Goalie Program - NSF G. Molander
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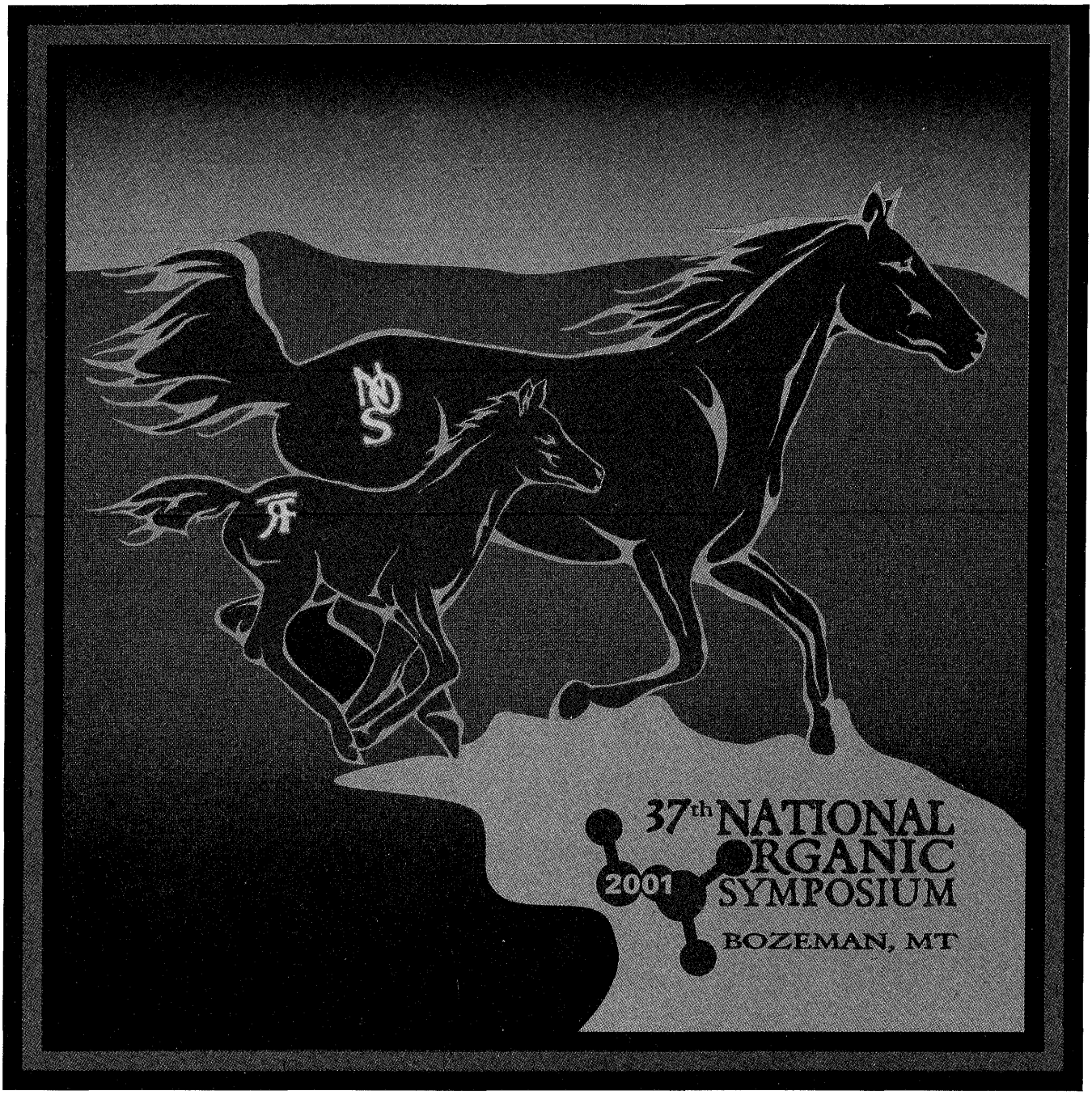

37th NATIONAL ORGANIC CHEMISTRY SYMPOSIUM

Montana State University • Bozeman

June 10-14, 2001

37th National Organic Chemistry Symposium

June 10-14, 2001
Montana State University
Bozeman, Montana

Table of Contents

National Organic Symposium
Schedule of Events

All lectures are in the Strand Union Ballroom.

All poster sessions and exhibitors are in the North Gym.

Exhibitor hours:
10:30am-2:30pm Monday, Tuesday, Wednesday and during poster sessions.

Saturday, June 9

7:00 a.m. – 7:00 p.m.	Yellowstone National Park Tour	Depart Strand Union

Sunday, June 10

7:00 a.m.-7:00 p.m.	Yellowstone National Park Tour	Depart Strand Union
1:00 pm - 9:00 pm	Registration	Strand Union
8:00 pm - 12:00 am	Opening mixer and Poster Session A Exhibitor booths	North Gym

Monday, June 11

Presiding: Cynthia McClure

7:30 am - noon	Registration	Strand Union
8:30 am - 8:50 am	Opening remarks: **Gary Molander**	Ballroom
8:50 am - 9:00 am	Welcome: MSU President **Dr. Geoffrey Gamble**	
9:00 am - 10:00 am	**Peter Stang** University of Utah "Nanoscale Molecular Architecture: Design and Self-Assembly of Metallocyclic Polygons and Polyhedra via Coordination"	Ballroom
10:00 am - 10:15 am	Questions	
10:15 am - 10:45 am	Break	
10:45 am - 11:45 am	**Josef Michl** University of Colorado at Boulder "Making and Using Molecular Rods and Connectors"	Ballroom
11:45 am - noon	Questions	

1:00 p.m. – 5:00 p.m.	Lewis & Clark Caverns Tour	Depart Strand Union

Monday Evening

Presiding: Mary Cloninger

7:00 pm - 8:00 pm	**Carolyn Bertozzi** University of California, Berkeley "Metabolic Cell Surface Engineering"	Ballroom
8:00 pm - 8:15 pm	Questions	
8:15 pm - 9:15 pm	**Jeffery Kelly** The Scripps Research Institute "Structure-Based Design, Synthesis and Evaluation of Transthyretin Amyloid Fibril Inhibitors"	Ballroom
9:15 pm - 9:30 pm	Questions	
9:30 pm - 12:00 am	Mixer and conclusion of Poster Session A Exhibitor booths	North Gym

Tuesday, June 12

Presiding: Amos B. Smith, III

8:30 am - 9:30 am	**Carl Johnson** Wayne State University "Using Nature's Catalysts: The Chemoenzymatic Synthesis of Bioactive Molecules"	Ballroom
9:30 am - 9:45 am	Questions	
9:45 am - 10:30 am	Break	
10:30 am - 11:30 am	**Gary Sulikowski** Texas A&M University "From Biosynthesis to Total Synthesis: Lessons from Natural Products"	Ballroom
11:30 am - 11:45 am	Questions	
11:45 am - 12:45 pm	**Manfred Reetz** Max-Planck-Institut für Kohlenforschung "Evolution in the Test Tube as a Means to Create Enantioselective Enzymes"	Ballroom

12:45 pm - 1:00 pm	Questions	
12 Noon – 7:00 pm	Yellowstone River Tour	Depart Strand Union
1:45 pm - 5:30 pm	Robert Rich, ACS-PRF Grant Proposal Writing Workshop.	Rm. 106E SUB

Tuesday Evening

Presiding: Robert Boeckmann

7:30 pm - 8:45 pm	**Roger Adams Awardee Address:** **Prof. Ryoji Noyori** Nagoya University "Asymmetric Hydrogenation via Architectural and Functional Molecular Engineering"	Ballroom
9:00 pm- 12:00 am	Mixer and Poster Session B Sponsored by Eli Lilly and Company Exhibitor booths	North Gym

Wednesday, June 13

Presiding: Paul Grieco

8:30 am - 9:30 am	**Bruce Lipshutz** University of California, Santa Barbara "New Synthetic Methodology Based on Late Transition Metal Catalysts"	Ballroom
9:30 am - 9:45 am	Questions	
9:45 am - 10:30 am	Break	
10:30 am - 11:30 am	**Andrew Evans** Indiana University "New Rhodium-Catalyzed Allylic Substitution Reactions: Mechanistic Insight and Synthetic Applications"	Ballroom
11:30 am - 11:45 am	Questions	
11:45 am - 12:45 pm	**John Hartwig** Yale University "Understanding and Discovery of Transition Metal-Catalyzed Reactions"	Ballroom

12:45 pm - 1:00 pm	Questions	

Wednesday Evening

Presiding: Gary Molander

5:00 pm - 7:00 pm	Western BBQ (tickets required)	Strand Union Patio
7:30 pm - 8:30 pm	**Jerrold Meinwald** Cornell University "Desperately Seeking Semiochemicals"	Ballroom
9:00 pm - 12:00 am	Mixer and conclusion of Poster Session B Sponsored by Organic Letters Exhibitor Booths	North Gym

Thursday, June 14

Presiding: Tom Livinghouse

9:00 am - 10:00 am	**Alois Fürstner** Max-Plank Institut für Kohlenforschung "Alkyne Metathesis: A Complementary and Competitive Tool"	Ballroom
10:00 am - 10:15 am	Questions	
10:15 am - 10:45 am	Break	
10:45 am - 11:45 am	**Ei-ichi Negishi** Purdue University "Highly Diastereoselective and/or Enantioselective Methods for the Syntheses of Terpenoids and Other Related Compounds via Organometallic Carbon-Carbon and Carbon-Heteroatom Bond Formation Catalyzed by Zr, Pd, Cu, and Other Transition Metals"	Ballroom
11:45 am - noon	Questions	
12:00 pm	Closing remarks	

GENERAL INFORMATION

Shuttle Schedule

Shuttles depart every half hour, unless otherwise specified, from the following hotels:

Comfort Inn, Ramada/Fairfield Inn, Hampton Inn, Holiday Inn, Best Western GranTree, Days Inn. The airport shuttle also stops at the MSU Residence Halls.

Saturday, June 9	Airport – Hotels – Residence Halls	12 Noon – Midnight
Sunday, June 10	Airport – Hotels – Residence Halls	12 Noon – Midnight
	Hotels – MSU Strand Union	1:00 p.m. – 12:30 a.m.
Monday, June 11	Hotels – MSU Stand Union	7:00 a.m. – 9:00 a.m. 12 Noon – 3:00 p.m. 6:00 p.m. – 12:30 a.m.
Tuesday, June 12	Hotels – MSU Strand Union	8:00 a.m. – 9:30 a.m. 1:00 p.m. – 3:00 p.m. 6:30 p.m. – 12:30 a.m.
Wednesday, June 13	Hotels – MSU Strand Union	8:00 a.m. – 9:30 a.m. 1:00 p.m. – 3:00 p.m. 4:30 p.m. – 12:30 a.m.
Thursday, June 14	Hotels – MSU Stand Union	8:30 a.m. – 10:00 a.m. 12 Noon – 1:00 p.m.
	Residence Halls – Hotels – Airport	5:30 a.m. – 9:00 a.m. (departs each hour) 10:00 a.m. – 3:00 p.m. 3:00 p.m. – 5:00 p.m. (departs each hour)
Friday, June 15	Residence Halls – Hotels – Airport	5:30 a.m. – 3:00 p.m. 3:00 p.m. – 5:00 p.m. (departs each hour)

Parking on the MSU Campus

For those staying in the MSU Residence Halls, the most convenient parking is in the North Hedges E Lot.

The closest lot to the Strand Union Building, where the sessions are held, is the S/B Lot on the corner of Grant Street and 7th Avenue. Your parking permit must be displayed at all times. Please do not park in restricted or handicapped parking areas.

Montana Travel

Montana Travel will have a table set up in the Registration area. There is still an opportunity to sign up for tours. Stop by and talk to representatives from Montana Travel about tours or travel arrangements. All tours depart from the Grant Street entrance of the Strand Union Building.

Accessing Email

The Renne Library has computers with Internet access that can be used free of charge during library hours. Construction is taking place outside the library this summer, and we have been advised that on-line capability could be intermittent, however. If you are staying in the residence halls, you can use the computer labs at no charge. If you would like Internet access in your room, you can order Resnet, MSU's high-speed Internet connection, for $15 per stay.

Renne Library Summer Hours

Sunday	1:00 – 9:00 p.m.
Mon. – Thur.	7:45 a.m. – 9:00 p.m.
Friday	7:45 a.m. – 5:00 p.m.
Saturday	10:00 a.m. – 5:00 p.m.

The Roger Adams Award in Organic Chemistry

The Roger Adams Award in Organic Chemistry is sponsored jointly by the American Chemical Society, Organic Reactions, Inc., and Organic Syntheses, Inc. The award recognizes the distinguished career of Roger Adams, who played a vital role in each of these three organizations. He was Chairman of the Board of Directors as well as President of the American Chemical Society, and he co-founded *Organic Syntheses* and *Organic Reactions.*

The award is made biennially to an individual, without regard to nationality, for outstanding contributions to research in organic chemistry. The award consists of a gold medal, a sterling silver replica of the medal, and an honorarium of twenty-five thousand dollars. It is presented at the biennial National Organic Chemistry Symposium of the Division of Organic Chemistry of the American Chemical Society. The awardee is a featured lecturer in the program of the symposium.

The recipient of this year's Roger Adams Award is Professor Ryoji Noyori of Nagoya University. His award address, entitled "Asymmetric Hydrogenation via Architectural and Functional Molecular Engineering," will be delivered on Tuesday evening, June 12.

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ACS Organic Division Graduate Fellows and Sponsors

Listed below are the thirty-four advanced graduate students who were awarded Division of Organic Chemistry Graduate Fellowships in the past two years. Many of these students are here at the Symposium with poster presentations. Also listed are the names of their institutions, faculty research advisors, and the companies that sponsored these awards. The Division is pleased to honor these extraordinary students and to gratefully acknowledge the substantial financial support provided by the generous sponsors.

1999-2000 **2000-2001**

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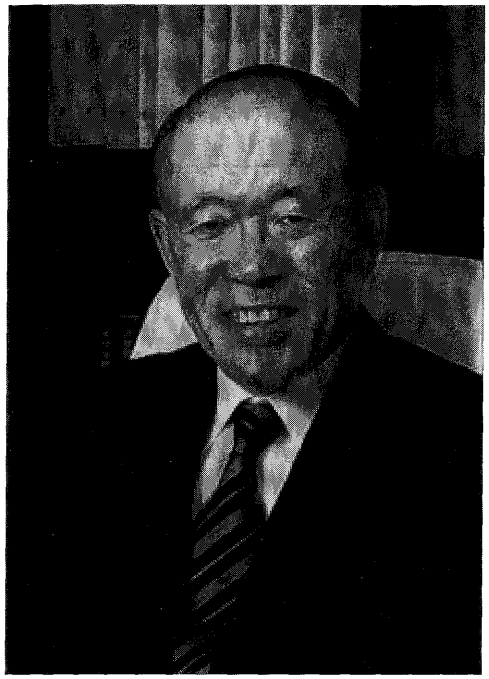
Please make sure to visit the **Wiley** booth, and browse our excellent selection of publications in the field. Books on display include *Basic Organic Stereochemistry*, by Eliel, Wilen, and Doyle; and *Solid Phase Organic Syntheses,* by Czarnik. Our standout journals include *The Chemical Record* and *International Journal of Chemical Kinetics.*



Asymmetric Hydrogenation via Architectural and Functional Molecular Engineering

Ryoji Noyori

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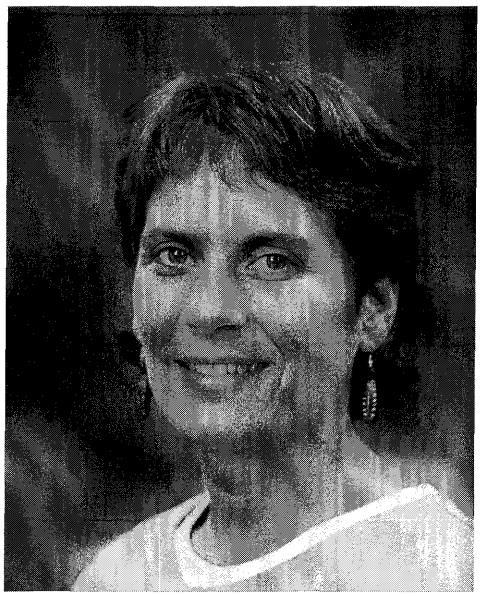
e-mail: noyori@chem3.chem.nagoya-u.ac.jp

Question: Is the substrate/metal complexation essential for hydrogenative saturation of unsaturated compounds? *Answer:* No, it is not always necessary. The metal–ligand bifunctional catalysis allows for direct saturation of carbonyl compounds with an 18-electron transition metal hydride without C=O/metal interaction.

$RuCl_2$(phosphine)$_2$(1,2-diamine) is an excellent precatalyst for homogeneous hydrogenation of simple ketones which lack any functionality capable of interacting with the transition metal center. The presence of an NH end in the diamine auxiliary is crucial for the catalytic activity. This catalyst system allows for the preferential reduction of a C=O function over a coexisting C=C linkage in a 2-propanol solution containing an alkaline base. The use of appropriate chiral diphosphines, particularly BINAP compounds, and chiral diamines results in rapid and productive asymmetric hydrogenation of a range of aromatic, heteroaromatic, and olefinic ketones and gives a consistently high enantioselectivity.

Asymmetric transfer hydrogenation of aromatic carbonyl compounds using 2-propanol/alkaline base or formic acid/triethylamine in the presence of RuCl[(*S,S*)-YCH(C_6H_5)CH(C_6H_5)NH_2](η^6-arene) (Y = O, NTs) gives the corresponding *S* chiral alcohols of high enantiomeric purity. The reaction is selective for C=O or C=N functions. The reaction proceeds via a coordinatively saturated 18-electron complex, RuH[(*S,S*)-YCH(C_6H_5)CH(C_6H_5)NH_2](η^6-arene), whose hydridic RuH and protic NH are simultaneously deliverd to a C=X (X = O or N) linkage.



Metabolic Cell Surface Engineering

Carolyn R. Bertozzi

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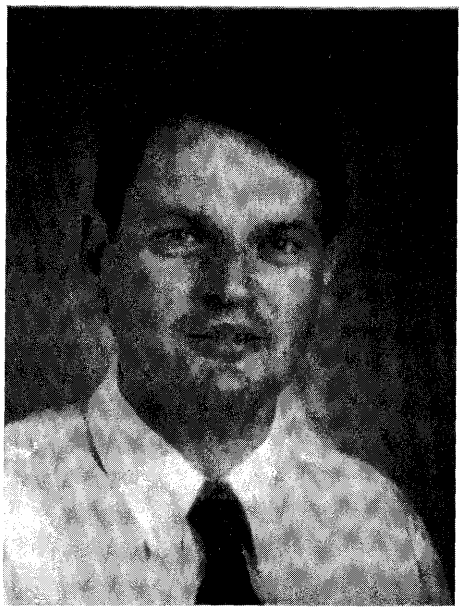
Cell surface molecules govern the 'social behavior' of cells and participate in fundamental processes such as cell-cell adhesion and virus-host cell binding. Consequently, the ability to chemically control the display of epitopes on cell surfaces would facilitate investigations of cell-cell interactions and enable one to engineer cells with novel properties. One of our goals is to apply the principles of organic chemistry to the problem of orchestrating cell surface chemistry. Toward this end, we harness the cell's metabolic machinery to remodel cell surfaces with reactive organic functional groups and to disrupt the expression of specific glycans associated with tumor metastasis. The foundation of our approach is the unnatural substrate tolerance of certain enzymes involved in oligosaccharide biosynthesis, which permits the incorporation of unnatural monosaccharides into cell surface-associated oligosaccharides. We exploit these pathways as vehicles for the delivery of uniquely reactive electrophilic functional groups, such as ketones and azides, to cell surface glycoconjugates. Their selective reaction with rationally-designed organic structures bearing a complementary nucleophile allows us to remodel the composition of the cell surface under physiological conditions. In some cases, metabolic incorporation of unnatural sugars serves to terminate growing oligosaccharide chains thereby modifying the carbohydrate landscape of the cell surface. This technique for cell surface engineering has prompted new directions in biomedical research.



New Rhodium-Catalyzed Allylic Substitution Reactions: Mechanistic Insight and Synthetic Applications

P. Andrew Evans

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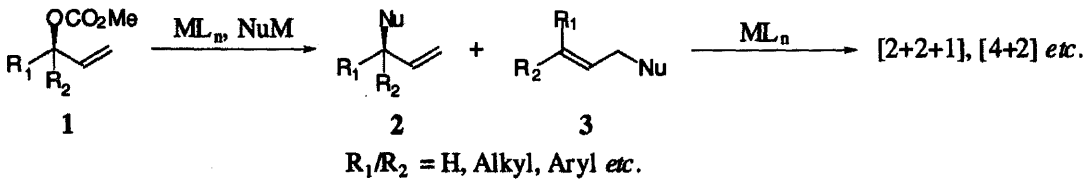
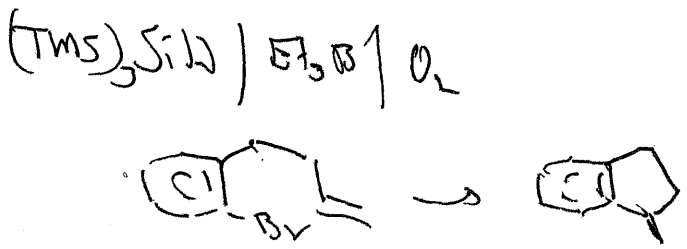
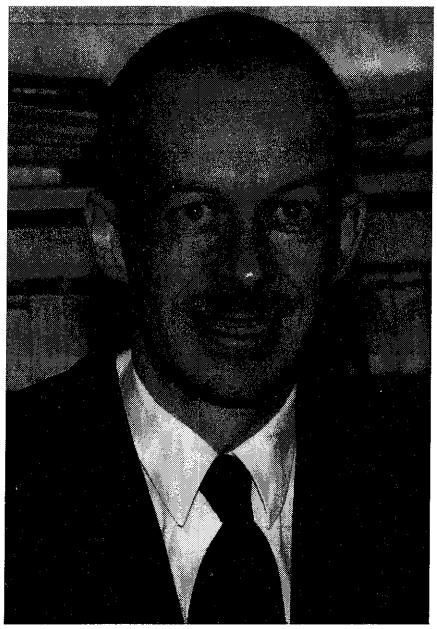
Bloomington, IN 47405, USA
e-mail: paevans@indiana.edu

The transition metal-catalyzed allylic substitution reaction represents a powerful and fundamentally important transformation, in which the enantiospecific version provides a conceptually useful method for the construction of vicinal ternary and quaternary stereogenic centers. Despite the enormous synthetic potential, this approach has been somewhat restricted to symmetrical or stereoelectronically-biased substrates in order to circumvent problems associated with regioselectivity. Furthermore, stoichiometric metal is often required to minimize the erosion of enantiospecificity due to metal-metal displacement reactions, which further limits the utility for target directed synthesis.



We recently demonstrated that Wilkinson's catalyst, [$RhCl(PPh_3)_3$], may be modified *in situ* to furnish a catalytically active species that facilitates the regioselective allylic substitution of acyclic *unsymmetrical* chiral non-racemic allylic alcohol derivatives with retention of absolute configuration, *vide supra*. The seminar will encompass many of the recent mechanistic developments, their implication for asymmetric catalysis and the disclosure of new results using hard nucleophiles that expand the scope of this important transformation. Finally, the development of new tandem metal-mediated allylic substitution/annulation reactions will be described.





Alkyne Metathesis: A Complementary And Competitive Tool

Alois Fürstner

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D-45470 Mülheim, Germany
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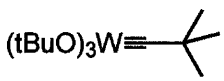
During the last decade, alkene metathesis has evolved into a very powerful and mature tool for advanced organic synthesis [1,2]. A short summary of the present state of the art will be presented which is largely defined by the excellent application profile of "second generation" ruthenium complexes bearing N-heterocyclic carbene ligands.

Despite the versatility of these novel catalysts, several problems remain unsolved. Most notable among them is the fact that the stereochemistry of the newly formed double bond can hardly be controlled. This handicap, however, can be overcome by a complementary approach based on alkyne metathesis followed by semi-reduction [3]. The available catalysts include the Schrock alkylidyne complex **1** [4] and a structurally yet unknown species formed in situ from the molybdenum complex **2** and a halide source such as CH_2Cl_2 [5]. Both reagents are distinguished by an excellent performance and a remarkable compatibility with polar functional groups.



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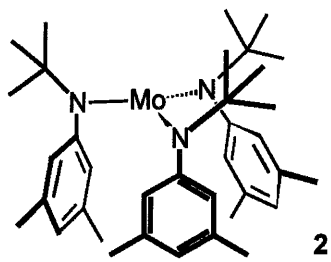
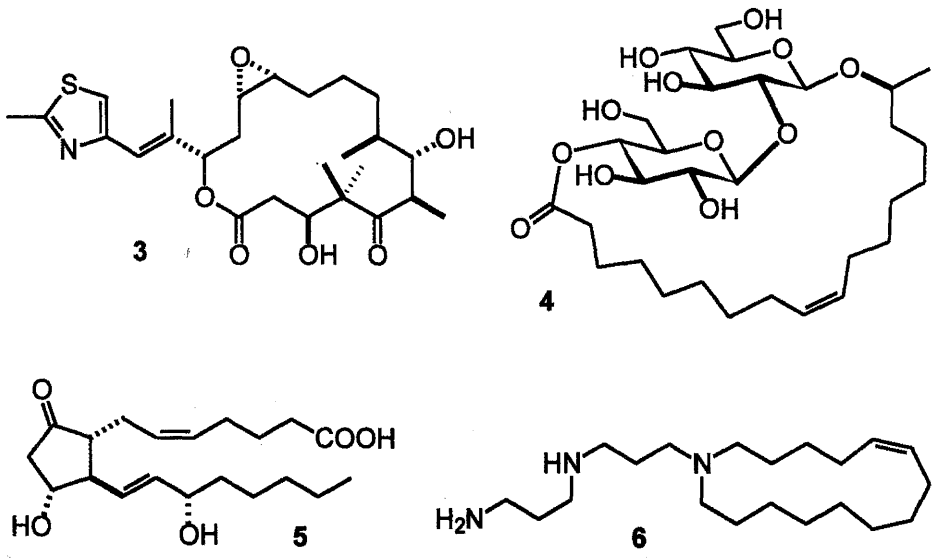


2

Prototype applications of alkyne metathesis to the total synthesis of bioactive natural products of different complexity such as **3** – **6** will be presented. These examples are meant to illustrate the wide scope of the reaction independent of whether it is performed in a ring closing- [5-9], homodimerization- [10], or a cross metathesis mode [11].



Selected references: [1] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18. [2] A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *122*, 3012. [3] A. Fürstner, G. Seidel, *Angew. Chem. Int. Ed.* **1998**, *110*, 1758. [4] R. R. Schrock, D. N. Clark, J. Sancho, J. H. Wengrovius, S. M. Rocklage, S. F. Pedersen, *Organometallics* **1982**, *1*, 1645. [5] A. Fürstner, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **1999**, *121*, 9453. [6] A. Fürstner, K. Grela, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **2000**, *122*, 11799. [7] A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, *121*, 11108. [8] A. Fürstner, K. Radkowski, J. Grabowski, C. Wirtz, R. Mynott, *J. Org. Chem.* **2000**, *65*, 8758. [9] A. Fürstner, A. Rumbo, *J. Org. Chem.* **2000**, *65*, 2608. [10] A. Fürstner, T. Dierkes, *Org. Lett.* **2000**, *2*, 2463. [11] A. Fürstner, C. Mathes, *Org. Lett.* **2001**, *3*, 221.

TL, 40, 4787 (1999)
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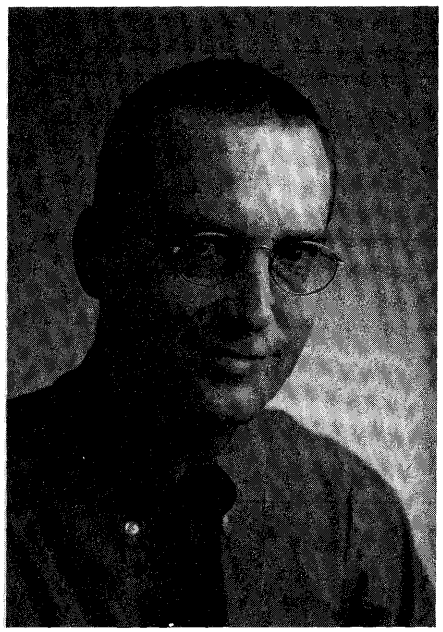
OL 12, 4475 (2000)
Org Lett., 2, 3731 (2000) } Smith, Snyder — Salicylihalamide



Understanding and Discovery of Transition Metal-Catalyzed Reactions

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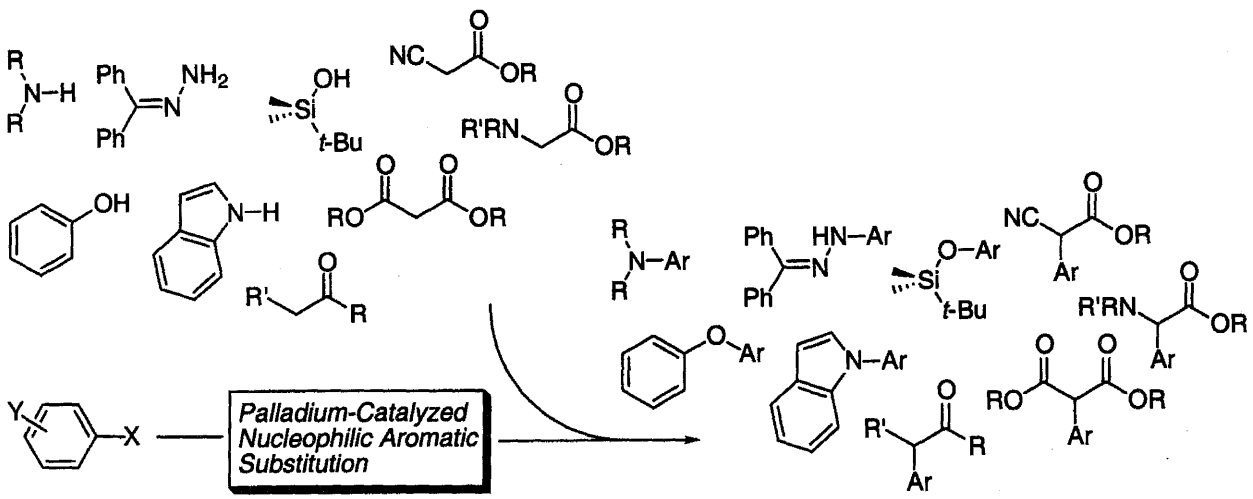
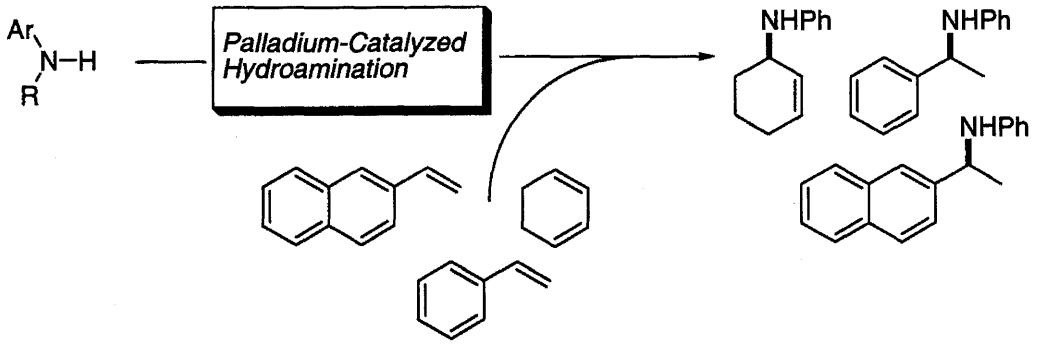
This talk will first present information on methodology and mechanism for one or more of the reactions developed recently in our laboratory. For several years my group has studied palladium catalyzed chemistry that forms aromatic carbon-nitrogen and carbon-oxygen bonds from aryl halides and triflates. In addition, we have recently reported chemistry that forms alpha-aryl carbonyl compounds by reaction of an aryl halides with α ketones, esters, malonates or cyanoester. These reactions are summarized in the Scheme below.

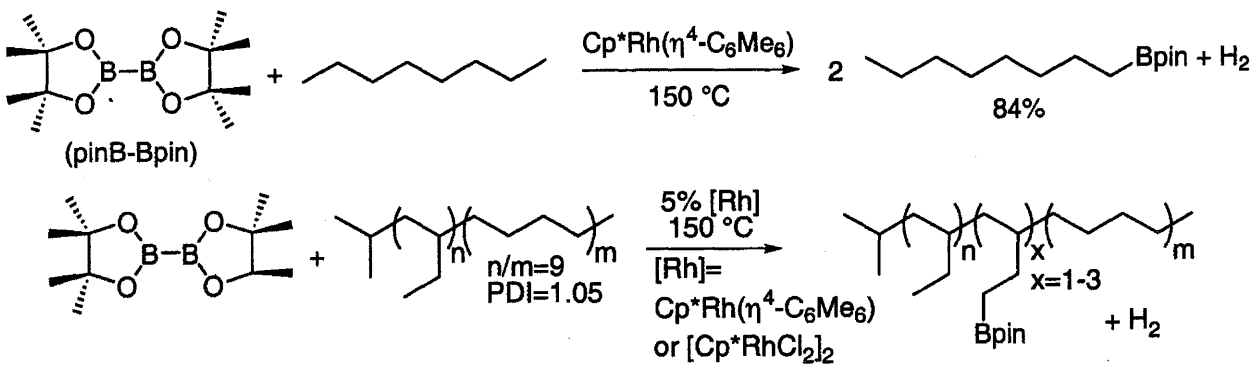


Mechanistic chemistry have been conducted hand-in-hand with studies on reaction scope and catalyst development. These studies have revealed new primary processes for organometallic compounds. In particular, C-N and C-O bond-forming reductive elimination of amines and ethers were unknown several years ago, and we uncovered examples of these reactions from isolated arylpalladium amides and phenoxides. Systems to observe directly reductive elimination from arylpalladium enolates have also been developed and these systems explain the trends in rates and regioselectivity of the alpha-arylation processes.

In addition, we have recently identified catalysts for the reaction of amines with dienes and vinylarenes to form the products of hydroamination as shown below. These catalysts were identified, in part, through a new high-throughput screening method for the reaction of amines. The scope of these reactions, mechanism for the process, and development of enantioselective versions has been a topic of recent studies.



Recently, we also have discovered of a catalytic, regiospecific functionalization of alkanes that occurs under thermal conditions. In this chemistry the reaction of a linear alkane with two diboron reagents shown below, or pinacolborane, produces linear organoboranes by regiospecific functionalization of the terminal position of the borane. The isolation of reaction intermediates and the reactions with macromolecules has been accomplished recently. The use of the organoborane products from polyolefin functionalization are precursors to alcohols by simple, well known chemistry, providing a route to the generation of polyolefins with polar functionality.



As part of these investigations, we have begun to develop general methods to screen for covalent bond formation from reactions employing homogeneous transition metal catalysts. We have focused on using substrates with fluorescent tags and on using simple spot-tests to analyze four palladium-catalyzed reactions: amination of aryl halides, Heck reactions, arylation of cyanoacetates, and hydroamination of dienes. Current progress on assay development and catalyst discoveries will be presented.

Using Nature's Catalysts: The Chemoenzymatic Synthesis of Bioactive Molecules

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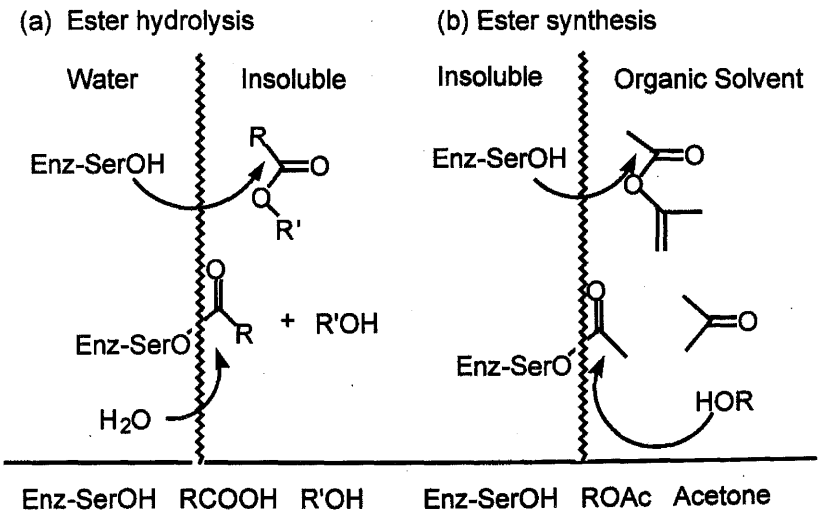
Although the concept of enzyme applications to asymmetric synthesis has been long recognized, it is only recently that these catalysts are attracting the attention of the non-specialist. The enzymatic desymmetrization of meso compounds has gained popularity in recent years and constitutes a highly effective approach for the synthesis of enantiomerically pure compounds. We will present in this lecture an overview of work from our laboratory involving the use of enzymes and fermentations in desymmetrizations and in resolutions for the production of enantiopure intermediates and the use of the latter in the synthesis of a variety of bioactive target molecules.

The molecular machinery of lipases is much like that of the serine proteases and consists of a catalytic triad of amino acids—serine, histidine and aspartic (or glutamic) acid. This machinery first transfers the acyl group of an ester (or other acyl derivative) to the hydroxyl group of the serine residue to form the acylated enzyme. The acyl group is subsequently transferred to an external nucleophile with return of the enzyme to its pre-acylated state to start the process over again. Because the natural substrates are water insoluble, lipases are specially structured to act at a water/organic interface. For this reason lipases appear to be optimum among the enzymes to operate in organic solvents, in this case the interface is between the insoluble enzyme with its essential water of hydration and the organic solvent containing an acylating agent, *e.g.*, isopropenyl acetate and a substrate to be acylated (Scheme 1).

Scheme 1



Structure-Based Design, Synthesis and Evaluation of Transthyretin Amyloid Fibril Inhibitors

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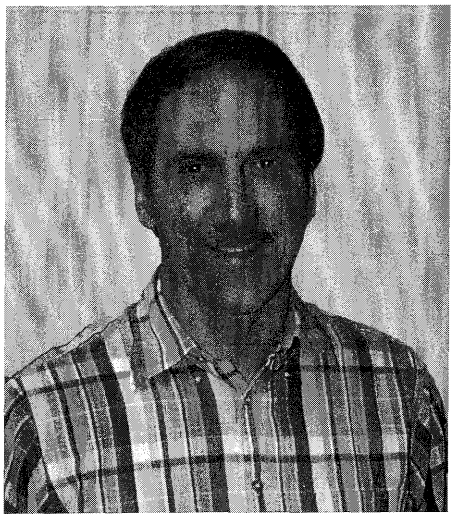
A detailed understanding of the kinetics and thermodynamics of transthyretin (TTR) amyloid fibril formation has led to a small molecule strategy to prevent the protein-protein interactions that are enabled by TTR conformational changes. The dissociation of the normally folded tetramer to an alternatively folded monomer is the rate-determining step in transthyretin amyloidogenesis. Small molecule inhibitors that block dissociation have been structurally characterized in complex to TTR to a resolution of 1.5 Å by X-ray crystallography. Several different inhibitor-TTR structures were used as a basis for structure-based designs of novel and optimized inhibitors. Several nM inhibitors have resulted from this effort. Chemistry will be described that allows preparation of aromatic oxime ether libraries that are exceptional inhibitors.



New Synthetic Methodolgy Based On Late Transition Metal Catalysis

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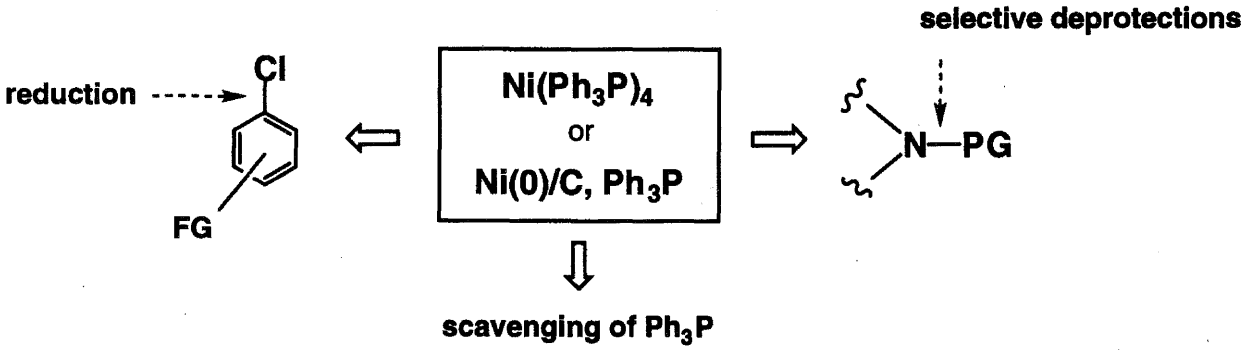
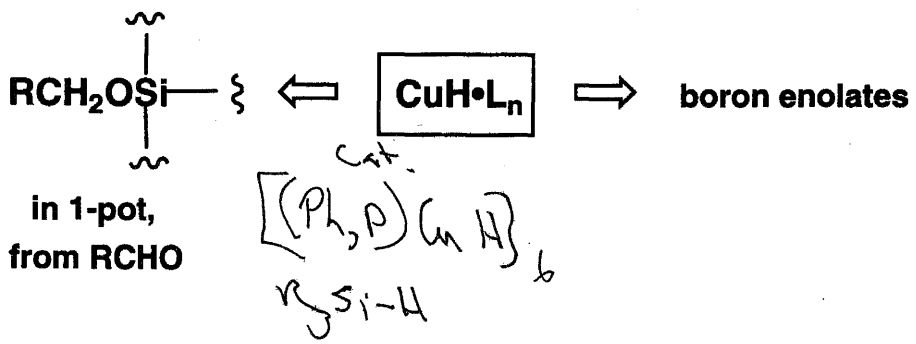
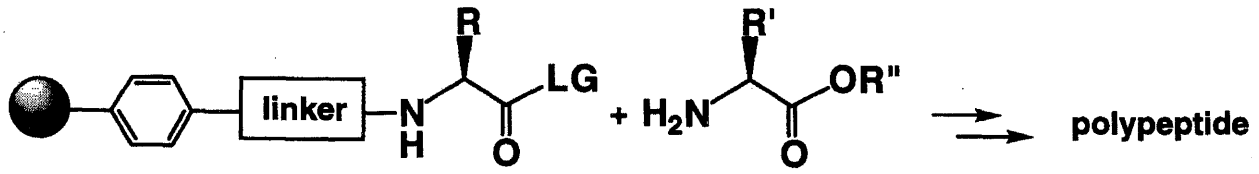
New methodologies which are based on catalysis by either nickel(0) or copper(I) will be described. Ni(0)-mediated couplings, where the ligated metal is used in a homo- $[Ni(Ph_3P)_4]$[1] or heterogeneous [Ni(0)/C] fashion,[2] will focus on aryl halide reductions, as well as applications to protecting group chemistry (of nitrogen).[3] A related study which has led to a novel, very effective means of scavenging monodentate phosphines (*e.g.*, Ph_3P) and oxides thereof (*e.g.*, $Ph_3P{=}O$), will be disclosed.[4]



Copper(I)-based technologies will focus on new catalytic uses of stabilized versions of copper hydride ($CuH{\bullet}L_n$).[5] Processes that include direct conversions of carbonyl derivatives to silyl-protected alcohols,[6] as well as unprecedented, regio- and stereo-specific boron enolate formation which does *not* rely on boron halides or triflates,[7] will also be presented.



Finally, time permitting, a novel traceless linker for (unconventional) solid phase polypeptide synthesis will be discussed.[8]



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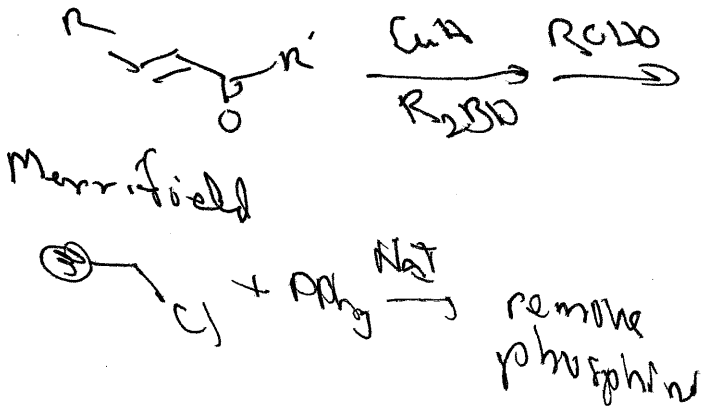

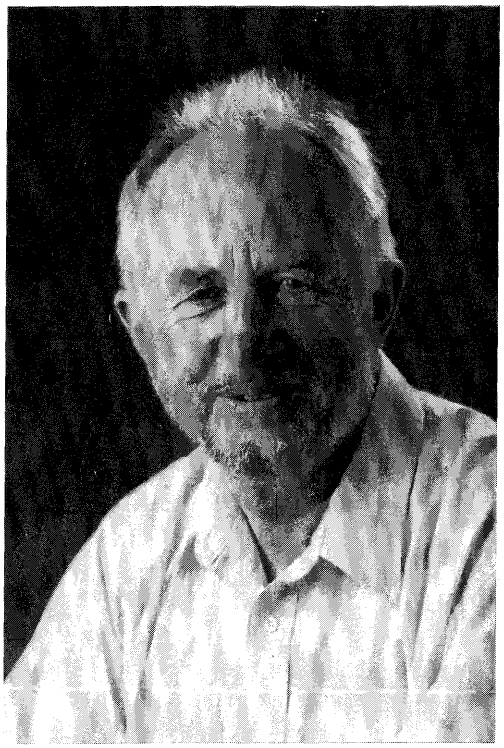

Making and Using Molecular Rods and Connectors

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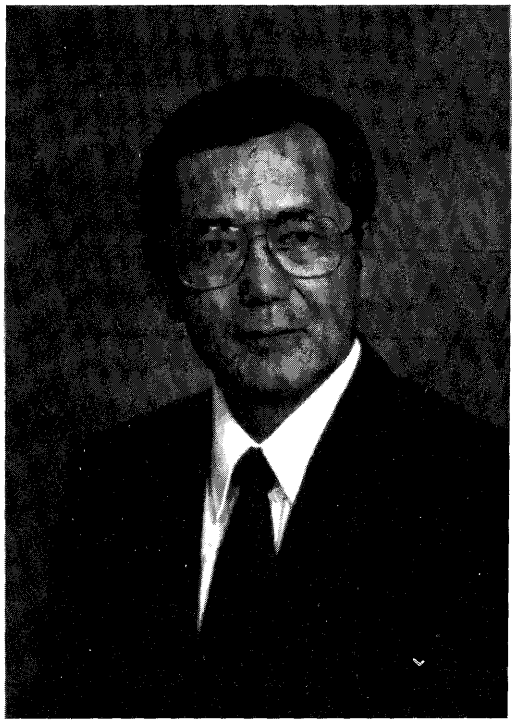
We survey our efforts to develop a molecular Tinkertoy-like construction kit for the synthesis of giant molecules based on one- and two-dimensional covalent assembly of rod-shaped with star-shaped modules. The project started when we noticed the oligomerization of [1.1.1]propellane to [n]staffanes. Numerous axially disubstituted rods were synthesized, using repetitive bicyclo[1.1.1]pentane, 10- and 12-vertex *p*-carborane, and other cage structures. Such rods can be used as purely structural elements and also as electrical resistors. Subsequent effort turned to the synthesis of electron-dopable rod-shaped electron-acceptor molecules, primarily concatenated extended viologen analogs. When doped with electrons, these molecular rods become electrically conducting. Their electron transfer properties are under examination by transient spectroscopy and electrochemistry, and their macroscopic electrical conduction has been measured after mounting them in small numbers (individually?) between a pair of electrodes at a continuously variable 0 to 5 nm separation, using terminal substituents that provide adhesion to gold. A third electrically insulated metallic electrode located nearby controls the current through such a molecular rod, as in ordinary field-effect transistors. We have also synthesized analogous hole-dopable electron-donor rods, concatenated sandwich complexes of tetraarylcyclobutadienes. Linear molecules combining electron-dopable and hole-dopable rod segments connected either directly or through one of the molecular resistor rods have permitted measurements of asymmetric electron transfer and electrical conduction that strongly hint at single-molecule current rectification ("Aviram-Ratner diode").

Two-dimensional synthesis of covalent grid-shaped structures from molecular rods and star-shaped connectors must overcome their natural tendency to cross-link three-dimensionally. We have devised methods for confining the motion of the star-shaped monomers to two dimensions during their coupling with linear linkers into a polymeric grid. The connectors used were trigonal (1,3,5-trisubstituted benzenes) or tetragonal (metal sandwich complexes of meso-tetraarylporphyrins and tetraarylcyclobutadienes). Surfaces and interfaces of liquids, particularly mercury and water, have been used to provide the needed confinement, and scanning tunneling microscopy (STM) has revealed the formation of sturdy and locally regular square grid polymer molecules up to about 150 nm by 150 nm in size. Adhesion to mercury is controlled by the electrical potential between the mercury surface and a counterelectrode. It appears that mercury cation complexation is responsible for the formation of extensive networks that preassemble the adsorbed molecules into regular

arrays, facilitating their subsequent covalent coupling into locally regular polymer grids. STM images of fragile grids resulting from monomer linking by linear couplers that depend on reversible weak intermolecular interactions (hydrogen or metal-ligand bonds) show much larger and nearly perfectly regular domains. We are presently attempting to combine the desirable properties of sturdiness, large domain size, and structural perfection in a single grid.

Various uses can be imagined for these grid polymers. One is the mounting of molecular dipolar rotors on the grid points, with axles normal to the surface. Some of the resulting dipole arrays should have ferroelectric ground states and promise novel dielectric properties. So far, experimental data have been obtained only for random arrays of dipolar rotors mounted on quartz. We have used molecular dynamics to simulate a single propeller-shaped dipolar rotor driven either by a stream of gas or by a rotating electric field, and explored the interplay of the driving force, friction, and random thermal motion in determining the nature of its response. The results can be viewed as prototypical for molecular-size mechanical nanomachinery in general.



Highly Diastereoselective and/or Enantioselective Methods for the Syntheses of Terpenoids and Other Related Compounds via Organometallic Carbon-Carbon and Carbon-Heteroatom Bond Formation Catalyzed by Zr, Pd, Cu and Other Transition Metals

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Transition metal-catalyzed cross coupling and carbometallation, the latter of which includes olefin metathesis, have been established as some of the most useful and general synthetic tools for the formation of carbon-carbon and carbon-heteroatom bonds. Of particular interest in this lecture are (i) the Zr-catalyzed carboalumination reported first in 1978[1], especially the more recently disclosed enantioselective version,[2] and (ii) the Pd-catalyzed cross coupling of organometals containing Al[3], Zn[4], Zr[5], and related metals.[6]

The Zr-catalyzed enantioselective carboalumination of "ordinary" terminal alkenes[2] can readily provide the desired isoalkylaluminum derivatives (**Scheme 1**). With Me_3Al as a reagent, the chemical yields and ee figures have been typically 70 – 90 % and 70 – 75%, respectively, while ethyl- and higher alkylalanes have led to 55 – 90% chemical yields and 90 – 95% ee. These results have been obtained by using $(NMI)_2ZrCl_2$[7] as a catalyst. Ten to a dozen other chiral Zr complexes were also tested, but the results were less satisfactory.[2] A more recent related study involving the use of cationic chiral zirconocene derivatives also led to comparable results.[8] The use of $(NMI)_2ZrCl_2$ derived from (-)-menthol has consistently led to the formation of the *R* isomers of isoalkylalanes, whereas the use of (+)-menthol has led to the *S* isomers. Thus, the reaction is fully reagent-controlled and predictably stereospecific. The origin of the uniquely and distinctly lower ee figures for methylalumination is still unclear. However, auxiliary asymmetric induction due to α-agostic interaction[9] involving Et and higher alkyl groups might be responsible for the persistently observed difference.

Mechanistically, the observed results are consistent with the bimetallic, *i.e.*, Zr and Al, and acyclic mechanism depicted in **Scheme 2**. Systematic, long-range investigations have established that, whereas acyclic monometallic carbozirconation involving zirconocene derivatives is virtually unknown, both monometallic and bimetallic cyclic carbozirconation reactions have been widely observed.[1d, 1e, 2c, 2d] In this connection, it is worth mentioning that a few other recently developed enantioselective carbozirconation reactions of allylically heterosubstituted alkenes[10] most likely proceed *via* monometallic cyclic carbozirconation and that high ee figures have been observed only with allylically heterosubstituted alkenes. Thus, these reactions must be synthetically and mechanistically discrete from those discussed herein.

In addition to the ongoing project for improving enantioselectivity of the Zr-catalyzed carboalumination itself, various different kinds of efforts to develop the reaction as a potentially useful synthetic tool have led to some fundamentally interesting and synthetically useful findings, such as those listed below. These will be elaborated in the lecture.

(i) Use of a terminal methylene group as a latent Me group and of mixed alanes, *i.e.*, $R(CH_2)_2Al(Bu\text{-}i)_2$, for high ee construction (~90% ee) of Me-substituted alkyl groups (**Scheme 3**).

(ii) Use of propene for attaining the same goal (**Scheme 3**).

(iii) An attendant development of a rate-accelerated and more reliable procedure with the use of isobutylaluminoxane (IBAO) along the line of a recent modification with H_2O or methylaluminoxane (MAO).[11]

(iv) Exploitation of statistical amplification[12] through a combination of two or more "independent" enantioselective carbon-carbon formation processes (**Scheme 4**).

(v) Exploitation of statistical amplification[12a–12c] for enantiomeric separation and purification (**Scheme 5**).

Although further improvements are clearly needed, the Zr-catalyzed carboalumination of alkenes indeed appears to be very promising as an enantioselective tool for the synthesis of chiral natural products and other chiral organic compounds. Highly efficient syntheses of several natural products, such as phytol, vitamins E and K, and stellettamides A and B,[12] will be discussed.

Also to be discussed are some highly selective and efficient syntheses of conjugated oligoenes, *e.g.*, β- and γ-carotenes,[3b] oligoenynes, *e.g.*, xerulin,[4g] and 1,5-diene-containing oligoenes, *e.g.*, coenzyme Q_{10}.[14]

Acknowledgments.

The author is deeply indebted to all of the cited coworkers, especially Drs. D. Y. Kondakov, S. Huo, F. Zeng, J. Shi, as well as Messrs. Z. Tan and L. Anastasia for their dedicated hard work. This work has been primarily supported by NSF, NIH, and Purdue University.

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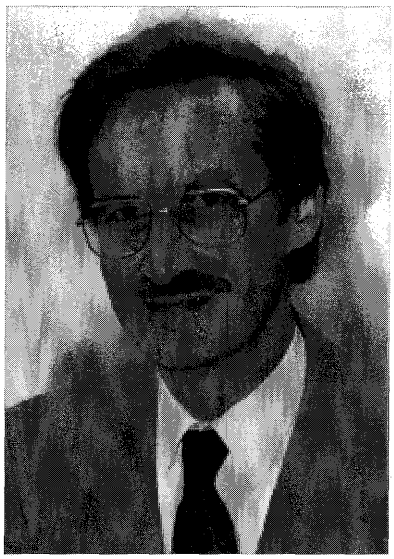

Evolution in the Test Tube as a Means to Create Enantioselective Enzymes

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In enantioselective transition metal catalysis, the development of a single highly effective chiral catalyst requires the laborious preparation and testing of a large number of ligands. Alternatively, biocatalysts can be used, but by nature the problem of substrate specificity persists.

A radically different approach to the development of enantioselective catalysts is described, namely directedevolution as a method to stepwise increase the enantioselectivity of a given unselective enzyme. The underlying principle - "evolution in the test tube" - does not require any knowledge of the enzyme structure or of its catalytic mechanism. Proper molecular biological methods for random mutagenesis and expression of genes coupled with an efficient screening system for the rapid identification of enantioselective mutants form the basis of our strategy. The principle is illustrated using a lipase from *Pseudomonas aeruginosa*, which shows an *ee*-value of only 5% in the hydrolysis of a chiral ester. An enantioselectivity of > 95% can be obtained by applying the evolutive method. Sequencing studies reveal the positions at which amino acid substitutions have occurred ("hot spots"), raising fundamental questions concerning enzyme catalysis.

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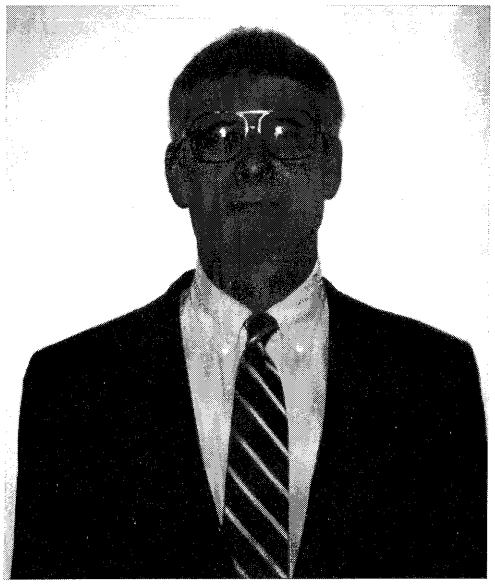

Nanoscale Molecular Architecture: Design and Self-Assembly of Metallocyclic Polygons and Polyhedra via Coordination

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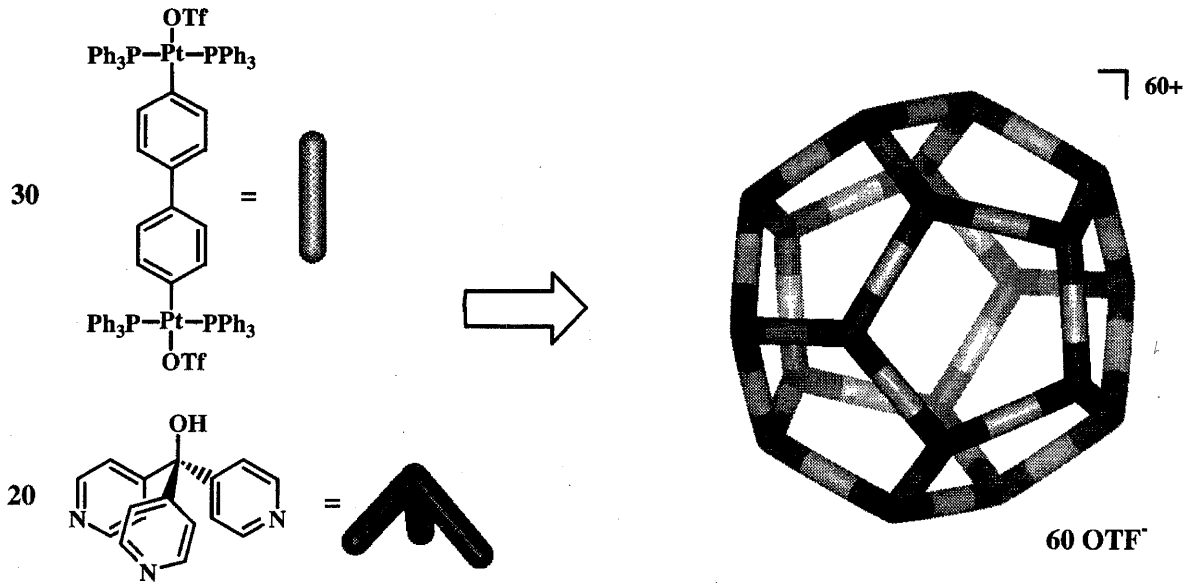
The use of just two types of building blocks, linear and angular, in conjunction with symmetry considerations allows the rational design of a wide range of metallocyclic polygons and polyhedra. via the coordination motif.[1,2] We have used this approach to self-assemble a variety of molecular polygons such as triangles, rectangles, squares etc. More recently we have used this methodology to construct via self-assembly the following polyhedra: truncated tetrahedra, cubooctahedra[3] and dodecahedra.[4] The methodology is illustrated in Figure 1. These novel, supramolecular ensembles are characterized by physical and spectral means. The design strategy, formation, characterization and potential uses of these novel metallocyclic assemblies will be discussed, along with our recent results in crystal engineering.

Figure 1



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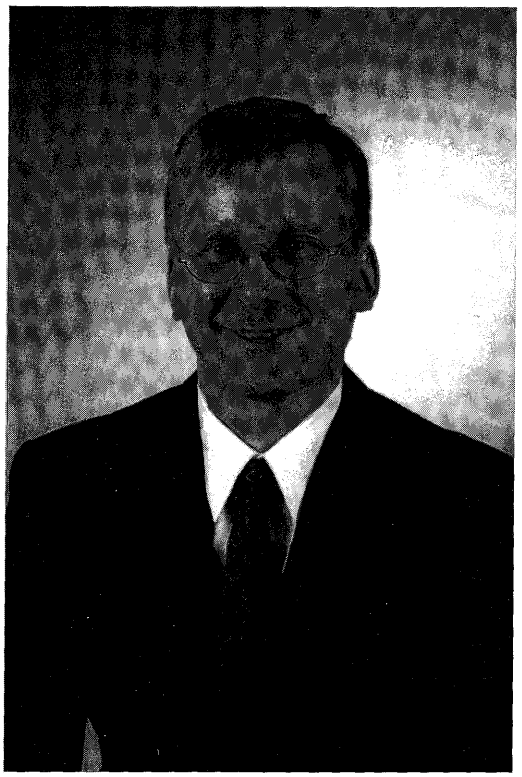

From Biosynthesis to Total Synthesis: Lessons from Natural Products

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The complex structures presented in the form of natural products frequently serve as inspiration for the development of new synthetic strategies and methods in the area of organic synthesis. Occasionally inspiration is derived from the biosynthetic pathway by which a natural product is itself assembled. In the latter case, the resulting biomimetic synthetic strategy is often characteristically concise and efficient in design. This lecture will describe progress on the total synthesis of several complex natural products, one inspired by a biosynthetic proposal currently under investigation in my group.

Phomoidride A (CP-225,917) and phomoidride B (CP-263,114) are produced by an unidentified fungus thought to be related to the *Phoma* species.[1] These secondary metabolites possess modest activity against farnesyl transferase and squalene synthase and were classified as nonadrides, a small group of natural products produced by various fungi. Due to their unique architecture and biological activity phomoidride A and B have been the subject of extensive synthetic investigations.[2] We reported on the biosynthesis of these compounds and described the biosynthetic scheme shown in Figure 1. Using ^{13}C-labeled precursors and whole cells we determined that succinic and acetic acid are precursors to the complete carbon skeleton of phomoidride B.[3] At the time of our initial publication, the relevance of the proposed C_{16} plus C_{16} dimerization (**2**) remained an open issue. Based on the biosynthetic pathway outlined in Figure 1 we investigated a biomimetic strategy aimed at the discovery of a template directed dimerization leading to the core structure of the phomoidrides in a single step.[4] This lecture will describe the latest experimental results supporting the biosynthetic scheme outlined in Figure 1 as well as progress on orchestrating a biomimetic synthesis of phomoidride A and B.

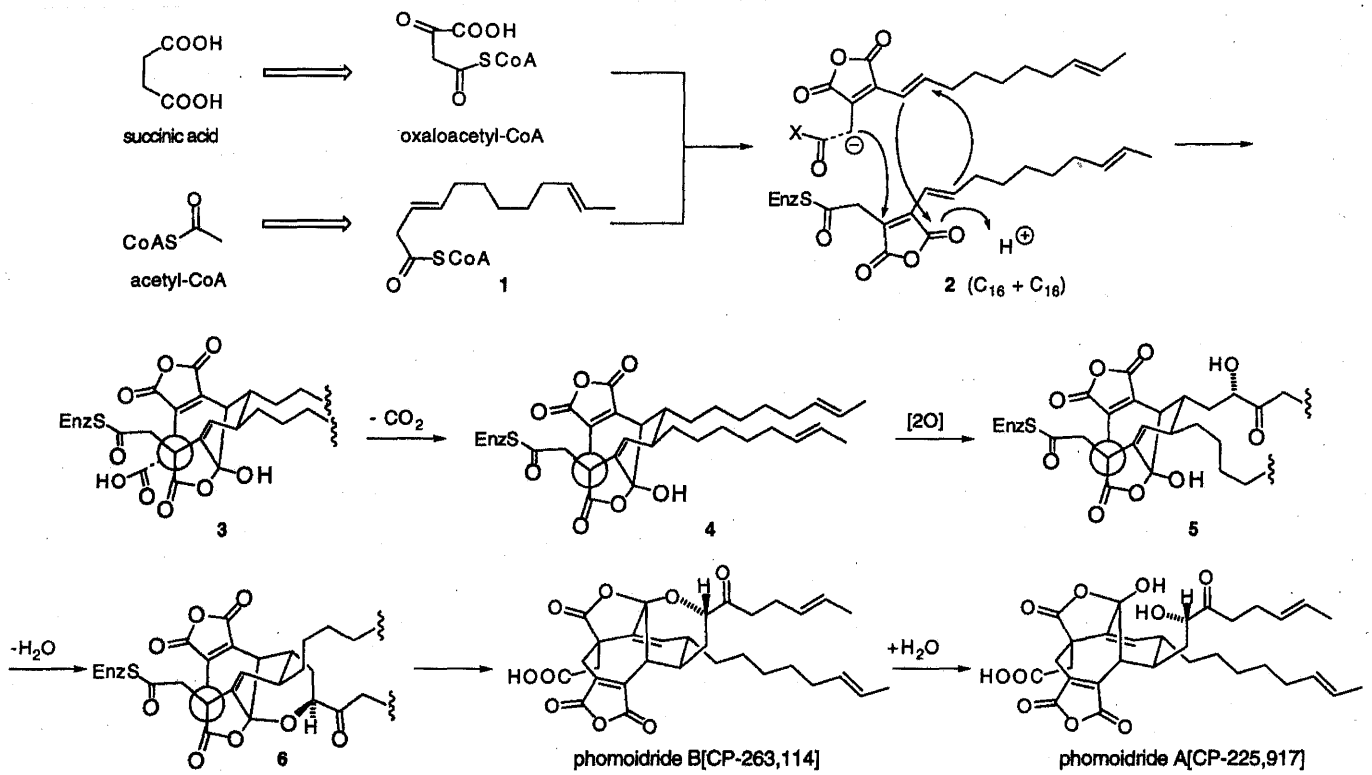
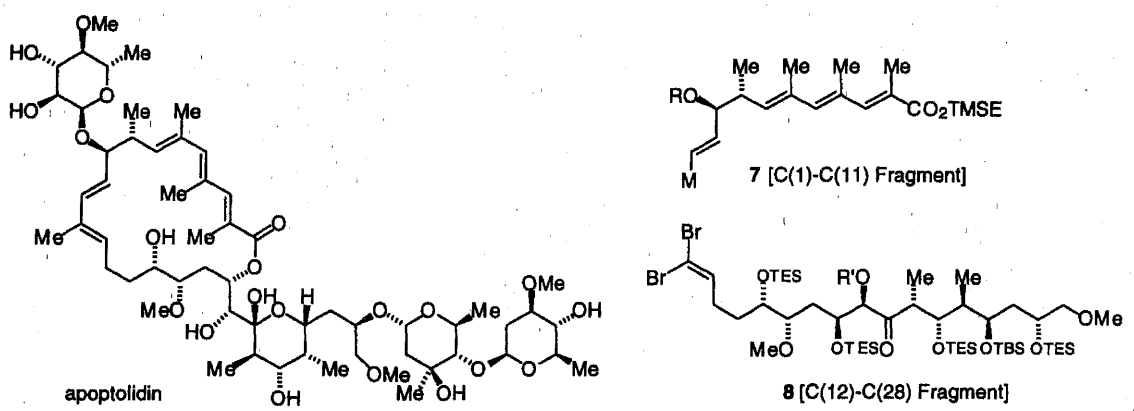


Figure 1. **Proposed biosynthesis of phomoidride A and B.**

50 In the second section of this lecture studies on the total synthesis of apoptolidin will be presented. In 1997 Seto and co-workers described the isolation and two-dimensional structure of apoptolidin and one year later a full structural assignment based on extensive NMR analysis was published.[5] Significantly, apoptolidin selectively sensitizes certain cancer cells to apoptosis induction. Recently, workers at Stanford suggested this selective mode of apoptosis induction is associated with apoptolidin's ability to inhibit mitochondrial F_0F_1-ATP synthase.[6] From the retrosynthetic perspective we divided apoptolidin in two fragments, C(1)-C(11) fragment (**7**) and C(12)-C(28) fragment (**8**).[7] The stereocontrolled assembly of **7** and **8** will be described as well as progress towards the completion of the apoptolidin aglycone and congeners.



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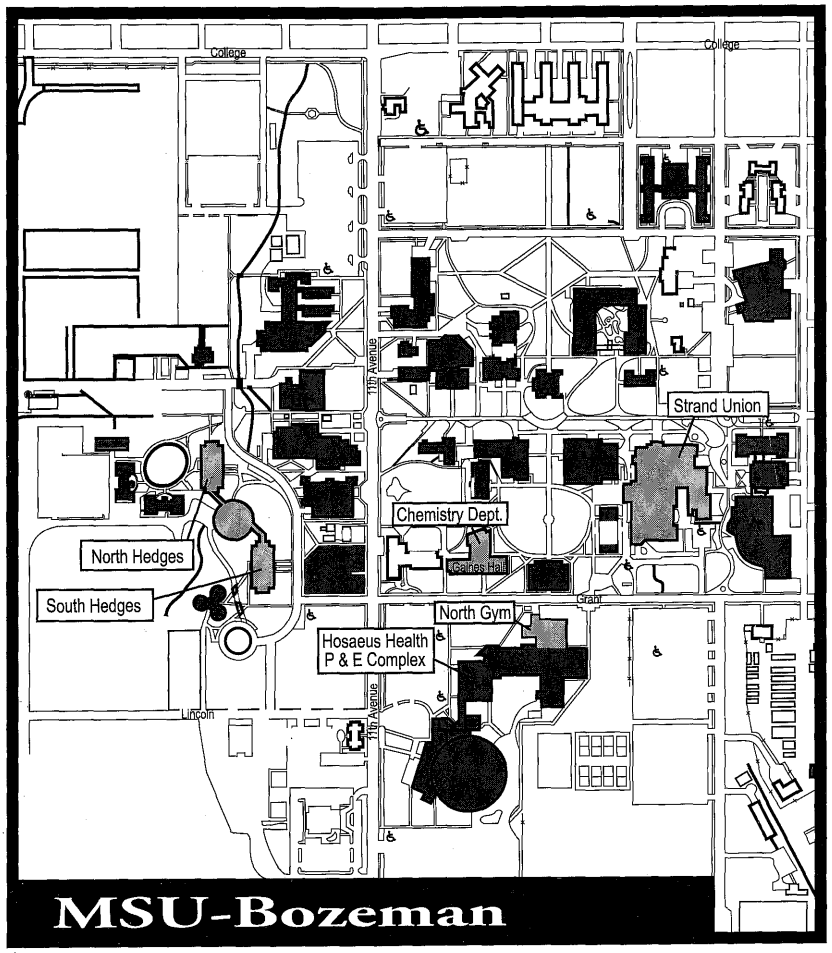

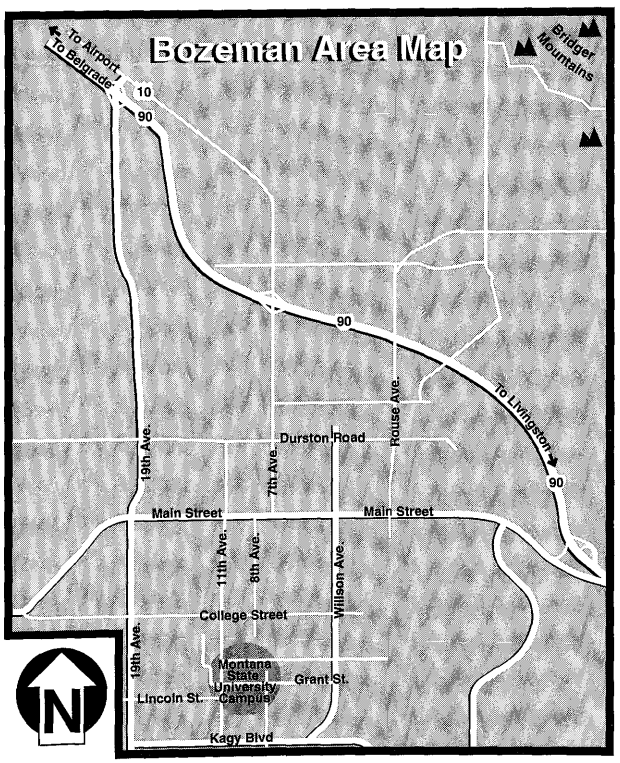

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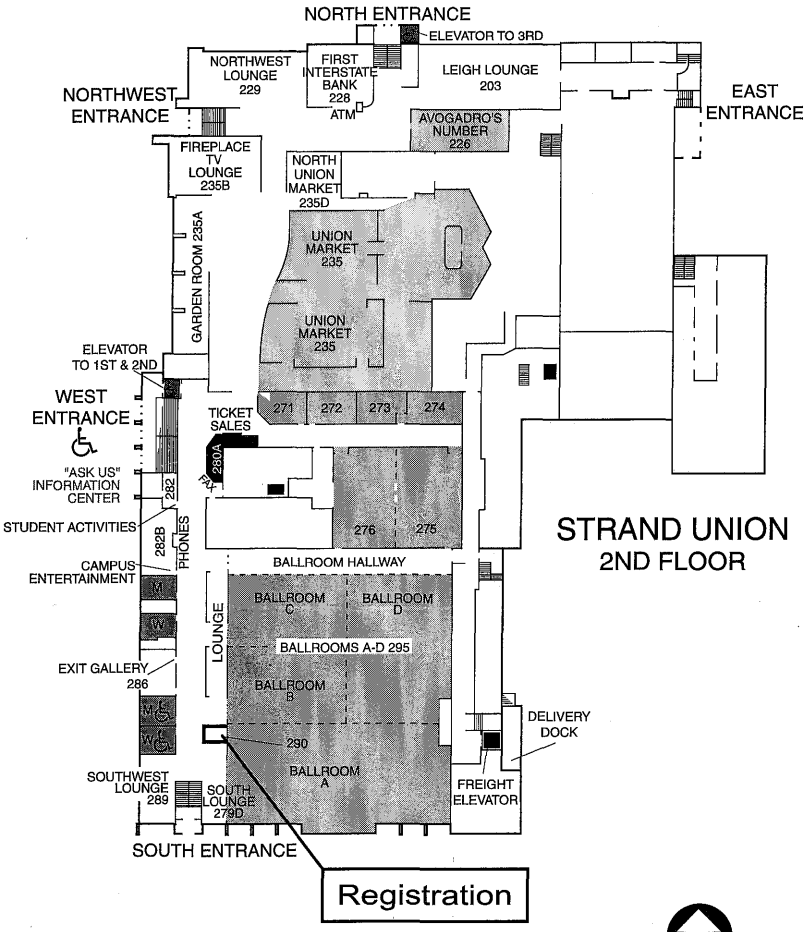

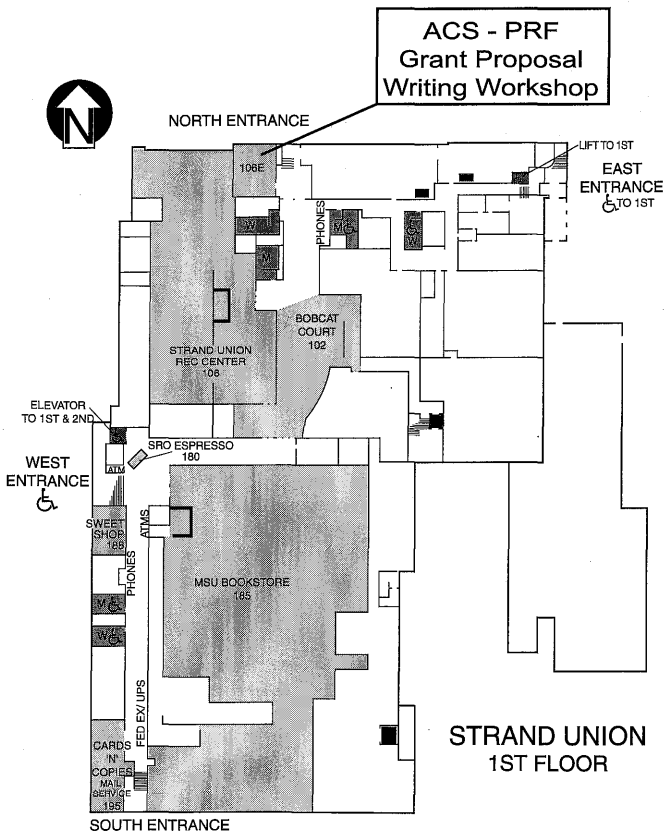

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