

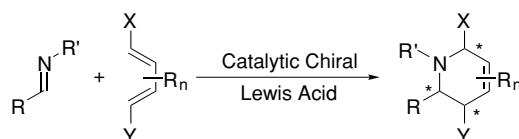
Catalytic Enantioselective Aza-Diels-Alder Reactions: Recent Advances in an Emerging New Methodology for the Construction of Nitrogen Heterocycles

Aaron Aponick

Department of Chemistry, University of Michigan, Ann Arbor, MI 48109-1055 USA.

aponick@umich.edu

ABSTRACT



The catalytic enantioselective aza-Diels-Alder reaction has been the focus of many recent synthetic studies owing to its potential application to the synthesis of nitrogen heterocycles. Reactions of achiral substrates mediated by chiral Lewis acids are presented and critically evaluated, as well as the limitations and scope of this emerging new methodology.

The development of methodology for the synthesis of enantiomerically pure compounds has become a core area of research in organic chemistry driven by increasing demand for these chemicals by industries such as the pharmaceutical industry. Since chiral, naturally occurring compounds are often too expensive for use as starting materials or stoichiometric reagents, a more economical approach is to employ substoichiometric amounts of chiral compounds in catalytic enantioselective processes which produce large quantities of optically pure compounds.

While literature reports of catalytic enantioselective reactions of carbonyl compounds using chiral Lewis acid complexes has become increasingly frequent,¹ analogous reactions of their nitrogen

counterparts, more specifically imines, are rarely seen. Several differences in the physical properties of imines are often cited as rendering these processes more formidable.² Increased Lewis basicity of the imino lone pair can effectively halt the catalytic cycle if a strong initial complex³ is formed. The choice of Lewis acid is limited due to the propensity of imines with α -protons to enolize. Facile *E/Z* isomerization may create addition species in solution, potentially eroding the stereoselectivity of the reaction. Perhaps due to the aforementioned difficulties, in comparison to carbonyl compounds, the chemistry of imines in catalytic enantioselective reactions is in its infancy, and many possibilities exist for the development of new synthetic methodology.

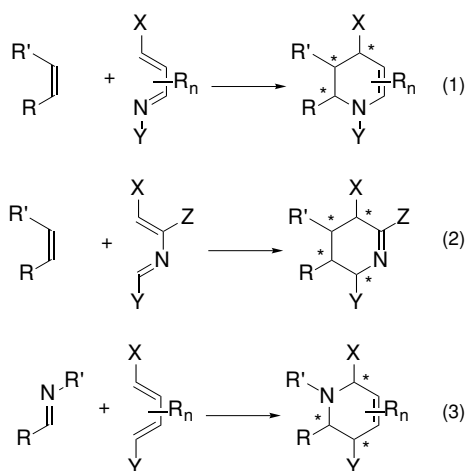
¹ For an excellent introduction to enantioselective catalysis see *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N., Pfaltz, A. and Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vols. 1-3.

² Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

³ Formation of stable amine-Lewis acid complexes as the reaction product may also interfere with catalytic cycles.

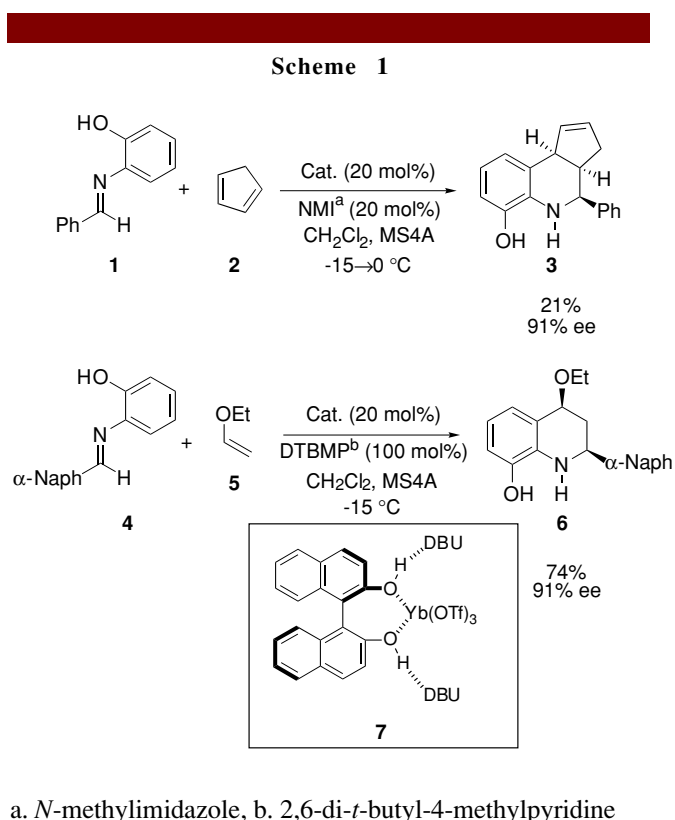
One such reaction that has only recently begun to receive attention from the synthetic community is the catalytic enantioselective aza-Diels-Alder reaction.^{2,4} Traditional aza-Diels-Alder reactions have long been known, and are highly efficient methods for forming heterocycles, particularly tetrahydropyridines.⁵ In the reaction, two new bonds and up to four stereocenters are formed rendering it an important and powerful method. Lewis acid catalyzed reactions have been reported but are comprised mainly of diastereoselective reactions catalyzed by achiral Lewis acids.^{4a} In this review, particular attention will be paid to enantioselective reactions in which a chiral Lewis acid complexes with the imino nitrogen of achiral substrates.⁶

The nitrogen component of the reaction can, in principle, be either the diene (Equations 1, 2) or the dienophile (Equation 3).



The first truly catalytic reactions were reported by Kobayashi in 1996,⁷ and were aza-heterodienes of the general type illustrated in Equation 2. The reactions between *N*-benzylidene-2-hydroxyaniline **1** and dienophiles were catalyzed by chiral lanthanide Lewis acid **7** derived from ytterbium triflate (Yb(OTf)₃), (*R*)-(+)-1,1'-bi-2-naphthol (BINOL), and DBU with various additives. It should be noted that these reactions are unusual in that the Lewis acid activates the diene, and that the cycloaddition occurs across an aromatic double bond. The reaction between **1** and cyclopentadiene (Scheme 1) was first studied and it was found that the highest ee (91%) was obtained when *N*-methylimidazole was used as an additive, however, a modest 21% chemical yield of **3** was observed. This could be improved by changing the additive to one equivalent of 2,6-di-*t*-butylpyridine, in which case a 92%

yield of **3** was obtained but only in 71% ee.⁸ With further optimization, tetrahydroquinoline **6** was produced in both high yield (74%) and ee (91%), as illustrated in Scheme 1.



In this reaction, additives are believed to hydrogen bond to the phenolic hydroxyl group of the substrate. Experimental observations have led the authors to propose the transition state assembly shown in Figure 1. Two molecules of DBU are believed to hydrogen bond to the BINOL hydroxyl groups, while the additive hydrogen bonds to the hydroxyl group of the substrate. The BINOL and substrate, now both bidentate ligands, chelate the ytterbium. The top face of the aza-diene is blocked by a DBU molecule, and the cycloaddition occurs from the bottom face.⁷ While this was the first report demonstrating that catalytic enantioselective aza-Diels-Alder reactions are feasible, certain features such as high catalyst loading, limited scope, and significant optimization required for each reaction necessitates further improvement.

⁴ a) Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558. b) Carmona, D.; Lamata, M. P.; Oro, L. A. *Coord. Chem. Rev.* **2000**, *200*, 717.

⁵ a) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 401. b) Boger, D. L. In *Comprehensive Organic Synthesis*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 451.

⁶ Catalytic enantioselective aza-Diels-Alder reactions between 2-azadienes and imide dienophiles have been reported, however, an imide(dieneophile)-Lewis acid complex is formed rather than complexation to the imino group. See Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617.

⁷ Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357.

⁸ The use of 2,6-dimethylpyridine and 2,6-di-*t*-butyl-4-methylpyridine as additives was also explored.

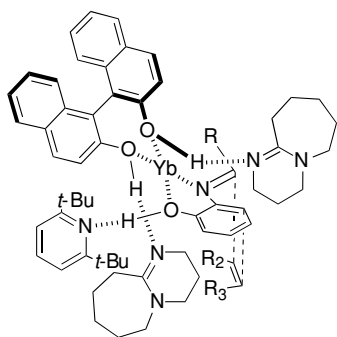


Figure 1. Proposed transition state.

Catalytic reactions in which the imine acts as the dienophile have also been reported. In these reactions, illustrated in Equation 3, a chiral Lewis acid complexes with the imine, activating it and rendering it transiently chiral. Cycloaddition and release of the product from the ensuing Lewis acid complex propagates the catalytic cycle. Zirconium^{9,10,11} and copper^{12,13} catalysts (Figure 2) have been employed in this reaction.

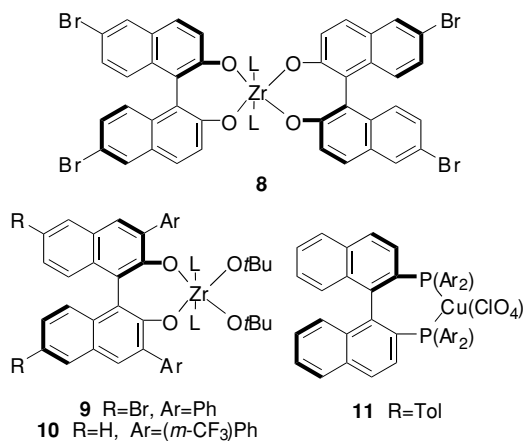


Figure 2. Chiral catalysts.

In a recent series of papers, Kobayashi has reported optimized reactions of aldimines and Danishefsky dienes catalyzed by zirconium complexes. Initial reports used catalyst **8**, prepared from two equivalents of (*R*)-6,6'-

⁹ Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 979.

¹⁰ Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220.

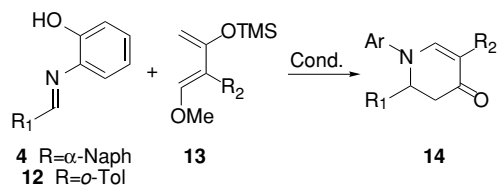
¹¹ Kobayashi, S.; Kusakabe, K.; Ishitani, H. *Org. Lett.* **2000**, *2*, 1225.

¹² Yao, S. L.; Johannsen, M.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 3121.

¹³ Yao, S. L.; Saaby, S.; Hazell, R. G.; Jorgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435.

dibromo-1,1'-binaphthol, zirconium *tert*-butoxide (Zr(O*t*Bu)₄), and various additives. The highest ee was obtained when the imine **4** was allowed to react with the diene **13** using 20% catalyst **8** and 1-methylimidazole as the ligand (Scheme 2, Entry 1).

Scheme 2



Entry	R ₁	R ₂	Cond.	Config.	yield (%)	ee (%)
1	α-Naph	Me	A	<i>S</i>	93	93
2	ο-Tol	H	B	<i>R</i>	93	91
3	α-Naph	Me	B	<i>R</i>	78	80
4	ο-Tol	H	C	<i>R</i>	93	91

A 20 mol% **8**, Tol, -45 °C
 B 20 mol% Zn(O*t*Bu)₄, 40 mol% (*R*)-Br-BINOL,
 60 mol% NMI, PhH, MS 3A
 C 5 mol% **9**, PhH, MS 3A

Interestingly, using slightly modified conditions, the antipode was obtained using the same *R*-BINOL ligand. The highest ee obtained was 91% and is illustrated in Scheme 2, Entry 2. Under these conditions, in the reaction between **4** and **13** (Scheme 2, Entry 3), the piperidine **14** (except of opposite configuration, *R*) was obtained in 80% ee and 78% yield, significantly lower than previously reported (Entry 1). Experimental evidence suggests that instead of forming catalyst **8**, under these conditions, **9** is the active catalyst. Preformed Lewis acid **9** was found to catalyze the reaction in comparable yield and ee.

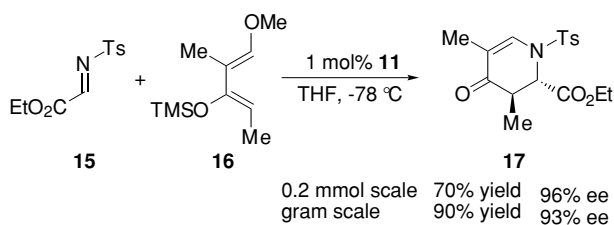
Most recently, the reaction was further optimized by systematically modifying the catalyst using a combination of solid phase and solution chemistry. It was found that the catalyst **10**, in only 5 mol%, catalyzed the reaction in Scheme 2 Entry 4, also giving a 91% ee and 93% yield.

Using chiral copper catalysts, Jorgensen has also developed enantioselective aza-dienophile Diels-Alder reactions (Scheme 3). Several types of ligands¹⁴ and metals¹⁵ were investigated but the copper BINAP catalyst **11** was found to be superior. Using **11**, the reaction between the *N*-tosyl imine **15** and diene **16** proceeds in 70% yield and 96% ee on a 0.2 mmol scale. On a gram scale, the ee is only reduced to 93%, but the yield increases to 90% using only 1 mol% catalyst.¹²

¹⁴ BINAP, bisoxazoline, and phosphino-oxazoline ligands have been utilized. See reference 13.

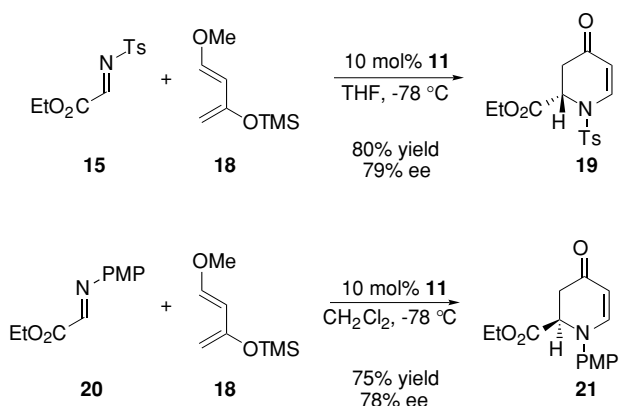
¹⁵ Salts of zinc, copper, silver, palladium, and ruthenium have all been explored. See reference 12.

Scheme 3



In addition to the obvious benefits of high optical and chemical yield with low catalyst loading, it has also been demonstrated that both enantiomers of the product can be accessed using the same catalyst but modifying the *N*-substitution and solvent (Scheme 4). The reaction of *N*-tosyl imine **15** and diene **18** provides the product of *S* configuration **19** while the *N*-*p*-methoxyphenyl imine **20** gives *R*-**21**.¹³

Scheme 4



The authors propose the change in stereochemical outcome to be due to a change in the ability of the *N*-substituent to chelate the metal. It is proposed that **20** forms an intermediate complex and acts as a bidentate ligand in CH₂Cl₂ (Figure 3). The bottom face of the imine is blocked by a tolyl group of the phosphine ligand, and

cycloaddition occurs from the top face. Using the *N*-tosyl imine **15**, the authors propose that an oxygen atom from the sulfonamide also coordinates to the metal.¹³ This would change the geometry of the ligands around the copper and also require difficult conformational changes of the imine. Determining the implications of changing to the coordinating solvent THF is also problematic.

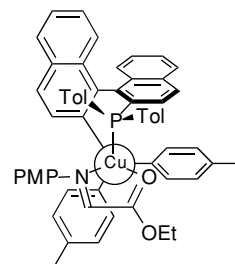


Figure 3. Proposed intermediate.

Despite the limitations of this reaction at its current stage of development, several drugs such as (-)-aristeromycin, carbovir, 1592U89, and (1*R*,2*S*)-amidinomycin can be synthesized from starting materials available by this technology.¹³ Other potential synthetic applications surely exist, but continued development to expand the scope of the reaction is necessary. Currently, only examples using non-enolizable aldimines with specific *N*-substitution has been reported.

The catalysts developed by both Kobayashi and Jorgensen rely on 2-point coordination of the imine to chiral metal center. In this respect the catalysts are fundamentally similar, and necessitate specific substrates to obtain products of high optical purity. Reactions which tolerate both enolizable aldimines and ketimines, and do not require specific *N*-substitution would be ideal.

To find widespread use, the catalytic enantioselective aza-Diels-Alder reaction still must be made more general. The chemistry of imines is rich with these opportunities and is entering into an exciting period of renewed development. The future of catalytic enantioselective synthesis using imines will be interesting, with literature reports of both new methodology and synthetic applications becoming much more common.