** Convenient synthesis of 2-aryl- α -carboline via synergistic methods. **K. Medas, R. Lesch,** F. Edima, S.P. Mulcahy
- 194.** Synthesis, characterization and bioactivity evaluation of heterocyclic chalcones and their ferrocenyl analogues. **A.M. Alsina-Sanchez,** I. Montes-Gonzalez, P.M. Bonilla Crespo, S.M. Delgado-Rivera
- 195.** Synthesis of organic thermoelectric materials with electron withdrawing groups. **J. Downs,** J. Pollard, M. Nahm Garrett
- 196.** Synthesis of fluorescent anthraquinone derivatives as sensors. **Y. Lysandrou,** S. Carter, W. Kylie, J. Markiewicz
- 197.** Cucurbit[7]uril-anchored porphyrin-based multi-functional molecular platform. **Y. Kumar**
- 198.** Synthesis of thermoelectric materials with a parent compound. **I. Agholor, M. Grey,** M. Nahm Garrett
- 199.** Synthesis of thermoelectric materials with an electron donating group. **A. Medina Hernandez,** M. Nahm Garrett
- 200.** Double conjugate addition reactions with olefinic N-heterocycles. D.A. Klumpp, M. Stentzel, **J. Hood,** M. Laporte, **A. Manz**
- 201.** Fundamental study on desulfurization of petroleum using synthesized novel ionic liquids and betaine moieties. **B. Blad,** K.K. Sharma, K. Dejesus
- 202.** Design and synthesis of soft porous crystal based upon organic cages for applications in gas separation. **w. zhifang,** Z. Zhang
- 203.** Studies towards synthesis of phakellin and its analogues such aza- and bis-aza- indolo phakellins. **Y. Huang,** V. Sammeta, S. Rasapalli
- 204.** One pot synthesis of angular-luotonins from quinazolinonylenones via novel aza-Nazrov chemistry. S. Rasapalli, **V. Sammeta,** z. murphy
- 205.** Design and synthesis of reverse amides of 4/5-acyl -2-amino imidazoles as oroidin analogues for biofilm inhibition. S. Rasapalli, **V. Sammeta**
- 206.** Synthesis of a precursor to an isoprene-derived Criegee intermediate and spectroscopic characterization. **C. Frost,** J.R. Scheerer, N.M. Kidwell
- 207.** Synthesis of pyrrolodiketopiperazine derivatives. **A. Leersnyder,** S. Maisto, J.R. Scheerer

Pennsylvania Convention Center
Exhibit Hall A

Metal-Mediated Reactions & Syntheses

E. C. McLaughlin, *Organizer*

5:30 - 7:30

208. Alkene dicarbofunctionalization by metallacycle contraction process. **R.K. Dhungana**, R. Giri

209. Computational studies of the transmetalation mechanism in Stille cross-coupling reactions. **V. Eng**, T. Zottarelli, B.L. Taylor

210. Lithium-halogen exchange studies of bromoalkyl bromothiophenes. **T. Chiarella**, D.A. Hunt

211. Cobalt-complexed acetylenic tetrads, a novel molecular scaffold for quadruple ionic functionalization reactions. **C. Herrera**, **N. Kalpakyan**, H. Chinchian, G.G. Melikyan

212. Vanadium-catalyzed intramolecular oxidative coupling of tethered phenols to generate phenol-dienone products. **P.H. Gilmartin**, M. Kozlowski

213. Gold(I) catalyzed synthesis of 1H-isochromenes. **J. Mouat**, Z.A. Grimm, D.M. Butler, C. Lacker, M.R. Gesinski

214. Gold-catalyzed Friedel–Crafts-like reaction of benzylic alcohols to afford 1,1-diaryllkanes. **A.K. Melanese**, R.G. Iafe

215. Generation of carbamate-derived nitrenes and evaluation of their inter- and intramolecular reactivity with alkenes. **B. Lee**, **W. Mohamed**, A.W. Bunnell, E.C. McLaughlin

216. Demystifying Cp₂Ti(H)Cl and its enigmatic role in the reactions of epoxides with Cp₂TiCl. **J.P. Gordon**, S. Hildebrandt, K. Dewese, S. Klare, A. Gansäuer, T. RajanBabu, B. Nugent

217. Synthesis of a variety of chiral triazolylidene-metal complexes and investigation on the catalytic activity. **k. torita**

218. Stereoselective synthesis of 1,2,3-cis oxazolidinone-containing 2-amino sugars via fully intramolecular amidoglycosylation. **A. Banerjee**, **E. Latif**, C.M. Rojas

219. Exploring nickel catalysis in allene synthesis. **S. Hejnosz**, T.D. Montgomery

220. Ru-catalyzed migratory geminal semi-hydrogenation of internal alkynes to terminal olefins. **Q. Feng**, J. Sun

- 221.** Copper-catalyzed disilane activation and hydrosilylation of aldehydes via an intermediate brook rearrangement. **C.E. Nuyen**, J. Wilkinson, R. Van Hoveln
- 222.** Synthesis of naturally occurring compounds via ketenimines. **A.K. Isaacs**
- 223.** Molybdenum-promoted synthesis of isoquinuclidines with bridgehead CF₃ groups. **J.H. Wilde**, W.D. Harman
- 224.** Synthesis and use of amidine ligands for catalyst development. **M. Laeini**, S.B. Luesse
- 225.** Convenient synthesis of spliceostatin derivatives. **J. Born**, A.K. Ghosh
- 226.** Synthetic and catalytic studies of metalloporphyrin and metallosalen complexes for biomimetic oxidations. **F. Bratcher**, A. Dames, R. Zhang
- 227.** Four-substrate guided inquiry scheme towards the synthesis of 2,2'-bipyridine adducts. **K. Wilkinson**, **F. Gruzmark**, **B. Aukszi**
- 228.** Synthesis and characterization of novel hybrid palladium (0) catalysts. **C.S. Strong**, M. Cadena, E. Thomas, D.E. Frantz
- 229.** Synthesis and characterization of ZNO nanoscale deposited on glass substrate at low temperature and atmospheric pressure for energy application in solar system. **L. Williams**, A. Kamara, L. Lewis
- 230.** Titanium promoted cross-electrophile coupling of imines with Weinreb amides: Modular approach to synthesize α -aminoketones. **O.a. Alkhamayseh**, S. Silwal
- 231.** Copper-mediated sp³-sp³ cross-coupling reactions with turbo Grignard reagents. **G. Petrucino**, S. Elahi-Mohassel, M. Paige
- 232.** Ring opening metathesis polymerization (ROMP) on [2.2.2]-diazabicyclic substrates. **M. Charlton**, J.R. Scheerer

MONDAY MORNING

Section A

Pennsylvania Convention Center
116

New Reactions & Methodology

S. M. Silverman, *Organizer*

8:00 233. Synthesis of indolines and derivatives via aza-Heck cyclization. **F. Xu**, K.M. Korch, D.A. Watson

8:20 234. Are aryl-aryl cross couplings and amidation reactions feasible and compatible under sunlight irradiation?. **A. Bugarin**

8:40 235. Hiyama cross-coupling of fully-substituted vinylsilanes. **S.B. Krause**, A. Conner, D.A. Watson

9:00 236. Palladium-catalyzed three component carbosilylation of internal symmetrical alkynes: Synthesis of tetrasubstituted vinylsilanes. **S.B. Krause**, M. Wisthoff, A. Cinderella, D.A. Watson

9:20 237. Generating dioxacarbenes from carbonates and thiocarbonates and the implications for the mechanism of the Corey-Winter olefination. **T.L. Troyer**, V. Sauve, K.E. Knopf

9:40 238. Halogenation of pyridines via heteroaryl phosphonium salts. **J. Levy**, R. Liu, J.V. Alegre-Requena, R.S. Paton, A. McNally

10:00 239. Solvent-free, methyl borate-catalyzed reductive amination with ammonia borane. **S. Choudhary**, A. Singh, P.V. Ramachandran

10:20 240. Amine-boranes as dual-purpose reagents for direct amidation of carboxylic acids. P.V. Ramachandran, **H. Hamann**

10:40 241. Ammonia-borane-catalyzed direct amidation of carboxylic acids and amines. **H. Hamann**, S. Choudhary, P.V. Ramachandran

11:00 242. Carbon dioxide-mediated synthesis of amine-boranes. **D.O. Reddy**, P.V. Ramachandran, A.S. Kulkarni

11:20 243. Rhodium-mediated electrophilic ^{18}F -oxyfluorination of diazoketones. **M.A. Cortes Gonzalez**, X. Jiang, P. Nordeman, G. Antoni, K.J. Szabo

11:40 244. Advances in NBS oxidation: Synthesis of symmetric and benzyl esters. **R.A. Koziel**, J.D. Fair, M.R. Luderer

Section B

Pennsylvania Convention Center
117

CH Activation

S. M. Silverman, *Organizer*

9:00 245. Hydrogen bond mediated supramolecular silver-phenanthroline catalyzed enantio- and site-selective intermolecular C(sp³)-H amination. **R. Annapureddy**, T. Bach

9:20 246. Carboxylate-assisted oxidative addition to aminoalkyl-Pd^{II} complexes: C(sp³)-H functionalization of alkylamines by distinct Pd^{II}/Pd^{IV} pathway. **W.G. Whitehurst**, H. Blackwell, G. Hermann, M. Gaunt

9:40 247. New monodentate directing groups for C-H bond functionalization. **H. Nguyen**, O. Daugulis

10:00 248. Orange-red fluorescent Cinnolino[2,3-*f*]phenanthridin-9-ium salts by palladium(II)-catalyzed C-H bond activation of 2-azobiaryls and alkenes. **S. Chuang**

10:20 249. Ir-catalyzed C-H functionalization of the alkaloid mitragynine : Late stage selective functionalization at indole via complex core restructuring. **S. Bhowmik**, J. Galeta, V. Havel, D. Sames, S. Majumdar

10:40 250. *N*-aminopyridinium ylide-directed C-H bond functionalization. **S. Kwak**, O. Daugulis

11:00 251. Explorations into a strain-mediated Norrish-Yang reaction and cross-coupling of cyclic amines. **R. LaLonde**

11:20 252. Fluoroalkenylidonium reagents in palladium-catalyzed ortho-C-H Activation of aromatic and heteroaromatic compounds. **B. Tóth**, G. Salyi, O. Egyed, A. Bényei, Z. Novák

Section C

Pennsylvania Convention Center
120A

Advances in Macrocyclic Design: Computational & Biophysical Methods

Cosponsored by COMP

A. N. Jain, M. Y. Reibarkh, E. C. Sherer, S. M. Silverman, *Organizers*

8:15 Introductory Remarks.

8:30 253. Macrocyclization of small-molecule ligands in drug discovery. **M.D. Cummings**

8:55 254. Toward ligand-based and structure-based macrocyclic design. **A.N. Jain**, A. Cleves

9:20 255. Discovery of bioactive, passively permeable cyclic peptides: Translating theory into practice. **S. Lokey**

9:45 256. Advances in macrocycle design, modeling and affinity estimation. **C.D. Christ**

10:10 Intermission.

10:35 257. Conformational analysis of macrocycles in solution and the solid-state. **P.C. Hawkins**, C.A. Sader, S. Wlodek

11:00 258. Novel and robust NMR-based conformational analysis to advance 3D structure characterization of cyclic peptides. **Q. Gao**, X. Wang, Y. Liu, E.C. Sherer, A.N. Jain, M. Reibarkh

11:25 259. Modeling macrocyclic peptides with integrated structure and sequence methods. **S. Posy**

Section D

Pennsylvania Convention Center
120B

Successful Products & Models of Undergraduate-Based Research: Good Science, Better Scientists

J. J. Reczek, K. A. Wheeler, *Organizers, Presiding*

8:20 Introductory Remarks.

8:25 260. Supramolecular ligands as extractants for *f*-elements. **S.M. Biros**, E.J. Werner

8:50 261. Exploring the intricacies of titanium alkoxide catalysts for ring-opening polymerization with undergraduate researchers. **C.B. Durr**

9:15 262. On the hunt for novel heterocycles: Nitrogen in small rings. **G. Moura-Letts**

9:40 263. Turning unexpected results into discoveries: Development of new tools to capture and study transient interactions of biosynthetic proteins. **L.K. Charkoudian**

10:05 Intermission.

10:20 264. Nickel catalyzed arylation of oxazoles using pharmaceutically relevant aryl halides. **D. Kalyani**

10:45 265. Uncovering the identity of the active species in ruthenium-catalyzed ester hydrogenation. **A.R. Chianese**, T. He, J.C. Buttner, J.C. Malek, E.F. Reynolds, J. Pham, J.M. Keith

11:10 266. Photochemical reactions of *S*-aryl thioformates: Toward a synthesis of oxetanes via formal formylation. **S.Z. Tasker**, O. Mautone, D. Alagic

11:35 267. Adventures with undergraduate research collaborators: Organic transformations driven by simple molecular interactions. **T.A. Davis**, A. Hornsby, S. Gardner, R. Miller

Section E

Pennsylvania Convention Center
118A

Importance of Innovative Synthetic Chemistry in Pharmaceutical Process Research & Development

S. M. Silverman, *Organizer*

K. M. Maloney, N. Patel, *Organizers, Presiding*

8:00 Introductory Remarks.

8:05 268. Amides and chemical education as vehicles for innovation. **N.K. Garg**

8:50 269. Development of a commercial manufacturing process for BRIDION® (sugammadex). **D. Thaisrivongs**

9:20 270. Biocatalysis and complex molecule synthesis. **A.R. Narayan**

10:05 Intermission.

10:15 271. Covering our bases: Development of scalable and reproducible cross-coupling reactions. **R.A. Green**

10:45 272. Enabling technology development and application in CDMO industry-practical examples of solving challenge synthetic problems. **J. Zhu**

11:15 273. Remote, selective C-H functionalization via radical chaperones. **D. Nagib**

Section F

Pennsylvania Convention Center
115A

James Flack Norris Award in Physical Organic Chemistry

8:30 Introductory Remarks.

8:35 274. Stereoselective addition reactions to carbon electrophiles: Conformational analysis, stereoelectronic effects, and reactivity. **K.A. Woerpel**

9:05 275. Making carbon–phosphorus bonds with visible light: Challenges and opportunities. **S. LAKHDAR**

9:35 276. Insights into organic reactivity through gas phase computational and experimental studies. **J. Lee**

10:05 Intermission.

10:25 277. Physical organic chemist's journey into fluoroalkylation chemistry. **S.G. Prakash**

10:55 278. Discovery and optimization of enantioselective catalysts through chemoinformatics. **S.E. Denmark**

11:25 Award presentation.

11:30 279. Award Address (James Flack Norris Award in Physical Organic Chemistry sponsored by the ACS Northeastern Section). Quantifying polar organic reactivity. **H. Mayr**

12:00 Concluding Remarks.

MONDAY AFTERNOON

Section A

Pennsylvania Convention Center
116

New Reactions & Methodology

S. M. Silverman, *Organizer*

1:00 280. Synthesis of 1,4-diketones via titanium-mediated reductive homocoupling of α -haloketones. **N.N. Le**, A.M. Rodriguez, J.R. Alleyn, M.R. Gesinski

1:20 281. Intercepted rearrangement reactions via iron catalyzed carbene transfer reactions with diazoacetonitrile. **C. Empel**, R.M. Koenigs

- 1:40 282.** Boracarboxylation of α -substituted vinyl arenes. **S. Knowlden**, B.V. Popp
- 2:00 283.** Innovation at a molecular level: Scaffold analysis of CAS registry. **T. Wills**, M. MCBRIDE
- 2:20 284.** Synthesis of *anti*- and *syn*-hydroxymethyl 1,3-diol motifs based on the regioselective cleavage of 2,3-epoxy diols using organomagnesium and organoaluminum reagents: Application to the polypropionate synthesis. **R.R. Rodriguez Berrios**, J.A. Prieto
- 2:40 285.** Synthesis of guaipyridine alkaloids cananodine and rupestines G and D. **J.R. Vyvyan**, P.M. Shelton, S. Grosslight, H.V. Spargo, B.J. Mulligan
- 3:00 286.** Diastereoselective transformations of macrocyclic 1,4-diketones and their application to the total synthesis of cyclobutane-containing natural products. **K.F. Johnson**, T.H. Barnes, B.L. Merner
- 3:20 287.** Pharmacophore-directed retrosynthesis applied to rameswaralide: Synthesis and bioactivity of *Sinularia* natural product tricyclic cores. **N.J. Truax**, S. Ayinde, K.N. Van, J. Liu, D. Romo
- 3:40 288.** Synthesis and structure activity studies of indene-based SHIP1 agonists. **J.D. Chisholm**, O.M. Dungan, B. Duffy, D.G. Effiong, S. Fernandes, W.G. Kerr
- 4:00 289.** Enantioselective total synthesis of oxazolomycin B, inthomycin C, and formal synthesis of neooxazolomycin. **C.M. Chaheine**, P.J. Sutter
- 4:20 290.** New strategies for *N*-nitrosation. **R. Baxter**
- 4:40 291.** Novel umpolung strategies enabled by hypervalent iodine reagents. **S. Wengryniuk**

Section B

Pennsylvania Convention Center
117

Molecular Recognition & Self-Assembly

S. M. Silverman, *Organizer*

- 1:20 292.** Supramolecular structures with intrinsic microporosity for "on-demand" separations and delivery applications. **N.M. Khashab**
- 1:40 293.** Fluorinated multiblock amphiphiles that transport ions across lipid bilayers. **K. Sato**, K. Nabeya, T. Muraoka, N. Hoshino, T. Akutagawa, K. Kinbara

- 2:00 294.** Cycloparaphenylene-based semiconducting host-guest complexes and rotaxanes stabilized by CH– π interactions. **H. Kwon**, C.J. Bruns
- 2:20 295.** Directing peptide self-assembly via chirality. K. McAulay, L. Marshall, B. Dietrich, E. Draper, A. Seddon, **D.J. Adams**
- 2:40 296.** Guest folding inside cucurbit[8]uril. **R. Rabbani**, H. Barbero, M. Raeisi, E. Masson
- 3:00 297.** Systematic investigation of chalcogen bonding interactions using X-ray analysis. **M.R. Ams**, A. Verardi, A. Verardi
- 3:20 298.** Self-sorting of ditopic Pt(II) terpyridyl thiolate complexes with cucurbiturils. **H. Barbero**, E. Masson
- 3:40 299.** Templating conformations with cucurbiturils. **N.A. Thompson**, H. Barbero, E. Masson
- 4:00 300.** Hydrocarbon sensing with cucurbit[8]uril and an auxiliary probe. **M. NAZIMUDDIN**, E. Masson
- 4:20 301.** Self-sorting in dynamic disulfide assembly: New unsymmetrical cyclophanes. **N. Phan**, L. Zakharov, D.W. Johnson
- 4:40 302.** Self-sorting networks using hydrogen-bonding building blocks. **A.J. Wilson**

Section C

Pennsylvania Convention Center
120A

Advances in Macrocyclic Design: Computational & Biophysical Methods

Cosponsored by COMP

A. N. Jain, M. Y. Reibarkh, E. C. Sherer, S. M. Silverman, *Organizers*

1:15 Introductory Remarks.

1:30 303. Accelerating the macrocycle pharmaceutical design pipeline *in silico*. **D.J. Sindhikara**, K. Borrelli

1:55 304. Development and application of computational analysis and prediction tools for macrocyclic peptide conformational space. **A. Brueckner**, Q. Deng, E.C. Sherer, A.N. Jain, P. Trigo Mourino, J. Frost, M. Reibarkh, D.M. Tellers

2:20 305. Structure-based design of potent macrocycles MCL1 inhibitors. **M.G. Cardozo**, S.P. Brown, h. Paul, p. leszek, D. Whittington

2:45 306. Design of cyclic peptide C5a antagonists guided with computational and NMR studies. **Y. Che**

3:10 Intermission.

3:25 307. Conformational analysis of peptide macrocycles for drug design. **J. Johnston**, Q. Deng, S.N. Ha, S. Schneider, G. Murphy, E.C. Sherer

3:50 308. Rationalization of the membrane permeability differences in structurally similar cyclic peptides. **S. Riniker**

4:15 309. Computational design of functional cyclic peptides. **P. Hosseinzadeh**

Section D

Pennsylvania Convention Center
120B

Advances in on-DNA Reaction Development for Encoded Library Technologies

Cosponsored by MEDI

Y. Ding, L. Marcaurelle, *Organizers, Presiding*

1:20 Introductory Remarks.

1:25 310. Diversity-based DEL development and construction. **X. Wang**

1:55 311. Reaction development for DNA-encoded library synthesis: Exploring heterogeneous systems. **A. Brunschweiler**

2:25 312. DNA-encoded libraries: Aryl fluorosulfonates as versatile electrophiles enabling facile on-DNA cross-coupling reactions. **H. Xu**, F. Ma, P. Ma, G. Yang, R. Lerner

2:55 Intermission.

3:10 313. DEL out of water: Expanding DNA compatible chemistry in organic solvents. **D. Flood**, P. Dawson

3:40 314. Application of enzymes to on-DNA reactions. **J. Chai**

4:10 315. Single electron processes to enable DEL synthesis. **G.A. Molander**

4:40 Concluding Remarks.

Section E

Pennsylvania Convention Center
118A

Importance of Innovative Synthetic Chemistry in Pharmaceutical Process Research & Development

S. M. Silverman, *Organizer*

K. M. Maloney, N. Patel, *Organizers, Presiding*

1:30 316. Molecular complexity the driving force for chemical process innovation at Amgen.
J.S. Tedrow

2:00 317. Deaminative cross-couplings via C–N bond activation. **M.P. Watson**

2:45 318. Development towards a potential commercial route for an IRAK4 inhibitor PF-06650833. **Z. Peng**, B. Li, E. McInturff, D. Place, R.A. Singer, L. Wei

3:15 319. Innovative process development to access 2-fluoroadenine for islatravir. **Y. Xu**

3:45 320. Stereocontrol in photochemical synthesis. **T.P. Yoon**

4:30 Concluding Remarks.

Section F

Pennsylvania Convention Center
115A

Ernest Guenther Award in the Chemistry of Natural Products

K. Maloney, *Presiding*

1:00 Introductory Remarks.

1:05 321. Chemical and functional characterization of natural products. **J. MacMillan**

1:40 322. Taking a deep dive into natural products chemistry and structure determination. **C. Bewley**

2:15 323. Discovery of bioactive marine natural products. **R.J. Andersen**

2:50 324. Progress in Absolute Stereochemical Determination of Organic Molecules via Exciton Coupled Circular Dichroism. **B. Borhan**

3:25 325. Evolution of the anion relay chemistry: Construction of architecturally complex natural products. **A.B. Smith**

4:00 326. Marine natural products: Discovery and invention from the 'wine dark sea'. **T.F. Molinski**

4:50 Award Presentation.

MONDAY EVENING

Section A

Pennsylvania Convention Center
Exhibit Hall A

Sci-Mix

E. C. McLaughlin, S. M. Silverman, *Organizers*

8:00 - 10:00

108, 111, 118, 120, 121, 128, 129, 143, 148, 150, 153, 156, 157, 158, 165, 166, 183, 185, 190, 193, 196, 202, 206, 212, 213, 216, 223, 229. See Previous Listings.

439, 446, 448, 450, 454, 455, 462, 466, 471, 473, 481, 484, 485, 489, 490, 495, 499, 505, 514, 518, 519, 522, 527, 529, 535, 537, 540, 549, 555, 661, 671, 673, 675, 676, 677, 681, 682, 689, 690, 693, 702, 709, 716, 718, 723, 724, 738, 741, 743, 747, 748, 749, 751, 752, 757. See Subsequent Listings.

TUESDAY MORNING

Section A

Pennsylvania Convention Center
116

New Reactions & Methodology

S. M. Silverman, *Organizer*

8:00 327. Pd-catalyzed preparation cyclic alkenylsulfonyl fluorides: New motif for sulfur fluoride exchange. **S.W. Bagley**, T. Lou, M.C. Willis

8:20 328. Chemoselective oxidation of equatorial alcohols with nitrogen-ligated λ^3 iodanes. **M. Mikhael**, S. Adler, S. Wengryniuk

8:40 329. Expanding the synthetic tool box: Methodology development of 1,3 dicarbonyls and α -alkylated azo-alkenes. **S. Aderibigbe**, D.M. Coltart

9:00 330. Amplification of N-halo reagent electrophilicity by organic dye visible-light photoredox catalysts for the halogenation of arenes and heteroarenes. **D. Rogers**, A. Lamar

9:20 331. Hypervalent iodine reagent-mediated formation of bioactive N-benzylsulfonamides from aryl and heteroaryl aldehydes. **M.D. Hopkins**, A. Lamar

9:40 332. Novel synthesis of 5-, 6-, or 7-iodoindenes. **A. Howlader**, K. Diaz, A.M. Mebel, R. Kaiser, S.F. Wnuk

10:00 333. Highly functionalized azetidines by visible light mediated [2+2] cycloadditions. **A.D. Richardson**, M. Becker, C. Schindler

10:20 334. Mitsunobu coupling enables the improved synthesis and simple purification of therapeutically relevant phosphoramidates. **V. Yan**, C. Pham, F. Muller

10:40 335. One-pot pyridine alkylation via traceless dearomatized pyridyl phosphonium ylides. **P. Fricke**, R. Dolewski, A. McNally

11:00 336. Modular approach to non-symmetric polycyclic aromatic hydrocarbons. **M. Ramirez**, N.K. Garg

11:20 337. Oxazoles from alcohols and nitriles via tandem hydrogen atom transfer. **J. Herbort**, D. Nagib

11:40 338. Photochemical reactions of benzophenone derivatives under microfluidic conditions. **X. Companyo**, J. Mateos, A. Cherubini-Celli, M. Bonchio, L. Dell'Amico

Section B

Pennsylvania Convention Center
117

Asymmetric Reactions & Syntheses

S. M. Silverman, *Organizer*

8:20 339. Ibuprofen as a probe of lipid metabolism. **J.A. Rosales**, J.M. Salvador

8:40 340. Synthesis of allyl and allenyl boronic acids and their applications in chiral organocatalysis. **S. Jonker**, J. Zhao, D.N. Meyer, G. Schulz, D. Tran, L. Eriksson, K. Szabó

9:00 341. Chiral anions with cobalt(III) hydrogen bond-donor catalysts. **C.Q. Kabes**

9:20 342. New stereoselective C-C and C-H bond formations enabled by flavoprotein photocatalysis. **S.J. Cooper**, K. Biegasiewicz, X. Gao, D. Oblinsky, J. Kim, S. Garfinkle, L. Joyce, B. Sandoval, G.D. Scholes, T. Hyster

9:40 343. *De novo* synthesis of phomopsolide E analogues. **A. Aljahdali**, S. Freedman, G.A. O'Doherty

10:00 344. Selective functionalization of heterocycles via myoglobin-catalyzed carbene transfer chemistry. **D. Vargas**, R. Fasan

10:20 345. Stereospecific synthesis of all-carbon quaternary centers via C–O bond activation. **J. Xu**, M.P. Watson

10:40 346. Catalytic enantioselective synthesis of cyclobutenes from alkynes and alkenyl derivatives. **M. Parsutkar**, V.V. Pagar, T.V. RajanBabu

11:00 347. Enantioselective, copper-catalyzed alkynylation of cyclic iminium ions lacking stabilizing groups. **W. Guan**, S. Santana, J. Liao, M.P. Watson

11:20 348. Catalytic asymmetric synthesis of cyclopentanones and tetrahydrofurans from ketenes and donor-acceptor cyclopropanes. **N. Kerrigan**, M. Mondal, M. Panda, C. Bergado

Section C

Pennsylvania Convention Center
120A

Green Methods & Syntheses

S. M. Silverman, *Organizer*

8:20 349. Scalable synthesis of a cyclobutane-1, 2-diacid and its derivatives from *trans*-cinnamic acid via photoreaction. **H.S. Amjaour**

8:40 350. Third or sustainable approach in synthesis of drugs or agrochemicals using cross-coupling reactions. **B. Takale**, R.R. Thakore, B.H. Lipshutz

9:00 351. Synthesis of sulfones from their component sulfides using $[\{\text{MoO}(\text{O}_2)_2\}_2(\mu\text{-O})]^{2-}$ catalyzed hydrogen peroxide reactions. **S. Wilger**, C.W. Cunningham, D. Thompson

9:20 352. New monomers from biomass. M. Wei, C. McNeff, E. Serum, C. Sutton, **M.P. Sibi**

9:40 353. Harnessing the power of biocatalysis and integrating cross-coupling chemistry to realize a novel greener synthetic routes for statins. **C.M. Amarasekarage**, K. Belecki

10:00 354. Green one-step synthesis of substituted oxoisoindolines. **B.J. Andersh**, J.M. Kuhns

10:20 355. Applying process intensification principles to the anti-retroviral drug lamivudine (3TC) to improve global health access. **S. James**, F. Gupton, K. Belecki

10:40 356. Biocatalysis and continuous processing as strategies to promote streamlined and green pharmaceutical processes. **K. Belecki**

11:00 357. Big-data driven solvent selection via deep learning to facilitate the discovery of green synthetic methodology. **A. Beck**, J. Fine, K. Jethava, **G. Chopra**

11:20 358. Regioselective, solvent- and metal-free approach to access C-5 chalcogenation of imidazo[2,1-*b*]thiazoles by employing I₂/DMSO as catalytic oxidation system. **J. Khan**

Section D

Pennsylvania Convention Center
120B

Modern Methods in Polymer Chemistry

Cosponsored by POLY

B. P. Fors, S. M. Silverman, *Organizers*

J. A. Kalow, *Organizer, Presiding*

J. P. Lutz, *Presiding*

8:00 Introductory Remarks.

8:05 359. Polymerization promoted by substrate photoexcitation. **J.A. Kalow**

8:35 360. Spatially controlled polymer properties through wavelength-selected cross-linking. **B. Buss**, G. Miyake

8:55 361. Photon energy upconversion photoredox catalysis. **L.M. Campos**

9:25 362. Effect of photo-ATRP components on oxygen consumption. **A. Anastasaki**

9:55 Intermission.

10:10 363. Designer molar mass distributions beyond dispersity variations. **T. Junkers**

10:40 364. Tuning molecular weight distribution of polymer through flow chemistry. D. Walsh, **D. Guironnet**

11:10 365. Designing functionalized and degradable polyphthalaldehyde derivatives. **J.P. Lutz**, O. Davydovich, M. Hannigan, J. Moore, P.M. Zimmerman, A.J. McNeil

11:30 366. Stereoselective cationic polymerization of vinyl ethers: New class of polar thermoplastics. **F.A. Leibfarth**

Section E

Pennsylvania Convention Center
118A

Approaches & Applications in Enzyme Engineering

S. M. Silverman, *Organizer*
M. Chiriac, M. Ford, *Presiding*

8:00 Introductory Remarks.

8:10 367. Unleashing the power of enzyme engineering in pharmaceutical research and development. **D.E. Fuerst**

8:45 368. Chiral synthesis of LSD1 inhibitor GSK2879552 enabled by directed evolution of an imine reductase. **C.M. MacDermid**, D. Roiban, M. Schober, A. Ollis, S. Chang, D. Khan, J. Hosford, J. Latham, L.A. Ihnken, M. Brown, D.E. Fuerst, M. Sanganee

9:20 369. Enantioselective C-H amination via directed evolution of cytochrome P450 enzymes. **Y. Yang**, F.H. Arnold

9:55 Intermission.

10:15 370. Computational pathway and enzyme design for synthetic biochemistry. **A. Zanghellini**

10:50 371. Computational enzyme modeling in development of a biocatalytic cascade for the manufacture of Islatravir (MK-8591). **L. Xiao**

11:20 372. Discovery and engineering of a biocatalytic cascade for the manufacture of Islatravir (MK-8591). H. Yang, **L. Xiao**

11:50 Concluding Remarks.

Section F

Pennsylvania Convention Center
Michael A Nutter Theatre

ACS Award for Creative Work in Synthetic Organic Chemistry

R. D. Broene, *Presiding*

8:00 Introductory Remarks.

8:05 373. *De novo* oligosaccharide synthesis and medicinal chemistry. **G.A. O'Doherty**

8:40 374. New catalysts and strategies that enable discoveries in natural product-based therapeutic development. **J.N. Johnston**

9:15 375. Chematica: Computer-planned syntheses of natural products and their experimental execution. **B. Grzybowski**

9:50 376. Metabolism before enzymes. **J. Moran**

10:25 377. Single electron processes enabling organic synthesis. **G.A. Molander**

11:00 Introduction of the Award Winner.

11:05 378. Hydrogen-mediated C-C bond formation. **M.J. Krische**

ACS Awards in Biological Chemistry (Bader, Breslow, Hach & Hirschmann Awards)

Sponsored by BIOL, Cosponsored by ORGN

TUESDAY AFTERNOON

Section A

Pennsylvania Convention Center
116

New Reactions & Methodology

S. M. Silverman, *Organizer*

1:00 379. Domino Michael/Mannich reactions of simple aliphatic (acyclic) substrates. **X. Jin**, V.K. Chatare, P. Yu, R.B. Andrade

1:20 380. Utilizing a [3+1] cycloaddition methodology for asymmetric synthesis of azetines and researching subsequent reactions. **N. Greco**, K. Marichev, M.P. Doyle

1:40 381. Blue light mediated photochemical carbene transfer reactions. **R.M. Koenigs**

2:00 382. To rearrange or not? Controlling the reactivity of onium ylides. **R.M. Koenigs**

2:20 383. Synthesis, Cytotoxic activity of novel tetracyclic acridone derivatives. **J. Anireddy**, R. V

2:40 384. Scope and recent applications of Co-mediated 1,3-diene isomerization. **K.r. Delgado**, D. Youmans, S.T. Diver

3:00 385. Rapid isocyanide-induced dearomatization to complex cyclohexadienes. **A.B. Altundas**, F.F. Fleming

3:20 386. Trifluoropropenyl iodonium salt: Platform for straightforward synthesis of trifluoromethylated vicinal diamines and substituted trifluoropropylamines. **F. Béke**, Á. Tóth, Á. Mészáros, Z. Novák

3:40 387. Lewis acid-catalyzed intermolecular ring-opening and cross carbonyl-olefin metathesis reactions. **H.L. Vonesh**, H. Albright, C. Schindler

4:00 388. Superelectrophilic aluminum(III)-ion pairs promote a distinct reaction path for carbonyl-olefin metathesis of medium-sized rings. **A.J. Davis**, R. Watson, C. Schindler

4:20 389. Unified strategy for the synthesis of pyridines, β - & γ -carbolines, and other fused azaheteroaromatics under mild, metal-free conditions. **D. Uredi**, D.R. Motati, E. Watkins

Section B

Pennsylvania Convention Center
117

Photoredox Chemistry

S. M. Silverman, *Organizer*

1:20 390. Development of a photoredox catalysis-mediated hydroazidation method for electron-rich olefins. N.P. Onuska, **M. Schutzbach-Horton**, J.L. Rosario Collazo, D.A. Nicewicz

1:40 391. Photo-catalyzed linear selective hydrocarboxylation of electron-deficient alkenes with CO₂ under flow. **k. guowei**

2:00 392. Opening a can of glow-worms: Tandem photoredox catalysis of $[\text{Ir}(\text{ppy})_2(\text{dtb-bpy})]^+$. **T.U. Connell**, C.L. Fraser, M.L. Czyz, D.E. Gomez, A. Polyzos, P.S. Francis

2:20 393. Exploring green photoredox routes for CO_2 reduction. K. Kron, **S. Mallikarjun Sharada**

2:40 394. Chemical method for selective functionalization at N^6mdA residues in DNA. **M. Nappi**, A. Hofer, S. Balasubramanian, M. Gaunt

3:00 395. Homolysis of alcohol O–H bonds via proton-coupled electron transfer. **H. Wang**, H. Yayla, K. Tarantino, E. Ota, N.L. Frye, E. Kran, R.R. Knowles

3:20 396. Light-driven depolymerization of native lignin enabled by proton-coupled electron transfer. **S. Nguyen**, P. Murray, R. Knowles

3:40 397. Water-soluble, organic fluorophores with powerful electrochemical and photophysical properties. **C. Fischer**, C. Sparr

4:00 398. Novel dioxolane mediated formylation of heteroarenes: Complementarity between photoredox and thermal conditions. **D.J. Berthelot**, C. Bosset, J.P. Edwards, L. Meerpoel

Section C

Pennsylvania Convention Center
120A

Total Synthesis of Complex Molecules

S. M. Silverman, *Organizer*

1:00 399. Michael-Dieckmann cyclisations in routes towards rishirilide A. **K. Ho**, M.J. Hall

1:20 400. Total synthesis of aspidosperma alkaloids utilizing a cascade Suzuki–Miyaura/Diels–Alder reaction. **D. Cain**, N. Anderson, A.J. Watson

1:40 401. Total synthesis of (–)-strictosidine. **S. Anthony**, N.K. Garg

2:00 402. Application of chemical network analysis toward the total synthesis of arcutinidine. **S. McCowen**, K.R. Owens, K. Blackford, S. Ueno, Y. Hirooka, M. Weber, R. Sarpong

2:20 403. Synthetic studies toward citrofulvicin. **K. Doytchinova**, J.D. Winkler

2:40 404. Synthesis and evaluation of novel ester derivatives of (+)-saxitoxin. **T.A. Bedell**, A. Elleman, J. Du Bois

3:00 405. Total synthesis of chalaniline B: Antibiotic xanthone from epigenetically-treated endophytic fungus *Chalara*. **M. Khoshbakht**, B. Thanaussavadata, Y. Cao, S. Loesgen, P.R. Blakemore

3:20 406. Application of a C–C cleavage strategy for the total synthesis of taxoid natural products. **M. Perea**, B.S. Wang, N. O'Connor, S. Nagasawa, B. Wyler, R. Sarpong

3:40 407. Total synthesis of altemicidin. **G. Tadano**, K. Tanino

4:00 408. Total synthesis of clavadinone B. **S. Chamberland**, M.T. Davenport, J.A. Dickson, M.R. Johnson

4:20 409. Total synthesis of the brocazine and chemical diversification. W. Hulangamuwa, C. House, A.C. Ebert, H. Dembele, **R. Rafferty**

4:40 410. Beyond total synthesis: Synthetic adventures in chemical screening library construction, therapeutic agent potentiation, and facilitated transport. P. Desman, W. Hulangamuwa, C. Weeramange, T. Nguyen, A.I. Lansakara, J. Dallman, H. Henderson, A. Torres, A. Bartels, **R. Rafferty**

Section D

Pennsylvania Convention Center
120B

Modern Methods in Polymer Chemistry

Cosponsored by PMSE

J. A. Kalow, S. M. Silverman, *Organizers*

B. P. Fors, *Organizer, Presiding*

M. Golder, *Presiding*

1:00 411. Discovering catalyst design rules for conjugated polymer synthesis. **M. Hannigan**, P.M. Zimmerman, A.J. McNeil

1:20 412. Tuning the twist in amide monomers for halide-rebound polymerization. **W. Gutekunst**

1:50 413. C-H functionalization: Viable route to materials. **C.N. Scott**, C. Rathnamalala, I. Rajapaksha, D. Feng

2:20 414. Design and study of bifunctional catalytic systems for polyester synthesis via the alternating ring-opening copolymerization of epoxides and cyclic anhydrides. **C. Lidston**, B.A. Abel, G.W. Coates

2:40 Intermission.

2:55 415. Building block strategies to functional polymers. **R.S. Klausen**

3:25 416. Organoborane strategy for polymers bearing lactone, ester, and alcohol functionality. **y. Ji, R.S. Klausen**

3:45 417. Radical cascade-driven polymerization. **J. Niu**

4:15 418. Controlled radical polymerisation using high frequency ultrasound. **J. Collins, T.G. McKenzie, G.G. Qiao**

4:35 419. Polymer mechanochemistry: Constructive approach. **J. Kim**

4:55 Concluding Remarks.

Section E

Pennsylvania Convention Center
118A

Chemical & Biological Synthesis of Anti-Infective Agents

J. G. Pierce, *Organizer*

M. K. Brown, *Organizer, Presiding*

J. Pierce, *Presiding*

1:00 Introductory Remarks.

1:05 420. Application of the seleno-Pummerer reaction to the construction of β -mannosides: Synthesis of the *K. pneumoniae* tetrasaccharide antigen. Y. Guan, **S.D. Townsend**

1:30 421. Slaying superbugs one natural product at a time. **W.M. Wuest**

1:55 422. Microbial synthesis of antibiotics and virulence molecules. J.B. Patteson, G.L. Morgan, **B. Li**

2:20 423. Adventures in the synthesis of antimicrobial natural products. **J.G. Pierce**

2:45 Intermission.

3:00 424. New antibiotics from old natural products. **I. Seiple**

3:25 425. Novel compounds towards overcoming resistance in tuberculosis. **S. Garneau-Tsodikova**

4:00 426. Winners and losers in early stage antifungal drug discovery. **M.K. Brown**

4:25 427. Total synthesis of natural product antibiotics. **S.E. Reisman**

Section F

Pennsylvania Convention Center
Michael A Nutter Theatre

Herbert C. Brown Award for Creative Research in Synthetic Methods

S. M. Silverman, *Organizer*

L. T. Scott, *Presiding*

1:30 428. Selective catalytic reactions in complex molecular scaffolds. **S.J. Miller**

2:15 429. Total biosynthesis of plant-derived therapeutics. **E. Sattely**

3:00 430. Recent advances in enantioselective cooperative catalysis. **M. Wasa**

3:45 431. Enantioselective synthesis with Cu-based catalysts and organoboron compounds. **A.H. Hoveyda**

Organic Chemistry Education: Research to Practice

Sponsored by CHED, Cosponsored by ORGN

TUESDAY EVENING

Section A

Pennsylvania Convention Center
Exhibit Hall A

Biologically-Related Molecules & Processes

E. C. McLaughlin, *Organizer*

5:30 - 7:30

432. Synthesis of glucosinolates via the nitronate pathway. **M.A. Anderson, M.R. Heiling, K.E. Ryan, J.R. Mays**

- 433.** Synthesis of an intermediate towards the total synthesis of the potential cytotoxic agent Callyspongamide A. E. Ruiz, A. Salazar, J. Lopez, K. Dankert, S. Rocha, **P.B. Carvalho**
- 434.** Synthesis and antibacterial evaluation of analogs of a new natural product of interest, denbinobin. **S. Wasserman**, A.L. Wolfe
- 435.** Evaluation of the antibacterial activity of simplified synthetic analogs of pestalone. **J. Hartig**, A.L. Wolfe
- 436.** Synthesis and antibacterial evaluation of pseudopyronine analogs. **J. Shumate**, A.L. Wolfe
- 437.** Synthesis of novel rearranged stemodane diterpenoids and their biotransformation by *Exophiala lecanii-corni*. **R. Pryce**, P.B. Reese
- 438.** Synthesis and characterization of nitric oxide donating poly(ester)s. **D.K. Mohanty**, C. Arnett-Butscher, A.W. Jensen
- 439.** Cross metathesis labeling with fluorescent probes for the identification and quantitation of unsaturated lipids. **O. Jayah**, R. Sapkota, J. Jarvis, T. Schaub, M. Talipov, J.B. Arterburn
- 440.** Synthesis and study of photophysical, redox properties of mixed melanin analogs of eumelanin and pheomelanin monomers. **E. Patel**, M. Brichacek
- 441.** Selenosulfides as versatile, electrophilic triggers for H₂S detection and imaging. **S.I. Suarez**, R. Ambrose, M. Kalk, J.C. Lukesh
- 442.** Synthesis of 3,4-dihydroxyhydrocinnamic acid analogues to investigate dioxygenase activity. **M. Betonio**, M.L. Cafiero, K.L. Colabroy, L. Peterson
- 443.** Synthesis of catechol derivatives as probes of dioxygenase mechanism. **E. Starr**, K.G. Sinojia, R. Mazumder, M.L. Cafiero, K.L. Colabroy, L.W. Peterson
- 444.** Biological ene reactions. **A.W. Jensen**, D.K. Mohanty, W.L. Dilling
- 445.** Design and synthesis of propargylglycine-based antibacterial compounds. **J.D. Greenberg**, R.J. Roldan, A.O. Pajarillo, M.L. Cafiero, E.R. Frawley, L.W. Peterson
- 446.** Ten-membered macrolides and other natural products isolated from the marine-derived fungus *Paraconiothyrium cyclothyrioides* through the manipulation of media composition. **O.K. Cherrington**, P.B. Reese, G. Nelson, D. Fearon
- 447.** Development of a benzothioate native chemical ligations-based cysteine-selective fluorescent probe. N. Kim, **H. Moon**, J. Kim, Y. Huh, Y. Kim, B. Kim, D. Kim
- 448.** Structure-activity relationships for beta-carboline behavior against the 5-Hydroxytryptamine receptor. **Y.A. Al-Issa**, S.P. Mulcahy

- 449.** Synthesis of quinoline-5,8-dione derivatives. **A. Jones, R.E. Sammelson**
- 450.** Cobalt III Schiff base inhibitor synthesis and biological protocol testing. **I.M. Haser, T. Whittemore, M.B. Ward, T.J. Meade**
- 451.** New bioorthogonal approaches for C-terminal protein modification. **H. Gu, S. Ghosh, N. Panitz, A. Ablicki, S.L. Bane**
- 452.** Development of enzyme responsive spin probes for non-invasive imaging of enzyme activity by EPR. **J. Huffman, U. Sanzhaeva, M. Poncelet, M. Tseytlin, V. Khramtsov, B. Driesschaert**
- 453.** Late stage derivation of podophyllotoxin using oxidative ring expansion. **A.J. Mellinger**
- 454.** Honokiol-inspired analogs as topical antibiotics. **H.F. Roenfanz, C. Ochoa, M. Kozlowski**
- 455.** Construction of an ethylene detecting metalloenzyme in *E. Coli* using a novel ruthenium-based probe. **M. Ellinwood, B.W. Michel, J.A. Latham**
- 456.** Optimization of fluorescent probes for the detection of ethylene in living systems. **S. Toussaint**
- 457.** Tethered glucose molecules in membranes: Can a longer spacer lead to closer approach?. **A.M. Hagwood, W.E. Allen**
- 458.** Diversification and exploration of the diazaxanthylidene scaffold toward highly florescent and efficient photoconvertible dyes for *in vivo* tracking of biomolecules. **C. Johnny, J.V. Jun**
- 459.** Simplification of method for hydrogen bond strength determination of various hydrogen bond donors. **T. Paniak**
- 460.** Phytochemical investigation of the non-polar extract of camu camu (*Myrciaria dubia*) roots. **D. Bandyopadhyay, J. Flores, F. Escamilla**
- 461.** Digging the waste: Phytochemical investigation of the non-polar extract of *Aloe vera* rind. **D. Bandyopadhyay, F. Castillo, R. Soliz**
- 462.** Synthesis and evaluation of purine analogs that target Xpt riboswitch gene. **S. Lundgren, B.P. Flores, A. Fallah, K. Gindinova, E.C. McLaughlin, S.S. Jain**
- 463.** Developing small molecules selectively targeting the sequence-based secondary structure of ssDNA, CCG repeats and their effect in biological processes. **M. Pfanner, W. Yang**
- 464.** Correlating bioactivity and reactivity for a series of guaianolide analogs. **D. Dempe, K.M. Brummond, D.A. Harki, P. Liu, P. Jackson, H. Schares, K.F. Jones, J.C. Widen, M. Cuellar, M.A. Walters, F. Grillet, T. Erbay**

- 465.** Riboflavin-biotin conjugate: Affordability in B2 vitamin determination. **S. Marincean, N. Patel**
- 466.** Development of imaging probes for fracture healing response. **S. Wah, K. Ha, K. Nagi, J. McCarthy, S. Moore-Lotridge, J. Schoenecker**
- 467.** Photochemical barcodes. **S. Tang**
- 468.** Synthesis of Rh(III)-catalyzed N-heterocyclic compounds and their application to inflammation imaging agent. S. Lee, Y. Han, J. Chin, Y. Jeon, S. Cho, **D. Kim**
- 469.** Synthesis and partial characterization of melamine Schiff bases and their antimicrobial activities. **M. ibrahem, L. Sreerama, S.M. Al-Hassan**
- 470.** Synthesis, structure, and preliminary biological activity of phenoxyalkyl esters of dithiocarbamic acids. **Z. Rakhimbekov**
- 471.** Quinoline-based fluorescent dyes as highly modular, environmentally sensitive probes for biological studies. **R.M. Lackner, J.V. Jun, C. Jones, E. Petersson, D.M. Chenoweth**
- 472.** Stereocontrolled total synthesis of eovanoids: Novel class of bioactive lipid mediators that protect cell integrity. **R. Nshimiyimana, N.G. Bazan, N.A. Petasis**
- 473.** Synthesis of hyaluronic acid-based phototsensitizers for tumor targeting. **G.A. Alvarez, J. Gilpin, S. Lindsay, J.A. Sizemore, N. Minanov, M. Parris, J.V. Ruppel, N.L. Snyder**
- 474.** Synthesis of flavonols as ligands for metal-flavonol complexes and as CORMs for therapeutic effect. **R. Dean, S. Zingales**
- 475.** Development of new methodology towards accessing 2-imidazoline scaffolds for combatting tuberculosis and multiple myeloma by proteasome modulation. **K. Saldarriaga**
- 476.** Synthesis and biological evaluation of novel thiazole derivatives as antimicrobial agents. **V. Petriti, G.P. Nora, J. Mitchell**
- 477.** Synthesis of maculosin derivatives via Horner Wadsworth Emmons reaction. **A. Boice, C. Frost, J.R. Scheerer**

Section A

Pennsylvania Convention Center
Exhibit Hall A

Carbon Allotropes, Materials, Devices & Switches

E. C. McLaughlin, *Organizer*

5:30 - 7:30

478. Thermotropic liquid-crystalline and light-emitting properties of bis(4-alkoxyphenyl) viologen bistosylate salts. H.D. Mandal, **R.G. Cortez**, **B. Gutierrez**, **K. Mendez**, P. Bhowmik, J. Kim, A. Ho, H. Han

479. Thermotropic liquid-crystalline and light-emitting properties of bis(4-alkoxyphenyl) viologen bis(triflimide) salts. H.D. Mandal, **R.G. Cortez**, **B. Gutierrez**, **K. Mendez**, P. Bhowmik, J. Kim, A. Ho, H. Han

480. Thermal and light-emitting properties of bis(3-alkoxyphenyl) viologen bis(triflimide) salts. H.D. Mandal, **R.G. Cortez**, **B. Gutierrez**, **K. Mendez**, P. Bhowmik, J. Kim, A. Ho, H. Han

481. Molecular engineering of organic molecules for applications in symmetric redox flow batteries. **R. Walser-Kuntz**, T.P. Vaid, M.S. Sanford

482. Synthesis and properties of new fluorinated aromatic molecules. **T. Lieu**, Z. Zhang, O. Daugulis, O. Miljanic

483. Electron-beam allowing simple nanostructuring of cinnamate-based materials. **M. Bojanowski**, K. Strunk, C. Huck, I. Wacker, R. Schröder, A. Pucci, C. Melzer, U. Bunz

484. Carbon nanotubes by pyrolysis of plastics and characterization techniques. R. Dohoney, N. Bagnell, **C. Magee**, **M.B. Jacobs**

485. Development of multicolor 3-dimensional photoactivatable light display. **A. Nakatsuka**, B. Li, U. Haris, M. Aljowni, A. Lippert

486. Spiropyran-based non-equilibrium self-assembling systems: Investigation of transient nanostructures. **T. Reardon**, C. Creemer, J. Parquette

Section A

Pennsylvania Convention Center
Exhibit Hall A

Molecular Recognition & Self-Assembly

E. C. McLaughlin, *Organizer*

5:30 - 7:30

- 487.** Transmembrane ion transport by asymmetric multiblock amphiphiles. **R. Sasaki**, K. Sato, K.V. Tabata, H. Noji, K. Kinbara
- 488.** Utilizing CB[8] to enhance activity of Pt photocatalyst in water reduction. **R. Rabbani**, S. Saeedi, T.A. White, E. Masson
- 489.** Investigating alkyl halogen- π interactions: Torsion balance approach. **T. Jones**, **P. Verardi**, M.R. Ams
- 490.** Recognition properties of 2,1,3-benzoselenadiazoles: Window into chalcogen bonding. **A. Verardi**, **A. Verardi**, M.R. Ams
- 491.** Suprastructures with tunable emission from assembled metallacages. **Y. Sun**, P. Stang
- 492.** Anion effects on reaction within hydrophobic yoctoliter spaces. **K. Wang**, B.C. Gibb
- 493.** Fluorescence approach for quantitative detection of H₂S in biosamples based on 1,8-naphthalimide. **H. Cao**
- 494.** Multicomponent synthesis of 1,4-disubstituted-1,2,3-triazoles using N-(phenyl)-N-2-pyridyl urea as ligands. **D. DiGrazia**, **L. Scott**, **O. Colon**, F. Damkaci, M.A. Knopp, C. Scalzo, K. Sprague
- 495.** Synthesis of Ru(II) 2,6-di-(quinolin-8-yl)pyridine substituted naphthalene diimide supramolecular polymers. **J. Bella**, D. Modarelli
- 496.** Arsenic recognition by azacryptand metallo-receptors. **S. Farshbaf**, P. Anzenbacher
- 497.** Binding of anionic guests in a face-capped Co₄L₄ supramolecular hosts. **J.D. Thoburn**
- 498.** Evaluation of small molecules that bind and stabilize G-Quadruplex DNA. **J. McCallum**
- 499.** Synthesis and spectroscopic studies of fluorophores for selective metal binding and single-molecule fluorescence imaging tags. P. Thapa, I. Arnquist, N.K. Brynes, **A.A. Denisenko**, F.W. Foss, B.J. Jones, A.D. McDonald, D.R. Nygren, K. Woodruff
- 500.** Influencing polymorphism of sulfameter. **M.D. Smendik**, D. Adsmond
- 501.** Removing the solubility barrier in ternary cocrystal formation. **T. Vincent**, D. Adsmond
- 502.** Crystal structure analysis of the chirality switching of the diastereomeric salt resolution of ($\pm$)-praziquanamine with two aryl esters of L-tartaric acid. **J. Hostetler**, T.A. Russell

Pennsylvania Convention Center
Exhibit Hall A

Peptides, Proteins & Amino Acids

E. C. McLaughlin, *Organizer*

5:30 - 7:30

503. Phenylalanine mutation to cyclohexylalanine facilitates triangular trimer formation by β -hairpins derived from A β . **S. Haerianardakani**, A. Kreutzer, P. Salveson, T. Samdin, J.S. Nowick

504. Efforts in the synthesis of auxiliary molecules for epimerization-free peptide ligation. **B.H. Williamson**, M.T. Peterson

505. Pyrene as an "unreliable narrator": Monitoring collagen triple-helicity by CD and fluorescence. **P. Banzon**, **M. Stoudt**, J. Keever, A.L. Sargent, W.E. Allen

506. Do antifreeze glycopeptides bind to ice reversibly or irreversibly?. **M. Koufas**, **B.R. Huggins**, W.E. Allen

507. Solid-phase synthesis of cysteine-containing potential anticancer depsipeptidic HDAC inhibitors. **C. Herr**, **S.A. Lewicki**, **K.M. Mullin**, L.G. Walker, **C. Cowie**, **J.S. Miller**

508. Design, synthesis, and development of new fluorescent unnatural amino acids for genetic incorporation into proteins. **Y. Venkatesh**, C. Jones, E. Petersson

509. Semi-synthesis of post-translationally modified and fluorescently labeled alpha-synuclein enables identification of protein behavior regulation by subtle changes in modification levels. **B. Pan**, E. Rhoades, E. Petersson

510. Diastereoselective methodology for the synthesis of 3a hexahydropyrrolo[2,3b]indole containing synthon (HO HPIC) containing synthon. **A. King**, C. Manion, F. Pachonka, A. Blanc

511. Effects of steric bulk on macrocycle formation. **A. Menke**, R.L. Miller, V. Sharma, J. Mars, A. Mehmood, E. Simanek

512. From nickel-catalyzed reductive coupling to cyclic peptide synthesis. **Y. Hong**, C. Twitty, S. Tsang, M.P. Watson

513. Illuminating the assembly and cellular interactions of a trimer derived from A β . **G. Guaglianone**, S. Yoo, A. Kreutzer, J.S. Nowick

514. Exploring conformation space for peptidomimetic macrocycles. **R.L. Miller**, A. Menke, V. Sharma, J. Mars, A. Saeid, A. Mehmood, B.G. Janesko, E. Simanek

- 515.** Intraresidue (C5) H-bonding mimicry of chloroalkene dipeptide isosteres. **T. Narumi**, Y. Kodama, K. Sato, N. Mase
- 516.** Chemical synthesis of sphingolipid activator protein for treating lysosomal disease. **K. Sato**, S. Tanaka, T. Narumi, N. Mase
- 517.** Impact of aza-glycine and aza-proline residues on triple helical collagen self-assembly and stability. **T.M. Harris**, A.J. Kasznel, S.D. Melton, Y. Zhang, D.M. Chenoweth
- 518.** Chemoselective peptide macrocyclization at tyrosine residues with 1,2,4-triazoline-3,5-diones. **D. Keyes**, **B. Alvey**, A. Smith, A. Roberts
- 519.** Quorum sensing inhibition in *Streptococcus pneumoniae* using optimized CSP1 modifications including a key E1A substitution. **E. Engler**, A.R. Buttner, T. Milly, K. Chichura, Y. Tal-Gan, M.A. Bertucci
- 520.** Side-chain protonation states of a fluorescent arginine. **S. Marshall**, A.L. Sargent, W.E. Allen
- 521.** Stapled peptides: Optimizing automated synthesis and ring-closing metathesis. **E. Denton**, J.R. Bickler
- 522.** Synthesis of an inhibitory peptide for quorum sensing in *Streptococcus pneumoniae* through optimization of the hydrophobic binding face and substitution of the N-terminus residue. **A.R. Buttner**, E. Engler, T. Milly, K. Chichura, Y. Tal-Gan, M.A. Bertucci
- 523.** Tools for citizen scientists interested in studying peptides and the origin of life. **P.J. Bracher**
- 524.** Effects of endcapping and truncation of a hydrogel-forming peptide on its structural and materials properties. **I. Angstman**, K.S. Akerfeldt, B. Pogostin, K. Godbe, N. Giovino, M. Lagator, B. Frohm, C.H. Londergan, S. Linse, U. Olsson, L. Gentile
- 525.** Identification of kinase substrates and interactors using Kinase-catalyzed CrossLinking and ImmunoPrecipitation (K-CLIP). S. Garre, **A.K. Kithulgoda Gamage**, A. Fouda, M. Pflum

Section A

Pennsylvania Convention Center
Exhibit Hall A

Physical Organic Chemistry: Calculations, Mechanisms, Photochemistry & High-Energy Species

E. C. McLaughlin, *Organizer*

5:30 - 7:30

526. Monomethylation and dimethylation of 1,3-diphenylpropane-1,3-dione and its derivative. **X. Song**, W. Li

527. Kinetic studies of the peroxyoxalate chemiluminescence in borate buffer. **M. Castro**

528. Novel acene-based singlet oxygen responsive materials. **Y. Yan**, S.W. Thomas

529. Computational determination of alkaloid chemical shifts with pH change. **A. Bellinghiere**, N.A. Doering, R. Sarpong, D.J. Tantillo

530. Functionalization of remote sp^2 carbon: [1, 5] sigmatropic shift controlled by an in-built donor-acceptor switch. D.V. Vidhani, **J. Gillette**

531. Computational investigation of the mechanism of HOCl-mediated cysteine oxidation in the conserved zinc-binding core of cytosolic chemoreceptor transducer-like protein D (TlpD). **L. Zumwalt**, O.M. Ogba

532. Copper-catalyzed aminoboration of *E*-alkenes. **L. Wells**, M. Kozłowski, L. Wu, O. Zatolochnaya, B. Qu, L. Wu, C.H. Senanayake, J.J. Song, Y. Zhang

533. Computational investigations into the mechanism of Lewis-acid mediated activation of sulfur(VI) fluorides. **M. Nwerem**, B. Han, O.M. Ogba

534. Computational studies of the formation of complex heterocycles through the cyclization of benzaldehyde oxime ethers containing a built-in azole group. **T. Tran**, D. Torres, A.S. Petit

535. Energetic scales built with new strategy for understanding α -C–H functionalization of tertiary amines: Case studies on tetrahydroisoquinolines. **W. Luo**

536. Illuminating the transformation of humulone. **E. Munder**, M.D. Mosher

537. Synthesis and evaluation of novel photosensitizers for photodynamic anti-pancreatic cancer therapy. **M. Abdelaziz**, D. Modarelli

538. Theoretical explanation of reaction site selectivity of a four armed dendrimer core. **T.J. Fuhrer**, K. Schoettinger

539. Gauche effects in 2-Fluorosulfonamides as a means for determining the acidity of organic compounds in DMSO. **B.U. Emenike**, S.S. Dhami

540. Photoreactivity of rigid divinyl azides. **N. Kitil**, U. Banerjee, A.D. Gudmundsdottir

541. Dme solvated mixed aggregates of lithium pinacolone enolate and lithium hexamethyldisilazide: Equilibrium of solvation states. **Q. Ye**, P.G. Williard

- 542.** Rotational barriers of substituted α,β -unsaturated diarylketones. **S. Rana, C. Lin, E. Orman, O. Gong,** S. Simpson, D.C. Merrer
- 543.** Quantum yields of photoredox catalyzed α -arylation of amines. **E. Spielvogel,** J. Swierk, B. Stevenson, E. Loiaconi
- 544.** Mechanistic insight into (DHQD)₂PHAL catalyzed asymmetric chloro-functionalization of olefins. **A. Sarkar,** R. Yousefi, D. Steigerwald, T. Kakeshpour, S. Bedford, B. Soltanzadeh, D. Holmes, J.E. Jackson, B. Borhan
- 545.** Study of pH-dependent H/D exchange from aromatic hydrogen in 1,8-diamino-2,7-naphthyridine-4-carbonitriles. **J. Ewald,** M. Pfanner, T.T. Truong, T.V. Albu, W. Yang
- 546.** Synthetic and mechanistic investigations on chromium salen-catalyzed oxidation of sulfides with iodobenzene diacetate. **A. Dames,** R. Zhang, F. Bratcher
- 547.** Zwitterionic red fluorophores as selective protein sensors. **R. Choudhury**
- 548.** Gasoline derived from food oil: DFT dynamics investigation. **A. Roy,** M.R. Siebert
- 549.** Investigation of silicon phthalocyanines as viable photocatalysts for organic transformations. **S. Dickerson**
- 550.** Synthesis, characterization, and initial membrane binding properties of mono- and gemini-decyl-chain lumazines. M.J. Sosa, M. Vignoni, J.L. Castro, P. Schilardi, M.N. Urrutia, H. Junqueira, M.S. Baptista, R. Itri, N. Walalawela, G. Ghosh, A.H. Thomas, **A. Greer**
- 551.** Broadening the understanding of selective microwave heating on the 1,2-Meisenheimer rearrangement. **A. Ziegelmeier,** M. Frasso, H. Fulo, G.B. Dudley
- 552.** Direct detection of airborne singlet oxygen from porous Vycor glass particles adsorbed with a brominated BODIPY photosensitizer. A.M. Durantini, **A. Greer**
- 553.** Deducing mobility of ethoxy and cumyloxy radicals on fumed silica surfaces based on recombination products. **S.J. Belh,** G. Ghosh, S. Jabeen, A. Greer
- 554.** Synthesis and characteristics of halogenated fused-ring cyclopropanes. **R. King,** J. Boone, C. Clinger
- 555.** Mallory photocyclizations: Enhanced twisted heli-acene formations. **S. Tannir,** E.L. Clennan, J. Weber

WEDNESDAY MORNING

Pennsylvania Convention Center
116

Physical Organic Chemistry: Calculations, Mechanisms, Photochemistry & High-Energy Species

S. M. Silverman, *Organizer*

8:20 556. Effect of water on the chemiexcitation step in peroxyoxalate chemiluminescence. **M. Castro**

8:40 557. Role of spin chemistry in photosynthesis: Approach for electron transport. **I.F. Cespedes-Camacho**, M. Vega-Cardenas

9:00 558. 1-Norbornyl cation may be in equilibrium with 2-norbornyl cation. **A. Mamantov**

9:20 559. Charge-transfer character in perylenediimide excimers self-assembled on anodic aluminum oxide membrane walls. **M. Myong**, J. Zhou, R. Young, M.R. Wasielewski

9:40 560. Hammett study of a resonance assisted hydrogen bond. **J.A. Jones**, T.M. Mathis, G.A. Mullins, D.J. Crouse

10:00 561. Computational investigations into the origins of reactivity at metal-sulfur centers. **O.M. Ogba**

10:20 562. Kinetics, mechanism, and chemoselectivity in multi-site proton-coupled electron transfer. **G. Qiu**, R. Knowles

10:40 563. Size-accelerated Lewis base catalysis. **H. Zipse**

11:00 564. Redefining our concept of the chemical bond. S.S. Shaik, D. Danovich, **J.M. Galbraith**, B. Braida, W. Wu, P. Hiberty

Pennsylvania Convention Center
117

Heterocycles & Aromatics

S. M. Silverman, *Organizer*
D. Chen, *Presiding*

8:00 565. Transformation of enantiopure homoallylic amines into nitrogen heterocycles via electrophilic addition. **M.G. Donahue**

8:20 566. Selective removal of *tert*-butyloxycarbonyl (BOC) groups from heterocyclic substrates utilizing addition-elimination with primary amines. **Z.Z. Gullledge**, J.D. Carrick

8:40 567. Diversity of tetrazole synthesis. **A. Doemling**, K. Neochoritis

9:00 568. BF₃.OEt₂-mediated formal [3+2]-cycloaddition of asmic to form heterocycles. **V. Chepuri**, F.F. Fleming

9:20 569. Green approach for the synthesis of ferrocenyl stilbene derivatives. **S.M. Delgado-Rivera**, S.A. Henriquez Lopez, A. Baerga-Ortiz, D.M. Pinero Cruz, I. Montes-Gonzalez

9:40 570. Catalyst behavior in carbonyl-olefin metathesis. **C. Hanson**, M. Psaltakis, J. Cortes, J.J. Devery

10:00 571. Fused azepine organic semiconductor via the cyclization of vinyl azide. **J.A. Schneider**

10:20 572. Total synthesis and investigation of metal-binding natural products. **K. Morrison**, J.A. Shapiro, R. Allen, S. Chodisetty, W.M. Wuest

10:40 573. Studies on maltol-derived oxidopyrylium ylides. **I. bejcek**, R.P. Murelli, A. Greer, E. Greer

11:00 574. Synthesis of a fluorinated nucleoside via an electrophilic fluorination/glycosylation strategy. **M. Pirnot**, E. Phillips, P. Maligres, C. Chung, J. Limanto, C. Lam

11:20 575. Efforts towards Rh(II)-catalyzed N-alkoxyazomethine ylide generation. **D. Chen**, E. Jones, B. Rocke, J. Trujillo, S.W. Wright, S.A. France

11:40 576. Synthesis approach to dramatically alter indole alkaloids leads to compounds with re-engineered biological activities. **R. Huigens**

Section C

Pennsylvania Convention Center
120A

Peptides, Proteins & Amino Acids

S. M. Silverman, *Organizer*

8:20 577. Pharmacology of motor proteins: Quest for better tool compounds and therapeutics. **B.I. Roman**

8:40 578. Synthesis and use of proteomics probes to identify the molecular targets of an anti-invasive agent. **B.I. Roman**

9:00 579. Positional effects of thioamides on serine protease activity: Mechanistic studies and application to stabilize cancer imaging peptides. **T. Barrett**, X. Chen, C. Liu, S. Giannakoulis, J. Wang, R.J. Karpowicz Jr., E. Petersson

9:20 580. Analysis of β -sheet mediated peptide assembly using a chemical biology approach. **A.J. Wilson**

9:40 581. Peptide-bile acid cyclisation as a tool for the development of a universal vaccine against influenza A. **D. Van Lysebetten**, B. Schepens, X. Saelens, A. Madder

10:00 582. Evolution of new enzymes for the synthesis of non-canonical amino acids. **C. Prier**, J. Vroom, S.A. Dockrey, H. Li

10:20 583. Devising a scalable solution-phase synthesis of peptidomimetics to probe the G protein-coupled receptor signaling pathway. **Y. Zhu**, M. Medcalf, K.D. Moeller

10:40 584. Fluorescent teixobactin probes. **M. Morris**, M. Malek, M. Hashemian, B. Nguyen, J.S. Nowick

11:00 585. Designing degradation resistance in therapeutic peptides using microwave-assisted SPPS. **S. Ly**, A. Brackbill, I. Gober, S. Singh

11:20 586. Synthesis of homogeneous cysteine-bridged N-glycoproteins via native chemical glycoligation. **N. Holloran**, P.P. Garner

Section D

Pennsylvania Convention Center
120B

Cross Coupling Reactions

S. M. Silverman, *Organizer*

8:00 587. Novel and efficient synthesis of SGLT2 inhibitors by means of Fukuyama coupling reaction. **M. Seki**, J. Talode, H. Tsurugi, K. Mashima

8:20 588. Carbon-hydrogen bond cross-coupling reactions: Carbon-carbon bond formation. Y. Zhou, M. Iqbal, **R. Hua**

8:40 589. Copper and iron catalyzed cross coupling reactions supported by a sterically bulky β -diketonate ligand platform. **M.P. Marshak**

9:00 590. Synthesis of *N*-pyridyl hydroxylamine derivatives via copper catalyzed cross-coupling and application towards design of new acetylcholinesterase reactivators. **C. Torruellas**, J. Myslinski, F. Hsu, A. Walz

9:20 591. Palladium catalyzed stereospecific arylation of biocatalytically derived dienes: Chirality transfer via a Heck-type mechanism. **P. Dunas**, A.J. Paterson, M. Rahm, P. Norrby, G. Kociok-Köhn, S.E. Lewis, N. Kann

9:40 592. Deaminative alkyl-alkyl cross-couplings of alkylpyridinium salts and alkenes. **K. Baker**, D.L. Baca, S.L. Plunkett, M.E. Daneker, M.P. Watson

10:00 593. Cross-coupling of amides by N–C activation. **M. Szostak**

10:20 594. Exploring the mechanism of Pd- and Ni-catalyzed carbonylative and decarbonylative coupling reactions. **A. Stirling**

10:40 595. Catalytic decarbonylative amination of carboxylic acid derivatives. **C.A. Malapit**, M. Borrell, M.W. Milbauer, C. Brigham, M.S. Sanford

11:00 596. Methylation of (hetero)aryl chlorides via halogen photoelimination. **S.K. Kariofillis**, B.J. Shields, M. Tekle-Smith, M.J. Zacuto, A.G. Doyle

11:20 597. Next-Gen MIDA enables automated Csp³ cross-coupling. **D.J. Blair**, M. Trobe, H. Haley, D.L. Gray, T. Woods, S. Ballmer, R. Hansen, A. Gill, M.J. Schmidt, R. Pipal, M.D. Burke

11:40 598. Synthesis of enantiomerically enriched 1,1-diarylalkanes using a Suzuki-Miyaura reaction catalyzed by an iron-based complex. **C.C. Tyrol**

Section E

Pennsylvania Convention Center
118A

Pharmaceutical Sciences: What Happens Next in Drug Delivery Development?

M. Gindy, R. Saklatvala, S. M. Silverman, *Organizers*
L. Austin, *Organizer, Presiding*

8:30 Introductory Remarks.

8:35 599. Next generation drug delivery and device opportunities for product development. **M. Gindy**

9:10 600. Delivering the insoluble: Amorphous solid dispersions. **L. Taylor**

9:45 601. Implantable drug delivery systems: How are they designed and developed?. **R. Teller**

10:20 602. Prodrug strategies for peptide drugs. **E.M. Topp**

10:55 603. Messenger RNA: Delivery challenges and encouraging first steps towards a novel modality. **M. Smith**

11:30 Concluding Remarks.

Section F

Pennsylvania Convention Center
Michael A Nutter Theatre

Green Chemistry & Engineering: Designing & Discovering Innovative Solutions to Achieve a Sustainable Future

I. Martinez, S. M. Silverman, *Organizers*
J. V. Obligation, *Presiding*

8:00 Introductory Remarks.

8:15 604. Catalytic oxidation methods for pharmaceutical synthesis. **S.S. Stahl**

8:55 605. Green chemistry at Pfizer: Applications to the oncology portfolio. **P. Richardson**

9:20 606. Trimming the waste-line in macrocyclic peptide synthesis: *N*-acyl urea cyclization and photodesulfurization. **J.L. Stockdill**

10:00 Intermission.

10:30 607. Metal-organic frameworks for sustainable catalysis. **W. Lin**

11:10 608. Beyond organic solvents: Synthesis of a 5-HT₄ receptor agonist in water. **D.K. Leahy, D. Bailey**

11:35 609. Inventing green chemistry in the context of implementation: Considerations beyond the bench. **P.D. Thornton**

WEDNESDAY AFTERNOON

Pennsylvania Convention Center
116

Physical Organic Chemistry: Calculations, Mechanisms, Photochemistry & High-Energy Species

S. M. Silverman, *Organizer*

1:20 610. Investigations into the reactivity and stability of the samarium diiodide-water system. **N. Boeckell**, R.A. Flowers

1:40 611. Exploring the reactivity of Sm(II)-proton donor systems. **C. Bartulovich**, R.A. Flowers

2:00 612. Method development of the competitive secondary kinetic isotope effect measurement for hydride transfer reactions of NADH/NAD⁺ models. **A.T. Beach**, Y. Lu, S. Wilhelm

2:20 613. Solvent effects on the temperature dependence of the primary kinetic isotope effects for hydride transfer reactions in solution. **P. Adhikari**, Y. Lu

2:40 614. Inhibiting excited state quenching mechanisms in donor-acceptor type chromophores with solvent-excluding substituents. **C. Hoelzel**, H. Hu, C. Wolstenholme, B. Karim, K.T. Munson, K. Jung, J.B. Asbury, X. Li, X. Zhang

3:00 615. SuFEx reactions and the role of silicon: Scope, kinetics, enantioselectivity and mechanism. D. Liang, D. Streefkerk, **H. Zuilhof**

3:20 616. Structural effects on the temperature dependency of the primary hydrogen kinetic isotope effects in solution: New physical organic chemistry research direction. **Y. Lu**

3:40 617. Stereochemical control of acetal photodeprotection. H. Pham, C. Yang, H. Wang, **S.M. Reed**

4:00 618. *N*-substituted open-shell π -conjugated material: Synthesis and optoelectronic properties. **M. Imran**, M.S. Chen, C.M. Wehrmann

Pennsylvania Convention Center
117

Photoredox Chemistry

S. M. Silverman, *Organizer*

1:20 619. Dual palladium-photoredox catalyzed C-H arylation of phenyl urea derivatives. **G. Purushothaman**

1:40 620. Sulfamate esters guide C(3)–H functionalization of alkanes. **S.K. Ayer**

2:00 621. Utilization of novel photocatalytic systems for functionalization and ring constructions reactions. **Z. Novák**, B. Varga, F. Béke, T. Földesi, B. Tóth, B. Nagy, G.V. Sipos, Z. Gonda, R. Adamik, T. Peelen

2:20 622. Accessing challenging fluorinated motifs using photoredox catalysis and enabling technologies. **R. Wiles**, J.P. Phelan, S.B. Lang, C.B. Kelly, G.A. Molander

2:40 623. Photoredox catalysis enables the modular installation of molecular complexity. **V.C. Polites**, J.A. Milligan, J. Phelan, C.B. Kelly, K.L. Burns, A.V. Le, Z. Wang, R.J. Wiles, G.A. Molander

3:00 624. Hydroetherification of unactivated alkenes enabled by light-driven proton-coupled electron transfer. **E. Tsui**, A.J. Metrano, Y. Tsuchiya, R. Knowles

3:20 625. Mechanistic and kinetic studies of photoredox cycles. **J. Swierk**, B. Stevenson, E. Spielvogel, E. Loiaconi

3:40 626. Anti-Markovnikov hydroamination of unactivated alkenes with primary alkyl amines. **J. Ganley**, D. Miller, A. Musacchio, T. Sherwood, W. Ewing, R. Knowles

4:00 627. Multiwavelength photoreactor for batch and flow chemistry: Development and applications. **G.V. Sipos**, I.K. Varga, K. Bodroghy

Section C

Pennsylvania Convention Center
120A

Peptides, Proteins & Amino Acids

S. M. Silverman, *Organizer*

1:20 628. Synthesis and the genetic encoding of N^ε-3-hydroxybutyryl lysine: Novel post translational modification. **S.A. Galbada Liyanage**, A.T. Cropp

1:40 629. Minimum increments of hydrophobic collapse within the N-terminus of human galanin. **M.W. Giuliano**

2:00 630. Constitutive activation of GLP-1R *via* covalent capture. **O. Unsal**, K.M. Sicinski, V. Montanari, K. Kumar

2:20 631. Utilizing interactions between enantiomeric peptides to sequester toxic dipeptide repeats for treatment of amyotrophic lateral sclerosis. **V.P. Gray**, R.A. Letteri

2:40 632. Variation in the Xaa and Yaa positions of collagen mimetic peptides containing azaglycine. **S.D. Melton**, D.M. Chenoweth

3:00 633. N,S-double labeling of N-terminal cysteines via an alternative pathway of 2-cyanobenzothiazole condensation. **W. Wang**

3:20 634. Metal-binding Q-proline macrocycles. **J. Northrup**, C.E. Schafmeister

3:40 635. Synthesis of molecular probes for the selective modification of tryptophan residues in peptides and proteins. S. Tower, W. Hetcher, **T. Myers**, M. Taylor

4:00 636. Site-specific isotopic labeling of peptides and proteins for biophysical studies. **J.M. Goldberg**

4:20 637. Molecular design of roteolytically stable peptide based therapeutics. **K.M. Sicinski**, V. Montanari, M. Beinborn, K. Kumar

Section D

Pennsylvania Convention Center
120B

Electrochemistry in Organic Synthesis

S. M. Silverman, *Organizer*

1:30 638. Efficient electrosynthesis of thiazolidin-2-imines via oxysulfurization of thiourea-tethered terminal alkenes using the flow microreactor. **M. Islam**

2:00 639. Electrochemical cross-coupling between alkyl and allylic halides with CuPd nanoparticles. **Z. Yin**, S. Sun

2:30 640. Boron-doped diamond electrodes as key for going beyond contemporary limits in electro-organic synthesis. **S.R. Waldvogel**, M. Zirbes, J. Panther

3:00 641. Fluorocyclization of *N*-allyl- and *N*-propargylamides by electrochemically generated ArIF₂. **J. Herszman**, M. Berger, S.R. Waldvogel

3:30 642. Electrochemical modulation of strong vibration-cavity coupling. **M. Sassin**, J. Pietron, K. Fears, J. Owrutsky, B. Simpkins

Section E

Pennsylvania Convention Center
118A

Molecular Recognition & Self-Assembly

S. M. Silverman, *Organizer*

1:20 643. Reductive coupling of *N*-aryl iminoboronates and B-N dynamic covalent chemistry. **A. McConnell**

1:40 644. Binding studies and anti-Zika activity of a library of synthetic carbohydrate receptors. **M.F. Bravo**, K. Palanichamy, A. Joshi, M.A. Shlain, F. Shiro, Y. Naeem, H. Garg, A.B. Braunschweig

2:00 645. Conformationally locked foldamers: Synthesis and properties of abiotic macrocycles. **T. Warnock**, P. Knipe

2:20 646. Supramolecular amphiphiles: Synthesis, characterization and applications of amphiphilic cyclodextrin and calix[4]arene inclusion complexes. E. Mobley, M. Martinez Rieder, **S. Ward**

2:40 647. Complexation by cucurbit[7]uril leads to increased cell potentials in aqueous redox flow batteries. **Y. Zheng**, A.E. Kaifer

3:00 648. Development of selective, dry-functional and single molecule sensitive on-off barium chemosensors for neutrinoless double beta decay. **P. Thapa**, A.A. Denisenko, N.K. Brynes, A.D. McDonald, K. Woodruff, D.R. Nygren, B.J. Jones, F.W. Foss

3:20 649. Synthesis of water-soluble dipyrins for sensing applications. **M.E. EL KHATIB**, S. Vinogradov

3:40 650. Synthetic ion transport systems for targeting cancer. **P. Talukdar**

4:00 651. Phosphorescence lifetime-based probe for oxygen and temperature. **S. Allu**, T. Esipova, I. Sencan, S. Sakadzic, S. Vinogradov

4:20 652. Hierarchical supramolecular assembly of an unusually stable viologen radical species. **J.J. Reczek**

4:40 653. Functionalized calixarenes: Synthesis, characterization and anion sensing applications.
N. Edwards, D. Schnable

Section F

Pennsylvania Convention Center
Michael A Nutter Theatre

Green Chemistry & Engineering: Designing & Discovering Innovative Solutions to Achieve a Sustainable Future

I. Martinez, S. M. Silverman, *Organizers*
J. V. Obligation, *Presiding*

1:00 Introductory Remarks.

1:10 654. Cobalt catalyzed C–H borylation: Unprecedented selectivity opens pathway to greener organic synthesis. **P.J. Chirik**

1:50 655. Biocatalytic routes to the drugs of the future. **A. Fryszkowska**

2:15 656. Sustainability in complex molecular settings. **M.D. Eastgate**

2:40 Intermission.

3:00 657. Safer sustainable recyclable solvent systems for catalysis and synthesis. **D.E. Bergbreiter**

3:40 658. Chevron Phillips Chemical LP Synfluid® high viscosity mPAO. **B.L. Small**

4:05 659. Role of green chemistry in the design of sustainable crop protection products. N. Foster, A. Hazari, M. Li, **G.T. Whiteker**

4:30 660. Homogeneous catalytic hydrogenation reactions towards fragrance and flavor ingredients: Industrial applications. **L. Saudan**

4:55 Concluding Remarks.

WEDNESDAY EVENING

Section A

Pennsylvania Convention Center
Exhibit Hall D

Electrochemistry in Organic Synthesis

Cosponsored by MEDI

E. C. McLaughlin, *Organizer*

7:00 - 9:00

661. Functionalization of Csp³-H bonds via copper catalyzed electro-organic chemistry. **L.K. Trigoura**, Y. Xing

662. Recent advances in the use of carbonyl compounds as active components in organic- based batteries. **C.E. Omaliko**, L. Hitler

Section A

Pennsylvania Convention Center
Exhibit Hall D

Flow Chemistry & Continuous Processes

Cosponsored by MEDI

E. C. McLaughlin, *Organizer*

7:00 - 9:00

663. Microwave-mediated continuous hydrogen generation method from methylcyclohexane and 2-propanol using carbon bead-supported Pt catalyst. T. Ichikawa, **T. Tachikawa**, T. Matsuo, T. Yamada, T. Yoshimura, M. Yoshimura, Y. Takagi, Y. Sawama, J. Sugiyama, Y. Monguchi, H. Sajiki

664. Flow chemistry used for optimization (DOE) of four-step synthesis of polysubstituted pyrroles. C. Perez Mandry, A. Kim, **R.N. Dominey**, E.W. Goldman, J.T. Gupton

Section A

Pennsylvania Convention Center
Exhibit Hall D

Green Methods & Syntheses

Cosponsored by MEDI

E. C. McLaughlin, *Organizer*

7:00 - 9:00

665. Investigating the formation of steroid derivatives from testosterone using free and immobilized filamentous fungi. **J.M. McKenzie**, P.B. Reese

- 666.** Aqueous solubility of new albuterol drugs in liquid form. **J. Thorn**
- 667.** Green approach: Metal free amination of aromatic alcohols. **D. Panhekar**, R.C. Sawant, M.D. Dongre, S.S. Pande
- 668.** Synthesis and structure investigation of dimethyl 2,2'-(5-amino-4,4,6-tricyano-3-methylcyclohexa-1,5-diene-1,3-diyl) diacetate obtained using one pot reaction. **Z.M. Almarhoon**
- 669.** Use of recyclable Brønsted acid catalysts in alternative alkane solvents. **C. Watson**, A. Keuchle, D.E. Bergbreiter
- 670.** Sustainable synthesis of 2/3-aryl indoles under Pd-catalysis in SPGS-550-M micellar medium. **G. Vaidya**, D. Kumar
- 671.** Scalable synthesis of a cyclobutane-1, 2-diacid and its derivatives from *trans*-cinnamic acid via photoreaction. **H.S. Amjaour**
- 672.** Verification of sulfonated compounds found in biodiesel produced from brown grease lipids (BGL). **S. Isah**, K. Jones, V. Wyatt, R. Cairncross, G. Ozbay
- 673.** Hydrodechlorination of aryl chlorides in biological media at neutral pH, ambient temperature and pressure. **E.E. Schultz**, M. AbuBakar, R. Shanker, S. Stubbs
- 674.** Synthesis of anilium based ionic liquid and ionic liquid hydrates. **D. George**, C. Cockram, **A.P. Cardenas**

Section A

Pennsylvania Convention Center
Exhibit Hall D

New Reactions & Methodology

Cosponsored by MEDI
E. C. McLaughlin, *Organizer*

7:00 - 9:00

- 675.** Reactions of disubstituted peroxides: Approach to the synthesis of strained bicyclic ethers. **T. Browning**, M. Locklear, P.H. Dussault
- 676.** Vanadium catalyzed oxidative regioselective homocoupling and trapping of alkenyl phenols to form lignan analogues. **W.C. Neuhaus**, A.L. Jemison, M. Kozlowski

- 677.** Remarkable rate enhancement of acidic Boc cleavage by hexafluoroisopropanol (HFIP) and application to acid sensitive substrates. **J.M. Humphrey**, C. Am Ende, E. Fisher, M. Bundesmann, J. Tucker, B.C. Vetelino
- 678.** Reaction of phenylsuccinic anhydride with Michael acceptors. **S. Lionetti**, D.A. Hunt
- 679.** ^{18}F -oxyfluorination of diazoketones by an electrophilic reagent. **M.A. Cortes Gonzalez**, X. Jiang, P. Nordeman, G. Antoni, K.J. Szabo
- 680.** Three-component olefin dicarbofunctionalization enabled by nickel/photoredox dual catalysis. **M.W. Campbell**, J. Compton, C.B. Kelly, G.A. Molander
- 681.** Preparation of benziodoxolone-based diaryliodine(III) compounds. **A. Yoshimura**, S. Larson, G. Rohde, M. Yusubov, A. Saito, V.V. Zhdankin
- 682.** Preparation of benziodoxolone-based vinyl iodine(III) compounds. **C. Huss**, M. Liebl, G. Rohde, M. Yusubov, A. Saito, A. Yoshimura, T. Kitamura, V.V. Zhdankin
- 683.** Preparation of chiral biaryl compounds via an asymmetric dimerization reaction. **Z. Zuo**, D.A. Watson
- 684.** Synthesis of highly functionalized piperidines via arylation of aza-Achmatowicz rearrangement products. **D. Canterbury**
- 685.** New bicyclo[1.1.1]pentanes via anionic reactivity of [1.1.1]propellane. **R. Shelp**, P.J. Walsh
- 686.** Methodology for the synthesis of thiophosphorus acids $\text{P}(\text{S})\text{OH}$ via amides. **K. Winters**, J.L. Montchamp
- 687.** On the cost of academic methodology. **A. Sabourin**, J.L. Montchamp, S.V. Dzyuba, K. Winters, O. Berger
- 688.** Asmic-based synthesis of tri-substituted oxazoles and imidazoles. **L. Mueller**, A. Chao, E.F. Alwedi, M. Natrajan, F.F. Fleming
- 689.** Synthetic studies on peganine A and B. **K.A. Leets**, J.D. Chisholm
- 690.** Stereoselective synthesis of quaternary centers via an Ireland-Claisen rearrangement of (*e*)- α -trialkylsilyl- β -alkyl- α,β -unsaturated esters. **C. Massey**
- 691.** Copper-catalyzed propargylation of nitroalkanes: Homopropargylic nitroalkanes as synthons to five-membered *N*-heterocycles. **R.S. Kim**, L.V. Dinh-Nguyen, K.W. Shimkin, D.A. Watson

692. Esterification and etherification with 2-(Trimethylsilyl)-2,2,2-Trichloroacetimidate. **W. Lin, S. Meyer, S. Dormann, J.D. Chisholm**

693. Progress toward late-stage functionalization of chiral bisphosphorylimides using Suzuki cross-coupling reactions. **A. Smolin, R.G. Iafe**

694. *N*-*tert*-butanesulfinyl metallodienamine in different methodologies. **A. Karmakar, P. Yu, X. Jin, V.K. Chatare, G. Dobereiner, R.B. Andrade**

695. Double allylboration reagent for the synthesis of chiral diols. **B. Hetzler, G. Volpin, D. Trauner**

696. Lewis acid promoted dialkylation of indoles with trichloroacetimidates for the Synthesis of 3,3'-disubstituted indolenines. **N. Mate, T. Suzuki, A. Adhikari, J.D. Chisholm**

697. Oxidative deamination of benzyl amines to carbonyl compounds promoted by (Diethylamino)sulfur trifluoride (DAST). **R. Belloso, M.A. Lnu**

698. Aryne-mediated phosphorylation of imines with dialkyl phosphites. **T. LIM, B. Kim**

699. Direct nucleophilic aromatic substitution of 2-halo-*N*-(1-ethoxyvinyl)pyridinium salts with *N*- and *O*-nucleophiles. **A.M. Blades, D. McConnell, A. Thayaparan, M.M. Majireck**

700. Efficient synthesis of cyclopropane-fused spiro-pseudoindoxyl derivatives through highly diastereoselective [2 + 1] annulation. **X. Tang, W. Huang, C. Peng**

701. Diastereoselective [4+1] annulations of ortho-quinone methides and bromides via direct sulfide catalysis. **Y. Liu, Q. Li, C. Peng, J. Li, B. Han**

702. Synthesis and purification of oxygen sensitive allenyl boronic acids. **S. Jonker, J. Zhao, D.N. Meyer, G. Schulz, D. Tran, L. Eriksson, K. Szabó**

703. Chemo- and stereo-selective cross Rauhut-Currier-type reaction of tri-substituted alkenes: Synthesis of trifluoromethyl-containing tetra-substituted olefins. **X. He, Q. Zhao, B. Han, C. Peng**

704. TFA mediated preparation of *S*-aryl thiosulfonates from electron-rich arenes using Mor-SS-Ts. **F. Koudai**

705. Alkeneisocyanides: Synthesis and reactions. **A. Bendia, F.F. Fleming**

706. Sulfur tetrafluoride as an effective reagent for semi-industrial fluorination of β -ketoesters: Safety vs efficacy. **D. Volochnyuk, S. Trofymchuk, S. Ryabukhin**

707. New method for the synthesis of pyrroloindolines via tandem alkylation-cyclization of tryptamines with trichloroacetimidates. **B.D. Joshi, J.D. Chisholm**

- 708.** Synthesis and use of bulky alkali metal amides. **S. Aderibigbe**, O. Daugulis
- 709.** Efficient synthetic pathways of replacing a pyrrole in porphyrins by an oxazole. **D.W. Thuita**, C. Brückner
- 710.** Copper-catalyzed conjugate additions to alkeneisocyanides. **J.R. Marrazzo**, A. Chao, F.F. Fleming
- 711.** Incorporation of heterocyclic aldehydes in Ugi-Smiles Diels-Alder reactions. **D. Scanlan**, S.B. Luesse
- 712.** Amine variation in oxy-Michael Ugi-Smiles processes. **J. Jones**, S.B. Luesse
- 713.** Tandem Michael Ugi-Smiles processes with thiols. **A. Robinson**, S.B. Luesse
- 714.** Re₂O₇ -mediated dehydrative cyclizations: Method towards 2,6-trans dihydropyran synthesis. **J. Lawrence**, P.E. Floreancig
- 715.** Re₂O₇ –Catalyzed dehydrative cyclization reactions in the synthesis of nitrogen containing heterocycles. **F. Rodrdriguez del Rey**, P.E. Floreancig
- 716.** Vicinal C-H functionalization of amines enabled by an interrupted Hoffman-Löffler-Freytag mechanism. **R. Dare**, L.M. Stateman, A. Paneque, D. Nagib
- 717.** Sulfuryl fluoride mediated synthesis of amides from ketoximes via Beckmann rearrangement. **J. Gurjar**, V.V. Fokin
- 718.** Dearomatization of electron-deficient phenols to *ortho*-quinones enabled by bidentate nitrogen-ligated I(V) reagents. **X. Xiao**, N. Greenwood, S. Wengryniuk
- 719.** Ring rearrangement of oxo- or aza-bridged 1,5-alkylidenemalononitrile-cycloheptenes. **E. Semenova**
- 720.** Diastereoselectivity of oxone-based oxidations of 1,3 thiazolidin-4-ones to sulfoxides. **K.C. Cannon**, A.Y. Nuriye, C. Craescu, Z. Khan, E. Bakiyev, J. Tierney
- 721.** Microwave-assisted aza-Prins reactions of unactivated imines. **H.A. Lindsay**, H. Vaughan, E. Burke, A. Martin
- 722.** Synthesis of 1,3,5-triarylbenzenes using sustainable metal triflates as catalysts. **T. Yamato**, T. Mathew, S.G. Prakash
- 723.** Development of an efficient method for fluorocyclization of tryptophol. **C. Chong**, Y. Xing

724. Access to highly functionalized cyclopentenones via diastereoselective Pauson–Khand reaction of siloxy-tethered 1,7-enynes. **O.A. Torres Herrera**, A.G. Gallagher, H. Tian, D.S. Martinez

725. 2,3-diketopirrolidines as perspective building blocks for medicinal chemistry: Synthesis and properties. **S. Ryabukhin**, S. Bondarenko, D. Volochnyuk

726. Synthesis of functionalized 1-azabicycloheptanes/octanes/nonanes: Perspective building blocks for medicinal chemistry starting from proline. **S. Ryabukhin**, S. Bondarenko, D. Volochnyuk

727. Microwave-assisted hafnium(IV) chloride-promoted self-coupling of D-glycal. **R.N. Yadav**, B.K. Banik

728. Microwave-induced preparation of 3-unsubstituted β -lactams with aqueous trimethylborane. **R.N. Yadav**, B.K. Banik

729. Microwave-assisted stereoselective synthesis of 3-phenylthio-4-carboethoxy β -lactams. **R.N. Yadav**, B.K. Banik

730. Acetylation of the amino group in β -lactams under aqueous conditions. **R.N. Yadav**, B.K. Banik

731. Microwave-assisted bismuth nitrate-catalyzed reaction of 3-amino β -lactams with enones. **R.N. Yadav**, B.K. Banik

732. Microwave-induced montmorillonite-mediated facile synthesis of enamines. **R.N. Yadav**, B.K. Banik

Section A

Pennsylvania Convention Center
Exhibit Hall D

Photoredox Chemistry

Cosponsored by MEDI
E. C. McLaughlin, *Organizer*

7:00 - 9:00

733. Photoinduced facile generation of vinyl radical from alkynes: Metal-free synthesis of 3-azabicyclo[3.1.0]hexan-2-ones. **B. Bankhead**, J. Markham, S. Chen, J. Zhang, Y. Deng

734. Oxidative photocatalytic homo- and cross-coupling of phenols: First non-enzymatic catalytic method for coupling tyrosine. **K. Niederer**, P.H. Gilmartin, M. Kozlowski

735. Expedient access to saturated nitrogen heterocycles by photoredox cyclization of imino-tethered dihydropyridines. **N. Bissonnette**, F. Romanov-Michailidis

736. Blue light-mediated catalyst free polyene cyclization. **S. Bhattarai**, A. Kafle, S.T. Handy

737. Carbon-carbon bond formation by visible light photocatalysis: [2 + 2] photocycloadditions of vinylogous esters and amides. **L. Cunden**, **M. Sheshova**, A. Waters, E.C. McLaughlin

738. Photocatalytic oxidative C-H thiolation: Synthesis of benzothiazoles and sulfenylated indoles. **A.N. Dinh**, **E. Millan**, A. Nguyen, S. Albright, M. Cedano, D. Smith, J.L. Gustafson

739. Green chemistry: Benzylic functionalization via visible-light induced photo redox catalysis. **J. Inoa**, M. Patel, G. Dominici

740. Photoreduction of quinolines: Nitro reduction to amines and *O*-debenzylation by proton-coupled electron transfer. **S. Aikonen**, A. Todorov, T. Wirtanen, M. Muuronen, J. Helaja

741. High-throughput kinetics screening of iridium catalyzed photo-dehalogenation of aryl bromines. **V. Mdluli**, S. Bernhard, S. DiLuzio, T.U. Connell

Section A

Pennsylvania Convention Center
Exhibit Hall D

Role of Synthetic Innovation in Delivering Clinical Candidates

Cosponsored by MEDI
E. C. McLaughlin, *Organizer*

7:00 - 9:00

742. Discovery and asymmetric synthesis of potent and selective small-molecule modulators of CXCR7 for treatment for cardiac fibrosis. **K. Hesp**, J. Albert, S.W. Bagley, M. Bayrakdarian, M. Boehm, D. Canterbury, S. Desjardins, F. Godin, W. Jiao, C. Limberakis, A.T. Londregan, E. Menhaji-Klotz, D.A. Perry, D.W. Piotrowski, B. Thuma, J. Xiao

743. Scaffold Diversity of Cyclic Organic Frameworks in CAS Registry. **M. MCBRIDE**, T. Wills

Section A

Pennsylvania Convention Center
Exhibit Hall D

Total Synthesis of Complex Molecules

Cosponsored by MEDI
E. C. McLaughlin, *Organizer*

7:00 - 9:00

744. Highly versatile synthetic approach to disciformycin and gulfmirecin antibiotics. **K. Ruehmann**, D. Trauner

745. Synthesis of 1,1'-dideaza-quinine: Proof of concept. **N. Schmitt**, J. Eber, A. Montoya, D.E. Minter

746. Elucidating the origin of preisolactone A via biomimetic synthesis. **A.J. Novak**, C.E. Grigglesome, D. Trauner

747. Progress towards the total syntheses of Impatiens A and Ochotensimine: Utilizing a novel cyclization. **K. Korch**, D.A. Watson

748. Concise total synthesis of ($\pm$)-lysergic acid. **N. Tasker**, P. Wipf

749. Convergent synthesis of anaphene B. **M.A. Baber**, J. Patrone

750. Synthetic studies on guaipyridine alkaloids rupestines D, L and M. **B.J. Mulligan**, P.M. Shelton, S. Grosslight, H.V. Spargo, J.R. Vyvyan

751. Biomimetic four-step access to the sesquiterpene natural product presilphiperfolan-1 β -ol via supramolecular catalysis. **L. Syntrivani**, I. Némethová, S. Levi, A. Prescimone, D.T. Major, K. Tiefenbacher

752. Divergent approach to the total synthesis of (–)-heliannuol A & D via hypervalent iodine-mediated oxidative ring expansion. **B. Hobbs**, C. Callas, S.E. Wengryniuk

753. Towards eleganine A total synthesis. **G. Smits**

754. Study of the semi-synthesis of (–)-conophylline. **J. Kang**, A.C. Gardner, M. Walia, R.B. Andrade

755. Efforts toward the total synthesis of various marine natural products. Z. Shultz, **S. Bradley**, J. Leahy

756. Steps towards the total synthesis of Amaryllidaceae alkaloids. **A. Montoya**, D.E. Minter

757. Synthesis of the carbocyclic core of thapsigargin using the asymmetric allenic Pauson–Khand reaction. **E.D. Deihl**, L. Burrows, K.M. Brummond

758. Progress in the synthesis of cryptomaldamide congeners. **D. McConnell**, R.B. Kinnel

- 759.** Construction of new classes of targeted chemical screening libraries: Investigating new avenues for drug delivery via natural product diversification. **H. Dembele, A.C. Ebert, C. House, D. Henderson, A. Fernando, W. Hulangamuwa, R. Rafferty**
- 760.** Synthetic modification of Reniochalistatin E to enhance drug delivery systems in cancer therapy. **B.N. Funk, A. Fatino, G. Baca, C. Weeramange, W. Hulangamuwa, R. Rafferty**
- 761.** Synthetic efforts toward balgacyclamide family of natural products: Total synthesis, new drug delivery vehicles, and beyond. **A. Bartels, R. Rafferty, P. Desman, H. Henderson, A. Torres Hernandez, T. Nguyen, Y. Zhang, V. Hoang**
- 762.** Halenium-ion induced cascade: Approach for the synthesis of agelastatin A. **E. Dzurka, H. Gholami, S. Torabi Kohlbouni, B. Borhan**
- 763.** Synthetic efforts towards the cahuitamycin family of natural products. **A.L. Fernando, P. Desman, W. Hulangamuwa, A. Jimenez, R. Rafferty**
- 764.** Synthetic efforts towards Lagunamide C and proposed Lagunamide E. **S.S. Perera, A. Fatino, B. Funk, Y. Zhang, J. Dallman, L. Lowlor, R. Rafferty**
- 765.** Utilizing an enantioselective chloroetherification strategy towards the total synthesis of napyradiomycin A1. **S. Torabi Kohlbouni, A. Jaganathan, N. Salehi Marzijarani, G.J. Rodriguez, N.R. Perry, B. Borhan**
- 766.** Optimizing the synthesis of 1-((4,9-dioxo-4,9-dihydronaphtho[2,3-b]thiophen-2-yl)oxy)-N,N,N-trimethylmethanaminium chloride as an organic redox flow battery material. **P.L. Cruz Parrilla, R.L. Broadrup**
- 767.** Progress towards the total synthesis of frondosin D via tandem cyclization/claisen rearrangement. **M. Pinto Pereira Junior, T.V. Ovaska, D. Chu**
- 768.** Synthetic studies towards ezomycin and related natural products. **J. More**
- 769.** Synthesis of new organic borazine compound derivated from 3-amino-2-naphthol as starting material for analysis of chemical and physical properties. **J.L. Rosario Collazo, M. Ortiz**
- 770.** Synthesis and evaluation of meroterpenoid derivatives of puupeheone. **A.D. Landgraf, N. Schulte, S. Sucheck**

THURSDAY MORNING

New Reactions & Methodology

S. M. Silverman, *Organizer*

8:20 771. Sulfonamide-induced gauche effect versus the Thorpe-Ingold effect in Richman-Atkins cyclization. **M.M. Sibley**, I.R. Ruohoniemi, C.L. Polito, **S.C. Temples**, C.J. Kelley, O. Bein, I.R. Cummings, W.A. Harris, M. Wetzler

8:40 772. Catalyst-controlled chemodivergent reaction of α -diazo- β -ketoesters and enol ethers: Regioselective synthesis of highly substituted indoles. **G. Guerra Faura**, T. Nguyen, S.A. France

9:00 773. Tropolonate salts as efficient acyl transfer catalysts. **C. Empel**, D.J. Lyons, R.M. Koenigs, T.V. Nguyen

9:20 774. Remote desaturation of amines by radical relay. **R. Dare**, L.M. Stateman, A. Paneque, D. Nagib

9:40 775. Sulfuryl fluoride: Lab scale synthesis and applications in SuFEx chemistry. **J. Gurjar**

10:00 776. Catalytic ring expansions of cyclic alcohols enabled by proton-coupled electron transfer. **K. Zhao**, R. Knowles

10:20 777. Reaxys-PAI predictive retrosynthesis: Rewiring chemistry and redesigning synthetic routes. **J. Swienty Busch**, A. Kumar, I. Krstic, T. Boettjer

10:40 778. Unusual salicyl-substituted triazole synthesis from aurones. **A. Kafle**, S. Bhattarai, S.T. Handy

11:00 779. Nickel-catalyzed Suzuki–Miyaura couplings of amides: Scope and applications. **T.B. Boit**, N.K. Garg

11:20 780. Development of silicon and boron tethered Pauson-Khand reactions. **D. Martinez-Solorio**, A.G. Gallagher, H. Tian, O.A. Torres-Herrera, S. Yin, A. Xie, D.M. Lang, M.R. Gau, P.J. Carroll

11:40 781. Semi-synthesis and biological evaluation of bis-indole alkaloid (–)-melodinine K: Case study in efficiency. **A.C. Gardner**, M. Walia, C. Tejjaro, T.M. Tran, J. Kang, S. Zhao, R.B. Andrade

Heterocycles & Aromatics

S. M. Silverman, *Organizer*

8:00 782. Reactions of thermally generated benzyne with *N*-heterocycles: Pathway and product diversity. **S. Arora**, J. Zhang, V. Pogula, V. Palani, T.R. Hoye

8:20 783. Iodine mediated one-pot cyclization-alkylation and cyclization-oxidation methodologies for the synthesis of 2,3-disubstituted benzo[*b*]thiophenes. **C.M. Cunningham**, S. Khan, T. Kesharwani

8:40 784. Synthesis and analysis of photoreactive activity-based troponoid chemical probes. **A. Berkowitz**, C. Parker, R.P. Murelli

9:00 785. Regioselective synthesis of fluorosulfonyl 1,2,3-triazoles from bromovinylsulfonyl fluoride. **J. Thomas**, V.V. Fokin

9:20 786. Enantioselective Synthesis of helically chiral boron chelated dipyrromethenes (BODIPYs) capable of circularly polarized luminescence. **M. Hall**

9:40 787. Rh(III)-catalyzed formal [4+1] approach to pyrrolidines from unactivated terminal alkenes and nitrene sources. **S. Lee**, H. Lei, T. Rovis

10:00 788. Diastereoselective synthesis of *trans*-2,3-disubstituted γ -butyrolactones. **A.Y. Nuriye**, C. Craescu

10:20 789. Use of microwaves to synthesize propargylic ethers as precursors of 1,2,3-triazoles in click reactions. **L.C. García-Sánchez**, M.A. García-Eleno, E. Cuevas-Yañez, **A.F. Becerra Buitrago**, J.A. García-Ortíz

10:40 790. Compared methods to synthesize 1,2,3-triazoles. **L.C. García-Sanchez**, M.A. García-Eleno, E. Cuevas-Yañez, **A.F. Becerra Buitrago**, J.A. García-Ortíz

11:00 791. Synthesis of highly oxygenated troponoids utilizing oxidopyrylium cycloaddition chemistry. **D. Schiavone**, R.P. Murelli

11:20 792. NIR emitting styryl dye with large stokes shift to enable *co*-staining study on Zebrafish neuromast hair cells. **L. McDonald**, D. Dahal, M. Konopka, Q. Liu, Y. Pang

11:40 793. Direct C–H arylation of enones with ArI(OCOR)₂ reagents. **F. Silva**, N. Van, S. Wengryniuk

Section C

Pennsylvania Convention Center
120A

Physical Organic Chemistry: Calculations, Mechanisms, Photochemistry & High-Energy Species

S. M. Silverman, *Organizer*

8:40 794. Steric effects on the temperature dependence of primary kinetic isotope effects in hydride transfer reactions in solution. **S. Koirala**, Y. Lu

9:00 795. Mechanistic insights of photoredox catalysis using an alpha-amino arylation. **B. Stevenson**, E. Spielvogel, E. Loiaconi, J. Swierk

9:20 796. On the mechanism of singlet oxygenation of the prenyl-containing natural product glycocitrine II. P.P. Mohapatra, **A. Greer**

9:40 797. Product distribution in the cross aldol condensation of 4,4'-bicyclohexanone with aromatic aldehydes. **A.M. Balija**, C.T. Burgin, W.J. Nape, K. Schoettinger, T.J. Fuhrer

10:00 798. Modulating aromatic pathways in porphyrins at the molecular level. **Y. Zhang**, S. Fatayer, I. gross

10:20 799. Mechanistic perspective to oxidative dehydrogenative intramolecular C-C coupling of (hetero)aryls with oxidized carbon materials. **S. Aikonen**, T. Wirtanen, D. Casadio, M. Muuronen, J. Helaja

10:40 800. Computationally guided design of cyclopentadiene click reactions for applications in bioorthogonal chemistry. **B. Levandowski**, N. Abularrage, R.T. Raines

11:00 801. Computational and crystallographic studies of heteroaromatic N-oxide halogen bonding. **C.N. Miller**

11:20 802. How to manipulate photodynamic behavior of crystals. **U. Banerjee**, S.K. Sarkar, J.A. Krause, M. Abe, A.D. Gudmundsdottir

Section D

Pennsylvania Convention Center
120B

Asymmetric Reactions & Syntheses

S. M. Silverman, *Organizer*

8:20 803. Asymmetric vinylogous aldol reaction of *N-tert*-butanesulfinyl metallodienamines. **P. Yu**, V.K. Chatare, R.B. Andrade

8:40 804. From desktop to benchtop: Paradigm shift in asymmetric synthesis. M. Burai Patrascu, **J. Pottel**, S. Pinus, M. Bezanson, P. Norrby, N. Moitessier

9:00 805. Development of chiral binaphthyl-based calcium disulfonimide complexes for asymmetric catalysis. **M. Benda**, M. Tang, S.A. France

9:20 806. Enantioselective hydroamination of alkenes with sulfonamides enabled by proton-coupled electron transfer. **C. Roos**, J. Demaerel, D.E. Graff, R.R. Knowles

9:40 807. Out-of-equilibrium stereocontrol: Light-driven deracemization enabled by excited-state electron transfer. **N.Y. Shin**, J.M. Ryss, X. Zhang, S.J. Miller, R. Knowles

10:00 808. Chameleon catalyst. **A. Mohammadlou**, B. Borhan, W.D. Wulff

10:20 809. Second-generation synthesis of illudinine, a potential MAO-B inhibitor. **R. Gaston**

10:40 810. Access to highly functionalized cyclopentenones via diastereoselective pauson-khand reaction of siloxy-tethered 1,7-enynes. **A.G. Gallagher**, H. Tian, O.A. Torres-Herrera, D. Martinez-Solorio

11:00 811. Oxidative dearomatization: One pot synthesis of chiral spiroimidazolidinone cyclohexadienones from amino acid chirons. **D.T. Do**

11:20 812. Enantioselective synthesis of cyclopropanone equivalents and its application for the production of chiral β -lactams by formal [3+1] cycloaddition. **V. Lindsay**

Section E

Pennsylvania Convention Center
118A

Molecular Recognition & Self-Assembly

S. M. Silverman, *Organizer*

8:20 813. Assembly of organic semiconductors into micro- and nano-crystals. **N. Gavvalapalli**, D. Jones

8:40 814. Macromolecular receptors for chemical fingerprinting in aqueous media. **M. Bonizzoni**

9:00 815. Effects of sterics and electronics on the binding modes and equilibrium binding constants of benzyl-4,4'-dipyridyl derivatives with cucurbit[7]uril. **S. Ellis**, U. Khadka, R. Cochran, R. Halterman

9:20 816. Creating a caged surfactant with thiazole orange moieties for the delivery of mRNA to cells. **J. Raise**, H. Han, D. Kerr, I. Li, C. Taing, N. Murthy

9:40 817. Computational and experimental optimization of cyclophane-guest complexes. **G. Lee**, M. Miller, K.N. Houk, E.M. Sletten

10:00 818. Functional capsules via subcomponent self-assembly. **D. Zhang**, T. Ronson, J. Nitschke

10:20 819. NMR insights into carbohydrate-carbohydrate interactions. **J. Muzulu**, B. Leeber, A. Basu

10:40 820. Correlation between the chirality of supramolecular aggregates of an azo dye to its plant proteoglycan binding ability. **R. Hoshing**, B. Leeber, H. Kuhn, D. Cainiello, B. Dale, R. Lusi, M. Saladino, S. Weingarten, N. Palaychuk, A. Basu

11:00 821. Synthesis and characterization of 4, 6-O-phenylethylidene acetal derivatives of D-glucosamine as molecular gelators. **P. Sharma**, A. Mao, G. Wang

11:20 822. DNA-directed assembly of supramolecular structures and nanoparticles. **S.T. Nguyen**

Section F

Pennsylvania Convention Center
120C

CH Activation

S. M. Silverman, *Organizer*

8:40 823. Metal-free C-H functionalization of *N*-Aryl amine compounds as drug scaffolds: Opportunities and current limitations. **M. Kim**, C. Mudithanapelli

9:00 824. Unusual reactivity of a palladium-catalyzed C(sp³)-H fluorination method. **M.T. Morales Colon**, M.S. Sanford

9:20 825. Improving sustainability in directing groups for C-H activation. **M. Young**

9:40 826. Cobalt(III) catalyzed C-H functionalizations through weak coordination: Synthesis of functionalized indole and indoline derivatives. **P. Ravikumar**, S.K. Banjare, T. Nanda

10:00 827. C-H activation of alcohols and ethers by a cationic iridium(III)-1,10-phenanthroline dichloride complex: Gas-phase study. **R.S. Corea**, S. Gronert

10:20 828. Dehydrogenation via C-H activation by a graphene-supported nickel single-atom catalyst model ion in the gas phase. **M. Borrome**, S. Gronert

10:40 829. Para selective iridium catalyzed CH borylation of sulfates and sulfamates directed by ion-pair electrostatic interactions. **J.R. Montero**, T.J. Oleskey, S.L. Miller, M.R. Smith, R.E. Maleczka

11:00 830. Rational development of remote C-H functionalization of biphenyl: Experimental and computational studies. **K. Bay**, Z. Fan, X. Chen, Z. Zhuang, H. Park, K.N. Houk, J. Yu

ORGN 1

Copper catalyzed reductive carbonylation of alkyl iodides

Siling Zhao¹, szhao48@uic.edu, **Neal P. Mankad**². (1) Chemistry, University of Illinois at Chicago, Chicago, Illinois, United States (2) Depart of Chemistry 4178 SES, UI Chicago, Chicago, Illinois, United States

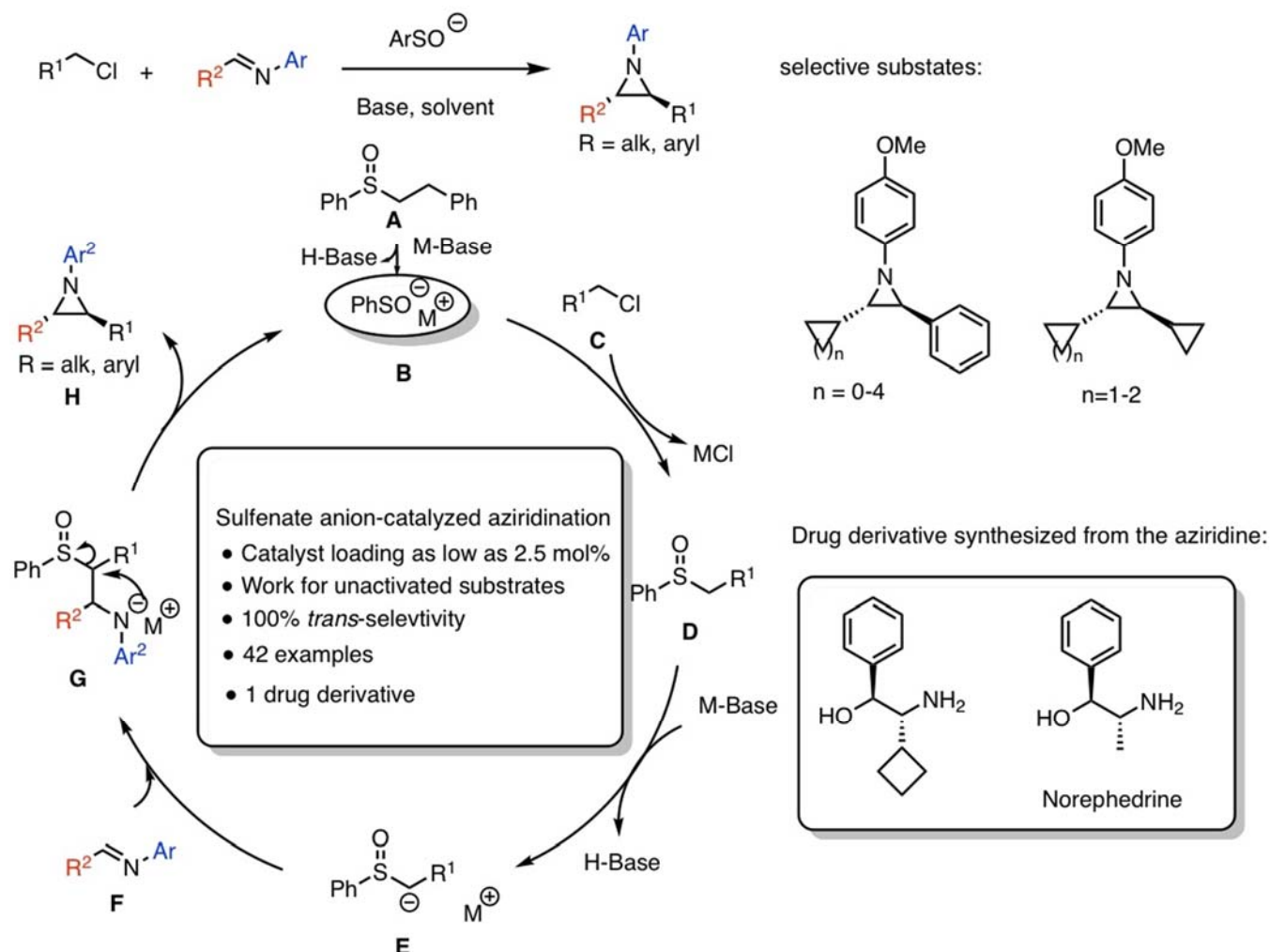
In this presentation, the ability of copper catalysts to mediate reductive carbonylation reactions of alkyl iodides will be discussed. First, a tandem carbonylation and reduction of alkyl iodides developed in the presence of a Cu catalyst to provide one carbon-extended alcohols will be presented. Mechanistic studies indicated that aldehydes served as intermediates and that radical atom transfer carbonylation (ATC) of alkyl iodides was involved. Second, a synergistic copper catalyzed carbonylation of alkyl iodides and reduction of nitroarenes to provide amides will be discussed. Both methods provided various carbonylated compounds in one pot under mild conditions. The supporting NHC ligands played an essential role in suppressing the side products in both C-C and C-N coupling reactions.

ORGN 2

Sulfenate-anion-catalyzed diastereoselective aziridination of imines

Zhipeng Zheng¹, zhengzh@sas.upenn.edu, **Patrick J. Walsh**², pwalsh@sas.upenn.edu. (1) Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States (2) Univ of Penn, Philadelphia, Pennsylvania, United States

Aziridines have been highly valued synthetic targets as well as building blocks in synthesis owing to its strained three-member ring and reactivity toward ring-opening reactions as well as cycloaddition reactions. Most of the existing synthetic methods to synthesize aziridines are stoichiometric reactions involving noble and expensive metals or potentially hazardous diazo compounds. In this work, sulfenate anions (PhSO^-) are utilized to catalyze diastereoselective aziridination of unactivated imines with benzylic or alkyl halides under basic condition. Forty substrates bearing heterocyclic rings, alkyl substitutes, and electron rich/poor aryl groups were shown to be compatible with this method, giving good yields and high diastereoselectivity (*trans*:*cis* > 20:1). Twelve ring-opening products and one norephedrine derivative were obtained with nucleophiles including water, thiol, azide, acetic acid and aniline.



ORGN 3

Cyanoalkylcopper species in carbon-carbon bond forming reactions

Daniel L. Silverio, dsilverio@adelphi.edu. Chemistry, Adelphi University, Floral Park, New York, United States

Traditional organocopper reagents have been utilized for decades as a reliable way to perform carbon-carbon bond forming reactions such as conjugate additions, allylic substitutions, and cross-couplings. Their mechanism of action has been well studied. However, this has not been the case for cyanoalkylcopper species, with only three extant reports about them. All of the previously reported species were cyanomethylcopper species, with none being derived from a nitrile that would yield a more complex cyanoalkylcopper reagent.

The scope and limitations of nitriles that can be utilized to prepare cyanoalkylcopper

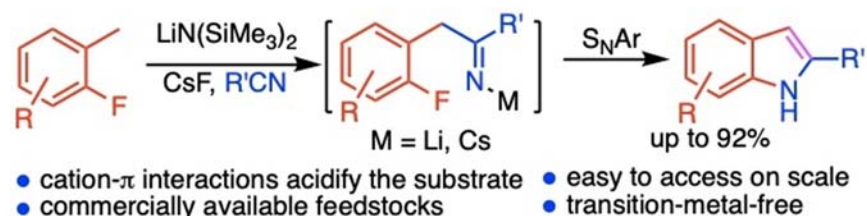
complexes for use in substitution reactions of allylic bromides will be discussed. Investigations of the extension of the method to include allylic leaving groups other than halides, optimization of reaction conditions, and the reactivity of cyanoalkylcopper species in conjugate addition and cross-coupling will also be presented.

ORGN 4

New reactivity enabled by cation- π interactions

Patrick J. Walsh, pwalsh@sas.upenn.edu. Univ of Penn, Philadelphia, Pennsylvania, United States

Cation- π interactions are electrostatic forces that can be used to control reactivity and selectivity in reactions. In the area of transition metal catalyzed processes, reactions presented include the arylation of 2-benzyl furan and arylation of toluenes using heterobimetallic Pd/K catalysts. Transition metal-free reactions involving the use of toluenes in the aminobenzylation of aldehydes and 2-fluorotoluenes in a novel indole synthesis will also be discussed. Support for cation- π interactions in these reactions will be outlined.



ORGN 5

Dipolar alkynyl-prins (DAP) cyclization for the rapid construction of complex polycycles

Shukree Abdul-Rashed, shukreea@buffalo.edu, Georgios Alachouzos, Alison Frontier. Chemistry, University of Rochester, Lockport, New York, United States

The development of a novel Dipolar Alkynyl-Prins (DAP) protocol for the expedient synthesis of unique, sp^3 -rich complex polycycles is described. This method relies upon a coupling of ampielectronic alkynyl and acetal building blocks under acidic conditions. The one-pot transformation consists of an intramolecular Prins cyclization of an alkyne and oxocarbenium ion (generated from an alcohol-acetal condensation), followed by nucleophilic capture of the incipient vinyl cation by the pendant (protected) amine functionality to furnish oxa-aza fused bicycles in a highly general, efficient and

stereocontrolled fashion. In this reaction cascade, molecular complexity is rapidly generated as three new bonds (C-C, C-O, and C-N) as well as two new rings are formed in one synthetic operation from simple and convenient precursors.



ORGN 6

Subphthalocyanines and perylene-diimide derivatives in organic photovoltaics

Lakshmi Chockalingam Kasi Viswanath, lakshmijeho@gmail.com. Dept of Chemistry, Oklahoma Baptist University, Shawnee, Oklahoma, United States

One of the greatest challenges for our modern society with burgeoning energy demand and inadequate reserve of traditional fossil fuel sources is to find clean and renewable energy sources. Modern technology has taken its stand to solve this energy challenge so as to harvest clean, renewable and abundant solar power by many attractive methods. The most important of all those techniques is the development of photovoltaic cells through the construction of donor acceptor conjugates involving supramolecular structures such as porphyrins, phthalocyanines etc. The specific aims of the proposed research are to construct precursors for the development of donor acceptor conjugates for harvesting energy.

ORGN 7

Silylated α -aminonitriles for late-stage functionalization

Thomas Mathew, tmathew@usc.edu, **Takehiko Yamato**, **Surya G. Prakash**. Loker Hydrocarbon Research Institute, Univ of Southern California, Los Angeles, California, United States

Successful ketonic Strecker reactions using a series of ketones including fluorinated ketones were achieved in our laboratories earlier using $Ga(OTf)_3$ giving the corresponding α -aminonitriles in high yields. Knowing the significance of bifunctional α -amino nitriles, which are versatile intermediates with broad range of synthetic and

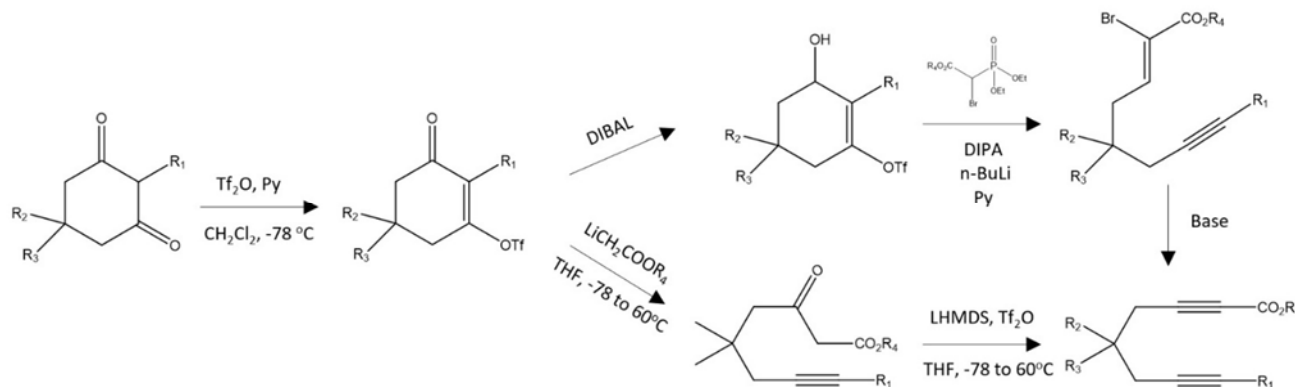
biological applications, development of convenient methods for their easy access is of great importance. A series of silylated α -aminonitriles are now synthesized in high yields using sustainable metal triflates as catalysts. Presence of trimethylsilyl group helps late-stage functionalization of the corresponding silylated α -aminonitriles. This safe and convenient methodology will be discussed in detail.

ORGN 8

Synthesis of differentially substituted diynes via tandem nucleophilic addition/fragmentation pathways

Amir Tavakoli, at0028@mix.wvu.edu, Gregory B. Dudley. Chemistry, West Virginia University, Morgantown, West Virginia, United States

As our ongoing interest, we have reported tandem processes to generate diverse keto-alkynes and 1,6-enyne hydrocarbons. These high-value substrates can undergo ring-opening fragmentation reactions to deliver valuable building blocks for many annulation and cycloisomerization strategies To obtain carbocycles and of natural product target structures. We have been developing our methodologies to access functionalized 1,6-diyne hydrocarbons that are otherwise hard to prepare.



ORGN 9

Analogues of Bestmann's ylide, $\text{Ph}_3\text{P}=\text{C}=\text{C}=\text{O}$: Syntheses, structures and Lewis acid catalyzed cyclizations with organic substrates

Clemens Krempner, clemens.krempner@ttu.edu. Dept of Chemistry Biochemistry, Texas Tech University, Lubbock, Texas, United States

Bestmann's ylide, $\text{Ph}_3\text{P}=\text{C}=\text{C}=\text{O}$, has been widely used as chemical linchpin reagent in the synthesis of natural products and was found to undergo various [2+2], [2+3] and [2+4] cycloaddition reactions. Herein, we report the synthesis, structures and spectroscopic properties of various structural analogues of Bestmann's ylide with general formula $\text{R}_3\text{P}=\text{C}=\text{C}=\text{E}$, where $\text{E} = \text{O}$ or S ; $\text{R} = \text{alkyl, aryl and NR}_2$ [1]. In addition, we will demonstrate that some of these structural ylide analogues readily undergo Lewis acid catalyzed cyclization reactions with nitrones and epoxides to selectively form heterocyclic compounds with exocyclic phosphonium ylide moieties [2]. These new phosphonium ylides serve as precursors in Wittig reactions to form the corresponding heterocycles with exocyclic $\text{C}=\text{C}$ double bonds. Substrate scope and mechanistic aspects of these new reactions will be discussed.

ORGN 10

Diastereoselective alkynylations of β -(Bromo)iminium ions via copper(I) catalysis

Samantha O. Santana¹, ssantana@udel.edu, **Weiye Guan**¹, **Mary P. Watson**². (1) University of Delaware, Baltimore, Maryland, United States (2) Chemistry & Biochemistry, University of Delaware, Newark, Delaware, United States

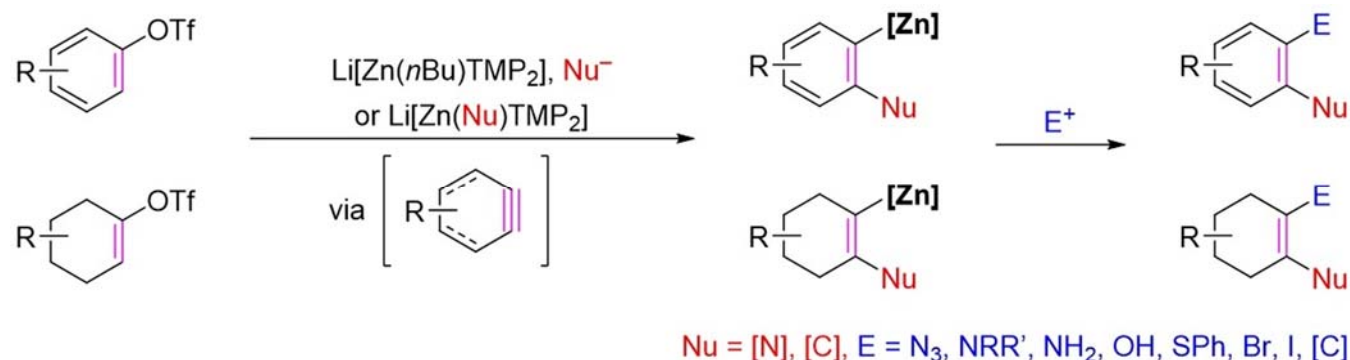
We have developed a diastereoselective copper-catalyzed alkynylation of cyclic β -(bromo)iminium ions, formed *in situ* from amins, to deliver *trans*-difunctionalized products. The β -(bromo)aminal substrates are readily prepared via bromination of cyclic enamine precursors, allowing an efficient route from dihydropiperidines and pyrrolidines to highly functionalized heterocycles. Piperidine and pyrrolidine derivatives can be prepared with high diastereoselectivity and good functional group tolerance.

ORGN 11

Modular three-component difunctionalization of aryl/cyclohexenyl triflates via aryne and cyclohexynes

Seoyoung Cho, seoyoung.cho@duke.edu, **Qiu Wang**. Chemistry Dept, Duke University, Durham, North Carolina, United States

A modular *ortho*-difunctionalization approach for aryl triflates has been achieved via a three-component reaction. The cascade transformation proceeds through a deprotonative formation of a highly reactive aryne intermediate, an *in situ* nucleophilic addition, and a coupling reaction of an organozinc intermediate. This approach enables the installation of a diverse range of functionalities, such as amines, anilines, oxygen, sulfur, halides, alkynyl, (hetero)aryl, vinyl, and alkyl groups. This strategy is also effective for difunctionalization of cyclic vinyl triflates by the deprotonative formation of strained cycloalkyne intermediates



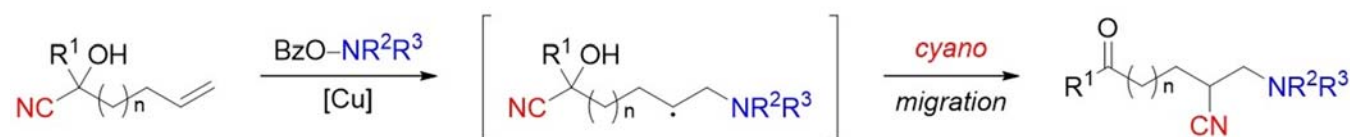
ORGN 12

1,2-aminocyanation of alkenes via distal migration

Yungeun Kwon¹, yungeun.kwon@duke.edu, **Qiu Wang²**. (1) Chemistry, Duke University, Durham, North Carolina, United States (2) Chemistry Dept, Duke University, Durham, North Carolina, United States

Synthesis of nitrogen containing molecules has been one of the major interests of organic chemists due to their prevalent biological activities. The incorporation of different transformations onto carbon–carbon double bond in a single step has been a powerful synthetic method to achieve various aminofunctionalization including diamination, aminooxygenation and aminohalogenation. Despite extensive progress in this field, aminocyanation of alkenes still remain underdeveloped. Due to the ubiquity of carbon–carbon and carbon–nitrogen bonds in nature, developing efficient methods for simultaneous formation of these two valuable bonds is highly desired. In our lab, we have developed diamination, amino lactonization and amino oxygenation transformations of alkenes by employing an umpolung strategy utilizing O-benzoylhydroxylamines as an electrophilic amine source. Inspired by these works and previous literatures of radical-mediated functional group migration, we utilized O-benzoylhydroxylamines as a radical initiator to trigger cyanide migration. This method allows us to achieve regioselective 1,2-aminocyanation of alkenes and form ketones simultaneously.

1,2-Aminocyanation through distal migration

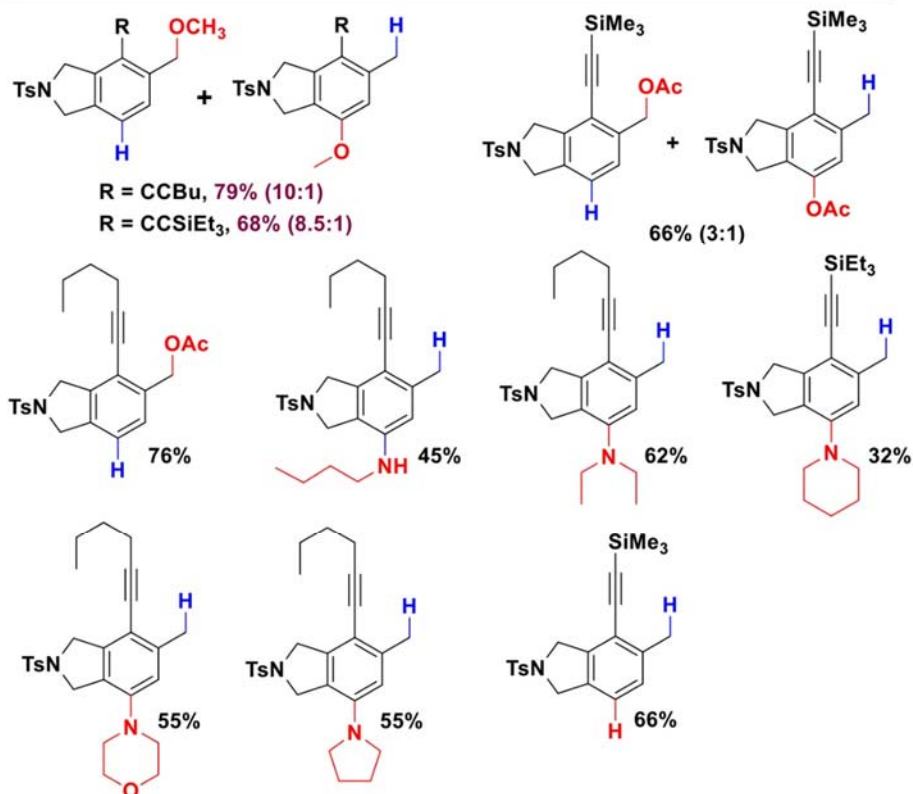
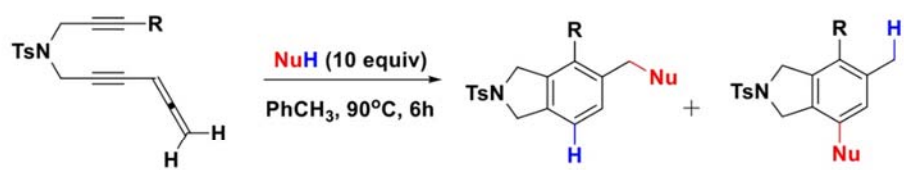


ORGN 13

Formal [4+2] cycloaddition between alkynes and allene-ynes to generate functionalized toluenes

Anh D. Le¹, *leducanh981991@gmail.com*, **Daesung Lee²**, **Saswata Gupta¹**. (1) Chemistry, University of Illinois at Chicago, Cicero, Illinois, United States (2) Univ of Illinois at Chicago, Chicago, Illinois, United States

A new type of thermal [4+2] cycloaddition reaction of an alkyne and an appropriately linked allene-yne is described. The reaction generates an α,β -dehydrotoluene intermediate which can behave as a zwitter ion or diradical depending on the reaction counterpart. The regioselectivity of nucleophile capture was examined with various nitrogen- and oxygen-based nucleophiles. Replacing the alkyne with nitrile induced a different mode of [4+2] cycloaddition through the formation of bis-allene under basic conditions, which led to functionalized picolines. Mechanistic investigation is in progress for this aromatization process by DFT calculations.



ORGN 14

Regioselective carbonylation of 2,2-disubstituted epoxides

Aran K. Hubbell¹, akh74@cornell.edu, **Jessica R. Lamb**¹, **Anne M. LaPointe**¹, **Kristine Klimovica**¹, **Geoffrey W. Coates**². (1) Chemistry and Chemical Biology, Cornell University, Ithaca, New York, United States (2) Cornell Univ, Ithaca, New York, United States

Carbon monoxide is an inexpensive and renewable feedstock for the production of biologically active small molecules. Epoxide carbonylation, therefore, has become a powerful, atom-economical synthetic method in the field of sustainable chemistry for the introduction of new carbon-carbon bonds. Resulting β -lactones are versatile intermediates that are frequently used in natural product synthesis, ring-opened to aldol adducts, and polymerized to form biodegradable polyhydroxyalkanoates. Different carbonylation catalysts were designed to target β,β -disubstituted β -lactones and α,α -disubstituted β -lactones as single regioisomers from 2,2-disubstituted epoxides. Improved mechanistic understanding facilitated reaction condition optimization, affording efficient, regioselective carbonylative routes to these disubstituted products. The resulting β -lactones were either ring-opened to generate a wide variety of challenging Mukaiyama aldol products or isolated for the formation of highly sought-after, biodegradable polyesters.

ORGN 15

Copper catalyzed N-arylation of 4-R-1,2,4-triazoles

Jeanne L. Bolliger, jeanne.bolliger@okstate.edu. Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma, United States

We are pleased to report an alternative synthetic route leading in two steps from primary amines to 1-aryl substituted 1,2,4-triazolium salts. The crucial step of this approach is a copper catalyzed quaternization of various 4-R-1,2,4-triazoles using diaryliodonium salts. Key features of the presented work are a reliable reaction protocol, short reaction times and high functional group tolerance, thus allowing the selective N-arylation of the triazole ring even in the presence of pyridine, pyrimidine and sulfide groups.

ORGN 16

Formation of tricyclic aromatic heterocycles mediated by oxidative disulfide coupling

Jeanne L. Bolliger, jeanne.bolliger@okstate.edu. Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma, United States

A new class of tricyclic aromatic thiazolium salts are conveniently obtained from air stable precursor via selective deprotection followed by oxidative disulfide coupling. Using this procedure, we are able to prepare a variety of thiazolium salts which contain both electron-withdrawing and electron donating aromatic substituents as well as aliphatic substituents. This method has proven to be tolerant towards many functional groups, thus allowing biologically relevant groups to be introduced either before or after the heterocycle formation.

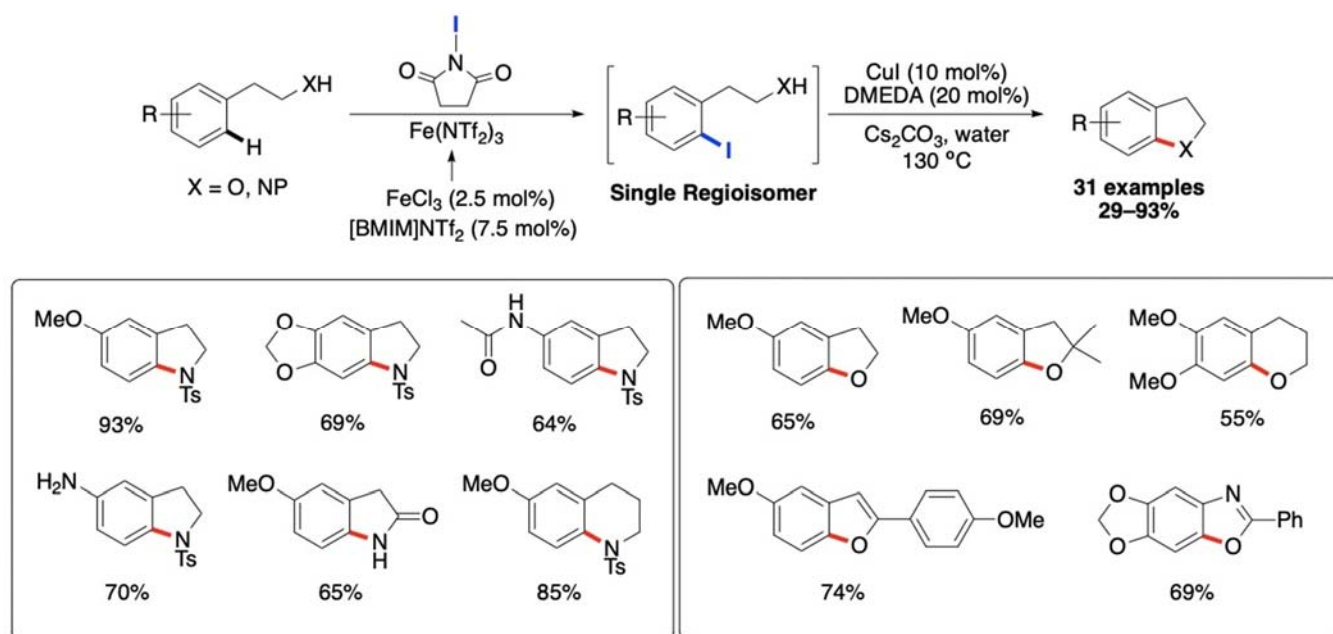
ORGN 17

New methods for aryl C-N and C-O bond formation using sequential iron and copper catalysis

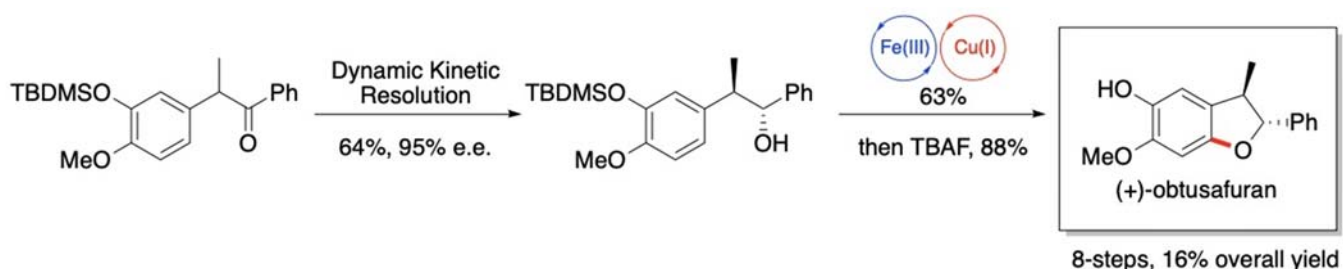
Martyn C. Henry, m.henry.1@research.gla.ac.uk. School of Chemistry, University of Glasgow, Renfrew, Renfrewshire, United Kingdom

Functional heterocycles such as indoline and 2,3-dihydrobenzofurans represent the core of many natural products and biologically active compounds. Rapid, selective and sustainable access to these privileged scaffolds is therefore of utmost significance. An emerging strategy for the synthesis of these heterocycles involves the direct, dehydrogenative cross coupling of tethered heteroatoms and aryl C-H bonds facilitated by precious transition metals such as Pd, Ru and Rh. This project has focused on the development of a one-pot, two-step intramolecular aryl C-N and C-O bond forming process for the preparation of diverse libraries of *N*- and *O*-heterocycles utilising readily available, non-toxic and inexpensive first row transition metals. The methodology involves activation of aryl rings by a highly regioselective, iron(III) triflimide-catalysed iodination, followed by copper(I)-catalysed intramolecular *N*- and *O*-arylation leading to indolines, oxindoles, dihydrobenzofurans, benzofurans, benzoxazoles and 6-membered analogues. This represents the direct transformation of a C-H bond into a C-N or C-O bond using sequential iron(III)- and copper(I)-catalysis in a one-pot process.

The versatility and functional group tolerance of this methodology was then demonstrated with a new total synthesis of (+)-obtusafuran, a neolignan natural product possessing antiplasmodial and anticarcinogenic activity. After preparation of a single diastereoisomer of the chiral benzyl alcohol, the one-pot iron(III)- and copper(I)-catalysed dehydrogenative type process was used as the key step for the efficient construction of the *trans*-substituted dihydrobenzofuran ring system.



One-pot iron and copper catalysed synthesis of functional heterocycles



Total synthesis of (+)-obtusafuran

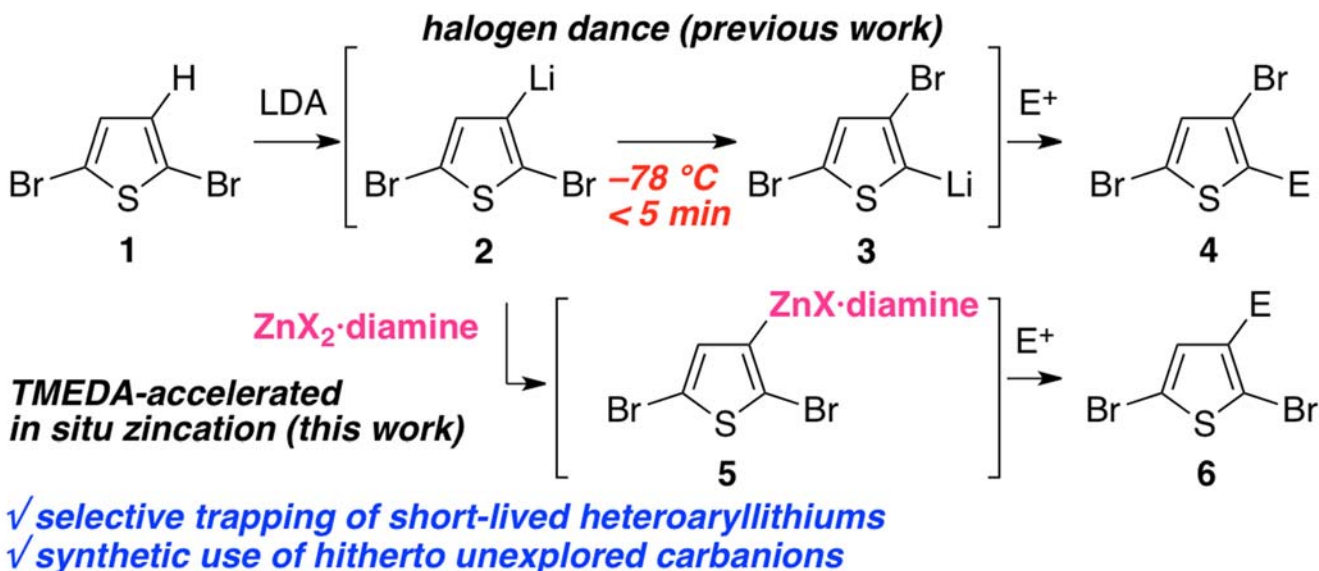
ORGN 18

Control of halogen dance and its application to the synthesis of substituted heteroaromatic compounds

Kentaro Okano¹, okano@harbor.kobe-u.ac.jp, **Suguru Hirai**¹, **Yuki Hayashi**¹, **Kengo Inoue**¹, **Masato Aoki**¹, **Atsunori Mori**^{1,2}. (1) Department of Chemical Science and Engineering, Kobe University, Kobe, Japan (2) Research Center for Membrane and Film Technology, Kobe University, Kobe, Japan

Deprotonation of a heteroaromatic ring continues to be the prevalent method for introducing functional groups, though transition metal-catalyzed C–H functionalization has reached a stage of maturity. Recently developed Knochel–Hauser-type magnesium amides and zinc amides allow the formation of mild organometallic species, which expands the substrate scope of the reaction. In contrast, its high reactivity is utilized for

halogen migration, which is known as halogen dance rearrangement; deprotonation of 2,5-dibromothiophene (**1**) gives β -lithiothiophene **2**, which is immediately converted to more thermodynamically stable α -lithiothiophene **3** within 5 min, even at $-78\text{ }^{\circ}\text{C}$, to furnish **4** upon treatment with an electrophile. Herein, we present trapping of short-lived thienyllithium **2** by TMEDA-accelerated *in situ* zincation to provide kinetically stable organozinc **5**. This method is applied to the synthesis of functionalized dibromothiophene **6** as well as to that of substituted furans and selenophenes.



ORGN 19

Development of 2-pyridinyl-1,2,4-triazine alkoxy-substituted scaffolds for minor actinide separations

Mariah L. Tedder, mariahtedder1@gmail.com, Jesse D. Carrick. Tennessee Technological University, Church Hill, Tennessee, United States

Increased interest in transitioning toward renewable cleaner energy sources like nuclear energy has amassed a necessity for the recycling of spent nuclear fuel. Environmental concerns, particularly regarding the handling of nuclear waste, has slowed the uptake of widespread usage in the U.S. This lab continues to be interested in developing complexants to aid in separations work of spent nuclear fuel, specifically with the separation of the minor actinides from lanthanides. Minor actinides possess the ability to adsorb neutrons which renders them not stable enough for usage in transuranic fuels, in addition to safety concerns with the resultant storage of these compounds.

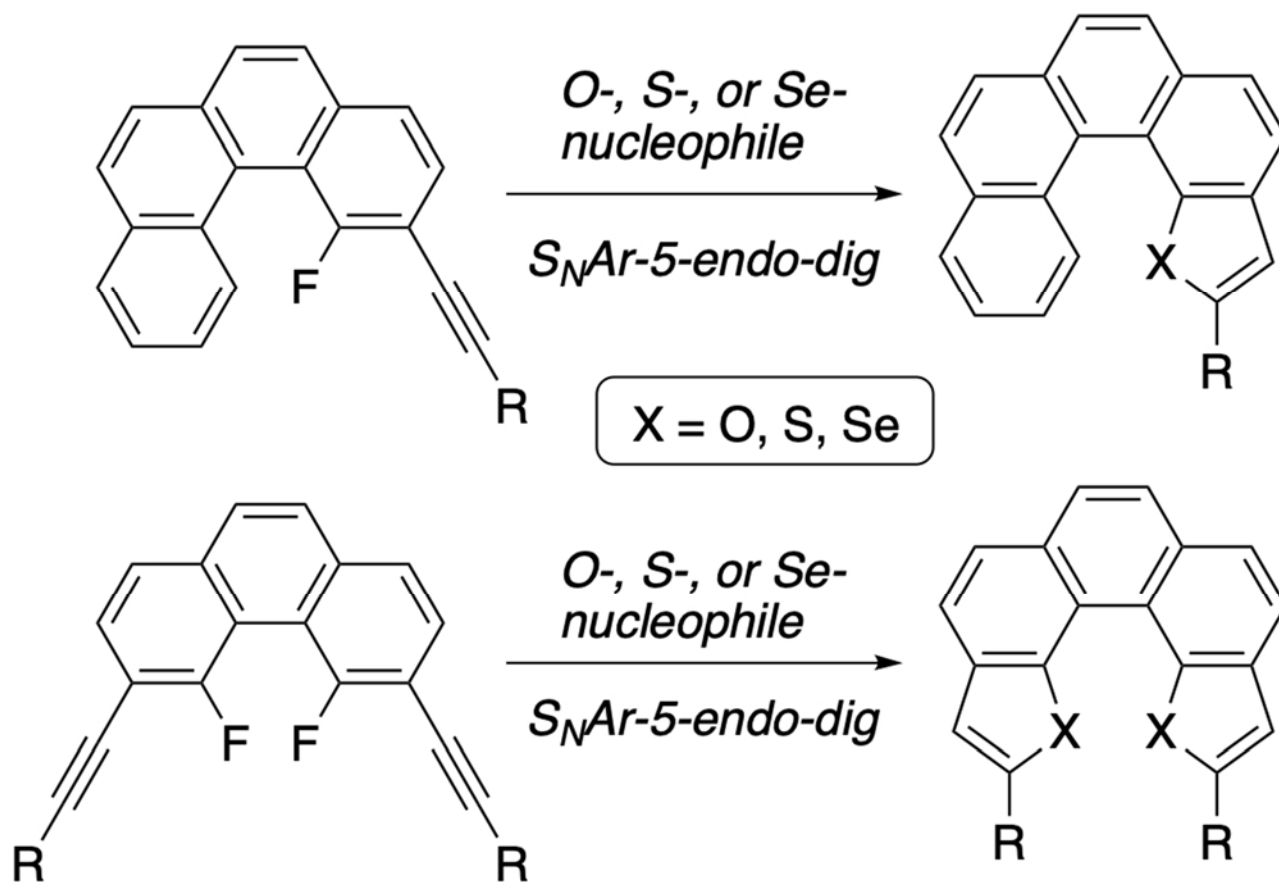
This project seeks to further improve 2-pyridinyl-1,2,4-triazine based scaffolds, which have demonstrated acumen in selective separations work of the minor actinides, by improving their solubility and selectivity by substituting these substrates with alkoxy chains of varying length. A three-step synthesis protocol using commercially available reagents was performed and afforded several new complexants featuring aliphatic chains to potentially improve solubility. Upon synthesis and characterization of the molecules, these compounds will be studied for both solubility and separations efficacy in comparison to previous complexants.

ORGN 20

Convergent strategy for the synthesis of oxa-, thia-, and seleno[5]helicenes by acetylene-activated S_NAr reactions

Jeffrey L. Katz, jlkatz@colby.edu, Samuel Hoenig, Youmian Yan, Emily Dougherty, Sava Petovic, Christopher Lee, Yusheng Hu, Lucas Gomez. Chemistry, Colby College, Waterville, Maine, United States

A tandem acetylene-activated S_NAr -anionic cyclization strategy is presented for the synthesis of chalcogen-containing [5]heterohelicenes. Oxa-, thia-, and seleno[5]helicenes are accessed from common *ortho*-fluoro-ethynylarene precursors, allowing the heteroatoms to be installed at the 1-position or 1- and 12-positions of the [5]helicene inner core.



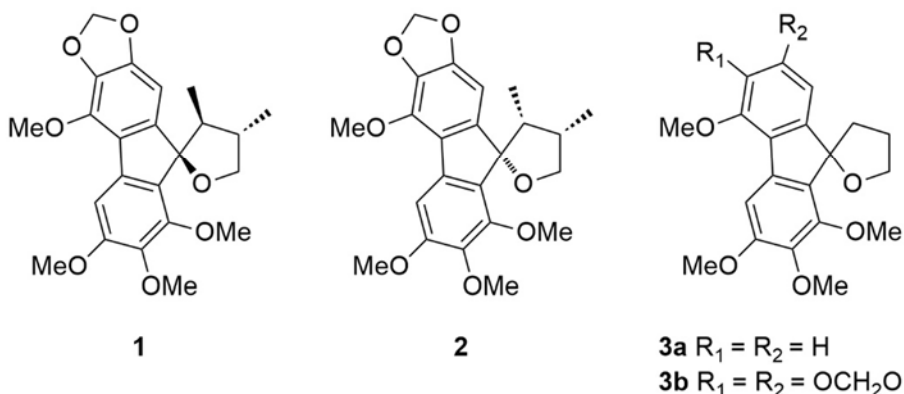
ORGN 21

Synthesis of polycyclic spiro lignan natural product model substrates

Ghada Ali, **Gregory D. Cuny**, gdc002y@yahoo.com. University of Houston, Houston, Texas, United States

Gymnothespirolignan A (**1**) and B (**2**) belong to a family of novel polycyclic spiro lignan natural products (Figure 1). They were isolated in 2014 from *Gymnotheca involucrate* and showed modest antiviral activities against respiratory syncytial virus (RSV). Our interest in these compounds arose from their conformationally restricted structure that provides fixed spatial orientation of functional groups that may be exploited for defining binding modes with biomolecular targets. As an initial study, polycyclic spiro lignan model substrates were used. In this presentation, a synthetic route to compounds **3a** and **3b** will be described.

Figure 1. Structures of polycyclic spiro lignans **1** and **2**, as well as model substrates **3a** and **3b**.

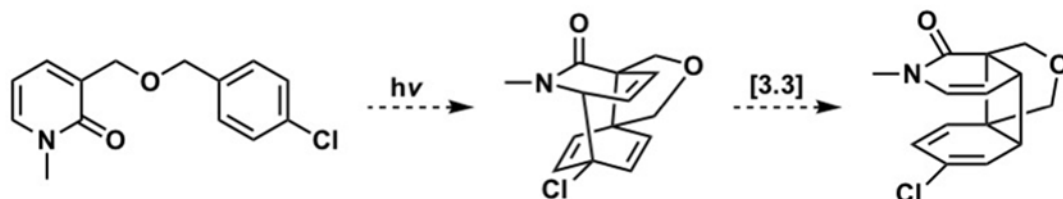


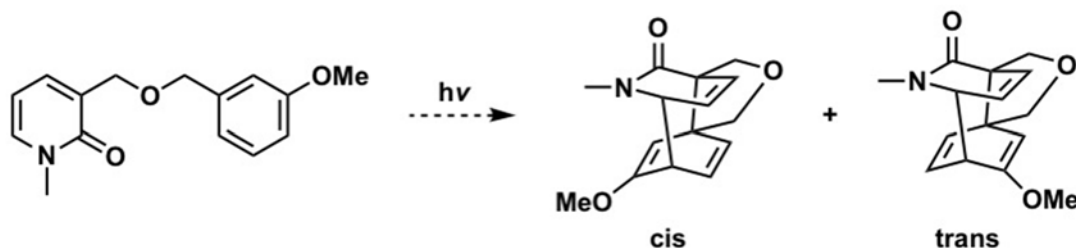
ORGN 22

Para- and [4+4] photocycloadditions in mixed pyridone–benzene systems

Lauren M. Rossiter¹, tug24975@temple.edu, **Steven Fletcher**¹, **Basheer Garas**¹, **Scott M. Sieburth**². (1) Temple University, Philadelphia, Pennsylvania, United States (2) Chemistry, Temple University, Flourtown, Pennsylvania, United States

Benzene can undergo photocycloadditions in three different ways, *ortho*, *meta* and *para*. Among these, *meta*-cycloadditions have received the most attention. Pyridones are well known for their propensity for [4+4] photocycloadditions with a broad selection of 1,3-dienes and 1,3-diene equivalents. In a mixed system designed to favor benzene–pyridone cycloaddition, the cycloaddition favors a *para* cycloaddition of the pyridone diene with the benzene. When the benzene has a substituent, cycloaddition can yield two *cis/trans* isomers. These highly strained molecules can undergo a thermal [3,3] rearrangement. A study of the chlorine and methoxy substituted benzene substrates will be discussed.





ORGN 23

Cyclopentannulation and cyclodehydrogenation of isomerically pure 5,11-dibromoanthradithiophenes leading to contorted aromatics

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This poster details the synthesis, characterization and cyclopentannulation of isomerically pure 5,11-dibromo-2,8-dihexylanthra[2,3-b:7,6-b']dithiophene **1**, which is a brominated analog of anthradithiophene (ADT). Cyclopentannulation with 3,3'-dimethoxyphenylacetylene using palladium catalysis was employed to synthesize 4,10-dihexyl-1,2,7,8-tetrakis(3-methoxyphenyl)cyclopenta[6,7]aceanthryleno[4,3-b:8,9-b']dithiophene **2**. Scholl cyclodehydrogenation of **2** with FeCl_3 resulted in the formation of contorted 2,14-dihexyl-5,10,17,22-tetramethoxytetrabenzo[4,5:6,7:11,12:13,14]rubiceno[2,3-b:10,9-b']dithiophene **3**. Compound **3** is a contorted aromatic that has low lying lowest unoccupied molecular orbitals capable of accepting electrons to make resonance stabilized cyclopentadienyl anions. Compound **3** was found to be more oxidatively stable compared to previously prepared pentacene derivatives that are isoelectronic to ADT. The contorted compound **3** is more soluble than traditional flat polycyclic aromatic hydrocarbons and possess a small HOMO-LUMO band gap (1.50 eV).

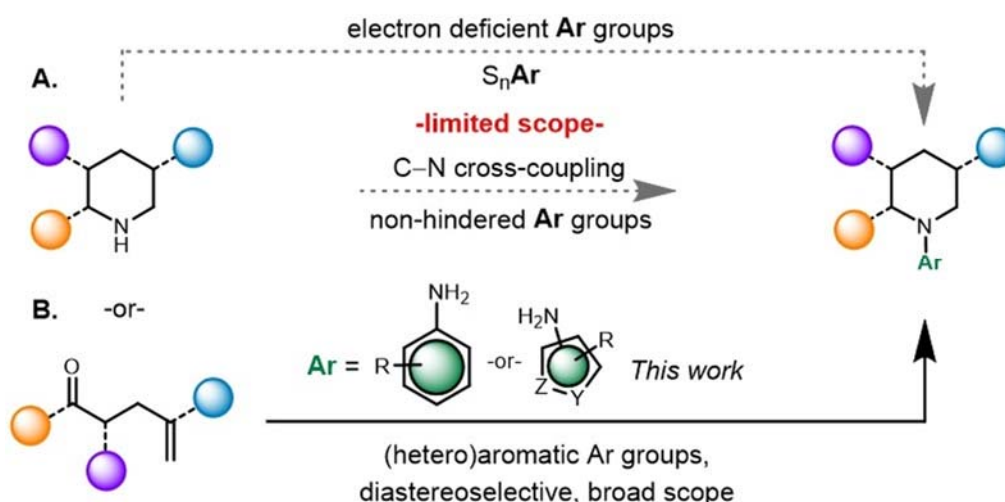
ORGN 24

Diastereoselective synthesis of *N*-(hetero)aryl-piperidines

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Piperidines are the most common nitrogen-containing heterocycle in FDA approved drugs, and these motifs are often substituted at the N-position. However, examples of

N-(hetero)arylation of piperidines via C-N coupling methods are sparse when the aryl electrophile is electron-rich, hindered, or a 5-membered heterocycle. We report an alternative approach that forms such products from a reductive amination/aza-Michael addition reaction sequence of an amino(hetero)arene and a bis-electrophile, forging both the piperidine ring and the desired *N*-aryl bond. The products of this sequence are formed in high diastereoselectivity, and this method allows for facile access to hindered *N*-(hetero)aryl piperidines containing electron-rich and 5-membered heteroaryl substituents on the piperidine nitrogen, which are challenging structures to form via Pd-catalyzed C-N coupling. The origins of the observed diastereoselectivity were investigated by DFT, and these studies suggest that a facially selective protonation of an enol intermediate leads to the often high observed diastereoselectivity.



ORGN 25

Approaches to scaling-up linked continuous flow photo-, electro- and thermal-chemistry: New reactors and new approaches

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Photochemistry is potentially a very powerful tool for manufacturing not least because energy is delivered to reacting molecules far more selectively than by bulk heating in an atom efficient manner. Indeed, more than a century ago, Ciamician, presented a very powerful vision of the where photochemistry could lead us [*Science* 1912, 36, 385-394]. Since then photochemistry has become a major strand of chemical research in academia. By comparison, its penetration into chemical manufacture remains comparatively modest because of a whole series of issues, mostly centred on the

problems of carrying out larger-scale photochemical reactions both efficiently and safely. In recent years, progress has been made in addressing the challenges of making photochemistry greener, more energy efficient and more widely accessible. This presentation will cover our activity particularly aiming for generic approaches for linking and scaling up continuous multi-step processes in the context of photo-, electro and thermal- chemistry on the kg/day scale with emphasis on singlet O₂ and the synthesis of the anti-malarial drug Artemisinin as well as recent advances in design of simpler reactors for both visible and UV photochemistry.

ORGN 26

"Machine-Assisted Synthesis: Programmable Precision Polymers by the Push of a Button"

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Contemporary macromolecular chemistry has matured to a point where virtually any polymer structure can be synthesized via combinations of controlled polymerization approaches, postpolymerization modification and efficient ligation strategies. Still, often large hurdles have to be overcome to take the next step in research, that is being able to provide such complex materials reliably on significant scale for use in advanced applications. A solution to this problem is to make use of continuous flow synthesis techniques. Flow reactors are associated with high reproducibility, intrinsically simple reaction scale-up and improved product qualities due to significant reduction of side reactions. Being an established method especially in the pharmaceutical chemistry domain, full potential with regards to macromolecular synthesis did not unfold until very recently. Among others, the benefits of using online-monitoring will be discussed and the development of fully autonomous machine-learning based reactor systems presented.

On the example of a variety of thermal and photochemically induced polymerizations, the potential of machine-learning in combination with flow chemistry will be highlighted. Specifically, the unmatched precision with respect to monomer conversion and average molecular weight that can be reached in self-optimizing reactor systems is elucidated. Various first applications of such systems will be shown. Among others, the ability to produce materials with an artificial molecular weight distribution opens new avenues in material design that classical approaches cannot provide. Applications in this realm stretches from precision thermal and mechanical material properties design to information encoding.

ORGN 27

Continuous plug flow antisolvent crystallization of active pharmaceutical ingredients

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Process-scale crystallization is important in pharmaceutical manufacturing given that nearly 90% of all drugs contain crystalline active pharmaceutical ingredients (APIs) or excipients owing to the high purity and predictable performance afforded by crystalline materials. As an alternative to batch crystallization in stirred tanks or continuous stirred tank crystallizers (MSMPR), continuous plug flow crystallizers with multiple antisolvent addition points and static mixers can provide a narrow size distribution of crystals less than 30 μm in size, thus making a milling step unnecessary when small crystals are needed. Results from ongoing development activities including batch antisolvent crystallization, solubility, kinetic, and preliminary continuous plug flow antisolvent crystallization studies using commercially relevant APIs will be presented. In addition, an approach to the flow synthesis and antisolvent crystallization of the acetaminophen (APAP) cocrystal with 2,4-pyridinedicarboxylic acid (PDA) will be discussed, as will the results of a demonstration at scale in a 230 mL α -prototype continuous flow crystallizer theoretically capable of producing over 6 kg cocrystal/day. Replicate and controlled studies show that competing crystallization of the synthons could be minimized while producing nearly 90% of the APAP-PDA cocrystalline material in the 20-30 μm size range.

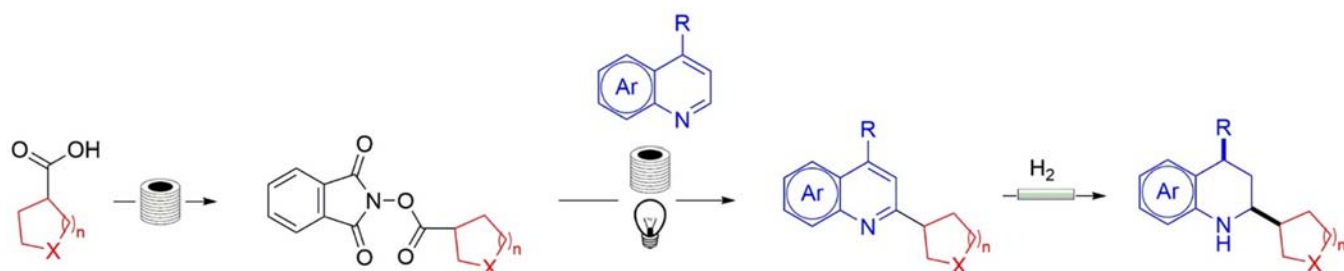
ORGN 28

Synthesis of substituted heteroarenes and their subsequent reduction using flow technology to produce novel heterocycles

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Construction of C(sp²)-C(sp³) bonds is relatively difficult in comparison to C(sp²)-C(sp²) bonds. Recently, photoredox catalytic and other photochemical methodologies, together with technological achievements expanded the scope of C(sp²)-C(sp³) bond constructions.

In particular, the Minisci reaction is a synthetically useful tool for the functionalization of heterocycles, nevertheless, it sometimes suffers from harsh conditions, low yields and selectivities. Building on batch results obtained in our multifunctional photoreactor we devised a continuous microflow procedure. In this an in situ formed N-(acyloxy)phthalimide esters (NAP) in combination with transition metal based photoredox catalysts or organic dyes were employed for the alkylation of six- and five-membered heteroaromatic ring systems. The flow procedure allowed for the convenient integration of NAP intermediate formation and the C(sp²)-C(sp³) coupling reaction. Subsequent reduction of the Minisci products gave access to novel heterocycles with even higher 3D character. The hydrogenations were carried out in automated flow systems affording the products in good stereoselectivities.



ORGN 29

Synthetic control of stoichiometry, size, and defect distributions: Beneficial impact on resultant electrochemistry

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Synthetic control of physicochemical properties of metal oxides is essential to realize the goal of fast ion transport and electron transfer in solid ionic matrices. Reducing the path length for ion transport both through crystallite size reduction and controlled introduction of ion vacancies can provide significant improvements. However, conventional nanostructuring techniques employing constraining media can lead to surface coatings manifesting as resistive interfaces, which are often detrimental in energy storage applications. Of particular benefit are composite materials incorporating both ion and electron conducting materials. However, intimate connection between the moieties to achieve full utilization is achieved synthetically rather than by mixing of dissimilar materials. Low temperature, scalable, direct synthetic approaches to achieve well defined stoichiometry, size, and defect distributions in energy storage materials and their composites will be described in this presentation, with an emphasis on materials employing earth-abundant transition metal centers (i.e. iron, manganese). The beneficial impact on the resultant electrochemistry will be highlighted.

ORGN 30

Making new materials for energy storage

Colin P. Nuckolls, cn37@columbia.edu. Columbia Univ, New York, New York, United States

This presentation will describe our efforts to create redox flow batteries from organic materials. We have focused on using perylene diimide and cyclopropenium cations as a

charge storage media and coupled with that membranes that are compatible with both high voltages and organic solvents for use in non-aqueous redox flow batteries. The membranes can be made via a processing-free fabrication method by polymerizing an ionic polymer inside a porous, commercially available scaffold. As the membrane in a non-aqueous redox flow battery, they are highly effective at preventing material crossover. For example, a perylene diimide derivative, when used as the anolyte, exhibits no detectible crossover and a new cyclopropenium cation, when used as the catholyte, exhibits less than 0.08% crossover per day. Cycling of a full battery yields a voltage of 1.7 V battery showing >99.5% coulombic efficiency and >99.5% capacity retention per cycle over a two-week period. This general membrane fabrication strategy supports rapid development and testing of new charge-storage molecules and battery components in fully functioning devices and fills a void in membrane candidates for testing high voltage non-aqueous redox flow batteries.

ORGN 31

Organic electrode material design for beyond lithium-ion batteries

Yan Yao, *yyao4@uh.edu*. University of Houston, Houston, Texas, United States

Electrochemically redox-active organic electrode molecules (OEMs) have attracted significant attention in the field of energy storage. In this talk, I will first present a case study of organic cathode materials in all-solid-state batteries that maintain reversible active material-electrolyte interfaces and intimate physical contact during battery cycling. A platform combining structural, chemical, and mechanical characterizations are being developed for multidimensional diagnostics of the interface evolutions in solid-state batteries to provide insights into the failure mechanisms. I will then discuss how OEMs can be designed to solve the short cycle life challenges of aqueous batteries for decades due to the structural and chemical instability of anode electrodes. We designed and synthesized three stable quinone anodes showing long cycle life of 3000 cycles and state-of-art energy density in a broad pH range from -1 to 15. An aqueous zinc-polymer battery and characterizations to understand the pressure-dependent reaction mechanisms will also be discussed.

ORGN 32

Diversity-oriented synthesis of new polymers for battery applications

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Here I will describe how diversity-oriented synthesis can be used to accelerate the identification of new polymers for batteries with properties that go beyond what has

been achievable with iterative advances on known materials. A particular emphasis will be placed on ion-conducting polymers, which are prominently featured as advanced membranes as well as solid- and semi-solid electrolytes. Characterization of libraries of such polymers, prepared using a variety of build/couple/pair strategies, have yielded information-rich structure–property maps from which lead polymers for a given application and battery chemistry were identified. I will also present our work in validating these hits in devices, including lithium metal batteries and redox-flow batteries.

ORGN 33

Going a step beyond: Isolating and characterizing the charged states of active battery materials

Susan A. Odom, *susan.odom@uky.edu*. University of Kentucky, Lexington, Kentucky, United States

When considering organic redox couples as active charge storage materials in redox flow batteries, the redox potential, solubility, and stability are all critical. Predicting stability in complex environments (e.g. electrolytes and their salts, charged electrodes, and membranes) remains a significant challenge, especially when considering the charged states of a material. My group is interested in characterizing the charged forms of organic molecules using methods that allow us to determine the sources and mechanisms of decomposition. Thus, in addition to the standard electrochemical methods and cycling studies, we have focused on the generation and isolation of charged species using chemical means. By isolating the charged species, we are able to measure solubility and analyze stability in controlled environments, choosing when to introduce any component that is not the active species itself. Here I will give an overview of the methods we have used to generate, isolate, and characterize charged organic molecules, as well as what we have learned, both independent of and complementary to electrochemical methods for analysis. In particular, I will focus on stability in the charged form.

ORGN 34

Design strategies for organic solids and solutions in hybrid redox flow batteries

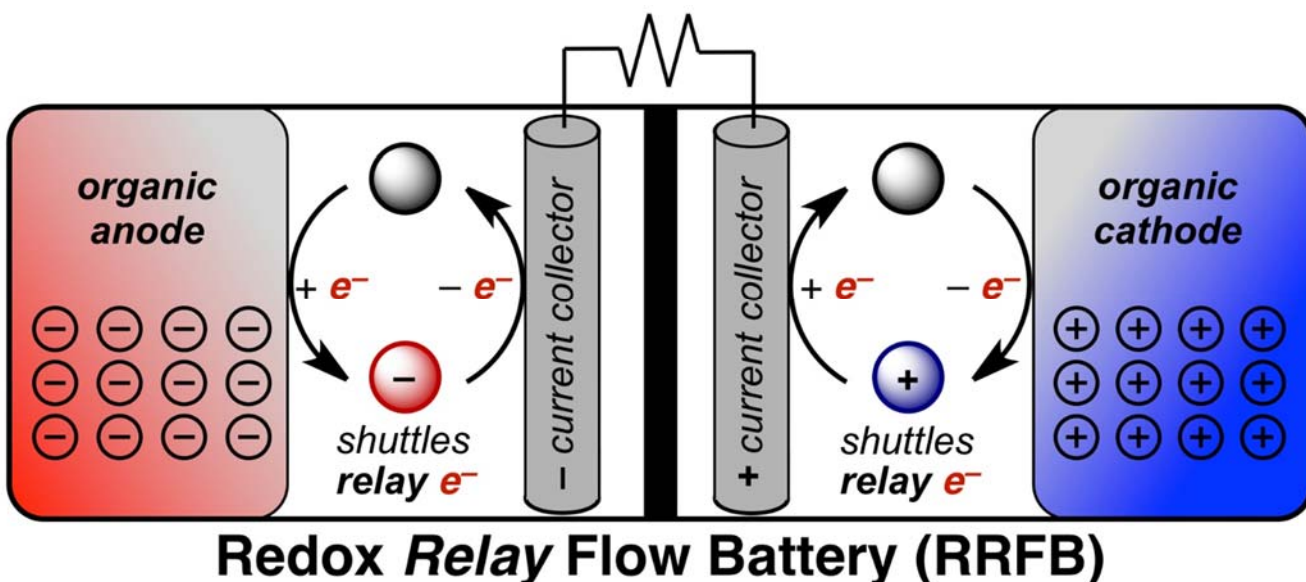
Christo S. Sevov, *sevov.1@osu.edu*. Chemistry and Biochemistry, The Ohio State University, Columbus, Ohio, United States

Large-scale penetration of electricity from renewable sources into the electrical grid has yet to be realized because technologies that can modulate the intermittence and variability of solar or wind energies are lacking. Redox flow batteries (RFBs) have attracted attention as a solution to grid-scale storage because they can be inexpensively scaled by simply adding redox liquids to large reservoirs. Because of this flow architecture, identifying redox-active solutions that are inexpensive, yet energy

dense, is critical to the deployment of RFBs. However, RFBs lack energy density and remain nearly an order of magnitude more expensive than what is necessary for cost-competitive energy storage.

This seminar details our efforts to address fundamental limitations in current RFBs by conceptually redesigning energy storage in flow. Specifically, redox-active organic solids (ROSs) serve as storage materials. Rather than forcing these solids to undergo redox directly at the electrode, small quantities of solvated redox-active organic molecules (ROMs) relay electrons between the ROSs and the distal current collectors. This redox *relay* flow battery is scalable because of the decoupled power and capacity, energy dense because of the solid storage materials, and tunable because of the organic materials.

The design principles that will be discussed include: (i) strategies to generate insoluble ROSs, (ii) the effect of size and shape on ROS charging and solution flow, (iii) the effect of a shuttle's redox potential on the accessible states of charge, and (iv) the effect of the shuttle's size on the rate of ROS charging and discharging. These key insights are the first steps to providing the community with fundamental guides for designing shuttles and solids for this new battery architecture.



ORGN 35

Use of high-pressure and high-throughput experimentation, and theory to optimize the catalytic borylation of methane with well-defined iridium complexes

Daniel J. Mindiola, mindiola@sas.upenn.edu. Chemistry, University of Pennsylvania, Bala Cynwyd, Pennsylvania, United States

A combination computational and experimental studies (high-pressure and high-throughput techniques) have allowed us to elucidate the mechanism and suggest a rational design and optimization strategies of a bis(phosphine)-supported iridium-catalyst for methane monoborylation. The activation of the C–H bond in methane via oxidative addition using tris(boryl) iridium(III) complexes bearing bis-chelating supporting ligands has been modeled computationally. This model shows that the use of the soft Lewis base ligand such as 1,2-bis(dimethylphosphino)ethane (dmpe) lowers the activation barrier of the rate-determining step as it facilitates polarization of the metal-center, lowering the barrier of the oxidative addition to afford a seven-coordinate iridium(V) intermediate. The experimental optimization of this reaction using high-throughput methods shows that we can obtain up to 170 turnovers at 150 °C (500 psi) within 16 h using bis(pinacolato)diboron, a well-defined homogeneous and monomeric catalyst (dmpe)Ir(COD)Cl that is readily available from commercial precursors. In this work we also establish decent selectivity for the monoborylation product H₃CBpinacolato. We have found that high-boiling cyclic aliphatic solvents such as decalin, cyclooctane, methylcyclohexane are also suitable for this reaction, while being inert toward borylation. In accordance with the lower calculated activation barrier, catalytic turnover is also observed at 120 °C but over a longer period of time. It was found that the borylation of methane is only achieved via one catalytic cycle, and buildup of pinacolborane, a side-product from methane borylation with bis(pinacolato)diboron, inhibits catalytic activity. New pre-catalysts, and high-pressure NMR spectroscopic studies have been further conducted to help understand the mechanism of this reaction.

ORGN 36

Utilizing high-throughput experimentation to catalyze diverse chemistry and collaborations within and outside of Merck

Dani M. Schultz, danielle.schultz@merck.com. Merck, Rahway, New Jersey, United States

Current examples will be discussed that highlight how approaching catalysis through high throughput experimentation (HTE) has addressed several synthetic challenges that have occurred during pharmaceutical development at Merck. Emphasis will be given towards recently published methodologies that focus on the direct functionalization of sp³ C-H bonds via decatungstate photocatalysis, Ni-catalyzed C-H arylation to afford oxazoles and lastly a Rh-catalyzed asymmetric hydroamination to yield 1,2-diamines. These methodologies were the result of strong academic-industrial collaborations that were ultimately enabled with HTE.

ORGN 37

Engaging esters, aldehydes, and alcohols in cross-coupling: High throughput approach to reaction discovery

Stephen Newman, *stephen.newman@uottawa.ca*. University of Ottawa, Ottawa, Ontario, Canada

With the use of hypothesis-driven high throughput experimentation,^[1] our group is exploring how the scope of electrophilic and nucleophilic reaction partners can be expanded to include more oxygenated functionality. In this presentation, strategies to engage esters, aldehydes, and alcohols in Ni-catalyzed C-C and C-N bond forming reactions will be described.^[2]

ORGN 38

Applications of HTE to the discovery and development of robust, scalable catalytic transformations for the synthesis of complex pharmaceutical intermediates

Eric Simmons, *eric.simmons@bms.com*. Chemical & Synthetic Development, Bristol-Myers Squibb, New Brunswick, New Jersey, United States

Many unique challenges are associated with the development of robust catalytic transformations that can be applied to the multi-kilogram scale synthesis of pharmaceutical intermediates. At BMS, our approach to the development of scalable catalytic processes relies upon the strategic application of high-throughput experimentation (HTE), along multi-variate design of experiments (DoE) and kinetic and mechanistic studies. This talk will describe our group's research philosophy and capabilities, and highlight some of our recent learnings through several case studies. Ongoing efforts to expand our research capabilities by exploiting base metals and photoredox catalysis to build the molecules that will become the medicines of tomorrow will also be discussed.

ORGN 39

High-throughput experimentation for the life sciences

Tim Cernak, *tcernak@med.umich.edu*. University of Michigan, Ann Arbor, Michigan, United States

Advances in chemical synthesis can be realized through rational experimental design, and a healthy dose of serendipity. We are exploring the use of high-throughput experimental methods to accelerate the discovery and optimization of new reactions. This talk will describe recent developments from our lab using miniaturized high-throughput experimentation in the development of reaction methods for the synthesis of complex molecules. Miniaturized chemical techniques enable the use of robotics for increased throughput. The ramifications of generating large amounts of data are that

new algorithmic planning approaches are needed. This talk will describe new hardware and software applications that enable explorations of chemical space and development of new reaction methods.

ORGN 40

Aryl amphiphile shape-directors for the shape-controlled synthesis of organic semiconductor micro- and nano-crystals

Dorothy Jones, *dkj32@georgetown.edu*, *Nagarjuna Gavvalapalli*. Chemistry, Georgetown University, Falls Church, Virginia, United States

Organic semiconducting micro- and nano-crystals (MNCs) are useful for active waveguiding (i.e., guiding the photoluminescence), photonic integrated circuits, optoelectronic applications, and laser applications. Specifically, the development of organic semiconductor based photonic integrated circuits may help overcome the limitations of silicon-based integrated circuits. Organic semiconducting MNCs also integrate electronics and photonics that is crucial for achieving high-density and high-speed optoelectronic circuits. It is well understood that properties and performance of MNC is highly dependent on the morphology and dimensionality of the microcrystals (MCs); in one-, two- or three-dimensional crystals the transport of photons and electrons can completely differ which can affect their use in different applications. While control over the particle shape as well as the molecular assembly within the particles is crucial to advance the burgeoning field of photonic integrated circuits for the above-mentioned applications, the methods for such control are limited. Aliphatic surfactants such as sodium dodecyl sulfate (SDS) and cetyltrimethylammonium bromide (CTAB) have been widely and successfully used for the shape-control of metal nanoparticles, but have much more limited success in the shape-control of organic crystals due to the weak interactions between the aliphatic surfactant tail and growing crystal surface. This talk will discuss the design, synthesis and use of novel aryl amphiphile as shape-directors for shape-controlled synthesis of organic MNCs. I will discuss the impact of the aryl hydrophobe structure on the MNC growth kinetics and thus the shape. The effect of the different morphologies of the MCs on the photophysical properties will also be discussed.

ORGN 41

Light-driven chiral liquid crystal nanostructures enabled by chiral molecular switches or motors: Dynamic photonics

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Liquid crystals (LCs) represent a fascinating state of matter that combines order and mobility at different hierarchical levels, i.e., from nanoscale to macroscale or in other

words from molecular level to macroscopic levels. The unique combination of order and mobility results in that LC is typically “soft” and responds to different external stimuli. The responsive nature and diversity of LCs provide tremendous opportunities as well as challenges for insights in fundamental science, and open the door to various applications. Conventional nematic LCs have become the quintessential materials of LC displays. With the LC displays ubiquitous in our daily life and annual more than \$100 billion market, the research and development of LCs are moving rapidly beyond display applications and evolving into entirely new and fascinating scientific frontiers. In my talk, I will focus on our recent development and investigation on light-driven chiral liquid crystal nanostructures for dynamic photonics enabled by chiral molecular switches or motors.

ORGN 42

Bisphenalenyl Radical Salts and their Uniquely Open-shell Optoelectronic Properties

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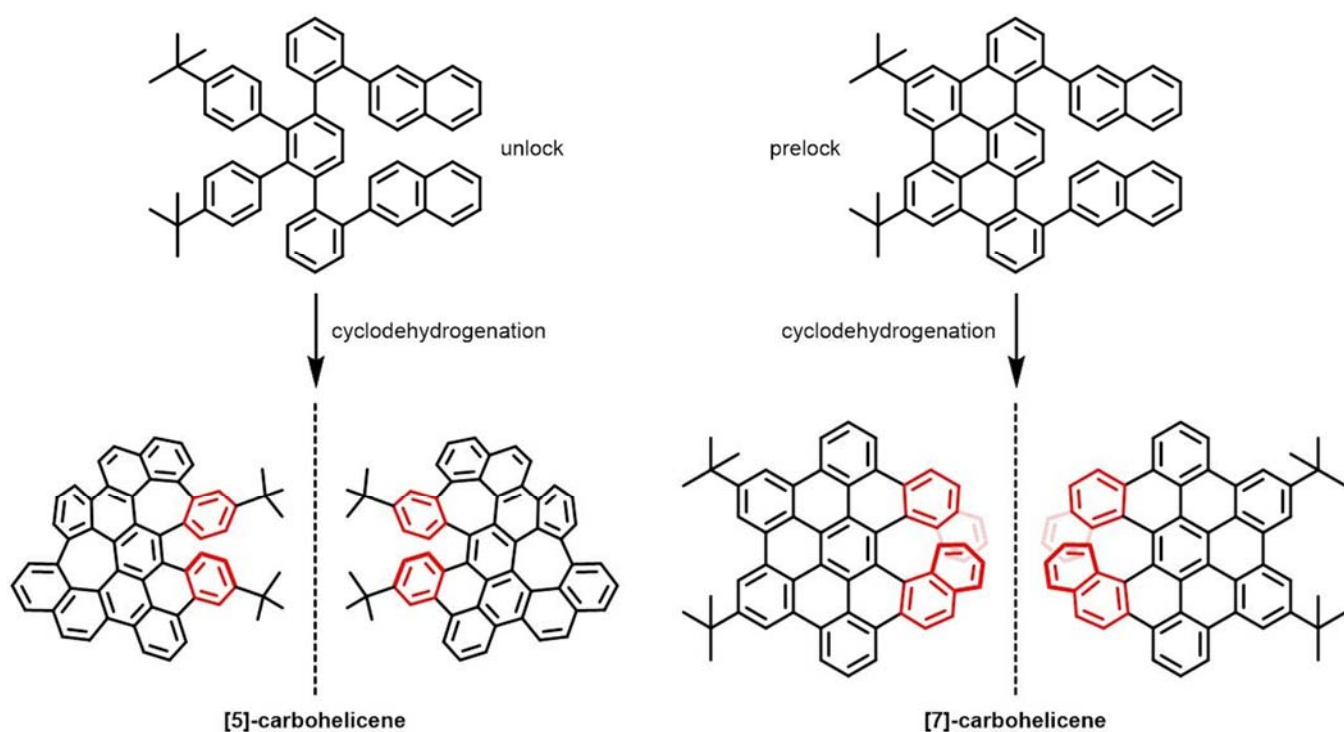
Classical organic materials used in optoelectronic applications are predominantly closed-shell in their electronic configuration, which limits their efficiency as charge carriers and functional materials. Open-shell materials, where some electrons are partially or wholly unpaired, represent a new approach to designing optoelectronic materials to overcome some of these limitations inherent to closed-shell systems. We have synthesized a new open-shell material in the form of a O-substituted bisphenalenyl π -radical cation salt that shows moderate electrical conductivity in single crystal measurements. Recent development of a solution-processable derivative has enabled the formation of thin films that demonstrate conductivities as high as 10 S/cm. The increase in conductivity allowed for Hall measurements which showed n-type behavior and mobilities ranging from 10-50 cm² V⁻¹ s⁻¹. These data are further supported by measuring the film's charge transport characteristics when applied to a FET device architecture. Physical studies suggest that the open-shell material is self-doped and achieves high electron mobilities due to remarkably strong intermolecular π - π interactions.

ORGN 43

Synthesis of [5]- and [7]-Carbohelicene through regioselective cyclodehydrogenation

Zijie Qiu¹, *zqiuaa@connect.ust.hk*, **Akimitsu Narita**^{1,2}, **Klaus Muellen**¹. (1) Max Planck Institute for Polymer Research, Mainz, Germany (2) Organic and Carbon Nanomaterials Unit, Okinawa Institute of Science and Technology Graduate University, Okinawa, Japan

Helicene molecules have attracted continuous attention because of their twisted molecular structures, inherent chirality, and contorted π -systems. Herein, we report the syntheses of [5]- and [7]-carbohelicenes through the regioselective cyclodehydrogenation from similar precursors, where unlock/prelock strategy plays a key role to achieve different products (scheme 1). The structure of [5]- and [7]-carbohelicenes are confirmed by NMR analysis, high-resolution MALDI-TOF mass spectrometry and single crystals analysis. The physicochemical properties are investigated by UV/Vis absorption, fluorescence spectroscopy, and cyclic voltammetry. DFT calculation is performed to study the isomerization processes. Their enantiomers are separated by chiral HPLC and the enantiopure [5]/[7]-helicenes are further characterized by circular dichroism spectroscopy.



Scheme 1

ORGN 44

Evidence of orientational order in thiophene derived carbon nanothreads

Arani Biswas¹, aqb5771@psu.edu, **Matthew Ward**², **Tao Wang**¹, **Li Zhu**², **Haw-Tyng Huang**¹, **John V. Badding**¹, **Vincent Crespi**¹, **Timothy A. Strobel**². (1) Pennsylvania State University, State College, Pennsylvania, United States (2) Geophysical Laboratory, Carnegie Institution of Washington, Washington, District of Columbia, United States

In an effort to synthesize novel carbon-based materials with various dimensionality and hybridization, success has been limited with only diamond, graphite, fullerenes and being a select few that exist in crystalline states as a discrete material. Among these predicted solids, one-dimensional sp^3 carbon nanomaterials offer much intrigue due to their structural organization with a diamond-like tetrahedral core that foreshadows the promise of novel mechanical, thermal and optical properties. These sp^3 carbon nanothreads live at the juncture of crystalline rigidity and polymeric flexibility. They were first synthesized from the slow, room-temperature compression and decompression of benzene or other small aromatics. However, limited long-range order along the thread axis and inter-thread registry was observed in the maiden synthesis of benzene-derived carbon nanothread.

Here we investigate the phase behavior of thiophene up to 35 GPa and establish a pressure-induced phase transition sequence that mirrors previous observations in low-temperature studies. Slow compression to 35 GPa results in the formation of a recoverable saturated product with a 2D monoclinic diffraction pattern along (0001) that agrees closely with atomistic simulations for single crystals of thiophene-derived nanothreads. Paradoxically, this lower-symmetry packing signals a higher degree of structural order, since it must arise from constituents with a consistent azimuthal orientation about their shared axis that is preserved over long axial distances. The simplicity of thiophene reaction pathways (with only four carbon atoms per ring) apparently yields the *first* nanothreads with orientational order, a striking outcome considering that a single point defect in a 1D system can disrupt long-range structural order. Orientational order of thiophene-derived nanothreads, in the face of sensitivity of 1D systems to structural disruption through defects, encourages efforts towards obtaining higher degrees of synthetic control over nanothread reaction outcomes. The high-pressure synthesis of ordered nanomaterials such as nanothreads can now be extended to aromatic systems with five-membered rings, a further increase in the diversity of compositions and structures achievable.

ORGN 45

Customizing the optoelectronic and chiroptical properties of carbon-based dots

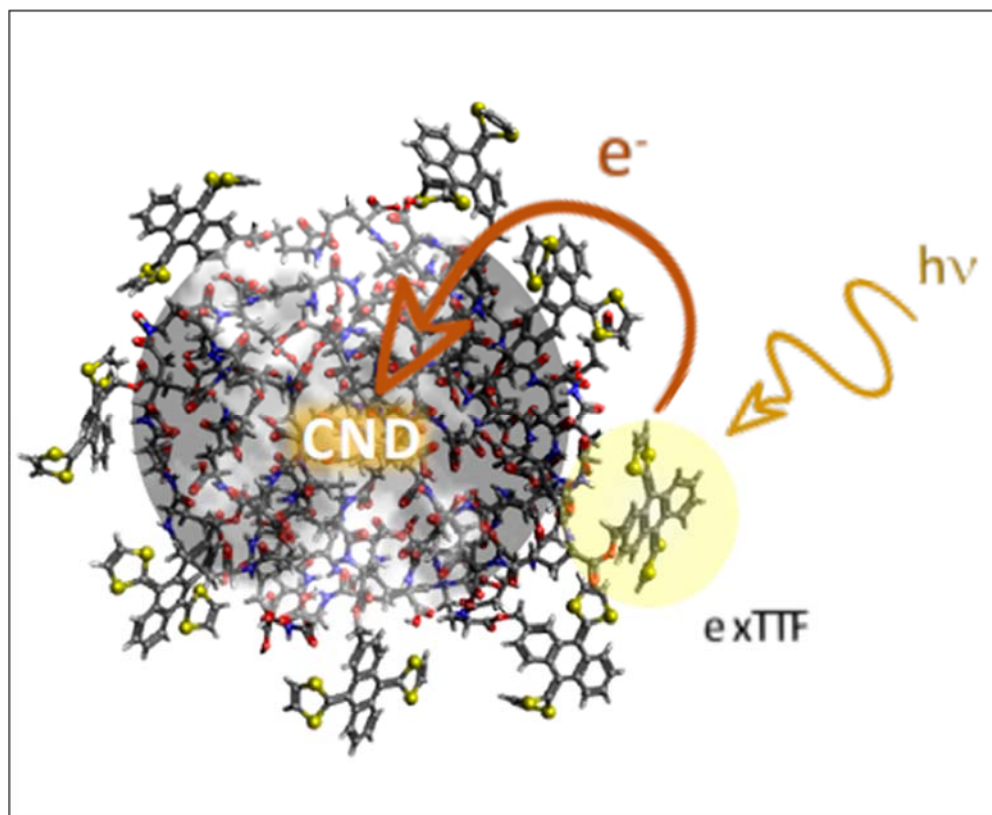
Mikiko Vázquez-Nakagawa, Andres Ferrer-Ruiz, Laura Rodríguez-Pérez, Nazario Martín, M. Ángeles Herranz, maherran@ucm.es. Química Organica, Universidad Complutense de Madrid, Madrid, Madrid, Spain

Fluorescent carbon nanomaterials, carbon nanodots (CNDs) and graphene quantum dots (GQDs), have triggered an increasing attention over the last years owing to their straightforward production methods, good photostability, biocompatibility and chemical inertness.

In this contribution, we will present our efforts toward the synthesis, characterization, and modulation of properties by chemical modification of these carbon nanostructures. Special attention was dedicated to customize the optoelectronic properties of CNDs obtained by bottom-up synthesis, and the electronic communication in CND-based functional materials.^{1,2} Both the electron-donating and -accepting performances of

CNDs make the charge-transfer chemistry of CNDs rather versatile. Charge-separated states formed by photoexcitation when CNDs have been combined with electron-donating extended tetrathiafulvalenes or electron-accepting tetracyano-anthraquinodimethane derivatives.

In a different approach, the top-down synthesis of chiral GQDs by covalent or supramolecular functionalization with chiral ligands will be also presented. A chiroptical response depending on the configuration of the organic ligands introduced was observed in solution experiments.^{3,4} Furthermore, by means of microscopic techniques on solid surfaces, an organization at the supramolecular level was observed in some of the systems.



Schematic representation of CND-exTTF nanoconjugate systems and photoinduced electron-transfer process.

ORGN 46

Tubularenes: Redefining carbon-based nanotubes

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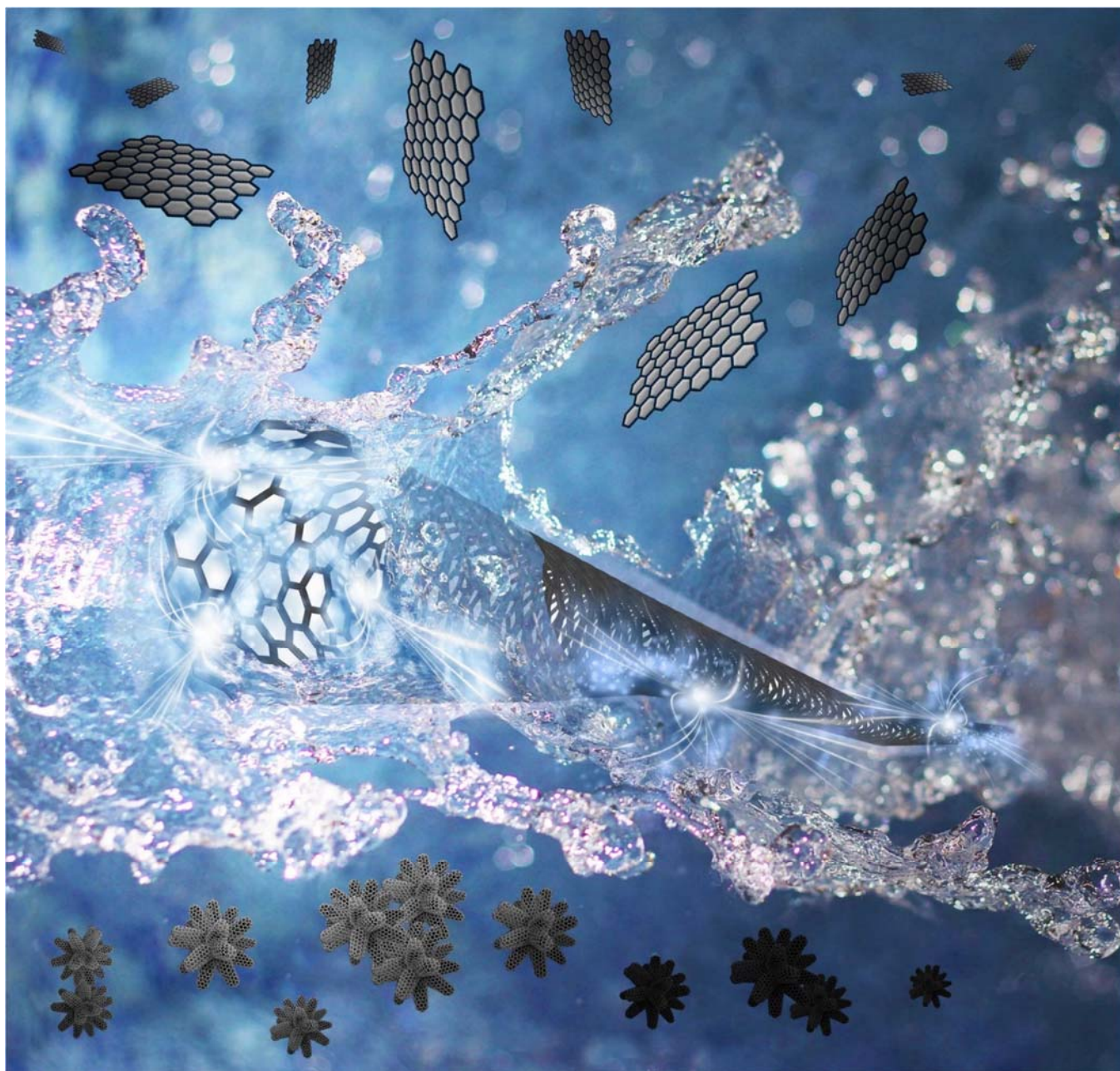
Carbon nanotubes hold promise to revolutionize molecular-scale electronics. This only holds true if methods are devised that allow for an exquisite control of their nature (multi versus single wall, diameter, length, and conductivity). In this regard, current bulk syntheses afford, in all cases, polydisperse materials. Thus, molecular strategies are much needed to provide atomic definition of the resulting species, which result in a single set of properties. Within this research endeavor, we have developed a viable and tunable methodology to synthesize atomically precise cylindrical organic frameworks—termed tubularenes. Our synthetic approach is based on a step-by-step growth, also referred to as *lego-style* build up. The target cylindrical structures are synthesized from a templating cap based on well-known resorcin[n]arenes. The tubular structure is achieved in the final step by a Suzuki cross-coupling cyclization. The as-synthesized tubularenes are a new family of organic compounds, which will open avenues for many applications such as fractional gas separation, intermediate size models for cryo-electron microscopy, and supercapacitors in device fabrication among others. The successful implementation of tubularenes will dramatically contribute to the development of the nanomaterial world.

ORGN 47

Nanocarbon morphology shapes hybrid functional matter

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Carbon nanostructures come in different morphology and size, which are well-known to affect their chemical reactivity. Yet it is still unclear how such properties affect nanocarbon behavior in composite or hybrid systems, and especially which nanocarbon is best suited for a higher performance of the final, multicomponent material. For instance, comparison between carbon nanotubes, few-layered graphene, and carbon nanohorns have revealed remarkable differences when used as scaffolds for the growth in situ of inorganic metal oxide nanoparticles, and thus in the resulting organic-inorganic hybrids, for applications in water, in areas as diverse as catalysis and phosphoproteomics. Another case of particular interest is the combination of nanocarbons and self-assembling tripeptides, whereby the latter can act as surfactants to disperse the former in aqueous buffer and still successfully self-organize, even in the presence of large amounts of nanocarbons. Interestingly, the similarity between the anisotropic morphology of carbon nanotubes and peptide fibrils can lead to the emergence of new properties such as self-healing behavior. The lessons learnt from unexpected properties that arise in multi-component materials featuring one or another carbon nanostructure will be discussed to gain insights for the design of the next-generation advanced materials for applications in polar solvents such as water.



A hybrid material composed of a supramolecular hydrogel and a carbon nanostructure, whereby carbon nanostructure morphology is a key factor for the hybrid properties.

ORGN 48

Tubular[n]arenes: Bottom-up approach to carbon-based nanotubes analogues

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Carbon nanotubes (CNTs) hold the promise to revolutionize many applications within the academic world and also in the industrial setting. Various ways have been proposed and tested to synthesize CNTs. However, synthesizing homogenous, single sized CNTs is currently an unmet challenge. Herein, we describe a new bottom-up approach to synthesize CNT shape-analogues that have been pioneered in our lab, where a resorcin[n]arene molecule serves as a templating cap where building blocks are attached in a programmatic fashion to create new tubular organic molecules, that we have termed *tubular[n]arenes*. By using different building blocks, tubularenes with various cavity sizes can be synthesized. In addition to exploring the fundamental chemistry in these tubular compounds, these have the potential for novel application in host-guest chemistry. Moreover, using the intrinsic porous nature of tubularenes, and by tuning the resorcin[n]arene backbone, we strive to decrease their melting point to medium temperature where we can explore their properties as liquids with permanent porosity. Herein, we describe an approach built upon well-known organic synthetic procedures, and utilizing macrocycles as templating caps, to construct carbon-based nanotubes with new and exciting properties and applications.

ORGN 49

Synthesis and polymerization of diynes containing thiocyanate and thiophene end-groups en route towards polydiacetylenes

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Polydiacetylenes (PDAs) have attracted much attention in recent years due to their potential electronic, biological, and optical applications. With backbones composed of sp^2 and sp hybridized carbons, these conjugated organic polymers can serve as precursors to graphene, sensor material, and as components in various electronic materials. The electronic properties of polydiacetylenes can be modified by attaching different end-groups, particularly those with electron-withdrawing or electron-donating capabilities. End-groups that contain sulfur have rarely been incorporated into PDAs, therefore this research focuses on the synthesis of diynes with thiocyanate- and thiophene- functionalities. The synthesis of 1,4-di(thiophen-2-yl)buta-1,3-diyne was achieved using previously reported methods; however 1,4-dithiocyanatobuta-1,3-diyne has not been reported in the literature. Polymerization experiments with both diynes are currently in progress.

ORGN 50

Award Address (ACS Award for Creative Invention sponsored by the ACS Corporation Associates). Photochromism and its commercial application

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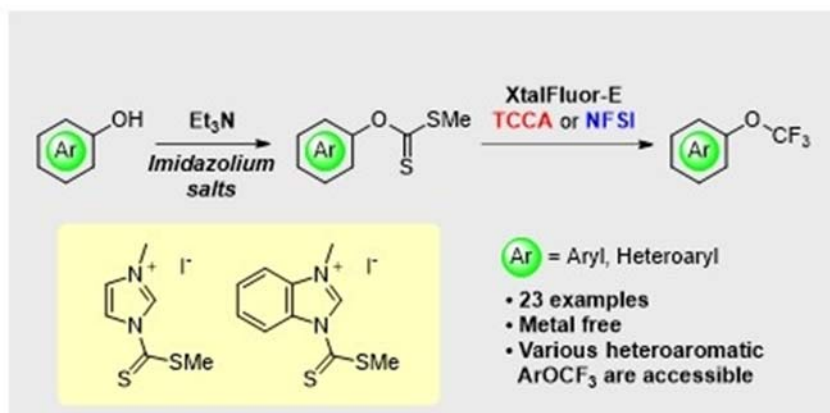
Organic photochromic compounds are an interesting class of materials that have the unique property of changing from colorless to colored when exposed to ultraviolet light, and revert back to a clear state in the absence of UV light. Various applications such as optical switches, optical data storage, sensors, light control windows and ophthalmic lenses have been demonstrated but the one application that has achieved substantial commercial success is photochromic plastic eyewear. Since the launch of photochromic plastic eyewear in the early '90s, major advancements have been made in photochromic technology that has improved performance and added attributes such as variable polarization. In this presentation, the author will talk about new innovations made in photochromic ophthalmic lenses.

ORGN 51

Metal-free trifluoromethylation of phenols via xanthates: New synthesis of aryl and heteroaryl-trifluoromethyl ethers

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A successful collaboration between the Hartwig Lab and Pfizer Medicinal Chemistry has resulted in a new method for the synthesis of aryl- and heteroaryl-trifluoromethyl ethers. There are relatively few established methods for the construction of aryl-trifluoromethyl ethers from phenols. Those that do exist proceed with very narrow substrate scope and rarely occur when heteroaromatic moieties are present. We report a two-step, metal-free, trifluoromethylation of aromatic and heteroaromatic alcohols via the intermediacy of aryl and heteroaryl xanthates, respectively. Utilizing a newly-developed xanthalating reagent, a variety of xanthates react under mild reaction conditions, with no strict moisture or atmospheric controls, to form the corresponding aryl and heteroaryl trifluoromethyl ethers. Reaction optimization and the workings of a successful collaboration will be discussed.

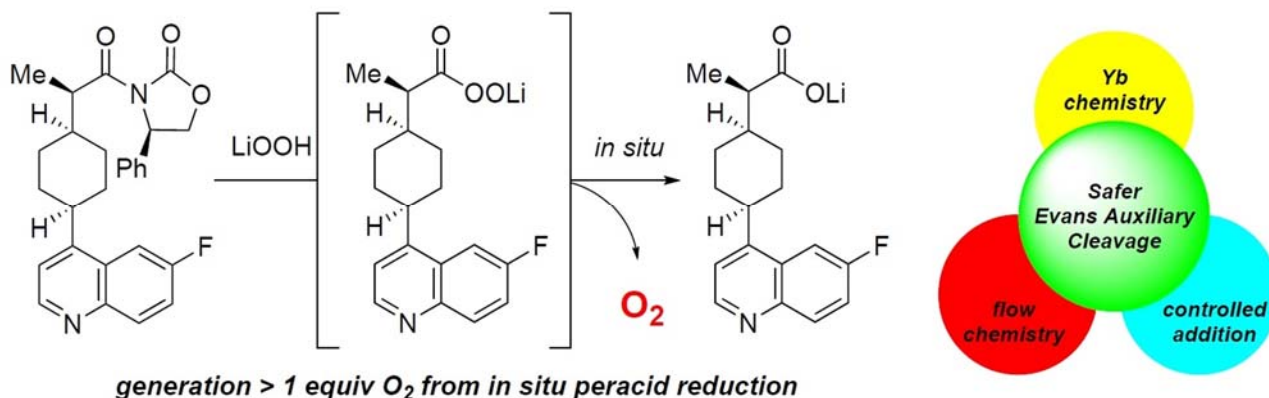


ORGN 52

Development of safer methods for cleavage of the Evans auxiliary

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The use of LiOH/H₂O₂ for cleavage of Evans oxazolidinones is a necessary step in utilizing this well-known, chiral auxiliary strategy in a synthetic route. The original conditions, disclosed more than 30 years ago, are now a textbook transformation and continue to be used with little modification from the original publication. During efforts to scale this procedure, we discovered the evolution of significant amounts oxygen under these conditions, presenting a risk for maintaining appropriate inertion and posing major safety risks. Driven by insights on the mechanism of the unanticipated release of oxygen, this talk will discuss three distinct solutions that were developed to address this issue, providing a safer manner for the cleavage of the Evans auxiliary with comparable performance to the original conditions.



ORGN 53

New strategies toward catalytic alkene dicarbofunctionalization

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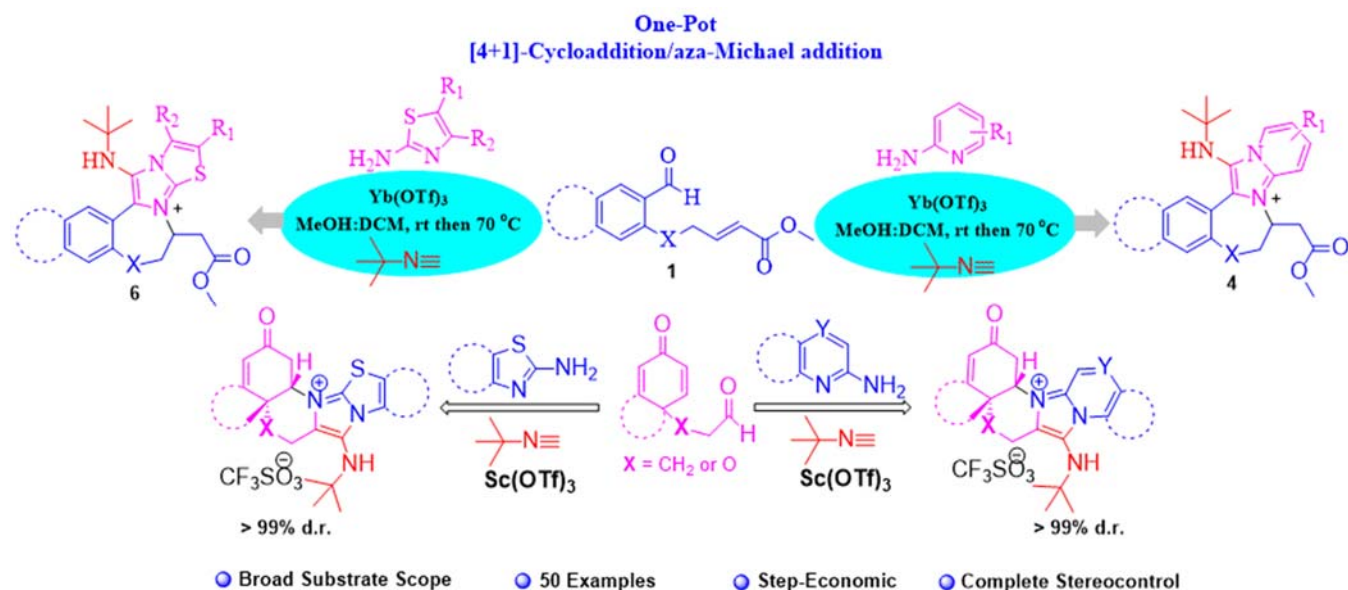
Alkenes serve as the most important feedstock for organic synthesis, having two vicinal sites for bond formation. Simultaneous construction of two carbon-carbon (C-C) bonds across these vicinal positions is a most powerful strategy, providing modular, convergent and expedient routes to generate complex products from simple starting materials. However, materializing such a process is fundamentally challenging due to the intrinsic natures of unactivated alkenes to undergo migratory insertion with slow kinetics, and alkylmetal intermediates to undergo β -H elimination with fast kinetics. In this talk, we introduce a novel concept of Bimetallic Cationic Catalysis – a strategy that addresses both fundamental issues of slow kinetics of migratory insertion and fast kinetics of β -H elimination during alkene difunctionalization. We also introduce another conceptually novel idea – Metallacycle Contraction Process – a strategy that harnesses the potential of alkylmetal intermediates to undergo β -H elimination to difunctionalize unactivated alkenes at the unusual 1,3-position rather than the usual 1,2-position that the alkenes occupy. Mechanistic pathways pertaining to these new reactions will also be discussed.

ORGN 54

Sequencing [4+1]-cycloaddition and aza-Michael addition reactions: Tandem cascades for the rapid and modular access of unique collections of anticancer and anti-superbugs motifs

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The design and synthesis of a quality compound library containing a small number of skeletally diverse scaffolds, whose members rapidly deliver new chemical probes active against multiple phenotypes, is paramount in drug discovery. In this meeting, the discovery of a one-pot build/couple/pair strategy that allows access to diversely functionalized hybrid architectures that encompasses benzoxazepinium or thiazolo[2',3':2,3]imidazo[1,5-a]quinolinium scaffolds fused to imidazopyridine or imidazothiazole systems, will be described. This new one-pot protocol features a tandem combination of Lewis acid-catalyzed [4+1]-cycloaddition with aza-Michael addition reactions. The cascade results in a rapid formation of these scaffolds *via* the utilization of the oxidative-dearomatization products of phenols or aldehydes suitably poised with Michael acceptor. Phenotypic screening of the developed mini library against multidrug resistant bacteria and a panel of cancer cell lines identified chemical probes as potential antibacterial and anticancer lead drug candidates. These findings hold the promise for the potential development of a new class of anticancer and antibacterial agents.



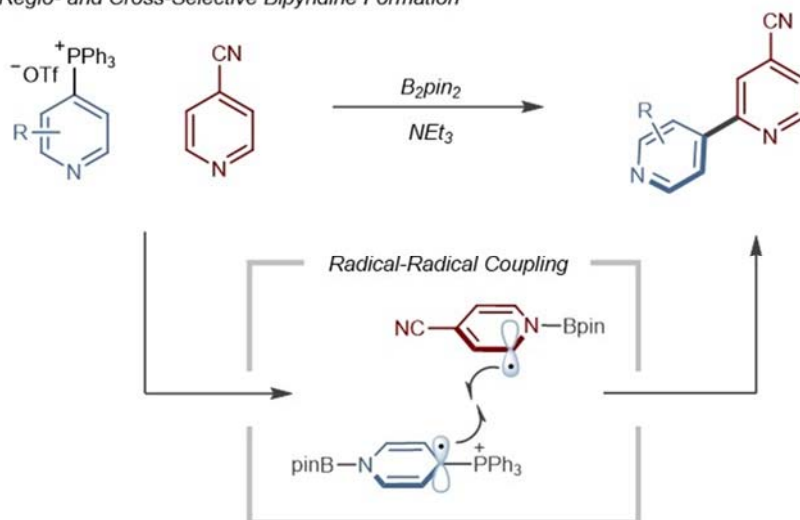
ORGN 55

Synthesis of 2,4'-bipyridines via a unique radical coupling of cyanopyridines and heteroaryl phosphonium salts

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Bipyridines are commonly found in a range of chemical applications including pharmaceuticals, materials, and ligands for metal catalysis. Due to the ubiquity of bipyridines, methods for the synthesis of this scaffold are in high demand. Metal-catalyzed cross-couplings are an essential part of the organic chemist's toolbox for biaryl synthesis, but these methods are less effective when coupling heteroarenes or even fail completely. A practical and powerful method for pyridine functionalization is the Minisci reaction in which a carbon-centered radical adds to an activated heteroaromatic ring; however, a Minisci coupling between two pyridine partners has not been reported. This is likely due to an electronic incompatibility between the activated pyridine and the pyridyl radical coupling partner as well as a lack of control over selectivity for the correct pyridine acceptor. Our lab made an unexpected observation that led to the development of an alternative, metal-free pyridine-pyridine cross-coupling reaction that overcomes these deficiencies of the Minisci reaction. Cyanopyridines were successfully coupled with pyridyl phosphonium salts with complete regio- and cross-selectivity to form a variety of 2,4'-bipyridines. Importantly, phosphonium salts were found to be the only effective radical precursors under the reaction conditions. After an extensive experimental and computational mechanistic investigation, the reaction was found to proceed through a unique coupling between two boryl-stabilized, dearomatized pyridyl radicals. This discovery provides a mild, mechanistically distinct method for the synthesis of valuable bipyridines.

Regio- and Cross-Selective Bipyridine Formation



ORGN 56

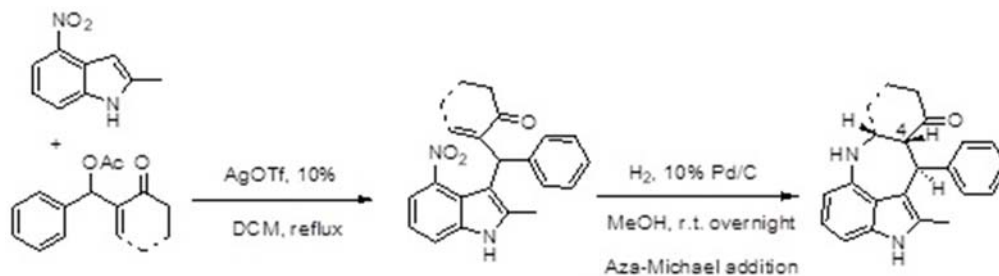
Regioselective nucleophilic substitution of the Baylis-Hillman (BH) adducts: Applications to the synthesis of heterocyclic derivatives

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C-C bond formation is the fundamental research to all organic chemistry and one of the most significant challenges faced by synthetic chemists is the selective construction of carbon-carbon bonds. The allylic alkylation or nucleophilic substitution (S_N) is an attractive route for the formation of C-C bonds because allylated/substituted products can be transformed into organic molecules possessing a variety of functional groups. The ability to control regioselectivity and stereoselectivity for different types of nucleophiles is desirable goal.

Recently, the Baylis-Hillman (BH) reaction has emerged as one of the most important C-C bond forming reaction and the Baylis-Hillman adducts, which possess versatile functionalities bearing allylic hydroxyl and Michael acceptor units, have been illustrated as valuable synthons and starting materials for the synthesis of heterocycles and many biologically active molecules.

The work describes the development of methodologies for regioselective C-C bond formation by nucleophilic substitution of the BH adducts employing Lewis acids and iodine as catalyst and their applications towards the synthesis of various novel and structurally important heterocycles.

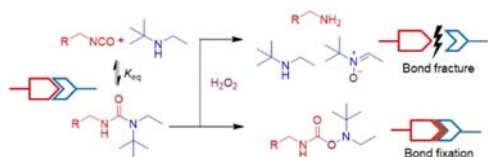


ORGN 57

Hindered urea bond: Bilaterally responsive chemistry to hydrogen peroxide

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As a type of safe, clean, and bio-relevant oxidant, hydrogen peroxide has been widely used as a trigger in the design of stimuli-responsive materials. Hindered urea bond (HUB) is a type of dynamic covalent bond which can reversibly dissociate into isocyanate and amine. Quenching of isocyanate or amine will shift the equilibrium and facilitate the degradation of HUB bond. Herein, we report that one of the HUB moiety – 1,1-tert-butylethylurea (TBEU) can react with hydrogen peroxide (H_2O_2) resulting in two opposing outcomes. Perhydrolysis of isocyanate and oxidation of amine lead to the bond fracture, while the formation of urethane product with oxygen inserted into the original TBEU structure was also observed giving a stabilized form of linkage. More precise kinetic control of the two distinct pathways is expected to make hydrogen peroxide a trigger to either degrade or fix the HUB based polymeric materials.



Bilaterally responsive behavior of HUB to hydrogen peroxide

ORGN 58

Shedding new light on squaraines: Utilizing squaraine dyes as building blocks in organic synthesis

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First discovered in 1965 by Treibs and Jacob, fluorescent squaraine dyes are boldly colored compounds well known for their applications in physical and analytical chemistry. Structurally, squaraine dyes contain a central, electron deficient cyclobutendione core flanked by two electron rich aromatic substituents in a 1,3-orientation, leading to a donor-acceptor-donor resonance stabilization. These unique electronic properties enable squaraine dyes to intensely absorb and emit light in the near-infrared region. Classically, these compounds have been utilized extensively in materials applications throughout physical and analytical chemistry, including biological imaging, photodynamic therapy, nonlinear optics, photovoltaics, and ion sensing. In contrast, there are surprisingly few reported studies that explore the use of squaraine dyes as synthetic building blocks, despite possessing multiple sites of potential reactivity. This research focuses on the development of functionally rich squaraine scaffolds as readily available starting materials for the construction of more architecturally complex small molecules and the exploitation of their inherent reactivity to design chemically-driven analytical protocols. To date, the applications of squaraine dyes has been successfully extended towards: (1) the development of squaraine dyes

as thermo- and chemoreversible imaging agents, (2) accessing highly functionalized oxindoles and benzofuranones via a phosphine-mediated ring expansion of appropriately substituted dianiline squaraine dyes, (3) the design of squaraine dyes as chiral transition metal ligands in enantioselective catalysis, and (4) squaraine dyes as novel organo-transfer reagents in synthesis.

ORGN 59

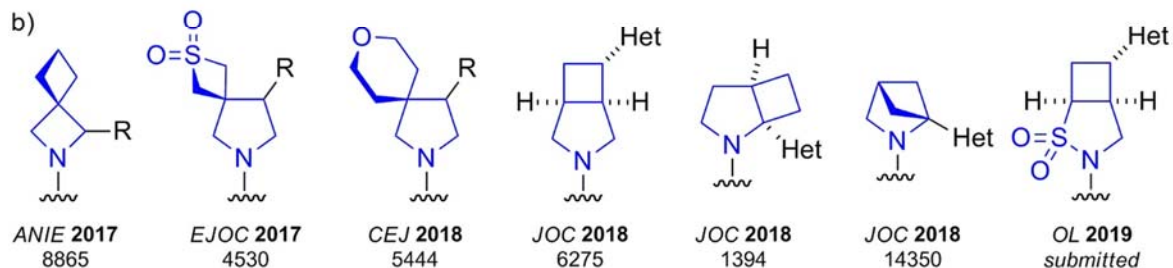
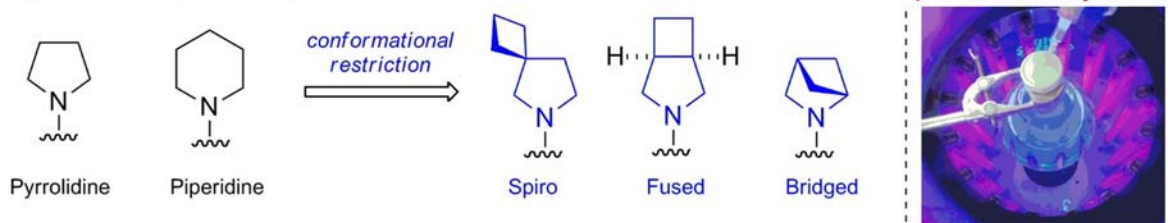
Photochemical synthesis of bicyclic amines for drug discovery

Pavel Mykhailiuk, *Pavel.Mykhailiuk@gmail.com*, Alexander Denisenko, Yevhen Skalenko, Alexander Kirichok, Bohdan Chalyk, Tetiana Druzhenko, Dmitry Dibchak.
Chemistry, Enamine Ltd, Kiev, Ukraine

Trends in drug discovery are changing rapidly. During the past decade, terms “*Scaffold hopping*,” “*Escape the Flatland*” and “*Conformational restriction*” have been introduced, and have already found huge practical application. In this context, in recent years medicinal chemists often use bicyclic Fsp^3 -rich building blocks in drug discovery projects.

In this work, we have designed synthesized and applied novel multifunctional bicyclic cores for drug discovery. The key synthetic step in many scaffolds was a [2+2]-photochemical cycloaddition. Details of the synthesis and application of the obtained compounds will be discussed.

a) >100 FDA-approved drugs

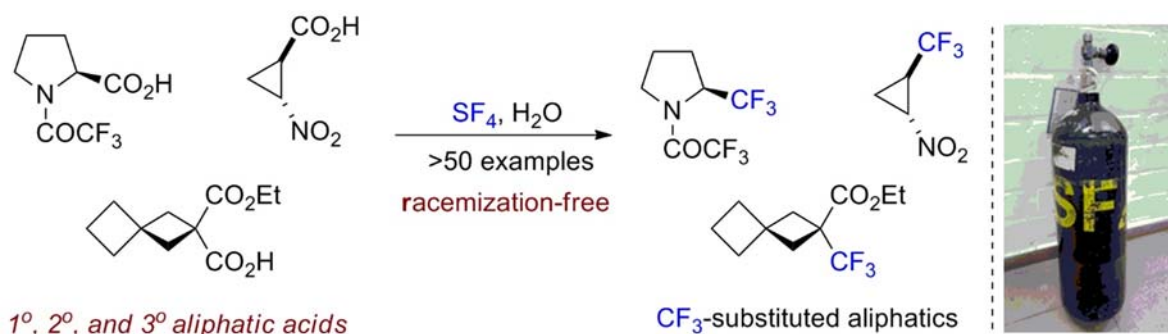


ORGN 60

Rapid access to functionalized trifluoromethyl-substituted aliphatic derivatives

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Practical method for the synthesis of functionalized aliphatic trifluoromethyl-substituted derivatives from aliphatic acids is developed. The transformation proceeds with sulfur tetrafluoride in the presence of water as a key additive. Compared to previous methods, the reaction gives products with full retention of stereo- and absolute configuration of chiral centers.



ORGN 61

Photoacid catalyzed C-C bond-formation: Synthesis of triarylmethanes and 3,3'-diarylindolin-2-ones

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The development of new catalytic processes is essential for organic synthesis. In this presentation, we will discuss a visible-light-induced, thiourea catalyzed C–C bond-forming reaction. Specifically, Schreiner's thiourea [(*N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea)] functions as a photoacid to facilitate a double Friedel-Crafts addition of indoles to aldehydes and isatins to form the corresponding triarylmethanes and 3,3'-diarylindolin-2-ones. We demonstrate that this protocol applies to a variety of aldehyde and isatin electrophiles and a range of electronically diverse indoles. Furthermore, this mild light-facilitated reaction is chemoselective for 1,2-addition to aldehydes over ketones and 1,4-conjugated systems. Mechanistic studies show that light is required for the reaction to be initiated.

ORGN 62

Direct decarboxylative functionalization of carboxylic acids via O–H hydrogen atom transfer

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A direct decarboxylative functionalization of aliphatic carboxylic acids using *N*-xanthylamides is reported in which the unique reactivity of amidyl radicals in hydrogen-atom transfer enables decarboxylative xanthylation under redox neutral conditions. This transformation exhibits a broad substrate scope, excellent functional group tolerance, and serves as a general platform for decarboxylative functionalization via subsequent synthetic elaboration of the xanthate group. Mechanistic data support a pathway

involving direct O–H HAT, which complements standard redox-based approaches to decarboxylative chemistry.

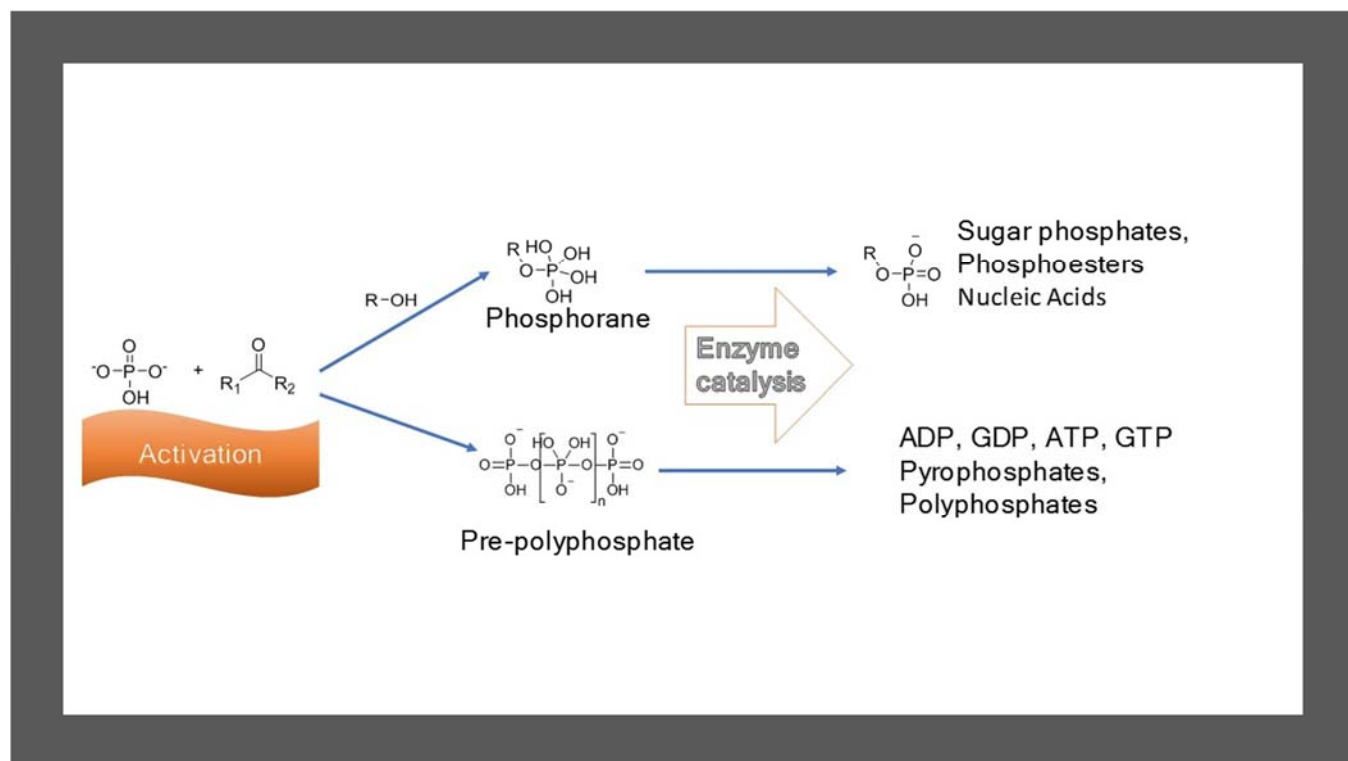
ORGN 63

Non-enzymatic synthesis of biologically important phosphates and polyphosphates

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Phosphorylation is a very important biochemical process utilized in metabolism and biochemical marking. The process of phosphorylation is thought to occur via enzymatic catalysis involving various phosphoesterases and kinases and the use of activated phosphates. We reported that the activation of phosphates toward phosphoesterification is a spontaneous non-enzymatic process which leads to the formation of the elusive pentacoordinated phosphoranes. Water soluble aldehydes and ketones combine with basic inorganic/organophosphates to form dioxaphosphetanes. Dioxaphosphetanes are activated phosphates that polymerize or phosphorylate alcohols without the requirement of any enzyme or additional activating agent. In five and six carbon monosaccharides, the activation-esterification occurs spontaneously and internally to give rise to the monosaccharide phosphorane. The pentacoordinated phosphoranes are then converted to the more stable phosphates via reductive dehydration.

During the polymerization of inorganic phosphates, we observed that monobasic phosphates dimerize, dibasic phosphates form straight chain polymers while the tribasic phosphates formed three-prong polymers. Thus, the type of polymerization depends on the basicity of the phosphate. This led us to us believe that a correct combination of phosphates of the right basicities would produce biologically important polymers like ATP, ADP and DNA. Indeed, we successfully achieved good yields of the precursors of the diphosphates and triphosphates of inorganic phosphates and combinations of dialkyl phosphates and inorganic phosphates. Conditions for the synthesis of precursors of the diphosphates and triphosphates of monoalkyl phosphates (ATP, GTP) as well as posible stepwise synthesis of nucleic acids are being optimised and will be discussed.



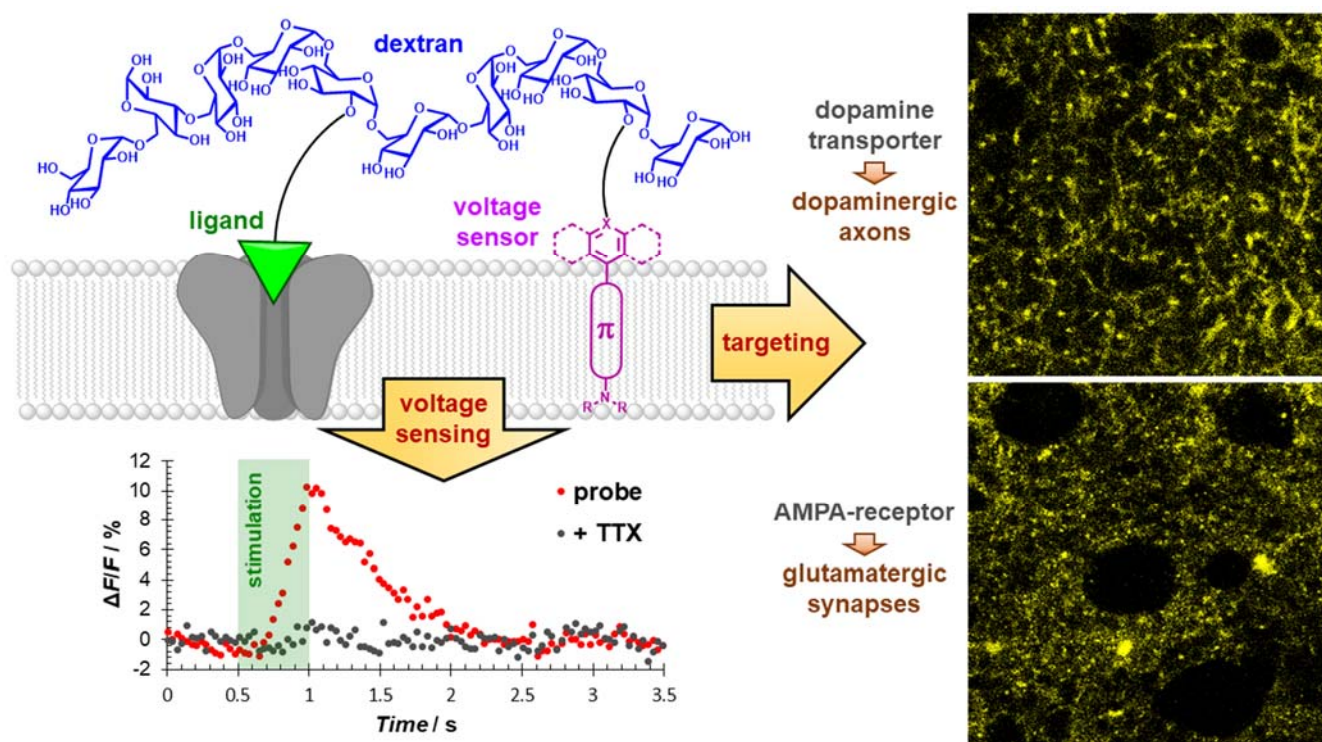
ORGN 64

Chemical targeting of voltage sensitive dyes to specific cell types in the brain

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Voltage sensitive fluorescent dyes (VSDs) are important tools for probing signal transduction in neurons and other excitable cells. These sensors, rendered highly lipophilic to anchor the conjugated π -wire molecular framework in the membrane, offer several favorable functional parameters including fast response kinetics and high sensitivity to membrane potential changes. The impact of VSDs has however been limited due to the lack of cell-specific targeting methods in brain tissue or living animals. We address this key challenge by introducing a non-genetic molecular platform for cell and molecule specific targeting of synthetic voltage sensitive dyes in the brain. We employ a dextran polymer particle to overcome the inherent lipophilicity of voltage

sensitive dyes by dynamic encapsulation and target the construct to specific neuronal populations using a small molecule ligand in acute mouse brain slices. Using the monoamine transporter ligand dichloropane, our probes label dense dopaminergic axons in the striatum and sparse noradrenergic axons in the cortex. The PFQX ligand in conjunction with ligand-directed acyl imidazole chemistry enables covalent labeling of AMPA-receptors in glutamatergic synapses. We demonstrate that probe variants bearing a state-of-the-art VoltageFluor dye respond to membrane potential changes in acute mouse brain slices under 1-photon or 2-photon illumination in whole-cell patch recording or after electric field stimulation respectively. Our platform enables targeting of diffusible VSD probes and voltage recording from specific neuronal cells using endogenous expression levels of native components of the neurotransmission machinery.

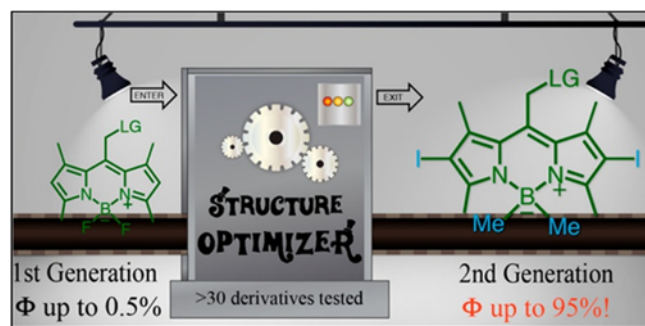


ORGN 65

BODIPY photocages: Structure-activity relationship in quantum yield of photorelease

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Photocages, also called photoremoval protecting groups, are light-activated chemical protecting group with an attractive feature: spatial and temporal control of the release process. Widely used photocages like O-nitrobenzyl groups absorb ultraviolet wavelength, which is hazardous for biological application, so we aimed to find the photocages which are activated by visible light, preferably infrared light as it can penetrate deeper in living tissue. Most photocages were discovered serendipitously or through empirical testing but a computational study found that structures with elevated ground state surface and stabilized excited state surface can lead to productive conical intersections favoring the photorelease. As predicted by our computational study *meso* substituted BODIPY dye releases acetic acid with green wavelength > 500 nm but the quantum yield of release is around 0.1%. To improve the quantum yield, we performed a structure-activity relationship study of *meso*-methyl BODIPY photocages and found that photorelease processes are highly sensitive to substituent effects. Derivatives with higher intersystem crossing have a higher quantum yield of photo release, which can be achieved by the introduction of heavy atoms on BODIPY core. Also, alkylation of the boron has remarkable improvements in the release rate whereas alkylation in the *meso*-methyl position has no effect. Furthermore, better-leaving groups are more efficient in the release process than poorer leaving groups. We found that these substituent effects are additive. For example, introducing iodine on the core and methyl on boron could improve the quantum yield of release to 28 % for acetate while for chloro it is 95%. Extension of the conjugation provides BODIPY photocages that absorb in the red-near IR range (600-700 nm). These near-IR photocages have improved quantum efficiencies on par with popular o-nitrobenzyl but absorb in the biological window.

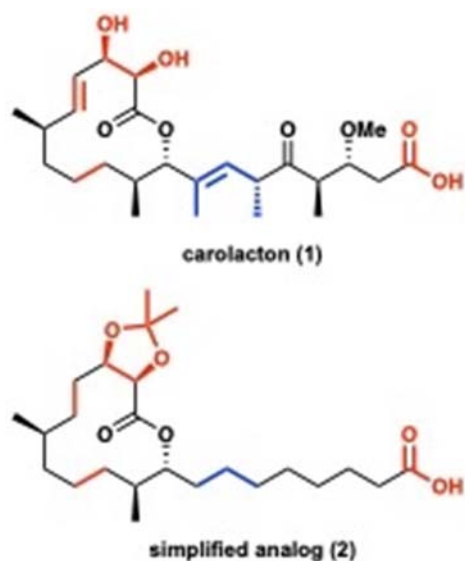


ORGN 66

Synthetic simplification of carolacton leads to identification of novel biofilm target

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Streptococcus mutans is a pathogenic bacterium that gives rise to the formation of dental caries, the most prevalent childhood disease. Specifically, *S. mutans* forms biofilm on the various surfaces in the oral cavity which leads to acidification and subsequent erosion of the dental enamel. Previously, we have studied the natural product carolacton (1) in the context of its anti-biofilm activity and developed a library of carolacton-inspired analogs. Herein we disclose the synthesis and biological investigation of our novel, more potent, biofilm inhibitor (2), as well as its use as a chemical tool to further understand the biofilm mechanisms involved in the action of these macrocyclic compounds. Target identification via affinity-based protein profiling (ABPP) and resistance selection assays were used to identify the protein target for (2). Furthermore, these results have implications in understanding complex biofilm mechanisms of the pathogenic bacteria, *S. mutans*, and other biofilm-mediated diseases. Combined these results demonstrate the power of chemical synthesis in elucidating the underpinnings of microbial pathogenesis.

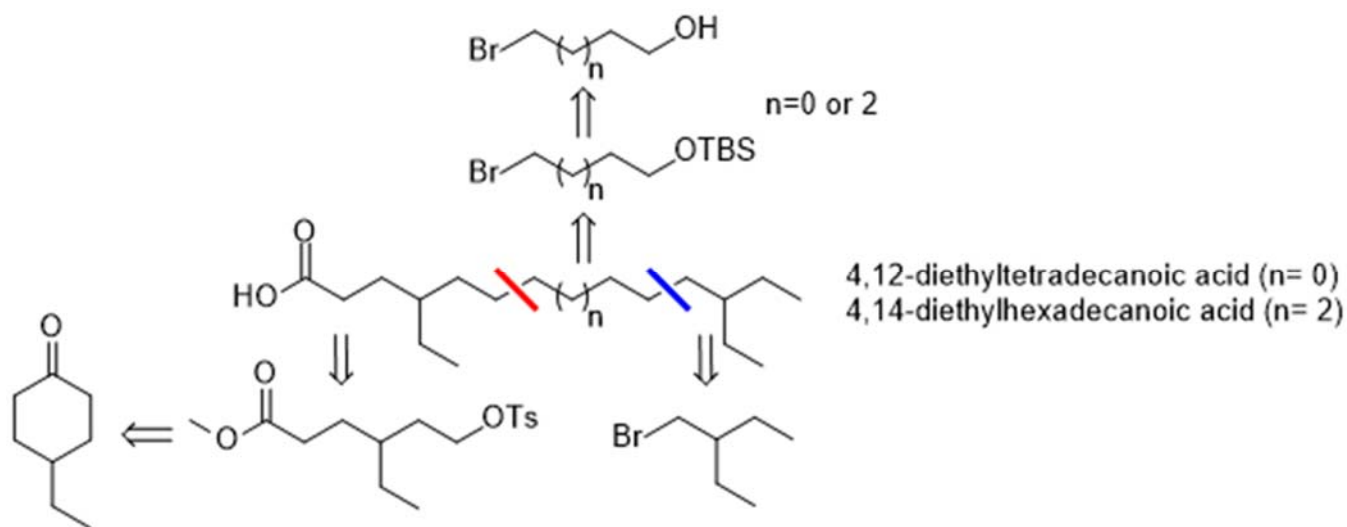


ORGN 67

Unusual ethyl branched chain fatty acids: Synthesis and biological evaluation

***Daiane Szczerbowski*¹**, daiszcze@tu-bs.de, *Jana Caspers*¹, *Masao Miyazaki*², *Rosimiriam P. de Freitas*³, *Stefan Schulz*¹. (1) Institut für Organische Chemie, Technische Universität Braunschweig, Braunschweig, Germany (2) Department of Agriculture, Iwate University, Morioka, Japan (3) Chemistry Department, Federal University of Minas Gerais, Belo Horizonte, Brazil

In this study, we have identified a great number of fatty acids present in domestic cat urine samples. GC-MS analysis of the extracts has shown the presence of two unusual ethyl branched fatty acids. Based on the mass fragmentation pattern, the structures proposal are 4,12-diethyltetradecanoic and 4,14-diethylhexadecanoic acid. To prove the identity of the compounds a synthetic route was developed. As shown in the Scheme below, the strategy is to combine building blocks in a convergent synthesis, coupling these blocks through a Fouquet-Schlosser approach of the Grignard reaction. The ethyl branches will rise from the commercially available materials 4-ethylcyclohexanone and 2-ethyl-1-bromobutane. The central building block will differ for the synthesis of the different structures of the two fatty acids, which will be 1-bromohexan-6-ol or 1-bromobutan-4-ol, determining the length of the main chain. After the synthesis, bioassays will be performed to observe if the compounds have activity against antibiotic-resistant strains of virus and bacteria. The structures will be tested alone and in combination with common antibiotics, to test whether they can also have a synergistic action.



Synthesis of a single chromophore for the development of photoluminescence switches: Detection of multiple analytes

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Based on the important applications of the fluorescent dyes and supramolecular photochemistry, a novel fluorescent dye was synthesized by reacting 5-(chloromethyl)quinolin-8-ol **1** with 2-(piperazin-1-yl)-1H-benzo[d]imidazole **2** 8-hydroxyquinoline to give dye **3**. The structure of the newly prepared dye **3** was confirmed through different spectroscopic methods such as ^1H -NMR, ^{13}C -NMR, mass spectrometry and elemental analyses. The work describes the utility of dye **3** with tunable-emission in aqueous solutions. The developed system employs a new principle, namely two distinct binding sites to achieve responsiveness to the multiple analytes: Al^{3+} , Cucurbit[7]urils (CB7), pH, and Cadaverine. The developed system obviates the need to mix more than one fluorescent agents, thus it paves the way to the fabrication of further non-toxic and bioactive tunable-emission materials for diverse biomedical applications.

ORGN 69

Synthesis and structural studies of peptidomimetic *N*-substituted azole-rich macrocycles

Amelia A. Fuller, *aafuller@scu.edu*, Somayeh Motevalli, Michelle Nguyen, Jiacheng Tan. Department of Chemistry & Biochemistry, Santa Clara University, Santa Clara, California, United States

Azole-rich oligoamide macrocycles are found as a variety of peptide-derived natural products including dendroamide and patellamides. A desire to replicate and/or modulate the biological activities of the natural products motivates the development of new methods to access diverse synthetic analogs for application and study. We have developed efficient synthetic methods to access *N*-substituted azole-containing amino esters as important building blocks for preparation of new peptidomimetics. *N*-substituents have been widely varied to introduce a range of functionality. Additionally, we have identified methods for the preparation of macrocycles that contain these building blocks and emulate natural product structures. Structural studies of the macrocycles in solution and in the solid state have revealed the influences of the azole identity, *N*-substituent, and ring size on the conformation of the ring. These findings will guide future applications of these new peptidomimetic molecules.

ORGN 70

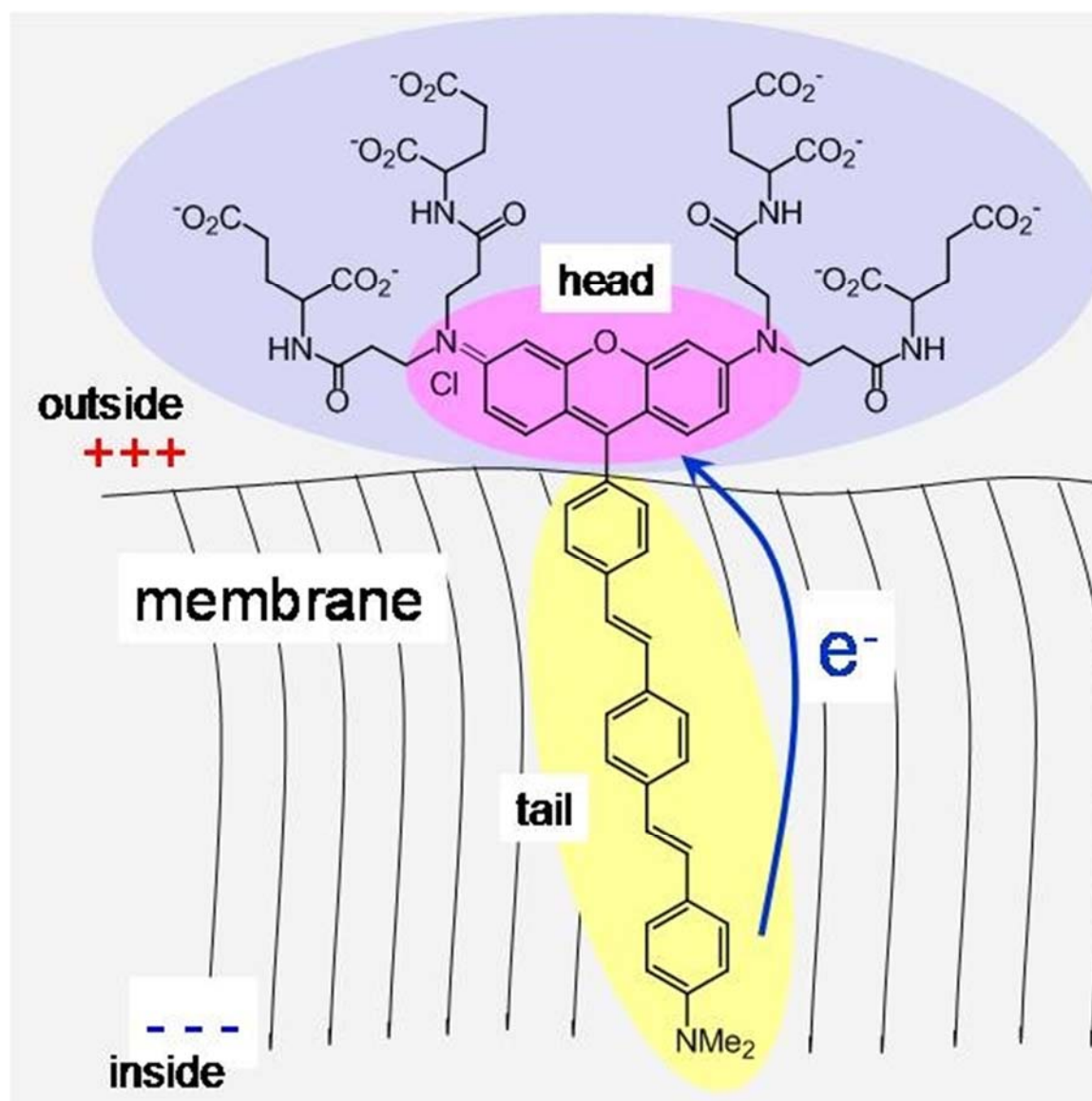
Water-soluble amphiphilic rosamine-based photoinduced electron transfer (PET) sensors for cell membrane potential

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Fluorescent voltage-sensitive indicators make up a useful tool for monitoring changes in local membrane potentials without perturbing underlying cellular physiology. When combined with *in vivo* imaging, such probes enable visualization of neuronal activity, making it possible to study communication between neurons in intact brain.

Amphiphilic voltage sensors based on photoinduced electron transfer (PET), have been developed by R. Tsien and E. Miller; however, all presently existing molecules suffer from poor aqueous solubility, precluding studies *in vivo* in the brain.

Here, we report the development of improved amphiphilic probes, in which a branched dendron-like polyanionic structure is attached to the fluorescent rosamine 'head' of the molecule, imparting water-solubility and enforcing the required orientation during partitioning into the plasma membrane. The new probes exhibit excellent aqueous solubility, allowing measurements in mouse cardiomyocytes, HEK cells and pituitary gland as well as in intact mouse brain, where they could be introduced without the use of organic solvent.



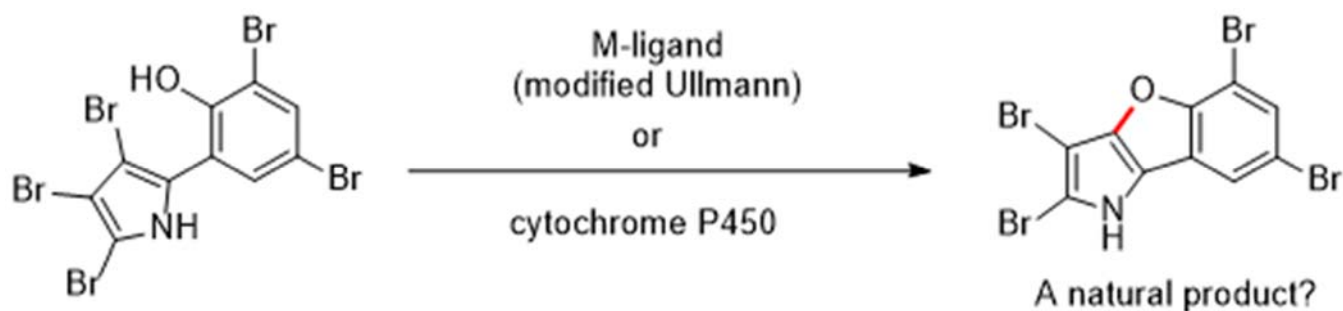
ORGN 71

Bio-inspired chemistry for synthesis of a polybrominated pyrrole marine alkaloid with antibacterial properties

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Polybrominated aromatics, such as polybrominated diphenyl ethers (PBDEs) and their derivatives dibenzo-*p*-dioxins have attracted attention due to their toxicity. The origin of such compounds in the marine environment has been ambiguous because some

PBDEs and their derivatives have been shown to be natural products while the majority of PBDEs are produced industrially as flame retardants. Recently isolated from *Pseudoalteromonas* collected from nudibranchs, 2,3,5,7-tetrabromobenzofuro[3,2-b]pyrrole (TBFP) has shown anti-MRSA (methicillin resistant *Staphylococcus aureus*) activities and possesses 3-phenoxy-pyrrole ether linkage similar to dibenzo-*p*-dioxins. To elucidate TBFP's biogenesis and to provide a facile access to this anti-MRSA compound with a novel scaffold, a bio-inspired chemical synthesis and a biocatalytic synthesis of TBFP are pursued. To this end, the putative biosynthetic precursor for TBFP, pentabromopsuedilin was synthesized in two-steps utilizing the MIDA boronate ester Suzuki-Miyaura coupling. For the chemical approach, modification of the Ullmann-type coupling reactions is investigated to allow for a low temperature nucleophile substitution of 3-bromopyrrole. For the latter biocatalytic approach, we employ the cytochrome P450 enzyme involved in the biosynthesis of pentabromopseudilin to cause the phenolic cyclization onto the pyrrole ring. Herein reported are our progress toward these complementary approaches to TBFP as well as the lessons learned along the way.



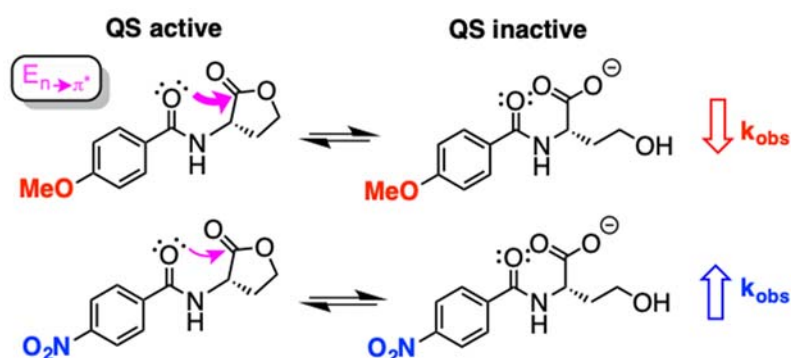
ORGN 72

Assessing the influence of $n \rightarrow \pi^*$ interactions on hydrolysis rates of *n*-acyl homoserine lactone derivatives

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In gram-negative bacteria, *N*-acyl homoserine lactones (AHLs) are a class of small molecules that enable cell density-dependent chemical communication known as quorum sensing (QS). QS permits colony-wide gene expression resulting in a variety of phenotypes, like virulence factor production and biofilm formation, that can have an

impact on human health. It has been proposed that the conformation of AHLs is influenced by $n \rightarrow \pi^*$ interactions that reduce the molecules' susceptibility to hydrolysis in an aqueous environment. To test this, seven AHL derivatives were modeled through gas-phase and implicit solvent DFT calculations and subjected to molecular dynamics (MD) simulations. Further, the AHL derivatives were synthesized so the rates of hydrolysis of each could be determined experimentally. Our combined data support that an increase in $n \rightarrow \pi^*$ energy ($E_{n \rightarrow \pi^*}$) correlates to a decrease in the hydrolysis rate constant (k_{obs}). AHL hydrolysis can be modified by manipulating steric and electronic effects that alter the electrophilicity of the lactone carbonyl. These results could inform the design of AHL-based quorum sensing modulators and help to elucidate nature's choice of AHLs as agents of density-dependent bacterial communication.



ORGN 73

Fluorous-soluble cyanines and their photophysical characterizations in aqueous, organic, and fluorous media

Irene Lim, lim.irene.16@gmail.com, **Ellen M. Sletten**. Chemistry and Biochemistry, UCLA, Los Angeles, California, United States

Highly fluorinated compounds, in which all $C_{\text{sp}^3}\text{-H}$ bonds have been replaced by $C_{\text{sp}^3}\text{-F}$ bonds, are referred to as “fluorous.” These compounds phase-separate from both aqueous and organic media. The orthogonality of the fluorous phase has led to many applications in biology, medicine, and materials. To better enable applications of the fluorous phase, especially in the context of biological experiments, there is a need to develop fluorous fluorophores. Various chromophore scaffolds with fluorous chain substitutions, such as BODIPY, rhodamine, perylene bisimide, and tetraphenyl porphyrin have been published. These previous reports either do not demonstrate fluorous solubility or have incomplete photophysical characterization. In this work, we report a synthesis of highly fluorinated indolenine cyanine dyes and create a panel of fluorophores with varied weight percent fluorine which allows for the photophysical

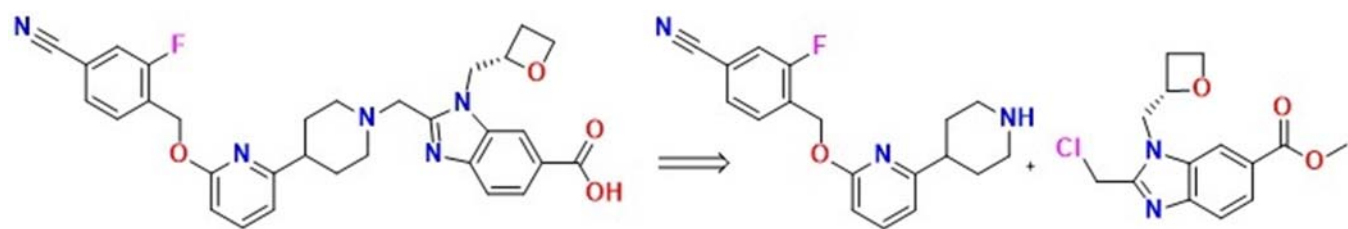
properties of these compounds to be fully characterized in fluoruous, organic, and aqueous media. We find that the cyanines are more fluoruous-soluble than another previously reported fluoruous fluorophore, the rhodamine. The fluoruous cyanines' fluorescence quantum yields are comparable to literature in fluoruous media, and the quantum yields increase in organic media. Furthermore, the fluoruous chains lend photostability to the dyes. This work provides insight into the synthesis of truly fluoruous-soluble fluorophores and allows for comparisons between how fluoruous, organic, and aqueous media affect photophysics.

ORGN 74

Discovery and synthesis of PF-06882961, a small molecule GLP-1 receptor agonist: From lead to clinical candidate

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Glucagon-like peptide-1 (GLP-1R) receptor agonists comprise a growing class of agents that deliver unprecedented efficacy in diabetes. Members of the class are also approved or under development for obesity and show further promise for the treatment of non-alcoholic steatohepatitis (NASH). GLP-1 is a 30 amino acid peptide hormone that activates the GLP-1 receptor, a class B GPCR that is particularly challenging to stimulate with small molecules. To date, all approved agents are large peptide drugs that are administered by injection, negatively impacting both the patient experience and uptake of these highly effective medicines. Recently, Pfizer disclosed the structure of the oral small molecule GLP-1R agonist PF-06882961 which is currently undergoing clinical trials. This presentation will discuss the synthetic strategy toward PF-06882961 from enabling the discovery of the lead (mg) by parallel medicinal chemistry to providing the clinical candidate (kg) for drug safety studies. Large scale amenable routes to the three key fragments (amino-oxetane, 4-pyridyl-piperidine and benzimidazole) will be highlighted with a focus on the discovery of a novel hydrolysis transformation utilizing an organic base in the penultimate step.



ORGN 75

New developments in palladium-catalyzed alkene diamination reactions of nitrogen electrophiles

Janelle K. Kirsch, *jakirsch@umich.edu*, **John P. Wolfe**. University of Michigan, Ann Arbor, Michigan, United States

Over the past 14 years, the Wolfe group has developed a series of Pd-catalyzed coupling reactions between alkenes bearing pendant nucleophiles and carbon-centered electrophiles, such as aryl halides, that afford substituted heterocycles. We have recently developed a new variant of these alkene difunctionalization reactions that utilize nitrogen-centered electrophiles, derived from acylated hydroxylamines. The coupling of these electrophiles with N-allylguanidines and ureas afford heterocyclic alkene diamination products. This presentation will describe our studies on the scope of this reaction, along with efforts to improve the stereospecific generation of products that result from either anti or syn addition to the alkene. Preliminary mechanistic findings will also be presented, including studies to determine whether these transformations proceed through a Pd(0)/(II) vs Pd(II)/(IV) catalytic cycle.

ORGN 76

Monosubstituted, anionic N-heterocyclic carbene complexes of palladium and their reactivity in cross coupling reactions

Erin Martinez, *chemistry.martinez7@gmail.com*, **Hadi Nazari**, **Alex Larson**, **Christopher Jensen**, **Karissa Kenney**, **David Michaelis**. Chemistry and Biochemistry, Brigham Young University, Provo, Utah, United States

Transition metal catalysts are an essential tool in cross-coupling reactions. Advances to improve these catalysts rely on tuning spectator ligands, with highly σ -donating N-heterocyclic carbene (NHC) complexes being among the most productive catalysts. By increasing the donating ability of NHCs, more electron density is placed on the metal to facilitate oxidative addition. While only a few examples exist, monosubstituted NHCs have the benefit of being less sterically hindered as well as increasing the electron density on the metal center after deprotonation of the imidazolium N–H. In the Michaelis lab, we have created a new class of monosubstituted NHC complexes of palladium by phosphinylating our monosubstituted NHC ligand and then going through a pseudo-oxidative addition to insert palladium(II) chloride into the carbene-phosphorous bond. These new complexes include a range of aryl, alkyl, and benzyl-substituted NHCs. In catalysis, these complexes perform Suzuki-Miyaura and Sonogashira cross-coupling reactions with exceptionally low catalyst loadings and tolerate a wide range of functional

groups. In the Suzuki-Miyaura reaction, catalyst loading can be lowered into the 1-10 ppm range and achieve a total of 250,000 turnovers.

ORGN 77

Nickel-catalyzed domino reactions

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Nickel-catalyzed domino reactions involving alkynyl substituted piperidines and tetrahydropyrans will be presented. These reactions proceed in moderate to good diastereoselectivity and excellent yield. The domino reaction allows for the efficient synthesis of motifs that would be otherwise difficult to prepare in one step. The scope of the reaction and the proposed mechanism will be discussed.

ORGN 78

Evaluating activity of transition metal catalysts of the salen/an framework and mechanistic pathway of oxidative coupling utilizing high throughput experimentation

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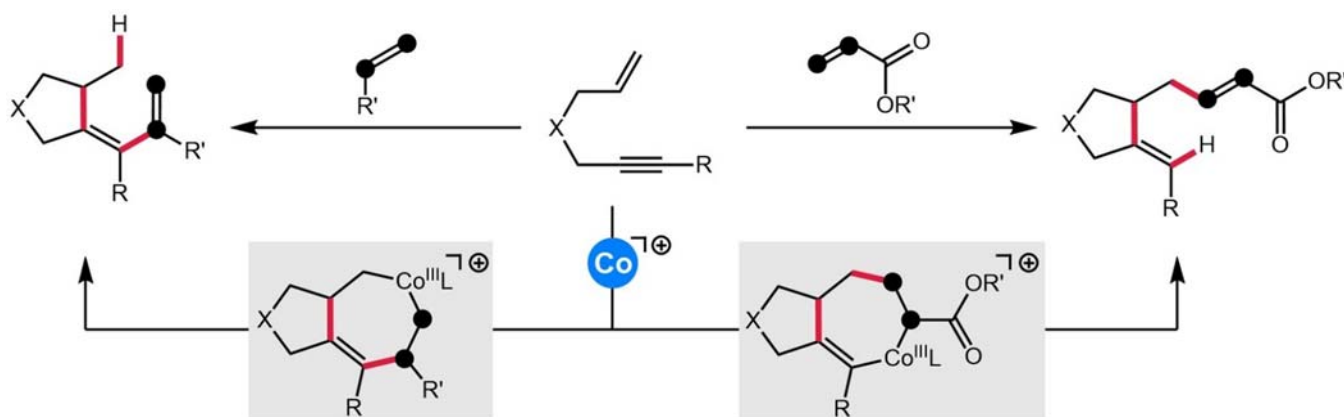
A library of related catalysts employing six first row transition metals and eighteen electronically and sterically diverse salen/an ligands have been developed in our laboratory for use in oxidative coupling reactions. Using high throughput experimentation (HTE), activity and selectivity were assessed for each of 24 unique catalysts with 24 phenolic substrates. Catalysts were then grouped into distinct categories using hierarchical clustering of the over 500 unique reaction outcomes. We are now probing the mechanism(s) and activity profiles of each cluster to uncover related reactivity. The small scale and rapid results of the method allow for quick assessment and discovery of subtle relationships among seemingly unrelated structures. In the future we hope to use this large data set to deduce which catalysts react by similar mechanisms and leverage this knowledge to develop new catalysts and methods.

ORGN 79

Cobalt catalyzed multicomponent cyclizations of enynes and alkenes

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Synthesis of complex organic molecules has relied heavily on the use of stoichiometric organometallic reagents. Strategies such as metal-catalyzed cycloisomerization bypass the need for these oftentimes harsh reagents and are valuable for constructing cyclic frameworks from simple unsaturated carbon sources. An important extension of this cyclization methodology is the incorporation of additional components accompanying the initial annulation. Through our studies we learned that cationic cobalt complexes can catalyze an intramolecular enyne cyclization, and subsequently form carbon-carbon bonds through intermolecular incorporation of feedstock alkenes into a presumed metallacycle intermediate. This strategy allows access to complex alicyclic and heterocyclic compounds from an earth abundant metal catalyst and readily available materials. Of note, is the complimentary reactivity and selectivity in this newly discovered cationic cobalt reaction manifold as compared to analogous rhodium and ruthenium catalysis. We discovered that product selectivity is dependent upon alkene identity, with activated alkenes and unactivated alkenes inserting into opposite sides of the cobaltacyclopentene intermediate. This remarkable selectivity provides access to two different motifs accompanying the cycle formed, either a linear diene or a styrene with a pendant functionalized acrylate. Over 25 different medicinally relevant pyrrolidines were accessed in this fashion and further elaborated on by post-synthetic modifications. In addition, the enantioselective variant of this reaction is also explored with selectivities up to 77% ee.

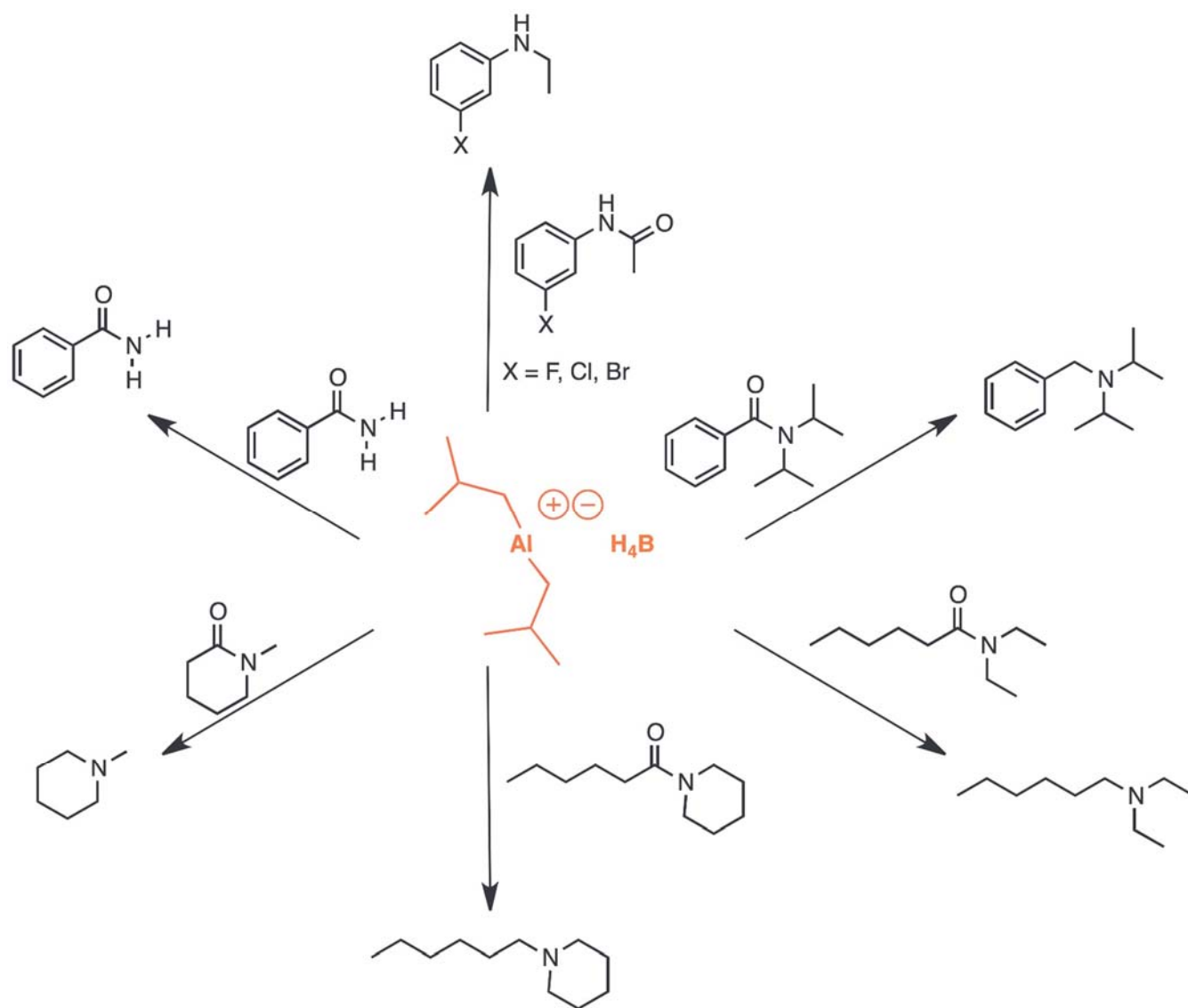


ORGN 80

Synthesis of diisobutyl aluminum borohydride for the reduction of tertiary amides at ambient temperatures

Rachel Snelling, rsnellin@ucsc.edu. Chemistry and Biochemistry, University of California, Ben Lomond, California, United States

Development of new reducing agents is an important tool in synthetic organic chemistry. Reduction of tertiary amides to the corresponding amine is commonly carried out using pyrophoric reagents, such as borane-tetrahydrofuran ($\text{BH}_3\cdot\text{THF}$) and lithium aluminum hydride (LiAlH_4), in refluxing THF. A new reducing agent has been developed for the reduction of tertiary amides, which can be used at ambient conditions and has the potential for use in a continuous flow reactor. The synthetically simple mixed metal hydride, diisobutyl aluminum borohydride [$(i\text{Bu})_2\text{AlBH}_4$], is easily generated from a 1:1 mixture of borane dimethylsulfide (BMS) and diisobutylaluminum hydride (DIBAL). Tertiary amides are reduced to the corresponding amine in fifteen minutes under ambient conditions using $(i\text{Bu})_2\text{AlBH}_4$. The enhanced reactivity may be due to the mixed hydride system acting in a synergistic fashion. The reaction progression can be easily monitored through ^{11}B NMR. The product is obtained through a simple acid-base extraction and no column chromatography is required for the isolation of the corresponding amine.



ORGN 81

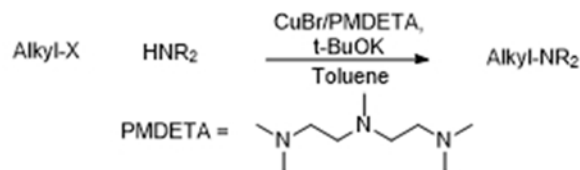
Ca-mediated SuFEx reaction toward the synthesis of sulfamides, sulfamates, and sulfonamides from S(VI) fluorides

Nicholas D. Ball¹, nicholas.ball@pomona.edu, **Subham Mahapatra**², **Cristian P. Woroch**¹, **Sabrina C. Kwan**¹, **Sabrina N. Carneiro**¹, **Samuel R. Khasnavis**¹, **Jason Dutra**², **Todd W. Butler**², **Christopher Am Ende**². (1) Chemistry, Pomona College, Pasadena, Massachusetts, United States (2) Pfizer Inc. , Mystic, Connecticut, United States

Cross-coupling chemistry has changed the face of synthesis since its inception

Cross coupling chemistry has changed the face of synthesis since it's inception. Although dominated by palladium based techniques, copper based cross coupling chemistry is experiencing a renaissance in the last decade. In this work, we examine

the utility of a cheap and stable ATRP catalytic system for copper cross coupling techniques.



Scheme 1. Generalised reaction for ATRP mediated Ullmann cross couplings

ORGN 83

Click chemistry assisted regioselective synthesis of new phosphorous moiety linked 1,2,3-triazoles

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Triazoles, one of the extensively studied 5-membered nitrogen heterocycles have shown a wide range of biological properties e.g. PDE4 inhibiting and anticancer properties, anti-HIV, antiallergic, antituberculosis, antifungal and antimicrobial activities. They also have shown p38 MAP kinase and PfPK7 protein kinase inhibitory properties. There are very few (1,2,3)-triazole containing molecules in the market e.g. tazobactam (β -lactam antibiotic), cefatrizine (cephalosporine antibiotic) etc and some are in the last stage of clinical trials.

1,2,3-triazole moieties are attractive linkers and moieties in medicinal chemistry because they are stable to metabolic degradation and capable of forming hydrogen bonds, which can be favorable in the binding of biomolecular targets and can improve the solubility. These moieties are valuable scaffolds and play an important role in bio-conjugation.

α -Hydroxy phosphonates (**Fig 1: A, B**) have attracted significant attention due to their fascinating biological activity, particularly as enzyme inhibitors, protective activity against influenza A, serine hydrolase inhibitors, antitumor, antibacterial and antimicrobial agents.

All these observations and reports prompted us to consider phosphorous moiety (**Fig 1: A, B**) to be incorporated as an integral part of the pharmacophore while designing antibacterial lead. Recently, we have reported the frame work, 1-((5-chloro-2,3-dihydrobenzo[b]oxepin-4-yl)methyl)-4-phenyl-1H-1,2,3-triazole (**Fig 1: C**) as a new template for potential antibacterial agents and the compounds synthesized based on this new template showed promising antibacterial and anticancer properties. In further

continuation of this research, we have now designed new template (**Fig 1: E**) via introducing a phosphorous moiety and a 1,2,3 triazole linker. Consequently, compounds based on diethyl (phenyl((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy) methyl)phosphonates **E** were synthesized and evaluated invitro against bacterial strains for their potential as new antibacterial agents and are found to possess excellent antibacterial properties.

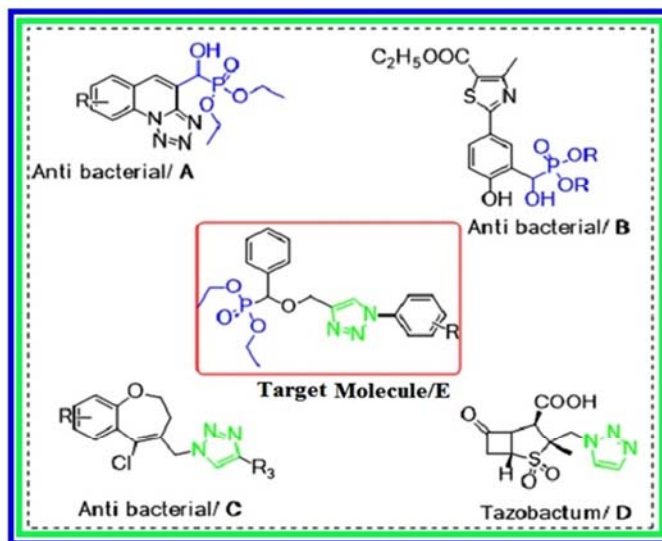


Figure 1: Design of hybrid target molecule

ORGN 84

Stereoselective synthesis of bile acid metabolites

Michael R. Krout, mrk020@bucknell.edu. Bucknell University, Lewisburg, Pennsylvania, United States

Bile acids and their metabolites serve various biological roles from detergents to cell signaling molecules that impact host physiology. Conventional bile acids are characterized by a cis-AB ring fusion, whereas an important class of metabolites feature a trans-AB ring fusion, also called allo bile acids. A highly chemo- and stereoselective synthesis of the allo bile acids was developed that leverages a key metal-catalyzed hydrogen atom transfer (MHAT) reaction with an accessible unsaturated intermediate. The C3 position of bile acids emerged as a critical element to control the stereochemical outcome and enabled the preparation of both allo and conventional bile acids in high

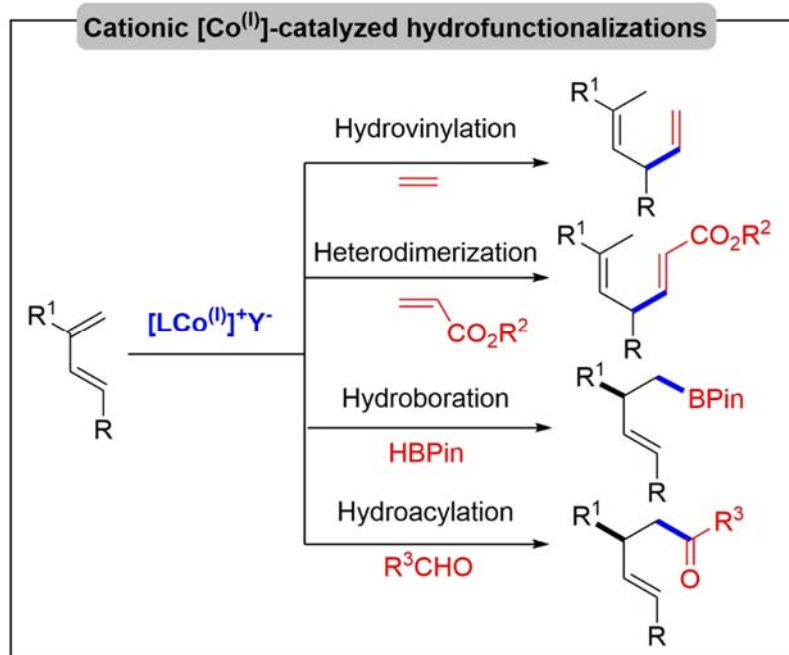
stereoselectivity. This modular MHAT approach enabled the gram-scale synthesis of a natural, anti-inflammatory metabolite of lithocholic acid.

ORGN 85

Cationic cobalt(I) intermediates in hydrofunctionalization reactions

Mahesh M. Parsutkar¹, parsutkar.1@osu.edu, Stanley M. Jing², Krishnaja Duvvuri¹, T. V. RajanBabu¹. (1) The Ohio State University, Columbus, Ohio, United States (2) Chemistry and Biochemistry, The Ohio State University, Columbus, Ohio, United States

Discovery of base metal-catalyzed methods for the preparation of chiral intermediates has garnered great attention. Recently, through a systematic study of activators and ligands, we have discovered Co(I)-catalyzed enantioselective heterodimerization of linear 1,3-dienes with ethylene and acrylates. In these studies, cationic cobalt(I) has been invoked as an active catalyst to carry out the transformation. However, the synthesis and isolation of such active Co(I)-complexes which could give insight into of reaction's mechanism, remains challenging. Herein, we disclosed a reliable procedure for the synthesis and isolation of Co(I)-complexes and characterized them by UV-Vis spectroscopy and X-ray crystallography. The *bis*-phosphine ligated Co(I) complexes in presence of activators, performed the regio- and enantioselective hydroboration of 2-substituted 1,3-diene with pinacolborane (HBPin) to obtain homoallylic boronates (enantiomeric excess, *ee* >90%). In the absence of activators, these complexes *do not catalyze* the reaction suggesting the key role of cationic Co(I)-species in the catalytic cycle. Currently, these Co(I) complexes are being further utilized in the hydroacylation of 1,3-dienes with simple aliphatic aldehyde to produce enantiopure ketones. The comprehensive protocols for the synthesis of Co(I) complexes and its application in hydrovinylation, heterodimerization with acrylates, hydroboration, and hydroacylation of 1,3-dienes will be discussed.



Cationic Co(I)-catalyzed hydrofunctionalization reactions

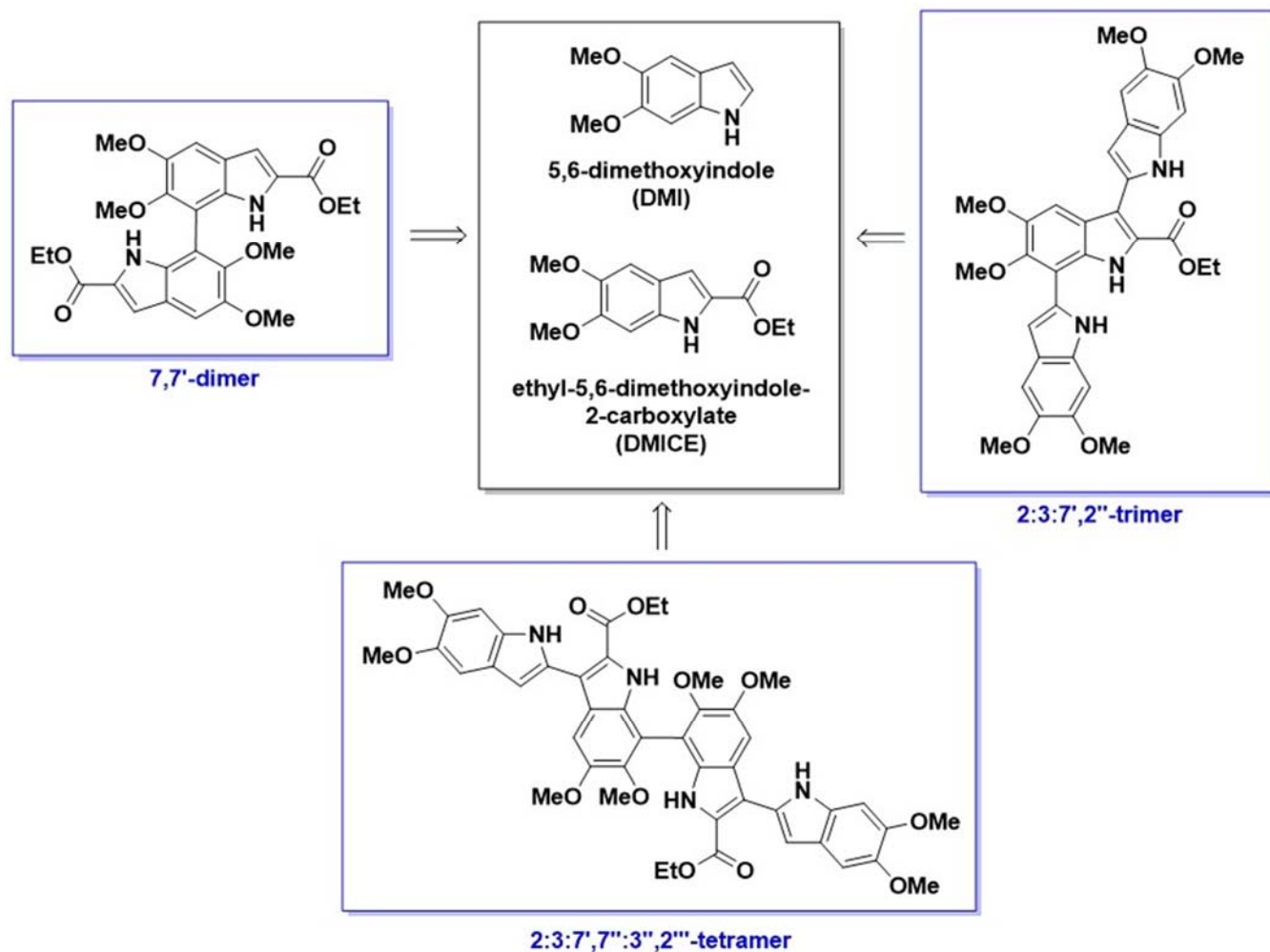
ORGN 86

Metal-mediated modular synthesis of eumelanin-inspired 5,6-dimethoxyindole oligomers

Andrew Aebly¹, aaebly@heidelberg.edu, **Benjamin J. Steger**², **Jeffrey Levy**³, **Jonathan C. Quirke**², **Jason M. Belitsky**². (1) Chemistry and Biochemistry, Heidelberg University, Tiffin, Ohio, United States (2) Chemistry and Biochemistry, Oberlin College, Oberlin, Ohio, United States (3) Chemistry, Colorado State University, Fort Collins, Colorado, United States

Eumelanin, the brown-to-black pigment present in mammals, is formed through the oxidative polymerization of dihydroxyindoles to form a heterogeneous mixture of oligomers. This complex natural pigment, along with numerous bio-inspired synthetic derivatives, have been of considerable interest in materials chemistry, finding applications in areas as diverse as modifiable surface coatings, organic electronics and metal remediation. Despite its broad and growing applications, the discrete molecules and supramolecular assembly of the oligomers that constitute eumelanin are still poorly understood. In order to explore the composition and unique physical properties of eumelanin, the Belitsky group has worked to develop a modular, metal-mediated synthetic approach to systematically create a library of biologically relevant oligomers, varying in regioconnectivity and monomer length. Specifically, commercially available 5,6-dimethoxyindole (DMI) and ethyl-5,6-dimethoxyindole-2-carboxylate (DMICE) have been functionalized via regioselective halogenation and iridium-catalyzed borylation at

the 2-,3-,4- and 7-positions of the indole. Using a Suzuki coupling, the functionalized 5,6-dimethoxyindoles were assembled into dimers, trimers and tetramers in good yields.



ORGN 87

Redox active organic materials

Dwight S. Seferos, dseferos@chem.utoronto.ca. Chemistry, University of Toronto, Toronto, Ontario, Canada

This talk will focus on our increasing interest in redox active polymers (redoxmers) and organic frameworks (redox-OFs). Some of these motifs derive their function from biological moieties, making them suitable for sustainable batteries. Other work has focused on unconventional designs that use ion intercalation in conjunction with redox

chemistry to maximize energy storage. The synthesis, properties, and applications will be the focus of the lecture.

ORGN 88

Phenazine-based covalent organic framework cathode materials with high energy and power densities

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Redox-active covalent organic frameworks (COFs) are promising materials for energy storage devices because of their high density of redox sites, permanent and controlled porosity, high surface areas, and tunable structures. However, the low electrochemical accessibility of their redox-active sites has limited COF-based devices either to thin films (<250 nm) grown on conductive substrates, or to thicker films (1 μ m) when a conductive polymer is introduced into the COF pores. Electrical energy storage devices constructed from bulk microcrystalline COF powders, eliminating the need for both thin-film formation and conductive polymer guests, would offer both improved capacity and potentially scalable fabrication processes. Here we report on the synthesis and electrochemical evaluation of a new phenazine-based 2D COF (DAPH-TFP COF), as well as its composite with poly(3,4-ethylenedioxythiophene) (PEDOT). Both the COF, and its PEDOT composite, were evaluated as powders that were solution-cast onto bulk electrodes serving as current collectors. The unmodified DAPH-TFP COF exhibited excellent electrical access to its redox sites, even without PEDOT functionalization, and outperformed the PEDOT composite of our previously reported anthraquinone-based system. Devices containing DAPH-TFP COF were able to deliver both high energy (250 Wh/kg) and power densities (2950 W/kg), validating the promise of unmodified redox-active COFs that are easily incorporated into electrical energy storage devices.

ORGN 89

New molecules for non-aqueous organic redox flow batteries

Koen Hendriks^{1,2}, k.h.hendriks@diffen.nl, Nicolas Daub², Rene A. Janssen². (1) Differ, Eindhoven, Netherlands (2) Molecular Materials and Nanosystems, Eindhoven University of Technology, Eindhoven, Netherlands

Non-aqueous organic redox flow batteries can provide a scalable technology that can be used to negate the impact of intermittency from renewable energy sources. The advantage of a non-aqueous system lies in the larger voltage window that can be utilized compared to aqueous systems, thereby allowing flow batteries with higher energy densities. In the quest for an all carbon-based system, challenges present themselves for the discovery and development of new redox active molecules that

combine high oxidation and low reduction potentials with outstanding solution stability and solubility. Here we present the development of novel molecules tailored to this application with an emphasis on multi-electron redox processes and redox amphoteric behaviour.

ORGN 90

Developing electrolyte chemistry for organic redox flow batteries

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Redox flow batteries are regarded as a promising technology for grid-scale energy storage. Viologen and quinone represent the state-of-the-art anolyte materials for both anion and cation exchange aqueous organic redox flow batteries (AORFBs) with a variety of catholyte materials. In this presentation, the most recent progress on viologen and quinone based AORFBs will be highlighted. Particularly, this presentation will discuss in-depth mechanistic understandings of viologen and quinone molecules regarding their chemical and electrochemical stabilities, which is crucial to develop new generations of redox active electrolytes for energy storage.

ORGN 91

Two electron storage using metal picolinamide complexes for redox flow batteries

Gabriel Andrade¹, **Celia R. Federico**¹, **Ivan A. Popov**², **Ping Yang**², **Enrique R. Batista**², **Benjamin L. Davis**¹, bldavis@lanl.gov. (1) MPA-11 Materials Synthesis and Integrated Devices, Los Alamos National Laboratory, Los Alamos, New Mexico, United States (2) Theoretical Division, Los Alamos National Laboratory, Los Alamos, New Mexico, United States

The lack of grid-scale energy storage is hindering the incorporation of more renewable energy generation. As such there has been significant interest in less expensive battery designs. Although traditional Li-ion batteries have been deployed in markets with higher utility costs (So Cal, Hawaii), substantial deployment and impact will likely result only if significant cost reduction is achieved. One technology that might fit this need is a redox flow battery, where the energy is stored in a redox reaction between dissolved molecular species, not in the electrode. The bulk of RFB research is focused on redox carriers that function in aqueous environments since water is essentially free. The inexpensive medium, however, comes at a cost – reduced cell potential, limited to ~2.4V under the best conditions. Our group, along with many others, are attempting to design new redox carriers for nonaqueous solvents to enable larger cell potentials, better cycle life, and lower cost.

In this talk our work using metal complexes with a linked picolinamide (pico) ligand will

be discussed. First the synthesis, characterization, and electrochemical performance of nickel complexes with two pico ligands will be detailed along with theoretical predictions of their redox behavior. This will be followed by showing our latest results with a new TREN based ligand incorporating three pico coordinate points and its unique two electron storage ability.

ORGN 92

High throughput experimentation as a tool for catalyst discovery with earth abundant transition metals

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Because of potential advantages in cost, sustainability and most importantly, new chemistry, there has been ongoing interest in catalysis with Earth-abundant metals such as iron, cobalt and nickel. One limitation in catalyst discovery has been the availability of reliable metal precursors for rapid catalyst discovery. Our laboratory has been engaged in developing new coordination and organometallic compounds of these metals that enable catalyst discovery by high throughput experimentation. Catalysts for the asymmetric hydrogenation of alkenes, Suzuki-Miyaura cross coupling and C–H borylation have been discovered using this approach. The role of industrial collaborations as well as mechanistic advances and unexpected findings will be highlighted.

ORGN 93

Democratization of high throughput experimentation for process chemistry

Kelsey F. VanGelder, *kelsey.x.vangelder@gsk.com*. Chemical Development, GlaxoSmithKline, Bryn Mawr, Pennsylvania, United States

High throughput experimentation is a powerful tool in modern process chemistry, enabling rapid optimization and route identification. Many pharmaceutical companies employ a dedicated group of users to conduct most of the high throughput screening, perhaps due to the increasing amount of complex automation equipment. As an alternative approach, the development and implementation of a walk-up platform will be discussed. Several case studies will also be presented, demonstrating how a walk-up high throughput chemistry platform can be used to address complex process chemistry problems at all stages of development.

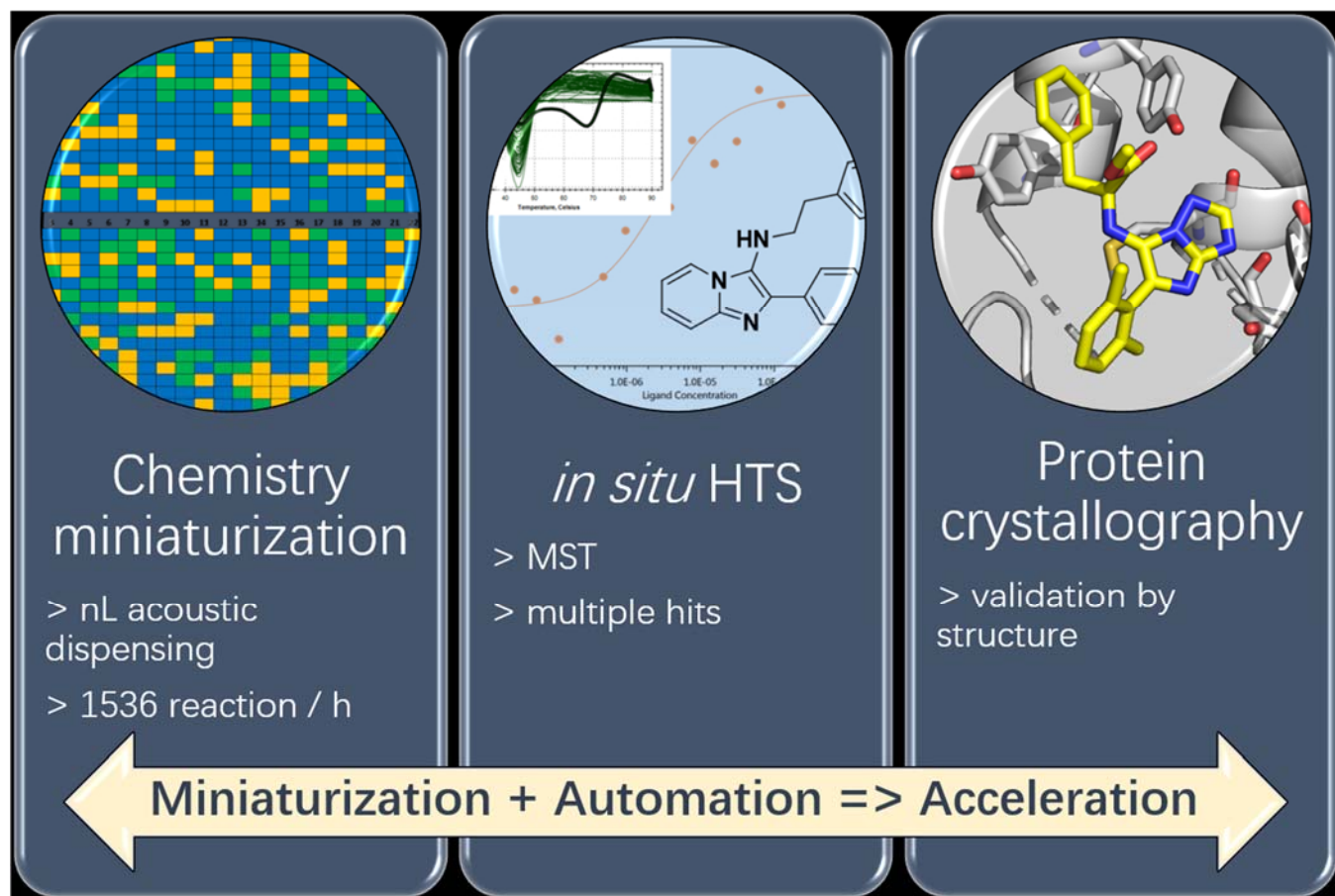
ORGN 94

Miniaturization + automation = Acceleration

Alexander Doemling, *a.s.s.domling@rug.nl*. Department of Drug Design, University of Groningen, Groningen, Netherlands

Automated, **miniaturized** and **accelerated** drug **discovery**, the **AMADEUS** platform, is a top-down reengineering of the currently performed lengthy, very expensive and unreliable drug discovery process (Figure). In a fully autonomous manner thousands of small molecules are synthesized per day in nano liter volumes, efficiently screened and optimized to drug candidates using artificial intelligence.

Industrially, early small molecule drug discovery involves a lengthy, personnel and resource intensive process with a very high attrition rate, resulting in lengthy development times and very expensive new medications for unmet medical needs. The slow cycle time within medicinal chemistry from synthesis to assay and data analysis is constantly being questioned to help improve the efficiency of the discovery process. With our project we want to challenge the early drug discovery process, which for over 50 years has, almost uniformly been pursued in all pharma companies around the world and comprises two blocks, 1) a HTS relying on millions of curated and stored compounds ('the compound library') resulting in hit lists and 2) the subsequent hit-to-lead (H-2-L) optimization phase often called 'design, make, test cycle'. In my talk I will showcase our automated and highly miniaturized synthesis platform. Moreover I will highlight screening and optimization projects resulting in potent Crisp/Cas9, IL17A-IL17r and menin/mlf inhibitors.

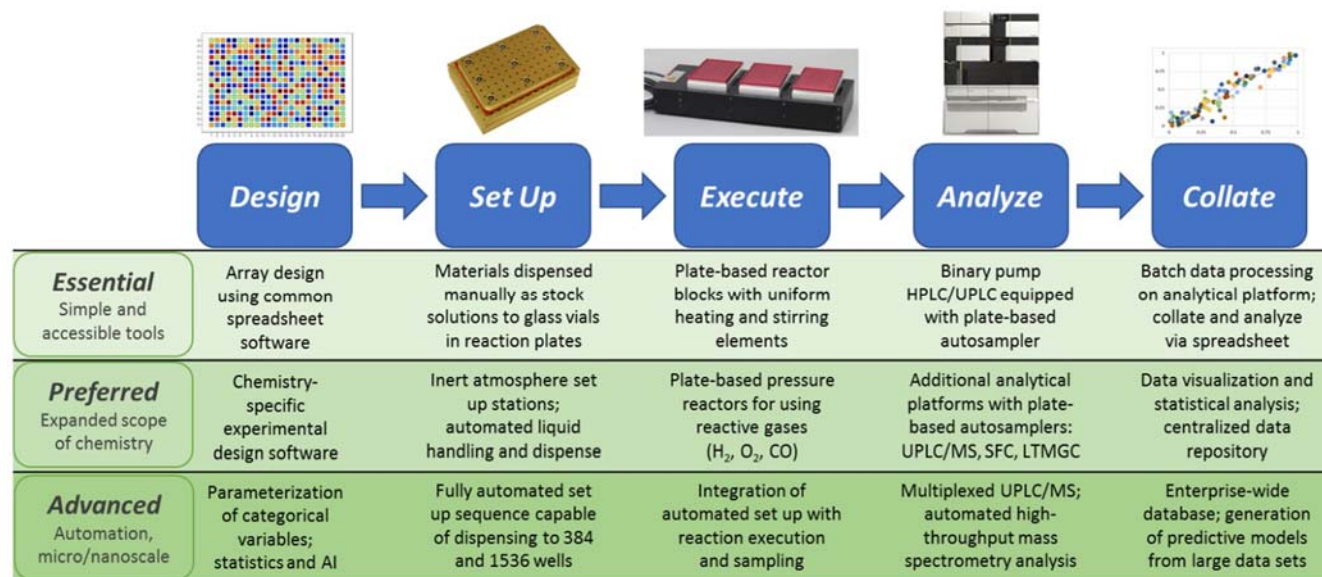


ORGN 95

High-throughput experimental approaches to mapping chemical reactivity

David Leitch, dcleitch@uvic.ca. Chemistry, University of Victoria, Victoria, British Columbia, Canada

High-throughput experimentation is increasingly being used to great effect in synthetic chemistry research, particularly when geared toward the optimization of a particular and specific reaction. Our group is establishing a program to use high-throughput experimentation to not just develop and optimize new methodology, but to thoroughly map and understand chemical reactivity within a multivariate parameter space. This talk will touch on aspects of setting up a high-throughput synthetic chemistry lab in an academic setting, and application of high-throughput experimentation to problems in transition metal catalysis.



ORGN 96

Nanoflow-HTE: Quick decision enablement for parallel medicinal chemistry

Simon Berritt, Simon.Berritt@pfizer.com. Pfizer Global Research & Development, Groton, Connecticut, United States

As Parallel Medicinal Chemistry libraries expand beyond amidations and SnAr reactions to metal-catalyzed reactions, the need to quickly identify best conditions covering a broad range of sterically & electronically diverse monomers and templates becomes paramount. Herein, we present ongoing efforts to rapidly test multivariate metal catalyzed reactions crossing both monomers and templates, detailing successes, failures, and the applicability of this workflow to Big-Data generation.

ORGN 97

Lessons learned and future opportunities for HTE

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Synthetic Development, Bristol-Myers Squibb, New Brunswick, New Jersey, United States (5) Process Research and Development, Merck and Co., Inc., Rahway, New Jersey, United States

This panel discussion assembles leaders in the area of high throughput experimentation with 50+ combined years of experience in the field. Planned as an interactive dialog, this presentation has the goal of sparking discussion about the impact and future of high throughput technologies in organic chemistry. Panelists will share stories around their experience and their visions for how HTE can drive efficiency in discovery, development, and beyond. Questions from the audience are welcome!

ORGN 98

Solving Ni puzzles in alkene difunctionalization reactions

Cristina Nevado, *cristina.nevado@chem.uzh.ch*. Department of Chemistry, University of Zürich, Zürich, Switzerland

The interaction of Nickel with π -systems represents a major focus in our research group. Catalytic transformations aiming at the straightforward functionalization of alkenes and alkynes in a chemo-, regio- and stereoselective manner utilizing radicals as well as studies on the mechanistic features underlying these transformations will be presented in this lecture[1].

ORGN 99

Strategic covalent bond transformations using mechanical force

Maxwell J. Robb, *maxwell.j.robb@gmail.com*. Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California, United States

The use of mechanical force to selectively activate covalent bond transformations is emerging as a powerful method to access stimuli-responsive polymers for applications ranging from sensing to drug delivery. In polymer mechanochemistry, polymer chains transduce mechanical stress to force-sensitive molecules called mechanophores that can be designed to undergo a wide variety of chemical reactions. Mechanochemical reactivity arises from a distortion of the potential energy surface under large forces, which fundamentally changes the reaction landscape. Force-induced chemical reactions that produce a change in optical properties such as color or luminescence are particularly useful because they enable molecular level stress sensing by simple visual detection methods. Mechanically triggered release of small molecules is also an underdeveloped, but potentially powerful approach for sensing and delivery. Our recent developments on a mechanophore design strategy that decouples mechanical activation from a functional response will be presented. This mechanically gated reaction methodology establishes unique opportunities for understanding and exploiting

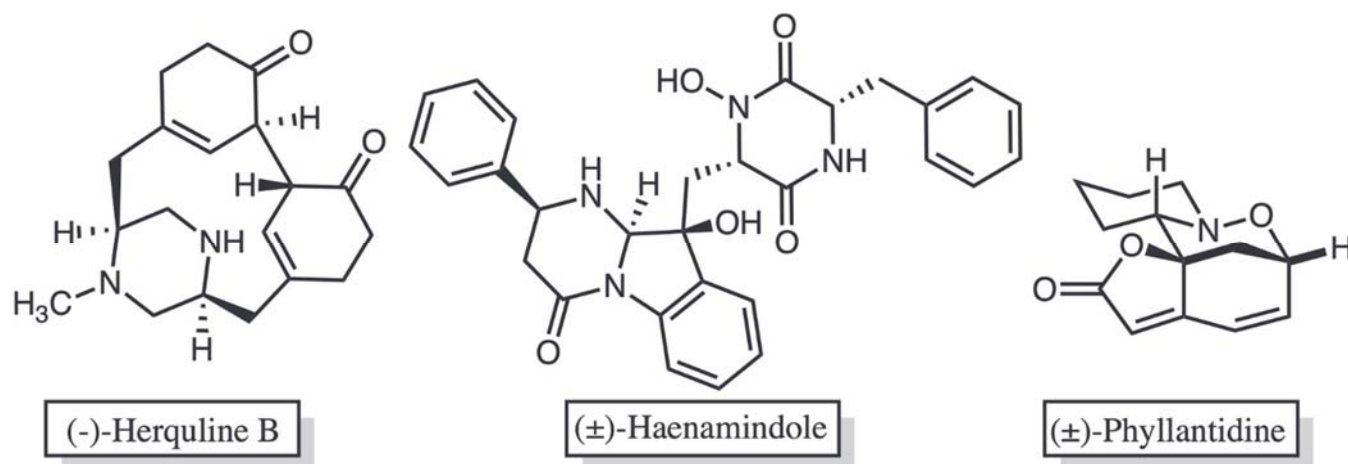
the structural features that govern mechanochemical reactions and creating stimuli-responsive polymers that impact a variety of useful technologies.

ORGN 100

Recent efforts in the synthesis of complex natural products: Efficient synthesis of phyllantidine and progress towards haenamindole

John L. Wood, John_L_Wood@baylor.edu. Department of Chemistry and Biochemistry, Baylor University, Waco, Texas, United States

Recent efforts in our laboratories have focused on syntheses of several complex alkaloids. Inspirations drawn from our recent synthesis of (-)-herquiline B have inspired further efforts that have culminated in an efficient synthesis of (±)-phyllantidine and intriguing approach to natural products possessing *N*-hydroxyl-diketopiperazine moieties (e.g., (±)-haenamindole).



ORGN 101

New directions in Ni-Catalyzed cross coupling

Abigail G. Doyle, agdoyle@princeton.edu. Princeton University, Princeton, New Jersey, United States

A central theme of our work is the demonstration that Ni can intercept common reactive intermediates in organic chemistry to effect previously inaccessible C(sp³)-C bond-forming reactions. These electrophiles include iminium ions, oxocarbenium ions, aziridines, and carbon-centered radicals. This lecture will describe recent examples of

synthetic methodology development and accompanying mechanistic studies from my group. In many cases, development of these methods has required the design and application of novel ligands because repurposing those designed for precious metal catalysts has failed. I will describe mechanistic studies to elucidate the structure-activity relationship of these ligands in Ni catalysis.

ORGN 102

Necessity is the mother of invention: Natural products and the chemistry they inspire

Sarah E. Reisman, *reisman@caltech.edu*. MC 101-20, California Institute of Technology, Pasadena, California, United States

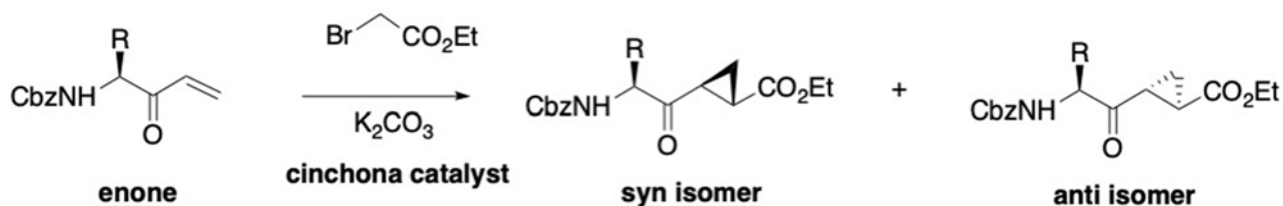
The chemical synthesis of natural products provides an exciting platform from which to conduct fundamental research in chemistry and biology. Our group is currently pursuing the synthesis of a number of structurally complex natural products, including the diterpenoids perseanol and talatisamine. The densely-packed arrays of heteroatoms and stereogenic centers that constitute these polycyclic targets challenge the limits of current technology and inspire the development of new synthetic strategies and tactics. This seminar will describe the latest progress in our methodological and target-directed synthesis endeavors.

ORGN 103

Stereoselective cyclopropanation of amino acid-derived enones using cinchona alkaloids

Norma K. Dunlap, *norma.dunlap@mtsu.edu*, Holli Kerns, Avraz Anwar. Middle Tenn State Univ, Murfreesboro, Tennessee, United States

A novel and efficient synthesis of cyclopropyl peptidomimetics has been previously reported by our group, using protected amino acids as starting materials. The key step is cyclopropanation of an amino acid-derived enone to afford cyclopropyl peptidomimetics. However, this step suffered from a lack of stereoselectivity, producing both *syn* and *anti* diastereomers in equal amounts. Investigation and application of the use of quinine and quinidine ethers as catalysts in this Michael-induced ring closure step has greatly enhanced the stereoselectivity. The methyl ether of quinine affords the *syn* diastereomer selectively, but only for enones with an alpha-branched substituent, such as the valine-derived enone. However, the quinine benzyl ether is selective for the *syn* diastereomer in all cases. The pseudoenantiomer quinidine benzyl ether is selective for the *anti* diastereomer in all cases. Results will be presented for seven different enones, with both catalysts.

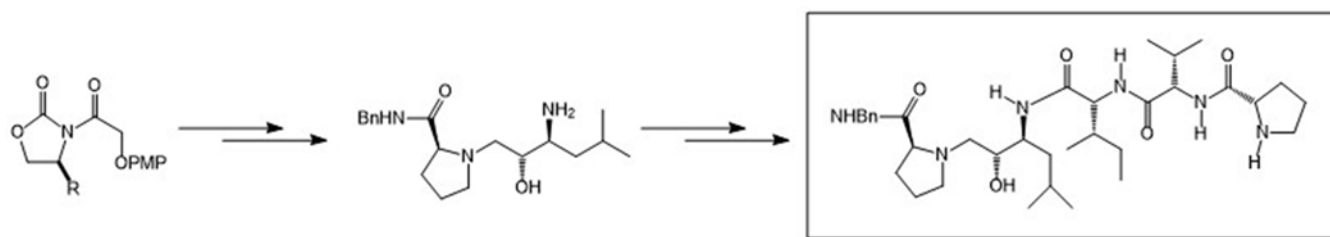


ORGN 104

Efforts towards the formal asymmetric synthesis of the Akaji Human T-cell leukemia virus (HTLV-1) protease inhibitor

Marian A. Addo¹, maaddo@ilstu.edu, **Shawn R. Hitchcock**². (1) Chemistry, Illinois State University, Normal, Illinois, United States (2) Dept of Chemistry, Illinois State Univ, Normal, Illinois, United States

The Human T cell leukemia virus (HTLV-1) was first isolated from patients with adult T cell leukemia/lymphoma (ATL) in the 1980s by researchers in both the United States and Japan. It was classified as the exclusive causative agent of ATL. HTLV-1 is a member of the deltaretrovirus family and has been established as the first retrovirus to directly be associated with human malignancy (cancer). It is estimated that 5-20 million people are infected with HTLV-1. HTLV-1 is endemic in southern Japan, parts of the Caribbean, most of Africa, South America, and is also be seen in a lower frequency over many other areas of the world. A commonality between HTLV-1 and other retroviruses is that it encodes a protease (PR) necessary for it to mature. In other retroviruses inhibition of the PR has shown to prevent the further spread of viral information. This makes the development of inhibitors specific to the HTLV-1 virus PR an attractive new direction for research. Compared to other retroviruses such as HIV, HTLV-1 has received very little attention with only a minimal literature occurrence. Building upon the work established by Aimoto and co-workers, Kenichi Akaji and co-workers were able to synthesize a protease inhibitor that successfully interacted with the Aimoto protease. The synthesis of the Akaji protease inhibitor was accomplished by the use of chiral auxiliary methodology combined with solid phase support chemistry to allow for the protection of a secondary alcohol and the addition of the tripeptide at the β -amino position. We recently became interested in the asymmetric synthesis of the protease inhibitor for the HTLV-1 using a glycolate aldol addition route. This poster will summarize the work that has been carried out on developing an efficient synthesis of the Akaji protease inhibitor. The summary will include the work that was accomplished with a variety of glycolate aldol additions directed by oxazolidine-2-thiones chiral auxiliaries. The aldol addition products that were obtained were reductively cleaved to generate the corresponding diol that was chemoselectively sulfonylated with toluenesulfonyl chloride. Treatment of this system with a variety of nucleophiles resulted in oxetane formation as the intermediate. The reactivity of the formed oxetane will be discussed as well as future plans for completing this body of work.



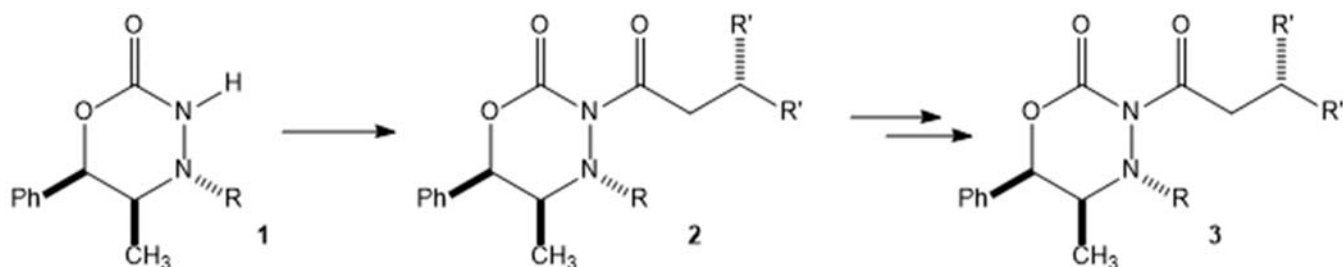
ORGN 105

Oxadiazinones as chiral auxiliaries: Asymmetric conjugate addition reactions with *Ephedra* based oxadiazinones

Fatima O. Obe¹, foobe@ilstu.edu, **Shawn R. Hitchcock²**. (1) Chemistry, Illinois State University, Normal, Illinois, United States (2) Dept of Chemistry, Illinois State Univ, Normal, Illinois, United States

The stereoselective formation of carbon-carbon bonds through the process of conjugate addition has proven to be a very important methodology in synthetic organic chemistry. We became interested in exploring the potential utility of oxadiazinones in asymmetric conjugate addition applications. In this context, oxadiazinones (**1**) are chiral auxiliaries that have been applied in the asymmetric aldol addition reaction. Our current efforts are directed towards employing these compounds as chiral scaffolds for the process of asymmetric conjugate addition with the ultimate objective of using this methodology in the preparation of gamma-amino acids such as Tolterodine. Our preliminary efforts focused on using an N4-p-methoxyphenyl substituted oxadiazinone. This oxadiazinone was acylated with *trans*-cinnamic acid via the Steglich reaction with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and catalytic N,N'-dimethylamino pyridine (DMAP). This substrate was then reacted with a Normant reagent, a mixture of the Grignard reagent, methylmagnesium bromide and copper (I) bromide-dimethylsulfide complex. The reaction was carried out in diethyl ether and in tetrahydrofuran. While tetrahydrofuran gave the superior result, still the diastereoselectivity of the conjugate addition was determined by 500 MHz NMR spectroscopy to be no greater than 3:1, a value unsuitable for meaningful asymmetric synthesis. This observation was in contrast to higher stereoselectivities observed in the asymmetric aldol reaction with *Ephedra* based oxadiazinones where ratios of 95:5 are commonly observed. It was reasoned that the electrophilic site of the conjugate addition was further away from the stereodirecting group at the N4-position than the aldol reactive site. To resolve this issue, a new series of oxadiazinones were prepared, namely N4-2-naphthylmethyloxadiazinone and N4-p-methoxybenzyloxadiazinone, and used in the asymmetric conjugate addition process. This poster will describe the chemistry that has been accomplished to this point, and

make projections for future efforts in the synthesis of the medically valuable target compound, tolterodine.

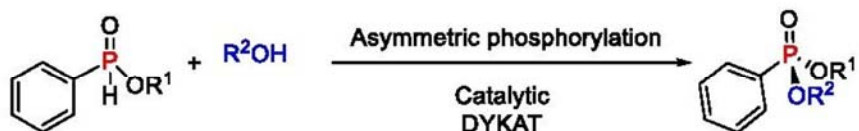


ORGN 106

Asymmetric synthesis of stereogenic phosphorous centers using chiral nucleophilic catalysis

Ahmed Numan¹, ahmed.numan@maine.edu, **Matthew Brichacek**². (1) University of Maine, Orono, Maine, United States (2) Department of Chemistry, University of Maine, Orono, Maine, United States

Organophosphonates are common motifs in nucleotides, pesticides, herbicides, and flame retardants. Commonly, phosphate mimics possess four unique substituents, and thereby a chirality centre. These chiral phosphate mimics are useful in transition metal catalysis and as nucleotide therapeutics. Use of phosphorus-stereogenic analogues in antisense therapy improves potency, stability toward enzymatic degradation, and bioavailability. The catalytic, stereocontrolled synthesis of phosphorous-stereogenic centres is challenging, and traditionally, depends on resolution or use of stoichiometric auxiliaries. Herein, enantioenriched phosphorous centres have been synthesized using nucleophilic catalysis. A racemic H-Phosphonate species were coupled to the nucleophilic alcohols under halogenating conditions. Chiral phosphonate products were synthesized in modest yield and enantioselectivity (62% ee) after identification of an appropriate chiral catalyst and optimization of the solvent, base and temperature. These products could be significantly utilized as phosphonate prodrugs and/or analogues for studies in a biological system.



ORGN 107

De novo asymmetric synthesis of purpurosamine

George A. O'Doherty², Chao Liang¹, Alhanouf Aljahdali¹, **Terrence Hopkins**¹, tmhopkins16@gmail.com. (1) Northeastern University, Malden, Massachusetts, United States (2) Dept of Chemistry Chem Biology, Northeastern Univ, Boston, Massachusetts, United States

The 2,6-diaminosugar, Purpurosamine C, is one of the two carbohydrate ring systems that make up the aminoglycoside antibiotic natural product Gentamicin C. As part of a study aimed at the discovery of new aminoglycoside antibiotic with lower toxicity and improved activity against resistant bacteria. We desired synthetic access to purpurosamine and its stereoisomers. To these ends, we have developed a *de novo* asymmetric synthetic approach to the purpurosamine ring system. The six-step asymmetric synthesis prepares either enantiomer of purpurosamine from the achiral starting material, *N*-Cbz-protected α-aminoacetylfuran. This new methodology starts with a Noyori catalyzed asymmetric reduction to install the D- or L-absolute stereochemistry. This was followed by a one-pot vanadium catalyzed peroxide mediated Achmatowicz rearrangement and *in situ* isocyanate annulation to form the desired pyran ring system with purpurosamine stereochemistry. A subsequent 4-step transformation, which involves the removal of a C-4 ketone, stereoselective glycoside formation and amine-deprotection provides the desired purpurosamine sugar. The details of the discover of this approach will be reported.

ORGN 108

Diverse derivatization of *trans*-cyclooctenes using diastereoselective functionalization of a scalable ketone-*trans*-cyclooctene precursor

Jessica E. Pigga, piggaj@udel.edu, **Joseph Fox**. University of Delaware, Newark, Delaware, United States

trans-Cyclooctenes (TCOs) are high strain energy compounds utilized in the realm of bioorthogonal chemistry. TCOs undergo inverse electron-demand Diels-Alder reactions with tetrazine molecules in the fastest bioorthogonal reaction to date, the tetrazine-*trans*-cyclooctene ligation. TCOs have been used for live-cell imaging, ¹⁸F labeling, biomaterials, and probing sulfenic acids formed on proteins experiencing high redox poise. With these applications, TCOs of diverse functionality that are also hydrophilic and synthetically accessible are desired. While the TCOs currently in the ever-growing “toolbox” have fast reaction kinetics, they are limited in scope, involve difficult separations, produce low yields of the desired isomers, and exhibit lower hydrophilicities. This work focuses on the synthesis of derivatized *hydroxy*-TCOs that are made from the diastereoselective functionalization of *keto*-TCO. Nucleophilic addition to *keto*-TCO results in the exclusive formation of the axial orientation of the hydroxyl group. This is pertinent for sulfenic acid tagging, affords higher yields of the ‘faster’ diastereomer, and makes purification more facile. Photoisomerization of *keto*-TCO is scalable and moderate yielding. The synthesized derivatives of *keto*-TCO include alcohol, propargyl, oxime, activated ester, amine, and etc. Several of these hydrophilic TCOs have been used as sulfenic acid probes as well as conjugated to a fluorophore for intracellular probing.

ORGN 109

Peptoid helices for the enantioselective trifluoromethylation of carbonyls

Katharine B. Toll, **Benjamin C. Gorske**, chld87stv@gmail.com. Bowdoin College, Brunswick, Maine, United States

The trifluoromethyl group is increasingly utilized in pharmaceutical design to enhance drug efficacy and biostability. Enantioselective nucleophilic trifluoromethylation of carbonyl groups to give trifluoromethyl alcohols is an attractive strategy for the incorporation of trifluoromethyl groups, although enantioselectivity can be difficult to achieve. Recent work has shown that peptoids are viable as chiral catalysts for enantioselective transformations. We present our progress toward developing a helical peptoid catalysts for the enantioselective trifluoromethylation of carbonyl groups.

ORGN 110

Peptoid turns for the enantioselective trifluoromethylation of carbonyls

Rebecca J. Londoner, **Benjamin C. Gorske**, chld87stv@gmail.com. Bowdoin College, Brunswick, Maine, United States

The trifluoromethyl group is increasingly utilized in pharmaceutical design to enhance drug efficacy and biostability. Enantioselective nucleophilic trifluoromethylation of

carbonyl groups to give trifluoromethyl alcohols is an attractive strategy for the incorporation of trifluoromethyl groups, although enantioselectivity can be difficult to achieve. Recent work has shown that peptoids are viable as chiral catalysts for enantioselective transformations. We present our progress toward developing chiral peptoid turns as catalysts for the enantioselective trifluoromethylation of carbonyl groups.

ORGN 111

Enantioselective synthesis of phenanthridinone analogs with quaternary carbons utilizing the Birch-Heck sequence

Mary Sexton¹, *mary.e.sexton@gmail.com*, **William P. Malachowski**². (1) Chemistry, Bryn Mawr College, East Norriton, Pennsylvania, United States (2) Department of Chemistry, Bryn Mawr College, Bryn Mawr, Pennsylvania, United States

Phenanthridinone is a flat aromatic structure that is commonly found in many biologically active molecules and drug candidates. However, its extensive bioactivity can be a problem when attempting to make drug candidates that are developed for selective interactions, thereby reducing side effects and toxicity. With this in mind, phenanthridinone derivatives were synthesized using the Birch-Heck sequence to produce analogs with chiral centers and all-carbon quaternary sp^3 carbons. This process entails the Birch-reduction/alkylation of benzoic acid followed by the formation of an acyl chloride, which is immediately reacted to form an amide. Finally, in the key step, an enantioselective desymmetrizing intramolecular Heck reaction is completed to produce these analogs. These derivatives of phenanthridinone could retain their bioactivity as well as be more selective and potent in their interactions with biological targets for therapeutic purposes.

ORGN 112

Asymmetric cyclopropanation using chiral group 11/N-heterocyclic carbene complexes

Peyton D. Kunselman, *pdk1750@rit.edu*, **Nathan Johnson**, **Michael G. Coleman**. School of Chemistry and Materials Science, Rochester Institute of Technology, Rochester, New York, United States

Cyclopropane rings have a uniquely rigid geometry that lends to their use in improving the pharmacokinetics of pharmaceutical compounds and in the ligand design of chiral molecular architectures. This work explores stereoselective cyclopropanation reactions using safer, environmentally-benign, and inexpensive Group 11 'coinage metals' complexed with commercially available chiral imidazol(in)ium salts. This system affords an operationally simple, single-step protocol resulting in a green and sustainable catalytic asymmetric cyclopropanation reaction in good yields, high diastereoselectivity, and good enantioselectivity.

ORGN 113

Light-triggered catalytic asymmetric allylic benzylation with photogenerated C-nucleophiles

Xavier Companyo, *xavier.companyo@unipd.it*, Suva Paria, Edoardo Carletti, Michela Marcon, Alessio Cherubini-Celli, Luca Dell'Amico, Marcella Bonchio. Department of Chemical Sciences, University of Padova, Padova, Italy

The asymmetric allylic alkylation (AAA) reaction lies amongst the most powerful strategies for the catalytic construction of C-C bonds in stereoselective manner. The pioneering works of Trost on the Pd-catalyzed AAA, together with the seminal reports of Kim and Lu on the organic Lewis base catalyzed AAA of Morita-Baylis-Hillman (MBH) derivatives, established the foundations of both the transition-metal catalyzed and the organocatalytic versions. Since then, extensive efforts have been devoted to expanding their generality and harness their asymmetric potential. Yet, these transformations are mainly restricted to the use of acidic or stabilized C-nucleophiles, such as alkali-metal salts, active methylene compounds or enolates. Conversely, the use of non-acidic or non-stabilized nucleophiles in asymmetric allylic alkylation remains largely underdeveloped.

Photochemistry is currently emerging as a complementary and more sustainable approach in synthetic chemistry. The unprecedented reactivity of excited organic molecules under light irradiation has tremendously expanded the playground for new reaction discovery. Herein is presented the asymmetric allylic benzylation of racemic MBH carbonates with 2-methyl benzophenone derivatives as non-stabilized benzylating C-nucleophiles. The dual activation of both reaction partners, chiral Lewis-base activation of the electrophile and light-activation of the nucleophile, enables the stereoselective installation of benzyl groups at allylic positions for the construction of tertiary and quaternary carbon centers.

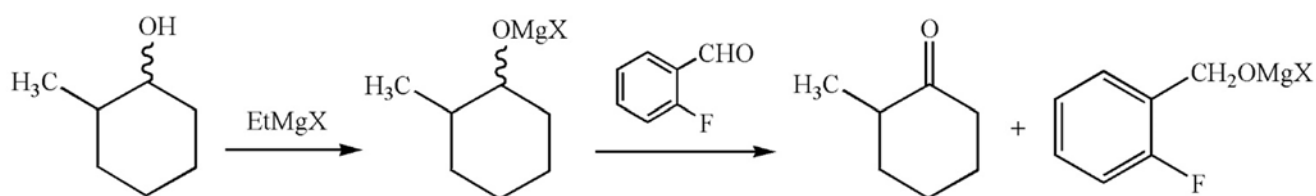
ORGN 114

Diastereomer differentiation in magnesium-oppenauer oxidation of chiral secondary alcohols

*Charles M. Martin, Chase M. Webb, **Kenneth J. Brown**, *kbrown@stmarys-ca.edu*.* Department of Chemistry, Saint Mary's College of California, Moraga, California, United States

Treatment of chiral 2° alcohols with an alkylmagnesium reagent to form the corresponding magnesium alkoxides, followed by addition of 2-fluorobenzaldehyde resulted in hydride transfer from the alkoxide to the aldehyde. Both the extent of this magnesium version of the Oppenauer oxidation and its stereodifferentiation between alkoxide diastereomers was determined for several different cyclic and acyclic alcohols. After quenching with acid, measured ratios of ketone product to recovered alcohols

showed a wide range of overall Oppenauer reactivity, with one alcohol being essentially unreactive while others showed substantial or complete conversion to the corresponding ketone. By measuring the ratio of diastereomers in the recovered alcohols after partial reaction, and comparing to their initial ratio, a range of stereoisomer ratio enhancements was determined. In the example shown here, the stereoisomer ratio increased from 1:1 to as high as 6:1, depending on conditions. For some of the other examples tested, this enhancement revealed a substantial difference in reactivity between the two alkoxide isomers, resulting in nearly complete disappearance of one diastereomer, while much of the other isomer remained unreacted. The effect on reaction outcomes resulting from use of different organomagnesium reagents and solvents was also explored.

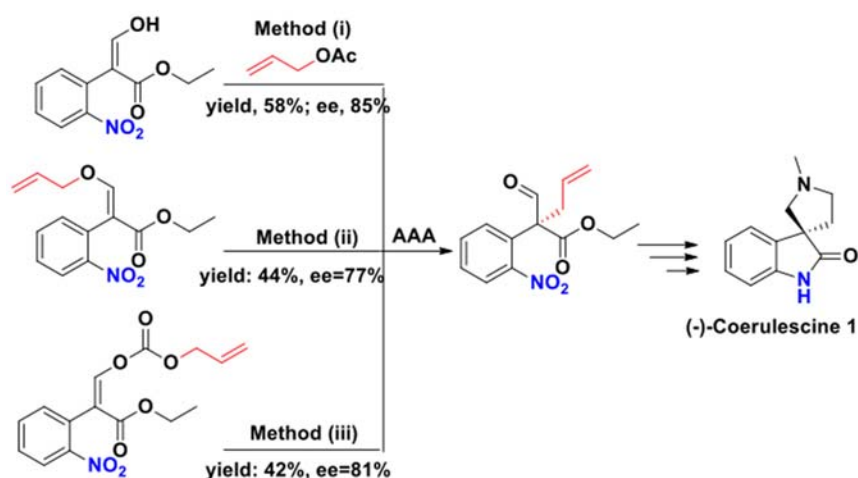


ORGN 115

Palladium-catalyzed asymmetric allylic alkylation of ortho nitro hydroxy acrylate: total synthesis of (-)-coerulescine

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The enantioselective synthesis of spiro architecture often associated with significant biological activity, render the spiro [pyrrolidine-3, 3-oxindole] alkaloids as an appealing synthetic target. We envisioned a novel approach of preparing 3,3-disubstituted oxindole from an acyclic stereogenic center. Consequently, we have screened three-way approaches of Pd AAA, (i) addition of Pd- L^* -allyl electrophile to acrylate, (ii) using O-allyl ether acrylate as a nucleophile, and (iii) in situ generation of enolate nucleophile by decarboxylation of carboxyallyl acrylate. Based on that thorough optimization on O- NO_2 substituted 3-hydroxy aryl acrylate, we obtained enantioselectivity up to 85%. Using the best method, we then prepared the tetra substituted oxindole and developed a 6 step shortest synthetic protocol for the asymmetric synthesis of (-)-Coerulescine (isolated from the blue canary grass "*Phlaris coerulescens*") with 40% overall yield. This approach can offer us an innovative tool and solution for the systematic and large-scale synthesis of target drug molecule.



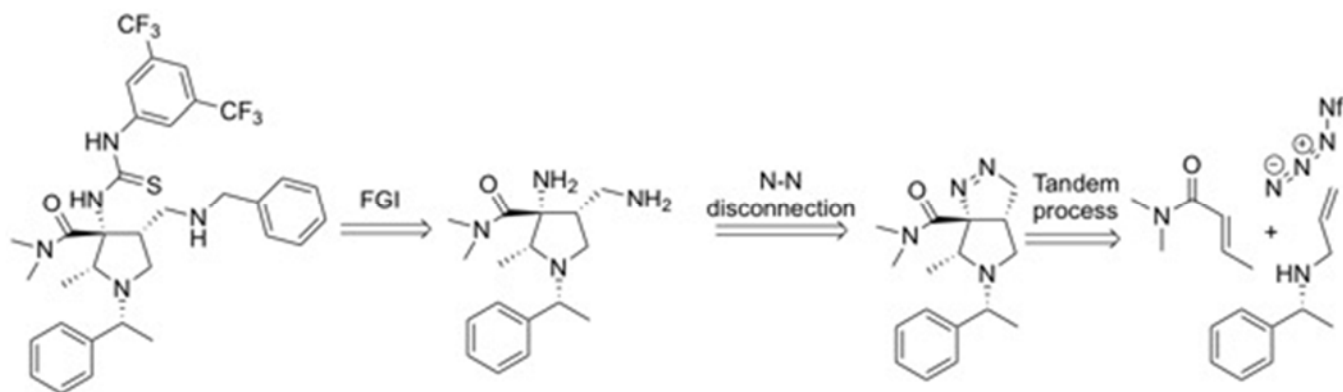
Overall synthetic route towards (-)-coerulescine via 3,3-disubstituted oxindole

ORGN 116

Synthesis of a chiral organocatalyst via a novel asymmetric tandem conjugate addition, diazo transfer and 1,3-dipolar cycloaddition

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In most synthetic systems, expensive and toxic transition-metal catalysts are often used to access chiral products with unique medicinal or material characteristics. In contrast, asymmetric organocatalysts modeled after naturally-occurring amino acids provide a similar catalytic ability, but with reduced toxicity and cost. These non-natural amino acids are especially of interest due to their unique stereochemistry and modifiability, which allow their catalytic ability to be carefully tuned for efficient asymmetric induction. As such, we are interested in non-natural amino acid derivatives containing sites for hydrogen bonding and enamine formation, allowing application in the catalysis of Michael additions between aldehydes and nitroalkenes. To approach this target molecule, a novel tandem conjugate addition, diazo transfer and 1,3-dipolar cycloaddition was employed to form a unique chiral non-natural amino acid scaffold. Subsequent reductive amination and isothiocyanation was then attempted. However, further optimization necessitated a reduction pathway to obtain the organocatalyst.



ORGN 117

Catalytic enantioselective synthesis of chiral esters from ketenes and allyl aryl ethers

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Transition-metal-catalyzed allylic alkylation is one of the most powerful methods for the enantioselective synthesis of molecules bearing new carbon-carbon bonds. However, the formation of simple allylated ester products bearing an α -quaternary stereogenic center still represents a major challenge for transition metal-catalyzed allylic alkylation chemistry. This is especially true when a disubstituted ketene is used as the reactant partner for allylic electrophiles. We have previously demonstrated that disubstituted ketenes can be converted in enantioselective fashion to a variety of four membered ring systems through phosphine or alkaloid nucleophilic catalysis. Recently, we investigated the catalytic asymmetric synthesis of chiral esters from disubstituted ketenes and allyl aryl ethers. We found that when a Pd(0) catalyst (2.5 mol%) and a chiral phosphine (5 mol%) was used as the catalytic system, to promote the reaction of disubstituted ketenes with allyl aryl ethers, that chiral aryl esters bearing an α -quaternary stereogenic center were formed in good to excellent yields (65-92%), with excellent regioselectivity, and with moderate to good enantioselectivity (up to 83% ee). Details of reaction optimization, substrate scope, reaction mechanism, including a rationale for regioselectivity and enantioselectivity, will be presented.

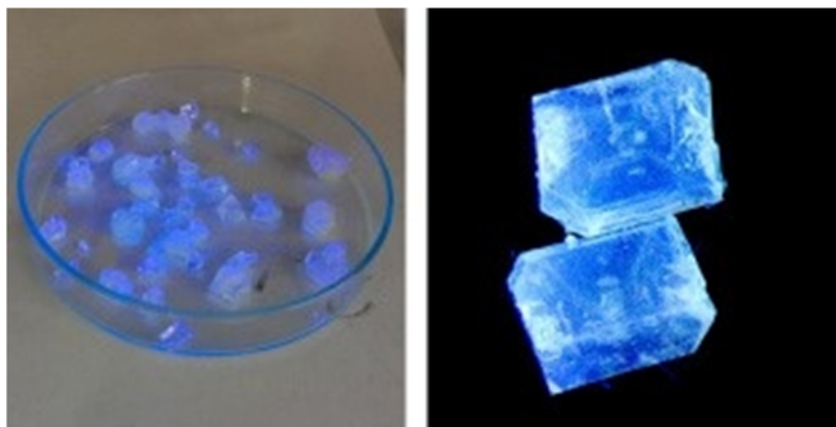
ORGN 118

Luminescent ionic materials toward neutron radiation sensors

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University of Strasbourg, Strasbourg, France (3) IPHC, University of Strasbourg, Strasbourg, France

Organic salts (functional ionic molecular liquids, FiMLs) in the liquid, liquid crystal, and crystalline states of matter incorporate ionic interactions that can counterbalance phase separation and even lead to molecular organizations that outperform traditional materials. Many FiMLs are ionic liquids at room temperature, display high thermal stability, offer easy synthetic purification routes, and exhibit a range of structural versatility by varying the side groups and counter anion. Despite growing interest in ionic materials properties based on imidazolium compounds, very little is known on systems which display luminescent behavior resulting from the organization in the liquid and crystal neat. One of the objectives of this project is to develop a new, solid material for the detection and identification of slow and fast neutrons. This work will focus on the design, optimization, and synthesis strategy for a series of solid, mesomorphic, and liquid ionic materials containing an imidazolium-fluorophore sub-unit to maximize quantum yield luminescence in the neat by preventing excimer formation via π - π interactions between fluorophore aromatic units. An improvement on traditional Ullman couplings using microwave assisted reactions allows easy gram scale access to *N*-substituted imidazole-based compounds without the need for solvent nor inert atmosphere. A subsequent nucleophilic substitution reaction with the imidazole compound and an alkyl halide will yield the FiML, whose transition temperature can be tuned through an anion metathesis reaction.

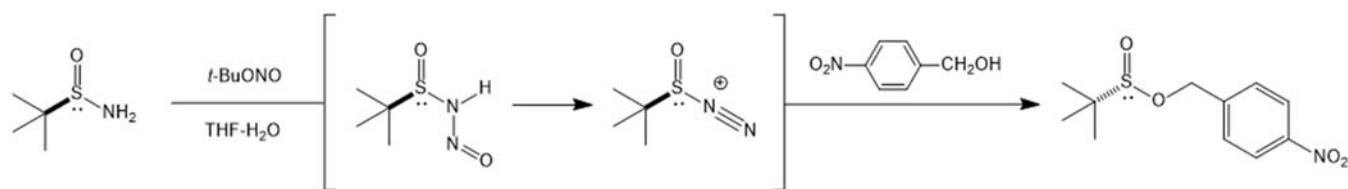


ORGN 119

Enantiomerically pure *tert*-butylsulfonamide as a template for synthesizing sulfinate esters and sulfonamides not accessible through direct alkylation

Jessica Shaw, jshaw@ilstu.edu. Chemistry, Illinois State University, Normal, Illinois, United States

This research is focused on the synthesis of chiral, non-racemic sulfinamides as organocatalysts for asymmetric reduction of imines and aldehydes. We seek to use *tert*-butylsulfinamide as a commercially available starting material that can be used to synthesize sulfinamides that would not be directly accessible through the alkylation or arylation of *tert*-butyl-sulfinamide. The first attempt at using (*R*)-*tert*-butylsulfinamide involved converting the amino group to a suitable leaving group via *N*-nitrosation using sodium nitrite combined with 3M hydrochloric acid. No product was observed under these conditions. It is proposed that the intermediate reacts too rapidly through a degradative mechanism that is independent of the presence of any nucleophile. In order to improve the reaction conditions to allow for the trapping of nucleophiles, *tert*-butyl nitrite was employed as the nitrosating agent. Using this reagent in combination with *p*-nitrobenzyl alcohol, the *p*-nitrobenzyl sulfinate ester was observed. This poster will feature the optimization of this transformation for the formation of enantiomerically enriched sulfinate esters via the *tert*-butyl nitrosation pathway.



ORGN 120

Discovery of an annulating reagent enabling the one-step and highly stereoselective synthesis of cyclopentanes

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The diastereoselective preparation of 5-membered carbocycles bearing three contiguous stereocenters using an unprecedented annulating reagent is described. The reagent reacts with a variety of Michael acceptors to forge cyclopentane rings in near total stereochemical control for one of the eight possible diastereomers. The ease of reaction setup, good yields, and high diastereoselectivity has enabled the application of this strategy toward the synthesis of biologically active compounds.

ORGN 121

Syntheses of pharmaceutically relevant *N*-heterocycles atropisomers via nucleophilic aromatic substitution

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Within this last decade, there has been a renewed interest in leveraging stable atropisomerism to synthesize more potent and selective *N*-heterocyclic pharmaceuticals. One unaddressed challenge is the narrowed scope of synthetic methodologies to directly access these important atropisomeric scaffolds on desired “gram-scale” quantities. Herein we report an atroposelective nucleophilic aromatic substitution towards a diverse range of these aforementioned compounds in optimal enantioselectivities and yields. With leaving groups such as a fluoride or chloride, we perform kinetic resolutions and dynamic kinetic resolutions using nucleophilic thiophenols. Twice oxidation to the sulfone can lead to a subsequent nucleophilic substitution to virtually any functionality that medicinal chemistry would be interested in (e.g. various amines, methoxy-groups). Examples of *N*-heterocycles we have directly functionalized with this chemistry include 3-aryl pyrrolopyrimidines (PPYs, a well-studied kinase inhibiting scaffold) and 3-aryl quinolines (which are found in many FDA-approved drugs and bioactive compounds). We have since synthesized several atropisomeric PPY inhibitors for our recent chemical biology efforts using this strategy, as well as currently investigating 3-aryl quinoline scaffolds in various bioactive compounds.

ORGN 122

Synthesis and characterization of *S*-camphorquinone derived quinoxalines and imines

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A common problem in organic chemistry is the resolution of enantiomers. Our approach involves the formation of diastereomeric imines of racemic aldehydes and ketones with a chiral amine. The resulting diastereomers may be separated by normal means, and the resolved imine hydrolyzed to produce the enantiomerically pure carbonyl compound (while also regenerating the chiral amine for future resolutions). Toward that goal, a chiral amine derived from the condensation and reduction of (*S*)-camphorquinone with 4-nitro-*o*-phenylenediamine was synthesized. Studies were undertaken to determine the optimal reaction conditions for imine formation. One such imine was synthesized and the x-ray structure was determined.

ORGN 123

Lewis acid carbocation catalyzed reduction of imines

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Amines are ubiquitous in nature and are found in amino acids, the building blocks of the cells molecular machinery. Strategies for imine reduction is highly researched topic in the field of organic chemistry. Here we propose to study the use of Lewis acid catalysts to form chiral amines, which have applications for the synthesis of pharmaceuticals and biologically relevant molecules, as well as potential uses in the context of materials, such as sensors. The goal of this research proposal is to investigate the use of carbocation catalysts such as triphenylcarbenium tetrafluoroborate in forming a chiral amine. The triphenylcarbenium acts as Lewis acid, binding to the nitrogen of the imine activating it for reduction with a hydride from Hantzsch ester forming a chiral center. The catalyst is then released producing a chiral amine and an oxidized Hantzsch pyridine. The preliminary results suggest that the reaction proceeds by Lewis acid carbocation catalysis. The most efficient carbocation so far is triphenylcarbenium tetrafluoroborate. The reaction with the highest yield in the presence of the proton sponge was achieved using trityl tetrafluoroborate as the carbocation (TR1, Figure 1), DCE as the solvent at 82 °C. This reaction was able to yield 72% of amine (table 1). The purpose of the proton sponge (2,6-Di-*tert*-butyl-4-methylpyridine) is to prevent catalysis of the imine by any potential adventitious Brønsted acid formed during the reaction. In the future, we will investigate the use of various imines and hydride sources to optimize the yield of reaction. Additionally, we will investigate the use of carbocations that contain a counterion in order to produce enantioenriched amines.

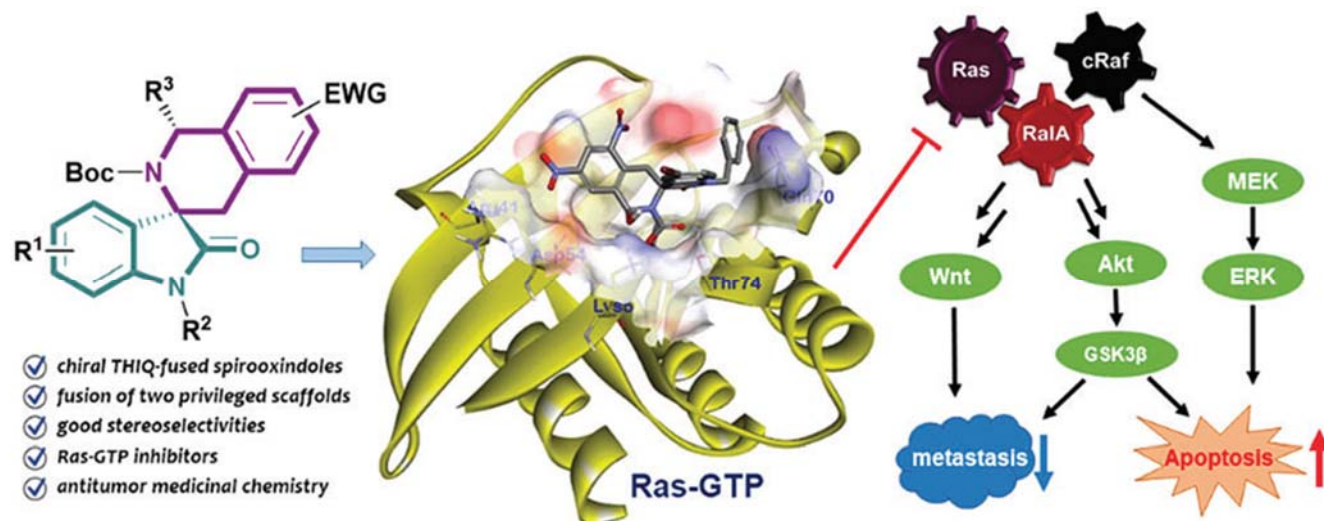
ORGN 124

Organocatalytic mannich-hemiaminalization cascade strategy for the asymmetric synthesis of spirooxindole tetrahydroisoquinoline derivatives as novel Ras-GTP inhibitors

Qian Zhao, *zhaoq584@sina.cn*, *Xiang-Hong He*, *Bo Han*, *Cheng Peng*. State Key Laboratory of Southwestern Chinese Medicine Resources, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Tetrahydroisoquinoline (THIQ) is a privileged scaffold with wide range of pharmacological activities, which are also existed in many natural alkaloids. For instance, the families of naphthyridinomycin, saframycin, quinocarcin and compound (+)-crispine A, noscapine possess remarkable antitumor activities. The fact that Trabectedin has even been licensed by the European Medicines Agency for the treatment of soft tissue sarcoma. For these reasons, the development of reliable synthetic approaches to synthesize THIQ derivatives become an extremely attractive area. Another attractive synthetic target is the C3-spirooxindole framework, which shows intriguing bioactivities, including antitumor effects. Previous studies have established a series of effective methods for the enantioselective synthesis of N-containing heterocycles fused spirooxindole. However, the combination of C3-

spirooxindoles and the antitumor THIQ skeleton has rarely been reported. Herein, we developed an organocatalytic Mannich/hemiaminalization cascade reaction for the construction of chiral THIQ-fused spirooxindoles, which hybridize two privileged scaffolds in antitumor natural products. Some of them can inhibit the proliferation and invasion of colon adenocarcinoma cells. Mechanistic studies demonstrated the most efficient compound, 3m, inhibits the activation of Ras-GTP, ultimately initiating mitochondrial apoptosis.



ORGN 125

Asymmetric synthesis of naturally occurring homoisoflavonoids having either 5,6,7- or 5,7,8-trisubstituted groups and their biological evaluation for antiangiogenic activity

Sang-Il Kwon, San-ha Lee, **Seung-Yong Seo**, syseo@gachon.ac.kr. College of Pharmacy, Gachon University, Incheon, Korea (the Republic of)

Naturally occurring homoisoflavonoids containing either 5,6,7- or 5,7,8-trisubstituted groups such as the antiangiogenic homoisoflavanone, cremastranone, were synthesized via three or four linear steps from the known 4-chromenone. This facile synthesis includes chemoselective 1,4-reduction of 4-chromenone and selective deprotection of 3-benzylidene-4-chromanone containing a C7-benzyloxy group. For the asymmetric synthesis of homoisoflavonoids, asymmetric transfer hydrogenation by Noyori's Ru-catalyst and TPAP oxidation were used. The synthetic homoisoflavonoids were evaluated for their antiproliferative activity against human retinal microvascular endothelial cells and human umbilical vein endothelial cells.

ORGN 126

Hydrogen-bonding effect directed stereodivergent synthesis of lactams bearing vicinal tertiary and fluorine-containing quaternary stereogenic centers via sequential approach

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The stereoselective construction of fluorine-containing quaternary center is a synthetically challenging task. We reported a novel stereodivergent synthesis of fluorinated lactams bearing vicinal C-F quaternary and tertiary center via sequential approach. A facile solvent changing under mild condition induced fluorine stereoselective switching was directed by hydrogen-bonding effect, both syn- and anti-diastereomers were obtained in excellent results (dr >20:1 and ee >99%). The mechanism of desymmetrization process on fluorine-containing quaternary center was elucidated via DFT calculation. The usefulness of the fluorinated lactam synthon was proved by total synthesis of natural product analogues and fluorinated central nervous system drug study.

ORGN 127

Towards cobalt catalyzed C-H activation with thio heterocycles

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Herein we will describe the method for the cobalt catalyzed C-H activation with thio heterocycles.

ORGN 128

Direct comparison of fluorination methods for the functionalization of biologically relevant molecules

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In 2018, about 50% of the FDA approved small-molecule drugs contained at least one fluorine atom, as the incorporation of a fluorine atom impacts many properties, including biological potency and metabolic stability. These drugs are mainly constructed from simpler fluorinated building blocks because their late-stage functionalization has proven to be difficult with common fluorination methods. Here we evaluated a variety of different C(sp³)-H fluorination reactions to directly compare their selectivity and

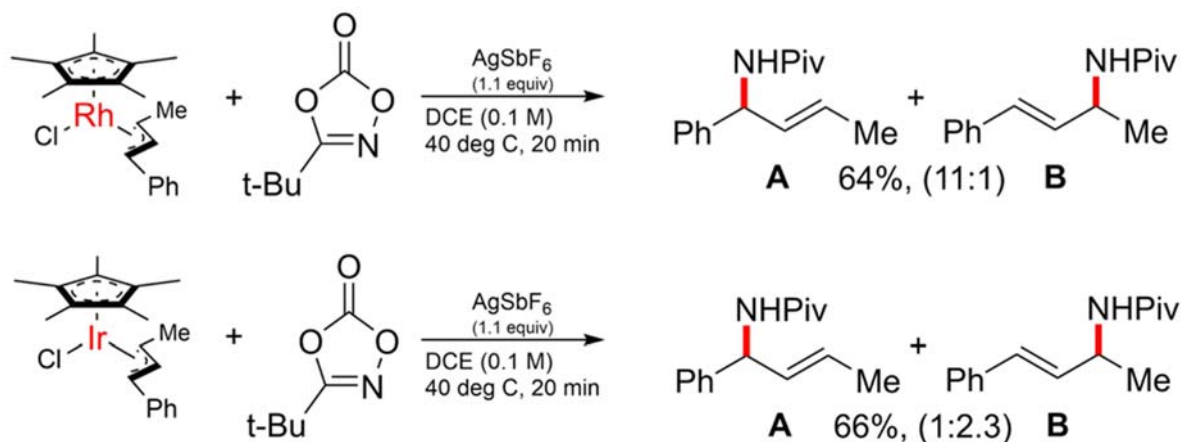
reactivity towards biologically relevant scaffolds. Common motifs in pharmaceuticals such as benzylic substrates, heterocycles such as pyridines and furans, and aliphatic amines were assessed. Our results have shown significant differences in reactivity and selectivity, even though these methods have been proposed to proceed via a similar mechanism.

ORGN 129

Differential regioselectivity profiles of rhodium(III) and iridium(III) catalysts in allylic C-H amidation

Thomas Kowal-Safron^{1,2}, tjkowal@emory.edu, **Jiyong Park**², **Joonghee Won**², **Bohyun Park**², **Jacob Burman**¹, **Simon Blakey**¹, **Mu-Hyun Baik**². (1) Chemistry, Emory University, Atlanta, Georgia, United States (2) Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Korea (the Republic of)

Experimental observations of the allylic C-H amidation of 1-phenyl-1-butene have demonstrated that Rh(III)Cp* catalysts induce marked regioselectivity for amidation to occur at the benzylic position following the formation of a pi-allyl complex. Complementary observations utilizing an Ir(III)Cp* catalyst have demonstrated slightly less pronounced regioselectivity for the other terminal carbon of the transient pi-allyl intermediate. In this computational study, complete energy profiles have been developed for both the Rh(III)Cp*- and Ir(III)Cp*-catalyzed C-H amidation of 1-phenyl-1-butene with tert-butyl dioxazolone, which reveal that the differential regioselectivities are determined due to a significant energy difference in the removal of carbon dioxide to form the metal-nitrene intermediate between the rhodium and iridium catalysts. The exact reason for this energy difference between the two isoelectronic metal centers is the subject of ongoing investigation.



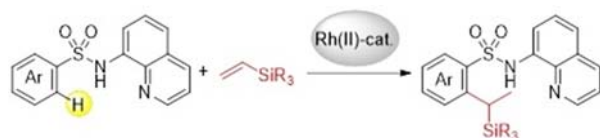
Recently published experimentally observed regioselectivity differences between the rhodium and iridium catalysts.

ORGN 130

Rhodium(II)-catalyzed branch-selective C-H alkylation of benzenesulfonamide derivatives with vinylsilanes

Supriya Rej, supriyo.rej@gmail.com, **Naoto Chatani**, chatani@chem.eng.osaka-u.ac.jp. Department of Applied Chemistry, Osaka University, Mino-shi, Osaka, Japan

The transition metal catalyzed directed C-H activation strategy is one of the most straightforward and site-selective approaches in organic chemistry for constructing C-C bonds. In particular, directed C-H alkylations with alkenes provides an atom economic protocol for forming the C-C bond. In 1993, Murai reported a ketone-directed strategy for the Ru-catalyzed *ortho*-C-H alkylation of aromatic ketones with alkenes. Following this pioneering reaction, numerous directing groups have been designed for use in regio-selective C-H alkylation reactions. It is noteworthy that most of the reports deal with linear-selective alkylation reactions. However, only a limited number of studies that deal with branch-selective C-H alkylation with alkenes have been reported. In this respect, all of these branch-selective alkylation reactions were achieved using styrenes, acrylate esters, vinyl ethers, and unactivated 1-alkenes. Nonetheless, branch-selective alkylation with vinylsilanes has not been achieved to date, although the linear selective alkylation with vinylsilanes with the aid of a directing group strategy have been widely explored. Given our long term interest in bidentate-chelation assisted Rh-catalyzed C-H alkylation reactions, herein we report an unusual Rh(II)-catalyzed branch-selective *ortho*-C-H alkylation of biologically important aryl sulfonamides with vinylsilanes by taking the advantage of an 8-aminoquinoline auxiliary. Moreover, deuterium labelling experiments provided insights into the reaction mechanism, in which involvement of two parallel catalytic pathways such as hydrometalation and carbometalation pathways are anticipated.



ORGN 131

Cascade C–H arylation/lactamization of benzylamines enabled by a transient directing group strategy

Pratibha K. Chand Thakuri, pchandt@rockets.utoledo.edu, **Vinod G. Landge**, **Mohit Kapoor**, **Michael C. Young**. chemistry and biochemistry, University of Toledo, Toledo, Ohio, United States

Amines are an important class of compound, yet their use as substrates in C–H activation has been hindered by the need to convert them into a better directing group. As a result, the development of cheap, easily available, and industrial friendly directing groups is still in demand. Our group has pioneered an approach using carbon dioxide as an inexpensive, catalytic, and transient directing group to allow the arylation of various amine substrates. Recently this methodology has been used to demonstrate a straightforward route to the synthesis of seven-membered lactams via directed C–H activation of a primary amine followed by subsequent cyclization with the newly installed functional group.

ORGN 132

Palladium–catalyzed gamma–arylation of allylamines using dry ice

Vinod G. Landge¹, vinodglandge@gmail.com, **Justin M. Maxwell**², **Pratibha K. Chand Thakuri**², **Mohit Kapoor**², **Evan Diemler**³, **Michael C. Young**². (1) The university of toledo, Toledo, Ohio, United States (2) chemistry and biochemistry, University of Toledo, Toledo, Ohio, United States (3) University of Toledo, Toledo, Ohio, United States

Allylamines are synthetically valuable and ubiquitous in various biologically active classes of compounds. The C–H activation of amines is very challenging because of complications with the coordination of the amine, including beta–hydride elimination and substrate decomposition in the presence of transition metal catalysts. Various approaches have been developed to functionalize the gamma position of primary amines using stoichiometric directing groups and specific ligands that do not offer step economy. Although transient directing groups have been developed to improve step economy, they only work with primary, and not secondary, amine substrates. Meanwhile, there are many challenges with performing C–H activation on allyl groups, including their increased sensitivity to hydrofunctionalization or difunctionalization (especially in the presence of Pd catalysts), as well as the regio and site–selectivity issues because of various accessible C–H bonds. This study describes carbon dioxide in the form of dry ice, as a transient directing group to selectively functionalize gamma C–H bonds of primary and secondary allylamines using a palladium catalyst.

ORGN 133

Protocol for the *ortho*-deuteration of acidic aromatic compounds in D₂O catalyzed by cationic Rh^{III}

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Current methods to exchange a hydrogen for a deuterium atom (H/D exchange) *ortho* to a carboxylic acid group of benzoic acid, require high catalyst loadings and additives to work. We have developed a method that uses D₂O as both as the solvent and deuterium source, while most current methods use D₂ gas as the deuterium source. We

have also been able to accomplish H/D exchange using low catalytic amounts of cationic Rh^{III} and with addition of only sodium acetate as a base (except in the few cases where the substrate is insoluble in D₂O and a co-solvent is necessary for H/D exchange to occur). We have been able to demonstrate the effectiveness of our developed method on a variety of carboxylic acid substrates.

ORGN 134

Exploration of new avenues for development of dirhodium catalysts for asymmetric C-H functionalization reactions

Jiantao Fu, *jfu38@emory.edu*, **Zachary Garlets**, **Zhi Ren**, **Huw M. Davies**. Department of Chemistry, Emory University, Atlanta, Georgia, United States

Rhodium-catalyzed C-H functionalization reactions via carbene insertion have been shown to be capable of achieving high site- and stereoselectivities. Previous work shows that Rh₂(S-TPPTLL)₄ is an exceptional catalyst for selective functionalization of substituted alkyl cyclohexanes through a desymmetrization reaction, and the observed selectivities are hypothesized to be imparted from the unique arrangement of the phenyl groups that surround the periphery of the catalyst. Through further development of a series of related dirhodium catalyst we provide new experimental results to corroborate this hypothesis and show that the desymmetrization reaction can be extended to more challenging substrates. These new results further highlight the synthetic potential of the catalysts.

ORGN 135

Heterogeneous palladium-catalyzed oxidative benzylation via benzylic C(sp³)-H activation

Prakash Basnet, *pbasnet@sas.upenn.edu*, **Charles E. Hendrick**, **Peter A. Amadeo**, **Marisa Kozlowski**. Chemistry, University Of Pennsylvania, Philadelphia, Pennsylvania, United States

Cross dehydrogenative coupling is a powerful means to form carbon-carbon bonds. This transformation avoids the use of pre-functionalized starting materials like organometallic reagents and organic halides contributing to overall efficiency. However, these reactions are predominantly catalyzed by homogeneous catalysts. Herein, we describe a novel benzylation of sterically challenging tertiary carbon centers with a heterogeneous palladium catalyst and readily available toluene derivatives. The reaction condition can be applied to various substrates ranges from azlactone to fluorene with good to excellent yields. Mechanism studies suggest that the reaction is catalyzed by heterogeneous palladium particles rather than Pd(OAc)₂ inputs, which was confirmed by activity with commercially available Pd/C. Pd/C provided several advantages in terms of substrate scope and provides motifs that are found in various agrochemicals, materials and drug molecules. Furthermore, a detailed mechanistic

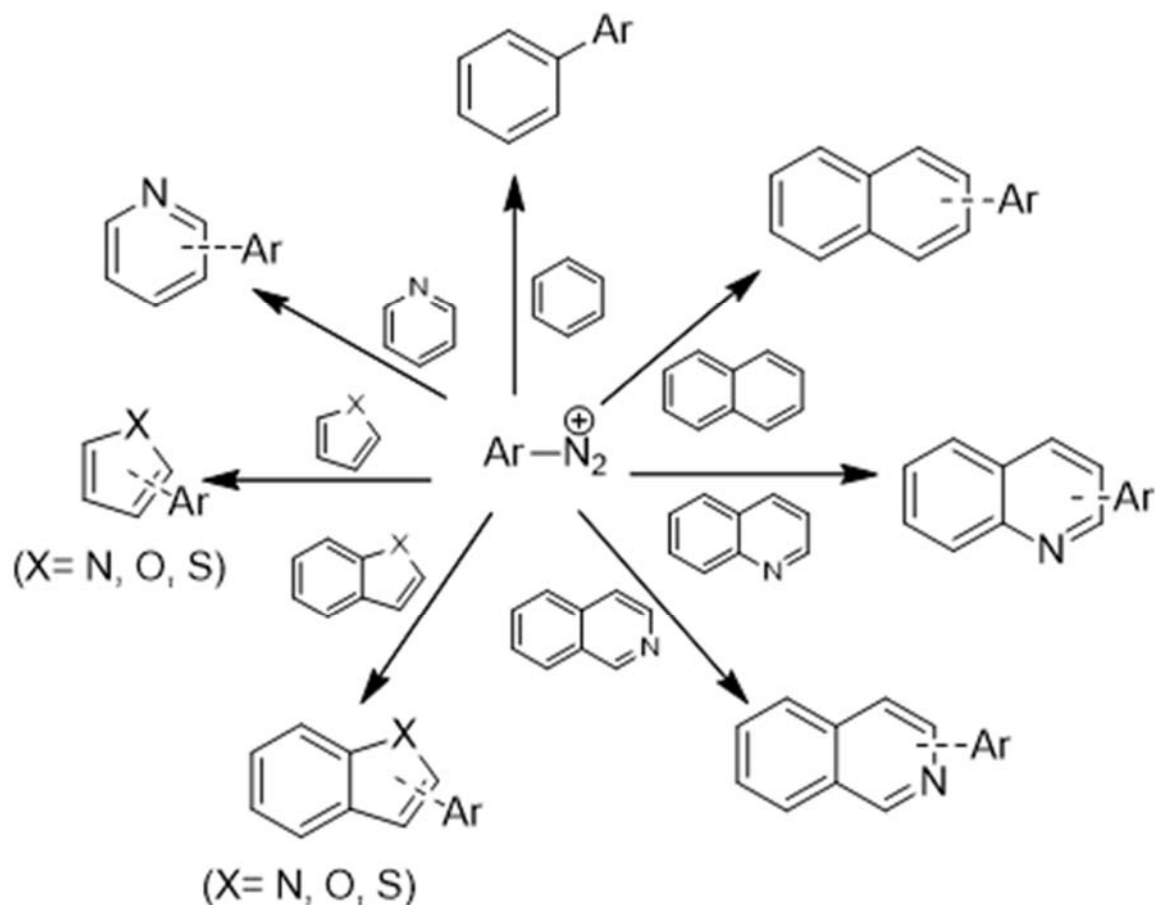
study reveals a framework to allow the discovery of other new transformations with heterogeneous catalysts.

ORGN 136

Environmentally benign solid acid-catalyzed coupling of diazonium salts with aromatic hydrocarbons and heterocycles for the syntheses of biaryls and heterobiaryls

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Biaryls and heterobiaryls are an important class of aromatic and heterocyclic compounds due to their diverse presence in natural products, pharmaceuticals, agrochemicals, ligands, polymers and organic materials. A new heterogeneous catalytic diazotization and subsequent coupling of diazonium salts with aromatics hydrocarbons and heterocycles for the synthesis of biaryls and heterobiaryls has been developed. This reaction involves *in situ* K-10 montmorillonite-catalyzed diazotization and subsequent C–C bond formation by the nucleophiles. The establishment and optimization of the approach for the direct synthesis of biaryls and heterobiaryls will be discussed. The synthetic route features the activity of diazonium salt at high temperature which becomes a partial C-electrophile and upon the nucleophilic attack a N₂ molecule leaves the system and a C–C bond is formed. Thus, the reaction is suggested to be of Friedel-Crafts nature from the nucleophile's point of view. This synthetic route provides a wide substrate scope with high yields and selectivities. As in this reaction no harmful products are generated, catalyst is recyclable and product isolation entails simple extraction and evaporation, this method also comply with green chemistry principles. The widespread industrial (pharmaceuticals, agrochemicals, and materials) interest in the target compounds this new process could significantly decrease the environmental impact of traditional syntheses of biaryls and heterobiaryls.



Syntheses of biaryl and heterobiaryls from aryl diazonium salts using solid acid-catalyzed method

ORGN 137

Efforts toward the total synthesis of trocheliophorolide A: Assessing a cadre of hydroboration techniques to afford a viable coupling partner

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Trocheliophorolide A is a natural product isolated from soft coral found in the Gulf of Aqaba in the Red Sea. This compound is of interest due to its antimicrobial effects and the structure of its unsaturated side chain. Our convergent route focuses on constructing the novel unsaturated side chain and coupling it via a Suzuki cross-coupling to a vinyl borane moiety. This presentation will address progress made toward the formation of the chiral vinyl borane and the challenges faced with the various hydroboration protocols.

ORGN 138

Cu₂O nanoparticles catalyzed C-N coupling of tetrazolones with boronic acids

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N-arylated heterocycles are widely found in pharmaceuticals, agrochemicals and functional materials. As a result, significant efforts have been dedicated to the development of efficient and versatile methods for N-arylation. Many of these C-N couplings involve palladium, nickel and copper-based catalysts. However, these are stymied by the need to require stoichiometric amount of the base, high reaction temperatures and harsh reaction conditions. Han and coworkers reported a green and atom-economical aerobic oxidation of tetrazoles with a variety of hetero(aryl) boronates in presence of catalytic Cu₂O in DMSO at 100°C. This coupling reaction occurs in the absence of any organic bases or ligands. In this study, we wish to investigate if this protocol can be extended for the N-arylation of other heterocycles utilizing Cu₂O nanoparticles. Briefly, phenyl isocyanate was reacted with trimethylsilyl azide via 1,3-dipolar cycloaddition to obtain phenyl tetrazolone. The latter was subjected to aerobic oxidation with aryl boronic acids in the presence of Cu₂O nanoparticles to obtain 1,4-diaryl tetrazolones. Different sizes of Cu₂O nanoparticles were prepared via low-temperature hydrothermal approaches to evaluate the size-dependent catalytic activity for this C-N coupling reaction. As expected, the N-arylation with nanoparticles proceeds faster and in higher yields compared to the amorphous catalyst. Currently, the substrate scope of this reaction is being investigated.

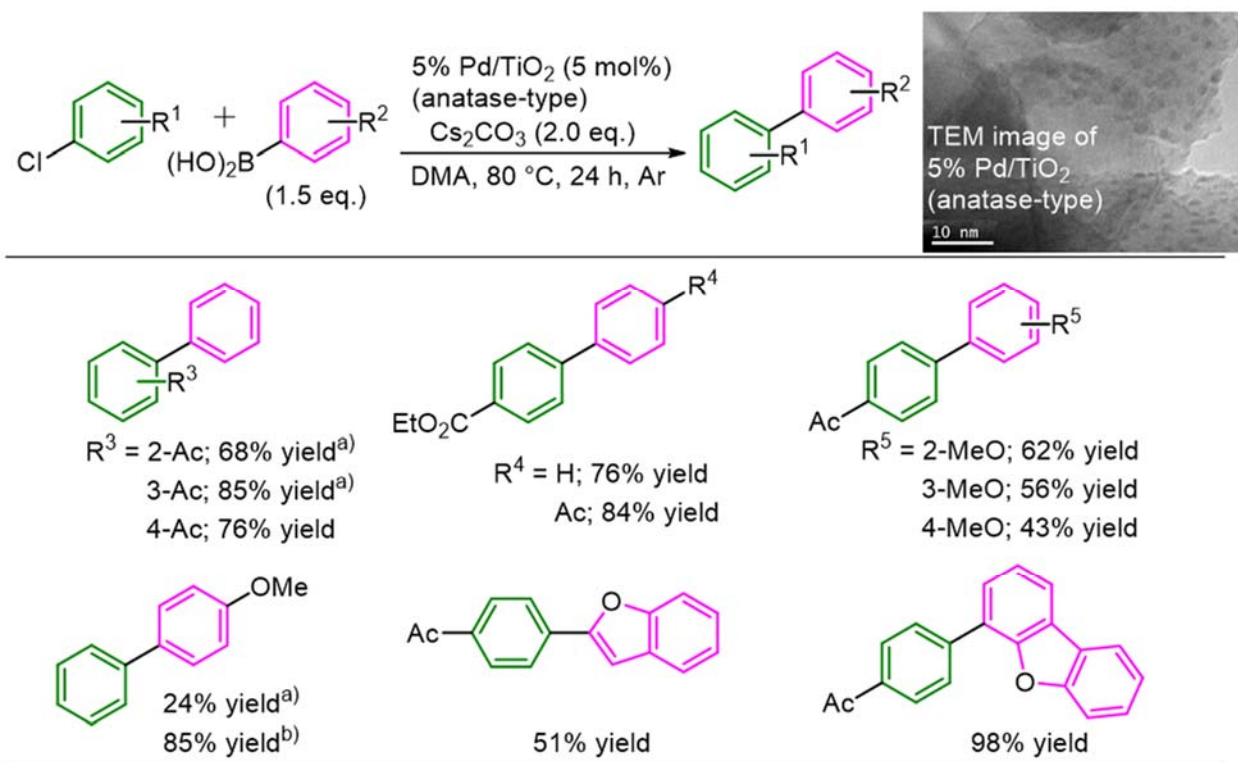
ORGN 139

Development of titanium oxide-supported palladium catalysts and evaluation of the catalyst activities for ligand-free Suzuki–Miyaura coupling using aryl chlorides

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Palladium (Pd)-catalyzed Suzuki–Miyaura coupling reaction of aryl halides and aryl boronic acid derivatives is one of the most useful synthetic methods for constructing biaryl derivatives as fundamental skeletons of various pharmaceuticals and functional materials. Heterogeneous Pd-catalyzed ligand-free Suzuki–Miyaura coupling reactions have attracted attention as environmentally friendly and metal-contamination-free (or low) methods. Aryl chlorides, which are readily available and less expensive organic compounds in comparison to aryl iodides and bromides, are preferred substrates for the Suzuki–Miyaura coupling reaction, although special ingenuity is necessary for activation

of the low-reactive carbon-chloride bond. We have prepared the anatase-, rutile- and brookite-type TiO₂-supported Pd catalysts and studied the physical properties of these catalysts by the use of X-ray photoelectron spectroscopy (XPS) and transmission electron microscopy (TEM). Furthermore, the effect on the catalyst activities depending on the crystal form of TiO₂ to the TiO₂-supported Pd-catalyzed Suzuki–Miyaura coupling reaction was investigated. Consequently, the anatase-type TiO₂-supported Pd catalyst was found to have an efficient catalyst activity toward the ligand-free Suzuki–Miyaura coupling reaction of aromatic chlorides due to the highly distributed small Pd nanoparticles (1–2 nm) on the anatase-type TiO₂.



^{a)} ArB(OH)₂ (2.0 eq.), 10 mol% of 5% Pd/TiO₂, and Cs₂CO₃ (3.0 eq.) were used.

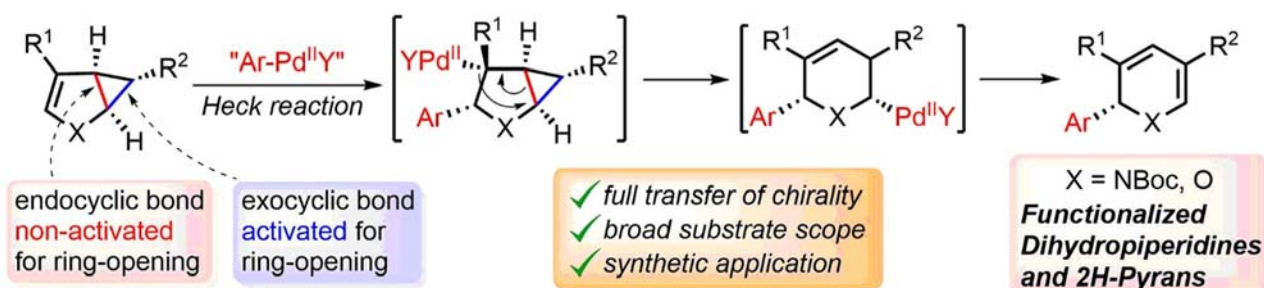
^{b)} 4-Bromoanisole was used instead of 4-chloroanisole.

ORGN 140

Regio- and stereoselective synthesis of functionalized dihydropyridines, pyridines, and 2H-pyrans: Heck coupling of monocyclopropanated heterocycles

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Here we would like to report a palladium-catalyzed coupling between monocyclopropanated pyrroles or furans and aryl halides or aryl boronic acids giving the corresponding six-membered *N*- and *O*-heterocycles. Key step of this transformation constitutes the selective cleavage of the non-activated, endocyclic C-C bond of the 2-heterobicyclo-[3.1.0]hexane framework triggered by a palladium chain walk. This protocol grants access to highly substituted piperidines and 2*H*-pyrans, that are challenging to synthesize by traditional methods. Furthermore, the synthetic application of the products was showcased by numerous transformations including the synthesis of a nipecotic acid derivative.



ORGN 141

Deaminative vinylation of pyridinium ions

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In the effort to identify new feedstocks for transition metal-catalyzed cross-couplings, we have been attracted to the use of alkyl amine derivatives. Amines are widely available, easily purified, and can be carried through multi-step sequences in protected form. Thus, they offer opportunities in late-stage functionalization and serving as simple building blocks. We and others have previously shown that benzylic amines can be used in nickel-catalyzed cross-couplings with aryl and vinyl boronic acids via conversion to trimethylammonium triflates. However, preparation of ammonium triflate is not compatible with the presence of other basic nitrogen atoms in the benzylic amine substrate, which limits the use of this chemistry to prepare heteroaryl-substituted products. Based on our recently developed strategy for C-N bond activation via the one-step conversion of alkyl amines into Katritzky pyridinium salts, we have developed cross-couplings of benzylic pyridinium salts with aryl and vinylboronic acids or esters. Via these benzylic pyridinium intermediates, benzylic amines can be engaged in these

cross-couplings via C-N bond functionalization. With the mild reaction conditions, heteroaryl substituents and a range of functional groups are well tolerated.

ORGN 142

Deaminative cross couplings of the side chain of lysine and its derivatives to synthesize unnatural amino acids

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Until recently, alkyl amine derivatives have been an underutilized substrate class in alkyl cross-couplings despite their ubiquity. We describe a method for the generation of unnatural amino acids from lysine, ornithine, and other derivatives via a deaminative reductive arylation of Katritzky pyridinium salts. This method enjoys high functional group tolerance, allowing for a wide variety of heteroaryl and aryl bromides to be incorporated.

ORGN 143

Deaminative reductive methylation of alkylpyridinium salts

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Alkyl amines are highly versatile, widely abundant feedstock chemicals. The ease with which they can be carried throughout multistep syntheses make them a highly sought-after candidate for further functionalization. Our group has discovered a powerful transformation of alkyl amines via activation of the carbon–nitrogen (C–N) bond to form mainly C(sp³)–C(sp²) bonds. Due to the high degree of saturated carbon–carbon bonds in bioactive molecules, we also recently developed a nickel-catalyzed cross-coupling of Katritzky alkylpyridinium salts and alkylzinc halides to create new C(sp³)–C(sp³) bonds. We now report a reductive cross-coupling utilizing alkylpyridinium salts and a simple methylating agent. The optimization, scope and mechanistic understanding will be presented.

ORGN 144

New methodology to controlling regioselectivity utilizing a copper-catalyzed boracarboxylation

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A methodology to achieve copper-catalyzed regioselective boracarboxylation of vinyl arenes has been reported by the Popp group. This transformation uses the cheap, abundant C1 feedstock of carbon dioxide to access highly functionalized α -aryl carboxylic acid derivatives. Expansion of boracarboxylation to vinyl indole, benzofuran, and benzothiophene substrates has been achieved to provide interesting organic moieties. The derivatization of the boron atom through Suzuki cross-coupling has led to a new method to synthesize 2,3-diarylpropionic acids, which find prevalence in pharmaceuticals. While other routes typically rely on the sterics and electronics of the aryl substituents, this new route allows for control of the regioselectivity of the carboxylic acid.

ORGN 145

Optimization of a Negishi cross-coupling reaction for the synthesis of β,β -disubstituted ketones

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Optimization of a palladium-catalyzed Negishi cross-coupling reaction between an α,β -unsaturated carbonyl with a β -leaving group and a monoorganozinc was performed to form a new carbon-carbon bond at the beta position. α,β -Unsaturated carbonyls are useful in the synthesis of natural products and pharmaceuticals and can be used as precursors to all-carbon quaternary stereocenters. Various metal catalyst and ligand combinations were screened in order to determine the optimized conditions. The catalyst loading ligand ratio was also investigated. Bulky, electron-rich phosphine ligands seem to block undesirable pathways, allowing for higher yields and efficiency. Further work includes examination of substrate scope with the current optimized conditions through varying both the organozinc and the α,β -unsaturated carbonyl.

ORGN 146

Toward an optimized copper-catalyzed sequential addition with functionalized monoorganozinc reagents

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α,β -unsaturated ketones (enones) represent an important motif in organic synthesis, with distinct chemical activity and reactivity patterns. Using functionalized

monoorganozinc reagents in concert with a copper(I) catalyst a cross-coupling type reaction at the beta position of a haloenone followed by a 1,4-conjugate addition could be accomplished. Optimization efforts focused on the addition of lithium halide salts, thought to increase the reactivity of organozinc reagents. In addition to overall reaction improvements, specifically, this enabled the use of an initial bromoenone substrate rather than the more facile coupling substrate, iodoenone. This was essential in order to remove iodide from the system which had been shown to inhibit the subsequent conjugate addition. Ultimately, this sequential addition results in a saturated sp^3 stereocenter at the beta position with two new functional groups. Initial work was motivated to access core sesquiterpene structures, specifically natural products like (+)- β -eudesmol. This reaction sequence could see wide scope based on overall reaction tolerance to different functionalities, providing access to a desirable set of products with a new chiral center.

ORGN 147

Synthesis of ammonium organotetrafluorosilicates from trialkoxysilanes

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Alkoxysilanes are powerful reagents and coupling partners, however they tend to suffer from low reactivity and poor benchtop stability. This has also been a problem that plagued organoboranes, however, organoboranes can be easily converted to organotrifluoroborate salts which are highly reactive and benchtop stable. Surprisingly, the analogous synthesis of organotetrafluorosilicates has not been developed, even though such a transformation should impart the same improvements in both stability and reactivity. Here, we present an accessible synthesis of ammonium organotetrafluorosilicates from trialkoxysilanes. The pentacoordinate tetrafluorosilicate should exhibit significantly different reactivity compared to neutral, tetracoordinate silanes. The optimization of the reaction, as well as the substrate scope will be discussed. Additionally, preliminary investigations into new transformations with tetrafluorosilicates will also be discussed.

ORGN 148

Nickel-catalyzed cross-coupling of ammonium organotetrafluorosilicates

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Coupling reactions are incredibly important transformations in organic synthesis, both in research and in medicinal chemistry. Current best coupling reactions, like Suzuki couplings and Sonogoshira couplings, are limited by their use of a Pd catalyst, which is costly and tends to perform poorly with sp^3 coupling partners. However, in over 30 years of research no reactions have been able to dethrone Suzuki couplings, or even Pd-

catalyzed couplings in general. Within the last 10 years, first row transition metal catalysts have become attractive alternatives to traditional Pd-catalyzed couplings, but currently none are as robust as the Suzuki. This reality suggests that a fundamentally new reaction must be developed if the limits of current couplings are to be overcome. In this respect, organotetrafluorosilicates show promise as a new coupling partner. Initial results show that tetrafluorosilicates will couple with a halogenated electrophile in the presence of a Ni catalyst, leaving behind non-toxic and easily removable byproducts. Optimization and substrate scope of this new transformation will be discussed.

ORGN 149

Synthesis of allenes using the alkynyl-Heck reaction

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The Heck reaction is one of the most synthetically versatile cross-coupling reactions used in both academia and industry. There have been various transformations and extensions to the Heck reaction including the heteroatomic-Heck, oxidative Heck, and decarboxylative Heck reactions. While all these extensions have led to different olefins as products, there has been little exploration using alkynes as the coupling partner. By substituting an alkyne for an olefin, the resulting products would be substituted allenes. This led to the discovery and development of the alkynyl-Heck reaction. In 2018, our group published the cationic alkynyl-Heck reaction using aryl triflates to access allenes. Since then, our group has been exploring the use of various starting materials to synthesize various functionalized allenes. The increasing synthetic utility of allenes in organic synthesis combined with their incorporation into a growing list of natural products and active pharmaceutical ingredients has stimulated an intense effort recently to identify efficient catalytic methods for their synthesis. Here, we wish to report the methodology that our lab has been investigating in order to synthesize allenes using the alkynyl-Heck reaction.

ORGN 150

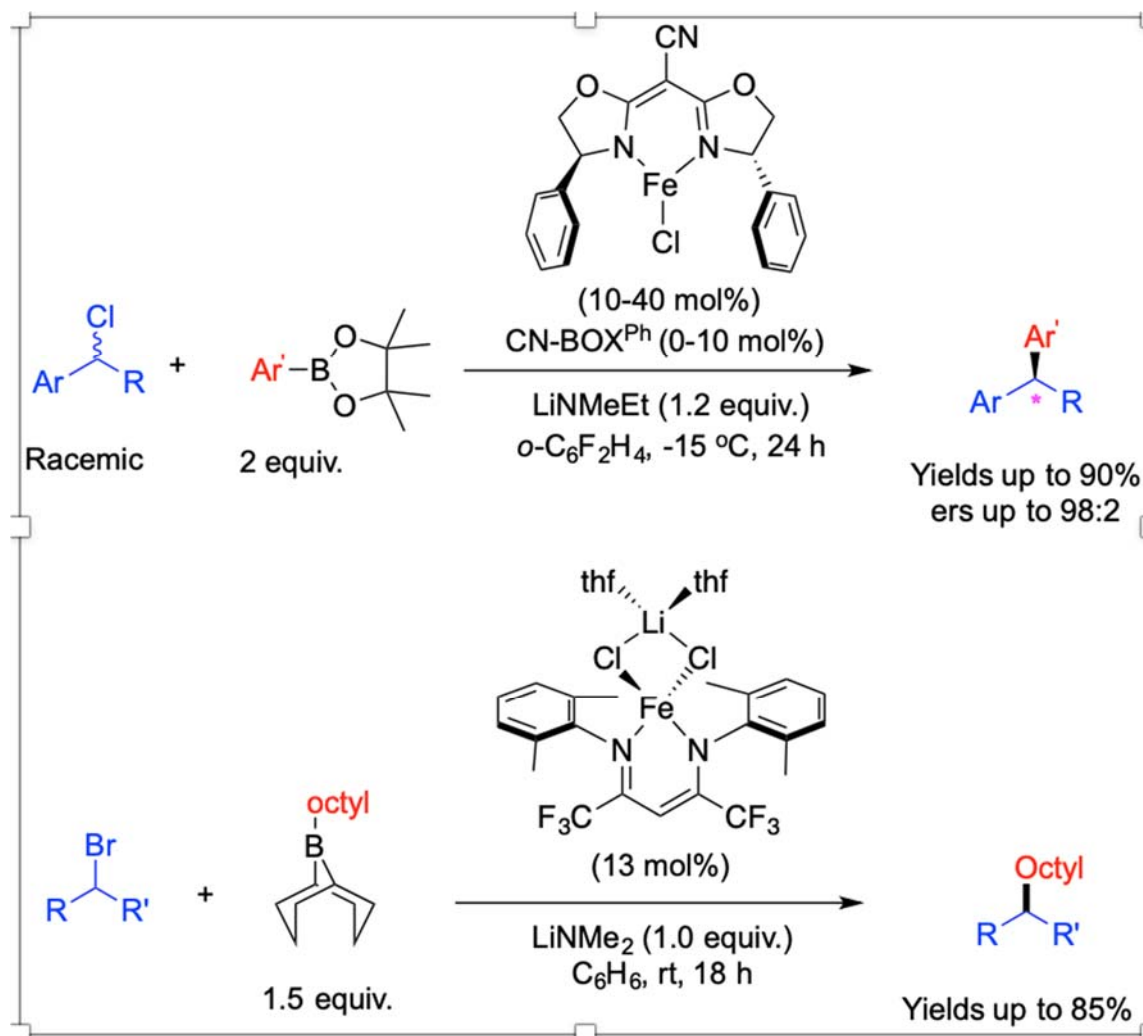
Iron-based catalysts for Suzuki-Miyaura cross-coupling reactions involving alkyl electrophiles

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Alkyl electrophiles are valuable reagents for cross-coupling, leading to more complex, three-dimensional molecules. One attractive area of research using alkyl electrophiles is the synthesis of chiral 1,1-diarylethanes which are common motifs in many natural products and pharmaceuticals. Herein, the first enantioselective Suzuki-Miyaura cross-coupling reaction catalyzed by iron-based complexes between benzylic chlorides and

unactivated arylboronic pinacol esters was developed to prepare enantioenriched 1,1-diarylalkanes. The use of a cyanobis(oxazoline) ligand framework and 1,3,5-trimethoxybenzene additive were essential to afford good yields and high enantioselectivities. Mechanistic investigations implicate a stereoconvergent pathway involving carbon-centered radical intermediates.

Another highly anticipated area of research using alkyl electrophiles is alkyl-alkyl cross-coupling which remains a difficult transformation, particularly with iron, due to competing β -hydride elimination. An investigation into alkyl-alkyl cross coupling between primary, secondary and tertiary alkyl bromides and alkyl 9-BBN reagents using a beta-diketiminate iron complex will be discussed.

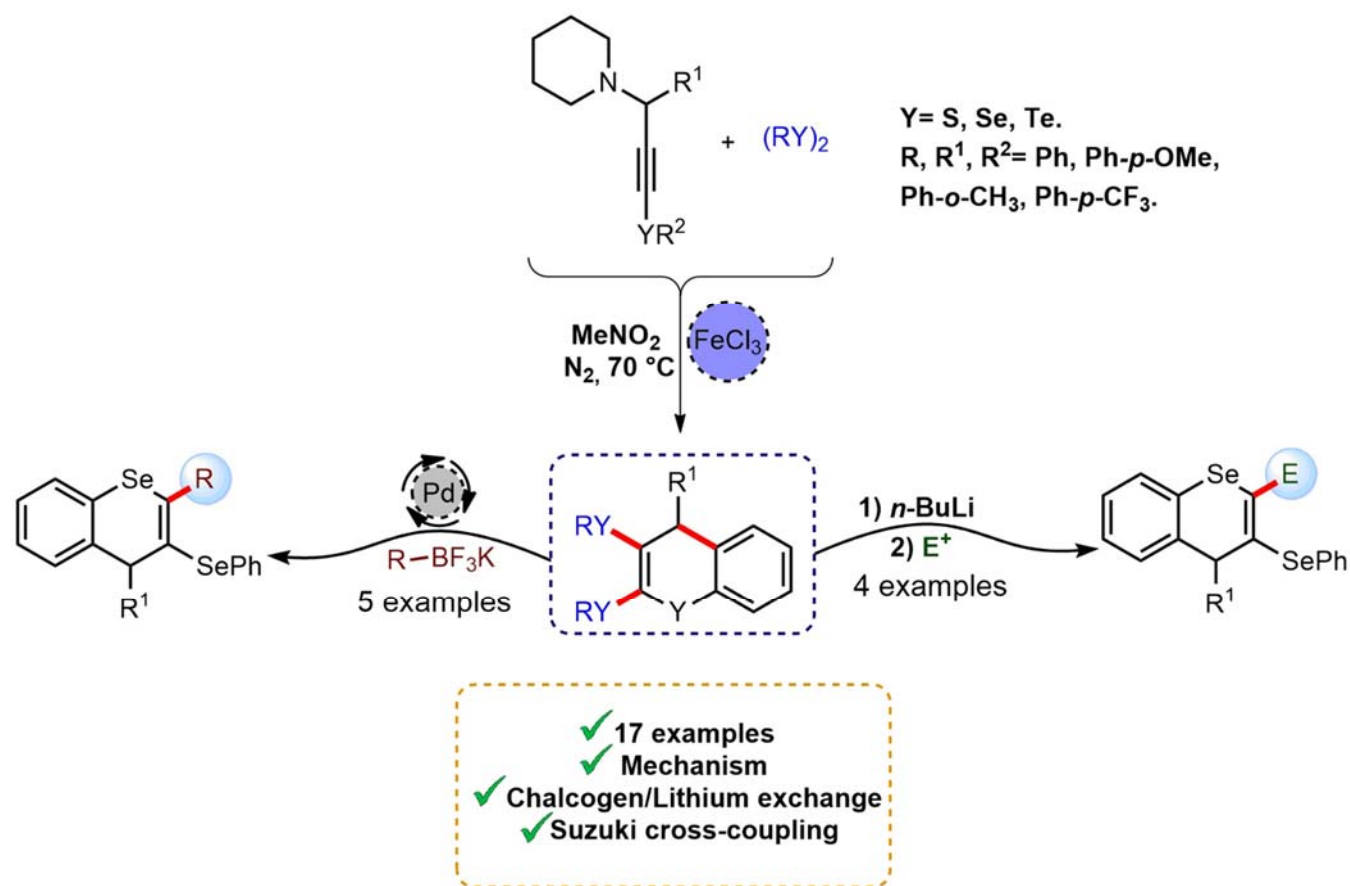


Synthesis of substituted 4*H*-chalcogenochromenes promoted by iron(III) and diaryl dichalcogenides

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Chromene derivatives are an important class of compounds found in natural products and biologically active molecules. Some of the activities described in the literature include anticancer, antiprotozoal, antibacterial, antiviral and insecticidal. The most common members of this family are 4*H*-chromenes, 2*H*-chromenes, 2*H*-chromen-2-one (coumarins) and 4*H*-chromen-4-one (chromones), whose syntheses have been accomplished via many different routes. Other chalcogenochromenes, such as 4*H*-seleno- and 4*H*-tellurochromenes, are rather unusual, with only very few examples described in the literature.

With these considerations in mind, we set out to design a useful and operationally simple route to 4*H*-chalcogenochromenes. The proposed methodology should be modular in order to accommodate a wide variety of functional groups, based on simple starting materials and at the same time allow the quick functionalization of the final product. We believed that a rapid cyclization process that at the same incorporated organochalcogenide substituents would meet these criteria as these groups are easily replaced by carbon-carbon, carbon-halogen and carbon-heteroatom bonds. These prerequisites led us to investigate iron(III)-promoted cyclization methodologies in which pendant alkynes are cyclized onto carbocyclic rings in the presence of dichalcogenides. In summary, we have described the synthesis of 4*H*-chalcogenochromene prepared via the iron(III)-promoted cyclization of organochalcogen propargylamines in the presence of diaryl dichalcogenides. Products with variations in the carbocyclic ring and at positions 2, 3 and 4 were obtained in moderate to excellent yields and a plausible mechanism based on HRMS experiments is proposed and discussed. In addition, we demonstrated the chemoselective C2-functionalization with four different electrophiles as well as the arylation of the same position with potassium aryl trifluoroborate salts via Suzuki- Miyaura reaction, adding nine more examples to the final scope.



ORGN 152

Purification of flavone derivatives: 3-Hydroxy-2-phenyl-4-chromenone via Algar-Flynn-Oyamada reaction

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 Massachusetts, United States

Studies of high energy particles require precise and accurate detector readings. Because many of these detector parts are made of polystyrene/polyvinyltoluene, fluorescent compounds that can undergo Excited State Intramolecular Proton Transfer (ESIPT) with suitable fluorescence characteristics and physical properties can be doped in plastic scintillators. The molecule 3-hydroxy-2-phenylchromen-4-one (3-hydroxyflavone or 3-HF) is known for its absorption near 350 nm and emission around 530 nm. With proper substitution of the phenyl ring, desired properties can be obtained. Our research focused on the synthesis and study of the mechanistic pathway of 3-hydroxy-2-phenylchromen-4-one and appropriately substituted molecules on C-2 that

could potentially enhance the extinction coefficient and the solubility to ease the inclusion of such in plastic. Purification lead to insightful mechanistic findings.

ORGN 153

Preparation of isoxazolines via ring closure of oximes

Ashley Kirsch, *kirs8052@bears.unco.edu*, **Michael D. Mosher**. Dept Chemistry Biochemistry, University of Northern Colorado, Greeley, Colorado, United States

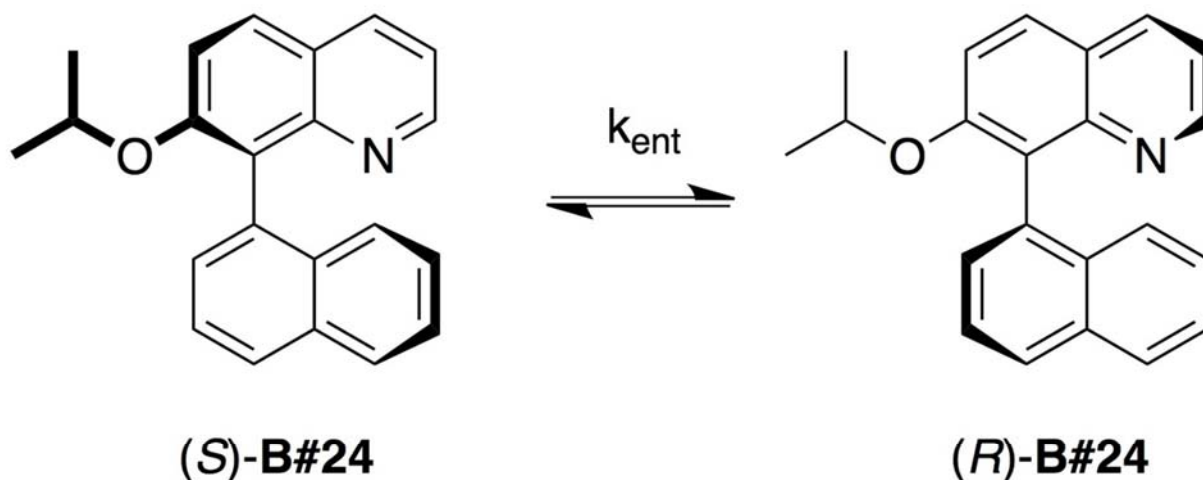
New methodologies for the preparation of the isoxazoline ring system are useful in drug design. One such methodology involves the ring closure of an α,β -unsaturated oxime. This method was explored using chalcones, which are readily available through the aldol condensation of a benzaldehyde and an acetophenone derivative. The oxime is formed by reaction of the chalcone with hydroxylamine hydrochloride and sodium acetate. The ring closure of the oxime was studied, and details of the synthesis and spectroscopic data will be discussed, including the effects of electron donating and electron withdrawing substituents.

ORGN 154

Synthesis, resolution, and configurational stability of 7-isopropoxy-8-(naphth-1-yl)quinoline and the influence of its absolute configuration on effectiveness of HIV-1 neutralization

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($\pm$)-7-Isopropoxy-8-(naphth-1-yl)quinoline (B#24) was recently identified as a low micromolar inhibitor of HIV-1, specifically its RNase H activity. However, whether or not the enantiomeric atropisomers of this azaBINOL derivative are configurationally stable, and, if so, how the absolute configuration of B#24 affects its biological activity, are issues yet to be addressed. It is here reported that the atropisomers of B#24 can be resolved by standard chiral stationary phase preparative HPLC and that the separated optical isomers retain their stereochemical integrity indefinitely at ambient conditions in the pure state (i.e., no change in %ee during ≥ 14 d at rt). Furthermore, it has been established that (+)-B#24 is 3-6 times more potent in its inhibition of HIV-1 in a single round HIV-1 infectivity assay as compared to its antipode (–)-B#24. These new findings will be presented in detail alongside the results of ongoing work to optimize the synthesis and resolution of B#24, to assign absolute configurations to its optical isomers, and to fully explore its enantiomerization kinetics via Eyring plot analysis. Knowledge of the parameters studied will aid future efforts to use B#24 as a lead compound en route to superior agents for HIV-1 neutralization.



- configurational stability? (enantiomerization kinetics)
- affect of absolute configuration on biological activity?

ORGN 155

Synthesis of bridged azapolycycles from tropone

Daniel Griffith, dan.griffith@gmail.com, Zaki K. Phelan, Yiqun He, Ziyang Guan, Philip Weiss. Lafayette College, Easton, Pennsylvania, United States

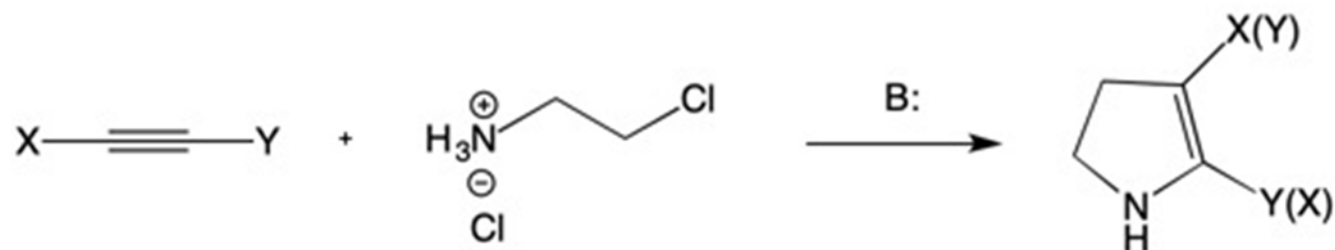
Bridged azapolycyclic motifs are embedded within a number of biologically active natural products, and ring systems containing a seven-membered carbocyclic ring are particularly challenging to access. This work describes the use of tricarboxyl(tropone)iron (synthesized in one step from tropone) to synthesize diverse bridged azapolycycles containing a seven-membered ring. Aza-Michael reactions with amine nucleophiles bearing functionalized side chains enables a variety of downstream transformations to forge diverse polycyclic skeletons. Some of these skeletons are novel while others resemble the core structures of alkaloid natural products.

ORGN 156

Michael additions to β -haloethyl amine derivatives

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In a prior study in our lab, the synthesis of a 2-phenylpyrrolidine ring system was attempted employing a Michael reaction between 2-chloroethylamine and β -nitrostyrenes. This study aims to better define reaction conditions and the use of other Michael acceptors in the reaction with 2-chloroethylamine.

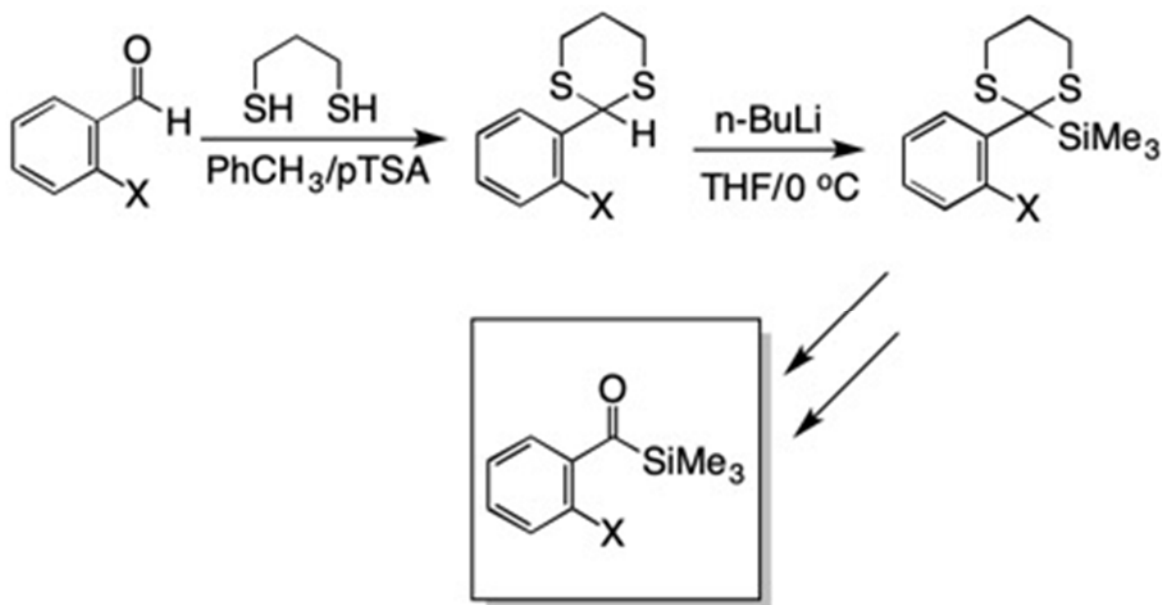


ORGN 157

Synthesis of aromatic silyl ketones for Brook Rearrangement studies

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Studies directed toward the preparation of aryl silyl ketones and related intermediates for use in mechanistic studies pertaining to the Brook Rearrangement will be presented.



ORGN 158

Intermolecular [3+3] ring expansion of bicyclic aziridines to access functionalized piperazines via aziridinium ylides

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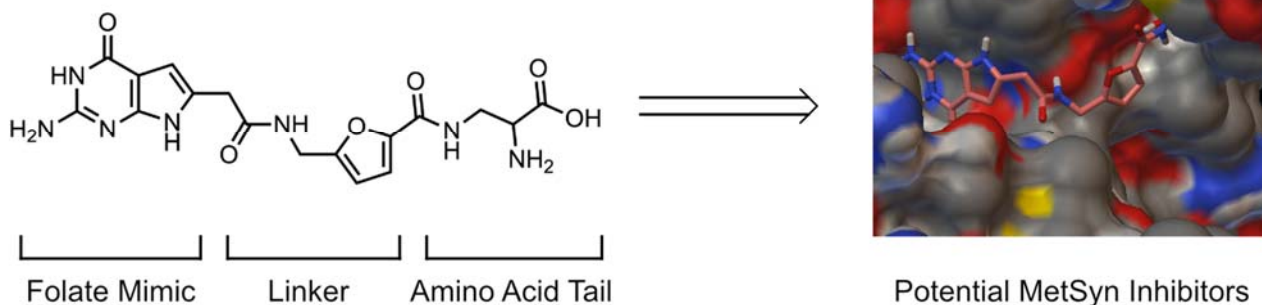
Nitrogen-containing structural motifs are prevalent in pharmaceutical scaffolds. According to a statistical analysis of nitrogen heterocycles in U.S. FDA-approved drugs, 59% of small-molecule drugs contain a nitrogen heterocycle. Among other nitrogen heterocycles, piperazines are the third most common nitrogen six-membered ring system found in pharmaceuticals. Traditional methods to synthesize piperazines often involve transition metal-mediated cyclization. However, these syntheses lack structural diversity, specifically carbon substitution diversity on the piperazine ring. This new method explores [3+3] ring expansion of bicyclic aziridines to access functionalized piperazines *via* aziridinium ylides. Asymmetric silver-catalyzed alkene aziridination is followed by an attack of the aziridine lone pair on the rhodium-stabilized imino carbene to produce the key aziridinium ylide intermediate. Subsequent concerted, asynchronous pseudo-[1,4]-sigmatropic rearrangement of the ylide delivers the piperazine scaffolds in high diastereoselectivity. DFT calculations support the current proposed mechanism in which this reaction proceeds through an aziridinium ylide. This work highlights a ring expansion of aziridines as a key strategy to access larger nitrogen-containing molecules.

ORGN 159

Synthesis of a library of folate mimics as inhibitors of fungal methionine synthase

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Fungal infections are of continuous concern, especially with regard to immunocompromised patients. In an effort to develop new potential anti-fungal agents, we have begun synthesizing a library of potential inhibitors of the fungal Methionine Synthase (MetSyn) enzyme. Key differences between the B₁₂-independant fungal MetSyn enzyme and the B₁₂-dependant mammalian form can allow for an antifungal drug to be developed to exclusively bind the fungal enzyme and inhibit fungal growth while leaving the host (patient) unaffected. We are currently exploring the synthesis of various pterin and deazaguanine-based molecules as these mimic folate, an essential substrate for MetSyn function. We have begun testing these new molecules for activity in a fungal growth assay, as well as a fluorescent assay for monitoring MetSyn activity.



ORGN 160

Synthesis of push-pull tetrazoles and investigation of their spectroscopic properties

Anna-Kay R. West, Joseph D. Huang, **Sundeep Rayat**, srayat@bsu.edu. Department of Chemistry, Ball State University, Muncie, Indiana, United States

Push-pull systems have a variety of applications in photonic devices. In this work, we designed and synthesized tetrazole-based push-pull molecules, the 1-alkyl-3-(5-aryl-2H-tetrazolyl) pyridinium and 1-alkyl-4-(5-aryl-2H-tetrazolyl) pyridinium salts, and investigated their absorption and fluorescence characteristics to evaluate their scope in

organic materials. A C-N coupling reaction of phenyl tetrazole with 3-pyridyl and 4-pyridyl boronic acid in the presence of copper(I) oxide and oxygen atmosphere in DMSO at 100 °C yielded the 3-(5-phenyl-2*H*-tetrazol-2-yl) pyridine and 4-(5-phenyl-2*H*-tetrazol-2-yl) pyridine. The latter were methylated upon reaction with methyl tosylate to form the 1-methyl-3-(5-phenyl-2*H*-tetrazol-2-yl) pyridinium and 1-methyl-4-(5-phenyl-2*H*-tetrazol-2-yl) pyridinium salts, respectively. The absorption and emission spectra of the synthesized compounds was obtained in water, methanol, ethanol and dimethyl sulfoxide. The UV-Vis bands were found to be not dependent on the solvent. Time dependent density functional calculations were employed to determine the nature of electronic transitions, and our data shows that UV bands are composed of π to π^* transitions.

ORGN 161

Progress toward catalytic enantioselective Friedel-Crafts reactions for the preparation of chiral tetraarylmethanes

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We have recently reported the first general method to prepare tetraarylmethanes with all-phenyl groups and diverse substitution using an intramolecular Friedel-Crafts reaction followed by a nickel-mediated desulfurization. Herein, we describe our progress toward developing an enantioselective variant of this methodology. Substrate preparation (2-thioaryl-triarylmethanols) is described along with our results using C2 symmetric Bronsted acids to enable cyclization giving quaternary stereocenters with four different aromatic groups. Subsequent desulfurization gives chiral tetraarylmethanes that could exhibit interesting properties/applications.

ORGN 162

Synthesis of GPCR and sigma-1 receptor ligands using allylic azides

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G-protein coupled receptors (GPCRs) are the largest and most diverse class of membrane receptors in the human body. GPCRs are pharmacologically relevant, with 34% of all drugs affecting at least one GPCR. The sigma-1 receptor is a GPCR that recent research has implicated as a target to potentially treat addiction, breast and colon cancer, and Alzheimer's disease, which makes it an exciting target. Previous work in the Topczewski group found that a class of small molecules are potent ligands for the sigma-1 receptor. The synthesis of these novel substituted chromanes was conducted via an allylic azide intermediate, which was further derivatized. These heterocycles contain the phenethylamine motif, which is common among many endogenous and

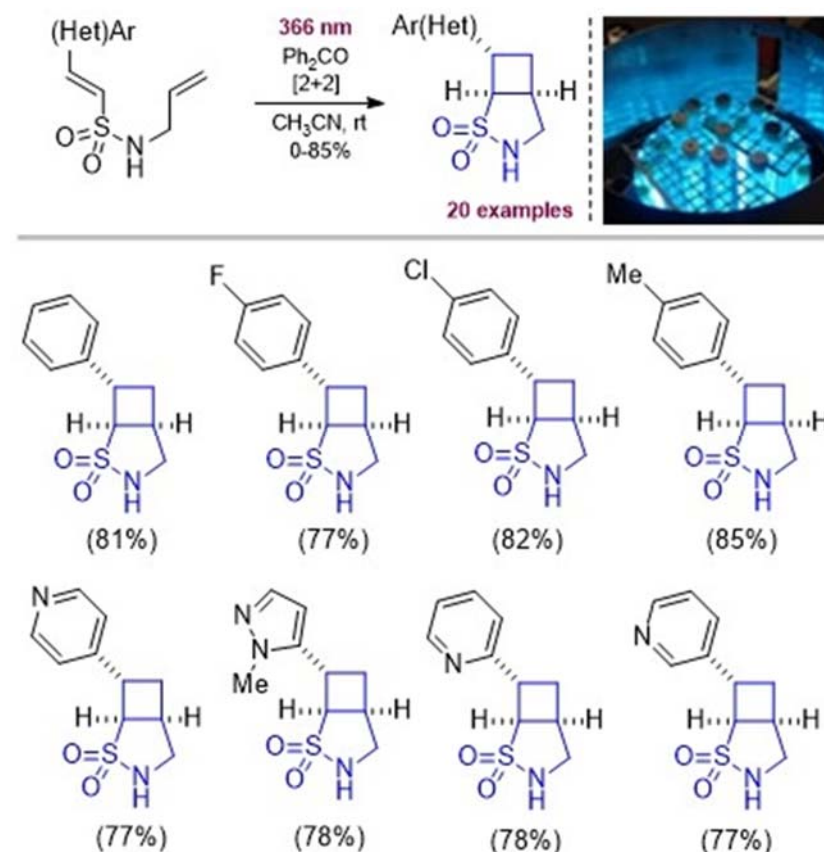
exogenous GPCR ligands. In this study, we separated the chromane core into its constituent enantiomers and then functionalized the enantiopure products, producing 36 novel compounds (18 pairs of enantiomers). These compounds have been submitted for assay against the human sigma-1 receptor.

ORGN 163

Convenient access to conformationally rigid sultams

D. Dibchak, V. Shcherbacova, A. V. Denisenko, **Pavel Mykhailiuk**,
Pavel.Mykhailiuk@gmail.com. Chemistry, Enamine Ltd, Kiev, Ukraine

Since the discovery of the first sulfonamide-containing drug - Prontosil - in the 1930s, sulfonamides and sultames, in particular, play an important role in agrochemistry and medicinal chemistry projects. During the recent decade medicinal chemists, however, tend to use more often compact bicyclic building blocks, in particular sultams. In this work, we synthesized the last missing scaffold in this compound class – bicyclic cyclobutane-fused sultam. The key synthetic step was a photochemical intramolecular cyclization of linear sulfonamides. The protocol allowed the synthesis of aryl and more importantly hetaryl-substituted bicyclic scaffolds on a milligram to gram scale.

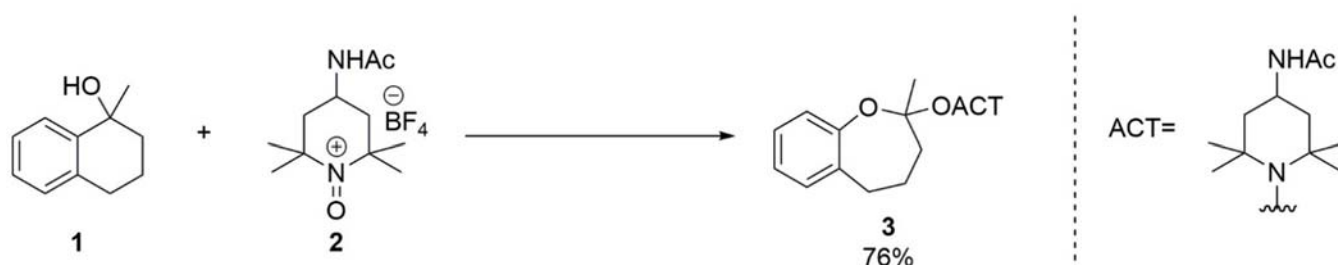


ORGN 164

Investigation of oxoammonium salt mediated oxidative rearrangements

Rowan Meador, rimeador@syr.edu, **John D. Chisholm**. Chemistry, Syracuse University, Syracuse, New York, United States

A number of natural products have medium sized cyclic ethers as core skeletal structures. However, medium sized heterocycles of 7-10 membered rings are often difficult to access via direct cyclization due to unfavorable entropic effects and transannular interactions. Other methods have been developed to access these systems, but often they rely on inefficient high-dilution and/or inconvenient slow-addition procedures to avoid polymerization side-products. The rearrangement of tertiary alcohols using oxoammonium salts provides a rapid entry into medium sized cyclic ethers and circumvents these requirements. To investigate this rearrangement, tertiary alcohol **1** was reacted with oxoammonium salt **2**, which provided rearranged acetal **3** in 76% yield. The commercially available oxoammonium salt **2** was shown to perform these rearrangements at room temperature. The oxoammonium salt is attractive as it is transition metal free, is readily synthesized from inexpensive reagents on large scale and is sustainable since the tetramethylpiperidine can be recycled to the oxoammonium salt after the acetal is deprotected. An evaluation of the substrate scope of these oxidative rearrangements will be presented.

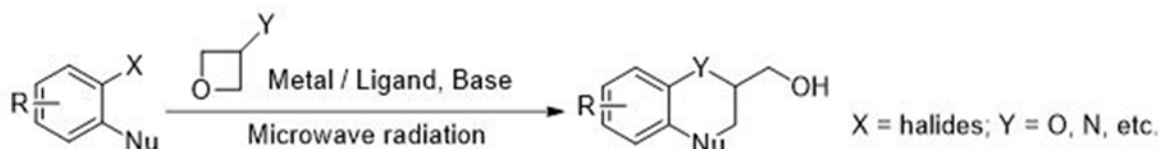


ORGN 165

Efficient synthesis of heterocycle rings through a one-pot cross coupling / intramolecular ring opening of oxetanes

Chao-Yuan Wang, cwang178@its.jnj.com, **Scott D. Kuduk**. Johnson & Johnson, Elmhurst, New York, United States

Heterocycles are important structural motifs that occur in a wide range of biologically active compounds. The efficient synthesis of these *N*, *O*-containing heterocycles has attracted significant attention in organic synthesis method developments. The present work demonstrates a one-pot cross coupling reaction followed by an intramolecular ring opening of 3-substituted oxetanes to provide various ring scaffolds.



ORGN 166

Diastereoselective multicomponent synthesis of tetrahydro-1*H*-pyrrolopyrazino[2,1-*b*]quinazolin-11(5*H*)-ones via sequential quinazolinone rearrangement & intramolecular ring closure of (*Z*)-benzamidines

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Densely functionalized 2-alkylaminoquinazolinones can be transformed into a variety of heterocycles. As part of our exploration of a regiospecific quinazolinone rearrangement, we recently described a telescoped, dual rearrangement strategy affording highly diversified, *N*-substituted (*E*)-amidoarylamidines. Further examination of the nature of the appended amine component of the quinazolinone revealed that the resulting product amidines could spontaneously cyclize to form tetrahydro-1*H*-pyrrolopyrazino[2,1-*b*]quinazolin-11(5*H*)-ones. Development of this tandem quinazolinone rearrangement-intramolecular ring-closure of *ortho*-amido-*NH*-(*Z*)-benzamidines afforded diastereomerically-enriched tetrahydro-1*H*-pyrrolopyrazino[2,1-*b*]quinazolin-11(5*H*)-ones. This highly efficient, four-step, seven-transformation method was used to generate 20 examples in up to 86% yield and with up to 89:11 dr. The protocol showed a wide tolerance for various electronic and steric substitutions and required only a single, final purification. Mechanistic considerations are bolstered by the isolation and characterization of an *ortho*-amido-*NH*-(*Z*)-benzamidine reaction intermediate. This work showcases our novel method for quinazolinone synthesis, broadening access to this understudied privileged structural class and related natural product frameworks.

ORGN 167

Cu-catalyzed heteroatom-vinylation for synthesis of 2-imidazolidinethiones, 2-imidazolidinones, and 2-iminoimidazolidines

Todd J. Eckroat, *tje146@psu.edu*. Penn State Behrend, Erie, Pennsylvania, United States

Five-membered heterocyclic rings are abundant in natural products and pharmaceuticals. Thus, continued investigation of new heterocyclic ring forming reactions are of interest to the synthetic community. 2-Imidazolidinethiones, 2-imidazolidinones, and 2-iminoimidazolidines have found a diverse array of biological applications. For example, 2-imidazolidinethiones have shown analgesic, antiserotonin, and herbicidal activity, while 2-imidazolidinones have shown anticancer activity and the ability to inhibit various enzymes, among them HIV protease. 2-Iminoimidazolidines have shown analgesic and antiparasitic activity. Current synthetic access to these scaffolds is as varied as their biological activity. Based on a recent report of Cu-catalyzed S-vinylation with N-(2-bromoallyl)butylamine and CS₂, it was hypothesized that additional heteroallenes of the general format R-Y=C=Z, namely isothiocyanates, isocyanates, and carbodiimides, could undergo similar heteroatom-vinylation to access 4-methylene-2-imidazolidinethiones, 4-methylene-2-imidazolidinones, and 4-methylene-2-iminoimidazolidines, respectively. Preliminary results show that N-(2-bromoallyl)butylamine reacts readily with phenyl isothiocyanate in the presence of CuI to form the resulting 4-methylene-2-imidazolidinethione. In the absence of CuI, the reaction stalls at the acyclic thiourea. Progress on the investigation of Cu-catalyzed heteroatom-vinylation between N-(2-bromoallyl)butylamine and isothiocyanates, isocyanates, and carbodiimides will be reported. Optimization of reaction conditions, catalyst screening, and substrate scope will be detailed. Additionally, the potential for a mixture of products based on regiochemistry of the ring formation and rearrangement of the exocyclic methylene will be addressed. This previously unreported reaction will enhance synthetic access to these important heterocycles.

ORGN 168

Functionalized heterocycles by nucleophilic substitution at olefinic groups

Douglas A. Klumpp, *dklumpp@niu.edu*, **Jacob C. Hood**. Northern Ill Univ, Dekalb, Illinois, United States

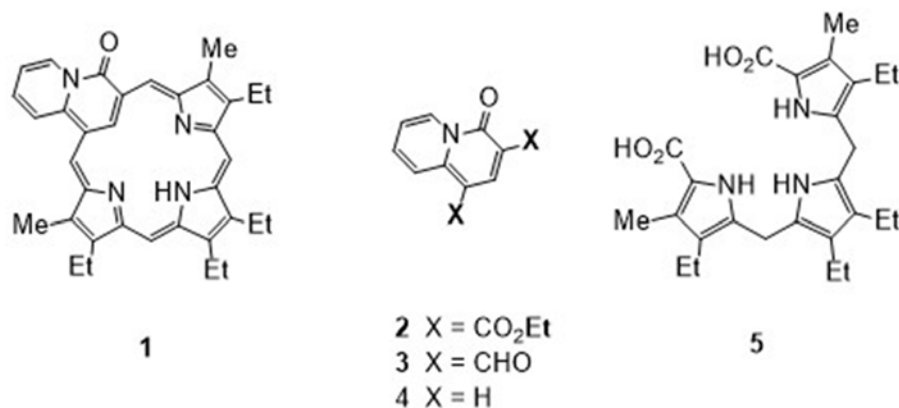
A series of heterocycles have been prepared having halogenated vinyl groups. Substitution occurs readily with carbon and heteroatom nucleophiles. The resulting functionalized heterocycles are useful scaffolds for further synthetic elaboration.

ORGN 169

Synthesis of Oxyquinoliziniporphyrin

Emma Cramer¹, ekcrame@ilstu.edu, **Timothy D. Lash**². (1) Illinois State University, Oak Forest, Illinois, United States (2) Chemistry, Illinois State Univ, Normal, Illinois, United States

Carbaporphyrinoids are porphyrin analogues where one or more of the internal nitrogen atoms have been replaced by carbons. Many examples of these systems have been reported and these show diverse reactivity and spectroscopic properties. In order to further extend this field, the formation of carbaporphyrinoid systems incorporating heterocyclic subunits is being investigated. Specifically, porphyrinoids **1** incorporating a 4*H*-quinolizin-4-one unit were targeted for synthesis. A quinolizinone diester **2** was synthesized from ethyl 2-pyridylacetate and diethyl ethoxymethylenemalonate. Refluxing **2** with conc. hydrochloric acid afforded quinolizinone **3** and subsequent Vilsmeier-Haack formylation gave the related dialdehyde **4**. Condensation of **4** with tripyrrane **5** using the MacDonald-type “3 + 1” approach gave the targeted oxyquinoliziniporphyrin **1**. Proton NMR spectroscopy indicated that this novel porphyrinoid has intermediary aromatic character. Ongoing studies are being directed towards the metalation, structural and spectroscopic characterization of **1**.



ORGN 170

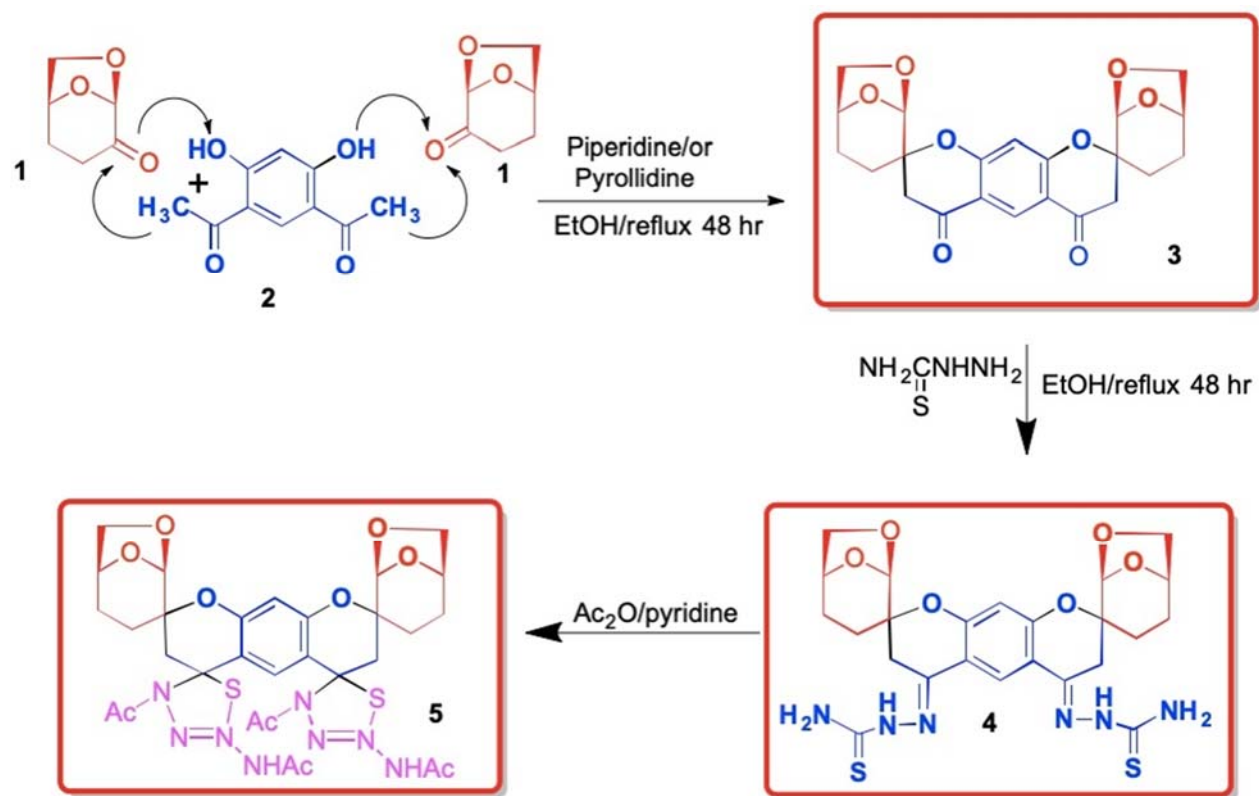
New approach to carbohydrate functionalized spiro-chromanone heterocycles

Jessie Lopez², jessie.lopez@wilkes.edu, **Zbigniew J. Witczak**¹, zbigniew.witczak@wilkes.edu, **Roman Bielski**¹, **Donald E. Mencer**². (1) Dept of Pharm SCI Sch of Phar, Wilkes Univ, Wilkes Barre, Pennsylvania, United States (2) Chemistry and Biochemistry, Wilkes University, Wilkes-Barre, Pennsylvania, United States

The reaction of dihydrolevoglucosenone **1** (DHLG) Cyrene^R with aromatic aldehydes in the presence of a base produces exo-cyclic enone^[1-2] as a main (and usually only) product. However, when DHGL **1** (2 moles) was reacted with 1,4-diacetyl-2,5-

dihydroxybenzene **2**, we noticed a formation of an entirely different product **3** in a good 58 % yield. Mass spectrometry and ^1H and ^{13}C NMR data of **3** ambiguously confirmed the formation of the cyclization product with a *spiro*-carbon structure. Interestingly, the product **3** derives from the reaction of the acetophenone anion attacking both C-2 carbonyl groups of DHLG **1**, via a standard Claisen-Schmidt condensation with a formation of a typical *spiro*-chromanone **3**.

We are in the process of studying the detailed mechanism leading to the formation of this product. The plausible mechanisms will be presented and discussed. The *spiro*-chromanone **3** was further converted to thiosemicarbazide **4**, which upon acetylation with acetic anhydride in pyridine produced **5**.

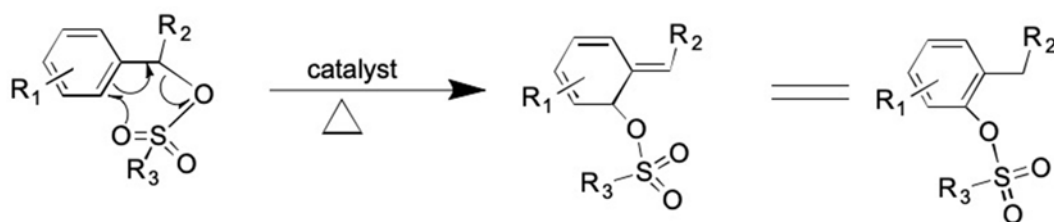


ORGN 171

Hetero-oxa-claisen rearrangement: New examples

Roman Bielski, **Zbigniew J. Witczak**, zbigniew.witczak@wilkes.edu. 2Dept of Pharm SCI Sch of Phar, 1Chemventive, LLC., 38 Ringfield Rd., Chadds Ford,, Pennsylvania, United States

There are four possible types of the Claisen rearrangement: allyl-vinyl, allyl-phenyl, benzyl-vinyl and benzyl-phenyl.¹ The rearrangement can still be successful when some of the carbon atoms of these groups or the focal oxygen atom are replaced with hetero-atoms. We call the Claisen rearrangements in which the oxygen atom is in the position 3 or 4 but one or more of the carbon atoms were replaced with hetero-atoms: Hetero-Oxa-Claisen Rearrangement.¹ The scope of Hetero-Claisen rearrangements has not been sufficiently studied. The poster will show our experimental results of new reactions belonging to the Hetero-Oxa-Claisen rearrangements such as the one below:



ORGN 172

Multicomponent protocol for the synthesis of novel substituted thiazoles Ayaa Shabana

Ayaa Shabana, as1404432@qu.edu.qa. Chemistry & Earth Sciences, Qatar University , Doha, Qatar, Qatar

The multicomponent reaction of some 1N,3S-dinucleophiles generated *in situ* with 1,2-dielectrophiles afforded novel substituted thiazoles. The reaction was studied under various conditions. Under the optimum reactions conditions, the target thiazoles were isolated in very good yields. The products were purified by crystallization. All new products were characterized by various spectroscopic methods to confirm their identities. The efficiency of this protocol is highlighted by utilizing commercially available starting materials, short reaction times, room temperature reactions and simple purification of the products

ORGN 173

Synthesis of novel substituted indeno pyrroles and their transformations Toka Farhat

Toka Farhat, tf1404704@qu.edu.qa. Chemistry & Earth Sciences, Qatar University , Doha, Qatar, Qatar

The reaction of ninhydrin with substituted enamines was studied under various conditions. Under the optimum reaction conditions, The reaction provided novel substituted indeno pyrroles in very good to excellent yields in short times. The products were purified by crystallization. These novel substituted indeno pyrroles were then transformed to variety of novel compounds including isocoumarins. All new products were characterized by various spectroscopic methods to confirm their identities.

ORGN 174

Hindered, solvatochromic, fluorescent naphthalimides

Alicia A. Pollock¹, pollocaa7411@uwec.edu, **David E. Lewis**². (1) University of Wisconsin-Eau Claire, Eau Claire, Wisconsin, United States (2) Chemistry Department, UW-Eau Claire, Eau Claire, Wisconsin, United States

The solvatochromism of the 4-amino-1,8-naphthalimide fluorophore is well established, with the wavelengths of maximum absorption and maximum emission showing a hypochromic shift as the dielectric constant of the solvent decreases. We have synthesized a new naphthalimide dye with bulky 2,2,6,6-tetramethylpiperidine (TMP) groups at both the 4-, and N- positions. This dye exhibits the normal solvatochromic behavior in a series of organic solvents ranging from cyclohexane to dimethyl sulfoxide. In preliminary trials, we have observed that this dye binds strongly to freshly isolated DNA that is not dissolved in buffer. There is no such staining with DNA dissolved in the same buffer. Herein, we report our findings of the solvatochromic behavior of this dye compared to a naphthalimide dye with sterically undemanding *n*-butyl substituents in the same positions, and our preliminary results of binding to undissolved DNA in buffer.

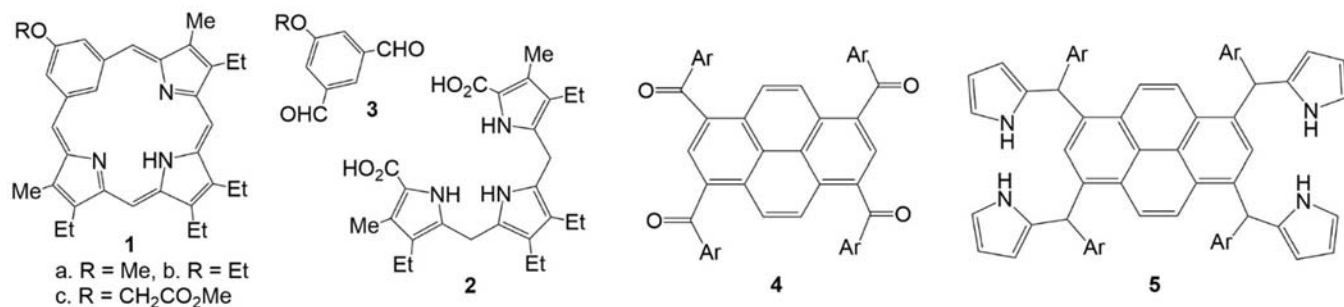
ORGN 175

Investigations into the synthesis of benziporphyrin and pyreniporphyrin dimers

Rachel A. Tomlovich¹, rtomlov@ilstu.edu, **Timothy D. Lash**². (1) Chemistry, Illinois State University, Decatur, Illinois, United States (2) Chemistry, Illinois State Univ, Normal, Illinois, United States

Benziporphyrins, e.g. **1**, are porphyrin analogues that incorporate a benzene moiety in place of one of the pyrrolic subunits. Although benziporphyrin is nonaromatic, many derivatives have global diatropic properties. The benziporphyrin cavity can also facilitate the formation of organometallic derivatives. In this work, the formation of dimeric benziporphyrin structures is under investigation. Novel benziporphyrin ethers **1a,b** have been synthesized from a tripyrrane **2** and alkoxybenzene dialdehydes **3** using a '3 + 1' MacDonald-type condensation. As expected, these new porphyrinoids show no overall diatropicity, but protonation afforded weakly aromatic dications. In addition, a related ether-linked ester **1c** has been prepared and its conversion into amide-linked dimers is being investigated. Furthermore, pyrene-derived tetraketones **4** have been converted into bis-benzitripyrrane-type structures **5**, and these have been reacted with a thiophene

dicarbinol to generate porphyrinoid products. Poor solubility has limited the characterization of these products and alternative substitution patterns are being considered to overcome these difficulties.

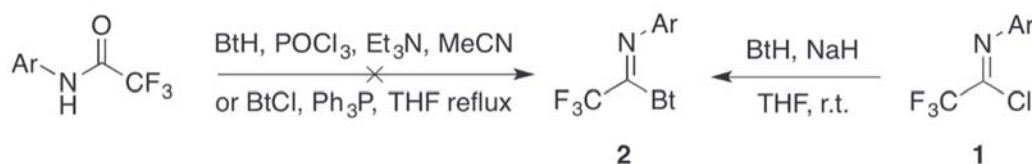


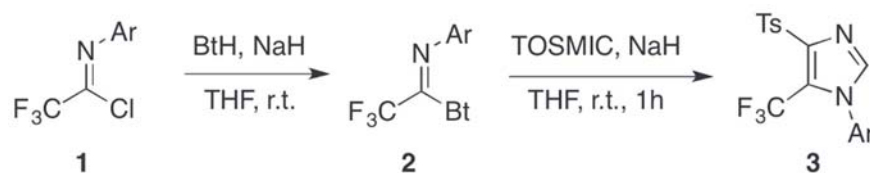
ORGN 176

Novel Reagents for the Synthesis of 1-Aryl-5-trifluoromethylimidazoles

Alexander S. Bunev, a.s.bunev@gmail.com. Medicinal Chemistry Center, Togliatti State University, Togliatti, Samara region, Russian Federation

1-Imidoylbenzotriazoles [N-aryl-1-(1H-benzotriazol-1-yl)-2,2,2-trifluoroethan-1-imines] reacted with tosylmethyl isocyanide according to van Leusen's procedure to give difficultly accessible 1-aryl-4-(4-methylbenzenesulfonyl)-5-(trifluoromethyl)-1H-imidazoles in good yields (81–94%). The initial imidoylbenzotriazoles were conveniently synthesized by reaction of sodium benzotriazolidine with the corresponding imidoyl chlorides in THF. The reactions were carried out with a wide series of imidoylbenzotriazoles containing various electron-donating and electron-withdrawing substituents in the N-aryl fragment.





1-3 Ar = Ph (**a**), 2-MeC₆H₄ (**b**), 4-MeC₆H₄ (**c**), 2,4-MeC₆H₃ (**d**), 4-MeOC₆H₄ (**e**), 4-CF₃C₆H₄ (**f**), 4-FC₆H₄ (**g**), 2-ClC₆H₄ (**h**), 4-ClC₆H₄ (**i**), 4-BrC₆H₄ (**j**), 4-NO₂C₆H₄ (**k**)

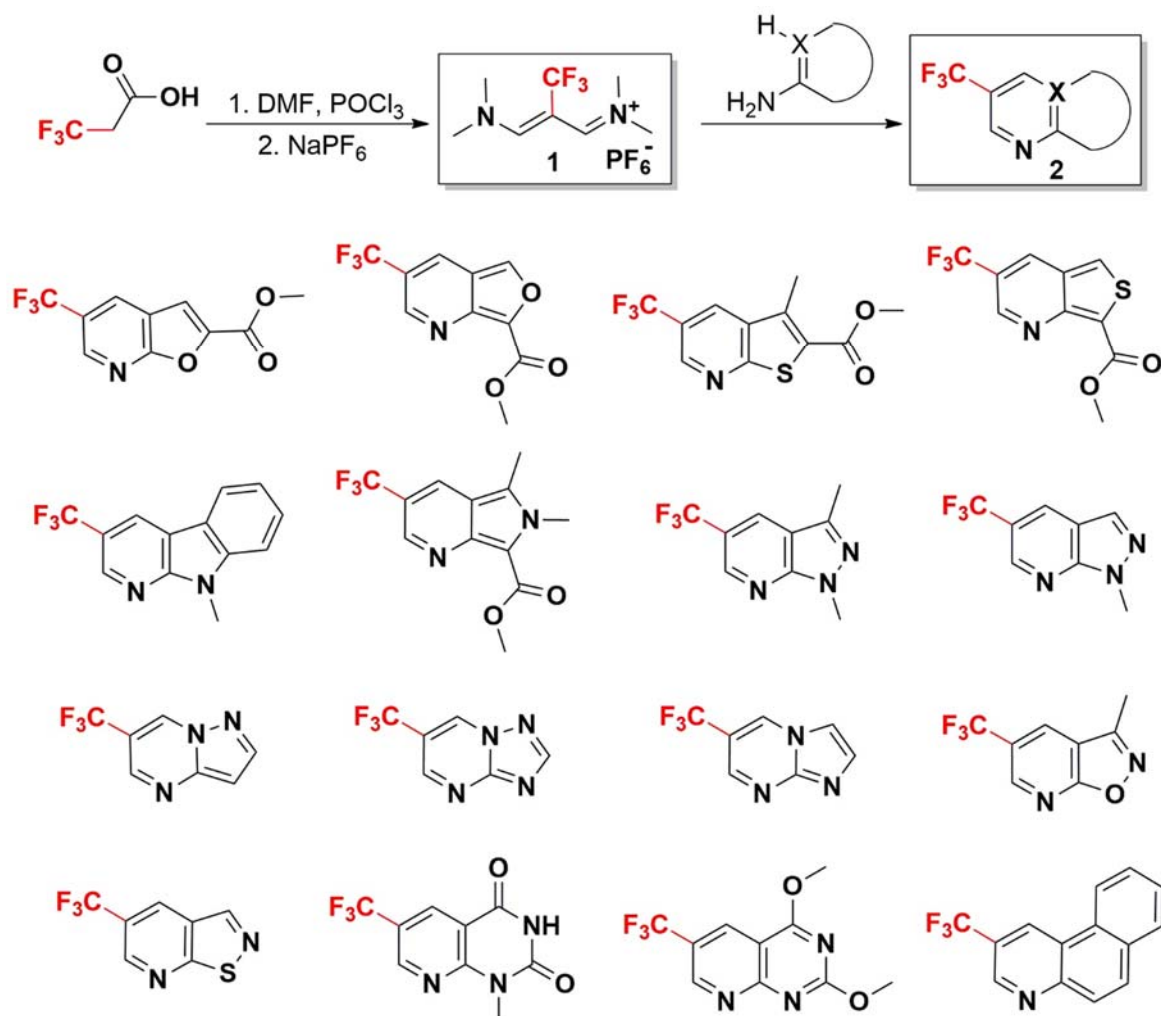
ORGN 177

Efficient route for the synthesis of diverse heteroannelated 3-trifluoromethylpyridines

Sergey Ryabukhin^{1,2}, s.v.ryabukhin@gmail.com, **Andrey Mityuk**¹, **Dmitriy Volochnyuk**^{1,2,3}. (1) Enamine LTD, Kyiv, Ukraine (2) The Institute of High Technologies, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine (3) Biologically Active Compounds, Institute of Organic Chemistry of NASU, Kyiv, Ukraine

Fused pyridines are widely applicable in various fields of medicinal chemistry. Last years different biological activities as antidepressants, antiallergics, antidiabetics, antihistaminics and so on are shown for them. Most of hits contained heterocycles annelated to the pyridine's core. The problematic of the functionalization of such type of compounds very often solved on the heterocyclization stage. The methodology for producing of heteroannelated 3-trifluoromethylpyridines based on the cyclization reaction of diverse aminoheterocycles with [3-(dimethylamino)-2-(trifluoromethyl)prop-2-en-1-ylidene]dimethylazanium hexafluorophosphate **1** were elaborated and adapted for multigram scale.

In this report, the synthesis of starting reagent [3-(dimethylamino)-2-(trifluoromethyl)prop-2-en-1-ylidene]dimethylazanium hexafluorophosphate in kilo scale is elaborated. The synthetic methodology for the cyclization is validated and optimized. The advantages and scope and limitation of the procedure are determined and will be discussed.



ORGN 178

Chemistry of a “bottleable” propargyl carbocation

Matthew Laprade, matthewlaprade@hotmail.com, Katherine Robertson, Jason A. Clyburne. Department of Chemistry, Saint Marys University, Halifax, Nova Scotia, Canada

Highly unsaturated organic molecules are reactive and readily undergo addition reactions. The reactivity of unsaturated molecules can be further increased by the inclusion of a carbocationic center. For instance, the propargyl cation possesses an alkyne moiety adjacent to a cationic carbon atom. It should exhibit a diverse reactivity reflecting the extreme nature of the unsaturation. In this poster we will describe the preparation of a family of propargyl cations and identify their spectroscopic and structural trends. Computational studies have been carried out, and preliminary

experimental results involving the reactivity of these cations with small reagents such as H₂O, N₃⁻, and the hydrogen atom will also be reported.

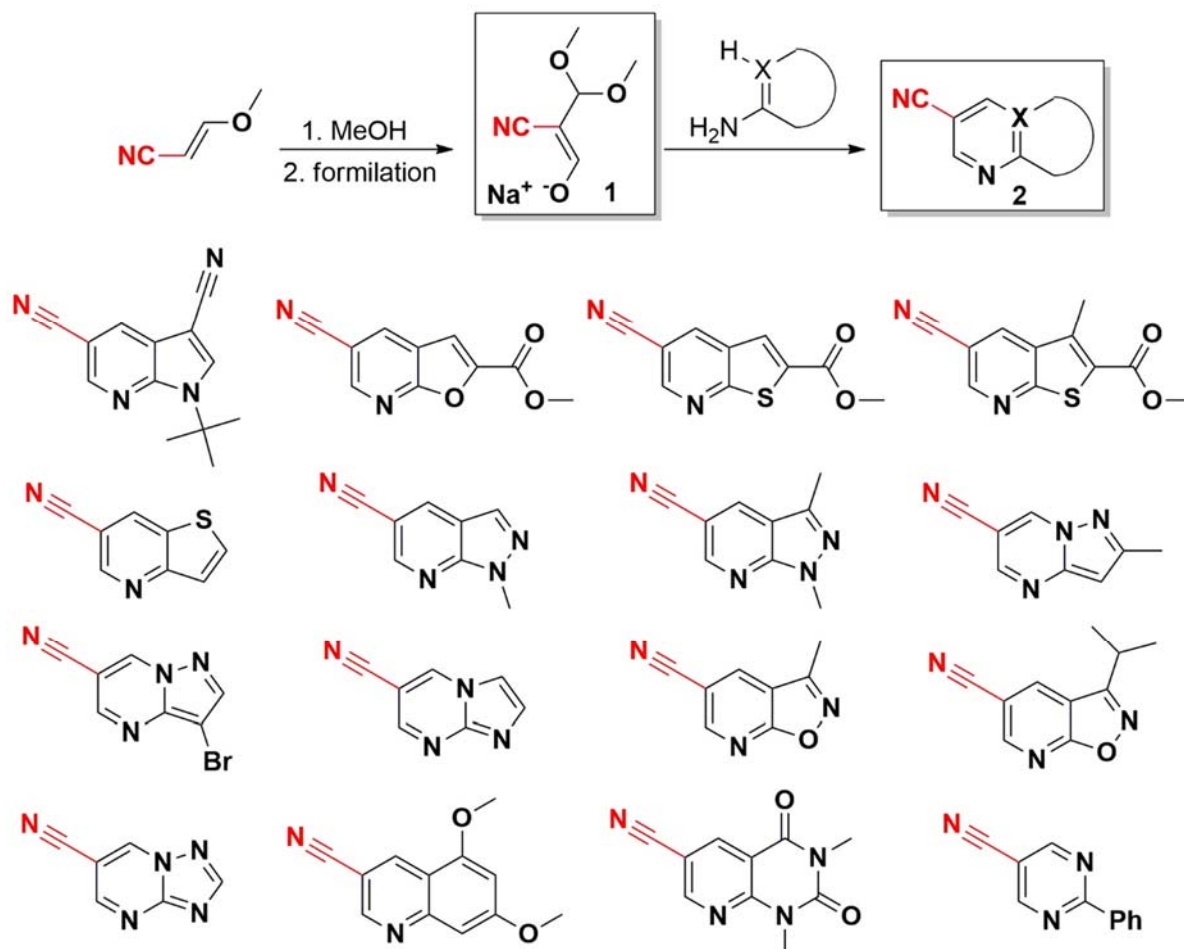
ORGN 179

Efficient route for the synthesis of diverse heteroannelated 3-cyanopyridines

Dmitriy Volochnyuk^{1,2,3}, *d.volochnyuk@gmail.com*, **Andrey Mityuk**¹, **Sergey Ryabukhin**^{1,2}. (1) Enamine LTD, Kyiv, Ukraine (2) The Institute of High Technologies, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine (3) Biologically Active Compounds, Institute of Organic Chemistry of NASU, Kyiv, Ukraine

Fused pyridines are widely applicable in various fields of medicinal chemistry. Last years different biological activities as antidepressants, antiallergics, antidiabetics, antihistaminics and so on are shown for them. Most of hits contained heterocycles annelated to the pyridine's core. The problematic of the functionalization of such type of compounds very often solved on the heterocyclization stage. The methodology for producing of heteroannelated 3-cyanopyridines based on the cyclization reaction of diverse aminoheterocycles with sodium 2-cyano-2-(dimethoxymethyl)eth-1-en-1-olate **1** were elaborated and adapted for multigram scale.

In this report, the synthesis of starting reagent sodium 2-cyano-2-(dimethoxymethyl)eth-1-en-1-olate in kilo scale is elaborated. The synthetic methodology for the cyclization is validated and optimized. The advantages and scope and limitation of the procedure are determined and will be discussed.



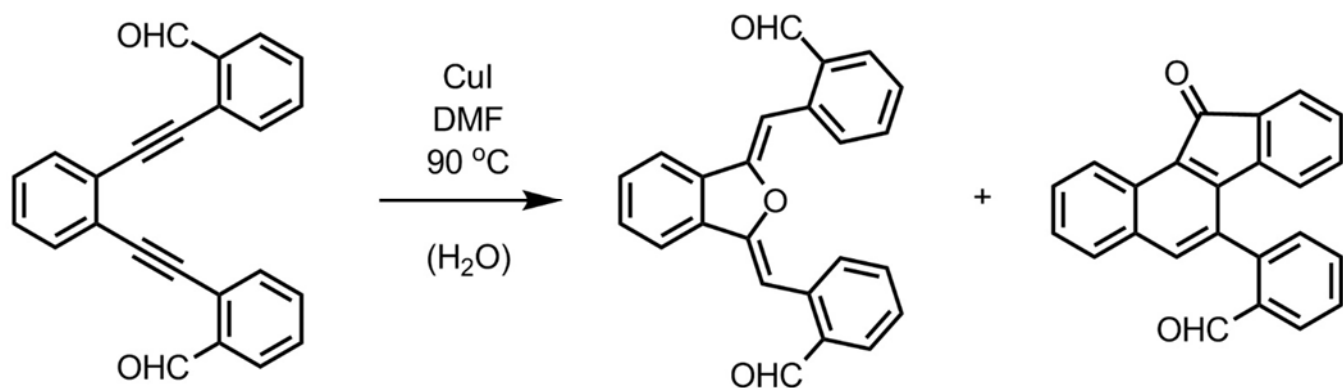
ORGN 180

1,3-Bis(benzylidene)isobenzofuran synthesis via copper(I) catalyzed hydration of ortho-diynearenes

Thomas S. Hughes, thughes@siena.edu, **Lino Gaglio**, l10gagl@siena.edu, **Hannah E. Hagearty**, h18hage@siena.edu, **Kelli M. Allen**. Chemistry and Biochemistry, Siena College, Loudonville, New York, United States

1,3-Dihydro-1,3-bis(benzylidene)isobenzofurans have been prepared in decent yields by heating 1,2-diphenylethynylbenzenes in the presence of copper(I) catalyst. Other products are also observed that do not involve the incorporation of water. The configurationally labile isobenzofuran has been isolated and crystallized in order to determine the geometry of the benzylidene alkenes. Activation of the alkyne by the copper appears to be the key mechanistic step, and the effects of different solvents and metals has been investigated. The presence of two ortho-aldehyde substituents is crucial to the formation of the isobenzofuran; the carbonyl oxygens may coordinate the

copper and stabilize the copper-alkyne complex enough to allow its intermolecular reaction with an adventitious water molecule. Substrates with only one ortho-aldehyde moiety do not produce significant quantities of the isobenzofuran products.



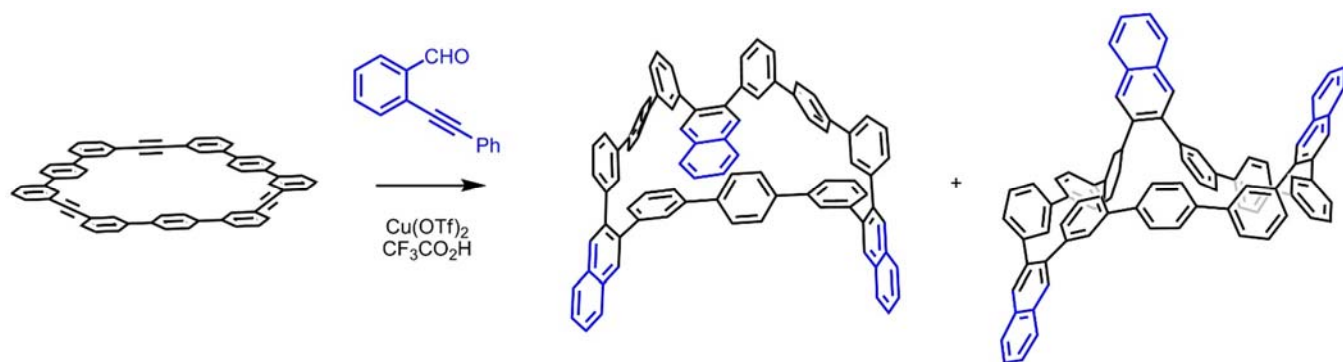
Tandem hydration of ortho-diynes gives 1,3-dihydro-1,3-bis(benzylidene)isobenzofurans

ORGN 181

Cyclooligo-(para, ortho)-phenylenes obtained by threefold Diels-Alder benzannulation of phenylene ethynylene macrocycles: Examination of the toposelectivity of cycloadditions to macrocycles by experiment and theory

Thomas S. Hughes, *thughes@siena.edu*, **Rajen H. Somwaru**, *rh06somw@siena.edu*,
Adam R. Bevilacqua, *ar06bevi@siena.edu*, **Julia Dunn**, *j29dunn@siena.edu*.
 Chemistry and Biochemistry, Siena College, Loudonville, New York, United States

Cyclotri(*m,p,m,o*)tetraphenylene macrocycles, which are precursors and models of carbon single-walled nanobelts, can be obtained by performing a Diels-Alder cycloaddition on each alkyne moiety in a cyclo(phenylene ethynylene) macrocycle. Computational modeling at the molecular mechanics, semi-empirical, and ab initio levels of theory predict the symmetrical triadduct to be preferred over the asymmetrical triadduct. The phenylene ethynylene macrocycles have been prepared using high dilution Sonogashira cross-coupling of ethynylaryl iodides. Diels-Alder cycloadditions of these macrocycles using both high temperature reactions with tetraphenylcyclopentadienone and lower temperature, copper(I) catalyzed benzannulations with phenylethynylbenzaldehyde are described. These cycloaddition products have been characterized with MALDI mass spectroscopy.



Threefold Diels-Alder benzannulation of phenylene ethynylene macrocycles to give cyclooligophenylenes

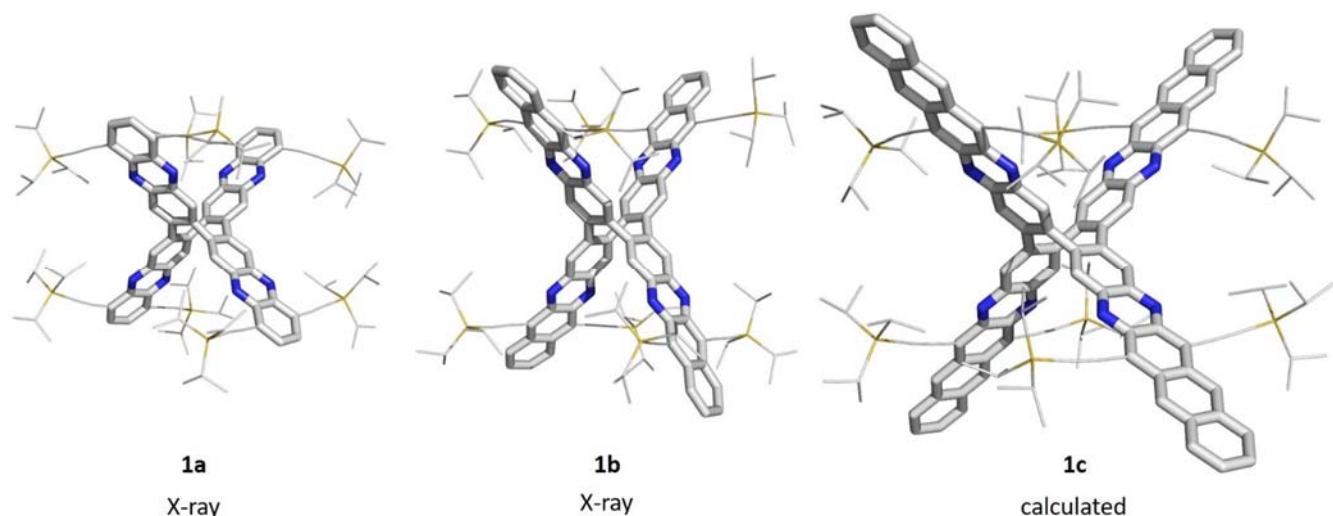
ORGN 182

Cyclooctatetraene-based acene tetramers

Victor Brosius, hf382@uni-heidelberg.de, **Lukas Ahrens**, **Frank Rominger**, **Jan Freudenberg**, **Uwe Bunz**. Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany

Small molecules like (aza-)acenes and arenes are important organic semiconductors with application in organic transistors (OFETs) or organic solar cells (OPV). Their tendency to crystallize forming π -stacked arrangements is beneficial for OFETs, but detrimental for OPV due to phase separation. For multilayer-devices such as bulk-heterojunction OPV cells, smooth films are desired. Appending alkyl-/alkoxy- or aryl-side-chains can lower the crystallinity significantly, but often results in a distinct reduction of the charge carrier mobilities due to increased distances between the aromatic systems.

This work focuses on the synthesis of azaacene tetramers, connected *via* cyclooctatetraene- (COT) backbones. The resulting constructs link the acene units *via* direct CC bonds without the need of an additional connector. The tetramers show strong interactions across the COT backbone resulting in a significantly redshifted absorption compared to their consanguine monomeric counterparts. The crystal structures of **1a** and **1b** show close packing of adjacent molecules and prove the tetrahedral shape spanned by the acene subunits. As expected, due to the three dimensional shape, **3a** and **3b** form smooth spin-coated films in contrast to their corresponding crystalline monomers.



X-ray structures of **1a** and **1b** and calculated structure of **1c**.

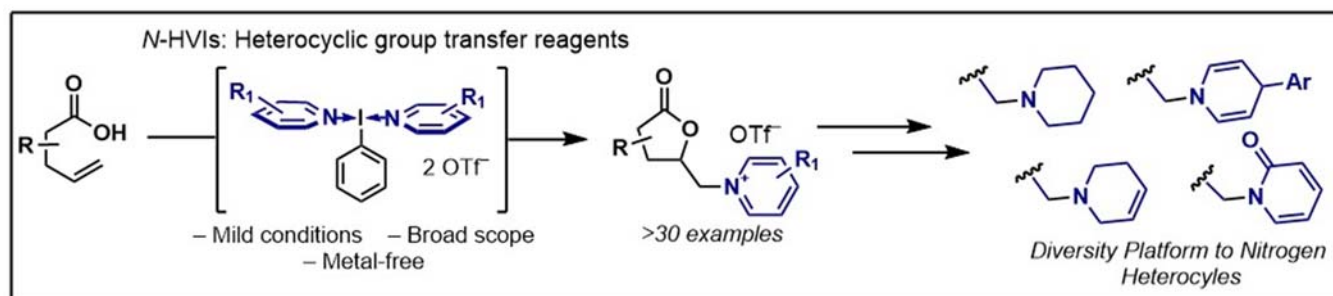
ORGN 183

Synthesis of diverse pyridinium salts via nitrogen-ligated hypervalent iodine mediated aminolactonization

Anthony Tierno¹, Jennifer Walters¹, **Andres Vazquez-Lopez¹**, a.vazquez1120@gmail.com, Xiao Xiao¹, Sarah Wengryniuk². (1) Chemistry, Temple University, Philadelphia, Pennsylvania, United States (2) Chemistry, Temple University, Philadelphia, Pennsylvania, United States

Pyridinium salts are advantageous structures which have diverse applications across materials science, biological processes, and organic synthesis. As synthetic intermediates, these scaffolds can be used as precursors to valuable piperidine derivatives and have recently emerged as important cross coupling handles for metal-catalyzed processes. Unfortunately, current methods to access pyridinium salts are limited; they require harsh conditions, rely on the presence of an amine functional handle, and are not amenable to diverse structural variation.

Herein, we report a novel strategy for pyridinium salt synthesis via aminolactonization of alkenoic acids promoted by *in-situ* generated nitrogen-ligated hypervalent iodine reagents (*N*-HVIs). This novel reagent class serves as “heterocyclic group transfer reagents”, incorporating diverse pyridinium salts under mild conditions and in excellent yields. The resulting pyridinium salts can be functionalized further, via simple known methods to access diverse piperidine motifs, providing access to substitution patterns that can be challenging to access. This strategy enables pyridinium salts to be viewed as a synthetic platform for diversity-oriented amine synthesis for the first time.



ORGN 184

N-(9-Acridinyl)-O-phenylhydroxylamines

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One way to combat cell growth is by targeting the DNA replication mechanism within a cell. The acridine class of molecules is known to intercalate DNA which then binds to Topoisomerase II. This ternary complex can then inhibit the reannealing process during supercoiling which ultimately leads to cellular apoptosis. N-(9-Acridinyl)-O-phenylhydroxylamines can be made in three steps starting from a commercially available aryl bromide. Condensation of the hydroxylamine combined with 9-chloroacridine will lead to the target compound. Substituents include NO₂, CH₃, OCH₃ and Cl which are used to observe the range of electronic effects. Thermal denaturation values and viscosity measurements, using calf thymus DNA, will be used to determine the effectiveness of the compound and electronic factors.

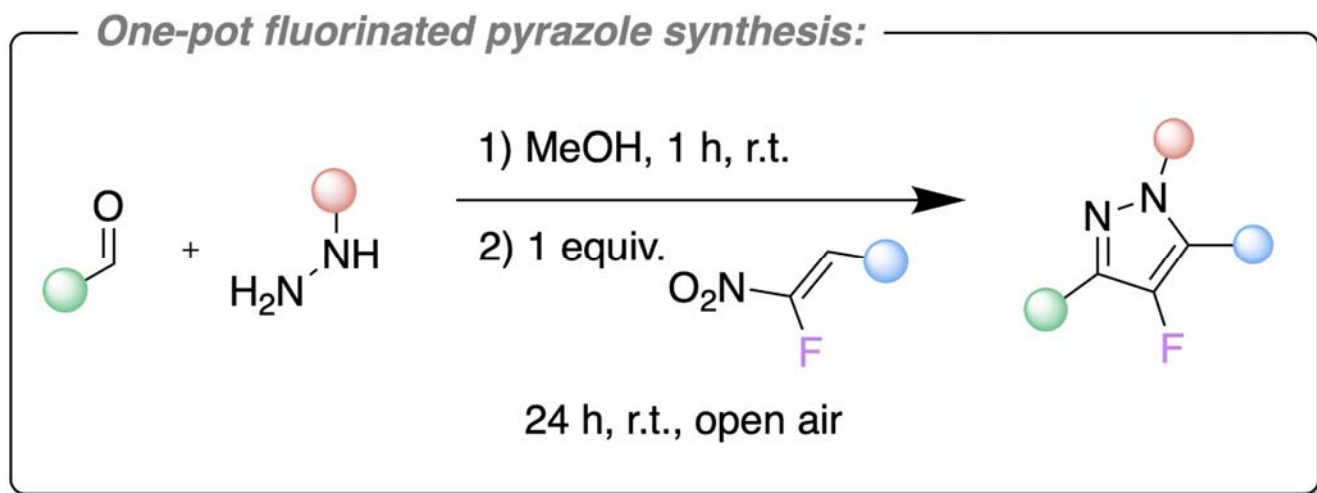
ORGN 185

One-pot synthesis of fluorinated pyrazoles from fluoroalkenes

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Pyrazole-based pharmaceuticals treat a wide array of diseases and conditions including obesity, diabetes, cancer, microbial and viral infections, pain and inflammation, and many neurological disorders. Syntheses for this biologically significant substrate have been well developed, but fluorinated pyrazoles remain to be directly accessible. By 2013, over 25% of all drugs available on the market contained the element fluorine due to its unique characteristics leading to improved target protein binding, bioavailability, and metabolic stability. In order to harness these pharmaceutical benefits of fluorine and overcome its difficulty in handling and stability, our lab sets out to develop new synthetic methods to achieve fluorinated heterocycles. From our recent studies we found that

fluoronitroalkenes can be employed in regioselective [3+2] dipolar cycloaddition reaction with organic azides to generate 1,5-disubstituted-fluorinated-1,2,3-triazoles. Here we show fluoronitroalkenes participate in regioselective cycloaddition in a similar fashion to afford fluorinated pyrazoles from organic hydrazones prepared *in situ*.



ORGN 186

Formation of stable anion radical oligomers from the one electron reduction of alkyl isothiocyanates

Steven J. Peters, **Zain Becerra**, zbecerr@ilstu.edu. Chemistry, Illinois State University, Normal, Illinois, United States

Isothiocyanates are unique heteroallene molecules that are derived in nature from cruciferous vegetables. These molecules have been shown to play an important role in inhibiting multiple metabolic pathways that can effectively show anti-cancer activity. With recent studies showing a correlation between high intake of cruciferous vegetables and lower cancer rates, the need to have a better understanding of the reactivity of these isothiocyanate molecules are important. Recently, our group has shown that isocyanates (RNCO), which are far more reactive than their isothiocyanate analogues (RNCS) due to the more electronegative oxygen, undergo rapid cyclotrimerization initiated by the one electron reduction of the isocyanate monomer (i.e., $\text{RNCO}^{\bullet-}$). The product formed is a stable isocyanurate anion radical, which has been detected via electron paramagnetic resonance (EPR) techniques. The results obtained reveal that the unpaired electron exhibits significant coupling to only two of the three nitrogens in the ring; a consequence of the unpaired electron localized in one of the carbonyl moieties. We are motivated to explore whether isothiocyanates exhibit similar chemistry

upon the reduction to anion radicals (RNCS^{•-}) in solution. Preliminary results reveal that the reduction of a solution containing alkyl isothiocyanates generates three unique anion radical species. It is also apparent that the formation of these anion radicals is much slower when compared to the results obtained from the analogous alkyl isocyanate reduction studies. We believe this is a consequence of the less electronegative sulfur atom in the isothiocyanate moiety. In this presentation, we will discuss the formation of these anion radical species and their structures as supported by EPR and NMR spectroscopic data. Density functional theory (DFT) calculations were also performed to further support the proposed structures resulting from these one electron reduction studies.

ORGN 187

Synthetic chemistry of superelectrophilic phosphonium ions

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A series of aryl-substituted phosphines have been prepared using superelectrophilic aromatic substitution chemistry. This chemistry includes reactive phosphonium-carbenium dications and related species. In addition to low molecular weight, aryl-substituted phosphines, we also are able to prepare macromolecular products. This includes a convenient method of preparing triphenylphosphine-functionalized resins or beads.

ORGN 188

Computational studies of intramolecular and intermolecular Diels–Alder reactions for heterocyclic syntheses

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Both octahydroquinoline and 2-azabicyclo[2.2.2]octane heterocycles are important motifs in the synthesis of alkaloid natural products. These valuable architectures can be constructed through intramolecular Diels–Alder reactions of *N*-substituted oxazolone trienes, and the intermolecular Diels–Alder reactions between α -amido acrylate dienophiles and dihydropyridine-derived dienes, respectively. Computational methods were utilized to explore the factors governing the stereoselectivity of these classes of cycloaddition reactions. Conformational analysis of starting materials, transition state estimates, and products were performed with Spartan'18 using Merck molecular force field (MMFF) and density functional theory (DFT) calculations at the B3LYP 6-31+G(d) level of theory. The resulting low energy conformations for each molecule were evaluated in Gaussian 16 using the M06-2X density functional and transition states were confirmed by intrinsic reaction coordinate (IRC) calculations. The results of this computational investigation will be described and reported herein.

ORGN 189

Charged aza-crown ethers and azolium-linked macrocycles for energy applications

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Nitrogen-containing macrocycles have been utilized in a number of fields, including catalysis, metal and anion complexation, biological applications, and development of materials and sensors. We have prepared a variety of multiply charged azamacrocycles via one-step cyclization and two-step alkylation reactions. The structures contain nitrogen heterocycles such as imidazoliums and 1,4-diazabicyclo[2.2.2]octane (DABCO) that are linked via alkyl and glycol chains of different lengths. We are exploring their use in various energy applications, including conversions to cyclic ionic liquids and carbon dioxide gas separations.

ORGN 190

Determination of reactivity and selectivity for the dearomative dehydro-Diels-Alder reaction of heteroarenes

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The dehydro-Diels–Alder reaction is a powerful synthetic method for preparing highly unsaturated six-membered rings when the initial Diels–Alder adduct involves a cumulated cyclohexadienyl intermediate. However, when the reaction involves the dearomatization of a heteroarene to produce a 1,4-cyclohexadienyl intermediate, harsh conditions and the formation of multiple products compromise its synthetic utility. We are using an iterative process involving experiment and computation to identify factors that influence reactivity and selectivity to expand the reaction scope. DFT transition state calculations and experimentally derived Gibbs free energies of activation are correlated for reactivity determinations. Identification of factors influencing product selectivity are accomplished by experimentally measuring product ratios under a variety of reaction conditions for precursors that differ electronically and sterically. The results from these experiments are guiding the computational studies required for selectivity determination. We will present our findings and mechanistic insight from these reactivity and selectivity studies.

ORGN 191

Synthesis of 2- and 6-substituted tryptophan spectroscopic reporters

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2D IR spectroscopy is a powerful technique used in the structural elucidation of many classes of biomolecules. Analyzing peptides or proteins with this approach requires the incorporation of non-native amino acids possessing IR-active functional groups with IR absorptions orthogonal to those of standard amino acids. Tryptophan is an important target because it is expressed in many functional regions of proteins, and the indole side-chain presents a reactive handle for modification, especially at the 2-position. Syntheses of cyano-, azido-, and thiocyno-labeled tryptophan derivatives have been developed, and the details of routes to these compounds will be described. This synthetic work has enabled experiments detecting peptide structural information through 2D IR spectroscopy.

ORGN 192

Copper iodide catalyzed imino-alkyne hydroamination

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Copper (I) iodide is a practical and efficient catalyst for the intramolecular hydroamination of scaffolds possessing an imino-alkyne array, such as propargyl imidates and propargyl thioimidates. The formation of dihydrooxazoles or dihydrothiazoles is catalyzed by CuI without concomitant aromatization. The reactions proceed in high yield and purity without chromatography or the use of inert/moisture-free atmospheres. Furthermore, these dihydroheterocycles are primed to react with a variety of electrophiles to produce useful functionality and afford the thermodynamically-favored aromatized systems. Example aromaticity-forming reactions include halogenations, borylations, and ene-processes. Preliminary mechanistic investigations support the intermediacy of an alkynyl-copper species, and suggest future opportunities and limitations.

ORGN 193

Convenient synthesis of 2-aryl- α -carbolines via synergistic methods

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Our research focuses on the development of new methodology in synthesizing nitrogen-containing heterocycles known as alpha-carbolines. We have previously reported a transition-metal catalyzed cyclization strategy to synthesize a different isomer, beta-carbolines. This strategy can be utilized for alpha-carboline synthesis through the formation of a cyanamide precursor molecule in five steps. From this precursor, we describe two parallel strategies for the addition of an iodobenzene substituent and subsequent [2+2+2] cyclization: a stepwise sequence using a Sonogashira cross-coupling followed by cyclization with a Rh(I) catalyst, and tandem catalysis using Pd(0). We first optimized the five-step synthesis of the cyanamide precursor to efficiently obtain the desired compound, followed by the optimization of the conditions for tandem catalysis by changing the solvent, catalyst, stoichiometry, temperature, and time. Next, we screened different solvents for Rh(I)-catalyzed cyclization. Finally, we report the synthesis of a series of different substituted alpha-carbolines via both pathways and compare the efficiency of the two strategies for each substituent.

ORGN 194

Synthesis, characterization and bioactivity evaluation of heterocyclic chalcones and their ferrocenyl analogues

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Chalcones consists of an α,β -unsaturated ketone containing two aromatic groups and are found in nature. Chalcones are usually synthesized by a Claisen-Schmidt condensation reaction. These compounds are very diverse synthetically and have shown significant biological activity against various diseases. Literature shows significant potential as antimalarial, antibacterial, antitumor and antioxidant agents, among others. Amongst the explored substituents are heterocyclic moieties such as pyrimidine, thiophene, thiazolyl and indolyl analogues. Due to their significant activity, chalcone analogues have been a very striking synthetic target. Moreover, ferrocenyl chalcones have become of medicinal interest, given that the presence of ferrocene has improved the biological activity of already active compounds. So far, we have synthesized various heterocyclic chalcones and its ferrocenyl analogues in good to moderate yields and have been characterized via ¹H-NMR and ¹³C-NMR spectroscopy. Moreover, we have been able to evaluate bioactivity of ferrocenyl and organic chalcones towards HeLa and MDA-MB-231 and antioxidant activity and establish a comparative between aforementioned analogues. In this presentation, synthetic methodology, analyses, and bioactivity results will be elaborated.

ORGN 195

Synthesis of organic thermoelectric materials with electron withdrawing groups

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The goal of this summer research project was to synthesize a tetracene that has fluorine substituents. When tetracene is bonded by two thio bridges and doped with iodine it forms a substance known as a thermoelectric material (TM). TM's are useful because of their capability to convert heat into electrical energy. Tetracene has already been successfully synthesized with electron donating groups (EDGs), but they have not been successfully synthesized with electron withdrawing groups (EWGs). The reason fluorine was chosen was because of its high electronegativity, and being one of the best EWGs. The possible benefit of a fluorinated tetracene would be that its electrical capacity would be increased, allowing for a better TM. The problem with synthesizing tetracene with EWGs, is that EWGs draw electron density towards itself. This makes it difficult for tetracene to form from its previous substrate due to it using a nucleophilic attack to close the ring forming the tetracene. The research team discussed ways on how to form tetracenes with EWGs, the group settled on a pathway. By starting with 2-butyne-1,4-diol the research team added iodine to form a diiodobutene diol product, with a 97.35%-97.65% yield, this step was the same for each of the groups. The next step was to add a fluorobenzyl compound to the diiodobutene diol product replacing the iodines, this ended with a 21.98% yield. The next step was to oxidize the hydroxyl groups producing aldehydes, giving a 66.37% yield. The last step that was reached during this eight-week period was replacing the aldehydes with dichlorogroups. The yield for this step was negligible. The final step that was not reached was the closing of the tetracene ring. Each product was observed by IR spectroscopy, ¹H NMR spectroscopy, ¹³C NMR spectroscopy, and GCMS. Future research will be conducted in the spring semester of 2020 in which another attempt will be made to develop tetracenes.

ORGN 196

Synthesis of fluorescent anthraquinone derivatives as sensors

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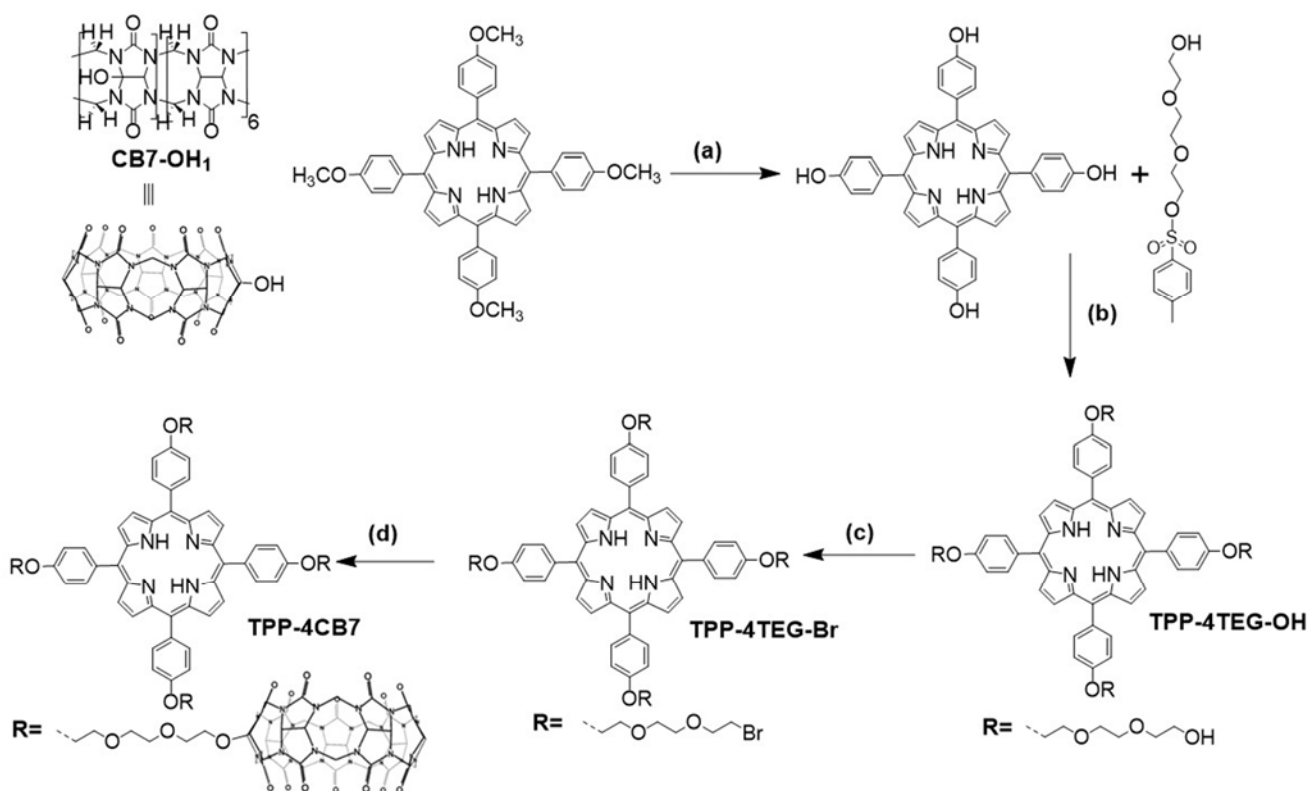
Substituted 1,8-diaminoanthraquinones were prepared, and their electric and optical properties were studied. These compounds further used in the preparation of heterocyclic compounds with fluorescent properties. Applications were investigated for use as ligands and sensors.

ORGN 197

Cucurbit[7]uril-anchored porphyrin-based multi-functional molecular platform

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We have successfully synthesized a novel photoactive supramolecular assembly in which a tetraphenyl-porphyrin core is decorated with four of the receptor molecule, CB7. This assembly (TPP-4CB7) has an appreciable amount of water solubility and thus, can be used in many applications due to its distinctive features including combined photo and chemotherapy, chemo-/bio-sensors and photocatalysis. In this study, we have shown its ability as a photocatalyst in the hydrogen production from water splitting. Although TPP-4CB7 by its own acts as a visible light triggered photocatalyst, its photocatalytic activity has enhanced significantly upon forming nanocomposite with TiO₂ as carbonyl portals of CB7 s act as anchoring groups and co-ordinate with TiO₂ to give rise homogenous mixture. The resulting nanocomposite, TPP-CB-TiO₂@Pt, is very efficient and stable photocatalyst and produces high amount of hydrogen (24.5 mmolh⁻¹g⁻¹, onset potential 10 mV, TOF of 0.202 s⁻¹) without the necessity of extra sacrificial agent in alkaline media.



Scheme 1. Synthesis of TPP-4CB7: (a) BBr₃, CH₂Cl₂, 0 °C 1 h, 25 °C 48 h, 92%; (b) K₂CO₃, KI, DMF, 80 °C, 50 h, 90%; (c) PPh₃, CBr₄, CHCl₃, 0 °C 30 min, 25 °C 60 h, 68% ; (d) CB7-OH₁, DMSO, NaH, 0 °C 10 min, 25 °C 70 h, 72%.

Synthesis of thermoelectric materials with a parent compound

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The goal of this research was to synthesize tetracenes, a promising compound that when combined with two thio bridges and doped with iodine creates an electron flow due to the resonance structures in the aromatic rings to be used as Thermoelectric (TE) materials. TE materials have been used in many aspects of power sources by converting heat to electric energy. Tetracenes with electron-donating groups (EDGs) have already successfully been synthesized at high percent yields, however electron-withdrawing groups (EWGs) have been less successful due to their nature of keeping electron density to themselves. This has led to difficulties in closing the aromatic ring structures of the synthesized tetracenes. The research team collaborated on a new technique of closing the aromatic rings for electron-neutral, electron-deficient, and electron-rich substrates. Our specific team focused on the neutral substrates by starting with 2-butyne-1,4-diol followed by three reported steps from literature. The first reaction is synthesizing the diiodo compound which had a 94-98 % yield. Using this compound and an aryl zinc chloride reagent, our next step was to synthesize symmetrical diols which after crystallization had a 2.24-19.5% yield. The final step our team reached was the synthesis of dialdehydes which had one excellent yield of 77%. We were unsuccessful to reach the next step of the tetrachlorides which theoretically would aid in the closing of the aromatic rings. Each compound was tested using infrared (IR) spectroscopy, TLC (thin-layer chromatography), ¹H NMR, and ¹³C NMR (nuclear magnetic resonance) spectroscopy analysis which was cross-referenced with the literature. Subsequent research is planned for the Spring 2020 semester to complete our original research goal.

ORGN 199

Synthesis of thermoelectric materials with an electron donating group

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The synthesis of tetracenes with electron-withdrawing groups (EWG) that could possibly act as thermoelectric materials, is the overarching goal of this research. Thermoelectric (TE) materials have the ability to use the free energy from waste heat to create a temperature difference that can then be used to conduct electrical energy. The synthesis of tetracenes with EDG has been successful in terms of producing them in high yields and in economically-friendly ways, yet the synthesis of tetracenes with EWGs, such as halogens remains unaccomplished. This specific project focused on the synthesis of tetracenes with electron-donating groups (EDG). By demonstrating that this new procedure is effective for substrates with EDGs, it gives hope that EWGs will also be successful. The synthesis of tetracenes was a multi-step project which began with the synthesis of (E)-2, 3-diiodobut-2-ene-1, 4-diol from 2-butyne-1, 4-diol, resulting in a

yield of 94-98%. The following step of converting (E)-2, 3-diiodobut-2-ene-1, 4-diol to (E)-2, 3-bis (4-methylbenzyl) but-2-ene-1, 4-diol was done under an atmosphere of nitrogen producing yields ranging from 7% to 49%. The yield was improved as purification and recrystallization techniques improved. The diol was then oxidized into 2, 3-bis (4-methylbenzyl) fumaraldehyde under aerobic conditions with a 74% yield. The identity of all compounds was confirmed using thin layer chromatography (TLC), single pulse ^1H and ^{13}C NMR, all which matched the data reported in literature. The progress of the research stopped with the synthesis of 2, 3-bis (4-methylbenzyl) fumaraldehyde due to time constraints, but upon completion of project, the possibility of these compounds demonstrating good heat conducting can be examined.

ORGN 200

Double conjugate addition reactions with olefinic N-heterocycles

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We have developed a series of reactions with vinylpyridines and related systems wherein double conjugate addition is accomplished at enol carbons. This chemistry provides convenient access to functionalized heterocycles. The work includes attempts to develop new polymerization reactions using this chemistry.

ORGN 201

Fundamental study on desulfurization of petroleum using synthesized novel ionic liquids and betaine moieties

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With conventional light and middle crude oil production in decline, efforts have increasingly turned to heavy and extra heavy crude oils production. However, these oils contain a much greater proportion of sulfur- and nitrogen-containing heterocycles than lighter crude, which is resistant to current desulfurization and denitrogenation processes. These compounds not only contribute to emission of SO_x and NO_x pollutants upon combustion, but also create difficulties in crude oil production, transport, refinery and its conversion to useful petrochemicals.

This research will alleviate that problem by focusing on the ionic liquid extraction of five of the most prevalent heterocyclic compounds - thiophene, dibenzothiophene, alkyldibenzothiophenes, dibenzopyrrole (carbazole), and alkyldibenzopyrroles. By using a two-stage process that first separates the nitrogen-containing pyrroles from the sulfur heterocycles we hope to simplify the purification of individual components for later resale.

Our strategy is to use glycine-derived, tetraalkylammonium carboxylate betaines for the

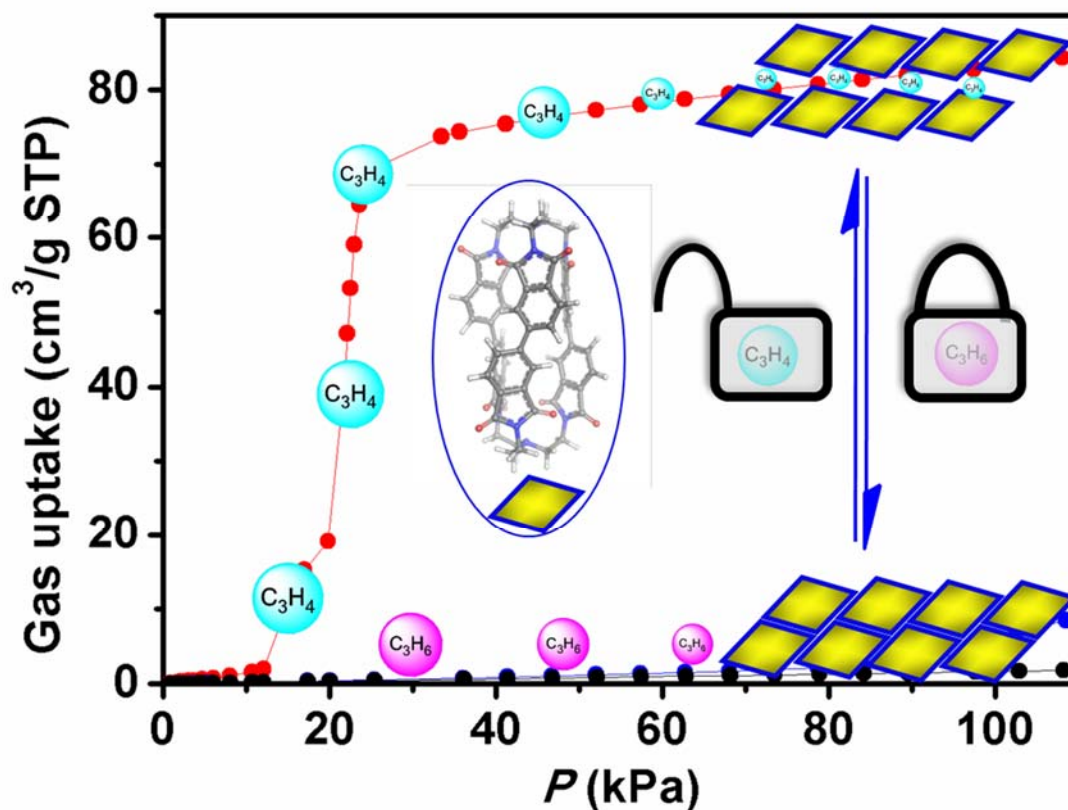
selective extraction of pyrroles taking advantage of the hydrogen bonding affinity of the pyrrole N-H to carboxylates. Subsequently, thiophenes will be extracted from the remaining crude using imidazolium ionic liquids. These ionic liquids will bear a tethered electron-poor aromatic ring, which will act in tandem with the electron-poor imidazolium core to π -stack with the electron rich thiophene core. The selectivity and extractive efficiency of each ionic liquid will be determined using a dodecane model system containing all five components and measuring the extraction content by spectroscopic means, primarily Nuclear Magnetic Resonance spectroscopy.

ORGN 202

Design and synthesis of soft porous crystal based upon organic cages for applications in gas separation

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Soft porous crystals (SPCs) as exemplified by third-generation metal–organic frameworks (MOFs) are attracting attention for their stimuli-responsive behavior that is accompanied by reversible structural transformations. Structural dynamism offers potential for applications as diverse as selective gas adsorption and separation, gas storage, sensing, smart materials, and so forth. However, the design and synthesis of SPCs is challenging. We report a new type of SPC based on a [2 + 3] imide-based organic cage (NKPOC-1) and find that it exhibits guest-induced breathing behavior. Various gases were found to induce activated NKPOC-1 crystals to reversibly switch from a “closed” nonporous phase (α) to two porous “open” phases (β and γ). The net effect is gate-opening behavior induced by CO₂ and C₃ hydrocarbons. Interestingly, NKPOC-1- α selectively adsorbs propyne over propylene and propane under ambient conditions. Thus, NKPOC-1- α has the potential to separate binary and ternary C₃ hydrocarbon mixtures, and the performance was subsequently verified by fixed bed column breakthrough experiments. In addition, molecular dynamics calculations and in situ X-ray diffraction experiments indicate that the gate-opening effect is accompanied by reversible structural transformations. The strategy of using organic cages to form SPCs has a broad scope and is likely to offer a new approach to utilizing molecular crystals for gas separations.



The NKPOC-1- α selectively adsorbs propyne over propylene and propane under ambient conditions

ORGN 203

Studies towards synthesis of phakellin and its analogues such aza- and bis-aza-indolo phakellins

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Phakellin belongs to the pyrrole–imidazole family of marine sponge derived alkaloids which contain intriguing structural features and potent bioactivities. We are involved in development of a novel and effective method to synthesize phakellin and its analogues from Imidazoformimidamide chemistry. This method provides a simple way to prepare the tricycle ring and can be used to prepare more complex members of the Phakellin family. The progress will be presented.

ORGN 204

One pot synthesis of angular-luotonins from quinazolinonylenones via novel aza-Nazarov chemistry

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We have uncovered a novel aza-Nazarov cyclization of quinazolinyl enones to tricyclic enols. TfOH/TFA system was found to be effective for this key aza-Nazarov cyclization step, and the regioselectivity of it is dependent upon proton availability in the reaction medium. We have successfully coaxed the Friedlander quinoline annulation step in to the aza-Nazarov reaction setup so as to trap the angular enols in to angular luotonins. The synthesized library of these luotonins (**10a-n**) are being evaluated for both general cytotoxicity and topo-I inhibition, and results will be reported along with the synthesis details.

ORGN 205

Design and synthesis of reverse amides of 4/5-acyl -2-amino imidazoles as oroidin analogues for biofilm inhibition

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We had developed acyl 2-aminoimidazoles as modified oroidin analogues. Further optimization efforts of this series via reverse amide strategy enabled an expedient generation of the library involving modification of the amide part. The synthesis details along with the bio-assay results will be presented.

ORGN 206

Synthesis of a precursor to an isoprene-derived Criegee intermediate and spectroscopic characterization

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(2) Chemistry, The College of William and Mary, Williamsburg, Virginia, United States

Isoprene, the most abundant organic molecule in the atmosphere, undergoes ozonolysis to produce Criegee Intermediates. These derived Criegee intermediates are an important source for the generation of atmospheric hydroxyl radicals. In order to perform selective analysis of the Criegee Intermediate methyl vinyl ketone oxide, an iodoallyl iodide precursor was prepared in 3 steps. Synthesis of this precursor, as well as photolysis and spectroscopic analysis of the derived Criegee intermediate, is described.

ORGN 207

Synthesis of pyrrolodiketopiperazine derivatives

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The pyrrolodiketopiperazine core is found in several natural products and bioactive molecules. The synthesis of pyrrolodiketopiperazines has been investigated starting with an intact diketopiperazine and appending the pyrrole motif. The key pyrrole annulation has been effected under two different reactions conditions which employ either protic acid or gold catalysis.

ORGN 208

Alkene dicarbofunctionalization by metallacycle contraction process

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Catalytic dicarbofunctionalization of unactivated alkenes is an emerging synthetic method that holds a great promise to furnish a modular, convergent, and expedient route to generate complex molecules rapidly from readily available starting materials. Although a tremendous progress has been made in the field, there is much more research problem yet to be solved. Here, we disclose a transmetalation-initiated Ni(I)-catalyzed regioselective β,δ -vinylarylation of γ,δ -alkenyl α -cyanocarboxylic esters with vinyl triflates and arylzinc reagents. This reaction proceeds via a simple functional group-assisted contraction of six-membered nickellacycles to five-membered nickellacycles to form two new carbon-carbon bonds at the nonclassical homovincinal sites, and provides expeditious access to a wide range of complex aliphatic α -cyanoesters, α -cyanocarboxylic acids, dicarboxylic acids, dicarboxylic acid monoamides, monocarboxylic acids, nitriles and spirolactones. Control, deuterium labeling and crossover experiments indicate that the nickellacycle contraction occurs by β -H elimination followed by hydronickellation on transiently formed alkenes, and that the Ni species are stabilized as Ni-enolates.

ORGN 209

Computational studies of the transmetalation mechanism in Stille cross-coupling reactions

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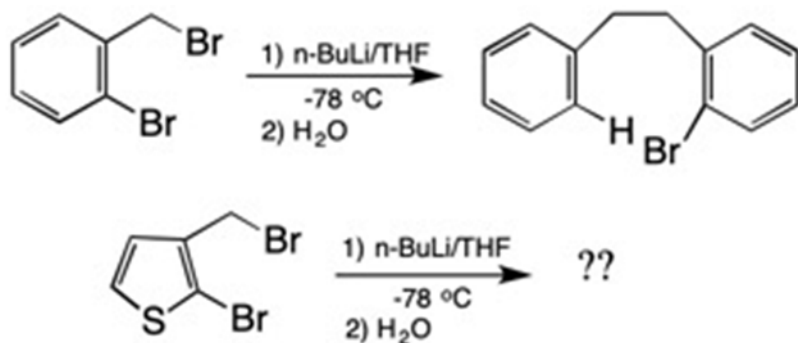
The Stille cross-coupling reaction is a mild and selective way to form C-C bonds with control of stereochemistry. Prior reports reveal that the transmetalation step governs the stereochemistry of the product when two chiral alkylstannane coupling partners are used. Two Sn-Pd transmetalation pathways are possible: the open transmetalation mechanism, which leads to inversion in stereochemistry, and the cyclic mechanism, which leads to retention. However, it is unclear how the structure of the reactants or catalysts may favor one mechanism over the other and thus dictate the stereochemistry of the final product. In this study, density functional theory was used to compare the open and cyclic mechanisms for several alkylstannanes. It was determined that benzyl stannanes favor the open transmetalation pathway, while other alkylstannanes favor the cyclic pathway. Additionally, the effect of the aryl halide was examined, and smaller halides result in lower barriers in the open pathway. These results provide clearer insight of ways to control stereochemistry in the Stille cross-coupling.

ORGN 210

Lithium-halogen exchange studies of bromoalkyl bromothiophenes

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Based on the lithium-halogen exchange behavior of o-bromobenzyl bromides, a study has been undertaken to ascertain if comparably substituted thiophenes exhibit the same reactivity. The work in this area to date will be described.



ORGN 211

Cobalt-complexed acetylenic tetrads, a novel molecular scaffold for quadruple ionic functionalization reactions

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Propargyl α,α' -diethers are scarcely studied substrates in transition metal-mediated ionic and radical reactions. In a purely organic setting, incorporation of nucleophiles into propargylic positions cannot be carried out efficiently due to acetylene-allene rearrangement, and also a lack of mechanistic tools that could control the regioselectivity of the C-C bond formation. In this account, novel methods are developed for introducing a variety of nucleophiles into α - and α' -positions of the acetylenic tetrad wherein the triple bond is immobilized by π -bonding to a dicobalthexacarbonyl core. The requisite unsymmetrical α,α' -propargyl diethers were synthesized in three steps (condensation-methylation-complexation), followed by the Lewis acid-assisted incorporation of a series of nucleophiles, such as aromatics (benzene, furan), enol ethers, allyl silanes, nitriles, and β -diketones. An excellent site-selectivity was achieved by fine-tuning the electrophilicity of the tetrad's competing termini with benzylic [α -phenyl, α -3,4,5-trimethoxyphenyl, α -(β -naphthyl)] and primary cationoid intermediates acting as alternative reaction sites. Novel synthetic protocols allowed for introducing either a given nucleophile to both termini of the acetylenic tetrad (α -Nu¹- α' -Nu¹; α -Nu²- α' -Nu²), or a pair of select nucleophiles arranged asymmetrically in opposing sequences (α -Nu¹- α' -Nu²; α -Nu²- α' -Nu¹). Overall, quadruple functionalization allowed for expansion of the reagent and product base, provided access to topologically and functionally diverse molecular assemblies, and also laid the groundwork for future studies on the 1,4-asymmetric induction and ionic-radical transformations.

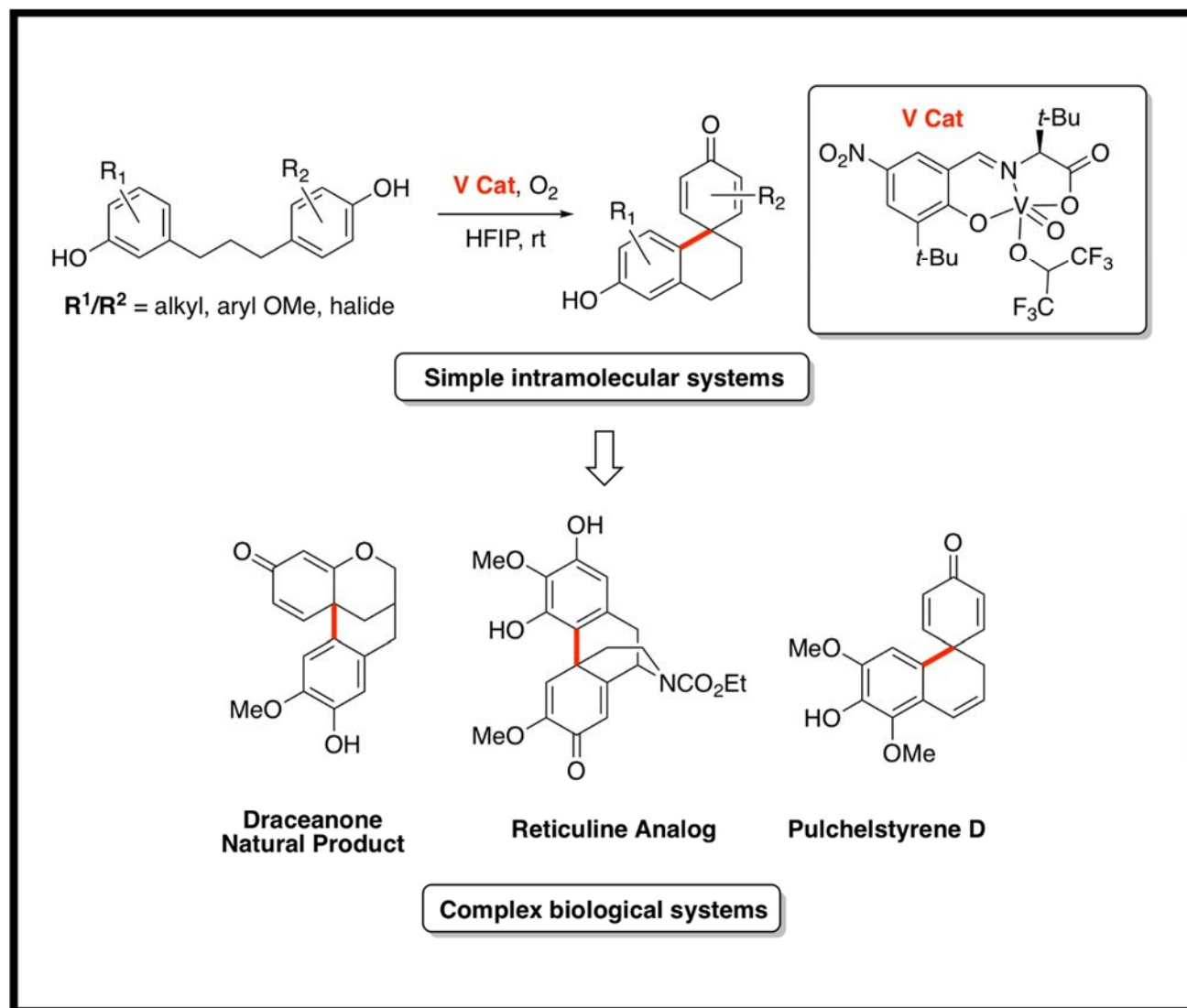
ORGN 212

Vanadium-catalyzed intramolecular oxidative coupling of tethered phenols to generate phenol-dienone products

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The oxidative, intermolecular homo- and cross-coupling of phenols has been an area of intense interest over the last decade. Despite this, the intramolecular coupling of unactivated C-H and C-C positions in tethered bisphenols to form complex molecular architectures remains a challenge to synthetic organic chemists. Inspired by prior work within our group, a simple, bench-stable vanadium(V)-oxo catalyst was developed for the intramolecular oxidative coupling of simple tethered phenols to form phenol-dienone products with a newly generated quaternary center. This mild reaction is catalytic in vanadium, utilizing oxygen as a co-oxidant, and demonstrates broad scope in substitution type and pattern on the tethered phenol rings. Given the prevalence of the phenol-dienone motif in natural products and related compounds, this method was applied to the syntheses of three biologically relevant molecules. Most notably, *N*-(ethoxycarbonyl)-5'-hydroxynorreticuline was oxidized catalytically to its corresponding salutaridine derivative, a chemical transformation which is biomimetic to the key

oxidative coupling step in the biosynthesis of morphine. This newly developed intramolecular coupling reaction proceeds in good yield with catalytic quantities of vanadium and may offer a mild, operationally simple alternative to similar reported transformations.



ORGN 213

Gold(I) catalyzed synthesis of 1H-isochromenes

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Belonging to a greater class of biologically active molecules known as benzopyrans, 1H-isochromenes and their isomers have been known to exhibit antitumor and antileishmanial activity. An atom economical synthesis of these valuable organic moieties has been developed utilizing a gold(I) catalyzed cyclization of o-alkynylbenzyl alcohols. The desired isochromene has been isolated in good yields exclusively yielding the 6-endo-dig product for most substrates. Moreover, selectivity for the 5-exo benzofuran product can be controlled by careful choice of gold catalyst. Current work is underway to investigate the mechanism of this reaction and expand its scope toward secondary and tertiary alcohols.

ORGN 214

Gold-catalyzed Friedel–Crafts-like reaction of benzylic alcohols to afford 1,1-diaryllkanes

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Microwave-assisted gold catalysis has been employed to promote Friedel–Crafts-like reactions of benzylic alcohols. Functional 1,1-diaryllkanes were prepared in good to excellent yields under mild conditions. The transformation showed good reaction scope, tolerating a range of cyclic and acyclic benzylic alcohols containing electron rich and electron deficient functional groups. Application of this gold catalysis methodology was also used to prepare a series of substituted fluorenes and pharmaceutically relevant compounds. Kinetic isotope effect and mechanistic considerations will be also discussed.



ORGN 215

Generation of carbamate-derived nitrenes and evaluation of their inter- and intramolecular reactivity with alkenes

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Though ubiquitous in nature, small molecules with carbon-nitrogen bonds are often difficult to prepare in the laboratory. Arguably, the most efficient method of C-N bond access is through nitrene intermediates. Nitrenes, neutral, monovalent, high-energy species, are can be effective as intermediates for skeletal rearrangements and electrophilic insertion into a variety of bonds, such as alkenes. Reactions reliant on the use of nitrenes often lack regiocontrol and selectivity. In this work, we investigate the formation of nitrenes by oxidation of carbamates using a hypervalent iodine oxidant and subsequent transfer to an alkene by means of a dirhodium catalyst, resulting in aziridination, C-N insertion, or [3 + 2] cyclization. Through optimization protocols, we evaluate the identity of the hypervalent iodine oxidant and the dirhodium catalyst in controlling nitrene formation and reactivity. We also report the effects of alkene geometry and substitution in the resulting products.

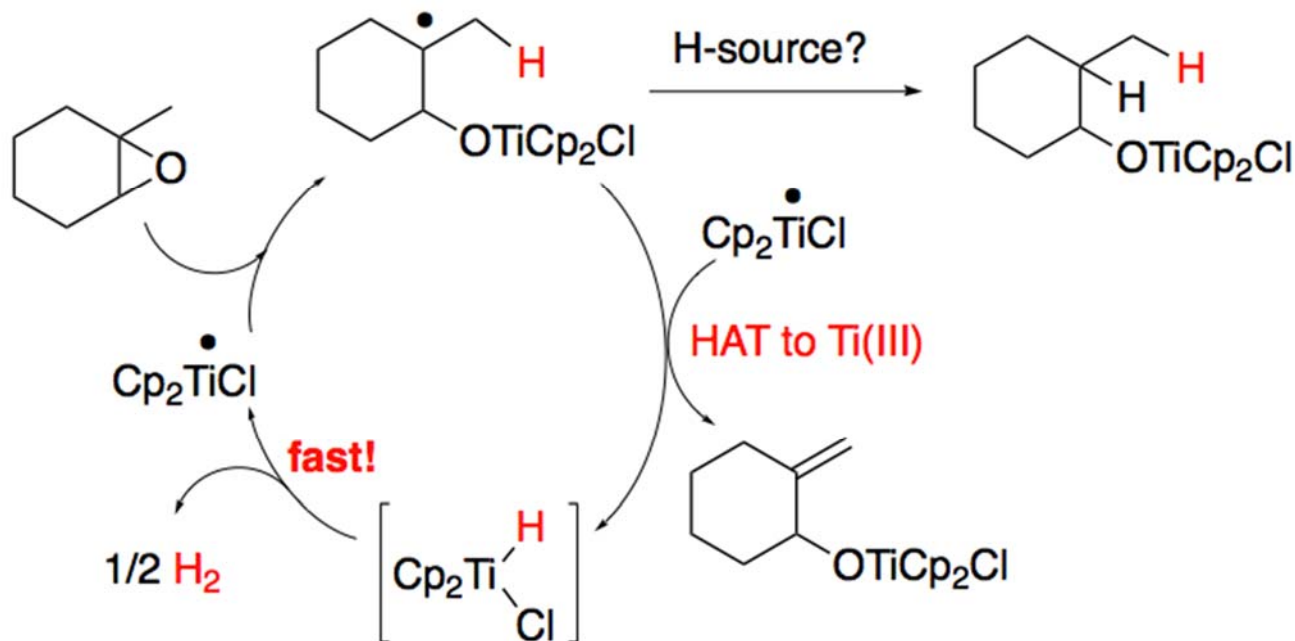
ORGN 216

Demystifying $\text{Cp}_2\text{Ti}(\text{H})\text{Cl}$ and its enigmatic role in the reactions of epoxides with Cp_2TiCl

Jonathan P. Gordon¹, *gordon.977@osu.edu*, **Sven Hildebrandt**², **Kendra Dewese**¹, **Sven Klare**², **Andreas Gansäuer**², **T.V. RajanBabu**¹, **Bill Nugent**¹. (1) Chemistry, The Ohio State University, Columbus, Ohio, United States (2) Kekulé-Institut für Organische Chemie und Biochemie, Universität Bonn, Bonn, Bonn, Germany

The role of $\text{Cp}_2\text{Ti}(\text{H})\text{Cl}$ in the reactions of Cp_2TiCl with trisubstituted epoxides has been investigated in a combined experimental and computational study. Although $\text{Cp}_2\text{Ti}(\text{H})\text{Cl}$ has generally been regarded as a robust species, its decomposition to Cp_2TiCl and molecular hydrogen was found to be exothermic ($\Delta G = -11$ kcal/mol when the effects of THF solvation are considered). In laboratory studies, $\text{Cp}_2\text{Ti}(\text{H})\text{Cl}$ was generated using the reaction of 1,2-epoxy-1-methylcyclohexane with Cp_2TiCl as a model. Rapid evolution of hydrogen gas was measured, indicating that $\text{Cp}_2\text{Ti}(\text{H})\text{Cl}$ is indeed a thermally unstable molecule, which undergoes intermolecular reductive elimination of hydrogen under the reaction conditions. The stoichiometry of the reaction ($\text{Cp}_2\text{TiCl}:\text{epoxide} = 1:1$) and the quantity of hydrogen produced (1 mol per 2 mol of epoxide) is consistent with this assertion. The diminished yield of allylic alcohol from these reactions under the conditions of protic versus aprotic catalysis can be understood in terms of the predominant titanium(III) present in solution. Under the conditions of protic catalysis, Cp_2TiCl complexes with collidine hydrochloride and the titanium(III) center is less available for “cross-disproportionation” with carbon-centered

radicals; this leads to byproducts from radical capture by hydrogen atom transfer, resulting in a saturated alcohol (2-methylcyclohexan-1-ol).



ORGN 217

Synthesis of a variety of chiral triazolylidene-metal complexes and investigation on the catalytic activity

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N-heterocyclic carbenes (NHCs), with their strong σ -donor ability, have structural diversity by tuning the electronic or steric properties of the nitrogen substituents. So they are recognized one of the most powerful ligand classes in transition-metal catalysis. Among the NHCs, mesoionic carbenes (MICs) have no neutral resonance form, and the electron-donating power can be further enhanced by reducing the number of heteroatoms stabilizing the carbene carbon than Arduengo-type normal imidazolylienes. The backbone triazol rings can be easily accessed through [3+2] cycloaddition of alkynes and azides, so many researchers have developed the MICs-complexes. However, despite significant progress there are few reports regarding the synthesis of chiral triazolylidene-metal complex.

Herein, we focused on planar chiral ferrocenes with large and rigid chiral environment. Based on this ligand design, we develop new chiral triazolylidene-metal complexes. In 2018, we reported ferrocene-based planar chiral triazolylidene-paradium complexes exhibited good enantioselectivity for the asymmetric Suzuki-Miyaura cross coupling reaction.

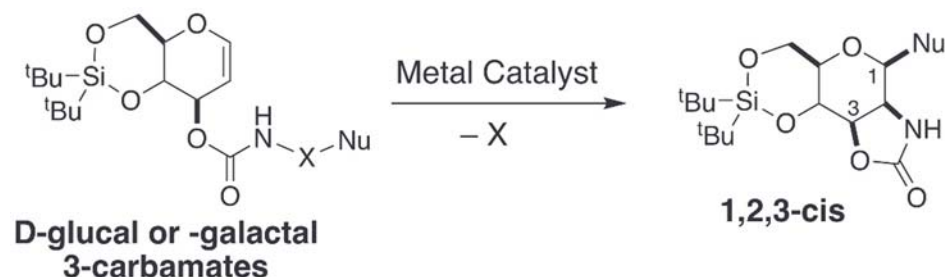
To expand the generality of triazolylidenes with planar chiral ferrocene, we synthesized a variety of chiral triazolylidene-metal complexes and investigated on the catalytic activity.

ORGN 218

Stereoselective synthesis of 1,2,3-cis oxazolidinone-containing 2-amino sugars via fully intramolecular amidoglycosylation

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2-Amino sugars are ubiquitous in biomolecules and pharmaceutically relevant molecules, necessitating versatile methodologies for their synthesis. This work involves all-syn-selective oxidative amidation of D-glycal derivatives to synthesize oxazolidinone-containing 2-amino sugars. We have investigated the stereocontrolled synthesis of 1,2,3-cis amidoglycosylation products by fully intramolecular routes. In this strategy, an acyl nitrene source tethered at the 3O-position of the glycal also incorporates a nucleophile, either directly, or through an extrudable linker. Metal-mediated N–X activation can lead to syn addition across the C1–C2 double bond, resulting in selection for the 1,2-cis anomer over the 1,2-trans product, while the 2,3-cis relationship is set by the intramolecularity of the initial enol ether amidation. We have examined catalysis by $[\text{Cp}^*\text{IrCl}_2]_2$ as well as Fe(II) with a variety of added ligands. Synthesis of the pre-*N*-oxidized (N–X-type) carbamate starting materials has been investigated and optimized, while studies for further development of the fully intramolecular amidoglycosylation reaction involve glycosyl acceptor diversification.



ORGN 219

Exploring nickel catalysis in allene synthesis

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Allenes have continuously attracted the attention of researchers for decades due to their presence in bioactive natural products and pharmaceuticals, unique geometry, and ability to transfer chirality. Allenes are also high value products in the medicinal chemistry community because they play key roles in the biological activity of numerous natural products, and serve as precursors to complex synthetic targets. As in other aspects of synthetic chemistry, many methods producing substituted allenenes require the use of a precious metal catalyst such as palladium, iridium, and silver. While palladium catalysts in particular have made substantial contributions to synthetic chemistry, relying on precious metal catalysts is not only expensive, but unsustainable due to their low natural abundances. The field of transition metal catalysis has been moving toward investigating the use of first-row transition metals because of their the relatively high natural abundances and sustainability. These qualities make first-row elements attractive candidates for catalysis in comparison to the corresponding precious second- and third-row transition metals which currently dominate the field. We are particularly interested in looking into how palladium can be replaced with nickel, its first-row counterpart, in allene formation. This work focuses on the reactions of in-situ formed metallo-allenes with various nucleophilic compounds. This will enhance the field's breadth and offer a more sustainable approach to allenic precursors for bioactive and synthetically interesting compounds.

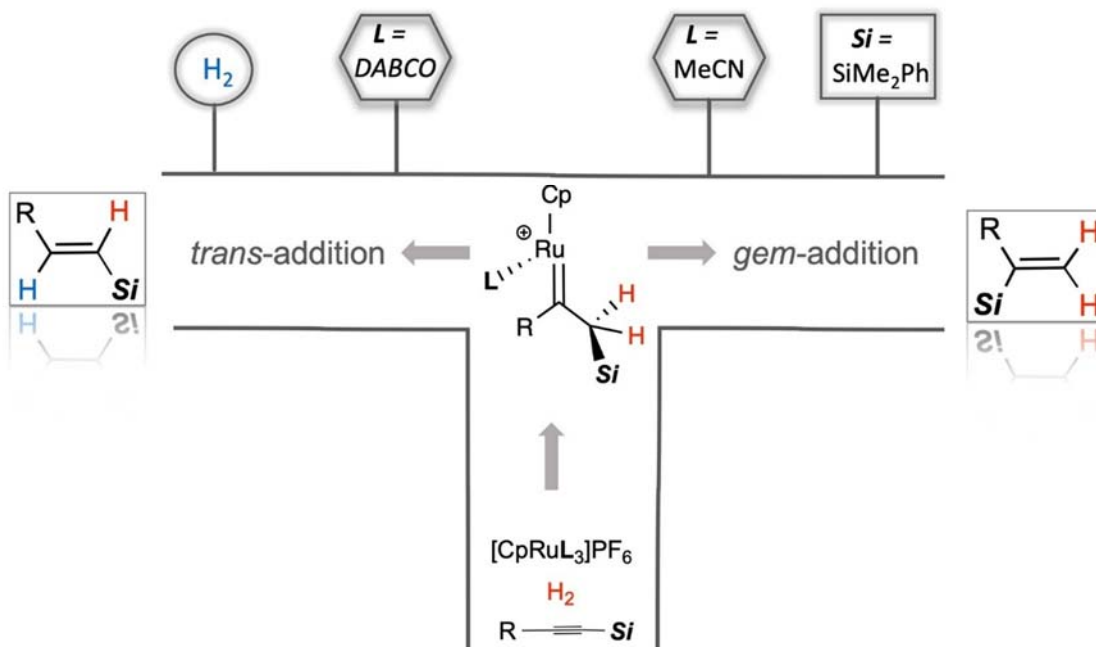
ORGN 220

Ru-catalyzed migratory geminal semi-hydrogenation of internal alkynes to terminal olefins

Qiang Feng¹, *qfengab@connect.ust.hk*, **Jianwei Sun**². (1) chemistry, HKUST, Hongkong, Hongkong, China (2) Chemistry Dept., Hong Kong U of Science and Technology, Kowloon, Hong Kong

Semi-hydrogenation of alkynes to alkenes represents a fundamentally useful transformation. In addition to the well-known cis- and trans-semi-hydrogenation, herein a geminal semi-hydrogenation of internal alkynes featuring 1,2-migration is described, which provides new access to the useful terminal vinylsilanes. This process also presents a new mode of reactivity of silyl alkynes. With the proper choice of the cationic $[\text{CpRu}(\text{MeCN})_3]\text{PF}_6$ catalyst and a suitable silyl group, both aryl- and alkyl-substituted silyl alkynes can participate in this highly efficient gem-selective process. Furthermore, dedicated condition optimization also allowed switching of selectivity from gem to trans by using a combination of parameters, including the suitable silyl group, additive and H_2 pressure. A systematic DFT study on the reaction mechanism revealed that the

formation of the gem-H₂ Ru-carbene might be the key intermediate in both gem- and trans-addition reactions, rather than the Ru-vinylidene intermediate. The DFT results were further supported by carefully designed control experiments. This uncommon gem-addition combined with 1,2-silyl migration in the metal-carbene intermediate should open up a new synthetic avenue for alkyne transformations.



ORGN 221

Copper-catalyzed disilane activation and hydrosilylation of aldehydes via an intermediate brook rearrangement

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Currently, the most efficient methods for developing organosilanes utilize expensive heavy-metal catalysts like platinum and palladium and expensive silylating reagents, such as silylboraness which are also air/water sensitive. Herein we report a hydrosilylation that uses a copper metal catalyst and a disilane silicon source. However,

unlike silylboranes which produce the α -silyl alcohol, silylations with disilanes tend to form the alkoxydisilane. The reasons for this divergence in reactivity are unclear, but mechanistic studies suggest that electron deficient silanes promote a Brook Rearrangement. Mechanistic studies that include computational studies and in situ reaction characterization will be discussed. Using a less electron-deficient disilane may be a possible means of reversing reactivity and may decrease the likelihood of the Brook rearrangement.

ORGN 222

Synthesis of naturally occurring compounds via ketenimines

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The copper catalyzed cycloaddition reaction of sulfonyl azides and terminal alkynes has been utilized in the synthesis of 1,2,3-triazoles and to access the highly reactive ketenimine intermediate. Ketanimines are very electrophilic and react with a wide range of nucleophiles that allow for their utility in total synthesis. Herein, we report a ketenimine/keteniminium strategy for the synthesis of indole and lactam naturally occurring compounds.

ORGN 223

Molybdenum-promoted synthesis of isoquinuclidines with bridgehead CF₃ groups

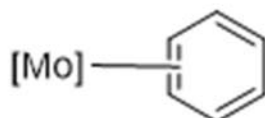
Justin H. Wilde, *jhw3au@virginia.edu*, **Walter D. Harman**. Chemistry, University of Virginia, Charlottesville, Virginia, United States

Although nitrogen-coordinated complexes of pyridine are ubiquitous in organometallic chemistry, other coordination modes are substantially less common. Especially unusual are η^2 -(C,C)-coordinated complexes, with only a few examples found in the literature. Dihapto-coordination is of considerable interest, as this binding mode promotes addition reactions that lead to dearomatization. This work explores the synthesis and organic reactivity of dihapto-bound pyridine complexes of a second-row metal, molybdenum, with the goal of producing substituted dihydropyridines via regio- and stereoselective additions. Given that molybdenum generally forms weaker bonds to arenes compared to analogous third-row dearomatization agents, it was uncertain whether such η^2 -pyridine complexes could be successfully isolated and carried through organic transformations. MoTp(NO)(DMAP)(4,5- η^2 -2-(trifluoromethyl)pyridine) (Tp = tris(pyrazolyl)borate, DMAP = 4-(dimethylamino)pyridine) was investigated to elucidate the effect of an electron-withdrawing substituent on dihapto-coordinate pyridine reactivity. N-methylation followed by treatment with nucleophiles, including Grignard reagents and organozinc compounds, allows the formation of various substituted

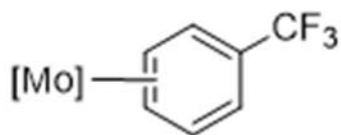
dihydropyridine complexes. The free dihydropyridines can be liberated from the metal without rearomatization by oxidation, and elaborated to form novel bridgehead CF₃-substituted isoquinuclidines. Additionally, an enantioselective variant has been demonstrated, illustrating the synthetic utility of this method to access compounds of potential medicinal relevance.

Known

Unstable

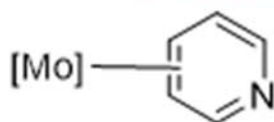


Electron-withdrawing group
stabilizes η^2 -benzene complex

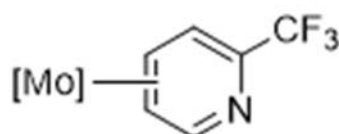


Proposed

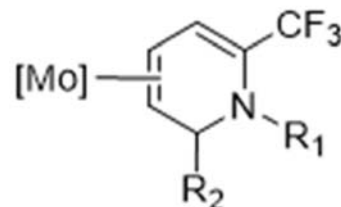
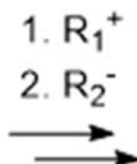
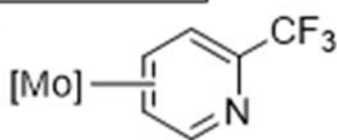
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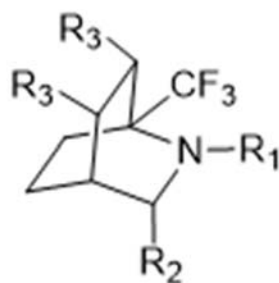
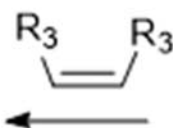
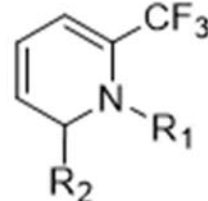
- M-L bond **strengthened**
- M more resistant to oxidation
- CF₃ group blocks N-coordination



Application



[O]



Synthesis and use of amidine ligands for catalyst development

Mohammad Sadegh Laeini, *mlaeini@siue.edu*, Sarah B. Luesse. Chemistry, Southern Illinois University Edwardsville, Edwardsville, Illinois, United States

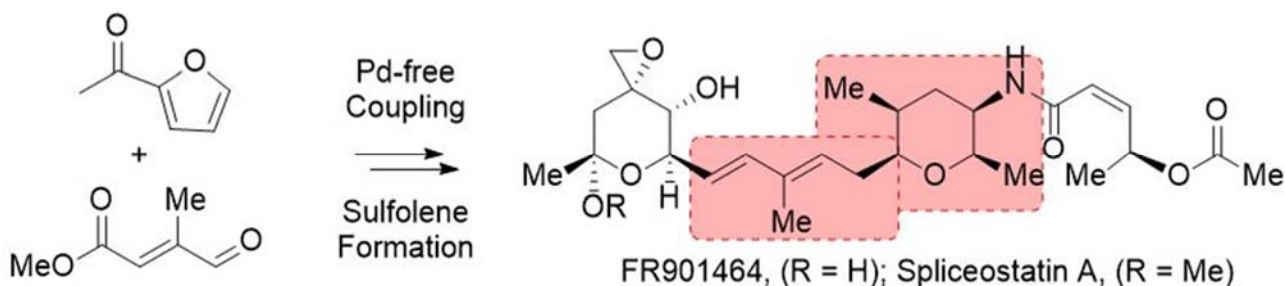
The development of organic and organometallic complexes to promote bond-forming processes is in demand. Bisamidine ligands have shown their utility as ligands and as organocatalysts. This work has focused on the preparation of amidine-derived ligands and efforts toward the preparation of new chiral catalysts. Initial complexation studies have provided important structural information, guiding our proposed reaction development.

ORGN 225

Convenient synthesis of spliceostatin derivatives

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Optically active synthesis of Spliceostatin derivatives via the construction of the tetrahydropyran (THP) core intermediate has been investigated. An optimization of a palladium-free transmetalative cross-coupling of the furan and diene allows for concise access to the THP core after minimal transformations. Formation of a sulfolene intermediate allows for protection over several steps to avoid the formation of an undesired triene byproduct. A detailed study of the Pd-free coupling will be presented.



ORGN 226

Synthetic and catalytic studies of metalloporphyrin and metallosalen complexes for biomimetic oxidations

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Cytochrome P450 (CYP450) enzymes catalyze important oxidation reactions in Nature which serve as inspiration for use of synthetic metal complexes as biomimetic catalysts. Several porphyrin free ligands containing different aryl groups and several salen ligands containing different substituents were synthesized according to well-documented procedures. Metals of iron, manganese, and ruthenium were inserted into the porphyrin ligands, while metals of chromium, manganese, and iron were inserted into the salen ligands and the resulting metal complexes were characterized by ¹H-NMR and UV-vis spectroscopies. With PhI(OAc)₂ and 2,6-Cl₂PyNO as a mild oxygen sources, the catalytic ability of the metal complexes were evaluated in alkene epoxidation, alkane hydroxylation, and sulfoxidation. High conversions and excellent chemoselectivity without overoxidation of sulfoxides into sulfones were obtained with various substrates. Of note, visible light irradiation was found to promote the ruthenium porphyrin-catalyzed oxidation in a significant way, which will be discussed in the presentation.

ORGN 227

Four-substrate guided inquiry scheme towards the synthesis of 2,2'-bipyridine adducts

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The project focuses on the preparation of 2,2'-bipyridine adducts for future use as ligands in novel organometallic ruthenium complexes. The first specific aim of the project includes utilizing substituted versus un-substituted bromo pyridines to explore the effects of electron donating groups on the efficiency of the reactions. The second specific aim of the project focuses on evaluating the differences of palladium(0) versus palladium(II) catalysts on the reactions.

Specifically, the compounds being synthesized are unsubstituted 2,2'-bipyridine versus a 4,4'-dimethylated, a 5,5'-dimethylated, or a 4,4'-diamino 2,2'-bipyridine. The synthetic method being explored is a homo-coupling reaction relying on a palladium catalyst. The catalyst being used is either tetrakis(triphenylphosphine)palladium(0) or a bis(triphenylphosphine)palladium(II) chloride in xylene as the choice.

The methodology has been developed to ensure an air-free environment, by assembling the closed reaction chamber in a nitrogen glovebox. The reaction is completed on a Schlenk-line assembly under an inert argon atmosphere, evaluated under different time frames varying from 12 to 72 hours. Reaction progress is monitored with thin layer chromatography. The product is isolated and purified via acidic extraction, and if needed, sublimation. Compound characterization is carried out utilizing NMR and FT-IR. The bipyridine building blocks, based on their excellent bidentate

ligands with complexing abilities, will be incorporated into ruthenium complexes in a collaborative project, increasing the photosensitivity of these complexes, and opening the doors for many applications ranging from synthetic photovoltaics to anti-cancer activity.

ORGN 228

Synthesis and characterization of novel hybrid palladium (0) catalysts

Christian S. Strong², *che.strong1@gmail.com*, **Melissa Cadena**¹, **Emerson Thomas**¹, **Douglas E. Frantz**¹. (1) Dept. of Chemistry, UTSA, San Antonio, Texas, United States
(2) Dept. of Chemical Engineering, UTSA, San Antonio, Texas, United States

Palladium catalysis has proven to be among the most adaptable tools in the organic chemist's toolbox throughout the late 20th and early 21st centuries. One class of transformations that involves palladium catalysis is cross-coupling reactions, capable of stitching together highly functionalized reacting partners through the establishment of new carbon-carbon or carbon-heteroatom bonds. In many cases, the active catalyst needed to induce oxidative addition, a key step in these processes, is palladium(0). Unfortunately, the air sensitivity of many palladium(0) phosphine complexes reduces their shelf-life, limiting their practicality. Further, other more stable palladium(0) dibenzylideneacetone (dba) complexes are limited in that dba ligands can impede oxidative addition, decreasing the overall productivity of a process. Because of this, a significant amount of procedures utilize air-stable palladium(II) sources that, alongside a reducing agent, are converted to the active catalyst in situ. A common drawback across these approaches is their non-quantitative nature caused by the ambiguity surrounding the state of a palladium atom at any given moment. Currently, the Frantz lab is working on the design of new hybrid catalysts which circumvent some of the issues currently present with comparable palladium(0) sources due to their high air stability which leads to easy handling and storage. Further, these catalysts are unique in that one of the ligands is easily removed in basic conditions, allowing the active palladium(0) phosphine species to undergo the catalytic cycle in a more controlled manner. These unique properties have been displayed in previous work done by the Frantz lab in which a newly designed catalyst, BobCat was employed in the alkynyl Heck reaction towards the synthesis of substituted allenes. This catalyst makes use of the easily removed ligand we are currently focused on and serves as a proof of concept for this technique.

ORGN 229

Synthesis and characterization of ZNO nanoscale deposited on glass substrate at low temperature and atmospheric pressure for energy application in solar system

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ZnO thin films are used in various applications such as transparent conductive film and window materials in solar cell applications due to its high optical transmittance in the visible light region. Metal organic chemical vapor deposition (MOCVD) offers the most flexible approach, by involving the chemical reactions of the gaseous reactants of each metal oxide on a heated surface. The objective of this work was to synthesize new ligands, characterize, and purify them. The isolated β -ketoimine ligands were dried over MgSO_4 and then distilled in vacuo. The synthesized ligands were characterized by proton NMR, GC/MS and FT-IR. Synthesis and characterization of Zinc β -ketoiminate complexes were prepared under an inert atmosphere of nitrogen, the appropriate ligand was added to a schlenk flask containing dried hexanes and a magnetic stirrer bar. The solvent is then removed under reduced pressure to afford a light yellow solid. Once synthesized the bond between Nitrogen and Hydrogen had an IR of 3277.78cm^{-1} and the C=O had an FT-IR of 1650.55cm^{-1} . The formula mass was 185 m/z and the percentage yield for the isolated structure was 79.75%. The infrared spectra analysis of all the free ligands studied, produces strong bands on the C=O, C=C bonds and weak bands for the N-H band. In the FT-IR spectrum the N-H stretching vibration appears in a frequency range between ($3292.18\text{-}3272.20\text{cm}^{-1}$). The C=O and C=C bond, vibration appears at a frequency range ($1654.07\text{-}1648.00\text{cm}^{-1}$) and ($1600.43\text{-}1599.10\text{cm}^{-1}$) respectively. The proton NMR spectrum for β -enaminoester free ligands studied is reported. The vinyl and amine protons have chemical shift values ranging (4.30-4.90 ppm) and (8.50-8.71 ppm).

ORGN 230

Titanium promoted cross-electrophile coupling of imines with Weinreb amides: Modular approach to synthesize α -aminoketones

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Compounds like bupropion, pyrovalerone, amfepramone, effient are studied as the potential pharmacotherapies for antidepressant and cocaine addiction. These compounds share a common structural motif, α -aminoketone. The α -aminoketones have also displayed numerous other biological applications and have been used as versatile intermediates in organic synthesis. Several methods exist to synthesize this structural motif, only few of them are used for small molecule library preparation. To address this, a synthetic protocol was necessary that could use wide range of readily available starting materials to synthesize diverse array of α -aminoketones. We have developed a titanium promoted cross electrophile coupling of imines with Weinreb amides to synthesize α -aminoketones in moderate to good yield in a chilled reaction.

ORGN 231

Copper-mediated $\text{sp}^3\text{-sp}^3$ cross-coupling reactions with turbo Grignard reagents

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Transition metal-catalyzed cross-coupling reactions have emerged as an effective technique to form sp^3 - sp^3 carbon-carbon bonds. The drawbacks associated with this transformation have necessitated the development of highly active catalysts and usage of reactive organometallic reagents. We implemented a combination of two methods for achieving cross-coupling between two sp^3 -hybridized carbon centers. First, a Turbo Grignard ($RMgX \bullet LiCl$) was generated at room temperature following the method of Knochel. Then, the hydrocarbon-ligated copper catalyst system by Kambe was used to perform the cross-coupling reaction, which was also carried out at room temperature and under low catalyst loading. The two-step sequence was effective for the cross-coupling of alkyl Grignards (1° , 2° , and 3°) with primary alkyl halides (Cl and Br). The yields for generation of the Grignard reagents ranged from 14-100% depending on the degree of substitution, and the yields for the subsequent cross-coupling reaction ranged from 60-80%.

ORGN 232

Ring opening metathesis polymerization (ROMP) on [2.2.2]-diazabicyclic substrates

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Since its development and commercialization in the 1970's, Ring Opening Metathesis Polymerization (ROMP) has been used to polymerize strained cycloalkenes derived from hydrocarbon precursors, most commonly strained [2.2.1]-bicyclic precursors such as dicyclopentadiene. Polymerization of related bicyclic scaffolds that contain heteroatoms (N, O) remains underexplored. We sought to evaluate polymerization efficiency of strained cyclic monomers containing a [2.2.2]-diazabicyclic motif. This method has the potential to create polymers with access to additional polar functionalities unavailable to those containing only hydrocarbon.

ORGN 233

Synthesis of indolines and derivatives via aza-Heck cyclization

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For the first time, an aza-Heck cyclization that allows the preparation of indoline scaffolds is described. Using *N*-hydroxy anilines as electrophiles, which can be easily accessed from the corresponding nitroarenes, this method provides indolines bearing pendant functionality and complex ring topologies. Synthesis of challenging indolines,

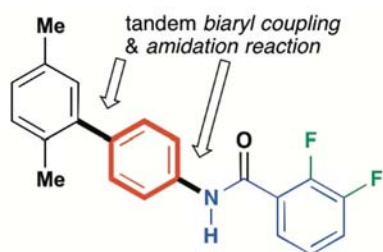
such as those bearing fully substituted carbon atoms at C2, is also possible using this method.

ORGN 234

Are aryl-aryl cross couplings and amidation reactions feasible and compatible under sunlight irradiation?

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Recently, we reported a room temperature and transition metal-free aryl-aryl cross coupling of several (hetero) arenes, under UV irradiation. At the time, we documented the synthesis of an interleukin-2 cytokine inhibitor as evidence of the synthetic utility of our method, albeit in couple of synthetic steps. This time, we are presenting the second-generation approach where we are now able to prepare this immunosuppressant (see the figure) in one pot procedure. The strategy involves two major transformations (aryl-aryl cross coupling and amidation reaction) occurring simultaneously. To the best of our knowledge, this work represents the first novel approach of two of the most useful transformations performed under mild/greener reaction conditions. Furthermore, it is a unique report on the use of natural sunlight to promote the title transformations. Therefore, this work and mechanistic insights can potentially open a new area of research to aid drug discovery.



ORGN 235

Hiyama cross-coupling of fully-substituted vinylsilanes

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The Hiyama cross-coupling of fully-substituted vinylsilanes has been historically challenging. We have developed general conditions for the Hiyama cross-coupling of tetrasubstituted vinylsilanes to form fully organosubstituted alkenes. Through analysis of

the mechanism of this reaction, we have further developed this method to eliminate the need for expensive and toxic additives. The development and scope of this process will be described.

ORGN 236

Palladium-catalyzed three component carbosilylation of internal symmetrical alkynes: Synthesis of tetrasubstituted vinylsilanes

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Vinylsilanes are useful synthetic intermediates in organic synthesis, however, methods for the preparation of fully-substituted vinylsilanes are limited. A three-component carbosilylation reaction for the preparation of fully-substituted vinylsilanes using a silyl-Heck approach has been developed. This method allows for the formation of both *cis*- and *trans*-fully-substituted vinylsilanes via ligand controlled stereoselectivity. The scope and limitations of this reaction will be discussed.

ORGN 237

Generating dioxacarbenes from carbonates and thiocarbonates and the implications for the mechanism of the Corey-Winter olefination

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The existence of dioxacarbenes have been reported, but have not yet realized any synthetic utility. A dioxacarbene has been suggested as an intermediate in the Corey-Winter olefination reaction where a thiocarbonate is reacted with trimethyl phosphite. Since thiocarbonates and carbonates are readily accessible from the corresponding diols, it would seem this represents a useful route to access a dioxacarbene. We envisioned that the dioxacarbene could be reacted with an olefin to afford a cyclopropanone acetal. This cyclopropanone acetal could be synthetically useful as it could be readily incorporated in to larger molecules. Provided that the dioxacarbene could react with a variety of olefins then this new methodology could be utilized in a diversity oriented synthesis approach. To realize this ultimate goal, we have synthesized a variety of carbonates and thiocarbonates. These carbonates and thiocarbonates have been reacted with several different olefins in the presence of trimethyl phosphite under a variety of conditions. Although a cyclopropanone acetal has not yet been isolated, important information has been discerned about the nature of any potential dioxacarbene and whether or not it is truly an intermediate in the reaction of a thiocarbonate with trimethyl phosphite.

ORGN 238

Halogenation of pyridines via heteroaryl phosphonium salts

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Halogenated arenes are important precursors in a myriad of chemical transformations. Despite this, halogenated pyridines and diazines are challenging to synthesize, particularly on complex substrates. Existing methods to selectively halogenate the 4-position of pyridine require either harsh conditions or preinstalled directing groups. We present a general method for the selective chlorination, bromination, and iodination of pyridines, diazines, and triazines using heteroaryl phosphonium salts. The phosphonium ion is installed in one-pot from C-H precursors with complete regioselectivity for the 4-position. By rationally designing the phosphine used in this transformation, the strategy is applicable on a range of simple building block azines, drug-like fragments, and complex bioactive molecules. Computation studies suggest that this reaction operates via an S_NAr-type mechanism, as opposed to a P(V)-mediated ligand-coupling pathway. This strategy allows for the mild and regioselective halogenation of azines that are valuable precursors in drug development.

ORGN 239

Solvent-free, methyl borate-catalyzed reductive amination with ammonia borane

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Reductive amination of carbonyls (or reductive alkylation of amines), the reaction of amines with aldehydes and ketones in the presence of a reducing agent, is one of the fundamental organic chemistry reactions with numerous applications in organic and medicinal chemistry. Several borohydrides and amine boranes, such as pyridine-BH₃, 2-picoline-BH₃, dimethylamine-BH₃, etc. have been utilized as reductants. However, each of these reagents suffers from drawbacks. We had reported that ammonia borane, a readily prepared, air-stable, low molecular weight reagent, acts as a reductant in the presence of titanium isopropoxide providing *pri*-, *sec*- and *tert*-amines in good to excellent yields. We have now discovered a solvent-free, sub-stoichiometric trimethyl borate-catalyzed, atom-economical reductive amination process using ammonia borane. This environmentally benign procedure has been employed for the amination of aldehydes and ketones with primary and secondary amines in excellent yields.

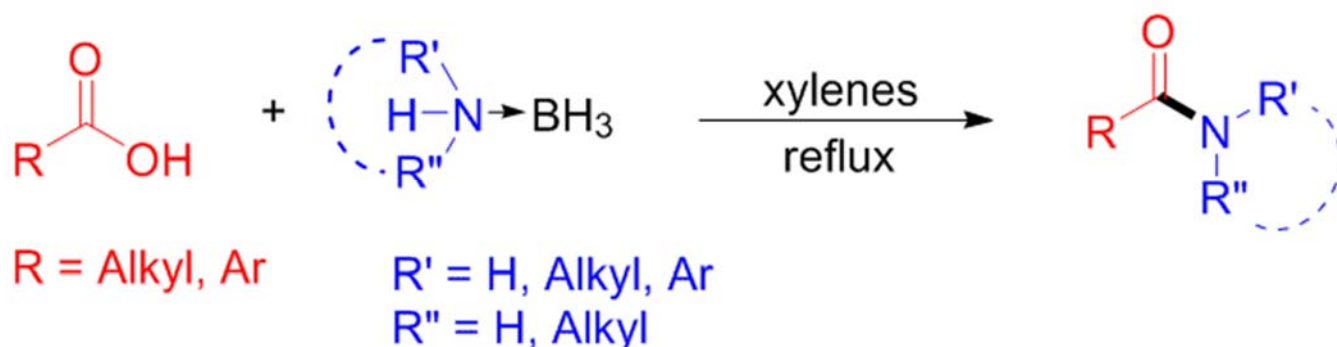


ORGN 240

Amine-boranes as dual-purpose reagents for direct amidation of carboxylic acids

P V. Ramachandran, Henry Hamann, hhamann@purdue.edu. Chemistry, Purdue University, West Lafayette, Indiana, United States

Amine-boranes act as dual-purpose reagents for the direct amidation of carboxylic acids. These reagents activate both aliphatic and aromatic carboxylic acids, and subsequently deliver amines to provide the corresponding amides in up to 99% yields with excellent chemoselectivity. This protocol offers several advantages over the current amidation procedures involving hazardous or unstable reagents with low functional group tolerance. It has a major advantage over other methodologies in that even gaseous or low-boiling amines, such as ammonia, methylamine, allylamine, etc. can be delivered as liquid or solid borane complexes. Employment of our recent synthesis of functionalized amine-boranes allows for the preparation of functionalized amides. This amidation protocol can be readily performed at mole-scale and has been demonstrated for the preparation of several bio-active molecules.

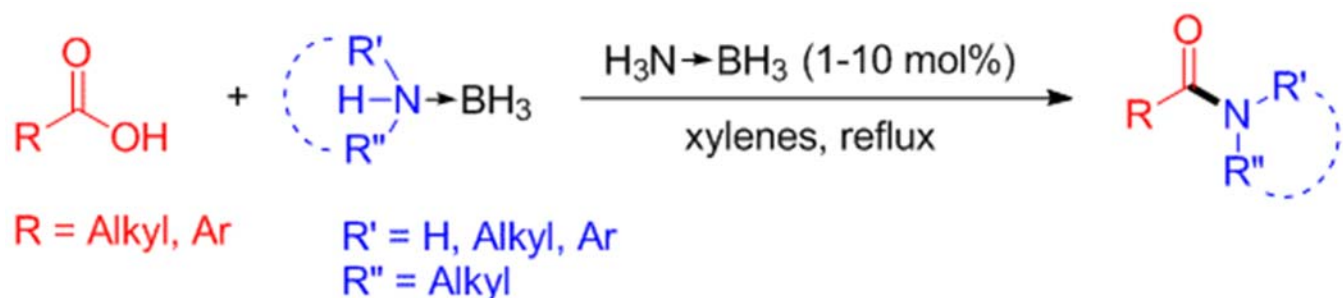


ORGN 241

Ammonia-borane-catalyzed direct amidation of carboxylic acids and amines

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Chemistry, Purdue University, West Lafayette, Indiana, United States

The ubiquity of amides in natural products and synthetic molecules makes direct amidation of carboxylic acids with amines a high priority reaction in modern organic chemistry. Current procedures, such as the N-acylation of amines using acid chlorides and the use of coupling reagents have several drawbacks. Limited reagent stability, hazardous reagent preparation, and inadequate functional group tolerance are examples of these. Several boron-mediated direct amidation protocols have been reported in the literature. We have now discovered that ammonia-borane catalyzes direct amidation with a loading as low as 1 mol%. Aliphatic or aromatic carboxylic acids, as well as aliphatic, cyclic, and aromatic amines undergo the reaction providing the corresponding amides in good to near quantitative yields. Readily prepared, air-stable, and low molecular weight ammonia-borane is an environmentally safe and non-toxic reagent, capable of promoting direct amidation even in the presence of water. The high chemoselectivity, good functional group tolerance and operational simplicity without the need of chromatographic purification make this attractive for laboratory and large-scale preparations.



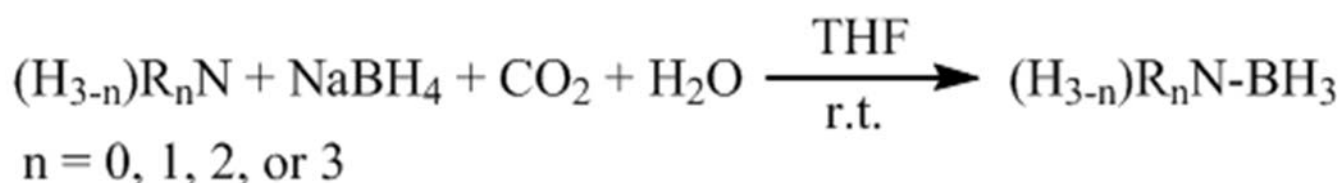
ORGN 242

Carbon dioxide-mediated synthesis of amine-boranes

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Chemistry, Purdue University, West Lafayette, Indiana, United States

Amine-boranes have been employed for several organic chemistry applications, such as reduction, reductive amination, aminoborohydride synthesis, etc. In addition, they have

seen applications as materials for energy storage, hypergolic fuels, and precursors to inorganic polymers. Yet, the chemistry of amine-boranes has not been explored to its full potential, probably due to its high cost or inconvenient syntheses. We have been involved in the chemistry of amine-boranes for over a decade and have developed various synthetic protocols, such as metathesis, trans-amination of borane-Lewis bases, amine-ammonium salt equilibration-metathesis, as well as a sodium bicarbonate-mediated synthesis. We have now developed a more convenient synthesis of amine-boranes involving gaseous or solid carbon dioxide. A variety of alkyl and aromatic amine-boranes have been prepared at ambient temperature and open-air conditions using this protocol in good-to-excellent yields within suitable reaction times. The details of this protocol will be presented.



ORGN 243

Rhodium-mediated electrophilic ^{18}F -oxyfluorination of diazoketones

Miguel Angel A. Cortes Gonzalez¹, miguel.cortes@su.se, **Xingguo Jiang**¹, **Patrik Nordeman**², **Gunnar Antoni**², **Kalman J. Szabo**³. (1) Organic Chemistry, Stockholm University, Stockholm, Sweden (2) Medicinal Chemistry, Uppsala University, Uppsala, Sweden (3) Department of Organic Chemistry, Stockholm University, Stockholm, Sweden

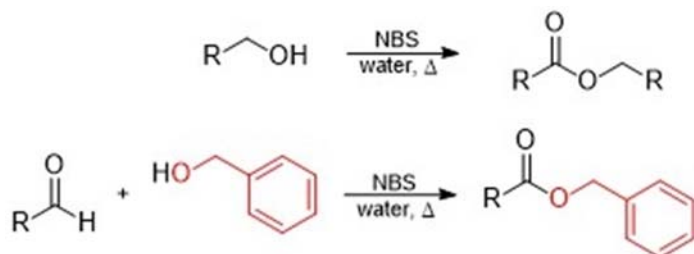
A geminal Rh-mediated ^{18}F -oxyfluorination of diazoketones has been developed using an electrophilic hypervalent iodine-based reagent. The reactions were carried out in short reaction times and typically mild conditions, affording radiochemical yields up to 98%. A preparative-scale experiment afforded a molar activity of 296 GBq/mmol.

ORGN 244

Advances in NBS oxidation: Synthesis of symmetric and benzyl esters

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N-halo reagents such as *N*-bromoacetamide, *N*-bromosuccinimide (NBS), and *N*-chlorosuccinimide are known to oxidize primary, secondary, and benzyl alcohol to aldehydes, ketones, and carboxylic acids. Using aqueous media to fine-tune the reactivity of NBS provides symmetric esters from primary alcohols without the need for further purification. While the conditions are more selective to aliphatic substrates, the resulting stability of benzaldehyde provides a unique synthetic route to benzyl aliphatic esters.



ORGN 245

Hydrogen bond mediated supramolecular silver-phenanthroline catalyzed enantio- and site-selective intermolecular C(sp³)-H amination

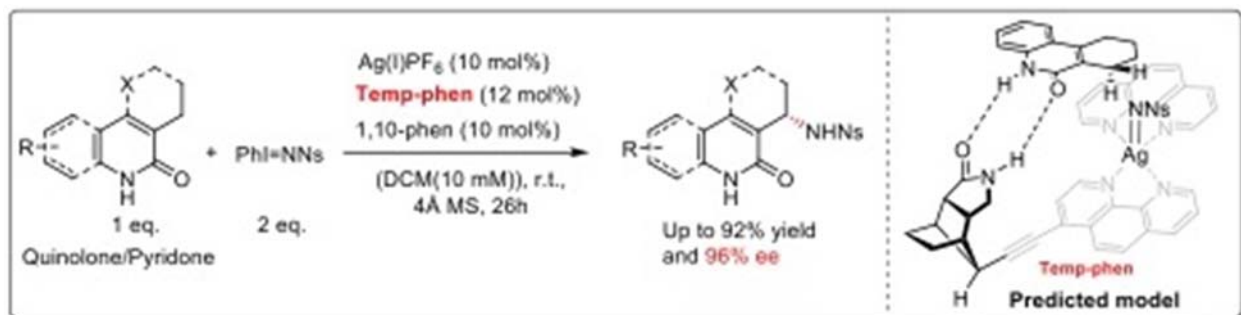
Rajasekar reddy Annapureddy, raj.annapureddy@tum.de, Thorsten Bach.

Department of Chemistry and Catalysis Research Center (CRC), Technical University of Munich, Garching, Munich, Germany

Inspired by nature's enzyme catalysis, supramolecular metal complexes have emerged, showing promising results in catalysis. Bifunctional ligands are very valuable and noteworthy tools in catalysis. These ligands have the ability to bind metal center at one site and an additional functional group, which is available for a second predefined task. The preorganization of a substrate's reactive position towards a catalytically active center can ideally allow for complete selectivity control in a chemical transformation.^a Direct C-H bond amination is a straightforward and atom-economic means for C-N bond formation.^b Although intramolecular C-H bond amination has found many important applications in complex molecule synthesis, in the case of intermolecular reaction the same success was not reproducible due to the selectivity issues, specifically lack of high enantioselectivity.

Considering all those factors, I have designed and synthesized templet coupled phenanthroline bifunctional ligands and used them in silver catalyzed intermolecular C-H bond amination. With supramolecular Silver-phenanthroline complex as catalyst, quinolone/pyridones undergo site specific intermolecular C-H amination with $PhI=NNs$ as nitrene source in good yields (up to 92%) and with an excellent enantioselectivities (up to 96%). The high enantio and regioselectivity originates from the substrate specific

orientation to the reactive metal center fix by hydrogen bondings between the chiral templet lactam moiety and the substrate. The key element is that the addition of extra dummy phenanthroline unit in silver complex synthesis could lead to drastic increase in reactivity by keeping the selectivity intact. Since supramolecular Silver-phenanthroline complex generated in situ, it allowed us to fine tune the reactivity and stereoselectivity by altering silver salts, phenanthroline moieties and position of the coupled templet on phenanthroline.



Silver-phen catalyzed intermolecular C(sp³)-H amination

ORGN 246

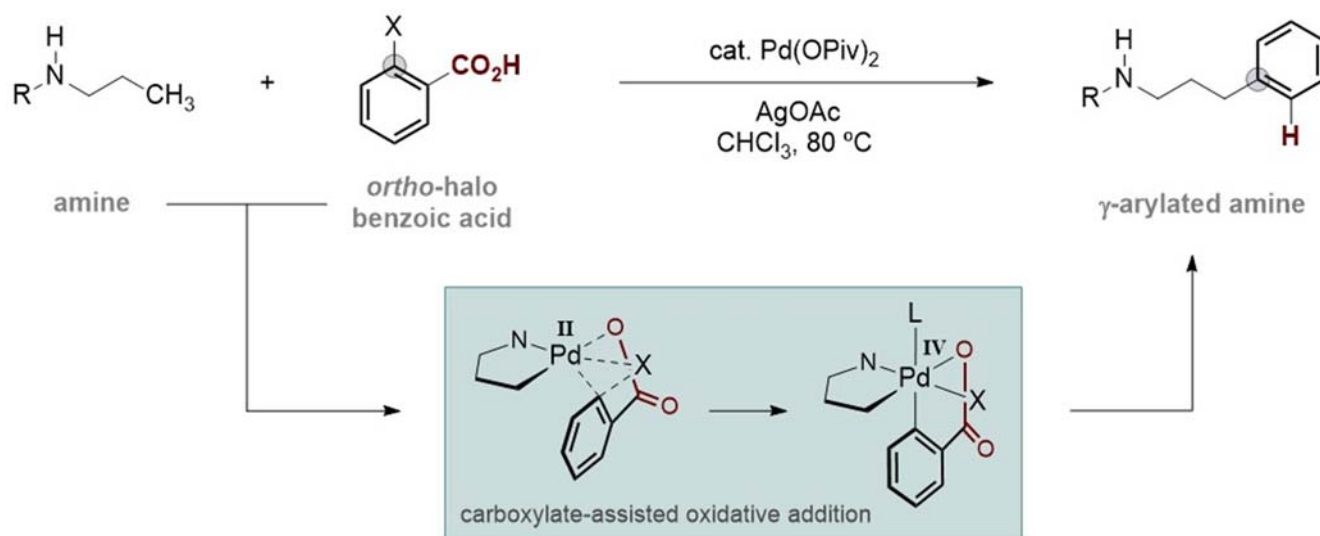
Carboxylate-assisted oxidative addition to aminoalkyl-Pd^{II} complexes: C(sp³)-H functionalization of alkylamines by distinct Pd^{II}/Pd^{IV} pathway

William G. Whitehurst¹, wgw22@cam.ac.uk, **Henry Blackwell¹**, **Gary Hermann²**, **Matthew Gaunt¹**. (1) Chemistry, University of Cambridge, Cambridge, United Kingdom (2) Chemistry, Scripps Research, La Jolla, California, United States

Pd-catalyzed C(sp³)-H functionalization of alkylamines has stimulated significant interest as the products of such a transformation display structural features that are highly represented in pharmaceutical agents. While a vast array of directing group auxiliaries have been designed to promote C(sp³)-H functionalization of amine derivatives, an alternative approach has been to exploit the innate coordinating ability of unprotected alkylamines for site-selective cyclopalladation. In this regard, the use of oxidative conditions to access a reactive Pd^{IV} intermediate has enabled a diverse range of reductive elimination pathways. However, previous methods have been limited to hindered cyclic alkylamines, and therefore the design of suitably mild oxidants compatible with a diverse range of alkylamines presents a significant challenge.

Herein, the discovery of an approach to functionalize secondary alkylamines using 2-halobenzoic acids is reported. These reagents promote a facile carboxylate-assisted oxidative addition to alkylamine-derived palladacycles. In the presence of Ag^I salts, a decarboxylative C(sp³)-C(sp²) bond reductive elimination leads to γ -aryl secondary

alkylamines and renders the carboxylate motif a traceless directing group. Stoichiometric mechanistic studies were effectively translated to a Pd-catalyzed γ -C–H arylation process for secondary alkylamines. Conversely, in the absence of Ag^{I} additives, selectivity of the reductive elimination switches to $\text{C}(\text{sp}^3)\text{--O}$ bond formation. Recent work focusing on extending this reactivity mode towards a general strategy for remote heteroatom incorporation within alkylamines will be discussed.



ORGN 247

New monodentate directing groups for C-H bond functionalization

Hanh Nguyen, hellorose4@gmail.com, **Olafs Daugulis**. Chemistry, University of Houston, Houston, Texas, United States

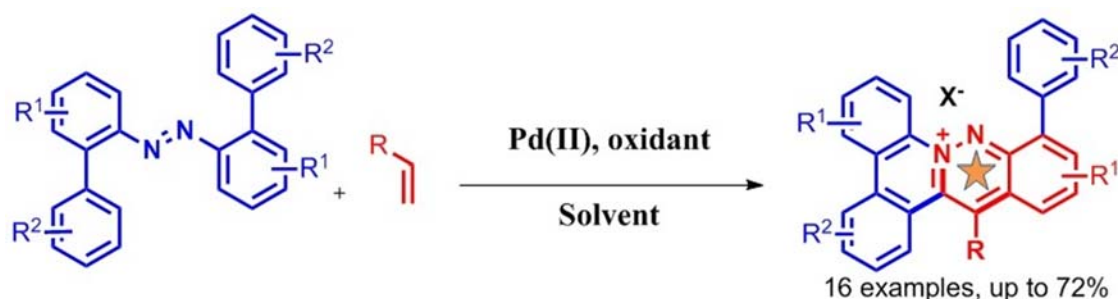
Direct C–H bond functionalization provides an efficient route for formation of C–C bonds from readily available starting materials. Palladium-catalyzed functionalization of sp^3 C–H bonds by using new monodentate auxiliaries will be presented. These zwitterionic directing groups can be easily cleaved under mild conditions. Preliminary mechanistic investigations will be disclosed as well.

ORGN 248

Orange-red fluorescent Cinnolino[2,3-*f*]phenanthridin-9-ium salts by palladium(II)-catalyzed C-H bond activation of 2-azobiaryls and alkenes

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Presented is the first palladium-catalyzed synthesis of quaternary ammonium salts through double oxidative C-H bond activation on 2-Azobiaryls in moderate to good yields. In this study, the chemistry of highly regioselective synthesis of orange-red fluorescent cinnolino[2,3-*f*]phenanthridin-9-ium salts and 15*H*-cinnolino[2,3-*f*]phenanthridin-9-ium-10-ide from 2-azobiaryls and alkenes catalyzed by palladium(II) will be discussed. The reaction mechanism is proposed involving an *ortho* C-H olefination of 2-azobiaryls with alkenes, intramolecular aza-Michael addition, concerted metalation deprotonation (CMD), reductive elimination and oxidation. These ammonium salts show strong absorption (π - π^*) bands around 330–360 nm and a charge transfer (CT) band around 460–490 nm. Their detailed photophysical properties will be presented too.



ORGN 249

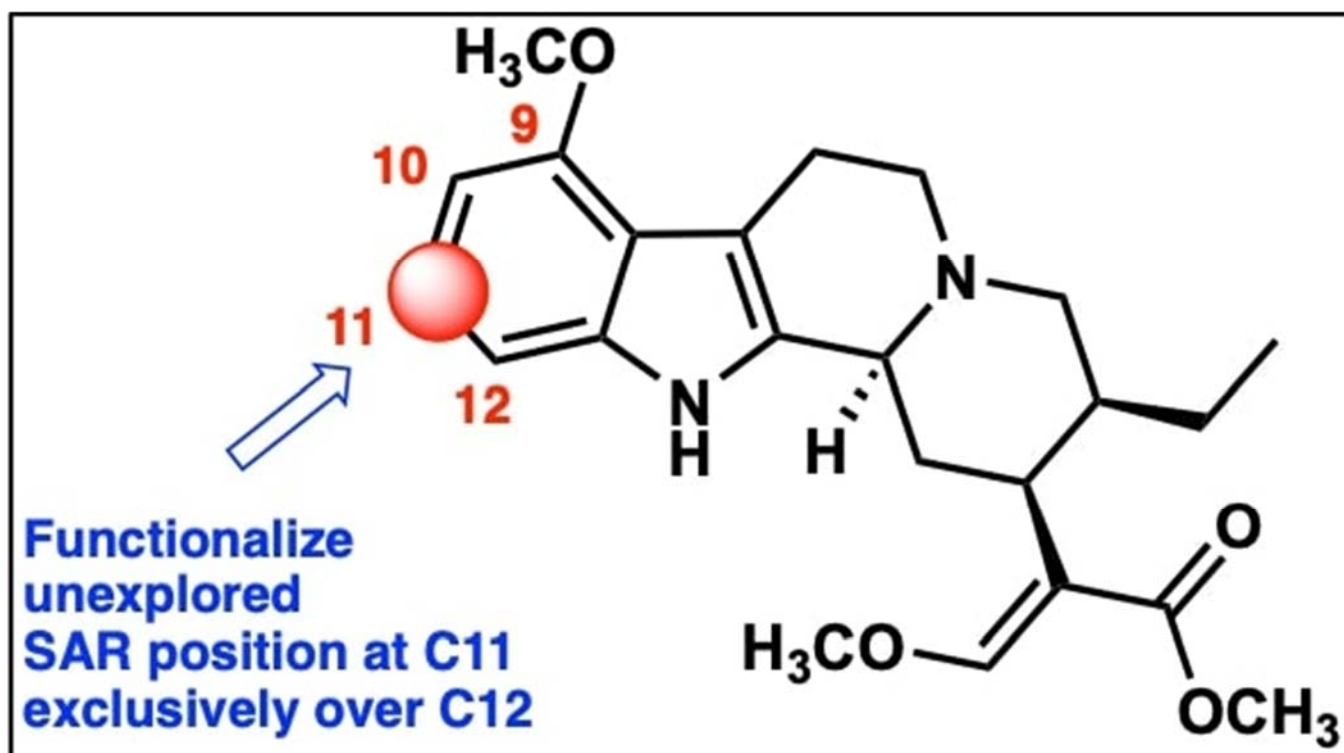
Ir-catalyzed C-H functionalization of the alkaloid mitragynine : Late stage selective functionalization at indole via complex core restructuring

Srijita Bhowmik¹, sb3890@columbia.edu, **Juraj Galeta**¹, **Vaclav Havel**¹, **Dalibor Sames**¹, **Susruta Majumdar**². (1) Chemistry, Columbia University, New York, New York, United States (2) Center for Clinical Pharmacology,, St Louis College of Pharmacy and Washington University,, St. Louis, Missouri, United States

Mitragynine, a corynanthe-type indole alkaloid, constitutes the major constituent of the plant Kratom which has a long history of use in many regions of South East Asia for treatment of various ailments including pain and opioid dependence. The use of kratom in the U.S. has been on the rise and numerous anecdotal reports suggest efficacy in self-medication for treatment-resistant pain syndromes, depression, anxiety, and substance use disorders. Mitragynine is a partial mu-opioid receptor (MOR) agonist with a G protein-biased signaling profile. Mitragynine analogs thus provide the opportunity for gaining new insights into the chemical biology of opioid receptors and access to new

chemical modulators of these receptors

Mitragynine is readily available from kratom by extraction, providing a strong incentive to develop “late-stage C-H functionalization”. The SAR of the indole ring of mitragynine has not been systematically examined and the C11 position in particular has remained unexplored mainly due to inability of chemical methods to target C11 position overriding the intrinsic propensity of indoles to direct functionalization at the C12 position. In our work we show that iridium-catalyzed borylation is compatible with the complexity of mitragynine’s structure, affording exclusively the C12 boronate ester. Re-routing the positional selectivity from C12 to C11 by temporarily converting mitragynine to the mitragynine-ethylene glycol adduct (**MG-EG**) gave high C11 selectivity (>16:1). Thus, we were able to synthesize various analogs of MG-EG. The ethylene glycol moiety can be readily removed under mild reductive condition in one step to yield C11-substituted mitragynine analogs. Mitragynine analogs can be converted to the corresponding 7OH series (more potent than mitragynine). *Our strategy enables, for the first time, CH functionalization of the C11 position with a wide range of substituents starting directly from the mitragynine natural product, thus permitting systematic exploration of SAR at this position.*



Developed functionalization at uninvestigated C11 position selectively.

ORGN 250

***N*-aminopyridinium ylide-directed C–H bond functionalization**

Sehun Kwak, sehunkwak@daum.net, *Olafs Daugulis*. University of Houston, Houston, Texas, United States

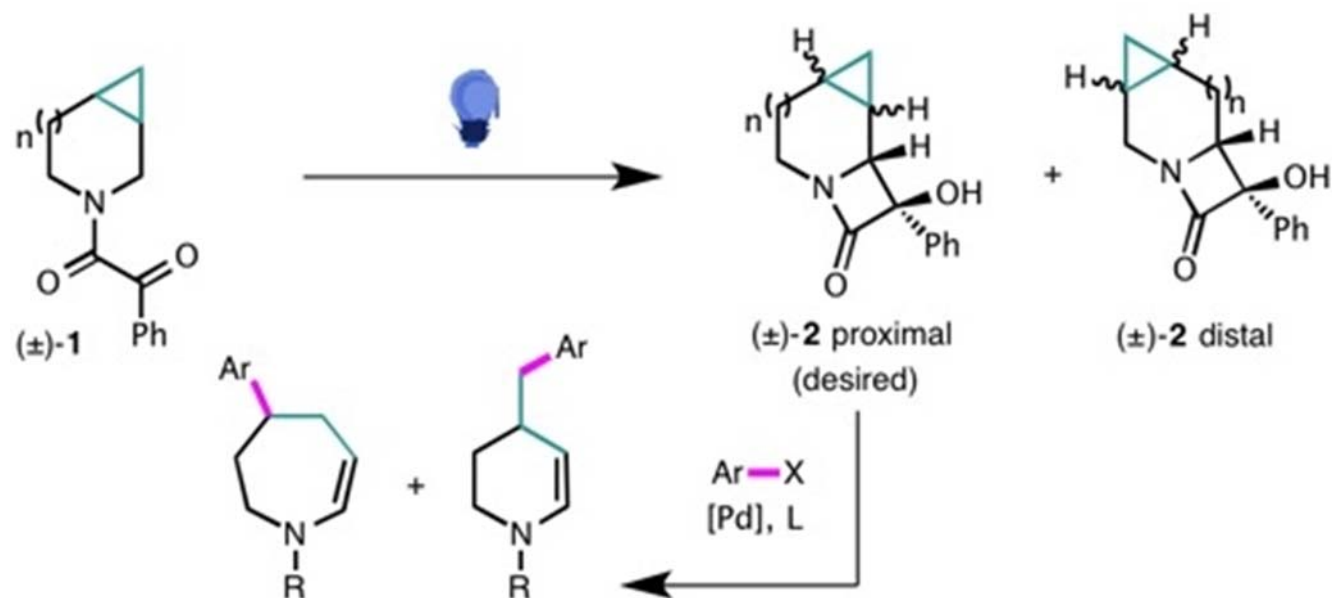
N-Aminopyridinium ylides are utilized as monodentate directing groups for C–H bond functionalization with first-row transition metals. Reaction of the ylides with compounds containing carbon–carbon multiple bonds as well as other reagents will be reported. Preliminary mechanistic studies will be presented as well.

ORGN 251

Explorations into a strain-mediated Norrish-Yang reaction and cross-coupling of cyclic amines

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New methods for late-stage diversification of biologically active cyclic-amine containing compounds are important for streamlining the drug discovery process. Strain-release was recently found to be important in the C–H functionalization of cyclic amines. We will describe our investigation into the impact of strain on the reactivity of cyclopropane-fused cyclic amines in the Norrish-Yang reaction and a subsequent C–C bond forming cross-coupling reaction.

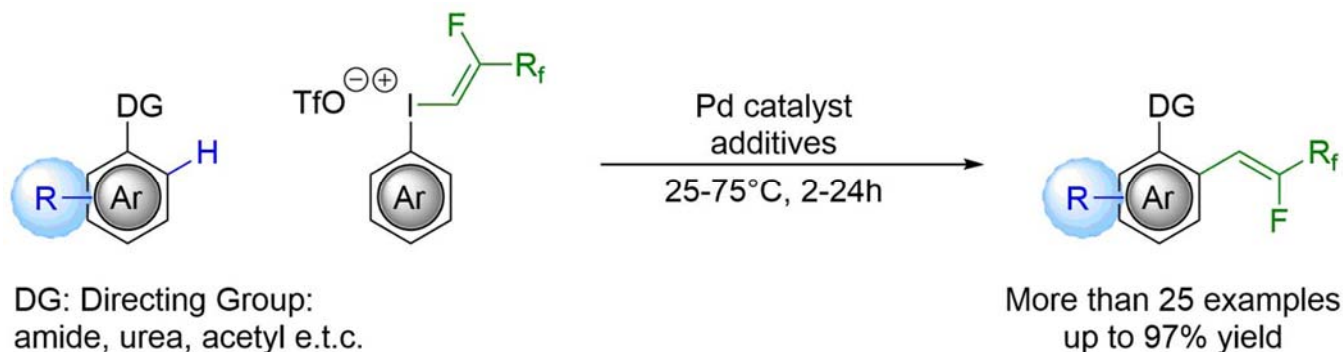


ORGN 252

Fluoroalkenylidonium reagents in palladium-catalyzed *ortho*-C-H Activation of aromatic and heteroaromatic compounds

Balázs Tóth¹, tothb@zng.elte.hu, **Gergo Salyi**¹, **Orsolya Egyed**², **Attila Bényei**⁴, **Zoltán Novák**³. (1) Eötvös University, Budapest, Hungary (2) Research Centre for Natural Sciences of the Hungarian Academy of Sciences, Budapest, Hungary (3) Eötvös Loránd University, Institute of Chemistry, Budapest, Hungary (4) University of Debrecen, Debrecen, Hungary

By the C-H activation methodology, aromatic C-H bonds can be easily substituted with different functional groups, without any previous functionalization of starting material. The introduction of a directing group (DG) allows regioselective metalation in the *ortho* position of the aromatic core. The application of hypervalent reagents opens new, shorter synthetic routes and facilitates mild reaction conditions. Due to their electrophilic character, high reactivity, easy preparation the +3 oxidation state organic iodonium salts are widespread in alkynylation and arylation reactions. Previously, our research group presented a simple and robust catalytic method for efficient and selective 2,2,2-trifluoroethylation reaction of aromatic compounds using the highly active trifluoroethyl(mesityl)iodonium salt.[1, 2] However, the application of alkenyliodonium salts is still underdeveloped. Here we present the first C-H activation reaction which utilize fluoralkenylidonium salts as alkenylating agents for direct C-C coupling of aromatic amides, benzamides, ureas and ketones. The reaction conditions, scope and limitations have been investigated, and with this simple methodology we prepared more than 25 new *ortho*-fluoroalkenylated molecules.



ORGN 253

Macrocyclization of small-molecule ligands in drug discovery

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Small-molecule macrocycles are of interest for drug discovery, and may prove especially well-suited to targeting protein-protein interactions or other systems where larger small-molecules may be required. In drug discovery, macrocycles are often discussed or grouped as a drug chemotype, but we distinguish purely synthetic small-molecule macrocycles from natural products or close analogs of natural products. We are interested in the structure-based design of small-molecule macrocycles, and we summarize our simple approach for the detection of bound ligand conformations that seem consistent with macrocyclization. Representative examples of such macrocycle-like compounds from the Cambridge Structural Database and the Protein Data Bank (PDB) will be presented and analyzed, and trends in PDB ligands will also be explored.



ORGN 254

Toward ligand-based and structure-based macrocyclic design

Ajay N. Jain¹, ajain@jainlab.org, Ann Cleves^{2,3}. (1) MC 0128, Bioeng Therapeutic Sciences, UCSF, San Francisco, California, United States (2) HDF Cancer Center, UCSF, San Francisco, California, United States (3) BioPharmics LLC, Santa Rosa, California, United States

Advances in multi-core computer hardware, cloud-based computing, and in parallel algorithms for macrocyclic conformation analysis have opened a significant fraction of macrocyclic design space to design-focused computational methods. Recently, we have shown that the ForceGen method is capable of producing conformational ensembles of macrocycles with up to a total of 21 rotatable bonds (including such bonds inside macrocyclic rings and those that are exocyclic) with accuracies that match those observed for non-macrocycles. Further, on workstation-level multi-core computers, processing typically requires only a minute or two in real wall-clock time. This tractable space of macrocycles includes molecules such as those recently developed as pharmaceuticals that inhibit enzymes such as BACE1 and HCV 3-4A protease. The ForceGen method and corresponding speed/accuracy results will be presented along with data supporting design-focused applications using ligand-based and structure-based techniques.

ORGN 255

Discovery of bioactive, passively permeable cyclic peptides: Translating theory into practice

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Cyclic peptides have undergone a renaissance in medicinal chemistry. Defying the decades-old assumption that peptides are hopelessly un-druglike, more and more cyclic peptides are being discovered with surprisingly high passive permeabilities and, in some cases, drug-like oral bioavailability. While we understand the general factors governing ADME properties in cyclic peptides, the question remains: Can we harness that understanding to generate molecules that are both membrane permeable and capable of inhibiting a given therapeutic target? I will describe new results from our efforts to translate our understanding of permeability in this interesting class into molecules with therapeutic potential.

ORGN 256

Advances in macrocycle design, modeling and affinity estimation

Clara D. Christ, *clara.christ@bayer.com*. Bayer AG, Berlin, Germany

In this talk we will show recent advances in macrocycle generation, modeling and property estimation. We will point out how recent improvements in computational modeling techniques can impact projects by prioritizing macrocycles prior to (the often challenging) synthesis and help rationalize experimental findings. Furthermore we will point out which open challenges we see when modeling macrocycles.

ORGN 257

Conformational analysis of macrocycles in solution and the solid-state

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Macrocycles have become of greater and greater interest to the drug discovery community over the past decade. Generating conformation ensembles that accurately reflect the behavior of a molecule in solution is a foundational task in drug design as nearly all molecular properties relevant to drug design are measured in solution. Accurate prediction of properties in solution is impossible without an accurate sampling of a molecule's conformations in solution. We will present our recent work on the use of distance geometry to generate macrocycle conformations that are validated against experimental data from NMR spectroscopy and new methods to analyse and interpret these conformational ensembles. We will pay particular attention to calculating conformational energies in solution using a variety of different levels of theory.

ORGN 258

Novel and robust NMR-based conformational analysis to advance 3D structure characterization of cyclic peptides

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The interest in peptides, including cyclic peptides, peptidomimetics and hybrid peptide macrocycles, as new scaffolds in the development of novel drugs has significantly increased for their potential to interact with novel and challenging biological targets. Facile and precise elucidation of structure, stereochemistry and the 3D conformation of such molecules can provide insights into structure-activity relationship, which in return illuminates molecular design with improved pharmacological performance, including on- and off-target activity, solubility, and cellular passive permeability. Nuclear Magnetic Resonance (NMR) spectroscopy is a powerful information-rich analytical technique that is broadly utilized in the drug discovery and development space for the structure and conformation characterization of drug candidates in solution. A variety of measurable NMR parameters, including chemical shifts, coupling constants, NOE-derived interatomic distances and anisotropic NMR parameters, facilitates a diverse range of applications of NMR in drug discovery. In this presentation, we will demonstrate a newly developed approach featuring rapid determination of high-resolution 3D conformation of cyclic peptides and macrocycles in solution using a small number of NMR restraints with an advanced conformational sampling mechanism. This complementary and integrated approach yields high-quality peptide solution ensembles in the cases where traditional NMR-based calculation methods have been either very time-consuming or unsuccessful. This developed methodology is applied to elucidate the 3D conformation

of aureobasidin A, a cyclic depsipeptide antifungal. Using sparse distance and torsional NMR constraints, the conformational ensemble generated is focused within an experimentally relevant space, confirmed by RDC analysis and RMSD from available crystal structure. Besides, by utilizing the complimentary approach, a minor conformer of aureobasidin A, where proline adopts a cis configuration on the peptide bond, has been successfully elucidated for the first time. As a comparison, traditional NOE-based structure determination of the same peptide using classical biomacromolecules structure calculation program, CYANA, has also been evaluated. The presented protocol can be expected to open the way to rapid structural characterization of cyclic peptides and to afford better insights for future molecular designs.

ORGN 259

Modeling macrocyclic peptides with integrated structure and sequence methods

Shana Posy, *sposy@gmail.com*. Bristol-Myers Squibb Co, Princeton, New Jersey, United States

Macrocyclic peptides have the potential to bind hard-to-drug targets and to have physicochemical properties that are comparable to those of small molecules therapeutics. Here we describe learnings from multiple peptide optimization campaigns across a diverse set of protein targets. We describe trends observed in peptide backbone structures and peptide-receptor interactions. We also touch on how to model novel peptides and design new sequences based on existing SAR with a toolkit of sequence approaches that enable rapid exploration and exploitation of large peptide datasets.

ORGN 260

Supramolecular ligands as extractants for *f*-elements

Shannon M. Biros¹, *biross@gvsu.edu*, **Eric J. Werner**². (1) Chemistry, Grand Valley State University, Allendale, Michigan, United States (2) The University of Tampa, Tampa, Florida, United States

The field of *f*-element coordination chemistry has gained recent attention due to the use of lanthanides and actinides in materials such as magnets, cellular phones, and bioprobes. Some actinides, particularly uranium, are also used as a source of alternative energy. Current research efforts are focused on the recycling of these metals from end-of-life materials, as well as the improvement of existing methods for their isolation from natural sources. To this end, our research group is focused on the development of supramolecular ligands that operate as selective extraction agents for lanthanide and actinide ions out of acidic, aqueous solutions.

ORGN 261

Exploring the intricacies of titanium alkoxide catalysts for ring-opening polymerization with undergraduate researchers

Christopher B. Durr, *cdurr2@gmail.com*. Chemistry, Amherst College, Amherst, Massachusetts, United States

Schiff-base supported titanium alkoxides are excellent candidates for the ring-opening polymerization of cyclic esters due to their low toxicity, electronic and steric variability and facile synthesis. Furthermore, these characteristics make for an ideal platform to conduct undergraduate research and allows students an opportunity to explore core concepts found throughout the curriculum. This presentation will describe how students have participated in various ways to this work by discussing three different families of titanium alkoxide catalysts. The synthesis, solution and solid-state analysis, and applications of these systems will be discussed through the lens of the undergraduate curriculum at Amherst College to best highlight connections between the classroom and the research lab.

ORGN 262

On the hunt for novel heterocycles: Nitrogen in small rings

Gustavo Moura-Letts, *moura-letts@rowan.edu*. Chemistry and Biochemistry, Rowan University, Cherry Hill, New Jersey, United States

Nitrogen-containing heterocycles are among the most important families of molecules due to their high occurrence among therapeutics. Despite efforts for the last 200 years, their synthesis remains a main challenge in the field of organic chemistry. Our group is interested in inventing new chemical reactions for the synthesis of nitrogen-containing small heterocycles and their respective reactivity patterns as substrates the synthesis of more complex molecules. These efforts have shed light on some highly unprecedented reactivity pathways, thus providing access to previously inaccessible regions of chemical space. Clues have been found, reactions discovered, but the hunt continues.

ORGN 263

Turning unexpected results into discoveries: Development of new tools to capture and study transient interactions of biosynthetic proteins

Louise K. Charkoudian, *lcharkou@haverford.edu*. Haverford College, Haverford, Pennsylvania, United States

Our undergraduate-fueled lab at Haverford College studies acyl carrier proteins (ACPs), which serve as central hubs in polyketide and fatty acid biosynthetic pathways. ACPs are notoriously challenging to study because the fast motions of the ACP and its phosphopantetheine (Ppant) arm make their conformational dynamics difficult to capture using traditional approaches. In this talk, I will share how unexpected results a

course-based undergraduate research experience (CURE) and independent research project led to the discovery of new spectrophotometric probes that enable us to capture and study the interactions of ACPs with their partner biosynthetic enzymes. These stories combine concepts and techniques spanning biochemistry, organic chemistry, physical chemistry, and chemical education, and therefore I hope this talk will be of interest to a broad audience.

ORGN 264

Nickel catalyzed arylation of oxazoles using pharmaceutically relevant aryl halides

Dipannita Kalyani^{1,2}, dipannita.kalyani@merck.com. (1) Chemistry, St. Olaf College, Burnsville, Minnesota, United States (2) Merck & Co., Inc., Kenilworth, New Jersey, United States

This presentation will detail the development of the nickel-catalyzed arylation of oxazoles and benzoxazoles using aryl halides. The use of microscale high-throughput experimentation for both the rapid identification of optimal reaction parameters and the investigation of the aryl halide scope will be discussed. The scope and efficiency of the arylation using several electronically and structurally varied pharmaceutically relevant aryl halides will be described.

ORGN 265

Uncovering the identity of the active species in ruthenium-catalyzed ester hydrogenation

Anthony R. Chianese¹, anthonychemist@gmail.com, Tianyi He¹, John C. Buttner¹, Jack C. Malek¹, Eamon F. Reynolds¹, John Pham¹, Jason M. Keith². (1) Chemistry, Colgate University, Manlius, New York, United States (2) Dept of Chemistry, Colgate University, Hamilton, New York, United States

Significant advances have been made in the last 15 years in the development of catalysts for the hydrogenation of polar molecules, based on a design principle of metal-ligand cooperativity. This seminar describes mechanistic studies of CNN- and PNN-pincer-ruthenium catalysts for ester hydrogenation, which feature dialkylamino groups on the pincer ligand. Both CNN- and PNN-based precatalysts undergo an unexpected transformation, resulting in the release of ethane or propane and the formation of five-coordinate ruthenium(0) species containing a nascent imine functional group. The ruthenium(0)-imine derivatives catalyze ester hydrogenation either at the same or a higher rate as their ruthenium(II)-amine precursors. The PNN-ruthenium(0) species reacts reversibly with two equivalents of hydrogen at room temperature to generate a ruthenium(II)-dihydride species, where the imine functionality has been hydrogenated to produce a protic amine. These results have potentially broad implications for our

understanding of the mechanisms of hydrogenation and dehydrogenation reactions catalyzed by ruthenium-pincer complexes.

ORGN 266

Photochemical reactions of S-aryl thioformates: Toward a synthesis of oxetanes via formal formylation

Sarah Z. Tasker, *stasker@fandm.edu*, **Olivia Mautone**, **Dzenis Alagic**. Chemistry, Franklin and Marshall College, Lancaster, Pennsylvania, United States

Oxetanes are an important structural motif found in a range of natural products and compounds of pharmaceutical interest. However, typical methods to make non-symmetrical oxetanes are lengthy and involve laborious functional group manipulation. Direct photochemical cycloaddition of aldehydes and alkenes (the Paternò–Büchi reaction) represents the most convergent synthetic method, but mechanistic limitations mean substrate scope is limited. We have explored the photochemistry of S-aryl thioformates as a possible general way to access 1,2-disubstituted oxetanes following reductive desulfurization to remove the necessary radical stabilization element, thereby accomplishing the unknown Paternò–Büchi formylation. Synthesis of a wide range of S-aryl thioformates with varying electronic properties was successful, and their reactivity under both direct UV irradiation and photoredox catalysis has been explored. In preliminary studies, a variety of products have been observed and isolated, including an interesting sulfoxide product. By understanding the photochemical mechanism leading to sulfoxide formation, we can synthesize it in good yields or eliminate it entirely. We will continue to explore the photochemical reactivity of S-aryl thioformates, with the ultimate goal of developing a new synthesis of oxetanes or discovering other novel reaction methodologies.

ORGN 267

Adventures with undergraduate research collaborators: Organic transformations driven by simple molecular interactions

Todd A. Davis, *todd.davis@usafa.edu*, **Audrey Hornsby**, **Steven Gardner**, **Rebecca Miller**. Chemistry, United States Air Force Academy, USAF Academy, Colorado, United States

Recently, our laboratory has focused on exploiting simple molecular interactions to develop new organic transformations in high yield and selectivity. In particular, we have focused on using Lewis base and hydrogen bonding catalysts to control both the reactivity of the substrate, and when applicable, the stereochemical outcome. This talk will focus on our recent efforts utilizing thiourea catalysts to activate carbonyls (esters and carboxylic acids) leading to the formation of amides in high yield. This method is advantageous in that it does not require the use of either a Bronsted-Lowry acid/base, is

solvent free, and minimal purification is required. The reaction optimization, substrate scope, and potential applications will be discussed in detail.



Scheme #1: Thiourea Catalyzed Amidation of Esters

ORGN 268

Amides and chemical education as vehicles for innovation

Neil K. Garg, neilgarg@chem.ucla.edu. UCLA Chemistry, Los Angeles, California, United States

This presentation will showcase recent methodological developments from our laboratory that rely on the use of nickel catalysis to break amide C–N bonds. Initiatives in the realm of chemical education will also be described.

ORGN 269

Development of a commercial manufacturing process for BRIDION® (sugammadex)

David Thaisrivongs, *david.thaisrivongs@merck.com*. Merck & Co., Inc., Cranford, New Jersey, United States

BRIDION® (sugammadex) is a γ -cyclodextrin-based medicine that is indicated for the reversal of the neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery. Its mechanism of action is unique in the field of pharmaceuticals: it is a host molecule for neuromuscular blocking agents, which upon encapsulation, are unable to bind to the nicotinic cholinergic receptors in the neuromuscular junction. This audacious idea for improving patient recovery after anesthesia required the development of a singular chemical structure, and this talk will focus on the unusual synthetic challenges encountered in the preparation of cyclodextrin-based molecules and on our efforts to develop a robust, efficient, safe, and environmentally-friendly commercial manufacturing process for sugammadex.

ORGN 270

Biocatalysis and complex molecule synthesis

Alison R. Narayan, *alison.narayan@gmail.com*. Chemistry and Life Sciences Institute, University of Michigan, Ann Arbor, Michigan, United States

Natural sources, such as plants, fungi and microbes, have historically provided compounds with potent pharmaceutical properties. While it can be challenging to build complex natural products in a lab using existing chemistry methods, Nature has perfected these biosynthetic pathways. The work described leverages the power of Nature's tools for building complex molecules to synthesize novel molecules with therapeutic potential. The reactivity and selectivity of enzymes from natural product pathways are often unparalleled in existing chemical methods. Enzymes with potential synthetic utility are used as a starting point for engineering biocatalysts with (1) broad substrate scope, (2) high catalytic efficiency, and (3) exquisite site- and stereoselectivity. These biocatalytic methods are employed to efficiently synthesize biologically active complex molecules.

ORGN 271

Covering our bases: Development of scalable and reproducible cross-coupling reactions

Rebecca A. Green, *rebecca.green@bms.com*. Chemical & Synthetic Development, Bristol-Myers Squibb, Monroe, New Jersey, United States

Pd-catalyzed C-N coupling reactions are ubiquitous in the syntheses of active pharmaceutical ingredients (APIs). The development of robust and scalable reaction processes is essential in order for these transformations to be suitable for large-scale manufacturing. The use of traditional weak inorganic base reaction conditions enable the desired transformation to proceed with broad functional group tolerance, but the

reaction profile is scale-dependent and contingent on the inorganic base particle size. The development of dual-base homogeneous reaction conditions that enable readily scalable processes will be presented along with mechanistic experiments to develop an understanding of the role of each component of the reaction.

ORGN 272

Enabling technology development and application in CDMO industry-practical examples of solving challenge synthetic problems

Jingyang Zhu, *Zhu_jingyang@wuxiapptec.com*. Process Enabling Technologies, STA Pharmaceutical Co. Ltd., A WuXi AppTec Company, Shanghai, China

The presentation will mainly focus on recent development and application of enabling technologies, such as biocatalysis, chemo-catalysis and flow chemistry, in pharmaceutical development at STA Pharmaceutical Co., Ltd. (a company of WuXi AppTec). It will also depict how such technologies overcome challenge synthetic problems to accelerate pharmaceutical development, and bringing green & cost-effective processes for manufacturing APIs.

Practical examples will share our experience in developing enabling technologies, challenges and solutions. Finally, it will give our view on the potential for application of these enabling technologies in pharmaceutical and chemical industries.

ORGN 273

Remote, selective C-H functionalization via radical chaperones

David Nagib, *nagib.1@osu.edu*. The Ohio State University, Columbus, Ohio, United States

Our research is focused on harnessing the untapped reactivity of abundant chemical feedstocks to enable late-stage functionalization of medicinally relevant molecules. We have recently developed new approaches for selective C-H functionalization of alcohols, amines, and (hetero)arenes, using a combination of radical (1e-) and closed shell (2e-) processes that act in concert with one another. These radical chaperone strategies have enabled discovery of new classes of reactivity to streamline the synthesis of complex molecules with biological and industrial significance.

ORGN 274

Stereoselective addition reactions to carbon electrophiles: Conformational analysis, stereoelectronic effects, and reactivity

Keith A. Woerpel, *kwoerpel@nyu.edu*. New York University, New York, New York, United States

Oxygen-stabilized carbocations (oxocarbenium ions) are important intermediates in synthetic chemistry and glycobiology. Consequently, a deeper understanding of their structures and reactivities would benefit both fields. Our research demonstrates that electronic effects exert powerful influences on the conformational preferences of these cations. Furthermore, nearby functional groups that can engage in neighboring-group participation may or may not be involved in the rate- and stereochemistry-determining steps of these reactions. As the nucleophile becomes more reactive, stereoselectivity can increase, decrease, or remain the same, which provides information regarding the structures and reactivities of intermediates. The insight gained from these studies can also explain the selectivities of reactions of carbonyl compounds with nucleophiles such as Grignard reagents.

ORGN 275

Making carbon–phosphorus bonds with visible light: Challenges and opportunities

Sami LAKHDAR, *sami.lakhdar@ensicaen.fr*. LCMT, CNRS- ENSICAEN France, Caen, Online Search, France

Reactions involving phosphorus centered radicals play a pivotal role in the construction of organophosphorus ligands, biologically active and p–conjugated molecules.[1] Common synthetic approaches for the generation of such radicals imply the use of harsh reaction conditions.

In this presentation, we show that access to a large variety of organophosphorus compounds can be achieved under mild reaction conditions through *i*) visible light photoredox catalysis or *ii*) visible light irradiation of Electron–Donor–Acceptor complexes (EDA). The scope and limitations of these methods will be discussed with a special focus on their mechanistic aspects.[2]

ORGN 276

Insights into organic reactivity through gas phase computational and experimental studies

Jeehiun Lee, *jeehiun@chem.rutgers.edu*. Rutgers Univ, Piscataway, New Jersey, United States

Through computational and mass spectrometric studies, we lend insight into various organic mechanisms. Work in the area of intrinsic nucleo- and electrophilicity will be discussed. Time permitting, recent work in the area of organic catalysis will also be presented.

ORGN 277

Physical organic chemist's journey into fluoroalkylation chemistry

Surya G. Prakash, gprakash@usc.edu. Loker Hydrocarbon Institute, University of Southern California, Los Angeles, California, United States

The protocols for the efficient synthesis of fluorinated molecules are booming because of fluorine's ability (high electronegativity and its relatively close size to hydrogen) to exert desirable properties on organic molecules. Past several decades have also seen the growth of fluorinated compounds in material science, agro-chemistry and pharmaceutical industry. Based on Physical Organic Chemistry knowledge, many decades ago, we discovered that (trifluoromethyl)trimethylsilane, TMSF₃, acts as an efficient nucleophilic trifluoromethylating agent for a variety of electrophiles under catalytic and autocatalytic conditions. This eventually led to isolation and characterization of the long-lived trifluoromethanide anion in solution. Our recent activities on nucleophilic as well as carbenoid fluoroalkylations will be discussed.

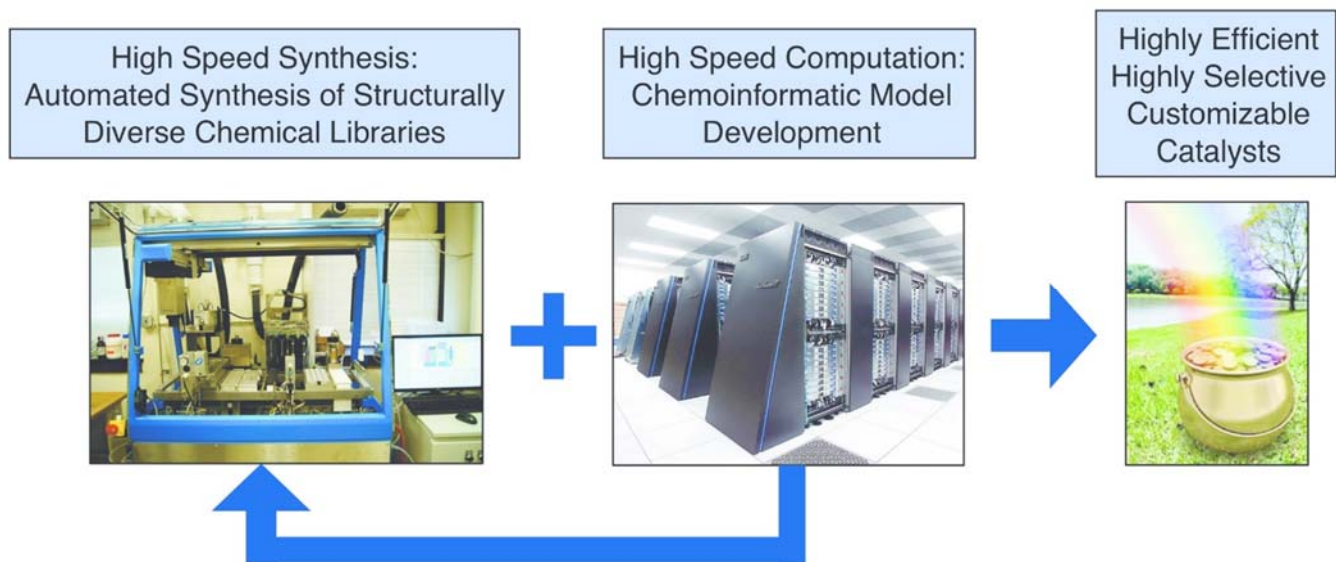
ORGN 278

Discovery and optimization of enantioselective catalysts through chemoinformatics

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The development of synthetic methods in organic chemistry has historically been driven by Edisonian empiricism. Catalyst design is no exception wherein experimentalists attempt to qualitatively recognize patterns in catalyst structures to improve catalyst selectivity and efficiency. However, this approach is hindered by the inherent limitations of the human brain to find patterns in large collections of data, and the lack of quantitative guidelines to aid catalyst selection. Chemoinformatics provides an attractive alternative for several reasons: no mechanistic information is needed; catalyst structures can be characterized by 3D-descriptors which quantify the steric and electronic properties of thousands of candidate molecules; and the suitability of a given catalyst candidate can be quantified by comparing its properties to a computationally derived model on the basis of experimental data. The ability to accurately predict a selective catalyst using a set of non-optimal data remains a Grand Challenge of machine learning with respect to asymmetric catalysis.

This lecture will describe a newly developed, chemoinformatic workflow that consists of the following components: (i) construction of an *in silico* library of a large collection of conceivable, synthetically accessible catalysts of a particular scaffold; (ii) calculation of robust chemical descriptors for each scaffold (iii) selection of a representative subset of the catalysts in this space. This subset is termed the Universal Training Set (UTS), so named because it is agnostic to reaction or mechanism. (iv) Collection of the training data, and (v) application of modern machine learning methods to generate models that predict the enantioselectivity of each member of the *in silico* library. These models are evaluated with an external test set of catalysts. The validated models can then be used to select the optimal catalyst for a given reaction.



ORGN 279

Award Address (James Flack Norris Award in Physical Organic Chemistry sponsored by the ACS Northeastern Section). Quantifying polar organic reactivity

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In a historic review, the development of nucleophilicity and electrophilicity scales from the 1950s to the 1970s will be described. Kinetic investigations of S_N2 reactions by Swain and Scott (1953) and Ritchie's studies of the rates of the reactions of tritylium and tropylium ions with amines, alkoxides and related anions (1972) are the most prominent examples. In the early 1980s we discovered methods for the selective formation of 1:1-products by additions of carbocations to olefins and used the kinetics of these reactions to generate the first nucleophilicity scales for π -systems. We found that the second-order rate constants of these reactions can be expressed by equation (1), where electrophiles are characterized by one parameter (E) and nucleophiles are characterized by two solvent-dependent parameters, the nucleophilicity N and the susceptibility s_N (typically $0.6 < s_N < 1.1$).

$$\lg k_{20^\circ\text{C}} = s_N (E + N) \quad (1)$$

By using para- and meta-substituted benzhydrylium ions (Ar_2CH^+) and structurally related quinone methides as reference electrophiles, which differ widely in reactivity, we have created the most comprehensive nucleophilicity scales presently available. In this way a direct comparison of the nucleophilicities of alkenes, allylsilanes and -stannanes, enol ethers and enamines, carbo- and heterocyclic arenes, carbanions, ylids,

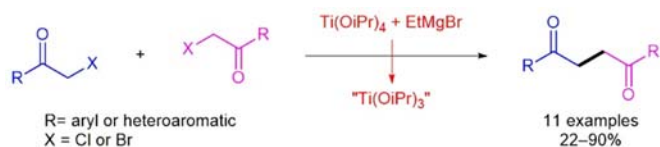
diazoalkanes, N-heterocyclic carbenes, isonitriles, O-, N-, S- and P-centered nucleophiles, as well as hydride donors became available. Data base: < <https://www.cup.lmu.de/oc/mayr/DBintro.html> >. In combination with analogously derived electrophilicity scales, absolute rate constants for numerous polar reactions can be calculated with an accuracy of factor 10-100 in a reactivity range of more than forty orders of magnitude which allows one to predict whether certain reactions will take place and whether they will proceed with activation or diffusion control.

ORGN 280

Synthesis of 1,4-diketones via titanium-mediated reductive homocoupling of α -haloketones

Nathan N. Le, le@southwestern.edu, **Aimee M. Rodriguez**, **James R. Alleyn**, **Michael R. Gesinski**. Chemistry and Biochemistry, Southwestern University, Georgetown, Texas, United States

1,4-Diketones have been synthesized via a reductive homocoupling of α -haloketones. Addition of a Grignard reagent to titanium(IV) isopropoxide affords a low-valent titanium(III) intermediate that is believed to mediate a radical dimerization reaction. The reaction works well for a variety of aromatic α -haloketones including heteroaromatic compounds



ORGN 281

Intercepted rearrangement reactions via iron catalyzed carbene transfer reactions with diazoacetoneitrile

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Diazoacetoneitrile is a close analogue of ethyl diazoacetate and was first described by T. Curtius in 1898. Despite their close resemblance, diazoacetoneitrile found only very little interest in organic synthesis methodology due to high risks associated to this diazoalkane.

Herein, we report on the safe and scalable synthesis of this important diazoalkane using in situ and flow techniques, which now allows applications in organic synthesis. Firstly,

we describe the implementation of an in situ protocol that allows efficient carbene transfer reactions with various nucleophiles. Importantly, the reaction of benzylic sulfides proceeds under an unexpected intercepted rearrangement reaction, which allows the formal exchange reaction of two alkyl groups. Secondly, we describe a continuous-flow protocol that now opens up applications of diazoacetonitrile in X-H functionalization reactions.

ORGN 282

Boracarboxylation of α -substituted vinyl arenes

Steven Knowlden¹, swk0005@mix.wvu.edu, **Brian V. Popp**². (1) Chemistry, West Virginia University, Morgantown, West Virginia, United States (2) Bennett Dept of Chemistry, West Virginia University, Morgantown, West Virginia, United States

Hetero(element)carboxylation of unsaturated organic substrates is useful due to the installation of a carboxylic acid as well as a synthetically versatile hetero(element)-functional group. In 2016, we reported the first method to achieve borolative-carboxylation of vinyl arenes. The mild method utilizes redox-neutral copper catalysis and a single atmosphere of CO₂ to obtain novel boron functionalized α -aryl carboxylic acids, including non-steroidal anti-inflammatory drugs (NSAIDs) such as bora-ibuprofen, bora-indoprofen, bora flurbiprofen, and bora-naproxen. Recently, we demonstrated that utilization of PPh₃ as a secondary ligand allows for extension of the substrate scope and improves overall reaction efficiency. However, boracarboxylation of α -substituted vinyl arenes presents another challenge, due to their steric bulk and the possibility of side reactions such as competitive copper-boryl reduction of CO₂ to CO, and base-mediated dimerization of the substrates. Tuning the electronics of the substrates in tandem with increased CO₂ pressure and modification of the base allows access to a wider variety of boron functionalized α -(hetero)aryl carboxylic acids with varying substitution at the benzylic position.

ORGN 283

Innovation at a molecular level: Scaffold analysis of CAS registry

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A set of 30M cyclic organic compounds was extracted from the CAS Registry and analyzed to study changes in structural innovation over time. Scaffolds, defined as the ring systems and the chain fragments connecting them, were used to assess the molecular novelty of the compounds. Our analysis presents findings on the pace of innovation and new regions of chemical space disclosed in recent years, including an assessment of FDA approved drugs suggesting that drug-hunters are pushing the boundaries and searching previously unexplored regions of the chemical space to find active organic small molecule drugs.

ORGN 284

Synthesis of *anti*- and *syn*-hydroxymethyl 1,3-diol motifs based on the regioselective cleavage of 2,3-epoxy diols using organomagnesium and organoaluminum reagents: Application to the polypropionate synthesis

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Polypropionates are large and complex metabolites found in many natural products that have a wide range of powerful therapeutic activities including antibiotics, antiviral, antitumor, antiparasitic and antifungal. The hydroxymethyl 1,3-diols motif appears in many natural and bioactive polypropionate and the development of synthetic methodologies for their construction represented a great endeavor. Up to date few regio- and diastereoselective methods for the synthesis of *anti*- and *syn*-hydroxymethyl 1,3-diols motif have been reported. Recently, we have reported and developed a second-generation methodology based on the regioselective cleavage of monoprotected-2,3-epoxy alcohols with alkynyl aluminum reagents for the synthesis of differentially monoprotected alkynyl triol derivatives with highly distereoselectivity. Here, we report a regiocontrolled epoxide cleavage methodology using Cu-catalyzed alkenyl Grignard reagents, for the synthesis of *anti*- and *syn*-hydroxymethyl 1,3-diols fragments (Scheme 1). Different alkenyl Grignard reagents were explored such as *cis*- and *trans*-1-propenylmagnesium bromide, vinyl magnesium bromide and (trimethylsilyl)vinylmagnesium bromide reagents with *cis*- and *trans*-TIPS-monoprotected epoxy alcohols. The successful results obtained with the Grignard reagents provided a direct access to the *cis*- and terminal homoallylic alcohols, avoiding the partial hydrogenation step, in moderate to good yields (46-88%) and excellent regioselectivities (>95:5) for the synthesis of *syn*- and *anti*-1,3-diols. The *trans* Grignard reagent produced a mixture of *trans* and *cis* alkenols in a moderate ~65:35 *trans/cis* selectivity. To access to the complementary *trans*-homoallylic alcohols in two steps we employed propynyl alane cleavage followed by *trans* reduction. Additionally, different alkynyl and alkylaluminum reagents were explored to compare the regioselectivity of the epoxide cleavage reaction using a variety of monoprotected 2,3-epoxy alcohols. These results open the door for the elaboration of new polypropionate targets that require hydroxymethyl 1,3-diols motif such as tedanolide, myriaporones, tylosin, mycinamicins and other natural products.

ORGN 285

Synthesis of guaipyridine alkaloids cananodine and rupestines G and D

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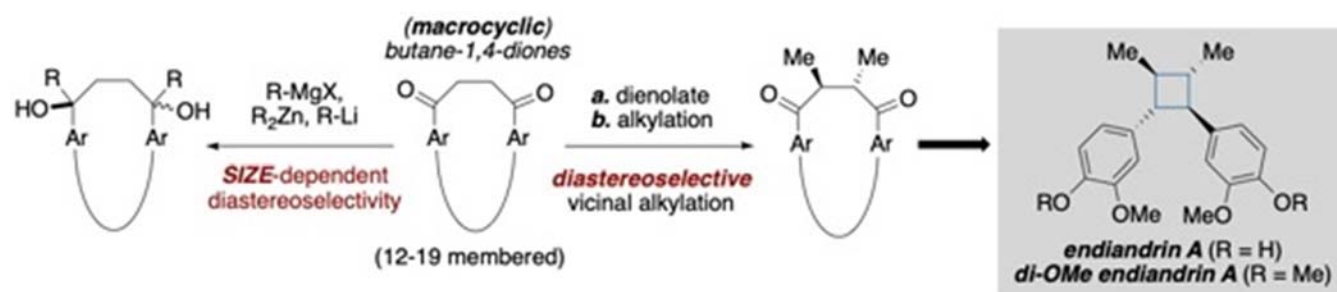
The guaipyridine alkaloids are a small family of natural products isolated from *Cananga odorata* and *Artemesia rupestris*, plants used in traditional medicine of China and Southeast Asia. One member of this family, cananodine, has reported activity against two hepatocellular carcinoma cell lines. A total synthesis of cananodine and rupestines G and D is reported. The synthesis hinges on an intramolecular Heck reaction to construct the seven-membered carbocycle of these targets.

ORGN 286

Diastereoselective transformations of macrocyclic 1,4-diketones and their application to the total synthesis of cyclobutane-containing natural products

Kara F. Johnson¹, *kfh0011@auburn.edu*, **Timothy H. Barnes¹**, **Bradley L. Merner²**. (1) Chemistry and Biochemistry, Auburn University, Auburn, Alabama, United States (2) Chemistry and Biochemistry, Auburn University, Auburn, Alabama, United States

High levels of diastereoselectivity have been observed for Grignard reactions of macrocyclic 1,4-diketones. In all of the macrocycles investigated, ring size proved to be the greatest contributor to diastereoselectivity. As the size of the macrocyclic (1,4-diketone) system employed decreases, the observed diastereoselectivity of the 1,2-addition increases. These results led to an investigation of enolate alkylations on the same macrocyclic 1,4-diketones as a means to alkylate the α and α' positions diastereoselectively. Similarly, high levels of diastereoselectivity were obtained in these vicinal alkylation reactions. The resulting macrocyclic 1,4-diketones were subsequently subjected to a five step sequence, featuring a transannular McMurry reaction, to afford the all trans relative stereochemistry of several lignan-type natural products.

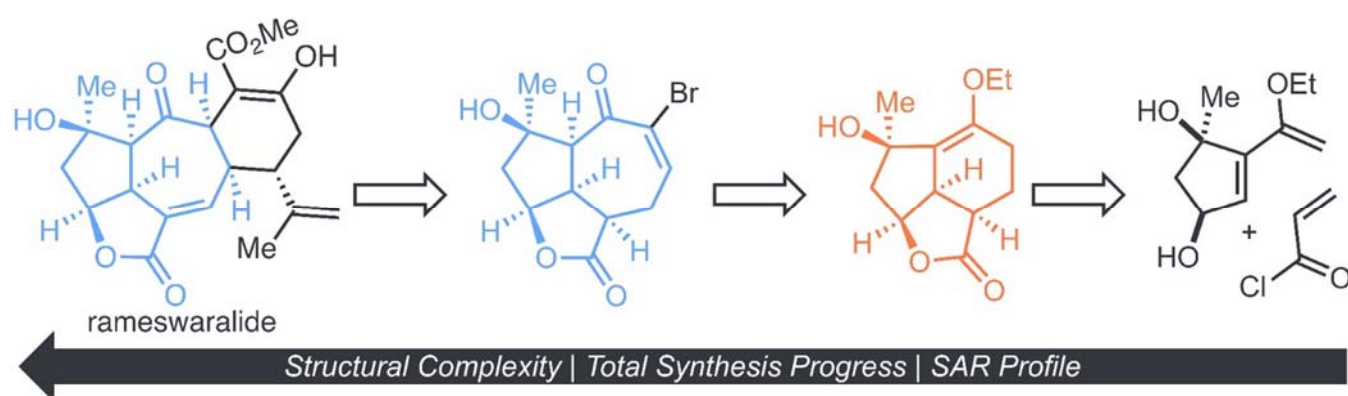


ORGN 287

Pharmacophore-directed retrosynthesis applied to rameswaralide: Synthesis and bioactivity of *Sinularia* natural product tricyclic cores

Nathanyal J. Truax¹, nathanyal_truax1@baylor.edu, **Safiat Ayinde**², **Khoi N. Van**¹, **Jun Liu**², **Daniel Romo**¹. (1) Chemistry and Biochemistry, Baylor University, Waco, Texas, United States (2) Department of Pharmacology and Molecular Sciences, John Hopkins School of Medicine, Baltimore, Maryland, United States

A pharmacophore-directed retrosynthesis strategy applied to rameswaralide has provided simplified analogs bearing the common 5,5,6 and 5,5,7 skeleton present in several cembranoid and norcembranoids from *Sinularia* soft corals. Given resemblance to many cembranoid and norcembranoid natural products, these core skeletons may be utilized as starting points to access other natural products in this family including yonarolide and ineleganolide. Key steps include a kinetic resolution Diels–Alder lactonization organocascade delivering the common 5,5,6 core and a subsequent ring expansion affording a 5,5,7 core serviceable for current studies toward the synthesis of rameswaralide. Initial structure–activity relationships of intermediates *en route* to rameswaralide have revealed interesting differential and selective cytotoxicity.



ORGN 288

Synthesis and structure activity studies of indene-based SHIP1 agonists

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The SH2-containing inositol 5'-phosphatase SHIP1 has been recognized as a key secondary regulator of the PI3K signaling pathway. Upregulation of SHIP1 has been implicated as a method to treat a number of inflammatory disorders. To facilitate our own studies on the role of SHIP1 in cell signaling, a new synthesis of the SHIP1 agonist AQX-1125 was developed. This synthetic route is significantly shorter than the route

previously reported, requiring only 12 steps from epiandrosterone. This sequence utilizes a hydroxy-acid intermediate which facilitates differentiation of the C6 and C7 positions, resulting in a completely regioselective synthetic route. Biological testing of intermediates and some analogs provides some insights into the structure activity relationships and their effects on SHIP1 agonist activity.

ORGN 289

Enantioselective total synthesis of oxazolomycin B, inthomycin C, and formal synthesis of neooxazolomycin

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Since the isolation and absolute structural assignment of peptide-polyketide secondary metabolites, oxazolomycin A and neooxazolomycin, by Uemura and co-workers in 1985, several other congeners now collectively referred to as 'oxazolomycins' have been isolated from terrestrial and marine strains of *Streptomyces* bacteria. These complex natural products have been the focus of research programs around the world aimed at the study of their bioactivity, biosynthesis, total synthesis, and, notably, the stereoselective synthesis of what we term the oxazolomycin 'core' (C1-C17). This core architecture features a densely functionalized pyroglutamate ring furnished with a strained spiro- β -lactone, four contiguous stereogenic centers— two of them being adjacent *oxa/aza*-quaternary centers— and a pendant amidomethyldiene chain (C8-C12). The bioactivity reported for these natural products includes anticancer, antibacterial, and antiviral. The scope of this activity with regard to the organisms affected may reflect the oxazolomycin structure as a general strategy of *Streptomyces* bacteria against competing organisms, which can potentially be leveraged in the development of a novel therapeutic chemotype to combat infectious disease. Thus an efficient, modular, and stereoselective synthesis of these natural products and analogues is highly desirable. Herein we report the outcome of our synthetic efforts toward these intriguing spiro- β -lactone natural products, which have culminated in an enantioselective total synthesis of oxazolomycin B and inthomycin C, as well as a concise formal total synthesis of neooxazolomycin. The synthesis commences with our group's nucleophile-catalyzed Michael-proton transfer lactamization to construct a simple γ -lactam in enantiopure form. Expedient functionalization of this ring was carried out with excellent stereocontrol, delivering an α -hydroxyaldehyde to which a key diastereoselective addition of a complex organolithium is mediated by a lanthanide salt. Future synthetic studies target alkyne-bearing molecular probes, predicated on the inherently reactive oxazolomycin core, to be applied in chemical proteomics investigations.

ORGN 290

New strategies for *N*-nitrosation

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N-Nitroso compounds display a wide range of biological activity. As nitric oxide donors, *N*-nitrosamines can exhibit either toxic or therapeutic properties depending on structure. In organic synthesis, *N*-nitrosamines are useful intermediates in the generation of α -amino compounds, or as reagents for electrophilic nitrosation or radical nitrosylation. Traditional methods for *N*-nitrosation involve harsh reaction conditions and are typically ineffective for nitrosating weakly nucleophilic amines or amides. To overcome this limitation, we have developed a series of bench-stable nitrosation reagents that successfully nitrosate a range of alcohols, thiols, amines, and amides under ambient conditions. These new reagents provide access to challenging nitroso compounds that were previously inaccessible by traditional methods, leading to a new class of potential nitric oxide donors.

ORGN 291

Novel umpolung strategies enabled by hypervalent iodine reagents

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Hypervalent iodine reagents in the I(III) oxidation state have emerged as a versatile, environmentally benign toolkit for the functionalization of organic molecules. Amongst their diverse reactivity is the ability to facilitate reversed-polarity, or “umpolung”, transformations of typically nucleophilic functionalities, enabling novel bond disconnections. Our laboratory has leveraged an underexplored class of I(III)-reagents, (bis)cationic nitrogen ligated lambda-3 iodanes (*N*-HVIs), as a platform to develop umpolung transformations of heteroatoms and alkenes. The presence of datively bound heterocyclic ligands leads to enhanced, highly tunable and novel reactivity relative to their well-established oxygen or halogen ligated counterparts. In this talk, applications to electrophilic oxygen activation, enone C–H arylation, and pyridinium group transfer reactions will be discussed.

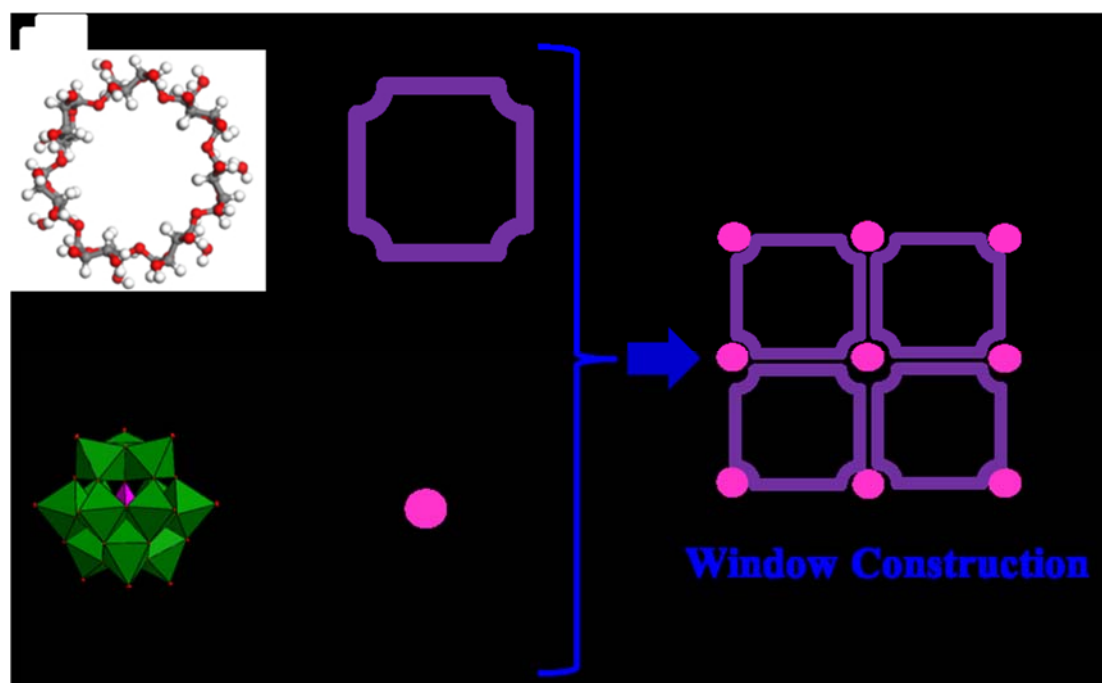
ORGN 292

Supramolecular structures with intrinsic microporosity for "on-demand" separations and delivery applications

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Nature embraces the principles of supramolecular chemistry, exploiting noncovalent interactions and coordination chemistry in various ways to facilitate all biological processes. Inspired by nature, the assembly of complex synthetic systems in both solution and the solid state is becoming increasingly feasible. This often requires that known systems be modeled, explored, and fine-tuned in order to develop further

systems of even higher complexity. Examples include the construction of globular self-assembled molecular capsules, which have potential applications as drug delivery agents, gas storage containers and catalytic nano-reactors. Moreover, fine-tuning porosity in such assemblies have expanded the scope of these systems to include gas and petrochemicals separation. Our approach to this class of functional self-assembled structures includes employing a "window construction" technique, which provides a new class of materials with intrinsic microporosity. Simple hydrogen bonding and/ or metal coordination were employed to construct a library of these suprastructures, which showed excellent selectivity towards gas separation together with easily tunable pore size. This talk will present an overview of the systems obtained so far and their applications in energy intensive separation and protein encapsulation/delivery.



ORGN 293

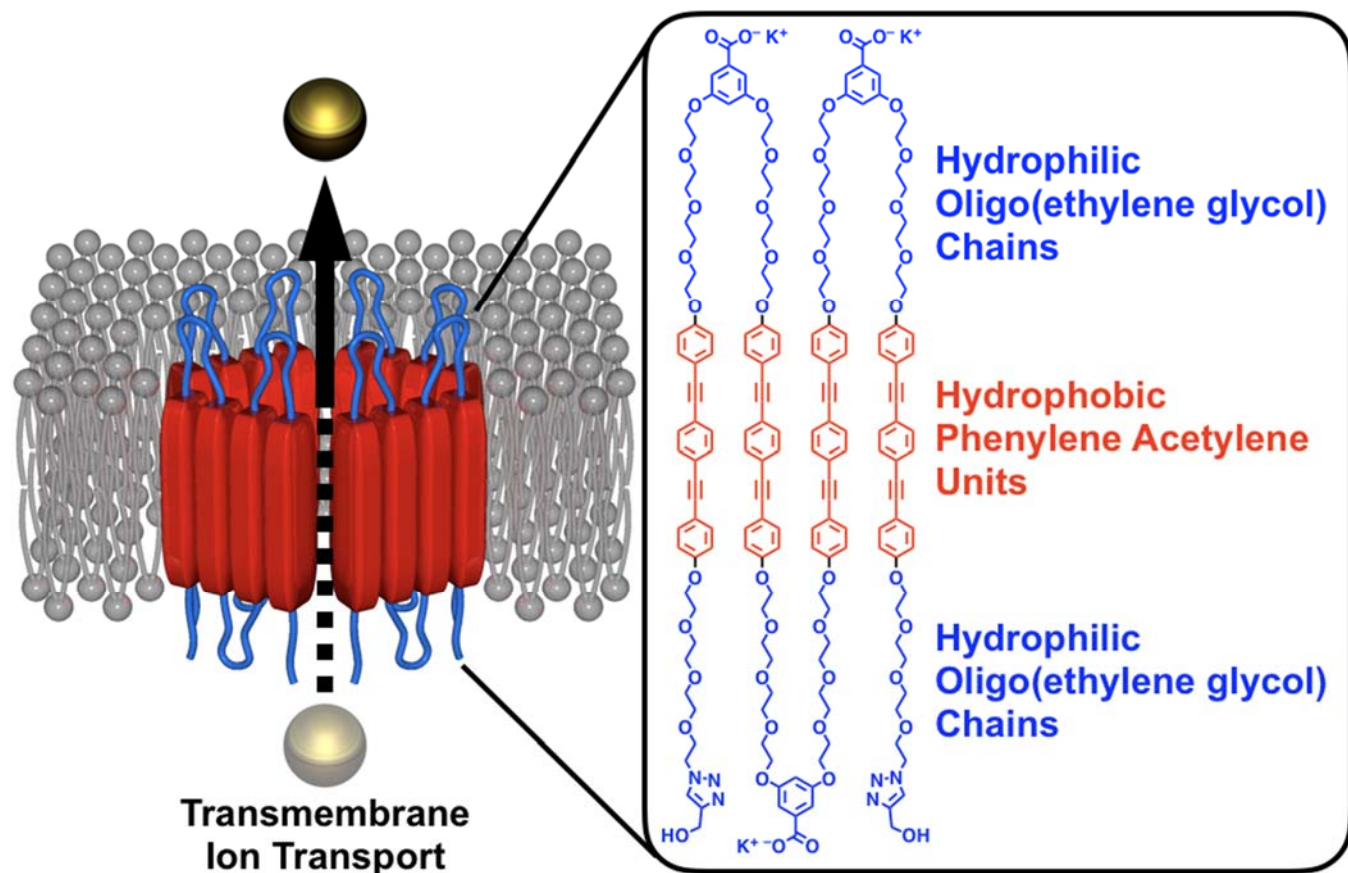
Fluorinated multiblock amphiphiles that transport ions across lipid bilayers

Kohei Sato¹, koheisato@bio.titech.ac.jp, Kota Nabeya¹, Takahiro Muraoka², Norihisa Hoshino³, Tomoyuki Akutagawa³, Kazushi Kinbara¹. (1) School of Life Science and Technology, Tokyo Institute of Technology, Yokohama, Kanagawa, Japan (2) Tokyo University of Agriculture and Technology, Koganei, Japan (3) Tohoku University, Sendai, Japan

Channel proteins that selectively transport ions across cell membranes play important roles in varieties of biological events, and synthetic mimetics of such biomolecules may offer novel therapeutic methods for channelopathies and material purification technologies in industries. In this regard, our research group has been developing a series of multiblock amphiphiles that are composed of hydrophilic oligo(ethylene glycol) chains and hydrophobic phenylene acetylene units. When the multiblock amphiphiles are incorporated into lipid bilayer membranes, the multiblock amphiphiles self-assemble and form transmembrane ion channels.

Here we newly developed fluorinated multiblock amphiphiles that incorporate perfluorophenylene acetylenes as hydrophobic units and hydrophilic oligo(ethylene glycol) chains as hydrophilic units, and investigated their ion transport properties across lipid bilayer membranes. Furthermore, we discovered that ion channels formed by the fluorinated multiblock amphiphiles show an unusual ion selectivity among alkali metal ions.

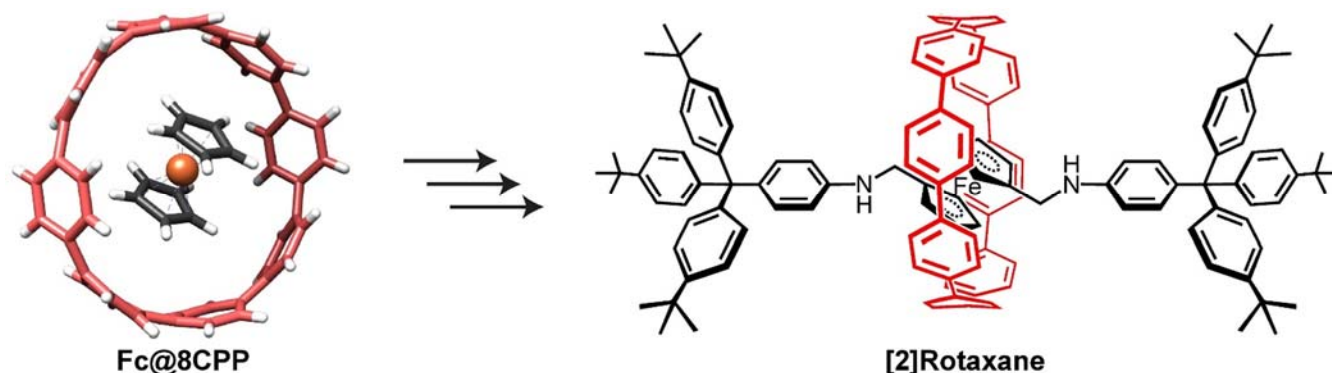
Further details will be presented at the conference.



Cycloparaphenylene-based semiconducting host-guest complexes and rotaxanes stabilized by CH–pi interactions

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The cycloparaphenylene (CPP) macrocycles represent the smallest cross-sections of armchair carbon nanotubes. Due to their unique optical and electronic properties, CPPs have been investigated as a new class of nanomaterials during the past decade. CPPs have been employed as supramolecular hosts, yet most CPP host-guest complexes, such as those involving fullerene guests, are stabilized by pi-pi interactions. We have found that CH–pi interactions between $[n]$ CPP ($n = 8$ or 10) and a variety of pi-conjugated guests drive the self-assembly of inclusion complexes, which may have advantageous properties as organic semiconductors or templates for the synthesis of mechanomolecules such as catenanes and rotaxanes. The host-guest complexes have been characterized by fluorescence, UV–visible–NIR, and ^1H / ^{13}C NMR spectroscopy. The single-crystal X-ray structure has been elucidated for the ferrocene@8CPP complex, which is stabilized by six CH–pi bonds. We employed this complex as a template in the synthesis of a pi-conjugated [2]rotaxane via a stoppering protocol. This new host-guest motif can open the avenue to new semiconducting materials based on molecular recognition as well as mechanically bonded molecular machines.



ORGN 295

Directing peptide self-assembly via chirality

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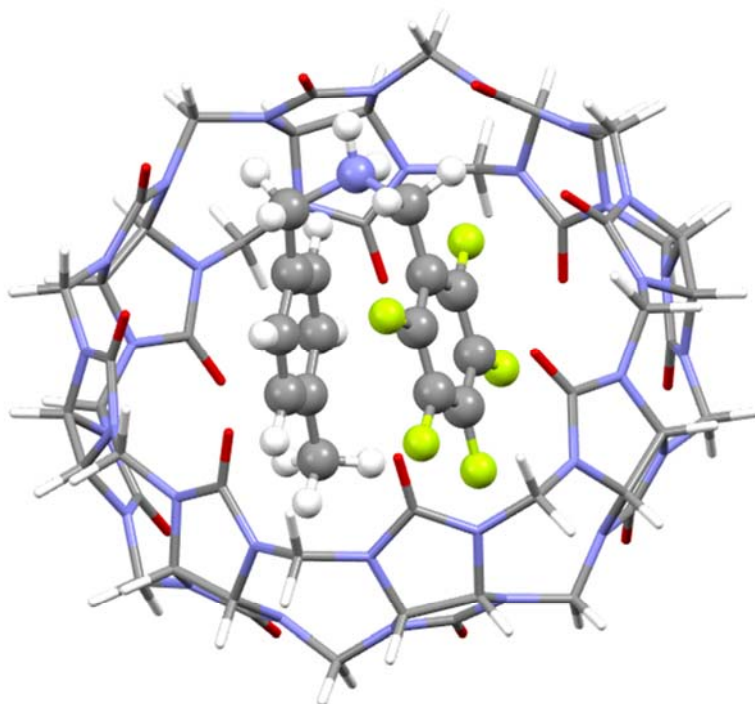
Functionalised dipeptides can self-assemble in water to give a range of supramolecular structures that lead to gel formation. Typically, homochiral dipeptides are used. Here, we discuss how the nature of the self-assembled aggregates can be affected and controlled by using different enantiomers, diastereomers and racemates of specific dipeptides. For example, it is possible to form fibres, tubes or thin-walled tubes from a single dipeptide depending on whether (L,L), (L,D), or the racemic dipeptide is used. We will show how this approach can be used to prepare very different materials.

ORGN 296

Guest folding inside cucurbit[8]uril

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Measuring the strength of intermolecular bonds in supramolecular assemblies is of critical importance to understand the non-covalent interactions that occur in nature. To evaluate the magnitude of π - π interactions in the non-polar and non-polarizable environment of the Cucurbituril family of macrocycles (CB[n]), we prepared eight dibenzyl ammonium guests, and titrated them with CB[8]. ^1H NMR spectroscopy reveals that the 1:1 "U" shape conformation of the guest inside the cavity of CB[8] is the dominant adduct even in sub-stoichiometric amounts of the host. The binding affinity of the guests towards CB[8] were measured by isothermal titration calorimetry (ITC). Intramolecular interactions (i.e. between the aryl substituents), intermolecular ones between the guests and the inner wall of CB[8], as well as differential solvation effects will be isolated and discussed carefully.



ORGN 297

Systematic investigation of chalcogen bonding interactions using X-ray analysis

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Chalcogen bonding (CB), defined as the interaction of a Group VIA element (O, S, Se, Te) and a Lewis-base partner atom, has an increasingly important role to play in diverse fields such as drug discovery, catalysis, and supramolecular chemistry. Much less is known about the energetic origins of CB recognition properties, however, and experimental data is lacking in this regard. We present a model system based on 2,1,3-benzochalcogenodiazole (**1**, Figure 1a) for experimentally investigating the various recognition classes of chalcogens (Figures 1b—d) using X-ray analysis, and what can be learned about the origins of their attraction.

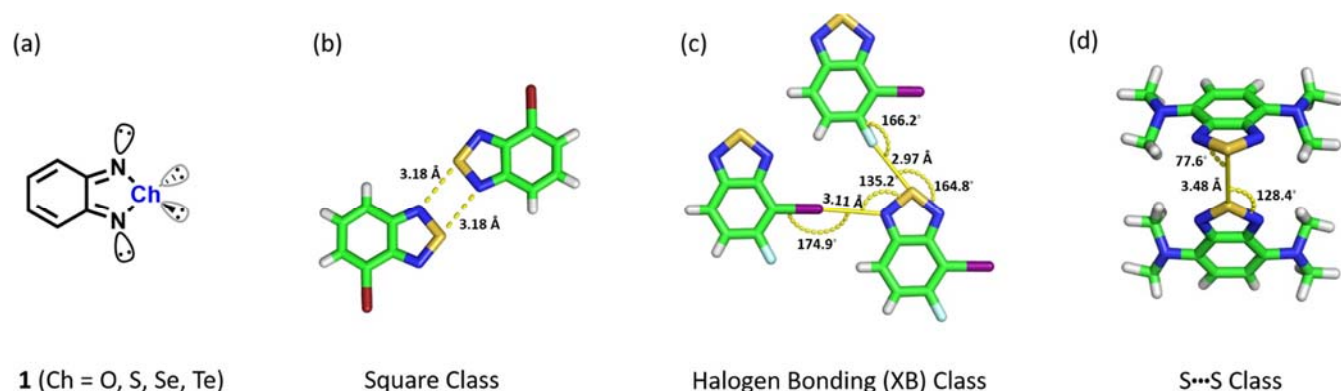


Figure 1. a) Top view of the 2,1,3-benzochalcogenadiazole core structure. b—d) Crystal structures showing various classes of CB interactions (Ch=S).

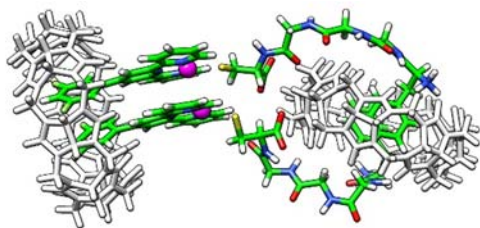
ORGN 298

Self-sorting of ditopic Pt(II) terpyridyl thiolate complexes with cucurbiturils

Hector Barbero, hb714618@ohio.edu, **Eric Masson**. Chemistry and Biochemistry, Ohio University, Athens, Ohio, United States

In order to maximize Coulombic interactions with positive guests, Cucurbit[8]uril (CB[8]) forms ternary complexes that distribute the positive charges over both portals of the macrocycle. However, our group showed that CB[8] and Pt(II) acetylides flanked by 4'-substituted terpyridyl (tpy) ligands form unprecedented 2:1 complexes with both Pt tpy units sitting on top of each other at the same CB[8] portal in a head-to-head (HH) fashion. We attribute the driving force to favorable “ π - π ” interactions between the extended aryl units, and to Pt-Pt interactions which counterweight Coulombic repulsion between the two positive guests.

Herein we explore the supramolecular self-sorting properties of Pt tpy thiolates bearing a peptide backbone with a CGGGF sequence. This design allows the compound to associate with CB[8] or CB[7] at either the 4'-substituent of the tpy ligand or at the phenylalanine residue. Assembly $\text{CB}[8]^{\text{Pt}} \bullet (\text{Pt} \bullet \mathbf{1})_2$ adopts the expected HH arrangement permitting the terminal phenyl moieties to recognize other CB[n] molecules. In fact, it can bind up to two additional molecules of CB[7] to afford assembly $\text{CB}[8]^{\text{Pt}} \bullet (\text{Pt} \bullet \mathbf{1})_2 \bullet \text{CB}[7]^{\text{Phe}}_2$. Likewise, it can also bind up to CB[8]. In this case, necklace $\text{CB}[8]^{\text{Pt}} \bullet (\text{Pt} \bullet \mathbf{1})_2 \bullet \text{CB}[8]^{\text{Phe}}$ is obtained with two CB[8] units, one that forms a “stacked 2:1” dimer of Pt complexes, and the other a HT assembly with the phenylalanine residues.



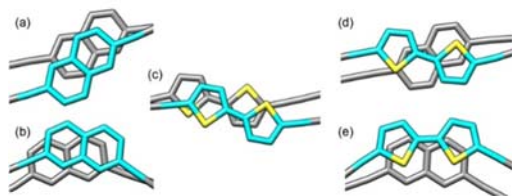
Supramolecular necklace $\text{CB}[8]^{\text{Pt}} \bullet (\text{Pt} \bullet \mathbf{1})_2 \bullet \text{CB}[8]^{\text{Phe}}$.

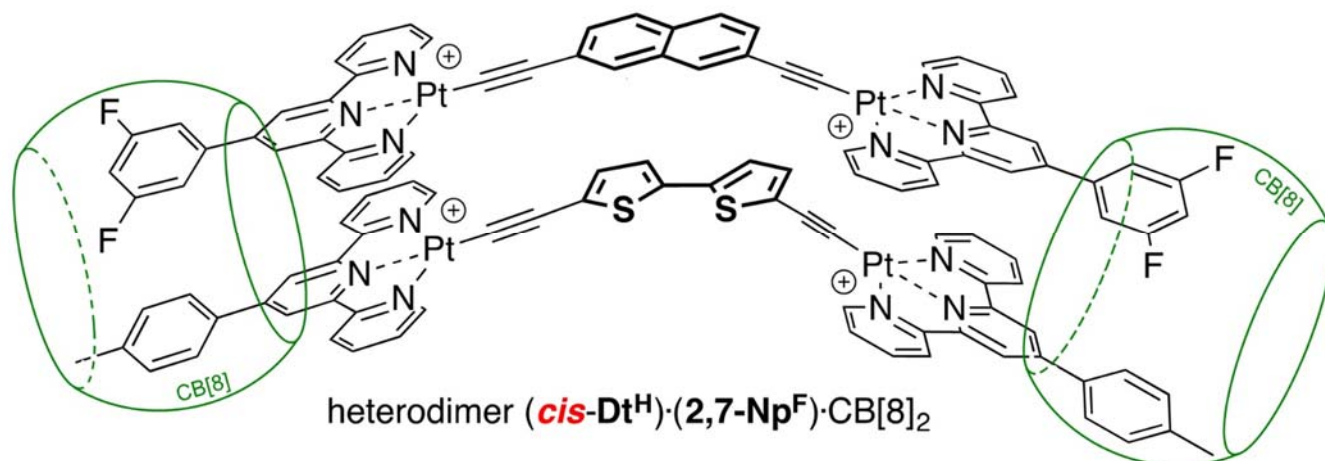
ORGN 299

Templating conformations with cucurbiturils

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Using rigid 2,6- and 2,7-substituted naphthalenes as templates, the *trans*- and *cis* conformations of 5,5'-substituted 2,2'-dithiophenes can be stabilized by the formation of heteroquaternary complexes with Cucurbit[8]uril macrocycles (CB[8]). The 2,6- and 2,7-substituted naphthalenes emulate the *trans*- and *cis*- conformations of dithiophene, respectively. Substituents are Pt(II) terpyridyl groups substituted at their 4' position with CB[8] binding sites, as these are known to form dimers in the presence of CB[8]. Formation of the dimers is caused by Pt-Pt interactions as well as favorable dispersive interactions between the terpyridyl groups. Formation of the heteroquaternary assemblies is driven in part by favorable quadrupole-quadrupole interactions between the terpyridyl heads inside CB[8].



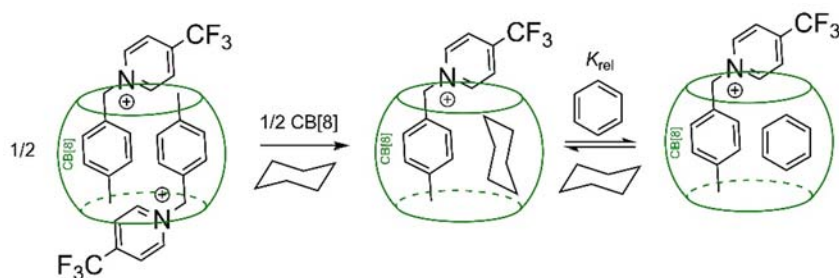


ORGN 300

Hydrocarbon sensing with cucurbit[8]uril and an auxiliary probe

MD NAZIMUDDIN, mn993916@ohio.edu, *Eric Masson*. Department of Chemistry and Biochemistry, Ohio University, Athens, Ohio, United States

Cucurbit[n]urils (CB[n]) are pumpkin-shaped, water soluble molecular containers which have a hydrophobic cavity and two hydrophilic carbonylated portals. In this study, we determined the relative affinities of a series of hydrocarbons for the cavity formed by the inner wall of Cucurbit[8]uril (CB[8]) and a tolyl unit linked to an auxiliary guest. The auxiliary guest is tagged with a trifluoromethyl group for quantification by ¹⁹F NMR spectroscopy. The CB[8]/probe pair was selective for cyclic hydrocarbons (cycloheptene and cyclooctatetraene, in particular). To the contrary, the affinity of benzene was approximately 450 times weaker than cycloheptene. Therefore, we conclude that unlike π-π interactions, CH-π interactions, as well as differences in hydrocarbon solvation, contribute significantly to the recognition process.



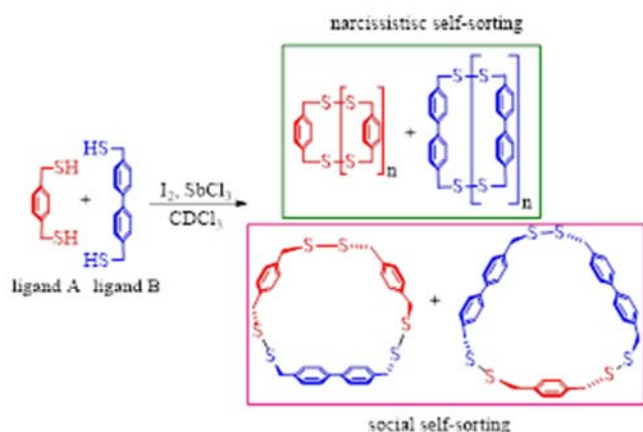
Formation of heteroternary complexes between CB[8], a probe and a reference hydrocarbon (cyclohexane), followed by competitive binding with benzene.

ORGN 301

Self-sorting in dynamic disulfide assembly: New unsymmetrical cyclophanes

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We report an approach combining dynamic covalent self-assembly and sulfur extrusion to synthesize new symmetrical biphenyl-linked disulfide and thioether macrocycles. This strategy also provides new unsymmetrical disulfide macrocycles when using two different thiols, and these can also be trapped as kinetically stable thioethers. This approach enables amplification and self-sorting of specific members of the disulfide libraries, improving a 20% statistical yield of two different unsymmetrical trimers up to 65% out of a small library of 21 different possible macrocycles. Finally, we use this method to synthesize two previously unknown unsymmetrical hydrocarbon cyclophanes, which are congeners of the venerable phenyl-bridged [2,2,2]-paracyclophane. NMR and/or single crystal x-ray diffraction confirm the structures of these new cyclophanes, which reveal that self-assembly followed by covalent capture and photochemical sulfur extrusion can be an effective strategy to synthesize new cyclophanes in high yields under mild conditions.



Scheme 1. Self-sorting of 2 different ligands, bis(mercaptomethyl) phenyl (A) and bis(mercaptomethyl) biphenyl (B), leads to narcissistic and social self-sorted products.

ORGN 302

Self-sorting networks using hydrogen-bonding building blocks

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A key challenge for self-assembly is to reproduce Nature's ability to assemble multiple functional entities in defined locations and at specific times. Such assemblies modulate complex adaptive networks that control biological processes (e.g. intracellular signalling cascades); multiple molecular recognition events happen simultaneously AND sequentially, requiring individual components to interact selectively with one partner at one point and then with another partner at a different point in a given process. This presentation will describe a series of new building-blocks capable of well-defined hydrogen-bonding interactions made in one or two steps.¹⁻² These motifs form heterodimers with tunable associations constants ($10^2 > 10^4 \text{ M}^{-1}$). The presentation will then describe how these hydrogen-bonding motifs together with others taken from the literature can be used to carry out sequential self-sorting and to develop self-sorting networks.³⁻⁴

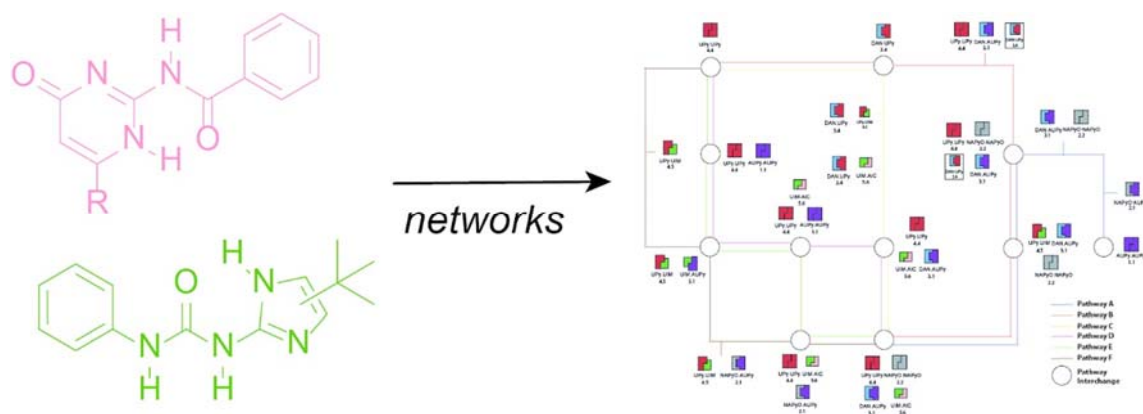


Figure 1. Schematic illustrating novel hydrogen-bonding motifs and their use in self-sorted networks

ORGN 303

Accelerating the macrocycle pharmaceutical design pipeline *in silico*

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Macrocycles are often attractive ligand matter for pharmaceutical projects from natural product optimization, to small molecule or peptide cyclization. Unfortunately significant hurdles still exist both in synthesis and in modelling. Here, we present some of the latest

tools we've developed to ameliorate these hurdles: automated macrocycle enumeration, conformational scoring, and rigorous free energy calculations.

ORGN 304

Development and application of computational analysis and prediction tools for macrocyclic peptide conformational space

Alex Brueckner¹, *bruecknera15@gmail.com*, **Qiaolin Deng**¹, **Edward C. Sherer**¹, **Ajay N. Jain**², **Pablo Trigo Mouriño**¹, **John Frost**¹, **Mikhail Reibarkh**¹, **David M. Tellers**¹. (1) Merck & Co., Inc., Kenilworth, New Jersey, United States (2) MC 0128, Bioeng Therapeutic Sciences, UCSF, San Francisco, California, United States

Macrocyclic peptides show promise as a class of pharmaceuticals capable of binding with targets previously undruggable by small molecules. Unfortunately, current computational tools and workflows have significant gaps for accurately predicting the chemical structure of complex systems such as macrocyclic peptides. The inherent conformational flexibility, as well as inter- and intra-molecular interaction possibilities, lead to an overabundance of seemingly relevant conformations. By incorporating select experimental data to computational methods, the conformational landscape is explored through the lens of a computational-experimental hybrid strategy to drive design toward the most pharmaceutically relevant conformational populations. The development of computational analysis and prediction tools to better define the conformational space of macrocyclic peptides, as well as several case studies, will be discussed.

ORGN 305

Structure-based design of potent macrocycles MCL1 inhibitors

Mario G. Cardozo^{2,1}, *mcardozo@nurix-inc.com*, **Sean P. Brown**¹, **hugues Paul**¹, **paul leszek**¹, **Doug Whittington**¹. (1) Amgen Inc, S San Fran, California, United States (2) Computational Chemistry, Nurix, Therapeutics, San Francisco, California, United States

The pro-survival BCL2 family member MCL1 is frequently dysregulated in cancer. To overcome the significant challenges associated with inhibition of MCL1 protein-protein interactions, we rigorously applied small-molecule conformational restriction, which culminated in the discovery of AMG 176, the first selective MCL1 inhibitor to be studied in humans. Using structure-based design and integrating conformational restriction as a guiding principle throughout the optimization process, we optimized a low microM HTS hit into a spiro-macrocyclic analogs series showing in vitro single digit pM inhibitory potency. Based on the hypothesis that high levels of nonbinding conformations increase the likelihood of poor selectivity and pharmacokinetic properties, we successfully used conformational restriction as a guiding principle for the optimization of these PPI inhibitors. NMR structure of a linear HTS hit series complexed with MCL1 showed a folded binding conformation, suggesting conformational restriction could be employed to form a macrocyclic ring. Combination of the conformationally restricted macrocyclic and

spirocyclic rings provided high-affinity MCL1 inhibition. The X-ray crystal structure of lead macrocycle complexed with MCL1 along with molecular modeling revealed that the population of the bound conformation is approximately 10% of the total conformations accessible in solution. This provided an opportunity to further rigidize the macrocycle to obtain compounds with suitable potency and selectivity profile to serve as a tool inhibitor for characterizing the mechanism of action of MCL1 inhibition in vitro. The gain in potency was presumably due to conformational restriction, where now the observed bound conformation in complex with MCL1 was the most abundant in the unbound state. Moreover, installation of an olefin reduced the number of energetically accessible conformations within 3 kcal/mol, these analogs had short half-lives and poor oral bioavailability. Simple methylation of a secondary alcohol led to a series of compounds with improved pharmacokinetic profiles, including increased oral bioavailability. This ultimately provided AMG 176, the first selective, orally bioavailable MCL1 inhibitor to advance into human clinical trials, validating our strategy of optimization guided by conformational restriction. MCL-1 inhibitor structure complexes, along with key biophysics assays, computational chemistry rational and design process will be illustrated.

ORGN 306

Design of cyclic peptide C5a antagonists guided with computational and NMR studies

Ye Che, *ye.che@pfizer.com*. Discovery Sciences, Pfizer, Groton, Connecticut, United States

C5a is one of the most potent proinflammatory mediators of the complement system. The effects of C5a are mediated through its interaction with C5a receptor (C5aR), which is a GPCR. However, targeting the C5a-C5aR axis has been extremely challenging, with one a single entity (eculizumab, an anti-C5 antibody) advancing to approval in the last 20 years. We have developed cyclic peptide C5a antagonists for both oral and i.v. administration with a goal to deliver an agent of lower cost, broader utility and higher patient satisfaction than the current standard of care. In this presentation, I'm going to highlight our efforts on design of bioactive cyclic peptides with tailored molecular properties guided with computational and NMR studies.

ORGN 307

Conformational analysis of peptide macrocycles for drug design

Jennifer Johnston¹, *jennifer.johnston@merck.com*, **Qiaolin Deng**¹, **Sookhee N. Ha**¹, **Sebastian Schneider**¹, **Grant Murphy**², **Edward C. Sherer**¹. (1) Computational and Structural Chemistry, Merck & Co., Jersey City, New Jersey, United States (2) Merck, Edison, New Jersey, United States

In the era of hit generation through exploration of large peptide macrocycle libraries facilitated by mRNA display technology, it is imperative for computational chemists to understand and even to predict the conformational preferences of identified hits. When considering large macrocycles, this is challenging using available technologies. Complicating factors include large conformational landscapes, and the workflow throughput required to match drug discovery timelines. Practical approaches to using macrocycle conformational searches to guide compound design will be covered.

ORGN 308

Rationalization of the membrane permeability differences in structurally similar cyclic peptides

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Cyclization and selected backbone N-methylations are found to be often necessary but not sufficient conditions for peptidic drugs to have a good bioavailability. Thus, the design of cyclic peptides with good passive membrane permeability and good solubility remains a challenge. To improve our understanding of the connection between structure and the ability to permeate membranes, we have developed a computational workflow to construct kinetic models based on extensive molecular dynamics (MD) data of the cyclic peptides in polar and apolar environments. By looking at "permeability cliffs", i.e. pairs or series of peptides with small structural variation but large changes in the permeability, we are able to establish the importance of the population of the membrane-permeable conformation in water as well as the time scales of the conformational interconversion processes [1-3].

ORGN 309

Computational design of functional cyclic peptides

Parisa Hosseinzadeh, *parisahoseinzade@gmail.com*. Biochemistry, University of Washington, Seattle, Washington, United States

Peptides have been considered as a promising alternative to small molecules and antibodies for targeting protein-protein interfaces. However, our inability to predict peptidic structures and to design peptides that selectively target a given interface has hampered their use as therapeutics. In this talk, I will go over our computational method to robustly and accurately design peptides with desired structures. I will then explain how we developed computational methods that lead to development of a peptide that inhibits histone deacetylase 2 with $IC_{50}=6$ nM without any library-based maturation. At the end I explain current challenges and future prospects of computational-based peptide binder design.

ORGN 310

Diversity-based DEL development and construction

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DNA-encoded library technology (DEL) has made noteworthy progress on small molecule drug discovery in the past few years in the pharmaceutical industry and academia. Speaking from the small molecular libraries construction, larger chemical space can improve the success rate of affinity selection. In order to achieve these purposes, on the one hand, we explored new DNA-compatible reactions, such as C-H activation reaction, which enables many previously considered mono-functional building blocks to act like bi-functional building blocks, and contemplated that more structurally diverse DELs can be efficiently constructed; meanwhile we also developed a series of DNA compatible Heck Coupling reaction conditions that can incorporate more building blocks into DELs; on the other hand, we employed diversity-oriented-synthesis (DOS) strategy combining with DNA-compatible reactions and high-throughput experiments, to construct DELs containing spiro-, unsaturated and disubstituted scaffolds. After affinity selection, the SAR and hit molecule's structural information can be decoded from attached DNA tags via high-throughput sequencing, which can be used as a basis for the lead optimization.

ORGN 311

Reaction development for DNA-encoded library synthesis: Exploring heterogeneous systems

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DNA-encoded chemistry translates molecular biology techniques for molecular evolution such as DNA barcoding, selection, DNA amplification, and DNA sequencing to combinatorial small molecule library synthesis and target-based screening. A broad scope of chemical reactions and diverse starting materials is desirable to furnish structurally diverse encoded libraries. Encoded library synthesis in homogeneous systems requires chemical methods that provide DNA-compatibility, water-tolerance and fast kinetics to operate on highly diluted DNA-tagged reactants. Ideally, they are operationally simple and furnish target compounds from diverse starting materials with high yields. Only a very few chemical reactions meet all these demands, access to encoded heterocyclic chemistry is even rare. Micellar catalysis is an attractive principle for encoded compound synthesis due to both reaction acceleration and DNA shielding. Amphiphilic block copolymers formed spherical nanoreactors and immobilized a catalyst in the DNA-inaccessible hydrophobic core. Sulfonic acid-substituted micelles converted DNA-tagged aldehydes by Povarov and Groebke reactions to diverse substituted tetrahydroquinolines and imidazopyridines without noticeable DNA degradation, and facilitated *t*Boc group removal from amines. Furthermore, a Cu(I)-immobilizing micelle

mediated the DNA-compatible oxidation of DNA-tagged alcohols to aldehydes by the Cu(I)/bipyridine/TEMPO system.

Initiating encoded library synthesis with solid phase-coupled barcodes is an alternative to solution-phase encoded chemistry. It benefits from freely selectable organic solvents and nucleobase-protection conferring increased chemical stability to the oligonucleotide tag. A solid phase-initiated barcoding strategy allowed for ready translation of several reactions to encoded library synthesis, among them heterocycle-forming cycloaddition reactions, isocyanide MCR chemistry, and phosphoric acid-mediated reactions.

ORGN 312

DNA-encoded libraries: Aryl fluorosulfonates as versatile electrophiles enabling facile on-DNA cross-coupling reactions

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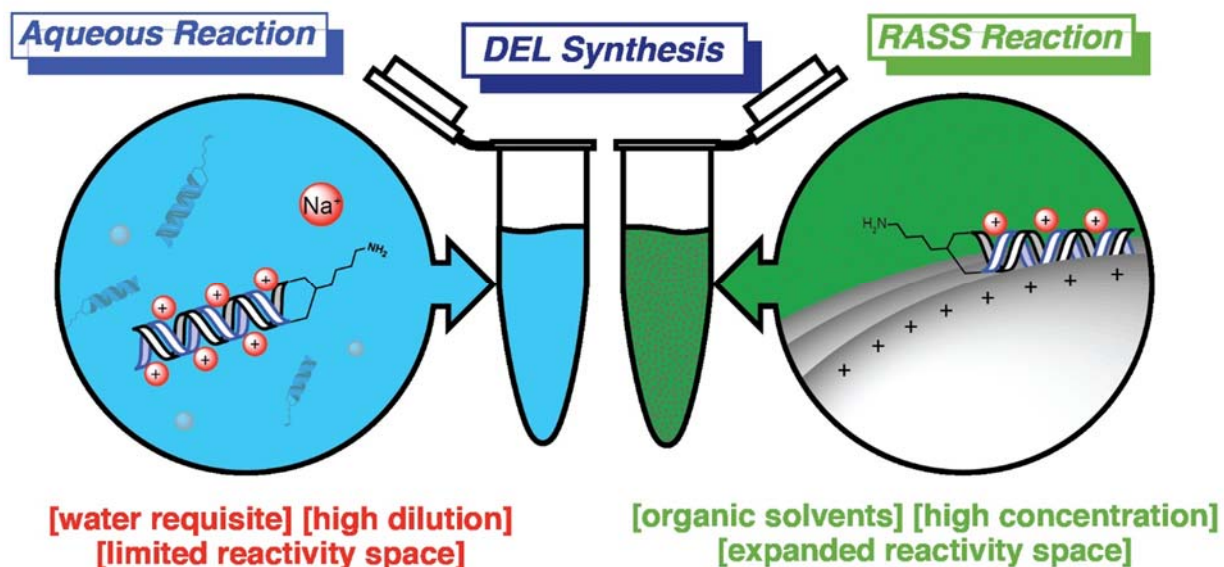
Despite the success of DNA encoded library (DEL) technology in new drug discovery and chemical biology, it's great potential has not yet fully realized. One of the major obstacles is the synthesis of high-quality DELs with more chemical structural diversities, which in turn depend on the development of novel solution-phase DNA-compatible reactions. As the two general approaches in the DEL synthesis, conventional split-pool synthesis in the presence of DNA tag and late-stage DNA annotation of bioactive natural products (NPs) both require chemical reactions that are orthogonal to DNA tags in aqueous reaction condition. Thus, new methodologies that could access the greater structural diversities of DNA tagged small molecules attract attentions of the academia and pharmaceutical industry. Herein, we identified that (hetero) aryl fluorosulfonate (-OFS) is a versatile electrophile in palladium-catalyzed on-DNA Suzuki, Sonogashira, and Buchwald cross-coupling reactions. We have optimized reaction conditions in terms of function tolerability, DNA compatibility, and heterocyclic coupling partners' diversity. Some of these reactions were facile at low temperature and under air. It is noteworthy, some of the catalytic systems distinguished between fluorosulfonate and other common electrophiles (Cl, Br), making them possible to carry out sequential on-DNA synthesis to form poly-substituted aryl and/or heteroaryl molecules in DELs. In addition, these new on-DNA coupling reactions could also be utilized in the late-stage on-DNA modifications of phenol containing natural products. Overall, these new DNA compatible reactions would provide more flexibilities in DEL's design and synthesis in the future.

ORGN 313

DEL out of water: Expanding DNA compatible chemistry in organic solvents

Dillon Flood, Dflood@scripps.edu, **Philip Dawson**. Scripps Research, La Jolla, California, United States

The structural diversity of DNA Encoded Libraries has been limited since the hydrophilic, anionic, and functional group rich nature of the DNA tag severely limits the repertoire of compatible chemical reactions. Rather than pursuing the optimization of individual synthetic organic reactions for water compatibility, we reasoned that a general strategy for transferring DNA-substrates into organic solvents could significantly expand the structural diversity explored by DEL. Reversible absorption of macromolecules to a solid support (RASS) has facilitated peptide and protein modification, enabling the use of anhydrous solvents and multistep synthetic procedures. This RASS strategy was adapted for DEL through a commercially available polystyrene based, quaternary ammonium resin. Adsorption of DNA headpiece substrates to this resin was found to facilitate transfer to organic solvents such as DMA, THF, EtOH, and CH₂Cl₂. This RASS approach for DEL has enabled the development of Ni mediated carbon-carbon (C(sp²)-C(sp³)) and carbon-heteroatom (C-N, C-S, C-P) cross couplings with broad substrate scope and DNA compatibility. The immobilization of the DNA has also facilitated the use of diverse reaction manifolds including electrochemical and photochemical transformations. In addition, this approach has been further optimized for use in industrial scale library building. This expanded scope of reaction conditions compatible with DEL library generation has the promise to contribute to the generation of conformationally diverse scaffolds with drug-like properties.



ORGN 314

Application of enzymes to on-DNA reactions

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DNA-encoded library technology (ELT) is a powerful tool for target validation and hit identification in early stage drug discovery. The attached DNA tagging limits the chemistry that can be applied to the technology. Enzymatic catalysis is a highly attractive alternative to classic chemical and chemocatalytic synthesis because it enables organic synthesis in aqueous environments with high stereoselectivity. In this presentation we will report Threonine Aldolase catalyzed on-DNA aldol reaction to form β -hydroxy- α -amino acids with high yield and good stereoselectivity. The broad aldehyde scope and three functional groups in the product make it a valuable reaction to DNA-encoded library.

ORGN 315

Single electron processes to enable DEL synthesis

Gary A. Molander, *gmolandr@sas.upenn.edu*. Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States

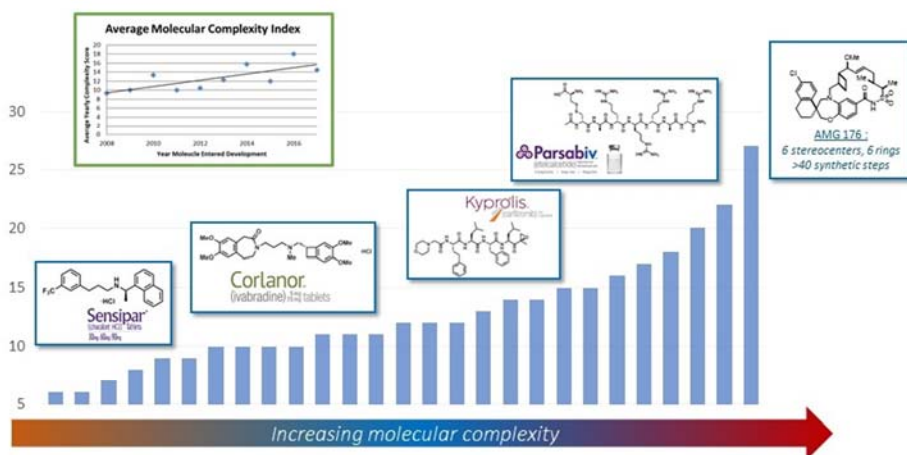
DNA Encoded Library (DEL) technology possesses the capability to sample four to five orders of magnitude more chemical space at a dramatically reduced monetary and temporal cost than any other available high-throughput screening method. As impressive as these numbers are, there are still many remaining challenges that prevent DEL methods from reaching their full potential. Thus, it is not only the speed, efficiency, cost, and size of the libraries that must be considered, but the quality of the libraries that will determine their ultimate value. The lack of variety and diversity in current medicinal chemistry libraries is exacerbated in DEL technology because any reactions used must be compatible with aqueous reaction media and the highly functionalized and sensitive nature of the DNA encoding material. It is widely acknowledged that the major hurdle to full implementation of DEL technology is the lack of structural diversity and 3D molecular complexity present in current DNA-encoded libraries. The photoredox/Ni dual catalytic reactions, photoredox radical reactions, and photoredox radical/polar crossover transformations to be discussed address this critical gap, and have the capability to enhance the quality of such libraries with structural motifs that would be otherwise challenging to evaluate. Not only are these protocols enabling for the creation of new chemical space in the DEL paradigm, but the reactions can be conducted open to the air in a matter of minutes, providing low-barrier access to these useful protocols.

ORGN 316

Molecular complexity the driving force for chemical process innovation at Amgen

Jason S. Tedrow, *jtredrow@amgen.com*. Process Development, Amgen, Inc, Salem, Massachusetts, United States

As the complex biology being interdicted by today's drug discovery groups increases, so too does the rise in overall synthetic complexity of the molecules themselves required to achieve selective therapies. At Amgen, the molecular of our small molecules entering development over time has increased requiring new and innovating methods to access these new molecular entities in efficient fashions. Often, these methods can lead to new molecular architecture previously difficult to come by even at discovery scale. This talk will take a historical perspective over Amgen's past 15 years of small molecule process development and build-up of novel innovative catalytic methodologies to assemble the drug targets. The topics will range from new catalysts for cross-coupling reactions to new stereoselective transformations executed on multikilogram scale.



Public Information

ORGN 317

Deaminative cross-couplings via C–N bond activation

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Alkyl amines are widely available, and easily prepared in high enantiomeric purity. In addition the amino group (NH₂) can be carried through multi-step syntheses in protected

form, and enables straightforward purification. These features are well appreciated in the use of alkyl amines for the preparation of nitrogen-containing products. We are expanding the toolkit of reactions of alkyl amines by developing cross-coupling reactions via cleavage of their carbon–nitrogen bonds. Capitalizing on the robust methods to prepare enantiopure benzylic amines, we have developed stereospecific cross-couplings of benzylic ammonium salts to deliver highly enantioenriched diaryl and triaryl alkanes, as well as benzylic boronates. This method was the first example of either an enantioselective or stereospecific cross-coupling of a benzylic electrophile with an arylboronic coupling partner.

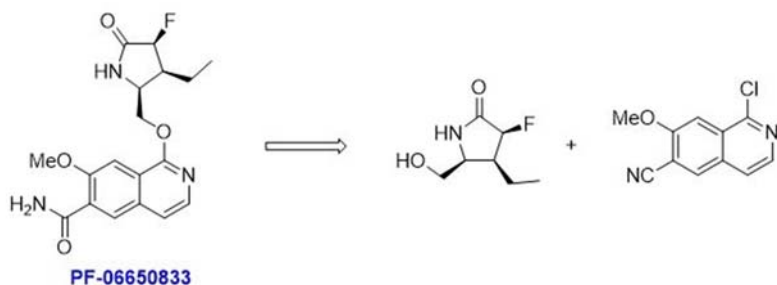
Recognizing the abundance of primary alkyl amines with unactivated alkyl groups (not benzylic, allylic, or strained), we have also developed cross-couplings of alkyl pyridinium salts. These reactions efficiently convert alkyl amine derivatives into alkyl arenes, and provide new opportunities for the use of amines in synthesis. Our method is the first example of the cross-coupling of an alkyl amine derivative in which the C–N bond is not electronically or strain-activated. We have also extended this chemistry to cross-couplings of benzylic pyridinium salts to enable transformation of benzylic amino groups to aryl or vinyl substituents. Our more recent work with new coupling partners and new classes of alkyl pyridinium salts will also be presented.

ORGN 318

Development towards a potential commercial route for an IRAK4 inhibitor PF-06650833

Zhihui Peng, chzpeng@yahoo.com, **Bryan Li**, **Emma McInturff**, **David Place**, **Robert A. Singer**, **Lulin Wei**. Chemical Research & Development, Pfizer, Inc., Groton, Connecticut, United States

The clinical supply route for PF-06650833 has successfully supported the advancement of the program through Phase 2 studies despite numerous synthetic challenges, most notably the all *cis* stereochemistry of the lactam fragment, including an α -fluoro stereocenter. Significant improvements have been made on the clinical supply route through innovative chemistry and process development. The improvements not only supported greater API demands with reduced cost and lead time, but also made the route a potential commercial route.



ORGN 319

Innovative process development to access 2-fluoroadenine for islatravir

Yingju Xu, *yingju_xu@merck.com*. Process Chemistry, Merck Sharp Dohme Corp., Rahway, New Jersey, United States

Islatravir is an investigational nucleoside reverse transcriptase translocation inhibitor (NRTTI) currently being evaluated in clinical trials for the treatment of HIV infection. The manufacturing route involves a novel enzymatic cascade between an elaborated ribose fragment and 2-fluoroadenine (2-FA). 2-FA is a significant contributor to the API cost and its commercial availability is limited. A green manufacturing process has been developed to deliver 2-FA from commodity chemicals, involves an efficient & mild difluorination reaction using readily available potassium fluoride at ambient temperature, a highly selective direct amination and a simple deprotection in water. Final in-situ release of 2-FA in water with a catalytic amount of acid provides the ideal particle size for the enzymatic cascade end game to deliver final API, eliminating isolation and pin-milling of 2-FA to maximize operation simplicity.

ORGN 320

Stereocontrol in photochemical synthesis

Tehshik P. Yoon, *tyoon@chem.wisc.edu*. Chemistry Department, Univ of Wisconsin Madison, Madison, Wisconsin, United States

Photochemistry is intriguing as a synthetic tool because the absorption of light by an organic molecule results in the formation of exceptionally energetic reactive intermediates that can react in ways that are inaccessible to ground-state molecules. However, this high reactivity is also a challenge for stereoselective synthesis: control over the stereochemistry of photochemical reactions, particularly using enantioselective catalysts, has been a long-standing challenging synthetic problem with few general solutions. We recently developed a class of functionalized Ir photocatalysts that combine the robust photophysical properties of metal polypyridyl chromophores with hydrogen-bonding elements that can recruit organic substrates and hold them in a fixed orientation as they react. This strategy offers a flexible new strategy for the design of highly enantioselective excited-state photoreactions.

ORGN 321

Chemical and functional characterization of natural products

John MacMillan, jomacmil@ucsc.edu. Chemistry and Biochemistry, University of California, Santa Cruz, Santa Cruz, California, United States

Natural products have played an integral role in the drug discovery process, providing therapeutic leads as well as chemical probes to unravel complex biological pathways. We have developed an integrative approach to the discovery of bioactive natural products through combination of chemical, biochemical and bioinformatic driven approaches. This has led to the discovery of a number of sub-type selective toxins against non-small cell, including products ikarugamycin, the bohemamines and discoipyrrole A. Furthermore, we have identified an unusual route to the biosynthetic formation of the discoipyrroles that utilizes a non-enzymatic, multi-component cyclization cascade. We have been able to harness this chemistry with discoipyrroles to generate analogs that have greater potency and PK properties. To follow on the non-enzymatic discovery of discoipyrroles, we have developed tools to increase the understanding of the function of non-enzymatic chemistry in natural products. Utilizing the natural products, dimaritimide A and oxazin A, I will highlight the use of isotope-labeling NMR studies to understand the non-enzymatic mechanism of formation and how the mechanisms can be used for improving biological activity of the natural products.

ORGN 322

Taking a deep dive into natural products chemistry and structure determination

Carole Bewley, caroleb@intra.niddk.nih.gov. Laboratory of Bioorganic Chemistry, NIDDK, National Institutes of Health, Bethesda, Maryland, United States

Nature's specialized metabolites or 'natural products' have inspired and motivated broad branches of basic and applied chemistry research and led to the development of over half of our drug therapies. Structure determination can be a complex yet prerequisite aspect of pursuing the chemistry or biology associated with natural products. Our group uses diverse methods for complete structure elucidation including NMR, x-ray diffraction and chiroptical measurements. In this symposium honoring Dr. Tadeusz Molinski, we will present detailed structural studies of new natural products from understudied environmental bacteria, structural surprises from old friends such as the marine alkaloids papu'amine and haliclonadamine and discuss related biological and ecological implications.

ORGN 323

Discovery of bioactive marine natural products

Raymond J. Andersen, raymond.andersen@ubc.ca. University of British Columbia, Vancouver, British Columbia, Canada

The secondary metabolites found in marine organisms represent an extremely rich source of novel chemical diversity for academic drug discovery and chemical biology

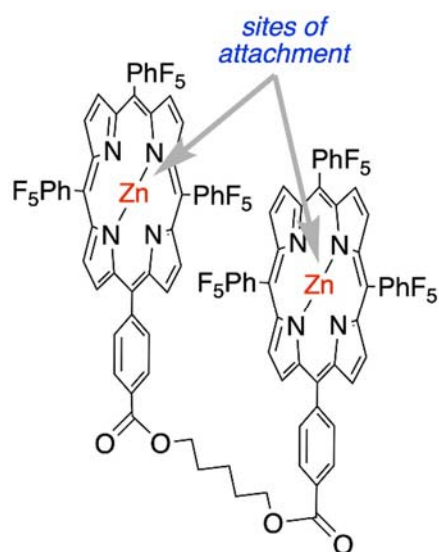
programs. Our group at UBC has amassed a sizable library of crude extracts from marine sponges, other marine invertebrates, and cultured marine microorganisms collected in many of the world's oceans. In collaboration with biologists, this crude extract library has been screened for activity in cell-based and pure enzyme assays designed to identify promising marine natural product lead compounds for the development of drugs. Bioassay-guided fractionation of crude extracts and extensive spectroscopic analysis has been used to identify the structures of pure natural products active in the assays. Biology-oriented chemical synthesis has been undertaken to probe the SAR for new natural product pharmacophores that we have discovered and to provide material for *in vivo* testing in animal models. We have used Click chemistry probes and protein x-ray diffraction analysis to study the interactions of bioactive natural products with their molecular targets. Several new drug candidates for the treatment of cancer, inflammation, type II diabetes, and infectious diseases have emerged from this research program. Four of them have progressed to phase II/III clinical trials in humans and others are in preclinical evaluation/development. The lecture will present some highlights from our academic 'Drugs from the Sea' and chemical biology research in the area of bacterial and viral infectious diseases.

ORGN 324

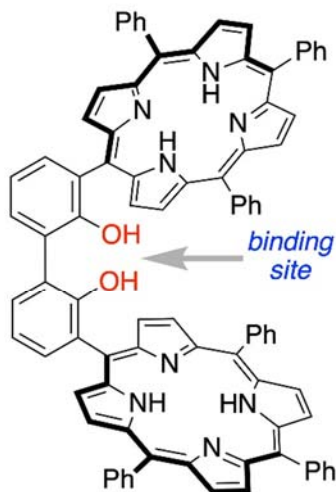
Progress in Absolute Stereochemical Determination of Organic Molecules via Exciton Coupled Circular Dichroism

Babak Borhan, babak@chemistry.msu.edu. Chemistry, Michigan State University, East Lansing, Michigan, United States

During the past 20 years, we have witnessed a great deal of activity directed towards the use of Exciton Coupled Circular Dichroism for the absolute stereochemical determination of organic molecules. The porphyrin tweezer method was among a number of innovative strategies that highlighted the power of ECCD analysis in host/guest complexation of chiral molecules. The use of a variety of zincated porphyrin tweezers as the chromophoric hosts will be discussed, with demonstration of the methodology's feasibility for the absolute stereochemical determination of a number of different classes of organic molecules. Application of a new host system, capable of binding molecules with a single site of attachment will be discussed also, with applications for absolute stereochemical determination of amines, cyanohydrins, alcohols, sulfoxides, phosphine oxides, etc.



Zn-TPFP porphyrin tweezer



MAPOL

ORGN 325

Evolution of the anion relay chemistry: Construction of architecturally complex natural products

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Multi-component union tactics in which three or more fragments are rapidly assembled are highly prized in the construction of architecturally complex natural products. Anion relay chemistry (ARC), a multi-component union tactic, has just such potential to elaborate structurally diverse scaffolds in a single operation with excellent stereochemical control. Recent advances and applications will be presented.

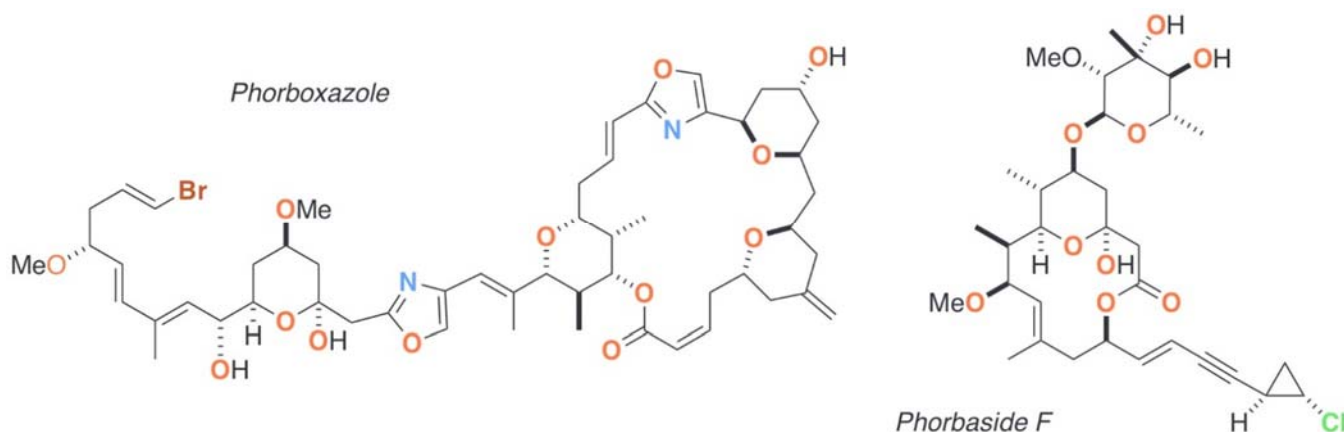
ORGN 326

Marine natural products: Discovery and invention from the 'wine dark sea'

Tadeusz F. Molinski^{1,2}, tmolinski@ucsd.edu. (1) Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California, United States (2) Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, California, United States

The wide chemical diversity of natural products from marine invertebrates (sea sponges, ascidians, soft corals, etc), algae and microbes, is often matched by potent biological activity; indeed, several marine derived-drugs have now been approved as

therapeutics. The history of natural products are linked to organic chemistry as the “engines of its development” (E. J. Corey), and structure elucidation is still at the heart of natural products discovery. Despite advancements in modern spectroscopy, challenging problems in establishing constitution and stereochemistry still arise. My research group has seized upon those as opportunities for development of inventive tools in marine natural products (MNPs); not only in NMR and CD spectroscopy (our 'nanomole-scale' project to fully characterize minute samples), but also synthetic methodology. Over the years, I have come to view the discovery of new molecules as not so much a matter of compound procurement, but bringing to light chemical information by uncovering the blueprints embodied in the bond constitution and stereochemistry that propels further investigation in multiple disciplines: pharmacology, chemical ecology included, and of course, total synthesis. In this talk, I will illustrate highlights of the past three decades of independent research in MNP chemistry, along with newer results. The objective is to share the extraordinary, rich landscape of structural and biological chemistry that first captured my imagination, and continues to inspire collaboration and exploration at the edge of new scientific frontiers.



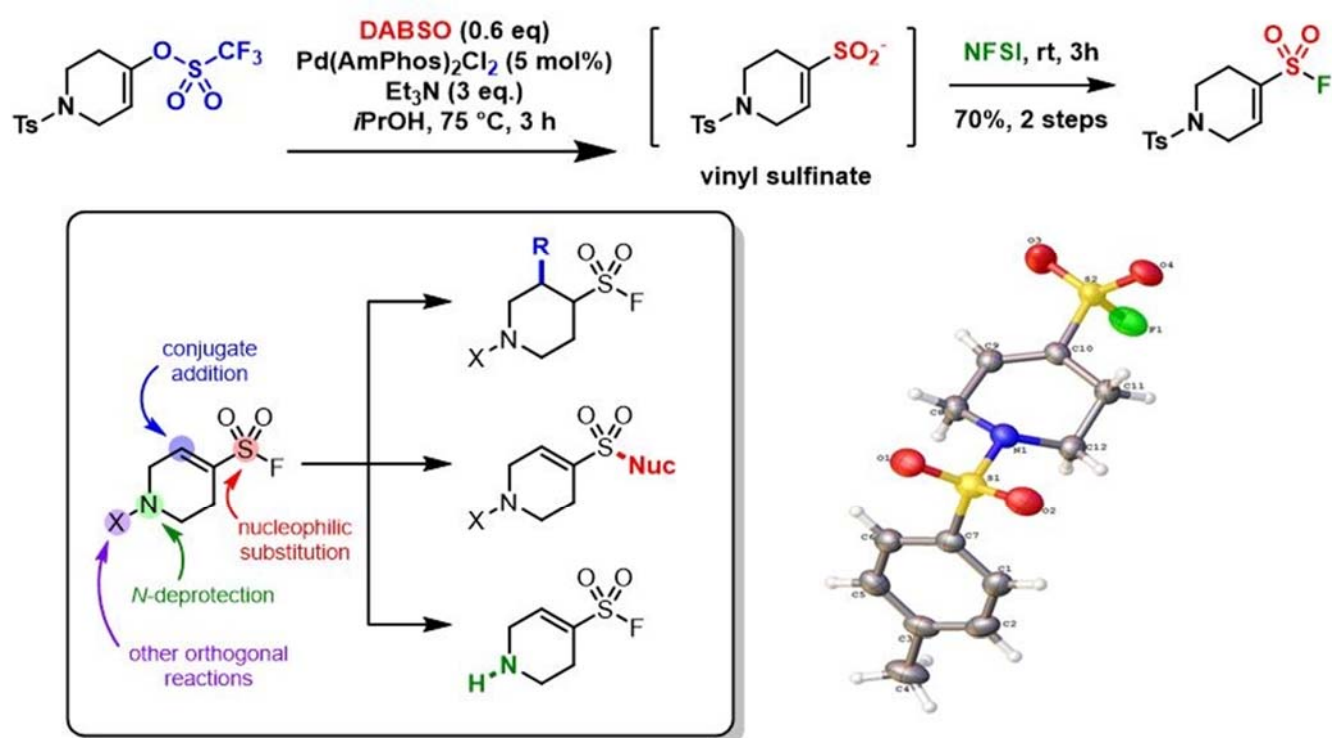
ORGN 327

Pd-catalyzed preparation cyclic alkenylsulfonyl fluorides: New motif for sulfur fluoride exchange

Scott W. Bagley¹, scott.w.bagley@pfizer.com, Terry Lou², Michael C. Willis². (1) Medicine Design, Pfizer, Inc., Groton, Connecticut, United States (2) Dept of Chem Univ of Oxford, Oxford, United Kingdom

Sulfonyl fluorides are gaining a wide use as chemical biology warheads for the exploration of protein active sites through covalent binding modes. In an effort to expand the available synthetic space around these important functional groups

Medicinal Chemistry at Pfizer has teamed up with the Willis lab at the University of Oxford to explore the synthesis of vinyl sulfinates as versatile synthetic intermediates to access a wide variety of reactions and products. A series of low molecular weight, compact and multifunctional cyclic alkenylsulfonyl fluorides are efficiently prepared from the corresponding alkenyl triflates under the action of palladium catalysis. A range of functional groups can be tolerated, and a correspondingly large range of derivatization reactions are possible, including substitution at sulfur, conjugate addition, and N-functionalization. This talk will describe the ongoing collaborative synthetic work towards the preparation of these vinyl sulfonyl fluorides as multifunctional tools for synthesis and chemical biology.



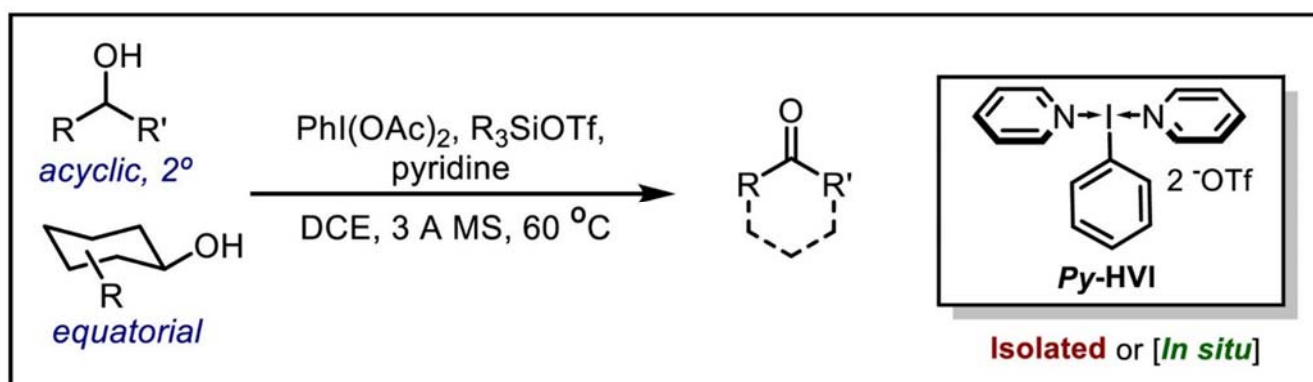
ORGN 328

Chemoselective oxidation of equatorial alcohols with nitrogen-ligated λ^3 iodanes

Myriam Mikhael, myriam.mikhael@temple.edu, Sophia A. Adler, Sarah E. Wengryniuk.
 Chemistry, Temple University, Philadelphia, Pennsylvania, United States

The chemoselective functionalization of complex molecules remains an outstanding synthetic challenge. Selective alcohol oxidation enables functionalization at a particular

α -carbon in polyol scaffolds through oxidation of a desired hydroxyl group to the corresponding carbonyl. Advancement in this area is scarce and the conventional methods usually require the use of toxic transition metals, which poses environmental and economic concerns. Moreover, in cyclic systems, the selective oxidation of axial alcohols can be readily achieved via Cr(VI) oxidants, however the complimentary equatorial selectivity remains elusive. Herein, an unprecedented level of selectivity in the oxidation of equatorial over axial alcohols is demonstrated via the utilization of a simple pyridine-ligated I(III)-reagent, or *Py*-HVI. The *Py*-HVI is a member of an emerging class of (bis)cationic nitrogen-ligated I(III) reagents known as *N*-HVIs, and is readily synthesized from commercially available PhI(OAc)₂ and pyridine upon activation with a silyl triflate. The *Py*-HVI can be pre-synthesized or we report a novel *in situ* protocol allowing the oxidation of alcohols directly from PhI(OAc)₂ under mild conditions. The method is shown to be quite general and displays exceptional levels of conformational selectivity for equatorial alcohols in both flexible and rigid systems. In conclusion, a novel tool for chemoselective oxidation of alcohols enabled by *N*-HVI reagents is established opening new doors for chemists for future synthetic applications.



ORGN 329

Expanding the synthetic tool box: Methodology development of 1,3 dicarbonyls and α -alkylated azo-alkenes

Sabrina Aderibigbe, sabrina.olunike@gmail.com, Don M. Coltart. Organic Chemistry, University of Houston, Houston, Texas, United States

Carbon-carbon bond formation is essential for most organic chemists within their synthetic toolbox. Its importance lies in applications in medicinal, petrochemical, and other industries. The focus of this research has been to expand the utility of classical synthetic routes such as, developing a Claisen reaction that uses crude material under soft enolization conditions towards 1,3 dicarbonyls and utilization of Umpolung-like

chemistry towards α -alkylation of ketones via azo-alkenes. Through our methodology development we will help provide organic chemists more synthetic options towards carbon-carbon bond formation.

ORGN 330

Amplification of N-halo reagent electrophilicity by organic dye visible-light photoredox catalysts for the halogenation of arenes and heteroarenes

David Rogers, *Dar006@utulsa.edu*, **Angus Lamar**. Chemistry and Biochemistry, University of Tulsa, Tulsa, Oklahoma, United States

The efficiency of electrophilic (hetero)aromatic halogenation by N-X reagents is significantly enhanced by select organic dye visible light-activated photocatalysts. According to mechanistic experiments, the polarization of the N-X bond within the electrophilic N-halo reagent is amplified via one-electron oxidation to the N-centered cationic radical. This approach allows for effective and convenient halogenation of arenes and heteroarenes under mild conditions, while avoiding traditional conditions or additives (such as metals or Lewis/Brønsted acids) that are typically required for N-X reagent activation. Our progress towards the development of a well-understood set of reagents and catalysts for the halogenation of a wide variety of arenes and heteroarenes will be presented.

ORGN 331

Hypervalent iodine reagent-mediated formation of bioactive N-benzylsulfonamides from aryl and heteroaryl aldehydes

Megan D. Hopkins, *mdh933@utulsa.edu*, **Angus Lamar**. Chemistry and Biochemistry, University of Tulsa, Tulsa, Oklahoma, United States

The sulfonamide moiety is an important bioisostere found in a wide range of pharmaceuticals. New synthetic methods for the direct installation of sulfonamides are desired for discovery and development of new bioactive compounds. The most common method of sulfonamide incorporation typically involves the use of a pre-installed amine and sulfonyl chloride under basic conditions. Sulfonamide installation at a carbonyl resulting in the formation of an intermediate imine is an alternative method. These imine-forming methods utilize high temperatures, costly catalysts, or acidic conditions. This results in limited substrate scope when it comes to acid-sensitive compounds containing a basic site capable of coordinating a Lewis or Brønsted acid. A new approach for the direct installation of sulfonamides using either an iminoiodinane/I₂ or sulfonamide/iodobenzene diacetate/I₂ system to form N-sulfonyl imine intermediate from aryl and/or heteroaryl aldehydes under mild conditions has been developed. These intermediate imines can then be reduced (one pot) in a second step to form N-benzylsulfonamides. This method is non-metal promoted, does not require removal of water, operates under mild reaction temperatures, and can be used for a wide range of

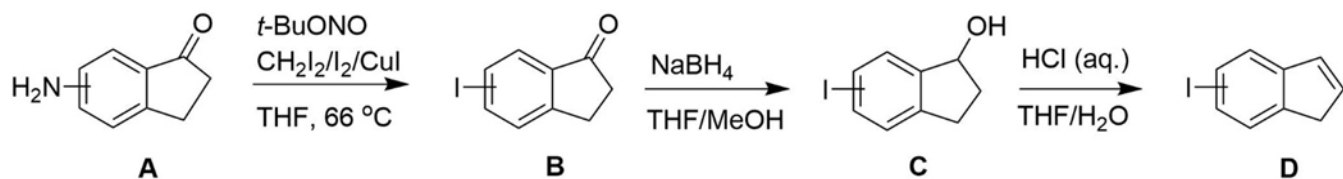
substrates including acid-sensitive compounds. Our recent progress regarding the development of a method for installation of N-sulfonyl units at carbonyls, along with results from a cytotoxicity screening and viability investigation of a library of synthesized compounds will be presented.

ORGN 332

Novel synthesis of 5-, 6-, or 7-iodoindenes

A. Hasan Howlader¹, *mhowl006@fiu.edu*, Keili Diaz¹, Alexander M. Mebel¹, Ralf Kaiser², Stanislaw F. Wnuk¹. (1) Florida International Univ, Miami, Florida, United States (2) Univ of Hawaii at Manoa, Honolulu, Hawaii, United States

The haloindenes are important synthetic precursors. We used haloindenes as precursors for the generation of various indenyl radicals (from 1-indenyl to 7-indenyl) which react with unsaturated hydrocarbons, such as acetylene and vinylacetylene, with formation of an additional aromatic ring, to study the growth mechanisms of polycyclic aromatic hydrocarbons (PAH). Methods for the synthesis of most reactive of iodoindenes are limited, although they could serve as convenient substrates for cross-coupling reactions. Reported synthesis of iodoindenes employs expensive nitroindanone as substrate and requires several steps which include separation of unstable aminoindene intermediate providing 5-iodoindene or 6-iodoindene in 20% and 7% respectively. We report straightforward synthesis of 5, 6, and 7-iodoindenes isomers from readily available 5, 6, and 7-aminoindanones which also employs simple ubiquitous reagents. Thus, diazotization-Sandmeyer reaction of 5, 6, and 7-aminoindanones **A** with *t*-BuONO/CH₂I₂/I₂/CuI in THF at 60 °C for 30 min afforded corresponding iodoindanone **B** (>90%). Reduction with NaBH₄ provided secondary alcohols **C** (>95%) and subsequent dehydration with aqueous HCl under reflux yielded selectively corresponding 5, 6, and 7-iodoindenes **D** (>70%). Isomerization of indenes was not observed during this reaction sequence. Application of iodoindenes for the synthesis of the corresponding enyne derivatives will be also discussed.



ORGN 333

Highly functionalized azetidines by visible light mediated [2+2] cycloadditions

Alistair D. Richardson, *adrich@umich.edu*, **Marc Becker**, **Corinna Schindler**.
Chemistry, University of Michigan, Ann Arbor, Michigan, United States

Azetidines hold great promise in current medicinal chemistry due to their desirable pharmacokinetic properties. However, a lack of efficient approaches to functionalized azetidines has impeded their incorporation into pharmaceutical lead structures. A [2+2] cycloaddition reaction between imines and alkenes, an aza Paternò-Büchi reaction, arguably represents the most direct route. The utility of this method has been hampered by competing reaction paths accessible upon photochemical excitation of the substrates. We have developed a visible light-enabled aza Paternò-Büchi reaction that surmounts existing limitations and provides a mild solution for the direct formation of functionalized azetidines from imine and alkene precursors.

ORGN 334

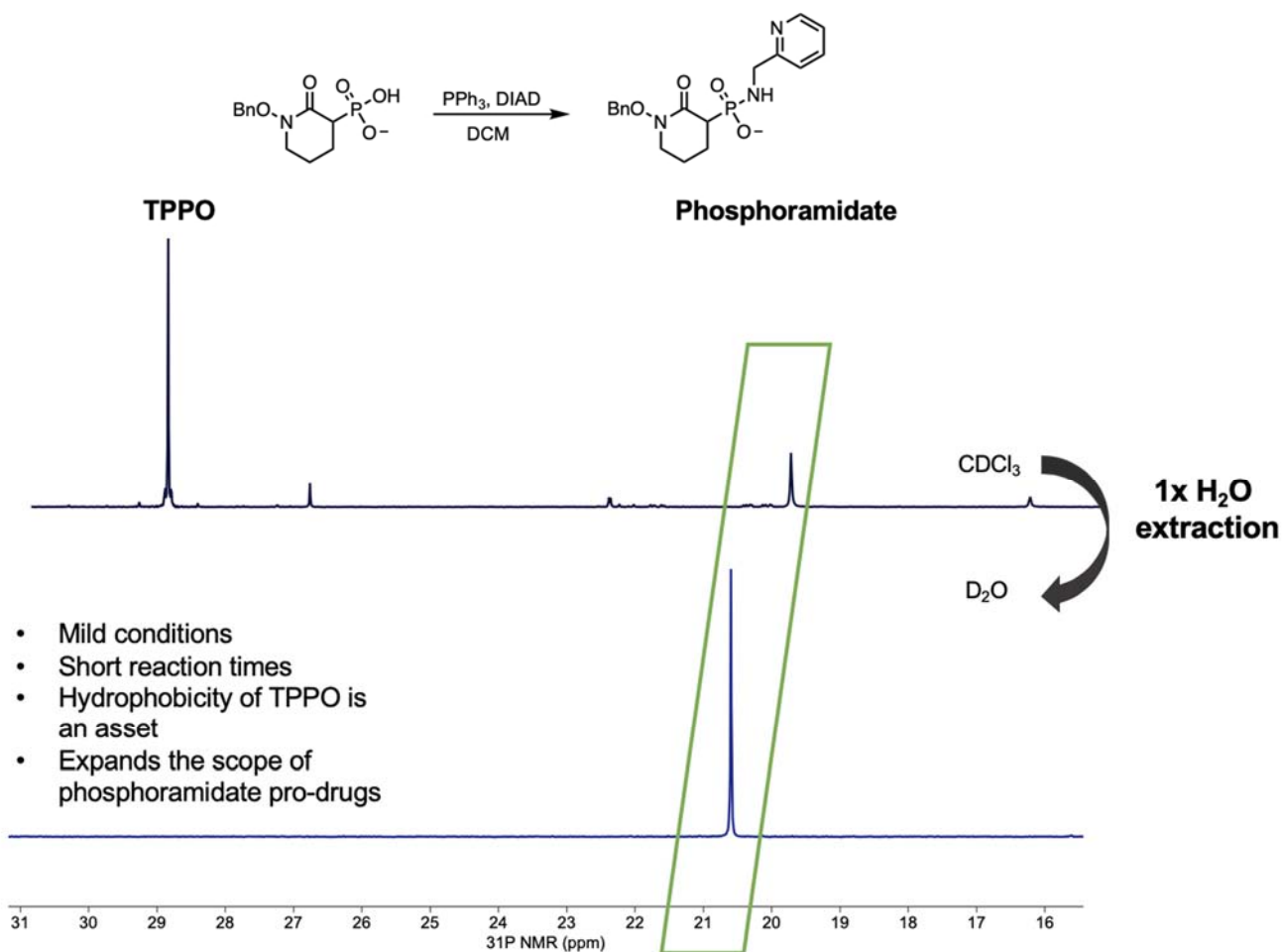
Mitsunobu coupling enables the improved synthesis and simple purification of therapeutically relevant phosphoramidates

Victoria Yan, *yan22v@mtholyoke.edu*, **Cong-Dat Pham**, **Florian Muller**. University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Phosphoramidates are structurally intriguing chemical moieties with high biological and therapeutic relevance. Inclusion of a phosphoramidate moiety has become an increasingly attractive pro-drug strategy for anionic phosphate- or phosphonate-containing drugs. Historically, phosphoramidates have been prepared using harsh reaction conditions involving toxic reagents, while peptide coupling strategies using DCC or EDC suffer from the difficulty of isolating the water-soluble mono-phosphoramidate from the water-soluble urea byproducts. In general, the development of phosphoramidate-containing molecules has been offset by the high variability in reaction efficiency and poor purification techniques to preserve the integrity of the acid-sensitive phosphoramidate.

The Mitsunobu reaction is a highly versatile reaction that converts an alcohol into a number of functional groups such as an ester or an ether. In more niche instances, it can be used to generate sulfonamides, thioesters, and N-alkylamines. However, since its initial inception in 1967, the Mitsunobu reaction has never been applied to a phosphate or phosphonate and an amine to generate the corresponding phosphoramidate. Here, we demonstrate the unprecedented synthesis of phosphoramidate-containing drugs using a novel variation of the Mitsunobu coupling. Unlike state-of-the-art approaches, our reaction occurs expediently and under mild conditions. By leveraging the hydrophilic, anionic nature of the mono-phosphoramidate and the hydrophobicity of the triphenylphosphine oxide byproduct, we show that isolation of the desired product can be accomplished by a single water extraction. As proof-of-concept, we show that our approach can be used to generate phosphoramidate-containing Enolase inhibitors and nucleotide analogues in good yields. With the growing interest in the medicinal properties of phosphoramidates, our

new reaction described herein stands to significantly ease the synthesis and purification of phosphoramidate-containing drugs.



ORGN 335

One-pot pyridine alkylation via traceless dearomatized pyridyl phosphonium ylides

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4-position alkylated pyridines can be found in several pharmaceuticals, and are common in natural products, materials, and ligands. Due to how frequent these

scaffolds are found, methods for synthesizing them directly from the pyridyl C-H bond are highly desired. Several methods already exist to alkylate pyridines directly, including Minisci-type reactions and C-H functionalization using transition metal-catalysis with alkenes. Although these methods have made significant progress, further developments in this field are still needed. Here, we report an alternative, one-pot method that goes through a traceless dearomatized pyridyl phosphonium salts. Sequential addition of a triazinyl chloride, *n*-tributylphosphine, and methyl lithium selectively yields a 4-position phosphonium ylide within the pyridine scaffold as a single isomer, in near quantitative yield. Upon addition of an aldehyde, Wittig olefination occurs with the ylide, resulting in a pyridine anhydrobase, which can be converted to the alkylated pyridine by an acidic workup. Additionally, we found that in the absence of an acidic workup, this pyridine anhydrobase could serve as a versatile intermediate for further derivatization. We demonstrate that a range of substituted pyridines can be alkylated from either alkyl or aryl aldehydes. Since our method relies on the well-established Wittig olefination reaction, various complex aldehydes are amenable, providing an extensive drug-fragment coupling scope. Finally, we demonstrate that under a similar set of conditions, methylation of pyridines and pharmaceuticals can be achieved.

ORGN 336

Modular approach to non-symmetric polycyclic aromatic hydrocarbons

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Polycyclic aromatic hydrocarbons (PAHs) have received significant attention due to their interesting optical and electronic properties. Anthracene derivatives, in particular, have seen applications in medicinal chemistry and materials chemistry, such as in the development of small-molecule fluorescent probes and organic field effect transistors. We report a modular synthetic platform using strained alkynes and arynes to access non-symmetric PAHs, as well as computational studies of the four sequential pericyclic reactions that take place in our methodology. The combination of strained intermediates and oxadiazinones enables the rapid access and controlled design of functionalized and extended PAHs. These studies demonstrate that strained alkynes and arynes can be exploited as powerful building blocks in the synthesis of novel, conjugated molecules.

ORGN 337

Oxazoles from alcohols and nitriles via tandem hydrogen atom transfer

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Oxazoles, five-membered aromatic heterocycles containing both nitrogen and oxygen atoms, have unique structural and physical properties that are desirable in both medicinal and materials chemistry. Generally, oxazole synthesis involves intra- or inter-

molecular carbonyl condensation chemistry in the presence of strong acid or harsh dehydrating agents. Through this study, a mild, radical-based strategy has been developed, which converts simple alcohols and nitriles to oxazoles via successive C-H functionalization of imidate intermediates. This modular approach allows for rapid synthesis of a library of oxazoles bearing diverse substitution patterns in high yields.

ORGN 338

Photochemical reactions of benzophenone derivatives under microfluidic conditions

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Synthetic photochemistry is emerging as a key enabling tool for the construction of molecular architectures using light as a renewable energy source. By exploiting the unprecedented reactivity of organic molecules under light excitation, photochemistry has tremendously increased the synthetic abilities of chemists towards the development of novel reaction pathways. Nevertheless, photochemical methodologies in batch suffer from some common drawbacks, such as irreproducibility problems owing to the home-made photochemical reactors, difficult up-scaling and reactivity issues related to reagents and product over-irradiation. In this scenario, the implementation of a microfluidic photoreactor (MFP) offers a decisive potential to address these fundamental issues related to photochemical batch protocols. MFPs present definite advantages considering enhanced surface-to-volume ratio, uniform irradiation and increased light penetration depth, short diffusion distance for efficient mass and photon transfer, and simple synthetic up-scaling in continuous flow for large-scale synthesis.

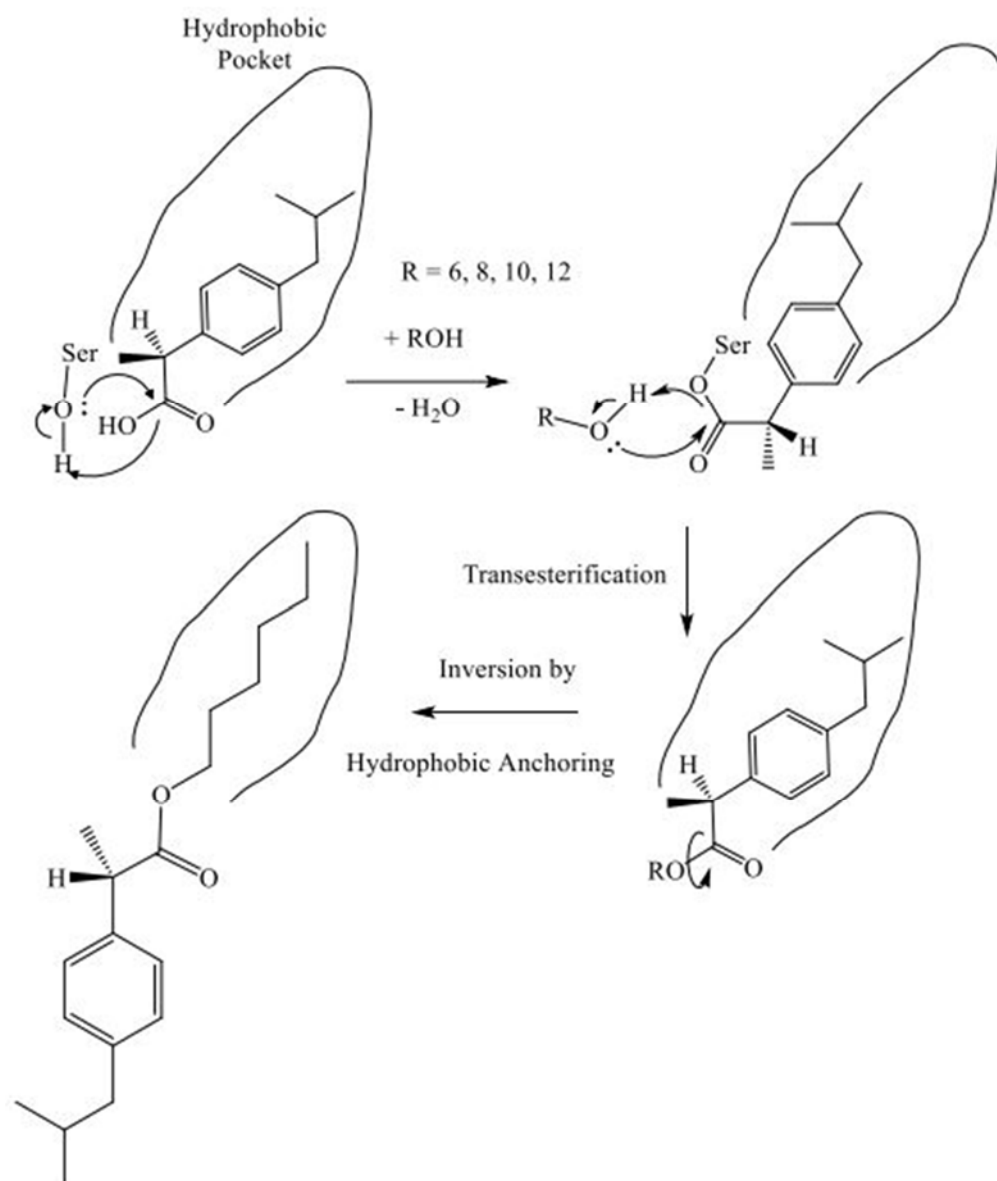
The ability of 2-methyl benzophenone (MBP) to generate the reactive photoenol intermediate upon UV-light irradiation is known since the 1960s. However, its potential as a versatile synthetic precursor has only been recognized very recently. Herein is presented how a microfluidic photoreactor (MFP) setup enables diverse light-driven 2-methyl benzophenone benchmark reactions to proceed with highly improved performances. Also, this setup allows the unprecedented Michael addition of the photoenol intermediate to coumarins for the synthesis of 4-benzylated cromanones. Further, the MFP setup permits the direct assembly of highly functionalized tetracyclic architectures through a [4+2] reaction manifold, for the synthesis of naphthocromene and benzoxanthene scaffolds. Remarkably, all these methods are easily scalable to gram-scale synthesis.

ORGN 339

Ibuprofen as a probe of lipid metabolism

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In previous work, racemic ibuprofen (IBU) was converted to (S)-IBU (deracemized) by reacting its racemic methyl ester with *Candida Rugosa* lipase (CRL) in water at 40°C and at pH 7.6. In this work, the hypothesis that the deracemization of racemic IBU occurs via the enolization of a CRL-IBU ester was disproven by reacting racemic IBU under the conditions that were used to deracemize IBU methyl ester (IME). However, at pH 7.6 longer chain length IBU esters were formed in-situ by reacting the corresponding primary alcohol with racemic IBU in the presence of CRL. Initially it was believed that the formation of ester corresponded with an increase of (R)-IBU but after isolating (R)-IBU and IBU ester, it was determined that the monitoring of the reactions by chiral HPLC was affected by the difficulties in recovering the ester. Molecular docking studies indicated that shorter chain length esters enter the hydrophobic pocket of CRL, isobutyl group first. However, longer chain IBU esters bind with the primary alkyl group in the hydrophobic pocket first. In addition, lower concentrations of the substrates, not using buffer, using the CRL supernatant versus the whole commercial enzyme, and reacting at pH 6.0 versus 7.6 all led to faster reactions of racemic IBU and longer chain length alcohols. For the reaction of racemic IBU and n-butanol catalyzed by CRL, formation of ester was favored at pH 6.0 and hydrolysis of the same ester was favored at 7.6, indicating that the hydrolysis of longer chain IBU esters is much slower.



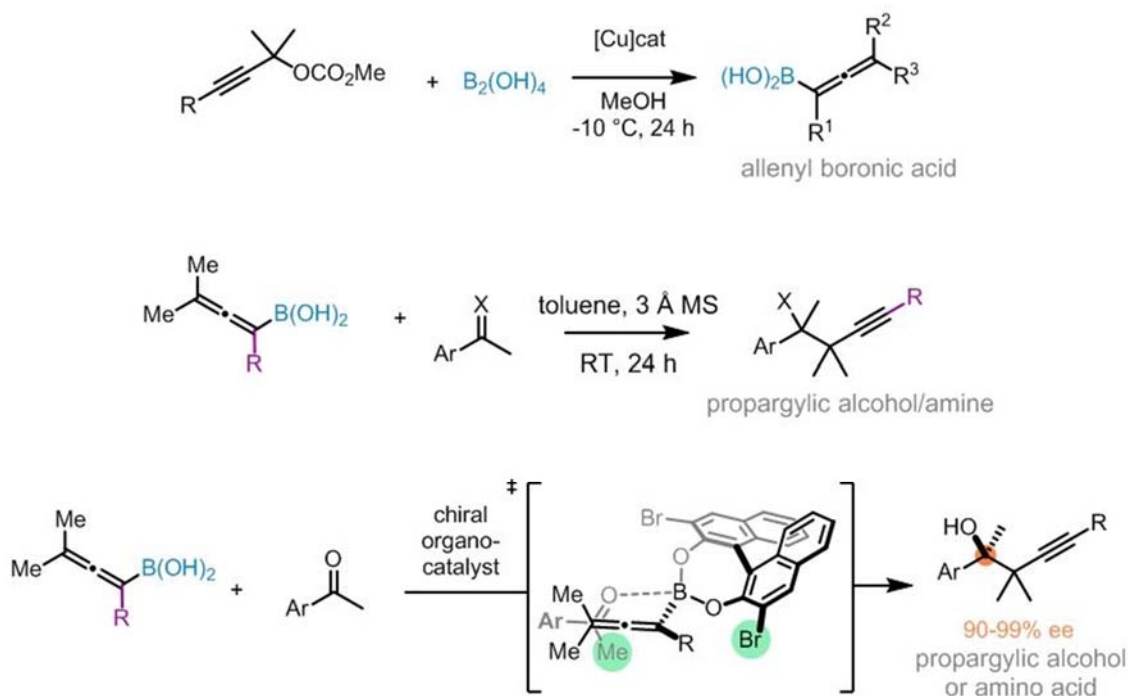
Esterification Reaction Scheme of (S)-IBU with Long Chain Length Alcohols and the Hydrophobic Anchoring of Long Chain (S)-IBU Esters

ORGN 340

Synthesis of allyl and allenyl boronic acids and their applications in chiral organocatalysis

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A copper-catalyzed synthesis of tri- and tetrasubstituted allenylboronic acids will be presented. The presentation contains examples of allenylboronic acids applied for the asymmetric synthesis of homopropargyl alcohols, imines, indolines, and amino acid derivatives. A new methodology for the synthesis of allylboronic acids will also be presented.



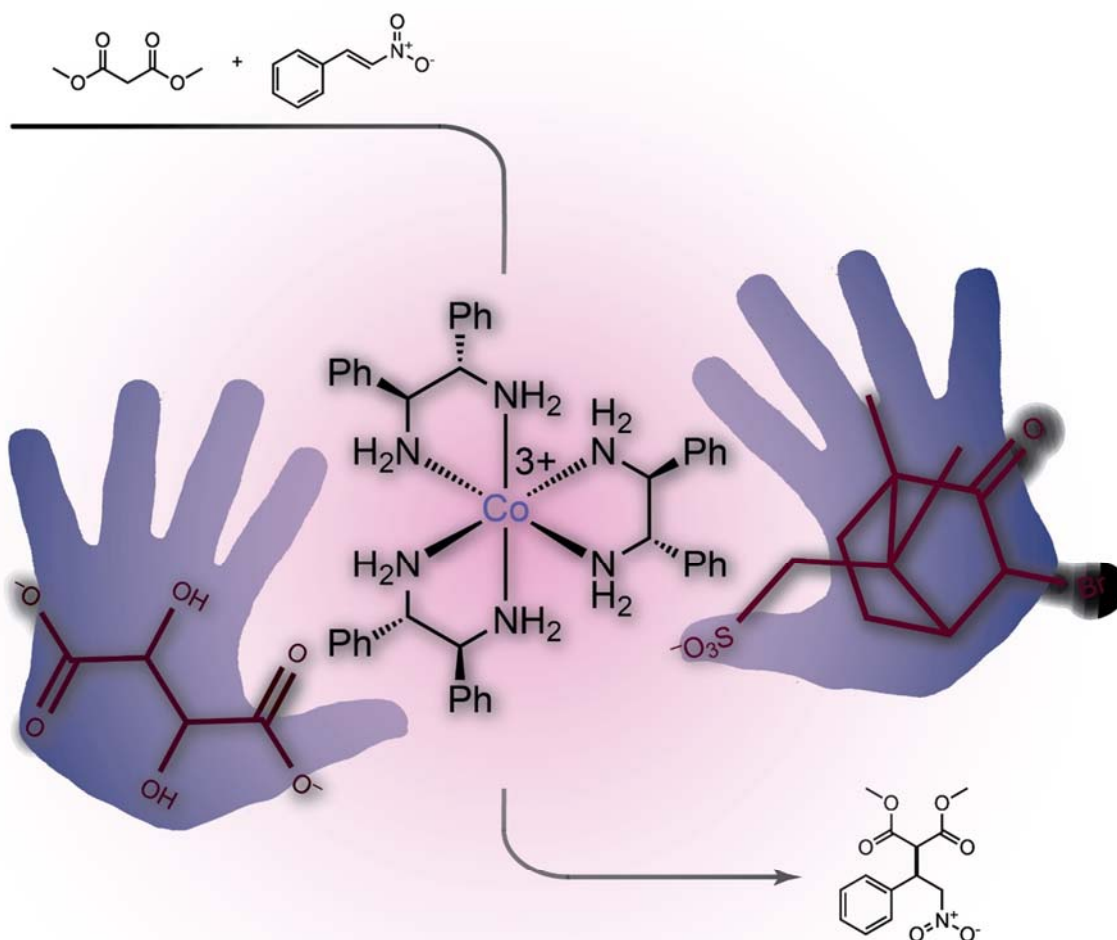
ORGN 341

Chiral anions with cobalt(III) hydrogen bond-donor catalysts

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In recent years, enantioselective catalysis has become a prominent field of chemical research. As novel pharmaceutical and agrochemical agents are becoming increasingly complex, an obvious motivation exists to produce chiral centers with the economy in mind (both the atom and financial economy, that is). Homogeneous transition metal catalysis has been well known for more than 50 years, but recent advances have shown the generation of catalysts which work through hydrogen bond-donation rather than classical Lewis acid interaction. Trications of cobalt(III) tris(1S,2S-diphenylethylenediamine) ($[Co(dpen)_3]^{3+}$) have been shown to be effective hydrogen bond-donors and are soluble in some organic solvents when paired with

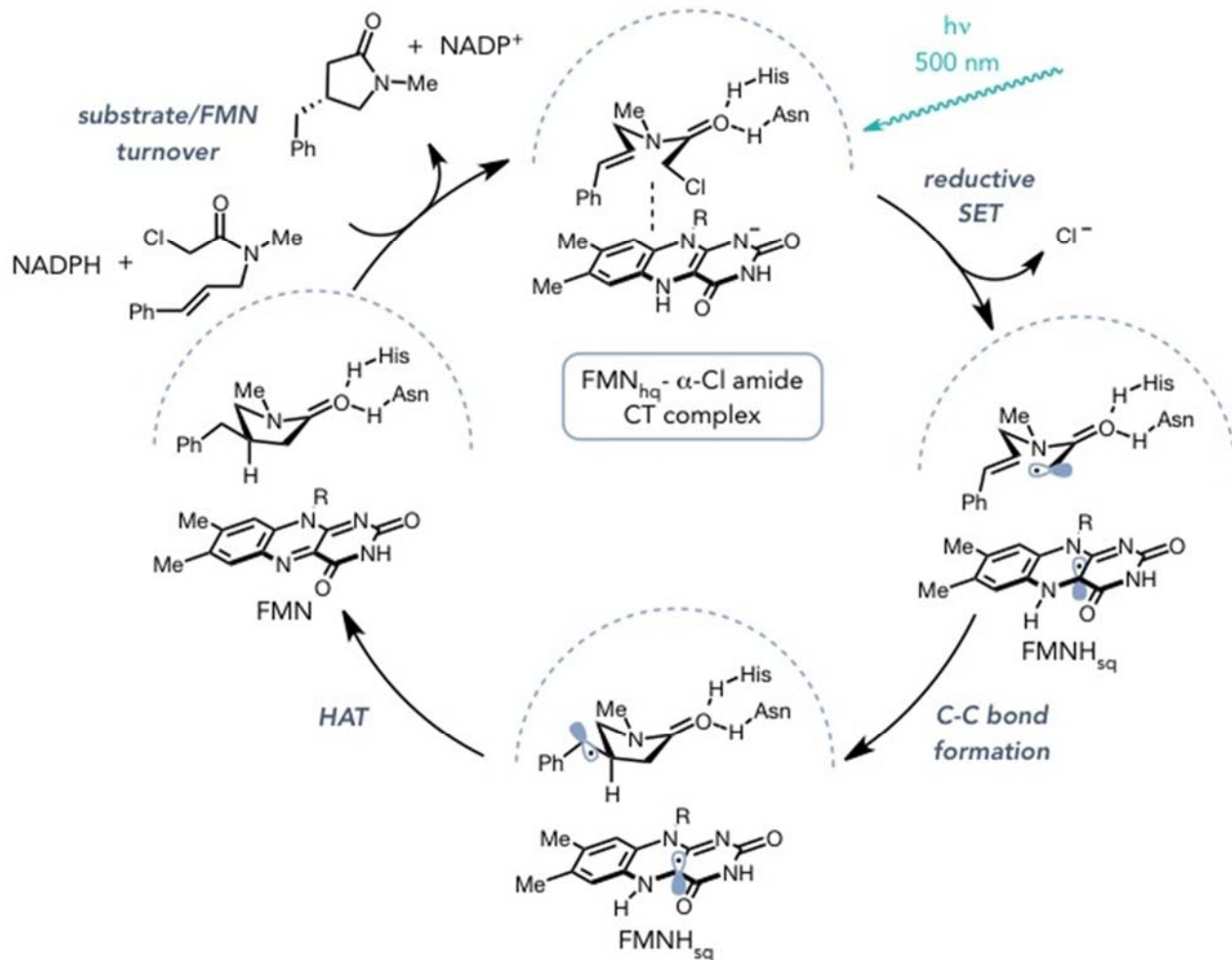
noncoordinating, lipophilic anions (BAr_4^- , BF_4^-). The pairing of chiral cobalt cations with chiral sulfonate, phosphate, and carboxylate anions improves solubility and allows for ee values up to 88%. Both affordable and commercially available, these anions can be paired in combination with other lipophilic anions to make mixed-anion salts, and also display high solubility and ee when used without companion anions. Finally, these complexes require no purification, are synthesized quickly, and afford product in near-quantitative yield.



New stereoselective C-C and C-H bond formations enabled by flavoprotein photocatalysis

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Irradiation of donor-acceptor complexes formed between alpha-chloroamides and the fully reduced flavin mononucleotide (FMN) of old yellow enzymes (OYEs) effects a reductive single electron transfer event that allows for selective alpha-amide radical generation within the confines of the active site. Alpha-amide radicals formed in this way can participate in enantioselective intramolecular C-C bond formations in 5-exo, 6-exo, and 7-exo trig cyclizations to form beta-substituted butyro-, valero-, and caprolactams. Alternatively, enantioselective hydrogen atom transfer (HAT) from flavin occurs in 5-endo and 8-endo trig cyclizations to yield gamma-substituted butyrolactams and azocan-2-ones, respectively. Additionally, 5-exo trig cyclizations onto trisubstituted olefins may combine the stereoselectivities of C-C and C-H bond formation to control the creation of two stereogenic centers in a single chemical step, yielding beta-substituted butyrolactams containing an additional exocyclic center. Taken collectively, these results demonstrate the ability of flavoprotein photobiocatalysis to address longstanding challenges in synthetic radical chemistry.



ORGN 343

De novo synthesis of phomopsolid E analogues

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This work explores a *de novo* asymmetric synthesis of several analogues of the biologically active carbohydrate natural product phomopsolid E. The proposed synthetic route improves upon routes previously developed by the O'Doherty Group for the 7-oxo and 7-aza analogues of phomopsolid E. The new route ascertains the stereocontrol by incorporating a second reagent-controlled Noyori reduction for the flexible introduction of the C-9 alcohol. Once complete the synthesis will allow for the efficient stereoselective synthesis of all eight possible stereoisomers of phomopsolid E

analogue for a stereochemical structure activity relationship (S-SAR) of this anticancer natural product analogue.

ORGN 344

Selective functionalization of heterocycles via myoglobin-catalyzed carbene transfer chemistry

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Transition metal-catalyzed carbene transfer reactions are powerful transformations for the construction of new carbon-carbon and carbon-heteroatom bonds, but current chemocatalytic methods often require rare and non-sustainable metals and/or lack of selectivity. Our group has previously established that engineered myoglobins are promising catalysts for catalyzing carbene transfer reactions with high degrees of catalytic activity and stereoselectivity. Building upon this progress, we developed and report here the first examples of biocatalytic strategies for the carbene-mediated functionalization of indoles and benzofurans. These heterocycles are prevalent motifs in drug molecules and bioactive natural products. Using engineered myoglobin as catalysts, we developed an efficient biocatalytic approach for the chemoselective C-H functionalization of unprotected indoles and for the stereoselective cyclopropanation of benzofurans with excellent degrees of diastereo- and enantiocontrol (>99% *de* and *ee*). The mechanism of these transformations was investigated experimentally and computationally, revealing the interplay of substrate- and catalyst-dependent factors in controlling the divergent reactivity of the biocatalyst (C-H functionalization vs. cyclopropanation) toward the structurally related heterocycles. Lastly, these biocatalytic methodologies could be applied to implement concise chemoenzymatic routes for the synthesis of two drug molecules.

ORGN 345

Stereospecific synthesis of all-carbon quaternary centers via C–O bond activation

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In the past few decades, alcohol derivatives have been developed as novel electrophiles in transition metal-catalyzed cross couplings via C–O bond activation. In particular, exceptional developments in stereospecific cross-couplings have harnessed highly enantioenriched benzylic alcohol-derived substrates. However, one of the widespread limitations in this field is the need for substrates substituted with naphthyl groups or other extended π systems. Additionally, most of these cross-couplings are limited to the formation of tertiary stereocenters. Herein, we report the development of a catalyst system that overcomes these longstanding limitations. Our nickel-catalyzed,

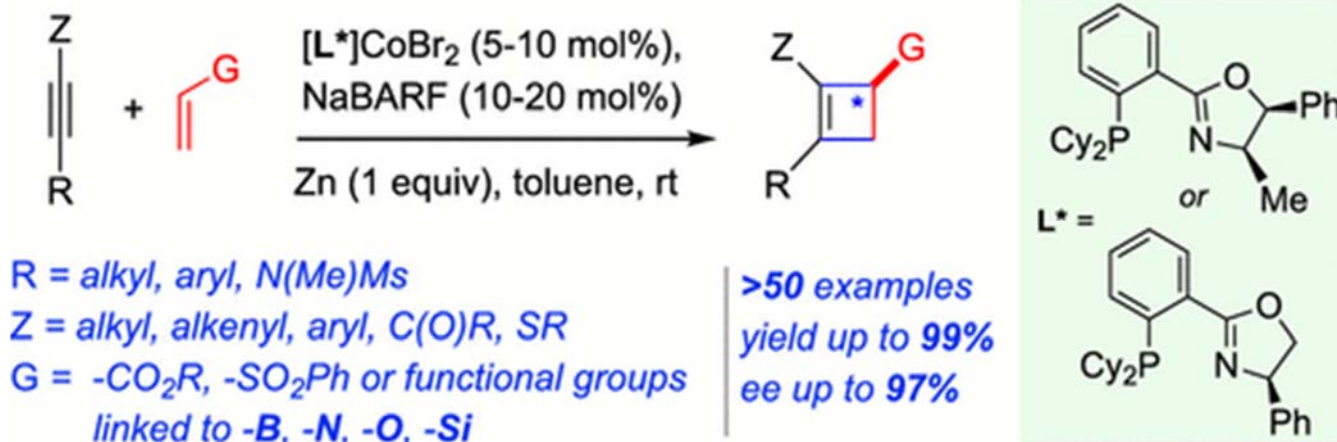
mild Suzuki-Miyaura coupling of tertiary esters harnesses readily available enantioenriched benzylic alcohol derivatives to access all-carbon quaternary stereocenters. Broad functional group tolerance, high yield, and high and stereochemical fidelity are observed. Our mechanistic investigations will also be presented.

ORGN 346

Catalytic enantioselective synthesis of cyclobutenes from alkynes and alkenyl derivatives

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Discovery of enantioselective catalytic reactions for the preparation of chiral compounds from readily available precursors, using scalable and environmentally benign chemistry, can greatly impact their design, synthesis, and eventually manufacture on the scale. Functionalized cyclobutanes and cyclobutenes are important structural motifs seen in many bioactive natural products and pharmaceutically relevant small molecules. The simplest approach to make cyclobutenes is through an enantioselective [2 + 2]-cycloaddition between an alkyne and an alkenyl derivative. Known reactions of this class that give acceptable enantioselectivities are of very narrow scope and are strictly limited to activated alkynes and highly reactive alkenes. Here, we disclose a broadly applicable enantioselective [2 + 2]-cycloaddition between a wide variety of alkynes and alkenyl derivatives, two of the most abundant classes of organic precursors. The key cycloaddition reaction employs catalysts derived from readily synthesized ligands and an earth-abundant metal, cobalt. Over 50 different functionalized cyclobutenes with enantioselectivities in the range of 86–97% ee are documented. In addition to this development, some of the novel observations made during these studies including a key role of a cationic Co (I)-intermediate, ligand and counter ion effects on the reactions, will be discussed.



Co-catalyzed enantioselective [2 + 2] cycloaddition

ORGN 347

Enantioselective, copper-catalyzed alkynylation of cyclic iminium ions lacking stabilizing groups

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The prevalence of α-chiral amines in pharmaceuticals, natural products, and other bioactive molecules makes them enticing targets for synthesis. A powerful approach for these compounds would be enantioselective addition to an iminium ion. We and others have previously shown that quinolinium, isoquinolinium, and pyridinium ions can be used in enantioselective alkynylation reactions. However, the iminium ions employed in these additions have been limited to benzylic and aromatic iminium ions. These iminium ions benefit from greater stabilization than their unconjugated counterparts, and lack acidic β-hydrogens, avoiding possible decomposition via E1 elimination. Here we have developed enantioselective, copper-catalyzed alkynylation of cyclic iminium ions lacking stabilizing groups. With the mild reaction conditions, a range of functional groups are well tolerated, and the reaction delivers alkynyl products in good yields and enantioselectivities.

ORGN 348

Catalytic asymmetric synthesis of cyclopentanones and tetrahydrofurans from ketenes and donor-acceptor cyclopropanes

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We have previously demonstrated that disubstituted ketenes can be converted to ketene homodimers, β -lactones and β -lactams through phosphine catalysis, and to ketene heterodimers through alkaloid catalysis. Recently we investigated the catalytic asymmetric synthesis of cyclopentanones from disubstituted ketenes and donor-acceptor (DA) cyclopropanes. We found that when a combination of an In(III) salt (30 mol%) and an Al(III) salt (15 mol%) was used as the catalytic system for the reaction of ketenes with enantioenriched DA cyclopropanes, that cyclopentanones were formed in good to excellent yields (84-99% for 15 examples), with good diastereoselectivity in many cases (dr up to 76:24), and with excellent transfer of chirality (17 examples with 90% ee to >99% ee). Furthermore, we observed a change in regioselectivity of cyclization when a Pd(0) catalyst (5 mol%) was used to promote the reaction; enantioenriched tetrahydrofurans bearing an exocyclic olefin substituent were formed as the major product with excellent olefin isomer selectivity. Details of reaction optimization, substrate scope, and proposed models rationalizing product selectivity, diastereoselectivity, and transfer of chirality will be presented.

ORGN 349

Scalable synthesis of a cyclobutane-1, 2-diacid and its derivatives from *trans*-cinnamic acid via photoreaction

Houssein S. Amjaour, houssein.amjaour@und.edu. Chemistry, University of North Dakota, Grand Forks, North Dakota, United States

Dicarboxylic acids and their derivatives have a variety of applications in many fields such as polymers, pharmaceuticals, and metal-organic materials. Cyclobutanedicarboxylic acids (CBDAs) represent a family of promising diacids that can be synthesized by using photoreaction.

It has been known for about a century that both CBDA-1 (α -truxillic acid) and CBDA-4 (β -truxinic acid) could be synthesized from two polymorphs: α - and β -*trans*-cinnamic acid, respectively. However, researchers had to take a detour to make CBDA-4 by turning *trans*-cinnamic acid into its *p*-nitrophenyl ester or 1,3-trimethylene diester for photodimerization, and then hydrolyzed the ester dimer back to CBDA-4. This is because that the metastable crystalline β -form (head-to-head packing) of *trans*-cinnamic acid is readily to transfer to the stable α -form (head-to-tail packing). The low energy barrier from the β -form to the α -form renders reliable synthesis of CBDA-4 challenging because the β -form gives CBDA-4 after photodimerization and α -form leads to CBDA-1, which also explained the conflicting experimental results about CBDA-4 synthesis in the literature.

In this presentation, we will show a facile and scalable preparation method of CBDA-4 accomplished by capturing and photodimerizing the metastable crystalline solid of *trans*-cinnamic acid. This synthetic approach builds a foundation for investigating the properties and applications of the useful diacid and its derivatives. The X-ray crystal structure of CBDA-4 was determined for the first time. The synthesis of a series of

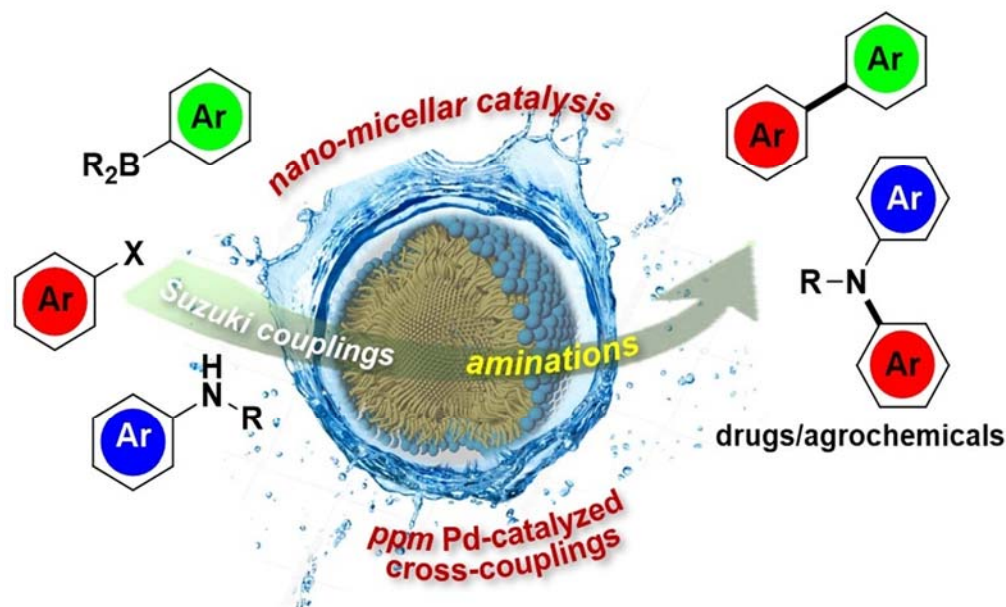
mono- and di-esters derived from CBDA-4, which have similar structure to the widely used phthalates, will also be discussed.

ORGN 350

Third or sustainable approach in synthesis of drugs or agrochemicals using cross-coupling reactions

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If nature does not need organic solvents to perform complex chemical reactions, which it efficiently does only in water then why would synthetic chemist choose to use environmentally egregious organic solvents to synthesize compounds of pharmaceutical/agrochemical/material interests? The partial and most arguable answer to this is a need of organic solvent (or so called first approach) to dissolve reactants so that they could react. Certainly, and quite forcefully (by policies), chemical industries are trying a “switch” to use sustainable solvents, ionic liquids, sCO₂, and in fact, water itself (second approach). However, this approach is mostly limited to academic purpose as there are several limitations when scale goes up. With selected case studies, this presentation will demonstrate that the presence of very small quantities of natural product-based surfactant in water could self-assemble into nano-reactors (nano-micelles) which remarkably increase the reaction rate and selectivity under mild conditions for cross coupling reactions using only *ppm* Pd-catalysts.



Cross coupling reactions in water

ORGN 351

Synthesis of sulfones from their component sulfides using $[\{\text{MoO}(\text{O}_2)_2\}_2(\mu\text{-O})]^{2-}$ catalyzed hydrogen peroxide reactions

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Sulfones are an important part in Julia-Kocienski Olefination, which can be used as an alternative to the Wittig reaction which uses hazardous reagents such as potassium tert-butoxide to achieve the same outcome. The original goal of this research was to synthesize the drug nalmefene from naltrexone using a modified Julia reaction, which requires sulfones as a reagent. Sulfones can be synthesized using a very large variety of reagents with different benefits and drawbacks. Clean reactions to make sulfones most often involve using H_2O_2 and some catalyst such as Na_2WO_4 or some molybdenum catalyst with the goal of minimizing cost or maximizing the reaction yield. The $[\{\text{MoO}(\text{O}_2)_2\}_2(\mu\text{-O})]^{2-}$ catalyst used in this reaction has shown to be very efficient, low cost, robust, clean, and very convenient to use, even in comparison to other catalysts used for this reaction under similar conditions, such as Na_2WO_4 . It required

very limited solvent at room temperature, using only 0.005 equivalents of catalyst and 2.1 equivalents of H₂O₂ at room temperature and made a variety of very pure sulfones, such as 2-(Methylsulfonyl)pyridine and 2-(Methylsulfonyl)benzo[d]thiazole, from their sulfide components at yields approaching 100%.

ORGN 352

New monomers from biomass

*Manqing Wei, Charles McNeff, Eric Serum, Catherine Sutton, **Mukund P. Sibi**, mukund.sibi@ndsu.edu.* Chemistry Molec Biology, NDSU Dept 2735, Fargo, North Dakota, United States

Our group's research is focused on the development of novel methods for the conversion of renewable resources to feedstock chemicals for use in polymer synthesis. In our work we have used three important renewable materials (1) oil seeds, (2) cellulose, and (3) lignin. In particular, we are investigating novel methodologies for the synthesis of furanic monomers and their application in polymer synthesis. I will discuss our recent results on the synthesis of biobased diamine and diacid monomers and details on the green metrics for these syntheses.

ORGN 353

Harnessing the power of biocatalysis and integrating cross-coupling chemistry to realize a novel greener synthetic routes for statins

***Chanaka M. Amarasekara**¹, amarasekaracm@vcu.edu, Katherine Belecki^{1,2}.* (1) Department of Chemistry, Virginia Commonwealth University, Richmond, Virginia, United States (2) The Medicines for All Institute, VCU, Richmond, Virginia, United States

As global and political awareness about sustainable practices sharpens in the face of dramatic climate change and environmentally harmful practices, one appealing strategy is to harness the catalytic potential of enzymes. Apart from the outstanding synthetic power of enzymes in the asymmetric synthesis of complex molecules, biocatalytic approaches reduce the environmental impact compared with organic synthetic pathways, as enzymes are renewable resources and often perform more efficiently than the analogous organic chemistry route. Our efforts are focused on engineering a novel deoxyribose phosphate aldolase (DERA) enzyme variant and employing it in the chemosynthesis of widely-prescribed cholesterol-lowering statin drugs, especially rosuvastatin (Crestor). Engineered DERA biocatalysts will utilize simple achiral feedstocks to construct a novel chiral synthon (containing the syn-3,5-dihydroxy acid pharmacophore that is universal to all statins), which can be incorporated into the statin core through atom-economical transition-metal catalysis. DERA, a ubiquitous bacterial enzyme, has been extensively studied owing to its ability to catalyze enantioselective tandem aldol reactions and its tolerance towards a broad range of polar substrates. Yet,

its application is hindered by poor tolerance towards high concentrations of aldehydes and even acetaldehyde, its natural substrate. In this work, we engineered a DERA variant to accept novel nonpolar substrates that, along with acetaldehyde, can generate functionalized intermediates to be deployed in valuable synthetic processes. Based on DERA crystal structures, rationally designed active-site variants have been produced by mutagenesis. Several of our mutants displayed elevated tolerance towards electrophilic aldehydes, including acetaldehyde, and showed successful incorporation of functionalized acceptor aldehydes into the targeted aldol product. Transition-metal catalyzed cross-coupling reaction strategies are being evaluated for efficient installation of the biocatalytically-prepared chiral side chain onto the heterocyclic core structure. Preliminary efforts towards immobilization of our engineered DERA enzyme to create an integrated flow-based system for the continuous synthesis of statins will also be discussed.

ORGN 354

Green one-step synthesis of substituted oxoisindolines

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The oxoisindoline (isindolin-1-one) core has recently received significant attention because of the varied biological activity that derivatives exhibit. For example, lenalidomide (Revlimid®) is used for treating multiple myeloma and mantle cell lymphoma, pazinaclo and pagoclo were investigated as antianxiety drugs, and recently various derivatives were found to possess antiviral activity against *Enterovirus* A71. We have identified a green method for preparing oxoisindolines with substituents on carbon 3. By treating 2-cyanobenzaldehyde with *beta*-keto esters, oxoisindolines can be prepared in high yield in one synthetic step when either a carbonate or alkoxide base is used in an alcohol solvent. Massa reported a similar two-step transformation using triethylamine in dichloromethane; however, concurrent acyl-transfer occurs under our reaction conditions, which eliminates the need for performing a subsequent decarboxylation reaction. Results from scope and limitation and mechanistic studies will be presented.

ORGN 355

Applying process intensification principles to the anti-retroviral drug lamivudine (3TC) to improve global health access

Sudhair James^{1,2}, *jamesa3@vcu.edu*, **Frank Gupton**^{3,2}, **Katherine Belecki**^{1,2,3}. (1) Chemistry, Virginia Commonwealth University, Richmond, Virginia, United States (2) The Medicines for All Institute, Virginia Commonwealth University, Richmond, Virginia, United States (3) Chemical Engineering, Virginia Commonwealth University, Midlothian, Virginia, United States

Many synthetic routes of active pharmaceutical ingredients (APIs) that are designed to access a variety of chemical analogs have limited regard for commercial consideration. Additionally, the innovator API processes are often still carried forward in manufacturing settings even after patent expiration, contributing to elevated costs of many generic and global health drugs and creating opportunities to address expensive starting materials and lengthy synthetic sequences. In developing countries, access to important medications can be limited for substantial portions of the population due to cost. Implementing chemical innovations and process intensification strategies can generate more efficient and greener processes while also helping to mitigate both local and global health crises.

Lamivudine (3TC) is a potent nucleoside drug targeting retroviral infections such as HIV-1 and HIV-2. It is a cytosine triphosphate analog in which the ribose has been replaced by a chiral 1,3-oxathiolane moiety. Access to the *cis*-(-)-enantiomer presents a major synthetic challenge, due to the need for stereo control of two labile stereocenters and regioselective N-glycosylation methodologies. Several creative routes have been reported in the literature to gain access to enantiomerically pure synthons for the chiral oxathiolane portion using L-menthol as a chiral auxiliary agent. The nucleophilicity of the exocyclic amine of cytosine makes pre-silylation a crucial step for glycosylation in these processes. We aimed to circumvent this problem with a cytosine analog that can be incorporated directly and is available at a lower cost. To test our hypothesis, uracil was examined as a potential nucleophile under different base-mediated reaction conditions. We have successfully glycosylated uracil with a chiral oxathiolane intermediate without pre-silylation, followed by conversion into the corresponding cytosine analog in over 80% yield. An evaluation of this alternative route for cost-effectiveness and chemical efficiency will enable identification of the optimum route for increasing access to this important medication for populations in need.

ORGN 356

Biocatalysis and continuous processing as strategies to promote streamlined and green pharmaceutical processes

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Developing green chemical processes for active pharmaceutical ingredients (APIs) has benefits beyond just a reduced environmental footprint. Access to life-saving medications remains a challenge in developing countries, but also for millions of Americans who cannot afford their prescriptions. By definition, environmentally friendly processes are more efficient, often generating manufacturing cost savings as an additional benefit. Chemical innovations and process intensification strategies can be harnessed to synergistically improve both the sustainability and the affordability of pharmaceutical processes. Through a series of vignettes about important global health targets and mainstream blockbuster drugs, a comprehensive and generalizable strategy

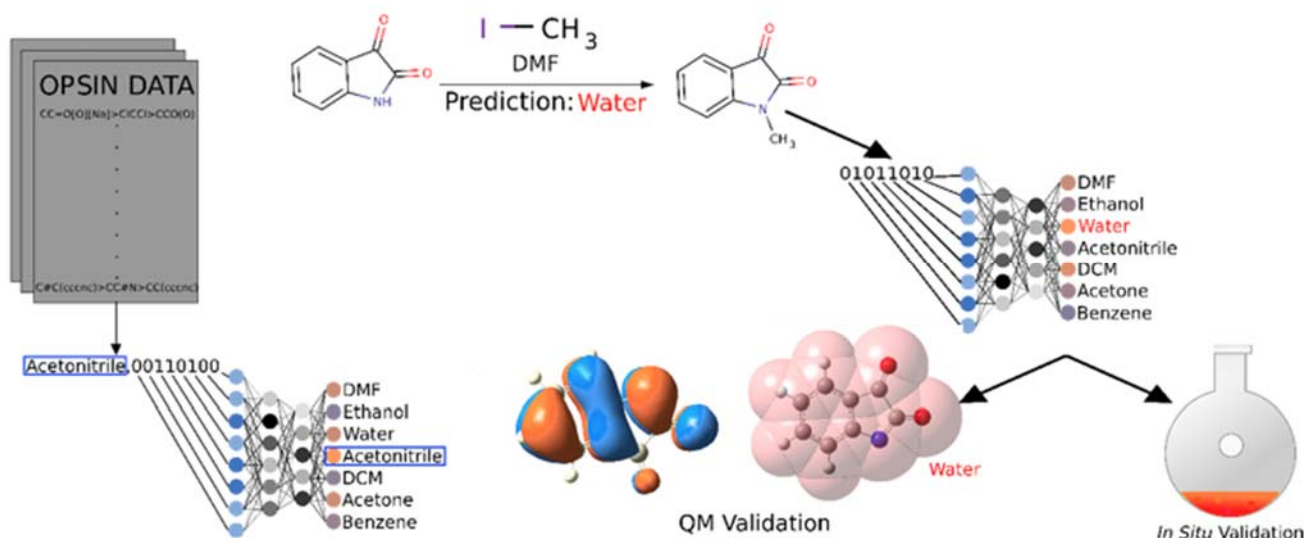
to develop streamlined process routes to molecular targets will be presented. The power of biocatalysis to efficiently install chiral centers to create novel synthons from achiral feedstocks will be demonstrated. An engineered aldolase variant has been deployed to access a novel chiral intermediate for use in a streamlined synthesis of widely-prescribed statin anti-cholesterol drugs, and progress towards a continuous application of this biocatalyst will be described. The application of a multifaceted approach to addressing API process inefficiencies will also be demonstrated for HIV drugs, along with the impact on global health sectors in developing countries. Principles of process intensification will be exemplified, and the metrics describing both process improvements and the impact of this route in terms of actual human lives saved will be presented. The potential and realized benefits of real-time monitoring techniques will also be discussed, along with opportunities and challenges in the incorporation of continuous flow technology to developing green approaches to API synthesis on scale. Current synthetic efforts towards additional global health drugs will also be presented.

ORGN 357

Big-data driven solvent selection via deep learning to facilitate the discovery of green synthetic methodology

Armen Beck, beck117@purdue.edu, **Jonathan Fine**, **Krupal Jethava**, **Gaurav Chopra**, gchopra@purdue.edu. Chemistry, Purdue University, West Lafayette, Indiana, United States

Solvent selection when developing synthetic methodology is typically facilitated by literature precedent or theory based approaches. While green solvent selection software has been developed, encoded rules can skew results and prevent discovery. We have developed a data driven pipeline for the selection of solvents in organic transformations, and have verified its utility both *in silico* and *in situ*. By training a neural network with reactions extracted from the patent literature we discovered that water is a viable medium, to facilitate N-alkylation of Isatin, replacing dimethylformamide as solvent. Additionally, the formation of N-Methylisatin proceeded under aqueous conditions without further modification of synthetic methodology that utilized dimethylformamide. By training the neural network to with functional moieties in reactions as input and their respective solvent as output, our model is capable of proposing non-intuitive yet suitable solvents. These results were supported by density functional theory calculations, and suggest that this approach can be used to discover various new green solvents unprecedented in the literature.



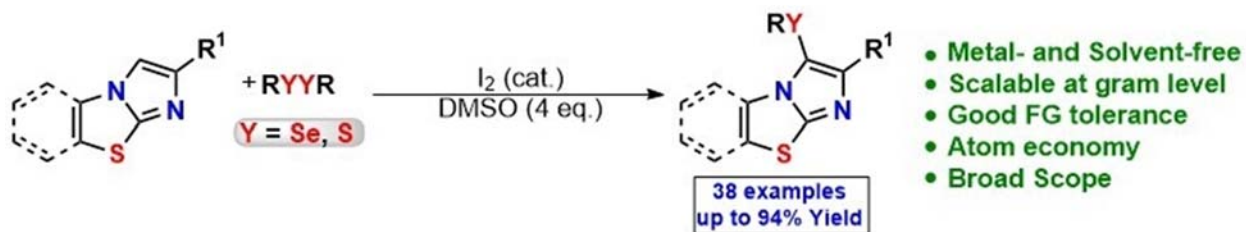
Workflow of green solvent selection pipeline

ORGN 358

Regioselective, solvent- and metal-free approach to access C-5 chalcogenation of imidazo[2,1-*b*]thiazoles by employing I_2 /DMSO as catalytic oxidation system

Jamal Khan, jamal.chm@gmail.com. Instituto de Química (INQUI), Universidade Federal de Mato Grosso do Sul (UFMS), Campo Grande, MS, Brazil

Herein, we report a greener protocol for the synthesis of C-5 chalcogenation (Se/S) of imidazo[2,1-*b*]thiazoles through direct C(sp²)-H functionalization using molecular iodine as catalyst and diorganoyl dichalcogenides under solvent free conditions. This approach afforded the desired products regioselectively in up to 94 % yields using an equivalent amount of DMSO as an oxidant in the absence of a metal catalyst and in an inert atmosphere. The reaction features are high yields, based on atom economy, ease of scale-up to gram scale, and metal- and solvent-free approach.



ORGN 359

Polymerization promoted by substrate photoexcitation

Julia A. Kalow, *jkalow@northwestern.edu*. Department of Chemistry, Northwestern University, Evanston, Illinois, United States

Photoredox catalysis has brought to light exciting avenues for the spatiotemporally controlled synthesis and modification of polymers and small molecules. In these reactions, a photoexcited transition-metal or organic dye (photocatalyst) performs single-electron transfer to oxidize or reduce a non-photoactive substrate, thus activating the substrate for bond-forming reactions. Alternatively, using a light-absorbing substrate, one can envisage that the substrate can be directly photoexcited, enabling a single-electron transfer event from a non-photoactive catalyst or reagent with the appropriate redox potential. Since different wavelengths of light deliver different amounts of energy, selectivity can be obtained in the presence of substrates with different photophysical properties by using narrow-bandwidth light sources (e.g. light-emitting diodes). I will describe the development of polymerizations enabled by substrate photoexcitation.

ORGN 360

Spatially controlled polymer properties through wavelength-selected cross-linking

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Wavelength-selective polymerization processes manipulating polymer sizes, compositions, or architectures offer significant opportunities in the advancement of photopolymer fabrication approaches, including for photoresists and stereolithography. One common strategy toward wavelength controlled polymer properties is reliant on strict manipulation of orthogonal polymerization systems, which can result in bulk inhomogeneities and residual monomers within the polymer matrix. In this work, a novel approach toward wavelength controlled properties using UV and visible light is presented. In this system, the degree of cross-link density is controlled within one polymerization manifold, realizing spatial control over polymer thermal and mechanical polymer properties.

ORGN 361

Photon energy upconversion photoredox catalysis

Luis M. Campos, *campos96@hotmail.com*. Chemistry, MC3124, Columbia University, New York, New York, United States

The net outcome in triplet fusion upconversion is that the process converts low-energy light into high-energy light (photon energy upconversion, PEU). This is a powerful system that can be exploited in next-generation photovoltaics, tissue engineering, sensing, etc, mainly because low-energy photons (infrared) can pass through various barriers with deep penetration. While there are a number of applications that can benefit from PEU, there are various challenges that have hampered implementation. This talk will be focused on recent advances in PEU and how the process can be exploited in photoredox catalysis and tissue engineering.

ORGN 362

Effect of photo-ATRP components on oxygen consumption

Athina Anastasaki, *ath.anastasaki@gmail.com*. ETH Zurich, Zurich, Switzerland

Photo ATRP has emerged as a powerful radical polymerization technique which, in contrast to other methods, allows for the *in-situ* deoxygenation of the reaction mixture in the absence of any additional reactants such as reducing agents. In this lecture I will discuss the effect of the various ATRP components on oxygen consumption. We found that the type of ligand, initiator, monomer and solvent significantly impact the rate at which the oxygen is being consumed and can subsequently affect both the kinetics of the polymerization and the dispersity of the resulting polymer. Importantly, we discovered that the inexpensive ligand TREN leads to the fastest oxygen consumption and polymerization time despite not participating in the reduction of CuBr_2 . The fast oxygen consumption may be attributed to a side reaction between the primary amine and the initiator which however does not significantly affect the control over the dispersity and the end-group fidelity of the obtained polymers.

ORGN 363

Designer molar mass distributions beyond dispersity variations

Tanja Junkers, *tanja.junkers@monash.edu*. School of Chemistry, Monash University, Clayton, Victoria, Australia

While numerous methods have been developed in the past decades that allow for the precise control of average molecular weights in polymerizations, relatively little is yet known about the control of dispersity and modality in polymerizations. Academic research often strives to create materials with as-low-as-possible dispersity, yet this may not always be desirable. Additionally, since dispersity is hardly controlled in polymerizations, only relatively few studies exist that study its effect on material properties.

Dispersity is typically given by chain statistics, and while some handles exist to tweak distributions in a purely chemical way, a straight forward approach to construct materials with precise molecular weight distribution shape is given by mixing and

demixing of distributions after polymerization. In here, different methods will be discussed, starting from chromatographic separation of polymers that allow to create libraries of monodisperse materials towards automated synthesis of materials in self-optimizing continuous flow reactors that allow for the direct synthesis of multi-modal distributions of any possible shape at will. Further, a distribution-based concept to encrypt information into a homopolymer will be introduced.

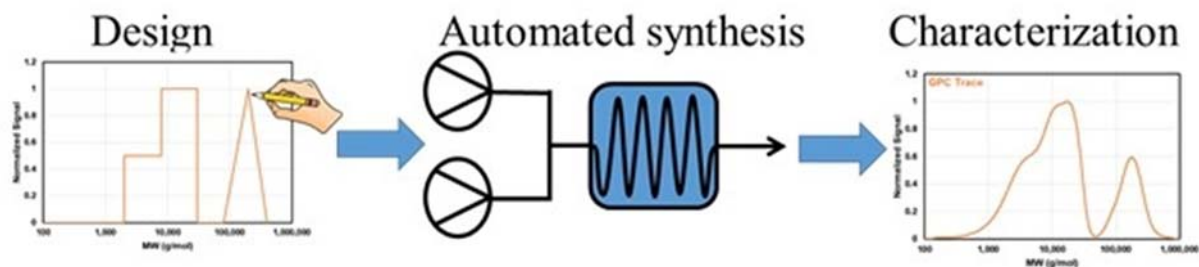
ORGN 364

Tuning molecular weight distribution of polymer through flow chemistry

Dylan Walsh², **Damien Guironnet**¹, damien.guironnet@gmail.com. (1) Chemical and Biomolecular Engineering, UIUC, Urbana, Illinois, United States (2) UIUC, Urbana, Illinois, United States

Flow chemistry has evolved as a versatile tool to prepare large libraries of polymers with precise compositions. This high throughput promises to accelerate the establishment of structure-function relationships. Apart from the high throughput, the polymers obtained in flow are, at best, identical to the material made in the classical round bottom flask, adding little additional benefit.

We will report on a methodology to yield polymers with any molecular weight distribution profile in a fully automated manner. Our approach consists of the blending of a large number of small quantities of polymer with narrow molecular weight distribution synthesized in a flow reactor. The development of our approach involves the combination of fundamental fluid mechanics principles, polymerization kinetics and a mathematical framework. We will demonstrate that this polymerization methodology is compatible with almost any living polymerization and the molecular weight of the polymer can be tuned over multiple orders of magnitude.

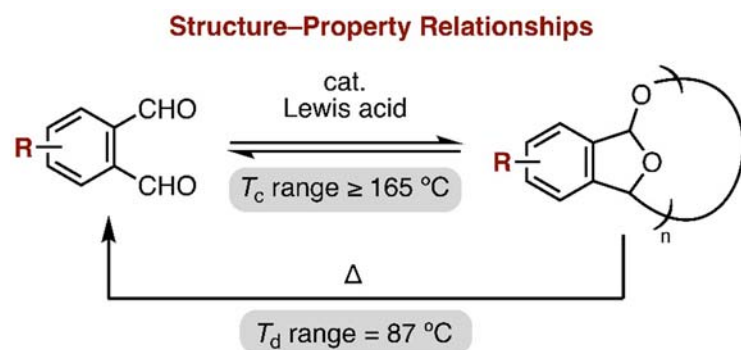


ORGN 365

Designing functionalized and degradable polyphthalaldehyde derivatives

John P. Lutz², lutzp@umich.edu, **Oleg Davydovich**¹, **Matthew Hannigan**², **Jeffrey Moore**¹, **Paul M. Zimmerman**², **Anne J. McNeil**². (1) Chemistry, University of Illinois Urbana-Champaign, Champaign, Illinois, United States (2) Chemistry, University of Michigan, Ann Arbor, Michigan, United States

Depolymerizable polymers are a class of transient materials that can be chemically recycled to monomers and repolymerized, reducing their environmental impact. Polyphthalaldehyde is one such polymer that undergoes rapid and quantitative acid-catalyzed or thermal depolymerization as a result of its low ceiling temperature. However, the ability to rationally modify the physical and chemical properties of polyphthalaldehydes is extremely limited due to the lack of systematic studies on polyphthalaldehyde derivatives. This talk will describe our computational and experimental investigation of the cationic polymerization of a range of substituted *o*-phthalaldehydes to access materials with a wide range of ceiling temperatures (<–60 to 106 °C) and decomposition temperatures (109–196 °C). We anticipate that these new polymers and their derivatives will lead to degradable materials with finely tunable thermal, physical, and chemical properties.



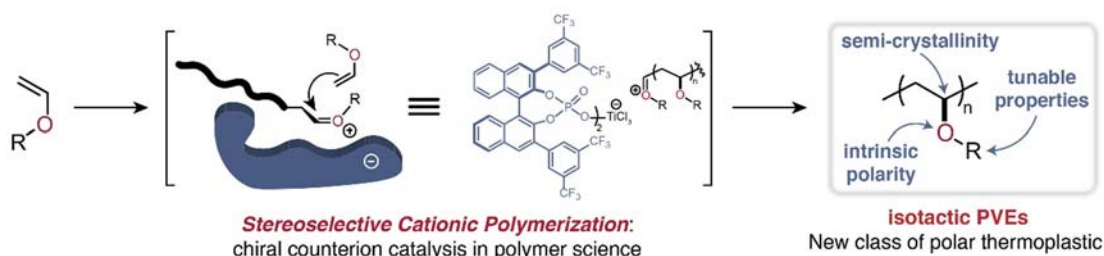
ORGN 366

Stereoselective cationic polymerization of vinyl ethers: New class of polar thermoplastics

Frank A. Leibfarth, FrankL@email.unc.edu. Chemistry, Massachusetts Institute of Technology, Boston, Massachusetts, United States

The stereochemistry of vinyl polymers, known as polymer tacticity, is intimately linked to their resultant material properties. Despite the well-developed stereoselective methods for the polymerization of propylene and other nonpolar α -olefins, general approaches to the stereoselective polymerization of polar vinyl monomers are not well developed. In

this lecture, we will discuss the design of chiral counterions that systematically tune the reactivity and chain-end stereochemical environment during cationic polymerization. This approach overrides conventional chain-end stereochemical bias to achieve the first catalyst-controlled stereoselective polymerization of vinyl ether monomers. We demonstrate that this method is general to vinyl ether substrate, providing access to a range of isotactic poly(vinyl ether)s with previously unprecedented degrees of isotacticity. Key mechanistic aspects of the polymerization will be presented from in depth kinetic and experimental studies. The obtained materials represent a new class of thermoplastics with a unique combination of mechanical and surface properties. Isotactic poly(vinyl ether)s display the tensile properties of commercial polyolefins but have an order of magnitude stronger adhesion to polar substrates, indicating their promise for next generation engineering applications.



ORGN 367

Unleashing the power of enzyme engineering in pharmaceutical research and development

Douglas E. Fuerst, doug.e.fuerst@gsk.com. GlaxoSmithKline, Collegeville, Pennsylvania, United States

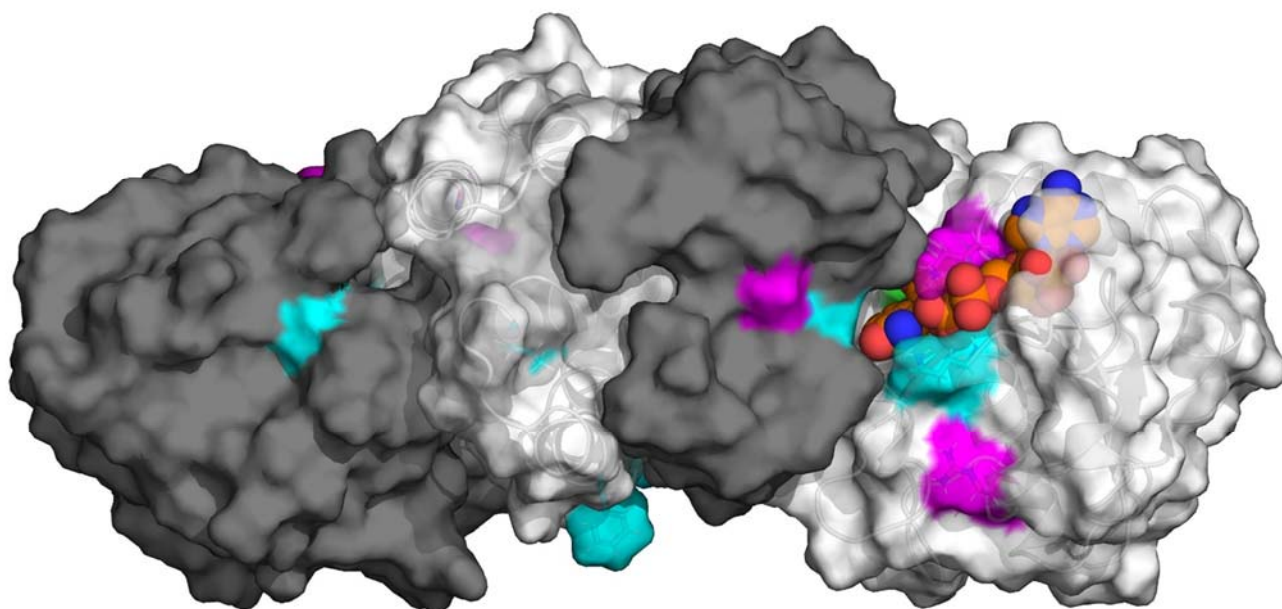
There continues to be increasing examples of the impactful application of biocatalysis for the research and development of pharmaceutical compounds. Thanks to advances in modern biotechnology the chemist's toolbox is no longer limited to commercially available enzymes. Chemists are now able to design processes in collaboration with enzyme engineers for enzymes with activities and properties that do not yet exist. The power of this approach to discover and engineer fit purpose enzymes will be highlighted with examples from drug discovery through commercial manufacture.

ORGN 368

Chiral synthesis of LSD1 inhibitor GSK2879552 enabled by directed evolution of an imine reductase

Christopher M. MacDermaid¹, chris.mac.dermaid@gmail.com, Doru Roiban², Markus Schober², Anne Ollis³, Sandy Chang³, Diluar Khan⁴, Joseph Hosford², Jonathan Latham², Leigh A. Ihnken³, Murray Brown², Douglas E. Fuerst⁵, Mahesh Sanganee⁴. (1) Data and Computational Science, GlaxoSmithKline, Collegeville, Pennsylvania, United States (2) Synthetic Biochemistry, GlaxoSmithKline, Stevenage, United Kingdom (3) Synthetic Biochemistry, GlaxoSmithKline, Collegeville, Pennsylvania, United States (4) Chemical Development, GlaxoSmithKline, Stevenage, United Kingdom (5) Glaxosmithkline UW2922, King of Prussia, Pennsylvania, United States

Imine reductases (IREDs) catalyse the reductive amination of aldehydes or ketones with amines to produce chiral amines - a key transformation in the preparation of fine chemicals and active pharmaceutical ingredients (APIs). Although significant progress has been recently made in the field, the industrial application for these enzymes has not yet been demonstrated. In less than one year, our team was able to re-engineer a wild type imine reductase to perform reductive amination with concomitant substrate amine resolution in a commercially relevant manufacturing process for lysine-specific demethylase-1 (LSD1) inhibitor GSK2879552. The evolved enzyme produced kilogram quantities of a key intermediate to GSK2879552 in 84% yield, 99.9% purity, and >99.7% enantiomeric excess, with improved process mass intensity. In this talk, I will describe the directed evolution process, which resulted in our selected enzyme variant showing >38000-fold improvement over wild type within three rounds of evolution.



ORGN 369

Enantioselective C-H amination via directed evolution of cytochrome P450 enzymes

Yang Yang¹, yang89@caltech.edu, **Frances H. Arnold**². (1) Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California, United States (2) Cal Tech, Pasadena, California, United States

The selective functionalization of ubiquitous C–H bonds can greatly streamline the construction of complex molecular architectures from easily available precursors. In particular, the development of general systems for the regio- and enantioselective transformation of C–H bonds lies at the forefront of current efforts to further advance transition-metal-catalyzed C–H functionalization. In this talk, I will discuss recent work from the Arnold lab at Caltech on using engineered cytochromes P450 for C–H amination processes. These genetically encoded enzymes are produced and function in bacteria, where they can be easily optimized by directed evolution. With this biocatalytic platform, a range of challenging C–H amination processes can be accomplished with excellent total turnover numbers in a regio- and stereocontrolled fashion.

ORGN 370

Computational pathway and enzyme design for synthetic biochemistry

Alexandre Zanghellini^{1,2}, az@arzeda.com. (1) Arzeda, Seattle, Washington, United States (2) Chemistry and Chemical Biology, Cornell University, Ithaca, New York, United States

Biocatalysis has proven its value in enabling new sustainable synthetic routes for complex chemistry, first and foremost for API manufacturing but also in the context of industrial chemicals. Its widespread use, however, has been hampered by two distinct challenges. The first one is our ability to rapidly and reliably identify and improve the required enzymes. To this end, Arzeda has been developing high-throughput computational methodologies to design *de novo* activity or exploit natural enzyme latent promiscuity to rapidly design new biocatalysts; these catalysts are further improved when needed using traditional directed evolution techniques. Successful academic and industrial applications of this methodology will be presented.

The second challenge is that of finding optimal ways to arrange natural and designed enzymes to biosynthesize a small-molecule of interest. To illustrate our progress towards solving this challenge, we will discuss a dedicated software (Scylax™) that Arzeda has been developing for the automated design of novel biosynthetic pathways. Inspired by retrosynthetic methods in organic chemistry, Scylax™ draws on databases of known natural enzymatic reactions as well as reactions that can be catalyzed by computationally designed enzymes to exhaustively enumerate biosynthetic routes from a set of desired metabolites down to any small molecule of interest. Such biosynthetic

routes can then be implemented in bioreactor or in the context of designer fermentation strains (designer cell factories).

ORGN 371

Computational enzyme modeling in development of a biocatalytic cascade for the manufacture of Islatravir (MK-8591)

Li Xiao, li.xiao2@merck.com. Merck, Cranbury, New Jersey, United States

Enzyme-catalyzed reactions are transforming pharmaceutical manufacturing, offering levels of selectivity and tunability that can dramatically improve chemical synthesis. Greater potential can be realized when combining enzymatic reactions into multi-step biocatalytic cascades. An in-vitro biocatalytic cascade synthesis of the investigational HIV treatment islatravir has been established. Five enzymes were evolved to construct the non-natural nucleoside islatravir from simple building blocks in a three-step cascade. In this presentation, the computational modeling approach applied to support design and development of this biocatalytic cascade will be addressed. Both successful case studies and lessons learned will be included to highlight opportunities and challenges for computational modeling of biocatalyst design.

ORGN 372

Discovery and engineering of a biocatalytic cascade for the manufacture of Islatravir (MK-8591)

Hao Yang, Li Xiao, li.xiao2@merck.com. Merck, Cranbury, New Jersey, United States

Enzyme-catalyzed reactions are transforming pharmaceutical manufacturing, offering levels of selectivity and tunability that can dramatically improve chemical synthesis. Greater potential can be realized when combining enzymatic reactions into multi-step biocatalytic cascades. In this presentation, discovery of an in-vitro biocatalytic cascade synthesis of the investigational HIV treatment islatravir will be described. Five enzymes were evolved to construct the non-natural nucleoside from simple building blocks in a three-step cascade. The unparalleled specificity of enzyme catalysis, enhanced by directed evolution, enabled us to design a fundamentally new and efficient synthesis of islatravir, demonstrating the great potential of biocatalytic cascades in sustainable manufacturing.

ORGN 373

***De novo* oligosaccharide synthesis and medicinal chemistry**

George A. O'Doherty, *g.odoherty@neu.edu*. Dept of Chemistry Chem Biology, Northeastern Univ, Boston, Massachusetts, United States

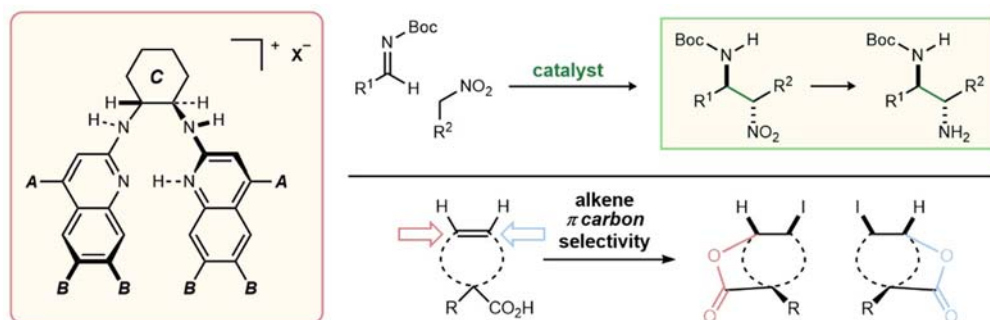
We possess a never-ending desire to mimic nature's elegances. This design principle has become a major aspiration in both art and science. For organic chemist this can be seen in the pursuit of the synthesis of natural products, as well as, in the design of new reaction catalysts that mimic enzyme efficiencies. Of all the aspects of enzyme catalyzed reactions to mimic of the selectivity of the glycosyltransferase stands as the "Holy Grail" in terms of substrate-, regio- and stereo-selectivity. Recently we have found that the use of the Taylor catalyst ($\text{Ph}_2\text{BO}(\text{CH}_2)_2\text{NH}_2$) as the regioselective activator component in a Pd(0)-catalyzed glycosylation (*i.e.*, pyranone installation) can result in a reaction with glycosyl-transferase like selectivities. A reaction where this dual B/Pd-catalyst system mimics the nucleophilic and electrophilic activation sites of the enzyme. Key to this mimicry is the recognition that pyranone rings can serve as atomlessly protected forms of monosaccharides. In this regard, we have been working to develop practical catalytic asymmetric approaches to the synthesis and study of stereochemically complex oligosaccharide structural motifs, using of asymmetric catalysis. This reliance on catalysis for stereocontrol can be seen in the asymmetric synthesis of the key pyranone building blocks from achiral furans, the diastereoselective assembly of these pyranones in to oligomers and finally the regio- and stereoselective bidirectional-functionalization of these oligomers in to oligosaccharides. This effort and its application for oligosaccharide synthesis and related medicinal SAR-chemistry studies will be discussed.

ORGN 374

New catalysts and strategies that enable discoveries in natural product-based therapeutic development

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Brønsted acid/base catalysts are no longer typically understood to function as *either* an acid or base, but more often as a hybrid of two or more functions. Enantioselective catalysis has driven our understanding of the principles of bifunctional catalysis, owing to the integral role that chiral ligands play in a reaction's mechanism. This characterization applies to chiral bis(amidine) [BAM] catalysis, an area that has played key roles in the development of nitroalkane and carboxylic acid-based reactions. Furthermore, these discoveries have been leveraged in the concise synthesis of therapeutics, facilitating hypothesis-driven research in the treatment of a broad range of disease types through key collaborations. Examples of these, with an emphasis on recent developments, will be described in this lecture.



ORGN 375

Chematica: Computer-planned syntheses of natural products and their experimental execution

Bartosz Grzybowski, nanogrzybowski@gmail.com. Chemistry, Institute for Basic Science, UNIST, Ulsan, Korea (the Republic of)

Planning of multistep syntheses leading to complex targets is often a creative but also a difficult and time-consuming process. Chemists were among the pioneers of using computers in various research tasks and, in particular, have strived for over five decades now to teach the machines the art of synthetic design. However, despite numerous and often ingenious approaches being pursued, there have been no examples of syntheses of non-trivial targets first planned by the machine and then successfully executed in the laboratory. With enormous improvements in computers' performance, with the modern methods of machine learning and graph theory, and with carefully encoded reaction mechanisms, our team has been able to develop the so-called Chematica platform that is finally capable of completely automated and chemically correct design of synthetic pathways leading to arbitrary targets, including complex natural products. In my talk, I will first discuss the theoretical basis of the program that emerged over many years of concerted effort, and then talk about its all-important validation in which this software designed, without human supervision, syntheses leading to numerous targets diverse both in terms of structure and complexity – these computer designed routes were later executed in the laboratory and in all cases offered significant improvements over previous approaches or identified efficient routes to targets for which previous synthetic attempts proved unsuccessful. With these results documenting the ability of machines to creatively apply known reaction types/mechanisms, I will also discuss their ability to discover completely **new** synthetic knowledge (ranging from previously unreported tactical combinations to new reaction types). Integration of such computer-driven discovery into mainstream synthetic effort appears an exciting opportunity – and a challenge – for the organic-synthetic research in the years to come.

ORGN 376

Metabolism before enzymes

Joseph Moran, *joseph.moran@me.com*. ISIS, University of Strasbourg, Strasbourg, France

How did life's chemical pathways emerge before there were enzymes to act as catalysts? Why does biochemistry use the reactions and pathways that it does and not others?

My group suspects that the metabolism underlying all living things started before the onset of Darwinian evolution as a self-organized reaction network. This prebiotic chemistry was driven into existence by a far-from-equilibrium environment and catalyzed by naturally occurring minerals and metal ions. To infer the conditions that would have been required for self-organization, we are searching for non-enzymatic versions of ancient, core metabolic processes. So far we have found non-enzymatic chemistry that resembles the acetyl CoA pathway, the reverse Krebs cycle, the Krebs cycle and glyoxylate cycle, and thioester-based energy conservation. With a few more non-enzymatic metabolic processes, we hope to triangulate the non-equilibrium conditions required to enable the self-organization of a primitive metabolism, and, ultimately, genetic polymers as well. Our results already support the hypothesis that biological metabolism was an outgrowth of geochemistry.

ORGN 377

Single electron processes enabling organic synthesis

Gary A. Molander, *gmolandr@sas.upenn.edu*. Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States

Many organic reactions are mechanistically driven by two-electron processes. Although such methods are highly effective for a vast number of transformations, there are still many such conversions that have proven challenging (e.g., cross-coupling of alkylmetallics) or that suffer from harsh reaction conditions or intolerance of sensitive functional groups.

The limitations of such transformations are often inherent to the mechanism of these processes at the most fundamental level, and thus predispose many of these reactions for failure. Processes transpiring via single electron mechanistic paradigms have promise to resolve some of the aforementioned limitations.

Described will be our efforts to develop a suite of radical precursors for alkyl cross-coupling with a variety of electrophiles, emphasizing the tolerability of the developed conditions to an unprecedented array of functional groups. The value of generating radicals in a process that is *synchronized and catalytic* will be emphasized. Sequential transformations and multi-component reactions based on radical chemistry will be

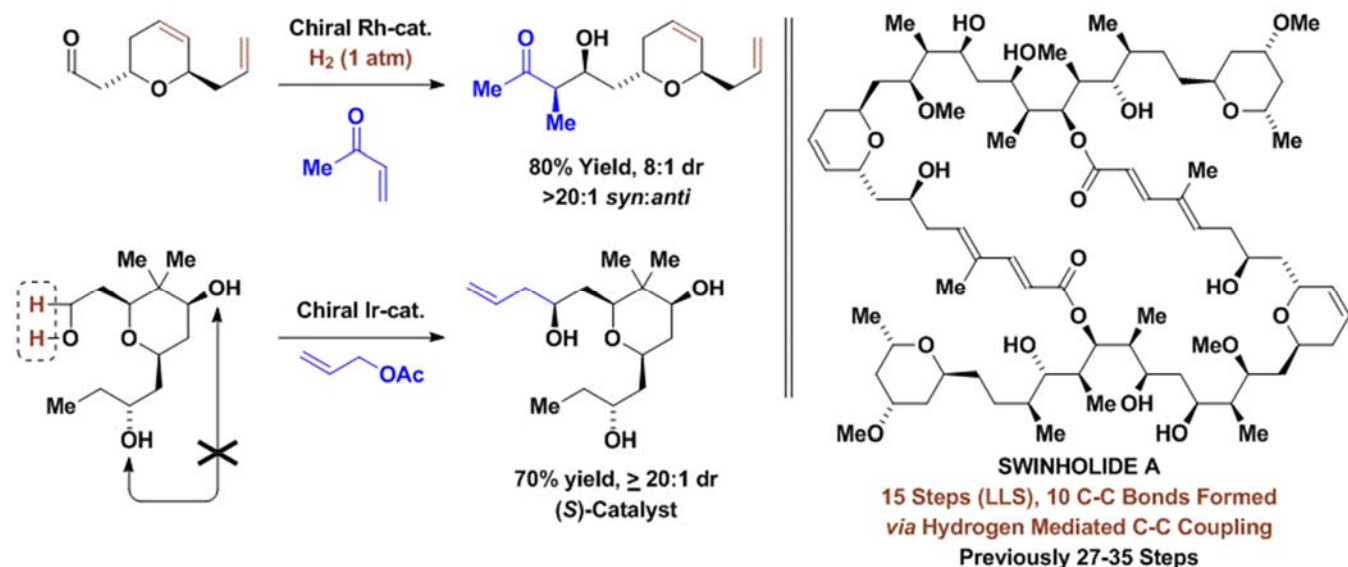
outlined, both in dual catalyzed processes and in radical/polar crossover processes where a subsequent catalytic transformation is not utilized.

ORGN 378

Hydrogen-mediated C-C bond formation

Michael J. Krische, mkrische@mail.utexas.edu. Chemistry, Univ Texas at Austin, Austin, Texas, United States

Stereo- and site-selective methods for the byproduct-free modification of unprotected organic compounds that occur through the addition or redistribution of hydrogen are natural endpoints in the advancement of methods for efficient, green chemical synthesis. Progress toward this goal requires a departure from reactants that embody non-native structural elements, such as premetalated reagents, directing/protecting groups and chiral auxiliaries. Our laboratory has developed a broad, new family of reductive C-C bond formations that merge the characteristics of catalytic hydrogenation and carbonyl addition. Hydrogenation or transfer hydrogenation of π -unsaturated reactants in the presence of C=X (X = O, NR) bonds delivers products of carbonyl or imine addition. In related hydrogen auto-transfer reactions, alcohols served dually as reductants and carbonyl proelectrophiles, enabling direct conversion of lower alcohols to higher alcohols. Such hydrogen-mediated C-C bond formations contribute to a departure from the use of stoichiometric organometallic reagents in chemical synthesis, and the issues of safety, selectivity, cost and waste associated with their use.



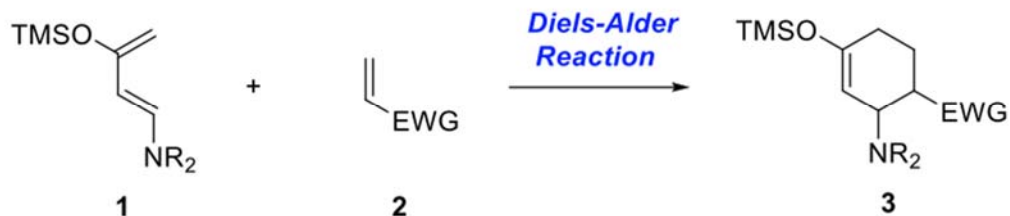
ORGN 379

Domino Michael/Mannich reactions of simple aliphatic (acyclic) substrates

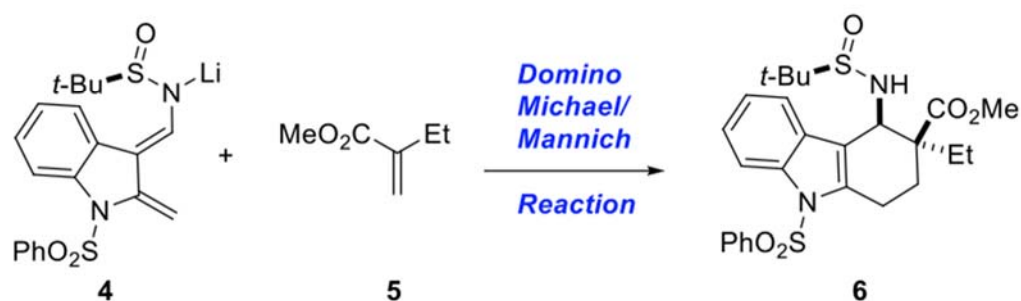
Xiao Jin², jinxiao08@gmail.com, Vijay K. Chatare¹, Po-Cheng Yu³, Rodrigo B. Andrade⁴. (1) Chemistry, Temple University, Philadelphia, Pennsylvania, United States (2) Fox Chase Chemical Diversity Center, inc, King of Prussia, Pennsylvania, United States (3) Temple University, Philadelphia, Pennsylvania, United States (4) Temple Univ, Philadelphia, Pennsylvania, United States

The domino intermolecular Michael/intramolecular Mannich (DMM) annulation reaction between an *N*-sulfinyl metallodienamine and an electrophilic alkene is an alternative to the Diels-Alder reaction of 1-amino-1,3-butadienes for the asymmetric synthesis of 2-amino cyclohexenes. In terms of FMO theory, the DMM reaction has a lower HOMO-LUMO gap compared to the Diels-Alder reaction that allows the reaction to proceed at lower temperatures while maintaining the stereochemical fidelity. In other words, the activation energy of DMM reaction is lower thus it may not require high temperatures or the Lewis acid catalysts. The purpose of this paper is to describe the discovery and utility of this important asymmetric route to 2-amino cyclohexenes, which are found in many alkaloid natural products.

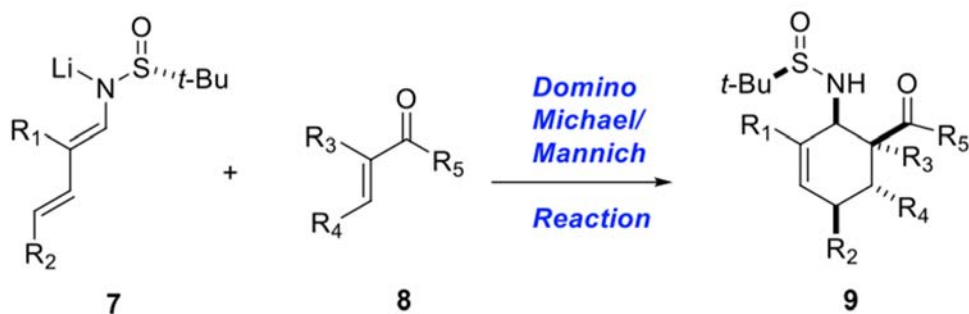
A: Rewal (1974)



B: Andrade (2013)

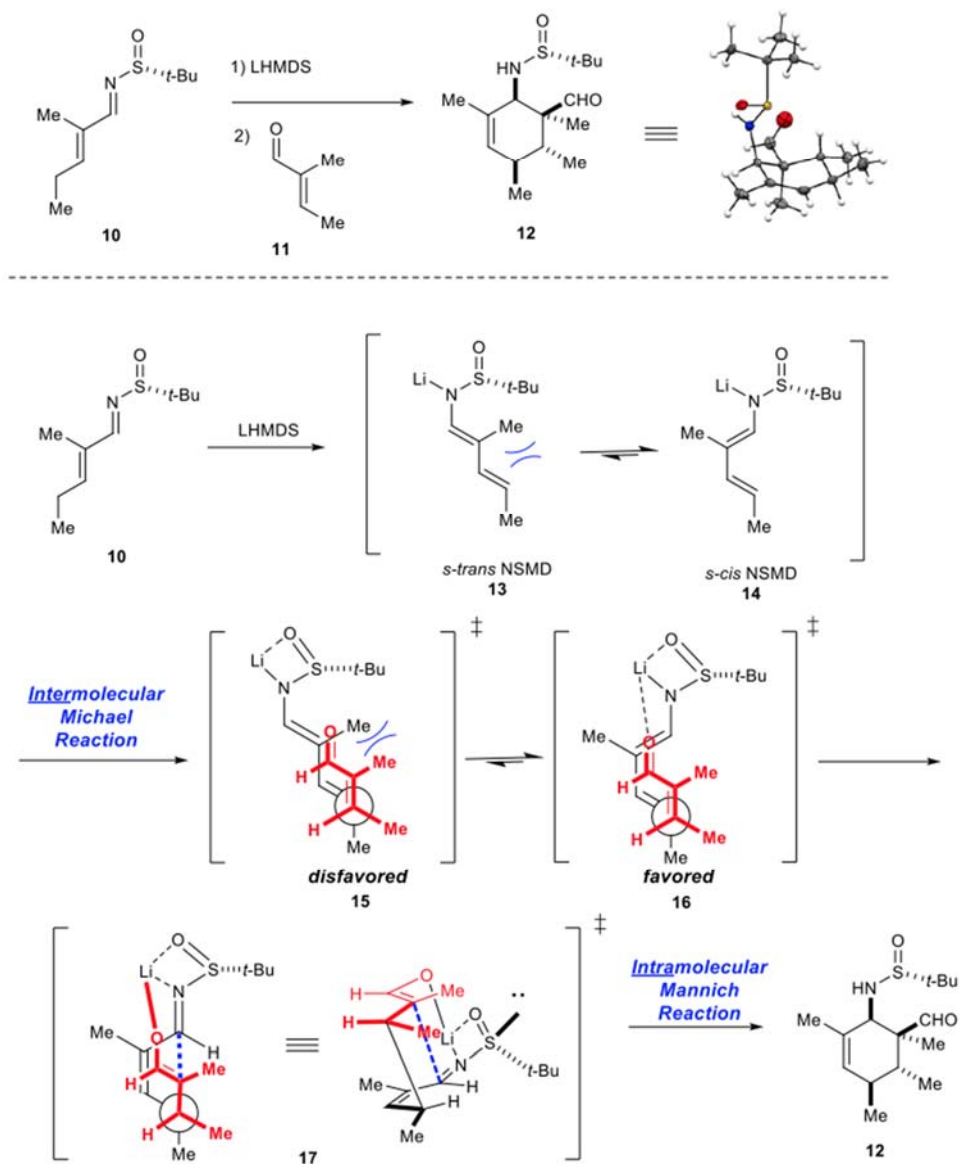


C: This work



Scheme 1. General context of amino-cyclohexene formation.

Scheme 2. Proposed stepwise mechanism for the acyclic DMM annulation reaction leading to *endo*-cycloadduct **12**.

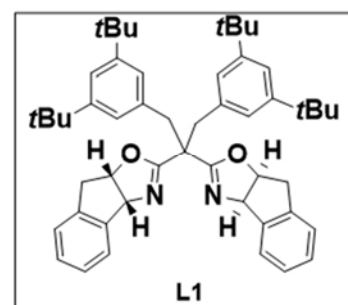
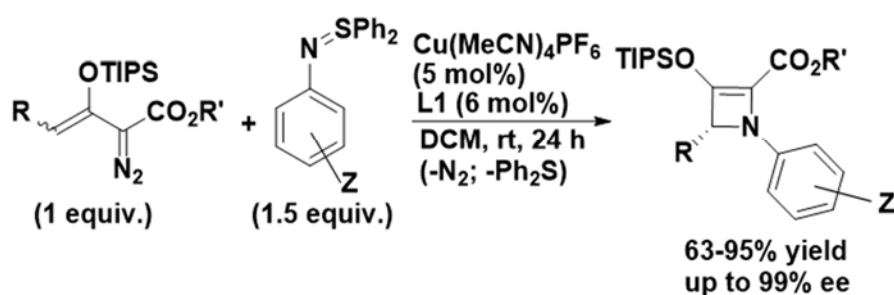


ORGN 380

Utilizing a [3+1] cycloaddition methodology for asymmetric synthesis of azetines and researching subsequent reactions

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The combination of *N*-arylimido sulfur ylides with enoldiazoacetates in the presence of a chiral catalyst form tetrasubstituted azetidine-2-carboxylic acid derivatives by [3+1]-cycloaddition. Only copper(I) catalysis was effective for this transformation, and Cu(MeCN)₄PF₆ was the catalyst of choice in the formation of 2-azetines. Product yields were the highest in dichloromethane, and diphenylsulfur ylides gave higher product yields than their dimethyl or methylphenyl analogues. Reactions were performed at room temperature to avoid electroreversion of the azetidine. [3+1]-Cycloaddition occurred with the triisopropylsilyl(TIPS)-protected enoldiazoacetate but not with the *tert*-butyldimethylsilyl(TBS)-protected enoldiazoacetate. This new cycloaddition methodology for azetines allows broad manipulation of substituents in high yields with excellent stereocontrol. Further research on azetidine-2-carboxylic acid derivatives is still being conducted in our laboratory.



ORGN 381

Blue light mediated photochemical carbene transfer reactions

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Carbene transfer reactions are an important transformation to conduct highly efficient cycloaddition, rearrangement, X-H or C-H functionalization reactions. They are typically conducted in the presence of expensive precious metal catalysts, which impacts on the process efficiency. Metal-free carbene transfer reactions are a timely strategy to overcome these shortcomings and are most often conducted under either thermal or UV photochemical conditions, yet limited due to harsh reaction conditions.

The visible light photolysis of diazoalkanes recently emerged as an interesting approach

to conduct carbene transfer reactions under mild and operationally simple conditions. Herein, we report on our recent work on the visible light photolysis of diazoalkanes to perform highly efficient cycloaddition and rearrangement that allow the synthesis of valuable functional small molecules with applications in medicinal chemistry.

ORGN 382

To rearrange or not? Controlling the reactivity of onium ylides

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Sigmatropic rearrangement reactions are a powerful tool for the construction of complex small molecules. They typically proceed via formation of an ylide intermediate that, depending on the nature of the substituents, can undergo either [1,2]- or [2,3]-sigmatropic rearrangement.

Herein, we report on our recent studies on sigmatropic rearrangement reactions of benzylic ylides that undergo either [1,2]- or [2,3]-sigmatropic rearrangement reaction with donor-acceptor diazoalkanes using a Rh(II) catalyst. The selectivity of this process can be controlled by the choice of solvent. We further investigated sigmatropic rearrangement reactions of small, strained heterocycles that proceed under ring expansion reaction of the heterocycle to give important furan or thiolane heterocycles. We conclude with our latest findings in interrupted rearrangement reactions, which can proceed under either dealkylation or ring opening of ethers.

ORGN 383

Synthesis, Cytotoxic activity of novel tetracyclic acridone derivatives

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Synthetic route was designed for a novel tetracyclic acridone skeleton along with its derivatisation. The biological activities of acridone derivatives (n=38) were evaluated to investigate their anti-proliferative/cytotoxic activities in three different types of human cell lines such as Breast cancer and neuroblastoma (MDA-MB-231 & IMR-32) and Human normal cell line (HEK293). The compounds were shortlisted based on the percentage inhibition that is greater than 50% at the selected 25 μ M concentration in the first step. The compounds with greater inhibition were tested for their GI₅₀ values through MTT assay. The results indicate that 6 compounds have shown significant anti-cancer activity on breast cancer cell line (MDA-MB-231) and 6 compounds on neuroblastoma (IMR-32) in a concentration-dependent manner (Table 1). It is apparent from the results that few derivatives are found to be more potent on breast cancer cell lines than the neuroblastoma cell line and vice-versa. The actives were further tested for

their cytotoxicity effect on human normal cell line and were found to be safe Invitro with lesser percentage toxicity at $25\mu M$.



S.No	Compound	MDA-MB-231 ^a (IC ₅₀ μM)	IMR-32 ^b (IC ₅₀ μM)	HEK293T ^c Toxicity at 25 μM
1	SK-6-7	>100	1.123	12.62
2	SK-6-11	16.87	0.949	21.36
3	Sk-6	1.878	1.284	5.53
4	SK-6-9	0.5814	1.081	18.54
5	SK-6-16	>100	4.526	31.96
6	SK-14	>100	0.4472	5.89
7	SK-6-10	6.545	>100	11.90
8	SK-6-4	6.977	>100	26.73
9	SK-6-13	13.77	>100	14.54
10	SK-6-14	3.939	>100	22.65
11	SK-5	3.497	>100	7.06
12	062	57.02	0.196	18.6
13	070	11.41	>100	2.69
14	066	0.03	16.55	5.64
15	Doxorubicin	1.00	0.043	-
16	Cisplatin	7.21	-	-

Table -1: Depicting GI₅₀ (μM) values of the selected compounds

ORGN 384

Scope and recent applications of Co-mediated 1,3-diene isomerization

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Our lab has recently developed an efficient cobalt-mediated 1,3-diene isomerization to highly substituted 1,3-dienes. Simple 1,3-dienes can be obtained by ene-yne metathesis using ruthenium carbene catalysts. A wide range of 1,3-dienes underwent isomerization regioselectively, with high isolated yields and modest to good isomeric ratios. Complete chemoselectivity towards diene isomerization in the presence of a terminal olefin was also observed. Mechanistic studies suggest a radical-mediated double bond migration which is consistent with a transition metal assisted hydrogen atom transfer (HAT) mechanism. Application towards a natural product total synthesis and future directions of the research will also be discussed.

ORGN 385

Rapid isocyanide-induced dearomatization to complex cyclohexadienes

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Isocyanides are a unique class of functional group that rapidly assemble heterocycles and peptidomimetics. Building on our recent anionic route to functionalized disubstituted and trisubstituted isocyanides with *Asmic* (Anisylsulfanylmethylisocyanide), we have discovered a remarkable dearomatization that occurs within 15 minutes at -78 °C to afford complex cyclohexadienes.

The cyclohexadiene incorporates two equivalents of disubstituted *Asmic* with formation of two all carbon quaternary stereocenters and three orthogonal functionalities: an enol ether, an isocyanide and a nitrile. The three functional groups provide different sites ideally suited for selective synthetic elaboration. The reaction scope, a mechanistic analysis, reactions that elaborate the cyclohexadiene scaffold will be presented.



ORGN 386

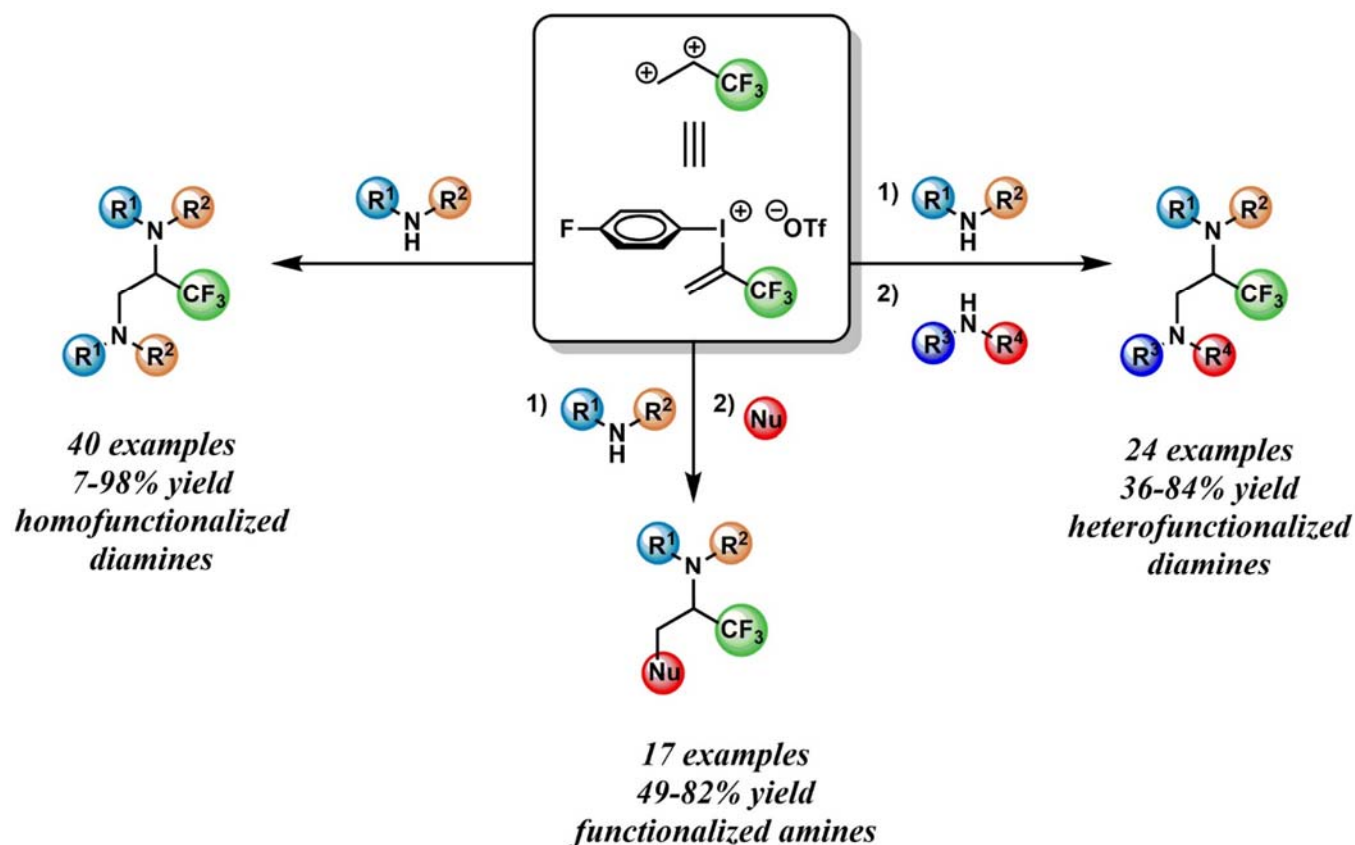
Trifluoropropenyl iodonium salt: Platform for straightforward synthesis of trifluoromethylated vicinal diamines and substituted trifluoropropylamines

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Difunctionalization of alkenes are well established transformation to introduce diversity in a single step in terms of structure and chemical reactivity. However, the difunctionalization of hydrocarbon olefins to introduce new C-N bonds (i. e. diamination, diazidation) are developed continuously in the last three decades, these transformations of fluorinated olefins are studied scarcely. On the other hand, different synthetic approaches towards the synthesis of vicinal diamines and amines containing α -trifluoromethyl group could be accomplished in multistep procedures. Therefore, we envisioned a synthetic approach, which uses trifluoropropyl biselectrophile synthon and simple secondary amines as nucleophiles. The desired reactivity of biselectrophile synthon could be achieved by application of a trifluoropropenyl iodonium salt, which reagent has been demonstrated as an efficient reagent in the synthesis of 2-trifluoromethyl aziridines.

In continuation of this work, we optimized reaction conditions to achieve simple and mild synthetic procedure for the preparation of *N,N'*-homofunctionalized α -trifluoromethyl containing vicinal diamines from secondary amines. We have investigated the scope of reaction, regarding the electronic and steric effects of secondary amines, and isolated the corresponding diamines up to 98 % yield.

In case of sp^3 -*N* containing secondary amines, the reaction mechanism was examined in details, which revealed the intermediacy of aziridinium ions. This intermediate was utilized in the regioselective synthesis of *N,N'*-heterofunctionalized α -trifluoromethylated vicinal diamines. Steric and electronic effects of different amines were evaluated at both stages of the reaction. Application of halides, other heteroatom (O, S, P) and carbon nucleophiles provided the corresponding substituted amines in moderate to good yields (49-82%), in a regioselective manner.



ORGN 387

Lewis acid-catalyzed intermolecular ring-opening and cross carbonyl-olefin metathesis reactions

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The development of a Lewis acid-catalyzed ring-opening cross-metathesis reaction has enabled selective access to acyclic, unsaturated ketones as the carbonyl-olefin metathesis products. While catalytic amounts of FeCl₃ were previously identified as optimal to catalyze ring-closing metathesis reactions, the complementary ring-opening metathesis between cyclic alkenes and carbonyl functionalities relies on GaCl₃ as the superior Lewis acid catalyst (22 examples, up to 47% yield). In depth mechanistic studies revealed that the reaction suffered from a competing carbonyl-ene reaction to form two distinct byproducts. More recently, advances for the intermolecular carbonyl-olefin metathesis reaction have been described relying on superelectrophilic Fe(III)-based ion pairs as stronger Lewis acid catalysts. This new catalytic system enables selective access to the corresponding (*E*)-olefins as the carbonyl-olefin metathesis

products. Initial mechanistic investigations suggest a regioselective formation and a stereospecific fragmentation of intermediate oxetanes as the origin of this selectivity observed. The optimized reaction conditions are general for a variety of aryl aldehydes and trisubstituted olefins and are demonstrated for 28 examples resulting in up to 64% overall yield.

ORGN 388

Superelectrophilic aluminum(III)-ion pairs promote a distinct reaction path for carbonyl-olefin metathesis of medium-sized rings

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Catalytic carbonyl-olefin metathesis reactions have emerged as a synthetically useful strategy for alkene formation. Successful approaches for carbonyl-olefin ring-closing, ring-opening, and cross metathesis have been developed in recent years, however, these transformations are limited in scope and general utility. Recent efforts have shown that stronger catalyst systems are required to selectively activate less reactive substrates for metathesis while impeding undesired off-target pathways. The presented work will explore the development of aluminum-based heterobimetallic ion pairs as powerful catalysts to expand the current scope of carbonyl-olefin ring-closing metathesis to the synthesis of medium-sized rings. The discussion will include both general scope of the catalyst system, as well as mechanistic insight into the transformation. The results presented are expected to inform future catalyst development to ultimately expand the synthetic utility of these transformations.

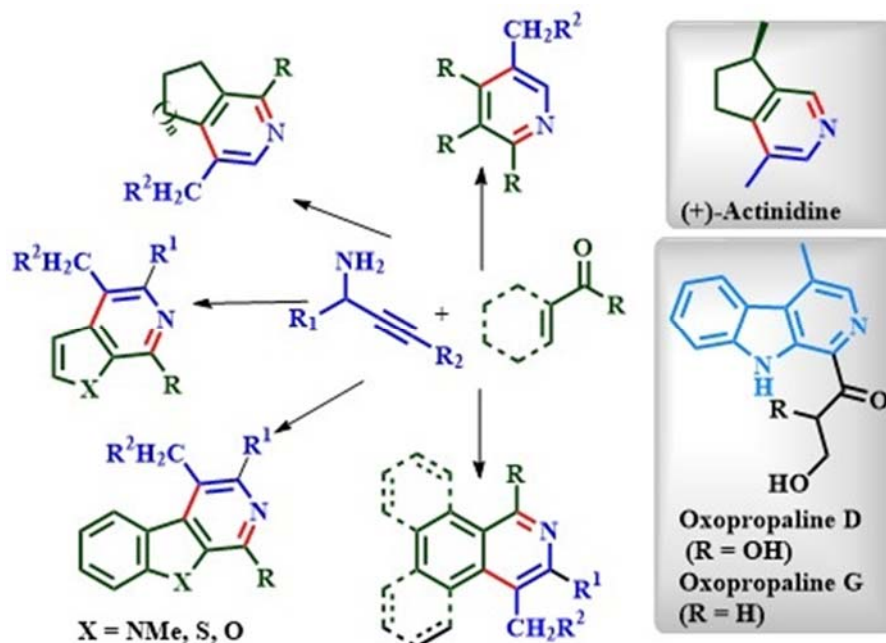
ORGN 389

Unified strategy for the synthesis of pyridines, β - & γ -carbolines, and other fused azaheteroaromatics under mild, metal-free conditions

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An efficient and unified approach for the synthesis of diversely substituted pyridines, β -carbolines, γ -carbolines and other fused azaheteroaromatics has been realized, under metal-free conditions, starting from propargylic amines and α , β -unsaturated carbonyl compounds. This unified strategy involves imine formation followed by concomitant cyclization through an allenyl intermediate to afford pyridines, β - and γ -carbolines as well as a range of fused azaheteroaromatics that include pyrrolopyridine, furopyridine, thienopyridine, benzofuropyridine, pyrrolodipyridine, benzothienopyridine, phenanthroline and benzisoquinoline, with a broad substrate scope and excellent

functional group compatibility. We have achieved the formal synthesis of oxopropalines D and G on a gram-scale, in a one-pot reaction from commercially available materials (previous shortest reported route was 5 steps) and one-step synthesis of the monoterpene alkaloid, (-)-actinidine, an ant-associated iridoid. Furthermore, we prepared an analogue of oxopropaline in two steps with a 69% overall yield. This mild strategy is also suitable for functionalization of natural products or other advanced intermediates having α , β -unsaturated carbonyl functionality.



ORGN 390

Development of a photoredox catalysis-mediated hydroazidation method for electron-rich olefins

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As precursors for amines, which are common motifs in biologically relevant molecules, organic azides are important synthetic targets. As such, significant attention has been given to the introduction of azide moieties into molecules resembling those with interesting properties. Organic azides are traditionally prepared using classical S_N2

chemistry, and more modern methods involve the use of transition metals or azido radicals. However, the use of these methods presents several challenges, including limited commercial availability of alkyl halide precursors or the use of explosive, toxic reagents such as hydrazoic acid. One area that has not been the subject of extensive study is the hydroazidation of activated olefins and styrenes, and this is perhaps due to the fact that such compounds are prone to oligomerization. However, the hydroazidation of these compounds could be used to access novel phenethylamine derivatives, which possess a variety of interesting biological activity. We envisioned the application of our organic photoredox catalysis platform to this synthetic challenge. We report the development of a mild, efficient method for the Anti-Markovnikov hydroazidation of activated olefins using an acridinium photoredox catalyst. This method was applied to the functionalization of 31 electron-rich olefins with the desired products formed in yields ranging from 22% –98%.

ORGN 391

Photo-catalyzed linear selective hydrocarboxylation of electron-deficient alkenes with CO₂ under flow

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A photo-catalyzed, linear selective hydrocarboxylation of electron-deficient alkenes employing CO₂ under flow conditions was developed. Several substrates participate in this process including unsaturated esters, unsaturated nitriles and enones and the reaction shows good functional group compatibility. The derived carboxylic acids are readily converted to beta-lactones through an alpha-halogenation-beta-lactonization pathway. Importantly, the required electron-deficient alkene substrates for this process are readily accessible from alkene and ketone-containing natural products, which renders it possible to tag these natural products with beta-lactones for subsequent activity-based protein profiling (ABPP) studies.

ORGN 392

Opening a can of glow-worms: Tandem photoredox catalysis of [Ir(ppy)₂(dtb-bpy)]⁺

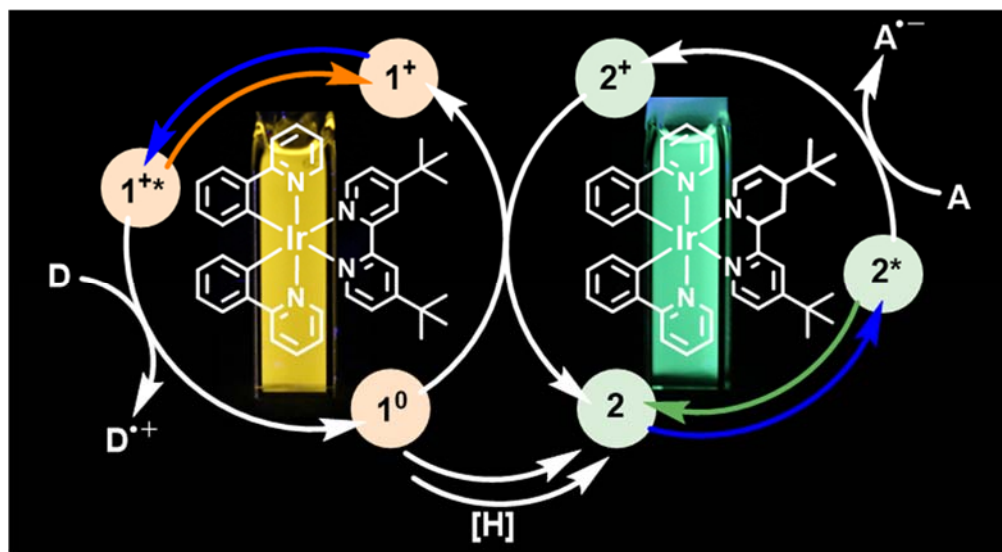
Timothy U. Connell¹, tim.connell@rmit.edu.au, Catherine L. Fraser², Milena L. Czyz³, Daniel E. E. Gomez¹, Anastasios Polyzos³, Paul S. Francis². (1) RMIT University, Melbourne, Victoria, Australia (2) Deakin University, Waurin Ponds, Victoria, Australia (3) The University of Melbourne, Parkville, Victoria, Australia

The emergence of photoredox catalysis over the last decade has facilitated small molecule activation under mild reaction conditions with minimal equipment overheads. This synthetic approach exploits the ability of predominantly homogenous d⁶ transition metal complexes to absorb visible-light and generate an excited state capable of single-

electron transfer (SET) reactions that either donate an electron to, or remove an electron from, simple organic substrates. Research efforts typically focus on the development of new synthetic methodologies, with often only a cursory investigation of the fundamental light-dependent interactions.

This work presents a unique photoredox reaction cycle comprised of two photoactive iridium(III) complexes working together. Following the first photoinduced electron transfer (PET) between the off-the-shelf catalyst $[\text{Ir}(\text{ppy})_2(\text{dtb-bpy})]^+$ and a sacrificial donor, subsequent reactions generate a previously unknown species distinguished by reduction and semi-saturation of the ancillary ligand. Rigorous structural characterization confirmed the nature of this new highly reducing metal complex and spectroscopic measurements demonstrated the PET properties of its excited state. Turnover of this new photocatalytic cycle occurs along with the reformation of $[\text{Ir}(\text{ppy})_2(\text{dtb-bpy})]^+$. These observations were rationalized by a mechanism containing two distinct yet interconnected photoredox cycles that provide access to an extended potential window.

Understanding the photochemical properties of this new metal complex help to both rationalize fringe cases of unexpected reactivity as well as expand the potential synthetic utility of this system. The application of this newly discovered photocatalytic cycle in other synthetic transformations will also be presented.



ORGN 393

Exploring green photoredox routes for CO_2 reduction

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Organic photoredox catalysts such as oligo(p-phenylenes) (OPPs) offer energy-efficient, sustainable alternatives to the otherwise energy-intensive, thermally activated process of CO₂ reduction. While optoelectronic properties of OPPs have been studied extensively, catalytic properties of OPP radical anions, especially towards CO₂ reduction, remain underexplored. To probe fundamental characteristics of electron transfer (ET) kinetics from para-substituted OPP radical anions to CO₂ under the Marcus theory framework, we utilize constrained density functional theory and energy decomposition analysis (EDA). Free energy changes, driven by substituent electrophilicities, dominate changes to the exponential term in the Marcus rate expression, yielding a parabolic correlation between log of rate coefficients and substituent Hammett parameters. EDA reveals that electrostatic contributions drive favorable formation of the reactant complexes, and charge transfer (interfragment electronic relaxation) contribute to substituent-dependent trends in reorganization energies. No direct or indirect (distance-driven) dependence of the charge transfer coupling element on electrophilicity is found, although the coupling element is responsible for outliers in rate coefficient trends. We explore the possibility of substituent-dependent quadrupole moments driving differences in coupling. We therefore report a comprehensive, fundamental analysis of substituent-dependence of ET kinetics and identify tunable features that enable enhanced activity towards CO₂ reduction.

ORGN 394

Chemical method for selective functionalization at N⁶mdA residues in DNA

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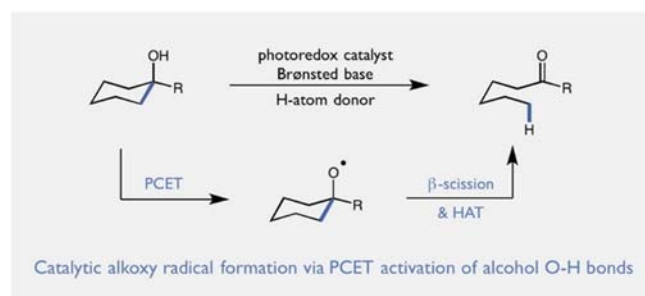
Methylation at specific positions of the nucleobases provides the most common means by which genomic DNA is reversibly marked. Although epigenetic modification occurs most commonly at C in DNA, methylation at the N⁶-position of A (N⁶mdA) has also been identified in eukaryotes, including mammals, and could play an important role in gene expression and disease regulation. N⁶mdA displays the only secondary amine motif in DNA, but no methods exist for its functionalization. Herein, we report the development of a synthetic method that introduces a covalent modification at the methylated DNA residue N⁶mdA. As a demonstration of the remarkably selective chemistry, we are able to modify and enrich oligonucleotide fragments comprising N⁶mdA, which is also proof-of-concept for a previously unknown method in which this methylated nucleotide could be detected in DNA.

ORGN 395

Homolysis of alcohol O–H bonds via proton-coupled electron transfer

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Direct homolytic activation of aliphatic and benzylic alcohol O–H bonds is achieved *via* proton-coupled electron transfer under photocatalytic conditions. The O–H bond is homolyzed by the joint action of a redox-active iridium photocatalyst and a mild Brønsted base. This strategy precludes the need for prefunctionalization of the alcohol functional group. The alkoxy radical generated in this reaction can undergo β -scission to form an alkyl radical, and ultimately give rise to contrathermodynamic isomerizations where cyclic alkanol substrates are transformed into linear carbonyl compounds. A mechanism is presented to rationalize this out-of-equilibrium behavior that may serve as a model for the design of other contrathermodynamic transformations driven by excited-state redox events.



ORGN 396

Light-driven depolymerization of native lignin enabled by proton-coupled electron transfer

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Lignin accounts for nearly 30% of the organic carbon on Earth, and is often proposed as a renewable alternative to petroleum for the production of aromatic feedstock chemicals. However, the selective conversion of native lignin into useful monomeric products is challenging due to its robust and complex structure. Accordingly, traditional lignin valorization methods require harsh reaction conditions and high temperatures or pressures, as well as produce stoichiometric chemical waste streams. As a consequence, these processes can suffer from poor product selectivity, product

repolymerization, and challenges associated with product separation and purification. In this context, photocatalytic approaches to lignin valorization have begun to garner significant interest. Here we present a catalytic, light-driven method for the redox-neutral depolymerization of native lignin biomass at ambient temperature. This transformation proceeds via a proton-coupled electron-transfer (PCET) activation of an alcohol O–H bond to generate a key alkoxy radical intermediate, which then drives the β -scission of a vicinal C–C bond. Notably, this depolymerization is driven solely by visible light irradiation, requiring no stoichiometric chemical reagents and producing no stoichiometric waste. This method exhibits good efficiency and excellent selectivity for the activation and fragmentation of β -O-4 linkages in the polymer backbone, even in the presence of numerous other PCET-active functional groups.

ORGN 397

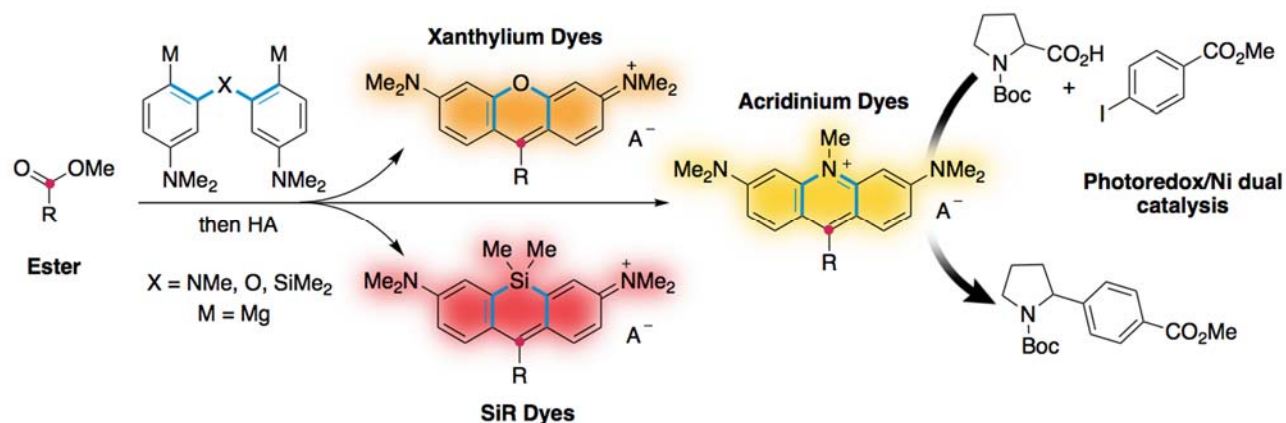
Water-soluble, organic fluorophores with powerful electrochemical and photophysical properties

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Small-molecule organic fluorophores are indispensable in material science, biological imaging and chemical synthesis. In order to cover the increasing demand for dyes with specific photophysical, chemical and electrochemical properties, synthetic approaches typically rely on the versatility of heterocyclic ring assembly. However, due to the incompatibility of the required reagents and conditions, established approaches frequently suffer from limitations in functional group tolerance needed for fine-tuning of the dye properties.

Hence, we envisioned that a double addition of 1,5-bifunctional organomagnesium reagents, such as 1,5-dimetallic dianilides, to a carboxylic acid ester would lead to the formation of a heterocyclohexadienolate intermediate which dehydrates upon acidic work-up to provide dyes with distinct heterocyclic cores and favorable photophysical properties within a single step.

The further development of this strategy led to the discovery of various unprecedented water-soluble organic fluorophores with powerful electrochemical and photophysical properties, capable of replacing expensive transition-metal based photocatalysts.



ORGN 398

Novel dioxolane mediated formylation of heteroarenes: Complementarity between photoredox and thermal conditions

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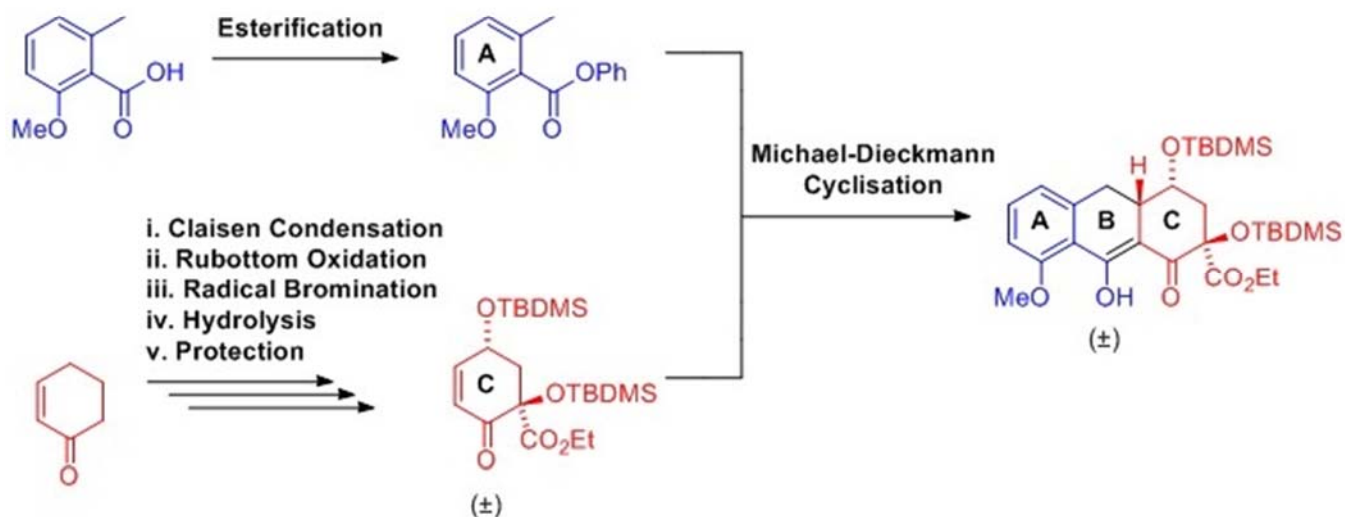
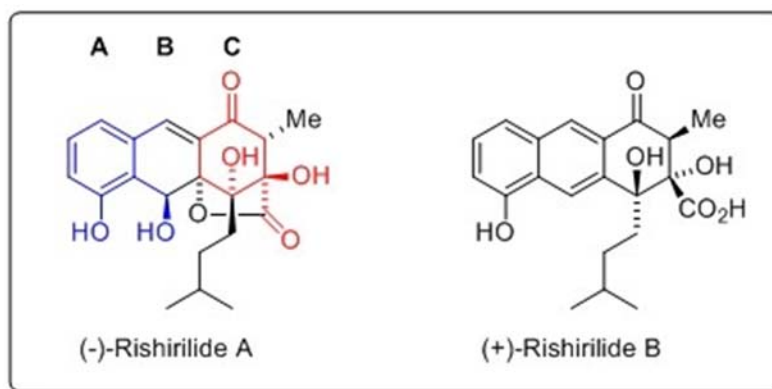
Photoredox catalysis has revolutionized C-C and C-X bond formation. The high functional group tolerance and versatility of these transformations make them directly applicable to elaborated compounds at the very late stage of the synthesis. Recently we demonstrated such utility for drug discovery with α -heteroarylation of N-protected secondary amines¹. We then envisioned a new protocol for the formylation of N-Heteroarenes under photoredox conditions first using 1,3,5-trioxane, thus showing also a broad substrate scope. During the course of these studies, the Merck group published a formylation methodology using trioxane under thermal conditions². The photoredox protocol was then extended further to dioxolane as a coupling partner allowing the subsequent formation of the formyl derivative under milder oxidative conditions compared to trioxane, therefore capitalizing fully on the functional group tolerance. Seeking broader impact in a drug discovery setting, the photoredox and thermal scope were compared, probed for complementarity yielding new conditions amenable to parallel synthesis.

ORGN 399

Michael-Dieckmann cyclisations in routes towards rishirilide A

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(-)-Rishirilide A and (+)-rishirilide B are two complex polycyclic natural products, originally isolated from *Streptomyces Rishiriensis* OFR-1056. Rishirilide B has been the focus of a number of synthetic efforts by Danishefsky, Pettus, Nagasawa and others. However the total synthesis of rishirilide A has yet to be achieved. Herein we present our efforts towards the synthesis of the fused tricyclic core of rishirilide A based on a key Michael-Dieckmann cyclisation.



Total synthesis of aspidosperma alkaloids utilizing a cascade Suzuki–Miyaura/Diels–Alder reaction

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Cascade reactions present a useful strategy in reaction design due to their ability to streamline chemical synthesis. The modularity with which complex molecules can be created by embedding downstream reactivity into small, simple precursors is an appealing strategy for chemists. Cascade reactions facilitate the use of reactive, non-isolable intermediates which can reduce step count and therefore lead to an overall increase in reaction efficiency. The Diels–Alder reaction is one of the most widely exploited reactions within cascade sequences in the synthesis of natural products. To this end, it was envisioned that a cascade reaction sequence could be employed in the total synthesis of Aspidosperma alkaloids. This family of alkaloids has been of significant interest to synthetic chemists, owing to their interesting topological structure and biological properties.

This work demonstrates the application of a Suzuki–Miyaura/Diels–Alder (SM/DA) cascade reaction in the synthesis of various Aspidosperma alkaloids. The SM/DA protocol allows the creation of the complex skeletal framework in a single reaction, which can then be subjected to a series of simple chemical manipulations to furnish a natural product library. The optimization of the SM/DA protocol will be presented, alongside showcasing the reaction through the shortest synthetic route to Aspidospermidine to date.

ORGN 401

Total synthesis of (–)-strictosidine

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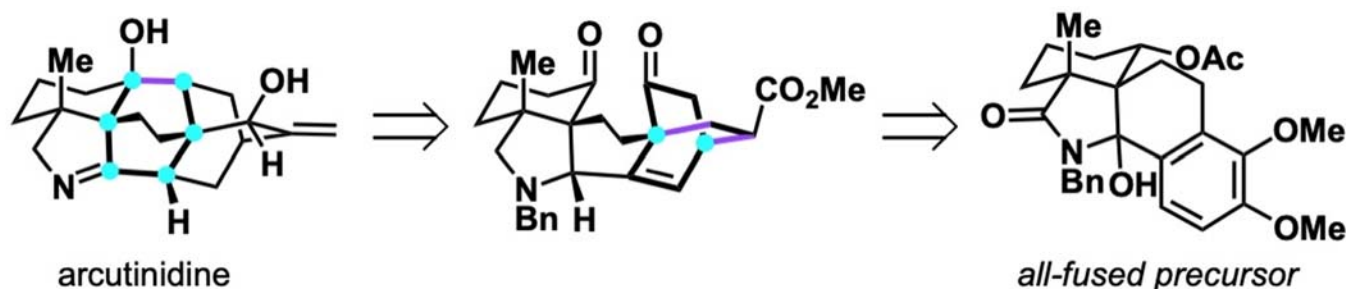
Monoterpene indole alkaloids (MIAs) are a large class of natural products with diverse and valuable medicinal properties. Thus far, over 3,000 structurally different MIAs have been isolated, all originating from the natural product strictosidine, the last universal biosynthetic precursor to all MIAs. This presentation will focus on our synthetic efforts toward accessing strictosidine. Specifically, the development of an inverse electron-demand hetero Diels–Alder reaction to build the core of the molecule and a late-stage enzymatic Pictet–Spengler reaction will be discussed.

ORGN 402

Application of chemical network analysis toward the total synthesis of arcutinidine

Shelby McCowen¹, shelby_mccowen@berkeley.edu, **Kyle R. Owens**¹, **Katherine Blackford**¹, **Sohei Ueno**¹, **Yasuo Hirooka**¹, **Manuel Weber**², **Richmond Sarpong**². (1) Chemistry, UC Berkeley, Berkeley, California, United States (2) Univ of California at Berkeley, Berkeley, California, United States

Bridged polycyclic natural products can display both useful bioactivities and interesting synthetic challenges. Bond-network analysis of a target molecule can guide the identification of strategic bonds, that when broken in a retrosynthetic sense, produces maximal simplification. We recently applied this topological analysis to develop the total synthesis of arcutinidine, a highly caged diterpenoid alkaloid. This translated in the forward sense to an intramolecular Diels–Alder cycloaddition to build the [2.2.2]bicyclic portion and a key SmI_2 -mediated pinacol coupling to forge the central maximally bridged six-membered ring. In addition, we developed an unprecedented oxopyrrolium Diels–Alder reaction to forge two vicinal all-carbon quaternary centers simultaneously. The synthesis was completed in 24 steps from known starting materials. The application of bond-network analysis in identifying strategies for the synthesis of other natural products will be discussed.



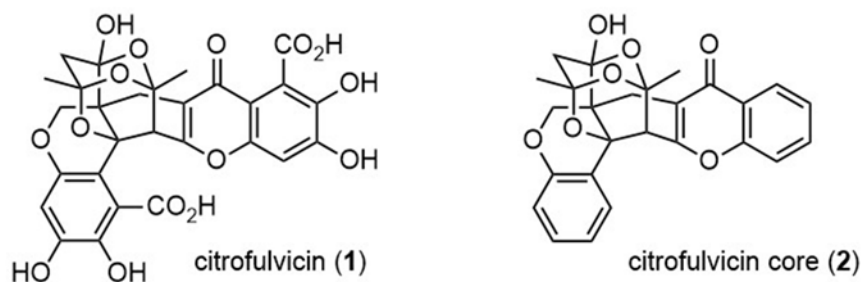
ORGN 403

Synthetic studies toward citrofulvicin

Kalina Doytchinova, kalinad@sas.upenn.edu, **Jeffrey D. Winkler**. Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States

Citrofulvicin (**1**) is a polyketide natural product recently isolated as a mixture of enantiomers from the *Penicillium velutinum* fungus, which shows antiosteoporotic activity against prednisolone-induced osteoporotic zebrafish. Its unprecedented skeletal framework features a 2,4,6-trioxaadamantane ring with two flanking aromatic rings with the same substitution pattern and its structure was confirmed by single crystal X-ray diffraction. Due to the inherent symmetry in the aromatic rings, a dimerization was envisioned to quickly build up the carbon framework, and an intramolecular acetalization to furnish the core trioxaadamantane ring. Current work is focused on a simplified model

system (2) to build up the core ring system of citrofulvicin, which will then be applied to the synthesis of this natural product.



ORGN 404

Synthesis and evaluation of novel ester derivatives of (+)-saxitoxin

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(+)-Saxitoxin (STX) is the archetype of a large family of tricyclic bis-guanidinium toxins commonly associated with red tides and infamous as the primary causative agent of toxicity in paralytic shellfish poisoning. STX targets voltage-gated sodium channels (Navs), transmembrane protein complexes responsible for the generation and propagation of action potentials, and binds to the extracellular pore to inhibit the passage of sodium ions into cells. The malfunction and mis-regulation of Navs is associated with several human pathologies including congenital insensitivity to pain and epilepsy. Thus, chemical tools for investigating Nav structure and function are highly desired to better understand these and other Nav-related diseases.

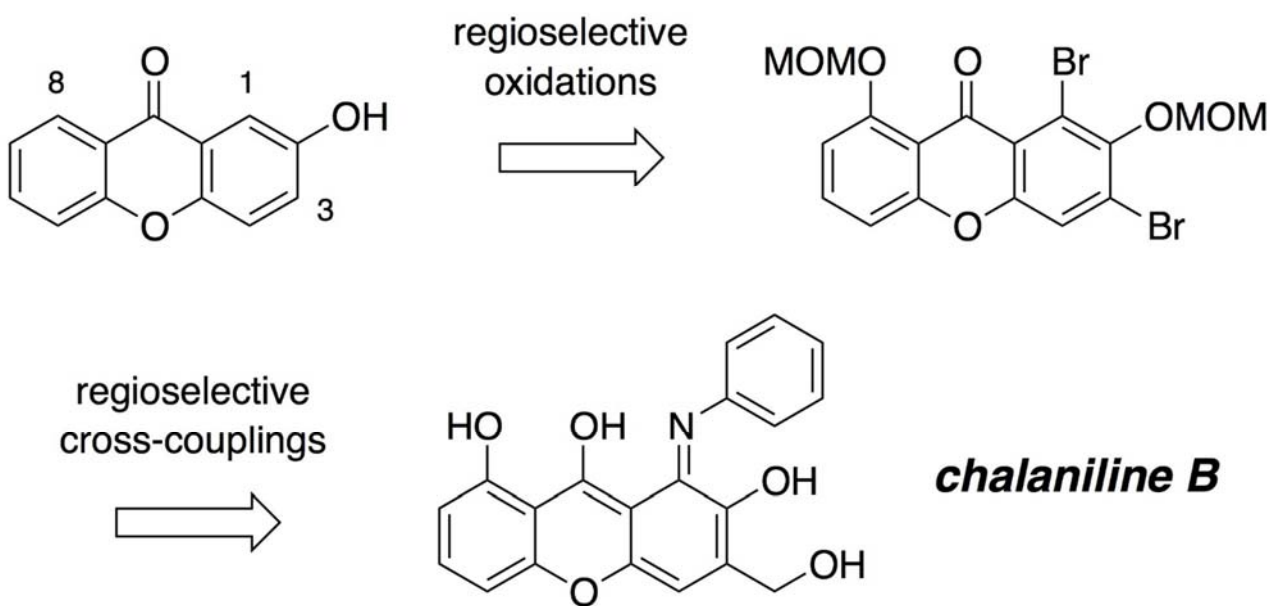
We have developed an efficient, step-economical synthesis of STX that enables access to natural and modified toxins, including ester derivatives that have not been previously prepared. Details of our improved route to these compounds will be presented along with results from electrophysiology studies. The latter reveal interesting structure-activity trends for toxin binding to different Nav subtypes.

ORGN 405

Total synthesis of chalaniline B: Antibiotic xanthone from epigenetically-treated endophytic fungus *Chalara*

Mahsa Khoshbakht¹, khoshbam@oregonstate.edu, **Bongkotrat Thanaussavadee**¹, **Yang Cao**¹, **Sandra Loesgen**², **Paul R. Blakemore**¹. (1) Department of Chemistry, Oregon State Univ, Corvallis, Oregon, United States (2) Whitney Laboratory for Marine Biosciences, University of Florida, St. Augustine, Florida, United States

Chalaniline B [2,8-dihydroxy-3-(hydroxymethyl)-1-(phenyl)aminoxanthone, CB] was identified by Loesgen and coworkers from an antimicrobial-bioassay guided fractionation of a culture of the endophytic ascomycete *Chalara* sp. 6661 that had been treated with the HDAC inhibitor vorinostat. In addition to activating the genes necessary to elicit production of xanthone CB, the epigenetic perturbation agent vorinostat was itself biotransformed and discovered to be the source of the anilino moiety found both within CB and another unusual xanthone (chalaniline A) that was also isolated. 1-Arylaminoxanthones represent a new chemotype and this fact, taken together with preliminary findings indicating that CB has moderate antimicrobial activity against a multidrug resistant *S. aureus* strain (ATCC BAA-44), prompted us to pursue a chemical synthesis. The development of a successful elaboration of CB from 2-hydroxyxanthone by a route incorporating strategic oxidations followed by regioselective introduction of nitrogen- and carbon-based moieties to the resulting 1,3-dibromo-2,8-dihydroxyxanthone derivative, will be presented and contrasted against alternate, and perhaps more obvious, approaches that failed. It is anticipated that the lessons learned from the total synthesis of CB will prove useful in the pursuit of analogous compounds for SAR and mode-of-action studies that may lead to the identification of antibiotics with heightened potency.

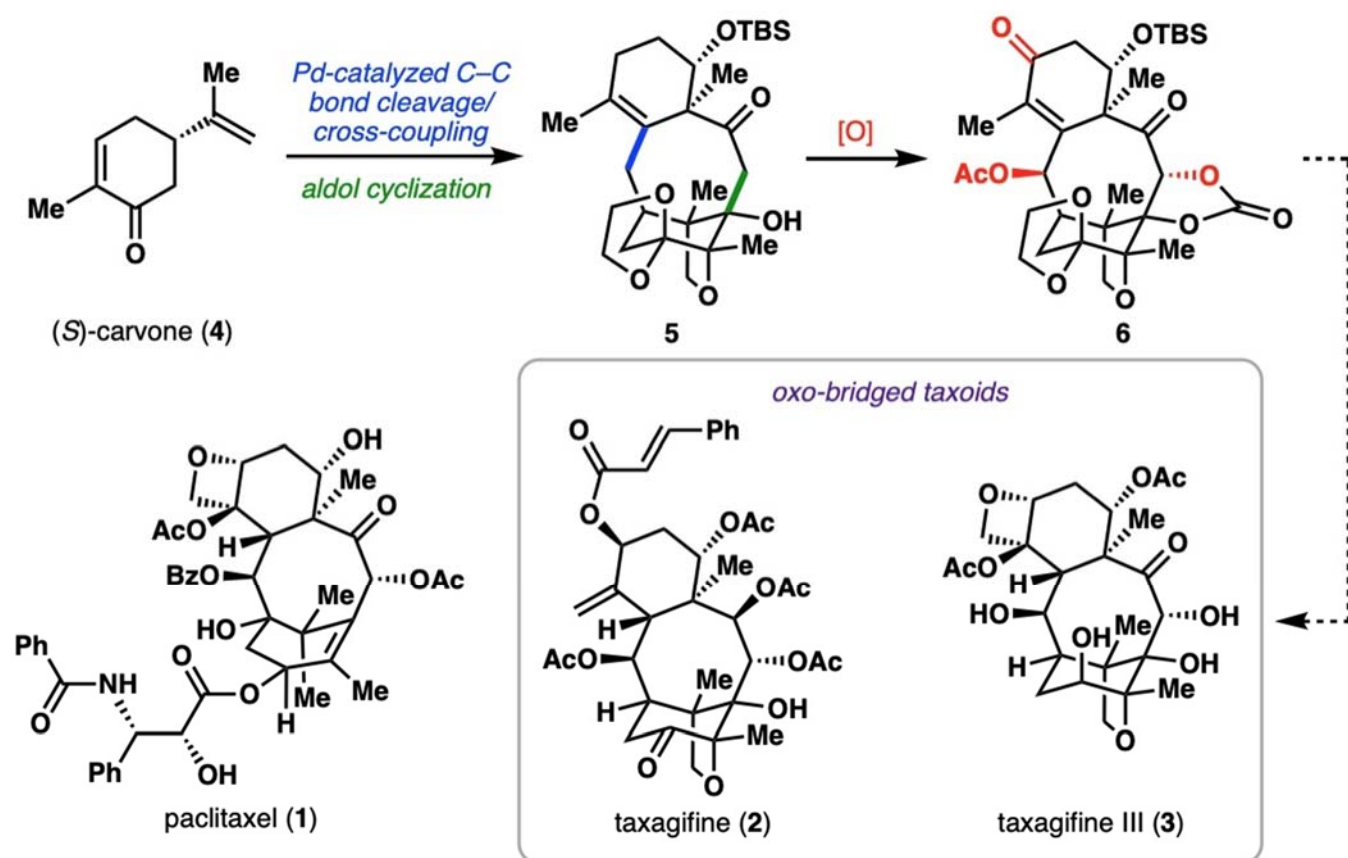


ORGN 406

Application of a C–C cleavage strategy for the total synthesis of taxoid natural products

Melecio Perea, *mperea@berkeley.edu*, **Brian S. Wang**, **Nicholas O'Connor**, **Shota Nagasawa**, **Benjamin Wyler**, **Richmond Sarpong**. Chemistry, University of California-Berkeley, Berkeley, California, United States

Cancer has become a prominent health crisis with millions of new cases diagnosed each year. In response, researchers have often turned to nature with the goal of discovering molecules, often structurally sophisticated, which can serve as viable therapeutics. The success of naturally occurring treatments has been evidenced by the widespread use of anti-cancer agents, such as paclitaxel (**1**). Paclitaxel belongs to the taxoid family of natural products, which are highly oxygenated diterpenoids isolated from Yew trees. While paclitaxel has proven its utility as a chemotherapeutic, emerging cases of cancer resistance have made it highly desirable to study other structurally diverse taxoids that may be used as alternative treatments. Herein we present recent progress toward the enantiospecific total synthesis of oxo-bridged taxoids, such as taxagifine (**2**) and taxagifine III (**3**), from (*S*)-carvone (**4**). Key features of this work include constructing the carbon skeleton (**5**) through a highly efficient Pd-catalyzed C–C bond cleavage/cross-coupling of two carvone-derived fragments followed by an intramolecular aldol cyclization to forge the central 8-membered ring. Additionally, we showcase the power of strategic oxidation tactics in elaborating this core to the fully oxygenated taxagifine skeleton (**6**).

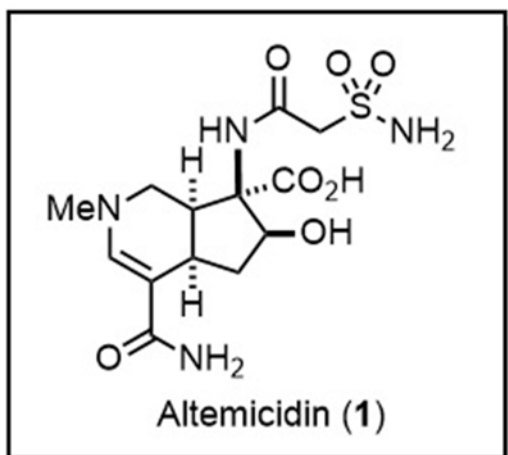


ORGN 407

Total synthesis of altemicidin

Genta Tadano¹, genta.tadano@shionogi.co.jp, **Keiji Tanino**². (1) SHIONOGI & CO., LTD., Toyonaka, Japan (2) Hokkaido University, Sapporo, Japan

Altemicidin (**1**), which was isolated from the *Actinomycete* strain *Streptomyces sioyaensis* SA-1758 by Takeuchi *et al.* in 1989, exhibits anti-brine shrimp activity as well as acaricide and antitumor activity. The total synthesis of altemicidin was accomplished on the basis of original strategy involving, (1) an intramolecular Mizoroki-Heck reaction of bromopyridine for the construction of the five-membered ring, and (2) the stereoselective partial reduction of methyl pyridinium salt leading to the hexahydro-6-azaindene skeleton.



ORGN 408

Total synthesis of clavatadine B

Stephen Chamberland, schamberland@uvu.edu, **Michael T. Davenport**, **Jordan A. Dickson**, **Matthew R. Johnson**. Department of Chemistry, Utah Valley University, Orem, Utah, United States

Chemists synthesize natural products to study their biological activity and architectural complexity. Guanidine-containing marine natural products exhibit antibiotic, anti-viral, anti-cancer, and anti-parasitic activity. Some act as peptide mimics and bind to the active sites of proteases. Serine proteases involved in blood coagulation are powerful targets for drug development to treat cardiovascular disorders such as thrombosis.

Two recently discovered aminoguanidine-containing marine natural products, clavatadine A and B, are specific inhibitors of coagulation factor XIa. Each alkaloid features a central carbamate moiety that is cleaved by a nucleophilic serine residue in the active site, as well as a linear aminoguanidine that increases their affinity to the active site through binding to an aspartate residue.

The first total synthesis of clavatadine B was completed by undergraduates and the PI at a teaching-intensive, primarily undergraduate institution. The principal synthetic challenge involved the disparate location of the aminoguanidine chain in clavatadine B in comparison with clavatadine A. Both molecules were conveniently prepared from 4,6-dibromohomogentisic acid lactone and the isocyanate derived from di-Boc agmatine. In practice, aminolysis of a protected 4,6-dibromohomogentisic acid lactone revealed the distal hydroxy group needed to unite both halves of the molecule in the key carbamate-forming step. The nearly identical chromatographic behavior of the aminolysis product and the carbamate required the development of a non-traditional method to separate

the carbamate from unreacted starting material. The entire synthesis required only one purification. Also notable was the fact that a primary amide survived and did not interfere with the final two reactions. An overall yield of 75% over four steps (longest linear sequence from known compounds) was achieved following global deprotection.

ORGN 409

Total synthesis of the brocazine and chemical diversification

*Wasundara Hulangamuwa¹, Casey House¹, Adam C. Ebert², Hawa Dembele², **Ryan Rafferty¹**, rjraff@ksu.edu. (1) Chemistry, Kansas State University, Manhattan, Kansas, United States (2) Biochemistry, Kansas State University, Manhattan, Kansas, United States*

Brocazines are natural products bearing a disulfide diketopiperazine core that was isolated by Meng et al in 2004 from an endophytic fungus derived from the marine mangrove plant *Avicennia marina* named *Penicillium brocae* MA-231. Six different brocazines (A-F) were isolated and of those brocazine F showed a strong activity against the prostate cancer cell line DU145 (IC₅₀ of 1.7 mM) and the lung cancer cell line NCI-H460 (IC₅₀ of 0.89 mM). Brocazine G was isolated two-year later, and also possessed anticancer activity. Given the potent cytotoxicity of brocazine F & G and its intriguing polycyclic core structure, our lab. has devised a total synthesis route to access this compd. To be presented is our route developed to gain access to brocazine F and G, biological evaluation (as sole agents and potentiation agents), and the development of a new targeted and designed chemical screening library to be used in the further investigations of charge location as a function of gram-negative bacteria porin mediated transport.

ORGN 410

Beyond total synthesis: Synthetic adventures in chemical screening library construction, therapeutic agent potentiation, and facilitated transport

*Prathibha Desman¹, Wasundara Hulangamuwa¹, Chamitha Weeramange¹, Thi Nguyen¹, Ashabha I. Lansakara¹, Johnathan Dallman¹, Hannah Henderson¹, Arnaldo Torres¹, Ashley Bartels², **Ryan Rafferty¹**, rjraff@ksu.edu. (1) Chemistry, Kansas State University, Manhattan, Kansas, United States (2) Department of Chemical Engineering, Kansas State University, Manhattan, Kansas, United States*

Natural products have been and continue to be the cornerstone in drug discovery. Either in the sole construction of therapeutic agents or as inspiration for the assembly of therapeutic scaffolds. Their role in the drug discovery process, while debated at times, continues to spark new innovation in therapeutic agent discovery. To this end, our laboratory focuses on the development of new synthetic routes towards bioactive and structurally intriguing natural products. To date we have accessed a new route towards the uvauretin class of natural products from which new chemical screening libraries have

been constructed. To be presented is this route and the biological evaluation of these library members, many of which have been found to possess strong potentiating properties with known therapeutics. Synthetic efforts towards the brocazone family of natural products will also be discussed, and the diversification of the advanced intermediates into new chemical screening libraries. The biological evaluation of these libraries, as sole agents and tools to understand gram-negative bacterial porin-transport will be presented.

ORGN 411

Discovering catalyst design rules for conjugated polymer synthesis

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Chemistry, University of Michigan, Ann Arbor, Michigan, United States

Fused-arene polymers are among the best-performing materials for organic electronics but are synthesized via methods that impart little control over molecular weight and dispersity. Methods that enable control over these properties, such as catalyst transfer polymerization (CTP), often fail to give polymer due to poorly understood off-cycle activity. The key to accessing fused-arene polymers via CTP therefore lies in identifying catalysts that minimize these off-cycle pathways. This work applies both computational reaction mechanism tools and experimental methods to avoid off-cycle reactivity, specifically by designing CTP catalysts for thienothiophene and other challenging monomers. Using these strategies, we observed unreported catalyst traps in thienothiophene polymerization and identified catalyst parameters that may enable polymerization of thienothiophene and similar monomers. We expect that this work will demonstrate the necessity of design strategies in expanding the scope of CTP and the importance of computational reaction mechanism tools in understanding organic processes.

ORGN 412

Tuning the twist in amide monomers for halide-rebound polymerization

Will Gutekunst, *willgute@gatech.edu*. Georgia Tech, Atlanta, Georgia, United States

Twisted amides have long been studied in physical organic chemistry due the unusual reactivity profiles that emerge from the reduced resonance interaction between the nitrogen atom and the neighboring carbonyl group. Our laboratory has recently leveraged the heightened nucleophilicity found in twisted amide structures to develop a new living polymerization that proceeds through a covalent electrophilic mechanism termed halide-rebound polymerization. This presentation will explore how remote substitution effects can be used to tune the geometric distortion of the amide, leading to significant changes in monomer nucleophilicity. In addition, halide and solvent effects on the polymerization reaction will be highlighted as a means to further tune monomer reactivity and alter the rate-limiting steps of the halide-rebound process. Through

greater understanding of the polymerization mechanism through kinetic studies and computational prediction of the ground state geometries, new monomers with enhanced performance have been designed to improve the livingness of the polymerization and increase solubility of the final materials.

ORGN 413

C-H functionalization: Viable route to materials

Colleen N. Scott, *cogst5@hotmail.com*, **Chathuranga Rathnamalala**, **Ishanka Rajapaksha**, **Daijun Feng**. Chemistry, Mississippi State University, Carbondale, Illinois, United States

The grand challenge for the efficient synthesis of known compounds and the development of new and interesting compounds using C-H functionalization reactions continue; specifically when the compounds to be synthesized are material focused. However, C-H functionalization is useful for the construction of new materials that are otherwise difficult to synthesize because the substrates are not compatible with the conventional reaction conditions. Also, C-H functionalization has been demonstrated to be a very useful technique for the synthesis of materials for organic devices such as OFETs, OLEDs, and OPVs. However, very few studies have been done to investigate the use of C-H activation reaction to prepare fluorescent dyes. Consequently, our group has been investigating the use of C-H activation reaction to prepare NIR fluorescent dyes for application as biosensors, and in deep tissue imaging. In this presentation, we describe our design rationale for a series of new water-soluble NIR dye that is readily accessible by the C-H activation reaction. These dyes have absorption and emission wavelengths between 700 nm – 1100 nm, are photostable and have moderate to good quantum efficiency.

Additionally, C-H functionalization has been demonstrated in the post-modification of commodity products to change their properties. However, our group has been investigating the use of C-H activation chemistry to post functionalized high-performance materials to discover new high-performance materials. C-H borylation is used to functionalize high-performance lubricants to convert them to high-performance sealants. We will discuss the properties of these materials in this presentation.

ORGN 414

Design and study of bifunctional catalytic systems for polyester synthesis via the alternating ring-opening copolymerization of epoxides and cyclic anhydrides

Claire Lidston, *lidstonc@gmail.com*, **Brooks A. Abel**, **Geoffrey W. Coates**. Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York, United States

Advances in catalytic methods have facilitated the ring-opening copolymerization of epoxides and cyclic anhydrides to afford aliphatic and semi-aromatic polyesters. By making use of commercially available, bio-renewable, and readily synthesized

monomers, epoxide/cyclic anhydride ring-opening copolymerization accesses structurally and functionally diverse polyesters with tunable thermomechanical properties. Unlike traditional step-growth approaches, this chain-growth strategy achieves atom economy, controlled molecular weight, and low dispersity. The most successful catalyst systems employ a metal salen complex in conjunction with a nucleophilic cocatalyst to initiate polymerization and control monomer enchainment. Yet current catalyst/cocatalyst systems typically require high loadings and are prone to transesterification and epimerization side reactions that degrade the polymer backbone. Recent efforts in catalyst development have afforded a bifunctional ring-opening copolymerization catalyst that maintains excellent activity at low concentrations. This strategy of tethering the catalyst and cocatalyst not only preserves catalytic activity under formerly unproductive conditions, but also controls chain-end reactivity to suppress deleterious side reactions. The bifunctional catalyst system thus affords desirable polyester materials with improved efficiency and fidelity.

ORGN 415

Building block strategies to functional polymers

Rebekka S. Klausen, *klausen@jhu.edu*. JHU/Chemistry Dept., Baltimore, Maryland, United States

This talk describes strategic synthetic approaches to fundamentally new materials with transformative potential, as well as methods to refine advanced materials through an understanding of structure-property-performance relationships. Key topics include (1) the design and synthesis of poly(cyclosilane)s, conjugated polymers inspired by the semiconductor crystalline silicon, and (2) the discovery of an innovative synthetic platform to poly(vinyl alcohol)s with atomic-level control of composition, sequence, and stereoregularity.

ORGN 416

Organoborane strategy for polymers bearing lactone, ester, and alcohol functionality

yuyang Ji, *yji14@jhu.edu*, *Rebekka S. Klausen*. JHU/Chemistry Dept., Baltimore, Maryland, United States

Vinyl acetate (VAc) is the traditional precursor to hydroxyl-functionalized polymers by radical polymerization and hydrolysis. However, VAc exhibits poor reactivity and copolymerization behavior due to the unstabilized radical intermediate, which limits the scope and versatility of poly(vinyl alcohol)s (PVA). Here, we will discuss an organoborane strategy using BN 2-vinylnaphthelene (BN2VN) as a comonomer with methyl methacrylate (MMA). BN2VN oxidation results in an unprecedented structure bearing MMA and lactone residues due to rapid lactonization of VA-MMA. Methanolysis

returns a copolymer bearing an equilibrium distribution of alcohol, lactone, and ester functional groups.

ORGN 417

Radical cascade-driven polymerization

Jia Niu, *jia.niu@bc.edu*. Chemistry, Boston College, Chestnut Hill, Massachusetts, United States

Cascade reaction is a chemical process in which one reaction sets off a chain of other reactions in a thermodynamically down-hill process. Cascade reactions have been widely used in the synthetic organic chemistry to rapidly increase the structural complexity of the resultant product in high atom economy. While a well-established concept in small molecule synthesis, cascade reactions were not applied to macromolecular synthesis until recently. In this presentation, I will discuss a new concept of radical cascade-driven polymerization, allowing the access of unprecedented polymer structures while maintaining good control over polymerization. First, a novel chain-growth, radical cascade-triggered ring-opening polymerization (RCT-ROP) approach for the rapid and controlled polymerization of macrocyclic monomers will be discussed. A systematic study correlating various designs of the ring-opening trigger and polymerization control were designed to allow optimized reaction kinetics and polymerization control. The optimized conditions were then employed to prepare multi-block copolymers with predefined block sequences and main-chain degradable functionalities. The discussion will be further extended to a radical cascade ring-closing polymerization, or cyclopolymerization. A consecutive ring-closing/ring-opening cascade polymerization will then be discussed to generate polymers with complex main-chain structures. In summary, the application of the cascade reactions to the polymer science provides new synthetic strategies for complex polymers that are inaccessible by previous techniques, laying the foundation for the generation of a series of novel polymers including biomimetic materials and sustainable polymers.

ORGN 418

Controlled radical polymerisation using high frequency ultrasound

Joe Collins¹, *joecol@mit.edu*, **Thomas G. McKenzie**², **Greg G. Qiao**². (1) MIT, Cambridge, Massachusetts, United States (2) University of Melbourne, Melbourne, Victoria, Australia

High frequency ultrasound (>200 kHz) has emerged as a new way to initiate and control radical polymerisations without the need for conventional initiators or additives. Through the sono-chemical generation of solvent-derived radicals, controlled polymerisation can be achieved via atom transfer radical polymerization (sonoATRP) and reversible addition-fragmentation chain-transfer (sonoRAFT) polymerization. By optimising the reaction conditions, sonochemically-controlled polymerisations were found to be well

controlled with the prepared polymers displaying good agreement between theoretical and experimental molecular weights, with low dispersity's and good temporal control. Interestingly, several factors were found to influence the polymerisation kinetics and resulting polymer properties such as the monomer vapor pressure and solubility, the solvent choice, and the polymer type. Overall, high frequency ultrasound is emerging as a powerful technique for the external control of radical polymerisations.

ORGN 419

Polymer mechanochemistry: Constructive approach

Jeung Gon Kim, jeunggonkim@jbnu.ac.kr. Department of Chemistry, Jeonbuk National University, Jeonju, Korea (the Republic of)

Mechanochemical reactions, chemical reactions that are induced by the direct absorption of mechanical energy, are promising methods to break and form chemical bonds. Beyond an alternative to thermo-, photo-, or electrochemical activation methods, mechanical-force-driven chemical synthesis can show unexpected reactivity and selectivity, which conventional approaches cannot achieve. Moreover, the exclusion of solvents reduces processing costs and minimizes environmental effects. While many areas of chemistry have enjoyed the merits of mechanochemistry, it has been unexplored in polymer synthesis. Applying mechanical stress on polymeric materials has been regarded to cause degradation. Recently, we started to pursue the use of mechanical force for the construction of macromolecules and a mechanochemical polymerization of lactide is developed using ball milling. Mechanical energy from the collisions between the balls and the vessel efficiently promoted an organic-base-mediated metal- and solvent-free solid-state polymerization. Also, solid-state post-polymerization modification and synthesis of block copolymers were achieved by means of mechanochemistry as well. The current status of mechanochemical polymer synthesis by our research team will be presented.



Mechanochemical Ring-Opening Polymerization of Lactide

- Metal Free
- Solvent Free
- High Molecular Weight



ORGN 420

Application of the seleno-Pummerer reaction to the construction of β -mannosides: Synthesis of the *K. pneumoniae* tetrasaccharide antigen

Yong Guan, Steven D. Townsend, steven.d.townsend@vanderbilt.edu. Chemistry, Vanderbilt University, Nashville, Tennessee, United States

The development of efficient glycosylation methods is critical for further advances in the assembly of complex carbohydrates. A new coupling procedure, that leverages the seleno-Pummerer reaction, is described for the construction of the challenging 1,2-cis glycosidic (β -mannoside) bond.

ORGN 421

Slaying superbugs one natural product at a time

William M. Wuest, wwuest@emory.edu. Chemistry, Emory University, Atlanta, Georgia, United States

The importance of natural products as starting points for antibiotic compounds is undisputed. In contrast to conventional broad-spectrum agents, the development of narrow-spectrum, pathogen-specific antibacterials would be of interest to the medical community serving as novel therapeutics and also to microbiologists as chemical probes to deconvolute complex bacterial communities. The talk will highlight our recent efforts in the diverted total syntheses of narrow-spectrum natural products and elucidation of their mechanisms of action which provide insight into their selectivity and potential for future development.

ORGN 422

Microbial synthesis of antibiotics and virulence molecules

Jon B. Patteson, Gina L. Morgan, Bo Li, elysee.libo@gmail.com. Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

Microorganisms conduct remarkable chemistries to synthesize unique, bioactive natural products. I will discuss our work on identifying and understanding the pathways that transform single amino acids into antibiotics and virulence factors. We characterized pathways for two different types of molecules, methoxyvinylglycine, a nonproteinogenic amino acid antibiotic, and (dihydro)pyrazine N -oxides, molecules made by a bacterial virulence pathway. Both biosynthetic pathways require unusual nonribosomal peptide synthetases and non-heme iron-dependent oxygenases. These enzymes catalyze novel

chemistry and could serve as tools for natural product engineering and synthetic biology.

ORGN 423

Adventures in the synthesis of antimicrobial natural products

Joshua G. Pierce, *joshuapierce6@me.com*. Dept of Chemistry, NC State University, Raleigh, North Carolina, United States

Natural products have historically been the main source of new antibiotics and there is an urgent need for new discoveries in this regard. This talk will discuss our efforts to develop creative and efficient approaches to complex natural products that have displayed promising antimicrobial activity. Through these efforts we aim to reveal new chemical reactivity and enable structure-activity studies often for the first time.

ORGN 424

New antibiotics from old natural products

Ian Seiple, *ian.seiple@ucsf.edu*. Pharmaceutical Chemistry, UC San Francisco, San Francisco, California, United States

Thousands of natural products have been discovered that possess potent antimicrobial properties. The vast majority of these natural products did not evolve in human hosts, and thus have not been evolutionarily selected to have desirable therapeutic properties as human drugs. While semisynthetic approaches have provided a repertoire of classes of antibiotics suitable for human use, many other classes have yet to reach their potential. Additionally, clinical resistance has been documented for every marketed class of antibiotics. By developing new chemistry for the assembly of known antibiotic scaffolds, we have been able to overcome several of the limitations that nature left behind, improving known antibiotics and opening the door to new classes.

ORGN 425

Novel compounds towards overcoming resistance in tuberculosis

Sylvie Garneau-Tsodikova, *sylviegtsodikova@uky.edu*. Pharmaceutical Sciences, University of Kentucky, Lexington, Kentucky, United States

Tuberculosis (TB) is a deadly global infection that has recently surpassed HIV/AIDS. ~250,000 of >1 million deaths were from multidrug-resistant (MDR) TB, with only ~50% success in treatment of MDR-TB. Unless new strategies to combat or prevent emergence of drug-resistant TB are found, the global spread of MDR-TB will be an epidemic of epic proportions. Kanamycin A (KAN) is an antibiotic of last resort used to treat MDR-TB. Resistance to KAN signifies extensively drug-resistant (XDR) TB, which

is nearly incurable. One-third of KAN-resistant TB is caused by upregulation of the acetyltransferase Eis in *Mycobacterium tuberculosis* (*Mtb*), caused by mutations in the *eis* promoter. We investigated the mechanism of Eis and discovered and validated several Eis inhibitor scaffolds. In this presentation, the discovery and development of compounds to combat tuberculosis will be presented: (1) new Eis inhibitors as KAN adjuvants, and (2) new stand-alone agents active against *Mtb*. Medicinal chemistry optimization, activity, structural, and preliminary animal studies will be presented.

ORGN 426

Winners and losers in early stage antifungal drug discovery

Michael K. Brown, brownmkb@indiana.edu. Department of Chemistry, Indiana University, Bloomington, Indiana, United States

Discovery of new drugs to treat *Cryptococcus neoformans* infections is one of the most important unmet objectives in clinical mycology. Described here are our efforts towards trying to meet this need through the synthesis of two natural products, hippolachnin A and hippolide J that are reported to be active against this fungal strain. In addition to the promising biological activity, the structures of these molecules have required the development of innovative strategies and methods. The synthesis and biological evaluation of these molecules are discussed.

ORGN 427

Total synthesis of natural product antibiotics

Sarah E. Reisman, reisman@caltech.edu. MC 101-20, California Institute of Technology, Pasadena, California, United States

Since the discovery of the antibiotic penicillin, natural products—small molecules isolated from plants, bacteria, and fungi—have played an essential role in the development of new anti-infectives. Synthetic organic chemists can use Nature's molecules as a starting point, and perform precise molecular edits to make new molecules with improved properties or efficacy. Although semi-synthesis has given rise to the vast majority of natural product-derived antibiotics, total synthesis can provide opportunities to prepare new derivatives not accessible through semi-synthesis. This seminar will describe recent efforts in our laboratory focused on the synthesis of natural product antibiotics.

ORGN 428

Selective catalytic reactions in complex molecular scaffolds

Scott J. Miller, scott.miller@yale.edu. Yale University, Dept of Chemistry, New Haven, Connecticut, United States

This lecture will describe recent developments in our efforts to develop catalysts for asymmetric reactions, in particular for the preparation of densely functionalized, stereochemically complex structures. Over time, our foci have been on enantioselectivity, site-selectivity and chemoselectivity. In much of our current work, we are studying issues of enantioselectivity as a prelude to extrapolation of catalysis concepts to more complex molecular settings where multiple issues are presented in a singular substrate. Moreover, we continuously examine an interplay between screening of catalyst libraries and more hypothesis-driven experiments that emerge from screening results. Some of the mechanistic paradigms, and their associated ambiguities, will figure strongly in the lecture. The catalysts themselves most often emerge from amino acids and peptides, as illustrated in the accompanying graphic.

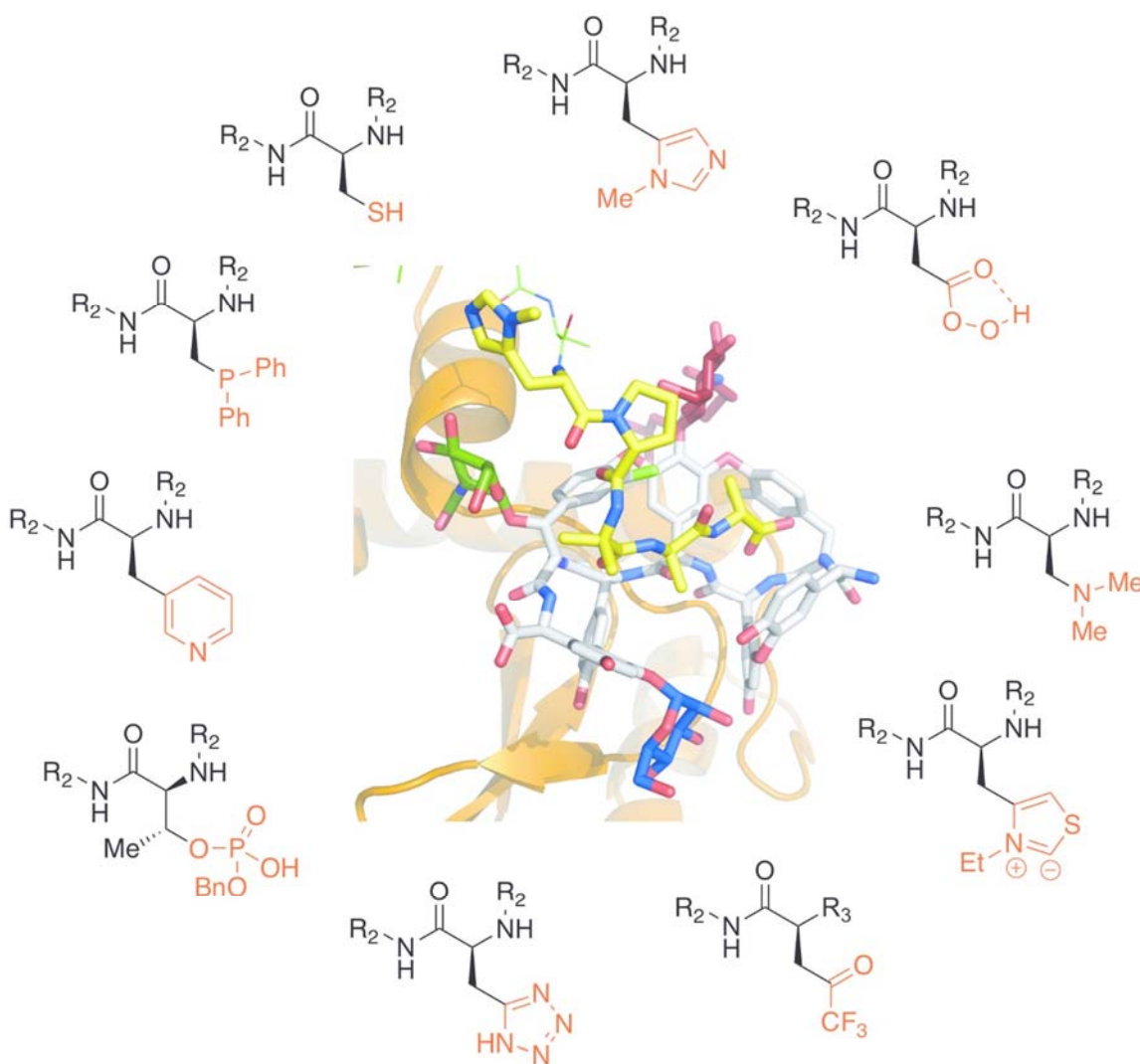


Figure 1. Survey of several catalyst chemotypes under study in our lab with a catalyst-substrate complex in the middle of the graphic.

ORGN 429

Total biosynthesis of plant-derived therapeutics

Elizabeth Sattely, *sattely@stanford.edu*. Stanford University, Stanford, California, United States

Molecules from plants play a critical role in human health as clinically-used therapeutics and dietary nutrients. Notably, 10% of the WHO essential medicines are plant natural products or derivatives (e.g., etoposide, taxol, digoxin, and vinblastine), and the food we eat contains abundant drug-like molecules from plants. Despite the major impact of plant chemistry on human health, numerous drugs are still isolated from difficult-to-cultivate native plants or plant cell culture and the chemistry of dietary crops is poorly understood and unoptimized. Engineering plant biosynthetic pathways in an exciting strategy for transforming how we use plant chemistry. The central challenge is identifying the genes that make up plant metabolic pathways without genetic tools or genome sequence in the producing plant. Our lab is focused on accelerating the discovery of both biosynthetic pathways in plants and plant natural product mechanism of action, and along the way we are developing new tools for engineering plant chemistry. In this talk, I will discuss recent advances in my lab that have allowed us to rapidly identify sets of enzymes that can be used to engineer the production of plant molecules of importance to human health.

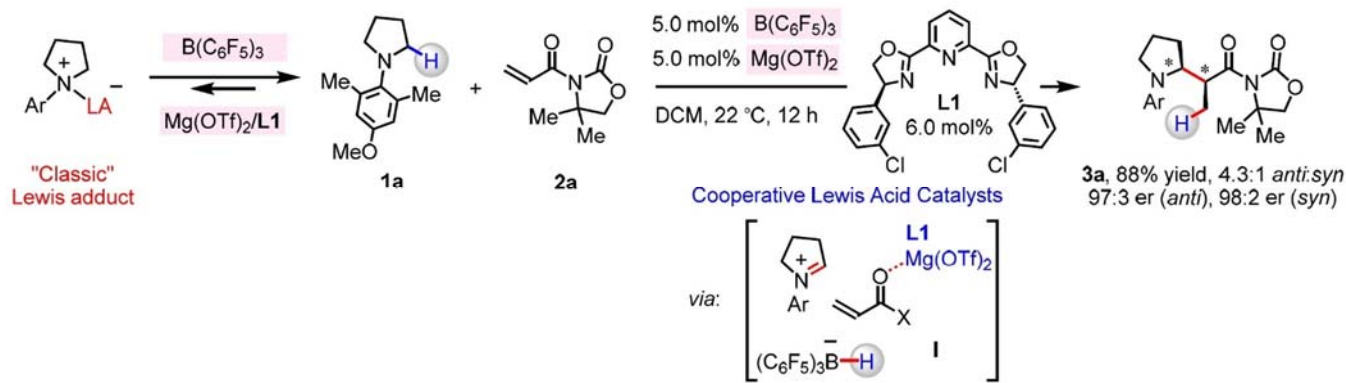
ORGN 430

Recent advances in enantioselective cooperative catalysis

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We have designed an enantioselective coupling of N-alkylamines and α,β -unsaturated compounds by implementing the cooperative action of two Lewis acid catalysts that possess overlapping functions. We have achieved this by developing catalyst/substrate combinations that form frustrated Lewis pairs (FLPs), namely, active acids and bases whose mutual quenching (formation of "classic" Lewis adduct) is sterically precluded. By tuning of different features of structurally and electronically different Lewis acids and substrates, the ability of Lewis acid catalysts to serve as a hydride acceptor from amines, or an activator of α,β -unsaturated compounds towards borohydride reduction to afford a chiral enolate, can be adjusted. Accordingly, enhancements in both the efficiency and stereoselectivity of C–C bond forming reactions between amines and α,β -unsaturated compounds can be attained without concomitant loss in enantioselectivity arising from any undesirable mode of catalysis by the achiral Lewis acid component. These principles serve as a conceptual

framework for the development of new processes that demand separate and independently operational Lewis acidic co-catalysts whose functions might overlap and the simultaneous use may have a negative impact on enantioselectivity.



ORGN 431

Enantioselective synthesis with Cu-based catalysts and organoboron compounds

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Design and development of new ligands, catalysts, strategies, and methods for enantioselective reactions that are promoted by a Cu-based catalyst and where an organoboron compound plays a central role will be presented. The rationale behind selection of the problems to be addressed, and the mechanistic basis regarding why the new catalysts are uniquely effective, as well as the application of such transformations to expeditious and practical total syntheses of complex bioactive molecules will be detailed.

ORGN 432

Synthesis of glucosinolates via the nitronate pathway

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Diets rich in *Brassica* vegetables provide a variety of anticancer benefits, largely due to the presence of glucosinolates, β -thioglucoside-*N*-hydroxysulfates, which are abundant in the plants. The action of the enzyme myrosinase on glucosinolates evolves biologically-active isothiocyanates (ITCs), cellular electrophiles which are believed to be partially responsible for the anti-cancer properties of these vegetables. The non-natural ITCs 4-(methylsulfinyl)benzyl ITC and 3-pyridylmethyl ITC have been shown to be potent inducers of antioxidant response element (ARE) promoted genes. Since myrosinase is known to be tolerant of non-natural glucosinolate substrates, this study describes efforts to utilize the nitronate synthetic pathway toward the preparation of four non-natural glucosinolate precursors related to these target ITCs: 4-(methylthio)benzyl glucosinolate, 4-(methylsulfinyl)benzyl glucosinolate, 4-(methylsulfonyl)benzyl glucosinolate, and 3-pyridylmethyl glucosinolate.

ORGN 433

Synthesis of an intermediate towards the total synthesis of the potential cytotoxic agent Callyspongamide A

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Marine organisms have been known to be a source of polyacetylenic compounds which have shown biological effects ranging from anti-inflammatory to anticancer activity. Callyspongamide A, a long, linear polyacetylenic amide, was extracted from *Callyspongia fistularis*, found in the Red Sea. Less than three milligrams were isolated, which was enough only for structural elucidation and biological testing against HeLa cancer cells. Despite its moderate cytotoxicity against HeLa cells our research group became interested in testing Callyspongamide A against different cancer cell lines and search for other possible biological activities of this unusual polyacetylenic amide. Extraction of significant quantities of Callyspongamide A from sponges is not practical, which makes the total synthesis of this natural compound the best alternative. Retrosynthetic analysis of its structure calls for the protection of a nine-carbon haloalkyl alcohol and a five-carbon acetylenic alcohol with different protecting groups, coupling of both moieties through lithium-mediated alkyne alkylation, sequential deprotection of one of the alcohols with subsequent oxidation to carboxylic acid and coupling to phenethylamine to finish one "half" of the molecule. Deprotection and controlled oxidation of the second alcohol to an aldehyde, followed by Stork-Zhao olefination and acetylene alkylation would yield Callyspongamide A. This presentation reports the current state of this total synthesis, where the intermediate monoprotected alkynol 14-((2-methoxyethoxy)methoxy)tetradec-4-yn-1-ol was synthesized with good yield and characterized through NMR spectrometry. Next steps involve the planned final synthetic reactions and establishment of the synthetic methodology for the preparation of analogs to explore structure-activity relationship.

ORGN 434

Synthesis and antibacterial evaluation of analogs of a new natural product of interest, denbinobin

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Antibiotic resistance is a serious and growing threat to human health. The increase in the number of resistant bacteria in recent years has been exacerbated by a decades-long lull in new antibiotic development. Accordingly, the rapid development of novel antibacterial compounds is vital to combatting antibiotic resistant bacteria. This study represents an initial investigation of the potential antibacterial properties of derivatives of denbinobin, a phytochemical and known cytotoxin produced by members of the family Orchidaceae. Precursor analogs of denbinobin were produced in house in accords with a seven-step denbinobin synthesis featuring a Claisen-Schmidt reaction. Analogs were evaluated for activity against a panel of Gram-positive and Gram-negative bacteria via standard broth microdilution assays. Screened derivatives include acid and methylester stilbenoid compounds. The results of this study serve to guide the field of novel antibiotic development towards a new natural compound of interest.

ORGN 435

Evaluation of the antibacterial activity of simplified synthetic analogs of pestalone

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Antibiotic resistance is one of the largest public health issues to date. One of the ways to combat antibiotic resistance is to create structurally unique antibiotic compounds with novel mechanisms of action. One such novel compound is Pestalone, a natural product produced from the co-culture of a deep-sea marine bacterium and fungus. Although potent against methicillin-resistant *Staphylococcus aureus* (MRSA) and other resistant bacteria, natural product isolation of Pestalone is difficult and previous syntheses has been low-yielding. This research focuses on the creation of simplified analogs of Pestalone that can be synthesized in 3-5 reactions. Typical overall yield for each 3-5 step synthesis ranges from 65%-99%. To date, nine simplified analogs of Pestalone have been synthesized and eight have been evaluated for antibacterial activity against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli*. Four of these eight analogs have shown antibacterial activity, with two showing activity against *S. aureus* and one showing activity against *E. coli*.

ORGN 436

Synthesis and antibacterial evaluation of pseudopyronine analogs

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As strains of drug resistant bacteria become more common, it is becoming increasingly necessary to synthesize novel compounds to overcome known resistance mechanisms. Natural products remain a robust source of novel bioactive molecules. One such family of natural products are the pseudopyronines, which are α -pyrone natural products isolated from *Pseudomonas* species of bacteria. This work derivatizes the α -pyrone core of short chain pseudopyronine analogs to probe the effects of electronegativity on antibiotic activity against *Escherichia coli*. All reactions were carried out over three steps in 74-86% yields, and used flash chromatography to purify crude reaction mixtures. Once complete, NMR and IR spectroscopy were used in order to verify the structural identity of each analog. Each analog was then tested for antibiotic activity against a panel of Gram-negative and -positive pathogens.

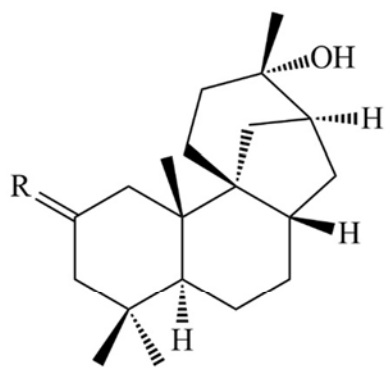
ORGN 437

Synthesis of novel rearranged stemodane diterpenoids and their biotransformation by *Exophiala lecanii-corni*

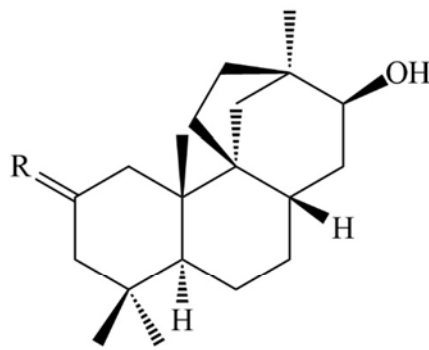
Ricaldo Pryce¹, ricaldo.pryce@mymona.uwi.edu, **Paul B. Reese**². (1) The Department of Chemistry, The University of the West Indies, Kingston, Kingston, Jamaica (2) Department of Chemistry, University of the West Indies, Kingston, Jamaica

Stemodin (**1**) is a biologically active natural product from *Stemodia maritima*. The compound possesses cytotoxic and antiviral properties and can be obtained in relatively large quantities from the plant. Stemodinone (**2**), also isolated from *S. maritima* (albeit in lower quantities), can be generated by simple oxidation of **1**. In the presence of aqueous acid, **2** undergoes solvolytic rearrangement to form 15(13→12)abeo-13 β -hydroxystemaran-2-one (**3**) and 15(8→9)abeo-8 β (H)-12 β -hydroxystachan-2-one (**4**). The skeleton of **3** is similar to that of the scopadulanes, which inhibit the porcine H⁺, K⁺-ATPase enzyme, and possess antitumour and antiviral activities against the *Herpes simplex* virus type 1. These natural products also interfere with the nutrient transport of the malarial parasite *Plasmodium falciparum*. The biological activity of compounds bearing the skeleton of **4** have not been explored.

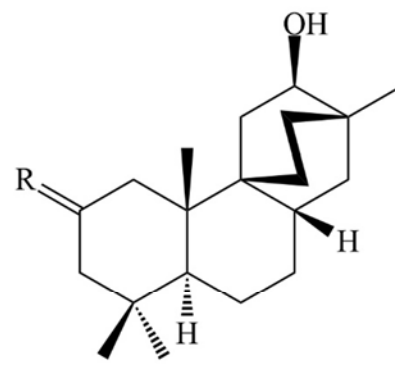
Diterpene **2** is readily chemically converted to analogues **5** and **6**. The solvolyses of **1**, **5** and **6** were carried out in order to generate similar products of rearrangement. These analogues served as substrates for transformation by the fungus *Exophiala lecanii-corni*. The aim is the production of a series of novel compounds for bioassay. *E. lecanii-corni* has previously been exploited as a catalyst for steroid biotransformation. However, its potential for microbial functionalization of terpenes is yet to be investigated.



1 R= α OH, β H
 2 R= O
 5 R= β OH, α H
 6 R= H₂



7 R= α OH, β H
 8 R= O
 9 R= β OH, α H
 11 R= H₂



8 R= α OH, β H
 9 R= O
 10 R= β OH, α H
 12 R= H₂

ORGN 438

Synthesis and characterization of nitric oxide donating poly(ester)s

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 Central Michigan Univ, Mount Pleasant, Michigan, United States

Nitric oxide (NO) is an extremely important signaling molecule, that has a variety of functions in multiple systems such as cardiovascular, immune, and nervous systems. Nitric oxide releasing compounds are of great therapeutic interest as a possible exogenous source of NO in the treatment of a variety disease-states associated with a shortage of *in vivo* production. The use of polymers, more specifically poly(ester)s in drug delivery applications has been a highly researched subject due to their mechanical strength and biodegradation via hydrolysis. Reported herein is the preparation of eight poly(ester)s with varied repeat units containing a secondary amine *ortho* to a nitro group. Various polymers were prepared using two diols, that differ by number of carbons between a secondary amine and terminal alcohol. After purification, each diol underwent polymerization with one of four diacid chlorides. After synthesis and purification of each poly(ester) the secondary amine was subjected to nitrosation, in order to obtain NO-release profiles. The poly(ester)s were also treated with lipase in an aqueous solution to observe if hydrolysis of the ester linkage took place.

ORGN 439

Cross metathesis labeling with fluorescent probes for the identification and quantitation of unsaturated lipids

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The position of carbon-carbon double bond(s) in fatty acid lipid molecules crucially affects their structure, reactivity, biological function and nutritional value. The accurate identification of double bond(s) position within lipid molecules has been investigated using a variety of specialized mass spectrometric techniques, but many limitations remain, particularly for rare and unusual lipids, and there is a great potential for approaches that involve a derivatization step prior to detection and analysis. Our work has focused on developing a simple, rapid, and reliable technique based on a cross metathesis approach for derivatizing double bond(s) in unsaturated lipids. We utilize a highly reactive allyl sulfone group conjugated to a hydrazinylpyridine-derived triazaborolopyridinium fluorescent probe (HPY-dye) that undergoes efficient cross metathesis with unsaturated lipid substrates, generating unique signature fluorescent fragments that are analyzed on HPLC/MS. The unsaturated fatty acid components yield corresponding labeled "HPY-head groups" and aliphatic "HPY-tails" as products suitable for optical chromatographic detection due to their strong absorption of UV light, and accurate mass analysis due to their characteristic boron isotopic pattern. Double bonds in long chain mono-unsaturated fatty acids are readily and unambiguously identified. Convenient identification of omega-3, omega-6 or omega-9 fatty acids were possible with this approach analyzing the aliphatic products from labeling at the terminal double bond position. This methodology was successfully applied to the omega fatty acid composition characterization of a series of triacylglycerol mixtures. Secondary metathesis processes can occur with polyunsaturated fatty acids, and we characterized the product distribution and computationally evaluated the energy profiles for competing ring closing metathesis pathways with linoleic and linolenic fatty acids.

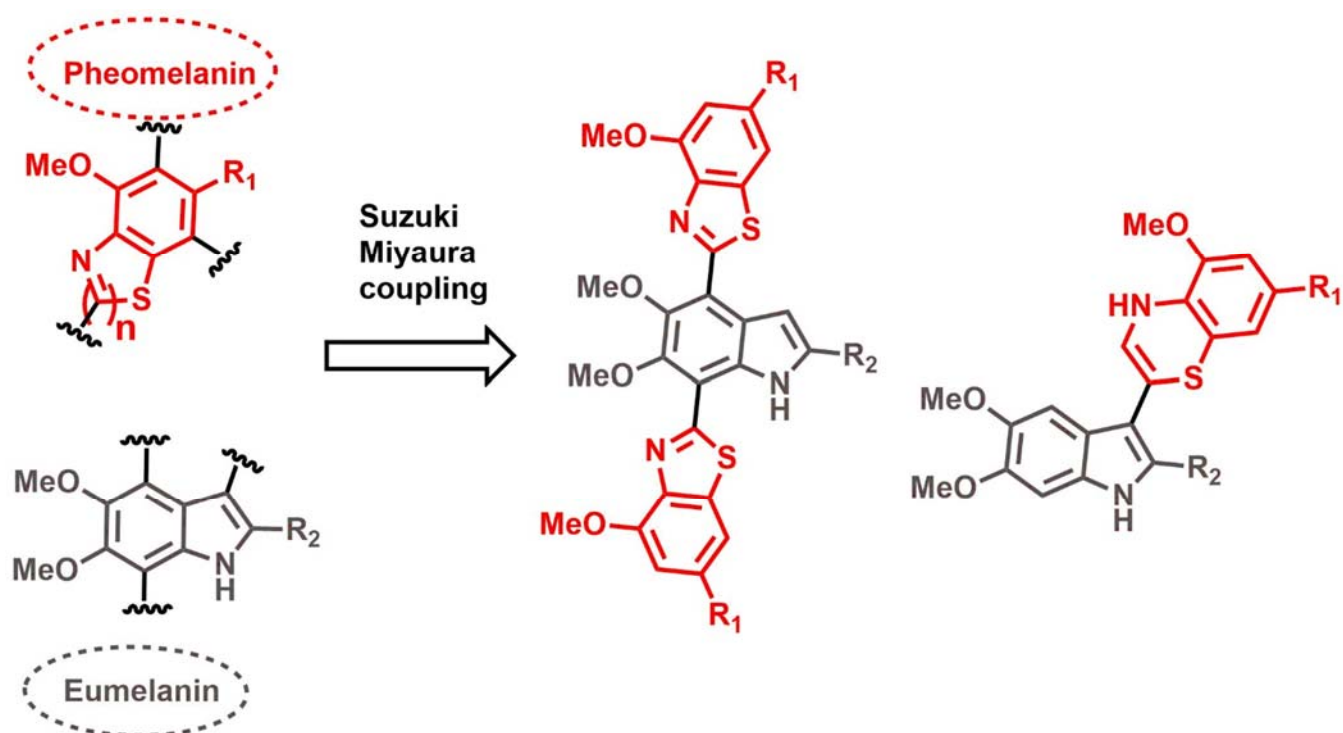
ORGN 440

Synthesis and study of photophysical, redox properties of mixed melanin analogs of eumelanin and pheomelanin monomers

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Eumelanin and pheomelanin are two major classes of natural pigments that are derived from L-dopa in nature. These molecules possess interesting photophysical and redox properties as well as amalgamate to form the enigmatic biopolymer, neuromelanin. Neuromelanin is a dark, polymeric pigment abundantly found in the substantia nigra and locus coeruleus of the brain. In Parkinson's disease, these pigmented neurons experience severe oxidative stress and reduced viability. Recent studies have hypothesized that eumelanin plays a protective role decreasing the oxidative stress while pheomelanin increases the oxidative stress. A definitive study of the biological,

photophysical, and redox properties of mixed melanins is lacking. The structure of mixed melanins have been formulated based on biosynthetic and degradation approaches. This study uses a bottom-up approach to synthesize dimers and trimers of mixed melanins from several eumelanin and pheomelanin monomers. The assembly of these neuromelanin mimics is accomplished using Suzuki-Miyaura couplings. A library of mixed melanins will be useful for deriving a structure activity relationship, understanding mixed melanogenesis, and advancing our understanding of neurodegenerative diseases.



ORGN 441

Selenosulfides as versatile, electrophilic triggers for H₂S detection and imaging

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The development of reaction-based fluorescent probes for H₂S detection has been of high interest in recent years. While numerous designs have been introduced, many of these scaffolds have displayed suboptimal selectivity and reactivity towards H₂S and with inadequate physicochemical properties which render their use impractical within biological systems. Herein, we report on a new approach for H₂S probe development

that utilizes a highly versatile selenosulfide functional group. With the heightened electrophilic character of selenium relative to that of sulfur, we demonstrate that the selenium half, when tethered to a second electrophilic partner, can selectively scavenge and detect H₂S while the sulfur half provides a suitable handle for tuning the probe's physicochemical properties such that it may be used effectively within a biological setting. With continued structural modifications to the sulfur half of these probes that further improve cellular delivery and/or tissue specificity, we foresee this framework serving as the foundation for a valuable set of chemical probes that may be used to further investigate the physiological importance of H₂S.

ORGN 442

Synthesis of 3,4-dihydroxyhydrocinnamic acid analogues to investigate dioxygenase activity

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Extradiol dioxygenase use metal chelation and oxygen activation to catalyze the cleavage of catecholic rings. The understanding of this powerful chemistry is limited by the substrates available for study. Electron withdrawing substituents on these catechols are attractive targets in semisynthetic applications of the extradiol cleavage products. To this end, the synthesis of 3, 4-dihydroxycinnamic acid analogues with bromo, nitro, and cyano groups were designed. Progress towards the synthesis of these compounds will be discussed.

ORGN 443

Synthesis of catechol derivatives as probes of dioxygenase mechanism

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Catechols are found as components of natural and man-made products, including flavors, fragrances, and pesticides. Extradiol dioxygenases cleave the catecholic rings coordinated at an iron center by the vicinal oxygen atoms. Our understanding of dioxygenase mechanism is limited by the substrates available for study. To broaden our understanding of substrate space in a way that informs mechanism, different substituents (electron donating or withdrawing) were placed at the 6-position of the catechol ring such that the interactions between these probes and the enzyme could be studied. Here we discuss progress toward the synthesis of substituted catecholic analogues, including derivatives of dopamine and 3,4-dihydroxyphenylalanine.

ORGN 444

Biological ene reactions

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Ene reactions take place when an allylic group reacts with a double bond. Both the allylic group and double bond may contain heteroatoms. For example, the double bond could be an alkene, carbonyl, or imine. The allylic group could be an allylic alcohol, a phenol, an aniline, or even an oxime. Recently reported findings suggest that NADH, FAD, FMN, vitamin C, the oxime intermediate of nitric oxide synthase, and many related biological molecules may all react through ene reactions. Thus, this reaction could be one of the most common chemical reactions in biology. Our continued progress studying biological ene reactions and their implications and applications will be reported.

ORGN 445

Design and synthesis of propargylglycine-based antibacterial compounds

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LpxC, an enzyme essential in the biosynthesis of a component of the outer membrane of Gram-negative bacteria, is an attractive target for inhibitor development. A series of propargylglycine-based compounds have been synthesized, characterized, and evaluated for antibacterial activity against Gram-negative bacteria. Antimicrobial activity was observed for compounds containing a phenyl propargyl ether tail or a biphenyl tail. A minimal inhibitory concentration of 16 µg/mL was achieved for the compound with the biphenyl tail in *Escherichia coli*, but inhibition was only possible in the absence of TolC-mediated efflux. The syntheses of these compounds and the design challenge of avoiding efflux activity will be discussed.

ORGN 446

Ten-membered macrolides and other natural products isolated from the marine-derived fungus *Paraconiothyrium cyclothyrioides* through the manipulation of media composition

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The exploration of fungal secondary metabolites as a source of, or lead to, new drug discovery is pertinent in the fight against antimicrobial resistance. The wide range of biological activities that these metabolites have been shown to exhibit and the vast potential for isolating new and more potent versions of natural products makes such investigations worthwhile. Secondary metabolites are the end results of activation of the gene clusters that code for their biosynthesis. These genes can be triggered by the manipulation of the environment in which the fungus grows.

Paraconiothyrium cyclothyrioides, isolated from the alga *Diginea simplex*, was grown on solid substrates, such as rice and breakfast cereals. The fermentations led to the isolation of a chromanone, 2-methyl-5-hydroxychroman-4-one, and three 10-membered macrolides – Modiolide A and Stagonolide E, along with a novel polyketide, provisionally named Modiolide C. Modiolide A and Stagonolide E exhibit antimicrobial and phytotoxic activities respectively. The effects of medium manipulation on the production of secondary metabolites is reported.

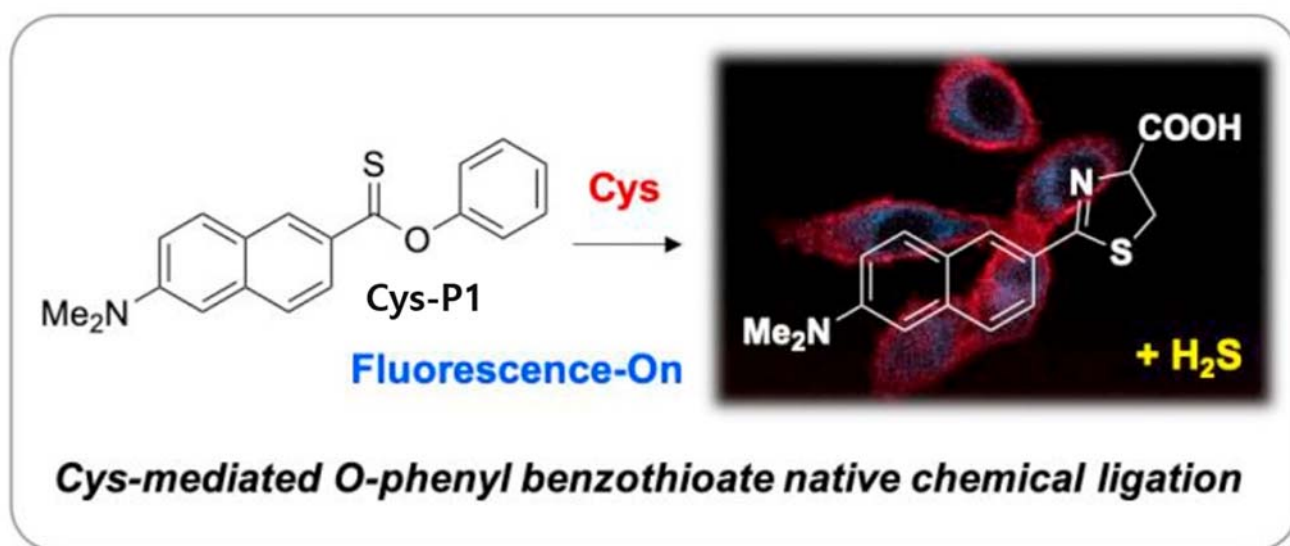
ORGN 447

Development of a benzothioate native chemical ligations-based cysteine-selective fluorescent probe

Na Hee Kim², **Heejo Moon**¹, hj.moon@snu.ac.kr, Jeong Hee Kim², Youngbuhm Huh^{2,3}, Yong Jun Kim^{2,5}, Byeongmoon Kim¹, Dokyoung Kim^{2,3,4}. (1) Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul, Korea (the Republic of) (2) Department of Biomedical Science, Graduate School, Kyung Hee University, Seoul, Korea (the Republic of) (3) Department of Anatomy and Neurobiology, College of Medicine, Kyung Hee University, Seoul, Korea (the Republic of) (4) Medical Reserach Center for Bioreaction to Reactive Oxygen Species and Biomedical Science Institute, Kyung Hee University, Seoul, Korea (the Republic of) (5) Department of Pathology, College of Medicine, Kyung Hee University, Seoul, Korea (the Republic of)

Biological thiols such as cysteine (Cys), glutathione (GSH), and homocysteine (Hcy) are known to play important roles in biosystems, the levels of which are closely related with diseases including cancer, matabolic diseases, and brain-related diseases. Therefore, the development of efficient biothiol sensing tools is highly desirable for chemical biology research.

In this work, we disclose for the first time a turn-on fluorescent probe, **Cys-P1**, for the detection of Cys, which functions based on Cys-mediated O-phenyl benzothioate native chemical ligation (NCL). We observed that **Cys-P1** shows fast responses as well as high selectivity towards Cys among amino acids, metal ions, and biothiols which might possibly be a source for interference. Moreover, we verified the generation of H₂S gas as a side product, which would make possible **Cys-P1** applied to H₂S delivery system as well. Furthermore, the probe showed superior sensing ability for Cys in cancer cells with low cytotoxicity. Taken together, we believe our study will provide a new platform for Cys sensing and warrant further related biological applications.



ORGN 448

Structure-activity relationships for beta-carboline behavior against the 5-Hydroxytryptamine receptor

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A class of compounds called beta-carbolines is known to have biological activity in the central nervous system by binding to a group of receptors important in signaling. In this research, we focused on synthesizing 1-aryl-substituted beta-carbolines in order to analyze their neuropharmacological behavior. A series of molecules were made using Suzuki cross coupling using aryl or heteroaryl boronic acids and a triflate precursor. A library of 26 of these molecules were made successfully, all of which were tested for biological activity by doing a neuropharmacological screen at 10 μ M against 40 protein receptors that are involved in brain signaling. Out of all these receptors, the most important interaction was with the serotonin 5-HT₂ receptors. By further refining these structures to enhance the interaction, several key points were learned regarding the interaction of these molecules with the receptors. Most important structural findings emphasize the importance of having a 3-indolyl substituent attached to the 1-position of the β -carboline and a 6-methoxy substituent on the β -carboline.

ORGN 449

Synthesis of quinoline-5,8-dione derivatives

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Lavendamycin, a naturally occurring quinoline-5,8-dione, has been shown to have anti-tumor properties by binding to the NAD(P)H:quinone oxidoreductase 1 (NQO1) enzyme which is over expressed in many cancer cells. The quinoline-5,8-dione ring is reduced to the corresponding diol which is cytotoxic. The over expression of the NQO1 enzyme in cancer cells made it a good target for bioreductive drug therapy. The focus of the project is to improve selectivity, activity, aqueous solubility, and cytotoxicity towards non-cancerous cells by altering the reactivity of the C2 position of the core quinoline-5,8-dione ring. The isoxazoline and isoxazole rings are synthesized via a 1,3-dipolar cycloaddition using a nitrile oxide as the 1,3-dipole and a terminal alkene or alkyne as the dipolarophile. Variation of the alkene and alkyne dipolarophiles, which are readily available, allows one to significantly alter the target molecule.

ORGN 450

Cobalt III Schiff base inhibitor synthesis and biological protocol testing

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Cobalt(III) Schiff base complexes are known to have inhibitory effects on zinc finger protein structural motifs. Targeted Co(III) Schiff base complexes have been synthesized to target Gli transcription factors known to be overactive in basal cell carcinoma (BCC) and medulloblastoma (Mb). In order to determine the effect of these drugs on cell mobility and invasiveness, scratch assays on BCC and Mb cell lines were conducted. It was determined that the Mb cell line was better suited to the scratch assay conditions used and that the hedgehog pathway controls the invasiveness of the cell line. Furthermore, synthesis of a dye arm for cobalt (III) Schiff base complex was completed through the addition of BOC-protected ethylenediamine to coumarin-3-carboxylic acid in basic conditions with the goal of monitoring drug binding to Gli protein. Product was recovered at 1.65 g (94% yield).

ORGN 451

New bioorthogonal approaches for C-terminal protein modification

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Protein modification enables the study and modulation of cellular events in which proteins play important roles. Our lab focuses on developing new bioorthogonal reactions for the site-specific protein conjugations, combining with approaches that

conveniently accessible to biological labs. Based on our previous investigations, we have designed and synthesized several peptides or unnatural amino acids that allow the incorporation of desired functionalities to the C-terminus of proteins through different chemoenzymatic methods or unnatural amino acid mutagenesis. These site-specific protein functionalities subsequently react with complementary probes with a fast speed, forming tricyclic boron-nitrogen heterocycles that are stable at physiological and acidic pHs.

In this work, we present the synthesis of a new unnatural amino acid that potentially can be attached to C-terminal protein through enzyme-mediated ligation. Model reactions with this unnatural amino acid were examined and characterized, including kinetics profiles and stability of the products at various pHs. The accessibility of attaching this unnatural amino acid to proteins through enzymatic methods will be presented. The reactivity and stability of the functionalized protein conjugation will be also discussed.

ORGN 452

Development of enzyme responsive spin probes for non-invasive imaging of enzyme activity by EPR

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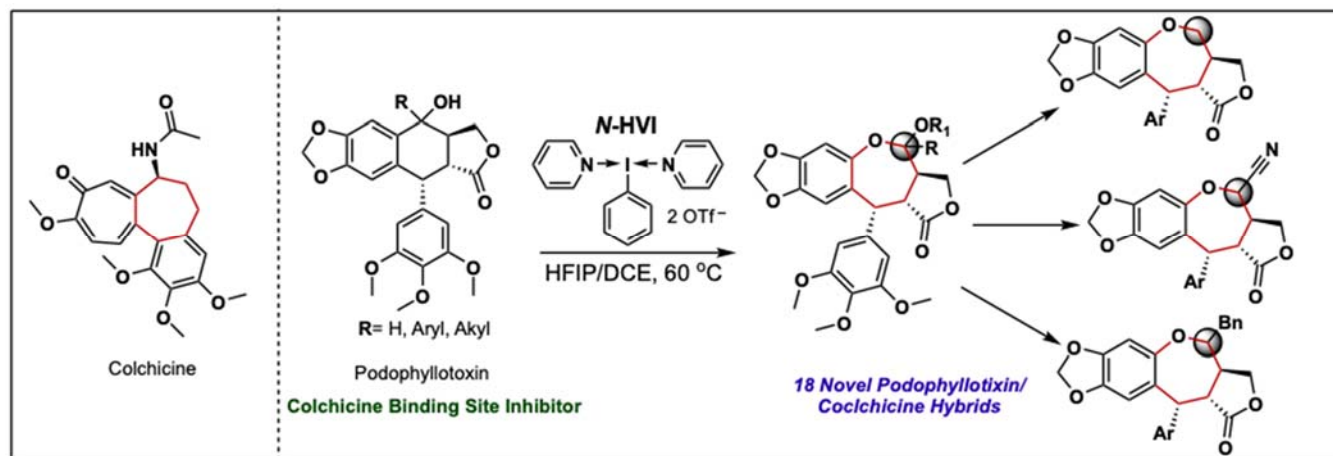
In this work, we report on the development of nitroxide and trityl radicals to measure enzyme activity directly *in vivo* using EPR imaging. This new concept is based on a modification of the EPR spectra of a spin probe substrate of a particular enzyme upon enzymatic transformation. The shift in EPR resonance between the enzyme substrate and product can be used to image both substrate and enzyme independently using 4D spectral-spatial EPR imaging. Our first example depicts a nitroxide-based radical whose spectrum is sensitive to alkaline phosphatase (ALP). This radical was used to image ALP activity *in vitro* using a homemade rapid-scan EPR imager operating at 800 MHz. However, the *in vivo* use of nitroxide radicals are limited by their fast bioreduction. Therefore, we are developing the first trityl radicals sensitive to enzyme activity. Indeed, trityl radicals are well known for their extraordinary stability in biological media, the narrow linewidth of trityl radicals also increases the sensitivity of detection and the spectral resolution between substrate and product. We report on the synthesis and characterization of an ALP sensitive trityl spin probe.

ORGN 453

Late stage derivation of podophyllotoxin using oxidative ring expansion

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Podophyllotoxin is a lignan natural product that has been pursued as a lead compound for therapeutic development. It is a World Health Organization essential medicine and its derivatives, etoposide, teniposide, and etopophos, have been advanced to clinical anticancer drugs. Podophyllotoxin targets the colchicine-binding site of tubulin, inhibiting the polymerization to microtubules causing cell death in a large variety of cancer cell lines with an average IC_{50} value of 52.7 nM. However, its further development has been hindered by significant off-target toxicity. While extensive SAR has been conducted, derivatizations have largely focused on alcohol appendages or sacrificing the D-ring lactone as a handle to introduce novel functionality. Herein we report on the synthesis and biological evaluation of novel medium-ring analogues of podophyllotoxin, which offer altered three-dimensional architectures that mimic that of the native ligand colchicine. The key transformation engages the benzylic alcohol in a hypervalent iodine-mediated oxidative ring expansion developed in our laboratory. The newly formed oxepane ring possess an acetal center that is then further functionalized with sterically and electronically diverse motifs, leading to the synthesis of 18 unique derivatives, all available within three steps from the natural product. Biological evaluation of the analogues has been paired with computational modeling to guide the continued development of improved compounds.



ORGN 454

Honokiol-inspired analogs as topical antibiotics

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Honokiol, a natural product isolated from the bark of magnolia trees, has been used for centuries in traditional eastern medicine as a therapeutic bactericide. Previous work has explored the use of honokiol-inspired analogs for the treatment of oral bacteria and biofilms, leading to the identification of CRO 215. This work explores the structure-activity relationship (SAR) of CRO 215 and other honokiol-inspired analogs for use as topical antibiotics. The minimum inhibitory concentration (MIC) of these compounds was determined for a variety of Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Acinetobacter baumannii* (See **Table 1**). While CRO 215 was very active against Gram-positive bacteria, it failed to target Gram-negative bacteria and the HD₂₀ (the concentration at which 20% of mammalian red blood cells are hemolyzed) indicated that this compound was toxic at low concentrations. Modifications to the substituents ortho to the phenol yielded CRO 263, a broad spectrum antibacterial with lower toxicity. Unfortunately, this modification led to a marked decrease in potency. Modification of the two-carbon linker of CRO 215 yielded HFR 115, a less toxic compound with activity similar to CRO 215 against Gram-positive bacteria. Presently, further modifications to the scaffold are underway to identify a more potent broad-spectrum antibacterial, and experiments are being undertaken to determine the bactericidal mechanism of action.

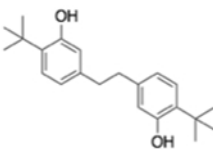
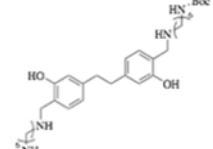
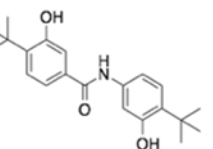
			
	CRO 215	CRO 263	HFR 115
MRSA	4 μ M	32 μ M	4 μ M
<i>A. Baumannii</i>	> 250 μ M	32 μ M	> 250 μ M
HD₂₀	32 μ M	2000 μ M	2000 μ M

Table 1. Honokiol-inspired Analog SAR

ORGN 455

Construction of an ethylene detecting metalloenzyme in *E. Coli* using a novel ruthenium-based probe

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Ethylene is a key modulator in the ripening of climacteric fruits and is commercially indispensable in the synthesis of common plastics such as polyethylene. Despite its multifaceted importance in society, there is a dearth of methodologies available to detect ethylene, with most techniques reliant upon complex instrumentation with limited potential within complex biological systems. Alternatively, small molecule probes grant insight into cellular systems and are used extensively in molecular biology. As such, we recently developed a small molecule probe that makes use of ruthenium catalyzed olefin metathesis to selectively release a fluorescent molecule in the presence of ethylene. Strategies for modifying this system for application as an artificial metalloenzyme will be presented. This system allows for not only the selective detection of ethylene within living systems, but also the localization of a metalloenzyme for location specific detection of ethylene in cells.

ORGN 456

Optimization of fluorescent probes for the detection of ethylene in living systems

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Ethylene is an important plant hormone that is involved in a variety of important developmental processes including agriculturally important ripening of certain fruits. Our group has recently developed the first approach for the selective detection of ethylene at the cellular level using an olefin metathesis complex appended with a BODIPY fluorophore. Low limits of detection in the single digit parts-per million range were found. The development of 2nd generation probes with improved sensitivity and functionalization for improved performance in biological systems will be presented.

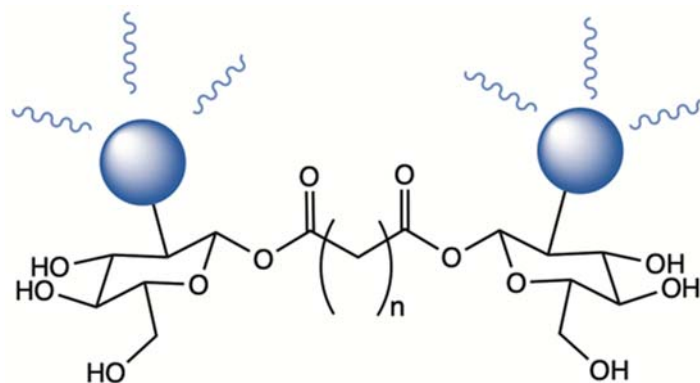
ORGN 457

Tethered glucose molecules in membranes: Can a longer spacer lead to closer approach?

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The disaccharide trehalose can be found in many organisms that are able to survive in extreme cold or arid environments. According to the "hydration hypothesis," trehalose interacts with the glycerol/phosphate regions of lipid bilayers and replaces water molecules, therefore preventing ice crystals from puncturing the cell membrane. Glucose, the monomer of trehalose, does not exhibit the same cryoprotective power. In this study, we aim to mimic the cryoprotective properties of trehalose by tethering two glucose molecules together using spacers of up to 20 carbons in length. We hypothesize that long spacers will be able to reach down to the hydrophobic region of the membrane, thus pulling the two glucose moieties within proximity of one another on the membrane surface. A naphthalimide attached to each glucose molecule is designed

to act as a water-sensitive fluorescence probe. The effects of these molecules on membrane dynamics, as studied by fluorescence spectroscopy and differential scanning calorimetry, will be presented. Long-term, these molecules may be useful in cryopreservation of red blood cells.



ORGN 458

Diversification and exploration of the diazaxanthylidene scaffold toward highly fluorescent and efficient photoconvertible dyes for *in vivo* tracking of biomolecules

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Although a great deal of progress has been made, the field of fluorescent bioimaging has a number of unmet needs. There are very few fluorophores that display low cytotoxicity, good cell permeability, and low molecular weight. Additionally, there is a lack of fluorescent probes that can provide single molecular precision for the *in vivo* tracking of biomolecules.

Recently, the Chenoweth laboratory has shown the emerging versatility of the diazaxanthylidene scaffold as a promising basis for fluorescent dye development. In 2013 the lab synthesized the reported structure of Xylopyridine A (a diazaxanthylidene natural product). In 2015, the lab discovered Xylopyridine A represented a new emissive and photoconvertible dye class, displaying low toxicity and good cell permeability. Furthermore, the lab then showed that Xylopyridine A could be used to selectively image lysosomes in HeLa cells. Most recently, in 2018 the lab then showed that a derivative of Xylopyridine A could be alkylated with an azide handle and subsequently used for the *in vivo* tracking of alpha synuclein fibril formation via copper click conjugation to alpha synuclein monomers.

Herein, we have further examined the utility of the diazaxanthylidene scaffold by (1)

synthesizing heterodimers to investigate the effects of a single nitrogen atom on the fluorescent qualities of the scaffold (2) synthesizing and evaluating the utility of the diazaxanthylidene dye alkylated with an IEDDA (Inverse Electron-Demand Diels-Alder) reactive handle for fast copper free conjugation to biomolecules, and (3) performing experimental and theoretical studies of “push-pull” analogs towards discovery of ultra-bright, ultra-responsive spatio temporarily photoconvertible dyes. These studies have resulted in the illumination of the versatility of the diazaxanthylidene scaffold as an emerging powerful new class of fluorophores.

ORGN 459

Simplification of method for hydrogen bond strength determination of various hydrogen bond donors

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The hydrogen bond strengths were determined for various classes of compounds, including organic acids, alcohols/phenols, carboxylate bioisosteres, dicarbonyls, and amides, using 7-methyl-2-phenylimidazo[1,2-a]pyrazine-3-(7H)-one as a colorimetric sensor. Our findings further support the ineffectiveness of using pK_a to estimate hydrogen bond strength. Additionally, full titrations were previously used to determine hydrogen bond strengths; however, from the compiled strength data, a simplified method for conducting the experiments was achieved. Single, double, or triple point measurements can be effectively employed to accurately determine hydrogen bond strengths.

ORGN 460

Phytochemical investigation of the non-polar extract of camu camu (*Myrciaria dubia*) roots

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Nature is the major source of variety of food and nutrients. In addition, huge number of pharmacologically privileged and industrially relevant compounds are obtained in nature. Camu camu (*Myrciaria dubia*) is an indigenous shrub found in the lowland region of Amazon rain forest. Camu camu fruits are widely consumed by the natives as a good source of vitamin C, minerals, and antioxidant flavonoids. High vitamin C content (about 2-3% of fresh weight) enabled the fruit to find its position in the international market. However, systematic phytochemical investigation of Camu camu roots has not been carried out. As a part of our ongoing research to identify medicinally privileged and industrially important molecules from neglected botanicals, phytochemical investigation of the low-polar extract of Peruvian camu camu (*Myrciaria dubia*) roots has been carried

out in order to identify a new source of advantaged natural compounds. Bioactivity-guided cold extraction in diethyl ether and subsequent gas chromatography-mass spectroscopy (GC-MS) studies of the non-polar extract have been accomplished. Findings that are related to low-polar fraction are summarized. Identification of industrially and pharmacologically privileged compounds from Camu camu roots may open a new frontier for meaningful utilization of this neglected natural resource.

ORGN 461

Digging the waste: Phytochemical investigation of the non-polar extract of *Aloe vera* rind

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Humans are indebted to Mother nature since the beginning of civilization. Nature provides foods, medicines, nutrients and many other useful things to humans forever. *Aloe vera*, a shrubby succulent plant belongs to the family *Asphodelaceae* and originated from the Arabian Peninsula, grows wildly in the tropical countries and cultivated worldwide for medicinal and nutritional uses. Historically *Aloe vera* gel is being used as traditional medicine to treat various skin ailments, minor burns, and as dietary supplement. After gel extraction the green exterior part (rind) is thrown away that might cause potential environmental pollution. As a part of our ongoing research of identifying precious compounds from agricultural and botanical waste, phytochemical investigation of *Aloe vera* rind has been carried out. Findings that are related to less polar (hexanes) fraction are summarized. Bioactivity-guided cold extraction in hexanes was performed and subsequent gas chromatography-mass spectroscopy (GC-MS) study of the extract has been accomplished. Identification of industrially and pharmacologically privileged compounds from the agricultural/botanical waste (*Aloe vera* rind) may open a new frontier for effective consumption of this waste.

ORGN 462

Synthesis and evaluation of purine analogs that target Xpt riboswitch gene

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Riboswitches are untranslated regions within bacterial mRNA that bind specific intracellular metabolites. The *xpt* riboswitch is a guanine responsive riboswitch involved in purine biosynthesis and transport pathways. This riboswitch inhibits purine gene expression in the presence of bound guanine. When guanine is bound, the mRNA changes its three-dimensional structure that subsequently inhibits transcription of the

xpt purine synthesis gene. In this work, we have synthesized purine nucleobase and nucleoside analogs in an effort to improve the binding affinity and solubility of compounds in our molecular assays. Our biochemical and cellular analysis looks at the binding and gene inhibition by the synthesized analogs in comparison to parent compounds.

ORGN 463

Developing small molecules selectively targeting the sequence-based secondary structure of ssDNA, CCG repeats and their effect in biological processes

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DNA exists primarily as a duplex. However, single-stranded DNA (ssDNA) is temporarily exposed in several cellular processes, such as DNA replication and transcription. ssDNA can form its self-folding (secondary) structure by sequences of DNA and the secondary structure of ssDNA affects the cellular processes. For example, the stable secondary structure of ssDNA can cause DNA mutations, both extension and contraction. Therefore, discovering selective binders that stabilize the secondary structure of ssDNA is important as a tool for understanding biological events more and as a potential treatment for diseases caused by the mutated DNA.

The target DNA strand (CCG)₇, which builds the stable secondary structure, was assayed with selected 80 compounds which have more than 80 % of similarity of the known C-C mismatched base pair binder. The six hits were tested for binding affinity and selectivity toward the secondary structure of (CCG)₇ repeats. The stabilization of the secondary structure of d(CGG)₇ repeats by the hit compounds was examined by measuring the T_m.

ORGN 464

Correlating bioactivity and reactivity for a series of guaianolide analogs

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Naturally occurring guaianolides with an α -methylene- γ -lactone show rich biological activity; however, high electrophilic reactivity of the lactone motif limits the value of

structure-activity relationship (SAR) studies. To address this limitation, we have substituted the α -methylene- γ -lactone of a guaianolide predisposed to binding to a particular protein target with electronically different α -methylene- γ -lactams to afford a series of analogs with variable reactivity. These analogs were reacted with glutathione or cysteamine under biomimetic conditions to measure their reaction rates. Cellular NF- κ B inhibition studies were performed to determine their bioactivity. Gibbs free energies of activation for the hetero-Michael addition reactions on a model system were computed using DFT. We will present the synthesis of these analogs, studies to correlate bioactivity, thiol reactivity, and computed Gibbs free energies of activation, and progress towards the next generation of α -methylene- γ -lactam analogs.

ORGN 465

Riboflavin-biotin conjugate: Affordability in B2 vitamin determination

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Riboflavin, a member of the B vitamin family, is a water-soluble vitamin that participates in energy metabolism processes via two coenzyme, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), in oxidized and reduced forms. Low levels of riboflavin have been associated with growth and developmental problems and have been reported in low-income countries due to inadequate intake of meat and dairy products. Thus, the need for a robust and accesible determination kit led to efforts to synthesize the key component, a riboflavin-biotin conjugate with the following characteristics: ability to interact selectively and simultaneously with the riboflavin binding protein (RBP) and avidin and stability at physiological pH. The synthetic scheme employs click chemistry methodology applied between a riboflavin derived azide and biotin related alkyne. Ab initio calculations were used to explore the role of hydrogen bonding on the riboflavin's flavin moiety structure and its ability to bind to RBP.

ORGN 466

Development of imaging probes for fracture healing response

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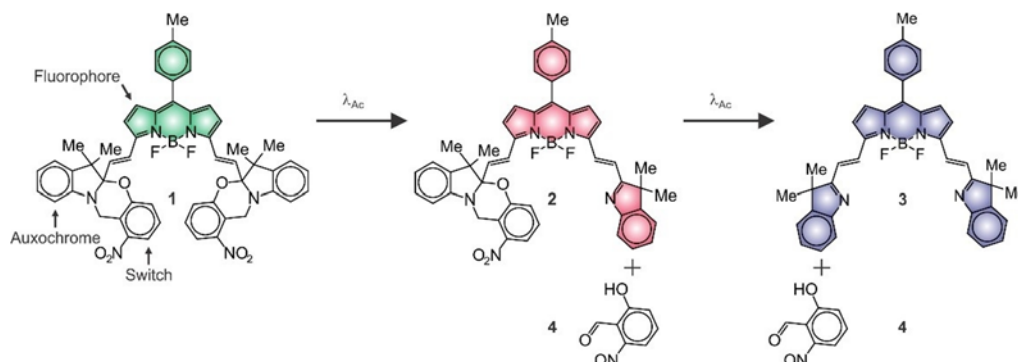
There are five primary problems created by bone fractures: bleeding, infection, disproportionate strains, vascular discontinuity, and inability to bear weight. The acute phase response (APR) is the body's natural response to injuries or trauma. Restoration of bones by APR is achieved through the formation of fibrin, hydroxyapatite crystals, collagens, and numerous other factors. In this project, we designed and synthesized imaging agents that enable high-resolution near-infrared fluorescence (NIRF) imaging of bone fracture APR. Synthesis of novel fluorescent probes for molecular imaging of fibrin, collagen and hydroxyapatite enables us to image and monitor bone healing process.

ORGN 467

Photochemical barcodes

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A photochemical strategy to encode fluorescence signals in vivo with spatial control was designed around the unique properties of a photoactivatable borondipyrromethene (BODIPY). The photoinduced disconnection of two oxazines, flanking a single BODIPY, in two consecutive steps produces a mixture of three emissive molecules with resolved fluorescence inside polymer beads. The relative amounts and emission intensities of the three fluorophores can be regulated precisely in each bead by adjusting the dose of activating photons to mark individual particles with distinct codes of fluorescence signals. The visible wavelengths and mild illumination sufficient to induce these transformations permit the photochemical barcoding of beads also in living nematodes. Different regions of the same animal can be labeled with distinct barcodes to allow the monitoring of their dynamics for long times with no toxic effects. Thus, our photochemical strategy for the generation of fluorescence barcodes can produce multiple and distinguishable labels in the same biological sample to enable the spatiotemporal tracking of, otherwise indistinguishable, targets.



Synthesis of Rh(III)-catalyzed N-heterocyclic compounds and their application to inflammation imaging agent

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The N-heterocyclic compounds represent ubiquitous structural motifs such as biologically active compounds and functional materials. With the many studies of C-H bond activation reactions, various method employing Rh(III)-catalysis have been developed for the synthesis of N-heterocyclic compounds. Recently, we developed new synthetic methods for the synthesis of pyridinium and benzoquinolinium salts using Rh(III)/Cu(II) complex. Interestingly, it has been found that these heterocyclic compounds are fluorescent materials and their emission wavelength can be adjusted by employing different internal alkynes. Based on these results, we have attempted the application of fluorescent materials to in vivo model diagnostic bioimaging. For successful application of fluorescent materials as imaging agent, several in vitro and in vivo experiments have been performed. As a result, we found that benzoquinolinizinium salt can act as an in vivo imaging agent for detection of inflammatory lesions. This result can be applied to the diagnosis of disease.

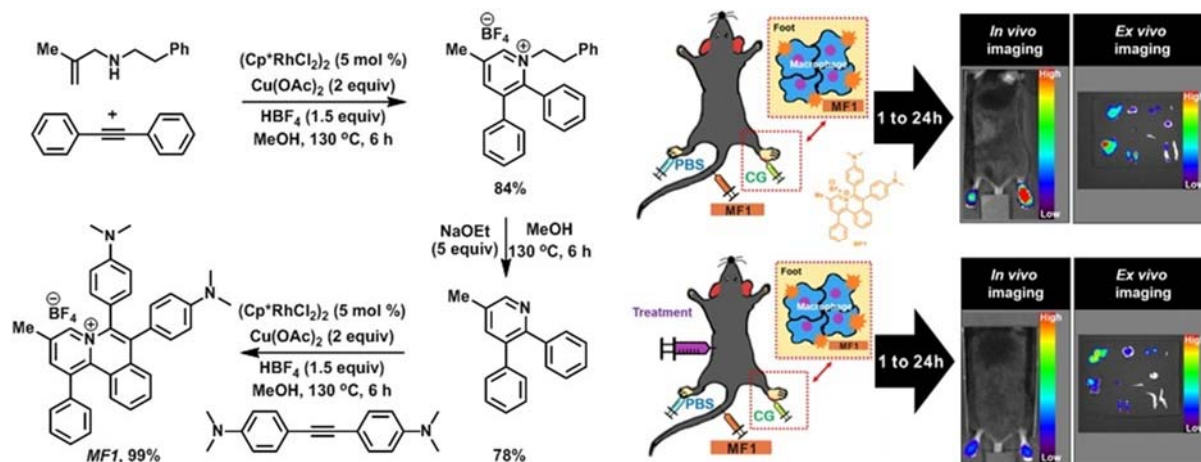


Figure 1. Synthetic route of MF1 and its in-vivo inflammation imaging

Synthesis and partial characterization of melamine Schiff bases and their antimicrobial activities

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Melamine (1,3,5-Triazine-2,4,6-triamine), a nitrogen-based compound used in commercial and industrial plastics, it is a component in adhesives and molding compounds; when mixed with resins, it has fire-retardant properties. Amines react with ketones to form Schiff bases and the Schiff-bases. The Schiff bases involving aromatic amines and quinones form bright colored compounds with applications in visualizing latent prints and dyeing industry. Further some of the Schiff bases when exposed to anions form charge transfer intermediates whose color is further enhanced, the latter is also beneficial in enhancing color of visualized latent fingerprints. In this study, melamine and Tetracyanoethylene (TCE) has been reacted with Tetrachloro-1,4-benzoquinone (TCBQ) and 2-hydroxy-1,4-naphthoquinone (HNQ, Lawsone). The reactions were carried out in a microwave at 150°C and 7 Barr pressure for 5-10 min. TLC analysis revealed the formation of a new product(s). The new compounds when exposed to ammonia in solution change colors/become brighter and causes their absorption bands to shift in a way that suggests that new compounds have sensory properties. The newly synthesized compounds inhibit bacterial growth suggesting possible pharmacological properties. In conclusion, we have successfully prepared three new Schiff bases with (i) novel anion sensory properties, and (ii) antimicrobial activities, that may be exploited to develop latent fingerprints.

ORGN 470

Synthesis, structure, and preliminary biological activity of phenoxyalkyl esters of dithiocarbamic acids

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The chemistry of organosulfur compounds is a relevant and rapidly developing field of science. Dithiocarbamic acids, particularly their salt derivatives with various metals, have a fundamental and applied agricultural importance and are actively used as herbicides and fungicides. With that thought in mind, conditions have been developed for the synthesis of cyclic amine dithiocarbamate phenoxyalkyl esters $\text{PhO}(\text{CH}_2)_n\text{Br}$ ($n=2,3,4$) with 1-methylpiperazine phenoxyalkyl bromides and carbon disulfide as the starting substrates. The reaction of 1-methylpiperazine with carbon disulfide and phenoxyalkyl halide was carried out in acetone in the presence of sodium phosphate at room temperature for 1.5 - 2 hours under a standard TCR synthesis. As a result, 2-phenoxyethyl-4-methylpiperazine-1-carbodithioate (PMC II) was synthesized with the corresponding yield (63.4%), as 3-phenoxypropyl-4-methylpiperazine-1-carbodithioate (PMC III) (78.7%), and 3-phenoxybutyl-4-methylpiperazine-1-carbodithioate (PMC IV) (80.4%). Synthesized phenoxyalkyl esters of methylpiperazindithiocarbamic acid (PMC

II-IV) were preliminarily confirmed by qualitative TLC and later characterized by HMRS and IR spectroscopies. Bioscreening of 3-phenoxypropyl-4-methylpiperazine-1-carbodithioate (PMC III) in the form of a water-soluble hydrochloride salt was conducted on model samples of a spring wheat *Triticum aestivum* varieties “Kazakhstan-10”, “Severyanka”, and “Miras”. Pre-sowing treatment of wheat with the PMC compounds was done in Petri dishes during the germination of seeds for 3 days. In the early biological testing of 15 plant samples, the seeds treated with procured compounds resulted in significant inhibition of plant height and root length - the stem length by an average of 30%, and the root length by an average of 52.7%. The hydrochloride of 3-phenoxypropyl-4-methylpiperazine-1-carbodithioate slows the growth of the stem, pointing out to potential use as a plant growth retardant.

ORGN 471

Quinoline-based fluorescent dyes as highly modular, environmentally sensitive probes for biological studies

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Fluorescent small molecule probes, which can be used as cellular stains, labels for biomolecules, environmental indicators, and biosensors, are essential tools for biomedical applications. Compared to fluorescent proteins, fluorophores often benefit from their small size, brightness, and photostability, although potential cell toxicity, impermeability, and low sensitivity can be a tradeoff. Unfortunately, these characteristics are difficult to predict through calculations or rational design, making the development of a core scaffold that is amenable to late stage functionalization particularly desirable.

We present a fluorescent dimethylamino quinoline (DMAQ) core that can be synthesized in two steps, yielding two variable domains that can then be functionalized sequentially. As demonstrated in previous work from the group, modification of one domain allows for the tuning of photophysical properties as a function not only of the electronics of the compound itself but also of the environment in which the molecule is present. Modification at a second domain would then allow for the installation of a reaction handle that can be used to label biomolecules for more targeted study. This work details the installation of an azide motif, which quenches fluorescence through photoinduced electron transfer (PeT) prior to bioorthogonal click chemistry, allowing for a no-wash labeling probe. We can observe both *in vitro* and *in cellulo* a primary turn-on in overall fluorescence following triazole formation as well as a secondary shift in fluorescence that indicates environmental change. To the best of our knowledge, this work presents the first multi turn-on quinoline probe that demonstrates both chemical and environmental turn-on.

ORGN 472

Stereocontrolled total synthesis of elovanoids: Novel class of bioactive lipid mediators that protect cell integrity

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Recent studies involving the role of lipid mediators in inflammation and disease led to the discovery of a novel class of bioactive lipids containing hydroxylated very long polyunsaturated fatty acid (VLC-PUFA) derivatives termed Elovans (ELVs). The precursors of ELVs are biosynthesized from docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA), which are also substrates that lead to the formation of anti-inflammatory and pro-resolving lipid mediators, with the help of an elongase enzyme (ELOVL4). ELVs have been found to enhance expression of pro-survival proteins in cells with oxidative stress, and possess protective and pro-homeostatic functions that preserve neural and retinal cell integrity. In order to validate the complete structures and stereochemistry of these novel molecules and to investigate their biological actions, we have developed a stereocontrolled chemical synthesis that produced stereochemically pure materials. Herein, we will present our efforts involving the stereocontrolled total synthesis of various elovanoids and related intermediates.

ORGN 473

Synthesis of hyaluronic acid-based phototsensitizers for tumor targeting

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Photodynamic therapy (PDT) has gained popularity as a non-invasive treatment for certain types of cancers. PDT consists of the administration of a photosensitizing agent, followed by laser-light activation to produce reactive oxygen species in the local vicinity of the tumor. Limitations for this form of treatment include selectivity and solubility. In this poster, we focus on our recent synthetic efforts towards the synthesis of several novel hyaluronic acid-based photosensitizers for targeting tumors overexpressing CD44 with the potential for overcoming the major limitations associated with PDT.

ORGN 474

Synthesis of flavonols as ligands for metal-flavonol complexes and as CORMs for therapeutic effect

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Flavonoids are a class of compounds that are natural components of plants, fruits, and vegetables and are primarily studied for their antioxidant, antimicrobial, and anticarcinogenic activity. Flavonols are a flavonoid that contains the 3-hydroxyflavone moiety and have the ability to release carbon monoxide (CO). Carbon monoxide-releasing molecules (CORMs) are chemical compounds designed to release controlled amounts of CO for potential therapeutic effects. Our research focuses on alternate methods for the Claisen-Schmidt condensation and subsequent Algar-Flynn-Oyamada reaction to synthesize novel flavonol-derived ligands and study the effect aryl substituents and metal-complexation has on the CO-releasing ability.

ORGN 475

Development of new methodology towards accessing 2-imidazoline scaffolds for combatting tuberculosis and multiple myeloma by proteasome modulation

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Multiple Myeloma (MM) is a disorder of differentiated B cells in which the inhibition of the proteasome is standard care. The current drug, bortezomib, used to treat MM is ineffective against drug tolerance where 97% of all patients become intolerant within a few years. Imidazoline scaffolds are capable of overcoming that resistance and delaying MM tumor growth. We believe we will be able to effectively yield imidazolines. Synthesis will occur with commercially available starting materials, making the process less expensive. The process involves 4 steps. While working under inert conditions, we took an acyl chloride, a highly reactive starting material, to make a desired amide. This amide was then transformed to the N-hydroxy amidine. Next, we reacted the hydroxy group on the amidine with an acyl chloride to install a good leaving group on the oxygen. Finally, a combination of secondary amine and α , β unsaturated aldehyde will invoke an iminium that will undergo a Michael Addition. This results in an aziridine that undergoes ring expansion to produce an imidazoline. Using IR analysis, melting point analysis, and nuclear magnetic resonance (NMR) of the products, we concluded that steps one and two yielded the desired compounds. The NMR for step 3 shows our product is present but requires purification to move on to the final step. Using column chromatography, we will separate the compounds based on UV absorption to isolate our purified product. That product will then be carried to step four. Steps 1 through 3 have worked and the outcome of step 4 will allow us to determine the success of our overall project.

ORGN 476

Synthesis and biological evaluation of novel thiazole derivatives as antimicrobial agents

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A few decades after the great discovery of antibiotics, scientists recognized the ability of bacteria and other microbes to resist antibiotics. Gram-negative bacteria are able to produce an enzyme known as β -lactamases, which makes them resistant to antibiotics. A particular group of thiazole sulfonamides extended ring structures attached to a sulfonamide group, inhibit β -lactamase. The present research synthesizes novel thiazole derivatives using multi-component microwave reactions and evaluates their activity against resistant microbial agents. Results described in this research will discuss compound extraction, purification and characterization using various methods such as: liquid chromatography separation (BiotageTM), Thin layer chromatography, liquid extraction, rotary evaporation and Nuclear magnetic resonance (NMR) analysis. Newly synthesized and purified compounds will be evaluated in microbiological assays using the Kirby-Bauer protocol to assess bacterial growth inhibition.

ORGN 477

Synthesis of maculosin derivatives via Horner Wadsworth Emmons reaction

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Maculosin, a substance produced by the fungus *Alternaria alternata*, has phytotoxic properties and can be used as a selective herbicide targeting the invasive spotted knapweed. A synthesis plan of Maculosin derivatives has been evaluated that employs a Horner Wadsworth Emmons reaction. The key HWE precursor can be prepared in 3 steps from commercially-available materials and permits easy access to diverse Maculosin analogues, which can be assessed for herbicidal activity.

ORGN 478

Thermotropic liquid-crystalline and light-emitting properties of bis(4-alkoxyphenyl) viologen bistosylate salts

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Six bis(4-alkoxyphenyl)viologen bistosylate salts ($n = 1, 6, 8, 12, 14, 16$), prepared from their bischloride salt precursors by the metathesis reactions, were characterized for thermotropic liquid-crystalline (LC) properties using differential scanning calorimetry (DSC) and polarizing optical microscopy (POM) studies. The salts with short alkoxy groups did not exhibit thermotropic LC phases on melting, but those with long alkoxy groups exhibited thermotropic smectic phases above their melting transitions (T_m) (Figure 1) and retained the LC phases up to their decomposition temperatures as determined using the hot-stage POM. Additionally, they exhibited crystal-to crystal transitions in the first heating cycles prior to their T_m s. All the salts had high thermal stability in the temperatures range of 303-311 degrees C as determined by thermogravimetric analysis (TGA). Their optical properties were also included using UV-Vis and luminescence spectrometry.

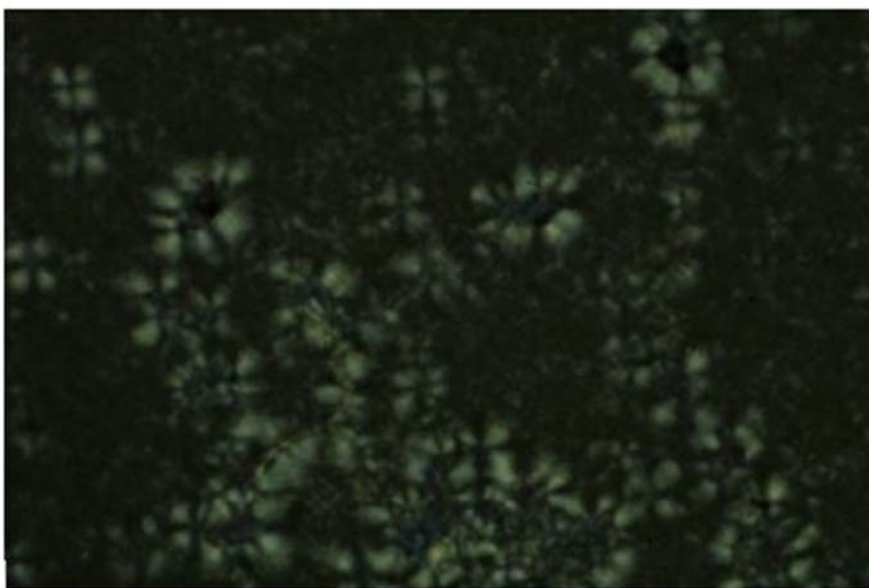


Figure 1. POM micrograph of the salt with $n = 14$ shows the smectic LC phase taken at 270 °C (magnification 400x).

ORGN 479

Thermotropic liquid-crystalline and light-emitting properties of bis(4-alkoxyphenyl) viologen bis(triflimide) salts

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Six bis(4-alkoxyphenyl)viologen bis(triflimide) salts (alkoxy chain length $n = 1, 6, 8, 16, 18, 20$), prepared from their bischloride salt precursors by the metathesis reactions, were characterized for thermotropic liquid-crystalline (LC) properties using differential scanning calorimetry (DSC) and polarizing optical microscopy (POM) studies. The salts with short alkoxy groups did not exhibit thermotropic LC phases on melting, but those with long alkoxy groups exhibited thermotropic smectic phases above their melting transitions (T_m s) (Figure 1) and also exhibited smectic-isotropic transitions (T_i s) as determined using the hot-stage POM. All the salts had high thermal stability in the temperatures range of ca. 330-370 degrees C as determined by thermogravimetric analysis (TGA). Their optical properties were also included using UV-Vis and luminescence spectrometry.



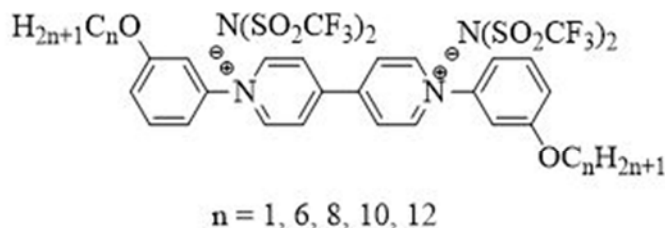
Figure 1. POM micrograph of the salt with $n = 8$ shows the smectic LC phase taken at 150 °C (magnification 400x).

ORGN 480

Thermal and light-emitting properties of bis(3-alkoxyphenyl) viologen bis(triflimide) salts

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Five bis(3-alkoxyphenyl)viologen bis(triflimide) salts ($n = 1, 6, 8, 10, 12$), prepared from their bischloride salt precursors by the metathesis reactions as shown in Scheme 1, were characterized for thermal properties using differential scanning calorimetry (DSC) and polarizing optical microscopy (POM) studies. All the salts exhibited crystal-liquid phase transitions (T_m s) that were detected in both the heating cycles of their DSC thermograms. The salt with $n = 1$ had the highest melting transition at 124 degrees C and that with $n = 6$ had the lowest melting transition at 108 degrees C. Therefore, they had melting transitions in the narrow temperatures range 108-124 degrees C, which is slightly higher than 100 degrees C. They had relatively high heats of fusion implying that they have potential as phase change materials. All the salts had high thermal stability in the temperatures range of 326-357 degrees C as determined by thermogravimetric analysis (TGA). Their optical properties were also included using UV-Vis and luminescence spectrometry.



Scheme 1. Chemical structures of viologen salts prepared by using Zincke salt.

ORGN 481

Molecular engineering of organic molecules for applications in symmetric redox flow batteries

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Crossover of electrolytes in redox flow batteries results in capacity fade and is commonly seen when using nonaqueous solvents. Symmetric cycling utilizes a single electrolyte acting both as the anolyte and catholyte, mitigating the impact of crossover. Herein we demonstrate the systematic synthesis and electrochemical study of organic molecules (specifically diaminoanthraquinone derivatives) as candidates for utilization in symmetric redox flow batteries.

ORGN 482

Synthesis and properties of new fluorinated aromatic molecules

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We report the preparation and properties of novel organic fluorophores. These molecules show a combination of [N–H–N] hydrogen bonds between the terminal pyrazole rings and [π–π] stacking between the electron-rich pyrazoles and electron-poor tetrafluorobenzenes. This material emits in the blue (442–446 nm) region when wet and in the green (497–503 nm) region when dry. Other related polyfluorinated materials will be discussed as well

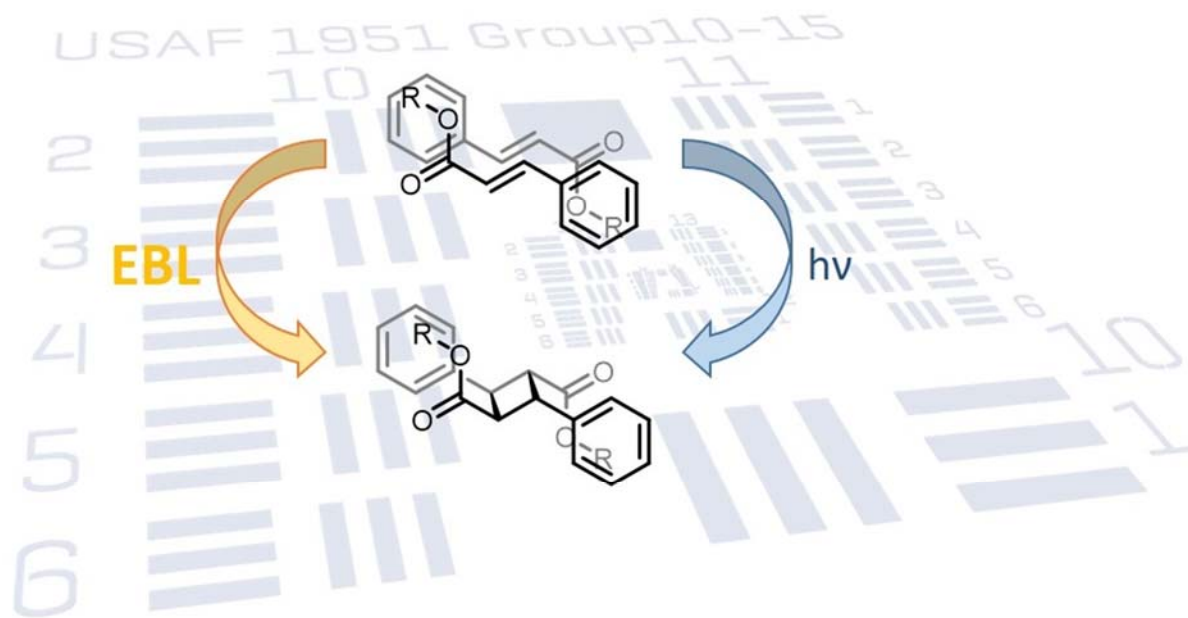
ORGN 483

Electron-beam allowing simple nanostructuring of cinnamate-based materials

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The production of electronic, photonic and metamaterial-based devices requires controlled deposition or structuring of functional materials. Electron-beam lithography (EBL) allows unparalleled miniaturization of those devices due to its high resolution. A tetrafunctional cinnamate is synthesized and EBL is performed as a proof-of-concept negative resist without the need for chemical amplification; structures with resolutions below 100 nm are easily achieved. Usually, EBL is accompanied by structure damage and material degradation as non-defined radicals are created. However, the combination of UV cross-linkable groups with low electron-beam intensities offers the advantages of selective crosslinking with high resolution. Electron impact promotes a cinnamic ester group to its excited state, which subsequently dimerizes according to the Woodward Hoffmann [2+2] cycloaddition formalism. Excitation of molecules by electron impact has been long known in the fields of mass spectrometry and electron impact fluorimetry and transferred to the condensed phase, which can thus serve as a

technique to achieve facile structures. EBL crosslinking of cinnamic acid-functionalized materials should allow patterning of advanced functional organic materials.



ORGN 484

Carbon nanotubes by pyrolysis of plastics and characterization techniques

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There has been an enormous amount of research done on carbon nanotubes (CNTs). Primarily due to the interesting properties and potential applications of CNTs. Herein we present methods for the synthesis of CNTs via pyrolysis of plastics using metal catalysts. The introduction of a transition metal/rare earth element (REE) is necessary for the synthesis. In addition, the substrate used for the formation of the CNTs has importance. We discuss further the different techniques used to characterize CNTs via spectroscopic, diffraction, microscopy techniques.

ORGN 485

Development of multicolor 3-dimensional photoactivatable light display

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Our group has shown that fluorescence emission from photoswitchable rhodamine B dye molecules can be used to generate 3-dimensional images and animations in a volumetric light photoactivatable display. The 3D light structures are formed by cross-projecting UV and visible light beams simultaneously through a solution of photoswitchable fluorescent dye. The first generation of our 3D light PAD utilized photoactivatable red-emitting N-phenyl spiro lactam rhodamine B derivatives. We have since built upon this to include multi-color display through synthesis of a fluorescent photoswitchable dyes with green emission. However, practical application of our 3D light PAD is limited by reaction kinetics. This talk will highlight the synthesis and characterization of various derivatives of both the red and green-emitting N-phenyl spiro lactam rhodamine B derivatives in order to optimize reaction kinetics and quantum yields of the molecules.

ORGN 486

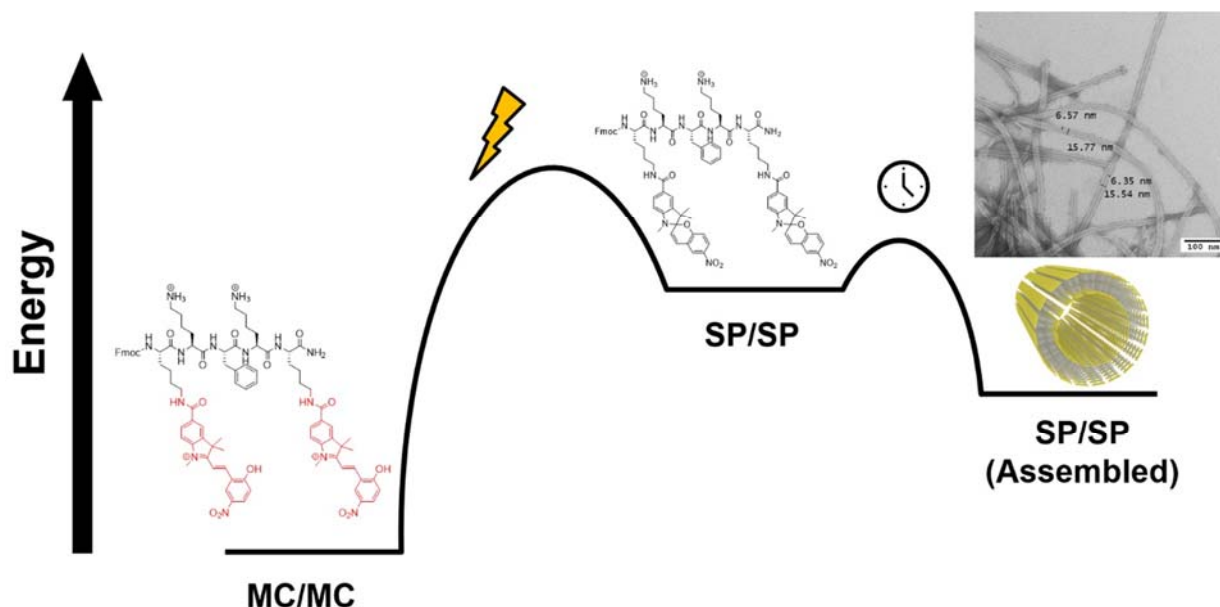
Spiropyran-based non-equilibrium self-assembling systems: Investigation of transient nanostructures

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Self-assembly is a key process in both nature and industry for the formation of larger aggregates from smaller monomeric components. While most of the focus in the field of self-assembly has been on static self-assembly, an area that many researchers have been striving to investigate more thoroughly is non-equilibrium/dynamic self-assembly. A system formed by dynamic self-assembly can have many useful abilities such as responsiveness to environmental changes, self-healing, and self-replication. However, when examining the literature dealing dynamic self-assembly it becomes clear that, in both applications and theory, it is still in its larval stage. To this end, our focus is the development of a dynamically self-assembling system which utilizes the energy of visible light to create metastable nanostructures.

We report the design, synthesis, purification, and characterization of a pentapeptide with spiropyran functionalization. The photochemical and thermal isomerization ability of this compound was studied along with its ability to self-assemble. In 30% MeCN/water with 0.75% TFA Fmoc-K(SP)KFKK(SP)-NH₂ completely isomerizes to its SP/SP form in visible light in 5 minutes, while the conversion to its MC/MC form occurs in 30 minutes of heat at 60°C. The changing of states can be observed via UV-Vis, NMR, HPLC, and even by the naked eye at sufficient concentration. The pentapeptide self-assembles into

nanotubes roughly 14 nm in diameter when incubated in visible light overnight. The pentapeptide also behaves as a dynamic self-assembling system in the presence of heat and light, assembling into metastable nanotubes only while constantly irradiated with visible light.



ORGN 487

Transmembrane ion transport by asymmetric multiblock amphiphiles

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Transmembrane proteins that can transport materials across the cell membranes and transduce signals are crucial for maintaining varieties of cellular activities. Intriguingly, some ion channels can transport ions in a selective and an anisotropic manner, which is driven by the difference of electrochemical potential across the cell membranes. In our group, we have developed synthetic mimetics of such ion channels that consist of hydrophilic oligo(ethylene glycol) chains and hydrophobic aromatic units. We found that these molecules localize within the lipid bilayer membranes and transport ions. Furthermore, the ion transport property can be controlled by ligand bindings or external stimuli such as mechanical stress.

However, development of synthetic ion channels that enable rectified ion transport still remains a major challenge in this field. For this purpose, we focused on the structure of a KcsA potassium channel, whose rectified ion transport is achieved with the help of dipole moments along the channel axis. Inspired by the structure and the function of KcsA, here we newly designed asymmetric multiblock amphiphiles that possess dipole moments along their molecular axis (**Figure 1**). We anticipated that such molecular design may bias the direction of their ion transport. Transmembrane ion transport of the asymmetric multiblock amphiphiles was evaluated by single channel current recordings under different voltage directions. Details will be reported at the conference.

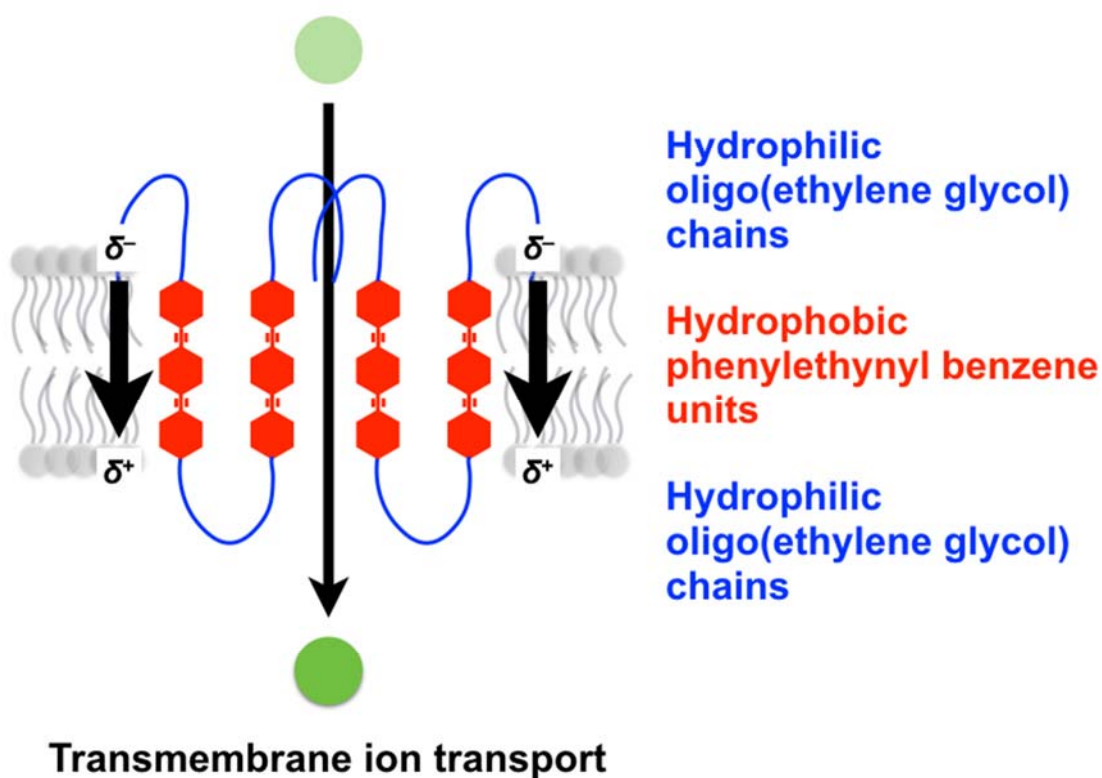
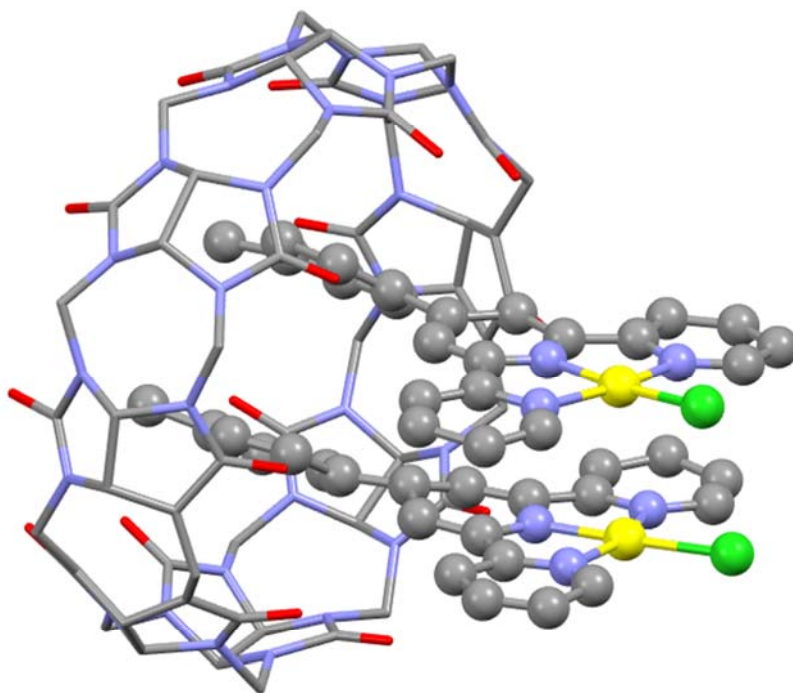


Figure 1. A schematic molecular structure of a multiblock amphiphile that has dipole moments along its molecular axis, and an illustration of a transmembrane ion channel formed within the lipid bilayer membranes.

Utilizing CB[8] to enhance activity of Pt photocatalyst in water reduction

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Hydrogen might be the best alternative to fossil fuels, yet the challenge is to produce it from a cheap and abundant source such as water. The research on developing molecular photocatalysts that can split water started in the late 80's. However, the efficiency of the catalysts needs to be improved to produce hydrogen on a large scale. A catalytic system for the photolysis of water consists of three components: an electron relay, a photosensitizer and a photocatalyst. Platinum terpyridine chloride ($[\text{PtCl}(\text{tpy})]^+$) is known to act as both photosensitizer and photocatalyst. The proposed mechanism for catalytic hydrogen production involves a close interaction between two Pt nuclei. Here, we use Cucurbit[8]uril (CB[8]) as a tool to secure Pt complexes together as dimers. We found that the formation of a 2:1 assembly between CB[8] and complex $[\text{PtCl}(\text{tpy})]^+$ efficiently promotes hydrogen formation upon irradiation of an aqueous solution of the supramolecular assembly.



ORGN 489

Investigating alkyl halogen- π interactions: Torsion balance approach

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Halogen— π interactions, such as those between halogenated drugs and aromatic amino acids, are well-known to improve drug-receptor binding affinities and are widely implicated in rational drug design. The focus has primarily been on aryl halide systems, while alkyl halogen— π interactions have been studied far less extensively (Figures 1a,b). We use a molecular torsion balance to investigate alkyl halogen— π interactions, which positions the C_{sp3}-halogen over the balance's bottom aryl shelf and allows for the direct, solution-phase quantification of the relative populations of folded versus unfolded

conformations (Figure 1c). We present our progress toward a systematic investigation of alkyl chlorine/fluorine— π interactions.

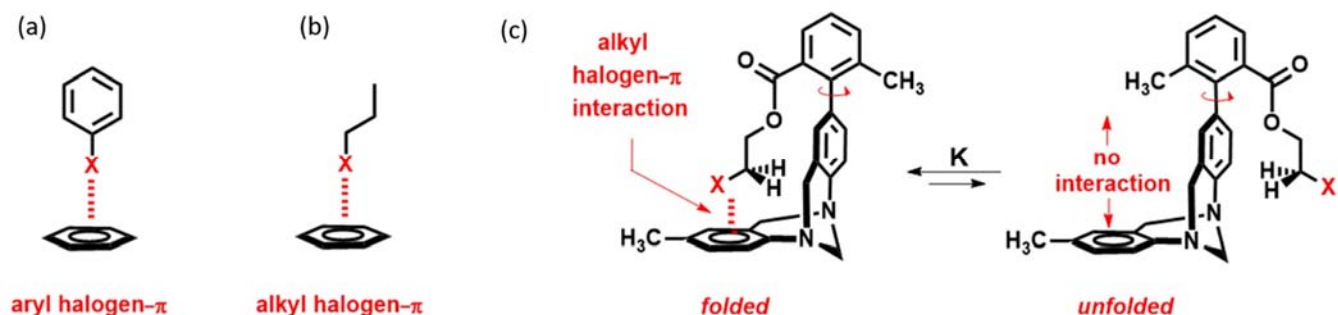


Figure 1. a) Aryl and b) alkyl halogen— π interactions. c) Conformational states of a molecular torsion balance for investigating alkyl halogen— π interactions (X = F or Cl).

ORGN 490

Recognition properties of 2,1,3-benzoselenadiazoles: Window into chalcogen bonding

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The 2,1,3-benzoselenadiazole scaffold has generated strong interest for its ability to form reliable 2Se—2N square dimer interactions in the solid state (Figure 1), leading to conducting, optoelectronic, and solar cell properties. However, many gaps remain in our understanding of the extent of square interactions, and when squares are overpowered by other recognition forces. We take advantage of 2,1,3-benzoselenadiazole's propensity for crystallization so that we may fully characterize its interactions using X-ray crystallography. This poster presents our progress in synthesizing a library of 2,1,3-benzoselenadiazole derivatives and their corresponding solid-state interactions.

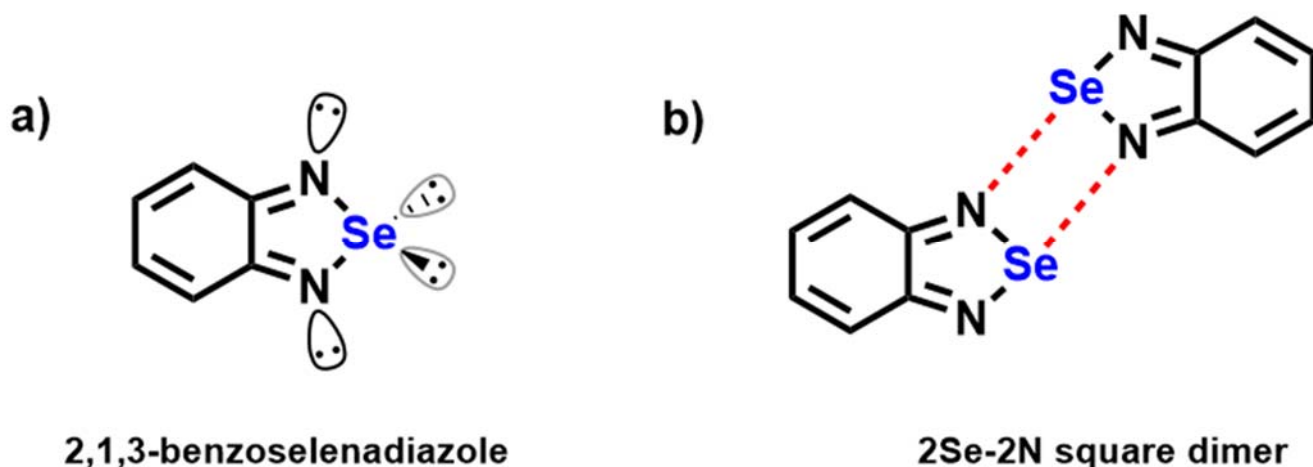


Figure 1. a) Top view of the 2,1,3-benzoselenadiazole core structure and location of the lone pair electrons: N in plane, Se out of plane. b) 2Se—2N Square dimer interaction.

ORGN 491

Suprastructures with tunable emission from assembled metallacages

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Suprastructures prepared from functional subcomponents are of growing importance as building blocks for the creation of synthetic hierarchical materials. The inspiration for using metal-organic complexes (MOCs) as subcomponents originates from their characteristic properties, such as the ease of fine-tuning the dimensions of the complexes, the coordination geometry, and the simple incorporation of essential functional groups. Here, two new shape-controllable, hybrid metallacages with modified substituents and tunable electronic properties were prepared using dicarboxylate ligands with various substituents (Naphthalene and pyrene), tetra-(4-pyridylphenyl) ethylene, and *cis*-(PEt₃)₂Pt(OTf)₂. The as-prepared metallacages were used as building blocks for further assembly. Diverse suprastructures with tunable emissions were prepared depending on the substituents and solvents used.

ORGN 492

Anion effects on reaction within hydrophobic yoctoliter spaces

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Studies of reactions within yocto-liter reaction flasks are an important part of the drive towards more efficient and/or unique chemical conversions. In our ongoing studies with water-soluble, dimeric capsules formed from Positand 1 (P1), we have been examining the effects of dissolved anions on cyclization reactions. In this presentation we will reveal how dissolved salts outside the host affect the cyclization of 12-bromodecane-1-thiol inside the capsule. Our studies utilizing ^1H NMR spectroscopy reveal that relatively charge-diffuse anions can bind to the outside of the capsule, attenuate the electrostatic field generated by the cationic water-solubilizing groups, and hence affect rates of cyclization. Thus, our results show that extrinsic species dissolved in the aqueous solution are capable of tuning reaction rates of processes within these yocto-liter flasks.

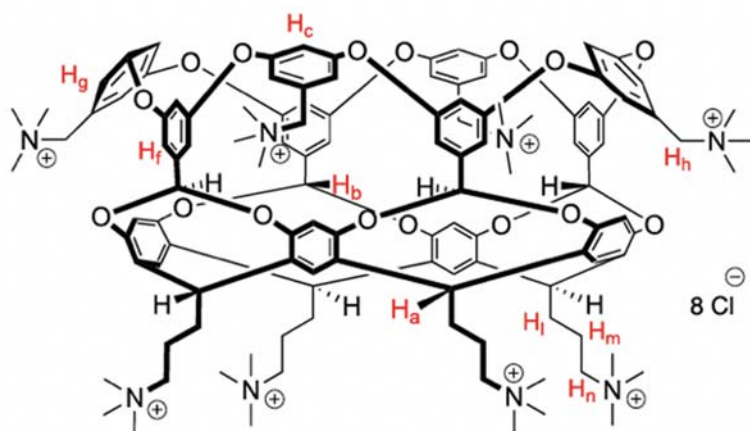


Figure: Positand 1

ORGN 493

Fluorescence approach for quantitative detection of H₂S in biosamples based on 1,8-naphthalimide

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H₂S play a crucial role in the biological system, including regulating vascular contractility, controlling stress tolerance, and maintaining cellular redox environment. Interestingly, these biofunctions are highly dependent to the local concentration, which determines the beneficial or detrimental effect. Therefore, developing a robust method for quantitative detections of H₂S molecules is highly desired. In past years, many efforts have been devoted to design fluorogenic approaches for detection of cellular H₂S in our research group. At here, we report a sensor for quantitative detection of H₂S based on 1,8-naphthalimide with a high affinity and selectivity.

ORGN 494

Multicomponent synthesis of 1,4-disubstituted-1,2,3-triazoles using N-(phenyl)-N-2-pyridyl urea as ligands

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Heterocyclic compounds such as 1,2,3-triazoles have been used in many different fields such as medicinal chemistry, biological science, and material science. 1,2,3-triazoles can be synthesized using a copper(I) catalyzed alkyl azide cycloaddition reaction, otherwise known as a click reaction. Click reactions produce 1,4-disubstituted 1,2,3-triazoles relatively quickly, with high yield, low byproducts, and can happen under mild conditions. In this research, an N-(phenyl)-N-2-pyridyl urea (NPPU) ligand is used to catalyze the click reaction. The NPPU ligand was chosen since it is easy to make using relatively inexpensive ingredients, compatible with copper, and compatible with green solvents.

After a series of tests, the optimized reaction conditions were determined to be: terminal alkyne (1 equiv.), halide (2 equiv.), sodium azide (1.6 equiv.), ligand (0.05 equiv.), and copper (I) oxide (0.05 equiv.) combined in a 50 mL round bottom flask with 8 mL of methanol. The reaction mixture was then stirred at room temperature for 16 hours, followed by the reaction mixture being filtered through Celite to extract the copper and ligand. The solvent was evaporated under reduced pressure to obtain the crude product which was then purified via column chromatography using hexanes and ethyl acetate as an eluent. Under these reaction conditions, a selection of different halides and alkynes were used in order to determine what steric and electronic factors affect the reaction.

ORGN 495

Synthesis of Ru(II) 2,6-di-(quinolin-8-yl)pyridine substituted naphthalene diimide supramolecular polymers

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Conversion of sunlight into energy through the use of organic photovoltaics (OPVs) devices may provide clean, renewable energy with potential low production costs, high flexibility, and low environmental impact. Production of efficient materials with these properties still lags behind conventional silicon-based materials. One approach toward increasing the charge-separation yield, and therefore the overall efficiency, of an OPV uses supramolecular polymers that have been prepared with redox active metal complexes that absorb visible light efficiently and have long excited-state lifetimes. Ruthenium polypyridyl groups are well-known for having long-lived triplet metal-to-ligand charge transfer state (³MLCT) excited state lifetimes, making them excellent donors in donor-acceptor polymers. In this presentation the synthesis of supramolecular polymers

containing ruthenium 2,6-di-(quinolone-8-yl)pyridine (dqp) complexes appended to core-substituted naphthalene diimide (NDI) groups are discussed.

ORGN 496

Arsenic recognition by azacryptand metallo-receptors

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Arsenate is a species known for its toxicity to living organisms. The International Agency for Research on Cancer (IARC) considers arsenic compounds highly toxic and classified them as group I (human carcinogens). For this reason, the U.S. Environmental protection agency (EPA) sets an arsenic maximum contaminant level for public water supplies at 0.010 mg/L (0.010 ppm). Bangladesh, Chile, Taiwan and the US are all countries that have high arsenic exposure via drinking water. Thus, a reliable and sensitive technique and portable detection tools are sought.

In this work, the changes of energy transfer of various aza-macrocyclic ligand to Eu^{3+} have been monitored. The detection method is based on switch OFF-to-ON of the Eu^{3+} luminescence in the presence of arsenate.

A sensing ensemble comprising a nitrogen-based cryptand ligand and the Eu^{3+} / Zn^{2+} cocktail in MeOH is capable of sensing of aqueous arsenate anion (HAsO_4^{2-}) with the attendant increase in luminescence while providing a clearly observable turn-On signal. The binding processes associated with the change of the luminescence signal has been investigated using luminescence spectroscopy.

Further plans include the incorporation of polymerizable cryptand receptors into hydrogels and polymerized colloidal crystal arrays. This leads us to an environmentally safe and easily portable arsenic detector.

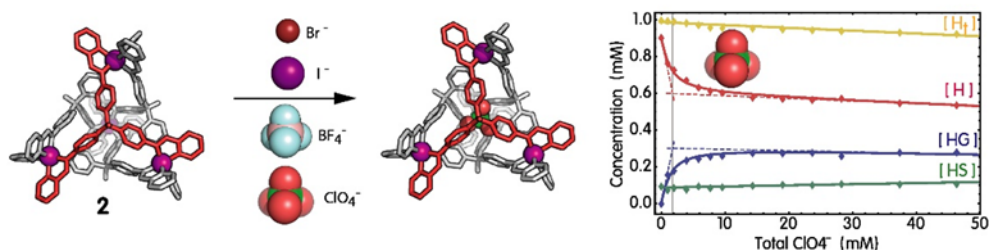
ORGN 497

Binding of anionic guests in a face-capped Co_4L_4 supramolecular hosts

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The thermodynamics of host-guest binding have played an important role in supramolecular chemistry since the inception of this field. In this presentation we will look at some of the challenges and strategies used to quantify the strength of host-guest interactions. Specifically, we will present titration isotherms for encapsulation of a series of anions (Br^- , I^- , BF_4^- , and ClO_4^-) in a supramolecular Co_4L_4 tetrahedral cage, where $\text{L} = \text{HO-C}(\text{PhNH}_2)_3$. We have found that smaller guests like Br^- and I^- show strong binding ($5,000$ - $15,000 \text{ M}^{-1}$) while larger anions such as BF_4^- and ClO_4^- show

weaker binding ($500\text{--}1,000\text{ M}^{-1}$) within the small cavities of these face-capped tetrahedral cages. The mathematical modeling is complicated by competition from solvent for the cavity, as well as competitive external ion-pairing with the TBA counter-ion added during the titration.



Anionic encapsulation of Co_4L_4 host and titration isotherm

ORGN 498

Evaluation of small molecules that bind and stabilize G-Quadruplex DNA

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G-quadruplexes are higher-order structures formed in guanine-rich sequences of nucleic acids. The quadruplex structure can occur naturally in G-rich sequences and have been identified in telomeres and gene promoter regions. Proteins and ligands can bind G-quadruplexes, stabilizing DNA and RNA, and inhibit or promote replication, transcription, and translation. As these structures are linked to such diverse functions, the development of small molecules to stabilize the G-quadruplex structure has garnered significant attention. The goal of our research is to synthesize and evaluate small molecules that stabilize the G-quadruplex structure. Through the derivatization of azobenzene and indigo based dyes, a small library of organic compounds was synthesized in 1-3 steps. These compounds, in addition to a small selection of RGG-motif peptides, were tested for G-quadruplex stabilizing abilities by measuring changes in melting point curves of DNA as measured by circular dichroism. Several of the drugs increased the melting temperature of the DNA, demonstrating that these core structures possess the ability to stabilize the telomeric G-quadruplex structure.

ORGN 499

Synthesis and spectroscopic studies of fluorophores for selective metal binding and single-molecule fluorescence imaging tags

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Neutrinos are fermion subatomic particles that interact only by the weak subatomic forces — making them almost impossible to detect. However, they can be produced in specific radioactive decay reactions, such as beta decay.

We hypothesize the detection of double beta decay through the tagging of the Ba^{2+} daughter ion from ^{136}Xe ($^{136}\text{Xe} \rightarrow ^{136}\text{Ba}^{2+} + 2n + 2b$). The proposal is to develop single-molecule fluorescence imaging (SMFI) technology to investigate gaseous chemical constituents in high-pressure gases (ca. 30-150 psi) at gas-solid interfaces. To achieve proper SMFI, of heterogenous self-assembled monolayers (SAMs) containing fluorophores that operate under dry conditions, and that is turned on when a covalently attached binding domain captures Ba^{2+} .

Different aza-crown-ether chelating agents with diverse fluorophores were designed and synthesized. The anthracene substituted aza-18-crown-6 ether specifically showed the fluorescent response to Ba^{2+} cation in a dry phase with a small intrinsic background from the unchelated state through Electron Multiplying CCD camera (EMCCD).

ORGN 500

Influencing polymorphism of sulfameter

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While attempting to grow co-crystals from 1:1 solutions of sulfameter and carboxylic acids, researchers at Ferris State University were surprised to obtain, instead, crystals of a polymorph (form III) of sulfameter from experiments containing benzilic, hydrocinnamic, or 2-nitrobenzoic acids. Subsequently, questions were raised about the role that the carboxylic acids played in inducing growth of form III and about whether sulfameter could be induced to crystallize in form III even when adding a much smaller amount of carboxylic acid. Graph sets were used as a tool to analyze the hydrogen-bond connectivity in previously published crystal structures of sulfameter (forms I and III) and 1:1 aspirin-sulfameter cocrystal. Insight gained from this analysis was applied in proposing a mechanism by which drug-acid association in solution might promote growth of form III. In an attempt to determine the smallest amount of acid required to induce the growth of form III from solution, crystals were initially grown by evaporation of solutions containing equal amounts of sulfameter and carboxylic acid. The experiment was repeated multiple times, each time cutting the amount of acid until 1/100th the molar quantity of drug was reached. The products were analyzed using infrared spectroscopy in order to determine which form of the drug had been obtained. It was discovered that under fast evaporation (2-4 days), the crystals obtained were usually a mixture of forms I and III, but under slow evaporation (9-24 days), pure

crystals were the norm. It was surprising to find that form III appeared even when there was a hundred times more sulfameter than acid; although with trace amounts of acid, occasionally mixtures of form I and III appeared. Results of the graph set analyses, a proposed mechanism, and results from the crystallization experiments of sulfameter are reported.

ORGN 501

Removing the solubility barrier in ternary cocrystal formation

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Attempting to grow a ternary cocrystal from solution often results in two of the components forming a binary cocrystal, while leaving the third component still dissolved in solution. In practice, merely changing the solvent or ratios of the components to favor the ternary cocrystal is frequently an ineffective strategy. The purpose of this research was to determine if ternary cocrystals and their competing binary cocrystals could be synthesized in the absence of solvent. Four ternary cocrystals that had been recently designed and synthesized, each containing a carboxyphenol as a ditopic hydrogen-bond donor and two types of acceptor compounds (an amidine and a pyridine), were selected. Initially the four known ternary cocrystals and their competing binary cocrystals were grown from solution, confirming their stoichiometry through solution pNMR and establishing a fingerprint of each cocrystal by infrared spectroscopy. Attempts were made to regenerate the ternary cocrystals and competing binary cocrystals through one or more of the following non-solution methods: a) neat grinding b) liquid-assisted grinding or c) melting. Two of the four known ternary cocrystals were solvates and consequently their synthesis could only be attempted through liquid assisted grinding. Synthesis of the other two ternary cocrystals was attempted using all the three non-solution methods. Product identity was determined by comparison of the infrared spectra to that of previously identified crystal phases, and all ternary non-solution experiments yielded products whose infrared spectra matched those of the ternary cocrystals obtained from solution. Six known binary cocrystals were regenerated by non-solution methods. Surprisingly, the binary non-solution experiments yielded eleven products whose infrared spectra differed significantly from all previously observed binary phases.

ORGN 502

Crystal structure analysis of the chirality switching of the diastereomeric salt resolution of ($\pm$)-praziquanamine with two aryl esters of L-tartaric acid

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The resolution of praziquanamine, a derivative of the anti-schistosomiasis drug Praziquantel, has an unusual change in enantioselectivity when using two different aryl esters of L-tartaric acid. Dibenzoyl-L-tartaric acid affords (*R*)-praziquanamine as the major enantiomer while di-*p*-anisoyl-L-tartaric acid affords (*S*)-praziquanamine as the major enantiomer. In this work, crystals of all four combinations of (*R*)- and (*S*)-praziquanamine with dibenzoyl-L-tartaric acid and di-*p*-anisoyl-L-tartaric acid were grown by slow evaporation with a mixture of isopropanol:water and analyzed by X-ray diffractometry. Preliminary results show tighter packing patterns and a higher propensity for forming crystals within the matched pair of enantiomers and resolving agents, with the mismatched pairs showing looser crystal packing. Intermolecular interactions leading to these tendencies will be presented.

ORGN 503

Phenylalanine mutation to cyclohexylalanine facilitates triangular trimer formation by β -hairpins derived from A β

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Oligomers of β -amyloid peptide, A β , are believed to play central role in pathogenesis and progression of Alzheimer's disease. Trimers and higher-order oligomers derived from trimers are believed to be the most potent neurotoxic of A β oligomers. Our laboratory has designed and synthesized macrocyclic peptides derived from A β_{17-36} to gain insights into structure and assembly of A β oligomers. In the current study, we found that mutating Phe₂₀ to cyclohexylalanine (Cha) of macrocyclic A β -derived peptides further stabilizes trimers and permits incorporation of more of the native residues including the A β_{24-29} loop. Using the F20Cha mutation, we were able to crystallize A β -derived peptides containing the A β_{24-29} loop. X-ray crystallography showed that A β -derived peptides containing the A β_{24-29} loop and the F20Cha mutation assemble to form hexamers and dodecamers. SDS-PAGE experiments corroborate the formation of dodecamers. Peptides containing the A β_{24-29} loop exhibit increase in cytotoxicity against neuroblastoma cell-line SH-SY5Y. Collectively, the studies demonstrate use of the F20Cha mutation to further stabilize oligomers of A β -derived peptides that contain more of the native sequence and better mimic the oligomers formed by full-length A β .

ORGN 504

Efforts in the synthesis of auxiliary molecules for epimerization-free peptide ligation

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Many fields of chemical research rely on a ready source of enantiomerically pure protein subunits that have been constructed to precise specifications. This necessitates that the synthesis of peptide chains is stereospecific. However, stereospecific synthesis of peptide fragments is challenging because epimerization of amino acid side chains commonly occurs alongside amide bond formation, or ligation. Epimerization in organic synthesis is a process by which a chiral center within a molecule temporarily transitions into an achiral form, such as by rearrangement or tautomerization, and then transitions back into a chiral form. Unfortunately, when the chiral center reforms, both chiral orientations (*R* and *S*) form, which reduces the enantiomeric purity of the peptide fragment. In particular, epimerization is commonly observed when overly reactive electrophiles, such as acid chloride derivatives of the C-terminus, are used during the ligation step. Zhang and others have developed synthetic peptide auxiliaries to support epimerization-free ligation, by providing an alternative to acid chlorides as precursors in peptide ligation. These auxiliary molecules provide a way to facilitate amide bond formation between the amino acid and peptides through a weak electrophile, which itself is not susceptible to epimerization. Once the peptide and amino acid are linked via the auxiliary molecule, intramolecular amide bond formation between the peptide and amino acid becomes energetically favorable. In this work, progress in the synthesis towards an aromatic peptide auxiliary, which prevents epimerization through steric bulk, is described. The long-term goal of the project is to develop an auxiliary that will make epimerization-free ligation between any two peptides possible.

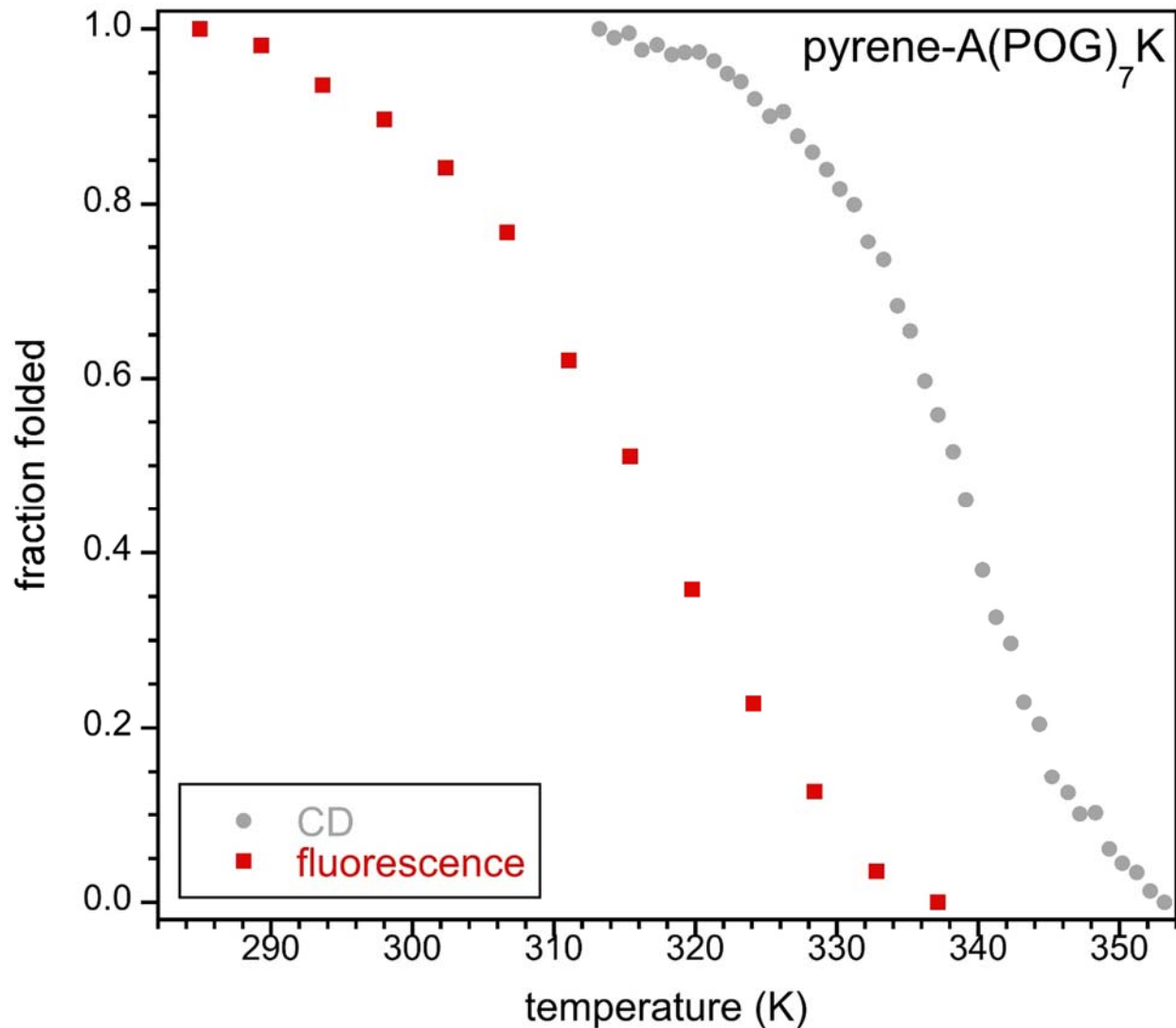
ORGN 505

Pyrene as an "unreliable narrator": Monitoring collagen triple-helicity by CD and fluorescence

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Research on collagen structural stability has largely focused on model peptides (CMPs) comprised only of (Pro-Hyp-Gly) repeat units. This investigation aims to develop collagen strands with heightened functionality. Thermal stabilities of triple-helical CMPs featuring the fluorophore pyrene at their *N*-termini have been evaluated using fluorescence spectroscopy and circular dichroism (CD). Flanking the (Pro-Hyp-Gly)_{*n*} core of the peptide monomers, the residues Ala, Asp, Glu, and Lys were introduced to impart varying degrees of "fraying." Triple helices derived from such peptides show a broad excimer emission at ~485 nm, indicative of close approach between pyrene units. The excimer intensity decreases upon heating. For sequences with a Lys residue adjacent to the pyrene probe, melting temperatures (*T*_m) obtained from fluorescence are within 2 °C of those determined using CD, even though the CD samples were typically

four times more concentrated. The most significant disagreement between the two techniques was found for the peptide with the least helix-disruptive residue (*i.e.*, Ala) adjacent to the fluorophore. This anomalous result will be discussed in detail in this presentation. In ongoing work, the linker between the pyrene unit and peptide has been modified with a proton-accepting amine group. By changing the pH, this bridge could be utilized as an “on-off” switch for higher-order assemblies of CMPs.

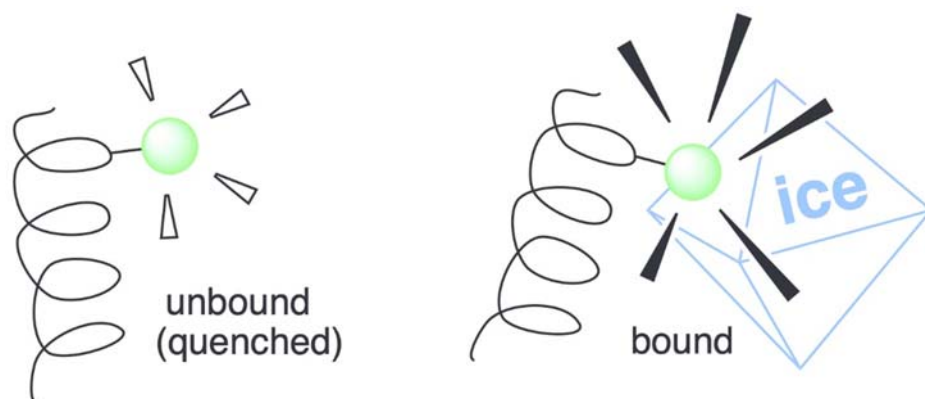


ORGN 506

Do antifreeze glycopeptides bind to ice reversibly or irreversibly?

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Antifreeze glycoproteins (AFGPs) are cryoprotective agents that occur naturally in cold-water fish. AFGPs consist of three-residue repeats (Ala-Ala-Thr*)_n or (Pro-Ala-Thr*)_n, in which a disaccharide is attached to the side-chain of Thr. They adopt a polyproline II helix, with hydrophobic methyl groups (from Ala) on one face and hydrophilic sugars on the opposite face. AFGPs are known to induce thermal hysteresis and to inhibit ice recrystallization. However, the mechanism by which they bind to ice is unclear. Recent molecular dynamics simulations suggest that the methyl groups can “walk” along the ice surface to find properly-spaced cavities, then can reversibly adsorb in order to prevent ice formation. Conversely, another study using fluorescence microscopy indicates that the disaccharides are irreversibly incorporated into the ice crystal lattice. We have attached a water-sensitive naphthalimide fluorophore at various locations throughout an AFGP in order to probe the mode of binding. Unravelling the AFGP-ice interaction would allow for advances in preservation of biological tissues and frozen foods.



ORGN 507

Solid-phase synthesis of cysteine-containing potential anticancer depsipeptidic HDAC inhibitors

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We describe the synthesis of Xyzidepsin and related molecules, all of which are depsipeptidic analogs of Romidepsin (FK228). Our solid-phase strategy generates

linear, protected precursors for these bicyclic molecules using a latent thioester solid-phase linker. Global deprotection followed by mild, selective conditions unmask the thioester functionality and provides the completed macrocycles. Our synthetic approach represents a generalizable route toward a range of analogs, including structures that can include acidic and basic amino acids, and is therefore well-suited to SAR.

ORGN 508

Design, synthesis, and development of new fluorescent unnatural amino acids for genetic incorporation into proteins

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Genetically encoded unnatural amino acids (Uaas) provide new chemical tools that can be site selectively incorporated into proteins. This offers the potential for addressing biological questions at the molecular and cellular level. Uaas can be genetically incorporated into proteins using orthogonal tRNA-codon-synthetase sets. Our efforts have been focused on designing and synthesizing new fluorescent Uaa's and improving their incorporation efficiency. Here, we show the successful incorporation of the Uaa acridonylalanine (Acd) into *E. coli* cells with minimal perturbation to the protein of interest. A new Acd derivative of interest is 2-aminoacridonylalanine (Aad), which has a substantially red-shifted emission in comparison to Acd. While Aad is a possible candidate FRET acceptor for chromophores such as methoxycoumarin and Acd, it has a relatively low quantum yield. Therefore, we are synthesizing new derivatives that are 3-4 times brighter than Aad. We additionally are synthesizing and testing novel ester derivatives of the Uaas for improved uptake and incorporation in both mammalian cells and *E. coli*. Our long-term goal is the development of a palette of fluorescent Uaas across the spectrum that can be fully genetically encoded to facilitate the monitoring of protein processes.

ORGN 509

Semi-synthesis of post-translationally modified and fluorescently labeled alpha-synuclein enables identification of protein behavior regulation by subtle changes in modification levels

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Semi-synthesis is a versatile technique that allows for the site-specific incorporation of biologically relevant modifications and biophysical probes into proteins of interest. Alpha-synuclein (α S) is an intrinsically disordered protein, the pathological aggregates of which are hallmarks of Parkinson's disease. A variety of post-translational

modifications (PTMs), including phosphorylation, arginylation, nitration, and N-terminal acetylation, are believed to affect the structure of α S and its interactions with other biomolecules. We develop semi-synthetic routes combining organic synthesis, peptide synthesis, unnatural amino acid mutagenesis, and native chemical ligation to introduce PTMs of interest along with fluorescent probes into α S. Following the synthesis of unnatural amino acids bearing a PTM of interest or a bioorthogonal handle, we incorporate them into α S via peptide synthesis or amber codon suppression. We also present a novel chemoenzymatic strategy to synthesize α S bearing one PTM and two fluorophores with improved yield. To compare α S bearing authentic PTMs to their corresponding mimics, we make such mimics both through common mutations and by synthesizing a small molecule that we react with recombinantly produced protein. Through biophysical measurements, we characterize the conformation, aggregation kinetics, and vesicle binding affinities of our multiply modified α S to elucidate how subtle differences in PTM levels dramatically alter the behavior of the protein. Our study demonstrates the robust reliability of incorporating authentic PTMs via synthetic strategies and provides an assessment of the utility of certain chemical modification mimics in studying biological processes.

ORGN 510

Diastereoselective methodology for the synthesis of 3a hexahydropyrrolo[2,3b]indole containing synthon (HO HPIC) containing synthon

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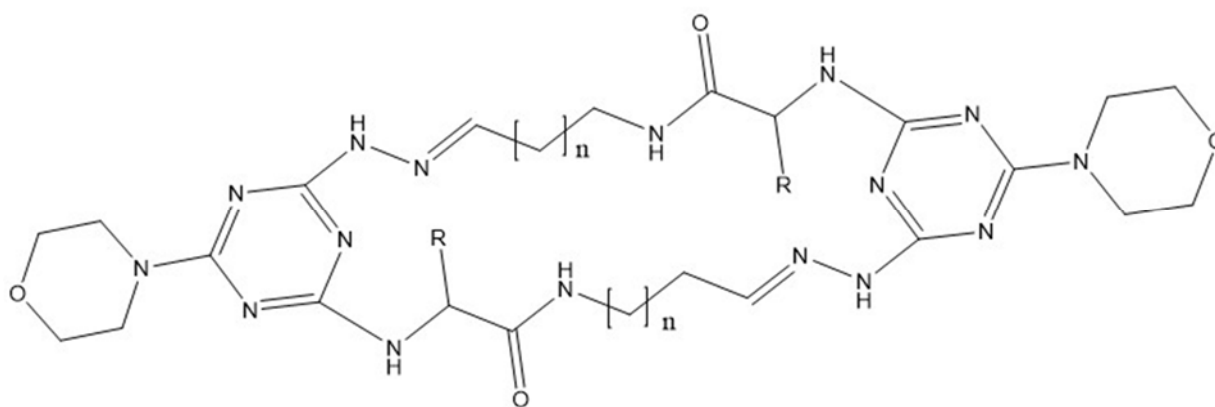
Currently, a natural 3a-hydroxyhexahydropyrroloindoline (HO-HPIC)-containing cyclopeptide family revealed encouraging medicinal properties. HO-HPIC-containing cyclopeptides extraction is tedious and low yielding, and consequently their potential medicinal properties are difficult to unravel. Furthermore, synthesis of HO-HPIC in laboratory often comes as a complex mixture of diastereoisomers which are difficult to purify from each other. Diastereoselective HO-HPIC synthesis was sought by reacting a N α -protected-tryptophan in aqueous solutions containing Oxone® (potassium peroxymonosulfate) and a series of commercially available constrained ketones in presence of ethyl lactate. Primary results suggested no clear diastereoselective effect from the various ketones used but ethyl lactate appeared to decrease the byproduct formation simplifying the product purification.

ORGN 511

Effects of steric bulk on macrocycle formation

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Macrocycles are clinically relevant. Interest in this class of molecules has grown in recent years because it is believed that these molecules have the ability to interfere with protein-protein interactions. However, due to synthetic challenges, macrocycles are not readily prepared. In early reports from our group, macrocycles resulting from spontaneous dimerization of monomers was reported. These studies and unpublished work shows that the ring size of these macrocycles can be varied from 22-28 members by varying the amino acetal subunit. Here, we look at the effect that ring size and steric bulk of the amino acid has on the conformation of these macrocycles in solution as well as solid state. This study specifically looks at macrocycles incorporating glycine, alanine, or valine in rings comprising 22, 24 or 26 atoms. Evidence for ring topology comes from ^1H and ^{13}C NMR and x-ray crystallography.



General structure for studied macrocycles

R changes depending on amino acid that is incorporated into the macrocycle

n changes depending on the length of the amino acetal subunit

ORGN 512

From nickel-catalyzed reductive coupling to cyclic peptide synthesis

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As drug candidates, cyclic peptides have significant therapeutic potential over other classes of peptides. For example, cyclic variants are more resistant to both exo- and endo-proteases. Therefore, in recent years, cyclic peptides have attracted an increasing amount of attention from both the scientific community and pharmaceutical companies. Multiple synthetic methods have been developed to obtain cyclic peptides; however, strategies utilizing natural amino acids in the macrocyclization are considerably limited. Recently, our group developed a strategy to harness alkyl amines as alkylating agents via C–N bond activation. We have now developed a reductive cross-coupling using pyridinium salts formed from the amino group of L-lysine's side chain. These reactions

proceed in good yields without loss of enantiomeric purity. Excitingly, this method has been advanced to a new peptide macrocyclization strategy harnessing L-lysine Katritzky pyridinium salts. The optimization and scope of these methods will be presented.

ORGN 513

Illuminating the assembly and cellular interactions of a trimer derived from A β

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Understanding the solution phase and biological behavior of the β -amyloid (A β) peptide is key to understanding Alzheimer's Disease (AD). Oligomeric assemblies of A β are suspected to be the leading cause of neurotoxicity, but their mechanism of action remains poorly understood. The Nowick lab has established a chemical model for A β oligomers by stabilizing fragments of A β in a macrocyclic β -hairpin structure and then stabilizing these macrocycles into covalently-linked trimers. Solution phase studies of the covalently-linked trimers have thus far been limited to SEC and SDS-PAGE, but fluorescent labeling has emerged as a new tool to study the solution phase and biological behavior of the trimers. These studies using fluorescence spectroscopy and fluorescence microscopy have provided insights into biological and solution-phase behavior of A β oligomers.

ORGN 514

Exploring conformation space for peptidomimetic macrocycles

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Spontaneous condensation of monomers comprising an amino acid acetal and arylhydrazine group leads to macrocyclic dimers, and not oligomers or polymers. Early proof-of-concept reports examined ring size through substitution of the amino acetal group. These studies showed that macrocycles ranging from 22-28 membered rings could be prepared. Here, different amino acids are explored to probe the generality of this methodology. Amino acids including G, A, V, S, K, and D all can be incorporated into monomers and yield a macrocycle upon dimerization. Initial studies of F and W suggest that there may be limits to the generality of this method. Evidence for macrocycle formation comes from ¹H and ¹³C NMR, mass spectrometry and x-ray crystallography. A diagnostic pattern of chemical shifts in both ¹H and ¹³C NMR as well as evidence for hydrogen formation suggests an opportunity to predict solution structure.

ORGN 515

Intraresidue (C5) H-bonding mimicry of chloroalkene dipeptide isosteres

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The new advances in the development of chemical tools for investigating biomolecular events could provide novel molecular strategies to understand and control those events. In particular, amide-to-alkene isosteric switching in the peptide backbone is a promising approach to probe the backbone-mediated interactions, including H-bonds in the molecular recognition of peptides. Despite there are many reports of backbone modifications, there are few reports to elucidate the functional mimicry of those-type isosteres.

In this study, we describe the unique ability of chloroalkene-type peptide bond isosteres to mimic the intraresidue hydrogen bonds between the carbonyl oxygen and the amide proton of the same residue. These interactions contribute significantly to the conformational stability of the beta-sheets of the amyloid state, which is linked with various neurodegenerative disorders. Kinetic studies of H/D exchange reactions of amide proton using Deg-type and Val-type compounds revealed that the chlorine atom of the (Z)-chloroalkene moiety could mimic the *p*-type H-bonding interaction to provide the protective effect slowing the H/D exchange reaction. In addition to the ¹H-NMR and infrared spectroscopic analyses, X-ray crystallographic analysis of the peptidomimetic containing a Val-D-Ala-type (Z)-chloroalkenetype dipeptide isostere revealed that there is an attractive interaction between the amide proton and the chlorine. To the best of our knowledge, this is the first example in which the basis of C5 H-bonding mimicry of alkene-type peptide bond isosteres has been uncovered. Details of the kinetic studies, spectroscopic, and structural analyses of those isosteres will be discussed.

ORGN 516

Chemical synthesis of sphingolipid activator protein for treating lysosomal disease

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Protein therapeutics containing glycoproteins have been increasing attention as attractive potential agents for treating diseases once thought incurable. In therapeutic development using proteins, a critical issue is how protein molecules are produced. Genetic engineering procedures using mammalian cells represent a significant advance in the production of naturally occurring proteins; however, strict control of post-translational modifications such as glycosylation using genetic protocols is far from satisfactory.

One alternative to genetic protocols is chemical synthesis of proteins in which the protein backbone is constructed using step-wise solid-phase peptide synthesis followed

by ligation chemistry to assemble peptide segments. Chemical synthesis enables us to produce proteins having any structures at any sites as a homogeneous molecule even proteins with complex post-translational modifications.

Sphingolipid activator proteins are small, nonenzymatic glycoproteins that are ubiquitously present in lysosomes. GM2 activator protein (GM2AP) is one of sphingolipid activator proteins involved in degradation of GM2 ganglioside by β -hexosaminidase A. Functional deficiency of GM2AP causes abnormal accumulation of GM2 in the nervous tissue. Protein replacement therapy, based on supplying a functional protein as an alternative to the defective protein, has served as a potential therapeutic approach to such disorders.

We have developed methodology for chemical synthesis of a protein and synthesized biologically active proteins for more advanced protein therapeutics. In this presentation, we will discuss about methods for chemical synthesis of proteins and synthesis of biologically active GM2 activator protein as protein therapeutics for lysosomal storage disease.

ORGN 517

Impact of aza-glycine and aza-proline residues on triple helical collagen self-assembly and stability

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We previously demonstrated aza-glycine considerably improves collagen's thermal stability and self-assembly properties without changing collagen's natural triple helix topology. We provided a firm structural basis for this stabilization with an atomic resolution crystal structure of collagen containing aza-glycine which revealed new cross-strand H-bonds within the triple helix interior. Here, using computational analysis, we show the enhanced properties of aza-glycine is a result of non-covalent forces (H-bonding) and backbone preorganization. The interplay of steric repulsion and hyperconjugative interactions in aza-glycine's backbone directly preorganizes the collagen peptide main-chain (ϕ , ψ) dihedrals for triple helical assembly. The synergy of multiple structural and electronic changes which originate at the residue level in the aza-glycine backbone and culminate at the macromolecular level of the triple helix lead to increased stability and faster refolding of collagen peptides containing aza-glycine.

Recent biophysical studies have demonstrated that natural L-amino acids can be replaced with non-natural achiral aza-amino acids in folded protein structures such as triple helical collagen. However, the structural consequences of achiral aza-amino acid incorporation has not been elucidated in the context of any relevant folded biomolecule. Here, we use X-ray crystallography to provide the first atomic resolution crystal structure of an achiral aza-amino acid residue embedded within a folded protein structure, definitively illustrating that achiral aza-proline has the capacity to effectively mimic the

stereochemistry of natural amino acids within the context of triple helical collagen.

We show an aza-proline residue exhibits identical thermal stability to proline when substituted in the Xaa position of the (Xaa-Yaa-Gly)_n collagen repeating unit but is detrimental to stability in the Yaa position. Aza-proline showcases the preorganizing power of a neighboring hydroxyproline residue on collagen stability and self-assembly. The inclusion of multiple configurationally labile aza-proline residues adversely affects collagen self-assembly due to the increased entropy present in aza-proline compared to a fixed proline stereocenter. These studies define aza-proline as a uniquely privileged amino acid to probe biomolecular systems and demonstrate the critical importance of stereochemical preorganization in biopolymer assembly and folding processes.

ORGN 518

Chemoselective peptide macrocyclization at tyrosine residues with 1,2,4-triazoline-3,5-diones

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Driven by an increasing demand for peptide-based drugs, method development for peptide synthesis and modification has grown substantially over the past decade. Peptide therapeutics can exhibit significant protein-target binding affinities at low concentrations due to high target specificity. Additionally, peptides offer an advantage relative to small molecules in part due to their low toxicity upon metabolism. However, this value is often overshadowed by their susceptibility to premature degradation and thus, the inability to reach an established target *in vivo*. The modification of bioactive linear peptides by means of cyclization has proven to be a useful strategy to minimize peptide degradation and maintain target specificity. We have developed a method to macrocyclize the N-terminus of peptides with internal and C-terminal tyrosine (Tyr) residues. The method is inspired by the chemoselective reaction of N4-substituted 1,2,4-triazole-3,5-diones with Tyr residues reported by Barbas and coworkers in 2010. Our method incorporates an electrophilic 1,2,4-triazoline-3,5-dione at the N-terminus of a given peptide sequence. Buffered, aqueous oxidation conditions permit internal Tyr residues to react with the *in situ* generated electrophilic 1,2,4-triazoline-3,5-dione moiety to produce macrocyclic peptides.

ORGN 519

Quorum sensing inhibition in *Streptococcus pneumoniae* using optimized CSP1 modifications including a key E1A substitution

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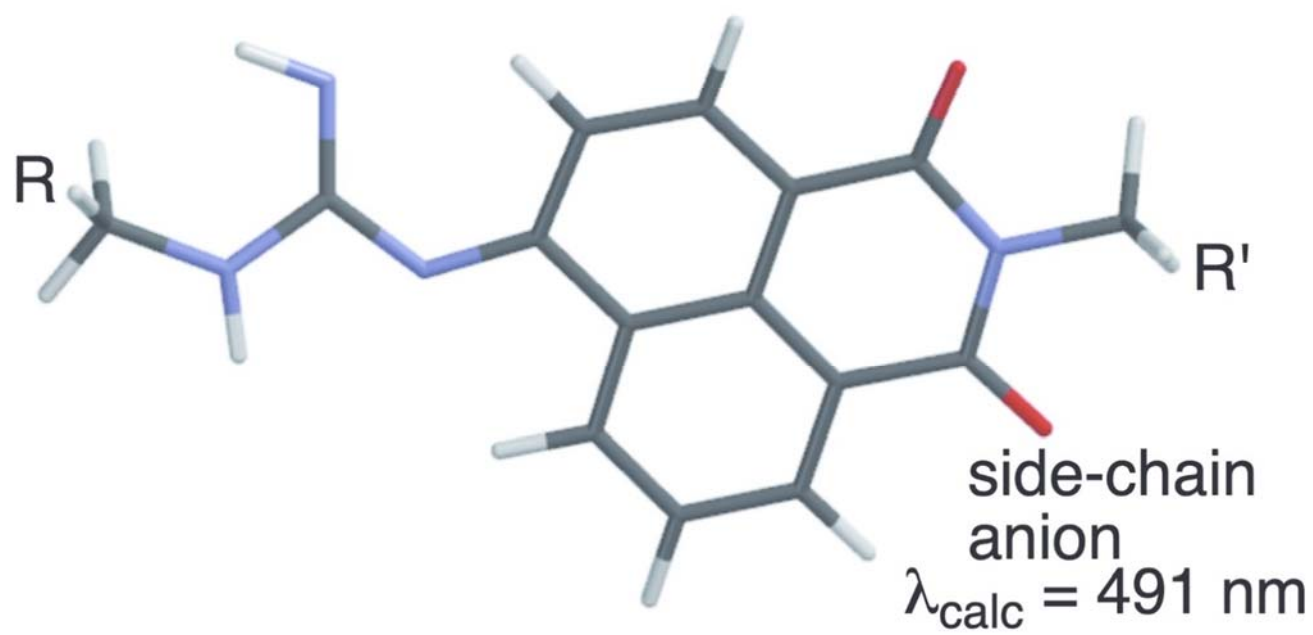
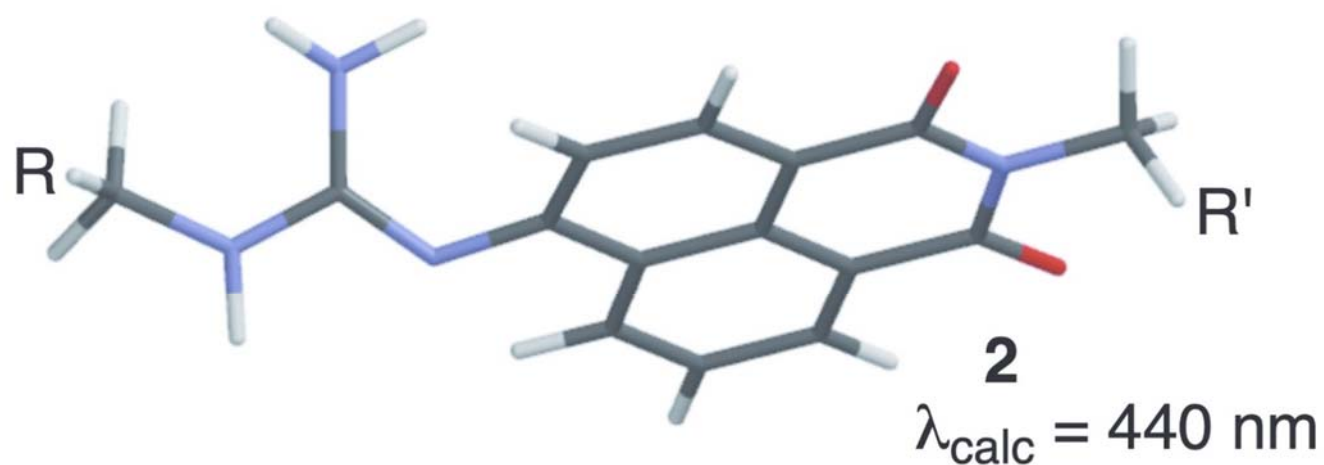
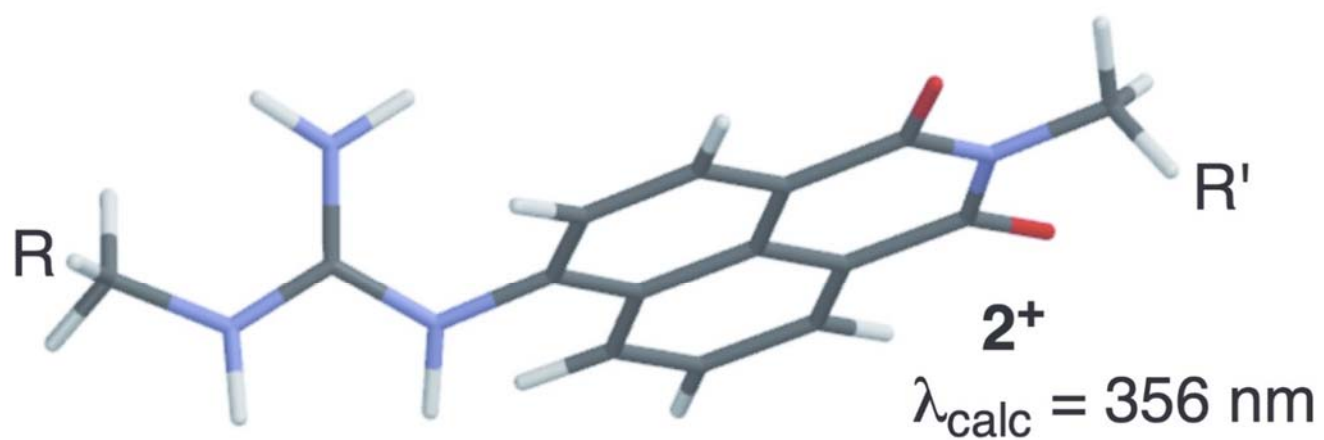
Quorum sensing, a cell-density dependent form of bacterial communication used by the notorious human pathogen *Streptococcus pneumoniae*, can result in the bacteria's ability to resist antibiotics, increased virulence, and increased pathogenic properties. *S. pneumoniae* utilizes its quorum sensing circuitry and associated signaling peptide, the Competence Stimulating Peptide (CSP), to regulate such properties. Strains of *S. pneumoniae* can be split into two different specificity groups based on their CSP signal produced. These two variants are CSP1 and CSP2; where CSP1 is the focus of this study. Through the modification of the six hydrophobic amino acid residues that comprise the quorum-sensing signaling peptide, a series more competitive, synthetic peptides were created to modulate quorum sensing in *S. pneumoniae*. From previous research, the substitution of alanine for glutamic acid at the *N*-terminus of the peptide eliminates activation at the ComD1 site, resulting in a conversion to a ComD1 inhibitor. Using this E1A substitution, and our peptides containing hydrophobic modifications made from previously successful peptides that exhibited high receptor activation, a library of inhibitory CSP1 peptides was created. It was hypothesized that increasing the binding efficiency in the peptide in combination with the E1A substitution could produce a peptide to out-compete the natural CSP1, resulting in blocking the bacteria's ability to initiate quorum sensing. Multiple notable ComD1 inhibitors were discovered including E1AL4NVI12NL, E1AI12NL, E1AL4NV, and E1AI2L. The E1AL4NVI12NL peptide was found to be the most potent ComD1 inhibitor to date, holding an IC₅₀ value of 54.58 nM. These results reveal important information about the structure of CSP1 and how it works as a ComD1 inhibitor in relation to the optimized hydrophobic residues.

ORGN 520

Side-chain protonation states of a fluorescent arginine

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An arginine derivative with a fluorescent side-chain, Boc-Arg(Nap)-OH, was prepared by palladium(0)-catalyzed coupling of Boc-Arg-OH with a 4-bromonaphthalimide. The presence of the fluorophore lowers the p*K*_a of the side-chain guanidinium group by several orders of magnitude, to 9.0 (± 0.1), allowing the derivative to access an electrically neutral protonation state that is not generally available to arginine itself. Computational modelling (DFT) predicts that protonation takes place at the side-chain C=N atom that bears the fluorophore. Calculated electronic absorptions for the protonated (356 nm) and neutral species (440 nm) are in good agreement with experiment. When irradiated with light, excited-state proton transfer (ESPT) occurs from cationic side-chains to suitably basic solvents, resulting in fluorescence emission from the neutral species. Arg(Nap) can be incorporated into peptides with sterically accessible N-termini using specially-adapted conditions of solid-phase peptide synthesis.



ORGN 521

Stapled peptides: Optimizing automated synthesis and ring-closing metathesis

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Peptides are increasingly utilized as tools to investigate the role of specific protein-protein interactions, often times with the ultimate goal of developing a therapeutic agent. Importantly, a well-defined secondary structure is typically required for the peptide to interact with either of the protein binding partners. However, peptide fragments of proteins are structurally hampered, minimizing any binding affinity and demanding a chemical strategy to stabilize an expected secondary structure.

As the complexity of synthetic peptides increases, additional strategies that simplify peptide synthesis are also required. Herein we present an optimization strategy for automating synthesis of helical peptides containing unnatural amino acids bearing an olefinic side chain functionality and constrained using on-resin ring-closing metathesis methods.

ORGN 522

Synthesis of an inhibitory peptide for quorum sensing in *Streptococcus pneumoniae* through optimization of the hydrophobic binding face and substitution of the N-terminus residue

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Streptococcus pneumoniae is a pathogenic bacterium that is the cause of many health issues such as bacterial infections, pneumonia, and sepsis. The ability of *S. pneumoniae* to infect a host organism (i.e. humans) and transform plasmid DNA to increase antibiotic resistance, is largely controlled through quorum sensing. Quorum sensing is a cell-density dependent form of bacterial communication where bacterial cells release a signaling pheromone once a population density is reached. This project uses Solid Phase Peptide Synthesis (SPPS) to create synthetic variants of the Competence Stimulating Peptide (CSP1), one of the main signaling pheromones in the *S. pneumoniae* quorum-sensing circuit. Substitutions were made that explored the steric limitations and electronic properties of residues involved in the hydrophobic binding face of CSP1. These substitutions at positions 4, 7, 12, and 13 in the primary structure resulted in increased binding efficiency to ComD1, the cognate receptor of CSP1. From these results, a second library of peptides was synthesized with alanine at the N-

terminus of CSP1 to convert our activating derivatives into inhibitory peptides for the *S. pneumoniae* quorum-sensing circuit. By creating inhibitory peptides with optimized binding, we seek to decrease quorum-sensing as the synthetic peptides can outcompete the native CSP1 peptides and, thus, decrease the pathogenicity of *S. pneumoniae*.

ORGN 523

Tools for citizen scientists interested in studying peptides and the origin of life

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The ubiquity of amino acids, peptides, and proteins across life on Earth suggests they appeared early in evolution—perhaps in the very first living system(s). While peptides have been a major focus of origins-of-life research, this work usually requires instrumentation that makes it inaccessible to prospective scientists outside of a university setting. This poster will present our recent work on (i) improving chemical shift dispersion in low-field (benchtop) NMR spectrometers such that they can be used to measure rates of peptide reactions and (ii) developing a kit to enable the characterization of peptide oligomerization reactions using equipment commonly available in high school laboratories. Our hope is that these tools will enable distributed research projects on peptides and the origin of life to be performed by a wide array of interested citizen scientists, educators, and students with access to home laboratories, local makerspaces, and/or labs in high schools and community colleges.

ORGN 524

Effects of endcapping and truncation of a hydrogel-forming peptide on its structural and materials properties

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A 13-residue peptide, referred to as the KD peptide, has previously been shown to form a hydrogel under physiological conditions by means of a cross-linked network consisting of extended β -sheet fibrils. This project investigates uncapped variants of this peptide and a series of truncated sequences, with the aim of finding an optimal hydrogel-forming core. The peptides were made using solid phase methodology and purified by HPLC. Hydrogelation properties were then assessed using visual inspection, rheology,

and cryo-TEM. It was found that Sequence 6 (S6) and Sequence 4 (S4), variants with 6 and 4 residues removed from the N-terminus, respectively, formed a hydrogel that underwent phase separation. Uncapped versions of KD (C-uncapped, N-uncapped, and both ends uncapped) formed a gel only at relatively high concentrations. Future directions of this project include the synthesis, purification, and hydrogelation studies of S5, as well as IR spectroscopy of the uncapped versions of the KD peptide and potentially other truncated sequences in order to identify the sequence with the most favorable hydrogelation properties.

ORGN 525

Identification of kinase substrates and interactors using Kinase-catalyzed CrossLinking and ImmunoPrecipitation (K-CLIP)

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Kinase enzymes phosphorylate protein substrates in a highly regulated manner in cellular signal transduction. Unregulated kinase activity is associated with a variety of disease states, most notably cancer. Therefore, deciphering of kinase signaling pathways in cells is critical to understand disease formation. However, still it has not been able to fully map the substrates and interacting proteins of kinases involved in cellular functions due to scarcity of available tools. Recently we developed kinase-catalyzed cross-linking to covalently connect substrate and kinase in a phosphorylation-dependent manner. And we introduced a new method combining kinase-catalyzed cross-linking and immunoprecipitation (K-CLIP) to identify kinase-substrate pairs and kinase-associated proteins. K-CLIP was applied to the substrate p53, which is robustly phosphorylated. Both known and unknown kinases of p53 were isolated from cell lysates using K-CLIP followed by LCMS/MS. In follow-up validation studies, MRCK was identified as a new p53 kinase. Beyond kinases, a variety of p53 and kinase-associated proteins were also identified using K-CLIP, which provided a snapshot of cellular interactions.

While K-CLIP is currently being utilized to study kinase-substrate relationships of different disease related proteins, with the use of ATP-photocrosslinkers, as the next stage of this tool, we developed an affinity-based crosslinking ATP cosubstrate, ATP-Mac to apply in K-CLIP. ATP-Mac has a methylacrylamide functional group that specifically react with a cysteine residue in the kinase active site, under more physiological conditions while avoiding UV light. Compared to ATP photocrosslinkers, the selectivity of the affinity-based ATP analogue towards cysteine residues will reduce nonspecific crosslinking. Out of 518 human kinases more than 200 are predicted to have a cysteine residue near the ATP binding pocket in the active conformation. Therefore, we are currently applying ATPMac in in-vitro K-CLIP and in-cellulo K-CLIP to identify novel kinase substrate interactions of highly regulated kinase EGFR. The K-CLIP method represents an immediately useful chemical tool to identify kinase-

substrate pairs and multiprotein complexes in cells, which will enhance our understanding of kinase activity in normal and disease states.

ORGN 526

Monomethylation and dimethylation of 1,3-diphenylpropane-1,3-dione and its derivative

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The reaction between 1,3-diphenylpropane-1,3-dione and iodomethane when potassium carbonate is present was investigated. Yields of the product of monomethylation and the product of dimethylation were obtained. Valuable kinetic information and structural data via NMR were collected.

ORGN 527

Kinetic studies of the peroxyoxalate chemiluminescence in borate buffer

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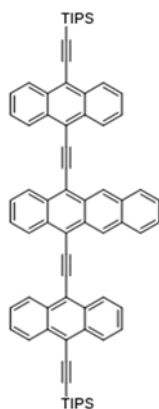
The peroxyoxalate reaction, one of the most important chemiluminescent systems today, is being widely used as an analytical tool. On the other hand, there are few kinetic studies of this system in aqueous media, obviously due to the occurrence of the parallel reaction of oxalic ester hydrolysis that makes it difficult to study the chemiluminescent reaction. In this work it was possible to perform a kinetic study on the peroxyoxalate reaction in exclusively aqueous media, using borate buffer as a catalyst. The concentration of borate buffer in the reaction of bis(2,4,6-trichlorophenyl) oxalate with hydrogen peroxide in the buffered medium pH = 8.2 was also varied using fluorescein and rhodamine 6G as activators and it was observed that the buffer concentration did not influence the rate constant, even with a 10-fold increase in the borate concentration. In the same way, the quantum yields did not seem to vary significantly with the concentration of the same. A linear dependence of the rate constant with the peroxide anion concentration was observed for two fixed borate concentrations. As the reaction rate was pH-dependent but not altered with different buffer concentrations, it can be concluded that the reaction of TCPO with H₂O₂ in this buffered aqueous medium occurs by specific basic catalysis.

ORGN 528

Novel acene-based singlet oxygen responsive materials

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Taking advantage of the cycloaddition reaction between singlet oxygen and acenes, various acene-based singlet oxygen probes have been developed. Singlet oxygen sensor green, for instance, is one of commercially available singlet oxygen probes based on anthracene. In the recent decade, our group has investigated the relationship between the lateral length of acene and its reactivity towards acenes. Notably, the longer acenes, namely tetracene and pentacene, respond to the singlet oxygen more rapidly. Thus, we have reported singlet oxygen probes based on longer acenes, which have merits of high sensitivity, rapid response, and significant changes in fluorescence. However, those probes disadvantage from self-sensitizing. The unintentionally generated singlet oxygen can damage the material itself and give a "fake" response. Aiming at the issue, we developed acene-based materials with a narrower band-gap and lower LUMO energy level, which have been reported as "unfavorable" for photosensitizing. Up to now, we have successfully synthesized 5,12-Bis{[(10-triisopropylsilyl)ethynyl]-9-anthracenyl} tetracene (TA-TET). This molecule shows a relatively rapid response to singlet oxygen ($k \sim 6.5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$) and a 200-fold turn-on of fluorescence is observed. Besides TA-TET is a bad photosensitizer. The CHCl_3 solution was irradiated by a lamp (60mW, with a filter blocking wavelength $< 435\text{nm}$) for half an hour and only neglectable change was observed. On the other hand, when irradiating with a photosensitizer, methylene blue, the molecule was fully degraded in 25min. In addition, as an organic semiconductor, acene has been used on organic transistors, photovoltaics, and LEDs. And one of the disadvantages of it is its instability against oxygen and light. TA-TET have shown good stability both in the solid and solution phase. Thus, we believe TA-TET can be a novel kind of potential organic semiconducting material.



Computational determination of alkaloid chemical shifts with pH change

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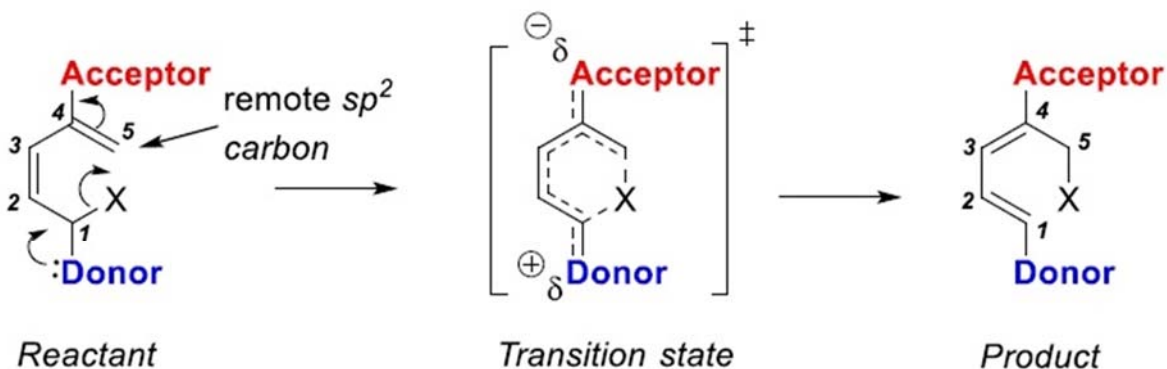
Verifying that the structures of synthetic alkaloids match those of natural products is often challenging due to changes in ¹H and ¹³C chemical shifts at different pHs of solutions used for recording NMR spectra. We are developing a computational method to determine the degree of protonation for alkaloids in solution by comparing the theoretical chemical shifts for the ammonium and free base forms of alkaloids to the experimental shifts. While combining the theoretical shifts for the two forms of the alkaloids into a weighted average for comparison against the experimental shifts at a given pH creates a new set of chemical shifts closer to the experimental data, predicted shifts were not accurate enough to describe the experimental data. Thus, additional methods of modelling the protonated alkaloids were investigated. DFT calculations were performed at the mPW1PW91/6-311+G(2d,p) (GIAO; PCM, chloroform)//B3LYP-D3(BJ)/6-31G+(d,p) level of theory.

ORGN 530

Functionalization of remote *sp*² carbon: [1, 5] sigmatropic shift controlled by an in-built donor-acceptor switch

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An investigation of [1,5] suprafacial halide shift and its competing [1,5] hydride shift in a boron activated diene system is presented. This functionalization of remote *sp*² carbon (C5) proceeds via a low energy concerted path when the carbon at the migration terminus (C5) is electrophilic. Incorporation of electron acceptors such as boronyl group at C4, assist in creating such electrophilic centre. As a result, transition state of this migration is strongly influenced by the combined effect of boron-acidity, interaction of halogen lone pairs with the migration terminus and the strength of carbon-halogen bond (C-X). In general, [1,5] halide shifts were favored when migration origin (C1) was substituted with bromide or chloride, whereas [1,5] hydride shift was favored when fluorine was attached to C1. Interestingly, the competing barriers for [1,5] hydride shifts were not only lower than the corresponding [1,5] halide shift and the parent 1,3 pentadiene substrate, but were also affected by the electron donating ability of groups at migration source (C1) and the acidity of boronyl group at C4 carbon.

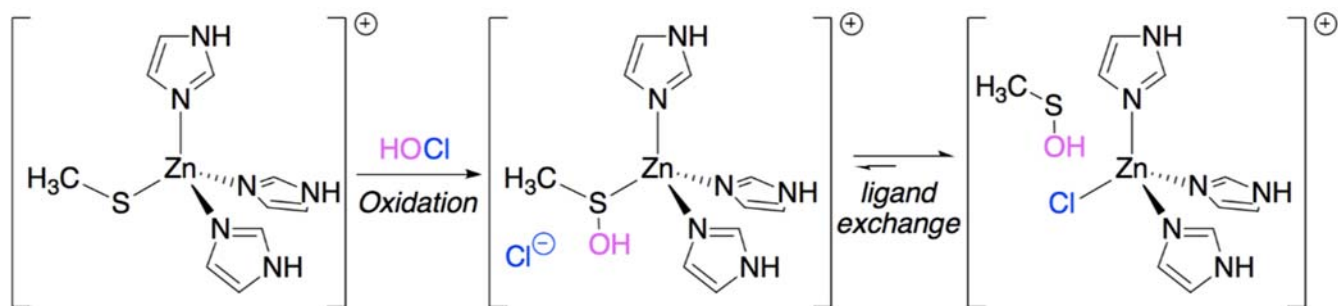


ORGN 531

Computational investigation of the mechanism of HOCl-mediated cysteine oxidation in the conserved zinc-binding core of cytosolic chemoreceptor transducer-like protein D (TlpD)

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Helicobacter pylori, a gastric pathogen present in about 50% of the global population, is known to facilitate gastritis, stomach ulcers, and stomach cancer. Previous experimental studies show that local unfolding at the conserved chemoreceptor zinc-binding (CZB) domain within the transducer-like protein D (TlpD) cytoplasmic chemoreceptor upon contact with hypochlorite (a known biological oxidant), is implicated in the mode in which *H. pylori* effectively colonizes the stomach. However, the mechanism of oxidation at the conserved zinc-bound cysteine residue upon HOCl contact, the role of the zinc complex in modulating the reaction, and the origins of selective oxidation are unknown. Our work utilizes DFT computations to probe plausible mechanisms for the oxidation process, illuminates the role of ligand exchange equilibria at the zinc complex in modulating the reactivity and regioselectivity, and provides new hypotheses for the origin of the chemoattractant response. Insights from our computational study will be presented.



HOCl-mediated oxidation at the zinc-bound cysteine within the CZB site of TlpD.

ORGN 532

Copper-catalyzed aminoboration of *E*-alkenes

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Amino groups are common fragments in pharmaceuticals and natural products while organoborons are versatile precursors. Copper catalyzed aminoboration has been shown to simultaneously add boron and nitrogen groups to alkenes under mild conditions. Cu-catalyzed aminoboration with a piv ZPhos ligand was investigated. Enantioenriched aminoborates are prepared in good yields and with good enantioselectivities. Greater than 99:1 er was obtained under the optimized conditions. The sensitivity towards the alkene geometry was investigated and the stereochemistry was rationalized and confirmed through computational studies.

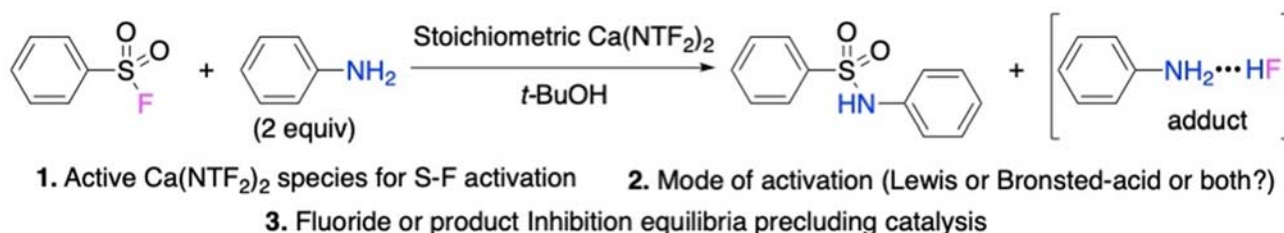
ORGN 533

Computational investigations into the mechanism of Lewis-acid mediated activation of sulfur(VI) fluorides

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Nitrogen-containing sulfur(VI) compounds, such as sulfamides, sulfonamides, and sulfones, are found in ~27% of sulfur-containing drugs administered by the United States Food and Drug Administration. Synthesis of these compounds have been historically performed via the oxidation of thiols or the substitution of sulfur(VI) chlorides precursors. The former occurs under harsh conditions, limiting functional group

compatibility; the latter is thermodynamically unstable and susceptible to hydrolysis and redox reactions. Sulfur(VI) fluorides have emerged as promising alternative precursors toward the synthesis of nitrogen-containing sulfur(VI) compounds via sulfur-fluorine exchange (SuFEx) chemistry. A recent experimental study has reported the use of stoichiometric calcium trifluoromethanesulfonate ($\text{Ca}(\text{NTf}_2)_2$) – one of the few reports that employ a Lewis-acid mediated process. However, given the difficulty in isolating Ca^{2+} intermediates along the reaction pathway, the mechanism of this process is unknown. Our work uses DFT computations to probe plausible mechanisms for the $\text{Ca}(\text{NTf}_2)_2$ mediated sulfur-fluorine activation process, specifically unraveling the calcium coordination complexes responsible for sulfur-fluorine bond activation. Furthermore, we probe various fluoride and product inhibition equilibria to provide new hypotheses for why stoichiometric Ca^{2+} is needed. Results from this computational study will be presented.



ORGN 534

Computational studies of the formation of complex heterocycles through the cyclization of benzaldehyde oxime ethers containing a built-in azole group

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Here we described our use of computational chemistry to investigate the overall scope of an oxime ether radical cation intramolecular cyclization pathway towards heterocycles. Heterocycles are a reoccurring structure in organic chemistry and are commonly found in pharmaceuticals, pesticides and dyes. One common way to synthesize heterocycles involves the cyclization of oximes or oxime ethers using either transition metal catalysts or strong acids. Recent experimental work in the de Lijser laboratory at California State University, Fullerton has concentrated on developing a more environmentally friendly approach using photo-induced electron transfer (PET) to produce oxime ether radical cation reactive intermediates that subsequently undergo intramolecular cyclization. This is a greener synthetic route as the reaction only requires light and an organic catalyst. Previous work has focused on the PET-induced cyclization of oxime ethers containing built-in aryl, thiophene, or furan groups. In this poster, we describe our efforts to predict the feasibility of the PET-induced

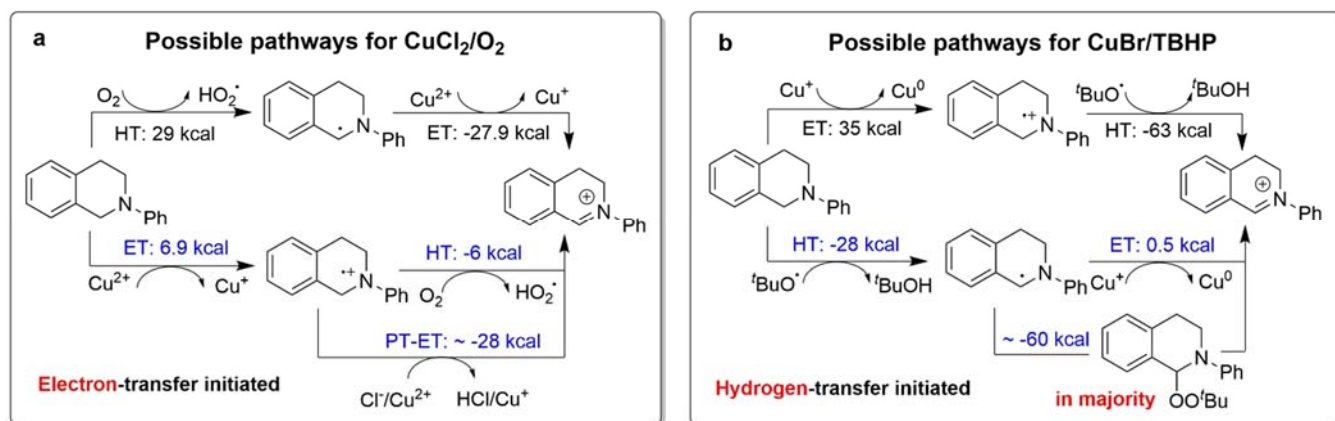
cyclization of benzaldehyde oxime ethers that contain a built-in azole group. Specifically, we use modern density functional theory approaches, ω B97M-V/def2-QZVPP// ω B97X-D/cc-pvdz, to understand how the formation and reactivity of the oxime ether radical cation is affected by the specific identity of the built-in azole nucleophile. We additionally examine the extent to which the thermodynamics and kinetics of radical cation formation through PET is tunable through substituents on the central benzene ring. As a whole, the presented work provides insights into the overall scope of this photoredox approach towards synthesizing complex heterocycles.

ORGN 535

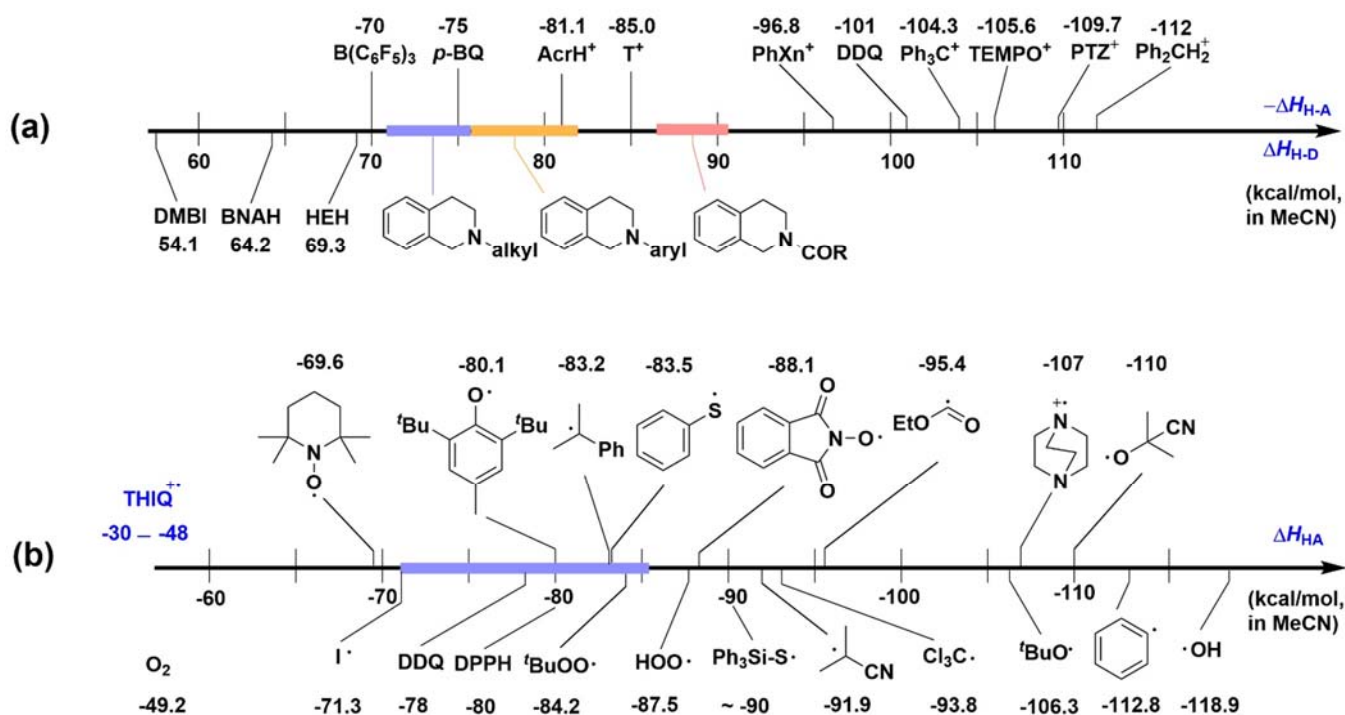
Energetic scales built with new strategy for understanding α -C–H functionalization of tertiary amines: Case studies on tetrahydroisoquinolines

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Functionalization of the α -C–H bonds of tertiary amines to form various α -C–X bonds (X = C, N, P, etc.) via CDC process has recently become a mainstream in contemporary synthetic chemistry. However, due to a lack of the comprehensive knowledge on various modes of bond-breaking energies corresponding respectively to releasing a proton, a hydrogen atom, or a hydride ion from the α -carbon of the parent or oxidized *tert*-amines, the long desired rational exploration of new methodologies, on the basis of the reactivity–energetics relationships, seems to remain a far-reaching anticipation. Consequently, the majority of research still has to be much kept on the conventional trial-error mode of practice. To help attenuating such bias, here we report a unique experimental approach, which starts with experimental measurement of the α -C–H hydricity in solution, to establish the so-called integrated α -C–H bond energy scale that is necessary for structure–property analysis towards understanding and further improving α -C–H functionalization of amines, as showcased here by the study on tetrahydroisoquinolines (THIQs). By virtue of the thermodynamic criteria, the feasibility and mechanisms of THIQ oxidation by common oxidants can be signified, that are found to correspond well with experimental observations.



Thermodynamic rationalization of possible pathways for oxidation of *N*-Ph-THIQ by (a) CuCl_2/O_2 and (b) CuBr/TBHP .



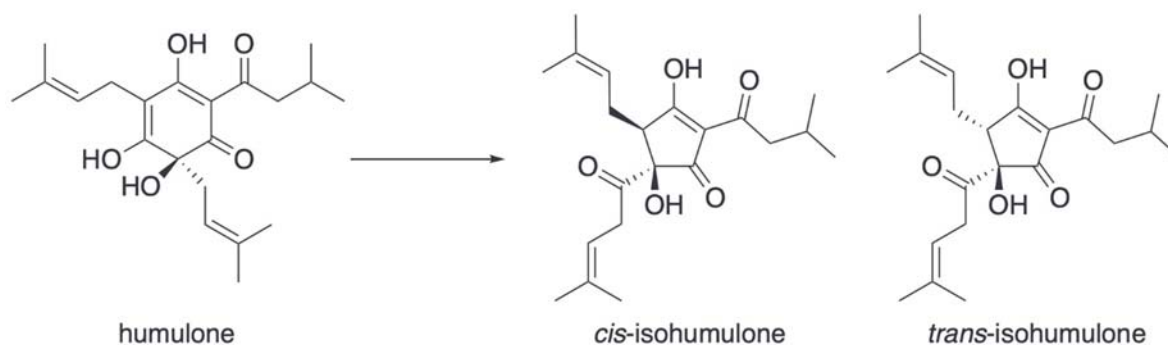
(a) Hydricity scale ($\Delta H_{\text{H-D}}$) of THIQQs (colored) and other donors and (b) Hydrogen-donating abilities ($\Delta H_{\text{H-D}}$) of THIQQs (blue bar) and hydrogen affinities ($\Delta H_{\text{H-A}}$) of common acceptors.

ORGN 536

Illuminating the transformation of humulone

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In the brewing industry, there are four main ingredients that are required to produce beer: water, yeast, barley, and hops. Hops are used in many different stages of brewing. The key reason for their use is the conversion of humulone (α -acids) during the boiling process to *cis*- and *trans*-iso-humulone (iso- α -acid). These compounds are the main contributors to the bitterness in beer. Humulone undergoes an acyloin condensation to form a 5-membered ring. Magnesium ion concentration and the pH of the solution are important mediators of this reaction. We envisioned exploration of this mechanism using UV-vis spectroscopy and polarimetry to determine the binding constant of metals to the humulone. The results, coupled with computational analysis, indicated that Mg^{2+} binds to the anion of humulone resulting in structural changes that promote the rearrangement. The kinetics, thermodynamics, and a proposed mechanism of the reaction that illustrates the retention of stereochemistry will be presented.



ORGN 537

Synthesis and evaluation of novel photosensitizers for photodynamic anti-pancreatic cancer therapy

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Photodynamic therapy (PDT) has attracted significant attention as an alternative approach to traditional cancer therapies such as radiotherapy, chemotherapy, and surgery. PDT involves irradiating a drug (the photosensitizer) with a photon of light to generate cellular oxygen that then proceeds to kill cancer cells. Porphyrin-based photosensitizers have been widely used in PDT. Porphyrins have a significant absorption in the visible region (400-700 nm), little dark toxicity, and long-lived triplet states that can lead to high singlet oxygen production. Porphyrins are known to accumulate in tumor cells in high concentrations, but aggregation resulting from π - π stacking often leads to a reduction in fluorescence and $^1\text{O}_2$ quantum yields. Porphyrins are also highly hydrophobic, leading to low bioavailability and making intravenous administration difficult. Ground state curcumin analogs have been shown to have

significant anti-cancer activity against various cancer lines, although these molecules have a low bioavailability due to poor absorption and fast metabolism. The aim of the research presented in this poster is to synthesize novel porphyrin-curcumin analog conjugates for use as photosensitizers in the photodynamic treatment of pancreatic ductal adenocarcinoma (PDAC). Porphyrin-curcumin analog conjugates have several advantages over the individual components: (1) improvement of stability, bioavailability, and tumor site accumulation of curcumin analogs, (2) the presence of two flexibly connected chromophores that will prevent aggregation of the porphyrin component, improving both fluorescence and $^1\text{O}_2$ quantum yields, (3) the presence of two chromophores that may maximize triplet-triplet energy transfer with $^3\text{O}_2$ and improve $^1\text{O}_2$ generation efficiency.

ORGN 538

Theoretical explanation of reaction site selectivity of a four armed dendrimer core

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Aldol condensation reactions create carbon-carbon bonds alpha to a carbonyl group with loss of water. Previous research has shown that reacting benzaldehyde derivatives with acetone provide solids that precipitate cleanly from solution. This reaction can be exploited to create dendrimers within minimal waste. Yet when reacting 4,4'-bicyclohexanone with two equivalents of benzaldehyde under basic conditions, two crossed aldol condensation compounds form, the kinetic and thermodynamic products. Herein we present computational evidence for the mechanisms leading to both products and a theoretical explanation for the reaction site selectivity observed.

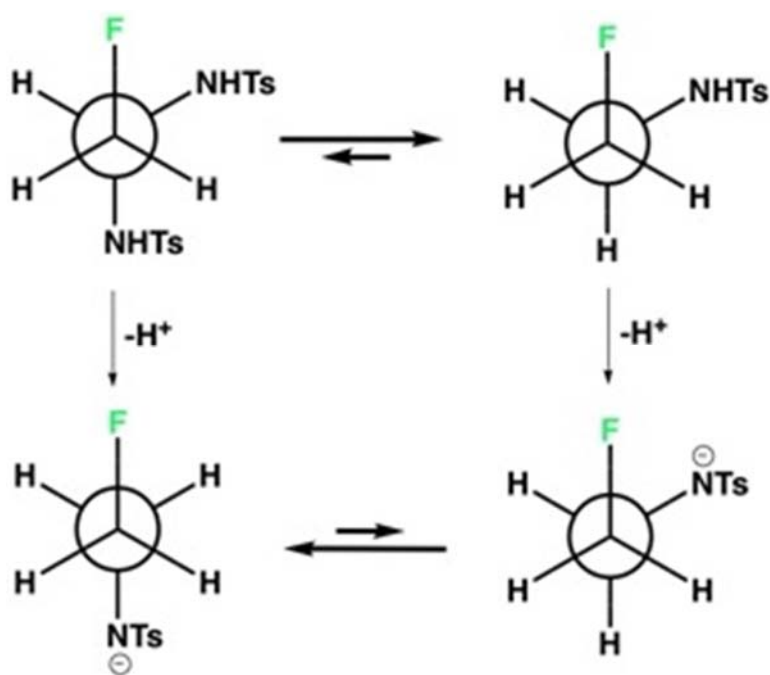
ORGN 539

Gauche effects in 2-Fluorosulfonamides as a means for determining the acidity of organic compounds in DMSO

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In conformational analysis, the gauche effect refers to the rotary property of a gauche conformer having a lower electronic energy than the corresponding trans conformer. Gauche effects are ubiquitous in compounds consisting of 2-fluoroethanes, and chemists have utilized this knowledge in the design of functional molecules, including but not limited to the design of drugs and catalysts. We have now extended the utility of the gauche effects to include serving as a means for determining the acidity of organic compounds in DMSO. This new approach to determining the acidity of organic compounds is both expedient and accurate because (1) only a single NMR measurement is needed in order to calculate the acidity of a given compound and (2) the accuracy of the measured $\text{p}K_{\text{a}}$ values are comparable to literature values. The new

method is based on our discovery that certain gauche effects (such as in the 2-fluoroethylsulfonamides used as model compounds) can be turned 'on' and 'off' through a proton-transfer reaction. The gauche effect was observed in the protonated state, whereas the trans conformer was preferred in the deprotonated state. A large change in the proton-fluorine vicinal coupling constants ($^3J_{\text{HF}}$, ~16 Hz) was observed in the transition between the gauche and the trans conformers. Thus, we showed that the accurate position of an acid-base equilibrium of a given proton-transfer reaction can be determined by measuring the extent of the gauche effect in the model compound—for which the gauche effect is reported by the changes in the $^3J_{\text{HF}}$ coupling constants. As the proof of concept, we accurately determined the $\text{p}K_{\text{a}}$ values of 15 known compounds, which ranged between the $\text{p}K_{\text{a}}$ values of 8.5 – 19.0 using DMSO as the solvent.



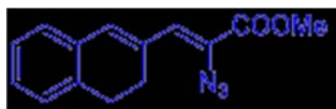
ORGN 540

Photoreactivity of rigid divinyl azides

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The quest for sustainable synthesis has sparked interest in using sunlight or ecofriendly LEDs to drive photoreactions. The photoreactivity of vinyl azides can be used to form various heterocyclic products that have relevance in medicinal and pharmaceutical chemistry. We investigated the photoreactivity of a ring-locked derivative of divinyl azide

(Scheme 1) in solution and the solid-state. We have gathered support for the reaction mechanism using transient absorption spectroscopy, matrix isolation and theoretical calculations. We will discuss the effect the ring-locked structure of the divinyl azide plays on the reaction mechanism.



Scheme 1. Structure of ring-locked divinyl azide

ORGN 541

Dme solvated mixed aggregates of lithium pinacolone enolate and lithium hexamethyldisilazide: Equilibrium of solvation states

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The structure and solvation state of DME solvated mixed aggregates of lithium pinacolone enolate and lithium hexamethyldisilazide in toluene-*d*₈ solution were determined by diffusion-ordered NMR spectroscopy (DOSY). Partial dissociation of DME was observed which implies the existence of monodentate DME and equilibrium between bidentate and monodentate mixed aggregates. The proposed solution structures and the equilibrium were further supported by calculation.

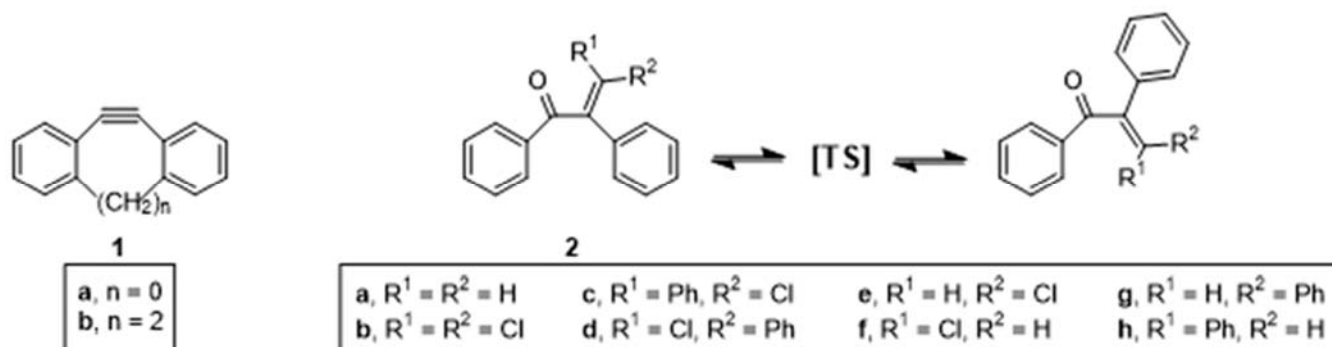
ORGN 542

Rotational barriers of substituted α,β -unsaturated diarylketones

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As a spinoff of our mechanistic studies of phenylchlorocarbene addition to dibenzocyclooctyne (**1b**) and its open-chain derivative **1a**, we are investigating computationally and experimentally the rotational barriers of relevant α,β -unsaturated diarylketones **2a-h**. Computationally, the barriers of rotation of **2a** and **2b** are 4.1-4.3 and 5.1-8.1 kcal/mol, respectively (M06-2X/6-31G(d)). The rotation of **2c** and of **2d** costs 7.6-8.5 and 9.1-9.8 kcal/mol, respectively (M06-2X/6-31G(d)). Experimentally, we are conducting steady-state room-temperature irradiation at 254 nm of **2b-d** in CH₂Cl₂. We have observed significant change in the UV-Vis spectrum of a mixture of

diastereomers **2c** + **2d** upon irradiation. We will also report our study of the photochemistry of **2b**. We have also planned variable temperature NMR experiments to experimentally measure the rotational barriers of **2b-d** with comparison to the calculated values.



ORGN 543

Quantum yields of photoredox catalyzed α -arylation of amines

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Photoredox Catalysis is a powerful tool for the formation of chemically challenging bonds that normally require high temperatures, high pressures, and harsh chemicals to synthesize. Despite widespread method development for use in pharmaceuticals and organic synthesis, a detailed mechanistic understanding of photoredox catalysis is needed. A major obstacle to understanding the photochemistry of photoredox catalysis is the lack of data on reaction quantum yields. In this study we analyze the quantum yields of an α arylation reaction of amines catalyzed by an Iridium polypyridyl photosensitizer. We will present our investigations into the quantum yields of this reaction with an emphasis on the effects of wavelength, light intensity, and reaction time.

ORGN 544

Mechanistic insight into (DHQD)₂PHAL catalyzed asymmetric chloro-functionalization of olefins

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(DHQD)₂PHAL and its analogs have been reported to catalyze numerous asymmetric halo-functionalization reactions. Yet, there is a critical dearth in detailed mechanistic studies of these reactions in the literature. In fact, recent reports on the mechanism of uncatalyzed olefin halo-functionalization has already begun challenging “conventional” mechanistic interpretations. For instance, recent reports have suggested that the nucleophile could be playing a role in pre-activating the alkenes before the electrophile could attack. This contradicts textbook schematics where the nucleophile is portrayed as just a trapping agent for the intermediate generated after the electrophilic attack of halirenium on the alkene. This inevitably demanded a deeper investigation into the mechanism of catalyzed, asymmetric versions of halo-functionalization reaction. We undertook a comprehensive kinetic analysis of these (DHQD)₂PHAL catalyzed asymmetric halo-functionalization reaction, that is backed by computational modeling. Kinetic analysis would provide insight into the molecularity of the rate determining step which ultimately would inform us about the catalytic cycle. Ultimately, our mechanistic studies have unearthed a surprisingly diverse set of mechanisms among various asymmetric halo-functionalization that switches with change in factors like, alkene functional group handle, solvent, as well as nucleophile.

ORGN 545

Study of pH-dependent H/D exchange from aromatic hydrogen in 1,8-diamino-2,7-naphthyridine-4-carbonitriles

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The instantaneous hydrogen-deuterium exchange (H/D exchange) is mostly applied to exchangeable protons and deuteriums such as those in hydroxyl or amine groups. Therefore, this quick H/D exchange of the hydrogens on the carbon in aromatic compounds has not been reported even with a metal catalyst to my knowledge. However, the unexpected pH-dependent aromatic H/D exchange in 1,8-diamino-2,7-naphthyridine-4-carbonitrile systems has been observed in NMR analysis immediately after adding D₂O. 1,8-diamino-3,6-bis(1-pyrrolidiny)-2-7-naphthyridine-4-carbonitrile and 1,8-diamino-3,6-bis(N-methylpiperazine)-2-7-naphthyridine-4-carbonitrile have been synthesized and characterized exhibiting unusual chemical properties. Both free and protonated forms of the compounds were studied by quantum calculation and experiments including NMR titrations and pH titrations by various methods. The outcomes showed that the protonation alters the structure and reactivity of the compounds.

ORGN 546

Synthetic and mechanistic investigations on chromium salen-catalyzed oxidation of sulfides with iodobenzene diacetate

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Chromium salen complexes efficiently catalyze the oxidation of organic sulfides to sulfoxides with iodobenzene diacetate [$\text{PhI}(\text{OAc})_2$] in the presence of a small amount of water. A series of thioanisoles were quantitatively oxidized to the corresponding sulfoxides with excellent selectivities for sulfoxides. The catalyst effects were investigated, showing a significant impact on the catalytic sulfoxidations based on the different catalysts used. The high-valent chromium (V)-oxo salens were generated and kinetically studied in the oxidation of thioanisole substrates, which provided mechanistic insights into the nature of the oxidizing intermediate and oxygen atom transfer mechanism.

ORGN 547

Zwitterionic red fluorophores as selective protein sensors

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In medical procedure, quantitative analysis of bioanalytes is performed to detect, diagnose, and monitor diseases. One important example is quantitative determination of human serum albumin (HSA) in body fluids—such as urine and blood. HSA is the most abundant protein in the circulatory system which plays a key role in maintaining oncotic pressure of blood, and in transportation of fatty acids, vitamins, hormones and drugs. Amount of HSA in urine between 20-300 mg per day is an indicator of microalbuminuria, which has been associated with diabetes and cardiovascular diseases. Hence, search for efficient HSA detection methods in body fluids has gained extreme importance among academic researchers and medical scientists. Several immunoassays are currently available and routinely used in medical diagnosis of HSA. But, they are time consuming and more often require well-equipped laboratory instrumentations. Recently, fluorescence techniques have gained considerable attentions for estimation of HSA in samples. Fluorescence techniques are sensitive and very quantitative. Moreover, with a suitable fluorophore a large number of samples can be analyzed. In this project, we aim to develop water-soluble fluorescent probes for simple, cost-effective, and selective detection of HSA in urine samples. We have reported development of two donor-acceptor fluorophores in two easy synthetic steps. Comparison of their photophysical properties in different solvents provides various structure-optical property relationships of the fluorophores. Fluorophore with electronegative fluorine atom selectively recognizes HSA to as low as 4.0 mg/L in

synthetic urine samples. The stereoelectronic effects of the substituents correlate with the intramolecular charge transfer and the non-covalent interactions with the amino acids, resulting zwitterion formation in normal urine pH. Currently, we are investigating the source of selectivity in presence of other common proteins and ions, and the assessment of efficacy of the fluorophores for quantitative albumin detection in biological samples is in progress.

ORGN 548

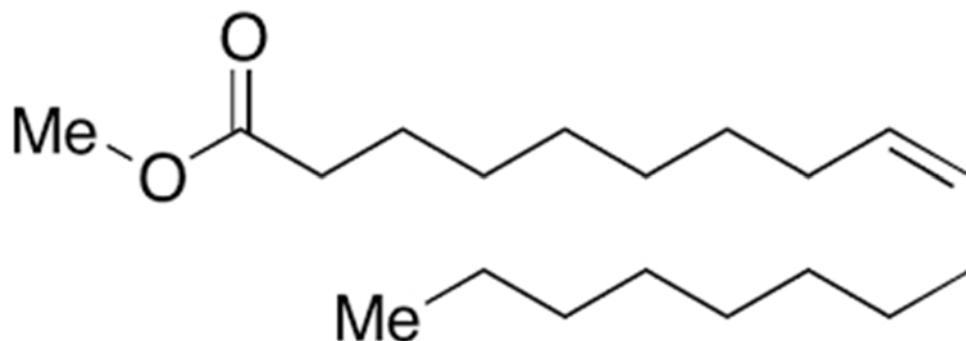
Gasoline derived from food oil: DFT dynamics investigation

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Petroleum products are found in all walks of life. From the plastic casing on a cell phone to the gasoline that runs most vehicles, all is derived from petroleum. Ubiquitous use of petroleum has adversely affected the environment. Toxic substances like SO_x and NO_x are released into the atmosphere during the processing and usage of petroleum products, which contributes to global warming. Inevitable oil spills cause devastating effects to marine ecosystems. The rate of regeneration of petroleum is way slower than the rate of usage that would lead to it being exhausted in the recent future. Hence, a more sustainable and ecological source of energy is needed.

Biodiesels are one of the common sources of alternate fuel. They mainly comprise of Fatty Acid Methyl Esters (FAMEs), and are synthesized by transesterification of triglycerides found in various food oils like soybean oil and canola oil in presence of methanol. Biodiesels claim some advantages over conventional fuels like lower SO_x and CO₂ emissions, high flash point and cetane number, biodegradable characteristics and non-toxic nature. But there are various disadvantages to it as well. FAMEs have higher NO_x emission than petroleum fuel, they gel at temperatures routinely reached in the United States (leading to clogged fuel filters), they dislodge previously deposited carbon due to surfactant properties, and they are more expensive to produce. A solution to such problems is pyrolysis or thermal cracking.

Pyrolysis breaks thermal cracking into smaller compounds that include petroleum products like plastic precursors and gasoline. Simulations at the (DFT) M06-2X/6-31G(d,p) level of theory show promising correlation to experimental work. The FAME of choice is Methyl Oleate, the most abundant FAME in Canola Oil, the largest source of biodiesel in Europe. Results from the simulations show formation of long alkyl chains, some containing a free radical, carbon monoxide and cyclization of 3-membered rings. After an ensemble is acquired, the final goal is to engineer a FAME for desired pyrolytic products.



Methyl Oleate, the most abundant source of biodiesel in Europe.

ORGN 549

Investigation of silicon phthalocyanines as viable photocatalysts for organic transformations

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Photocatalysis has increasingly become a major focus as a sustainable pathway for chemical reactions with visible light photocatalysts performing a large range of reactions such as redox reactions, cyclization reactions, and energy transfer reactions. Silicon phthalocyanines (SiPcs) have been largely ignored as photosensitizers in photocatalytic reactions, despite their low energy excitation, long triplet lifetimes, and their ability to form singlet oxygen. By incorporating alkyl, aryl, and silicon protecting groups as axial ligands on the silicon center, three SiPcs have been generated by the Wiskur research group with the goal of developing three novel photocatalysts for organic synthesis. Using cyclic voltammetry and Stern Volmer quenching studies, we have shown SiPcs are capable of exchanging electrons with appropriate substrates, including Hünig's base and dimethylaniline (DMA) with varying redox potentials. We have also successfully used a SiPc catalyst in a reductive quenching reaction where Hünig's base served as a sacrificial electron donor in the reaction. In addition to being redox-active, our preliminary data also shows SiPcs are capable of performing energy transfer reactions, by performing a reaction that utilizes singlet oxygen as a reactant under visible light conditions. This reaction, in combination with cyclic voltammetry studies, has also served as a model to understand how axial substitution on the silicon center seems to influence the photostability of these species. These results, as well as the photophysical and electrochemical experiments for each SiPc, will be presented.

ORGN 550

Synthesis, characterization, and initial membrane binding properties of mono- and gemini-decyl-chain lumazines

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In an effort to tune fluorescent versus photosensitizer properties in biomembranes, decyl-chain and bis-decyl-chain $[-(\text{CH}_2)_9\text{CH}_3]_n$ ($n = 1$ and 2) lumazine [pteridine-2,4(1,3*H*)-dione] conjugates are being synthesized and characterized. A nucleophilic substitution ($\text{S}_{\text{N}}2$) reaction with iododecane and K_2CO_3 was used for the coupling of the decyl chain to the N1 and N3 sites. Evidence is pointing to two main products, namely, 3-decylpteridine-2,4(1,3*H*)-dione and 1,3-didecylpteridine-2,4(1,3*H*)-dione based on NMR (^1H , ^{13}C , HSQC, HMBC), HPLC, TLC, and UV-VIS data. Measurements of fluorescence quantum yields and the degree of interaction of these lumazines with biomembranes are being studied with large unilamellar vesicles (LUVs) as a biomimetic system. Data on their binding constants and ability to photooxidize the vesicles is forthcoming. Our study aims to expand on a wider series of lipophilic, photooxidatively active lumazines.

ORGN 551

Broadening the understanding of selective microwave heating on the 1,2-Meisenheimer rearrangement

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Microwave reactors are common and safe devices that allow for the heating of reactions more rapidly and facilitate the use of solvents above their boiling points, in comparison with conventional heating. Some reactions carried out in microwave reactor give results that are not reproducible using conventional heating when conducted at the same apparent temperature. These results generally manifest as faster apparent reaction rate, and they are poorly understood. We hypothesize that in solutions containing a weakly microwave absorbing solvent and a strongly absorbing solute, that the microwave energy can selectively heat the solute. This selective heating of solutes can lead to an increased local temperature and thus a higher reaction rate. The 1,2-Meisenheimer rearrangement of an amine *N*-oxide to an *N*-alkoxy amine in nonpolar solvents was used to test the hypothesis. Preliminary results show that there is a rate enhancement when using microwave heating. Unexpected differences in solvent effects are presented as well.

ORGN 552

Direct detection of airborne singlet oxygen from porous Vycor glass particles adsorbed with a brominated BODIPY photosensitizer

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We present a physical organic study of an 8-acetoxymethyl-2,6-dibromo BODIPY photosensitizer (PS) dispersed onto ground porous Vycor glass (PVG_{PS}) for the production of airborne singlet oxygen (¹O₂). Green-light photosensitization of dry PVG_{PS} particles led to the direct detection of ¹O₂ phosphorescence at 1270 nm. Decay curves for singlet oxygen show two lifetimes (τ_1 and τ_2). A short lifetime ($\tau_1 = 68 \mu\text{s}$) was attributed to ¹O₂ residing at the air/PVG_{PS} surface with some spurious light that scattered and reached the near IR detector (Figure). However, the long lifetime ($\tau_2 = 1810 \mu\text{s}$) was attributed to airborne ¹O₂. Also, experiments adding a ¹O₂ chemical quencher (9,10-anthracene dipropionic acid, Q) adsorbed on separate PVG particles or the ¹O₂ physical quencher (H₂O surface) caused τ_2 to disappear. Finally, the presence of airborne ¹O₂ was assessed by conducting experiments in anaerobic conditions. Upon pre-purging the PVG_{PS} with nitrogen, the 1270-nm signal intensity drops significantly. Further, after purging the sample with molecular oxygen (re-oxygenation) the lifetimes were restored. Our results provide insight on how airborne ¹O₂ may be exploited to eradicate dry biofilms in healthcare settings.

ORGN 553

Deducing mobility of ethoxy and cumyloxy radicals on fumed silica surfaces based on recombination products

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In an effort to study the migratory aptitude of alkoxy radicals, fumed silica nanoparticles were adsorbed with cumylethyl peroxide and 4,4'-dimethylbenzil photosensitizer then irradiated with UV light ($280 < \lambda < 700 \text{ nm}$). The radical mobility was probed by detecting recombination products. Namely, the photosensitized homolysis of cumylethyl peroxide led to ethyloxy and cumyloxy radicals, which recombine in ~0.15% yields to diethyl peroxide and dicumyl peroxide products. Based on the yield of dicumyl peroxide, a cumyloxy radical migration distance of ~2-3 nm on the surface was deduced. Studies of the formation of ethanol and cumyl alcohol from the reaction of these radicals with surface SiOH in propagating silicate-type SiO• radicals is underway. Our study aims to expand on deciphering downstream reactions from initial photosensitized processes.

ORGN 554

Synthesis and characteristics of halogenated fused-ring cyclopropanes

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For a number of years, halogenated cyclopropane compounds have been routinely synthesized from dihalocarbenes formed from haloforms in basic solution and allowing them to attack an unsaturated ring. While a number of these compounds have been reported in the literature, few structural studies on these ring structures have been undertaken. This method has been used in the present study to synthesize fourteen chlorinated and brominated 4,4,8,8-tetrahalotricyclo[4.1.0.0^{3,5}]octanes and 5,5,10,10-tetrahalotricyclo[7.1.0.0^{4,6}]decanes in order to examine the structure of these tricyclo ring systems. Five of these compounds are reported for the first time in this presentation. This includes compounds with two chlorine atoms on one side of the ring and two bromines on the other, compounds with a bromine and a chlorine on each side of the ring, and compounds which have three of one halogen and one of the other.

ORGN 555

Mallory photocyclizations: Enhanced twisted heli-acene formations

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The photochemical dehydrogenation, referred to as the Mallory photocyclization, is a pioneer reaction for formation of helicenes and other polyaromatic hydrocarbons. Four bis-Mallory photocyclization substrates have been examined from both experimental and computational (B3LYP/6-311+G(2d,p)) perspectives. Only one of the substrates showed the formation of all the three possible regioisomers at room temperature. The other three substrates only produced the two C₂-symmetric products and not the C₁ product. For these three reactions, it was found that a low photocyclization temperature (< 0°C) resulted in the exclusive formation of the helicene regioisomer despite the fact that the other potential isomers that could form are 11.0, 10.7, and 12.2 kcal/mol more stable. This is due to three factors: (1) the DHP (dihydrophenanthrene) precursors of these two sets of regioisomers are closer in energy (<5 kcal/mol) than the helicene products; (2) the extinction coefficients of the DHP precursors to the helicenes are smaller than that of the DHP precursors of their competitively formed regioisomers by a factor of 4.8-9.2; (3) thermal decomposition of intermediates are suppressed at low temperatures. These factors taken together allow the formation of a photostationary state dominated by the helicene DHP precursor. We have further synthesized helicenes with extended acene appendages that have been studied photophysically and show interesting chiroptical properties such as large optical rotations and higher g_{lum} values. We have also conducted calculations at the B97D/cc-pVDZ computational level for

these twisted heli-acene compounds to further explore the scope of photostationary state-driven helicene formation.

ORGN 556

Effect of water on the chemiexcitation step in peroxyoxalate chemiluminescence

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A wide variety of analytical and bioanalytical applications are based on the highly efficient peroxyoxalate chemiluminescence reaction. This system can be easily carried out by the reaction of an oxalic ester with hydrogen peroxide, catalyzed by a base and in the presence of an activator. Although, this transformation has been intensively studied in anhydrous medium, obtaining quantum yields of up to 50%, there are only few mechanistic studies in aqueous conditions, where the efficiency of this reaction is much lower. In this work we report our results of a study on the chemiexcitation step of the peroxyoxalate reaction using two oxalic esters with different reactivity in organic solvents like 1,2-dimethoxyethane, containing small amounts of water, in order to understand why the chemiexcitation quantum yields of this transformation are drastically lowered in aqueous media.

The quantum yields showed to increase in the presence of water up to a maximum value for a molar fraction of 0.06 of water, decreasing with still higher water content of the reaction medium. A possible explanation for these results can be given by assuming that small amounts of water stabilize the pair of radical ions formed within the solvent cage and the solvation initially contributes to keeping these species together, allowing the occurrence of the electron back-transfer step, responsible for the formation of states excited. From a certain limiting value of polarity the radical ions can be solvated individually by the water molecules avoiding the possibility of an electron back-transfer and leading to a decrease in the chemiexcitation quantum yields. The variation of the ACT concentration allows the study of the chemiexcitation step and the determination of the chemiluminescence parameters of this transformation, which showed to be critically influenced by the presence of small amounts of water. For three different water fractions the electron transfer coefficients α were obtained. The α value of 0.10 indicates an early transition state with respect to electron transfer and, presumably, also O-O bond cleavage, since these two steps should be simultaneous. In a preliminary conclusion it can be observed that the low chemiexcitation quantum yields obtained for the peroxyoxalate reaction in aqueous medium are not mainly due to concurrent oxalic ester hydrolysis but to the influence of water on the efficiency of the chemiexcitation step.

ORGN 557

Role of spin chemistry in photosynthesis: Approach for electron transport

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Investigations on electron transport (ET) focus mostly on the charge of the electron and not much on its spin property. ET results in both charge and spin transfer, and a full understanding of the conversion of light energy into chemical energy requires an analysis of the spin transport.

In the photosynthetic reactions centers (RC), the photochemical charge and spin separation in the primary reactions creates a spin-correlated radical pair that can be detected by electron paramagnetic resonance (EPR) showing strong electron spin-hyperpolarization, normally called CIDEP (chemically induced dynamic electron polarization). The spin-hyperpolarization refers to a non-Boltzmann spin polarization, which can be detected as a change in signal intensity by magnetic resonance techniques. Since the electron Zeeman energy in typical EPR experiments is small compared to the thermal energy and in particular to chemical reaction energies, a purely energetic view of the photosynthetic reaction process tends to underestimate the role of spin dynamics, but even the smaller nuclear spin energies can decide the fate of the chemical reaction.

CIDEP effect has been observed in several photosynthetic systems and properly explained by the radical pair mechanism (RPM).

The photo-CIDNP (chemically induced dynamic nuclear polarization) is another spin-hyperpolarization effect that has been observed, by magic-angle spinning (MAS) solid-state NMR, in various frozen RC of different photosynthetic organisms. It appears that this effect is an intrinsic property of efficient photosynthetic electron transfer and that is highly conserved in the evolution of photosynthetic organisms. The solid-state photo-CIDNP effect opens the possibility for an efficient method to analyze the electronic structures of cofactors in RC proteins and has been developed into a fully-fledged analytical method to study the structure and function of different RC in various organisms.

As can be seen, spin-hyperpolarization plays a significant role in photosynthesis, for both its functional relevance and the analytical research on it.

ORGN 558

1-Norbornyl cation may be in equilibrium with 2-norbornyl cation

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New ^1H and ^{13}C NMR 400 MHz spectra of the 2-Nb cation under stable ion conditions, e.g., in $\text{SbF}_5 / \text{SO}_2\text{F}_2 / \text{SO}_2\text{ClF}$, -80°C , show besides the usual ^1H NMR resonances at $\delta 4.93$ (4H), 2.82 (1H), 1.85 (6), the never before seen singlet, $\delta 9.63$, and doublet, $\delta 2.97$ ($J_{2,6} = 16.6$ Hz), ratio 1.00 : 1.07, proposed to be due to resonance stabilized bridgehead 1-Nb cationic enantiomers in equilibrium with 2-Nb cation. The corresponding ^{13}C proton-coupled NMR spectrum, -80°C , has a C3,5,7 triplet, δ

30.45, $J(\text{CH}) = 139.14$ Hz, and C4 doublet, δ 37.7, $J(\text{CH}) = 154.54$ Hz. The C1,2,6 absorption, δ 91.04 is relatively broad, whereas previously at -70°C , it was a pentuplet. The ^{13}C proton-decoupled spectrum at -80°C shows the C4 doublet and C3,5,7 triplet collapsed to a singlet but the C1,2,6 resonance is still broad.

Analyses support slowing exchange between resonance stabilized enantiomeric 2-cations at $\leq -159^\circ\text{C}$. Quenching the 2-Nb cation solution with aqueous MeOH at -66°C yielded 42.8 % of 1-substituted products (37.7 % 1-hydroxynorbornane, 4.2% 1-chloronorbornane, 0.9 % 1-methoxynorbornane, 43.5% dinorbornylether, 0.4% 2-hydroxynorbornane and 13.3% unidentified products) indicating resonance stabilized 1-Nb cation is indeed present in solution along with the 2-Nb cation. These results complement previous quenching results of 1-chloronorbornane in $\text{SbF}_5\text{-SO}_2$ at -70°C which, e.g., after warming to -50°C yielded 65 % of 1-norbornanol and 0.5 % exo-2-norbornanol.

It is crucial to recognize that some previous interpretations of NMR studies at $\leq -150^\circ\text{C}$ are not secure. These interpretations did not consider (1) recent evidence indicating anchimeric assistance of 2-exo leaving group displacement by bridgehead hydrogen orbital (2) presence of a pair of stereospecific front-face C1,2,6 hydride shifts via the bridgehead C1 rather than the assumed nonstereospecific 6,2,1 hydride shift for which there is no evidence (3) possibility of C1 instead of C6 carbon bridging, and (4) sigma aromaticity.

ORGN 559

Charge-transfer character in perylenediimide excimers self-assembled on anodic aluminum oxide membrane walls

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Chromophore aggregation strongly impacts the efficiency of organic photovoltaics (OPVs). Perylene-3,4:9,10-bis(dicarboximide) (PDI)-based electron acceptors have been shown to be excellent alternatives to fullerenes in OPVs, provided their supramolecular assemblies do not form excimers. In order to study this phenomenon in a controlled fashion, we have prepared two PDI derivatives that were incorporated into an anodic aluminum oxide (AAO) membrane. In one system, the PDI molecule has an *n*-propyl silatrane attached to one of its imide nitrogens, while a 12-tricosanyl group is attached to the other imide nitrogen. The silatrane reacts with the AAO surface to covalently bind the PDI. The other PDI has 12-tricosanyl groups on both imide nitrogens, which intercalate with *n*-octadecylsilane chains covalently bound to an AAO membrane. Since aluminum oxide is a wide bandgap semiconductor, photoexcitation of PDI does not result in charge injection into the AAO membrane; thus, the intrinsic electronic properties of the aggregated PDI molecules within the membrane can be studied. Both PDI derivatives form excimers with and without solvent in the AAO

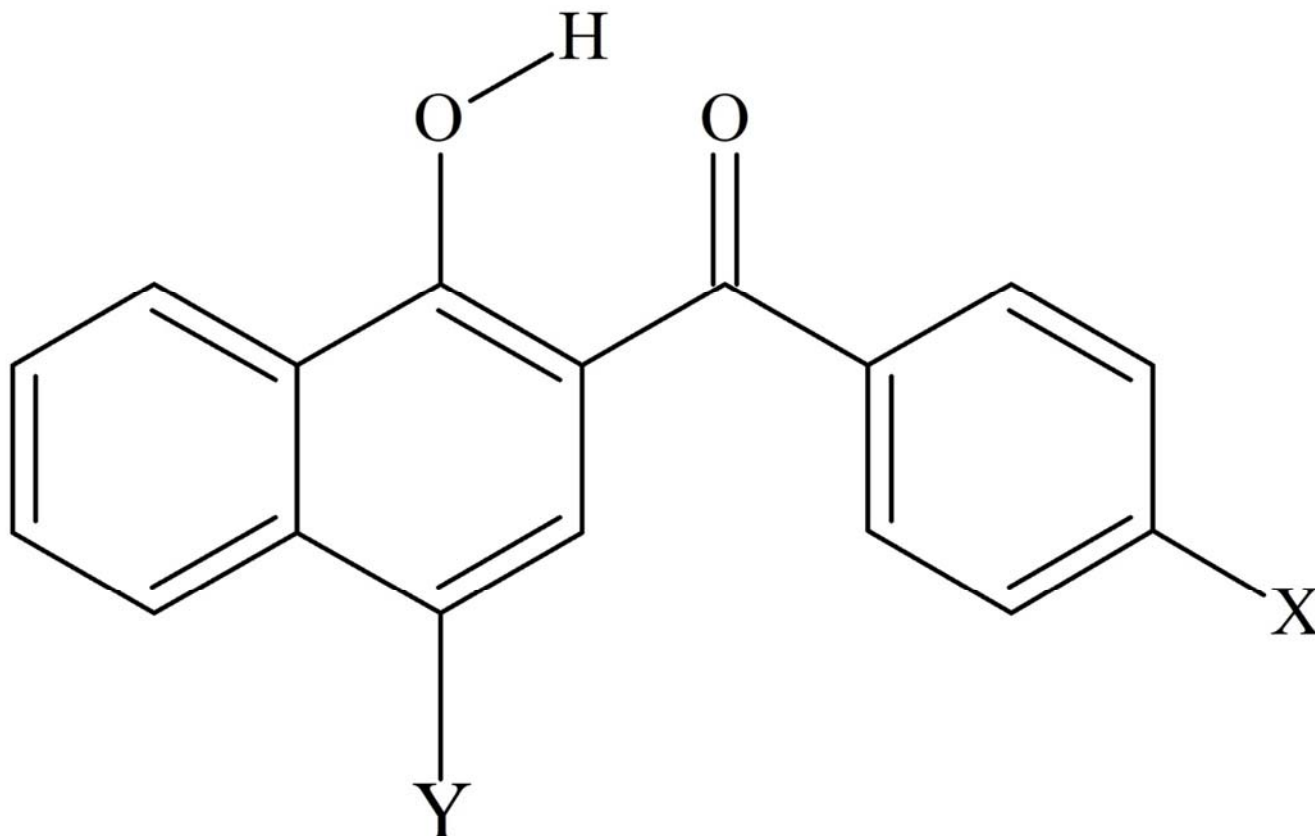
membrane pores and display increasing charge transfer character with increasing solvent polarity. Since the AAO membrane allows for any choice of solvent to be infiltrated into its pores, the PDI photophysics can be modulated over an arbitrary range irrespective of whether PDI is soluble in a particular solvent. The results presented here show how to tune the intermolecular interactions of PDI and related rylene dyes attached to walls of the AAO pores to understand the intermediate regime between solution and the solid state.

ORGN 560

Hammett study of a resonance assisted hydrogen bond

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Resonance assisted hydrogen bonds (RAHBs) are among the strongest forms of hydrogen bonding known to occur and are found in specific intramolecular hydrogen-bonding systems. Two series of *ortho*-acylnaphthols were synthesized, as in the figure below, where X or Y = CH₃O, CH₃, H, Br, Cl, NO₂. One series was substituted on the 4-naphthol position (Y), and the other substituted on the 4-benzoyl position (X). A Hammett study was carried out using ¹H NMR and ¹³C NMR to determine the nature of the electronic effects on the internal hydrogen bond in this system. The OH exhibited ¹H NMR shifts higher than 13ppm in these compounds.



General structure of the two series of *ortho*-acynaphthols synthesized. X or Y = CH₃O, CH₃, H, Br, Cl, NO₂.

ORGN 561

Computational investigations into the origins of reactivity at metal-sulfur centers

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Reactivity at metal-sulfur sites plays a central role in modulating protein function and cell signaling processes in biology, and the push to harness metal-sulfur reactivity beyond biological systems is of growing interest. An ongoing discussion is on the role of the metal complex in modulating the reactivity at the coordinating sulfur atom. In this talk, our computational investigations of two systems will be presented: (1) plausible mechanisms, and origins of regio- and chemoselective oxidation at a zinc-sulfur coordination site; (2) origins of varying reactivity at an iridium-sulfur and a rhodium-sulfur coordination site toward cooperative bond activation. Computational insights into the role of the metal, the ligand coordination geometry, and ligand dissociation and

exchange equilibria in governing reactivity across metal-sulfur centers will be presented, and implication in biological systems will be discussed.

ORGN 562

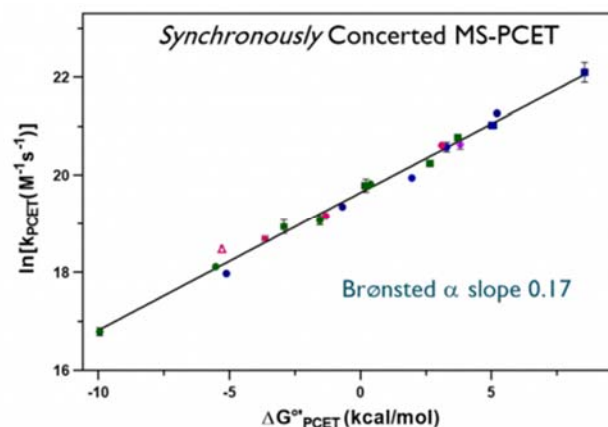
Kinetics, mechanism, and chemoselectivity in multi-site proton-coupled electron transfer

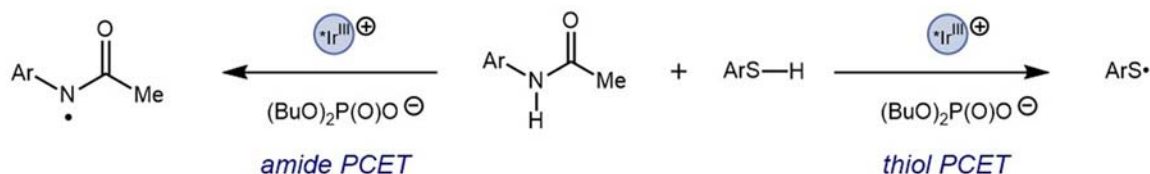
Guanqi Qiu, gqiu@princeton.edu, Robert Knowles. Chemistry, Princeton University, Princeton, New Jersey, United States

Here we present a detailed kinetic study of the multisite proton-coupled electron transfer (MS-PCET). As a model system, we elect the activations aryl ketones using a variety of Brønsted acids and excited-state Ir(III)-based electron donors. We formulated a simple method that simultaneously extracting both the hydrogen-bonding equilibrium constants and the rate constants for the PCET event from deconvolution of the luminescence quenching data. These experiments confirm that these activations occur in a concerted fashion, wherein the proton and electron are transferred to the ketone substrate in a single elementary step. The rates constants for the PCET events were linearly correlated with their driving forces over a range of nearly 19 kcal/mol. However, the slope of the rate-driving force relationship deviated significantly from expectations based on Marcus theory. A rationalization for this observation is proposed based on the principle of non-perfect synchronization, wherein factors that serve to stabilize the product are only partially realized at the transition state. Similar studies were carried that provide a quantitative basis for understanding the chemoselectivity in competitive PCET activations of amides and thiols relevant to catalytic olefin hydroamidation reactions. These results demonstrate how the interplay between PCET rate constants, hydrogen-bonding equilibria, and rate-driving force relationships jointly determine PCET chemoselectivity under a given set of conditions. In turn, these findings predict reactivity trends in a model hydroamidation reaction, rationalize the selective activation of amide N-H bonds in the presence of much weaker thiol S-H bonds, and deliver strategies to improve the efficiencies of PCET reactions employing thiol co-catalysts.

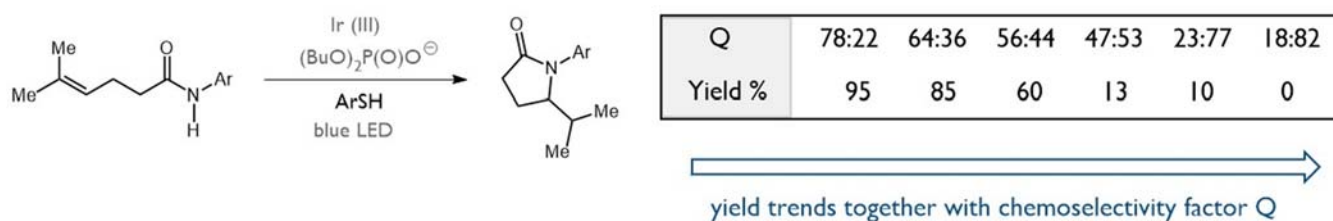


- 20 distinct combinations of ketone, acid, and reductant
- Linear rate-driving force relationship over 19 kcal/mol range





Quantitative Basis of Chemoselectivity ?

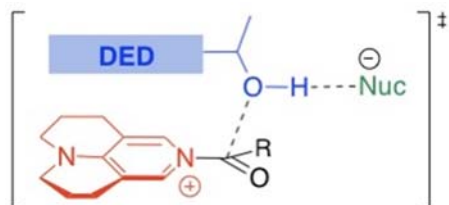


ORGN 563

Size-accelerated Lewis base catalysis

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The idea of guiding molecular transformations in organic chemistry through London dispersion forces has seen numerous examples in recent years. We here explore the question, whether properly placed dispersion energy donor (DED) units can alter the reactivity and selectivity patterns observed in Lewis base-catalyzed reactions of alcohols. For the acylation of secondary alcohols it can indeed be found that reaction rates for the Lewis base-catalyzed process increase with increasing size of the reacting alcohols. This can most easily be rationalized with transition state structures showing a close proximity between substrate alcohols and Lewis base catalysts.



ORGN 564

Redefining our concept of the chemical bond

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The foundation of our understanding of the chemical bond dates back to the pioneering work of G. N. Lewis. Lewis's ideas were then framed in the language of quantum mechanics by Pauling and Slater resulting in the present day classification of chemical bonds as either covalent/polar covalent or ionic. However, in the early 1990's Sason Shaik and Philippe Hiberty began to challenge this paradigm with a new form of chemical bond that is neither covalent nor ionic alone, but due to the resonance mixing of both together. This new type of bonding was named charge-shift bonding (CSB). Originally CSB was seen as an anomaly of valence bond theory by which it was discovered. However, in recent years CSB has been gaining attention and is being recognized by other forms of theory and being verified experimentally. In this talk I will discuss my work with Shaik and Hiberty on CSB over the past several decades. I will start by defining CSB in the context of VB theory and then show how it extends to other forms of theory as well. I will then show some experimental manifestations of this unique bonding situation and discuss its potential applications. The chemical bond is at the heart of chemistry and the way we view bonds has remained unchanged for over 100 years. CSB is a real and unique form of chemical bond that has the potential to completely change the way we think about chemistry.

ORGN 565

Transformation of enantiopure homoallylic amines into nitrogen heterocycles via electrophilic addition

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In this presentation, the transformation of enantiopure homoallylic amines to nitrogen heterocycles will be described utilizing a variety of chemical methods. Virtually any aldehyde, especially aromatic ones, can be condensed with enantiopure R or S-tert-butanesulfinamide (the Ellman stoichiometric chiral ammonia reagent) to access chiral, non-racemic imines. In relatively straightforward fashion, the indium mediated allylation with allyl bromide in tetrahydrofuran provides access to homoallylic amines in a highly diastereoselective manner. This chemistry is extremely robust and has been performed

by high school, undergraduate and graduate students on milligram to decagram scale. The value added amines have been examined under a variety of strategies to produce nitrogen heterocycles. In one vignette, oxidation of the secondary sulfinamide to the sulfonamide with mCPBA allowed for BOC protection of the nitrogen. Subsequent electrophile initiated cyclization with halogens (Br₂, I₂, NCS, NBS, NIS) allowed for the difunctionalization of the pendant alkene. This intramolecular cyclization created a 1,3-aminoalcohol with excellent diastereoselectivity at the newly created stereogenic carbon due to transfer of chirality. The bulkiness of the tert-banesulfonamide (BUS) group forces C2 substituents to be axial in a the chair like transition state. The halogen atom can be reduced under radical conditions with tin-hydride or transformed into azide or alcohol via standard S_N2 chemistries. In a second vignette, acidic deprotection of the secondary N-sulfinamide to the free amine allowed for preparation of homoallylic guanidines using commercially available guanidinyllating reagents. These substrates cyclize in an intramolecular fashion as well to access cyclic guanidines. Factors controlling the cyclization will be discussed based on 1D/2D NMR and x-ray crystallization data.

ORGN 566

Selective removal of *tert*-butyloxycarbonyl (BOC) groups from heterocyclic substrates utilizing addition-elimination with primary amines

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Pursuant to the exploration of utilizing 2-(5,6-diphenyl)-mono-1,2,4-triazinyl-pyrid-2-yl)-6-1H-indoles as complexant molecules for the extraction of minor actinides from lanthanides post-PUREX, a protocol has been developed for the removal of the BOC group where typical methods, such as treatment with TFA or mineral acids / Lewis acid activation, were unsuccessful. Treatment of a wide scope of nitrogen-containing heterocycles such as: indazoles, pyrazoles, indoles, and imidazoles with primary amines and gentle heating results in clean, deprotected products. The mildness of these conditions can potentially find use when deprotection is desired and substrate sensitivity to acidic conditions is of concern. The development of this protocol, its optimization, and full substrate scope will be described.

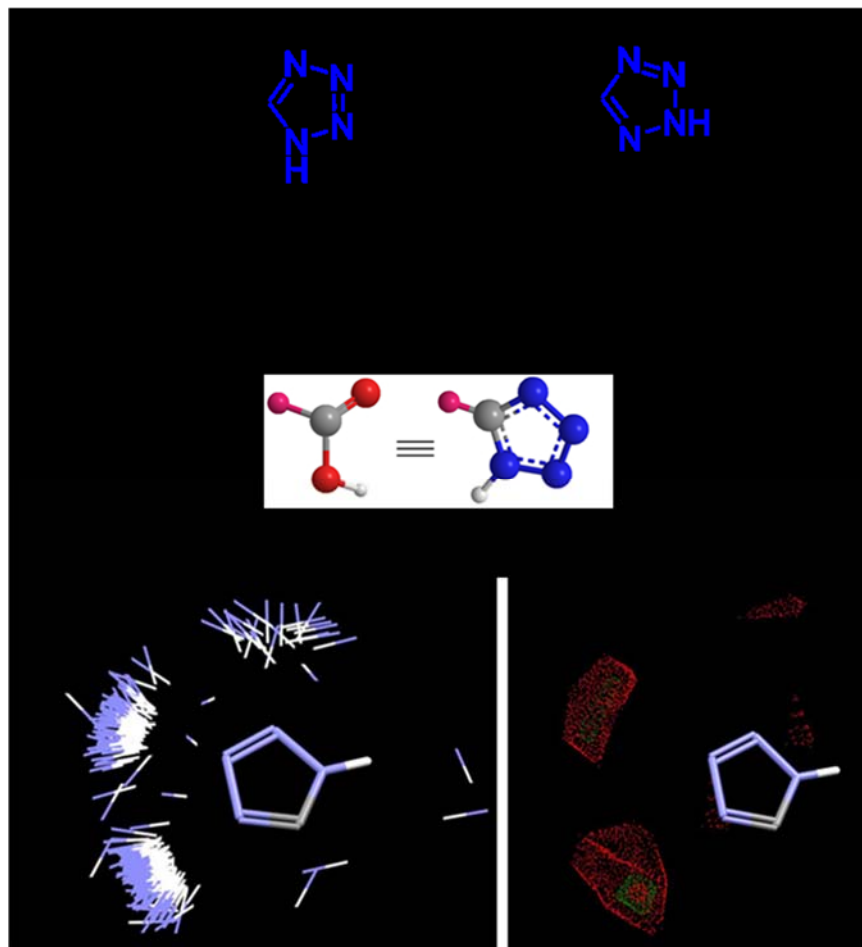
ORGN 567

Diversity of tetrazole synthesis

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Tetrazoles are a privileged scaffold bioisosteric to cis amides and carboxylic acids with a lot of applications in medicinal chemistry. Here I will give an overview on the synthetic world of tetrazoles by multicomponent

reactions with a focus on our own work, highlighting novel scaffolds intermediates towards oxadiazoles, 1-tetrazolylimidazo[1,5-a]pyridines, tetrazole in DNA encoded library synthesis and miniaturized HT synthesis of tetrazoles on a nano scale (1).



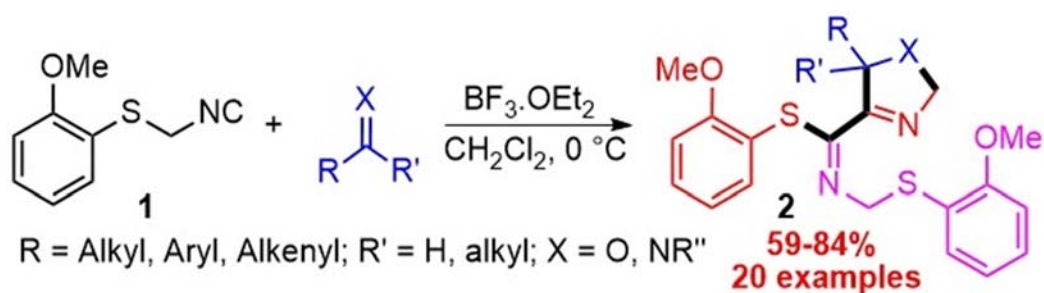
ORGN 568

BF₃.OEt₂-mediated formal [3+2]-cycloaddition of isocyanides to form heterocycles

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Isocyanides are unique functionalities that can act as both electrophiles and nucleophiles. Their utility is demonstrated in the multicomponent reactions to generate a variety of heterocycles, peptidomimetics and their use as dipoles in [3+2]-cycloadditions.

Anisylsulfanylmethylisocyanide (Asmic) **1**, is a powerful isocyanide building block that provides access to a variety of di- and trisubstituted isocyanides through alkylation and exchange processes. A conceptually orthogonal alkylation strategy has been developed with Asmic that provides a rapid route to the synthesis of dihydrooxazoles and dihydroimidazoles **2** (**Equation 1**). This strategy rests on the highly unusual deployment of $\text{BF}_3 \cdot \text{OEt}_2$ with electrophilic *p*-acceptors such as carbonyl compounds and activated imines to efficiently generate various heterocycles. The structure of heterocycles incorporates two Asmic units and one benzaldehyde unit with the breaking of C–S and C–C bonds. This novel one-step protocol is highly efficient for accessing the heterocycles. We will provide a detailed mechanism and reaction scope in the presentation.



Equation 1: Asmic based heterocycles synthesis

ORGN 569

Green approach for the synthesis of ferrocenyl stilbene derivatives

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Stilbene derivatives like Resveratrol are found in natural products and their capacity as antioxidants is well known. They also act against free radical effects related to diseases like some type of cancers. Ferrocenyl stilbenes derivatives have been usually prepared via olefination reactions, Wittig or Horner-Wadsworth-Emmons. Moreover, the Heck reaction has also been used as well as the Knoevenagel condensation, but all these methodology approaches include conditions of the reactions, work up and purification process that are not environmentally friendly. For this reason, our interest is to apply a

greener approach to the synthesis of Ferrocenyl stilbenes. We also aim to explore its radical scavenging and biological activity. Ferrocenyl stilbenes compounds were synthesized applying a greener approach for the Heck reaction using water as a solvent and Aliquat 336 as a phase transfer catalyst or using a mixture of water and acetone without the catalyst. Products were obtained in shorter times and better yields while compared with the reported methodology for the Heck reaction using DMF as a solvent under a Nitrogen atmosphere. Some of the compounds are novel. Most of the compounds were purified using crystallization process avoiding extractions and column chromatography techniques. The complete synthetic methodology, IR, ^1H and ^{13}C NMR characterization and the radical scavenging activity of these compounds will be presented. Also, the X-Ray crystallographic structure of some of the compounds was obtained.

ORGN 570

Catalyst behavior in carbonyl-olefin metathesis

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Chemistry and Biochemistry, Loyola University Chicago, Chicago, Illinois, United States

The utilization of Lewis acids to activate substrates containing carbonyls is ubiquitous in organic synthetic methods. Importantly, Lewis acid-catalyzed carbonyl-olefin metathesis represents a powerful reaction manifold for the construction of C=C bonds from functional groups that are broadly utilized in the construction of complex molecules. The Fe(III)-catalyzed process developed by Schindler and coworkers triggered a series of synthetic developments that expand the use of Fe(III), employ Ga(III), as well as employing Bronsted acids with supramolecular hosts, or as organic catalysts. Because of the widespread application, effort has been devoted to characterizing the interactions of Lewis acids and bases, historically relying on solid state IR and X-ray crystallography, as well as in situ NMR. A fundamental understanding of how the carbonyl specifically interacts with Lewis acid in solution will provide synthetic chemists with mechanistic information crucial for developing high yielding procedures as well as opening new reaction trajectories via structural modification of the catalyst. Experiments designed to elucidate the relevant Lewis acid-carbonyl solution structures to specify their impact in catalytic methods will be presented.

ORGN 571

Fused azepine organic semiconductor via the cyclization of vinyl azide

Julia A. Schneider, *jschneider43@fordham.edu*. Chemistry, Fordham University, Bronx, New York, United States

Continued growth in organic electronics is linked to the synthesis of novel conjugated structures. A key strategy toward tunable optoelectronic properties is the incorporation of nitrogen heteroatoms into polycyclic aromatic compounds. Increasing the electron

affinity in azaacenes, for example, yields excellent electron transport properties. Their synthesis, almost exclusively via the condensation of o-diamines, however, severely limits possible structures. Our work utilized the visible-light photocyclization of vinyl azides to synthesize thiophene-fused benzodiazepine. This Hemetsberger-like reaction is the first example of 7-membered ring formation from vinyl azides. Additionally, 7-membered rings, and azepines in particular, are rare in organic semiconductors, so the optical and electronic properties of thiophene-fused benzodiazepine will be presented.

ORGN 572

Total synthesis and investigation of metal-binding natural products

Kelly Morrison, *krmorr4@emory.edu*, Justin A. Shapiro, Ryan Allen, Shreya Chodisetty, William M. Wuest. Emory University, Atlanta, Georgia, United States

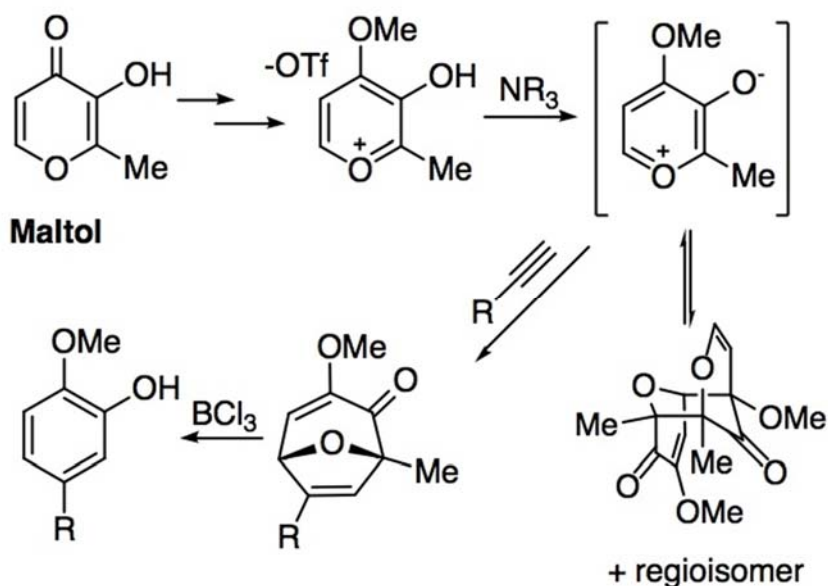
Antibiotic resistance is one of the greatest challenges scientists are currently confronting. A rigorous investigation of how bacteria respond in an infection state, both individually and as a community, is essential to understanding their complex and varied processes. In order to survive the hostile host environment, bacteria must acquire key nutrients to gain a competitive advantage and ensure survival. One of these key nutrients is bio-unavailable ferric iron which is severely limited, and sought after by both bacteria and the host itself. Bacteria acquire iron by secreting siderophores – small molecules with a high affinity for iron – which are then actively transported into the cell and used in cellular processes. We propose that learning more about the iron cycle may lead to a greater understanding of bacterial infection responses, and potentially lead to bacterial inhibitors. Our approach consists of synthesizing natural products which contain privileged iron-binding motifs and then testing them for metal binding capabilities and biological activity. Ulbactin F is a unique, cysteine-derived, marine natural product with preferential binding for iron and anticancer activity. Other iron-binding natural products, the watasemycins and thiazostatins, are two families of molecules have specific methylation patterns which effect their three-dimensional structure and therefore, their reported antibiotic activity. Therefore, the total synthesis of ulbactin F, watasemycins, and thiazostatins will be reported. By synthetically accessing these small molecules and analogs, we can further investigate their role in metal acquisition as well as their antibiotic properties.

ORGN 573

Studies on maltol-derived oxidopyrylium ylides

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Oxidopyrylium ylides are useful intermediates in synthetic organic chemistry because of their ability to form structurally complex cycloadducts via a [5 + 2] cycloaddition with a variety of diverse dipolarophiles. They can also self-dimerize via [5 + 3] cycloaddition, which has been historically referred to as a byproduct of the [5 + 2] cycloaddition. We have shown that these dimers can be isolated and used as the source of oxidopyrylium ylide in the synthesis of cycloadducts and that the substitution pattern of the ylide governs both the cycloaddition and dimerization processes. We have further demonstrated through experimental rate studies and DFT calculations that maltol-derived oxidopyrylium ylides have a higher energy barrier to dimerization compared to their allomaltol regioisomeric counterpart, and thus can be trapped more efficiently with dipolarophiles. In addition, under acidic conditions the oxabicyclic structures formed from these cycloadditions can afford biologically relevant functionalized biaryl structures in high yields.



ORGN 574

Synthesis of a fluorinated nucleoside via an electrophilic fluorination/glycosylation strategy

Michael Pirnot, mpirnot@gmail.com, Eric Phillips, Peter Maligres, Cheol Chung, John Limanto, Colin Lam. Process Research and Development, Merck & Co., Inc., Rahway, New Jersey, United States

This talk will describe the commercial route development for a fluorinated nucleoside that relies on a highly diastereoselective electrophilic fluorination/glycosylation process for the synthesis of this intermediate. Initial discovery of the process, subsequent optimization, and evolution of a through-process that culminates with a multi-kilogram delivery will be detailed.

ORGN 575

Efforts towards Rh(II)-catalyzed N-alkoxyazomethine ylide generation

Doris Chen¹, *dchen2@gatech.edu*, **Elizabeth Jones**¹, **Benjamin Rocke**², **John Trujillo**², **Stephen W. Wright**², **Stefan A. France**¹. (1) School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, Georgia, United States (2) MS 8220-3431, Pfizer PGRD, Groton, Connecticut, United States

Azomethine ylide cycloaddition reactions are some of the most powerful and well-studied chemical transformations to construct (hetero)cyclic frameworks. On the other hand, the cycloadditions of azomethine ylides bearing *N*-alkoxy substituents has largely been overlooked. This has been the case despite the potential for accessing heterocycles with a useful cleavable tether which can be manipulated downstream (via N-O bond cleavage). Herein, we describe our efforts in the pursuit of intramolecular *N*-alkoxyazomethine ylide generation from oximes with a diazoketone moiety tethered to the oxygen atom and the disparate reactivities observed. The research plan discussed will probe three key questions: (1) Does the desired [3+2] cycloaddition take place in the presence of a catalyst and dipolarophile? (2) What is the effect of having a diazo ketone vs an α -diazo- β -ketoester moiety tethered to the oxime oxygen? (3) How does the transition-state ring size effect the intramolecular ylide formation and stability?

ORGN 576

Synthesis approach to dramatically alter indole alkaloids leads to compounds with re-engineered biological activities

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Today, drug discovery efforts primarily involve the screening large compound libraries of structurally simple organic molecules against drug targets of interest. Despite many success stories related to such efforts leading to the discovery new and effective clinical agents, we continue to face significant challenges in the treatment of disease. The lack of chemical diversity within screening libraries (i.e., compounds without stereocenters, or low sp^3 character) is a limitation in the types of targets that can be effectively drugged. To address this problem, our group is working to optimize an array of indole-based synthetic methods to enable rapid and dramatic structural alterations of the complex molecular architectures of indole alkaloids. Our goal in doing this chemistry is

to re-engineer the biological activities of indole alkaloids to discover new compounds with new biological activities of significance to human health. This presentation will detail our synthetic strategy and results. In addition, select biologically active compounds identified from the screening of this unique compound library will be discussed.

ORGN 577

Pharmacology of motor proteins: Quest for better tool compounds and therapeutics

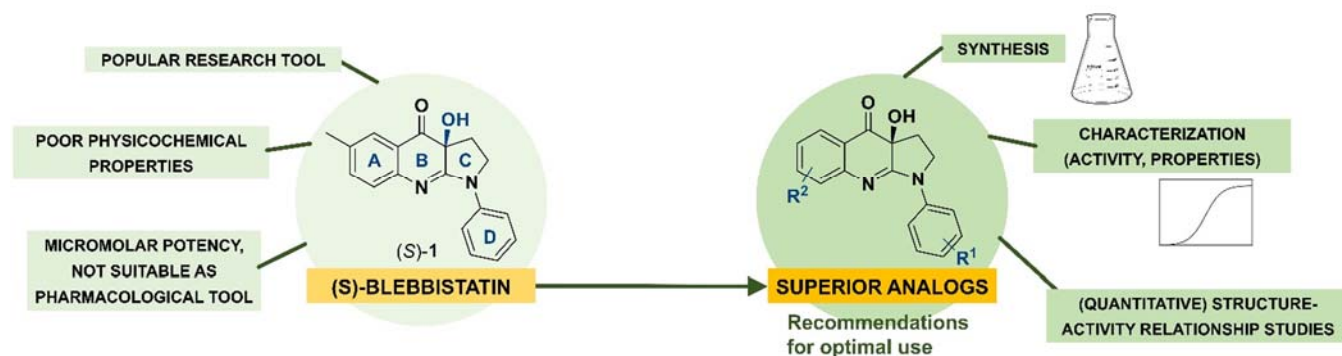
Bart I. Roman, *bart1.roman@ugent.be*. Department of Sustainable Organic Chemistry and Technology, Ghent University, Ghent, Belgium

This talk is an introduction to the pharmacology of motor proteins, in particular to the medicinal chemistry of blebbistatin. (S)-Blebbistatin (S)-**1**, a chiral tetrahydropyrroloquinolinone, is a widely used and well-characterized ATPase inhibitor selective for myosin II. The central role of myosin II in many normal and aberrant biological processes has been revealed with the aid of this small molecule.

Given the multiple roles of myosin II in a diverse range of motility-based diseases, potent and drugable inhibitors of particular isoforms of this protein could be valuable pharmacological tools. The potency of (S)-blebbistatin is however too low to serve this goal. (S)-blebbistatin also has severe physicochemical deficiencies that trouble its use as a research tool in advanced biological systems: low solubility, fluorescence interference, (photo)toxicity and stability issues. As a consequence, there is a large unmet need for better myosin inhibitors.

Over the last years we have developed and field-tested a toolbox of (S)-blebbistatin analogs as improved myosin inhibitors in which several of the above shortcomings have been addressed. We have designed a user's guide for their optimal application. We have also strived for potency enhancement via modification of rings A, C and D of the molecule, in search of lead compounds. We have analyzed the resulting structure-activity relationships using *in silico* methods, which have provided unexpected but interesting insights.

The present talk will provide an overview of these efforts, as well as an outlook to future developments in the fast moving area of motor pharmacology.



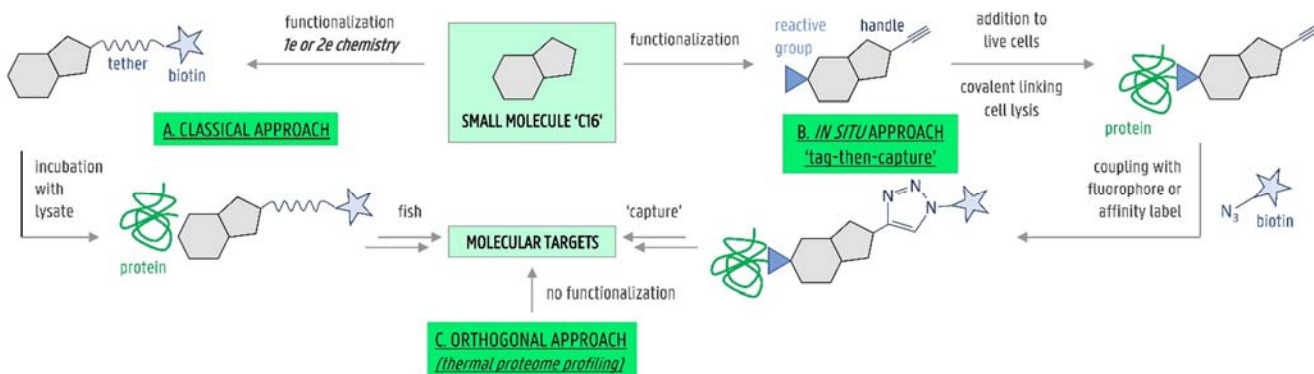
ORGN 578

Synthesis and use of proteomics probes to identify the molecular targets of an anti-invasive agent

Bart I. Roman, bart1.roman@ugent.be. Department of Sustainable Organic Chemistry and Technology, Ghent University, Ghent, Belgium

Ninety percent of cancer patients die because of the local or distal dissemination of their disease. The related phenotypic hallmarks of malignancy, invasion and metastasis, remain incompletely understood phenomena. In search of new drugable mechanisms driving the process of invasion, and in search of pharmacological tools to modulate invasion, we have screened a large library of molecules in a phenotypic, organotypic invasion assay. From this screen we have identified the small molecule C16 as a nanomolar inhibitor of invasion.

In this communication, we present our synthetic and biological work on the identification of the molecular targets of this inhibitor using C16-derived probes. We have used both classical, two-electron transfer, and novel one-electron transfer-type chemistry to prepare three families of probes for use in either classical fishing methodology or *in situ* (*tag-then-capture*) approaches. We will discuss the synthesis of these probes and the outcome of the proteomics experiments using them, and will compare these methods against an orthogonal approach that uses the unmodified inhibitor to identify direct binders: thermal proteome profiling.



ORGN 579

Positional effects of thioamides on serine protease activity: Mechanistic studies and application to stabilize cancer imaging peptides

Taylor Barrett¹, taybar@sas.upenn.edu, **Xing Chen**¹, **Chunxiao Liu**¹, **Sam Giannakoulis**¹, **Jieliang Wang**¹, **Richard J. Karpowicz Jr.**², **E Petersson**¹. (1) Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States (2) Center for Neurodegenerative Research, University of Pennsylvania, Philadelphia, Pennsylvania, United States

Thioamide substitution in the peptide backbone has several applications in studying proteolysis, including as protease probes and selective protease inhibitors. To date, we have used model substrates to investigate the positional effects these thioamide substitutions have on proteolysis rates, as well as examining the ability of thioamides to stabilize peptides for imaging applications. In order to determine the positional effects of thioamides, we have examined several model peptides with a thioamide scanned from the P3 position to the P3' position and identified thioamide perturbing and non-perturbing positions. Further mechanistic investigation showed that the primary effect of the thioamide is often to prevent binding to the protease. Finally, incorporation of a thioamide into a peptide scaffold that is known to selectively bind the neuropeptide Y Y1 receptor showed increased serum stability, while retaining affinity for the receptor. These studies show that thioamides can be used to create stabilized imaging peptides and are helping to guide our understanding of where is best to place thioamides to obtain the desired effects.

ORGN 580

Analysis of β -sheet mediated peptide assembly using a chemical biology approach

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A key problem in life-sciences research is to understand protein-protein interactions (PPI) with molecular and temporal resolution – this would allow the identification of the transient intermediates that play key roles in the function of biomacromolecular machines, signalling, translocation and folding to illuminate our understanding of disease development e.g. aberrant intracellular cell signalling in cancer and aggregation in amyloid disease. This presentation will outline the use of diazirines as powerful reagents to study β -sheet mediated PPIs specifically assembly of peptides into amyloid fibrils and will illustrate how, in combination with state-of the art mass-spectrometry, cross-linking encodes non-covalent structure in cross-linked peptides.¹⁻² Alongside these studies, the presentation will outline how a suite of biochemical and computational methods can be harnessed to provide, for the first time, an analysis of the structural mechanism of surface-catalyzed secondary nucleation in amyloid assembly.³

ORGN 581

Peptide-bile acid cyclisation as a tool for the development of a universal vaccine against influenza A

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Peptide cyclisation is considered to enhance the therapeutic properties of peptide drugs because it allows to modulate for example the conformational flexibility, susceptibility to proteases, potency and selectivity of such drugs. In this work, cyclisation is achieved by grafting the peptide sequence onto a bile acid scaffold, more specifically deoxycholic acid. Apart from being rigid, the scaffold is also very cheap and has amphipathic properties which equips the molecules with a hydrophobic side. In this way, the scaffold can constrain the peptide as well as help to increase cellular uptake, bioavailability, albumin binding, protease stability, etc.

This bile acid cyclisation can be used for a variety of targets. Here, we present a conjugate peptide antigen designed to generate broadly protective antibodies against Influenza A. We chose to graft a peptide corresponding to the extracellular part of matrix protein 2 (M2e) onto the scaffold because M2e is conserved across different influenza A virus subtypes and can thus act as a universal antigen for influenza A. The M2e peptide adopts a U-shape when bound to a M2e-specific and protective monoclonal antibody (mAb 65). Therefore, we hypothesized that constraining this peptide can promote the induction of mAb 65-like antibodies. The grafting reaction involves an easy one-step synthesis delivering two regioisomers, which can be separated and purified with optimised HPLC conditions. Interestingly, the cyclic peptide-bile acid conjugates are recognized by M2e-specific monoclonal antibodies and polyclonal serum in an ELISA assay. In addition, the immunogenicity of the constrained M2e peptide that best competed with the linear M2e peptide for mAb 65 binding was evaluated *in vivo*.

Immunization of laboratory mice with the cyclic M2e peptide induced serum antibodies that were specific for M2e, and for M2 expressed by mammalian cells. We conclude that constraining a peptide antigen on a bile-acid scaffold is an efficient method to design a universal influenza A vaccine candidate.

ORGN 582

Evolution of new enzymes for the synthesis of non-canonical amino acids

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Non-canonical amino acids (ncAAs) are required for a range of applications in drug discovery, but these compounds are challenging targets for chemical synthesis, often requiring synthesis via long and inefficient routes. Biocatalysis can offer uniquely direct and selective methods to access ncAAs, either by using enzymes that naturally perform amino acid synthesis or by designing alternative enzymatic strategies. We have explored enzymatic methods for the synthesis of tryptophan analogs as well as hydroxylated amino acids. Using engineered tryptophan synthases, a range of unnatural tryptophan derivatives can be accessed in a single step from the condensation of an indole with serine. To create amino acids bearing functionality for cross-linking, we evolved a tryptophan synthase to act on N-allyl indoles, providing allyl-containing tryptophans that can be used to link peptides via olefin metathesis. To access hydroxyprolines, another desirable class of amino acids, we developed a ketoreductase-catalyzed dynamic kinetic resolution. This reaction delivers all four isomers of 3-hydroxyproline with high diastereo- and enantioselectivities, and can also be used to access 3-hydroxyproline derivatives. We have additionally explored the use of alpha-ketoglutarate- and Fe(II)-dependent oxidases for the C-H hydroxylation of amino acids. In particular, we evolved a proline hydroxylase for the highly selective and efficient preparation of a desired hydroxyproline isomer. These biocatalytic approaches to ncAAs are more efficient and greener than alternative chemical routes, and they have been enabling for the large-scale synthesis of clinical candidates as well as the early-stage evaluation of novel chemical space.

ORGN 583

Devising a scalable solution-phase synthesis of peptidomimetics to probe the G protein-coupled receptor signaling pathway

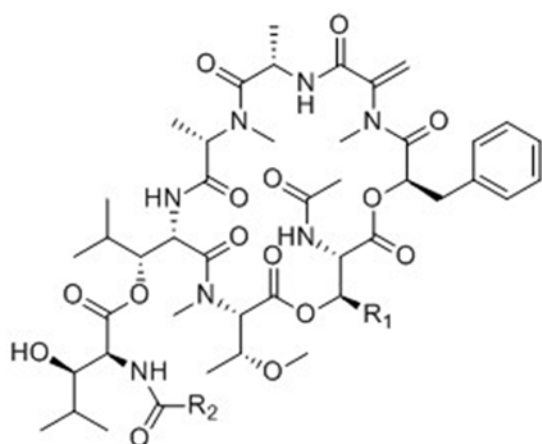
Yu Zhu, *yu.zhu@wustl.edu*, **Matthew Medcalf**, **Kevin D. Moeller**. Department of Chemistry, Washington University in St. Louis, St. Louis, Missouri, United States

The G protein-coupled receptor (GPCR) signaling pathways provide therapeutic opportunities in Alzheimer's, metabolic, cardiovascular, neurologic, and oncologic diseases. However, GPCR-targeted therapeutics can be ineffective when multiple receptors with redundant or overlapping functions drive diseases pathogenesis or progression, or mutationally activated $G\alpha$ subunits drive disease independently of GPCRs. Accordingly, pharmacological inhibitors that directly target $G\alpha$ or $G\beta\gamma$ subunits are emerging as important leads for drug discovery.

Two closely related cyclic depsipeptides, YM-254890 (YM) and FR900359 (FR), isolated from *Chromobacterium* sp. QS3666 and *Ardisia Crenata* respectively, potently and selectively inhibit signaling by Gq/11 class G protein α subunit by trapping them in their inactive GDP-bound states. This class of natural products could serve as a wonderful tool to selectively regulate the signalling pathways and give us a better understanding of the pathways. We hope to develop a panel of synthetic, bioavailable inhibitors, each of which targets selected $G\alpha$ subunits as probes and therapeutic leads.

While solid-phase peptide synthesis can be used to generate a series of analogs for screening, we eye animal tests that require larger amounts of the compounds. This requires a scalable solution-phase synthesis. Along these lines, we have successfully prepared multiple simplified analogs used to probe the GPCR signaling pathway. While these analogs are not as potent as YM or FR, they do selectively bind to $G\alpha_q$.

Currently, we are developing the synthesis of a new family of analogs that retain more of the functionality found in the natural products. The analogs have the intact "bottom bridge" moiety that was found to bind with $G\alpha_q$ in crystal structures of the YM- $G\alpha_q$ complex and such change is expected to improve the potency of the analogs. The synthetic gains made with this new approach will be discussed.



YM-254890 ($R_1 = \text{Me}$, $R_2 = \text{Me}$)

FR900359 ($R_1 = i\text{-Pr}$, $R_2 = \text{Et}$)

ORGN 584

Fluorescent teixobactin probes

Michael Morris, morrisma@uci.edu, **Melody Malek**, **Mohammad Hashemian**, **Betty Nguyen**, **James S. Nowick**. Chemistry, UC Irvine, Irvine, California, United States

We report the syntheses and applications of fluorescent teixobactin analogues that exhibit antibiotic activity and bind to the cell walls of Gram-positive bacteria. The teixobactin probes have a fluorescent tag at position 9 and an arginine in place of the natural *allo*-enduracididine residue at position 10. The probes retain partial antibiotic activity, with a minimum inhibitory concentrations of 4–16 µg/mL across a panel of Gram-positive bacteria, as compared to 1–4 µg/mL for the parent antibiotic. The rhodamine-labeled teixobactin analogue is prepared by a regioselective labeling strategy using solid phase peptide synthesis and the BODIPY-labeled analogues are regioselectively tagged using NHS ester chemistry. Treatment of the teixobactin probes in a panel of Gram-positive bacteria results in septal and lateral staining of the bacteria, which is consistent with an antibiotic targeting peptidoglycan precursors. Concurrent treatment of rhodamine-teixobactin and BODIPY FL vancomycin results in septal and sidewall co-localization in a panel of Gram-positive bacteria, providing further evidence that the teixobactin probe binds to peptidoglycan precursors. Controls with either Gram-negative or an inactive fluorescent homologue with Gram-positive bacteria showed little or no staining in micrographic studies. On-going efforts include FRET microscopy of BODIPY-labeled teixobactin probes to study the self-assembly of the antibiotic on bacterial surfaces. This study provides functional fluorescent teixobactin probes that can be further utilized to investigate the mechanism of action of the antibiotic.

ORGN 585

Designing degradation resistance in therapeutic peptides using microwave-assisted SPPS

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Despite the challenges that initially stymied their development as drugs, peptides have demonstrated to be effective in biomedical applications such as tissue engineering, drug delivery, and vaccines. Their rapid growth in the global drug market over recent decades has prompted demand for highly efficient synthetic methods of peptide synthesis targeting biological applications. This presentation will cover strategies to design physiochemically robust peptides using microwave-assisted solid phase peptide

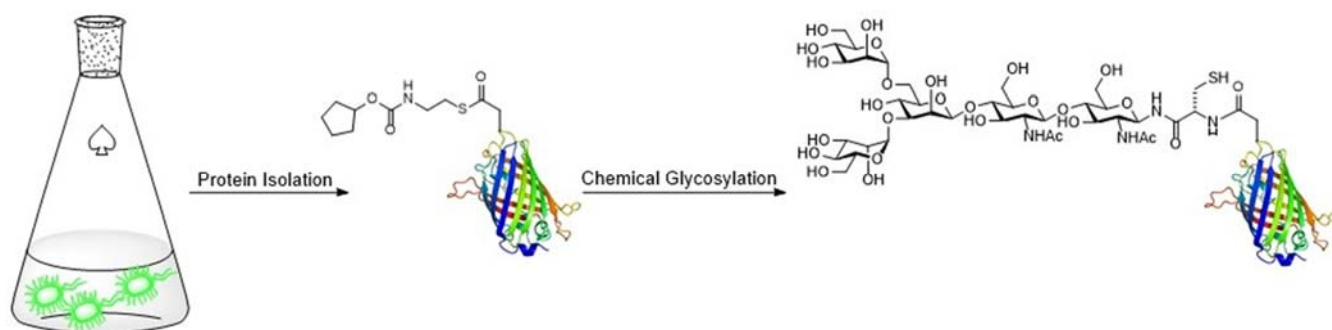
synthesis. Applications to be covered include backbone modification and various secondary structural enhancements to improve peptide stability as therapeutic molecules.

ORGN 586

Synthesis of homogeneous cysteine-bridged N-glycoproteins via native chemical glycoligation

Nicholas Holloran, nicholas.holloran@wsu.edu, **Philip P. Garner**. Dept of Chem, Washington State Univ, Pullman, Washington, United States

Glycosylation is one of the most common post-translational modifications of proteins, and proteins affected by this modification can have altered conformation, solubility, activity, and antigenicity. N-glycoproteins are a class of glycoproteins characterized by the attachment of a chain of sugars (glycans) to one or more asparagine residues through an amide bond. The study of N-glycoproteins has been hindered by the difficulty in obtaining homogeneous samples for testing their biological effects because natural samples of glycoproteins appear as complex mixtures of proteins with many different glycosylation patterns. Here, we describe our efforts toward chemospecific glycosylation of a recombinantly generated protein to produce a homogeneous sample of N-glycoprotein. The protein is produced recombinantly by *E. coli* which have been modified to insert a non-canonical amino acid containing a reactive thioester side chain at a specified internal site. This thioester handle can then undergo a chemoselective reaction with a modified glycan to give a cysteine-bridged N-glycoprotein. Because natural sources of glycoproteins contain a high degree of heterogeneity, this method of chemical synthesis is attractive because of its ability to generate homogeneous samples which can be used in biological research.



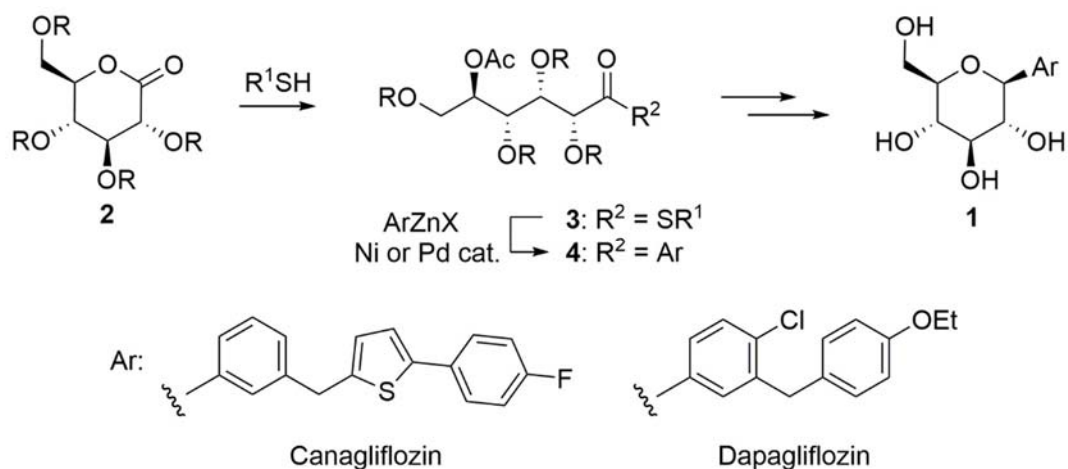
General scheme for the synthesis of cysteine-bridged N-glycoproteins.

ORGN 587

Novel and efficient synthesis of SGLT2 inhibitors by means of Fukuyama coupling reaction

Masahiko Seki^{1,2}, ma-seki@tokuyama.co.jp, **Jalindar Talode**², **Hayato Tsurugi**², **Kazushi Mashima**². (1) Life Amenity Department, Tokuyama Corporation, Tsukuba, Ibaraki, Japan (2) Department of Chemistry, Osaka University, Toyonaka, Osaka, Japan

A novel and efficient synthesis of SGLT2 inhibitors **1** for the treatment of type 2 diabetes will be presented. Pd- and Ni-catalyzed Fukuyama coupling reaction of thioesters **3**, derived from protected D-gluconolactone **2**, with aryl zinc reagents provided aryl ketone intermediates **4** at ambient temperature. Subsequent simple structural modifications involving stereoselective reduction and deprotection provided the final SGLT2 inhibitors **1** in excellent yields.



ORGN 588

Carbon-hydrogen bond cross-coupling reactions: Carbon-carbon bond formation

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Department of Chemistry, Tsinghua University, Beijing, China

Carbon-carbon bond formation via the cross-coupling reactions of carbon-hydrogen is an important and useful synthetic route with high atom-utilization. We are interested in development of not only the synthetic methods for the synthesis of cyclic compounds by annulations of alkyne with C-H bond, but also the carbon-carbon formation via C-H bond cross-coupling reactions. In this presentation, we would like to report several catalytic systems for C-C bond formation via the cross-coupling reactions of C-H bond

and their application in the synthesis of Tröger's base analogues, α -arylpyridines, α -cyanostyrenes and biaryls, which have been developed in our group.

ORGN 589

Copper and iron catalyzed cross coupling reactions supported by a sterically bulky β -diketonate ligand platform

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Cross coupling catalysis has benefited from the development of sterically bulky phosphine and N-heterocyclic carbene ligands. Although cross coupling reactions can also be catalyzed by simple metal β -diketonates such as $\text{Fe}(\text{acac})_3$ and $\text{Cu}(\text{acac})_2$ (acac = acetylacetonate), the corresponding application of large functional groups has never been systematically applied to the β -diketonate framework. Here, we report the synthesis of a β -diketonate functionalized with two *m*-terphenyl groups, projecting sterics back towards the metal with axial C_2 symmetry. Upon metalation, this ligand inhibits the formation of $\text{M}(\text{acac})_2$ ($\text{M} = \text{Fe}, \text{Cu}$), enabling isolation of $\text{M}^I(\text{acac})$ complexes that can perform bimetallic oxidative addition reactions. Iron-catalyzed Kumada coupling and copper-catalyzed Ullmann-type reactions as well as mechanistic considerations will be discussed.

ORGN 590

Synthesis of *N*-pyridyl hydroxylamine derivatives via copper catalyzed cross-coupling and application towards design of new acetylcholinesterase reactivators

Carilyn Torruellas, *carilyntorruellas@gmail.com*, James Myslinski, Fulian Hsu, Andrew Walz. Chemical Sciences Division, CCDC Chemical Biological Center, Aberdeen Proving Ground, Maryland, United States

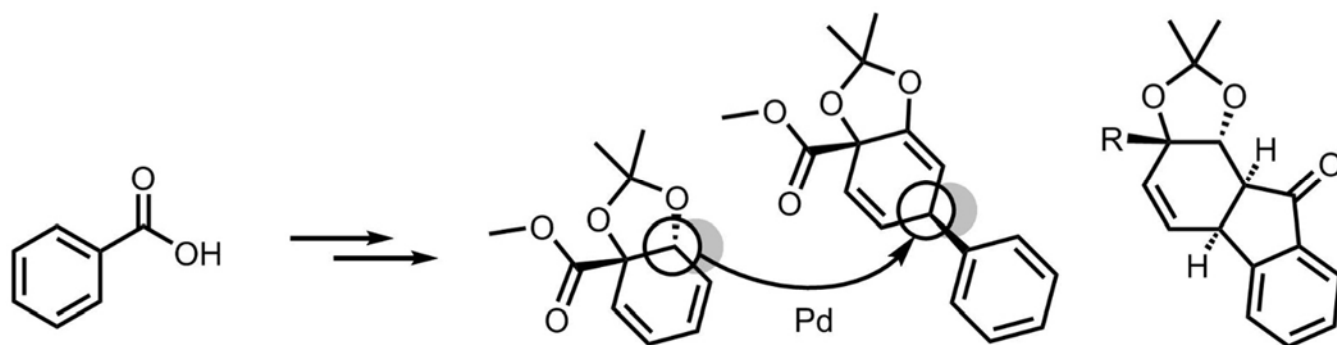
N-pyridyl hydroxylamine scaffold is found in anti-bacterial, anti-viral, anti-osreoclastogenic and anti-cancer agents. *N*-Pyridyl hydroxylamine derivatives were prepared via copper-catalyzed cross-coupling of *N,O*-difunctionalized hydroxylamines and iodopyridines. Various traditional amino- and hydroxyl-protecting groups were tolerated and a total of 24 examples were synthesized in 28-91% yield. This method was employed towards the synthesis of a new class of hydroxylamine-based reactivators for nerve agent-poisoned acetylcholinesterase (AChE). A total 8 reactivators were prepared and the reactivation efficiency was evaluated against several organophosphorus nerve agents (OPNAs).

ORGN 591

Palladium catalyzed stereospecific arylation of biocatalytically derived dienes: Chirality transfer via a Heck-type mechanism

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A selective Heck-arylation of a chiral highly functionalized cyclohexadiene, easily obtained by biocatalytic oxidation of benzoic acid is demonstrated. Interestingly, the reaction effects a 1,3-chirality transfer, yielding a non-conjugated diene. The mechanism and selectivity of the reaction were investigated using DFT calculations. A palladium catalyzed cascade reaction is triggered when a benzaldehyde moiety is present in the *ortho* position of the aryl halide coupling partner. In this way, a highly functionalized tetrahydrofluorenone skeleton, containing two new stereocenters, is obtained as a single diastereomer. This cascade reaction is also under investigation as a key step in the synthesis of a natural product synthesis.



ORGN 592

Deaminative alkyl-alkyl cross-couplings of alkylpyridinium salts and alkenes

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Alkyl amines are inexpensive and widely abundant chemicals in organic synthesis, making them attractive substrates for further functionalization. Functionalization via cleavage of the carbon–nitrogen (C–N) bond has recently been discovered as a powerful transformation of these abundant, easily protected alkyl amines. Due to the prevalence of C(sp³)–C(sp³) bonds in bioactive molecules, methods to create alkyl-alkyl bonds have become increasingly desirable. By using High-Throughput Experimentation

interfaced with traditional reaction optimization, we have developed a nickel-catalyzed cross-coupling of alkyl pyridinium salts with alkyl boron species formed in situ from an alkene. The optimization, scope, and mechanistic understanding of these reactions will be presented.

ORGN 593

Cross-coupling of amides by N–C activation

Michal Szostak, *michal.szostak@rutgers.edu*. Rutgers University, Newark, New Jersey, United States

Development of new strategies encompassing activation of inert bonds has revolutionized organic synthesis. Transition-metal-catalyzed coupling of amide N–C bonds holds an enormous potential for widespread practical applications. In this lecture, recent developments in the selective activation of amide bonds by ground-state-destabilization-controlled metal insertion into the amide double bond will be presented. These reactions are enabled by virtue of decreased amidic resonance, which is a recurring theme of this new cross-coupling manifold. The selectivity in amide bond cross-coupling will be described. Representative examples to be discussed include Pd-, Ni- and Rh-catalyzed acyl- and aryl-decarbonylative cross-couplings.

ORGN 594

Exploring the mechanism of Pd- and Ni-catalyzed carbonylative and decarbonylative coupling reactions

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In this talk I present our recent mechanistic explorations of Pd- and Ni-catalyzed coupling reactions. Pd-catalyzed carbonylative cascade reaction leading to site-selective cyclization of amide/amine tethered ortho-anilylanilines will be shown and the selectivity issues will be specifically addressed. We have also scrutinized the reactivity of Ni-phosphine complexes that catalyze the base-free Suzuki-Miyura coupling with acid fluorides disclosed very recently by Sanford et al. The active intermediates and the decarbonylative routes leading the formation of the transmetalation-active NiP₂(Ar)F complexes are successfully identified. Additional QMMM and metadynamics simulations have helped to understand the reactivity differences induced by ligand change.

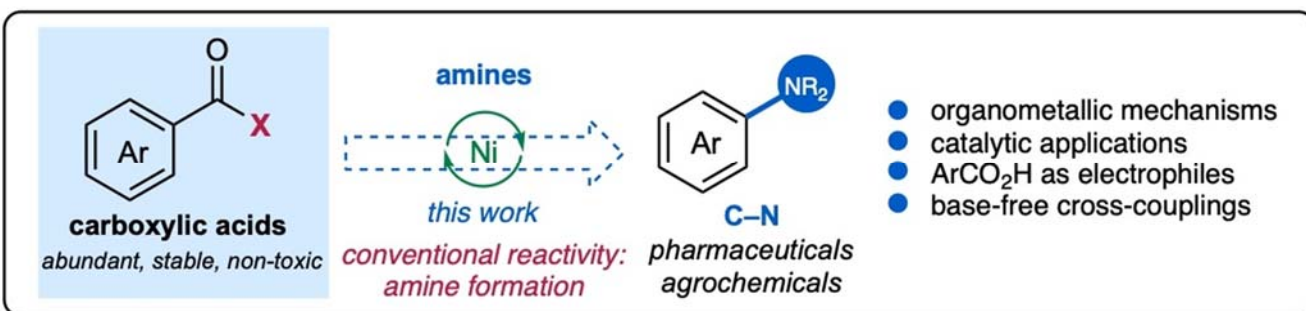
ORGN 595

Catalytic decarbonylative amination of carboxylic acid derivatives

Christian A. Malapit^{1,2}, *cmalapit@umich.edu*, **Margarida Borrell**¹, **Michael W. Milbauer**¹, **Conor Brigham**¹, **Melanie S. Sanford**¹. (1) Chemistry, University of Michigan,

Ann Arbor, Michigan, United States (2) University of Utah, Salt Lake City, Utah, United States

Aromatic carboxylic acids and their derivatives are highly abundant, inexpensive, and stable molecules, and these properties render them attractive building blocks for organic synthesis. The strategic conversion of aromatic carboxylic acids to C(sp²)–nitrogen bonds would be particularly valuable reactions for organic chemists, as these products appear in numerous pharmaceuticals and agrochemicals. The success of this strategy is predicated on providing understanding of fundamental organometallic mechanisms (e.g. decarbonylation and base-free transmetalation), careful design of the catalyst, carboxylic acid derivative, and appropriate coupling partners to achieve the selective formation of the desired aryl amines over the conventional amide bonds. This presentation will highlight our recent development on the mechanism and scope of a novel nickel-catalyzed decarbonylative coupling of carboxylic acid derivatives to aryl amines.



ORGN 596

Methylation of (hetero)aryl chlorides via halogen photoelimination

Stavros K. Kariofillis¹, stavrosk@princeton.edu, **Benjamin J. Shields**¹, **Makeda Tekle-Smith**¹, **Michael J. Zacuto**², **Abigail G. Doyle**¹. (1) Princeton University, Princeton, New Jersey, United States (2) Cellegene, Summit, New Jersey, United States

Direct methylation of organohalides represents a valuable but challenging transformation, typically requiring harsh reaction conditions or reagents. We report a radical approach for the methylation of (hetero)aryl chlorides using metallaphotoredox catalysis wherein trimethyl orthoformate, a common laboratory solvent, serves as a methyl source. This method permits methylation of (hetero)aryl chlorides and acyl chlorides at an early and late-stage with broad functional group compatibility.

Mechanistic investigations indicate that trimethyl orthoformate serves as a source for methyl radical via beta-scission upon chlorine-mediated hydrogen atom transfer.

ORGN 597

Next-Gen MIDA enables automated Csp³ cross-coupling

Daniel J. Blair¹, *daniel.james.blair@gmail.com*, **Melaine Trobe**¹, **Hannah Haley**¹, **Danielle L. Gray**¹, **Toby Woods**¹, **Steve Ballmer**², **Rich Hansen**², **Adrian Gill**², **Michael J. Schmidt**¹, **Robert Pipal**¹, **Martin D. Burke**¹. (1) Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois, United States (2) Revolution Medicines, Redwood City, California, United States

The iterative assembly of interchangeable parts (or the building block-based approach) is increasingly transforming chemists' capacity to synthesize chemical matter. Such methods facilitate the synthesis of complex organic molecules as both functionality and stereochemistry can be installed upfront in the reagents, which are then assembled in a controlled manner. There is a growing body of evidence which indicates that a building block-based approach to small molecule synthesis stands to unlock the tremendous synthetic potential that this class of chemical matter possesses. In this regard much important progress has been made in the synthesis of small biopolymers such as polypeptides, oligosaccharides and oligonucleotides. Automated methods now exist for their synthesis in part due to the obvious common linkages and building blocks required for their construction. Applying similar methods to small organic molecules, especially natural products, is significantly more challenging as the common repeating units and assembly methods non-obvious.

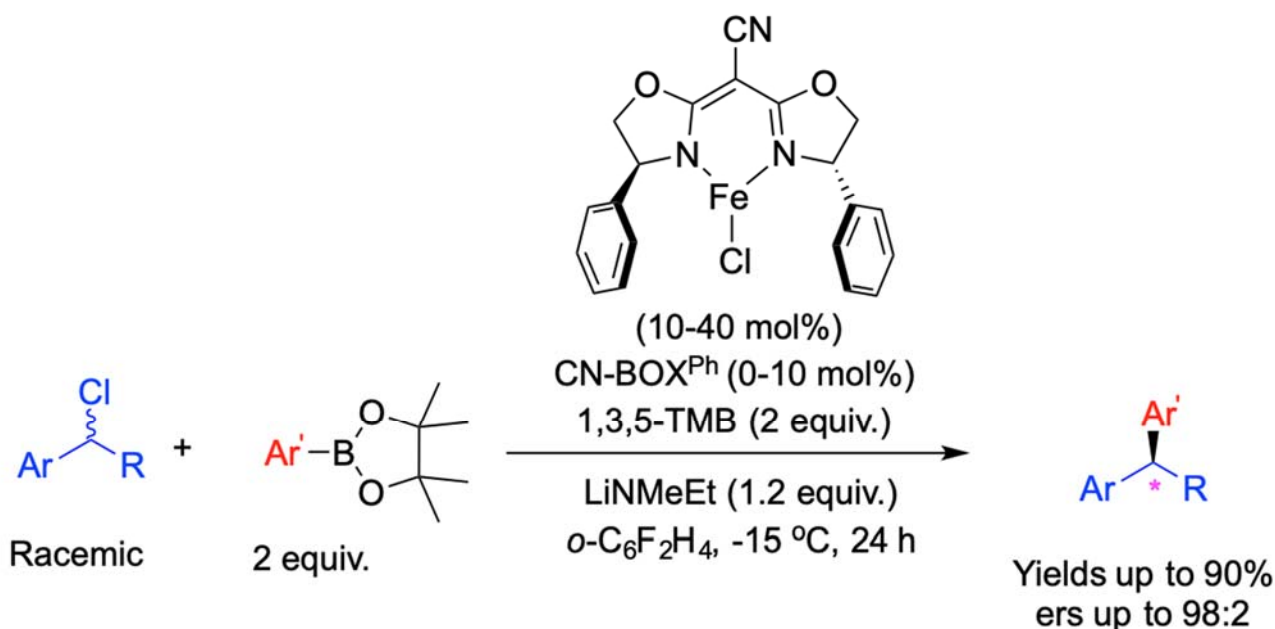
However, if cross-coupling chemistry were to be regarded as sufficiently general it could be envisioned that the C-C bonds themselves would then become the common linkages for building block-based assembly. Our ongoing research program focuses on developing a strategy for small molecule synthesis by employing organoboron-based coupling reactions to iteratively form C-C bonds. Specifically, we have found that the ligand MIDA can reversibly attenuate the reactivity of a boronic acid within Suzuki-Miyaura cross-coupling reactions and thereby enable iterative cross coupling cycles. On the basis of this advance we have developed an automated synthesis machine which can iteratively assemble Csp²-Csp² bonds performing all the required steps including purification – preparing 14 distinct classes of small organic molecule. A limitation of this platform is that many of the natural products/natural product fragments which represent exceptionally promising starting points for new drug development are rich in sp³ and not the sp² carbons assembled by this approach. Moreover, the aqueous conditions permissive of many common Csp³ cross coupling reactions lead to cleavage of our MIDA ligand and prevent practical iterative synthesis. We herein report the development of a next-gen MIDA which tolerates aqueous Suzuki-Miyaura reactions and enables automated iterative synthesis via Csp³ cross coupling.

ORGN 598

Synthesis of enantiomerically enriched 1,1-diaryllkanes using a Suzuki-Miyaura reaction catalyzed by an iron-based complex

Chet C. Tyrol, cctyrol@eckerd.edu. Chemistry, Boston College, Chestnut Hill, Massachusetts, United States

The first enantioselective Suzuki-Miyaura cross-coupling reaction catalyzed by iron-based complexes between benzylic chlorides and unactivated arylboronic pinacol esters has been developed. The enantiomerically enriched 1,1-diarylalkane products are common motifs within many blockbuster pharmaceuticals such as Zolof and Zyrtec. It was found that a cyanobis(oxazoline) ligand framework and 1,3,5-trimethoxybenzene additive were essential to afford good yields and high enantioselectivities. Mechanistic investigations implicate a stereoconvergent pathway involving carbon-centered radical intermediates. This approach provides a route toward synthesizing sterically-challenging ortho-substituted 1,1-diarylalkanes with high selectivities.



ORGN 599

Next generation drug delivery and device opportunities for product development

Marian Gindy, marian_gindy@merck.com. Pharmaceutical Sciences, Merck & Co., West Point, Pennsylvania, United States

Decades of translational research have established the value of drug delivery and device innovation for the advance of new pharmaceutical, biological and viral therapeutic and prophylactic products. Transformative technologies have been used to

enhance product attributes impacting efficacy and tolerability, such as drug absorption, distribution, stability and clearance. Delivery- or device-enabled commercial product examples abound, from oral and injectable dosages to ophthalmic, inhaled, transdermal and implanted products. Nonetheless, as drug developers pursue more personalized medicines and biological targets of greater complexity, new delivery challenges have emerged that compel next-generation innovations, particularly for biologic, cellular and gene therapies. Technologies that improve intracellular drug delivery, oral absorption of biomolecules, local/ targeted drug delivery or the overall patient experience are currently of great interest. In this talk, I will share emerging research exemplifying such opportunities.

ORGN 600

Delivering the insoluble: Amorphous solid dispersions

Lynne Taylor, *ltaylor@purdue.edu*. Purdue University, West Lafayette, Indiana, United States

For oral delivery, a drug must first dissolve in the intestinal fluids, and then be absorbed across the gastrointestinal membrane. Unfortunately, many new drugs are poorly soluble in water and are consequently difficult to deliver to the patient. To improve this situation, drugs can be formulated as supersaturating delivery systems such as an amorphous drug-polymer blends or other metastable solid forms. Such systems generate a supersaturated solution *in vivo*, improving membrane transport rate and ultimately absorption relative to stable crystal forms. However, supersaturated solutions are meta- or unstable and phase transformation to a lower energy state(s) is thermodynamically favored. Such phase transformations include liquid liquid phase separation and crystallization. The nature of the phase transformation and the characteristics of any precipitate formed is important since these can impact the supersaturation profile and the redissolution kinetics of the phase separated material. Herein, different phase transformations and their potential implications for the oral delivery of poorly water soluble drugs are considered.

ORGN 601

Implantable drug delivery systems: How are they designed and developed?

Ryan Teller, *ryan.teller@abbott.com*. Abbott, Los Angeles, California, United States

Implantable drug-eluting devices have many potential advantages over conventional oral or parenteral drug delivery methods. For instance, implants can provide localized, site specific drug delivery that improves effectiveness and minimizes side effects (e.g. drug-eluting stents), reduce the need for difficult or dangerous repeated injections (e.g. ophthalmic indications), or enable improved patient compliance via less frequent dosing compared to frequently administered conventional dosage forms (e.g. contraception and opioid withdrawal). Nonetheless, within the past two decades only a limited number of

drug-eluting devices have been approved. This reflects the technically challenging and expensive development pathway associated with combination medical devices. To successfully develop a long-acting drug-eluting device, potent and stable active pharmaceutical ingredients are required but not sufficient as the design of the device, the physical and chemical properties of drug and excipients, especially rate-controlling polymers, and the manufacturing process will impact the drug release kinetics. Implantable drug-eluting devices can be categorized by the design of the drug-elution portion, for example matrix and reservoir designs, and primary mode of action of the device, for example the drug delivery could be primary (e.g. contraceptive drug-eluting implant) or secondary (e.g. medical device with a drug-eluting coating or component). In this talk, I will provide an overview of different drug delivery technologies and how they have been utilized in a range of disease areas.

ORGN 602

Prodrug strategies for peptide drugs

Elizabeth M. Topp, topp@purdue.edu. Industrial and Physical Pharmacy, Purdue University, West Lafayette, Indiana, United States

The development of peptide drugs can be complicated by chemical and physical instabilities inherent in the molecules, which often cannot be resolved by sequence modifications without unacceptable loss of efficacy. This presentation describes the discovery and development of reversibly phosphorylated derivatives of glucagon, which resist fibrillation and have enhanced solubility at neutral pH. This is essentially a prodrug strategy, an approach long used to improve the solubility and delivery of small molecule drugs. Phosphoglucagons are presented as a case study to inspire the application of similar prodrug strategies to other peptides with formulation and/or delivery challenges.

Glucagon is a 29-amino acid peptide hormone used in the emergency treatment of severe hypoglycemia. Glucagon is poorly soluble in aqueous solution at neutral pH and is administered in acidic solutions. However, glucagon is not stable even in acidic solution, in which it rapidly and irreversibly forms insoluble amyloid β -fibrils. Glucagon amyloid fibril formation compromises the potency of the drug, has the potential to generate toxic effects, and increases solution viscosity which causes difficulty in delivering the formulation using an infusion pump or injection pen. Due to these solubility and stability issues, glucagon is currently formulated as a lyophilized powder that is reconstituted just prior to administration, and any surplus solution is discarded immediately. This presentation summarizes computational and experimental studies of the mechanisms of glucagon fibrillation, and presents novel glucagon derivatives that resist fibrillation through phosphorylation of amino acid side chains. Phosphorylation at selected sites increases glucagon solubility at neutral pH by shifting the pI, and inhibits fibrillation through charge repulsion. On administration, the phosphate group is cleaved by ubiquitous phosphatase enzymes, regenerating native glucagon. The approach is promising for glucagon and other peptide drugs that are prone to fibrillation.

ORGN 603

Messenger RNA: Delivery challenges and encouraging first steps towards a novel modality

Mike Smith, *mike.smith@modernatx.com*. Drug Product Development, Moderna, Cambridge, Massachusetts, United States

The combination of messenger RNA and lipid nanoparticles (mRNA LNPs) represent a novel therapeutic modality with a range of potential applications. However, mRNA is challenged by unavoidably large molecular size, instability, and immunogenicity. Preclinical efforts have shown the utility of LNPs for efficient mRNA encapsulation and tissue-selective delivery. Through advancement in mRNA and lipid chemistry, together with progression in nanoparticle formulation and process science, many barriers were overcome towards robust protein expression in vivo. In addition, more recent evidence has emerged suggesting the ability to encapsulate multiple mRNA cargo within LNPs, enabling the expression and assembly of multi-subunit proteins. The totality of clinical outcomes exemplify progress in the past few years, driving enthusiasm for RNA therapeutics and the area of nanoparticle-mediated oligonucleotide delivery.

ORGN 604

Catalytic oxidation methods for pharmaceutical synthesis

Shannon S. Stahl, *stahl@chem.wisc.edu*. Univ of Wisconsin, Madison, Wisconsin, United States

Oxidation chemistry is among the most challenging classes of chemical transformations in pharmaceutical synthesis and is often avoided, especially in large scale applications. Over the past 13 years, we have partnered with numerous process chemistry groups in the pharmaceutical industry to develop safe, scalable, and sustainable oxidation methods suitable for application to complex molecule synthesis. This talk will highlight key advances in the development of aerobic and electrochemical oxidation methods, many of which are amenable to large-scale application.

ORGN 605

Green chemistry at Pfizer: Applications to the oncology portfolio

Paul Richardson, *paul.f.richardson@pfizer.com*. Medicine Design, Pfizer, San Diego, California, United States

Pfizer actively strives to find innovative ways to minimize our impact on the environment during the manufacturing of pharmaceuticals and is continuously "greening" the process. In particular, we leverage our Green Chemistry programs to advance scientific innovation to help develop processes that are more sustainable, environmentally sound

and cost-effective. Whereas the impact can easily be quantified with tangible metrics during the manufacturing phase of a pharmaceutical, there exists the opportunity for significant contributions to be made within medicinal chemistry during the discovery phase. However, thinking “Green” is often perceived to be contrary to the mindset of a traditional medicinal chemist. This talk will focus on the challenges faced in changing this culture, and how enabling technologies such as flow chemistry, *in situ* reaction monitoring and reaction screening can help to overcome these. In addition, case studies will be provided detailing the significant benefits these changes have made within our Oncology Drug Discovery programs.

ORGN 606

Trimming the waste-line in macrocyclic peptide synthesis: *N*-acyl urea cyclization and photodesulfurization

Jennifer L. Stockdill, stockdill@wayne.edu. Chemistry, Wayne State University, Berkley, Michigan, United States

Macrocyclic peptides are important lead targets for pharmaceutical development, and methods for their synthesis have been an area of focused study by the peptide community for decades. Strategies that utilize a native chemical ligation (NCL)-like approach (i.e.; a cysteine-mediated macrocyclization) are particularly powerful because of the enhanced nucleophilicity and easily exploitable pKa differences of the Cys thiol vs. other potential nucleophiles. However, NCL methods, including Cys and non-Cys NCL followed by desulfurization have not employed industrially because of the unmanageable amount of waste generated due to dilution requirements and large excesses of phosphine and thiol reagents. This seminar will describe our recent efforts to minimize waste in both the cysteine-mediated cyclization of peptides and in the subsequent radical-mediated desulfurization process.

ORGN 607

Metal-organic frameworks for sustainable catalysis

Wenbin Lin, wenbinlin@uchicago.edu. Dept of Chemistry Bldg GCIS RM E519A, University of Chicago, Chicago, Illinois, United States

Metal-organic frameworks (MOFs) have emerged as an interesting class of crystalline molecular materials whose structure-property relationships can be readily established by taking advantage of the detailed knowledge of their atomic structures. The modular nature of and mild conditions for MOF synthesis have permitted the rational design of numerous catalytic MOFs by incorporating various functionalities as constituent building blocks. In this talk, I will discuss our recent works on designing porous MOFs for sustainable catalysis. We have designed a series of chiral porous MOFs using privileged chiral ligand-based linkers and demonstrated their applications in highly efficient heterogeneous asymmetric catalysis. We have also incorporated earth-

abundant metal complexes of simple ligands, such as bipyridines, salicylaldimines, and 1,3-diketimines, into MOF frameworks and demonstrated their unique catalytic activities. Finally, we have shown that MOFs provide an interesting platform for discovering efficient molecular catalysts that do not have homogeneous counterparts. I will also present preliminary results on integrating MOF catalysts into flow reaction systems for continuous synthesis of fine chemicals.

ORGN 608

Beyond organic solvents: Synthesis of a 5-HT₄ receptor agonist in water

David K. Leahy, *david.leahy@takeda.com*, **Dan Bailey**. Process Chemistry Development, Takeda Pharmaceuticals, Cambridge, Massachusetts, United States

Organic solvents are estimated to make up 60% of all waste generated during API manufacturing, accounting for some 9 billion kg of waste per year industry-wide. Disposing of this waste is costly, but, perhaps more concerning, many widely-used solvents are hazardous to workers and the environment and are derived from non-renewable petroleum. As a result, organic solvents have come under increasing regulatory scrutiny in recent years. Amid growing concerns over the use of organic solvents in chemical manufacturing, water has emerged as a promising alternative reaction medium. A growing body of research has demonstrated that a wide variety of organic reactions can be successfully adapted to aqueous reaction media using micelle-forming surfactants, often providing superior outcomes over conventional solvents. Inspired by this work, we set out to demonstrate the feasibility of implementing aqueous reaction media in Takeda's portfolio using the TAK-954 process as a test case. We redeveloped the six-step TAK-954 manufacturing sequence to be run entirely in water, replacing five separate organic solvents used in the enabling route, while implementing five direct isolations from aqueous media. Key transformations carried out in aqueous media include a benzimidazole cyclization, amidation, reductive amination, and a selective oxidation of an aliphatic alcohol.

ORGN 609

Inventing green chemistry in the context of implementation: Considerations beyond the bench

Paul D. Thornton, *pdthornton@gmail.com*. Thornton Chemistry, Kingston, Ontario, Canada

The discovery and manufacture of drug molecules presents both challenges and opportunities for organic chemists inventing new reactions, catalysts, and other technologies that can positively impact the sustainability of the pharmaceutical industry. However, the sustainability impact of a new chemical technology will depend on the success of that technology being implemented in widescale industrial application.

Chemists and innovators aiming to invent new solutions to the myriad of challenges presented by the chemical synthesis of APIs should consider the parameters for successful implementation in guiding their discovery and development efforts. Researchers must consider whether they are developing solutions for those challenges that are most relevant to improving sustainability and have the potential to fill an unmet need in industry. Innovators should also consider the potential economics of their inventions as the successful adoption of a new technology will require a compelling business case relative to incumbent solutions. Thus, for an innovation to have an impact, not only does the chemistry need to work well, it needs to address unmet sustainability challenges and be economically viable.

This presentation will discuss a systems-based approach to aligning academic and early-stage research with critical sustainability needs in drug-discovery and process development and give insight into how addressing techno-economic considerations can help better position an innovation for successful implementation. Models for collaborative projects and potential business partnerships will also be discussed in the context of case studies.

ORGN 610

Investigations into the reactivity and stability of the samarium diiodide-water system

Nick Boekell, ngb217@lehigh.edu, Robert A. Flowers. Lehigh Univ Dept of Chem, Bethlehem, Pennsylvania, United States

Samarium diiodide (SmI_2) has been used extensively as a powerful and versatile single electron reductant in synthesis since its introduction by Kagan in 1977. Recent work on SmI_2 has demonstrated its ability to reduce a number of electron-rich nitrogen containing substrates. Expanding upon this precedent, we have developed a method for the selective reduction of a diverse array of aromatic heterocycles, including quinoline and pyridine, using a SmI_2 - H_2O reducing system. Further, by modifying the reducing system to SmI_2 - D_2O , we are able to selectively deuterate the reduced substrates. These reactions have potential applications for the discovery and development of novel pharmaceutical compounds.

The rapid and quantitative reduction of challenging substrates such as pyridine by SmI_2 - H_2O raises important questions about the stability of the $\text{Sm(II)}\text{-H}_2\text{O}$ complex since H_2 should be readily evolved from the reagent system. This unusual stability was examined through mechanistic experiments to elucidate the nature of the intermediate(s) responsible for the unique stability of the SmI_2 - H_2O reagent system.

ORGN 611

Exploring the reactivity of Sm(II) -proton donor systems

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Sm(II)-based reagents are potent single electron reductants and when used in conjunction with proton donors display unexpected reactivity. The addition of water to Sm(II)-based reductants produces a Sm(II)-water complex where the O-H bond of coordinated water is significantly weakened. As a consequence, reductions proceed via a proton coupled electron transfer (PCET) that enables the reduction of substrates typically difficult to reduce through electron transfer.

We propose that the concept of coordination induced bond weakening can be utilized to design extremely powerful reaction systems which can facilitate PCET, thereby enabling the reduction of a variety of substrates initially thought to be outside the range of reduction by Sm(II)-reagents. Several combinations of Sm(II) reductants and proton donors containing both oxygen and nitrogen donor atoms have been examined with results demonstrating that these complexes can be pushed well beyond the range thought possible using Sm(II) reducing systems.

ORGN 612

Method development of the competitive secondary kinetic isotope effect measurement for hydride transfer reactions of NADH/NAD⁺ models

Amanda T. Beach, *mandykt3@gmail.com*, *Yun Lu*, *Samantha Wilhelm*. Chemistry, Southern Illinois University Edwardsville, Edwardsville, Illinois, United States

Secondary hydrogen kinetic isotope effect (KIE) is central to the understanding of the transition state (TS) structure of chemical reactions. It is especially important for study of the H-tunnelling reactions, as H-tunnelling could inflate secondary KIEs to sometimes be outside of the semi-classical limits. Accurate measurement of the secondary KIEs for H-tunnelling reactions could help explore the correct structure of the TS and thus design efficient enzyme inhibitors and drugs. We report a competitive secondary KIE method for hydride transfer reactions involving NADH/NAD⁺ models. These methods use either proton NMR spectroscopy or Mass Spectrometry to measure the secondary KIE. The KIEs obtained from the competitive measurement method will be compared with the ones from the conventional spectroscopic non-competitive method.

ORGN 613

Solvent effects on the temperature dependence of the primary kinetic isotope effects for hydride transfer reactions in solution

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We study the solvent effects on the temperature dependence of primary (1°) kinetic isotope effects (KIEs) for H-transfer reactions in solution in an attempt to understand the KIE observations in wild-type versus mutated enzymes. A hypothesis following the contemporary vibrationally assisted activated H-tunnelling model is that a greater temperature dependence of 1° KIEs, with a larger isotopic activation energy difference $\Delta E_a (= E_{aD} - E_{aH})$, should be observed in H/D-transfer reaction systems that have a loosely associated tunnelling ready state (TRS). The latter TRS requires more energy to sample the shorter donor-acceptor distances (DADs) for H-tunnelling to occur. Hydride transfer reactions from several dihydropyridines to various hydride acceptors, in acetonitrile versus a more polar protic water-alcohol mixture solvent, were studied to investigate this hypothesis. It is expected that the latter mixed solvent will solvate and thus stabilize the TRS well but meanwhile the solvation would pull the reaction centers away from each other loosening the TRS. The solvent effects on ΔE_a 's will be discussed to provide insight into the hypothesis.

ORGN 614

Inhibiting excited state quenching mechanisms in donor-acceptor type chromophores with solvent-excluding substituents

Conner Hoelzel¹, *CHoelzel52@gmail.com*, Hang Hu³, Charles Wolstenholme¹, Basel Karim¹, Kyle T. Munson⁴, Kwan Ho Jung¹, John B. Asbury¹, Xiaosong Li³, Xin Zhang². (1) Chemistry, Pennsylvania State University, State College, Pennsylvania, United States (2) The Pennsylvania State University, University Pk, Pennsylvania, United States (3) Department of Chemistry, University of Washington, Seattle, Washington, United States (4) Chemistry, Penn State University, University Park, Pennsylvania, United States

Provided the advantage of spatiotemporal control with low-energy, visible light, organic donor-acceptor (D–A) type chromophores are employed in an array of techniques ranging from organic synthesis to cellular imaging. Still yet, the application of D–A type dyes is limited in many regards often due to low quantum yields, short excited state lifetimes, an inherent polarity sensitivity that inhibits photochemical processes. While methods have been developed to inhibit excited state quenching mechanisms such as external conversion and twisted intramolecular charge transfer (TICT), the task of engineering a practical and generalized method to control these dynamics in a bifunctional manner remains persistent. In this work we characterize and apply a novel method to improve excited state lifetimes and quantum yields through the inhibition of solvent-solute interactions with molecular excited states while simultaneously mitigating effect of TICT. Our designed dialkylamino donor utilizes a subtle amide based modification of the beta-position to create a structural buffer to exclude solvent interactions. Using fluorescence lifetime and quantum yield as readout methods, we

show nearly 9-fold improvements in the photophysical properties of these 4-amino-7-nitrobenzoxadiazole beta-amide derivatives in ethanol relative to a dimethylamino control. Further we demonstrate that this modification works cooperatively with TICT inhibiting, small azacyclic donors, and that its application is broadly effective in D–A type chromophores, including coumarin, naphthalimide, and PRODAN based scaffolds. Using computational modeling and empirical characterization, we demonstrate that the beta-amide donor effectively inhibits solvent interaction with the excited state while simultaneously increasing the energy barrier of rotation about the donating group. We have applied these dyes to cellular imaging, showing quantitative increases in brightness, and future applications include application to chemical systems such as photolabile protecting groups.

ORGN 615

SuFEx reactions and the role of silicon: Scope, kinetics, enantioselectivity and mechanism

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The SuFEx reaction is one of the most promising novel reactions, displaying many of the characteristics of 'click reactions'. Characteristically, a silyl-protected phenol (Ar-O-SiR₃) reacts with high efficiency under mild reaction conditions with a S-F bond in a range of sulfur-based compounds, forming both an Aryl-O-S bond in a novel functional molecule and a R₃Si-F bond. While highly successful in a range of applications, ranging from biological to materials chemistry, the mechanism of this reaction is still highly unclear. In the current paper we outline the role of the silicon-based protection groups, the scope of the reaction, and outline the mechanism by investigating the kinetics, enantioselectivity and study of substituent effects by both experimental and quantum-chemical investigations.

ORGN 616

Structural effects on the temperature dependency of the primary hydrogen kinetic isotope effects in solution: New physical organic chemistry research direction

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The change from temperature independence of the primary (1°) H/D kinetic isotope effects (KIEs) in wild-type enzyme catalyzed H-transfer reactions ($\Delta E_a = E_{aD} - E_{aH} \sim 0$) to strong temperature dependence with the mutated enzymes ($\Delta E_a \gg 0$) have recently been frequently observed. This has prompted some enzymologists to develop new H-tunneling models to correlate ΔE_a with the donor-acceptor distance (DAD) at the tunneling-ready state as well as the protein thermal motions/dynamics that sample the short DADs for H-tunneling to occur. The contemporary H-tunneling model is the

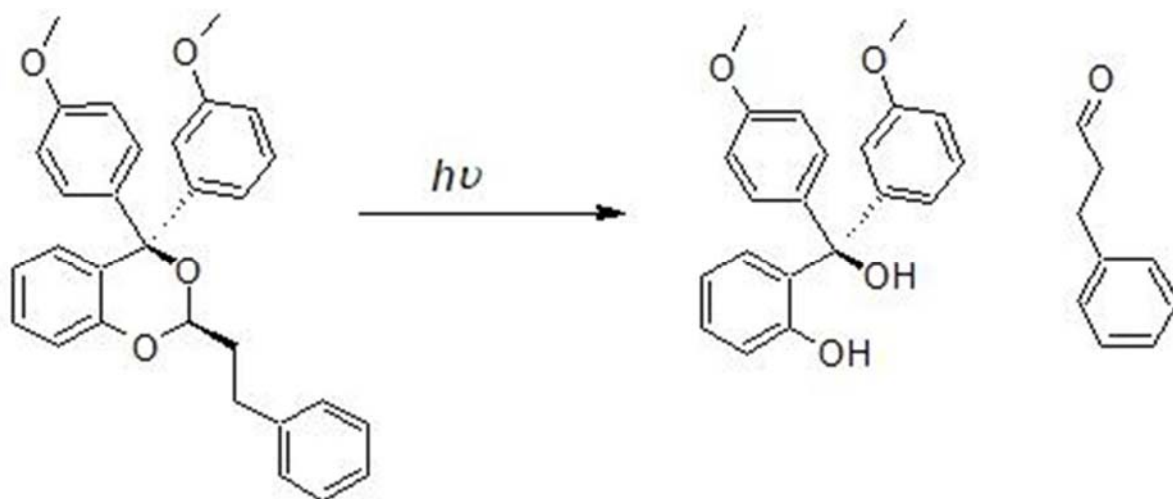
vibrationally assisted activated hydrogen tunneling model. The model predicts that the more rigid the reaction centers the smaller the ΔE_a . To test the thermally activated DAD sampling concept, we designed a series of hydride transfer reactions in solution to study the rigidity – ΔE_a relationship. Steric, electronic as well as solvent effects on ΔE_a 's are studied and the rigidity – ΔE_a relationship is discussed. Results are compared with those from enzymes in order to provide insight into whether there is a role of enzyme's local fast motions in catalysis.

ORGN 617

Stereochemical control of acetal photodeprotection

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Photolabile protecting groups (PPGs) are useful tools in the synthesis of organic compounds as they can be removed with light under mild conditions. Photoactive acetals have been shown to release carbonyl compounds under neutral conditions. We have designed a new pathway for synthesizing acetal PPGs that allows for the placement of two different groups on the benzylic positions of a salicyl alcohol derived PPG. In this design, one of the groups contains a meta positioned electron donating group (EDG) known to facilitate photorelease and the other contains a para EDG. Coupling of this PPG to an aldehyde produces a mixture of stereoisomers and we find the stereoisomers react differently to light. To elucidate the corresponding photochemical processes, electronic structure theory calculations and quantum dynamics simulations were used to investigate the reaction mechanism. Our computational study suggests that each stereoisomer returns to a ground state after photoexcitation and prior to dissociating. Only in two of the stereoisomers is the excitation energy released into the ring containing the EDG in the meta position while in the other two, the para ring is favored. Confirming that different pathways exist for these stereoisomers, we find that two of the stereoisomers react with light much more readily than the other two.



ORGN 618

***N*-substituted open-shell π -conjugated material: Synthesis and optoelectronic properties**

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Unlike closed-shell compounds, open-shell compounds have unpaired electrons that reside in non-bonding molecular orbitals. Stabilization of unpaired electron density through π -delocalization enables open-shell compounds to demonstrate unique optoelectronic properties that are not accessible to their closed-shell counterparts. Additionally, these properties can be electronically tuned by incorporating heteroatoms into the π -conjugated backbone. Here I will present the synthesis of an open-shell *N*-substituted bisphenalenenyl π -radical cation and our investigations into its optoelectronic properties. Its molecular structure was confirmed by X-ray diffraction, and conductive single crystals (1.3×10^{-2} S/cm) revealed that unusually close π -stacking interactions occur in the solid-state. The ambient stable π -radical cation showed fluorescence through doublet emission and notably demonstrated one of the highest photostabilities amongst luminescent organic radicals. Furthermore, conductive films of the π -radical cation can achieve balanced hole and electron mobilities ($\mu_e/\mu_h \geq 1.48 \times 10^{-2}$ cm² V⁻¹ s⁻¹) in FET devices, which is an extremely rare example of a small molecule material capable of ambipolar conduction.

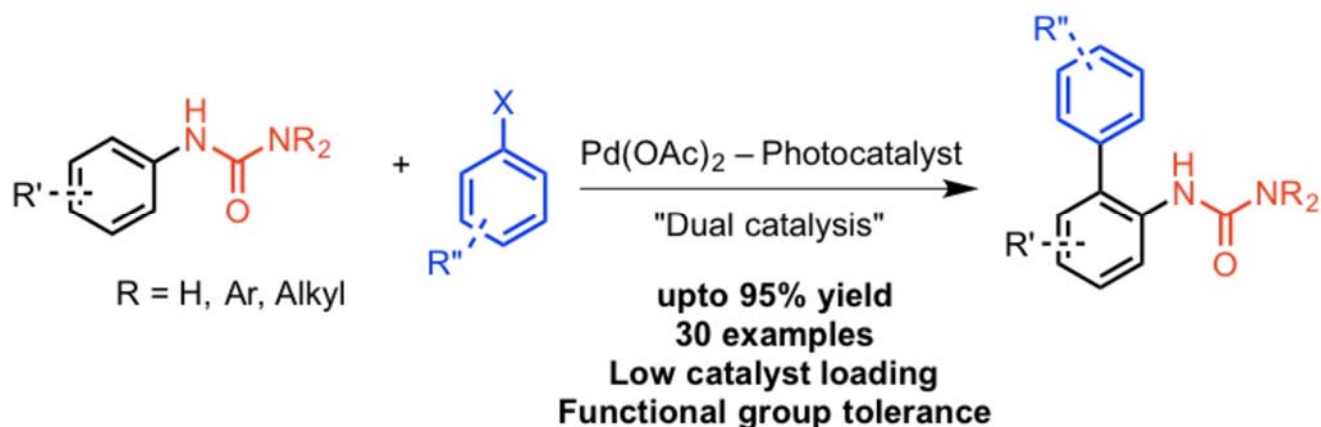
ORGN 619

Dual palladium-photoredox catalyzed C-H arylation of phenyl urea derivatives

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Visible light photoredox catalysis, a rapidly growing field of organic chemistry, harnesses the energy from light (visible light) to catalyze organic reactions using some metal complexes and organic dyes as photocatalysts. Photoredox catalysis when merged with other modes of catalysis (dual catalysis) such as transition metal catalysis, organocatalysis, etc. can perform many novel transformations that are not possible for both the catalysis independently. In light of the biological importance of phenyl urea derivatives in various drugs and natural products, we embarked on the development of a robust protocol for the C-H functionalization of phenyl urea derivatives under very mild conditions. Although C-H functionalizations of phenyl urea derivatives are reported in the literature, most of them require higher temperatures or harsh reaction conditions. Till date, most of the phenyl urea derivatives studied for C-H functionalization reactions are limited to phenyl urea derivatives of the type, ArNHCONR_2 , wherein R = alkyl group.

Phenyl urea derivatives with a free amino group (ArNHCONH_2) on the other hand are generally not suitable substrates or reacting partners due to undesired side reactions or formation of a complex reaction mixture with the palladium catalyst at higher temperatures. But given the synthetic advantage of simple phenyl urea derivatives, ArNHCONH_2 (which can be further derivatized after the initial C-H functionalization step), we focused our efforts towards the C-H functionalization of this special class of molecules. In this presentation, I'll discuss our groups efforts for C-H arylation of phenyl ureas of the type ArNHCONH_2 using dual palladium-photoredox catalysis under room temperature without any additives or metal oxidants. Additionally, N,N-diaryl substituted phenyl ureas of the type, $\text{ArNHCONHAr}'$ are shown to be viable substrates using this method by a careful choice of aryl substituents, which previously was not viable due to difficulties in the regioselective functionalization of aryl moieties.



Scheme 1: C-H arylation of Phenyl urea derivatives

ORGN 620

Sulfamate esters guide C(3)–H functionalization of alkanes

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Owing to the pervasiveness of hydroxyl groups in natural isolates, alcohol derivatives are alluring directing groups. Herein, an alcohol-anchored sulfamate ester guides the xanthylation and alkylation of aliphatic C(3)–H bonds. The disclosed methods rely on light and photoredox mediated processes to generate sulfamyl radicals. These sulfamyl radicals template, otherwise rare, 1,6-hydrogen-atom transfer (HAT) processes via seven-membered ring transition states to enable C(3)–H functionalization. The developed reactions proceed with predictable selectivity offering a valuable tool for late stage modification of pharmacologically relevant small molecules.

ORGN 621

Utilization of novel photocatalytic systems for functionalization and ring constructions reactions

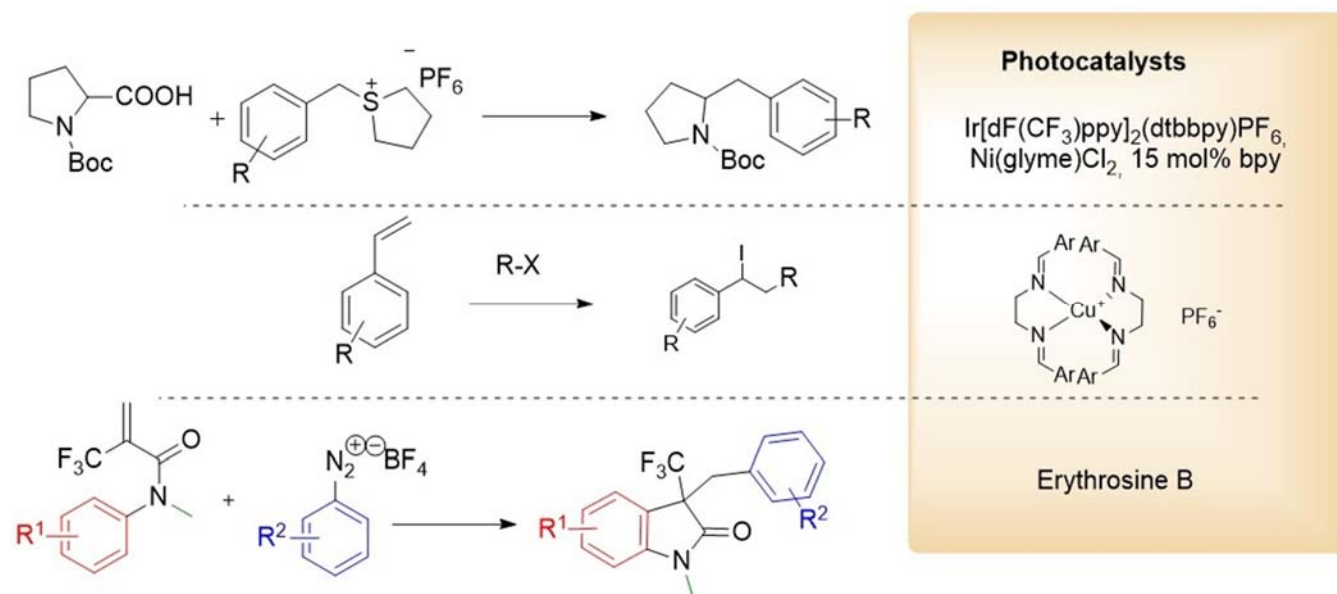
Zoltán Novák¹, *novakz@elte.hu*, **Bálint Varga**¹, **Ferenc Béke**¹, **Tamás Földesi**¹, **Balázs Tóth**², **Bálint Nagy**¹, **Gellert V. Sipos**³, **Zsombor Gonda**¹, **Réka Adamik**¹, **Tim Peelen**⁴. (1) Eötvös Loránd University, Institute of Chemistry, Budapest, Hungary (2) Eötvös University, Budapest, Hungary (3) Thalesnano Inc., Budapest, Hungary (4) Chemistry, Lebanon Valley College, Lebanon, Pennsylvania, United States

Renewable resources became very important in the last decades. Accordingly, applying visible light in organic synthesis became one of the most examined area of the synthetic chemistry.[1-3] In a photocatalytic reaction, a metal complex, organic dye or electron-donor-acceptor complex could generates radicals which could take part in a catalytic cycle. One of the critical aspects of this synthetic technique is the use of expensive metal based catalysts such as iridium and ruthenium. However, these metals are the most effective.[2] However, many attempts were performed to use non-precious metals, for example copper.[4]

In our work we developed novel copper catalyst complexes for the ATRA reaction of halides and styrene derivatives. [5] Using copper as the metal core and diimine based ligand obtained from ethylenediamine and aromatic aldehydes we prepared a series of complexes, which could be used in photocatalytic reactions. After optimization of an initial atom-transfer radical addition (ATRA) reaction using styrene and carbon tetrabromide, an extensive structure-reactivity relationship was performed by systematic modification of the structure of the ligands.

Additionally, a new method has been developed for the synthesis of 2-benzylpyrrolidines utilizing cross-coupling and photoredox catalysis. Using a well-established dual Ni-Ir system, we were able to successfully couple benzylsulfonium salts with a proline utilizing radical photochemistry. [6]

Beyond the transition metal based photocatalysts we used Erythrosine B as novel organic dye for the synthesis of 3-Trifluoromethyl-indoline-2-one derivatives in a visible light photocatalytic transformation of acrylamides with aryl diazonium salts.



ORGN 622

Accessing challenging fluorinated motifs using photoredox catalysis and enabling technologies

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The rapidly rising prevalence of fluorinated motifs in pharmaceutical compounds has spurred interest in the development of synthetic methods which allow for the efficient incorporation of such fluorinated groups into complex molecules. Two fluorinated functional groups of interest are the α-trifluoromethyl alkene and the *gem*-difluoroalkene, which are particularly sought after due to their properties as bioisosteres. Two orthogonal methods have been developed which allow rapid access to diversely functionalized α-trifluoromethyl alkenes. The first method relies on the development of a novel cross-coupling reagent, and the second pushes the boundaries of the capabilities of Peterson olefination chemistry. In addition to their utility as bioisosteres, α-trifluoromethyl alkenes also serve as a uniquely well-suited starting point for the synthesis of *gem*-difluoroalkenes. Photoredox catalysis via radical polar crossover

enables the alkylation and arylation of α -trifluoromethyl alkenes to allow access to a library of diversified *gem*-difluoroalkenes.

ORGN 623

Photoredox catalysis enables the modular installation of molecular complexity

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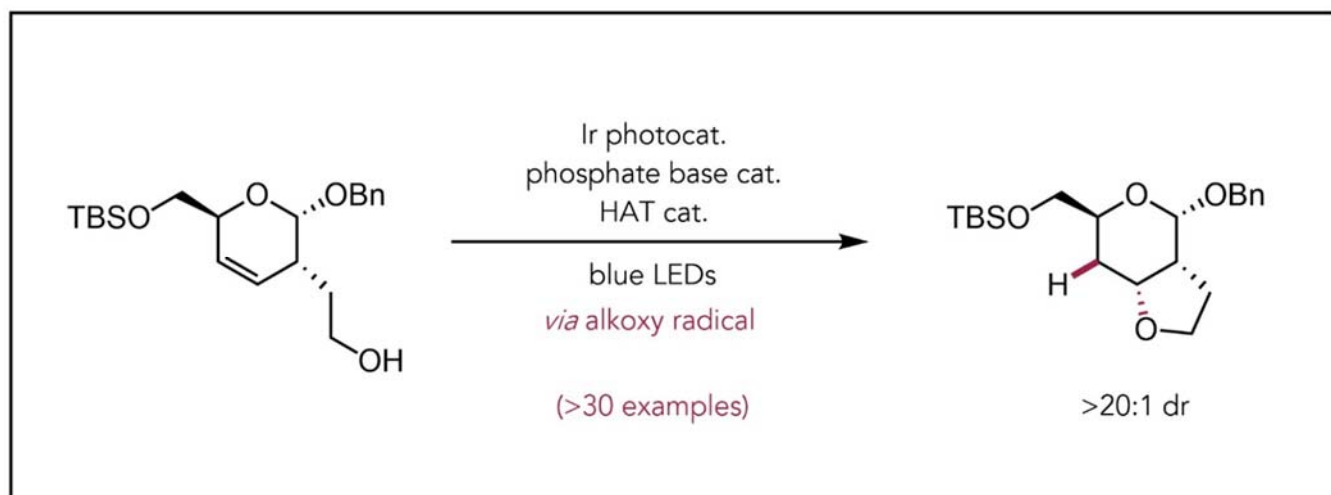
Photoredox catalysis has become a strategy for novel sp³ bond construction under mild conditions. Here, we demonstrate new applications towards radical-polar crossover reactions and nickel/photoredox cross-coupling.

ORGN 624

Hydroetherification of unactivated alkenes enabled by light-driven proton-coupled electron transfer

Elaine Tsui, elaine.tsui@princeton.edu, Anthony J. Metrano, Yuto Tsuchiya, Robert Knowles. Princeton University, Princeton, New Jersey, United States

Olefin hydroetherification reactions have long been sought after, as they represent a versatile and atom-economical approach to C–O bond formation. Here, we report a general protocol for the light-driven, intramolecular hydroetherification of unactivated alkenols to furnish cyclic ether products. Facilitated by proton-coupled electron transfer (PCET) activation of alcohol O–H bonds, these reactions proceed through an alkoxy radical intermediate, followed by addition to a pendent olefin. These transformations occur under visible light irradiation in the presence of an iridium(III) photocatalyst, a Brønsted base, and a hydrogen atom transfer catalyst. This method exhibits a broad substrate scope, high functional group tolerance, and applicability to a diverse range of alkene substitution patterns. Taken together, this strategy represents an advance in radical-based hydroalkoxylation methods. Results demonstrating the extension of this catalytic system to carboetherification are also presented.



ORGN 625

Mechanistic and kinetic studies of photoredox cycles

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While photoredox catalysis has demonstrated a potential to transform small molecule synthesis, a detailed mechanistic understanding is generally lacking. Using a combination of steady state photochemical measurements, transient absorption spectroscopy, and electrochemistry, we are able to interrogate each step of a photoredox cycle to directly observe reaction intermediates and assign rate constants to each step. This talk will begin with a discussion our studies on an α -amino arylation photoredox reaction before transitioning to our more recent work on dual cycle photoredox catalysis involving organic and organometallic nickel catalysts.

ORGN 626

Anti-Markovnikov hydroamination of unactivated alkenes with primary alkyl amines

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We report here a photocatalytic method for the intermolecular anti-Markovnikov hydroamination of unactivated olefins with primary alkyl amines to selectively furnish

secondary amine products. These reactions proceed through aminium radical cation (ARC) intermediates and occur at room temperature under visible light irradiation in the presence of an iridium photocatalyst and an aryl thiol hydrogen atom donor. Despite the presence of excess olefin, high selectivities are observed for secondary over tertiary amine products, even though the secondary amines are established substrates for ARC-based olefin amination under similar conditions.

ORGN 627

Multiwavelength photoreactor for batch and flow chemistry: Development and applications

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Recently, photoredox catalytic and other photochemical methodologies, together with technological advancements has enabled the invention of a vast number of powerful methodologies for bond construction.

Having the right technology in hand is oftentimes crucial in order to achieve high yielding photochemical transformations. Our team developed a multifunctional photoreactor capable of performing batch and flow chemistry applying multiple wavelengths at a time. We present here the first applications of this instrument to a variety of photochemical transformations. The reactor was tested on a range of literature methodologies such as the photoinduced Wohl-Ziegler bromination, Cu-catalyzed atom transfer radical addition, and photoredox C-C couplings (e.g decarboxylative C-C couplings, trifluoromethylations, and the Minisci reaction) catalyzed by organic dyes or late transition metal complexes.



ORGN 628

Synthesis and the genetic encoding of N^ε-3-hydroxybutyryl lysine: Novel post translational modification

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United States

Post translational Modifications (PTMs) play a major role in regulating cell signaling and communication, enzymatic activity, protein-protein interactions, protein localization, protein turnover, cell and DNA repair. The study of post-translational modification (PTM) of proteins and their major biological functions inside the cell is a critical question in the understanding biological function and the development of new medicines.

Hydroxybutyrylation of lysine residues in histone proteins has been identified recently. Zhao (2016) and co-workers were able to show the direct coupling of the 3-hydroxybutyrate lysine (K_{bhb}) modification with the gene expression. This demonstrated a connection between metabolism, epigenetics and gene expression, and opens up a gateway to study in-depth, how cell metabolism controls the gene expression and *vice versa*. To study the PTM in depth, it is critical to obtain homogeneously modified proteins. Due to the complexity, technical challenges and inefficiency, it is difficult to obtain proteins with post-translationally modified form using total synthesis or peptide synthesis.

Here we report the synthesis of N^ε-3-hydroxybutyryl Lysine (K_{bhb}) and genetic encoding using an aminoacyl-tRNA synthetase (aaRS)/tRNA system. This allows for the production of proteins containing the site-specifically incorporated lysine PTM. The ability to obtain a homogenous composition of proteins with the post-translationally modified form, which is focused site specifically will greatly enable further studies directed at understanding the biological function of these PTMs.

ORGN 629

Minimum increments of hydrophobic collapse within the N-terminus of human galanin

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The neuropeptide galanin has a thirty-five-year history as an intriguing target in drug design, owing to its implication as a potential anticonvulsant and neuronal trophic factor among many other therapeutically interesting functions including analgesia and mood alteration. However, despite years of medicinal chemistry study and some biophysical characterization, there are still no high-resolution descriptions of the intrinsic three-dimensional structure of galanin. We present the NMR structural characterization of several fragments of the galanin N-terminus in buffered aqueous solution. This analysis utilizes modified hydrogen-bonding and dihedral angle restraints to reflect chemical shift patterns in the data suggestive of a weakly-folded helix - a long-standing hypothesis regarding the conformation of this functionally critical portion of the galanin sequence. The presented structures depict a core of hydrophobic residues that cluster together regardless of the presence of helical structure, and correspond to residues in the N-terminus of galanin that have been previously shown to be critical for binding its

receptors. The fact that multiple peptide backbone arrangements can accommodate a nearly identical sidechain display raises interesting questions regarding the relationship between a given peptide's sequence patterning and its ability to present a functional and, often, selective protein-binding epitope.

ORGN 630

Constitutive activation of GLP-1R via covalent capture

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The gut-derived peptide hormone glucagon-like peptide-1 (GLP-1) is essential for regulating glucose homeostasis and is currently used for metabolic diseases such as type two diabetes (T2D) and obesity. The physiological effects that GLP-1 initiates are mediated by the peptide binding to, and activating its cognate receptor, GLP-1R. We report here a chemical-biological strategy to enable constitutive activation of GLP-1R by the peptide and the receptor reacting covalently *in situ* after binding. This "covalent capture" is achieved by careful structural analysis of basic and aromatic residues residing on the extracellular domain of the receptor and design of a GLP-1 derivative that is adorned with synthetic unnatural amino acids providing the reactive partner. The basic residue on the receptor is only reactive when the peptide is proximal to the receptor resulting in high effective molarity to undergo covalent capture. The effort here is to build a tightly engaged interaction between GLP-1 and its cognate receptor that (1) induces prolonged activity of the receptor to obtain all the beneficial metabolic functions of GLP-1; and (2) enables the administration of a peptide candidate that is short that may have lower potency but still possess full efficacy to achieve receptor activation over extended periods of time. We present here a design to constitutively activate GLP-1R by exogenously added synthetic GLP-1 analogues that have the potential to be used for the treatment of T2D and other metabolic deficits.

ORGN 631

Utilizing interactions between enantiomeric peptides to sequester toxic dipeptide repeats for treatment of amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a lethal, rapidly spreading neurodegenerative disease targeting motor neurons of the brain and spinal cord, causing patients pain, depression, and paralysis. In one of the most prevalent forms of the disease, dipeptide repeats (DPRs) that are toxic to motor neuron cells are produced due to a genetic mutation. We aim to utilize enantiomeric biomaterials to sequester and clear these toxic

DPRs, and thereby slow or halt disease progression. Mixtures of enantiomeric peptides, *i.e.*, stereocomplexes, have been shown to result in blends with enhanced material properties relative to the individual component peptides (*e.g.* yielding fibers with four times greater moduli than individual component fibers and protease-resistant hydrogels) due to strong peptide-peptide noncovalent bonds. Inspired by these results, we investigate the differences in interaction affinity between DPRs with the same and complementary stereochemical configurations. ALS-relevant D- and L-DPRs were prepared by microwave-assisted solid phase peptide synthesis methods and purified by preparative-scale high performance liquid chromatography (HPLC); characterization shows that synthetic DPRs recapture native DPR structure. We perform isothermal titration calorimetry measurements to determine enthalpy of binding and binding affinity, comparing L- and L-DPRs to D- and L-DPRs. Preliminary binding data for D- and L-DPRs show an approximately 5-fold increase in binding enthalpy over L- and L-DPRs. These results support the hypothesis that enantiomeric peptide complexes have higher binding affinity than individual component peptide complexes. Ongoing binding affinity studies modulating factors of length and sequence mismatches, informing the design of a toxic DPR sequestration system, where D-DPRs conjugated to a biocompatible polymer will bind toxic L-DPRs and yield therapeutic outcomes.

ORGN 632

Variation in the Xaa and Yaa positions of collagen mimetic peptides containing aza-glycine

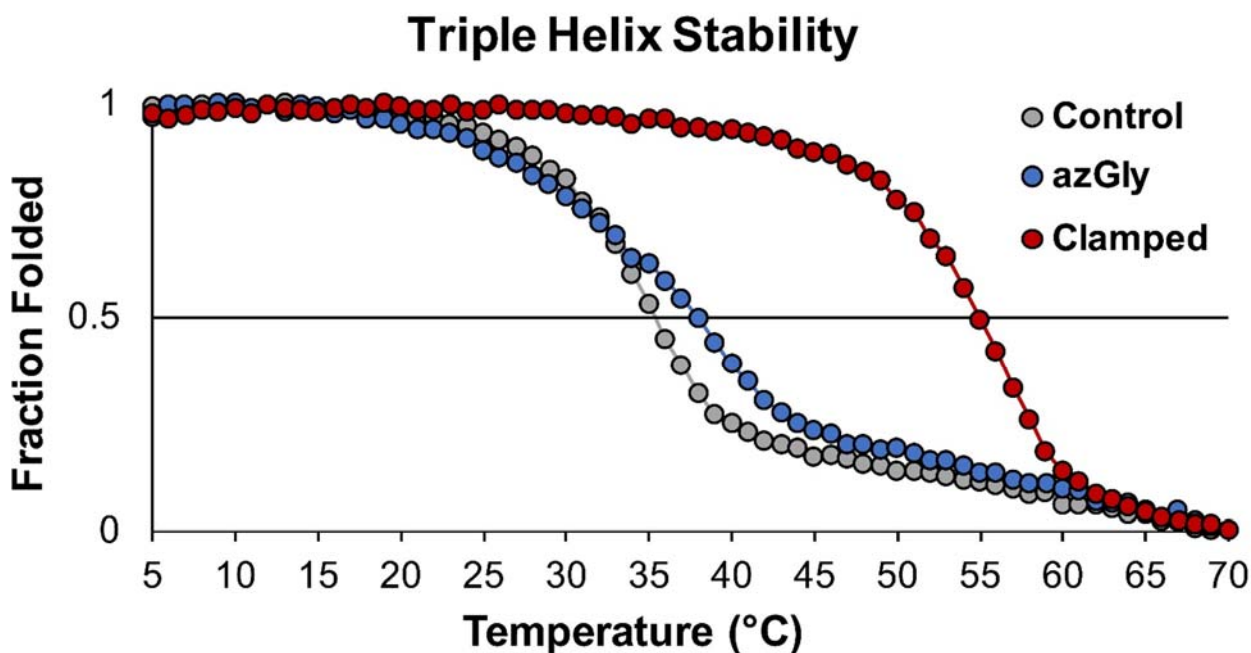
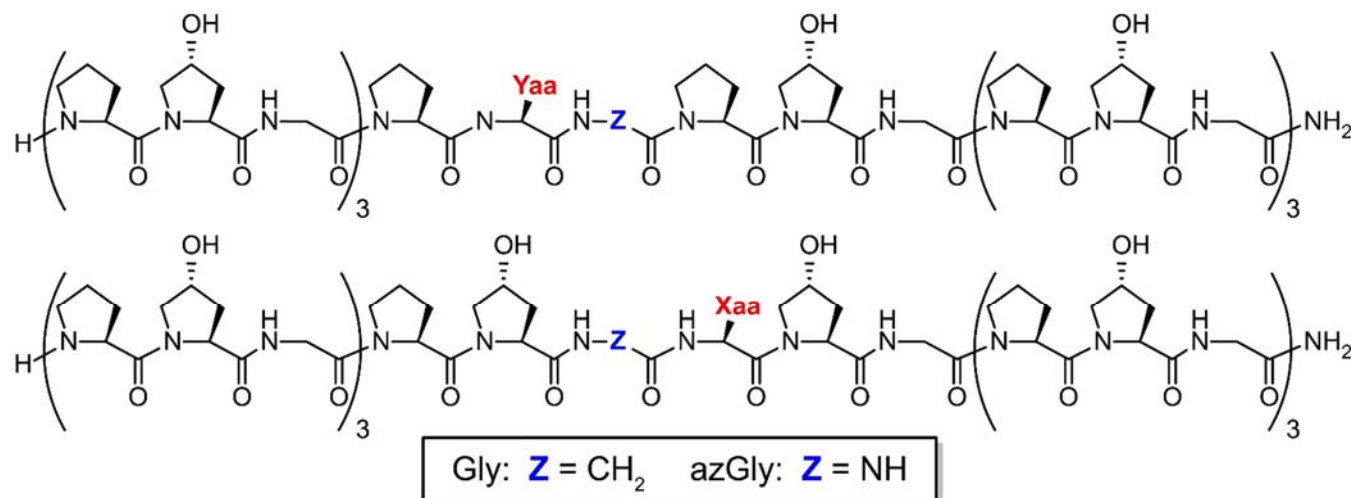
Samuel D. Melton, smelton@sas.upenn.edu, **David M. Chenoweth**. Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States

Protein folding is carefully regulated through a network of intra- and intermolecular interactions resulting from amino acid side chains, backbone functional groups, and solvent. Hydrogen bonding is one of the most critical forces stabilizing protein structure. Unnatural modifications to the protein backbone or side chains can affect modulate these interactions and are commonly used to alter the physical and chemical properties of proteins. One important class of modifications are aza-amino acids, which are typically characterized by substitution of the α -carbon with nitrogen.

This substitution can result in aza-residues exhibiting restricted conformational flexibility compared to natural amide linkages, making them valuable tools for structural studies and peptidomimetics. Mimetic peptides are indispensable for studying natural proteins including collagen, the most abundant protein in mammals. Collagen's folded structure involves three individual chains intertwining to form a triple helical bundle. Collagen's primary structure is often represented using repeating (Xaa-Yaa-Glycine) triplet sequences; the Xaa and Yaa positions are variable, but glycine is largely conserved.

Our group has previously shown substitution of glycine residues with azaglycine in a collagen peptide results in increased triple helix thermal stability. In this work, we demonstrate aza-glycine's effect on the triple helix stability is surprisingly dependent on

its neighboring Xaa and Yaa residues. To counteract this, we present a sequence-independent strategy for stabilizing the triple helix using aza-glycine residues as “clamps” around a central substitution.



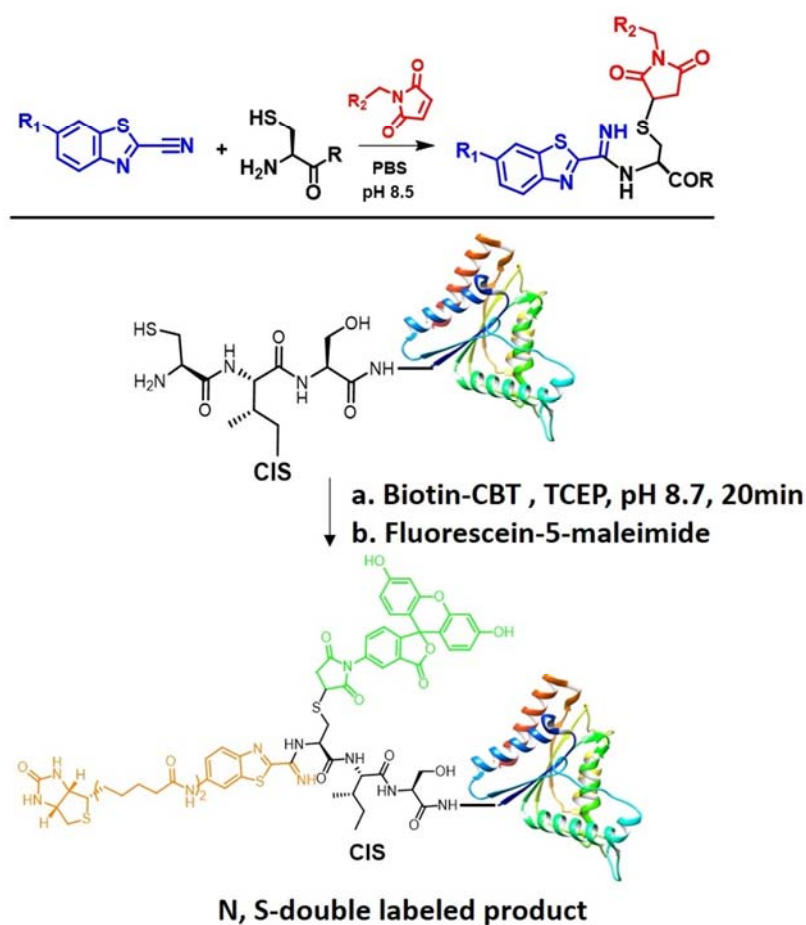
ORGN 633

N,S-double labeling of N-terminal cysteines via an alternative pathway of 2-cyanobenzothiazole condensation

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Condensation of 2-cyanobenzothiazole (CBT) and cysteine yielding luciferin has been applied to selectively label proteins containing N-terminal cysteine. Herein we report a new reaction pathway where CBT reacts with NCys forming an amidine product which allows the side chain thiol for further modification. This non-luciferin pathway is favored under basic conditions and dependent on the peptide sequence downstream of the NCys. Especially, a tripeptide tag CIS which can afford N, S-double labeled product with the excellent yield was discovered. These features would enhance the applicability of CBT-Cys chemistry for site-specific labeling of proteins.

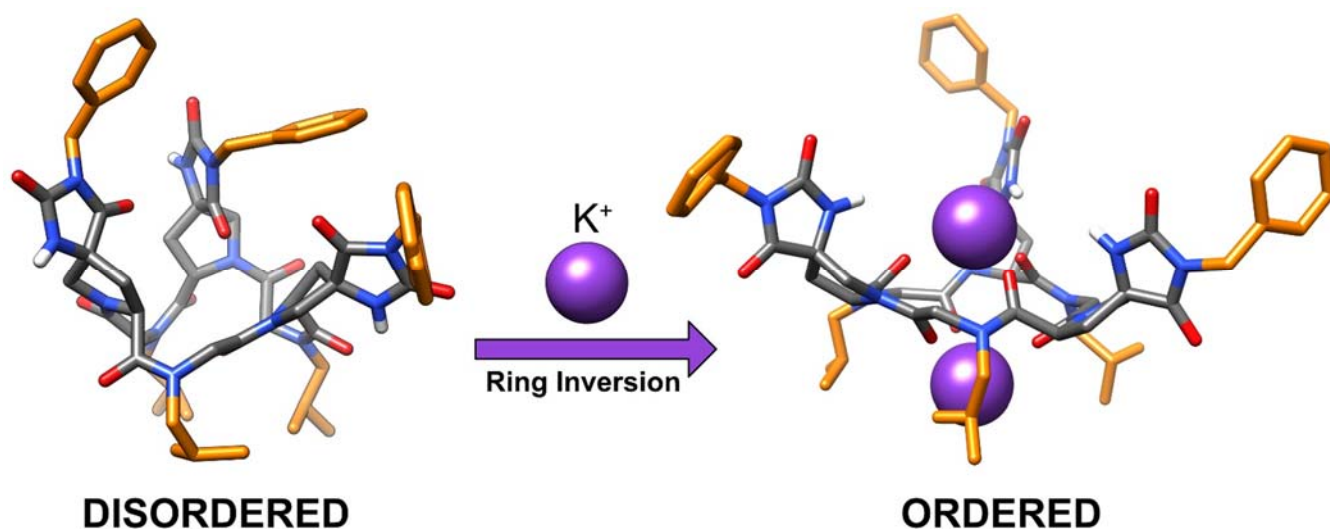
A strategy to N, S-doubly label N-terminal cysteines via an alternative pathway of 2-Cyanobenzothiazole condensation was reported. Especially, a tripeptide tag CIS which can afford N, S-double labeled protein with an excellent yield was discovered.



Metal-binding Q-proline macrocycles

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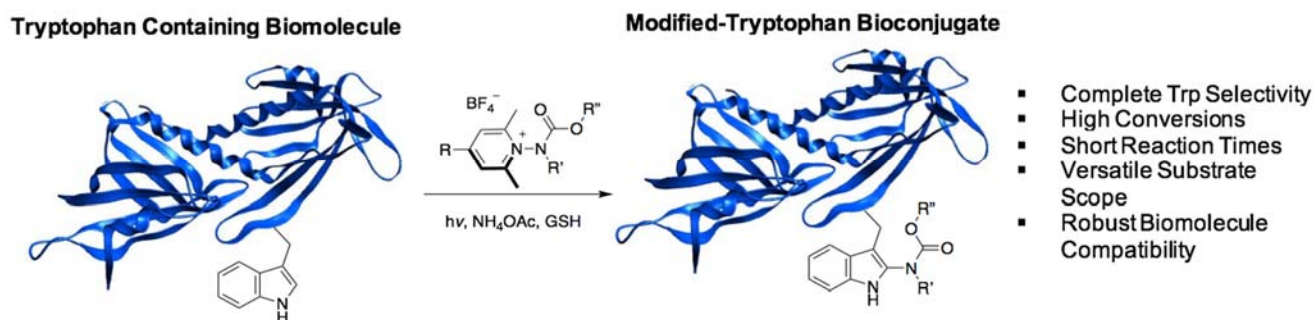
We introduce the efficient synthesis of highly preorganized Q-proline (Q-Pro) amino acids, which display two functional groups that are added after the stereochemistry has been defined. These amino acids have been synthesized on multigram scale with a single purification in good yields (58-78% over 3 steps). Synthesis of 8 Q-Pro macrocycles (QPM) was achieved through standard Fmoc-SPPS and peptoid chemistry. We show that QPM are disordered in the absence of a metal cation, as evidenced by NMR and a crystal structure of **QPM-3** obtained through racemic crystallization. However, in the presence of a metal cation, these macrocycles adopt an ordered, uniform core structure regardless of the functional groups on the macrocycles. Late stage functionalization of the Q-Pro macrocycles via alkylation chemistry allows the installation of a reactive functional group as the final step in a synthesis. Furthermore, the addition of this second functional group to the hydantoin amide position (R_2) converts the proline ring from a Cgamma-endo to a Cgamma-exo conformation, most likely due to the steric crowding caused by the addition of this functional group. Future work will be focused on application of these new amino acids towards catalytic, peptidomimetic, and materials research.



Synthesis of molecular probes for the selective modification of tryptophan residues in peptides and proteins

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The bioconjugation of proteins with chemically relevant molecular probes mimic nature's ability to selectively modify proteins and can directly improve the human condition. Therefore, the aim of this research is to develop new, *chemically distinct*, reagents for selective protein modification. Molecular probes able to undergo photo-induced bioconjugation are of particular interest as photochemical reactions allow for spatiotemporal control over reactivity. We consider a means to achieve an effective photo-bioconjugation process by utilizing the photolability of tryptophan (Trp). Being the most photolabile of all the naturally occurring amino acids coupled with its low-abundance, makes Trp an ideal candidate for bioconjugation. We report the synthesis of a variety of *N*-carbamoyl pyridinium salts that, upon irradiation with UV-B light, have shown complete tryptophan selectivity over other redox active or photo-labile amino acid, verified *via* Tandem MS, in a range of protein and peptides of varying structural complexity. Furthermore, modified Trp containing biomolecules have been isolated confirming the location of the labelling group to be at the C2 position of the indole. The reaction has been demonstrated to be a viable mode for selectively modifying Trp as high conversions has been achieved at varying biomolecule concentrations, in completely aqueous media, in short reaction times, and is aided by the addition of glutathione.



ORGN 636

Site-specific isotopic labeling of peptides and proteins for biophysical studies

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Site-specific incorporation of isotopically labeled oxygen atoms in peptides and proteins facilitates a number of biophysical studies, including some of those employing advanced vibrational spectroscopy or mass spectrometry techniques. Here, we present a general method for installing a given oxygen isotope in a specific amide bond in a protein backbone. This approach allows for late-stage functionalization of derivatized peptides or proteins in such a way that oxygen-16, -17, or -18 isotopes can be incorporated into a common precursor with minimal purification required to obtain pure material. Additionally, this chemistry can also be applied to produce isotopically labeled asparagine or glutamine sidechains. Applications to small model systems will be described.

ORGN 637

Molecular design of roteolytically stable peptide based therapeutics

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Chronic health conditions such as type II diabetes, obesity, Alzheimer's disease, and Parkinson's disease have potential to be treated by a single gut hormone, glucagon-like peptide-1 (GLP-1). GLP-1 binds to and activates its cognate G protein-coupled receptor (GPCR), GLP-1R, to stimulate secretion of insulin in a glucose dependent manner and has been shown to display neuroprotective effects. Unfortunately, when GLP-1 is in systemic circulation, it is inactivated within ~90 seconds by the serine protease, dipeptidyl peptidase-IV (DPP-IV). Enzymatic hydrolysis by DPP-IV results in removal of the two *N*-terminal amino acids, His-Ala, resulting in a truncated peptide that is orders of magnitude less potent. Common strategies to circumvent enzymatic degradation and delay renal clearance include mutation of the second *N*-terminal amino acid, alanine, to aminoisobutyric acid and/or lipidation at Lys26 to facilitate binding to serum albumin. Unfortunately, all clinically successful GLP-1 analogues are still susceptible to DPP-IV proteolysis or require administration by subcutaneous injection. We describe here efforts to (1) prevent DPP-IV degradation of GLP-1 by altering the pK_a, polarity, or steric bulk of the *N*-terminal amine and (2) increase oral uptake of protease stable peptides by the addition of side chains to facilitate barrier transport all while still retaining receptor potency and efficacy. These chemical modifications will be achieved through alkylation by reductive amination or fluorination with a trivalent iodonium salt. We present here several GLP-1 analogues obtained through chemical design that have extended half-lives *in vivo* and promise for delivering the next generation of orally administered peptide therapeutics.

ORGN 638

Efficient electrosynthesis of thiazolidin-2-imines via oxysulfurization of thiourea-tethered terminal alkenes using the flow microreactor

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Sulfur-containing scaffolds play a significant role in many important biological processes. The thiazole-2-imine derivatives have gained significant biological attention due to their interesting pharmacological activities and act as potential therapeutic agents. Many of their syntheses suffer from the drawbacks such as the handling of toxic reagents, harsh reaction conditions, longer reaction times and tedious separation procedures. To their easy access, we applied first time flow electrochemical approach under free supporting electrolytes conditions and without the use of expensive catalysts and reagents. This is not only the first electrochemical cyclisation to access thiazolidin-2-imines also represents the first intramolecular sulfurisation of unfunctionalised terminal alkenes. This flow electrolysis of N-allylic thioureas generates radical intermediates of nitrogen and sulfur that cyclised via oxysulfurisation of terminal alkenes and gives thiazolidin-2-imines with good to high yields under mild, green and environmentally friendly conditions.

ORGN 639

Electrochemical cross-coupling between alkyl and allylic halides with CuPd nanoparticles

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Organic electro-synthesis could use electricity as the power for organic oxidation and reduction, which has great potentials for green chemical industry. The traditional organic electro-synthesis focuses on searching for electro-intermediates and reagents search. However, only few works are exploring the effects of the electrode. Here, for the first time, we apply nanomaterials as the catalysts for electrochemical C-C cross coupling. To be specific, our as-synthesized 2.5 nm CuPd nanoparticles could cross connect one inactivated halide (allylic halides) and one activated halide (allyl halides) with over 90% yield in water/isopropanol condition. Compared with traditional halide coupling which needs large amount of Pd salt and toxic electrolyte, our CuPd NP catalyst is more economical, efficient and environment friendly. Additionally, we investigate the mechanism of C-C cross coupling with Pd ions as the control and the results show that the nucleation of Pd ions to form Pd clusters is the key step of C-C coupling.

ORGN 640

Boron-doped diamond electrodes as key for going beyond contemporary limits in electro-organic synthesis

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Johannes Gutenberg-University Mainz, Mainz, Germany

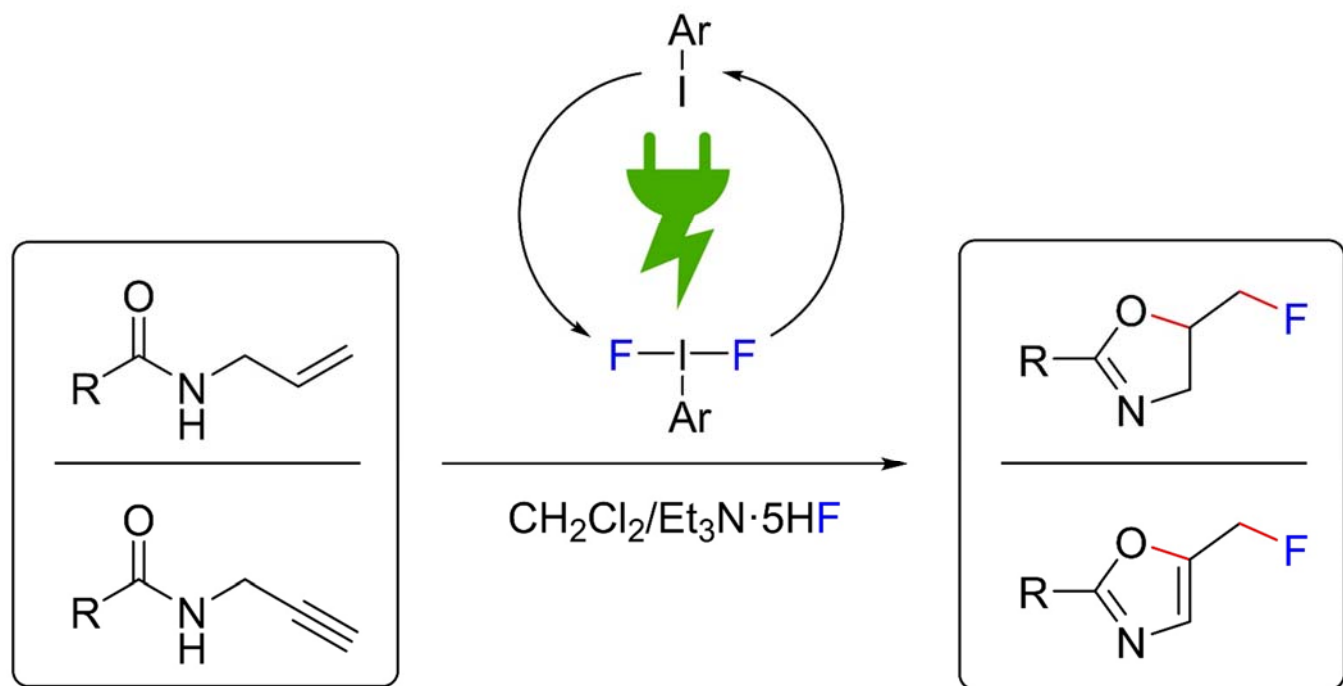
The use of electrochemistry for the generation of reactive intermediates can have major advantages over conventional synthetic strategies. Less or no reagent waste is produced and new reaction pathways are accessible. In this context, we present the use of boron-doped diamond anodes for a sustainable synthetic approach for the generation of valuable organic arylation products and other target molecules. The general benefits of these novel and extreme robust carbon electrodes are outlined. Particular fields wherein BDD electrode outperform other electrode materials in electroorganic synthesis are: (i) Unique reactivity of boron-doped diamond electrodes (ii) Enabling electroorganic synthesis via smooth electron transfer (iii) Fouling-free operations of electrodes.

ORGN 641

Fluorocyclization of *N*-allyl- and *N*-propargylamides by electrochemically generated ArIF₂

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Johannes Gutenberg University Mainz, Mainz, Germany

A sustainable protocol for the synthesis of oxazolines and oxazoles containing a fluoromethyl moiety by use of electrochemistry has been established. Thereby, hypervalent difluoroiodoarene (ArIF₂) is generated in-situ by direct electrochemical oxidation of iodoarene (ArI) in Et₃N*5HF and mediates the fluorocyclization of *N*-allyl- and *N*-propargylamides to fluoromethyl oxazolines and oxazoles, respectively. The fluorocyclization provides the synthesis of the heterocycle and the fluorination in a single step. Furthermore, this electrochemical approach is easy to conduct under constant current conditions and offers a green and safer alternative over conventional reagent-based pathways.



ORGN 642

Electrochemical modulation of strong vibration-cavity coupling

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Modulation of strong coupling has implications for on-demand reactivity, optical modulation devices, and more thorough understanding of molecule-cavity coupling effects. We electrochemically switch the benzoquinone–dihydroquinone redox couple, BQ–dHQ, within an optical cavity and find that the BQ carbonyl species can be reduced, under appropriate biases, resulting in the complete elimination of the Rabi splitting, the signature of strong coupling. We achieve optical signal modulation of ~100 % at frequencies near the fundamental BQ carbonyl absorption and the polariton bands, and experimentally evaluate the switching rate of such systems finding that repeated cycling degrades performance, attributed to compositional changes in the electrochemical medium. We observe that cavity resonances shift over time in correlation with the change of the solvent dielectric constant during electrochemical cycling. Although this consequent detuning influences the magnitude of optical modulation at the fundamental

BQ resonance frequency, optical modulation is possible at many frequencies simultaneously since cavity fringe position scales with the refractive index. These results expand the understanding and utility of strong vibrational-cavity coupling and may lead to demonstrations of modified electrochemical response for technologically relevant material systems.

ORGN 643

Reductive coupling of *N*-aryl iminoboronates and B-N dynamic covalent chemistry

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N-Aryl iminoboronates are appealing platforms for the investigation of reductive coupling reactions as they are readily self-assembled from an amine, 2-formylphenyl boronic acid and a diol, enabling tuning of their electronic and steric properties. The reductive coupling of a series of iminoboronates using cobaltocene gave three isomeric products following the C-C bond formation: the diastereomeric **rac**₅ and **meso**₅ products with coupled five-membered rings and the enantiomeric **rac**₆ with fused six-membered rings (Figure 1). The **rac**₅ and **rac**₆ isomers were observed to interconvert through a rearrangement of the dynamic covalent B-N bonds. Investigations into the mechanism for the C-C bond formation and this unusual B-N bond rearrangement will be presented.

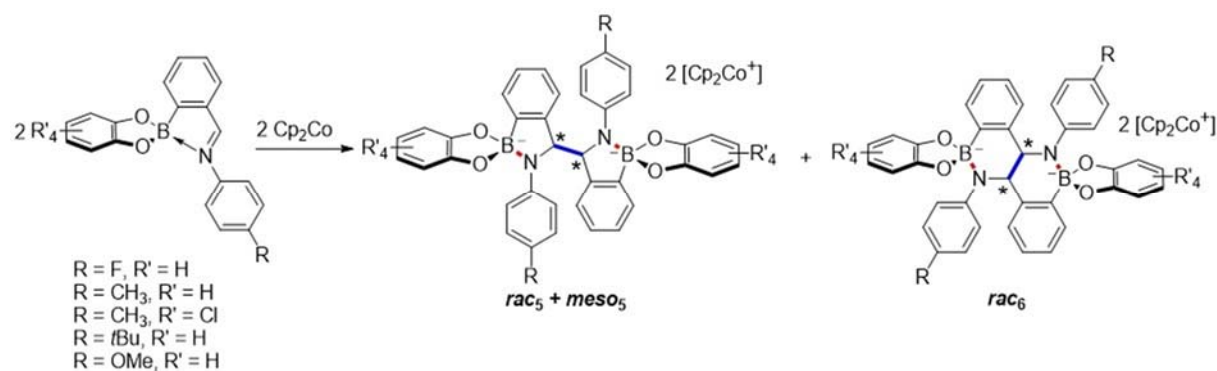


Figure 1. Reductive coupling of *N*-aryl iminoboronates giving three isomeric products, **rac**₅, **meso**₅ and **rac**₆, from C-C bond formation (blue bold bonds) and in the case of the **rac**₆ isomer, rearrangement of the dynamic covalent B-N bonds (bold red).

ORGN 644

Binding studies and anti-Zika activity of a library of synthetic carbohydrate receptors

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Zika virus (ZIKV) has become a global health concern because of its link with acute neurological illnesses, and there are no currently approved vaccines or antiviral therapies. Although several compounds have advanced to phase I clinical trials, without an approved method to treat the infection, there still remains a persistent necessity to explore molecules that inhibit ZIKV using alternative, less conventional approaches. Developing small molecule-based synthetic carbohydrate receptors (SCRs) that bind glycans on the cell surface can lead to potent ZIKV inhibitors by disturbing virus attachment to the host cell. Herein, we present the binding studies and anti-Zika activity of a small library of SCRs. Binding of these SCRs with 5 distinct octyloxy pyranosides was measured by mass spectrometry and by ¹H NMR titrations showing high selectivity for mannosides. Using a ZIKV Reporter Virus Particle (RVP)-based infection assay, we evaluated the anti-Zika activity of the SCRs, and our data demonstrates these SCRs have IC₅₀'s as low as 0.16 μM and negligible toxicity, and thus much more potent than Suramin, an FDA-approved drug for the treatment of trypanosomiasis, which has been shown to have activity against ZIKV by inhibiting different aspects of the virus lifecycle. Time-of-addition studies indicated that these SCRs inhibit the early stages of the virus infection process in Vero and Hella cells, which are consistent with the proposed mode of action, where the SCRs likely inhibit binding between the virus and cell-surface glycans. Further studies are underway to determine the mechanism of action and create more potent SCRs.

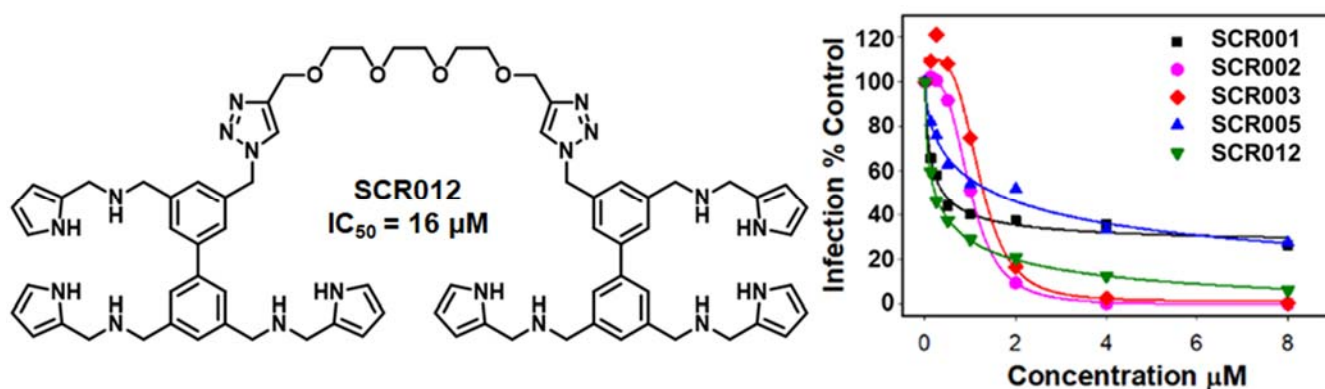


Figure 1. Structure and anti-Zika activity of a series of SCRs

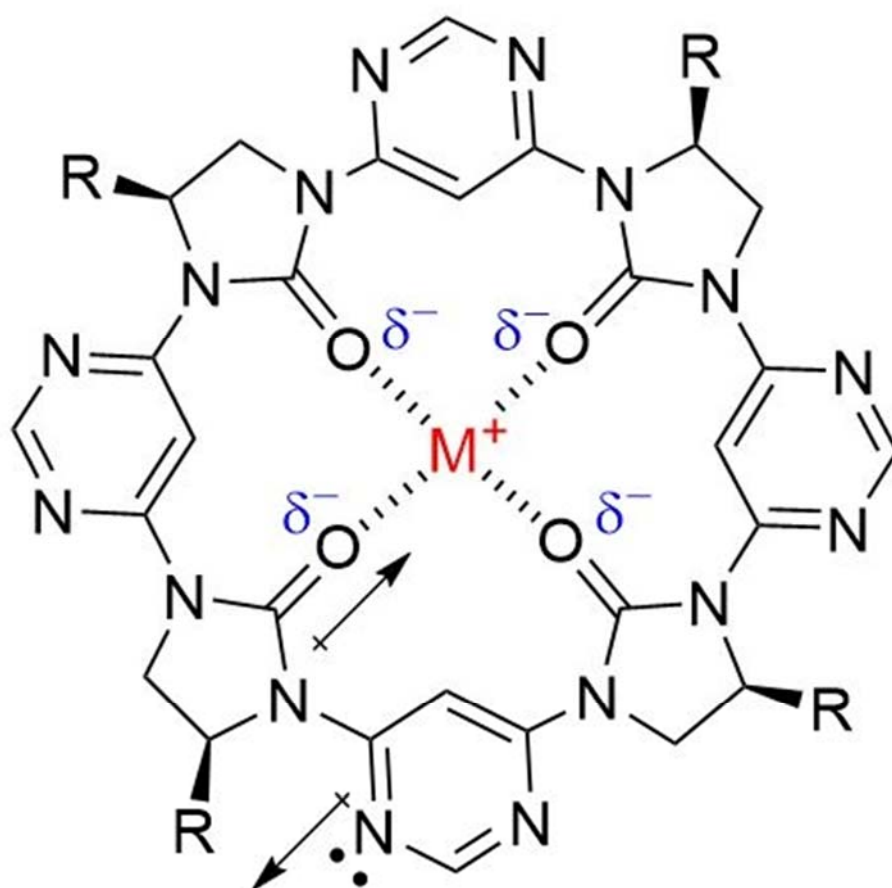
Conformationally locked foldamers: Synthesis and properties of abiotic macrocycles

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Foldamers are unnatural macromolecules with potential applications in medicine, materials science and catalysis. For example, their abiotic nature and ability to bind ions makes foldamers ideal antibiotic candidates in the fight against antimicrobial resistance.

We have synthesized a library of chiral macrocyclic foldamers featuring a dipole-dipole repulsion stabilized urea-pyrimidine backbone. This unique skeleton provides structural rigidity and creates a central cavity that is highly electron-rich—conducive to the binding of common metallic and non-metallic cations.

We have observed reversible cation binding in solution through NMR and mass spectroscopy techniques. We have sought to exploit this strong binding by employing the macrocycles as phase-transfer catalysts, achieving promising enantioselectivities in Michael addition reactions and in the synthesis of α -amino acid derivatives from *N*-(diphenylmethylene)glycine esters. Furthermore, such ion binding is reminiscent of the mode of action of common peptide ionophore antibiotics, indicating that future applications in this area may be productive.



Cationic binding

ORGN 646

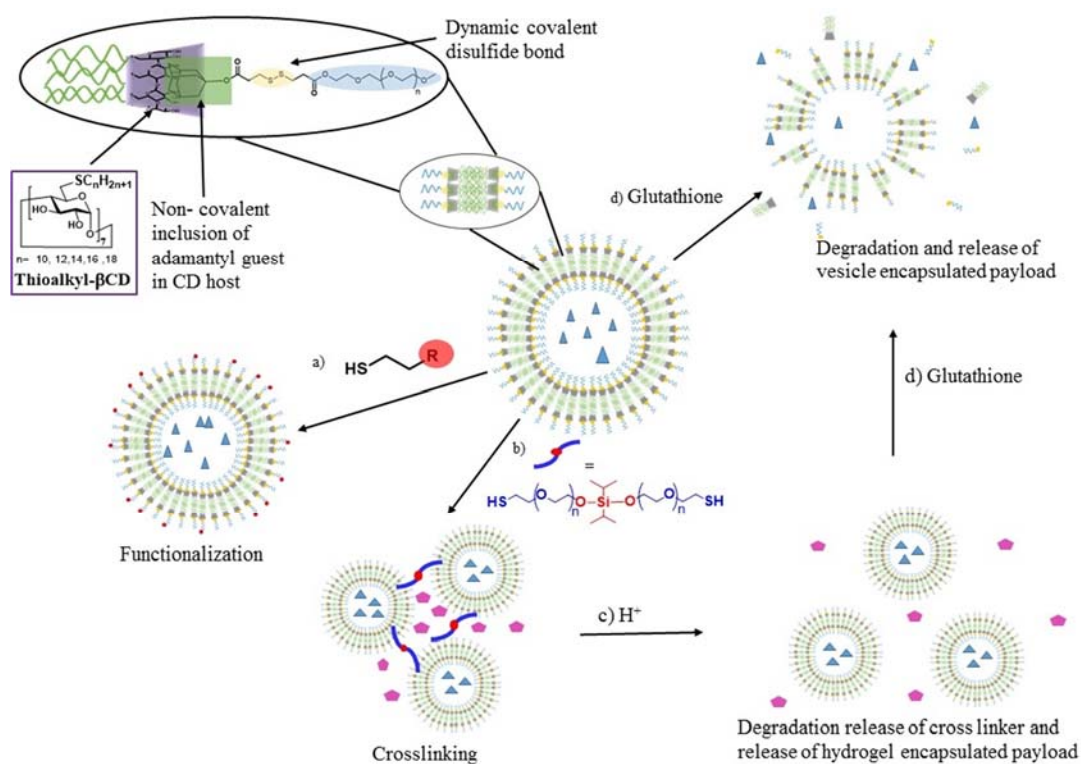
Supramolecular amphiphiles: Synthesis, characterization and applications of amphiphilic cyclodextrin and calix[4]arene inclusion complexes

Emily Mobley, Maya Martinez Rieder, **Sandra Ward**, sward07@calpoly.edu. Chemistry & Biochemistry, California Polytechnic State University, San Luis Obispo, California, United States

Amphiphiles are ubiquitous compounds found in nature as lipids in cell membranes and in industry as detergents or dispersants. The hydrophobic and hydrophilic regions of the molecules allow the compounds to self-assemble in water making them excellent building blocks for the design of self-assembled systems such as vesicle or micelles. In

this presentation, we use non-covalent inclusions chemistry to minimize lengthy organic synthesis steps. Cyclodextrin or calix[4]arene host derivatives form inclusion complexes with functionalized adamantyl or naphthyl guest derivatives to produce novel supramolecular amphiphiles

The supramolecular amphiphiles are able to further self-assembly into vesicles confirmed through dynamic light scattering and fluorescence studies. A dynamic covalent sulfide bond in the supramolecular amphiphile has been exploited to degrade the vesicles by treatment with the free thiol glutathione. We are currently making progress toward using the dynamic covalent bond to crosslink the vesicles into a hydrogel or functionalize the vesicles at the bilayer surface.

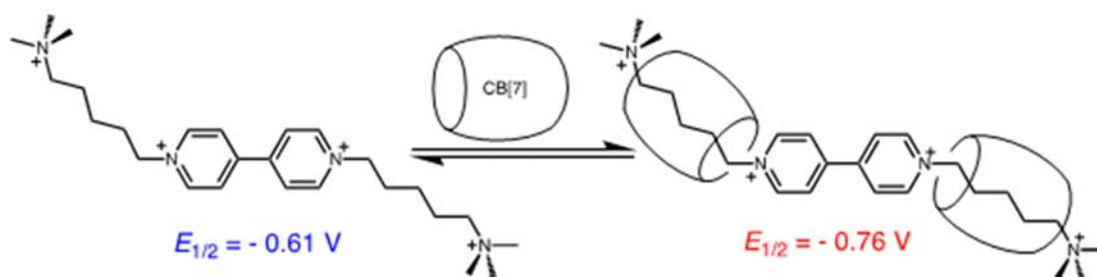


ORGN 647

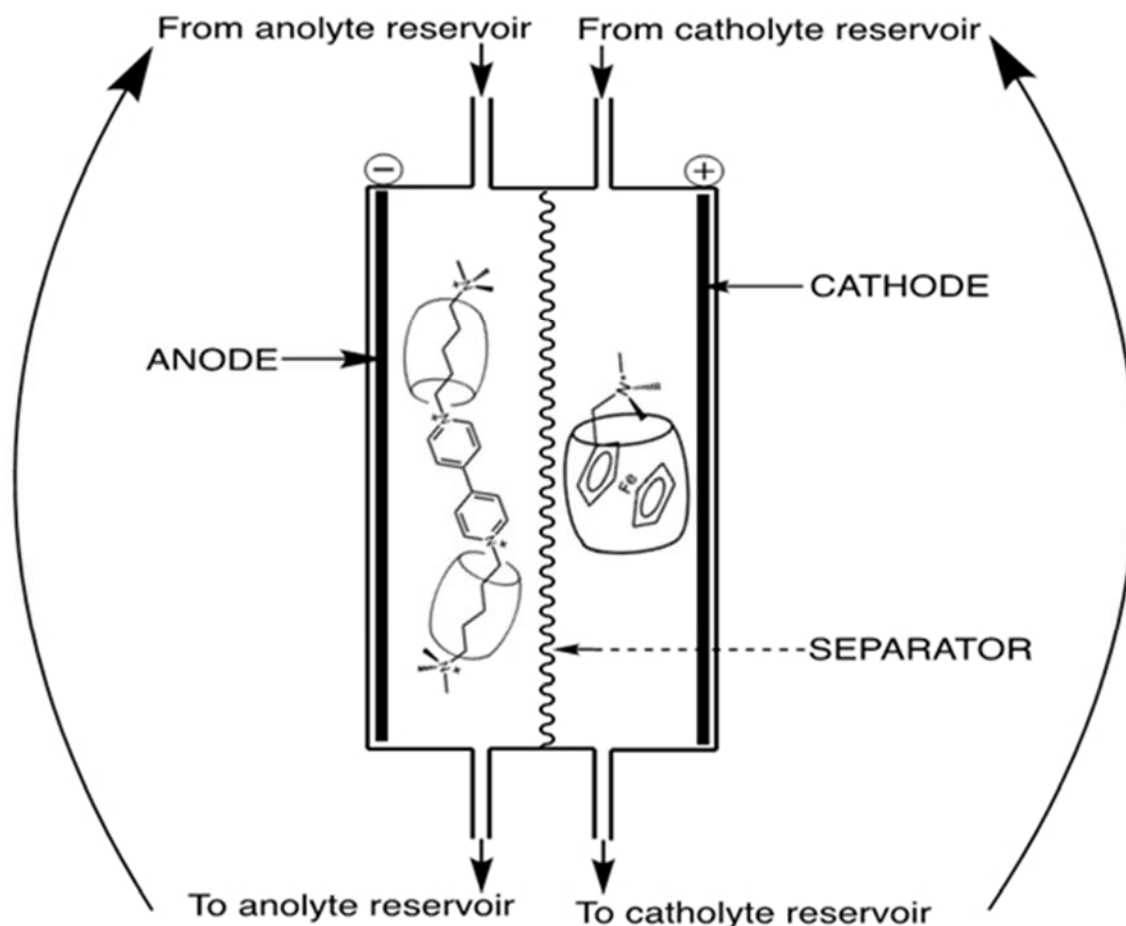
Complexation by cucurbit[7]uril leads to increased cell potentials in aqueous redox flow batteries

Yeting Zheng¹, y.zheng8@umiami.edu, **Angel E. Kaifer**². (1) Chemistry, University of Miami, Miami, Florida, United States (2) Univ of Miami, Coral Gables, Florida, United States

Future power networks will rely heavily on renewable energy sources that are often intermittent in nature. Therefore, these networks must include energy storage components to compensate for the relatively sporadic nature of energy generation. Redox Flow Batteries (RFBs) are among a number of storage devices under strong consideration at this time. The effects of supramolecular complexation by cucurbit[7]uril (CB[7]) on the cell potential of aqueous Redox Flow Batteries (RFBs) based on ferrocene and 4,4'-bipyridinium (Viologen) electroactive materials are reported. It was previously known that the oxidation potential of cationic ferrocene derivatives is shifted to more positive values by the formation of highly stable 1:1 binary complexes with CB[7]. Here, we found that the formation of 1:2 ternary complexes between suitably designed viologens and CB[7] leads to a pronounced shift to more negative values in the first one-electron reduction potential of the viologen. Combining these two effects, we show that the corresponding aqueous RFB -containing cationic ferrocene in the catholyte and viologen in the anolyte- will exhibit a potential of 1.04 V in the absence of CB[7] and 1.30 V in the presence of suitable concentrations of CB[7]. Clearly, CB[7] complexation has a substantial effect on the cell potential, increasing it by 0.26 V or 25%. This substantial potential increase might be improved in future research, as the supramolecular complexation effect seems to be rather general.



Potential changes induced by CB[7] complexation



Schematic Representation of a Redox Flow Battery

ORGN 648

Development of selective, dry-functional and single molecule sensitive on-off barium chemosensors for neutrinoless double beta decay

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The search for Neutrinoless Double Beta Decay, an unobserved extremely rare nuclear process, is recognized as the key to understanding the nature of the neutrino and the dominance of matter over antimatter in the Universe. One nuclear reaction that shows special promise for probing Neutrinoless Double Beta Decay is $^{136}\text{Xe} = ^{136}\text{Ba}^{2+} + 2e^-$. Successful detection of this nuclear reaction requires an extremely sensitive detector, which may be realized by detecting the Barium daughter ions ($^{136}\text{Ba}^{2+}$) from the decay

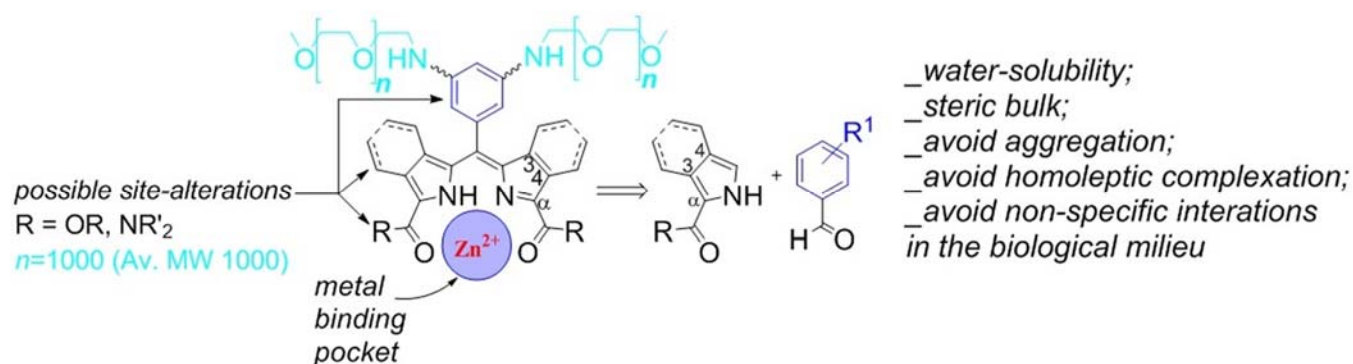
of ^{136}Xe at the single molecule level. Our group has developed the fundamentally new approach of Single Molecule Fluorescence Imaging as a technique to achieve this ultra-low background sensitivity to neutrinoless double beta decay. In this report, we present the synthesis and application of Ba^{2+} selective chemosensors specially designed to function under the conditions of a Neutrinoless Double Beta Decay experiment. Several classes of chemosensor films including polymeric chemosensor and monolayers are assessed for their relative responsiveness, dry-phase activity, and single molecule sensitivity through fluorescence Imaging. One promising candidate—a naphthalimide based chemosensor—is found to be highly selective and sensitive to Barium ions and can be resolved at the target single molecule level. Future work regarding design, synthesis, and challenges of self-assembled monolayer (SAM) of these chemosensors on silicon substrate and glass will also be discussed.

ORGN 649

Synthesis of water-soluble dipyrins for sensing applications

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We report the development of water-soluble dipyrins with different affinities for Zn^{2+} , potentially suitable for sensing Zn^{2+} in biological environments. The new dipyrins possess excellent water-solubility. Their optical absorption spectra in aqueous media are nearly identical to the spectra of the parent lipophilic dipyrins in organic solvents, indicating lack of aggregation. Addition of Zn^{2+} causes characteristic changes in the absorption spectra of the dipyrins and induces strong fluorescence. Notably, the mechanism underlying fluorogenicity of the dipyrins is different from that in photoinduced electron transfer-based sensors, developed earlier. The dissociation constants (K_d) of the complexes we found to be strongly dependent on: (1) the basic structure of the dipyrin skeleton, whereby p-extension *via* 3,4-pyrrolic positions (as in benzo-dipyrins) significantly increases the Zn^{2+} binding affinity; (2) substituents in the pyrrolic α -positions, where dipyrin-esters exhibit higher binding affinity than amides. The new water soluble dipyrins may be useful for sensing Zn^{2+} in the micromolar range, where only a few sensors are currently available.



ORGN 650

Synthetic ion transport systems for targeting cancer

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The ion transport process across the cell membrane is facilitated by a certain class of membrane-embedded proteins such as channels, carriers, etc.¹ This process is essential for diverse biological functions such as maintenance of ion homeostasis of cells, sensory transduction, cell proliferation, osmotic stress response, etc. Homeostasis of sodium, potassium, calcium, and chloride are involved in apoptotic cell death.² Evasion of apoptosis is long observed in cancers and chemotherapeutic agents that initiate apoptosis in cancer cells are already applied for the treatment of cancer.³ In this lecture, our recent approaches to the development of synthetic ion transporters would be discussed.⁴ Understanding of ion recognition and the mechanism of ion transport by these systems would be addressed. The effect of the transporter-mediated ion transport on cells would be discussed.⁵ Further, our strategies to activate the ion transport across the lipid membranes by certain types of stimuli would be presented.^{6,7,8} The effect of stimuli-responsive ion transport on cells would also be presented. The potential of such ion transport systems in targeting cancer would be addressed.

ORGN 651

Phosphorescence lifetime-based probe for oxygen and temperature

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We report the development of a molecular probe for *in vivo* high-resolution imaging of temperature concurrently with oxygen. The probe is based on a chromophore capable of microsecond-scale emission occurring simultaneously from two well spectrally resolved excited electronic states, existing in thermal equilibrium with one-another: phosphorescence and delayed fluorescence. While the emission decay time is sensitive to both temperature and oxygen, the ratio of the decay intensities is sensitive only to temperature. Because ratiometric measurements (i.e. the ratio of decay intensities at two different wavelengths) *in vivo* are jeopardized by optical heterogeneities of the medium (differential absorption and scattering by endogenous tissue chromophores), the probe is supplemented by a second molecule of nearly identical structure, but emitting regular prompt fluorescence at the wavelengths matching those of the phosphorescence and delayed fluorescence of the probe. The second chromophore is excited simultaneously with the probe, serving as a fluorescent correction standard to account for absorption/scattering uncertainty, since prompt fluorescence is independent of temperature and/or oxygen. The microsecond-scale emission of the probe and the nanosecond emission of the standard are measured simultaneously, taking advantage of their significantly different time scales. Synthesis, photophysical characterization and *in vivo* tests will be discussed.

ORGN 652

Hierarchical supramolecular assembly of an unusually stable viologen radical species

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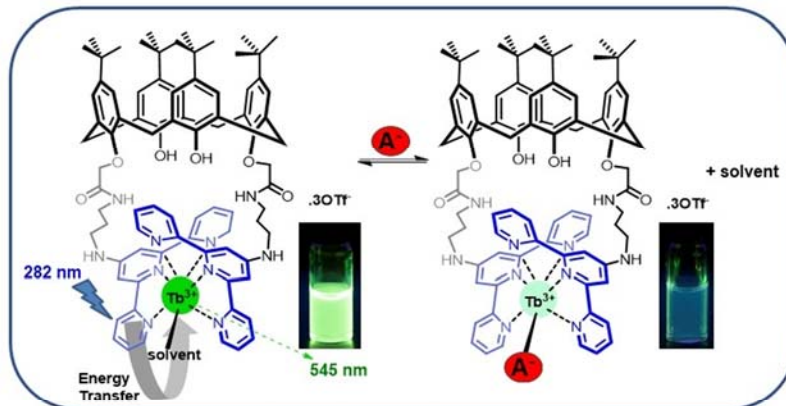
Viologens are an important class of redox-active compounds, often used as electron acceptors in fundamental photochemical and electrochemical studies, as well as redox components in rotaxane-based molecular electronics and electrochromic devices. However, viologens are often limited in redox-based applications by the instability of their reduced forms to Oxygen. Here, we discuss the design, self-assembly, electrochemical behaviors, and Oxygen stability of viologen species incorporated in a hierarchical supramolecular assembly in water. Two different bis-viologen dimers are presented, each reduced in the presence of the macrocyclic host cucurbit[8]uril (CB[8]). This results in the sequential folding and then encapsulation of the reduced viologen dimers. Interestingly, the normally degenerate 2 e⁻ redox wave (4⁺/2⁺ transition) of the bis-viologen species separates into two separate 1 e⁻ redox waves in the presence of CB[8]. This new 3⁺ mono-radical complex displays unique UV/Vis absorbance and a significant stabilization to molecular Oxygen. The supramolecular chemistry leading to the formation and stability of these reduced viologen dimers will be discussed.

ORGN 653

Functionalized calixarenes: Synthesis, characterization and anion sensing applications

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There is keen interest in the development of anion sensors in supramolecular chemistry due to the crucial roles that these sensors play in many arenas including environmental, biological and medicinal arenas. Lanthanide-based complexes are particularly attractive targets for use as optical anion sensors. These complexes boast excellent photophysical properties and are potent Lewis acids; coordination of anions to the lanthanide results in changes in the photophysical properties of the complex that can be harnessed in a sensing scheme. This presentation will describe the synthesis, characterization and anion sensing studies of lanthanide-chelated terpyridine functionalized calixarenes. These functionalized calixarenes have been synthesized in two steps and characterized via NMR, UV-Vis and fluorescence spectroscopy using a range of spectroscopic techniques. Lifetime measurements and quantum yields of these functionalized calixarenes have also been determined. The binding ability of these functionalized calixarenes for various anions, including NO_3^- , HSO_4^- , H_2PO_4^- (as their tetrabutylammonium salts) was tested in organic media by monitoring the changes in their UV-Vis and fluorescence spectra as a function of added anions.



Terpyridine-functionalized calixarene chelated with Tb^{3+} in the presence of the dihydrogen phosphate ion.

ORGN 654

Cobalt catalyzed C–H borylation: Unprecedented selectivity opens pathway to greener organic synthesis

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The direct, selective conversion of ubiquitous C–H bonds in to synthetically versatile C–B bonds is attractive in organic synthetic and potentially enabling in green chemistry as synthetic steps are potentially eliminated. Our laboratory has discovered a class of cobalt catalysts supported by various tridentate pincer ligands that promote the borylation of C(sp²)–H bonds. With fluorinated arenes, control over *ortho*, *meta* and *para* selectivity has been achieved. The various catalyst types operate in distinct kinetic regimes and the observed selectivity derives from whether the C–H bond breaking step is under kinetic or thermodynamic control. Importantly, the observed reactivity and selectivity derives from inherent electronic differences in the C–H bonds rather than from more traditional (and limited) directing group strategies. The various kinetic regimes and how the properties of the supporting ligands enable the selectivity of the reaction will be discussed as well applications to important synthetic intermediates.

ORGN 655

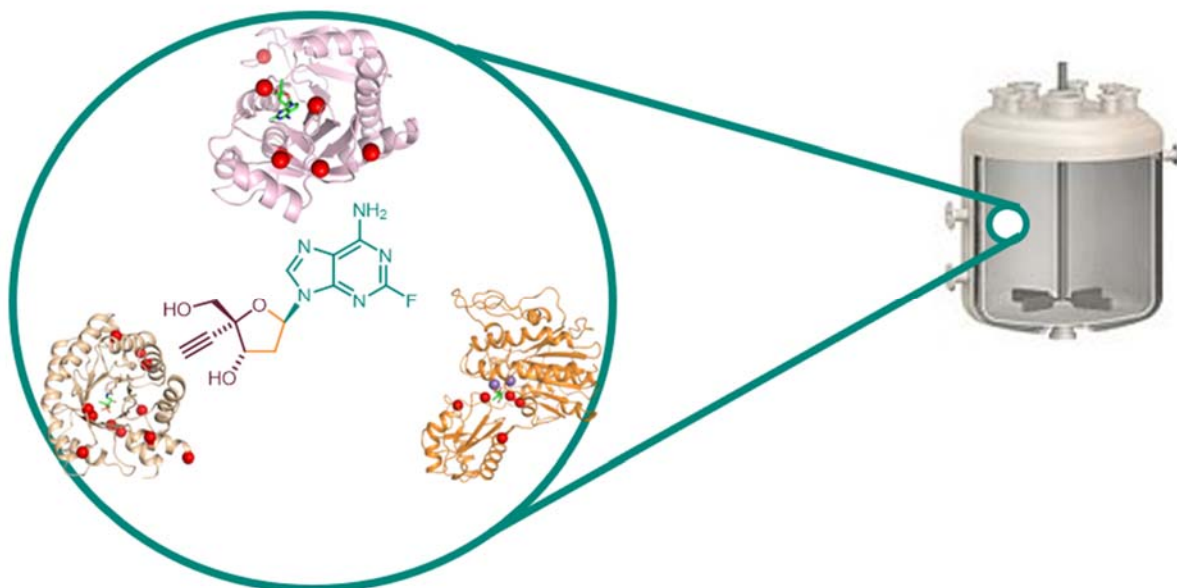
Biocatalytic routes to the drugs of the future

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Biocatalysis has begun to transform the pharmaceutical industry. Recent advances in directed evolution and protein engineering, combined with the explosion of genomic information, mean that we can now identify and improve enzymes for new reactions at unprecedented speed. The benefits of enzyme-catalyzed reactions for sustainable syntheses are well known, but perhaps most powerful is their unique suitability for combination into multi-step sequences. Such cascade processes can lead to fundamentally different synthetic design, where the step-count and the number of isolations are significantly reduced. Merck team has constructed and engineered biocatalytic cascades starting from simple achiral building blocks to furnish complex molecules with non-natural structural features. Our work demonstrates that it is now feasible to design robust (multi)enzyme processes to active pharmaceutical ingredients, characterized by high synthetic efficiency and atom economy.

Today, biocatalytic transformations have a great potential to accelerate the pace of drug discovery and manufacture, expanding the synthetic chemistry toolbox beyond the traditional boundaries of small-molecule synthesis. Continued investment in enzyme catalysis and protein engineering technologies will advance the development of

greener, sustainable manufacturing routes of the drugs of the future, paving the way to their continuous manufacture.



ORGN 656

Sustainability in complex molecular settings

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Modern pharmaceuticals are both increasingly complex¹ and increasingly diverse. Today's clinical candidates often contain challenging stereochemistry, unique molecular architectures, and uncommon heterocyclic frameworks; they range from small molecules to natural products, peptides, oligonucleotides, antibody-drug conjugates and other modalities. Developing safe, scalable and sustainable routes to molecules, in the context of increasingly short development timelines, requires an approach focused on maximizing impact through innovative chemical solutions – so called 'disruptive innovations'.² However, increases in molecular complexity bring new challenges to the decision making process, complicating our ability to identify the synthetic strategies which will produce the most sustainable outcomes. These decisions can be aided by predictive decision making tools, cognizant of potential environmental impact, and recent advances have begun to establish such methodologies.³

This presentation will cover the synthetic strategies and chemical innovations developed

to address several clinical candidates from the Bristol-Myers Squibb portfolio. Our approach² has led to the invention of several new synthetic approaches,⁴ new chemical methods,⁵⁻⁸ and new concepts in predictive data analytics.³

ORGN 657

Safer sustainable recyclable solvent systems for catalysis and synthesis

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While designing sustainable reaction systems can include many factors, the issue of solvents is of paramount importance since solvents constitute the major component of most reactions. The focus of our recent work has been to address this issue by exploring how to develop inexpensive safer, separable, and recyclable solvent systems that can be used to facilitate reactions that use recyclable homogeneous catalysts. Initial studies have shown the poly(α -olefin)s (PAOs) that are commercially available fractionated hydrocarbon mixtures with 20-48 carbons and modest viscosities can replace hexane or heptane in many reactions. Such PAOs are readily separable from polar organic solvents by a gravity separation. They can be reused multiple times in homogeneous catalysis and readily recycle PAO-anchored catalysts without significant contamination of the isolated organic products. They are also safer solvents with reduced flammability and volatility due to their higher molecular weight. They themselves are simply alkanes with the limitations of any alkane solvent. However our studies show that mixtures of PAO with both low molecular weight and PAO-anchored cosolvents can be prepared and that such cosolvent systems are in effect polarized alkanes. Such solvent systems have much of the polarity of a pure polar solvent based on changes in the fluorescence of solvatochromic dyes using dansyl and Nile Red as dye probes of microheterogeneity in otherwise miscible solvent mixtures. Such solvent systems too can be designed to be fully recyclable by designing the cosolvent so that it is phase anchored in the PAO host solvent.

ORGN 658

Chevron Phillips Chemical LP Synfluid® high viscosity mPAO

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The past decade has witnessed a variety of new lubrication technologies, as markets have continued to migrate toward higher performing base oils. High viscosity oils are no exception, as improvements in low temperature properties, thinning behavior, and energy efficiency benefit a variety of applications. Chevron Phillips Chemical's high viscosity base oil, Synfluid® High Viscosity mPAO, is a poly(α -olefin) produced using a proprietary metallocene catalyst system and a continuous flow reactor. The properties of mPAO are in many cases superior to traditional high viscosity PAO

(HVPAO), and mPAO can be produced in a wide range of viscosities to meet the demands of a growing market.

ORGN 659

Role of green chemistry in the design of sustainable crop protection products

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Green Chemistry principles are especially impactful in agriculture due to the sheer size of the food value chain. Unlike the relatively small volumes of active pharmaceutical ingredients, typical annual manufacturing volumes for crop protection active ingredients are hundreds to thousands of metric tons. The Green Chemistry principles focused on waste reduction and process safety are highly relevant to the design of agrochemical manufacturing processes. However, the emphasis of green chemistry on product safety and degradation in the environment is even more critical to the design of products that are applied to crops. Corteva Agriscience is committed to the development of sustainable agrochemical products and is a leader in the development of agrochemicals that are derived from fermentation processes. To learn from experts in Green Chemistry, Corteva recently joined the ACS Green Chemistry Institute Pharmaceutical Roundtable as an affiliate. This talk will describe recent products from Corteva that have been awarded the Green Chemistry Challenge award.

ORGN 660

Homogeneous catalytic hydrogenation reactions towards fragrance and flavor ingredients: Industrial applications

Lionel Saudan, *lionel.saudan@firmenich.com*. Product & Process Research, Firmenich SA, Geneva, Geneva, Switzerland

The research into new industrial catalytic processes is at the forefront of *Firmenich's* R&D and constitutes one of the main strategic pillars towards realizing its sustainability targets. In particular the need for industrial processes which will generate less waste, use less solvent, and minimize energy requirement.

The development of industrial homogeneous catalytic hydrogenation processes was pioneered almost 20 year ago with the launch of the iconic *Paradisone*[®] process and has since expanded into a well-established domain of research at *Firmenich*.

In this presentation, several examples will be presented to show how the implementation of new catalytic homogeneous hydrogenation led to less hazardous and less waste generating processes towards the synthesis of some key Perfumery

ingredients.

A special emphasis will be on the newly developed catalytic processes towards efficient preparation of Muguet type aldehydes. Aldehydes are key ingredients of the Perfumery palette with examples such as Lilial® and more recently Hivernal Neo®.

(Figure 1)

Herein we will show the development of chemo- and regioselective hydrogenation of conjugated dienals into their corresponding gamma-delta unsaturated aldehydes, as an alternative to the *Claisen*-rearrangement, all while avoiding the formation of over-hydrogenated alcohol side products.

(Figure 2)

This innovative catalytic process provides a new direct method, with a low environmental footprint, towards making gamma-delta unsaturated aldehydes (either aliphatic or aromatic), accessed until now through a *Claisen*-rearrangement of allyl-vinyl ethers.

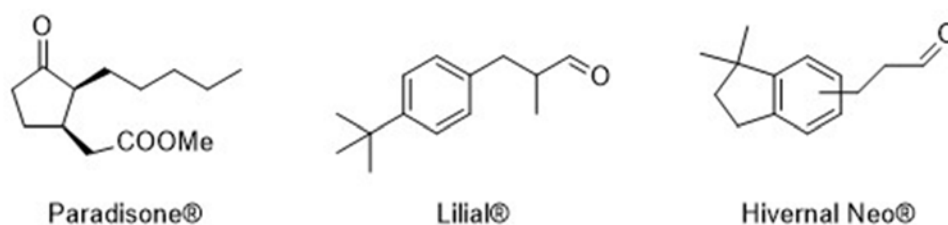


Figure 1. Examples of Perfumery ingredients

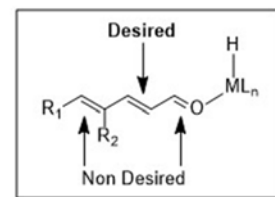
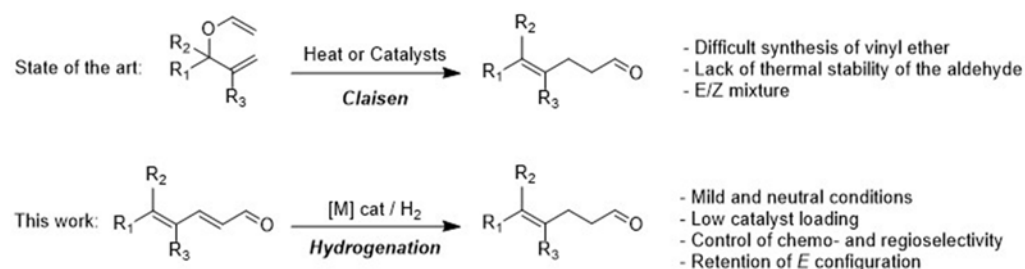


Figure 2. Catalytic hydrogenation of dienals versus Claisen rearrangement

ORGN 661

Functionalization of Csp³-H bonds via copper catalyzed electro-organic chemistry

Leslie K. Trigoura¹, *ltrigoura25@gmail.com*, **Yalan Xing²**. (1) Chemistry, William Paterson University, Waldwick, New Jersey, United States (2) Chemistry Dept-SCIE 4059, William Paterson University, Wayne, New Jersey, United States

Electrochemistry has made major contributions to organic synthesis through its “green” methodology, higher atom economy, and minimal waste. Organic electrosynthesis utilizes electrical current to drive the activation of organic molecules via the removal or addition of electrons. Due to its selective redox of organic molecules, organic electrosynthesis can perform reaction transformations that have not been generated traditionally through the use of conventional chemical reagents. Electrochemistry is a beneficial asset for chemists providing clean transformations, mild reaction conditions, simple scalability, high functional group tolerance, low energy consumption, and a step away from the use of toxic redox reagents. Through this research, we have developed a strategic electrochemical approach to perform this Csp³–H bond functionalization on C–H bonds adjacent to oxygen and nitrogen, using an undivided electrolytic cell with graphite electrodes as both anode and cathode. The identification of the optimal conditions are currently under investigation in the laboratory.

ORGN 662

Recent advances in the use of carbonyl compounds as active components in organic- based batteries

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The quest for green and sustainable energy storage systems has brought about the need for a material system that can satisfy the following requirements; low cost of production, environmental benignity, flexibility, redox stability, renewability and structural diversity. Interestingly, organic compounds of carbonyl functionality have been identified as potential candidates to proffer solutions to the above-mentioned challenges. This review therefore discusses various classes of carbonyl compounds as active components in some rechargeable batteries, highlighting their major strengths and drawbacks.

ORGN 663

Microwave-mediated continuous hydrogen generation method from methylcyclohexane and 2-propanol using carbon bead-supported Pt catalyst

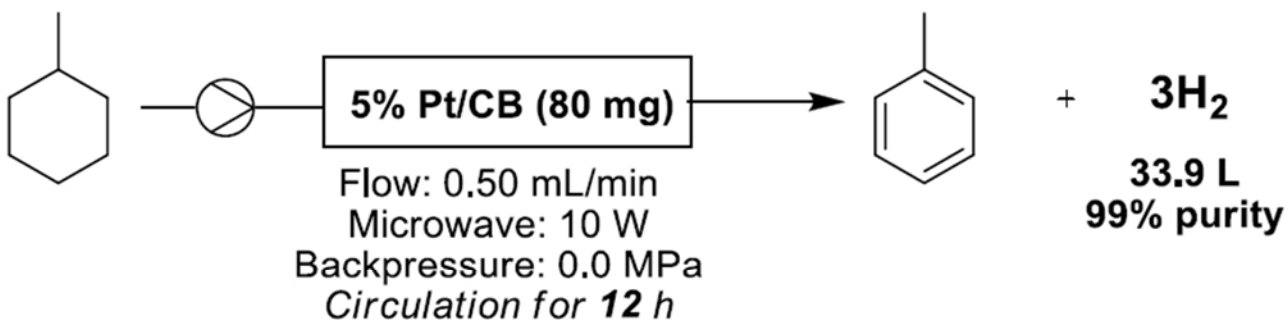
Tomohiro Ichikawa¹, **Takumu Tachikawa¹**, *156024@gifu-pu.ac.jp*, **Tomohiro Matsuo¹**, **Tsuyoshi Yamada¹**, **Takeo Yoshimura²**, **Masatoshi Yoshimura³**, **Yukio Takagi³**, **Yoshinari Sawama¹**, **Jun-ichi Sugiyama⁴**, **Yasunari Monguchi⁵**, **Hironao Sajiki¹**. (1) Org

Chem Lab, Gifu Pharm Univ, Gifu, Japan (2) SAIDA FDS INC., Yaizu, Shizuoka, Japan (3) Catalyst Development Center, N.E. Chemcat Corporation, Numazu, Shizuoka, Japan (4) Tsukuba Central, National Institute of Advanced Industrial Science and Technology, Tsukuba, Ibaraki, Japan (5) Laboratory of Organic Chemistry, Daiichi University of Pharmacy, Tamagawa, Fukuoka, Japan

Hydrogen, which never released CO₂ during the combustion, has received attention as a clean energy source alternative to fossil fuels. However, hydrogen is industrially produced by the steam reforming of methane and methanol along with the production of CO₂. Besides, the extremely low boiling point, the low energy density per unit volume, and the flammability of hydrogen gas leave serious problems with hydrogen storage and transport. Therefore, there has been a great interest in the concept of hydrogen storage in liquid organic hydrocarbons (LOH). However, since dehydrogenation from LOH such as cyclic hydrocarbons and alcohols is an endothermic reaction, and energy input is required, problems remain in terms of practicality.

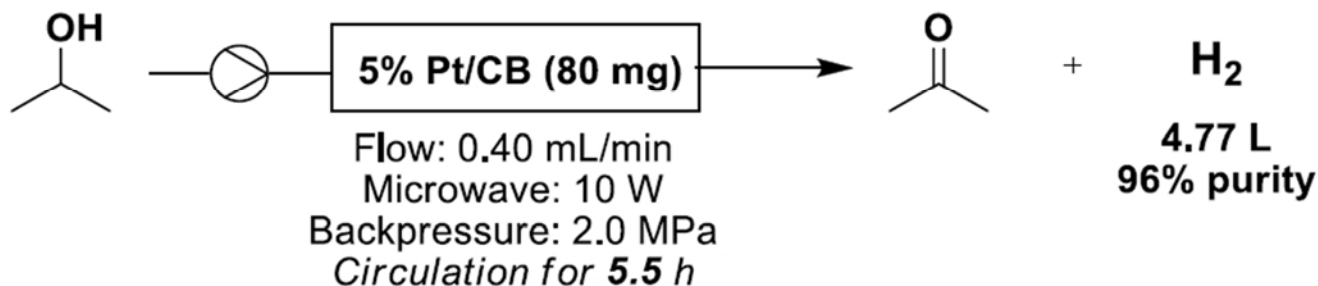
We have developed an only 10W microwave-mediated continuous flow dehydrogenation method from methylcyclohexane (MCH) and 2-propanol (2-PrOH) catalyzed by platinum on carbon bead (Pt/CB). Both MCH and 2-PrOH were transformed into corresponding toluene and acetone, and 33.9 L and 4.77 L of hydrogen gas were generated, respectively, under only 10W MW irradiation during the circulation flow path equipped with a 5% Pt/CB-packed. The turnover number of Pt/CB during the reaction achieved 67773 and 12945 times, respectively.

The selective and local heating effect toward carbon beads as the catalyst support in the catalyst cartridge of the flow reaction system by microwave irradiation enables a new sustainable, cost-friendly and versatile continuous hydrogen generation method from MCH and 2-PrOH.



Turnover number: 67773 times

ACS Sustainable Chem. Eng., **2019**, 7, 3052



Turnover number: 12945 times

Catalysts, **2019**, 9, 655

ORGN 664

Flow chemistry used for optimization (DOE) of four-step synthesis of polysubstituted pyrroles

Carlos Perez Mandry, Ariana Kim, **Raymond N. Dominey**, rdominey@richmond.edu, Emma W. Goldman, John T. Gupton. Univ of Richmond, Richmond, Virginia, United States

Vinylogous amines, and chloroenals derived therefrom, are very versatile reagents for the regioselective synthesis of unsymmetrical polysubstituted pyrroles and isoquinolones based on extensive research by Gupton. We report here our attempts at using a flow chemistry platform to accelerate optimization of individual reaction steps as well as for the overall telescoped four-step syntheses of polysubstituted pyrroles. In particular, a Design of Experiment (DOE) for optimizing the final ring closure step will be presented.

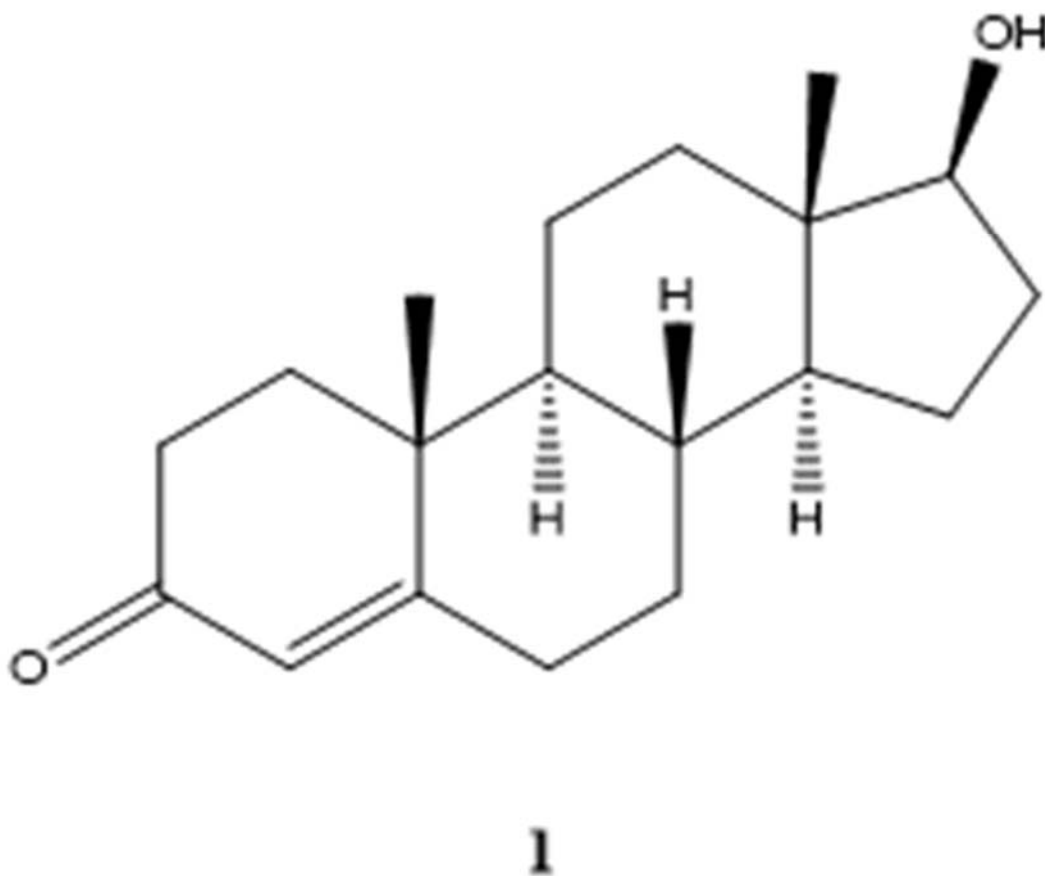
ORGN 665

Investigating the formation of steroid derivatives from testosterone using free and immobilized filamentous fungi

Jordan M. McKenzie¹, jordan.mckenzie@mymona.uwi.edu, **Paul B. Reese²**. (1)
Chemistry, The University of the West Indies, St. Catherine, Spanish Town, Jamaica (2)
Department of Chemistry, University of the West Indies, Kingston, Jamaica

For decades, microbial transformation has been exploited by scientists for its applications in green chemistry and the facile conversion of substrates to oxygenated analogues. Hydroxylation reactions are typical among these transformations as microorganisms, through the use of cytochrome P450 enzymes, perform remote functionalization on a number of substrate carbons. The current investigation explores the potential of seven fungi, namely, *Actinomucor elegans*, *Aspergillus ochraceus*, *Beauveria bassiana*, *Calonectria decora*, *Mucor plumbeus*, *Rhizopus stolonifer* and *Penicillium chrysogenum* to effect the biotransformation of 17 β -hydroxyandrost-4-en-3-one, commonly known as testosterone (**1**).

These transformations have been carried out by incubating **1** with fungal mycelia growing in nutrient media, or separately to calcium alginate cells suspended in water. The conditions for successful bioconversions have been optimized and yields of products from both methods have been compared. The approach can be extended to examine the products formed when **1** is fed to a single vessel with a mixture of two sets of beads, each derived by encapsulating a single fungal strain. This approach has the potential for generation of a library of compounds.



ORGN 666

Aqueous solubility of new albuterol drugs in liquid form

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One of the most recurrent issues encountered in the world of active pharmaceutical ingredients (APIs) is their low bioavailability, which is in part due to their poor dissolution in aqueous media. Researchers are actively pursuing a solution to this issue. Multiple studies have shown that the conversion of the solid state pharmaceuticals into liquid state or ionic liquids (ILs, ionic salts in liquid state comprised of a 1:1 cation to anion molar ratio) is one of the most promising routes to address these issues. An increase in the drugs solubility can be also achieved when three or more pharmaceuticals are combined in different molar ratios into a more complex IL, namely a double salt ionic liquid (DSIL). Albuterol is one of the most commonly used drugs in asthma treatment.

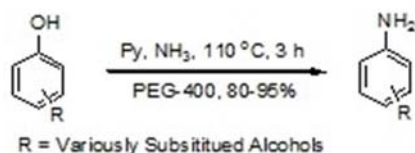
Due to the aliphatic and aromatic regions present in its structure, the aqueous solubility of this drug is low, and its bioavailability hence is diminished. However, albuterol contains a basic amine site making it an ideal candidate for its conversion into a cationic form which can then be paired with organic anions to form new liquid state asthma medication. Our previous research showed that albuterol cation, a non-steroidal anti-inflammatory drug anion, and docusate anion can be successfully combined in different molar ratios to form the corresponding DSILs. Here, our research efforts are directed towards the aqueous solubility of the novel liquid state albuterol derivatives. Solubility studies were performed in phosphate buffered saline (PBS, an aqueous medium that mimics the ionic concentration, osmolality, and pH of blood) by following the reported procedures and the amount of the desired compound in the aqueous solution was quantified *via* UV-Vis spectroscopy.

ORGN 667

Green approach: Metal free amination of aromatic alcohols

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A simple and convenient reaction protocol for the clean and high-yielding synthesis of various aromatic amines derived from reactions of phenols with ammonia under transition metal-free reaction conditions is described here. PEG-400 (Polyethylene Glycol-400) is employed as green reaction solvent. Pyridine was found to be the ideal catalyst and base for this transformation. The conversion rates and yields observed are excellent and in the majority of the reactions significantly higher yields were obtained than in their catalyzed versions. The reactions were performed with substituted benzyl alcohol and phenols. Phenols which are supposed to be harder to convert under metal free conditions, gave high yielding products under these newly developed reaction conditions. After optimization, the best reaction condition was found to be use of catalytic amount of Pyridine (0.1 equiv) and ammonia (1.2 equiv) for amination.



ORGN 668

Synthesis and structure investigation of dimethyl 2,2'-(5-amino-4,4,6-tricyano-3-methylcyclohexa-1,5-diene-1,3-diyl) diacetate obtained using one pot reaction

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By utilizing green chemistry, dimethyl 2,2'-(5-amino-4,4,6-tricyano-3-methylcyclohexa-1,5-diene-1,3-diyl) diacetate was synthesized successfully via one step reaction between methylacetoacetate, malononitrile in presence of piperidine. This reaction product was also obtained using same procedure with adding aliphatic aldehyde. Structural investigations are pursued via different techniques; such as: FTIR, ^1H NMR, ^{13}C NMR, mass and single crystal structure analysis. The compound is being estimated for anti-inflammatory and antifungal activities. The results showed that the compound with the molecular formula of $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_4$ crystallized in the Monoclinic, Pc, $a = 6.4194$ (14) Å, $b = 9.374$ (2) Å, $c = 13.071$ (3) Å, $\beta = 98.761$ (7)°, $V = 777.4$ (3) Å³, $Z = 2$. The propose mechanism for this reaction will be described.

ORGN 669

Use of recyclable Brønsted acid catalysts in alternative alkane solvents

Christopher Watson¹, christopher.watson@chem.tamu.edu, **Adrianna Keuchle**¹, **David E. Bergbreiter**². (1) Texas A&M University, Bryan, Texas, United States (2) Texas AM Univ, College Station, Texas, United States

While heterogeneous polymer bound Brønsted acid catalysis has been of regular interest, it is also advantageous to look at phase anchored homogeneous catalysis. The use of acid catalysts for reactions such as esterifications, acetalysis, and multicomponent reactions is well documented; however these reactions often have the significant drawback of having small ΔG values and thus needing to be driven by Le Chatelier's Principle. This causes either a waste of heat to boil off products or the use of excess starting materials to drive the reaction. However, this work shows that with the use of a proper phase anchor such as polyisobutylene (PIB) and a suitably acidic end group such as a sulfonic acid, these reactions can be carried out in poly- α -olefins (PAOs), which due to their very low polarity, will exclude the water byproducts. This serves to drive the reactions without the need for apparatuses such as Dean-Stark traps or the need for excess of reagents. Additionally, this work demonstrates that the initial reaction rates in PAO are comparable to those in traditional toluene solvent systems. This work shows that even stoichiometric amounts of alcohol and acid can be driven to the ester in excellent yields by the exclusion of water at moderate temperatures. The significant nonpolar nature of these solvents also allow for simple purifications of the product materials. This reaction coupled with either extractions or distillation of the products allows for recyclability of not only the acid catalyst, but also the solvent in excess of ten times, due to its near nonexistent vapor pressure, which constitutes a significant reduction in the waste materials and loss of solvent for these reactions. While this solvent system does have the drawback of normal alkane solvent systems (namely

the issue of solubility of reagents) we have shown that it does also have significant advantages that can outweigh many of its drawbacks.

ORGN 670

Sustainable synthesis of 2/3-aryl indoles under Pd-catalysis in SPGS-550-M micellar medium

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The selective control over multiple competing C–H sites would enable straightforward access to functionalized indoles. In this context, we report here a modular and selective C–H arylation of indoles via the micellar catalysis approach using the third generation “designer” surfactant SPGS-550-M in the presence of 1 mol % of [(cinnamyl)PdCl]₂ under mild conditions. Thus, access to high value C-arylated (C-3 and C-2) indoles was achieved fulfilling the “triple bottom line philosophy” of green chemistry. The nature of the phosphine ligand was found to be critical for achieving site-selectivity, DPPF and DPPP being the most effective in promoting the arylation at C3–H and C2–H, respectively. The reaction is scalable and offers high chemo- (C vs. N) and regio-selectivity (C-3 vs. C-2) with a wide range of functional group tolerance. The surfactant aqueous solution can be recycled and reused without compromising on product yields.



Micellar approach for C-H arylation of indoles

ORGN 671

Scalable synthesis of a cyclobutane-1, 2-diacid and its derivatives from *trans*-cinnamic acid via photoreaction

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Dicarboxylic acids and their derivatives have a variety of applications in many fields such as polymers, pharmaceuticals, and metal-organic materials. Cyclobutanedicarboxylic acids (CBDAs) represent a family of promising diacids that can be synthesized by using photoreaction.

It has been known for about a century that both CBDA-1 (α -truxillic acid) and CBDA-4 (β -truxinic acid) could be synthesized from two polymorphs: α - and β -trans-cinnamic acid, respectively. However, researchers had to take a detour to make CBDA-4 by turning trans-cinnamic acid into its p-nitrophenyl ester or 1,3-trimethylene diester for photodimerization, and then hydrolyzed the ester dimer back to CBDA-4. This is because that the metastable crystalline β -form (head-to-head packing) of trans-cinnamic acid is readily to transfer to the stable α -form (head-to-tail packing). The low energy barrier from the β -form to the α -form renders reliable synthesis of CBDA-4 challenging because the β -form gives CBDA-4 after photodimerization and α -form leads to CBDA-1, which also explained the conflicting experimental results about CBDA-4 synthesis in the literature.

In this poster, we will show a facile and scalable preparation method of CBDA-4 accomplished by capturing and photodimerizing the metastable crystalline solid of trans-cinnamic acid. This synthetic approach builds a foundation for investigating the properties and applications of the useful diacid and its derivatives. The X-ray crystal structure of CBDA-4 was determined for the first time. The synthesis of a series of mono- and di-esters derived from CBDA-4, which have similar structure to the widely used phthalates, will also be discussed.

ORGN 672

Verification of sulfonated compounds found in biodiesel produced from brown grease lipids (BGL)

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This project reports the development or modification of protocols used to synthesize and characterize methyl 8-(2'5'-hexylthienyl) octanoate (23%), epithiostearate (27%), cross-linked disulfide (10%), crosslinked sulfide (7.5%) and epidithiostearate (55%). Our research team is interested in these molecules because a combination of distillation, extraction, and analytical techniques (GC-FID, GC-PFPD, and GC-MS) have identified them as possible sulfur (S)-bearing contaminants in biodiesel derived from brown grease lipids (BGL). BGLs are the primary components of dewatered grease trap waste and sewage scum grease. It has recently been used as a low-value feedstock for biodiesel production; however, the S content of the resultant biodiesel is too high to meet industry specifications. The S-bearing compounds described herein do not exist in the MS library. Therefore, this project was devised to generate the analytical data

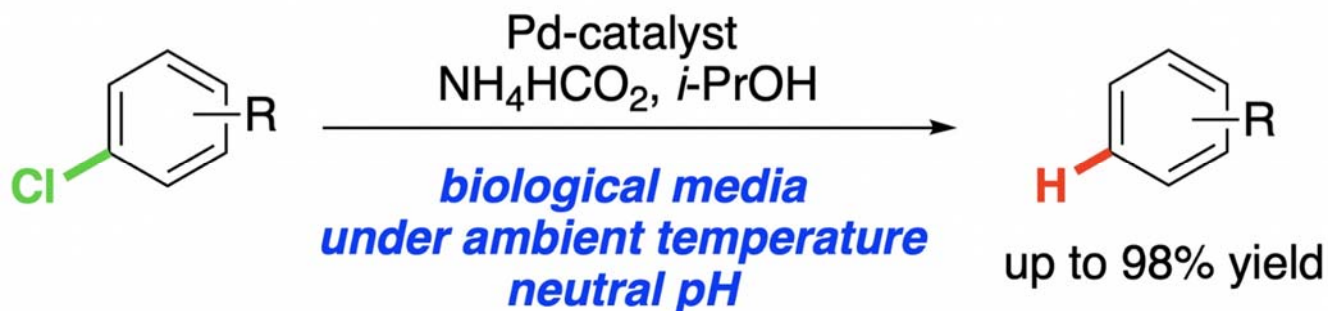
necessary to verify the existence of the S-bearing compounds presumed to exist in BGL-biodiesel. The identification of S-bearing compounds in BGL-derived biodiesel is necessary to devise effective desulfurization protocols needed to reduce the concentration of S-bearing impurities in biodiesel to < 15 ppm, as specified by ASTM.

ORGN 673

Hydrodechlorination of aryl chlorides in biological media at neutral pH, ambient temperature and pressure

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The hydrodechlorination of substituted aryl chlorides using a heterogeneous palladium catalyst and ammonium formate in biological media under physiological conditions at neutral pH, moderate temperature, and ambient pressure is presented. The reaction conditions were successful for a range of aryl chlorides with activating and deactivating groups, limited by solubility of substrate in aqueous media. Soluble substrates gave good yields (60-98%) of the reduction product within 24 hours. The relative toxicities of each reaction component were tested against bacteria, and we have found preliminary results for the hydro-dehalogenation in bacterial cultures containing aryl chlorides.



ORGN 674

Synthesis of anilium based ionic liquid and ionic liquid hydrates

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The interest for ionic liquid has been growing in the past decades to its promising application as a solvent and as an ionic liquid electrolyte. In this study, simple ionic liquid was

synthesized using varieties of aniline. The subtle changes in structure leads to a dramatic change in melting points. Physical properties and solid state structural characterizations were done to relate the crystal packing to its melting point. This presentation is a part of a Course-Based Undergraduate Research Experience (CURE) course where undergraduate students perform research lab as part of a curriculum.

ORGN 675

Reactions of disubstituted peroxides: Approach to the synthesis of strained bicyclic ethers

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The formation of strained bicyclic ethers, a substructure found in important natural products such as the clot inducing thromboxane A₂, remains a significant synthetic challenge. The purpose of this research is to evaluate and establish a new approach to bicyclic ethers via intramolecular reactions of carbanions with disubstituted peroxides. Previous research from our lab has demonstrated that this strategy, which reverses the polarity of traditional ether synthesis based upon reactions of oxygen nucleophiles and carbon electrophiles, can give high yields of monocyclic, spirocyclic, and bicyclic ethers with the focus of this research being the latter. Our investigations, which will initially employ a model series of substrates derived from the peroxidation of dihydrocarvone, will investigate the intramolecular reaction of enolates with various substituted peroxides as an approach to the bicyclic ether. The peroxide intermediate and bicyclic ether will be characterized using ¹H and ¹³C nuclear magnetic resonance, infrared spectroscopy, and mass spectrometry. The results gained in the model study will be applied to a model system for the synthesis of the core bicyclic ether ring structure of thromboxane A₂.

ORGN 676

Vanadium catalyzed oxidative regioselective homocoupling and trapping of alkenyl phenols to form lignan analogues

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The oxidative homocoupling of para-alkenyl phenols and subsequent trapping of the resulting quinone methide with a variety of common nucleophiles was demonstrated. Selectivity was achieved by thorough optimization of catalyst electronics, solvent conditions, and reaction concentration. A qualitative predictive model for the

regiochemistry of the coupling was synthesized based upon data from mechanistic experiments.

ORGN 677

Remarkable rate enhancement of acidic Boc cleavage by hexafluoroisopropanol (HFIP) and application to acid sensitive substrates

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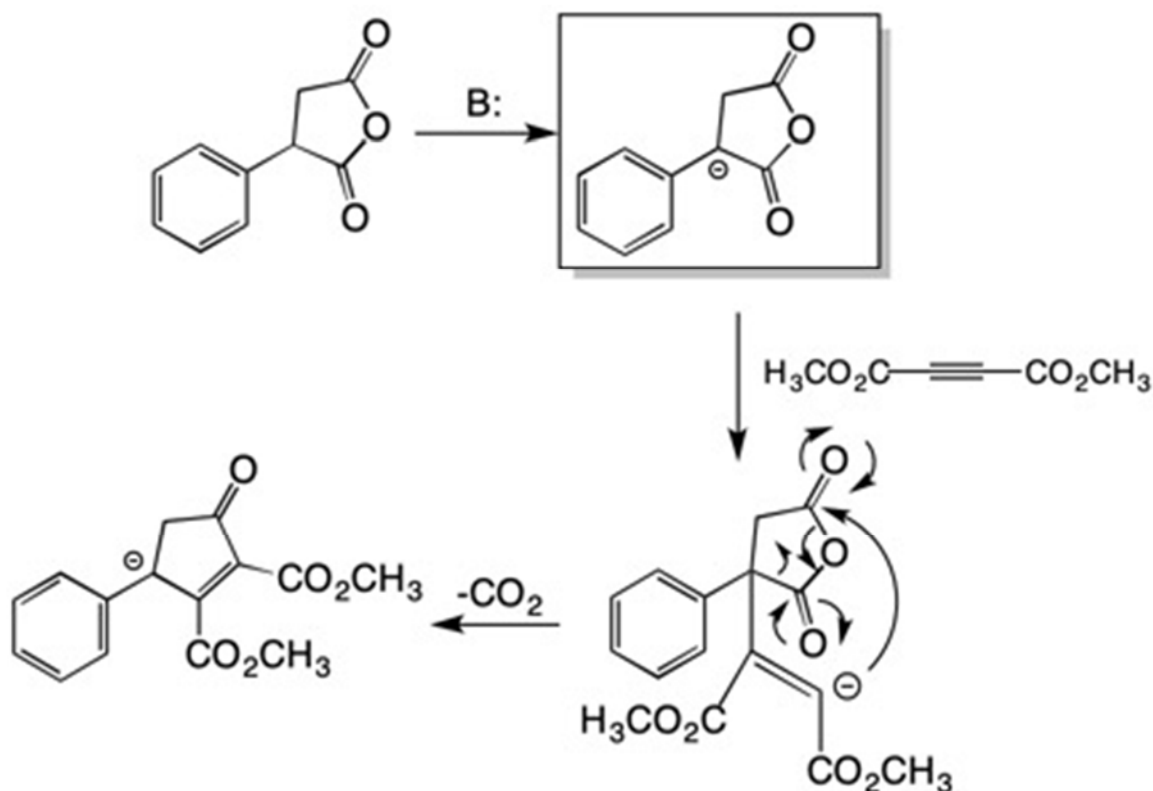
The solvent hexafluoroisopropanol affords remarkable acceleration of acid-catalyzed Boc cleavage and related reactions. This observation can be leveraged in the selective removal of the Boc group over other acid sensitive functionalities, including certain epoxides and silyl protecting groups, with stoichiometric acid. Acidic HFIP is also promotes cleavage of the amino PMB group and acetals.

ORGN 678

Reaction of phenylsuccinic anhydride with Michael acceptors

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This work details a study on the reaction of phenylsuccinic anhydride with Michael acceptors under basic conditions to afford highly substituted cyclopentanones. Our efforts to date will be discussed.



ORGN 679

¹⁸F-oxyfluorination of diazoketones by an electrophilic reagent

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Geminal ¹⁸F-oxyfluorination of diazoketones was performed using an electrophilic hypervalent iodine reagent and rhodium mediators. The reactions took place in short reaction times and mild reaction conditions. High radiochemical yields (up to 98%) and molar activity (296 GBq/mmol) were obtained.

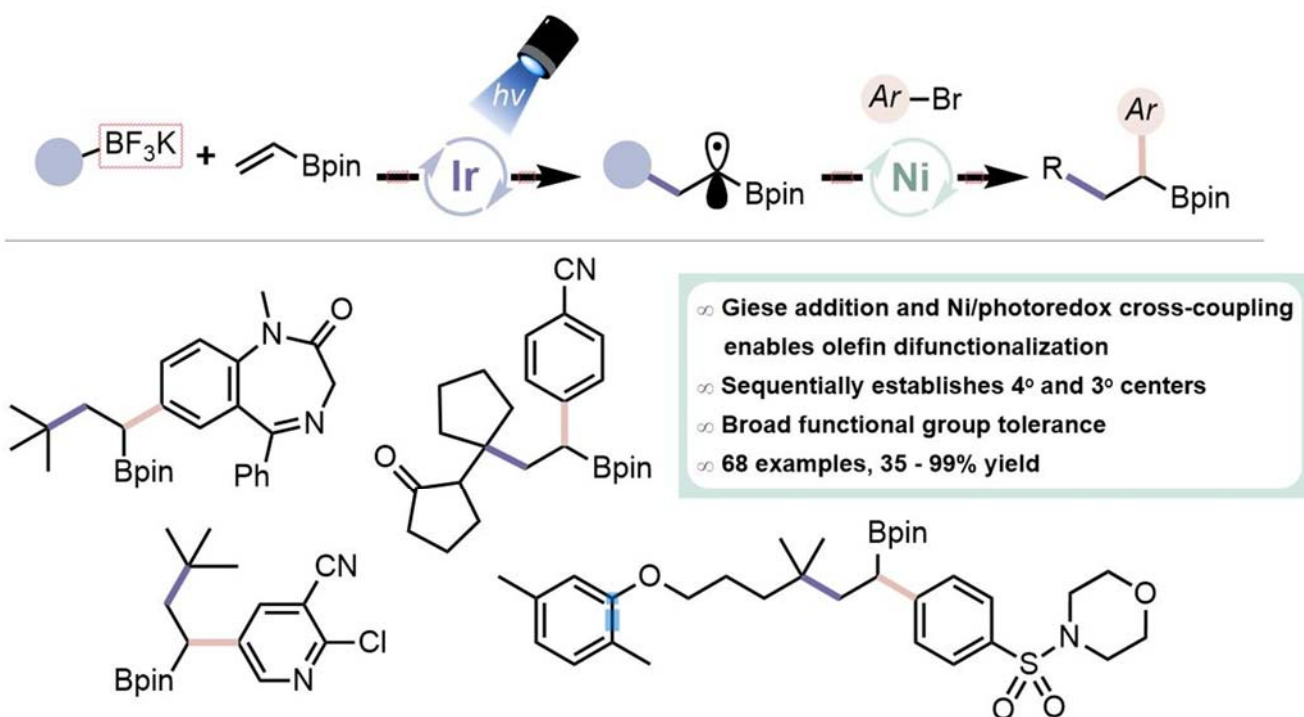
ORGN 680

Three-component olefin dicarbofunctionalization enabled by nickel/photoredox dual catalysis

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Pennsylvania, United States (2) Chemistry, Virginia Commonwealth University, Richmond, Virginia, United States (3) Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States

An intermolecular, photocatalytic dicarbofunctionalization (DCF) of olefins enabled by the merger of Giese-type addition with Ni/photoredox dual catalysis has been realized. Capitalizing on the rapid addition of 3° radicals to alkenes and their reluctance toward single electron metalation to Ni complexes, regioselective alkylation and arylation of olefins is possible. This dual catalytic method not only permits elaborate species to be assembled from commodity materials, but also allows quaternary and tertiary centers to be installed in a singular, chemoselective olefin difunctionalization. This technology was directly applied to the synthesis of an intermediate to a preclinical candidate (TK-666) and its derivatives.



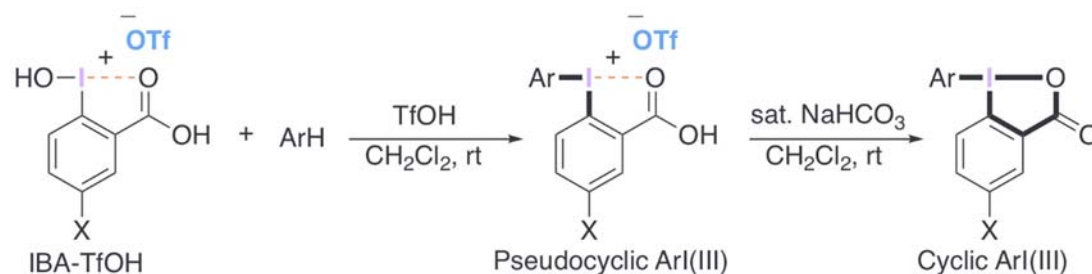
ORGN 681

Preparation of benziadoxolone-based diaryliodonine(III) compounds

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Russian Federation (3) Marshall School, Duluth, Minnesota, United States (4) Tokyo University of Agriculture and Technology, Tokyo, Japan (5) Department of Chemistry and Biochemistry, University of Minnesota Duluth, Duluth, Minnesota, United States

Diaryliodine(III) salts are versatile reagents and well investigated compounds in organic synthesis. Most of diaryliodine(III) compounds can be prepared from hypervalent iodine(III) reagents with arenes under oxidative reaction conditions. Recently, our group reported the synthesis and structural investigation of a new active hypervalent iodine(III) species, 2-[hydroxy(trifluoromethanesulfonyloxy)]-iodobenzoic acid (IBA-TfOH), which was prepared by the treatment of 2-iodosylbenzoic acid with trifluoromethanesulfonic acid, and the prepared reagent could be used as an oxidant for many substrates. Herein, we report a synthesis and structural investigation of pseudocyclic diaryliodine(III) salts, which can be prepared from IBA-TfOH and arenes in the presence of trifluoromethanesulfonic acid. Prepared pseudocyclic diaryliodine(III) salts can be converted to the cyclic diaryliodine(III) compounds.



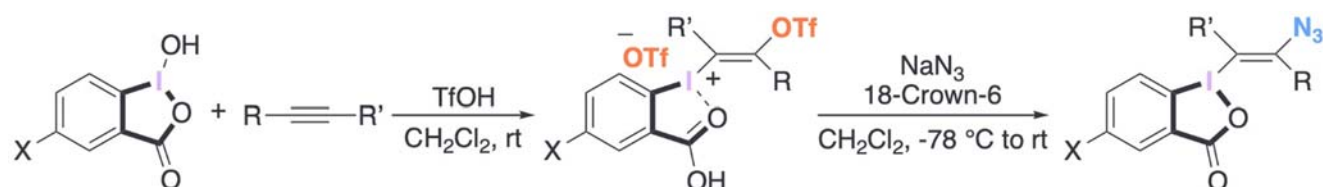
ORGN 682

Preparation of benziodoxolone-based vinyl iodine(III) compounds

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Vinyl iodine(III) compounds are versatile reagents that can be used as efficient synthons for: i) vinylic nucleophilic substitution, ii) α -elimination reaction, iii) Michael addition, and iv) ligand coupling. Numerous preparation methods and reactivity of vinyl iodine(III) compounds have been reported. However, the preparation and reactivity of

pseudocyclic vinylidene(III) compounds have not been previously investigated. Herein, we report a synthesis and structural investigation of pseudocyclic vinylidene(III) compounds, which can be prepared from 2-iodosylbenzoic acid and alkyne in the presence of trifluoromethanesulfonic acid. Prepared pseudocyclic vinylidene(III) compounds can be converted into the cyclic vinylidene(III) compounds.



ORGN 683

Preparation of chiral biaryl compounds via an asymmetric dimerization reaction

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Biaryl atropisomers are particularly valuable chiral scaffolds in numerous natural products and biologically active molecules. They have also been widely used as chiral ligands or auxiliaries in asymmetric synthesis. Due to their great importance, substantial efforts have been made in the past decades to developing methods for efficient synthesis of axially chiral biaryls. In spite of several reports including metal-catalyzed and organo-catalytic processes for making biaryl atropisomers, straightforward synthetic routes to axially chiral biaryls in high enantiomeric purity that do not rely on resolution still remain scarce. Within this regard, the transition metal-catalyzed asymmetric dimerization of simple aromatic substrates for the efficient construction of axially chiral biaryl compounds is described. The development of the reaction conditions and the scope of this new process will be discussed.

ORGN 684

Synthesis of highly functionalized piperidines via arylation of aza-Achmatowicz rearrangement products

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The first Pd-catalyzed arylation of Aza-Achmatowicz rearrangement products with arylboronic acids is achieved, providing versatile 2-aryldihydropyridinones (>26

examples) for facile synthesis of medicinally valuable, highly functionalized 2-arylpiperidines. Enantiomerically pure 2-aryldihydropyridinones can be obtained by either kinetic resolution with Noyori asymmetric transfer hydrogenation or highly diastereoselective arylation of chiral C6-substituted dihydropyridinones derived from Aza-Achmatowicz rearrangement of enantio-enriched furfuryl carbamates.

ORGN 685

New bicyclo[1.1.1]pentanes via anionic reactivity of [1.1.1]propellane

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To optimize the performance of bioactive molecules, medicinal chemists must fine-tune drug properties such as water solubility, metabolic stability, and permeability through the cell membrane. Towards this goal, bicyclo[1.1.1]pentanes (BCPs) have recently attracted significant attention as bioisosteres of benzene rings, an abundant feature in drug molecules. Despite three decades of literature on the synthesis of BCPs, efficient methods to incorporate them into target drug molecules are limited. In our effort to prepare BCP analogues of ubiquitous diaryl methylamines ($\text{Ar}_2\text{CH-NH}_2$), we have discovered new reactivity of [1.1.1]propellane, the highly strained parent structure from which many BCPs are derived. 2-Azaallyl anions, which are derived from *N*-benzyl ketimines, add reversibly with [1.1.1]propellane. Though this equilibrium lies far to the side of the 2-azaallyl anion, protonation of the BCP anion drives reactivity forward to enable C—C bond formation at room temperature with no external additives. This principle of anionic “propellerization” can be extended to the reaction of other pronucleophiles with [1.1.1]propellane as well as to the synthesis of 1,3-difunctionalized BCPs.

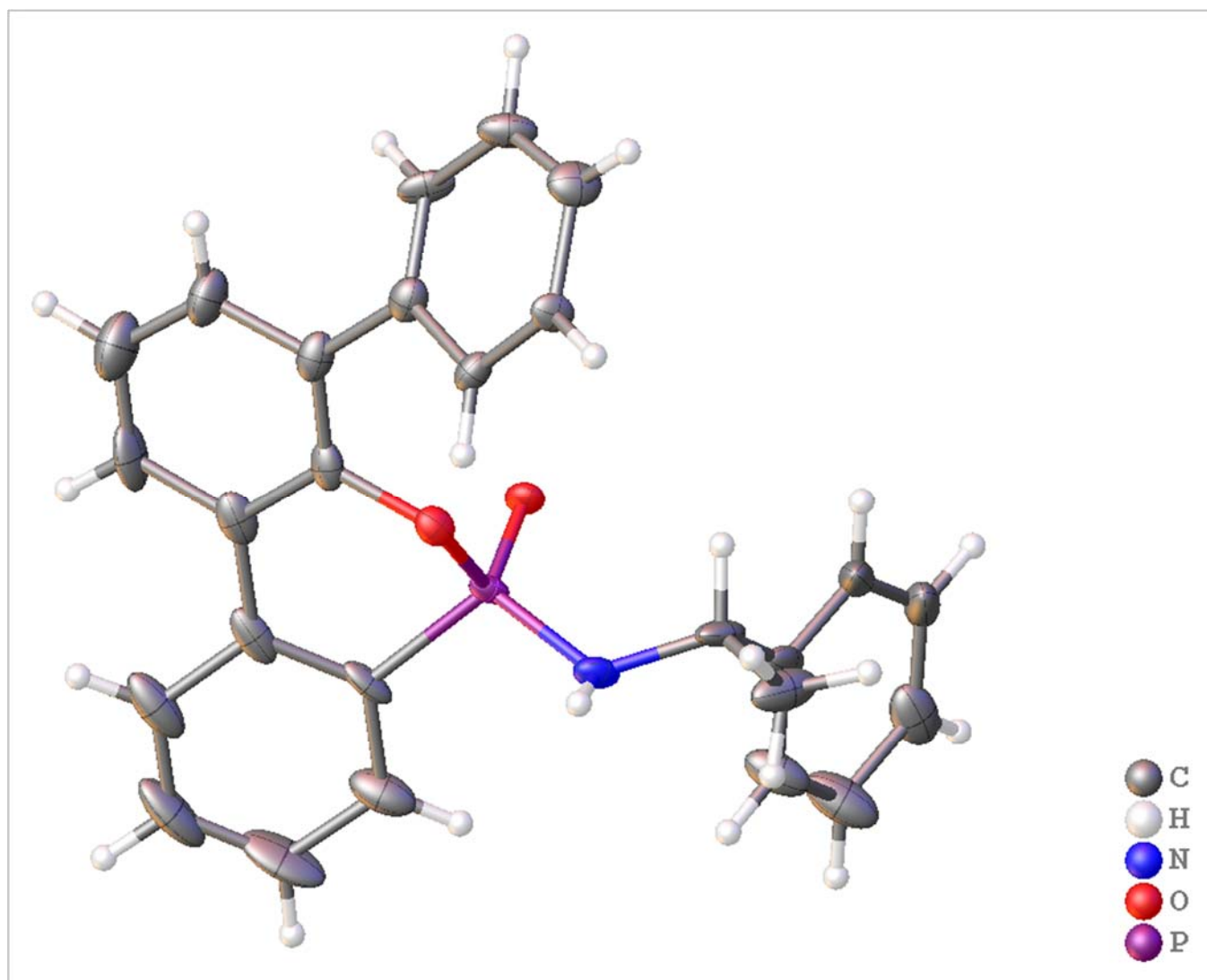


ORGN 686

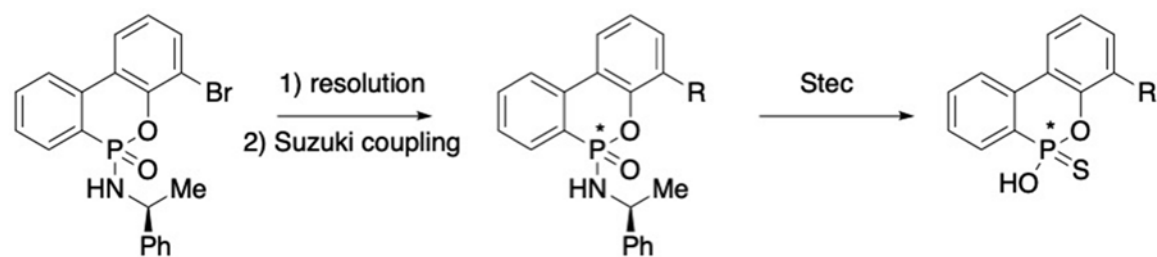
Methodology for the synthesis of thiophosphorus acids P(S)OH via amides

Karen Winters¹, *k.winters@tcu.edu*, **Jean L. Montchamp**². (1) Chemistry and Biochemistry, Texas Christian University, Fort Worth, Texas, United States (2) Chemistry, Texas Christian Univ, Fort Worth, Texas, United States

The Stec-Wadsworth-Emmons reaction is a powerful transformation which allows the synthesis of thiophosphorus acids $P(S)OH$ from $P(O)NH$ via deprotonation, then reaction with carbon disulfide. The reaction is stereospecific and has been extensively employed by Stec in nucleotide chemistry. However this transformation's scope has never been fully explored to its maximum potential. We explored the effects of the substituents at phosphorus, the effects of the amine, bases and other conditions. Using a chiral amine as the nitrogen source allows for 1) the chirality to be introduced late in the synthesis to get both enantiomers, 2) a straightforward resolution, and 3) avoid the use of thionating agents that often have difficult purification steps and/or a stench. DOPO (9,10- dihydro-9-oxa-10-phosphaphenanthrene-10-oxide) derived chiral phosphorus acids were easily obtained by using inexpensive chiral 1-phenylethylamine as the nitrogen source. These phosphorus acids will be tested as novel chiral Brønsted organocatalysts.



(R = Ph)



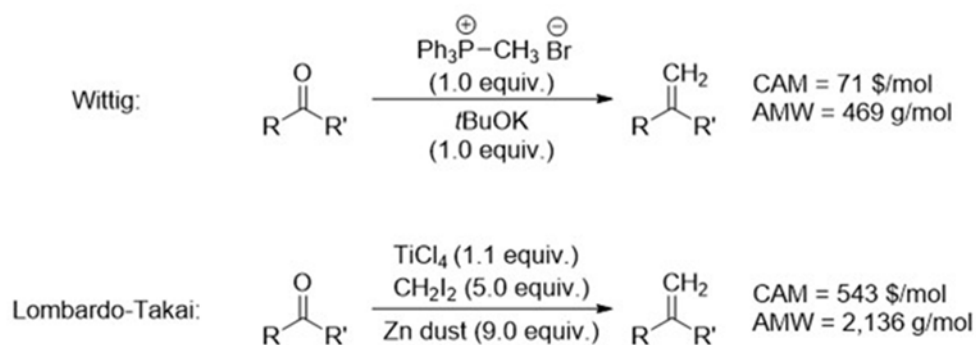
Scheme: DOPO-Based Chiral Phosphorus Acids

ORGN 687

On the cost of academic methodology

Axel Sabourin¹, *a.sabourin@tcu.edu*, **Jean L. Montchamp²**, **Sergei V. Dzyuba³**, **Karen Winters⁴**, **Olivier Berger¹**. (1) Chemistry & Biochemistry, Texas Christian University, Fort worth, Texas, United States (2) Chemistry, Texas Christian Univ, Fort Worth, Texas, United States (3) Department of Chemistry, Texas Christian University, Fort Worth, Texas, United States (4) Chemistry and Biochemistry, Texas Christian University, Fort Worth, Texas, United States

The cost of reagents and catalysts employed in synthetic methodologies developed in academia is very rarely discussed. Yet these costs are very real as they represent a significant portion of any grant proposal budget. The Cost of Academic Methodologies (CAM) is a novel concept, which should be considered when evaluating synthetic methodologies. CAM will allow for one to quantitatively evaluate a particular synthetic methodology that prepares a particular product. CAM will allow for a comparison among distinctly different reactions conditions, reagents, catalytic versus stoichiometric systems, etc. We also introduce an associated concept: Aggregate Molecular Weight (AMW). Cost considerations are almost always avoided in academic publications; however, CAM is a parameter that can be useful to gauge seemingly non-comparable methodologies. Unlike specious or poorly-defined considerations often seen in manuscripts, such as “harshness” of conditions, “metal-free”, “precious metals are expensive”, etc., the CAM/AMW parameter is a real, tangible two-point criterion of academic methodologies, which is applicable to any chemical reaction.



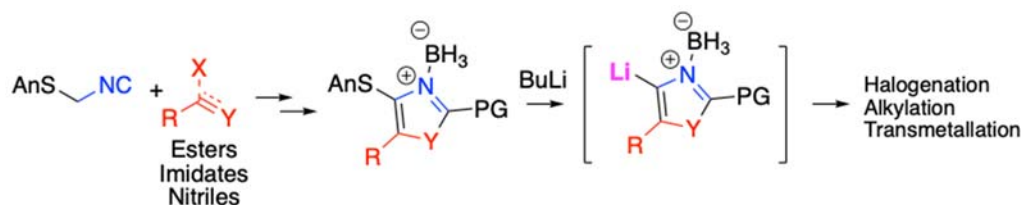
Scheme: CAM and AMW comparison of Wittig olefination and Lombardo-Takai olefination

ORGN 688

Asmic-based synthesis of tri-substituted oxazoles and imidazoles

Louis Mueller¹, lomueller.jr@gmail.com, **Allen Chao**², **Embarek F. Alwedi**¹, **Maanasa Natrajan**¹, **Fraser F. Fleming**¹. (1) Chemistry, Drexel University, Philadelphia, Pennsylvania, United States (2) Wistar Institute, Philadelphia, Pennsylvania, United States

Anisylsulfanylmethylisocyanide (**Asmic**) is a valuable building block that has been used to access a diverse range of trisubstituted isocyanides. In this work, Asmic was sequentially deprotonated and trapped with esters to prepare oxazoles. An analogous deprotonation-trapping sequence using imidates or nitriles afforded imidazoles. The oxazoles and imidazoles bear an anisylsulfanyl group which serves as an excellent handle for introducing an additional substituent to the heterocycles. We demonstrated a first-in-class sulfur-lithium exchange reaction that generates a lithiated heterocycle which can be trapped with an array of electrophiles. This sulfur-lithium exchange provides a short, efficient method to selectively control all three substituents on oxazoles and imidazoles. We will discuss the scope of the method as well as the discovery of a unique role of borane in activating the heterocycles for lithiation.



ORGN 689

Synthetic studies on peganine A and B

Katelyn A. Leets, kaleets@syr.edu, **John D. Chisholm**. Chemistry, Syracuse University, Syracuse, New York, United States

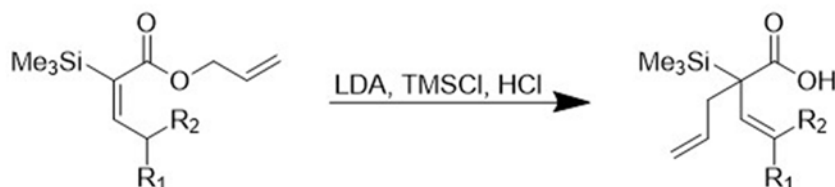
Recently the pyrroloindoline natural products peganine A and B were isolated from the seeds of *Peganum harmala*. These pyrroloindolines have an unusual carbon skeleton with a methyl group at C2 of the pyrroloindoline core. To access these natural products a new method for the synthesis of pyrroloindolines that are oxygenated at the C3a was developed utilizing an oxidative cyclization of tryptamines employing the oxoammonium salt 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate. This oxidizing agent effectively cyclizes tryptamine derivatives to access the core structure of the peganine natural products as well as a number of other pyrroloindolines. The substrate scope of the oxidative cyclization and its application to the synthesis of the peganines will be described.

ORGN 690

Stereoselective synthesis of quaternary centers via an Ireland-Claisen rearrangement of (E)- α -trialkylsilyl- β -alkyl- α,β -unsaturated esters

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Sigmatropic rearrangements provide a reliable and predictable method for the stereoselective construction of carbon-carbon and carbon-hetero bonds in a large collection of natural products. Specifically, the Ireland-Claisen rearrangement makes use of strong bases for the kinetic deprotonation of allyl esters and subsequent conversion to β,γ -unsaturated carboxylic acids via a silyl-stabilized enolate which rearranges into a silyl ester that undergoes hydrolyzation during workup. Using said method allows for the transformation of (E)- α -trialkylsilyl- β -alkyl- α,β -unsaturated esters into α -allyl- α -trialkylsilyl- γ -alkyl- β,γ -unsaturated carboxylic acids which serve as precursors for a multitude of polyfunctionalized structures.



Ireland-Claisen rearrangement of unsaturated esters into unsaturated carboxylic acids

ORGN 691

Copper-catalyzed propargylation of nitroalkanes: Homopropargylic nitroalkanes as synthons to five-membered N-heterocycles

Raphael S. Kim¹, *raphsk9@gmail.com*, **Linh V. Dinh-Nguyen**¹, **Kirk W. Shimkin**¹, **Donald A. Watson**². (1) University of Delaware, Newark, Delaware, United States (2) Chemistry/Biochemistry, University of Delaware, Newark, Delaware, United States

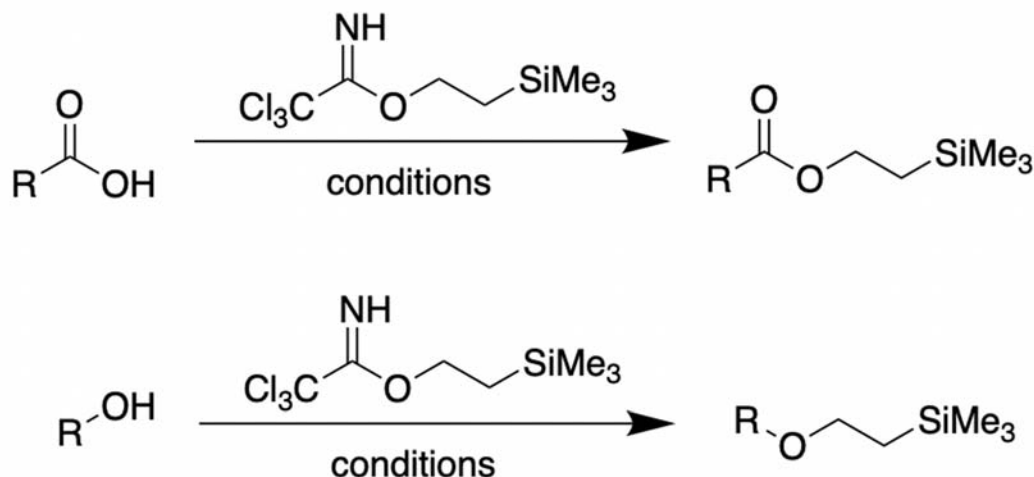
Under a commercially available, inexpensive, and abundant copper-catalyst system, an efficient C-alkylation of nitroalkanes with propargyl bromides is now established. This mild and robust method is highly functional group tolerant and provides a simple access to complex secondary and tertiary homopropargylic nitroalkanes. Moreover, the usefulness of these α -propargylated nitroalkanes is demonstrated through downstream functionalization to biologically relevant, five-membered N-heterocycles such as pyrroles and 2-pyrrolines.

ORGN 692

Esterification and etherification with 2-(Trimethylsilyl)-2,2,2-Trichloroacetimidate

Wenhong Lin¹, wlin11@syr.edu, **Shea Meyer**¹, smeyer@syr.edu, **Shawn Dormann**³, **John D. Chisholm**². (1) Chemistry, Syracuse University, Syracuse, New York, United States (3) Syracuse University, Syracuse, New York, United States

2-(Trimethylsilyl)ethyl esters and ethers have served as effective protecting groups throughout organic chemistry. Their prevalent use can be attributed to their stability under acidic conditions and their relative ease of deprotection with fluoride sources. An investigation into the alkylation activity of 2-(trimethylsilyl)ethyl-2,2,2-trichloroacetimidate (TMSEtlm) was undertaken. TMSEtlm is a bench stable reagent and is easily synthesized from 2-(trimethyl)silylethanol and 2,2,2-trichloroacetamide in excellent yields. This imidate offers an effective reagent for the formation of 2-trimethylsilylethyl esters and 2-trimethylsilylethyl ethers. The substrate scope and optimal conditions for formation of these protecting groups will be presented.

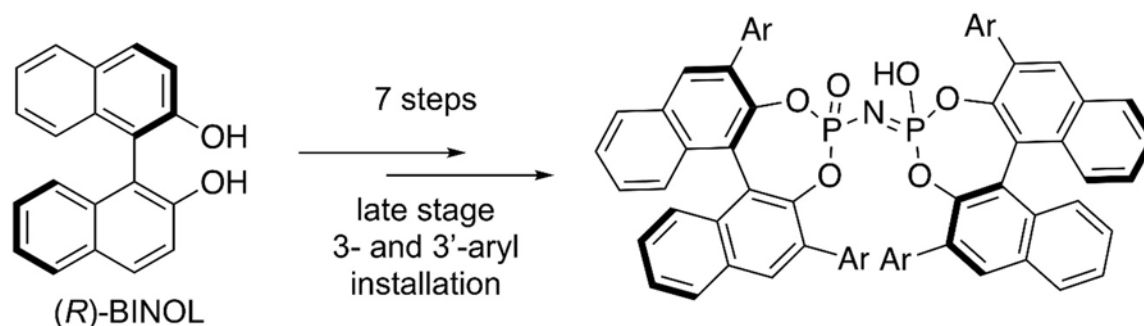


ORGN 693

Progress toward late-stage functionalization of chiral bisphosphorylimides using Suzuki cross-coupling reactions

Amanda Smolin, smoli001@cougars.csusm.edu, **Robert G. Iafe**. Chemistry & Biochemistry, California State University San Marcos, San Marcos, California, United States

Conformationally restricted bisphosphorylimides derived from readily available 1,1'-bi-2-naphthol (BINOL) are highly effective in asymmetric catalysis, however access to a diverse suite of 3- and 3'-substituted bisphosphorylimides for reaction optimization is labor-intensive and expensive. Late stage functionalization of these catalysts would be advantageous for reaction investigations. Our lab has developed a rapid process to access different 3- and 3'-aryl-substituted bisphosphorylimide catalysts starting from (*R*)-BINOL utilizing Suzuki-Miyaura reaction methodology at the final step. We have chosen sterically demanding aryl groups to optimize the protocol. Details and example substrates will be described in detail.



ORGN 694

N-*tert*-butanesulfinyl metallodienamine in different methodologies

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The omnipresent technique that has been used in organic chemistry to generate C-C bond is reaction between two carbon centers of different 'philicity', one of the common example would be alkylation of enolates. Enolates are the most widely explored nucleophilic carbon source. But the shortcomings with enolates are their high reactivity hence they are less selective and sometimes they undergo self-condensation. The discovery of enamine and metalloenamine posed as the solution of the high reactivity hence less selectivity of the enolates. Extensive investigation on the chemistry of enamines and metalloenamine had been done in the past after the discovery of those reactive intermediates. Different methodologies had been developed with these species by varying the electrophiles as well as the substrates. *N*-*tert*-butanesulfinyl metallodienamine are interesting reactive intermediates, where N is attached to a chiral

sulfur which directs the stereochemistry of incoming electrophile and also the imine serves as a latent amine or in the later steps it can be interconverted to other functionality. In 2013 we reported a methodology of annulation through a Domino-Michael-Mannich fashion with the *N*-*tert*-butanesulfinyl metallodienamine derived from 2-methyl-1H-indole-3-carbaldehyde resulting tetrahydrocrazole moiety with two contiguous stereocenters which maps onto core structure of *Aspidosperma* alkaloids. We also reported vinylogous aldol reaction on *N*-*tert*-butanesulfinyl metallodienamine. The work expanded to oxidation of the metallodienamines by Davis oxaziridine and dioxxygen on which most of my work is focused. We found out that if we change the base from LiHMDS to NaHMDS to KHMDS the diastereoselectivity increases drastically and most interestingly the stereochemistry gets inverted. We are still working on the substrate scope of this methodology. Also we investigated the efficacy of dioxxygen opposed to Davis oxaziridine in the oxidation of metallodienamine. We investigated the amination reaction on metallodienamine with DIAD which we found out extensively goes to gamma. We are currently working on the substrate scope and the natural product on which we can apply these methodologies.

ORGN 695

Double allylboration reagent for the synthesis of chiral diols

Belinda Hetzler², beh302@nyu.edu, **Giulio Volpin**¹, **Dirk Trauner**². (1) Bayer AG, Dr. Giulio Volpin, Germany (2) New York University, New York, New York, United States

In target-oriented chemical synthesis, the encounter of challenging transformations often leads to the necessity to develop new methodologies, and such contributes as a large driving force to chemical innovation. The use of multifunctional reagents that display chemodivergent reactivity are of great interest for the preparation of novel organic compounds due to the rapid access to complexity. Allylboron reagents are widely employed in the transfer of an allyl group to carbonyl compounds owing to their configurational stability, predictable stereoselectivity and tunable reactivity. Here, we report the development of a bis-allyl boronate reagent that can be synthesized on a large scale in a single-step procedure. We show that the mono-allylation can be carried out asymmetrically under phosphoric acid catalysis. The reagent can be transformed in-situ to the more reactive bis-borinic ester, allowing allylation of two aldehydes. The second allylation step shows substrate-dependency and gives C₁- or C₂-symmetric products. We apply this methodology towards the synthesis of strained alkaloids to investigate congeners with previously inaccessible stereoconfigurations.

ORGN 696

Lewis acid promoted dialkylation of indoles with trichloroacetimidates for the Synthesis of 3,3'-disubstituted indolenines

Nilamber Mate, namate@syr.edu, **Tamie Suzuki**, **Arijit Adhikari**, **John D. Chisholm**. Chemistry, Syracuse University, Syracuse, New York, United States

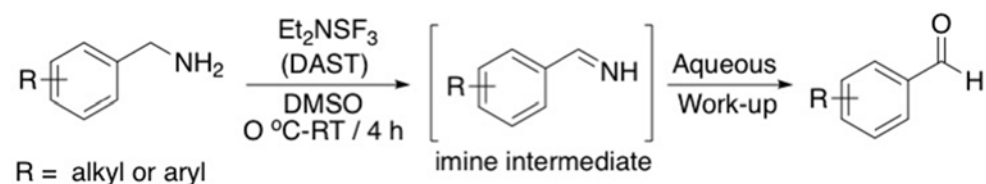
3,3-Dialkyl indolenines and related structures are widely present in the natural products and medically relevant structures. Here we report a new method for converting 2-substituted indoles to 3,3-dialkyl indolenines using trichloroacetimidate electrophiles and a Lewis acid such as TMSOTf. This method furnishes a cost effective and facile alternative to the use of transition metal catalysis. The 3,3'-indolinines are readily transformed into 3,3'-spiroindoline systems which are privileged nonplanar scaffolds often utilized in medicinal chemistry studies.

ORGN 697

Oxidative deamination of benzyl amines to carbonyl compounds promoted by (Diethylamino)sulfur trifluoride (DAST)

Ricardo Belloso, *rb21879@georgiasouthern.edu*, **Mohammed A. Lnu**. Department of Chemistry, Georgia Southern University, Statesboro, Georgia, United States

Amine oxidation is a potent tool for the production of a broad range of synthetic intermediates, such as imines, amides, oximes, nitro compounds, nitriles, aldehydes, and ketones. The conventional route to aldehydes and ketones involves the oxidation of primary and secondary alcohols, alternatively, the synthesis of carbonyl compounds could be achieved from readily available and abundant precursors like amines. Herein, we report an efficient protocol for oxidation of benzyl amines to corresponding aldehyde or ketone. Our new method involves use of commercially available (diethylamino)sulfur trifluoride (DAST) as reagent combined with DMSO as solvent and oxidant. The reaction provided carbonyl compounds in excellent yields with high purity and short reaction times. All the reactions were carried out in a screw-cap glass vial at ambient temperature without maintaining moisture-free or inert conditions. In all cases, formation of the corresponding carbonyl compounds was observed exclusively without any traces of carboxylic acid as further oxidation product.



ORGN 698

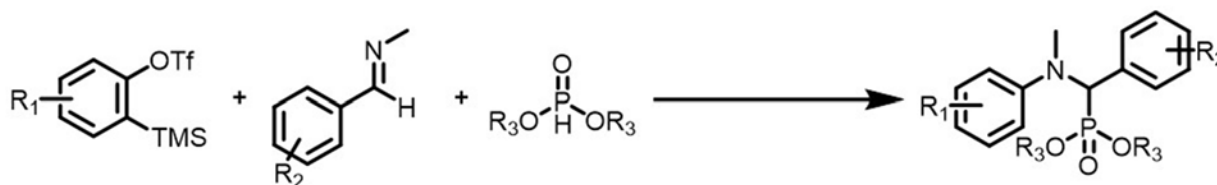
Aryne-mediated phosphorylation of imines with dialkyl phosphites

TAEHYUN LIM, *hyun722@snu.ac.kr*, **Byeongmoon Kim**. Seoul National University, Seoul, Korea (the Republic of)

Organophosphorus compounds are becoming increasingly useful in many applications such as industrial, agricultural and medicinal chemistry. In particular α -aminophosphonic acids and esters are structurally analogous to peptidomimetic compounds possessing diverse biological activities such as enzyme inhibition and antibiotic activities.

A number of methods have been developed for the synthesis of α -aminophosphonates. Lewis acid or transition metal catalysts containing [Rh], [Co] and others have recently attracted much attention. However, those methods require harsh reaction conditions and use of toxic metal catalysts.

To improve these methods, we envisioned the use of arynes as a part of a new synthetic pathway. In this work, we have developed a multicomponent phosponylation reaction without using metal-based reagents, which is a three-component coupling system involving arynes, imines and dialkyl phosphites. This method provides a more efficient and mild procedure applicable to various substrates, which obviates the use of transition metal-based reagents. A plausible mechanism is as follows: an iminium zwitterion, generated from a nucleophilic addition of an imine to an aryne abstracts a proton from a dialkyl phosphite in the reaction. Then the phosphite anion adds to the iminium ion to form α -aminophosphonates. Also, we have found an evidence for the nucleophilic addition of a deprotonated phosphite to an iminium intermediate using a deuterium isotope study.



ORGN 699

Direct nucleophilic aromatic substitution of 2-halo-*N*-(1-ethoxyvinyl)pyridinium salts with *N*- and *O*-nucleophiles

Alisha M. Blades, ablades@hamilton.edu, **Danielle McConnell**, dmcconne@hamilton.edu, *Ashley Thayaparan*, *Max M. Majireck*. Chemistry, Hamilton College, Clinton, New York, United States

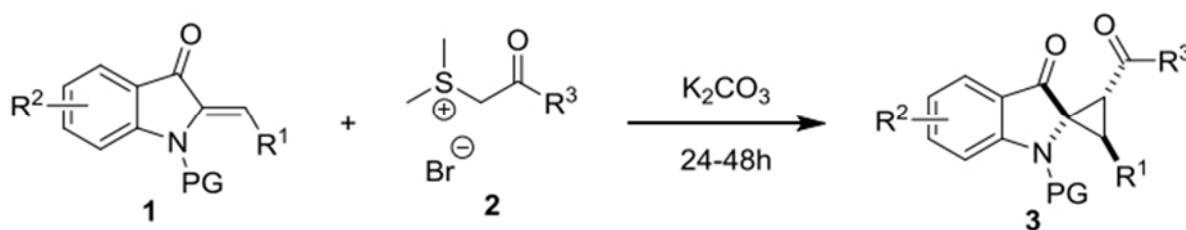
A variety of amine, alcohol, and related *N*- and *O*-nucleophiles can participate in room-temperature S_NAr reactions with readily prepared and bench-stable 2-halo-*N*-(1-ethoxyvinyl)pyridinium salts. This procedure adds to the repertoire of synthetic methods for production of bioactive 2-aminopyridine and 2-alkoxypyridines, but offers notable advantages including a simple protocol, mild conditions, and avoidance of transition metals, coupling reagents, and their persistent impurities.

ORGN 700

Efficient synthesis of cyclopropane-fused spiro-pseudoindoxyl derivatives through highly diastereoselective [2 + 1] annulation

Xue Tang, *xuexuetang92@163.com*, Wei Huang, Cheng Peng. Chengdu University of Traditional Chinese Medicine, Chengdu, China

Spirooxindole is an important scaffold found frequently in natural products and biologically active molecules. Easy construction of spirooxindole derivatives with simple starting material is significant for natural product synthesis, drug discovery and biomedical research. Compared with the intensively studied C3 spirooxindoles, the development of reliable approaches for the formation of a structurally analogous spiro-pseudoindoxyl scaffold containing a spirocyclic quaternary carbon center at the C2 position is finite. We have learned that sulfur ylides as excellent synthons are widely used for the construction of aziridines or cyclopropanes with imines or electron-deficient olefins. We hypothesize that sulfur ylides can readily react with easily available (Z)-2-ylideneoxindoles to assemble a spirocyclopropane moiety at the C2-position of indole through 1,4-addition/substitution cyclization. Here, we report our development of a mild and efficient method for diastereoselective synthesis of cyclopropane-fused C2-spiro-pseudoindoxyl derivatives.



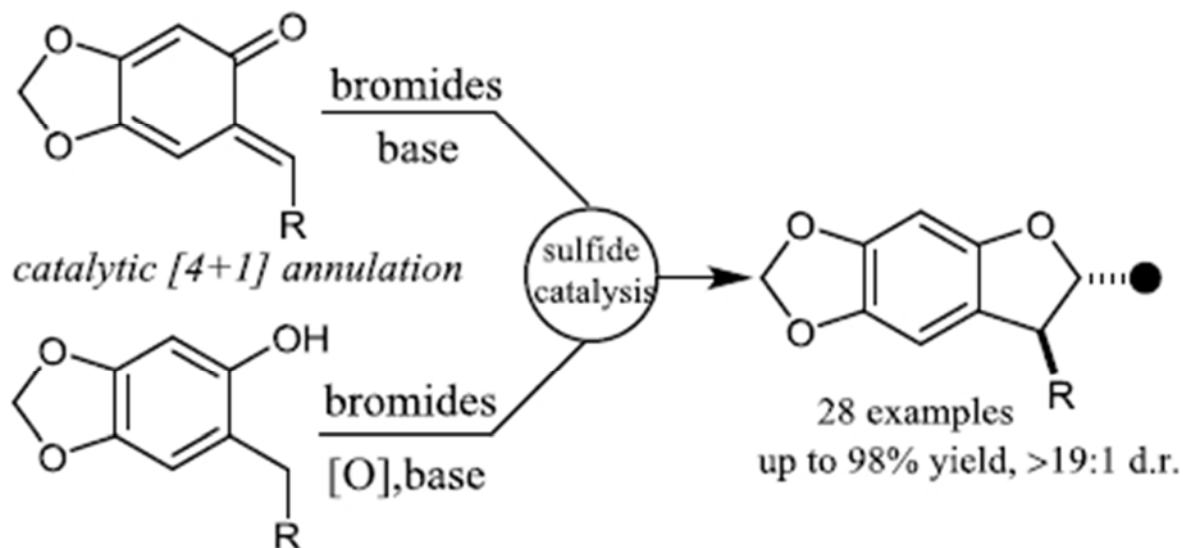
25 examples, up to 88% yield, > 20:1 dr

ORGN 701

Diastereoselective [4+1] annulations of ortho-quinone methides and bromides via direct sulfide catalysis

Yanqing Liu¹, lyq82893@163.com, Qingzhu Li², Cheng Peng¹, Junlong Li², Bo Han¹.
(1) Chengdu University of Traditional Chinese Medicine, Chengdu, China (2) Chengdu university, Chengdu, China

It is one of the most attractive objectives of modern organic synthetic chemistry to develop an efficient catalytic technology for previously noncatalytic reactions. Sulfur ylide chemistry as a powerful tool is pervasively applied to various cyclization reactions, especially the synthesis of three-membered carbo- and heterocycles. For the past few years, a smart and efficient strategy that sulfides are directly used as organocatalysts in ylide-mediated cyclization has attracted considerable attention of chemists and it has become an emerging topic in organic chemistry research. In our previous work, we have successfully developed an environmentally friendly and facile method to synthesis functionalized cyclopropanes through the direct sulfide-catalyzed cyclopropanation of electrondeficient dienes. In view of our continued interest in direct sulfide organocatalysis, we desire to extend our synthesis method from the established [2+1] cyclization to an unprecedented catalytic [4+1] annulation. Here, we report an unprecedented sulfide-catalyzed diastereoselective [4+1] annulation of (in situ generated) ortho-quinone methides and bromides. Meanwhile, we have performed the catalytic reaction under oxidative conditions and there was no significantly affection about the reaction outcome which demonstrated the robustness of such sulfide organocatalysis.

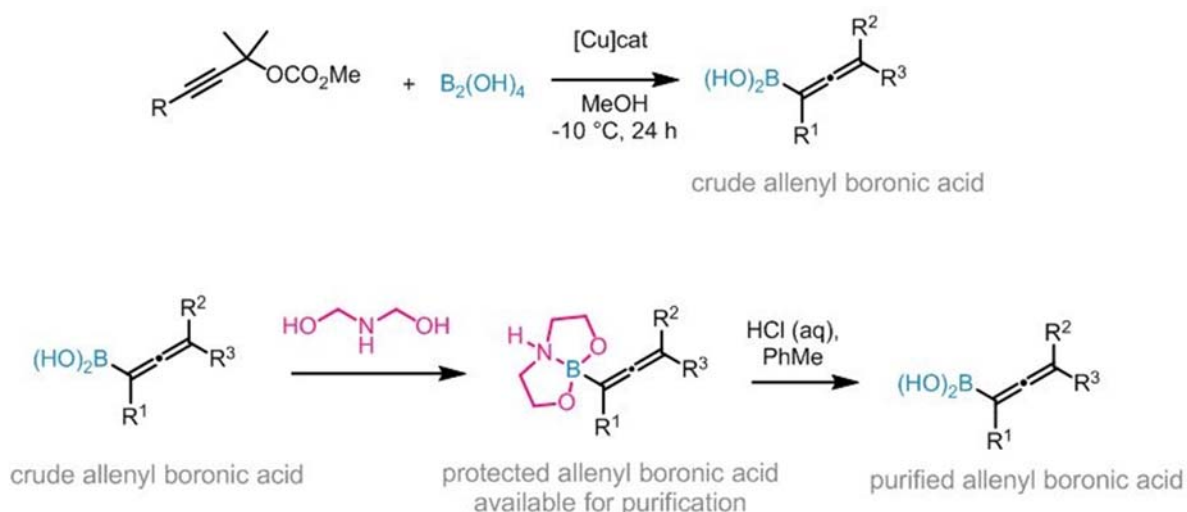


ORGN 702

Synthesis and purification of oxygen sensitive allenyl boronic acids

Sybrand Jonker, sybrand.jonker@su.se, Jian Zhao, Denise N. Meyer, Göran Schulz, Duc Tran, Lars Eriksson, Kálmán Szabó. Stockholm University, Stockholm, Sweden

A procedure has been developed for the preparation of tri- and tetrasubstituted allenylboronic acids using a copper catalyst. These oxygen sensitive boronic acids can be purified after protection with diethanol amine. Subsequent hydrolysis of the protection group results in free boronic acid.



ORGN 703

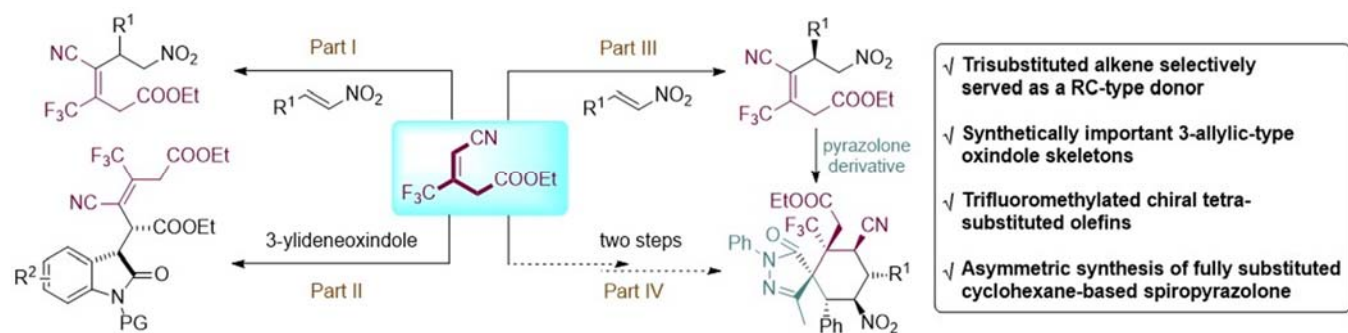
Chemo- and stereo-selective cross Rauhut-Currier-type reaction of tri-substituted alkenes: Synthesis of trifluoromethyl-containing tetra-substituted olefins

Xiang-Hong He¹, hexianghong0806@sina.com, Qian Zhao², Bo Han¹, Cheng Peng¹.

(1) Chengdu University of TCM, Chengdu, China (2) State Key Laboratory of Southwestern Chinese Medicine Resources, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Trifluoromethyl (CF₃) is a privileged structural motif playing a crucial role in many drugs, so organic chemists continue to spend considerable efforts on constructing CF₃-containing organic compounds. On the other hand, the Rauhut-Currier (RC) reaction is an efficient, atom-economic approach to multi-substituted alkenes and has been applied

to the synthesis of several biologically important targets and natural products. Much more challenging is the so-called 'cross Rauhut-Currier reaction' between two different activated alkenes, which normally proceeds with poor selectivity. Previous studies have demonstrated that 1,2,2-tri-substituted alkenes are poor donors in cross RC reactions, which means that few methods exist to generate tetra-substituted RC-type products. Herein, a chemoselective cross Rauhut-Currier-type reaction has been developed involving a trifluoromethyl-containing tri-substituted alkene and a di- or tri-substituted alkene to yield tetra-substituted double bonds in RC-type products. This approach can support the synthesis of trifluoromethylated tetra-substituted olefins and synthetically important, structurally complex 3-allylic-type oxindole skeletons. The asymmetric version of this RC-type reaction can be realized by combining a Brønsted acid and Lewis base for bifunctional H-bonding-tertiary amine catalysis. Subsequent transformation of multi-functionalized RC-type product leads to pharmacologically interesting cyclohexane-based spiro-pyrazolones bearing six contiguous chiral centers and two highly congested, vicinal quaternary carbon centers.



ORGN 704

TFA mediated preparation of S-aryl thiosulfonates from electron-rich arenes using Mor-SS-Ts

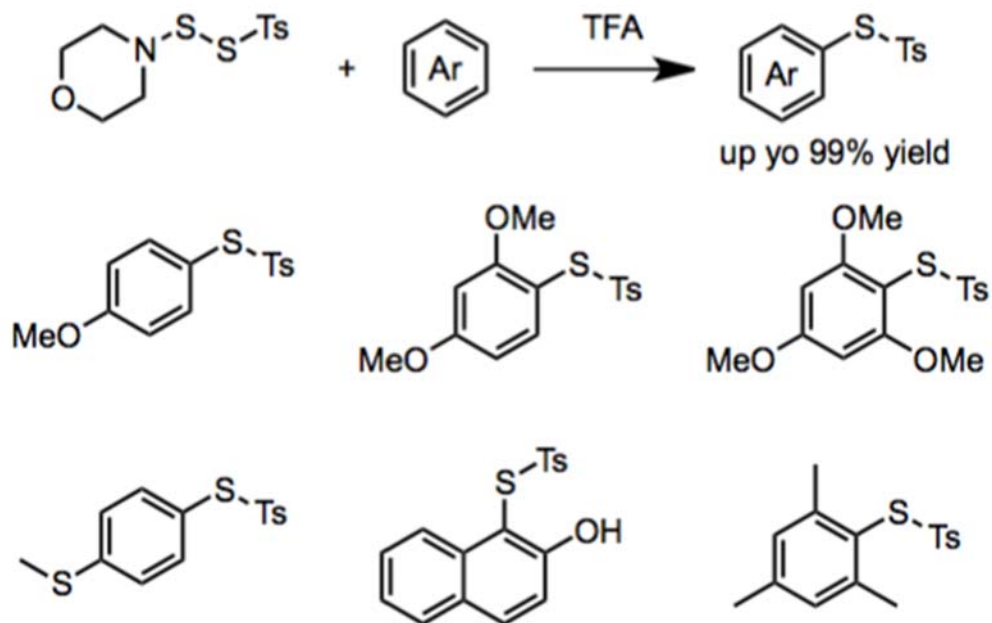
Furuhashi Koudai, a15.f5rt@g.chuo-u.ac.jp. Applied Chemistry, Chuo university, Tokyo, Japan

Organosulfur compounds have a broad range of applications in the fields of medicinal chemistry and materials science. For the convenient access to these compounds, thiosulfonates have attracted attention as useful electrophilic sulfur surrogates, which are transformable into various organosulfur compounds in mild conditions without unpleasant odor. In spite of the utility, the preparation of S-aryl thiosulfonates through C–S bond formation are still limited.

In this context, we conceived that the selective activation of morpholino group of Mor-SS-Ts using TFA could enable the efficient preparation of S-aryl thiosulfonates. Herein,

we report the TFA mediated thiosulfonate synthesis from electron-rich arenes with Mor-SS-Ts. This reaction exhibited a broad substrate scope, which allowed for the convenient synthesis of diverse aryl sulfides from easily available starting materials.

The Friedel–Crafts type reaction



ORGN 705

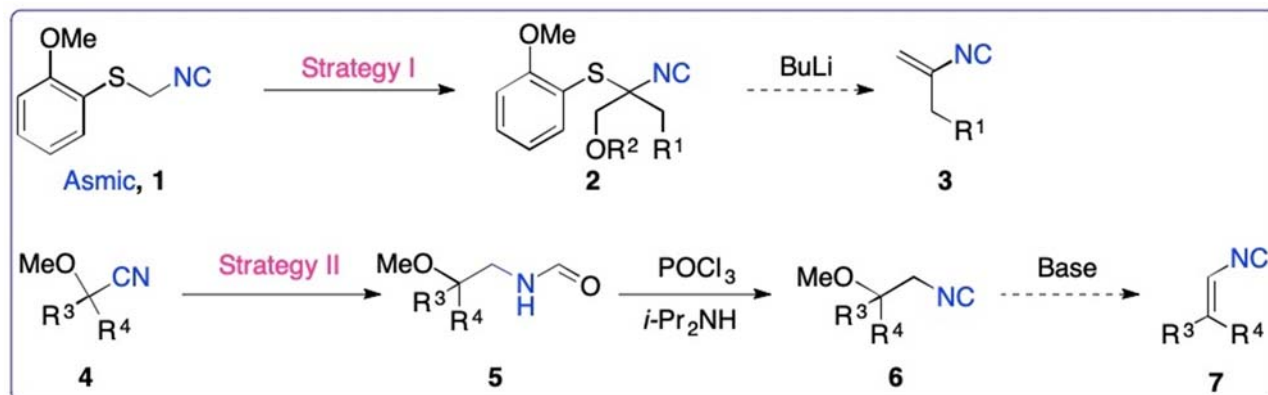
Alkeneisocyanides: Synthesis and reactions

Aicha Bendia, aicha.bendia@drexel.edu, Fraser F. Fleming. Chemistry, Drexel University, Philadelphia, Pennsylvania, United States

Alkeneisocyanides are valuable intermediates for heterocycle synthesis and display a range of antibacterial and antifungal activities. Rapid modular assembly of isocyanides is a challenge because isocyanides are intolerant toward many reagents, difficult to store and purify.

This presentation will describe two distinct strategies to access alkeneisocyanides. The first uses anisyl sulfanyl methyl isocyanide (Asmic), a powerful new building block that permits a facile route to alkeneisocyanides via a beta-elimination strategy (**1**→**3**). The

second relies on reduction-formylation of cyanohydrins followed by a dehydration-elimination (4→7).



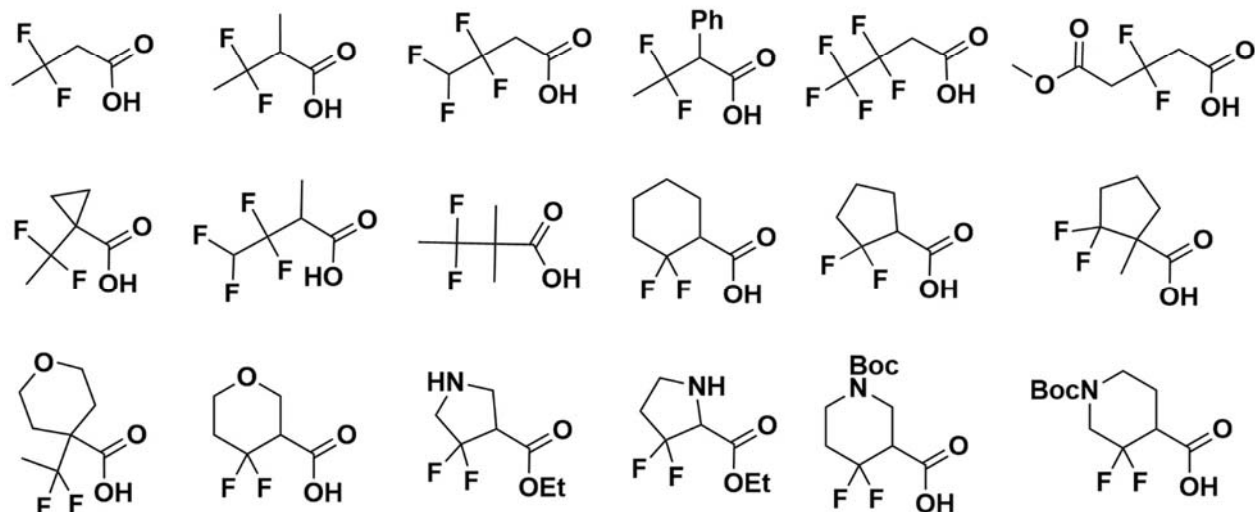
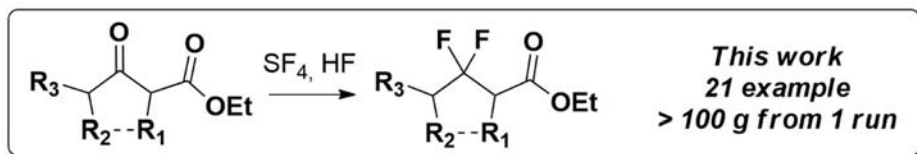
ORGN 706

Sulfur tetrafluoride as an effective reagent for semi-industrial fluorination of β -ketoesters: Safety vs efficacy

Dmitriy Volochnyuk^{1,2,3}, d.volochnyuk@gmail.com, **Sergii Trofymchuk**¹, **Sergey Ryabukhin**^{1,2}. (1) Enamine LTD, Kyiv, Ukraine (2) The Institute of High Technologies, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine (3) Biologically Active Compounds, Institute of Organic Chemistry of NASU, Kyiv, Ukraine

There are many well-known efficient reagents for the organic synthesis from the classical textbooks, but not all of them are popular among chemists for real using in the laboratory practice. Despite the great achievements in the development of modern reagents and techniques some synthetic transformations, which require using of extremely toxic and hazard gaseous reagents is still remained useful. The SF_4 is one of such reagents. Result as high toxicity and hazardous of this reagent many more safe analogues like DAST (Et_2NSF_3), Morph-DAST ($\text{O}[(\text{CH}_2)_2]_2\text{NSF}_3$), XtalFluor-E ($[\text{Et}_2\text{N}^+=\text{SF}_2]\text{BF}_4^-$) etc. are researched. But unique properties of SF_4 to replace the carbonyl oxygen with two fluorine atoms in some cases cannot be replaced by other analogues with keeping the efficiency of the process.

So in this report we propose a very efficient methodology of obtaining of β - CF_2 acids by direct fluorination of β -ketoesters using SF_4 as deoxofluorinating agent. The synthetic methodology is validated and optimized for multigram scale. The advantages and scope and limitation of the procedure are determined, the efficacy are and will be discussed.



ORGN 707

New method for the synthesis of pyrroloindolines via tandem alkylation-cyclization of tryptamines with trichloroacetimidates

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The pyrroloindoline core is present in an important class of natural products exhibiting significant biological activity. Reported here is a rapid construction of the pyrroloindoline polycyclic ring system employing an acid-catalyzed alkylation-cyclization process utilizing tryptamine derivatives and trichloroacetimidates. Two key steps (alkylation and cyclization) are accomplished in a single reaction, providing rapid access to a fully functionalized pyrroloindoline. A variety of alkyl groups have been incorporated in the pyrroloindoline core, and a number of different tryptamine derivatives participate in these processes. This reaction provides an alternative to transition metal-catalyzed and base promoted approaches to synthesize pyrroloindoline natural products.

ORGN 708

Synthesis and use of bulky alkali metal amides

Sabrina Aderibigbe, sabrina.olunike@gmail.com, **Olafs Daugulis**. Organic Chemistry, University of Houston, Houston, Texas, United States

Synthesis, characterization, and use of new, extremely bulky alkali metal amides will be reported. Specifically, these bases will be used in deprotonative functionalization of several substrate classes. Low temperature *in situ* quench with electrophiles allows us to functionalize C-H bonds of sensitive substances.

ORGN 709

Efficient synthetic pathways of replacing a pyrrole in porphyrins by an oxazole

Damaris W. Thuita, damaris.thuita@uconn.edu, *Christian Brückner*. Chemistry, University of Connecticut, Willimantic, Connecticut, United States

Methodologies to modify the electronic properties of porphyrins include the preparation of porphyrin analogues containing non-pyrrolic building blocks, so-called pyrrole-modified porphyrins (PMP). Total synthesis approaches toward PMPs are frequently taken but for their brevity the conversion of porphyrins – particularly along the ‘porphyrin breaking and mending’ route – remain an attractive option. The replacement of one of the pyrrole rings in *meso*-tetraarylporphyrins with an oxazolone moiety generates a class of PMPs referred to as porpholactones. Porpholactones, and their downstream derivatives (porpholactols, porpholactams, thionolactones, imidazoloporphyrins, etc.) have found broad utility in catalysis, chemosensing, and photomedicine. The formation of porpholactones along more than a dozen routes was described (either by design or chance), but the success of most routes is dependent on the specific *meso*-arylporphyrin considered or the central metal present. In most cases, however, no systematic assessment of the scope and limits of the method was performed. We evaluate here which routes are the most suitable for the preparation of which *meso*-aryl(metallo)porpholactone. We thereby make this attractive PMP more readily accessible to a wider range of fields.

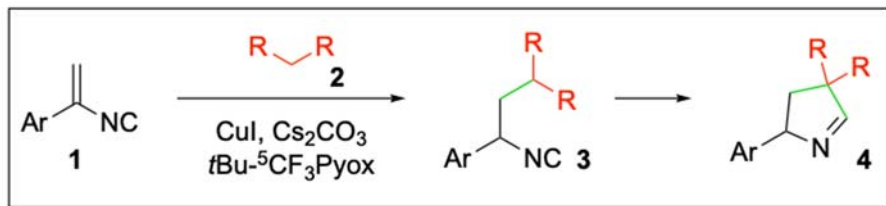
ORGN 710

Copper-catalyzed conjugate additions to alkeneisocyanides

John-Paul R. Marrazzo¹, jp.marrazzo@gmail.com, *Allen Chao*², *Fraser F. Fleming*¹. (1) Chemistry, Drexel University, Philadelphia, Pennsylvania, United States (2) Wistar Institute, Philadelphia, Pennsylvania, United States

The development of catalytic syntheses of complex isocyanides is paramount in providing diverse substrates for isocyanide-based reactions. Structurally complex isocyanides are difficult to synthesize because of the highly reactive nature of the isocyanide with most transition metals. The alkeneisocyanide **1** is readily available from commercially available nitriles in a two-step operation. We have discovered the first copper-catalyzed conjugate additions to alkeneisocyanides by activating the alkeneisocyanide with a pyridine oxazoline complexed copper(I) salt. Conjugate additions have been achieved using thiols, malonates, malononitriles, ketoesters, and

arylacetonitriles (**1**+**2**→**3**), which can be further reacted to access dihydropyrroles (**4**) and cyclopropanes in a one-step fashion.



ORGN 711

Incorporation of heterocyclic aldehydes in Ugi-Smiles Diels-Alder reactions

Drew Scanlan, dscanla@siue.edu, **Sarah B. Luesse**. Southern Illinois University Edwardsville, Edwardsville, Illinois, United States

Epoxyisoindoline scaffolds can be efficiently assembled through a tandem Ugi-Smiles intramolecular Diels-Alder (US-IMDA) process. Two separable diastereomeric products are obtained through the one-pot multicomponent reaction. Studies have been directed at examination of epimerization conditions for the diastereomers and expanding the scope of this reaction with a range of substituted phenol and isocyanide components. Bromo-substituted 2-nitrophenol has provided significant improvements in reaction yields (80-96%) over non-halogenated analogs. Recent efforts are focused on the use of thiophene-derived components.

ORGN 712

Amine variation in oxy-Michael Ugi-Smiles processes

Joshua Jones, jjones7331@gmail.com, **Sarah B. Luesse**. Chemistry, Southern Illinois University Edwardsville, Edwardsville, Illinois, United States

Multicomponent coupling reactions (MCRs), such as the Ugi-Smiles reaction, can provide direct access to diverse scaffolds from simple starting materials. In the presence of methanol and a conjugated aldehyde, a novel five-component oxy-Michael Ugi-Smiles reaction was observed. This process tolerates a range of substituted alcohols and isocyanides, with moderate, but promising, yields (45-65%). Current efforts are focused on variation of the amine and aldehyde components, as well as minimization of a competitive Ugi-Smiles product.

ORGN 713

Tandem Michael Ugi-Smiles processes with thiols

Ashley Robinson, *arobiag@siue.edu*, Sarah B. Luesse. Chemistry, Southern Illinois University Edwardsville, Edwardsville, Illinois, United States

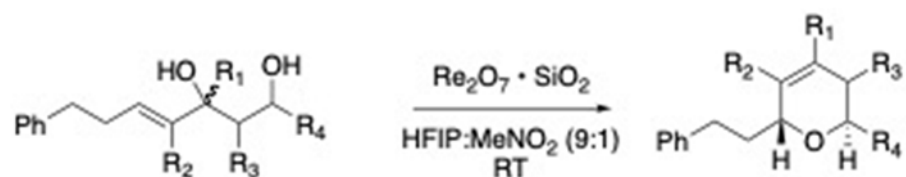
The Ugi-Smiles reaction is a one-pot multicomponent coupling used to assemble functionalized *N*-aryl amides. Use of acyclic conjugated aldehyde components in the presence of alcoholic solvents led to observation of a novel five-component oxa-Michael Ugi-Smiles reaction. Current efforts are focused on examination of the scope of the reaction through use of related thiol components.

ORGN 714

Re₂O₇ -mediated dehydrative cyclizations: Method towards 2,6-trans dihydropyran synthesis

Jean-Marc Lawrence, *jmgolf94@gmail.com*, Paul E. Floreancig. Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Dihydropyrans are highly attractive targets in chemical synthesis based on their prevalence in numerous biologically active natural products. This poster describes the development of a method for obtaining dihydropyrans using Re₂O₇ catalyzed dehydrative cyclization of 1,3-diols, in which one of the alcohols serves as a precursor to allyl cation formation. These reactions proceed to give the dihydropyrans that afford the 2,6-trans isomer as the major product. We initiated a mechanistic investigation through manipulating functional groups and olefin geometry. A solvent screen was done to determine the optimal system for yield and stereocontrol. A substrate scope was investigated to determine the functional group tolerance, effects of pendant stereocenters and application to synthesizing enantiopure monosubstituted dihydropyrans successfully.

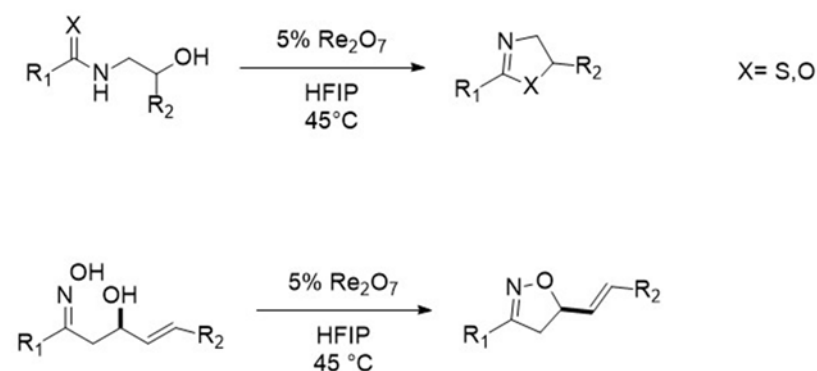


ORGN 715

Re₂O₇ –Catalyzed dehydrative cyclization reactions in the synthesis of nitrogen containing heterocycles

Freddy Rodrdriguez del Rey, *for3@pitt.edu*, **Paul E. Floreancig**, Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania, United States

The synthesis of various heterocycles through dehydrative cyclization is of great importance to medicinal and natural product chemistry. Heterocycles such as oxazolines and thiazolines are prominent in biologically active natural products and compounds with medicinal properties. Previously reported methods used to prepare these heterocycles require stoichiometric use of a dehydrating reagent or suffer from a limited scope. This poster describes a mild catalytic method for dehydrative cyclization reactions using allylic alcohols as electrophilic surrogates and Re_2O_7 as the catalyst. This method enables the synthesis of 5-membered heterocycles including oxazolines, isoxazolines, and thiazolines, as well as a 6-membered dihydro-1,3-oxazines and dihydro-1,3-thiazines. A wide range of hydroxylamides and α -hydroxyl oximes were converted to the corresponding heterocycles in good to excellent yields.



ORGN 716

Vicinal C-H functionalization of amines enabled by an interrupted Hoffman-Löffler-Freytag mechanism

Ross Dare, *dare.20@osu.edu*, **Leah M. Stateman**, **Alyson Paneque**, **David Nagib**, Chemistry, The Ohio State University, Columbus, Ohio, United States

Alkenes are one of the most ubiquitous functional handles in organic chemistry. In this study, a strategy to introduce alkenes through the remote desaturation of aliphatic C-H bonds was investigated. Utilizing Copper and Iridium catalysts, a series of distal desaturated amines were synthesized. The versatility of this privileged scaffold is showcased by the streamlined synthesis of pharmaceutically relevant piperidines and pyrrolidines.

ORGN 717

Sulfuryl fluoride mediated synthesis of amides from ketoximes via Beckmann rearrangement

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A metal free and redox-neutral, method for Beckmann rearrangement, employing inexpensive and widely available SO₂F₂ gas, is described. The reported room temperature transformation is compatible with wide array of sterically and electronically diverse aromatic, heteroaromatic, and lignin model oximes to afford amides in good to excellent yields. The reaction proceeds through the formation of an imidooyl fluoride intermediate that can also be used for synthesis of amidines.

ORGN 718

Dearomatization of electron-deficient phenols to *ortho*-quinones enabled by bidentate nitrogen-ligated I(V) reagents

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Ortho-quinones are versatile functional groups which find application in Nature, materials science, and as synthetic intermediates. Despite their broad applications, the synthesis of o-quinones remains a significant challenge. Challenges include regioselective oxidation (*ortho*- vs. *para*-) as well as the sensitivity of the resulting o-quinone products, which are often not compatible with the harsh conditions required for oxidation. In particular, access to electron-deficient derivatives remains an unsolved problem, with most oxidants only being applicable to the use of electron-rich substrates. Hypervalent iodine reagents in the I(V) oxidation state, namely IBX and its analogues, have been found to give high regioselectivity for o-quinones via intramolecular oxygen delivery, however these methods are restricted to highly reactive, electron-rich phenols. Herein, we report the first general method for the synthesis of electron-deficient o-quinones via the direct dearomatization of phenols, enabled by a novel class of bidentate nitrogen-ligated I(V)-species. The first example of these reagents, which we have termed Bi(N)-HVIs, was reported by Zhdankin in 2002, however no studies on its reactivity or synthetic applications were reported. The reaction scope is extremely general and proceeds with excellent regioselectivity for the ortho over para isomer. Functionalization of the o-quinone products was also examined, resulting in a facile one-pot synthesis of highly functionalized catechols and diversely substituted catecholic derivatives. This represents the first synthetic application of Bi(N)-HVIs and demonstrates their potential as a tunable platform for the further development of I(V) reagents.

ORGN 719

Ring rearrangement of oxo- or aza-bridged 1,5-alkylidenemalononitrile-cycloheptenes

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We discovered that oxo- or aza-bridged alkylidenemalononitrile-cycloheptenes, substrates prepared via [4+3] cycloaddition then Knoevenagel condensation from haloacetone, furan or pyrrole derivative, and alkylidenemalononitrile, undergo a [3,3] ring rearrangement to yield cyclopenta-fused dihydro furans or pyrroles.

ORGN 720

Diastereoselectivity of oxone-based oxidations of 1,3 thiazolidin-4-ones to sulfoxides

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Oxidation of *meta*- and *para*-substituted 2-phenyl-3-aryl thiazolidin-4-ones with Oxone at room temperature in methanol typically resulted in the formation of a mixture of diastereomeric sulfoxides. The ratio of diastereomers can be determined by integration of the hydrogen on C2 of the thiazolidin-4-one ring. Changing the reaction solvent to either acetone or acetonitrile in most cases yielded a single diastereomer. This solvent-based diastereoselectivity was further evaluated for a series of *meta*- and *para*-substituted 2-trichloromethyl-3-aryl-thiazolidin-4-ones, which yielded similar results.

ORGN 721

Microwave-assisted aza-Prins reactions of unactivated imines

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The aza-Prins reaction is a facile method for preparing functionalized piperidines, which are extremely common pharmaceutical scaffolds. The reaction proceeds by condensation of a homo-allylic amine with an aldehyde. The resulting iminium cation readily undergoes cyclization. However, strongly electron withdrawing amine protecting groups are frequently required for reasonable yields. To add to the versatility of this reaction and to obviate the need for a protecting group, we have developed a microwave-assisted aza-Prins reaction of an unprotected (and thus unactivated) imine as a method for preparing *cis*-2,4-disubstituted piperidines. Herein we report the scope

and limitations of varying the aldehyde to form a variety of piperidines. Additionally, the significance of the preforming the imine prior to the aza-Prins reaction compared with a one-pot condensation/aza-Prins reaction will be described.

ORGN 722

Synthesis of 1,3,5-triarylbenzenes using sustainable metal triflates as catalysts

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1,3,5-Triarylbenzene core is shown to be an important synthetic motif in the development of organic light emitting diodes (OLEDs), synthesis of dendrimers and fullerene fragments. Direct synthesis of 1,3,5-triarylbenzenes by self-condensation from the corresponding acetophenone derivatives was achieved earlier in our laboratories using Nafion-H as reusable catalyst. However large amount (30 wt%) of the catalyst and higher temperatures are required for the reactions. Now, we are able to obtain the products using sustainable metal triflate catalysts such as Ga(OTf)₃ in much lower amounts (2 mol%) and lower temperatures. The reaction occurs in toluene as solvent and under neat conditions. The products can be separated by simple crystallization in most cases. Details of the reactions and the conditions will be presented.

ORGN 723

Development of an efficient method for fluorocyclization of tryptophol

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Heterocyclic compounds, particularly indoles, are of interest due to their unique biological applications. The development of efficient methods for fluorocyclization reactions of Tryptophol catalyzed by Selectfluor were investigated. Selectfluor has been proven to be a good electrophilic fluorination agent in the presence of a base. This methodology provides a convenient approach for Fluorocyclization of Tryptophol under mild conditions.

ORGN 724

Access to highly functionalized cyclopentenones via diastereoselective Pauson-Khand reaction of siloxy-tethered 1,7-enynes

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A diastereoselective Co₂(CO)₈-mediated Pauson–Khand reaction (PKR) of siloxy-tethered 1,7-enynes for the synthesis of cyclopentaoxasilinones has been developed. This transformation can be performed on a multigram scale and is characterized by a broad substrate scope, functional group compatibility, and high chemo- and diastereoselectivity. Oxidation of the resulting cyclopentaoxasilinones delivers stereo-enriched β -alkylated cyclopentenones, which are inaccessible by intermolecular PKRs. This research provides a practical solution to the challenges associated with the classical intermolecular PKR.

ORGN 725

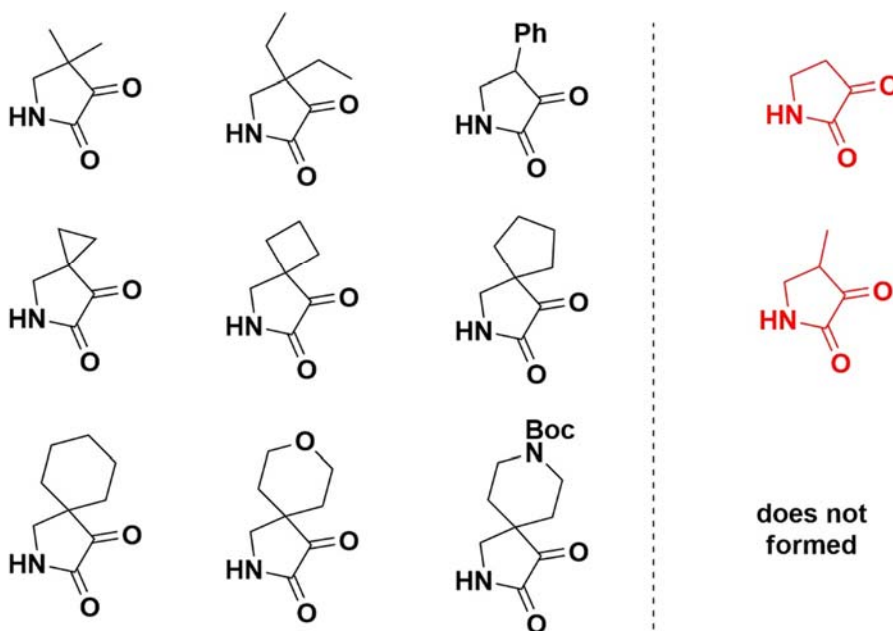
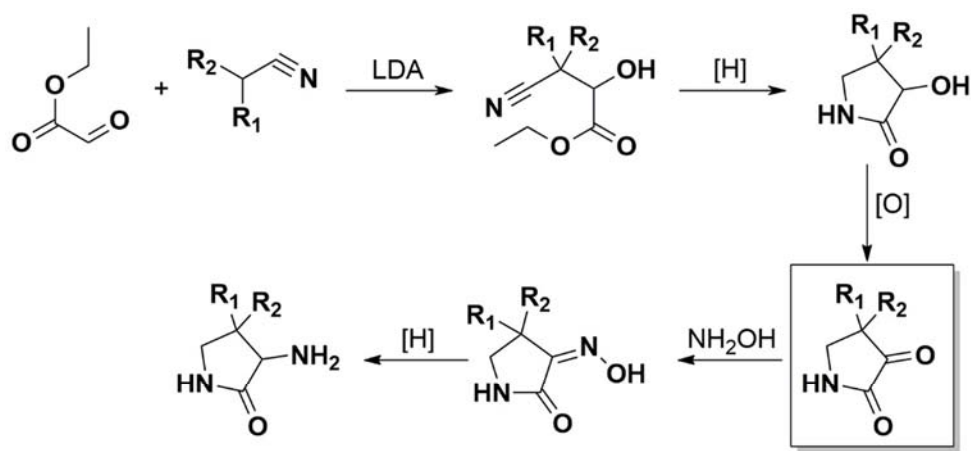
2,3-diketopyrrolidines as perspective building blocks for medicinal chemistry: Synthesis and properties

Sergey Ryabukhin^{1,2}, *s.v.ryabukhin@gmail.com*, **Semen Bondarenko**¹, **Dmitriy Volochnyuk**^{1,2,3}. (1) Enamine LTD, Kyiv, Ukraine (2) The Institute of High Technologies, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine (3) Biologically Active Compounds, Institute of Organic Chemistry of NASU, Kyiv, Ukraine

The shifting from “traditional” heteroaromatic design concepts in modern Medicinal Chemistry leads to increasing complexity of the synthesis of medicinally relevant molecules. The one of the best way for solving this problem is to apply in the synthesis the robust well-known procedures and achieves complexity by using the sophisticated, commercially available (if it is possible), building blocks. Therefore, the interest to 3D-shaped building blocks with high fractions of F(sp³)-hybridized carbon atoms continuously growth and now its synthesis become a part of the industry. Therefore, the procedures, which can effectively lead to the formation of targeted products in 10-100 gram scale become more and more demanded.

We focused our attention on the elaboration of the effective multigram scale procedure for the synthesis of diverse 4-substituted 2,3-diketopyrrolidines. These ketones are a very rare class of organic compounds. For today there are only a few methods for obtaining such compounds in milligram scales. From the other hand these products have been a perspective building blocks for Medicinal Chemistry needs.

In this report the synthetic methodology for the obtaining of 2,3-diketopyrrolidines is validated and optimized. The advantages and scope and limitation of the procedure are determined and will be discussed.



ORGN 726

Synthesis of functionalized 1-azabicycloheptanes/octanes/nonanes: Perspective building blocks for medicinal chemistry starting from proline

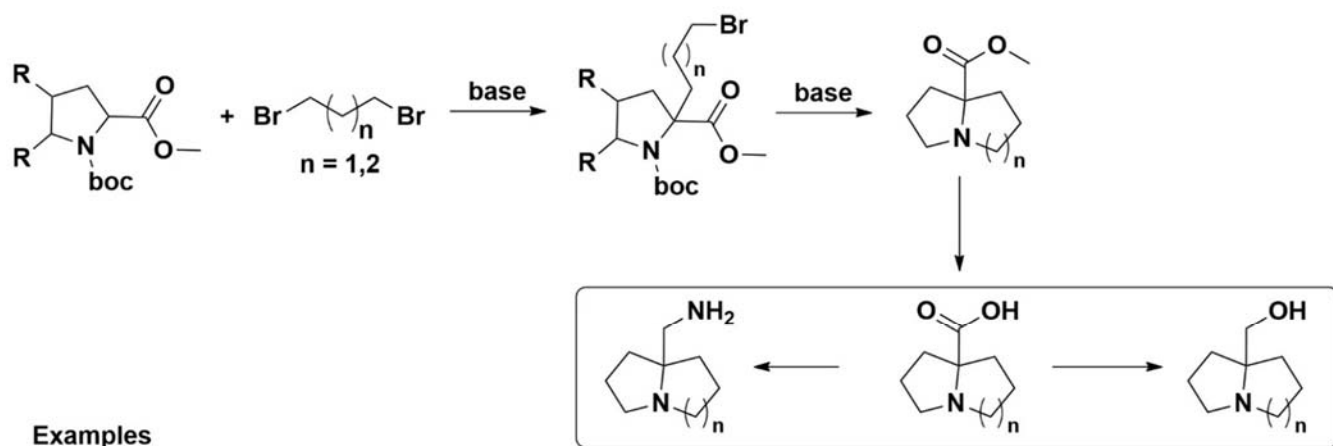
Sergey Ryabukhin^{1,2}, s.v.ryabukhin@gmail.com, **Semen Bondarenko**¹, **Dmitriy Volochnyuk**^{1,2,3}. (1) Enamine LTD, Kyiv, Ukraine (2) The Institute of High Technologies, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine (3) Biologically Active Compounds, Institute of Organic Chemistry of NASU, Kyiv, Ukraine

The shifting from “traditional” heteroaromatic design concepts in modern Medicinal Chemistry leads to increasing complexity of the synthesis of medicinally relevant

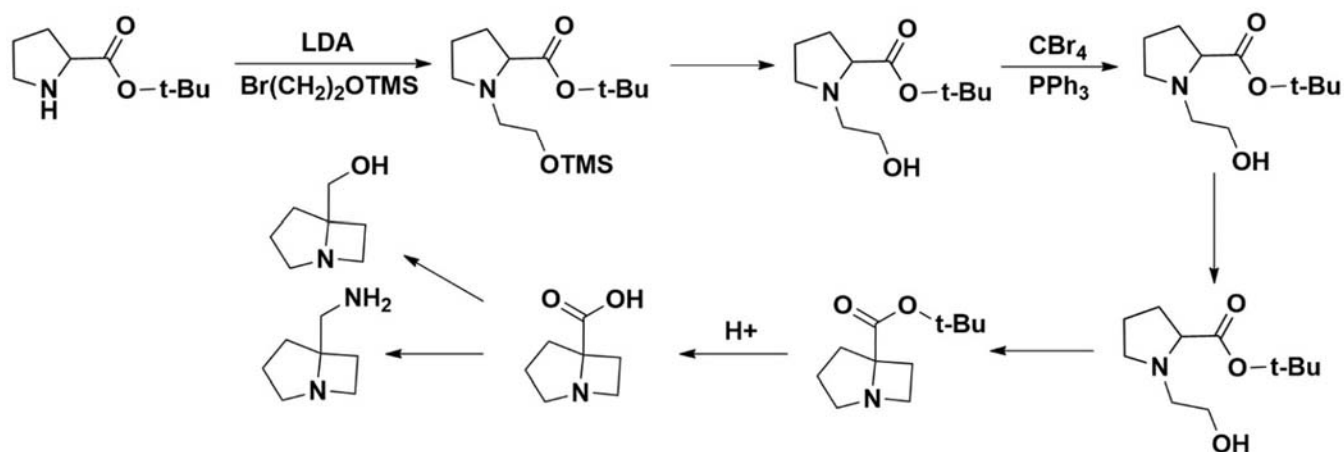
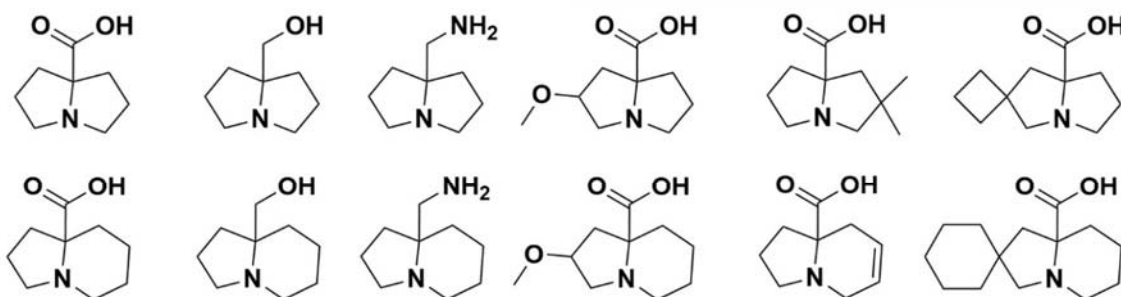
molecules. The one of the best way for solving this problem is to apply in the synthesis the robust well-known procedures and achieves complexity by using the sophisticated, commercially available (if it is possible), building blocks. Therefore, the interest to 3D-shaped building blocks with high fractions of $F(sp^3)$ -hybridized carbon atoms continuously growth and now its synthesis become a part of the industry. Therefore, the procedures, which can effectively lead to the formation of targeted products in 10-100 gram scale become more and more demanded.

The effective multigram scale procedure for the synthesis of functionalized 1-azabicycloheptanes/octanes/nonanes is proposed in our research. The method depends on using common organic reagents and simple reactions which highly increase its efficiency. From the other hand the products have been a perspective building blocks for Medicinal Chemistry needs.

In this report the synthetic methodology for the obtaining of of functionalized 1-azabicycloheptanes/octanes/nonanes is validated and optimized. The advantages and scope and limitation of the procedure are determined and will be discussed.



Examples

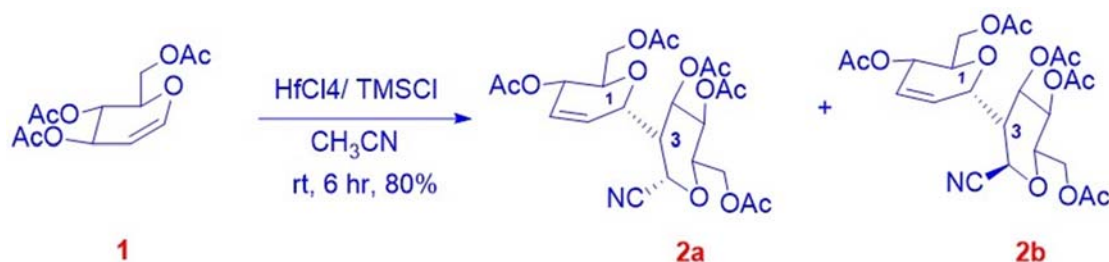


ORGN 727

Microwave-assisted hafnium(IV) chloride-promoted self-coupling of D-glycal

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Ferrier rearrangement has been extensively used for the synthesis of 2,3-unsaturated glycosides. C-glycoside analogous of the O-glycosides is used as intermediates for the synthesis of numerous medicinally active molecules. Our group has developed numerous novel methods for synthesizing glycosides through Ferrier rearrangement. We herein synthesize glycosyl nitrile from glucal *via* carbon Ferrier rearrangement of glycal and silyl nitrile in the presence of Hafnium (IV) chloride under microwave irradiation method. Hafnium tetrachloride (HTC) is an efficient catalyst for this purpose.

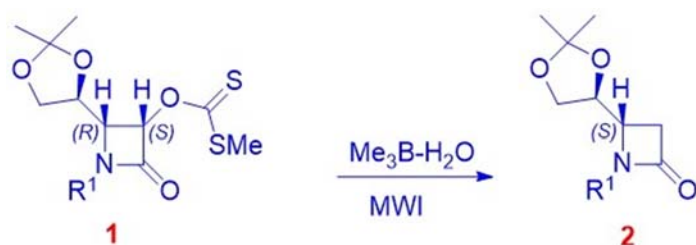


ORGN 728

Microwave-induced preparation of 3-unsubstituted β -lactams with aqueous trimethylborane

Ram N. Yadav, nareshutpa@gmail.com, **Bimal K. Banik**. Chemistry, Veer Bahadur Singh Purvanchal University Jaunpur-222003 UP INDIA, Jaunpur, Uttar Pradesh, India

A microwave-induced procedure for the preparation of 3-unsubstituted β -lactams is explored *via* aqueous trimethyl borane-mediated reaction of the xanthates. We have been engaged in the synthesis and biological evaluation of β -lactams for many 25 years. It is conceivable that 3-oxygen substituted β -lactams on deoxygenation can produce 3-unsubstituted β -lactams.

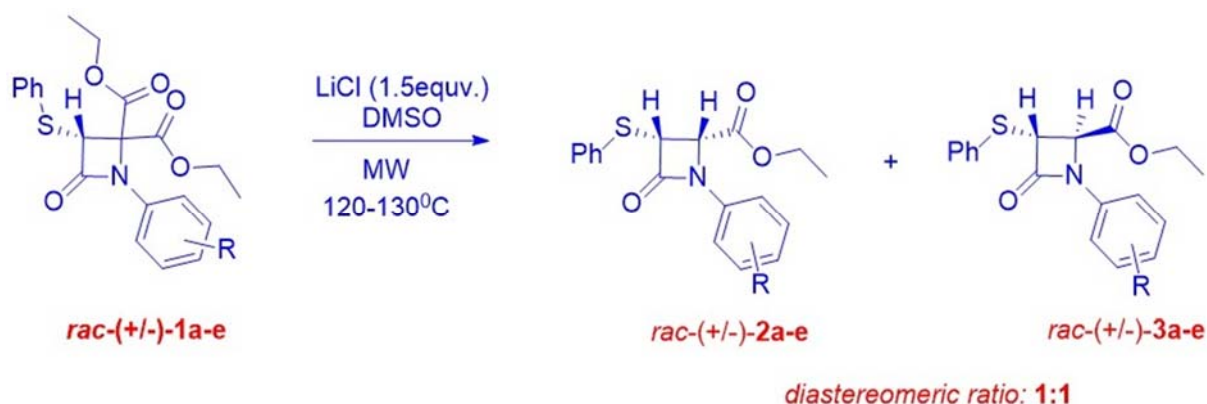


ORGN 729

Microwave-assisted stereoselective synthesis of 3-phenylthio-4-carboethoxy b-lactams

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Cycloaddition of dicarboethoxy-substituted imines with phenylthioacetyl chloride under microwave irradiation is investigated toward the preparation of C-4 dicarboethoxy-substituted b-lactams. One of the ester groups of the products is removed through a decarboethoxylation process by lithium chloride in DMSO. This procedure results in the formation of functionalized *cis* and *trans* b-lactams.

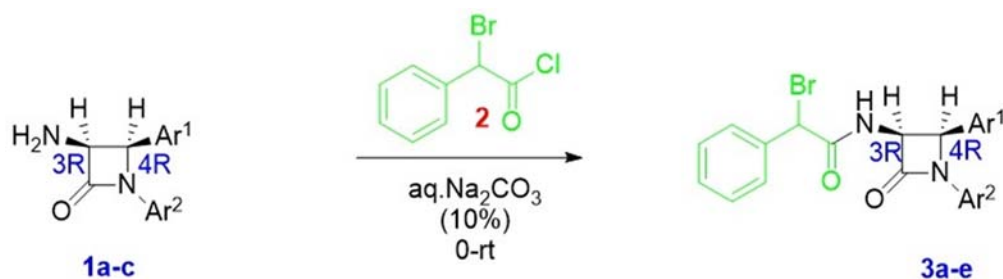


ORGN 730

Acetylation of the amino group in β -lactams under aqueous conditions

Ram N. Yadav, nareshutpa@gmail.com, **Bimal K. Banik**. Chemistry, Veer Bahadur Singh Purvanchal University Jaunpur-222003 UP INDIA, Jaunpur, Uttar Pradesh, India

We report acetylation of *cis* and *trans* amino β -lactams in aqueous sodium bicarbonate solution and further extended to this strategy to 6-aminopenicillanic towards the synthesis of important heterocyclic compound, oxazolone through a ring rupture-rearrangement reaction. This study suggests that the stability of monocyclic β -lactams is superior to bicyclic β -lactams in aqueous alkali solution.

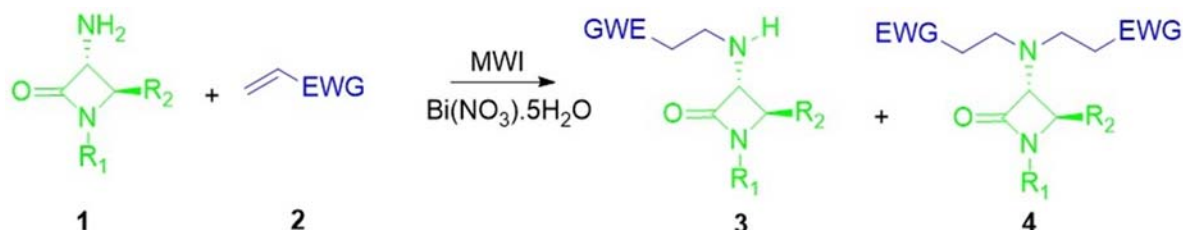


ORGN 731

Microwave-assisted bismuth nitrate-catalyzed reaction of 3-amino b-lactams with enones

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Synthesis of substituted amino b-lactams is an important operation because of the medicinal activities of the products derived from them. Microwave-induced bismuth nitrate-catalyzed reaction of 3-amino b-lactams with unsaturated ketones is performed in order to obtain substituted amino b-lactams. The amino b-lactams is obtained through the strategy of [2+2] ketene-imine cycloaddition followed by the deprotection of the phthalimido b-lactams with ethylenediamine.



EWG: Electron-withdrawing groups

ORGN 732

Microwave-induced montmorillonite-mediated facile synthesis of enamines

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The synthesis of enamines is an important operation in synthetic chemistry. Montmorillonite clay- mediated simple and high yielding protocol to synthesis of various enamines with secondary amines and ketones is developed under microwave condition. This protocol is very convenient to access the enamines from cyclic amines with various carbonyl compounds in very high yield under mild reaction conditions with very short reaction time.

Different types of clay-mediated reactions are easy to perform because they are not soluble in organic solvents. Most of the clays or solid surfaces are acidic or neutral in nature. Clays have the capability to absorb water and organic compounds inside the cavity in their structures. It is reported that clays are catalyzed a diverse organic reaction including substitution, addition, elimination, hydrogenation, hydrogenolysis, dehydration, aromatization, annulation, Diels-Alder, and isomerization. These methods are efficient in the synthesis of a wide range of diverse molecules of biological and medicinal interests. Montmorillonite K-10 has been proven its versatile catalytic efficiency in organic synthesis.



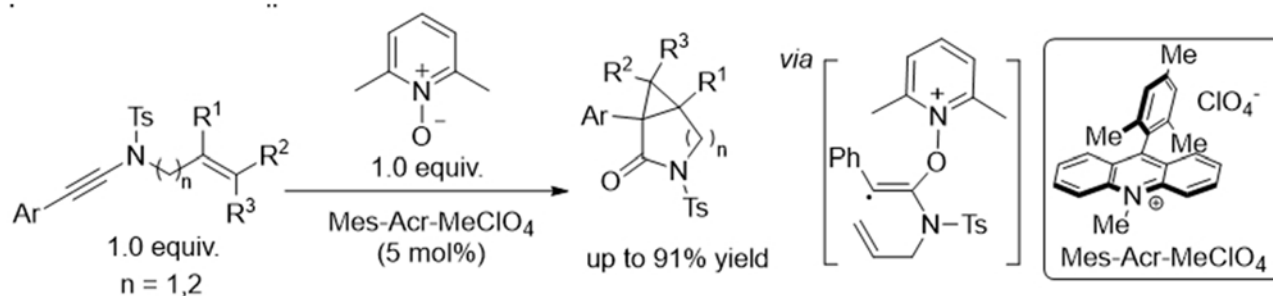
ORGN 733

Photoinduced facile generation of vinyl radical from alkynes: Metal-free synthesis of 3-aza-bicyclo[3.1.0]hexan-2-ones

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Recently, our group reported a novel strategy for the facile generation of vinyl radical through the photoredox catalyzed oxidative activation of alkynes with pyridine N-oxide. With our continuous efforts to explore new synthetic applications of this strategy, we report here a metal-free photoredox catalyzed oxidative cycloaddition of ene-ynamides for the synthesis of 3-aza-bicyclo[3.1.0]hexan-2-ones. Our research indicates that this transformation undergoes the formation of a distonic cation vinyl radical intermediate from photoinduced oxidative addition of ene-ynamide with pyridine N-oxide. This methodology provides a metal-free facile synthesis of 3-azabicyclo[3.1.0]hexane

skeletons, which is one type of important synthetic intermediate for several bioactive molecules and pharmaceuticals.



ORGN 734

Oxidative photocatalytic homo- and cross-coupling of phenols: First non-enzymatic catalytic method for coupling tyrosine

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The first oxidative photocatalytic method for homo-coupling phenols is described and isolated yields of up to 76% are obtained. Additionally, nucleophilic phenols are arene were cross-coupled with easily oxidized phenols improving upon recently reported cross-couplings. Selectivity was high and yields of up to 97% are reported. Finally, the first non-enzymatic catalytic method for coupling tyrosine is revealed.

ORGN 735

Expedient access to saturated nitrogen heterocycles by photoredox cyclization of imino-tethered dihydropyridines

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A large proportion of medicinally relevant molecules bear nitrogen and sp³-hybridized carbon functionalities. Overwhelmingly, these atoms are found as part of (hetero)cyclic structures. Despite their importance, synthetic approaches to saturated nitrogen heterocycles are limited to several established stoichiometric alkylation techniques, as well as a few methods involving C–H bond activation. The synthetic community remains

interested in more general, mild, and sustainable ways to access these motifs. Here we describe a dual-catalyst system composed of an iridium photocatalyst and a lithium phosphate base that is capable of selectively homolyzing the N–H bond of 4-alkyl-1,4-dihydropyridines, presumably by proton-coupled-electron-transfer (PCET), and mediating efficient cyclization of the resultant carbon-centered radicals with tethered imines. The outcome of this transformation is access to a broad range of structurally complex nitrogen heterocycles obtainable from simple aldehyde starting materials in a highly chemoselective manner.

ORGN 736

Blue light-mediated catalyst free polyene cyclization

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Polyene cyclization reactions are highly efficient and unique biomimetic transformations that yield complex polycyclic molecules from their acyclic precursors. The process involves a concerted step in the formation of stereo-controlled multiple C-C bonds. Over the years, various cation-mediated and radical-mediated synthetic methods have been developed to obtain highly enantioselective cyclization, along with the use of visible-light in the recent years. However, all these strategies demand using expensive and toxic transition metal complexes or organic dyes as catalysts to accomplish the desired reaction. In contrast, here, we report a visible-light-mediated, catalyst free cascade cyclization of geranyl phenols and farnesyl phenols containing bromo- and chloro-groups at different positions of the phenolic ring. The desired cyclization product was obtained with high stereoselectivity using a blue LED light in hexafluoro-2-propanol without any photocatalyst.

ORGN 737

Carbon-carbon bond formation by visible light photocatalysis: [2 + 2] photocycloadditions of vinylogous esters and amides

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In this work, we target new methods to prepare the cyclobutene carbon scaffold, a structural feature found in both natural and non-natural products. It has long been known that cyclobutanes can be synthesized with through [2 + 2] cycloadditions promoted by ultraviolet (UV) light; however, UV light sources are expensive, hazardous to use, and often lead to undesired reactivity. To avoid the challenges of using high

energy, UV light, our reactions were carried out under lower energy visible light (blue LEDs). In this project, we report cyclobutane syntheses with vinylogous esters/vinylogous amides and enones, in the presence of iridium transition metal catalysts. Examples result in modest yields and excellent regio- and diastereoselectivity. The substrate scope was investigated to probe how structural modifications impact both reactivity and selectivity of the photocycloaddition. In an effort to understand the mechanism by which these reactions proceed, photophysical properties: phosphorescence and absorbance, of the substrates and catalysts, are reported.

ORGN 738

Photocatalytic oxidative C-H thiolation: Synthesis of benzothiazoles and sulfenylated indoles

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A variety of sulfur containing scaffolds widely exists in both natural products and pharmaceuticals. There are many synthetic routes that have been developed to synthesize aryl sulfides from aryl halides, commonly using various sulfenylating reagents like N-thiosuccinimide. These methods result in a milder yet efficient conversion of simple substituted arenes to aryl sulfides, however sulfenylation via photoredox catalysis is not as widely explored. The use of photoredox catalysis allows for the generation of a more reactive radical intermediate that can be employed to generate a C-X bond, or C-S in this case.

We report studies on the photocatalytic formation of C-S bonds to form benzothiazoles via an intramolecular cyclization and sulfenylated indoles via an intermolecular reaction. Cyclic voltammetry (CV) and density functional theory studies (DFT) suggest that benzothiazole formation proceeds via a mechanism that involves an electrophilic sulfur radical, while the indole sulfenylation likely proceeds via a nucleophilic sulfur radical adding into a radical cationic indole. These conditions were successfully extended to several thiobenzamides and indole substrates.

ORGN 739

Green chemistry: Benzylic functionalization via visible-light induced photo redox catalysis

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Visible-light photoredox catalysis offers a promising synthetic technology which replaces traditional methods due to its mildness and high compatibility with functional groups.

Visible light is considered as a clean energy because of its high abundance, greenness, benign environmental impact, and sustainability. We developed a visible-light induced photoredox catalysis for an efficient functionalization of benzylic/allylic C-H bonds with peroxides. This research was primarily conducted to functionalize various substrates at the benzylic position by the addition of a peroxide group. Each experiment performed in the presence photocatalyst (an organic dye) and various LED lights under room temperature. The overall strategy of the reaction was to use the Hydrogen Atom Transfer strategy to create radicals which would ultimately create a peroxide radical which would then have bonded at the benzylic position.

ORGN 740

Photoreduction of quinolines: Nitro reduction to amines and O-debenzylation by proton-coupled electron transfer

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Arylamines are common substrates amongst pharmaceuticals, agrochemicals, dyes, and pigments. Typically, these are synthesized via (aryl nitration and) reduction of nitro-groups either with catalytic transition metal reduction under H₂ atmosphere, or with stoichiometric reagents. However, the above-mentioned methodologies are often unselective and have poor functional group tolerance. Recently, different reductive photocatalytic approaches for nitrophenyls have been developed with and without sacrificial reductants.

Previously, our research group has developed a photoreductive methodology for O-debenzylation of N-heterocycles, where reduction potential of the protonated N-heterocycle was used to select either a milder ([Ru(bpy)₃]²⁺) or more powerful ([Ir(dF(CF₃)ppy)₂(dtbbpy)]³⁺) photoreductant. The reduction was selective in the presence of a wide set of functional groups, but proved to be unsuitable for nitroquinoline derivatives. A closer examination of the product distribution revealed reduction of the nitro-group to be a competing reaction, and optimization of the reaction conditions allowed for a selective conversion of nitro-groups to amines. Computational analysis, control experiments, and photocatalyst quenching experiments revealed that the reduction is a multi-site proton-coupled electron transfer (MS-PCET) reaction between the photocatalyst (electron acceptor), nitroquinoline (proton acceptor) and ascorbic acid (electron and proton donor).

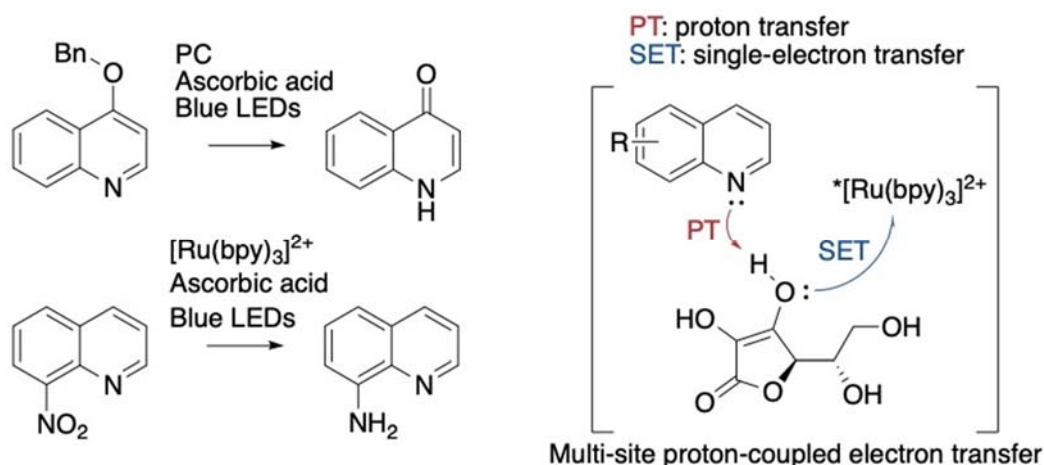


Figure 1. Photoreduction reactions with quinolines and MS-PCET reaction.

ORGN 741

High-throughput kinetics screening of iridium catalyzed photo-dehalogenation of aryl bromines

Velabo Mdluli¹, vmdluli@andrew.cmu.edu, **Stefan Bernhard**¹, **Stephen DiLuzio**², **Timothy U. Connell**³. (1) Chemistry, Carnegie Mellon University, Pittsburgh, Pennsylvania, United States (2) Carnegie Mellon University, Landenberg, Pennsylvania, United States (3) RMIT University, Melbourne, Victoria, Australia

The photo-induced electron transfer from sacrificial donor amines to aryl bromides generates highly reactive aryl radical intermediates that are useful in a wide variety of photoredox cross coupling reactions. We present a novel approach to “online” high throughput screening (HTS) to evaluate photocatalysts’ (PCs) performance in such reactions (Figure). Cationic iridium complexes $[\text{Ir}(\text{CN})_2(\text{NN})]^+$ are perfectly suited for combinatorial screening of such transformations because of their modular ligand arrangement and charge transfer excited state. Judicious design of the cyclometalating (CN) and ancillary (NN) ligands results in structurally very diverse PCs with a wide range of photophysical and chemical properties. We developed an indicator dye-based colorimetric technique that allowed us to measure the reaction rate of over a thousand debromination reactions on aryl halides substrates using libraries of such PCs. The discovered structure-activity relationships revealed that the careful choice of PC and sacrificial electron donor can help pinpointing desirable chemoselective and rapid reaction conditions.

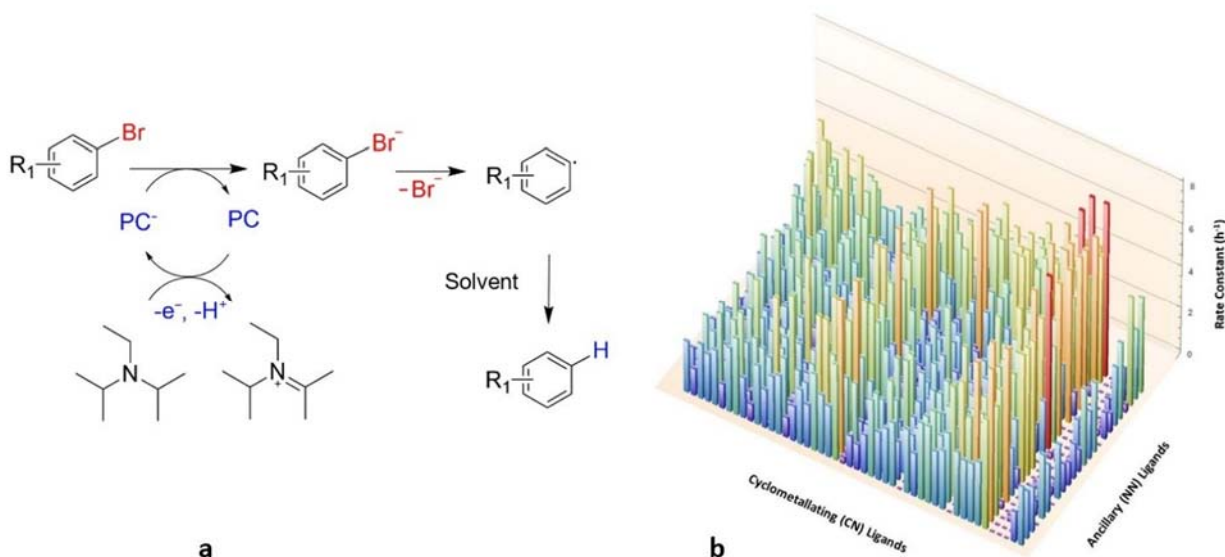


Figure: a) Photo-induced electron transfer from a sacrificial donor (DIPEA) via a visible-light excited photocatalyst (PC) to an aryl halide creates reactive aryl radicals. **b)** A 3D bar chart depicting the rate constants of 1152 Ir(III) photocatalysts (PCs) screened for their dehalogenation reactivity.

ORGN 742

Discovery and asymmetric synthesis of potent and selective small-molecule modulators of CXCR7 for treatment for cardiac fibrosis

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In conjunction with CXCR4, the G protein coupled receptor CXCR7 has been reported to play a protective role following a cardiac event to improve both function and cardiac injury repair processes. It was postulated that a potent small molecule CXCR7 modulator could interact with the target receptor to prevent binding, internalization, and degradation of its natural ligand SDF1 α . Following a rigorous medicinal chemistry campaign targeting upregulation of the systemic circulation of SDF1 α , a sterically hindered tertiary beta amino amide was identified as a promising candidate. The work presented herein highlights the project rationale, key SAR developed en route to the discovery of our in vivo tool compound, and the practical asymmetric synthesis that

bridged our initial discovery route to enable the delivery of bulk quantities to support critical in vivo studies.

ORGN 743

Scaffold Diversity of Cyclic Organic Frameworks in CAS Registry

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Scaffold analysis of 30M cyclic organic compounds from the CAS Registry was performed to study changes in structural innovation over time. Scaffolds, defined as the ring systems and the chain fragments connecting them, were used to assess the molecular novelty of the compounds. Our analysis presents findings on the pace of innovation and new regions of chemical space disclosed in recent years.

ORGN 744

Highly versatile synthetic approach to disciformycin and gulfmirecin antibiotics

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The advent of antibiotics has increased our quality of life significantly by changing the status of infectious diseases from life threatening to easily treatable. Bacterial evolution, however, has led to the development of various mechanisms of resistance, while at the same time the number of newly approved antibiotics is in decline. The combination of these trends together with the appearance of multi-resistant bacteria underlie the need for ongoing research. The natural product families of disciformycins and gulfmirecins are highly potent inhibitors of the bacterial RNA polymerase, presumably exhibiting a new mechanism of inhibition. A highly versatile synthetic approach towards this antibiotic family would lead to easy access of further analogs and thus an efficient exploration of their unknown binding site.

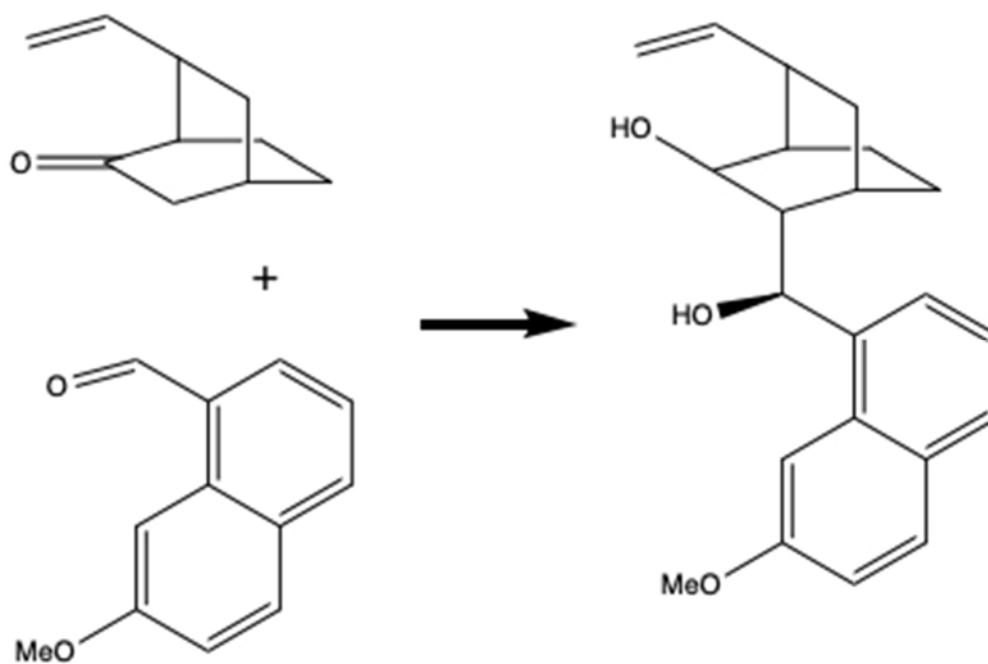
ORGN 745

Synthesis of 1,1'-dideaza-quinine: Proof of concept

Nate Schmitt, *nate.schmitt@tcu.edu*, Jackson Eber, Adam Montoya, David E. Minter. Texas Christian Univ, Fort Worth, Texas, United States

Quinine is a naturally occurring alkaloid with substantial medicinal relevance due to its historical role as an anti-malarial agent, although it is now used judiciously for special cases where the organism is resistant to newer drugs. While quinine is easily extracted from the bark of the Cinchona tree, the challenge of engineering a set of reactions to synthesize stereochemically pure quinine has captivated chemists for generations. Due

to its four stereocenters, the synthesis of this molecule can yield up to sixteen different stereoisomers. The purpose of this study is to validate the conceptual route proposed by Stotter, Friedman, and Minter¹ for a total synthesis of stereochemically pure quinine via the preparation of racemic 1,1'-Dideaza-Quinine—a model system that lacks both nitrogen atoms. While the total synthesis of quinine has been completed successfully by several other groups, our proposed route simplifies the process by relying on a tandem, diastereoselective aldol addition and reduction to establish two of the four chiral centers in a single operation. This route avoids overly expensive reagents and provides a more concise synthetic scheme.



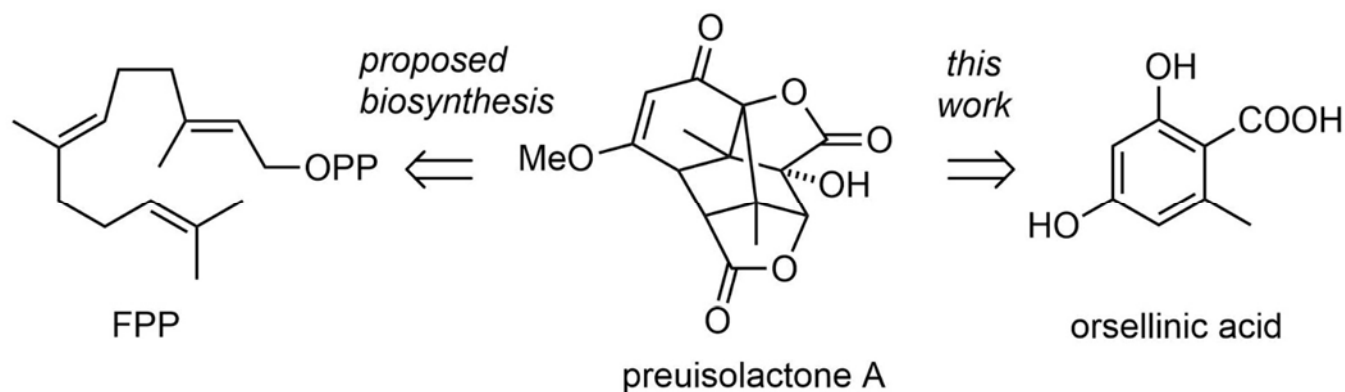
ORGN 746

Elucidating the origin of preisolactone A via biomimetic synthesis

Alexander J. Novak, alexander.j.e.novak@gmail.com, Claire E. Grigglesome, Dirk Trauner. Chemistry, New York University, New York, New York, United States

Preisolactone A is a recently isolated, racemic natural product from the endophytic fungus *Preussia isomera*. It is marked by a caged structure that contains seven adjacent stereocenters, two of which are quaternary. Biosynthetically, preisolactone A was proposed to be formed via the terpene pathway featuring several oxidative editing

steps. We propose an alternative biosynthetic hypothesis and have completed a short, biomimetic synthesis that follows our proposal. Its features are a purpurogallin-type [5+2]-cycloaddition, followed by a retro-Dieckmann reaction, vinylogous aldol addition, oxidative lactonization and a final, unprecedented benzilic acid rearrangement. The synthesis furnished preisolactone A in essentially three steps in high overall yield. Our work explains why preisolactone A has been isolated as a racemate and suggests that it is not a terpenoid but a phenolic polyketide.



ORGN 747

Progress towards the total syntheses of Impatien A and Ochotensimine: Utilizing a novel cyclization

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Impatien A, an isoindolone natural product isolated from *Corydalis impatiens*, and ochotensimine, a tetrahydroisoquinoline natural product isolated from *Corydalis ochotensis*, both possess a similar carbon scaffold featuring a spirocyclic stereogenic center. While ochotensimine and its des-methyl analog ochotensine have been shown to inhibit TNF- α , have been characterized as single enantiomers by optical rotation studies and by x-ray diffraction, and have been prepared via racemic syntheses, much less is known about the related impatien A. A unified approach to the preparation of the spirocyclic centers of these natural products poses a synthetic challenge both in its racemic and enantioenriched forms. We envision a metal-catalysed approach to the creation of these spirocyclic centers, which would be amenable to asymmetric induction. From readily available starting material, the southern indane half (identical to both natural products) and an appropriate northern arene half tagged with a cross-coupling handle can be synthesized with minimal chromatographic steps. Key palladium-

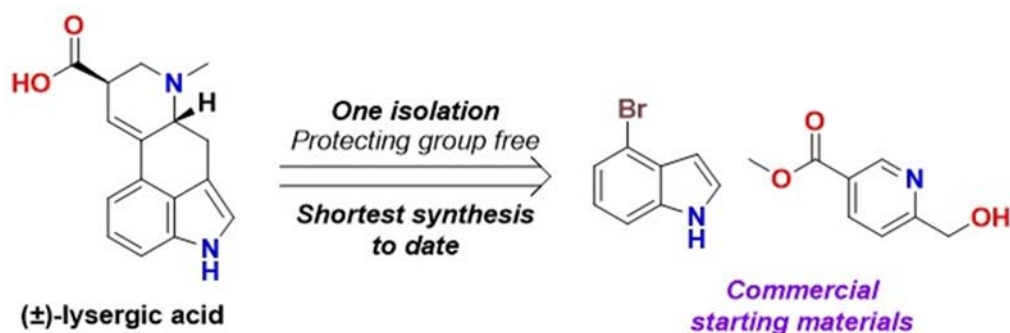
catalysed arylation and cyclization allow for the construction of the spirocyclic framework.

ORGN 748

Concise total synthesis of (±)-lysergic acid

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Ergot alkaloids have been of wide interest for almost a century, and new methodologies to synthesize the ergoline core are continuously being explored. We have developed a streamlined, protective group free synthesis of lysergic acid that will enable an expedient access to peptide ergot alkaloids. Key steps include a transition metal-free borrowing hydrogen reaction and an intramolecular coupling to construct the ergoline core. This sequence describes the shortest synthesis to date and allows for scaleup of tetracyclic intermediates. Lysergates, direct precursors to lysergic acid, can be telescoped and synthesized with only one chromatographic purification. Finally, during the pursuit of the total synthesis, a novel lysergate regioisomer was discovered, and a structure-activity relationship study is in progress.



ORGN 749

Convergent synthesis of anaephene B

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As strains of bacteria continuously evolve and become resistant to modern antibiotics, there exists a need for the development of new treatments to combat bacterial infection. *Staphylococcus aureus* (*S. aureus*) is known to develop such resistance and remains a leading cause of invasive infections and biofilm formation on prosthetic medical devices.

In 2018, Brumley *et al.* isolated Anaephenes A–C, natural products from a marine bacterium. Anaephene B was of particular interest as it was the only member of the series to demonstrate moderate antibacterial activity against *S. aureus* and *Bacillus cereus*. Because of the potential clinical utility of Anaephene B, investigation into synthetic production was warranted. A convergent synthesis of Anaephene B will allow for facile production of analogs consisting of various substituents on the aromatic ring and alterations in alkyl chain length, composition, or saturation.

ORGN 750

Synthetic studies on guaipyridine alkaloids rupestines D, L and M

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The guaipyridine alkaloids are isolated from plants native to China and Southeast Asia. One member of this family, cananodine, has activity against two types of hepatocellular carcinoma cell lines. We are targeting the synthesis of the rupestines to see if they, too, have biological activity. A total synthesis of rupestine D from 5-hexenenitrile and 5-hydroxy-2-methylpyridine is reported. An intramolecular Heck reaction forms the 7-membered carbocycle of the targets. Progress on the synthesis of rupestines L and M from rupestine D is also reported.

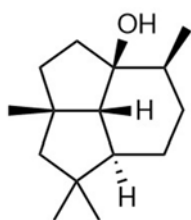
ORGN 751

Biomimetic four-step access to the sesquiterpene natural product presilphiperfolan-1 β -ol via supramolecular catalysis

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Terpenes are amongst the most structurally varied classes of natural products, and much of this variety arises from the complex cyclization/rearrangement cascade reactions catalysed by type I terpene synthase enzymes. Man-made, non-enzymatic catalysts able to promote this reactivity are currently lacking. Our group recently reported that a hexameric resorcinarene capsule can mimic terpene synthase enzymes by catalysing the tail-to-head terpene cyclization reaction. Additionally, we used this system to prepare a number of monoterpenes (such as α -terpinene and eucalyptol) and sesquiterpenes (such as isolongifolene and δ -selinene). However, these are commercially available compounds; to showcase the applicability of supramolecular catalysis to natural product synthesis, it would be highly desirable to identify capsule-catalyzed cascade reactions that lead to complex biologically active terpenes, difficult to

access by other means. In this context, we will present here our studies on the synthesis of the complex sesquiterpene presilphiperfolan-1 β -ol in four steps from inexpensive, commercially available starting material, employing the resorcinarene capsule as the catalyst for the key step. Importantly, in addition to the natural product itself, this approach provides access to unnatural analogues that would be inaccessible using the biosynthetic machinery.



(-)-presilphiperfolan-1 β -ol

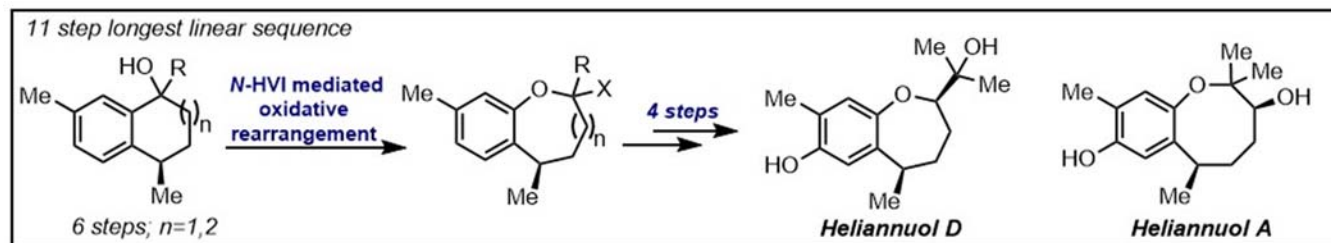
ORGN 752

Divergent approach to the total synthesis of (-)-heliannuol A & D via hypervalent iodine-mediated oxidative ring expansion

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The heliannuols are a family of phenolic allelochemicals extracted from *Helianthus annuus* which hold promise as a novel class of environmentally benign herbicides. The challenging medium-ring benzofused ether scaffold common to many family members has attracted much synthetic attention. Specific effort has been dedicated to the syntheses of heliannuols A and D, which possess 8- and 7- membered rings respectively and have striking similarities in their biosynthetic pathways. A common approach to these molecules has relied on an early stage kinetic resolution to set the key benzylic stereocenter and a biomimetic epoxide opening to access the key medium ring ether; unfortunately, this approach is low yielding and in particular, heliannuol A is accessed only in trace amounts. Herein, we describe a divergent approach to the asymmetric synthesis of the heliannuol family which efficiently constructs either the 7- or 8-membered medium ring ether scaffold; to date this has resulted in the efficient total syntheses of both (-)-heliannuol A and D. Central to this strategy is the synthesis of the medium-ring scaffolds via a novel oxidative ring expansion of benzylic alcohols with (bis)-cationic nitrogen-ligated hypervalent iodine reagents (*N*-HVIs) which was developed in our laboratory. The necessary alcohol substrates possessing the benzylic stereocenter were readily accessed in just 6 steps via a stereoretentive lithiation-borylation sequence. Late stage aryl hydroxylation delivers each of the natural products

in 11 steps in the longest linear sequence. It is envisioned that this strategy will enable rapid synthesis of analogues and further their development as novel herbicides.

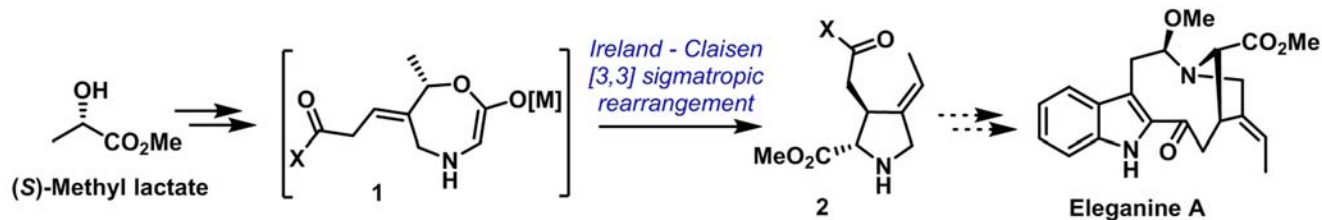


ORGN 753

Towards elegance A total synthesis

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Elegance A is an indole alkaloid possessing anticancer activity. The unique azabicyclo[6.2.1]undecane core as well as the intriguing biological properties makes this natural product an attractive target both from the medicinal and organic chemistry point of view. Retrosynthetically, the key building block for the total synthesis of elegance A is a substituted ethylidene proline ester **1**. This crucial fragment was successfully obtained starting from the readily available methyl lactate, employing an Ireland-Claisen rearrangement. The methodology developed for the synthesis of building block **1** as well as our attempts for completion of the total synthesis of elegance A will be presented.

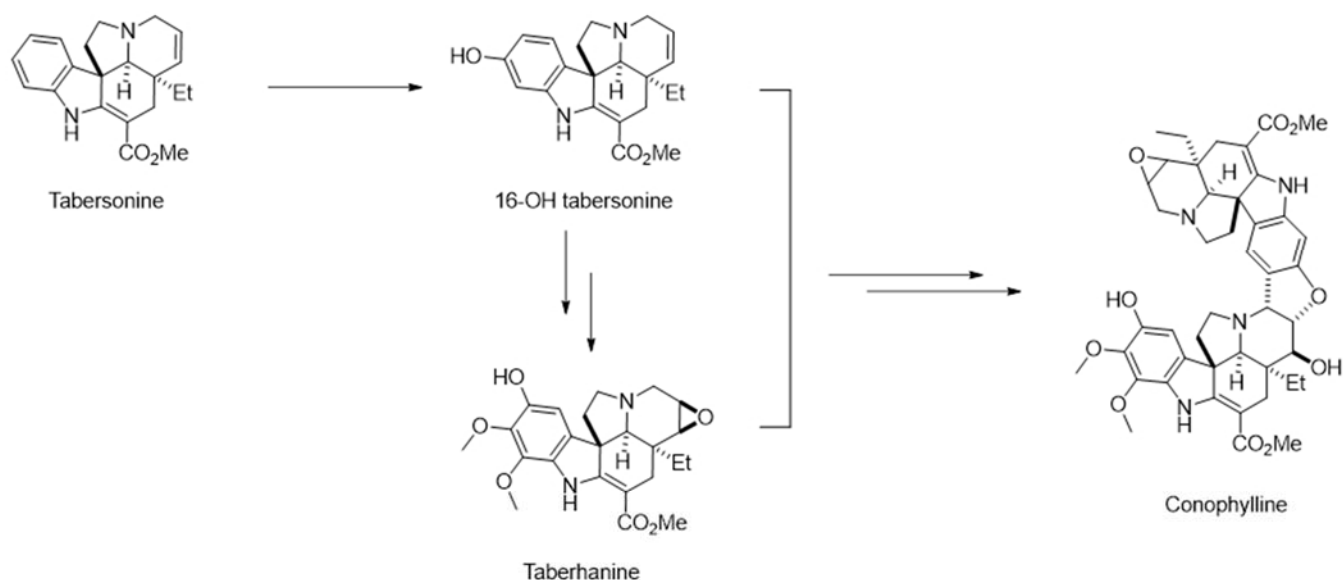


ORGN 754

Study of the semi-synthesis of (–)-conophylline

Jinfeng Kang, tuj50963@temple.edu, Alexander C. Gardner, Manish Walia, Rodrigo B. Andrade. Department of Chemistry, Temple University, Philadelphia, Pennsylvania, United States

(–)-Conophylline, a member of *aspidosperma-aspidosperma* type alkaloids, was first isolated from leaves of *Tabernaemontana divaricata* in 1992 and was believed to be a potential lead compound against cancer, diabetes, etc. Due to low isolation yields, structural complexity, as well as a limited number of synthetic routes, the more efficient access to (–)-conophylline has long been a challenging task. Based on our previous work, we have devised a new semi-synthetic route combining both synthetic and biochemical reactions towards (–)-conophylline from (–)-tabersonine, a commercially available monomeric *aspidosperma* alkaloid. The northern fragment of (–)-conophylline can be afforded via a site-selective C-H oxidation on (–)-tabersonine performed in yeast, and then applied to a sequential halogenation/borylation/Chan-Lam reaction to synthesize the southern fragment, (–)-taberhanine, a multiple-oxidized tabersonine derivative. A key Polonovski-Potier reaction will then be utilized in the coupling of these two fragments. This novel synthetic route offers a rapid and more efficient access to (–)-conophylline for the extensive evaluation of its bioactivities.



ORGN 755

Efforts toward the total synthesis of various marine natural products

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Today, we are seeing tremendous issues with the presence of multi-drug resistant bacterial infections and still don't have a very good way to treat these infections. Membranolide is a natural product that's produced by the Antarctic sea sponge *Dendrilla membranosa*. Membranolide was found to have a high bioactivity in breaking up Methicillin-Resistant *Staphylococcus aureus* (MRSA) biofilms. Due to this high bioactivity, we are currently working on the first enantioselective total synthesis of Membranolide. Another set of natural products, the Oxeatamides, are produced by the sea sponge *Darwinella oxeata* and are structurally similar to Membranolide. Due to this similar structure, we are also working towards the enantioselective total synthesis of these natural products, in order to potentially find multiple bioactive compounds that can be used to break up MRSA biofilms.

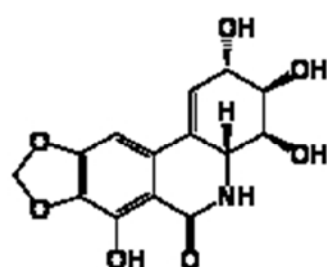
ORGN 756

Steps towards the total synthesis of Amaryllidaceae alkaloids

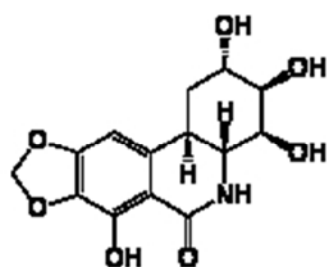
Adam Montoya, *a.p.montoya@tcu.edu*, **David E. Minter**. Chemistry and Biochemistry, Texas Christian University, Fort Worth, Texas, United States

Amaryllidaceae isoquinoline alkaloids, as well as their analogs, have long been of interest in research for drug discovery due to their biologically active nature. Many of these compounds have been found to be anti-tumor agents. Moreover, there have also been studies that show the effectiveness of these molecules against diseases such as Yellow Fever and other RNA-containing flaviviruses. Though these compounds are pharmaceutical prospects, their low natural abundance lowers their potential to become useful drugs. For this reason, many synthetic chemists have pursued novel routes to synthesize a wide variety of these compounds.

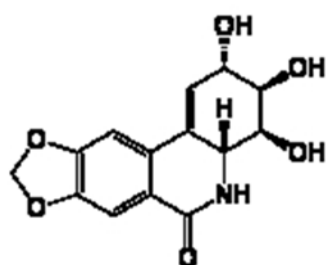
Techniques toward the synthesis of Amaryllidaceae natural products are presented herein. Manipulations were tested and optimized on a model system to save both time and funds while developing a synthetic pathway to be utilized in the formation of more complex compounds. Setbacks such as introducing additional hydroxyl groups have been encountered. However, adjustments are being made to alleviate such difficulties. Ultimately, the proposed scheme will allow for the synthesis of multiple biologically active alkaloids.



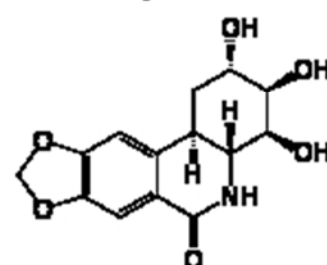
Narciclasine



Trans-
dihydronarciclasine



Lycoricidine



Trans-
dihydrolycoricidine

target molecules



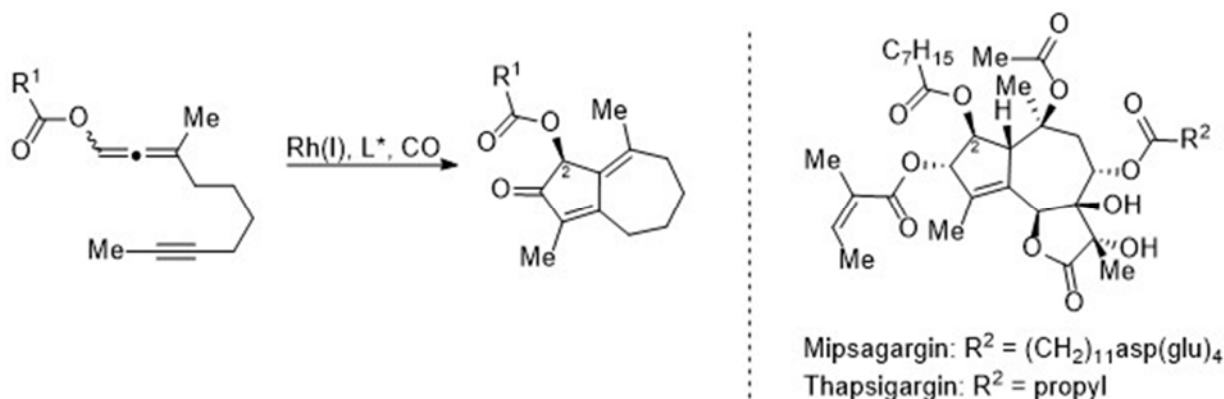
example of key step

ORGN 757

Synthesis of the carbocyclic core of thapsigargin using the asymmetric allenic Pauson–Khand reaction

Eric D. Deihl¹, edd25@pitt.edu, **Lauren Burrows**², **Kay M. Brummond**¹. (1) Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania, United States (2) National Energy Technology Lab, South Park Township, Pennsylvania, United States

Mipsagargin, a prodrug of the potent SERCA inhibitor thapsigargin (Tg), recently completed phase II clinical trials for several types of cancer. Currently, Tg and its analogs are only accessed using chiral pool starting materials limiting the structural and stereochemical diversity of these compounds. To address this limitation, we have developed an enantioselective synthesis of 5,7 ring systems using a Pauson–Khand reaction involving a dynamic kinetic asymmetric transformation (DyKAT) of allenyl acetates. This process has the potential to afford the complete carbocyclic skeleton of Tg as a single enantiomer at the C2 stereocenter. The functional group at C2 will direct the desired stereochemistry at the remaining chiral centers. Our progress towards these goals will be presented.



ORGN 758

Progress in the synthesis of cryptomaldamide congeners

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New methodologies for cleaving the terminal ester of cryptomaldamide precursors in the presence of the guanidine group were investigated. The poster will report on the variety of attempts and the successful conversion to the free carboxylic acid without affecting the guanidine group.

ORGN 759

Construction of new classes of targeted chemical screening libraries: Investigating new avenues for drug delivery via natural product diversification

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It is estimated that by 2050, gram-negative bacterial resistance to antibiotics will result in over 10 million deaths, surpassing cancer death rates. Structurally, gram-negative bacteria have evolved to develop mechanisms of drug resistance, which involve restricting the entrance of cytotoxic species into their cytoplasm and the ability to remove said agents via active efflux pumps. The ability to develop antibiotic resistance is correlated to the efficiency of removal by efflux pumps which results in a nonfatal concentration of antibiotics within the bacteria but allows for construction of resistance machinery. Our laboratory proposes that the restrictive transport mechanisms that limit antibiotic movement into the bacterium must be investigated. Porin channels upon the outer membrane of gram-negative bacteria are responsible for nearly 90% of antibiotic transport into the cytoplasm, however movement through porins is highly restrictive and dependent upon multiple physicochemical properties, such as molecular weight, cLogD, fraction sp³ centers, planarity, and spatial orientation. Investigating these properties are currently impossible via commercially available libraries. Our laboratory uses complex intermediates from total synthesis routes towards natural products for initial library construction, in which individual properties can be altered without altering the molecule's core structure. To date, we have shown that the charge and its location on the scaffold are critical for porin-mediated transport. Consequently, our group is synthesizing a library derived from the intermediates of the total synthesis of natural products brocazine F & G. These molecules were chosen for their antibacterial activity and rigid core structure with functional group amenability for diversification. Using commercially available L-Tyrosine and an array of reactions, a base scaffold was synthesized. To this scaffold various amino acids were attached, thus creating a small library. Currently, work is underway to synthesize additional libraries by coupling amino acids to varying groups on the scaffold.

ORGN 760

Synthetic modification of Reniochalistatin E to enhance drug delivery systems in cancer therapy

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Reniochalistatin E, is a natural cyclic peptide from a marine sponge, *Reniochalina stalagmitis*, that was found to be cytotoxic against myeloma (RPMI-8226, IC₅₀ of 4.9 µM), gastric (MGC-803, IC₅₀ of 9.7 µM), and ovarian (HeLa, IC₅₀ of 17.3 µM) cancer. Our laboratory completed the first total synthesis of Reniochalistatin E in 15 steps with 5% yield overall. Compared to the natural compound, the synthetic compound showed very similar cytotoxicity in myeloma (RPMI-8226, IC₅₀ of 4.5 µM) and ovarian cancer (HeLa, IC₅₀ of 16.9 µM). We are now interested in harnessing this molecule as a targeting agent against multiple myeloma. To do this, we hypothesize a covalent conjugation of 6-thiopurine (6TP) through a disulfide linkage will allow for targeted delivery. 6TP has been a primary anti-metabolite used to treat blood cancers since 1952. However, there are dosage limits for 6TP treatments due to severe cytotoxicity; including bilirubin, jaundice, and hepatotoxicity. Our laboratory has been interested in reapplying this molecule in ways that can reduce this off-target toxicity. A potential method to increase effectiveness and decrease dosage is to target the cancer cells with an appropriate drug delivery vehicle. We hypothesize that 6TP can be attached to a cysteine residue positioned where tryptophan resides on Reniochalistatin E and still retain activity because this was previously proven by substituting phenylalanine in the same position. After 6TP incorporation to Reniochalistatin E, in house *in vitro* testing will assess changes in cellular uptake and accumulation. The results from this research will serve as a guide for future syntheses of novel drug delivery systems for blood cancer treatment. To be presented is the construction of the phenylalanine analog and its biological evaluation, and as well as efforts towards a cysteine analog and potential drug conjugation and evaluation.

ORGN 761

Synthetic efforts toward balgacyclamide family of natural products: Total synthesis, new drug delivery vehicles, and beyond

Ashley Bartels¹, atbartels@ksu.edu, **Ryan Rafferty**², **Prathibha Desman**², **Hannah Henderson**³, **Arnaldo Torres Hernandez**³, **Thi Nguyen**³, **Yichao Zhang**¹, **Vinh Hoang**³. (1) Department of Chemical Engineering, Kansas State University, Manhattan, Kansas, United States (2) Chemistry, Kansas State University, Manhattan, Kansas, United States (3) Chemistry Department, Kansas State University, Manhattan, Kansas, United States

The balgacyclamide family are members of macrocyclic natural products composed of oxazoline and thiazole rings. The family was isolated from *Microcystis aeruginosa* EAWAG 251 in 2014 and was found to have three members, Balgacyclamide A-C (BagA-C). While these natural products are not notably cytotoxic towards cancerous cell

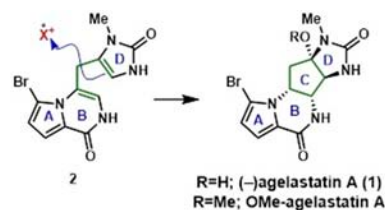
lines, they have shown selective penetration of rat myoblasts. Balgacyclamide A and B were shown to have activity against *Plasmodium falciparum* K1. These biological characteristics of this family drew the attention of our laboratory, as we suspect they can be used for drug delivery by conjugating cancer agents to them, since the problem with cancer agents is their low selectivity. We have focused on developing a synthetic route to BagA, composed of two oxazoline and one thiazole units. To be presented are our works towards these units, synthesis of BagA and its biological evaluation, construction of BagA analogs and applications into cellular delivery, and utilizing these cores to develop new chemical screening libraries.

ORGN 762

Halenium-ion induced cascade: Approach for the synthesis of agelastatin A

Emily Dzurka, erdzurka@svsu.edu, Hadi Gholami, Saeedeh Torabi Kohlbouni, Babak Borhan. Department of Chemistry, Michigan State University, East Lansing, Michigan, United States

Recent advances in the asymmetric halofunctionalization of alkenes has elevated the potential of these transformations to equal those that have had a significant role in enantioselective reactions of olefins in organic chemistry, such as dihydroxylations, epoxidations, aminohydroxylations, and aziridinations. Halofunctionalizations provide direct access to a variety of molecular families, including oxazolidinones, oxazolines, dihydrooxazines, etc. Yet, to establish its place, halofunctionalizations must be challenged in synthetic transformations of complex architectures such as those that appear in natural products. Numerous total syntheses of agelastatin A (**1**) have been reported to date, however, only two of these syntheses involve the late-stage construction of the densely functionalized C-ring. We envisioned the 5,6,5,5-tetracyclic core of agelastatin A (**1**) could be accessed from amide **2** through an asymmetric halenium-ion initiated cascade while simultaneously establishing all four contiguous stereocenters diastereoselectively in a single pot, and thus building the C-ring in a late stage operation. Mechanistic investigations using *HalA* (halenium affinity), a method developed for predicting reactivity of functional groups for halenium ions, reveal nuances that determine regio-, and chemoselectivity of electrophilic alkene halogenation reactions. Ultimately, we are guided by *HalA* values in our key step of the synthesis, to achieve high chemo- and regioselectivity of halogenation and subsequent halenium ion induced cyclization to synthesize agelastatin A.



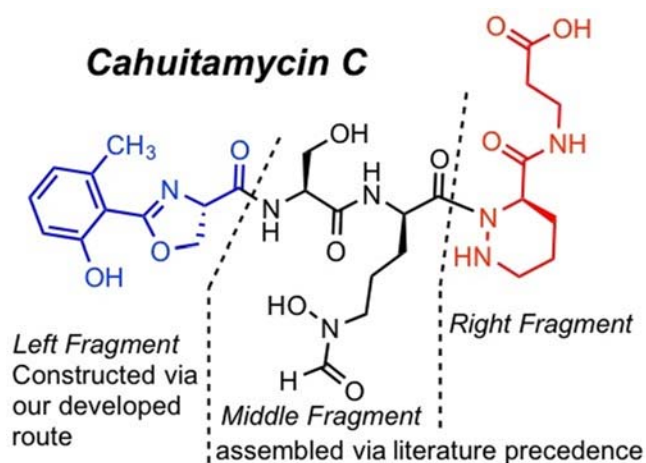
ORGN 763

Synthetic efforts towards the cahuitamycin family of natural products

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In the treatment of bacterial infections, antibiotic resistance is one of the major issues alongside the lack of novel antibiotics available for treatment. One of the major causes contributing to resistance are the biofilms that form within some bacteria, which acts as a shield to antibiotics. Iron has been identified as a factor that increases the biofilm forming ability of many bacteria. Hence siderophores which chelate iron could potentially assist in inhibiting biofilm formation. In 2016, the Cahuitamycin family of natural products were reported to be found in marine microbe *Streptomyces gandocaensis* and shown to inhibit biofilm formation of *Acinetobacter baumannii*, one of the ESKAPE group of major nosocomial opportunistic resistant pathogens. Of the three Cahuitamycins discovered, Cahuitamycin C possessed the highest potency with an IC_{50} of 14.5 mM. Given the strong activity of Cahuitamycin C and our lab's interest in development of new methods for general transport of agents into gram-negative bacteria, we have undertaken to develop a synthetic route towards this bioactive agent.

Construction of the Middle and Right Fragments have been accomplished upon building from literature precedence. Accessing the Left Fragment required the development of new protocols, which has resulted in a route that allows for synthetic manipulation upon the phenol ring. Currently, synthetic efforts at the coupling of these fragments are underway. To be presented will be the synthetic chemistry gaining access to these fragments, the anticipated total synthesis of Cahuitamycin C, and the biological evaluation of the natural products and fragments. Investigations into identifying the mode of transport into *A. baumannii* will be undertaken with the aims of determining the portion of Cahuitamycin C responsible.



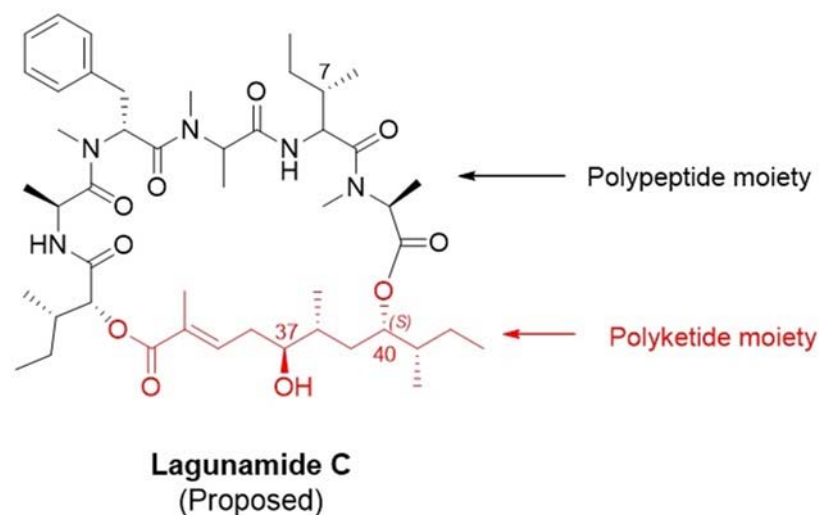
ORGN 764

Synthetic efforts towards Lagunamide C and proposed Lagunamide E

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Lagunamides are macrocyclic depsipeptides that belongs to the aurilide class of natural products. Isolated from the marine cyanobacteria *Lyngbya majuscula* in Singapore, these lagunamides show very high cytotoxicity against the cancer cell lines; lymphoma (P388), lung (A549), prostate (PC), ileocecal colorectal adenocarcinoma (HCT8), and ovarian (SK-OV) with IC₅₀ values in nanomolar concentrations of 2.4, 2.6, 2.1, and 4.5 respectively. Furthermore, they possess antimalarial properties towards *Plasmodium falciparum* with an IC₅₀ in micromolar range. Lagunamide C (LagC) is specially found to display high potency against human colon carcinoma cell line (HCT8) with an IC₅₀ of 2.1 nM, antimalarial activity with an IC₅₀ of 0.29 μM and weak anti swarming activity

against Gram-negative bacterial strain *Pseudomonas aeruginosa* (PA01). LagC has been shown to have the most diverse, as well as most potent cytotoxic properties of the family. Structurally, the family is comprised of a polypeptide backbone and a polyketide unit, the latter differs between the family members. The presence of an extra methylene unit within LagC, ambiguity of two stereocenters of the polyketide, and its potent biological activity drew our lab's attention. To be presented is our current efforts on the development of a modular route towards the polyketide, allowing for final structural determination, and the assembly of the polypeptide unit. Our synthetic work towards the first total synthesis of this potent natural product will also be disclosed. Furthermore, our efforts at elucidating how LagC enters cells and the determination of the pharmacophore will be presented. In 2019 Lagunamide D was isolated, differing from LagA in a methyl group deletion upon the exocyclic sec-butyl group (here a propyl). Based upon the discovery of LagD and our synthetic endeavours, we will be proposing the structure of LagE, its synthesis, and plans for searching for it in *L. majuscula*.



ORGN 765

Utilizing an enantioselective chloroetherification strategy towards the total synthesis of napyradiomycin A1

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With prior experience in chlorofunctionalization of olefins, we had surmised that a chloroetherification route to Napyradiomycin A1, a natural product with demonstrated high anti-microbial activity against gram-positive bacteria, would not pose a major

challenge. Nonetheless, the enhanced reactivity of the phenolic hydroxyl group proved detrimental in our initial attempts, with substantial non-catalyzed reactivity that substantially reduced enantioselectivity. Our efforts to tame this reaction, yielding synthetically useful yields and enantioselectivities will be discussed. Furthermore, strategies towards finalizing the total synthesis of Napyradiomycin A1 will be presented. Key to these efforts is a regioselective Michael addition to an electronically differentiated quinone, with anticipated stereocontrol resulting from the stereogenic chlorine substituted carbon. SAR studies with this family of natural products are lacking, and thus we hope to alleviate this through our modular synthetic route, enabling alterations to the A ring (resulting from a Diels-Alder reaction), and the geraniol appendage, which is installed via the Michael reaction.



ORGN 766

Optimizing the synthesis of 1-((4,9-dioxo-4,9-dihydronaphtho[2,3-b]thiophen-2-yl)oxy)-N,N,N-trimethylmethanaminium chloride as an organic redox flow battery material

Peter L. Cruz Parrilla, pcruzparri@haverford.edu, **Robert L. Broadrup**, Department of Chemistry, Haverford College, Haverford, Pennsylvania, United States

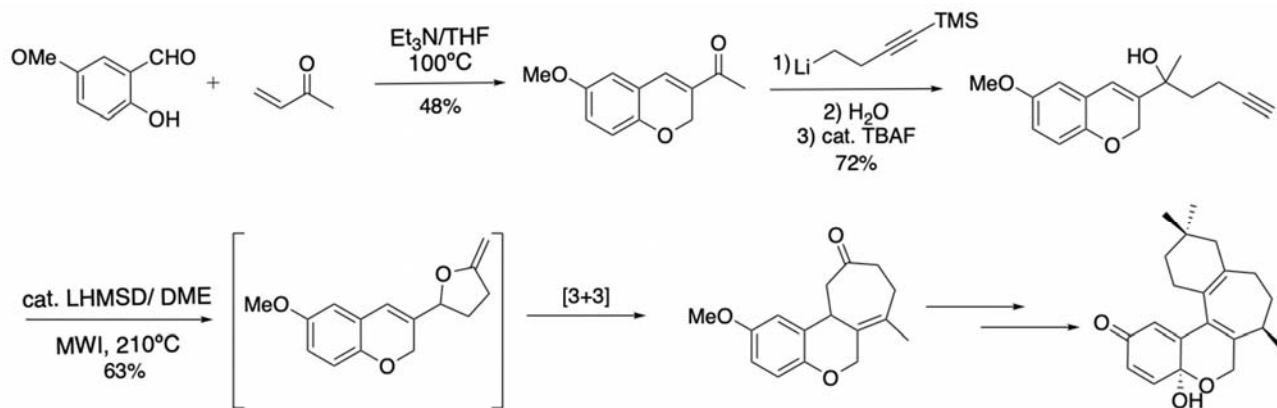
In light of the evident environmental problems we face, there is a high demand for greener energy storage methods. Organic redox flow batteries (ORFBs) are a promising green method to replace common, heavy metal-dependent energy sources, for they may be cheaper to make, highly scalable, and better suited for dissolution in aqueous as opposed to organic solvents. Additionally, many biological processes found in nature, such as photosynthesis, depend on redox active compounds for energy transfer, and such processes may offer structural clues for the development of ORFBs. Furthermore, it has been reported that functional group substitutions may allow for tunable reduction potential in these redox-active species. Here we present the progress toward the synthesis of 1-((4,9-dioxo-4,9-dihydronaphtho[2,3-b]thiophen-2-yl)oxy)-N,N,N-trimethylmethanaminium chloride, a substituted thiophenoquinone inspired from aerobic *Sulfolobus* archaeobacteria, as a promising organic redox flow battery material.

ORGN 767

Progress towards the total synthesis of frondosin D via tandem cyclization/claisen rearrangement

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The frondosin family of natural products, consisting of five compounds A-E, was first isolated in 1997 from the marine sponge *dysidea frondosa*, and they have been determined to have anti-inflammatory, anti-tumor and HIV- inhibitory activity. There is currently no synthetic pathway for the total synthesis of frondosin D. This study explored two distinct pathways for the synthesis of the tetracyclic structure of frondosin D. Both of the explored approaches include a 7-membered ring tricyclic compound as the key intermediate which can be obtained via tandem 5-exo dig cyclization/Claisen rearrangement methodology developed by the Ovaska group.



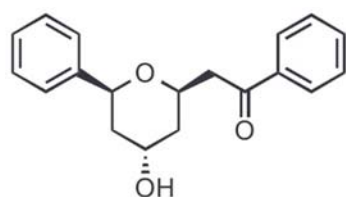
ORGN 768

Synthetic studies towards ezomycin and related natural products

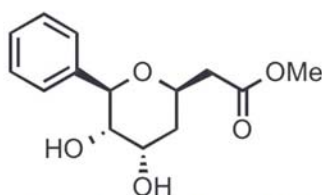
Jesse More, jdmore@loyola.edu. Chemistry, Loyola University Maryland, Baltimore, Maryland, United States

The ezomycins are structurally interesting bacterial natural products which have a rich history in the synthetic community, including a number of total and partial syntheses. These molecules and related natural products invite chiron approaches to their syntheses, starting with commercially-available and stereochemically rich molecules.

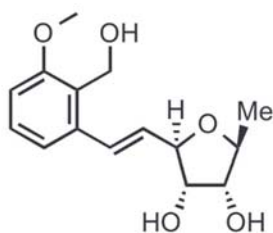
The advantages of such chiral-pool type strategies are balanced by many stereochemical issues that must be solved. Past studies in our lab focused on the molecules varitriol and diospongin A, which required inventive stereochemical strategies to edit the native chirality in the starting materials into that of the final target molecules. More recent efforts have been directed towards the ezomycin class of natural products, which have required not only new stereochemical strategies, but also the development of new annulation tactics. Results from a chiral-pool based synthetic study, focusing on new ring-forming reactions will be presented.



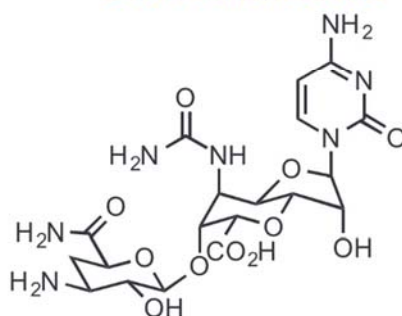
Diospongin A



Goniothalesdiol



Varitriol



Ezomycin A₂

ORGN 769

Synthesis of new organic borazine compound derivated from 3-amino-2-naphthol as starting material for analysis of chemical and physical properties

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Borazines are inorganic compounds with alternate B-H and N-H bonds. Its best known by the name inorganic benzene due to the similarities with the benzene ring. The organic borazine compounds is not well developed, but it is well known that the compound can be used for hydrogen storage and optoelectrical properties. Among the different functionalization approaches, the replacement of carbon atoms by isostructural

elements has emerged as a versatile strategy to tune their optoelectronic and mechanical characteristics. In particular, the replacement of C=C bonds by covalent B-N couples leads to molecular isosteres displaying a strong local dipole moment responsible for their peculiar electronic. Our research group is highly interested in the synthesis of a new oxazaborolidine compound. This compound will be used for the trimerization of a new 3-amino-2-naphthol Borazine. To achieve the preparation of the borazine a series of synthesis steps were developed. First, THF was added followed of 3-amino-2-naphthol. In a round bottom flask, $\text{BH}_3\cdot\text{DMS}$ was added and dissolved in THF. The 3-amino-2-naphthol solution was slowly added using injection pump for 1 hour. The reaction mixture was left stirring for 3 hour at room temperature. This step represents the synthesis of Noval Oxazabororolidine derived from 2-amino-3-nathphol and this product is the precursor to the new borazine. The synthesis keeps in optimization for best result. The future plan will be to work with O-phelynenediamine, the product is already a more stable compound for the synthesis of diazaborolane followed trimerization of the borazine.

ORGN 770

Synthesis and evaluation of meroterpenoid derivatives of puupeheone

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Marine life creates a large variety of structurally diverse and bioactive compounds and metabolites. One class of these compounds is the Meroterpenoid family of polyketide and terpenoid precursors. These compounds have activity encompasses possible uses as antitumor, antibiotic, antiviral, and antifungal agents¹. Our lab is currently focusing on the cytotoxic meroterpenoid Puupeheone originally isolated in 1979 from and encrusting yellow sea sponge in Hawaii, but has since been isolated from sea sponges of the orders *Verongida*, *Dictyoceratida*, *Dendroceratida*, and *Haplosclerida*. Puupehedione, a metabolic derivative of puupehenone, has 87.6 $\mu\text{g/ml}$ activity against active tuberculosis (TB) and 15.4 $\mu\text{g/ml}$ activity in an induced dormancy model of TB. Isolation of these compounds from natural sources in large quantities is difficult. We are interested in creating derivatives of these compounds for antibiotic screening purposes. Our synthesis started with commercially available (+) scalareolide modified to access a borono-sclareolide terpenoid donor. With this intermediate terpenoid donor in hand functionalization of the boronic acid with a quinone was tested, this method was originally reported by the Baran lab. Using benzoquinone and 2-methoxybenzoquinone we formed (+)-chromazonarol with a 60% yield and 8-epi-19-methoxypuupehenol with a 20% yield respectively. The same intermediate was subjected to Suzuki coupling to form (+)-Yahazunol in 16% from borono-sclareolide. These compounds will be tested for activity against *Mycobacterium tuberculosis*.

ORGN 771

Sulfonamide-induced gauche effect versus the Thorpe-Ingold effect in Richman-Atkins cyclization

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Polyazamacrocycles are some of the strongest and most versatile ligands, with just one example, cyclen, being coordinated to every metal from lithium to plutonium. Richman and Atkins's transformatively high-yielding cyclization of polyazamacrocycles, reported in 1974 without the use of high dilution or template effects, has long been attributed to the Thorpe-Ingold effect. The Thorpe-Ingold effect (also known as the *gem*-dimethyl or *gem*-disubstituent effect) can be described as an angle compression or a conformational restriction due to steric interactions between large substituents. The steric repulsion of the bulky toluenesulfonyl protecting groups in Richman-Atkins cyclization is thought to restrict internal rotation in the macrocyclic precursors, resulting in curved conformations which differ little from the conformation of the cyclic product. Surprisingly, in the 45 years since the report of the Richman-Atkins cyclization there has been no evidence of the Thorpe-Ingold effect, which the present work demonstrates using multiple crystal structure overlays of protected precursors with the protected macrocycle.

More surprisingly, additional work successfully achieved Richman-Atkins cyclization with exceedingly small groups (formyl, methyl, hydrogen) on the center nitrogen of the diethylene triamine precursor. These results at least partially contradict the Thorpe-Ingold effect, indicating that sterics on the central nitrogen are not responsible for the curvature required for cyclization. The solid-state and solution-state conformations of toluenesulfonyl(diethylene triamine) and toluenesulfonyl(diethanolamine) derivatives have been studied via X-ray diffraction and NOESY. Potential energy surfaces show, with respect to each ethyl "arm," sulfonamide and sulfonate moieties adopt a *gauche* conformation which is lower in energy than the *anti* conformation, similar to the so-called fluorine *gauche* effect. The effects of electrostatic polarization and hyperconjugation contributing to the observed *gauche* effect are weighed.

The sulfonamide protecting groups provide significant steric bulk but also require extremely acidic deprotection conditions that have greatly hindered functionalization of azamacrocyclic backbones. Hopefully, an understanding of the electronic effects contributing to Richman-Atkins cyclization as presented herein will allow a wider variety of protecting groups to be used to enable more facile synthesis of polyazamacrocycles.

ORGN 772

Catalyst-controlled chemodivergent reaction of α -diazo- β -ketoesters and enol ethers: Regioselective synthesis of highly substituted indoles

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Highly substituted indoles are among the most privileged structures in medicinal chemistry, found in a vast array of biologically active natural products and pharmaceutical compounds. Due to their relevance, methodologies that allow for the regioselective synthesis of indoles are highly desirable. Herein, we would like to discuss our efforts towards the indole core by exploring the chemodivergent reactions of α -diazo- β -ketoesters and enol ethers. We found that copper (II) catalysts led to the exclusive formation of 1,2-Dihydrofuran (DHF) acetals, which upon Lewis-Acid treatment afforded the corresponding indoles. In contrast, rhodium (II) catalysts led to the direct formation of the regioisomeric indoles through an alternative reaction mechanism. Furthermore, the choice of enol ether dictated the regioselectivity of the reaction products, allowing for a modular and regioselective synthesis of highly substituted indoles.

ORGN 773

Tropolonate salts as efficient acyl transfer catalysts

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The synthesis of carboxylic acid esters is an important chemical transformation in organic synthetic toolbox. Steglich's pioneering work using DMAP as acyl transfer catalyst in conjunction with DCC in esterification reactions in 1978 opened up the research field of esterification reactions under mild reaction conditions. Since then, the development of new efficient methods for acylation reactions of alcohols, thiols and amines is still of widespread interest, especially for the synthesis and functionalization of complex bio-relevant compounds like peptides or proteins.

Based on our previous studies on tropone-promoted chlorination and oxidation of alcohols, we envisioned that tropolonate salts can be used as suitable Lewis bases for acyl transfer catalysis. Indeed, the esterification reaction of alcohols with carboxylic acid anhydrides or acid chlorides using catalytic amounts of tropolonate salts proved to be an efficient way to give the corresponding carboxylic acid esters and thioesters on a wide range of substrates.

ORGN 774

Remote desaturation of amines by radical relay

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A dual-catalytic mechanism to enable remote desaturation of amines has been developed. This mechanism proceeds through an N-centered radical that is initiated by an iridium photocatalyst. Subsequent 1,5-hydrogen atom transfer (HAT) translocates the radical, which can be trapped by the copper catalyst and undergo elimination furnishing a distal alkene product. Mechanistic Investigations provide insight into the HAT and elimination as well as the nature of the selectivity of this transformation.

ORGN 775

Sulfonyl fluoride: Lab scale synthesis and applications in SuFEx chemistry

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Sulfur (VI) fluoride exchange (SuFEx) is a new click reaction, which creates stable structures via sulfate or sulfonate linkages. SuFEx has already found many applications, from synthesis of macromolecules, surface chemistry, medicinal chemistry, and biological probes. However, very limited availability of SO_2F_2 for lab purposes has limited wider use of this chemistry. We have developed an ex-situ, on water, safe and inexpensive route for SO_2F_2 synthesis and applied in the synthesis of high molecular weight polysulfates from parent phenols. The reaction developed here is atom economical and results in complete cycle where byproduct generated can be reused in the same reaction cycle, virtually eliminating the chemical waste. The SO_2F_2 was also found to be a stable electrophilic dehydrating reagent in various organic transformation for synthesis of nitriles and amides.

ORGN 776

Catalytic ring expansions of cyclic alcohols enabled by proton-coupled electron transfer

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Aliphatic rings are key structural elements in functional molecules ranging from pharmaceuticals and natural products to ligands and polymers. Accordingly, methods that enable direct interconversion between ring-size isomers are important technologies that can provide useful retrosynthetic disconnections and facilitate the evaluation of structure–function studies. While appealing in principle, the development of general catalytic methods for ring-size modulation remains limited in practice, as successful transformations require orchestrating non-degenerate C–C bond-breaking and bond-forming events to occur in a controlled and sequential fashion. Moreover, the conversion of readily accessible 5- and 6-membered ring starting materials to either medium- or small-ring compounds is often thermodynamically challenging due to a concomitant increase in ring-strain.

We report here a catalytic method for the modular ring expansion of cyclic aliphatic

alcohols. In this work, proton-coupled electron transfer activation of an allylic alcohol substrate affords an alkoxy radical intermediate that undergoes subsequent C–C bond cleavage to furnish an enone and a tethered alkyl radical. Recombination of this alkyl radical with the revealed olefin acceptor, in turn, produces a ring-expanded ketone product. The regioselectivity of this C–C bond-forming event can be reliably controlled via substituents on the olefin substrate, providing a means to convert a simple n -membered ring substrate to either $n+1$ or $n+2$ ring adducts in a selective fashion. In addition, the strategy can also apply to various classes of cyclic and acyclic olefin substrates, affording $n-1$ or $n-2$ ring contraction products, as well as inter- or intramolecular [1,3] sigmatropic rearrangement products.

ORGN 777

Reaxys-PAI predictive retrosynthesis: Rewiring chemistry and redesigning synthetic routes

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Synthetic organic chemistry is one of the cornerstones of the drug discovery process and is crucial for rapid navigation of increasingly complex druggable chemical space. It is also critical in determining discovery cycle times and development speeds associated with drug candidates. The knowledge and experience of researchers has always been the key to combining chemical reactions into successful synthetic schemes.

However, chemical synthesis and route design is still a significant challenge. Merck quotes that 55% of the time, a benchmarked reaction fails. Therefore, a radical and innovative step change in synthesis is needed. Computer-aided retrosynthesis would be a valuable tool but until recently it was slow and provided results of unsatisfactory quality. Further to this, software that devise effective schemes for synthetic chemistry have depended on the input of rules from researchers.

Waller and Segler *et al.* in collaboration with Elsevier have developed a ‘deep learning’ computer program that produces blueprints for the sequences of reactions needed to create small organic molecules, such as drug compounds. This artificial-intelligence tool has digested nearly every reaction ever published (> 15 million) and has the potential to transform the way synthetic & medicinal chemists work in the future. Segler & Waller *et al.* tested the synthetic routes that the program generated in a double-blind trial with 45 organic chemists from two institutes in China and Germany and the routes have proven scientifically sound and robust.

Increasing the success rate in synthetic chemistry would have a huge benefit in terms of speed and efficiency on drug-discovery projects, as well as cost reduction. Reaxys-PAI Predictive Retrosynthesis solution developed in collaboration between Elsevier and Waller and Segler *et al.* deploys next generation technologies to augment chemical synthesis and chemist knowledge helping drive innovation, time and cost savings. This talk will discuss the solution and with feedback from chemists demonstrating its utility with some examples from recent drug development programs.

ORGN 778

Unusual salicyl-substituted triazole synthesis from aurones

Arjun Kafle¹, *ak3y@mtmail.mtsu.edu*, **Shrijana Bhattarai**¹, **Scott T. Handy**². (1) Molecular Biosciences, Middle Tennessee State University, Murfreesboro, Tennessee, United States (2) Chemistry, MTSU, Murfreesboro, Tennessee, United States

Attempts to prepare azido-aurones for potential use as photoaffinity labels via a copper-catalyzed azidation of halo-aurones failed to afford the desired compounds. Instead, it was determined that the reaction resulted in unusual salicyl-substituted triazoles. This transformation has proven to not require a metal catalyst but simply proceeds thermally in the presence of sodium azide in polar protic solvents such as DMSO and DMF. A wide range of substitution patterns was tolerated to afford triazoles in modest to excellent yield featuring two clear sites for alkylation chemistry, along with the great opportunity for modification in the ring system. Given this potential utility and the ease of access, they could prove to be a new and unexplored scaffold for further development.

ORGN 779

Nickel-catalyzed Suzuki–Miyaura couplings of amides: Scope and applications

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The Suzuki–Miyaura coupling has become one of the most important and prevalent methods for the construction of carbon–carbon bonds. Although palladium catalysis has historically dominated the field, the use of nickel catalysis has become increasingly widespread due to its unique ability to cleave carbon–heteroatom bonds that are unreactive toward other transition metals. This presentation will focus on the development of the nickel-catalyzed Suzuki–Miyaura coupling of aliphatic amides derived from aliphatic carboxylic acids. In addition, a mild reduction protocol uncovered during these studies will be described. Lastly, applications and extensions of these methodologies will be disclosed to allow for unconventional synthetic conversions. Collectively, these studies reinforce the notion that amides, despite classically being considered inert substrates, can in fact be harnessed as synthons for use in C–C bond forming reactions through cleavage of the amide C–N bond using non-precious metal catalysis.

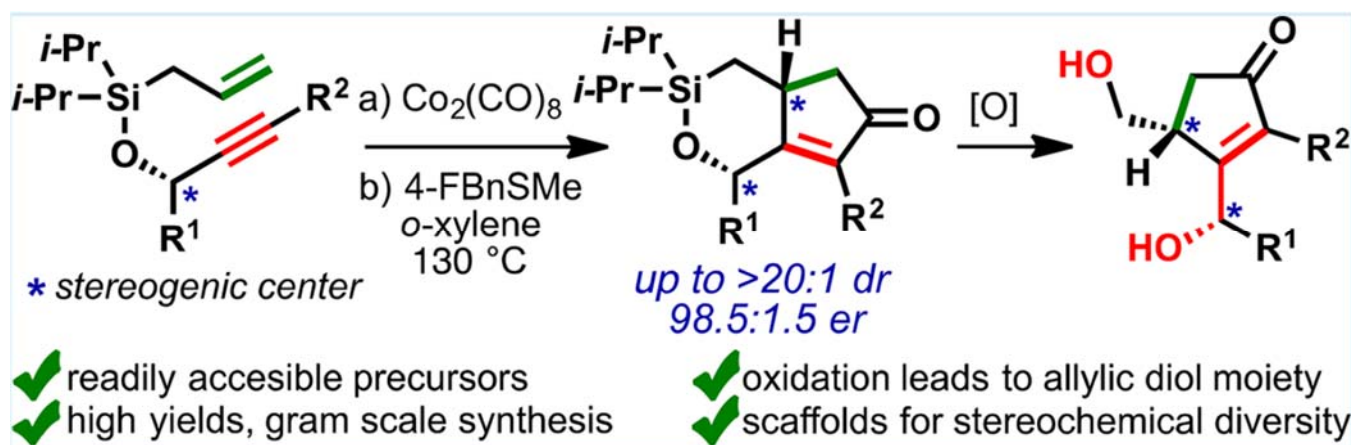
ORGN 780

Development of silicon and boron tethered Pauson-Khand reactions

Dionicio Martinez-Solorio¹, *nicho.orgchem@gmail.com*, **Austin G. Gallagher**¹, **Huan Tian**¹, **Osmar A. Torres-Herrera**¹, **Shuai Yin**¹, **Anxin Xie**¹, **Daniel M. Lang**¹, **Michael R. Gau**², **Patrick J. Carroll**². (1) Chemistry, Drexel University, Philadelphia, Pennsylvania,

United States (2) Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania, United States

The Pauson-Khand reaction (PKR) is a prominent transformation for the synthesis of cyclopentenones. In particular, the intramolecular variant has been widely exploited. Although notable advances have been made, the intermolecular PKR remains restricted to strained, cyclic, or symmetrical olefins. Problems arise from alkene regioselectivity, and mixtures of cyclopentenones are often observed. A tactic to define the regioselectivity is to use a removable tether, preferably one that allows further functionalization. Our research group is currently developing silicon and boron-containing tethers in the PKR reaction because of the excellent potential for post-cyclization manipulation. This talk will focus on our efforts that have now led to the successful development of the first diastereoselective $\text{Co}_2(\text{CO})_8$ -mediated Pauson-Khand reaction (PKR) of siloxy-tethered 1,7-enynes for the synthesis of cyclopentaoxasilinones. Oxidation of the resulting cyclopentaoxasilinones delivers densely functionalized, stereoenriched β -alkylated cyclopentenones, which are inaccessible by intermolecular PKRs. Preliminary results towards the development of a catalytic variant, future directions, and advantages/disadvantages of boron vs. silicon tethers in the PKR will also be discussed.



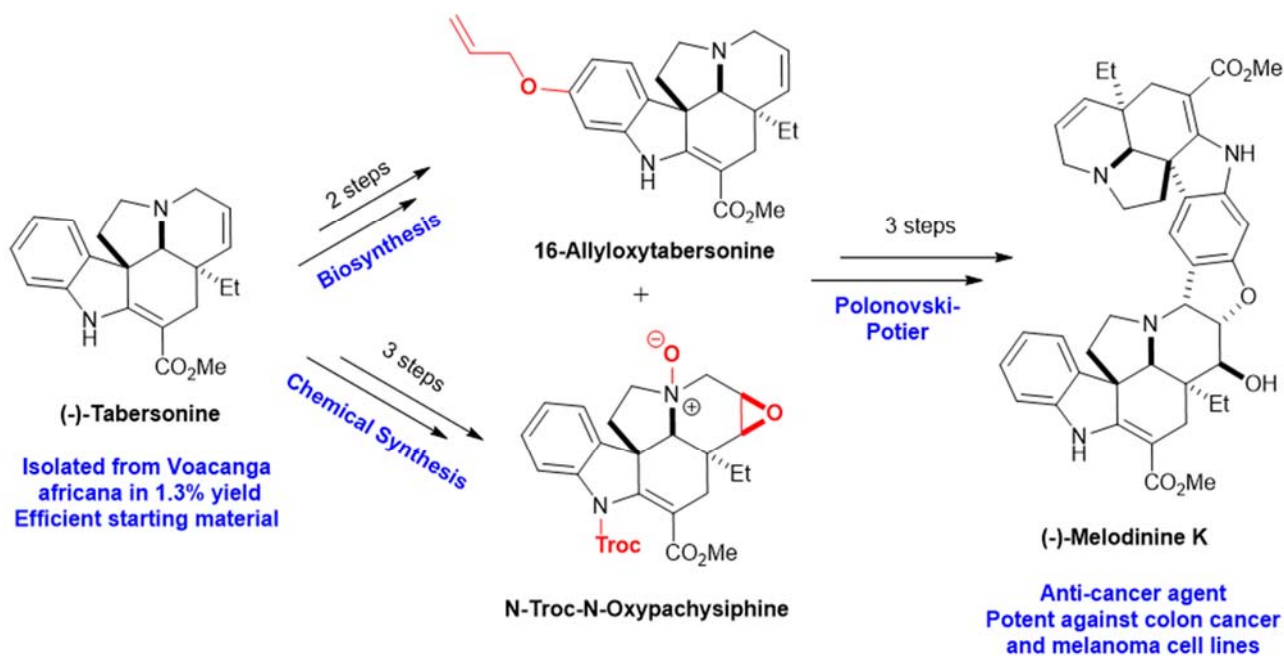
Access to Highly Functionalized Cyclopentenones via Diastereoselective Pauson-Khand Reaction of Siloxy-Tethered 1,7-Enynes

ORGN 781

Semi-synthesis and biological evaluation of bis-indole alkaloid (–)-melodinine K: Case study in efficiency

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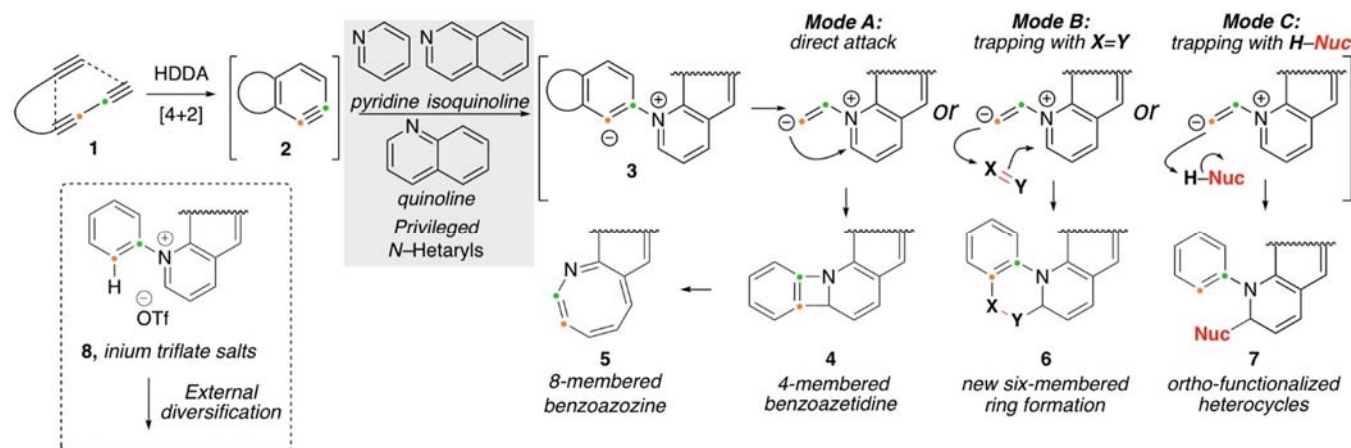
Efficiency has become a key organizing principle in modern natural product synthesis. In assessing a synthetic target, practical criteria such as time, cost, and effort invariably track with step-count and production scale. Therefore, the principle of minimum chemical distance must be employed. Access to bioactive *Aspidosperma-aspidosperma* bis-indole alkaloid scaffolds have been limited due to low isolation yields and long synthetic routes. In 2011, Kam and coworkers isolated (–)-melodinine K, a promising anti-cancer agent, from *Melodinus tenuicaudatus* leaves, in 0.001% yield. Through a combination of chemistry and biochemistry, the first novel semi-synthesis of (–)-melodinine K is reported in eight steps from a commercially available mono-indole alkaloid, (–)-tabersonine. This monomeric alkaloid can be isolated from *Voacanga Africana* seeds in a staggering 1.3% yield, eliminating the need for a multistep total synthesis. This efficient route utilizes an enzymatic biotransformation in yeast to perform site-selective C-H oxidation which enables multigram quantities of late-stage monomers. Synthetic reactions then allow coupling of the two monomers through a key Polonovski-Potier reaction. Evaluation of semi-synthetic (–)-melodinine K by the National Cancer Institute found that it was potent against various colon cancer and melanoma cell lines. This novel synthetic route establishes a template for fast access to diverse scaffolds of various bioactive bis-indole alkaloid natural products as well as new bis-indole alkaloid analogs to probe biological activity.



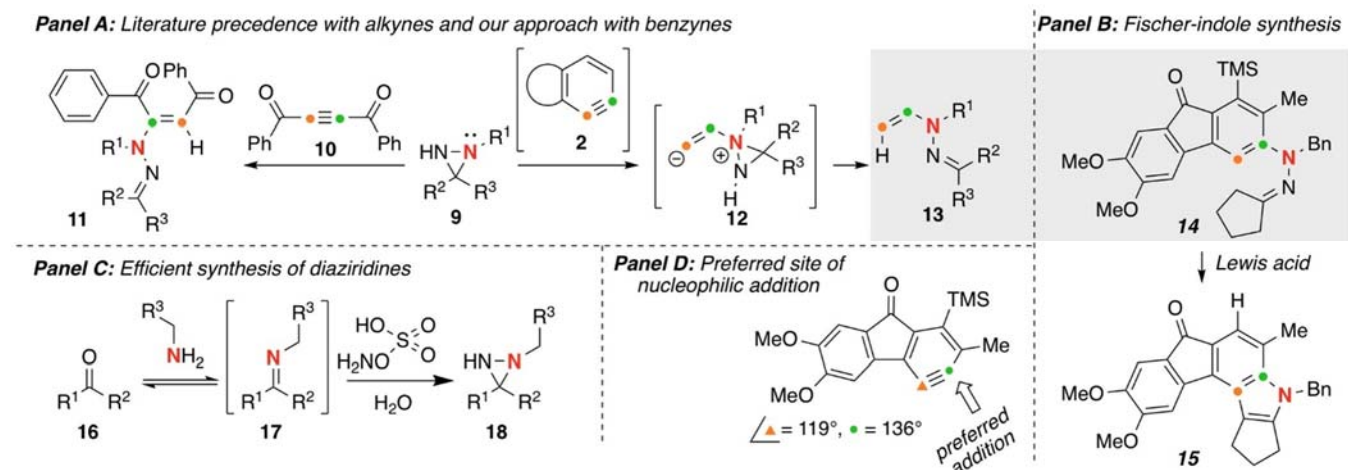
Reactions of thermally generated benzyne with *N*-heterocycles: Pathway and product diversity

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Thermally generated arynes (by the hexadehydro-Diels–Alder (HDDA) reaction) can undergo trapping reactions with *N*-heterocycles such as *N*-heteroaromatics (quinoline, isoquinoline and pyridine) and strained cyclic amines (diaziridines). The initially formed 1,3-zwitterionic species (a) can collapse intramolecularly to give novel 1 : 1 adducts of the heterocycle and benzyne; (b) protonate intramolecularly within the zwitterion, followed by a ring-opening event to generate hydrazones; (c) can react with an externally added, electrophilic third-component to give functionalized heterocyclic products; or (d) can react with an external protic nucleophile to produce, following collapse of the ion pair resulting from protonation of the zwitterion, a variety of three-component assemblies. Mechanisms for formation of some of the 1 : 1 adducts are supported by DFT methods. The hydrazones generated from this strategy can be used to synthesize fischer indole adducts. I will present these different modes of reactions that can be realized to construct multifunctional heterocyclic motifs and also to gain some of their mechanistic insights.



Reactions of thermally generated benzyne with six-membered *N*-heteroaromatics: pathway and product diversity



Reactions of diaziridines with benzynes give *N*-arylhydrazones

ORGN 783

Iodine mediated one-pot cyclization-alkylation and cyclization-oxidation methodologies for the synthesis of 2,3-disubstituted benzo[*b*]thiophenes

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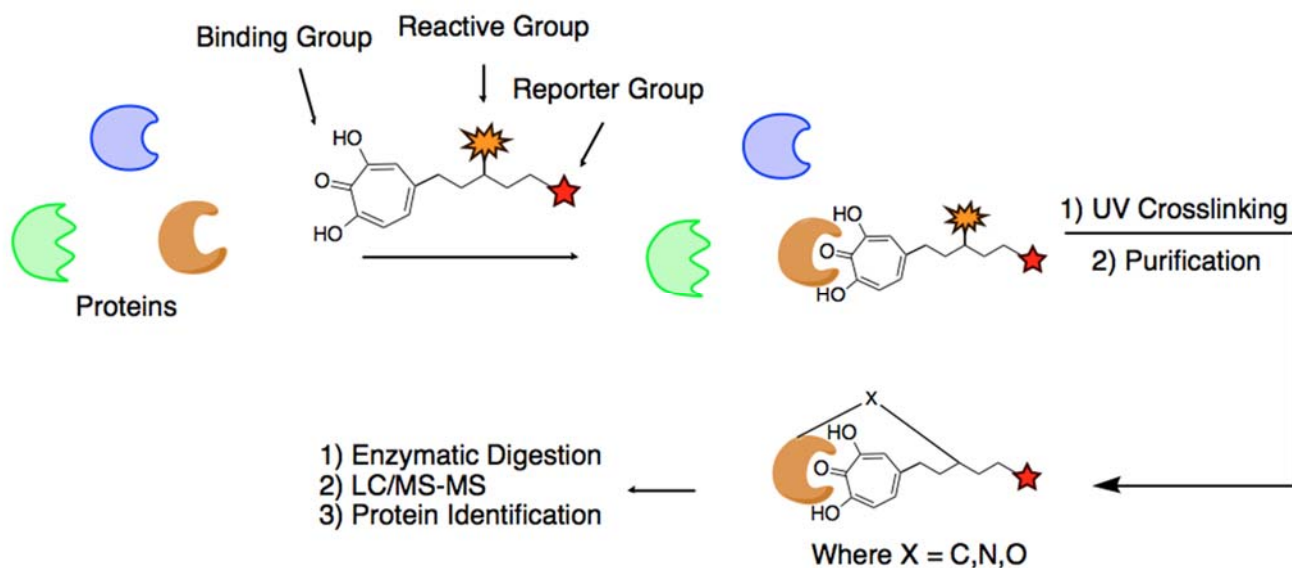
Herein, we report two methodologies for the synthesis of 2,3-disubstituted benzo[*b*]thiophenes. In the first methodology we report a one-pot cyclization-alkylation reaction where iodine acts as a cyclizing agent as well as a catalyst. Iodine mediated cyclization of various propargyl alcohols resulted in the formation of benzo[*b*]thiophen-2-ylmethanol, which undergoes iodine catalyzed alkylation reaction using various 1,3-dicarbonyl molecules. In the second one-pot methodology we report another iodine mediated cyclization reaction in combination with an alcohol oxidation reaction. In this cyclization-oxidation methodology benzo[*b*]thiophene obtained from an iodocyclization reaction of alkynyl thioether is further reacted with potassium carbonate and iodine to give an aldehyde or a ketone moiety. Both methodologies employ mild conditions and results in high yield of desired functionalized benzo[*b*]thiophenes. Sulfur heterocycles are well established in the field of material science and pharmaceuticals. The properties of benzo[*b*]thiophenes have been showed case in phosphorescent organic light-emitting diodes and dye-sensitized solar cells due to thermal stability and electronic properties. Benzo[*b*]thiophenes are also well-known for their range of biological activities They are known to exhibit antiviral, antimalarial, anti-inflammatory, anti-tumor, anti-mitotic activities. Benzo[*b*]thiophene core structures are also well established as estrogen receptor modulator and kinases inhibitor.

ORGN 784

Synthesis and analysis of photoreactive activity-based troponoid chemical probes

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Successfully profiling the entire suite of proteins encoded for by the human genome would have far-reaching implications for human health and drug discovery. One of the most powerful techniques utilized for protein identification is activity-based protein profiling (ABPP), a method in which a small molecule binds to a protein's active site irreversibly, and in so doing tags the biomolecule with a reporter group that is then used to visualize, isolate, and characterize the bound protein. ABPP has a broad range of applications that include the determination of upregulated proteins in diseased cells, as well as identification of novel protein-ligand interactions that could be useful for drug development. Herein, we will describe our ongoing efforts towards the synthesis and evaluation of troponoid-based ABPP probes. We will introduce a novel cyclopropanation/autoxidation approach that has enabled access to a wide variety of troponoid classes in a single step, including tropolones and hydroxytropolones. These troponoid probes have been successfully utilized in a variety of chromatography-tandem mass spectrometry-based proteomics experiments, and have identified several therapeutically-relevant protein targets in mammalian cells. Furthermore, the experiments have unveiled a unique property of troponoids' photolability more generally.



ORGN 785

Regioselective synthesis of fluorosulfonyl 1,2,3-triazoles from bromovinylsulfonyl fluoride

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A regioselective metal-free preparation of 4-fluorosulfonyl 1,2,3-triazoles from organic azides and a hitherto underexplored bromovinylsulfonyl fluoride building block is described. This reaction is very general and was extended to the synthesis of various sulfonates, sulfonamides, and sulfonic acid derivatives of triazoles and other azole heterocycles which would otherwise be difficult to access by existing methods.



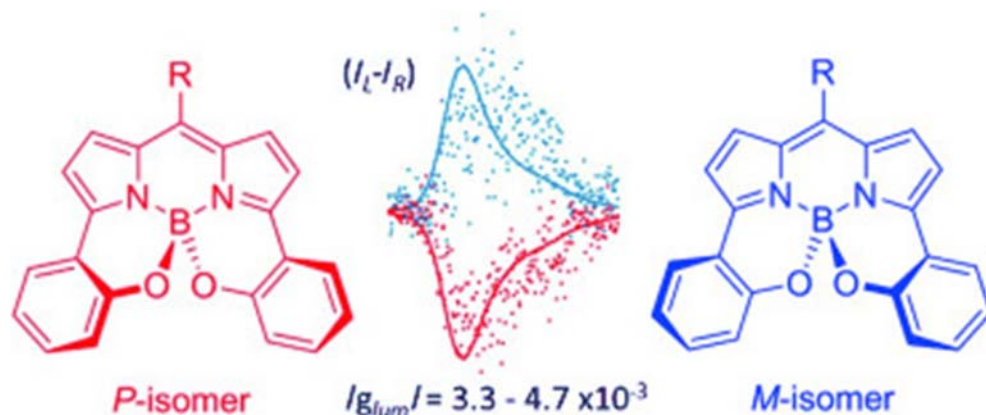
ORGN 786

Enantioselective Synthesis of helically chiral boron chelated dipyrromethenes (BODIPYs) capable of circularly polarized luminescence

Michael Hall, Michael.Hall@newcastle.ac.uk. Newcastle University, Newcastle upon Tyne, United Kingdom

Helically chiral boron chelated dipyrromethenes showed solution phase circularly polarized luminescence (CPL) in the red region of the visible spectrum. Desymmetrisation of the parent BODIPYs can be achieved through O chelation of the central boron atom by one or more *ortho* phenolic substituents at the 3/5 positions. The resulting helical perturbation of the fluorophore resulting in CPL with high luminescence dissymmetry factors and fluorescence quantum yields. In this presentation, we will both

advances in molecular design, leading to improved CPL efficiencies, as well as novel synthetic approaches for enantioselective synthesis of helically chiral BODIPYs.



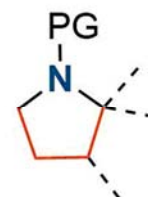
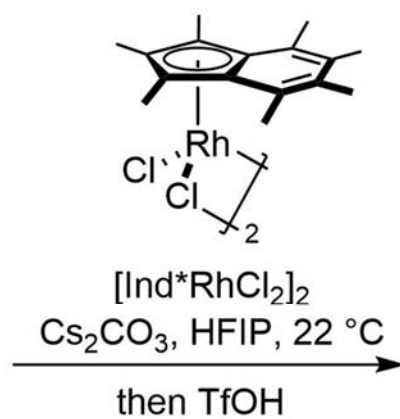
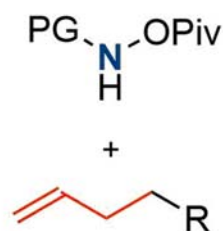
CPL from a helically chiral *N,N,O,O*-boron chelated dipyrromethene

ORGN 787

Rh(III)-catalyzed formal [4+1] approach to pyrrolidines from unactivated terminal alkenes and nitrene sources

Sumin Lee, sl4060@columbia.edu, **Honghui Lei**, **Tomislav Rovis**. Chemistry, Columbia University, New York, New York, United States

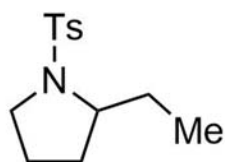
We have developed a formal [4+1] approach to pyrrolidines from readily available unactivated terminal alkenes as 4-carbon partners. The reaction provides a rapid construction of various pyrrolidine containing structures, especially for the diastereoselective synthesis of spiro-pyrrolidines. The reaction underwent smoothly with alkenes containing substituents at C4 and C5 positions, giving desired products in good yields. A variety of functional groups were well tolerated, providing corresponding products in moderate to good yields. The reaction was particularly efficient for the synthesis of spiro-pyrrolidines. It is also worth noting that greater than 20:1 diastereoselectivities were achieved regardless of trans/cis ratio of starting cyclohexanes. Mechanistic investigation suggests a Rh(III)-catalyzed intermolecular aziridination of the alkene and subsequent acid-promoted ring expansion for the pyrrolidine formation.



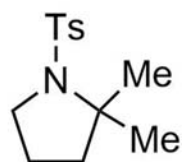
*simple unactivated alkenes
as 4-carbon coupling partner*

Formal [4+1]

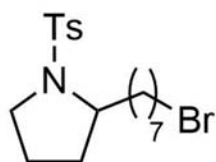
22 examples
 40-75% yield
 > 20 : 1 dr



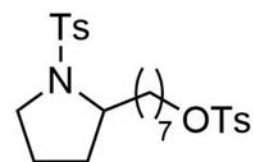
61%



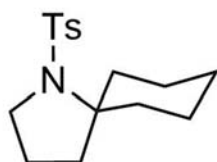
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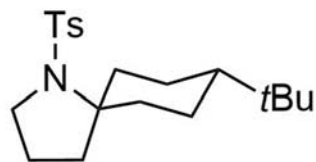
57%



71%



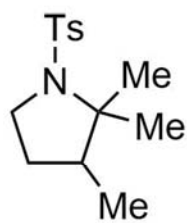
60%
>20 : 1 *dr*



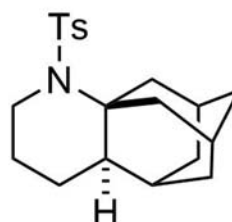
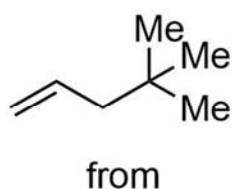
73%
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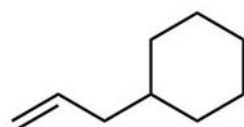
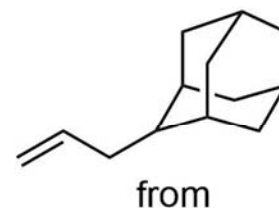
53%
>20 : 1 *dr*



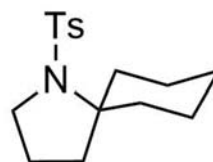
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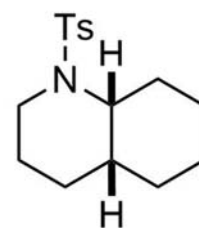
71%



Ts-NH-OPiv
[Ind* RhCl_2] $_2$
 Cs_2CO_3
HFIP, 22 °C
then TfOH
T °C



or



At **22 °C**: 18 : 1 (71%)
At **60 °C**: 1 : 14 (66%)

ORGN 788

Diastereoselective synthesis of *trans*-2,3-disubstituted γ -butyrolactones

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A short strategy for the synthesis of dimeric *trans*-2,3-disubstituted γ -butyrolactones from simple esters is described. This three-step process uses the diastereoselectivity of titanium enolate homocoupling chemistry to dimerize and set the *trans* stereochemistry in very high selectivity in the molecules described. The resulting diesters are converted to 1,4-diols which are then lactonized by a one-pot selective oxidation-lactonization sequence to give the desired γ -butyrolactones. The method is used in the synthesis of various 2,3-diaryl and dialkyl γ -butyrolactones.



ORGN 789

Use of microwaves to synthesize propargylic ethers as precursors of 1,2,3-triazoles in click reactions

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Use of click chemistry as an effective way to synthesize triazolic compounds have grown in recent years. Click reactions can be done under normal conditions of temperature and pressure; nevertheless, they need the use of azides and terminal alkynes as precursors. At present, many click reactions involve propargylic ethers as precursors of new 1,2,3-triazoles, providing different and important radicals to the compound. These alkynes are mostly synthesized using phase transfer catalysts, as TBAB (tetrabutylammonium bromide), and many hours of reaction (on average 24 h). Therefore, reported methodology for these ethers delay the fast development of new triazoles. Changing conditions and using microwave reactor it is possible to decrease time and increase efficiency of these reactions.

Putting phenol derivatives, K_2CO_3 , DMF and propargyl bromide at temperature of 100°C,

power of 100 W and 20 minutes is a way to synthesize propargylic ethers. The mixture reaction is cooled and final product is purified via liquid-liquid extraction or vacuum filtration.

ORGN 790

Compared methods to synthesize 1,2,3-triazoles

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Recently, the use of 1,2,3-triazoles have been important in medicine, because these compounds have a broad spectrum of biological activities. This involves that the development of new methodologies to synthesize them in the laboratory will be necessary in research in organic chemistry. Currently, the use of microwaves in the synthesis processes has been useful, since these allow the reduction of reaction times and the increase of yields.

The methodology consists to synthesize triazoles using aromatic azides and propargyl ethers, modifying the conventional protocol for click reactions. Two modified methods are carried out: the first is a temperature increase at 60 ° C for 6 h in a heating plate, and the second is the introduction of microwaves to heat the reaction at the same temperature for 30 min. A click reaction is performed under normal conditions (room temperature, 24 h) as a control in the comparison of the methods

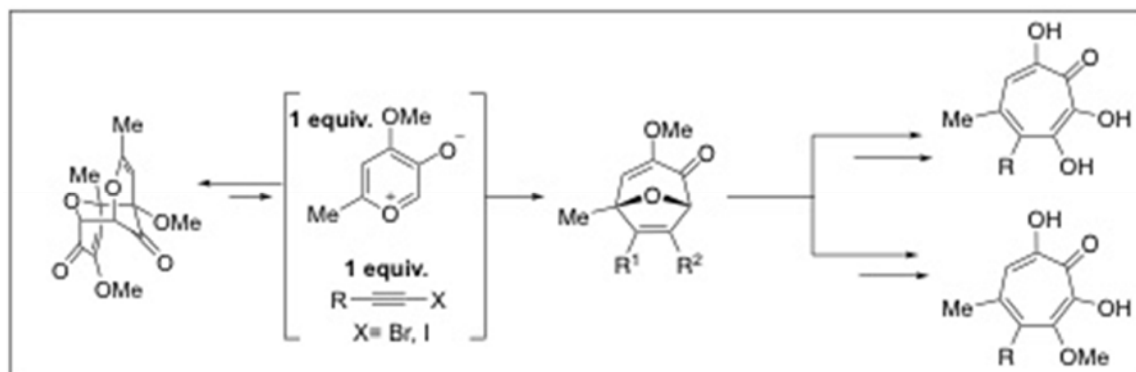
ORGN 791

Synthesis of highly oxygenated troponoids utilizing oxidopyrylium cycloaddition chemistry

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α -Hydroxytropolones (α HTs) are a class of molecules that have been identified as lead compounds for several human diseases. Prior to Murelli group studies of [5+2] oxidopyrylium cycloaddition/ring opening strategies towards α HTs, structure activity relationship studies on these molecules have been limited due to a scarcity of efficient synthetic methods to access them. Recently, we've described the successful adaptation of this [5 + 2] oxidopyrylium cycloaddition/ring-opening for 3,7-dihydroxytropolone (3,7-dHT) synthesis. During these studies it was found that that a stoichiometrically equivalent reaction between oxidopyrylium dimer and halogenated alkyne takes place quantitatively at elevated temperatures. The oxidopyrylium ylides are generated through the cycloreversion of oxidopyrylium dimers, which provides a 'clean' source of ylide

absent from base and/or acid commonly present as reagents or byproducts using standard intermolecular oxidopyrylium cycloaddition procedures. Therefore, in cases where the reaction is quantitative, the reaction mixture only contains product and solvent, and thus highly pure material can be obtained after removal of solvent. As the method works particularly well with iodoalkynes, we also describe examples of modifications of the resultant iodide-containing bicycles. Finally, we describe how by adding an alcohol incorporation, α HTs, as well as 3,7-dHTs, can be synthesized using stoichiometrically equivalent, intermolecular [5+2] oxidopyrylium cycloadditions with halogenated alkynes.



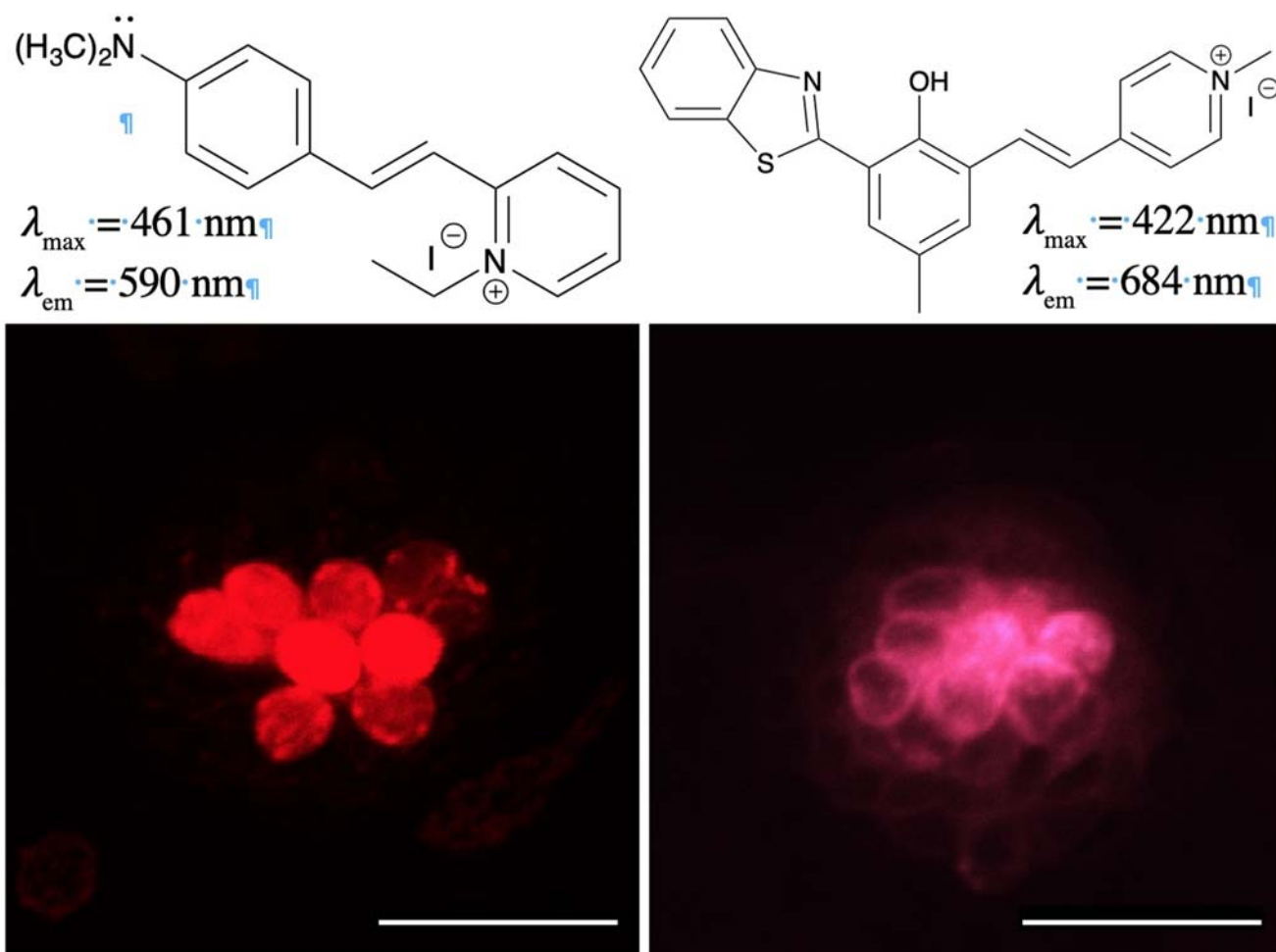
ORGN 792

NIR emitting styryl dye with large stokes shift to enable co-staining study on Zebrafish neuromast hair cells

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Hearing loss is a significant public health problem, and the “loss of sensory hair cells” is one of two leading causes in humans. Advanced imaging reagents are desirable for understanding the role of the surrounding support cells on the loss or regeneration of the hair cells. A styryl dye was found to exhibit NIR emission ($\lambda_{em} \gg 684 \text{ nm}$) with a very large Stokes shift ($\Delta\nu \gg 9190 \text{ cm}^{-1}$), due to incorporation of excited state intramolecular proton transfer (ESIPT) mechanism. When used to stain live zebrafish embryos, the probe was found to exhibit good selectivity in targeting neuromasts, which are sensory organs on the surface of the fish’s body. The finding was verified by direct comparison with the known neuromast-labeling reagent, 4-Di-2-ASP. In contrast to the existing styryl

dyes that label neuromast hair cells, the new probe labeled *both* neuromast hair cells *and* the surrounding support cells, while giving discernable signals. The study thus illustrated a useful tool to aid the developmental study of two closely related cell types on the mechanosensory sensory organ of zebrafish, which is a powerful animal model for hearing loss research.

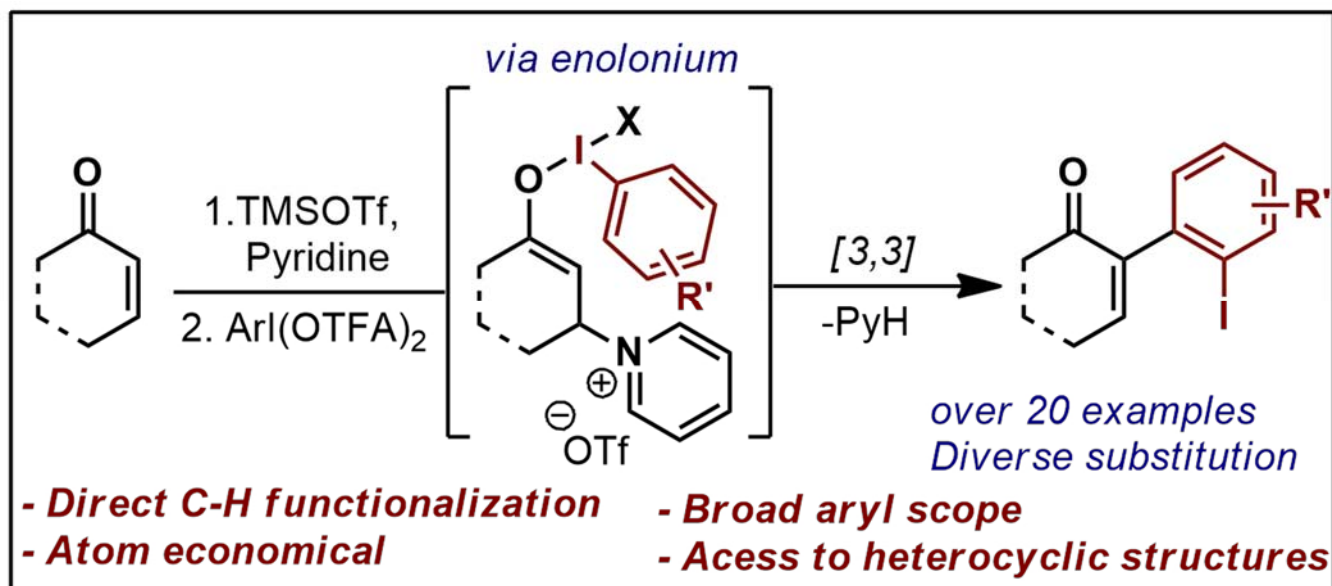


ORGN 793

Direct C–H arylation of enones with $\text{ArI}(\text{OCOR})_2$ reagents

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α,β -Unsaturated ketones constitute a versatile building block for the synthesis of complex molecules and efficient methods for their functionalization are of continued interest. In particular the α -arylation of enones is a powerful and ubiquitous transformation, however there exists only one method for direct C–H arylation and it is limited in both practicality and scope. Enone α -arylation is most commonly achieved via a stepwise halogenation/cross-coupling sequence. Although highly enabling, the required pre-functionalization, as well as the use of expensive and toxic catalysts detract from the efficiency and practicality of this approach. Herein, we demonstrate the direct C–H α -arylation of enones via a reductive iodonium-Claisen rearrangement of *in situ* generated pyridinium silyl enol ethers and I(III) reagents. The method utilizes $\text{ArI}(\text{OTFA})_2$ species as the aryl source, which are readily accessed from the parent iodoarenes and tolerant of a wide range of substitution. Furthermore, the arylated products retain the valuable iodide functional handle, and further derivatization to diverse indoles and benzofurans is demonstrated. Mechanistically, the reaction proceeds through formation of an O–I enolonium species followed by reductive iodonium-Claisen rearrangement and this reactivity is contingent on the presence of the *b*-pyridinium moiety. This method represents an atom and step economical approach to access diverse α -(2-iodo)arylated enone motifs, providing rapid entry to heterocyclic structures and complex molecular architectures.



ORGN 794

Steric effects on the temperature dependence of primary kinetic isotope effects in hydride transfer reactions in solution

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Temperature dependence of primary (1°) kinetic isotope effects (KIEs) for H-transfer reactions has been used as a measure to determine the H-tunneling mechanism. How structure affects such dependency has never been systematically studied. The weaker the temperature dependence of the 1° KIEs, the smaller the isotopic activation energy difference ($\Delta E_a = E_{aD} - E_{aH}$). It has been recently frequently observed that the ΔE_a value is small and close to zero with wild-type enzymes but increases as the active site of the enzyme is deformed due to mutation. This has been explained in terms of different structures of tunnelling ready states (TRS's) that have different donor-acceptor distances (DADs), following a full-tunneling model within which the 1° KIE is DAD dependent. The wild type enzyme has a tightly associated TRS with DAD whose change is not sensitive to temperature resulting in weak temperature dependence of 1° KIEs, whereas a mutant has a loosely associated TRS whose DAD could vary and hence is readily altered by temperature resulting in stronger temperature dependence of 1° KIEs. In this study, we hypothesize that a smaller ΔE_a value would be observed in H-transfer systems that have a more sterically hindered thus more rigid TRS. Hydride transfer reactions with various sterically hindered substrates (NADH/NAD⁺ models) in acetonitrile were designed to investigate this hypothesis. The steric effect on rigidity of the TRS's and ΔE_a 's will be discussed. The relationship between structure and ΔE_a will be compared for reactions in solution *versus* in enzymes.

ORGN 795

Mechanistic insights of photoredox catalysis using an alpha-amino arylation

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Photoredox reactions offer great potential for use in synthetic organic chemistry. Using photoredox catalysis has allowed synthetic chemists to generate radical intermediates under mild conditions by using photosensitizers to convert light into chemical energy. Despite these promises, a detailed, experimentally-validated mechanistic understanding of photoredox cycles is often lacking. Using an alpha-amino arylation as a model reaction, we have investigated the kinetic pathways, rate constants, and reaction intermediates of the individual steps within photoredox cycle using steady state photochemical methods, transient absorption spectroscopy, and electrochemical techniques. This report will detail these atomic-level interactions and how they control the overall reaction yield.

ORGN 796

On the mechanism of singlet oxygenation of the prenyl-containing natural product glycocitrine II

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We present a density functional theoretical study, implicating two independent elimination reactions to reach a dihydrofuran rutacridine in the singlet oxygenation of the C-prenylated natural product glycocitrine-II. This study predicts a reaction between singlet oxygen and glycocitrine-II to reach rutacridine first by an H₂O₂ expulsion process, and second by an intermolecular O atom transfer to glycocitrine-II and a subsequent alcohol dehydration step. The computed results presented here reveal an aspect of the singlet oxygen chemistry to reach a hydroperoxide product by a non-¹O₂ 'ene' reaction. The study is proposed to be significant in the biosynthesis mechanism of acridinone natural products.

ORGN 797

Product distribution in the cross aldol condensation of 4,4'-bicyclohexanone with aromatic aldehydes

Amy M. Balija¹, *abalija@radford.edu*, *Cooper T. Burgin*¹, *William J. Nape*¹, *Kateri Schoettinger*¹, *Timothy J. Fuhrer*². (1) Chemistry, Radford University, Radford, Virginia, United States (2) Chemistry/Physics Department, Radford University, Radford, Virginia, United States

Dibenzylidenecyclohexanone are prepared by condensing benzaldehyde derivatives with cyclohexanone under basic conditions with minimal by-products and no purification. Due to these desirable features, the cross aldol reaction has been utilized to prepare macromolecular frameworks. Thus, a library of macromolecules can be prepared readily with simply modifying the starting materials. In this presentation, benzaldehyde derivatives were condensed with 4,4'-bicyclohexanone to form cross-aldol condensation products. Because 4,4'-bicyclohexanone contains four potential sites where an aldol condensation can occur, this reaction can construct unique 3D architectures in a single step. Studies were initiated to control the site-selectivity of the cross-aldol condensation of 4,4'-bicyclohexanone with excess benzaldehyde derivatives. Kinetic and thermodynamic aldol condensation products were discovered by ¹H NMR spectroscopy and LC-MS. The mechanistic implications of these results were explored using computational studies and substituent group effects.

ORGN 798

Modulating aromatic pathways in porphyrins at the molecular level

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Porphyrins have been studied extensively in various fields including chemistry, biology, physics, nanotechnology, and materials sciences due to the unique reactivity and properties associated with the aromatic macrocyclic structure. The [18]-annulene model originally proposed by Vogel in the 1960s has been central to understand the electronic structure of porphyrins. Although verified in numerous experimental and theoretical studies, basic questions remain and have been continuously studied to obtain new insights about this molecule. Recently, we applied non-contact atomic force microscopy (nc-AFM) to visualize directly the structure of the porphine on the surface. Moreover, atomic manipulation by charging the molecules enabled us to produce new species and monitor the structural changes in situ. The changes in aromaticity pathways upon charging were studied with DFT calculations of the aromaticity indices using the HOMOA, NICS, and ACID methods. Our results indicate a neutral porphine structure (P_0) consistent with [18]annulene, which provides direct proof for this model. The radical anion (P^{-1}) produced by adding one electron is an antiaromatic species. The aromaticity is reversed again to become an aromatic species (P^{-2}) upon adding another electron. Calculations suggest the dianion has an aromatic triplet ground state and slightly disfavored singlet state which is antiaromatic, in accordance with predictions of Baird's rule.

ORGN 799

Mechanistic perspective to oxidative dehydrogenative intramolecular C-C coupling of (hetero)aryls with oxidized carbon materials

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Oxidative dehydrogenative (ODH) C-C coupling of aryls, *i.e.*, Scholl reaction, has been proposed to proceed *via* radical cationic (rc) and arenium cationic (ac) mechanistic pathways. Typically, homogeneous oxidants, such as a molecular quinoidic oxidant; DDQ, or a Lewis acidic 1-electron oxidant; $FeCl_3$, are used as stoichiometric reagents in various intra- and intermolecular C-C coupling reactions with earliest examples dating back to the 19th century. Yet, the mechanistic understanding of Scholl reactions remains elusive. Efforts have been put into investigation of Lewis acid mediated Scholl reactions with and without external oxidants. The challenge is that, for instance, $FeCl_3$ can act both as a (Lewis) acid and as a 1-electron oxidant, for which reason it is difficult to differentiate between the rc and ac mechanisms.

Recently, we have investigated the ODH C-C coupling mechanism of terphenyls and tetraheteroarenes (Figure 1) with oxidized carbon materials in the presence of Brønsted acid additive, methanesulfonic acid. Both substrate classes could be concluded to operate

via either mechanisms, oxidant and substrate dependently. Importantly, the oxidative power and basicity of the catalyst's quinoidic groups would favour either rc or ac mechanism, while the nucleophilicity of the substrate was found to be decisive for the choice of operative mechanism. Mechanisms proved to selectively give different products in the ODH C-C coupling of tetraheteroarenes, as rc mechanism lead to a formal cyclooctatetraene product, while ac strongly favoured dearomatized-migratory 6-ring product.

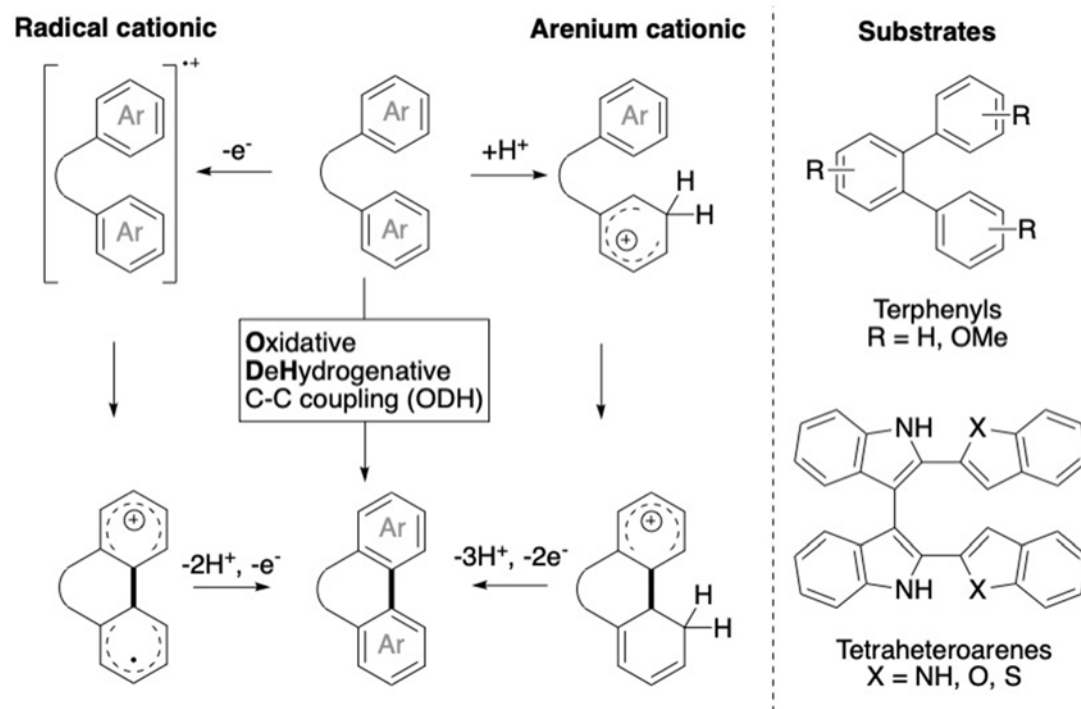


Figure 1. Mechanistic scheme of ODH-reaction and substrate sets used for the study.

ORGN 800

Computationally guided design of cyclopentadiene click reactions for applications in bioorthogonal chemistry

Brian Levandowski, levandbj@ucla.edu, **Nile Abularrage**, **Ronald T. Raines**. MIT, Cambridge, Massachusetts, United States

Bioorthogonal reactions are powerful tools capable of visualizing and altering biological processes. While there are a number of organic reactions that have been applied as bioorthogonal reactions, these reactions are often limited by factors such as poor solubility, stability, synthetic yields, and reaction kinetics. The ability to develop organic reactions into bioorthogonal reactions has the potential to advance the field of chemical biology and bring forth new applications. Using a computationally guided rational design

approach we have developed cyclopentadiene as a bioorthogonal reagent with rapid kinetics towards strained alkynes and robust biological stability.

ORGN 801

Computational and crystallographic studies of heteroaromatic N-oxide halogen bonding

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Various complexes of nitrogen N-oxide heterocyclic and organic halide compounds were synthesized and simulated computationally. Computational results were compared to previous efforts for the non-oxide complexes and compared to experimental results. Interaction energies and geometrical parameters were computed using the DFT method, and SCXRD was used to quantitatively measure the geometrical parameters. SCXRD results for several of these complex pairs will also be presented. Both experimental and computational results revealed strong halogen bonds within the structure, strongly supporting N-O halogen bond formation. This talk will focus on several of our recent halogen bonding structures.

ORGN 802

How to manipulate photodynamic behavior of crystals

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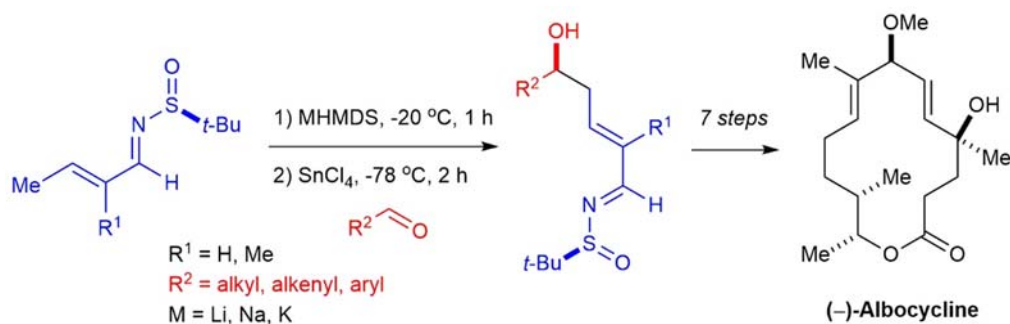
Molecular machines have gained interest recently due to their versatile applications in mimicking biological processes effectively. Studies have shown that organic crystals can be sufficiently dynamic to be utilized in developing molecular machines e.g. actuators, transistors, rotors and bioelectronics. Although one of the advantages for these organic crystals are relatively easier structural manipulation, the biggest challenge lies in developing a bridge between the structure and function of dynamic crystals. In most cases, these dynamic organic crystals are serendipitous discoveries. To overcome this limitation, we need to strive towards understanding the factors that control the dynamic nature of the organic crystals. Our research aim is to develop a method to understand the different controlling factors behind making a crystal rigid or flexible upon irradiation of light. Crystal packing and intermolecular forces must play a crucial role in controlling the photodynamic nature of the crystals. To explore the role of these factors on photodynamic behavior, we compared organic alkyl azides with similar chemical structure and reactivity but varying the crystal packing by changing the location of substituents.

ORGN 803

Asymmetric vinylogous aldol reaction of *N*-*tert*-butanesulfinyl metallodienamines

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The asymmetric vinylogous aldol reaction has emerged as an efficient way to generate a large size structure with chiral, homoallylic alcohols and has found widespread utility in the total synthesis of natural products. Recently, our group developed a novel asymmetric vinylogous aldol reaction of *N*-sulfinyl metallodienamines with aldehyde toward the concise asymmetric total synthesis of the macrolactone antibiotic, (-)-albocycline. The strategic use of enolizable chiral *N*-sulfinyl imine derivatized vinylogous aldol reaction showed they can react regioselectively at the γ -position with aldehydes to afford vinylogous aldol products with high levels of 1,7-asymmetric induction. The reaction has been systematically optimized and scope investigated with various aldehydes and ketones. The yields ranged from 68-91% and diastereomeric ratios observed as high as 5.9:1 with α,β -unsaturated aldehydes. Further investigation of stereoselectivity mechanism revealed that stereochemical erosion occurred when using tin tetrachloride accompany with LiHMDS but not with NaHMDS or KHMDS. A transition state supported by DFT calculations has been advanced to rationalize the stereochemical course of the reaction.



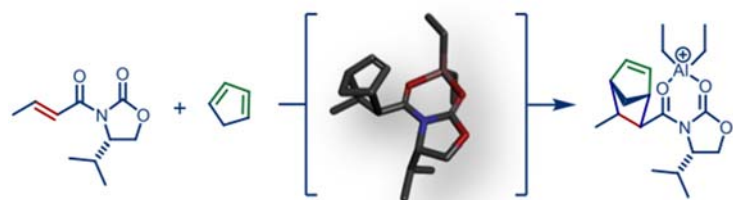
ORGN 804

From desktop to benchtop: Paradigm shift in asymmetric synthesis

Mihai Burai Patrascu², **Joshua Pottel**¹, josh.pottel@molecularforecaster.com, **Sharon Pinus**², **Michelle Bezanson**², **Per-Ola Norrby**³, **Nicolas Moitessier**². (1) Molecular Forecaster Inc., Montreal, Quebec, Canada (2) McGill University, Montreal, Quebec,

Canada (3) Pharmaceutical Technology & Development, AstraZeneca, Mölndal, Sweden

The organic chemist's toolbox is vast with technologies to accelerate the synthesis of novel chemical matter. Asymmetric catalysis is one way to access new areas of chemical space and computational power is today sufficient to assist in this exploration. Our new software platform, Virtual Chemist, allows bench chemists to predict outcomes of asymmetric chemical reactions ahead of testing in the lab, in just a few clicks. Modular workflows facilitate the simulation of various sets of experiments, including the following scenarios: one-by-one design, library screening, hit optimization, and substrate scope investigation. Catalyst candidates are screened within hours and the enantioselectivity predictions provide substantial enrichments compared to random testing. The achieved accuracies within ~1 kcal/mol of experimentally observed selectivities provide new opportunities for computational chemistry in asymmetric catalysis. The tools presented herein are available for free for academic research.



ORGN 805

Development of chiral binaphthyl-based calcium disulfonimide complexes for asymmetric catalysis

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The Niggemann catalyst is a very powerful Lewis acid that has shown great promise in promoting a wide array of organic transformations with low catalyst loadings. To date, no chiral analogues of this catalyst have been explored. Herein, the design, synthesis, and characterization of chiral Niggemann-type, calcium catalysts derived from

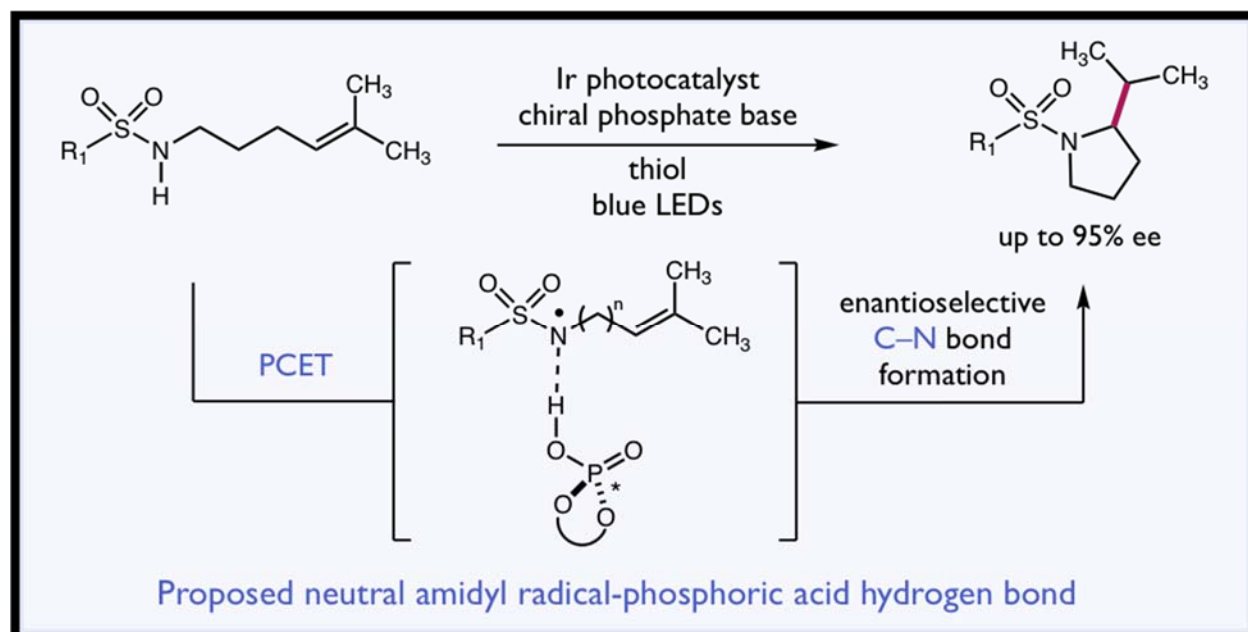
binaphthyl-based disulfonimide ligands will be presented. Furthermore, optimization of catalytic performance will be discussed utilizing the potential variability at the 3,3'-positions inherent to the binaphthyl-backbone of this ligand-type. This variability leads to unique control of both the steric environment and metal acidity of this system.

ORGN 806

Enantioselective hydroamination of alkenes with sulfonamides enabled by proton-coupled electron transfer

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Herein, we report an enantioselective hydroamination of alkenes with sulfonamides, enabled by proton-coupled electron transfer (PCET). The PCET step proceeds through the simultaneous oxidation and deprotonation of a sulfonamide N–H bond by an iridium photocatalyst and chiral phosphate base, respectively. We propose that residual hydrogen bonding interactions between the resulting neutral sulfonamidyl radical and neutral conjugate chiral phosphoric acid induce asymmetry during the subsequent C–N bond formation. This reaction has been demonstrated for a variety of sulfonamides in an intramolecular cyclization reaction with selectivities up to 95% ee. These results demonstrate that neutral, open-shell hydrogen bonding interactions can be applied as a design principle for asymmetric reactions with radical intermediates.

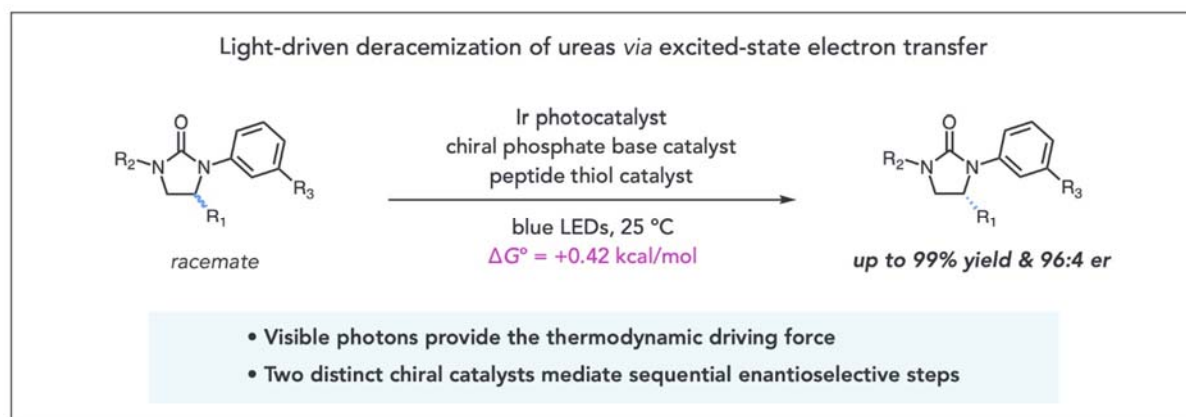


ORGN 807

Out-of-equilibrium stereocontrol: Light-driven deracemization enabled by excited-state electron transfer

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A new strategy for catalytic deracemization is presented, wherein amine derivatives undergo spontaneous optical enrichment upon exposure to visible light in the presence of three distinct molecular catalysts. Initiated by an excited-state iridium chromophore, this reaction proceeds *via* a sequence of favorable electron, proton, and hydrogen atom transfer steps that serve to break and reform a stereogenic C–H bond. The enantioselectivity in these reactions is jointly determined by two independent stereoselective steps that occur in sequence within the catalytic cycle, giving rise to a composite selectivity that is higher than that of either step individually. These reactions represent a distinct and potentially general approach to creating out-of-equilibrium product distributions between substrate enantiomers using excited-state redox events.

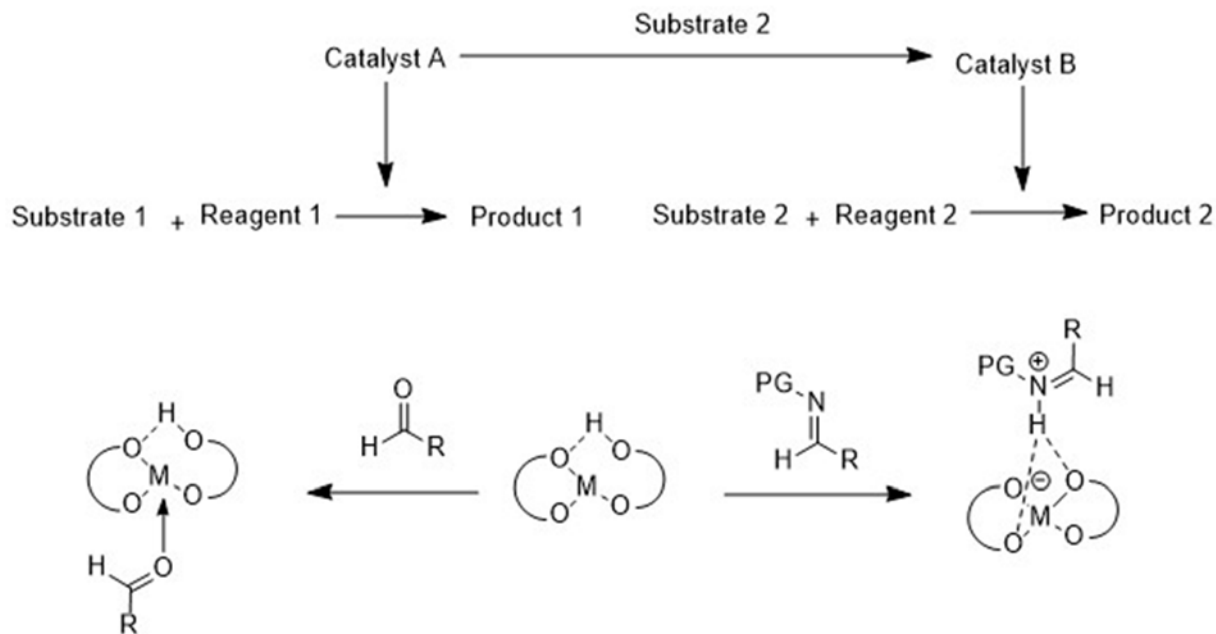


ORGN 808

Chameleon catalyst

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Department of Chemistry, Michigan State University, East Lansing, Michigan, United States

Chiral borate esters attract a lot of attention in organic synthesis because of their applications in asymmetric catalysis and the kinetic resolution of chiral ligands such as BINOL. Yamamoto reported the first chiral biaryl borate ester as an effective catalyst in a Diels-Alder reaction. The structure of this catalyst was proposed to be a three coordinated boron species with an intramolecular hydrogen bond between the hydroxy group and an oxygen of the ligand. Yamamoto named his catalyst BLA (Brønsted acid-assisted chiral Lewis acid) because the acidity of the boron was increased as a result of the intramolecular hydrogen bonding. The BLA also mediated a Mannich reaction in a stoichiometric manner. Yamamoto proposed the mechanism of the BLA, which involves the activation of the aldehyde in the Diels-Alder reaction and of the imine in the Mannich reaction via coordination to the boron Lewis acid (unified mechanism). Recently our lab found that a chiral biaryl borate ester with two VANOL ligands and one boron is an extremely active catalyst in the epoxidation of aldehydes, Diels-Alder reaction and the aziridination of imines. Our mechanistic study casts doubt about the Yamamoto proposal. Our findings suggest that the chiral borate ester catalyst acts as a Lewis acid in the presence of less basic substrates such as aldehydes, and as a Brønsted acid in the presence of more basic substrates such as imines. We define this new class of catalyst as Chameleon catalysts, which can catalyse two different reactions with two different mechanisms. The mechanistic study of the Chameleon catalyst calls into question Yamamoto's unified mechanism.



Second-generation synthesis of illudinine, a potential MAO-B inhibitor

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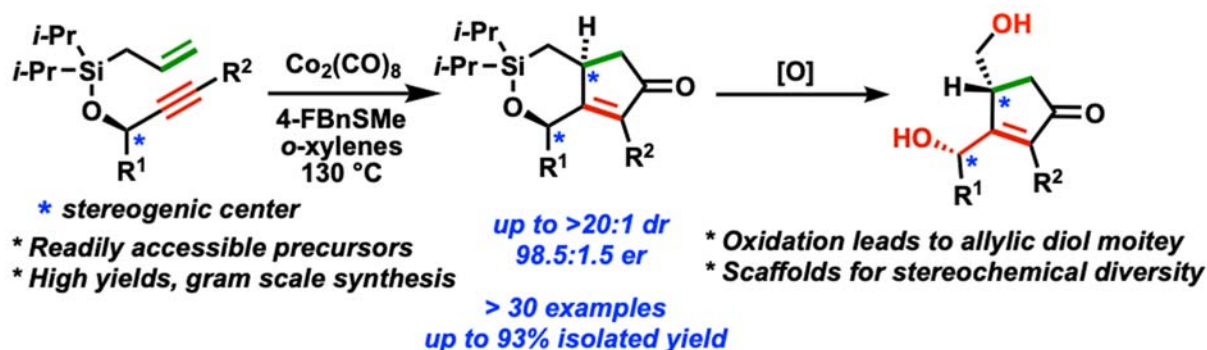
A more efficient second-generation synthesis of illudinine, an illudalane sesquiterpene, has been achieved in seven steps (54% overall yield) from dimedone. The previously reported first-generation synthesis delivered illudinine in 8-steps (14% overall yield) from dimedone using tandem fragmentation-olefination and an inverse-demand Diels-Alder as key steps. Tactical innovations, most notably incorporating a nitrile functional group as a masked carboxylic acid helped improve several steps and increased the overall yield of illudinine. Preliminary monoamine oxidase (MAO) assays of illudinine analogues indicated illudinine as a potential MAO inhibitor.

ORGN 810

Access to highly functionalized cyclopentenones via diastereoselective pauson-khand reaction of siloxy-tethered 1,7-enynes

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A diastereoselective $\text{Co}_2(\text{CO})_8$ -mediated Pauson–Khand reaction (PKR) of siloxy-tethered 1,7-enynes for the synthesis of cyclopentaoxasilinones has been developed. Oxidation of the resulting cyclopentaoxasilinones delivers stereo-enriched β -alkylated cyclopentenones, which are inaccessible by intermolecular PKRs. Since its initial discovery in 1973, the intra- and intermolecular PKRs have been exemplified as a convergent, atom-economical, and fundamental reaction for the [2+2+1] synthesis of cyclopentenones. However, the intermolecular PKR has generally been limited to strained or symmetrical alkenes due to the difficulty controlling the alkene regio- and stereoselectivity. Therefore, a general stereoselective PKR strategy to access highly functionalized monocyclic cyclopentenones remains an unsolved challenge. Herein, we describe the use of 1,7-enynes bearing a removable silicon tether, that upon oxidation of the Si-C bond, gives rise to highly functionalized and stereo-enriched monocyclic cyclopentenones bearing functionalizable handles, allowing the rapid introduction of stereochemical complexity and structural diversity. We are currently developing a catalytic variation of the above method that invokes the *ex-situ* formation of carbon monoxide, as well as exploring the use of the more labile tethers to access monocyclic cyclopentenones in milder reaction conditions.



ORGN 811

Oxidative dearomatization: One pot synthesis of chiral spiroimidazolidinone cyclohexadienones from amino acid chirons

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A series of chiral spiroimidazolidinone cyclohexadienones was synthesized under operationally mild conditions via a one pot reaction of N-carbamate protected chiral amino acids, N-alkyl aminophenol, and iodobenzene diacetate (IBD). The sequence of oxidative dearomatization/ipso nucleophilic addition of a carbamate nitrogenous nucleophile to construct the new C-N bond was realized for the first time. The chirality of amino acids is preserved during the transformation. The novel chiral spiroimidazolidinones with many distinctive functional groups could potentially be used as new organocatalysts or as chiral templates for building up molecular complexity.

ORGN 812

Enantioselective synthesis of cyclopropanone equivalents and its application for the production of chiral β -lactams by formal [3+1] cycloaddition

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Cyclopropanone derivatives have long been considered unsustainable synthetic intermediates due to their important kinetic instability. In this work, we have achieved the first enantioselective synthesis of 1-sulfonylcyclopropanols, acting as stable yet powerful equivalents of the corresponding cyclopropanone derivatives under basic conditions. Both the electronic and steric nature of the sulfonyl moiety were found to have a crucial impact on their rate of equilibration to cyclopropanone, highlighting the modular reactivity of these reagents. Their utility is demonstrated in the development of

a mild and stereospecific formal [3+1] cycloaddition with sustainable nitrenoid equivalents, leading to the efficient formation of chiral β -lactam derivatives.

ORGN 813

Assembly of organic semiconductors into micro- and nano-crystals

Nagarjuna Gavvalapalli, *ng554@georgetown.edu*, Dorothy Jones. Chemistry, Georgetown University, Washington, District of Columbia, United States

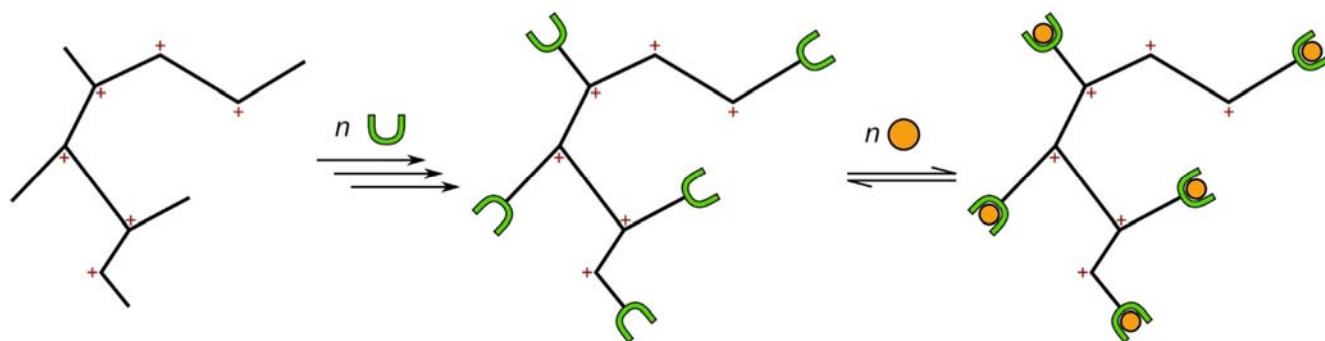
Organic semiconducting micro- and nano-crystals (MNCs) are useful for optical active waveguiding, solid-state lasers, photonic transistors, photonic integrated circuits, and field-effect photonic applications. Particle shape as well as molecular assembly within particles is known to control the photonic and optoelectronic properties. Thus, development of synthetic strategies that result in organic MNCs of different shapes and provide control over molecular packing within the particles is crucial to advance the field of organic photonics. Nature uses peptides and proteins to control the nanocrystal size and shape to achieve key functionalities in biological systems. Examples include the size and shape control of Fe_3O_4 or Fe_3S_4 nanostructures by magnetotactic bacteria for their alignment and migration, and growth and assembly of apatite nanocrystals in apatite bone for optimal mechanical performance. Synthesis of organic MNCs with precise control over their size and shape requires directed assembly of molecules onto the growing nucleating seed. Currently, there are no existing synthetic strategies for organic MNCs that can rival nature's precision in controlling the size and shape. Availability of synthetic strategies that predictively generate different shaped organic MNCs, especially of organic π -conjugated molecular MNCs, will enable efficient use and realization of the full potential of π -conjugated organic molecules in photonic and electronic applications. Currently, aliphatic surfactants such as CTAB and SDS are used for the synthesis of organic MNCs. Most of the time there is no advantage of using one over the other because both these surfactants use their aliphatic tail to interact with the particle facet and control growth rate. Thus, the lack of tunable interaction energies between particle facets and aliphatic surfactants results in limited control over particle growth and hence the possible particle shapes. Recently, we proposed to use aryl surfactants to control the organic MNC growth and the shape. Using the novel aryl surfactants, psuedooctahedron and elongated octahedron shaped triptycene MNCs were synthesized. In this talk, I will discuss the synthesis of a series of aryl surfactants and their impact on the growth and shape of triptycene and perylene MNCs.

ORGN 814

Macromolecular receptors for chemical fingerprinting in aqueous media

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Artificial supramolecular receptors often rely on relatively weak intermolecular interactions for their chemical recognition properties, so they may struggle to work in competitive media, chief among which are water solutions. However, aqueous media are extremely important in analytical, environmental, and biomedical applications, so it is valuable to adapt our supramolecular tools to them as well. In fact, even the weakest among noncovalent interactions can be effectively put to use in aqueous media. We have been using water-soluble polymers (e.g. dendrimers, hydrogels, conjugated polymers) as scaffolds to build multivalent supramolecular sensors that take advantage of the large number of interactions and of the preorganization of receptor sites afforded by such scaffolds. We will show instances of this use resulting in improved affinity in competitive media, with a particular focus on neutral buffered aqueous solutions for the detection of a variety of interesting guest families, including carboxylate anions, common antibiotics, simple saccharides, and polycyclic aromatic hydrocarbons. These are examples of a general approach that, in our opinion, has two key advantages. On the one hand, decorating an existing polymer scaffold with known receptor sites affords a modular approach to multivalency without requiring a significant design and synthesis effort, which may improve the affinity of weak interactions and allow them to overcome desolvation costs in water. On the other hand, water-soluble scaffolds impart such solubility to receptor groups that would otherwise require significant modification to make soluble. This simple approach is particularly valuable when designing chemical fingerprinting systems, which typically use a large number of receptors, each one poorly selective, and recovers selectivity from judicious interpretation of the ensemble response.



A modular approach to soluble multivalent chemical receptors is based on water soluble macromolecular scaffolds (black) that can be synthetically modified with simple, proven receptors (green). The resulting system recognizes similar analytes (orange) as the monovalent receptor, but it can be designed to display multivalent advantages and improved affinity.

ORGN 815

Effects of sterics and electronics on the binding modes and equilibrium binding constants of benzyl-4,4'-dipyridyl derivatives with cucurbit[7]uril

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Macrocycles of all types have found useful application in chemistry in recent years, including supramolecular self-assembly, reaction catalysis, drug delivery, removal of heavy metals, molecular machines, nanosensors, and physical property enhancement. Though initially the majority of these applications have employed the use of cyclodextrin and crown ethers, more recently, cucurbit[n]urils have shown unique properties that have expanded the field. By the use of hydrophobic interactions, and to a smaller extent electrostatic interactions, these macrocycles can bind various small molecules with abnormally high binding constants in the range of 10^5 to 10^{12} M⁻¹. In building complex supermolecular structures, it can be useful to understand the positions of binding as well as equilibrium binding constant. The binding mode of the host-guest complex between benzyl-4,4'-dipyridyl derivatives and cucurbit[7]uril was studied and suggest steric and electronic effects can dramatically alter position of binding. Competitive ¹H NMR studies were performed to measure the equilibrium binding constants of the 1 : 1 complexes.

ORGN 816

Creating a caged surfactant with thiazole orange moieties for the delivery of mRNA to cells

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Lysosomal degradation of therapeutic nucleic acids such as pDNA and mRNA is a central issue in the field of drug delivery. Upon cell uptake, the nucleic acids are transported through endosomes to lysosomes, where nucleases hydrolyze the entrapped nucleic acids. One way of increasing delivery of pDNA and mRNA is through the lysis of the endosomal membrane, allowing for release of the entrapped nucleic acids before lysosomal degradation. There are several strategies for the delivery of nucleic acids, mainly revolving around the use of amine-rich "proton sponges" that lyse the endosome by destabilizing the pH balance, causing a rise in osmotic pressure. However, these positively charged proton sponges, such as PEI and poly-lysine, often struggle with toxicity issues, making them hard to adopt for in vivo use. Despite the issues with amine-containing proton sponges, there has been a lack of new delivery strategies that do not depend on these molecules.

In this study, we use a multi functional molecule (CS8-TO2) consisting of two nucleotide chelators, thiazole orange (TO), connected to a surfactant through an acetal linkage. The thiazole orange groups acts as a complexation agent, allowing for assembly of CS8-TO2 around nucleic acids such as mRNA and pDNA. Upon acidification, such as in

the endosomal compartment, the acetal bond in CS8-TO2 hydrolyses, releasing free surfactant into the endosomal membrane. This strategy is independent of proton sponges, and endosomal disruption is caused by a release of surfactant, rather than by disrupting the osmotic balance. We show here that CS8-TO2 can lyse membranes selectively at acidic conditions (pH 5.5), but shows no measurable membrane disruption in neutral conditions. We also show here that CS8-TO2 binds pDNA at concentrations < 2 TO/P, meaning the TO does not have to be in great excess for proper assembly. Finally, we showed that when mixed with mRNA encoding for mCherry, CS8-TO2 is able to deliver mRNA into cells, as measured by the expression of mCherry in transfected cells. CS8-TO2 proves to be a useful structure for nucleic acid delivery, and is an alternative to the existing library of proton sponges. We therefore think CS8-TO2 has great potential in the field of drug delivery.

ORGN 817

Computational and experimental optimization of cyclophane-guest complexes

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Chemistry and Biochemistry, UCLA, Los Angeles, California, United States

Host-guest chemistry uses a combination of small non-covalent interactions between a guest and rigid, preorganized host to result in an overall high affinity complex. In biological systems, host-guest complexes such as enzymes or antibodies ($K_a \sim 10^{15} \text{ M}^{-1}$ in H_2O) have evolved around their specific natural substrates to enhance selectivity and binding affinity in a sea of various functionalities. Several synthetic systems, such as cucurbiturils, cyclodextrin, calixarenes, and pillarenes, have not only shown to mimic this stability and strengths (K_a upto 10^{17} M^{-1} in H_2O) but also exhibit larger scope of guests. Traditionally, this is achieved by the discovery of host macrocycles followed by screening of high-affinity guests, yielding multiple host-guest pairs with a range of K_a values.

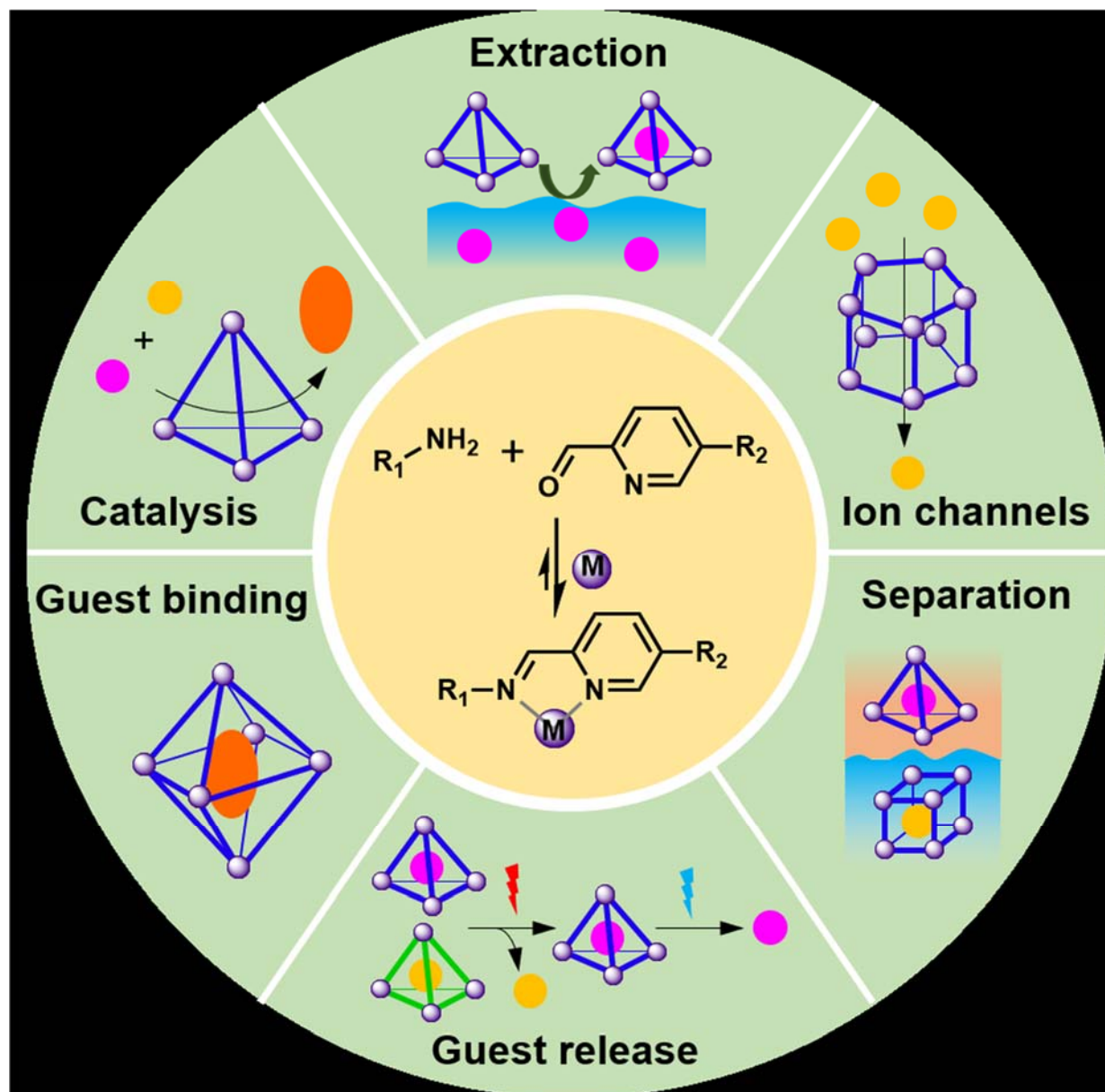
In this study, we take a biomimetic approach where we rationally design a macrocycle host around a specific guest of interest. This was aided by computational modeling, to provide useful insights into binding geometry and structure-based lead optimization prior to synthesis. To develop our host, we templated cyclophanes as they are synthetically tunable and allowed for π - π interactions to be leveraged. To promote more efficient π - π interactions, we first quantified its energetics and studied several variables, such as ring size and solvent effects, using both computational and experimental data. Then we subsequently engineered these interactions into host-guest complexes using DFT calculations. Finally, synthesis and binding affinity assays in solution were performed to yield several novel host-guest complexes. We anticipate that this novel approach in the rational design of host-guest systems will spark interests in chemistry, biology, and materials science.

ORGN 818

Functional capsules via subcomponent self-assembly

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We have employed subcomponent self-assembly to prepare metal-organic capsules from simple building blocks *via* the simultaneous formation of dynamic coordinative and covalent bonds. Fundamental investigations into the host-guest chemistry of capsules prepared through subcomponent self-assembly have led to the design of useful functions and new applications. We use two strategies here to construct functional capsules: capsule construction directly from functional building blocks and preparation of cages with enclosed cavities and excellent guest binding properties. The former strategy allows us to achieve the selective extraction of perchlorate anion from water to an organic phase by using an azaphosphatane-functionalized $\text{Fe}^{\text{II}}_4\text{L}_4$ tetrahedron. Based upon a tritopic triazatruxene ligand, we have prepared face-capped $\text{M}^{\text{II}}_4\text{L}_4$ ($\text{M} = \text{Fe}$ or Zn) capsules with enclosed cavities. The excellent guest binding properties of the capsules lead to a new class of supramolecular Russian-dolls, selective separation of polyaromatic hydrocarbons, and the function of thermo-responsive guest uptake and release.



Functions and applications of subcomponent self-assembled capsules

ORGN 819

NMR insights into carbohydrate-carbohydrate interactions

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Carbohydrate-carbohydrate interactions (CCIs) mediate cell-cell adhesion and are involved in processes that include embryo development, metastasis and myelin

compaction. Herein, we will focus on myelin sheath CCI, particularly between either galactose (Gal) or glucose (Glc) with sulfo-galactose (SGal). To understand how sugars bind sugars, various NMR techniques that include diffusion oriented spectroscopy (DOSY) have been employed.

ORGN 820

Correlation between the chirality of supramolecular aggregates of an azo dye to its plant proteoglycan binding ability

Raghuraj Hoshing¹, *raghuraj_hoshing@brown.edu*, **Blaise Leebert**¹, **Helene Kuhn**¹, **David Cainiello**¹, **Brandon Dale**¹, **Robert Lusi**¹, **Michael Saladino**¹, **Sarah Weingarten**¹, **Natalie Palaychuk**¹, **Amit Basu**². (1) Chemistry, Brown University, Providence, Rhode Island, United States (2) Chemistry Dept., Brown University, Providence, Rhode Island, United States

Yariv reagents are glycosylated triphenylazo dyes that bind arabinogalactan proteins (AGPs); proteoglycans found in plant cell walls. This property of Yariv reagents is widely utilized to disrupt AGP functionality, stain and isolate AGPs. However, the exact mechanism of the Yariv-AGP interaction remains unknown. The Yariv reagents are known to form supramolecular aggregates in solution. We use circular dichroism to show that the Yariv reagent aggregates possess helical chirality, and the AGP binding ability of the Yariv reagents is correlated to its helical chirality.

ORGN 821

Synthesis and characterization of 4, 6-O-phenylethylidene acetal derivatives of D-glucosamine as molecular gelators

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Over past few decades, low molecular weight gelators (LMWGs) have gained increasing attention for the preparation of novel functional soft materials. Carbohydrate derivatives are interesting molecules for the preparation of these advanced materials due to their natural abundance, biocompatibility and intrinsic chiral functional groups. The driving force governing the formation of self-assembled networks by LMWGs are non-covalent forces such as hydrophobic interactions, hydrogen bonding, π - π interactions and CH- π interactions. Previously, various urea, amide, and carbamate derivatives of 4, 6- O-benzylidene acetal protected glucosamine were synthesized and their gelation properties were analyzed. In this study, we introduced a $-\text{CH}_2$ unit between the sugar ring and the aromatic protecting group to afford two 4, 6-O-phenylethylidene acetal derivatives of D-glucosamine as the headgroups. A series of aliphatic and aromatic carbamate derivatives at the 2- and 3-positions of the glucosamine headgroups were synthesized and analyzed. Several compounds were found to be gelators for organic solvents and aqueous mixtures with organic solvents.

The gels were characterized using optical microscopy and atomic force microscopy for the morphology of the assemblies. These LMWGs are currently being studied for applications as soft biomaterials for enzyme immobilization and drug delivery. In this presentation, the synthesis, characterization and potential applications of these sugar derivatives will be reported.

ORGN 822

DNA-directed assembly of supramolecular structures and nanoparticles

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Small molecule-DNA hybrids (SMDHs), comprising multiple DNA strands covalently attached to small-molecule cores, have recently emerged as well-defined DNA-containing building blocks for supramolecular materials with “valencies” that can be precisely tuned through the number and orientation of the strands. SMDHs greatly increase the scope and versatility of the design and construction of DNA-based nanostructures because branched building blocks can be synthesized efficiently from relatively short oligonucleotides and a broad range of organic cores. Notably, the precisely defined, compact nature of SMDHs has greatly facilitated their use as key models for deciphering macroscopic DNA-mediated assembly behaviors from both experimental and theoretical perspectives. This presentation will discuss the experimental and computational efforts that our group has undertaken to understand the parameters that control how SMDHs are assembled into discrete supramolecular nanostructures such as cage and face-to-face (ff) dimers, polymers, and nanoparticles.

ORGN 823

Metal-free C-H functionalization of *N*-Aryl amine compounds as drug scaffolds: Opportunities and current limitations

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Metal-free C-H functionalization is a future-oriented approach for sustainability and safety control (eg. due to the limitation of regulatory science on non-predefined impurity) in our future world. In particular, hypervalent iodine chemistry has been frequently used for metal-free redox reaction, C-H functionalization, and cross-coupling based on transition metal-like and benign property. In order to synthesize novel and versatile drug scaffolds, SAR based scaffold hopping (core hopping) and side-chain hopping is a useful strategy to investigate promising drug structure in chemical space. Hypervalent iodine chemistry can contribute to the realization of the hopping strategy from virtual into our real world. In this presentation, I introduce iodine or hypervalent mediated C-H functionalization applicable to the hopping method. Concretely, my research focused on the C-H functionalization of *N*-aryl amine compounds. Firstly, α -C(sp^3)-H functionalized

oxidative cyclization of tertiary *N,N*-diaryl amino alcohols is presented through cross-dehydrogenative coupling (CDC) reactions [1]. The methodology can add anomeric *N,N*-diaryl amino tetrahydropyran scaffold as a new drug scaffold into core hopping strategy. Secondly, I present solvent-controlled selective functionalization of C(sp²)-H or C(sp³)-H: nitration via C-N bond cleavage of CH₃NO₂, cyanation, or oxygenation in water [2]. Surprisingly, NO₂ transfer from CH₃NO₂ to the aromatic group of the substrate is firstly reported under I(III)/NaCN conditions via a novel C(sp³)-N breaking/C(sp²)-N formation mechanism. In addition, the solvent-controlled C(sp²)-H functionalization can shift to an α-C(sp³)-H functionalization (cyanation or oxygenation) of the α-C(sp³)-H of cyclic amines. The methodology can be used for side-chain hopping at late-stage synthesis.

ORGN 824

Unusual reactivity of a palladium-catalyzed C(sp³)-H fluorination method

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The development of fluorination methods has become very important for the synthesis of many pharmaceuticals, agrochemicals, and ¹⁸F-labeled radiotracers for positron emission tomography (PET). Current palladium-catalyzed methods for C(sp³)-H fluorination require the use of directing groups, which limit the scope of the reactions. Here we report a new palladium-catalyzed method for non-directed C(sp³)-H fluorination. Low loadings of a palladium catalyst afford moderate to good yields for C-H fluorination products. This presentation will discuss the optimization, scope, and mechanism of this transformation.

ORGN 825

Improving sustainability in directing groups for C-H activation

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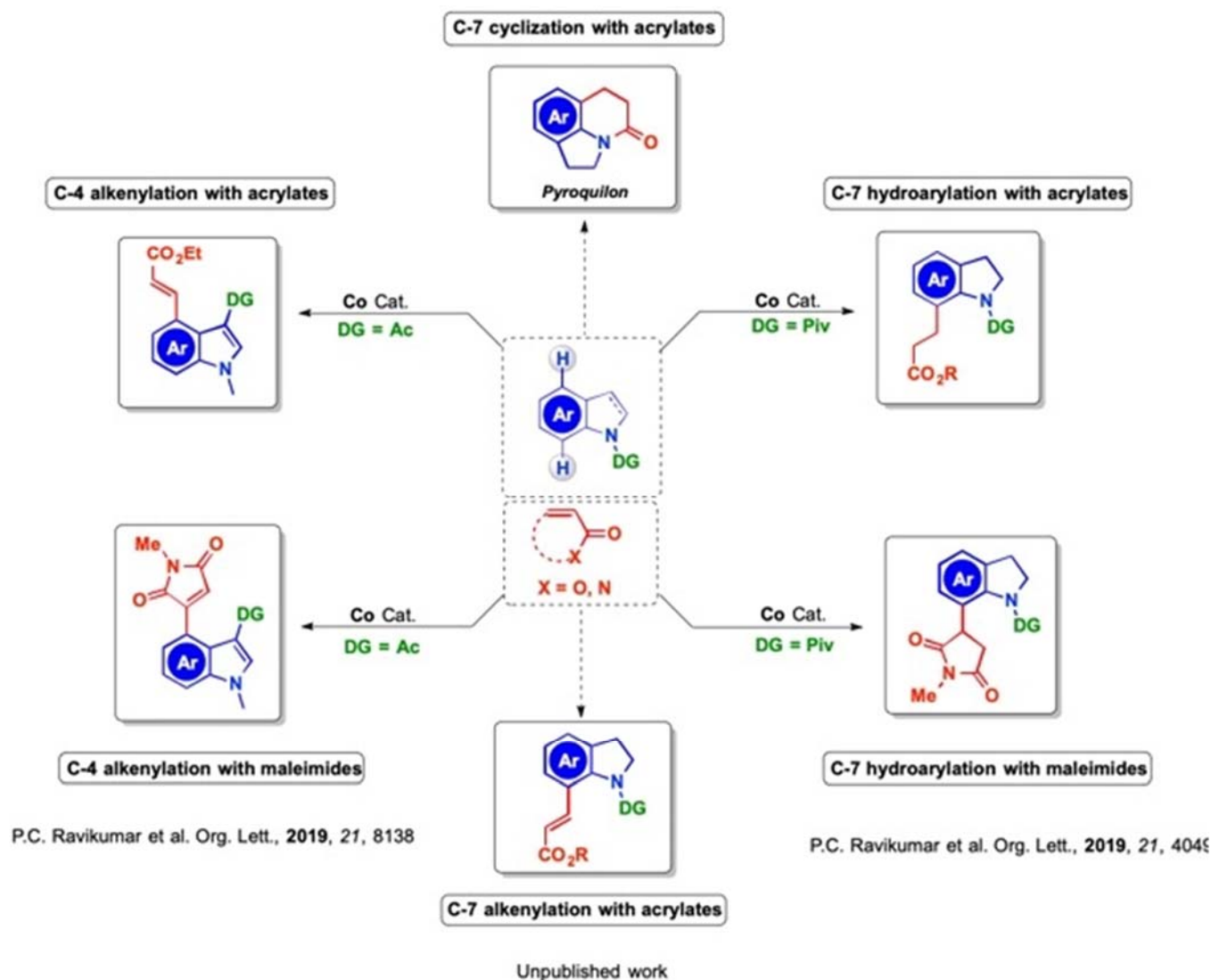
Our group is interested in developing more sustainable strategies for site selective C-H functionalization, using either reversibly covalent or non-covalent interactions. This talk will feature our work using CO₂ as a transient directing group to enable C-H activation-initiated cascade reactions, halogenation (using native amines as directing groups), and if time permits some of our new work on developing ligands for C-H functionalization through non-covalent interactions.

ORGN 826

Cobalt(III) catalyzed C-H functionalizations through weak coordination: Synthesis of functionalized indole and indoline derivatives

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Indole and indolines are commonly found in numerous bioactive molecules and pharmaceuticals. Indole is considered as the fourth prominent heteroaromatic moiety present among the currently marketed drugs. Owing to its biological importance, the synthesis of various functionalized indole derivatives has been an active area of research. Traditionally functionalization on the benzenoid ring system of indole has been achieved through metal-catalyzed coupling reactions using pre-functionalized substrates. In recent years second and third-row transition metal (Rh, Ru, Pd, Ir) catalyzed direct C-H activation and functionalization has been used to achieve derivatives of indole and indolines. The high cost, low availability, and toxicity of noble metals restricts its use in pharmaceutical industries. Therefore there is an urgent need to mimic noble metals using less toxic, more abundant and less expensive first-row transition metals. In this context, cobalt catalysts offer an alternative option to noble metals. In recent years cobalt catalysts have been shown to perform numerous C-H activation reactions, however, in most cases, a strong directing group is required to effect the reaction. Cobalt catalyzed C-H functionalizations mediated through weak coordination is very less explored, therefore in our group we have initiated a program to explore cobalt catalyzed C-H functionalization of indole and indolines using weakly coordinating directing groups. A brief account of our recent results will be presented.



Cobalt catalyzed C(4)-H and C(7)-H functionalizations of indoles and indolines through weak coordination

ORGN 827

C-H activation of alcohols and ethers by a cationic iridium(III)-1,10-phenanthroline dichloride complex: Gas-phase study

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This study is focused on examining the mechanism and selectivity of C-H activation by the iridium(III)-1,10-phenanthroline dichloride catalyst on 1-butanol and 1-methoxybutane. Ethers are compounds with inherent low reactivity and alcohols are one

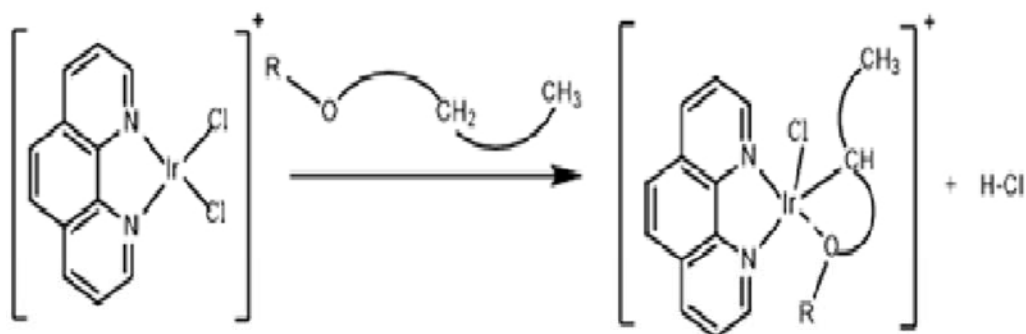
of the most widely used precursors in synthesis. Therefore, the selective activation of these molecules will be greatly beneficial in many synthetic applications.

The experiments were carried out on a modified mass spectrometer where the iridium complex is introduced via the ESI and trapped. Our modified mass spectrometer allows introduction of a second reagent into the ion trap via the helium flow. Thus the ion trap behaves as a reaction cell.

As shown in Figure 1, the initial study showed that C-H activation is accompanied by a loss of HCl. By using selectively deuterated compounds, the loss of DCI instead of HCl would indicate the site of activation. The substrates used in this study were selectively deuterated butanol and methoxybutane. The selectively deuterated methoxybutane ethers were synthesized from the corresponding alcohols. The experimental results were further supported using DFT calculations.

Studies carried out with the substrates showed that the iridium(III) complex selectively activates the C-H bonds in the gamma position of methoxybutane while activation in butanol occurs on both the gamma and delta carbons. Kinetic isotope effect studies showed that there is a higher preference of activation on the delta compared to the gamma carbon in butanol. This indicates that the iridium(III) complex can selectively activate C-H bonds in methoxybutane but in moving towards butanol, the selectivity is compromised. DFT calculations show that the driving force of these reactions are the formation of either a 6-membered (delta) or 5-membered (gamma) ring transition state. In methoxybutane the presence of the methyl group tilts the preference towards the 5-membered ring transition state thus allowing selective C-H activation on the gamma position.

This study proves that the iridium(III)-1,10-phenanthroline dichloride complex can be used as a potential catalyst for selective C-H activation.



ORGN 828

Dehydrogenation via C-H activation by a graphene-supported nickel single-atom catalyst model ion in the gas phase

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Drastic improvements in transition metal heterogeneous catalysts have been observed by decreasing catalyst size and anchoring them to a support scaffold. Size reduction offers two important benefits: (i) the number of surface atoms able to participate in catalysis increases, and (ii) the coordination number of the metals decrease, resulting in higher catalytic activity. Since transition metal heterogeneous catalysts are widely used in various industries, many studies have focused on smaller scale catalysts. This led to the conception of single-atom catalysts (SACs), a class of catalysts based on isolated metal atoms anchored to a support scaffold. SACs are often much more reactive and can offer better selectivity when compared to nano-scale catalysts. In order to realize the full potential of SACs, a sound understanding of the underlying catalytic mechanisms is required. However, surface analysis tools can become less effective in studying catalytic mechanisms at the atomic scale.

Mass spectrometry has proven to be a robust technique for studying organometallic catalytic mechanisms at the single-molecule level. Using a modified linear triple quadrupole ion trap mass spectrometer (modified Thermo Electron LTQ XL™) equipped with an electrospray ionization (ESI) source, we can isolate a specific ionic species and probe its reactivity via ion-molecule reactions. By employing established gas-phase synthetic techniques, we have developed the first example of a zero-valent Ni complex that can act as a model ion for a pristine graphene-supported SAC. Reactions with linear, branched, and cyclic alkanes reveal that the Ni SAC model ion is capable of the dehydrogenation of alkanes via two sequential C-H activations: metal insertion into a C-H bond and β -hydride elimination. By introducing energy into the system, additional dehydrogenations occur, enabling processes such as the transformation of cyclohexane to benzene. In addition to the formation of alkenes, the Ni SAC model ion is also capable of selectively producing other unsaturated functional groups, such as imines, via a similar dehydrogenation pathway. Kinetic isotope effects and DFT calculations support the proposed mechanism. Our work suggests that graphene-supported Ni SACs are capable of dehydrogenation via C-H activation.

ORGN 829

Para selective iridium catalyzed CH borylation of sulfates and sulfamates directed by ion-pair electrostatic interactions

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Direct functionalization of CH bonds reduces the number of synthetic steps for a target molecule enhancing efficiency and avoiding undesired waste material. Iridium catalyzed CH activation-borylation (CHB) is now an established method to access aryl boronic esters. Regioselectivity challenges can arise when multiple hydrogens are present in the molecule. CHB are traditionally directed by sterics yielding a mixture of meta and para products for monosubstituted arenes. Reactions that produce exclusively the meta or para regioisomer are more challenging. This presentation will show a method to direct para CHB via ion-pair electrostatic interactions of sulfated phenols, benzyl alcohols and anilines with bulky counteranions. It is proposed that the tetraalkylammonium cation shields the meta position, while leaving the para accessible. The effects of additional/different substituents, ligands, additives, and chain length of the tetraalkylammonium on regioselectivity will be discussed.

ORGN 830

Rational development of remote C-H functionalization of biphenyl: Experimental and computational studies

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Control of distance and geometry between directing groups and possible sites of functionalization has been very effective in achieving site selectivity of remote C–H activation when differentiation through electronic and steric effects are ineffective. A number of nitrile templates have been designed to achieve *meta*- or *para*-selectivity for carboxylic acids, alcohols and amines. We now report simple and efficient nitrile-directed *meta*-C–H olefinations, acetoxylation and iodinations of biaryls. Compared to our previous approach of installing a complex U-shaped removable template, biaryl nitriles are readily available and the functionalization products can be easily converted to amines, acids, amides or other heterocycles. This reaction provides a useful method for modifying biaryl compounds which make up an important class of molecules in both medicinal chemistry and synthesis. Notably, the remote *meta*-selectivity of biphenyl nitriles could not be expected from previous results with a macrocyclophane nitrile template. However, DFT computational studies now show that a Pd–Ag heterodimeric transition state (TS) favors the desired remote *meta*-selectivity. Control experiments demonstrate the directing effect of the nitrile and exclude the possibility of non-directed *meta*-C–H activation. Substituted 2-pyridone ligands were found to be key in assisting the cleavage of the *meta*-C–H bond in the concerted metalation-deprotonation (CMD) process.

