

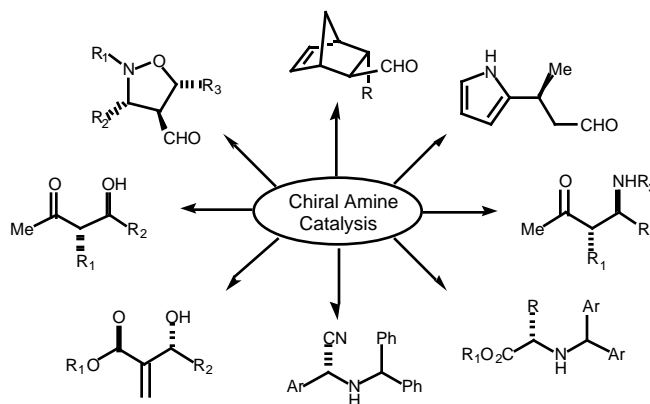
# Enantioselective Catalysis by Simple Chiral Amines: The Search for a General Strategy

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## ABSTRACT



The development of enantioselective catalytic methods employing chiral amines as catalysts has become an area of vigorous research interest. Approaches to this type of organocatalysis are discussed.

In the last 30 years, the field of enantioselective catalysis has become the subject of extensive research activity, resulting in the development of numerous organometallic asymmetric catalysts. These catalysts have shown broad utility in mediating a variety of synthetically useful transformations with high selectivities.<sup>1</sup> Until recently, relatively few enantioselective reactions have been reported that utilize purely organic reagents as asymmetric catalysts, despite their attendant potential for cost-savings and operational ease. A variety of organocatalytic methods have been described recently, and these studies have established that an array of organic molecules can serve as selective catalysts for a large number of chemical processes. However, these catalysts often lack general applicability to

a range of transformations.<sup>2</sup> Simple chiral amines, however, have shown promise in (1) catalyzing a broad

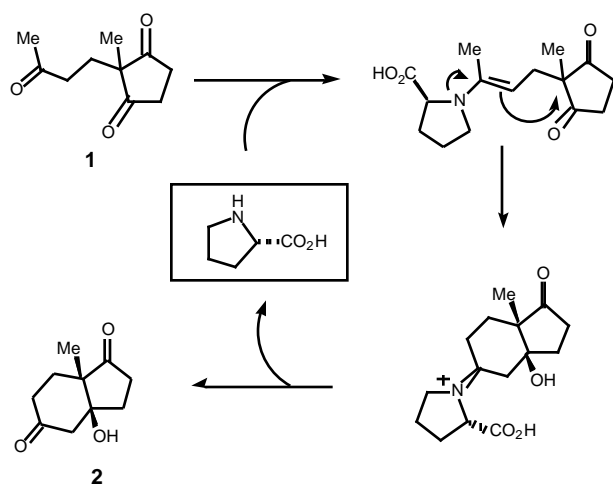
<sup>1</sup>For leading references, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; Springer: Heidelberg, 1999. (b) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed; Wiley: New York, 1994. (c) *Asymmetric Synthesis*; Ojima, I., Ed; VCH: New York, 1993.

<sup>2</sup>For other notable organic catalysis, see the following: Epoxidation: (a) Tian, H.; She, X.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (b) Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Yang D.; Wong, M.; Yip, Y.; Wang, X.; Tang, M.; Zheng, J.; Cheung, K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (d) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. Phosphorus catalysts: (e) Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377, and references therein. Phase transfer catalysis: (f) O'Donnell, M. J.; Bennett, W. D.; Wu, S.; *J. Am. Chem. Soc.* **1989**, *111*, 2353. (g) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *118*, 12414. (h) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097. Catalytic antibodies: (i) Hilvert, D. *Annu. Rev. Biochem.* **2000**, *69*, 751, and references therein. Peptide catalysts: (j) Horstmann, T. E.; Guerin, D. J.; Miller, S. *J. Angew. Chem. Int. Ed.* **2000**, *39*, 3635. (k) Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.* **1990**, *55*, 6047. (l) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. (m) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. Strecker synthesis: (n) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279. -halogenation: (o) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531.

range of transformations and (2) affording selectivities matching or exceeding those of Lewis Acid catalysts, two goals which must be fulfilled to make organocatalysis a viable field within organic synthesis.

The use of chiral amines as asymmetric catalysts was first reported in 1974 by Hajos and Parrish in the context of a Robinson annulation catalyzed by L-proline.<sup>3</sup> As seen in Scheme 1, ketone **1** associates with proline to form an enamine which then undergoes annulation. Dissociation of the proline catalyst affords the cycloadduct **2** in 92% yield and 88% ee. Twenty-six years later, Barbas found that L-proline was capable of catalyzing both steps of the Robinson annulation.<sup>4</sup> Accordingly, **1** was synthesized *in situ* by combination of methyl vinyl ketone and 2-methylcyclohexane-1,3-dione in the presence of 35 mol% L-proline in DMSO for 89 hours to afford the dehydrated adduct **2** in 49% yield and 76% ee. In this case, an enamine mechanism was again implicated, with proline functioning as a catalyst for the initial bimolecular reaction and the subsequent annulation to form **2**.

**Scheme 1.** Robinson Annulation Catalyzed by L-Proline

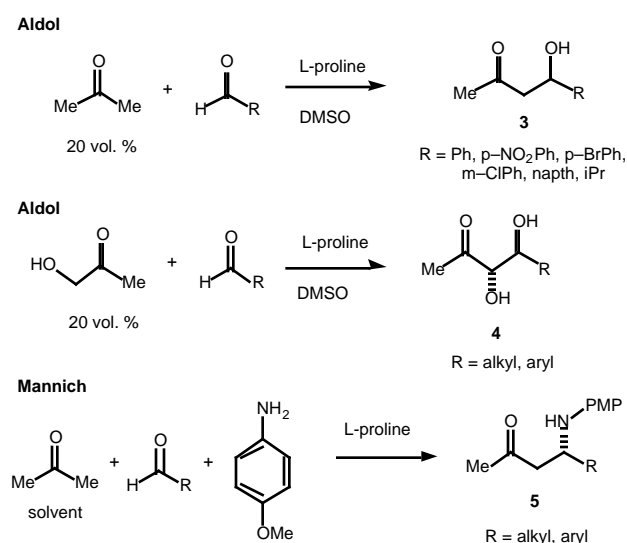


List has recently probed the generality of L-proline as a catalyst for the aldol reaction. Using 30–40 mol% of proline, acetone undergoes the aldol reaction with various aldehydes to produce the  $\beta$ -hydroxy ketones **3** in moderate to good yield (62–97% yield) and enantiomeric excess (60–96% ee)<sup>5</sup> (Scheme 2). Subsequent research has shown that the analogous aldol reaction between hydroxy acetone and a range of aldehydes is also amenable to proline catalysis, providing *anti*-1,2-diols **4** (40–95% yield, 67–99% ee)<sup>6</sup> (Scheme 2). This method is particularly valuable as it provides the ability to perform

enantioselective aldol reactions utilizing unmodified ketones.

This enamine catalysis has been applied to a three-component asymmetric Mannich reaction, of which very few enantioselective catalytic variants are known<sup>7</sup> (Scheme 2). List achieves the three-component coupling of acetone with various aldehydes and *p*-anisidine to afford  $\beta$ -amino ketones **5** (35–90% yield, 70–99% ee) using 35 mol% of L-proline. While the scope of this process is somewhat narrow, the novelty of the transformation renders this limitation less significant. Notably, this enamine approach to organocatalysis, though applied successfully to both aldol and Mannich reactions, has not yet become a broadly general process.<sup>8</sup>

**Scheme 2.** Aldol and Mannich Reactions



A number of other novel approaches to organocatalysis using chiral amines have been accomplished. One interesting example is Corey's synthesis of  $\beta$ -amino nitriles using chiral bicyclic guanidine catalyst **7** (Figure 1).<sup>9</sup> With 10 mol% catalyst, the  $\beta$ -amino nitrile products **6** are formed in high yields and good enantioselectivity with a variety of aryl imines. The mechanism of the process is believed to involve a pre-transition state assembly of imine and HCN with the bifunctional catalyst. At present, no extensions of this catalytic platform to other reactions have been developed.

<sup>7</sup> List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

<sup>8</sup> There have been independent reports of the L-proline catalyzed conjugate addition of nitroalkanes to enones and enals (30–88% yield, 29–93% ee). An iminium ion intermediate is likely: (a) Hanessian, S.; Pham, V. *Org. Lett.*, **2000**, *2*, 2975. (b) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hiram, M. *Tetrahedron* **1997**, *53*, 11223. (c) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hiram, M. *Tetrahedron Lett.* **1994**, *35*, 8233.

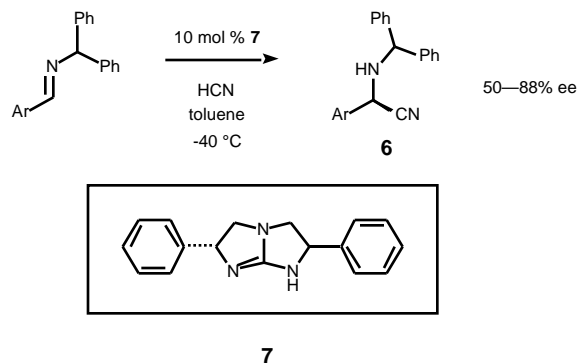
<sup>9</sup> Corey, E. J.; Grogan, M. *J. Org. Lett.* **1999**, *1*, 157.

<sup>3</sup> Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

<sup>4</sup> Bui, T.; Barbas, C. F. *Tetrahedron Lett.* **2000**, *41*, 6951.

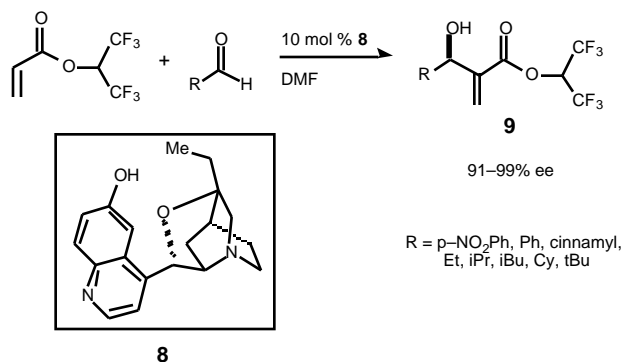
<sup>5</sup> List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

<sup>6</sup> Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.



**Figure 1.** Corey's amine catalyzed Strecker synthesis.

Another example of a unique transformation involving a specialized catalyst is the chiral amine-catalyzed Baylis-Hillman reaction (Figure 2).<sup>10</sup> Hexafluoroisopropyl acrylate reacts with a range of aldehydes in the presence of 10 mol% quinidine-derived catalyst **8** to afford the adducts in moderate yields and excellent enantioselectivity (31–58% yield, 91–99% ee). Cinchona alkaloid derivatives similar to **8** have also found use in the catalytic asymmetric dimerization of methylketene. Calter reports enantioselectivities as high as 98% ee, though the scope of his reaction is limited to one substrate.<sup>11</sup> Thus, similar organic architecture has been catalytically viable in two different reactions.

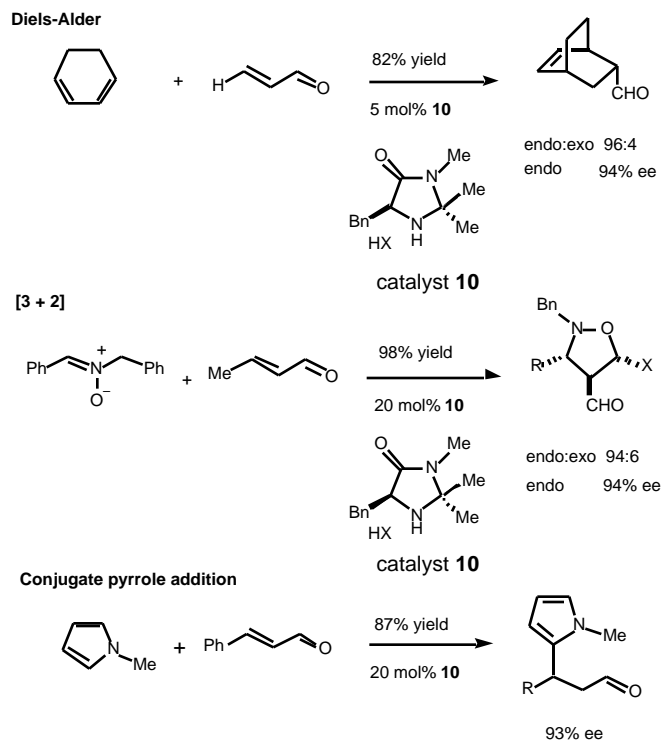


**Figure 2.** Amine-catalyzed Baylis-Hillman reaction.

Recent reports from the MacMillan laboratories have described a new chiral imidazolidinone catalyst that enable high levels of enantiocontrol in a range of asymmetric transformations, including Diels-Alder<sup>12</sup> and [3+2]

cycloaddition<sup>13</sup> reactions, as well as the first enantioselective catalytic conjugate pyrrole addition.<sup>14</sup> In all cases, a diverse group of aldehydes and reactant partners undergo high-yielding reactions with excellent enantioselectivities (Scheme 3).

### Scheme 3. Imidazolidinone Catalyzed Reactions



In designing this catalytic strategy, we reasoned that LUMO-lowering activation and the kinetic lability toward ligand substitution that enables Lewis acid-catalyst turnover might also be available with a carbogenic system that exists as a rapid equilibrium between an electron-deficient and a relatively electron-rich state. We hypothesized that the reversible formation of iminium ions from  $\alpha,\beta$ -unsaturated aldehydes and amines might emulate the equilibrium dynamics and  $\pi$ -orbital dynamics that are inherent to Lewis acid catalysis, thereby providing a new platform for the design of organocatalytic processes (Scheme 4).

In fact, a key feature of this chiral imidazolidinone system is that *the same catalyst framework* is able to mediate cycloadditions as well as conjugate additions, demonstrating a level of utility typically associated with a general catalyst for asymmetric synthesis. Further, the *mode of catalysis* is consistent across reaction type, allowing rational design of new enantioselective reactions using the same catalytic platform. Preliminary results

<sup>10</sup> Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

<sup>11</sup> (a) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006. (b) Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308.

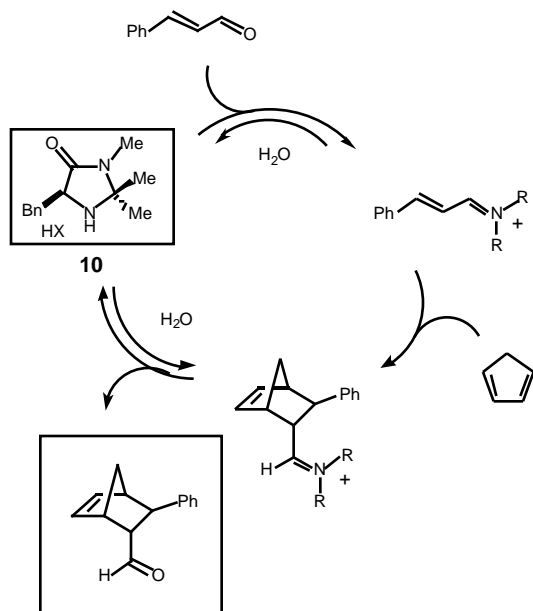
<sup>12</sup> Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

<sup>13</sup> Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

<sup>14</sup> Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

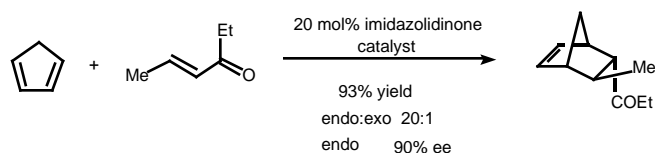
indicate that this LUMO-lowering activation strategy can also be applied to  $\alpha,\beta$ -unsaturated ketones (Scheme 5).<sup>15</sup> Ongoing studies have revealed that this iminium activation strategy is applicable to conjugate addition reactions of a range of  $\alpha,\beta$ -nucleophiles including furans, thiophenes, indoles, and anilines to  $\alpha,\beta$ -unsaturated aldehydes (Scheme 6).<sup>16</sup>

**Scheme 4.**



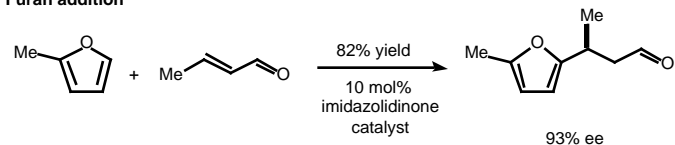
From initial reports to current developments, enantioselective organocatalysis has represented a challenging and intriguing field within organic chemistry. Whereas approaches to catalysis using purely organic molecules once encompassed a highly selective series of singular catalysts for singular transformations, efforts are being made to design catalysts that are general, in addition to being highly selective. Indeed, research efforts involving simple chiral amines are now beginning to achieve the high levels of enantioselectivity and broad generality required of a general catalyst in the realm of asymmetric synthesis.

**Scheme 5.** Organocatalytic Diels-Alder Reaction of Ketones

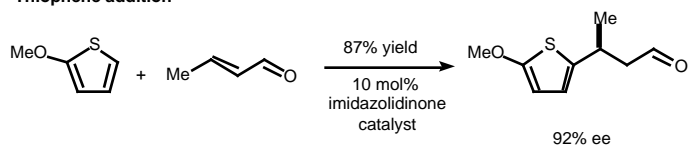


**Scheme 6.** Organocatalytic Asymmetric Conjugate Additions

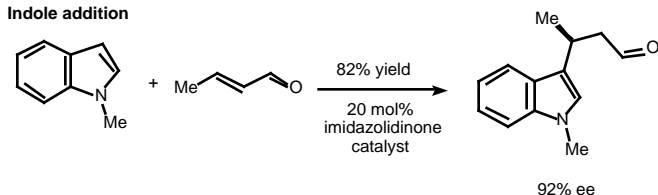
**Furan addition**



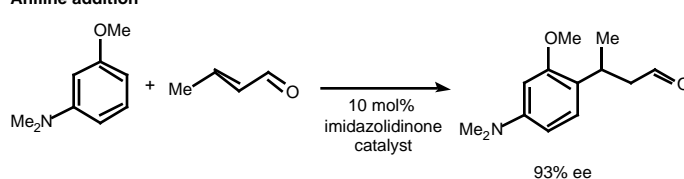
**Thiophene addition**



**Indole addition**



**Aniline addition**



<sup>15</sup> Northrup, A. B.; MacMillan, D. W. C., manuscript in preparation.

<sup>16</sup> Brown, S. P.; Austin, J. F.; Paras, N. A.; MacMillan, D. W. C., manuscript in preparation.

