Chapter 1

Organocatalysis

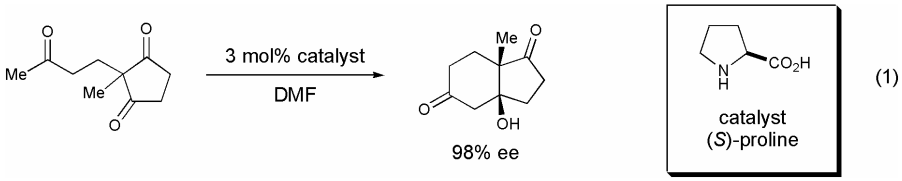
I. Background

Organocatalysis

For the last 40 years, enantioselective catalysis has been in the forefront of research in synthetic organic chemistry. This growth has seen the development of a wide variety of chiral Lewis acidic organometallic catalysts capable of effecting a broad range of transformations.[1-5] These catalysts have proven successful at the enantioselective catalysis of many organic transformations including asymmetric oxidations, reductions, cycloadditions, conjugate additions, and π-bond activation reactions.

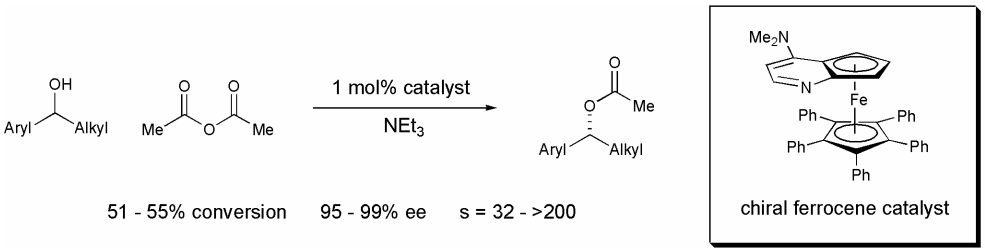
However, relatively few asymmetric transformations have been reported which use wholly organic molecules as catalysts. Since organometallic catalysts typically involve an air- or moisture-sensitive metal as the catalytically active species, moving towards using completely organic molecules would prove beneficial from a variety of perspectives. Organocatalysts have the potential of avoiding the sensitivities of organometallic catalysts, eliminating the need to exclude oxygen or water from reaction conditions. Organocatalysts could possibly be discovered within the great number of naturally occurring enantiopure organic compounds such as carbohydrates, amino acids, nucleic acids, and their oligomers, facilitating access to effective chiral catalysts. Using catalysts that can be accessed more directly from a naturally occurring chiral source would most likely prove more cost-effective and efficient than a corresponding

organometallic catalyst, a catalyst which typically involves a multi-step synthesis from the same naturally occurring chiral starting materials. As such, this field offers a unique opportunity for the development and elucidation of conceptually novel enantioselective transformations.



(1)

The concept of utilizing an organocatalyst for enantioselective transformation has not been lost on the chemical community, and there have been reports of enantioselective organocatalysts as early as 1912.[6] One of the best known early asymmetric organocatalytic reactions is the proline-catalyzed intramolecular aldol reaction, the Hajos-Parrish-Eder-Sauer-Wiechert reaction (equation 1).[7,8] This reaction has been used extensively in natural product synthesis and elsewhere since its development.

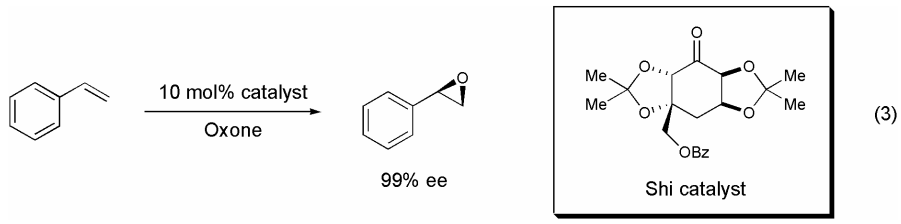


(2)

A variety of chiral nucleophilic amines have been developed as catalysts for kinetic resolutions, cycloadditions, halogenations reactions, Baylis-Hillman reactions, anhydride desymmetrizations, acylations, and cyanation reactions.[9] Cinchona alkaloids

and organocatalysts discovered through rational design, such as the ferrocene-based catalyst of Fu, have been utilized for the kinetic resolution of alcohols by acylation (equation 2).[10]

Several groups have developed chiral ketones that can function effectively as catalysts for the enantioselective epoxidation of olefins.[11-15] These organocatalysts can efficiently epoxidize a wide range of olefins with high yields and selectivities (equation 3).



(3)

Additionally, other chemotypes have proven successful as organocatalysts.[9,16-19] Antibodies have been developed as catalysts for organic transformations.[20] Quaternary ammonium salts have been developed as selective phase-transfer catalysts.[21] Hydrogen bond donors have also functioned as catalysts.[22-24] Even synthetic peptides have been used as catalysts for organic transformations.[16]

Although there have been many reports of organocatalysts, these chiral catalysts differ from successful organometallic catalysts in one significant respect. Organometallic complexes derived from BINOL, BINAP, Salen, and bisoxazoline ligands have been successful at catalyzing a broad range of transformations with excellent selectivity.[25] Catalysts derived from these ligands have been termed “privileged” catalysts by the chemical community, and for good reason. A small number of chiral organometallic

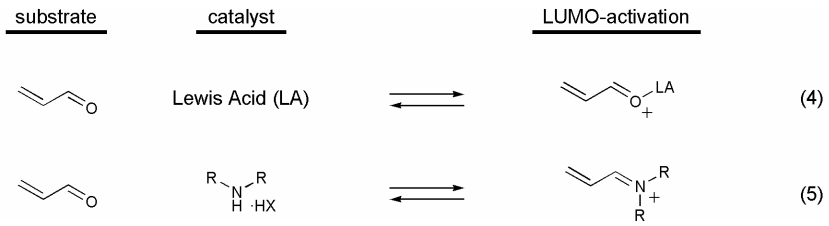
catalysts are able to affect most of the asymmetric transformations that have been realized. These catalysts have been successful because of general nature of Lewis acid-activation and the strong ability of their asymmetric ligands to transmit their chirality. While organometallic catalysts operate through Lewis acid-activation, a means of activation applicable to a wide variety of synthetic transformations, organocatalysts appear to operate through reaction-specific means of activation.

II. Developing a General Approach towards Enantioselective Organocatalysis

LUMO-Lowering Catalysis

We began our research program with the intent of developing a general strategy for organocatalysis based on the most successful aspects of Lewis acid catalysis (Scheme 1). The equilibrium of a Lewis acid catalyst system and the effect of that catalyst on the energy of a substrate's π-orbital system were two features of Lewis acid-activation that we sought to mimic using a wholly organic system. In doing so, we believed we could develop a catalyst capable of affecting the same broad range of transformations possible with Lewis acid-catalysis.

Scheme 1. LUMO-lowering activation of α,β-unsaturated aldehydes by secondary amines.



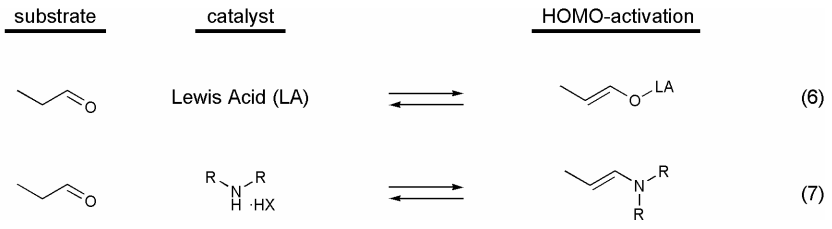
An organic system that exists as a rapid equilibrium between a relatively electron-rich and electron-deficient state should mimic these features of Lewis acid catalysis. The reversible formation of an iminium ion from the corresponding secondary amine and α,β-unsaturated aldehyde was chosen as a platform for the development of a general organocatalytic strategy (Scheme 1, equation 5). The formal cationic charge and electronegative heteroatom should both serve to lower the LUMO of the α,β-unsaturated iminium ion relative to the corresponding α,β-unsaturated aldehyde starting material.

This chemical activation through LUMO-lowering and reversible iminium ion formation is analogous to the Lewis acid catalysis of reactions involving α,β-unsaturated carbonyl compounds (Scheme 1, equation 4). Most significantly, this proposal led to the hypothesis that secondary amines should be able to catalyze the same range of chemical transformations as Lewis acids.

HOMO-Raising Catalysis

Another mechanism of activating a chemical species toward a transformation is HOMO-raising, and this is another avenue for developing a general method of organocatalysis (Scheme 2). This form of organocatalysis accelerates a reaction by increasing the energy of the HOMO of one reacting partner. An enamine can be formed by the condensation of a secondary amine and an aldehyde (Scheme 2, equation 7). The resulting enamine has a higher HOMO than the corresponding aldehyde, and, therefore, is activated towards further transformation. This is analogous to the formation of a nucleophilic enol from a carbonyl compound (Scheme 2, equation 6). Research on proline-catalysis led to the hypothesis that secondary amines should also be able to catalyze a broad range of organic transformations through HOMO-raising catalysis.[7,8,26,27]

Scheme 2. Organocatalytic HOMO-activation.



Efforts towards General Enantioselective Organocatalysis

The following chapters detail efforts towards developing a general organocatalytic methodology. Chapter Two discusses the development of a general strategy for organocatalysis using LUMO-lowering activation and the development of the first enantioselective organocatalytic Diels-Alder reaction. Chapter Three details the development of a second-generation organocatalyst and the extension of organocatalytic methodology to an enantioselective Mukaiyama-Michael reaction. Chapter Four describes investigations into HOMO-raising organocatalysis, the proline-catalyzed α-oxidation of ketones.

III. References

(1) Procter, G. *Asymmteric Synthesis*; Oxford University Press: Oxford, 1996.

(2) Lin, G. Q.; Li, Y. M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; Wiley-Interscience: New York, 2001.

(3) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. *Comprehensive Asymmetric Catalysis*; Springer: Heidelberg, 1999.

(4) Noyori, R., Ed. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(5) Ojima, I., Ed. *Asymmetric Synthesis*; VCH: New York, 1993.

(6) Bredig, G.; Friske, P. S. *Bichem. Z.* **1912**, *46*, 7.

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

(8) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.

(9) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.

(10) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412.

(11) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491.

(12) Yang, D.; Wong, M. K.; Yip, Y. C.; Wang, X. C.; Tang, M. W.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 5943.

(13) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.

(14) Tian, H. Q.; She, X. G.; Shu, L. H.; Yu, H. W.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551.

(15) Denmark, S. E.; Wu, Z. C. *Synlett* **1999**, 847.

(16) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481.

(17) List, B. *Synlett* **2001**, 1675-1686.

(18) List, B. *Tetrahedron* **2002**, *58*, 5573.

(19) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726-3748.

(20) Schultz, P. G.; Yin, J.; Lerner, R. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4427.

(21) Carter, C.; Nelson, A. In *Organic Synthesis Highlights V*; Schmalz, H. G., Wirth, T., Eds.; Wiley-VCH: Weinheim, Germany, 2003, p 125.

(22) Kelly, T. R.; Meghani, P.; Ekkundi, V. J. *Tetrahedron Lett.* **1990**, *31*, 3381.

(23) Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259.

(24) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407.

(25) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

(26) List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

(27) Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260.