

Trifunctional Organocatalysis

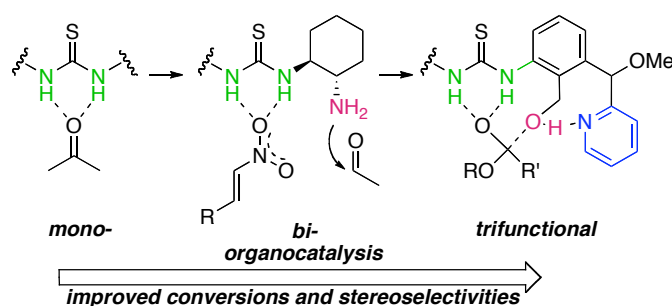
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ABSTRACT



The scope and stereoselectivities achieved by organocatalysts have grown remarkably over the past decade. However, the high catalyst loadings and low temperatures often required remain limitations in the field. Recent reports of *trifunctional* organocatalysts to overcome these shortcomings have begun to appear in the literature. This mini-review covers trifunctional catalysts and their applications.

Organocatalysts have emerged as powerful tools for organic transformations.¹ Reports describing the catalysis of organic reactions by cinchona alkaloids² and proline³ date back to the last century. At the turn of the millennium, List and co-workers reported a proline-catalyzed enantioselective intermolecular aldol reaction,⁴ and MacMillan and co-workers discovered a highly enantioselective imidazolidinone-catalyzed Diels-Alder cycloaddition.⁵ The use of these effective, environment-friendly catalysts surged.

In the short time that has passed since the seminal work of these two groups, organocatalysis has grown “from infancy to adolescence.”^{1b} More than 1500 manuscripts report the use of these catalysts in over 130 discrete reaction types,^{1a} including carbon-carbon bond formation, oxidation, reduction, pericyclic, and halogenation reactions. These small molecules are remarkably efficient, catalyzing cascade⁶ and multi-component⁷ reactions. Extensive theoretical studies have allowed for mechanistic elucidations and predictions⁸ and effective syntheses of drugs and natural products.⁹

¹ (a) MacMillan, D. W. C. *Nature*, **2008**, *455*, 304-308. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2-25. (c) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516-532. (d) List, B. *Chem. Rev.* **2007**, *107*, 5413-5415. (e) Buckley B. R. *Annu. Rep. Prog. Chem., Sect. B* **2007** *103*, 90-106. (f) Houk, K. N.; List, B. *Acc. Chem. Res.* **2004**, *37*, 487. (g) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138-5175. (h) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *41*, 3726-3748.

² (a) Bredig, G.; Fiske, P. S. *Biochem. Z.* **1912**, *46*, 7. (b) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9-22. (c) Wynberg, H.; Staring, E. M. J. *J. Am. Chem. Soc.* **1982**, *104*, 166-168.

³ (a) Hajos, Z. G.; Parrish, D. R. *DE* 2102623, Jul 29, 1971. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621. (c) Eder, U.; Sauer, G.; Wiechert, R. *DE* 2014757, Oct. 7, 1971. (d) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Eng.* **1971**, *10*, 496-497.

⁴ List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

⁵ Ahrendt, K. A.; Borths, C. J.; MacMillan D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.

⁶ For a minireview, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570-1581. For examples, see: (b) Bui, T.; Barbas, C. F., III *Tetrahedron Lett.* **2000**, *41*, 6951-6954. (c) Yang, J. W.; Hechavarria, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036-15037. (d) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986-14991. (e) Enders, D.; Huettl, M. R. M.; Grondal, C.; Raabe, G. *Nature*, **2006**, *441*, 861-863. (f) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498-7499.

⁷ For a review on organocatalytic multi-component reactions, see: Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693-700.

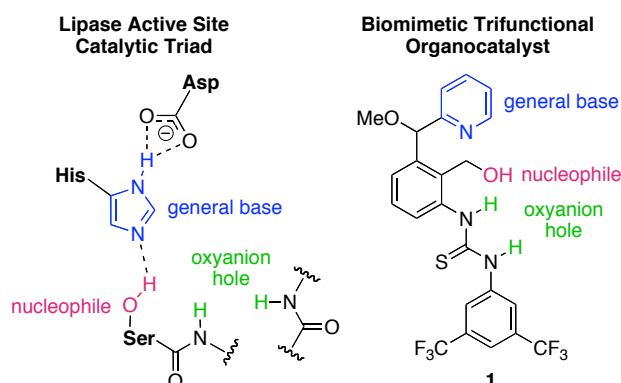
⁸ Houk, K. N.; Cheong, P. H.-Y. *Nature*, **2008**, *455*, 309-313.

⁹ For reviews on organocatalysis in drug and natural product syntheses, see: (a) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8-27. (b) Marcia de Figueiredo, R.; Christmann, M. *Eur. J. Org. Chem.* **2007**, *16*, 2575-2600.

The success of these small molecules may largely be attributed to *bifunctionality*, bearing a Lewis/Brønsted acidic moiety for the activation of electrophiles, and a Lewis/Brønsted basic moiety for the activation of nucleophiles.¹⁰ Despite these successes, the need for high catalyst loadings (usually 20-30 mol% is required) and low temperatures to achieve high stereoselectivity are serious limitations. In an effort to further enhance these catalysts and ultimately mimic enzyme activity, researchers have recently developed *trifunctional* organocatalysts. Trifunctional catalysts bear (in addition to the bifunctional motifs) a third functional group, such as an additional hydrogen bond donor or a general base, in order to enhance reactivity and stereoselectivity. This mini-review describes the accomplishments that have been achieved with trifunctional catalysts.

One of the first—and arguably most impressive—reports of a trifunctional organocatalyst rate acceleration involves the transesterification of vinyl acetates to alcohol.¹¹ Sakai and co-workers mimicked the known active site of serine hydrolases and performed MO calculations to hone in on **1** as the catalyst of choice (Scheme 1). The pyridine is proposed to act as a general base for the deprotonation of the hydroxyl group, which attacks the carbonyl group of the trifluoroacetate. The thiourea mimics an oxyanion hole.

Scheme 1



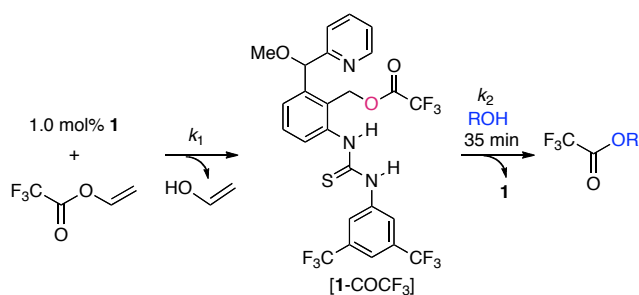
The rate-determining step, deacetylation of the acyl-catalyst intermediate (k_2 , Scheme 2), was measured to be approximately $10^{-1} \text{ M}^{-1}\text{s}^{-1}$, which corresponds to rate accelerations (k_2/k_{uncat}) of 10^3 and 10^5 for methanol and isopropanol, respectively. For comparison, the rate constants ($k_{\text{cat}}/K_{\text{M}}$) for bimolecular enzyme-catalyzed reaction often approach the diffusion-controlled collision

¹⁰ For minireviews of bifunctional organocatalysis, see: (a) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785-795. (b) Connon, S. J. *Chem. Commun.* **2008**, *22*, 2499-2510. (c) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7496-7504.

¹¹ Ema, T.; Tanida, D.; Matsukawa, T.; Sakai, T. *Chem. Commun.* **2008**, 957-959.

frequency of two reactants in water ($10^9 \text{ M}^{-1}\text{s}^{-1}$),¹² and catalytic proficiencies ($(k_{\text{cat}}/K_{\text{M}})/k_{\text{uncat}}$)¹³ of enzymes generally range from 10^8 to 10^{27} M^{-1} . Although the efficiency of **1** is still far from that of known enzymes, this work demonstrates the strong potential of multifunctional organocatalysts. When the same reaction was run with three control catalysts lacking either the pyridine, hydroxy, or thiourea moiety, little or no acceleration was observed.

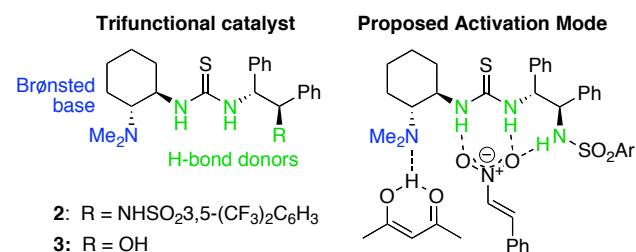
Scheme 2



R	k_{uncat} ($\text{M}^{-1}\text{s}^{-1}$)	k_1 ($\text{M}^{-1}\text{s}^{-1}$)	k_2 ($\text{M}^{-1}\text{s}^{-1}$)	k_1/k_{uncat}	k_2/k_{uncat}
Me	7.6×10^{-5}	14.4	0.63	1.9×10^5	8.3×10^3
<i>i</i> -Pr	4.0×10^{-6}	14.9	0.61	3.7×10^6	1.5×10^5

The Michael reaction has been a favorite target for trifunctional catalysis. Wang et al. described new catalysts bearing *two* hydrogen bond donors and a basic site (**2** and **3**, Scheme 3) for the addition of diketones¹⁴ and cycloketesters¹⁵ to nitroolefins. Results for the addition of acetylacetone to a variety of nitroolefins are shown in Scheme 4. With only 1 mol % of **2**, unsubstituted, electron-rich, and electron-deficient aryl nitroolefins all reacted in less than two hours with excellent yields and stereoselectivities. Furthermore, **2** was able to promote the first known asymmetric addition of acetylacetone to *alkyl* nitroolefins, albeit with less efficiency.

Scheme 3



¹² Fersht, A. *Structure and Mechanism in Protein Science: A Guide to Enzyme Catalysis and Protein Folding*, 3rd ed.; W. H. Freeman and Company: New York, 2000.

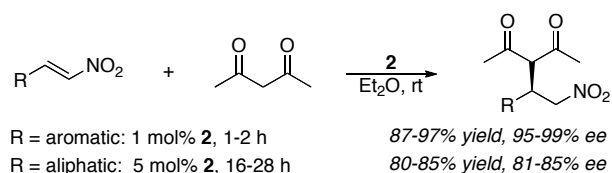
¹³ Miller, B. G.; Wolfenden, R. *Annu. Rev. Biochem.* **2002**, *71*, 847-885.

¹⁴ Wang, C.-J.; Zhang, Z.-H.; Dong, X.-Q.; Wu, X.-J. *Chem. Commun.* **2008**, 1431-1433.

¹⁵ Zhang, Z.-H.; Dong, X.-Q.; Chen, D.; Wang, C.-J. *Chem. Eur. J.* **2008**, *14*, 8780-8783.

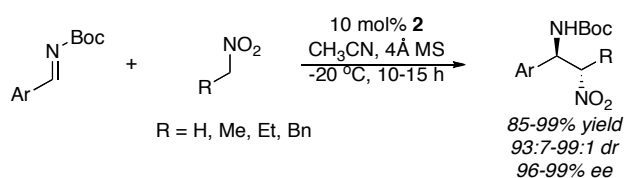
The tertiary amine of the catalyst is believed to deprotonate the diketone and stabilize the resulting enolate (Scheme 3), while the remaining two functional groups (thiourea and sulfonamide) stabilize the nitro oxygens via hydrogen bond donation. Mesylate and tosylate analogs of **2**, as well as *N*-methyl sulfonamides, gave poor conversions and enantioselectivities, which strongly suggests that a triple activation mode is essential for effective catalysis.

Scheme 4



The same catalyst **2** catalyzes an *anti*-selective nitro-Mannich reaction (Scheme 5).¹⁶ Prior to this point, only a few organocatalyzed *anti*-selective nitro-Mannich reactions with excellent diastereo- and enantioselectivity had been known.¹⁷ The authors did not discuss possible activation modes, but Takemoto et al.^{17c} had proposed an activation mode by a related bifunctional catalyst in which the tertiary amine deprotonates the nitroalkane and stabilizes the resulting anion, and the protonated amine and thiourea activate the imine for electrophilic attack (Scheme 6, left).

Scheme 5

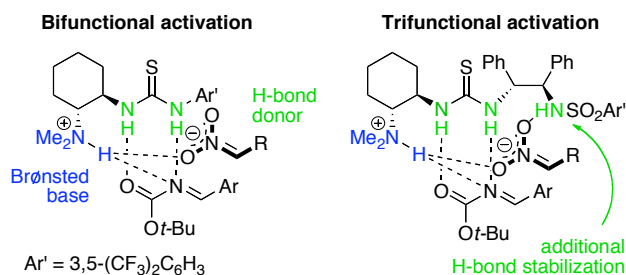


The sulfonamide hydrogen of trifunctional catalyst **2** may provide further stabilization to the nitroalkane anion (Scheme 6, right). The nitro-Mannich reactions reported by Takemoto required 24-60 hours for good yields (compared to 10-15 hours with trifunctional **2**), and *N*-methylation of **2** resulted in sluggish reactions and diminished stereoselectivities. These results show the advantage of having multiple hydrogen-bond donors in the catalysis of the nitro-Mannich reaction.

¹⁶ Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8606-8607.

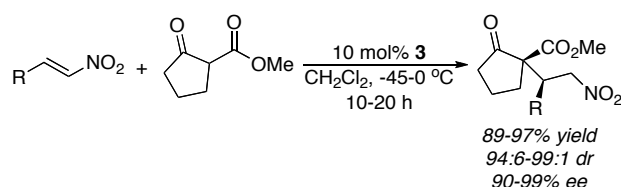
¹⁷ (a) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625-627. (b) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466-468. (c) Xu, X. N.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466-476. (d) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110-15111. (e) Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008**, *10*, 1707-1710.

Scheme 6



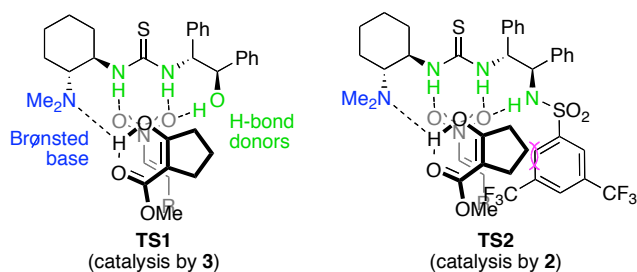
Attempts to use **2** to promote the Michael reaction of α -substituted- β -ketoesters with nitrostyrene gave poor results. The reaction proceeded smoothly but with low stereoselectivity. The authors attributed the poor selectivity to the bulkiness of the sulfonamide group. Indeed, upon replacing the sulfonamide moiety with a hydroxy group (**3**), very good yields and stereoselectivities were achieved over a wide substrate scope, including aliphatic nitroalkenes (Scheme 7). The *O*-methyl analog of **3** causes long reaction times and decreases in enantioselectivity to as low as 29%, demonstrating the prominent role of the hydroxy group in the reaction.

Scheme 7



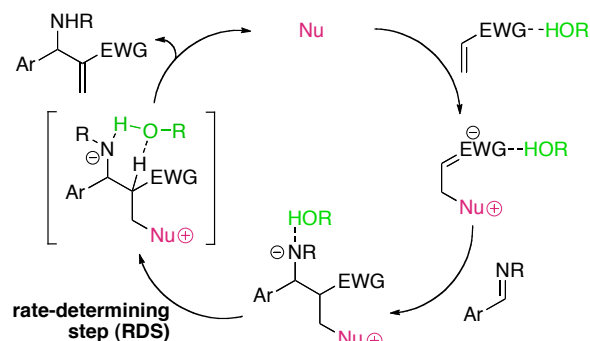
The proposed transition structure according to the observed enantioselectivities is shown in Scheme 8 (**TS1**). Like **2**, the tertiary amine of **3** activates the dicarbonyl, while the thiourea and hydroxy hydrogens activate the nitroalkene. The inactivity of **2** in catalyzing this reaction may be explained by a steric repulsion between the cyclopentane and aryl moieties (**TS2**). Wang's work shows that a few similar organocatalysts (**2** and **3**) can be effective in catalyzing a variety of reactions and substrates.

Scheme 8



The aza-Morita-Baylis-Hillman (aza-MBH) reaction has also been catalyzed by a trifunctional organocatalyst. Although this atom-economical reaction has been known for decades, poor conversion, limited substrate scope, and unpredictable enantioselectivities have hampered its widespread use.¹⁸ Theoretical¹⁹ and experimental²⁰ evidence point towards the alcohol-assisted deprotonation of the nucleophile-alkene-imine adduct as the rate-determining step of the reaction (Scheme 9).

Scheme 9



Drawing upon the known efficiencies of bifunctional BINAP-phosphines bearing hydrogen donors as catalysts for the reaction,²¹ Liu envisioned a catalyst that contains a third motif, a chiral ion pair.²² The protonated Brønsted base is proposed to stabilize the imine nitrogen and alcohol, while the counterion “gates” (i.e., selectively assists) the proton, thereby accelerating the reaction rate and stereoselectivity (Scheme 10).²³ The catalysts, **4** and **5**, proved to be the most effective of a variety of screened catalysts. The relatively low catalyst loading, ambient temperature, and good conversion achieved by Liu et al.

¹⁸ For recent reviews, see: (a) Masson, G.; Zhu, J.; Housseman, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614-4628. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-891.

¹⁹ (a) Xu, J. *THEOCHEM* **2006**, *767*, 61-66. (b) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 15513-15525. (c) Roy, D.; Sunoj, R. B. *Org. Lett.* **2007**, *9*, 4873-4876. (d) Fan, J.-F.; Yang, C.-H.; He, L.-J. *Int. J. Quantum Chem.* **2009**, *109*, 1311-1321.

²⁰ (a) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1706-1708. (b) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980-3987. (c) Price, K. E.; Broadwater, S. J.; Jung, H. N.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147-150. (d) Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701-1708. (e) Buskens, P.; Klankermayer, J.; Leitner, W. *J. Am. Chem. Soc.* **2005**, *127*, 16762-16763. (f) Amarante, G. W.; Milagre, H. M. S.; Vaz, B. G.; Ferreira, B. R. V.; Eberlin, M. N.; Coelho, F. *J. Org. Chem.* **2009**, *74*, 3031-3037.

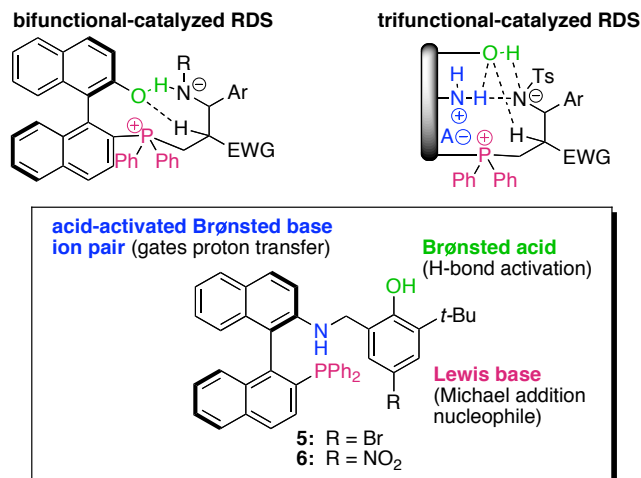
²¹ For examples, see: (a) Shi, M.; Chen, L.-H. *Chem. Commun.* **2003**, 1310-1311. (b) Shi, M.; Chen, L.-H. *J. Am. Chem. Soc.* **2005**, *127*, 3790-3800. (c) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680-3681. (d) Liu, Y.-H.; Shi, M. *Adv. Synth. Catal.* **2008**, *350*, 122-128.

²² (a) Liu, F. *Org. Biomol. Chem.* **2009**, *7*, 1272-1275. (b) Garnier, J.-M.; Anstiss, C.; Liu, F. *Adv. Synth. Catal.* **2009**, *351*, 331-338.

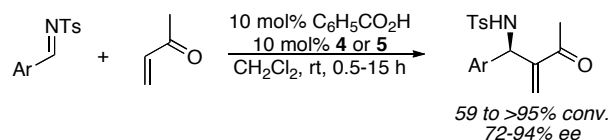
²³ For a highlight on enantioselective counterion catalysis, see: (a) Lacour, J.; Linder, D. *Science* **2007**, *317*, 462-463. For an example of a chiral ion pair-catalyzed MBH reaction, see: (b) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Chen, J.-P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093-3097.

(Scheme 11) represent notable improvements in the catalysis of the aza-MBH reaction.

Scheme 10



Scheme 11



Trifunctional organocatalysis is a promising approach to selective acceleration of reactions. The incorporation of multiple hydrogen bond donors or bases into bifunctional frameworks results in enhanced reactivity and stereoselectivity. The reactions described here require no more than 10 mol% catalyst, and in most cases can proceed at room temperature with good stereoselectivities. However, it would be advantageous to reduce catalyst loadings even more and perform all reactions at ambient temperature, especially if these catalysts are to be used for industrial-scale syntheses. It will also be interesting to see the array of structures that will be designed, the ease of synthesis of the catalysts, and the reaction scope that can be achieved.