C h a p t e r 1

Enantioselective LUMO-Lowering Organocatalysis.

I. Introduction.

The presentation of the Nobel Prize in 2001 to William S. Knowles, Ryoji Noyori, and K. Barry Sharpless recognized the influence and power of asymmetric catalysis in organic synthesis.[1] These laureates demonstrated that chiral ligands bound to metals imparted high levels of selectivity and catalytic activity to a diverse range of organic transformations and industrial processes.[2] Building on their seminal work, the area of asymmetric catalysis using chiral Lewis acids has expanded to a variety of metal-mediated, catalytic enantioselective reactions and now covers a range of reaction mechanisms and conditions.[3]

In contrast to the vast literature on Lewis-acid and metal-catalyzed processes, there are fewer asymmetric transformations catalyzed by organic molecules. This is surprising because chiral organometallic Lewis acids require enantiopure ligands, which generally require a multi-step synthesis from organic building blocks. The metals employed often are expensive and require inert atmospheres for preparation and storage.

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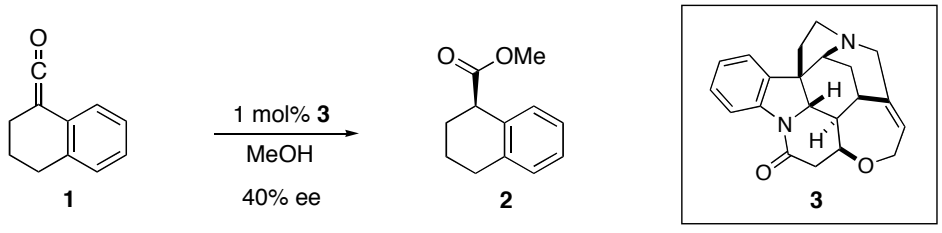
[1] (a) Knowles, W. S. *Angew. Chem. Int. Ed. Engl.* **2001**, *41*, 1998. (b) Noyori, R. *Angew. Chem. Int. Ed. Engl.* **2001**, *41*, 2008. (c) Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **2001**, *41*, 2024.

[2] For an example of industrial process, see L-DOPA synthesis: Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, 1445.

[3] (a) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, 1994. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Heidelberg, 1999.

Organocatalysts, on the other hand, are insensitive to air and moisture, thus making them more practical for use in synthetic laboratory procedures. Moreover, nature provides us with an array of enantiopure organic compounds from which to develop organic catalysts. These include α-amino acids, α-hydroxy acids, nucleic acids, and carbohydrates.

There are some reports of organocatalyzed reactions that date back almost a century. In 1912, Bredig and Fiske reported the use of alkaloids to catalyze the syntheses of cyanohydrins, noting that the opposite enantiomers were generated in the presence of quinine and quinidine.[4] Almost 50 years later, Pracejus demonstrated the use of strychnine (**3**) to catalyze the asymmetric methanolysis of a ketene **1** to provide an enantioenriched methyl ester **2** (eq. 1).[5]



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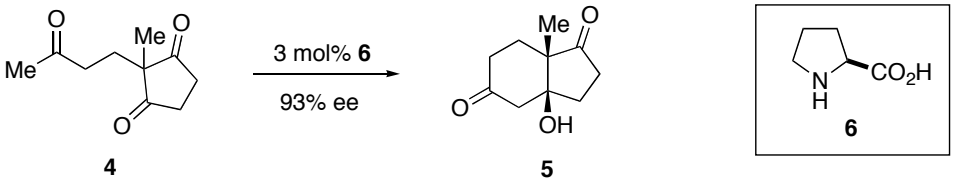


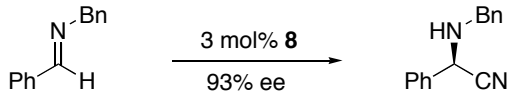
(2)

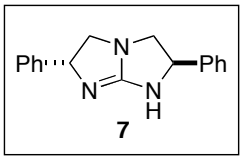
[4] Bredig, G.; Fiske, P. S. *Bichem. Z.* **1912**, *46*, 7.

[5] (a) Pracejus, H. *Annalen Der Chemie-Justus Liebig* **1960**, *634*, 9. (b) Pracejus, H. *ibid.* **1960**, *634*, 23.

Weichert,[6] and Hajos and Parrish[7] separately reported what is perhaps the most well-known example of an organocatalyzed reaction. Sub-stoichiometric quantities of proline (**6**) were able to effect the highly enantioselective Robinson annulation of triketone **4** to provide the Wieland-Mieschler ketone **5** (eq. 2).

Over the next 25 years, there were limited reports of the use of organic molecules to catalyze synthetic transformations. Corey and Jacobsen reported the use of imidazole-type catalysts **7** to effect the hydrocyanation of imines (eq. 3).[8,9] Shi, Yang, and Denmark demonstrated that the asymmetric epoxidation of styrenes can be affected in a highly stereoselective manner using fructose-derived ketone **8** (eq. 4).[10] The quaternary cinchonidine-derived alkaloid **9** was employed initially by O'Donnell as well as Corey to do enantioselective alkylations under phase transfer conditions (eq. 5).[11,12]





(3)

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[6] Eder, U.; Sauer, G.; Weichert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496.

[7] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

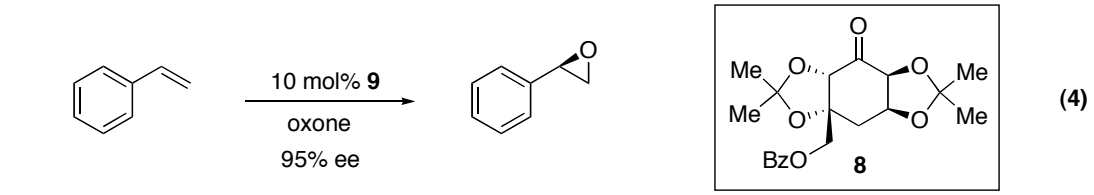
[8] Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.

[9] (a) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279. (b) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867.

[10] (a) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Tian, H. Q.; She, X. G.; Shu, L.-H.; Yu, H. W.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (c) Yang, D.; Wong, M. K.; Wang, X. C.; Tang, Y. C. *J. Am. Chem. Soc.* **1998**, *120*, 6611. (d) Denmark, S. E.; Wu, Z. C. *Synlett.* **1999**, 847.

[11] O'Donnell, M. J.; Bennett, W. D.; Wu, S. D. *J. Am. Chem. Soc.* **1989**, *111*, 2353.

[12] Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.



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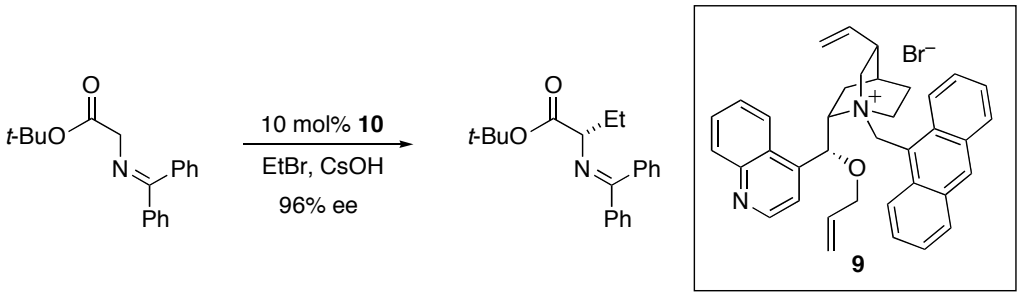
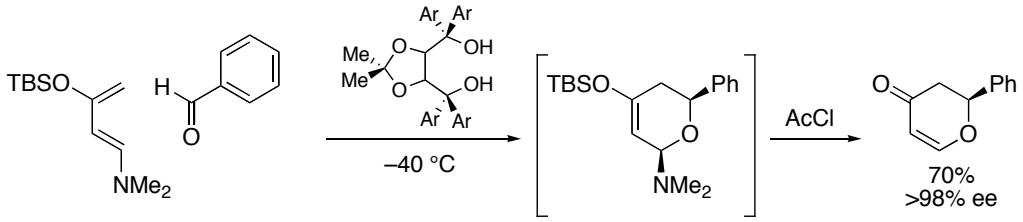


(5)

More recently, chiral diols and phosphoric acids have opened a new field of organocatalysis. Rawal and Huang showed that TADDOL derivatives can act as enantioselective hydrogen bonding catalysts to effect a highly selective hetero-Diels-Alder reaction (eq. 6).



(6)

While each of these examples has been a major contribution to synthetic chemistry, each of the organocatalysts shown above only affects a single transformation. The MacMillan group became interested in rediscovering the field of organocatalysis by developing a novel organocatalytic platform that would be effective for a broad range of transformations.

II. A General Approach to Enantioselective LUMO-lowering Catalysis.

Lewis acids have long been used to activate various π-systems towards nucleophilic attack. As depicted in figure 1, the mechanism of Lewis acid activation occurs via reversible binding of the Lewis acid to an electrophilic substrate, which lowers the energetic potential of the lowest unoccupied molecular orbital (LUMO). This electronic redistribution, in turn, decreases the energy gap between the LUMO of the electrophile and the HOMO of the nucleophile, thus facilitating the reaction between the two reacting partners. After bond formation occurs, the Lewis acid can then dissociate from the product to allow for catalyst turnover.

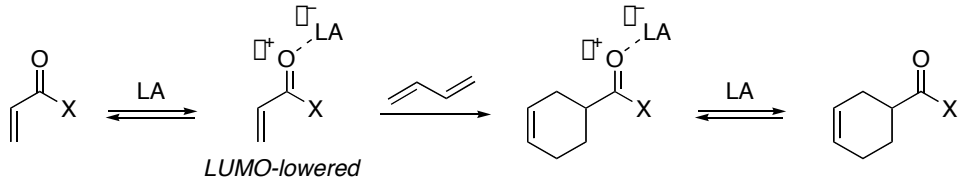


Figure 1. Lewis-acid catalysis of the Diels-Alder reaction.

Our group recognized that this type of Lewis acid LUMO-lowering activation could be emulated by secondary amines (Fig. 2). The reversible condensation of a secondary amine with an α,β-unsaturated aldehyde to form an iminium ion achieves the LUMO-lowered π-system that would have enhanced susceptibility to nucleophilic attack. A variety of chiral secondary amines are readily available, thus providing a new platform for enantioselective catalysis.

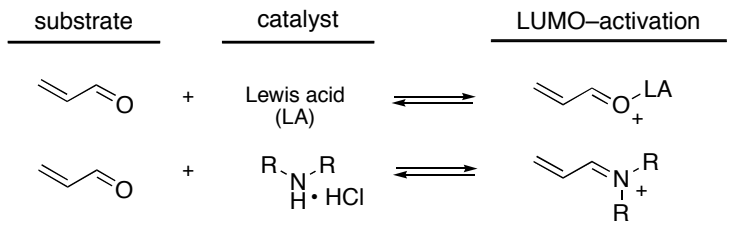


Figure 2. Complementary modes of LUMO-lowering catalysis.

i. *Chiral imidazolidinones as privileged organocatalysts.*

In order to achieve enantiocontrol in the nucleophilic attack onto activated iminium systems, there are a few requirements that must be met. First, the catalyst must be able to control iminium ion geometry. As shown in figure 3, the larger group (R_L) of the amine will partition the iminium to be oriented on the same side as the smaller group (R_S) in order to avoid non-bonding interactions with the β-proton of the iminium.

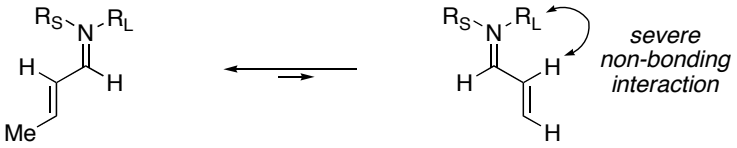


Figure 3. Iminium geometry control with imidazolidinones.

Second, the catalyst must be able to provide enantiofacial discrimination of the *Re* and *Si* faces of the π-system by protecting one face from nucleophilic attack. A variety of amines were tested for these requirements, and chiral imidazolidinones emerged as the

most successful catalyst framework. Using (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (Fig. 4), the larger *tert*-butyl and benzyl groups of the catalyst framework shield the *Si* face effectively to leave the *Re* face exposed for nucleophilic attack.

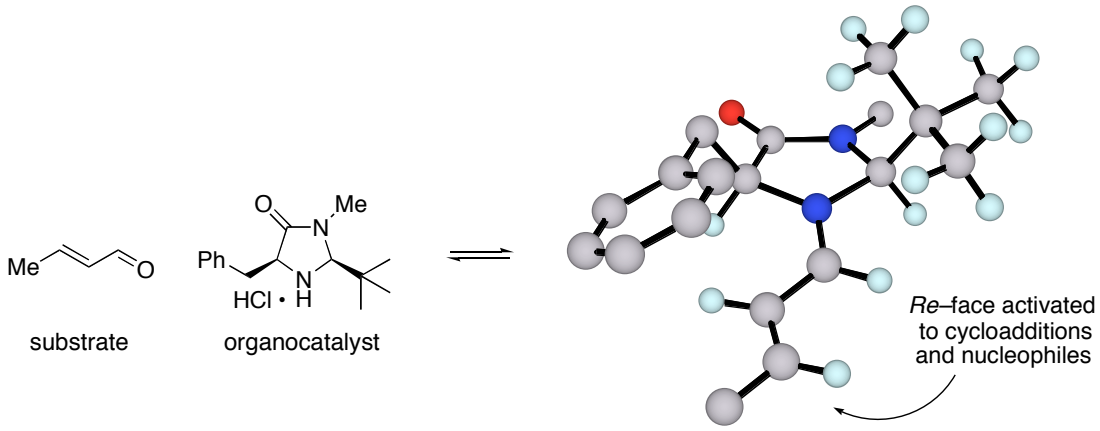


Figure 4. Enantiofacial discrimination of chiral imidazolidinones.

In 2004, Houk reported a thorough computational study to explain the observed enantioselectivities in the organocatalytic conjugate additions of pyrroles and indoles.[13] The calculated preferred conformations of the iminium intermediates are similar to the structure presented in figure 4. The most stable conformers **(*E*)-11a** and **(*E*)-11b** constitute 92% of all the existing species in the gas phase at 25 °C (Fig. 5). This work complements the proposed reasons for the high levels of stereoselectivity typically observed in these organocatalytic reactions.

[13] Gordillo, R.; Carter, J.; Houk, K. N. *Adv. Synth. Cat.* **2004**, *346*, 1175.

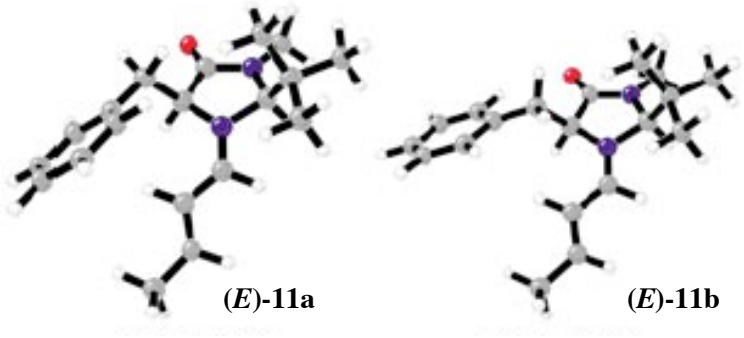


Figure 5. Calculated minimized structures for the iminium in figure 4.

Unlike the chiral ligands often employed in Lewis acid catalysis, preparation of chiral imidazolidinones does not require a lengthy synthetic sequence. In fact, they are available in two steps from readily-available amino acids (Fig. 6). Preparation of the amide derived from phenylalanine is accomplished via the acid chloride. Iron trichloride-mediated condensation of pivaldehyde onto the amine and subsequent cyclization of the amide gives a mixture of *cis* and *trans* isomers of imidazolidinone **11**, which are easily separable by silica gel chromatography.

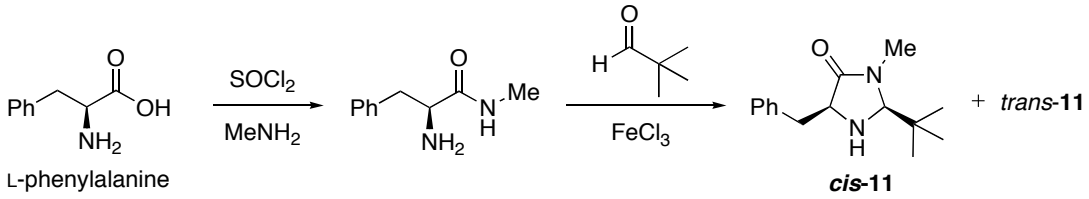


Figure 6. Easy access to imidazolidinones.

Over the past six years, different variations of this catalyst framework (Fig. 7) have been shown to be widely effective for a broad range of transformation. Initial investigations into the Diels-Alder and nitrone cycloadditions as well as limited use in

1,4-conjugate additions of electron-rich heteroaromatic π-nucleophiles commenced with *gem*-dimethyl imidazolidinone **10**.[14] When the research described in this thesis began, the MacMillan group had already developed *tert*-butyl imidazolidinone **11**,[15] and it is this catalyst that appears throughout much of this work. The imidazolidinone framework has been adjusted for different reactions. For example, catalyst **12** was developed for the asymmetric ketone Diels-Alder cycloadditions[16] and catalyst **13** was developed for 1,4-conjugate hydride reduction[17] – a reaction that will appear in Chapter 4 of this work.

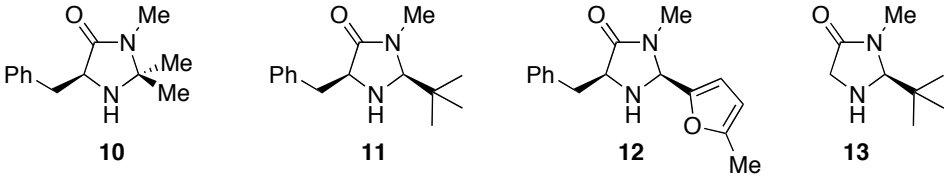


Figure 7. Imidazolidinones developed and used within the MacMillan group.

The organocatalytic, enantioselective transformations developed in our labs display a wide scope of aldehydes and nucleophiles with superior enantio- and diastereoselectivity. However, to test the true utility and generality of these transformations, they must be utilized in the total synthesis of natural products where substrates are more complicated than those used in methodology studies.

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[14] (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

[15] (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

[16] Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

[17] Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.

III. Summary of Thesis Research.

The following chapters describe the application of iminium activation technologies towards the total syntheses of natural products. The development of the first organocatalytic vinylogous Mukaiyama-Michael reaction is presented in Chapter 2. This methodology, which generates highly stereoselective butenolide architectures, is then applied to the total syntheses of spiculisporic acid and 5-*epi*-spiculisporic acid. The remainder of the research in this thesis has been devoted to investigations towards the cylindrocyclophanes. Chapter 3 introduces the *B*-alkyl nickel(0)-catalyzed cross-coupling of trimethylanilinium salts and its application towards the total synthesis of cylindrocyclophane F. Chapters 4 and 5 feature two different trimethylanilinium cross-coupling strategies towards cylindrocyclophane A: a Suzuki cross coupling with a vinyl potassium trifluoroborate and a Stille cross-coupling with an activated vinyl stannane, respectively. The latter chapter culminates with a formal synthesis of cylindrocyclophane A.