

Module 1 Reactions using Chiral Lewis Acids and Brønsted Acids

Lecture 1 Reactions Using Chiral Lewis and Brønsted Acids I

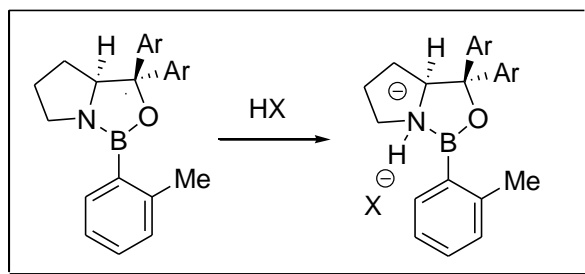
This module presents the recent developments in chiral Lewis acid and Brønsted acid catalysis, especially the systems having the combination of Lewis acids and Brønsted acids. This combined catalytic system has been useful in asymmetric synthesis over the past 20 years.

1.1 Brønsted Acid-Assisted Lewis Acid (BLA)

Chiral Brønsted acid-assisted Lewis acids (BLAs) are efficient and versatile chiral Lewis acids for a wide range of catalytic asymmetric cycloaddition reactions. Some of the representative examples follow:

1.1.1 Diels Alder Reaction

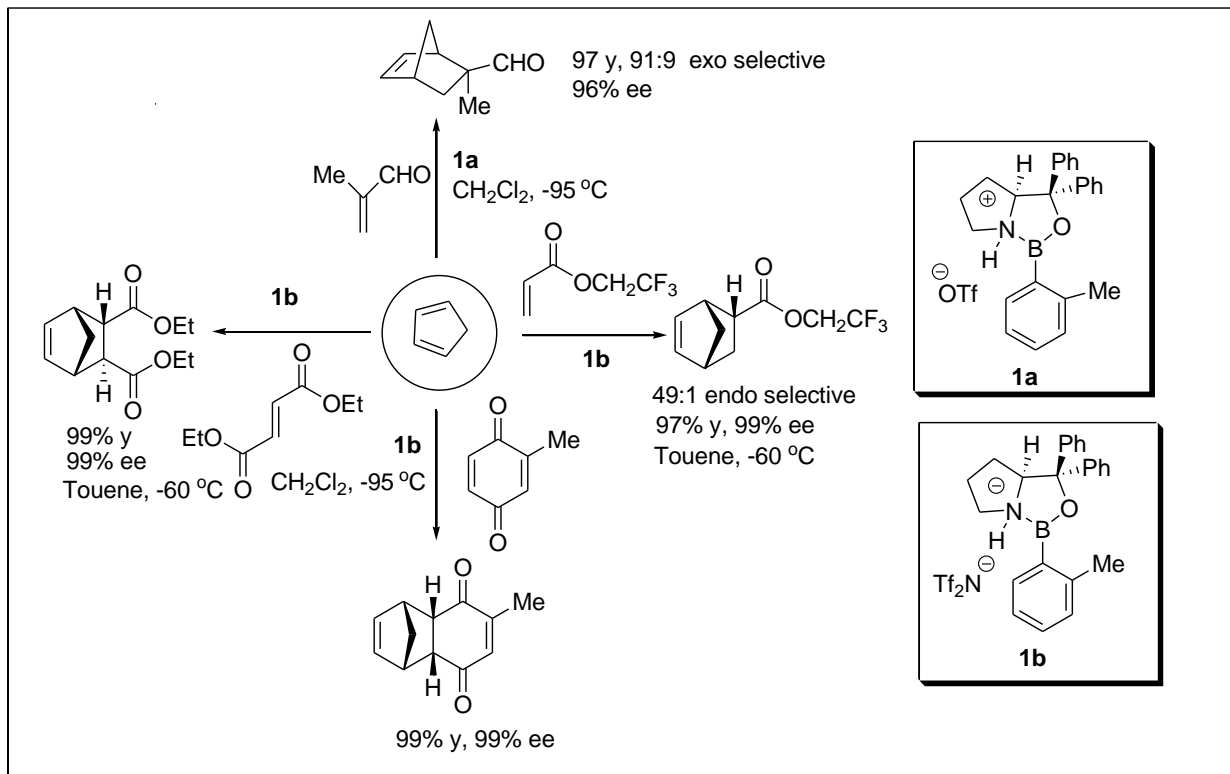
Brønsted acid-assisted chiral oxazaborolidine-based Lewis acids have been found to be versatile chiral Lewis acids for asymmetric Diels-Alder reactions. These chiral BLAs can be readily prepared by protonation of the chiral proline-derived oxaborolidines using protic acids such as trifluoromethanesulfonic acid (TfOH) and *bis*(trifluoromethane)sulfonamide (Tf₂NH) (Scheme 1).



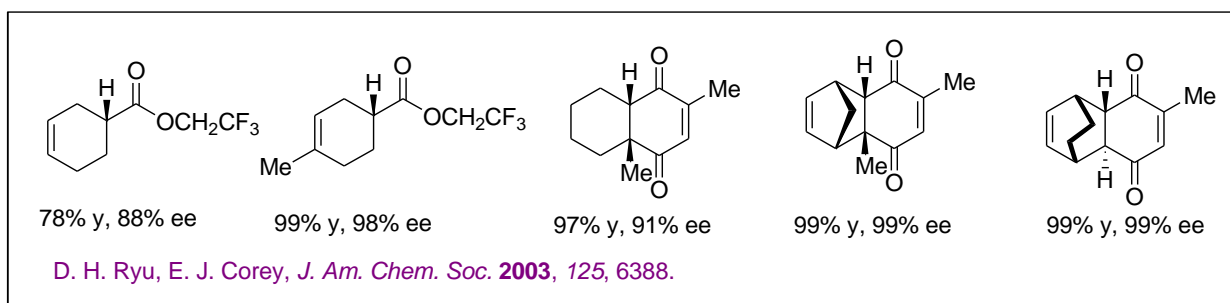
Scheme 1

BLAs **1a-b** activate various electrophiles, including α,β -unsaturated ketones, esters, carboxylic acids, lactone, enals and quinones towards Diels-Alder reaction with various dienes (Scheme 2). The stereochemical outcome can be

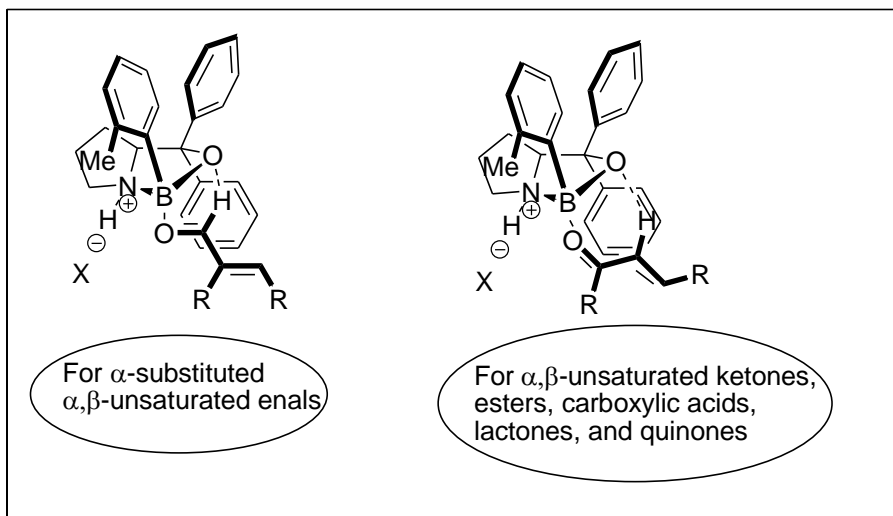
predicted using the transition state assemblies shown in Scheme 3. The face selectivity of α -substituted α,β -unsaturated enals is found to be opposite to α,β -unsaturated ketones, esters, and acrylic acids.



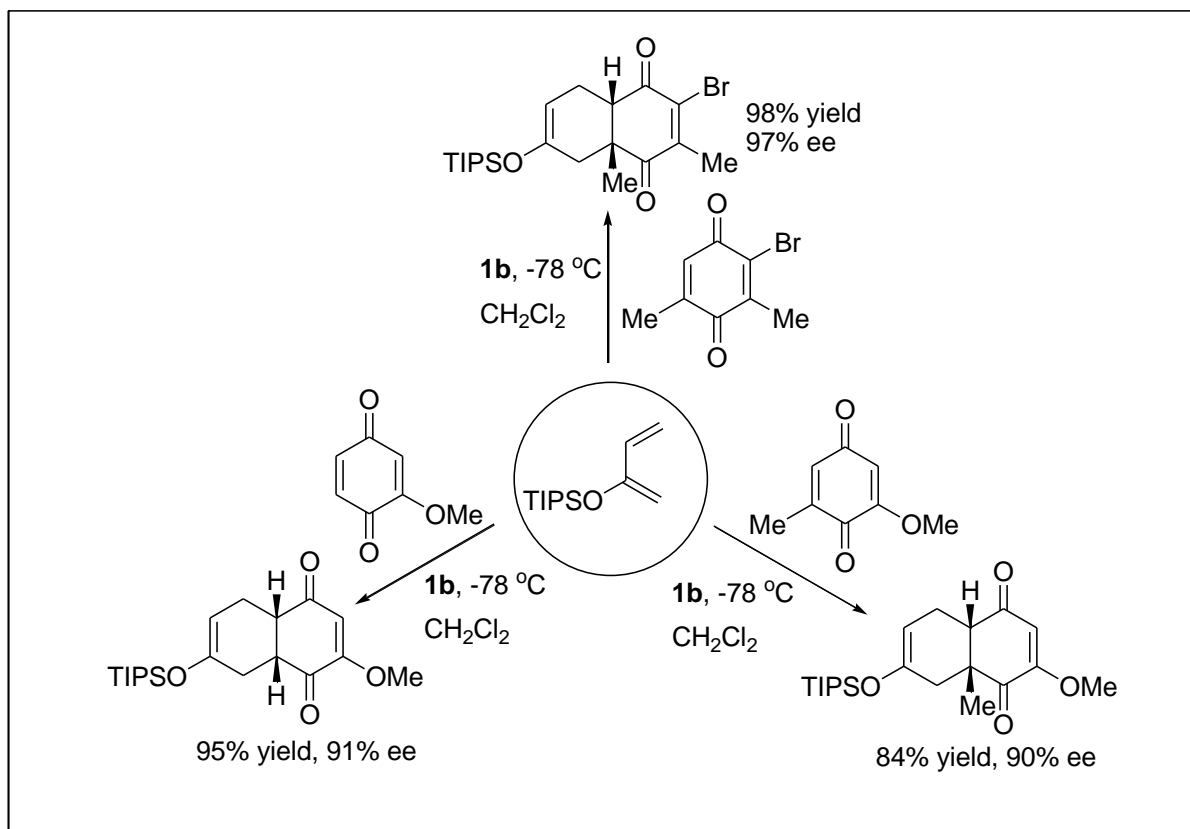
Examples using **1b**:



Scheme 2



Scheme 3

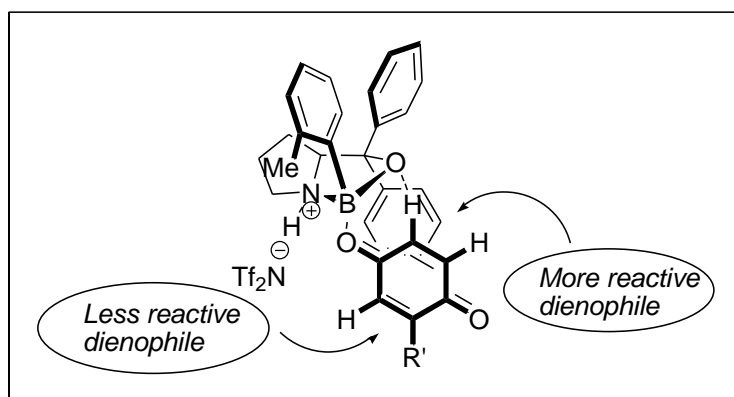


Scheme 4

The chiral BLAs having counteranion triflimide ($\text{ Tf}_2\text{ N}^-$) provides remarkable catalytic stability compared to that bearing triflate ($\text{ CF}_3\text{ SO}_3^-$). In addition, BLAs with triflimide are found to be versatile catalysts for wide range of Diels-Alder

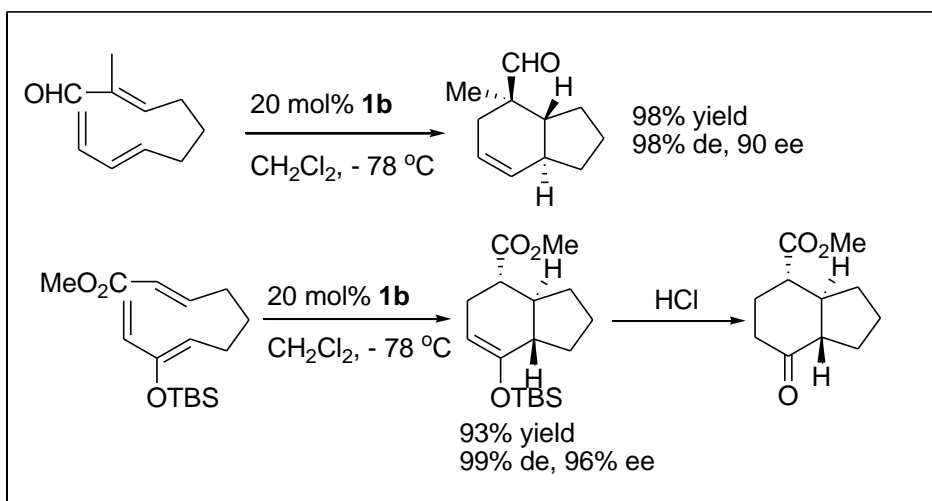
reactions. For examples, the reactions of the challenging unsymmetrical benzoquinones with 2-triisopropoxy-1,3-butadiene has been shown with excellent enantio- and regioselectivities (Scheme 4).

The observed results suggest that the BLA coordination to the oxygen of unsymmetrical quinones takes place as shown in Scheme 5. The coordination predominately takes place with the more basic oxygen of the quinones.



Scheme 5

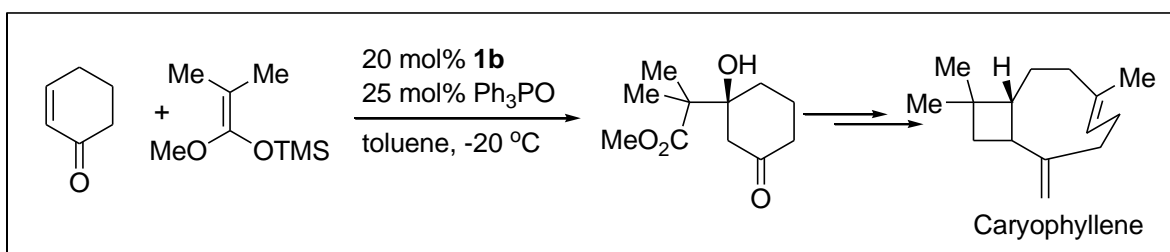
The catalytic system is also effective for intramolecular reactions to afford *trans*-fused bicyclic structures with excellent enantioselectivity (Scheme 6).



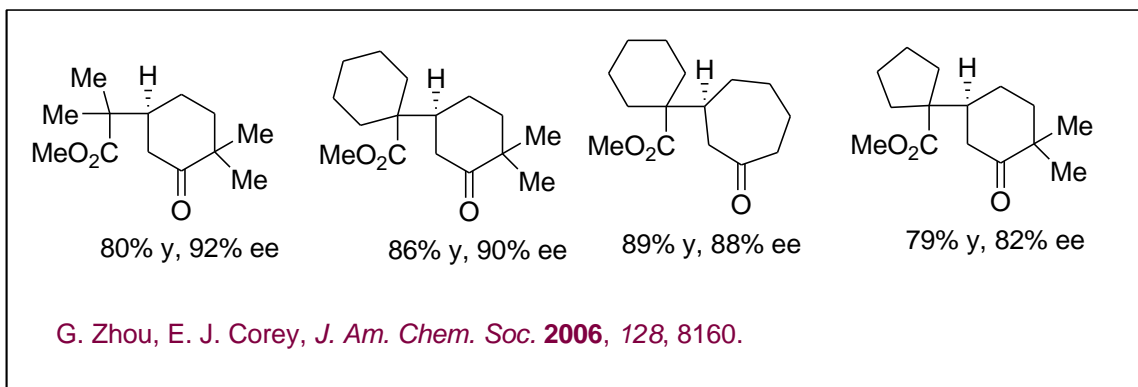
Scheme 6

1.1.2 Michel Addition

Michel addition of silyl ketene acetals to cyclic and acyclic α,β -unsaturated ketones has been studied. In these reactions, the addition of catalytic amount of Ph_3PO increases the enantioselectivity because it could trap Me_3Si species that could form during the reaction. For example, BLA **1b** has been used for the Michel addition of cyclohexenone with silyl ketene acetal to afford key intermediate for the enantioselective synthesis of caryophyllene (Scheme 7). The absolute stereochemical course of the reaction can be rationalized by the above proposed transition states.



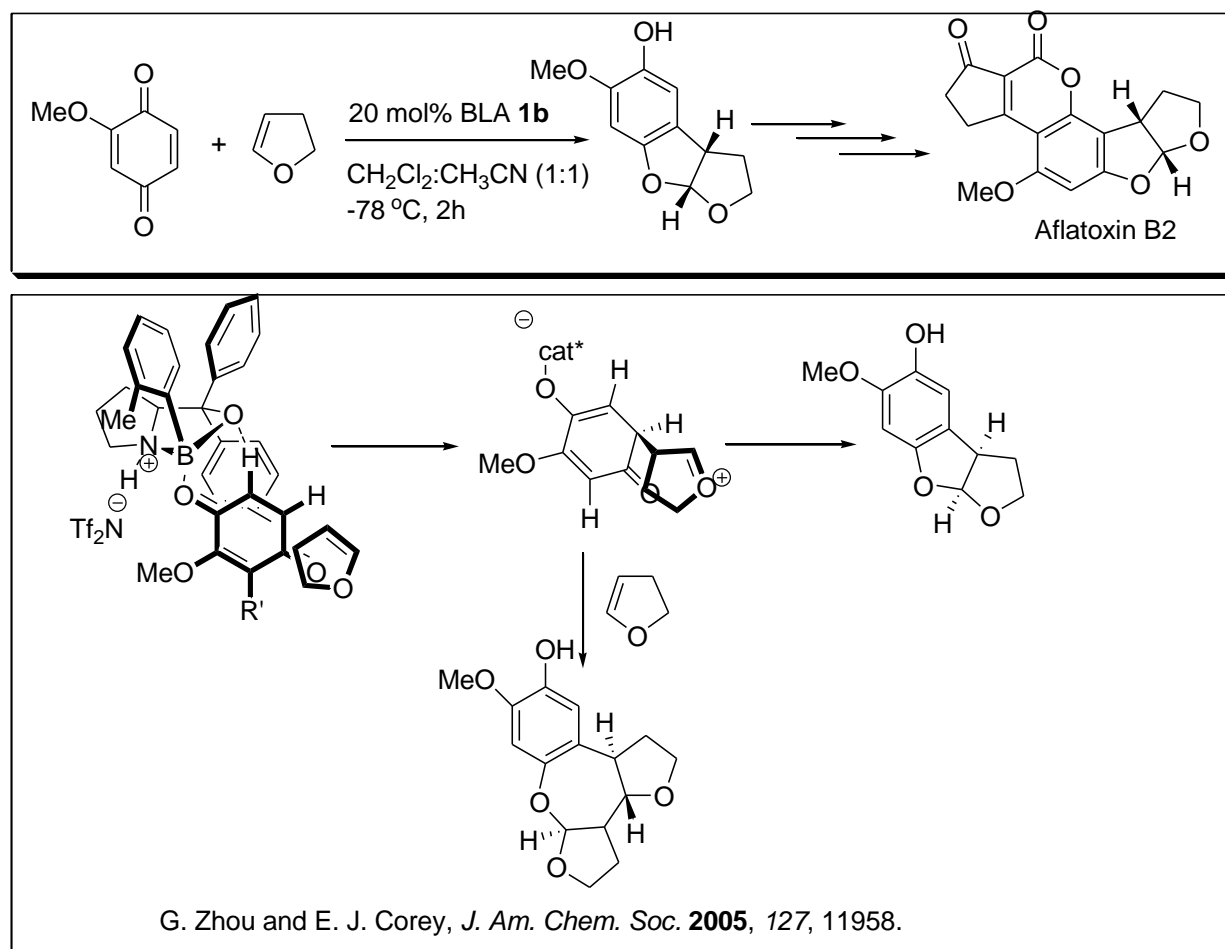
Examples:



Scheme 7

1.1.3 [3+2] Cycloaddition

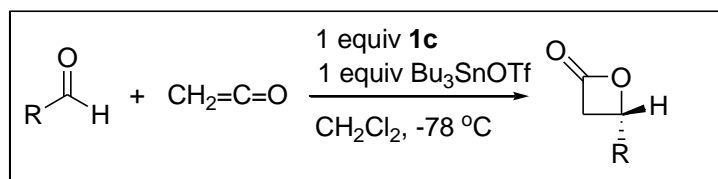
Several benzoquinones proceed reactions with 2,3-dihydrofuran in the presence of BLA **1b** to afford a variety of chiral phenolic tricycles with high enantioselectivities. The application of this reaction has been demonstrated in the total synthesis of aflatoxin B₂. The reaction pathway has been elucidated by performing the reaction in the presence of excess of 2,3-dihydrofuran (Scheme 8).



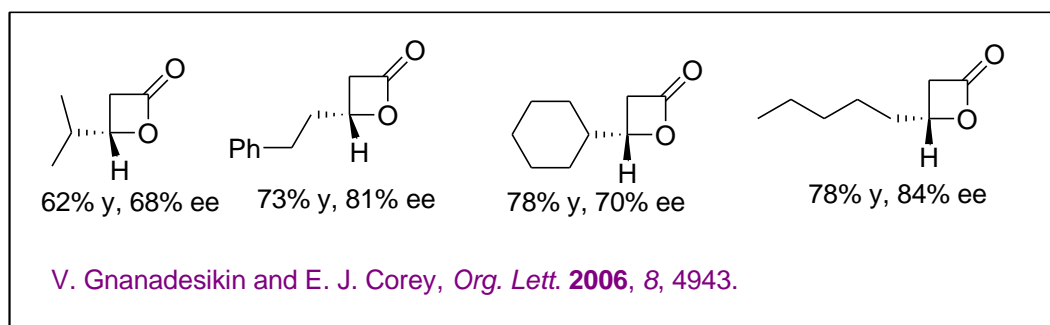
Scheme 8

1.1.4 β -Lactone Synthesis

Chiral BLA **1c**, derived from precatalyst zwitterions and tributyltintriflate, has been investigated for the reaction of aldehydes with ketene to afford β -lactones (Scheme 9).

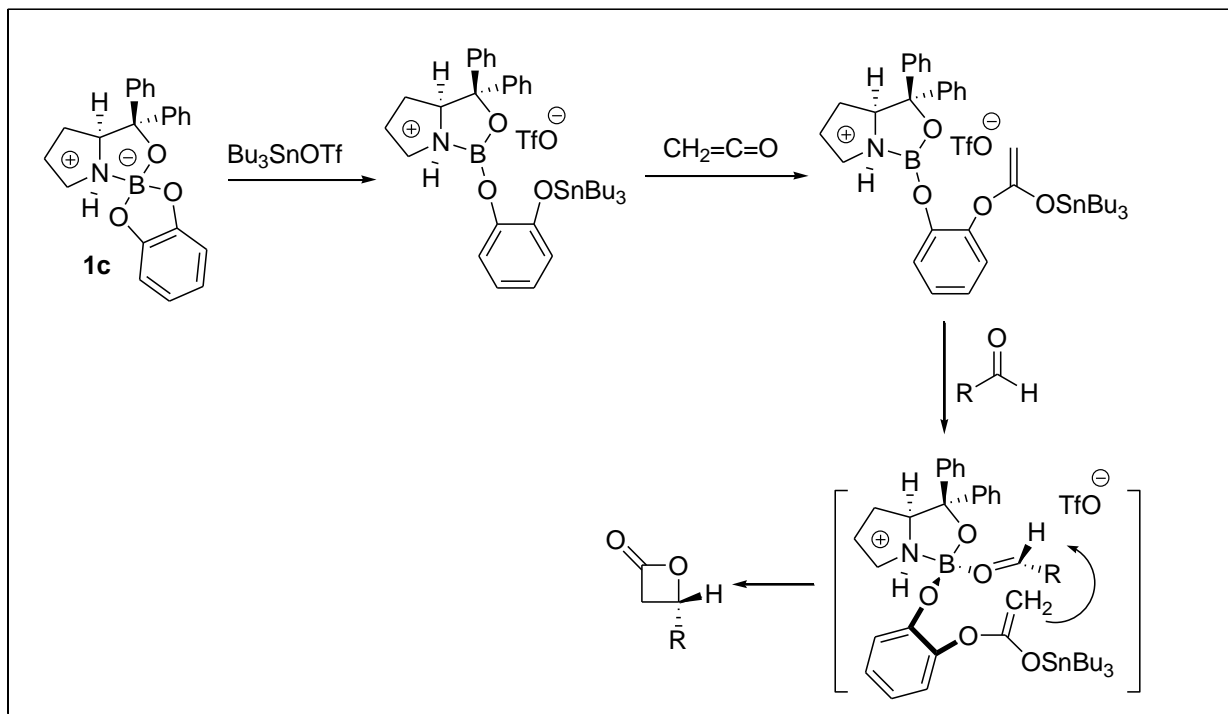


Examples:



Proposed Mechanism

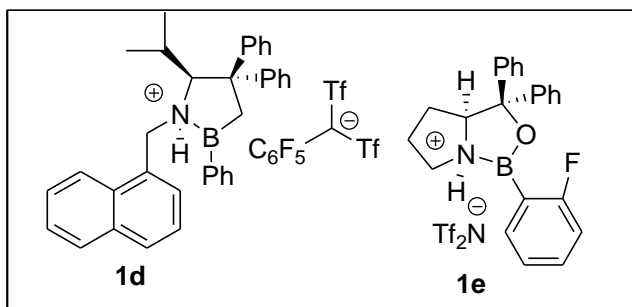
Reaction of the precatalyst **1c** with tri-*n*-butyltintriflate may give an ion pair that could react with ketene to give sufficiently strong Lewis acid intermediate to make chelation with aldehydes. It is important to note that the formation β -lactone from α -branched aldehydes has been demonstrated for the first time.



Scheme 9

1.1.5 Modified BLA Catalysts

The following modified BLA catalysts **1d-e** has been subsequently developed. These catalysts have also been demonstrated as powerful catalysts for Diels-Alder reactions.

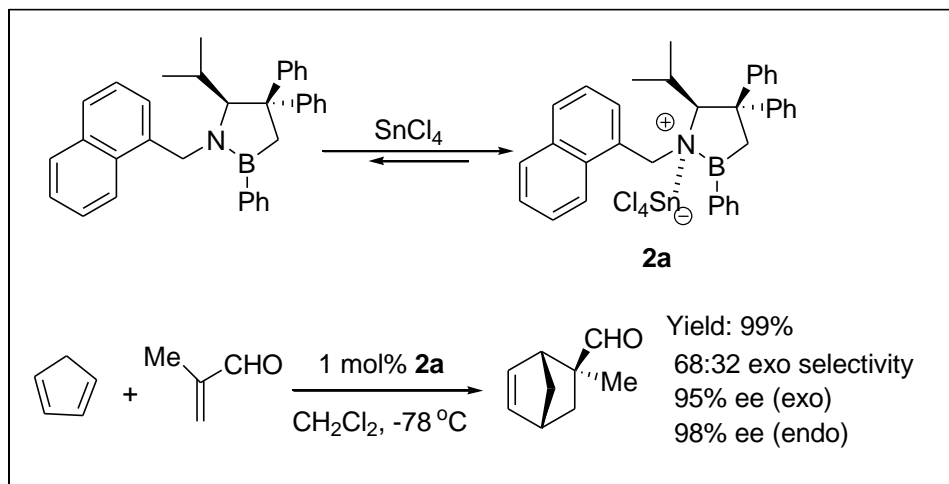


1.2 Lewis Acid-Assisted Lewis Acid (LLA)

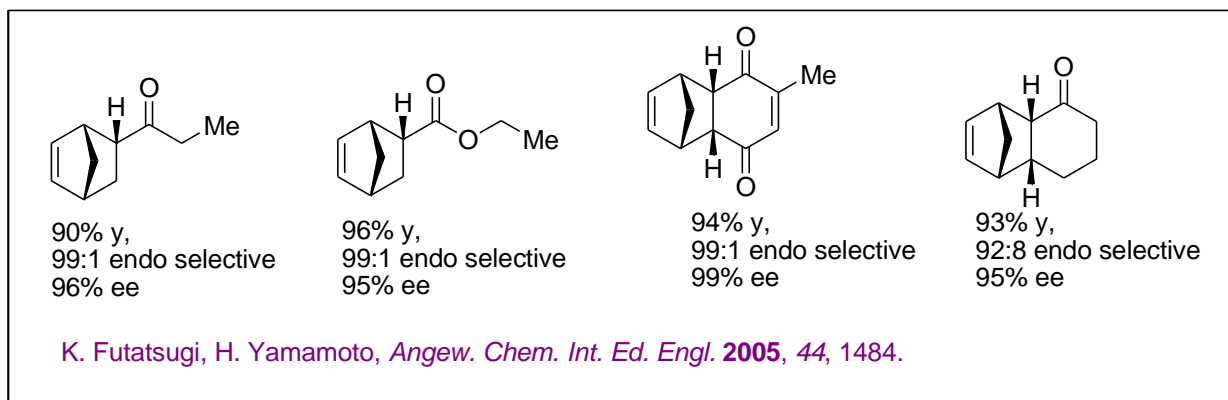
In Lewis acid assisted chiral Lewis acids (LLAs), achiral Lewis acid is added to activate chiral Lewis acid via complex formation. The reactivity of LLA is much greater compared to that of achiral Lewis acid, and thus, the latter's presence does not affect the selectivity of the reaction.

1.2.1 Diels-Alder Reaction

The LLA **2a**, derived from chiral valine-based oxazaborolidine and SnCl_4 as an activator, has been utilized as an efficient catalyst for the Diels-Alder reaction of wide range of substrates (Scheme 10). In this system, the LLA **2a** is more reactive compared to SnCl_4 and the *ee* is not affected because of the addition of excess SnCl_4 .

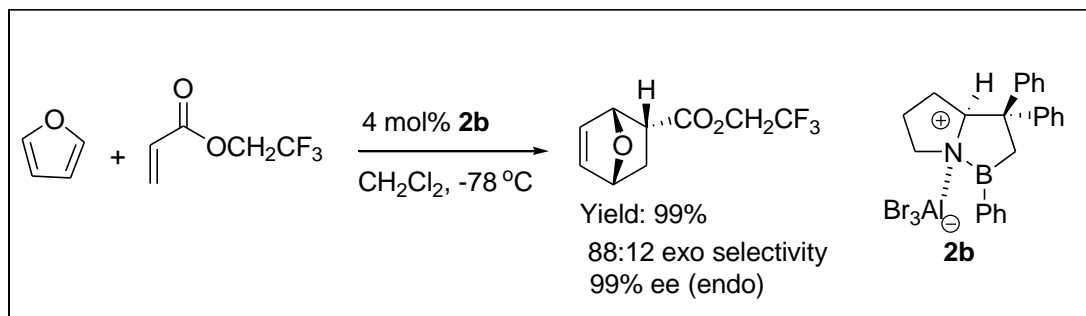


Additional examples:

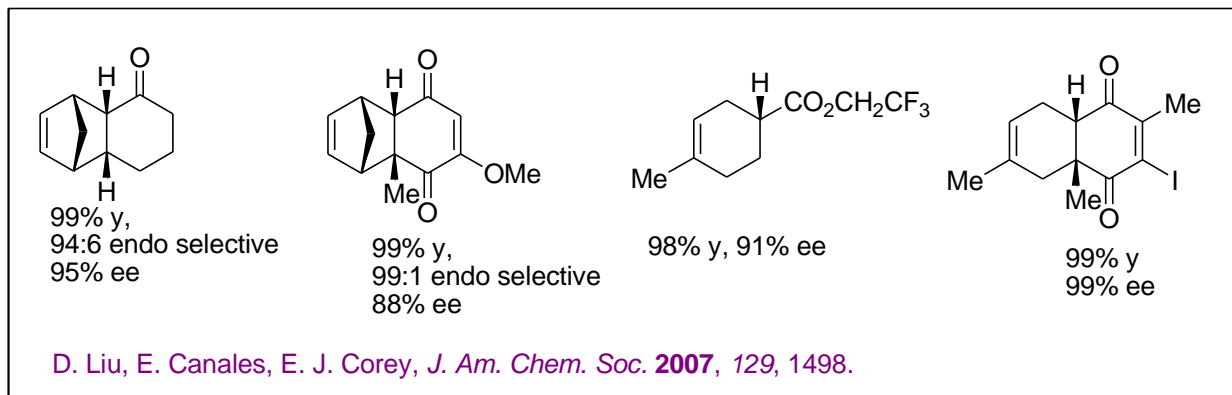


Scheme 10

The LLA **2b**, derived from the complexation of AlBr_3 with chiral oxazaborolidine, has been shown as useful catalyst for Diels-Alder reaction (Scheme 11). The observed results suggest that LLA **2b** is considerably more efficient catalyst than the corresponding BLA **1a** or **1b** since 10-20 mol% of BLA is usually needed for the optimum results.



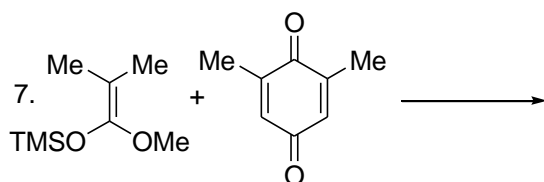
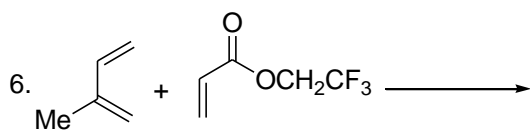
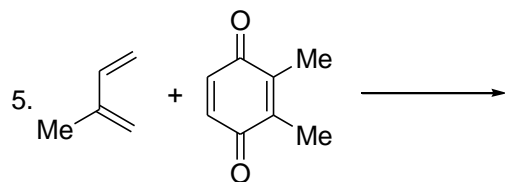
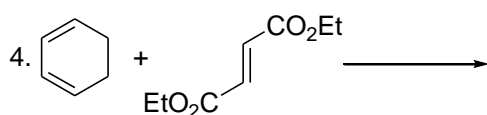
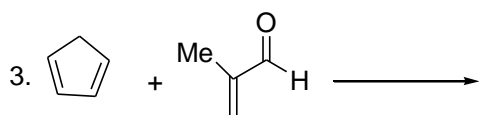
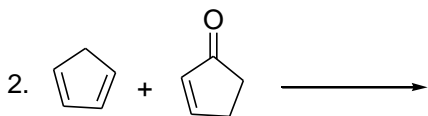
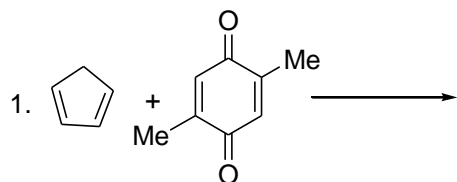
Additional examples:



Scheme 12

Problems:

What products would expect from the following reactions using BLA **1b** as a catalyst?



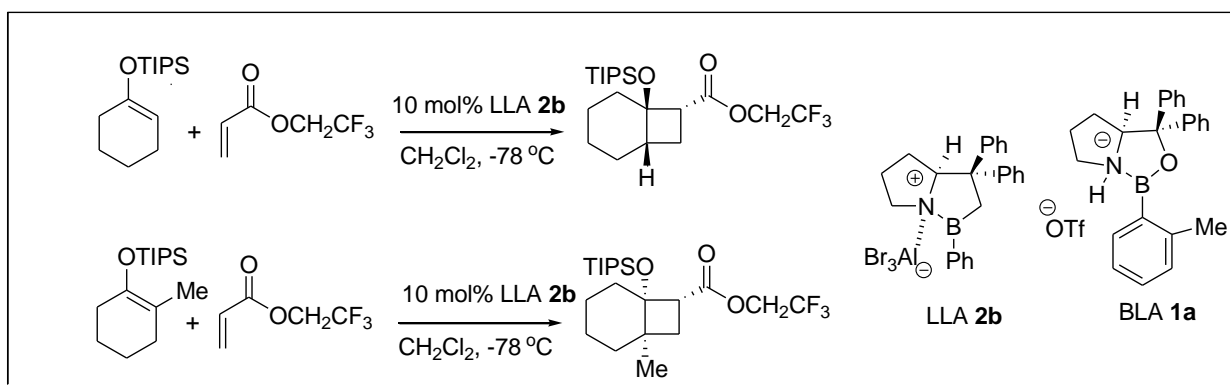
Reference/Text Book

1. I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., Wiley, New Jersey, 2010.
2. M. B. Smith, *Organic Synthesis*, 2nd edition, McGraw Hill, New Delhi, 2004.

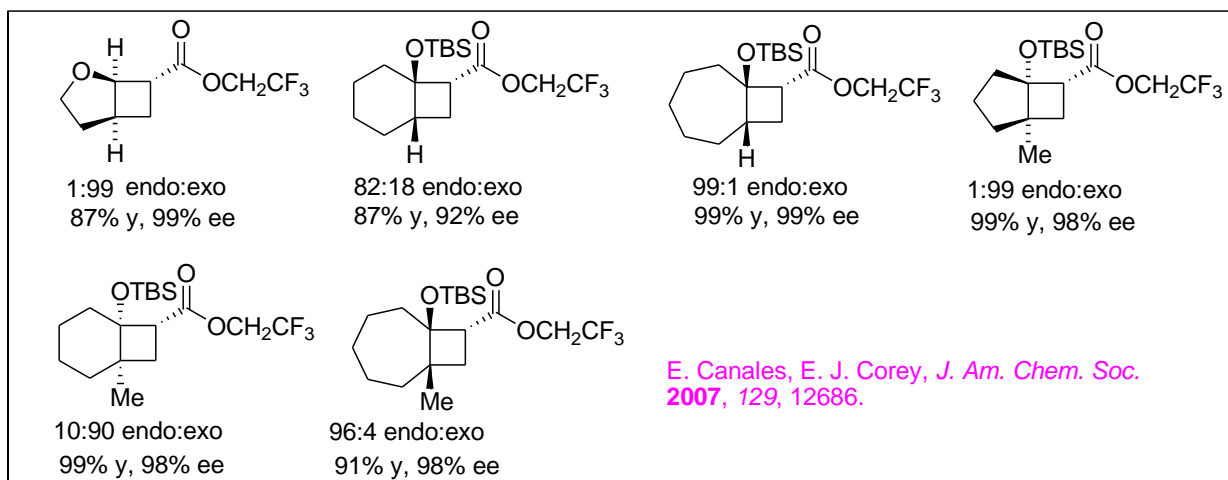
Lecture 2 Reactions Using Chiral Lewis and Brønsted Acids II

1.2.2 [2+2]-Cycloaddition

The utility of LLA**2b** has been further extended to [2+2]-cycloaddition reactions of trifluoroethyl acrylate with enol ethers (Scheme 1). The protonated BLA**1a** was found to be inferior to LLA**2b** in catalyzing the [2+2]-cycloaddition due to side reactions involving the enol ether component. The stereochemical outcome could be predicted using the transition states proposed earlier in Scheme 3, Lecture 1.



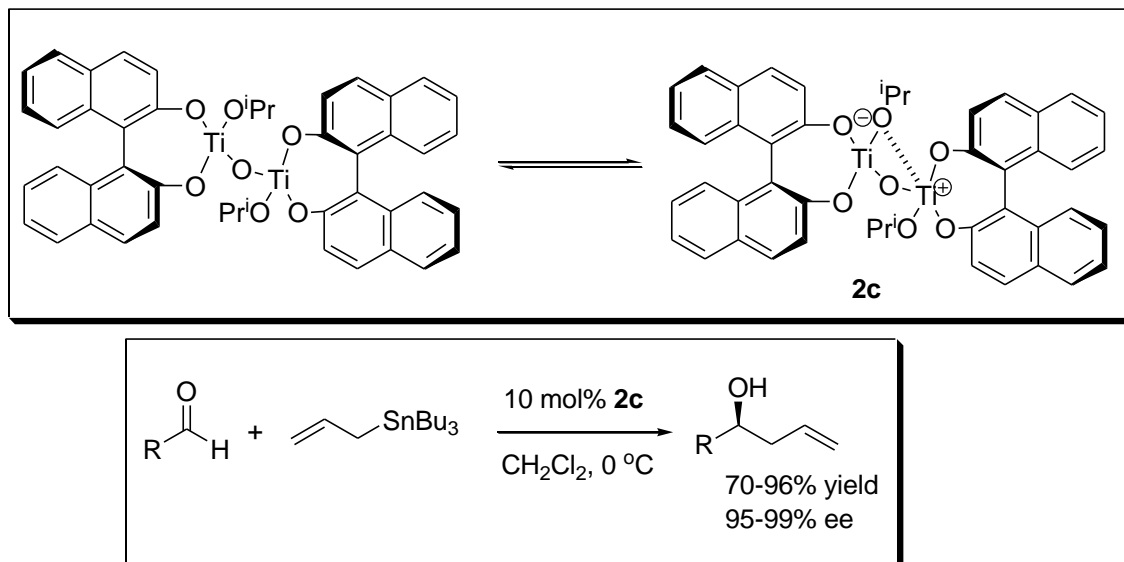
Examples:



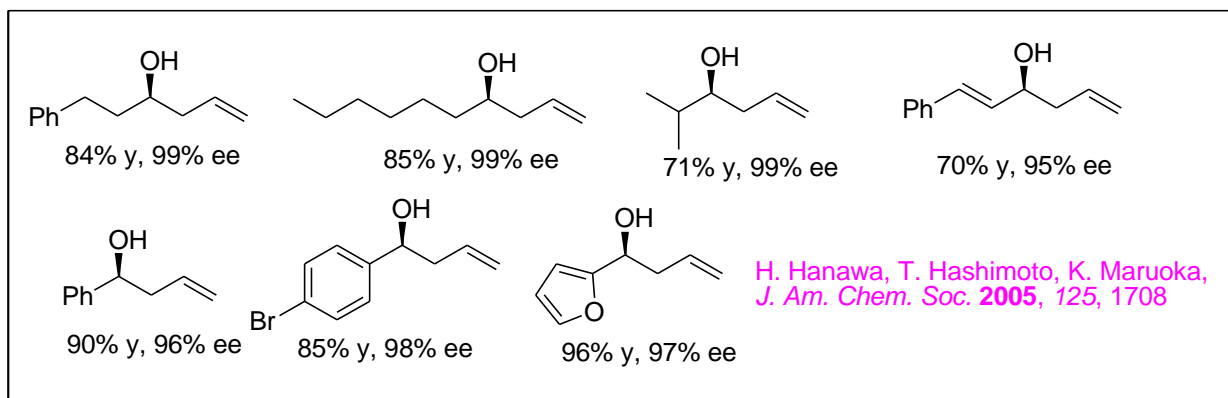
Scheme 1

1.2.3 Allylation

Maruoka group has developed chiral *bis*-Ti oxide complex **2c** as LLA (Lewis Acid-Assisted chiral Lewis Acid) for the enantioselective allylation of aldehydes with allylbutyltin (Scheme 2).



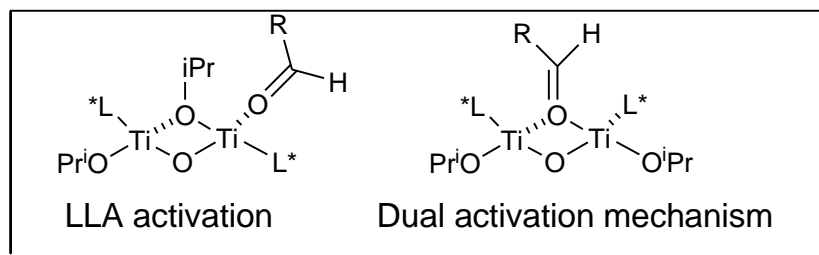
Examples:



Scheme 2

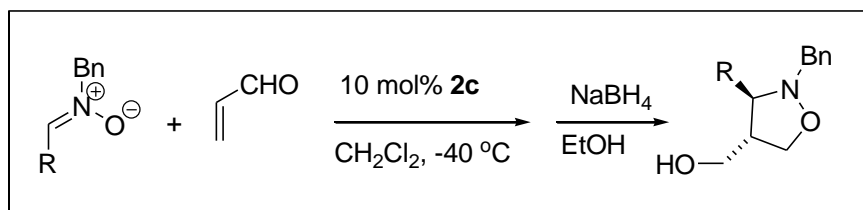
For the high reactivity of the catalyst **2c**, two different transition states are proposed (Scheme 3). In the first, intramolecular coordination of one isopropoxy oxygen to the other titanium has been proposed which could lead to enhancement in Lewis acidity of the original Ti center for the carbonyl activation. In the second system, the simultaneous coordination of the two Ti

centers to the carbonyl group has been proposed which may also lead to the high reactivity.

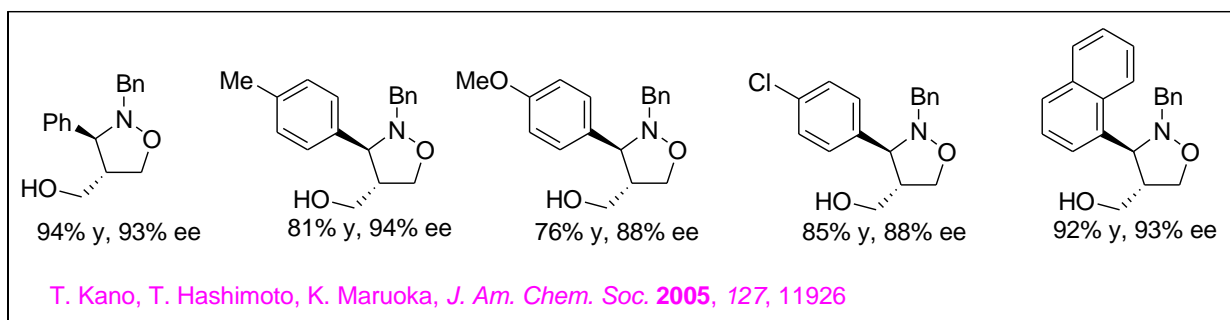


Scheme 3

The catalyst **2c** has also been found to be effective for 1,3-dipolar cycloaddition reaction between diazoacetates and α -substituted acroleins to give 2-pyrazolines with a quaternary carbon centre (Scheme 4).



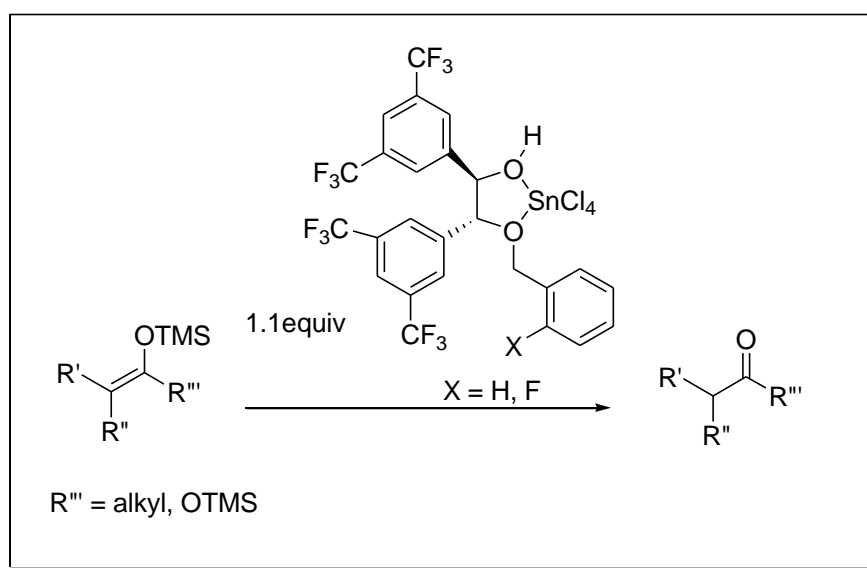
Examples:



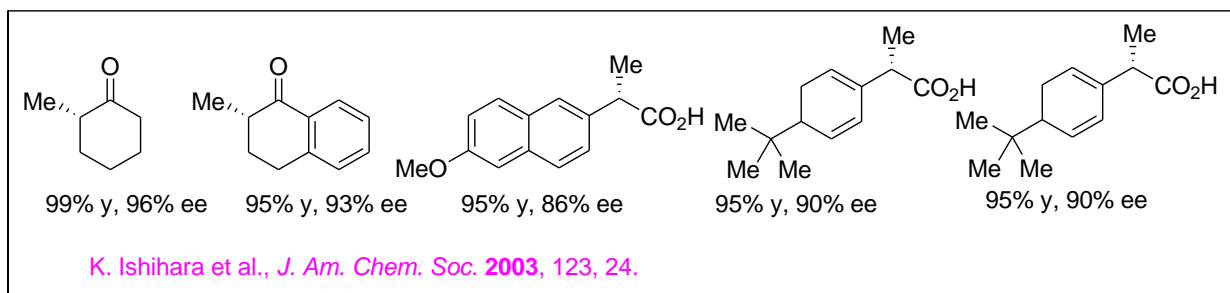
Scheme 4

1.3 LBA Catalysts

The combination of Lewis acids and chiral Brønsted acids affords LBA catalysts. In this system, the coordination of the Lewis acids to the heteroatom of the chiral Brønsted acid results in increase the acidity of the latter. For examples, the LBA, derived from optically active monoalkylated-1,2-diarylethane-1,2-diol and SnCl₄, has been found to be an effective catalyst for the enantioselective protonation of silyl enol ethers and ketene disilyl acetals (Scheme 5).

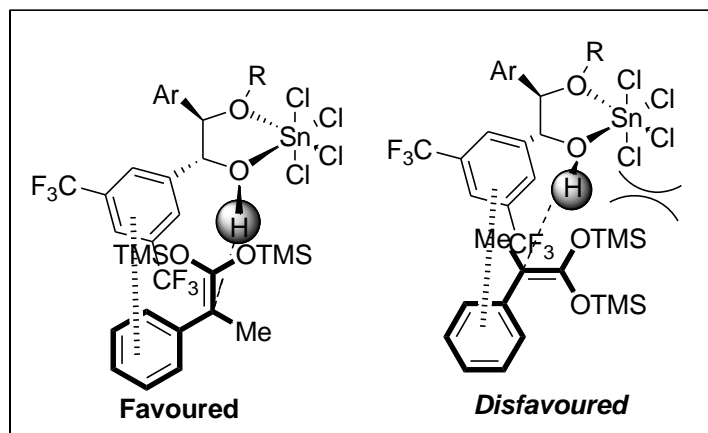


Examples:



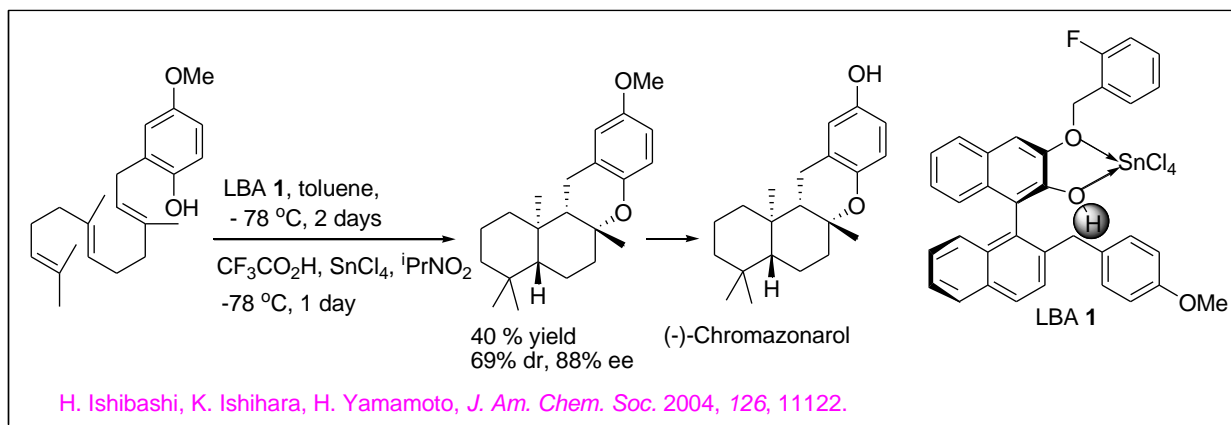
Scheme 5

Based on the related X-ray crystal structure, the following transition states, controlled by a linear O-H— π bonding interaction, are proposed for the stereochemical course of the reactions (Scheme 6).

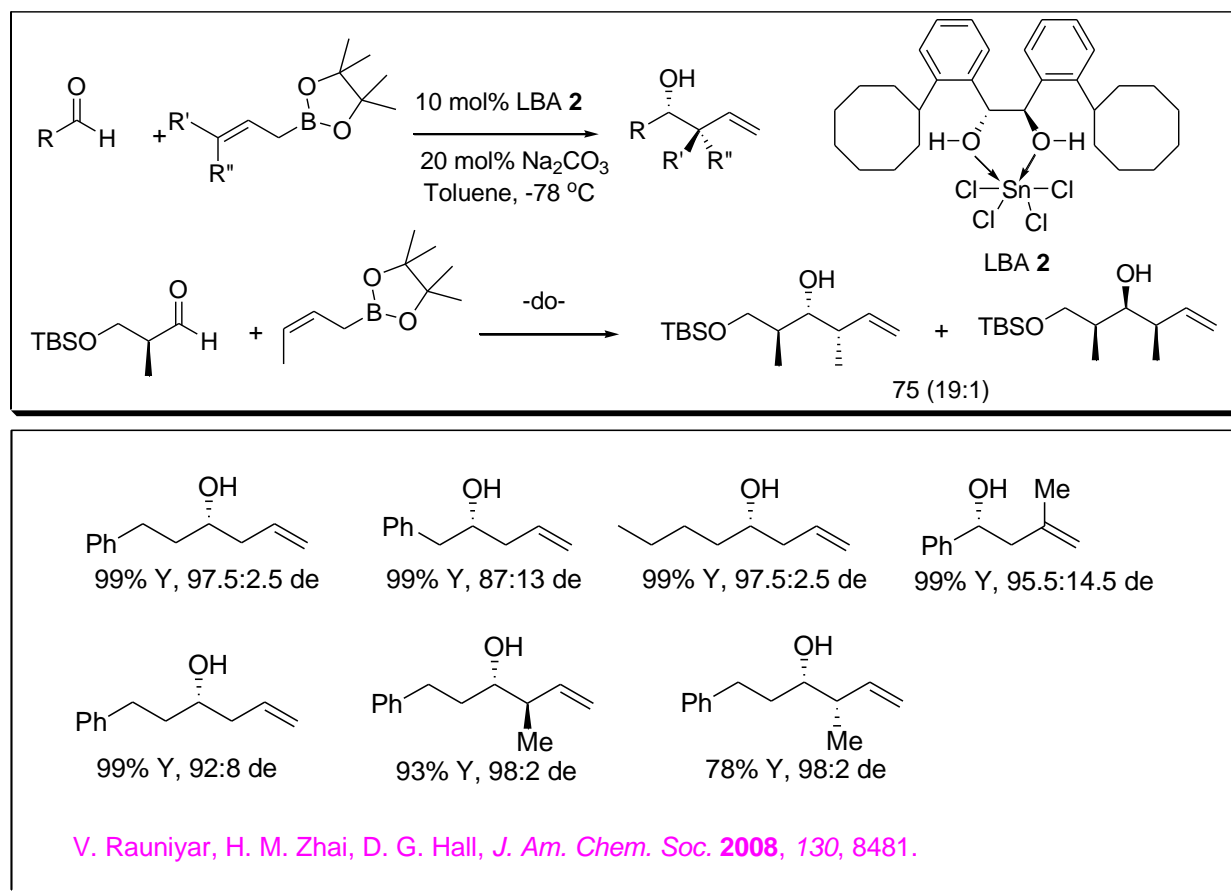


Scheme 6

The chiral catechol-derived LBA **1** has been employed as an artificial cyclaze for the cyclization of various 2-(polyprenyl)phenol derivatives with good yield and enantioselectivity. For example, a short total synthesis of (-)-chromazonarol can be accomplished with 88% enantioselectivity (Scheme 7).



Scheme 7



Scheme 8

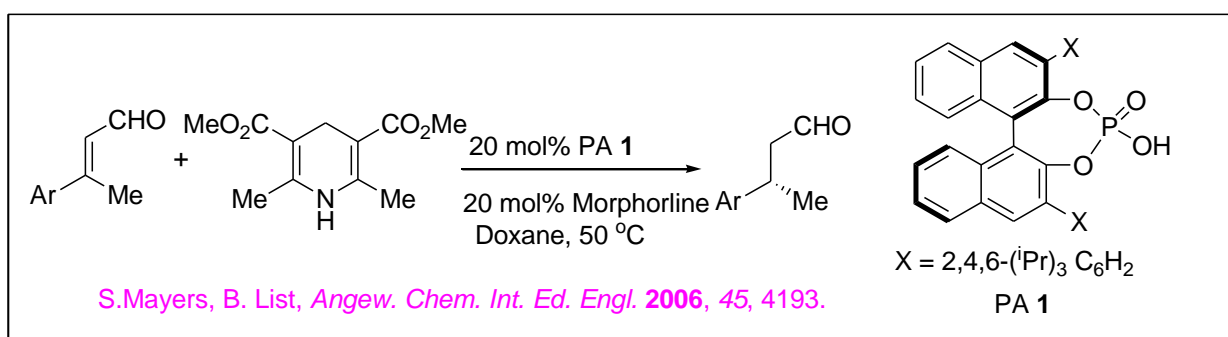
In addition, LBAs have been used as powerful catalysts for allylation reactions. For examples, LBA **2** has been used as an effective catalyst for allylation of aldehydes with high diastereofacial selectivity (Scheme 8).

1.4 Chiral Phosphoric Acids (PAs)

Chiral phosphoric acids (PAs) derived from optically active BINOL carrying 3,3'-substituents have been utilized as effective chiral catalysts to various organic transformations. Phosphoric acids act as bifunctional catalysts bearing both Brønsted acidic site and a Lewis basic site and the 3,3'-substituents play a crucial role in attaining high stereoselectivity by controlling the structural and electronic properties.

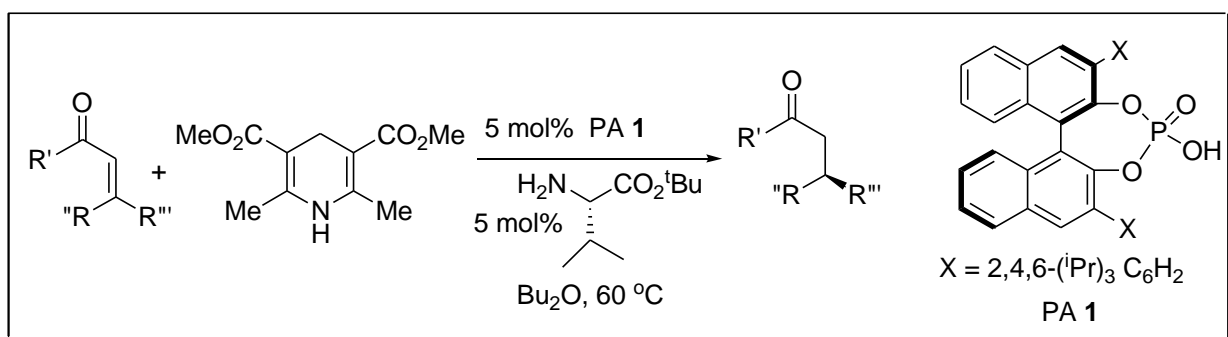
1.4.1 Asymmetric Counterion Directed Catalysis (ACDC)

ACDC is a new concept of enantioselective synthesis. In 2006, List group first reported ACDC concept for the 1,4-hydrogenation of α,β -unsaturated aldehydes using the combination of morpholine and PA **1** at moderate temperature (Scheme 9). In this reaction, PA**1** reacts with morpholine to give the morpholine salt of chiral anion PA **1** that catalyzes the reaction. The reaction takes place via the formation of iminium salt, wherein phosphate anion is believed to effectively shield one of the enantioface of the iminium salt.

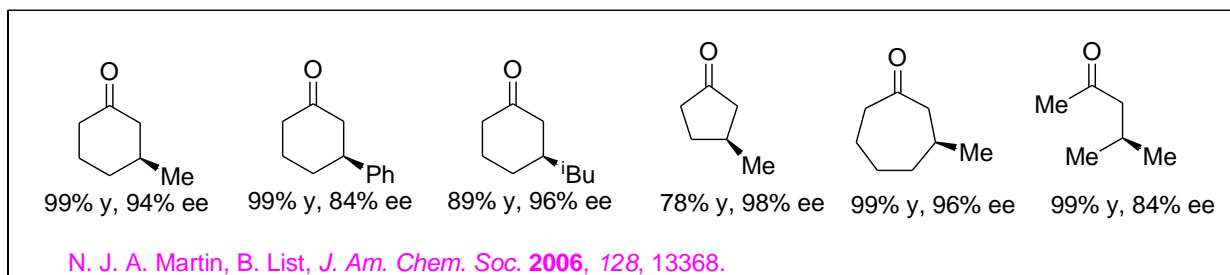


Scheme 9

This method has been subsequently utilized for the reduction of α,β -unsaturated ketones (Scheme 10). In which both cation and anion are chiral that catalyze with high enantioselectivity.

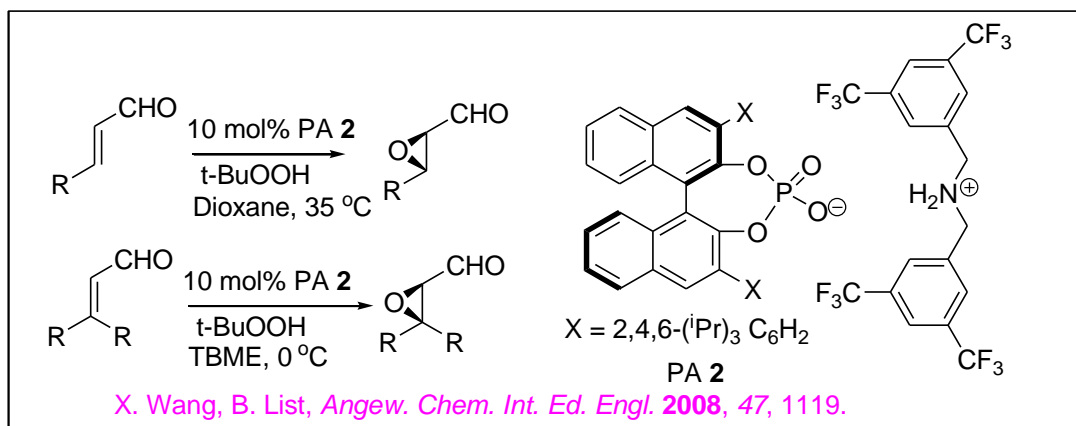


Examples:



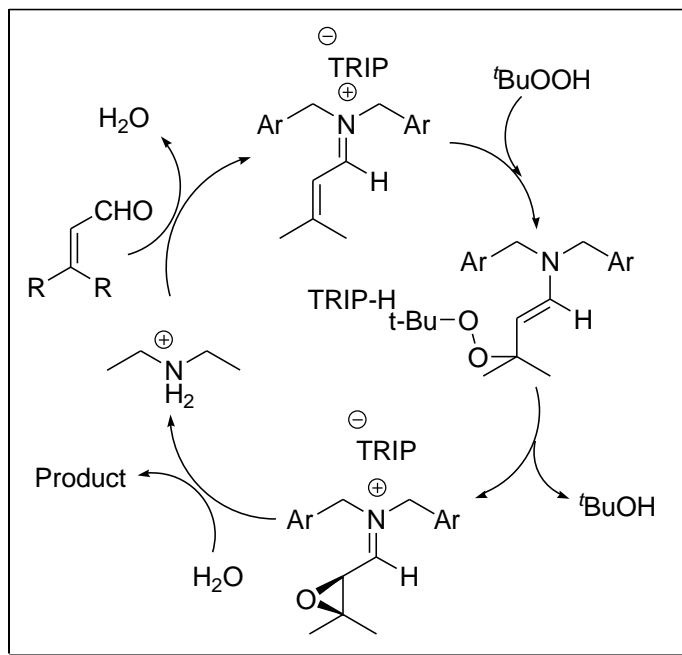
Scheme 10

The PA **2** has been further utilized for the asymmetric epoxidation of α,β -unsaturated aldehydes in the presence of t-BuOOH (Scheme 11). The proposed catalytic cycle is shown in Scheme 12. The initial addition product is achiral and the subsequent cyclization to iminium ion leads to the stereogenic center.

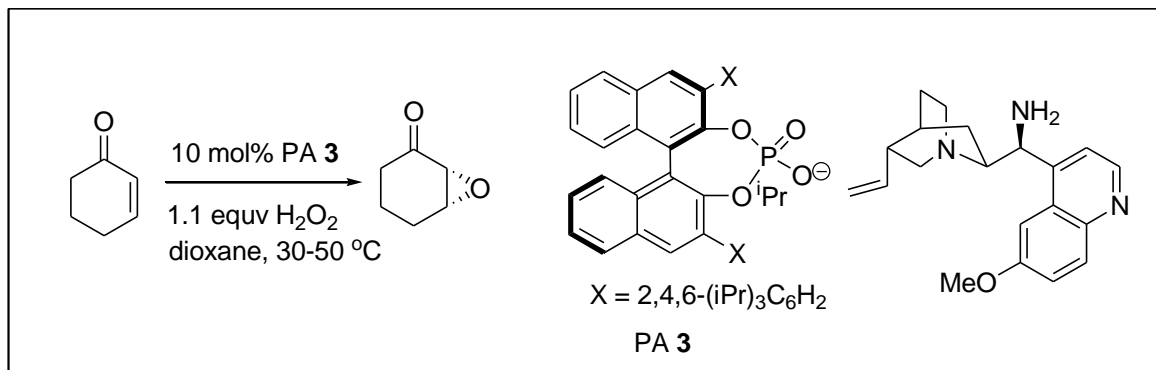


Scheme 11

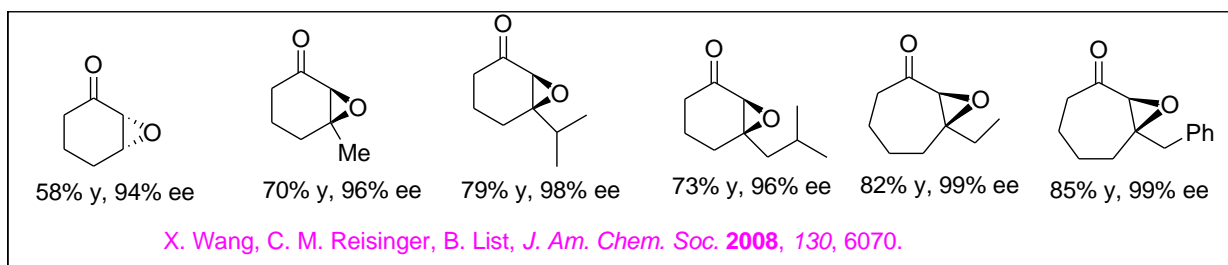
This methodology has been further extended for the epoxidation of α,β -unsaturated ketones (Scheme 13). In this system, the diamine salt may serve as a bifunctional catalyst to possibly activate the enone substrate via iminium ion formation and hydrogen peroxide via general base catalysis as shown in Scheme 14.



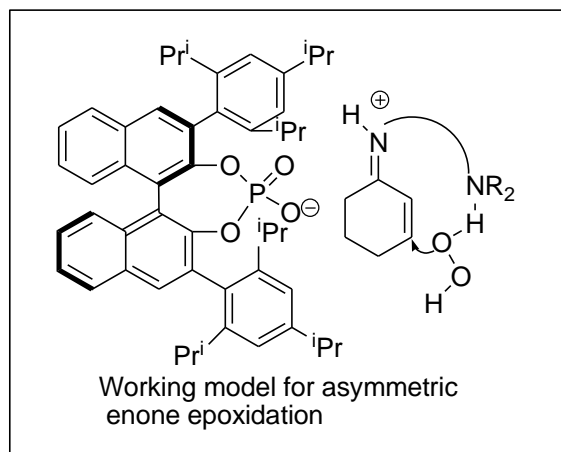
Scheme 12



Examples:

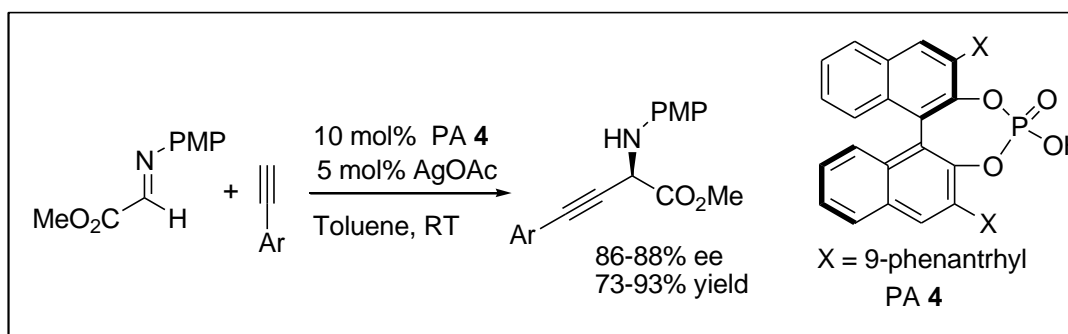


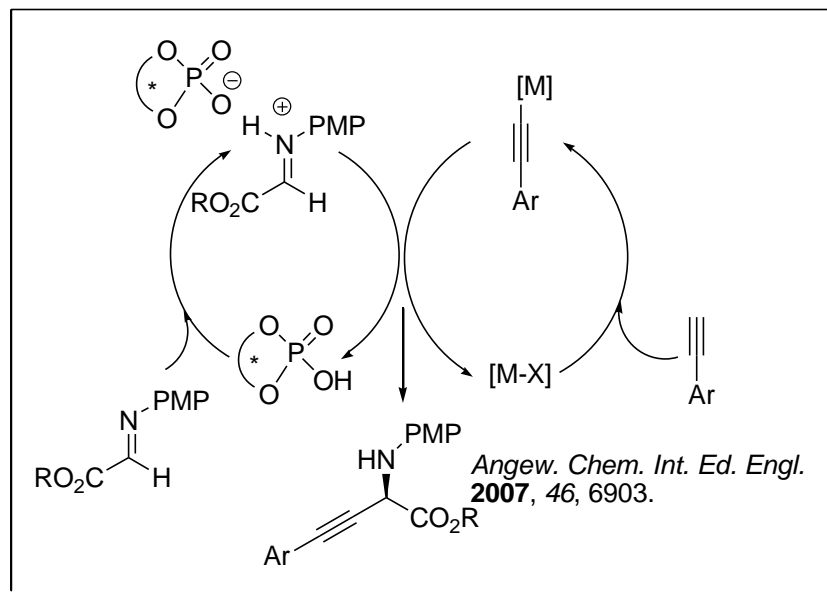
Scheme 13



Scheme 14

A dual catalytic procedure has been developed for the enantioselective activation of imines by a Brønsted acid combined with BINOL phosphate complex that results in a new metal catalyzed reaction in which the chiral counterion induces the enantioselectivity (Scheme 15).

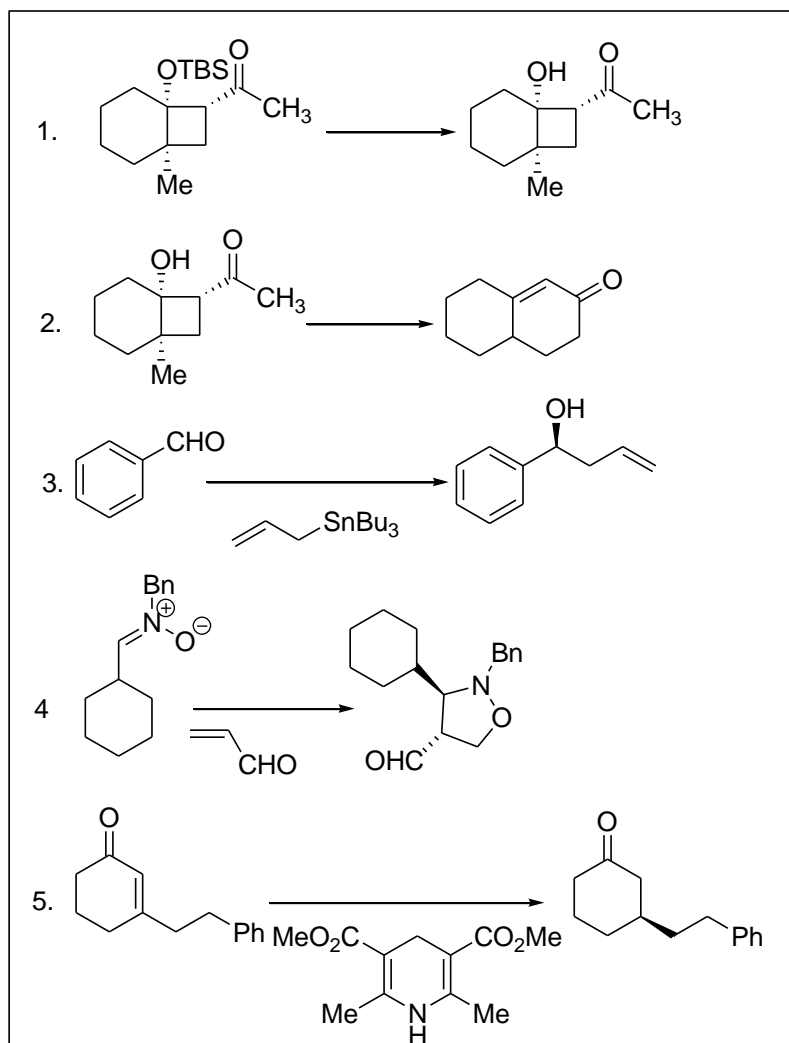




Scheme 15

Problems

Provide suitable catalysts/reagents for the following conversions.



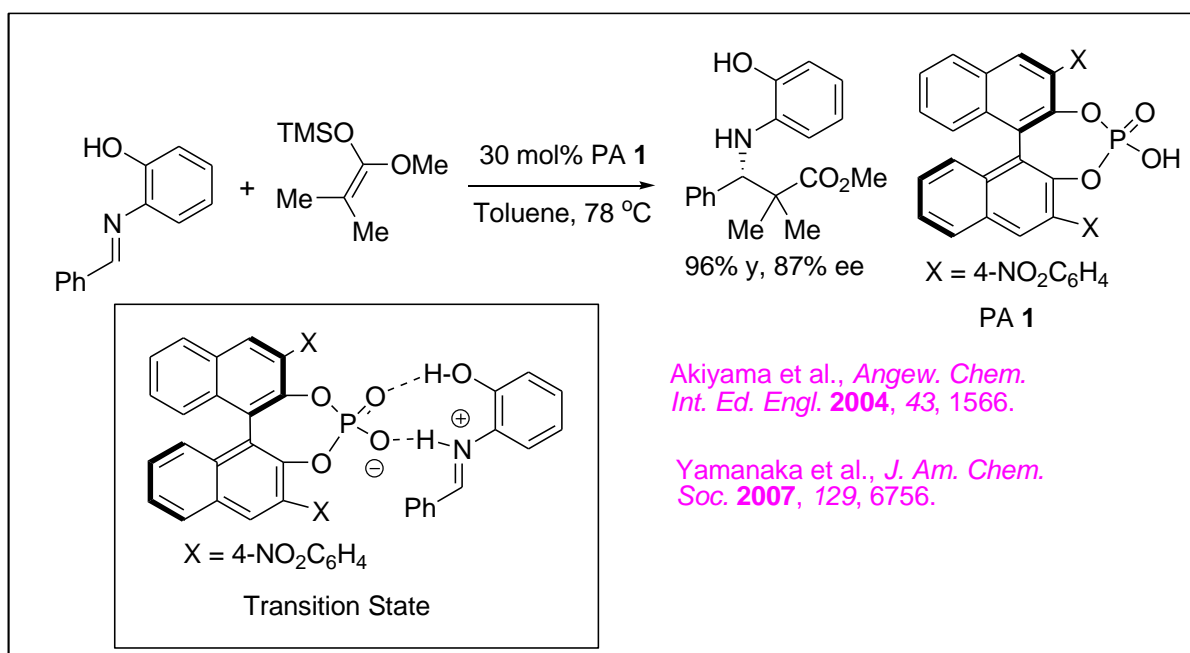
Reference

- I. Ojima, *Catalytic Asymmetric Synthesis*, John Wiley & Sons, New Jersey, 2010.

Lecture 3. Reactions Using Chiral Phosphoric Acids I

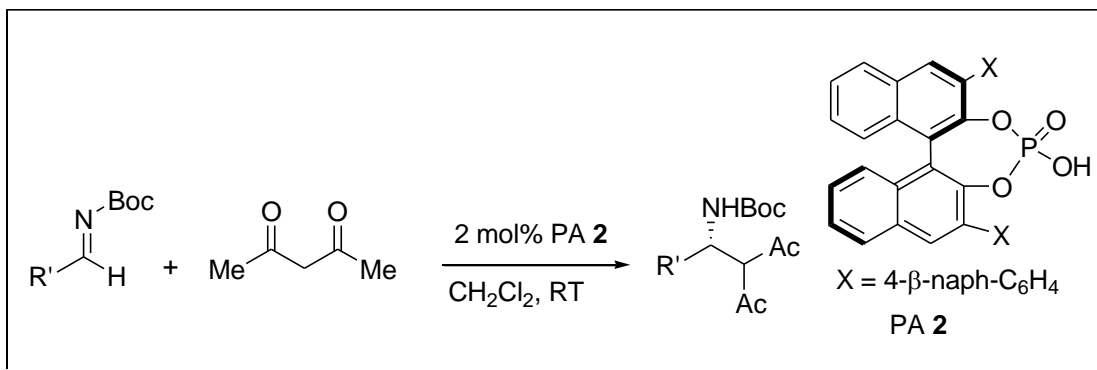
1.4.2 Nucleophilic Additions of Aldimines

Chiral phosphoric acids (PAs) have been investigated as effective catalysts for Mannich type reactions. For examples, the reaction of imines with ketene silyl acetals has been studied using PA **1** in which introduction of 4-nitrophenyl substituents at 3,3'-positions has a beneficial effect on obtaining the high enantioselectivity (Scheme 1). Based on DFT calculations a nine-membered zwitterionic transition state has been proposed to explain the stereoinduction.

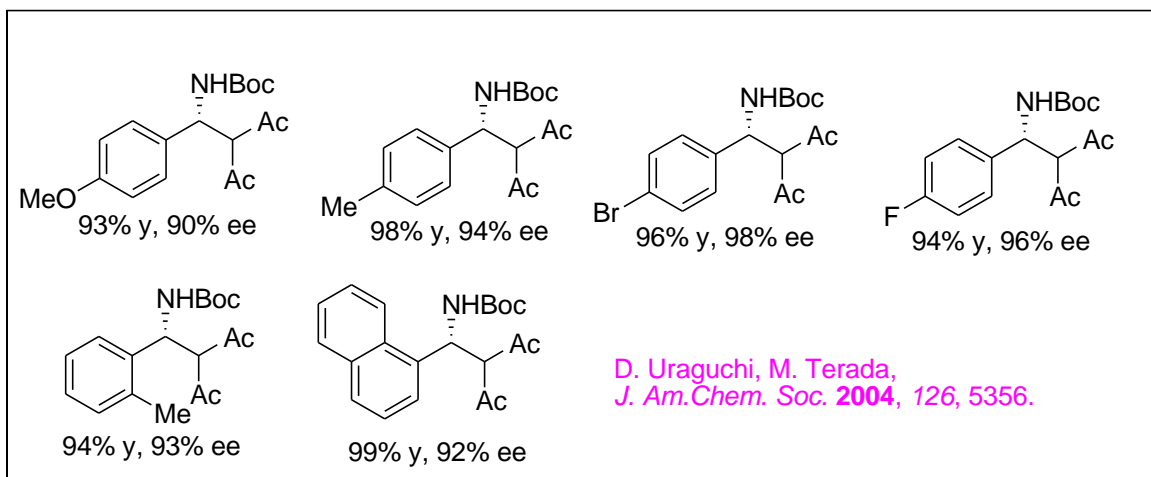


Scheme 1

The reaction of acetylacetone with *N*-boc-protected imines has been subsequently reported employing 2 mol% PA**2** with excellent yield and enantioselectivities (Scheme 2). The procedure is compatible with a series of substrates to afford target products in high enantioselectivities.

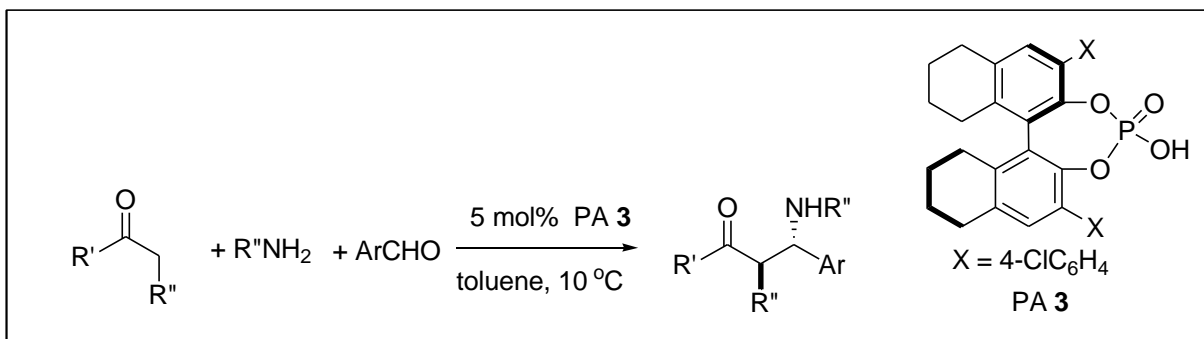


Examples:

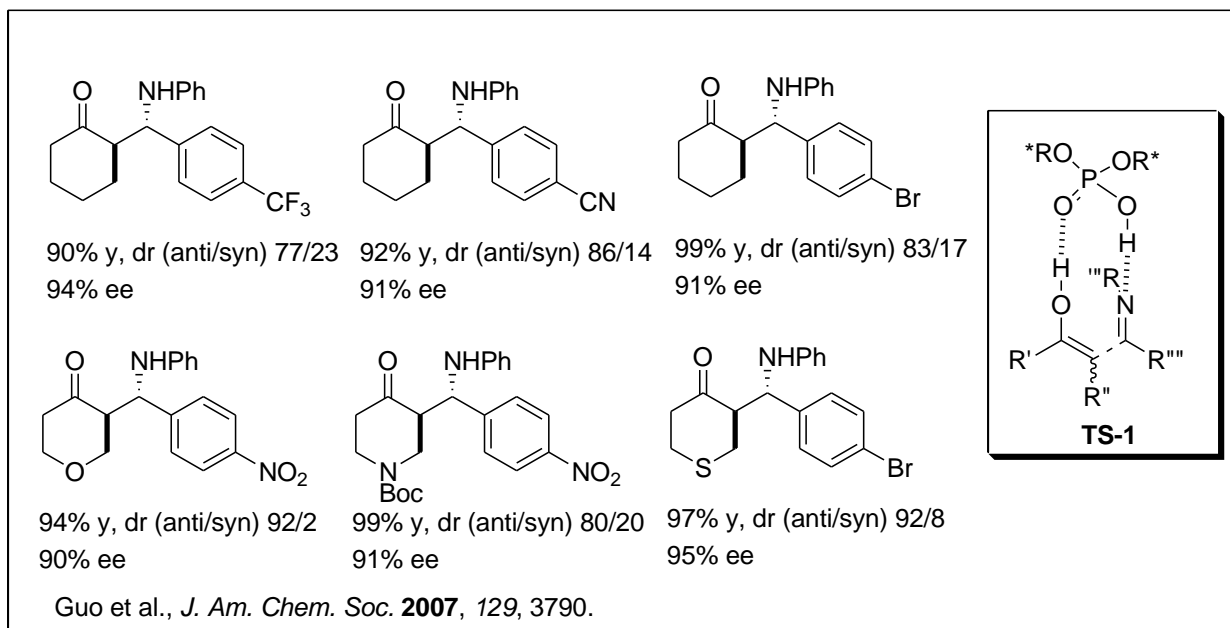


Scheme 2

Phosphoric acid PA 3 derived from H₈-BINOL derivative has been further studied for the direct Mannich reactions between *in situ* generated *N*-aryl imines and ketones (Scheme 3). The authors have proposed TS-1 for the acid-promoted enolization of the ketone and its addition to the protonated aldimine.

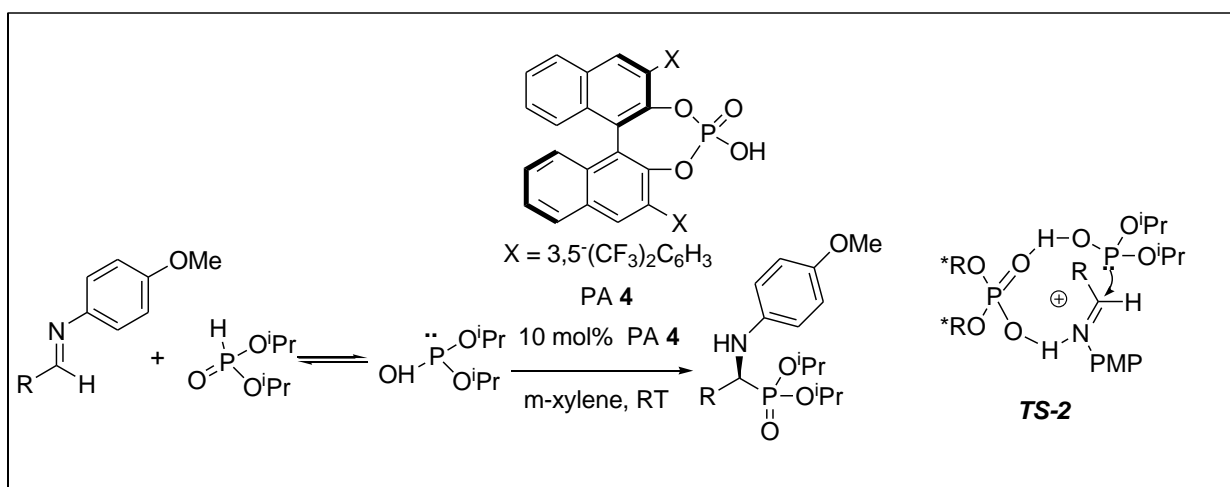


Examples:

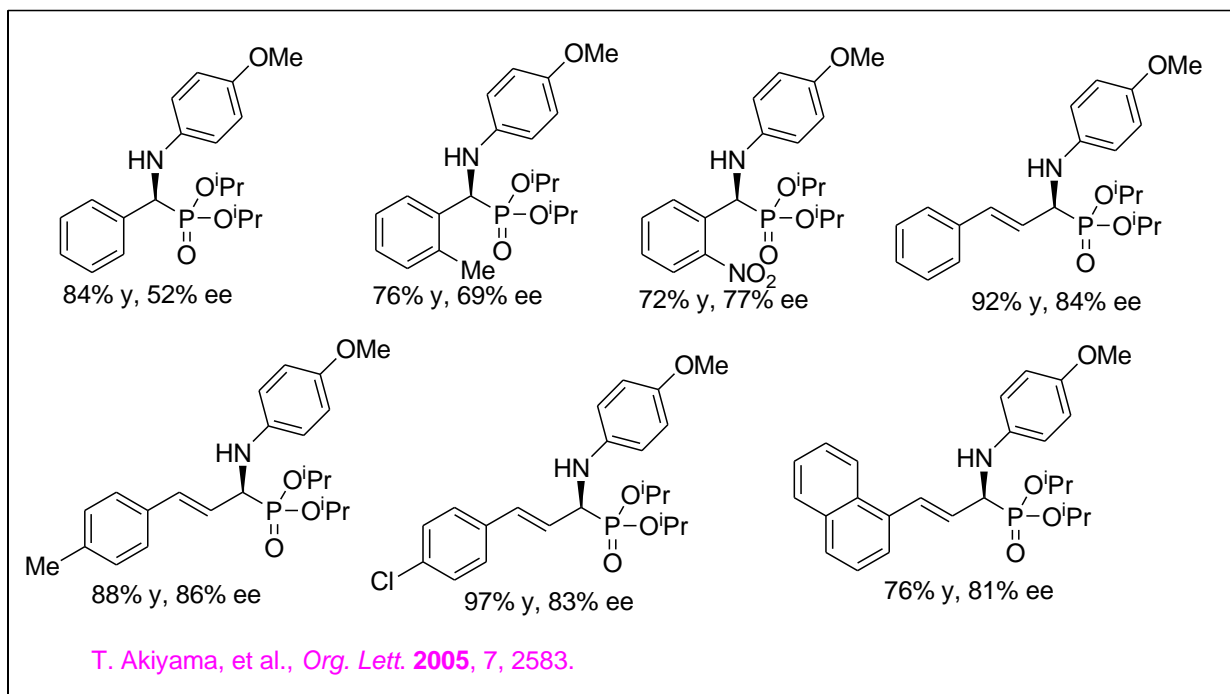


Scheme 3

Hydrophosphorylation of aldimines with dialkyl phosphate has been studied using PA **4** to afford optically active α -amino phosphonates in good to high yields and enantioselectivities (Scheme 4). The proposed transition state is shown in TS-2, where PA **4** acts as a bifunctional catalyst: the OH in phosphoric acid activates the aldimine as Brønsted acid and the phosphoryl oxygen activates the nucleophile as a Lewis base, thereby orienting both nucleophile and electrophile.



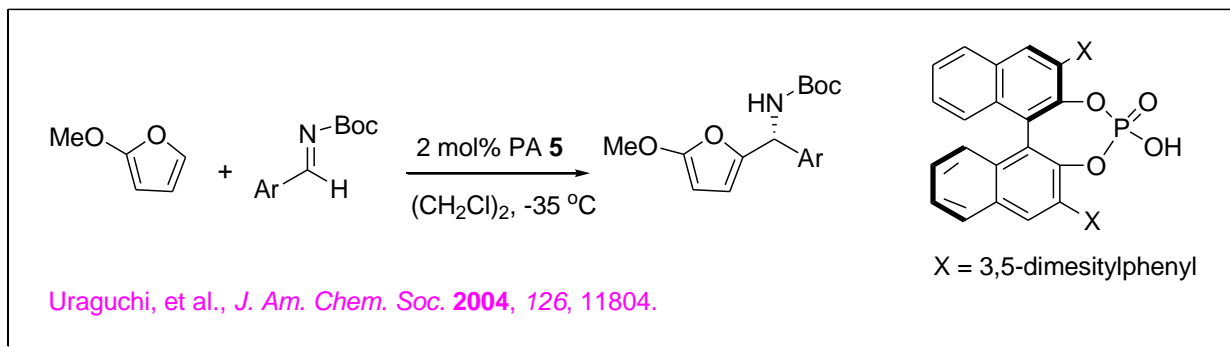
Examples:



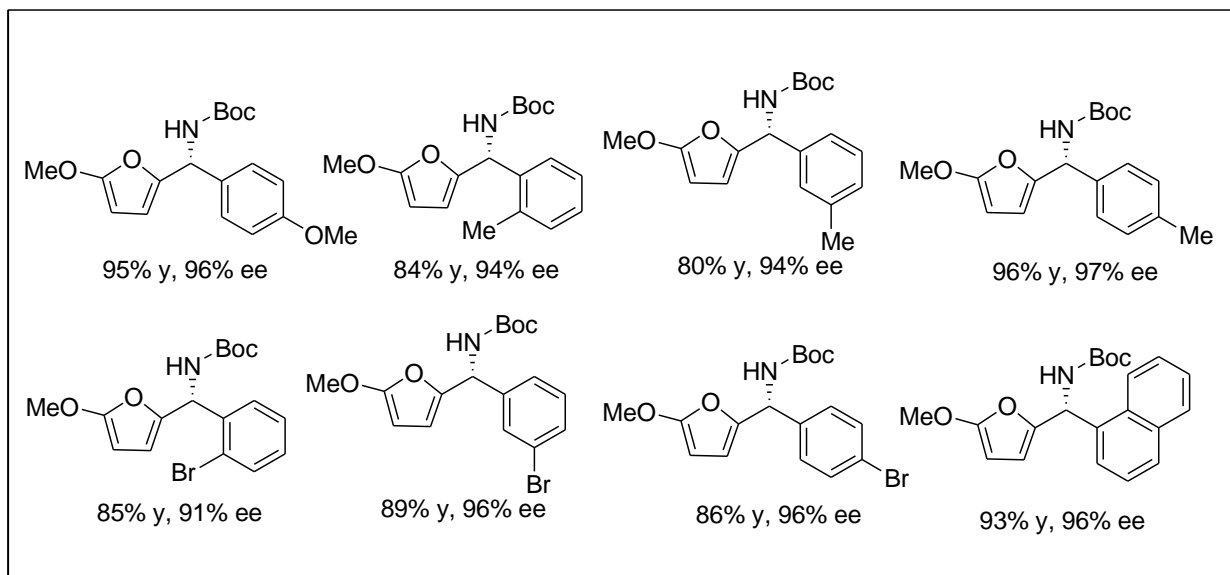
Scheme 4

1.4.3 Aza-Friedel-Crafts Reactions

The first organocatalytic aza-Friedel-Crafts reaction of aldimines has been accomplished using PA **5** (Scheme 5). It is important to note that *N*-boc-protected aryl imines having electron-donating or –withdrawing groups at either the *ortho*-, *meta*-, or *para*- positions are compatible with the reaction condition.

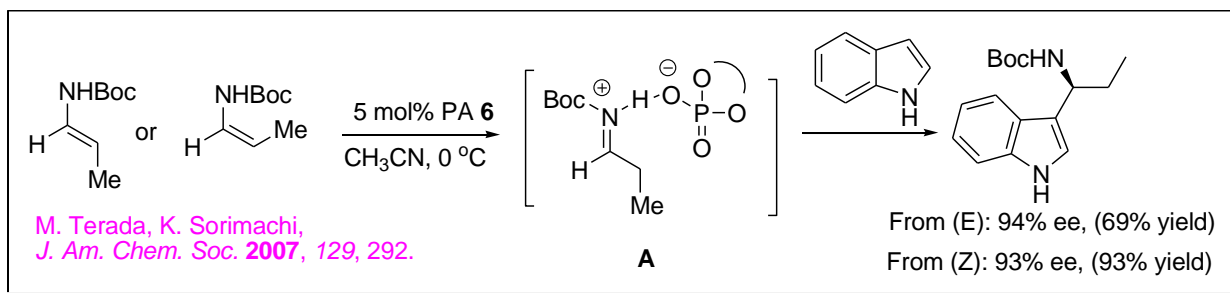


Examples:

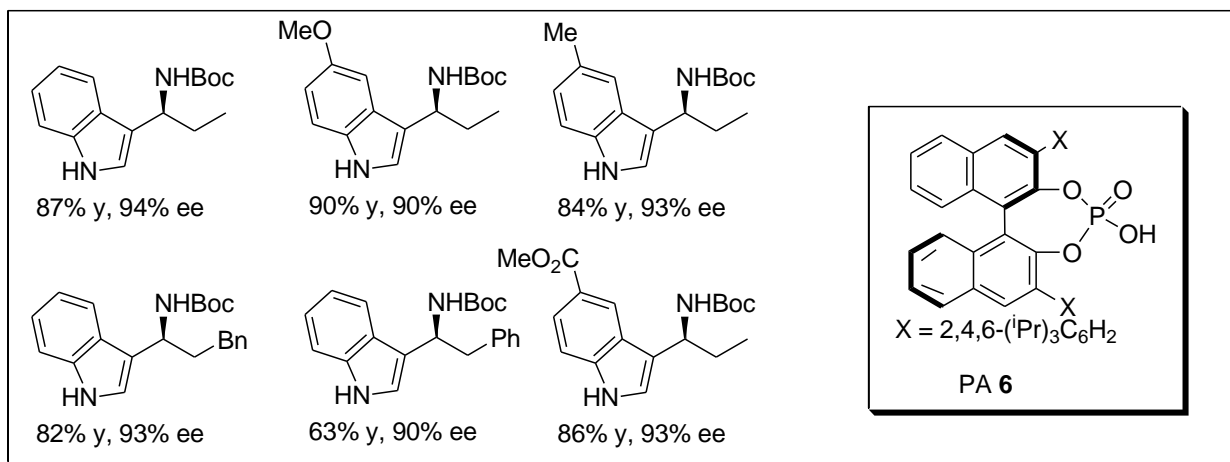


Scheme 5

The reaction of indoles with encarbamates has been successfully accomplished in the presence



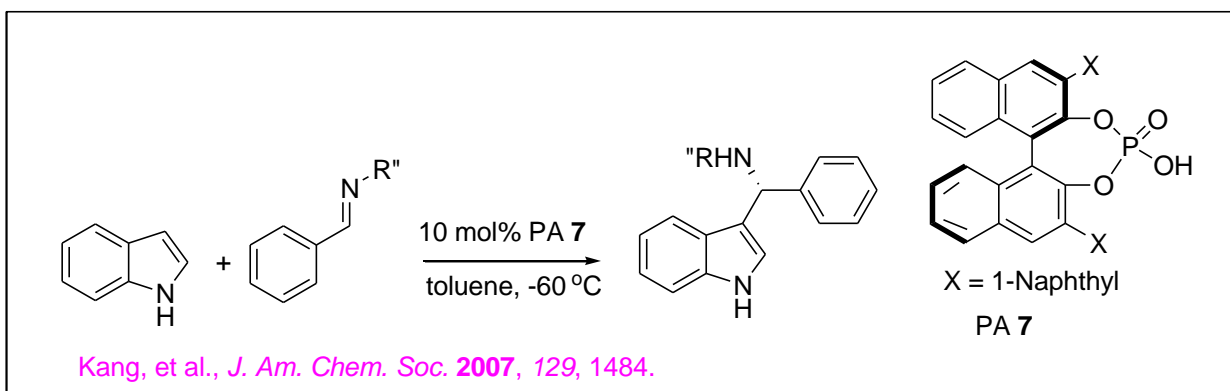
Examples:



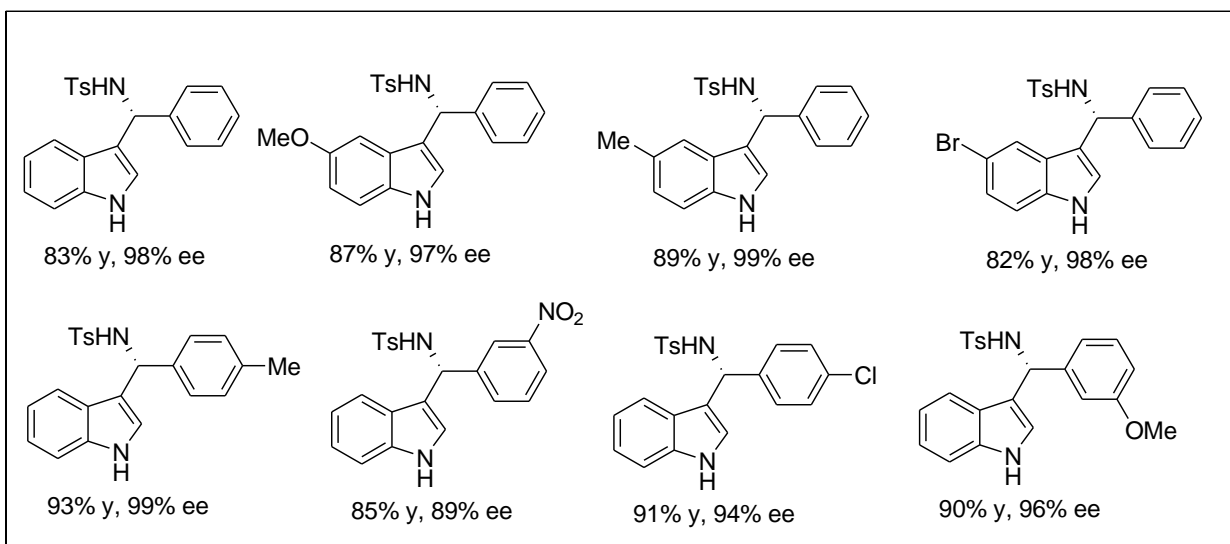
Scheme 6

of PA **6** (Scheme 6). Use of either pure regioisomers (*E*) or (*Z*)-enecarbamate gives the same product with similar enantioselectivities. Thus, the reaction is believed to take place via a common intermediate **A** that could be generated by the protonation of the enecarbamates.

The reactions of indole with a wide range of imines, derived from aromatic aldehydes, have been demonstrated using PA **7** with excellent enantioselectivities (Scheme 7).

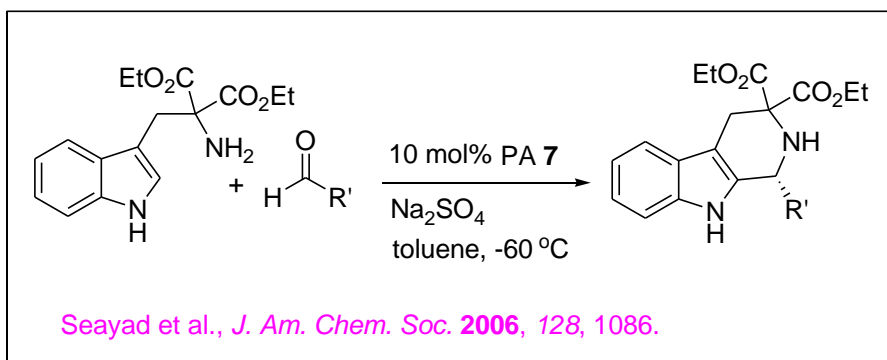


Examples:

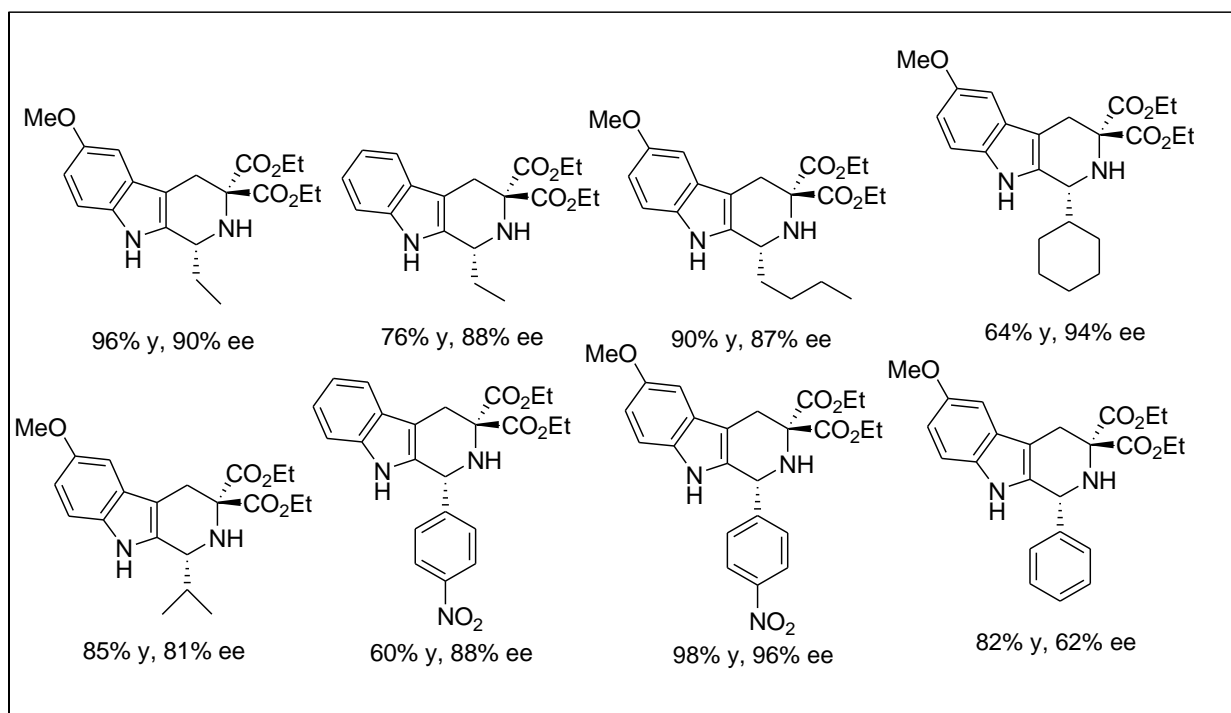


Scheme 7

The Pictet-Spengler reaction of *N*-tritylsulfonyl tryptamines with various aliphatic and aromatic aldehydes has been accomplished using PA **7** (Scheme 8). The sulfonyl substituent stabilizes the intermediate iminium ion and favours the Pictet-Spengler cyclization compared to the undesired enamine formation.



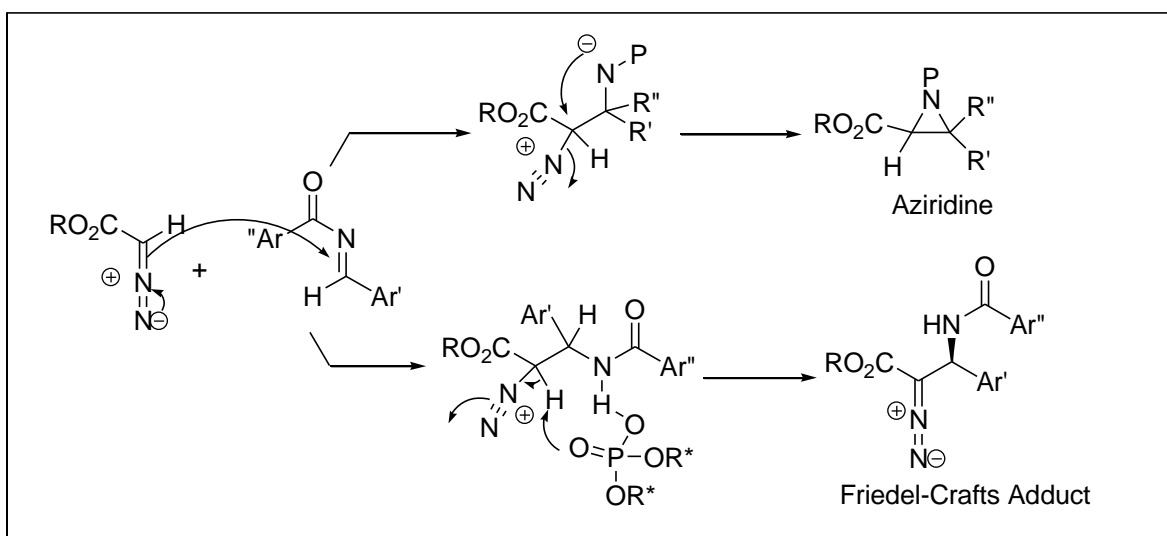
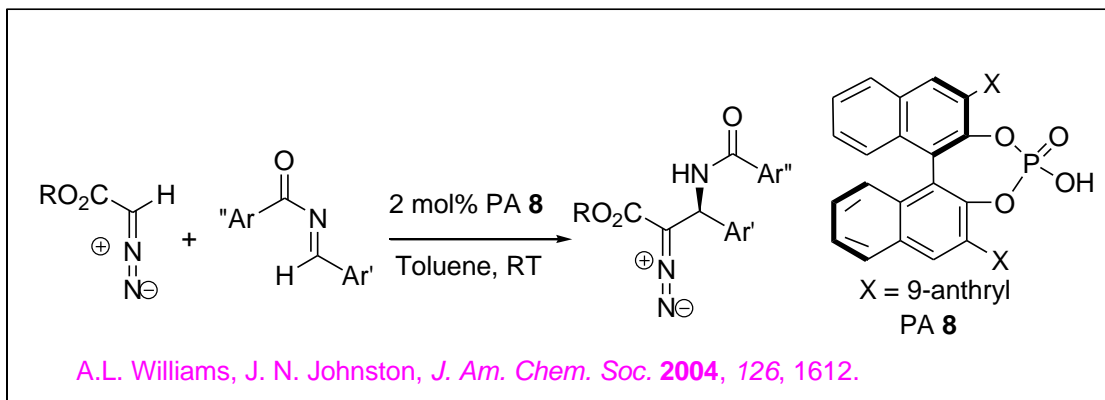
Examples:



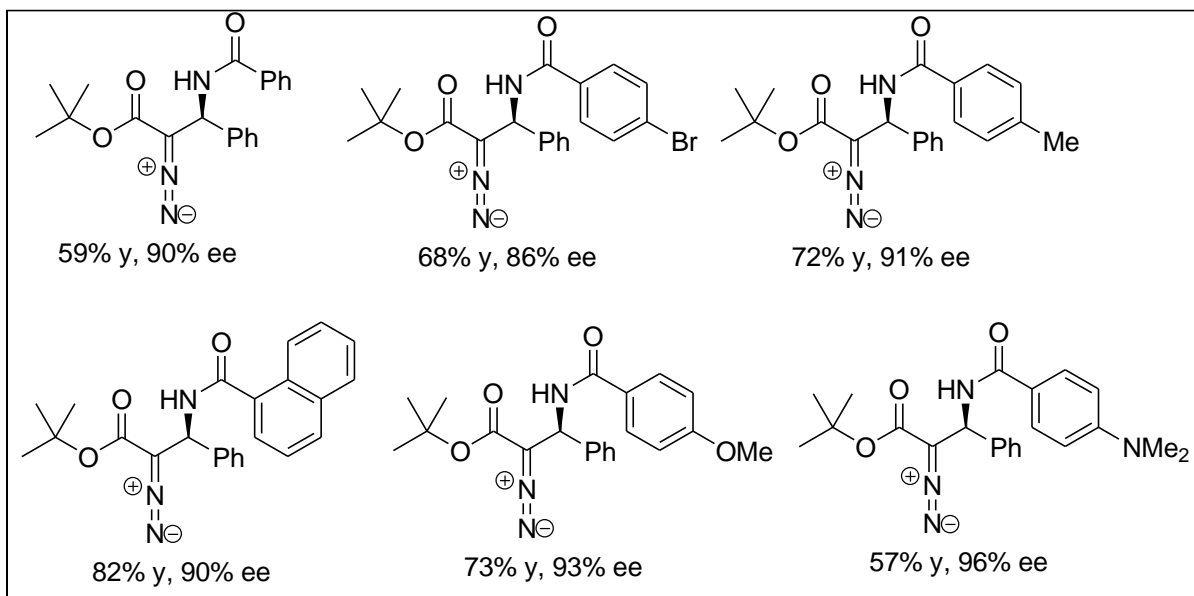
Scheme 8

The quite interesting alkylation of α -diazoesters with *N*-acyl imines has been shown using PA **8** with high enantioselectivities (Scheme 9). Diazoacetate is generally used in aziridine formation in the presence of Lewis acidic and Brønsted acidic conditions. Under these conditions, the competing aziridine formation has been eliminated by decreasing nucleophilicity of resulting amine

intermediates and thus, the Friedel-Crafts adduct could be formed via C-H bond cleavage by the phosphoryl oxygen of phosphoric acid.



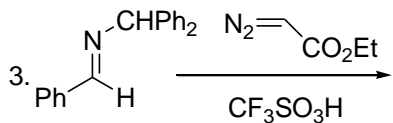
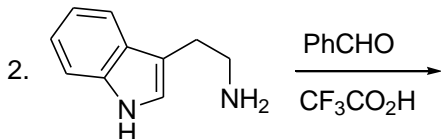
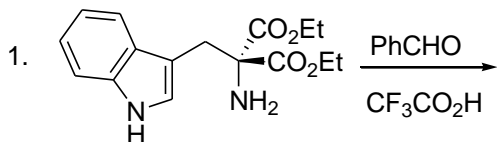
Examples:



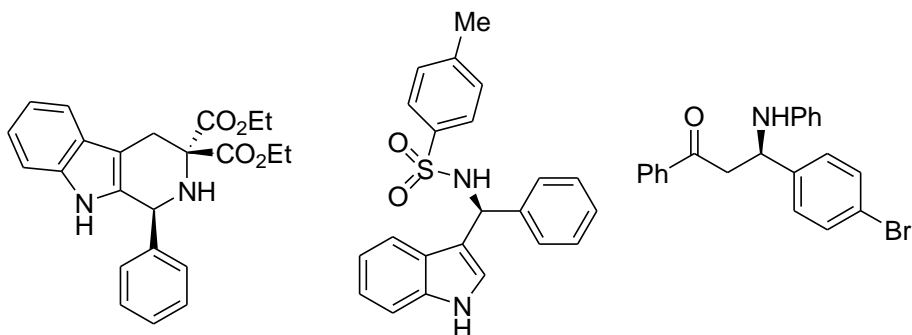
Scheme 9

Problems

A. What major products would you expect from the following reactions?



- B. Write synthetic routes for the following compounds using chiral phosphoric acid catalysts.



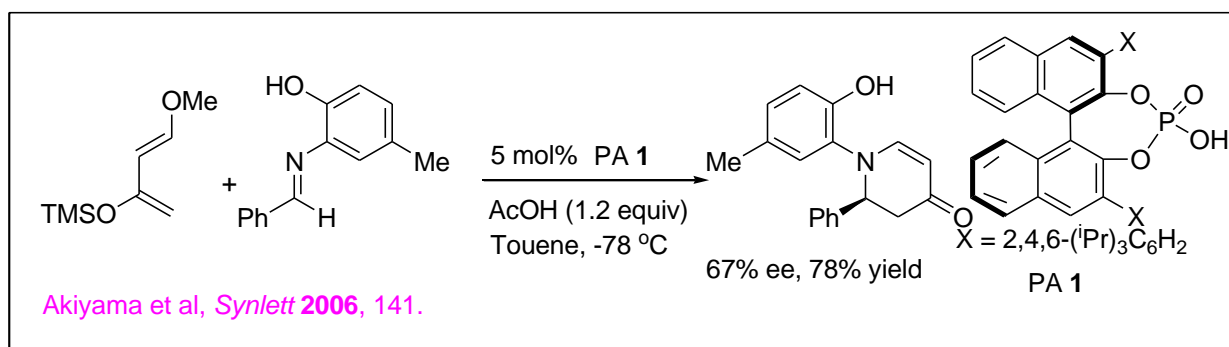
Reference

- I. Ojima, *Catalytic Asymmetric Synthesis*, John Wiley & Sons, New Jersey, 2010.

Lecture 4 Reactions Using Chiral Phosphoric Acids II

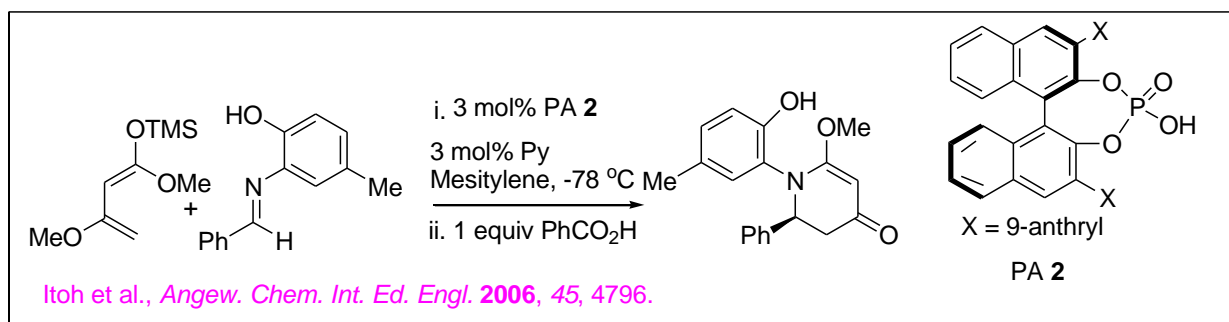
1.4.4 Diels-Alder Reaction

Chiral phosphoric acids (PAs) are excellent catalysts for the Diels-Alder reaction. For examples, the aza-Diels Alder reaction of Danishefsky's diene with aldimines is effective using PA **1** with good enantioselectivities (Scheme 1). The addition of acetic acid leads to increase significantly the yield and enantioselectivities.



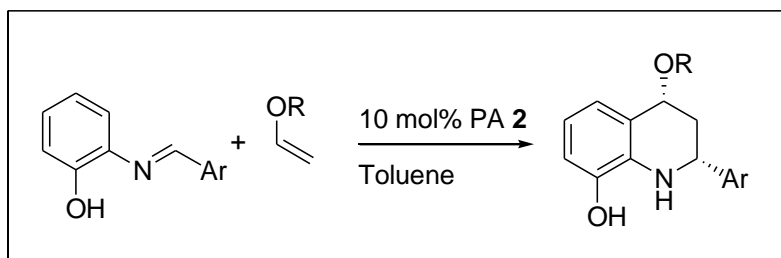
Scheme 1

Although the aza-Diels Alder reaction of Brassard's diene using a Brønsted acid is rare due to the lability of the diene in the presence of a strong Brønsted acid, PA **2** has been found to be an effective catalyst for the aza-Diels Alder reaction of Brassard's diene (Scheme 2). The yield of the product could be improved using the pyridinium salt of the phosphoric acid as catalyst.

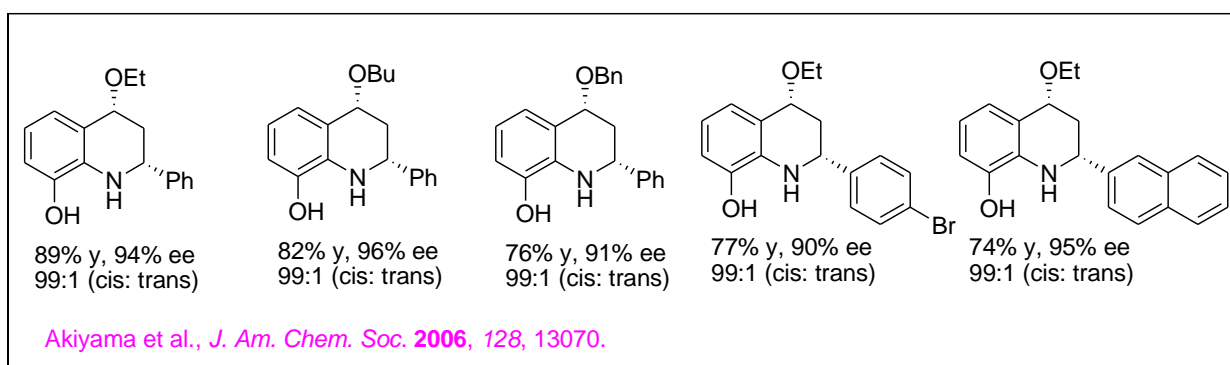


Scheme 2

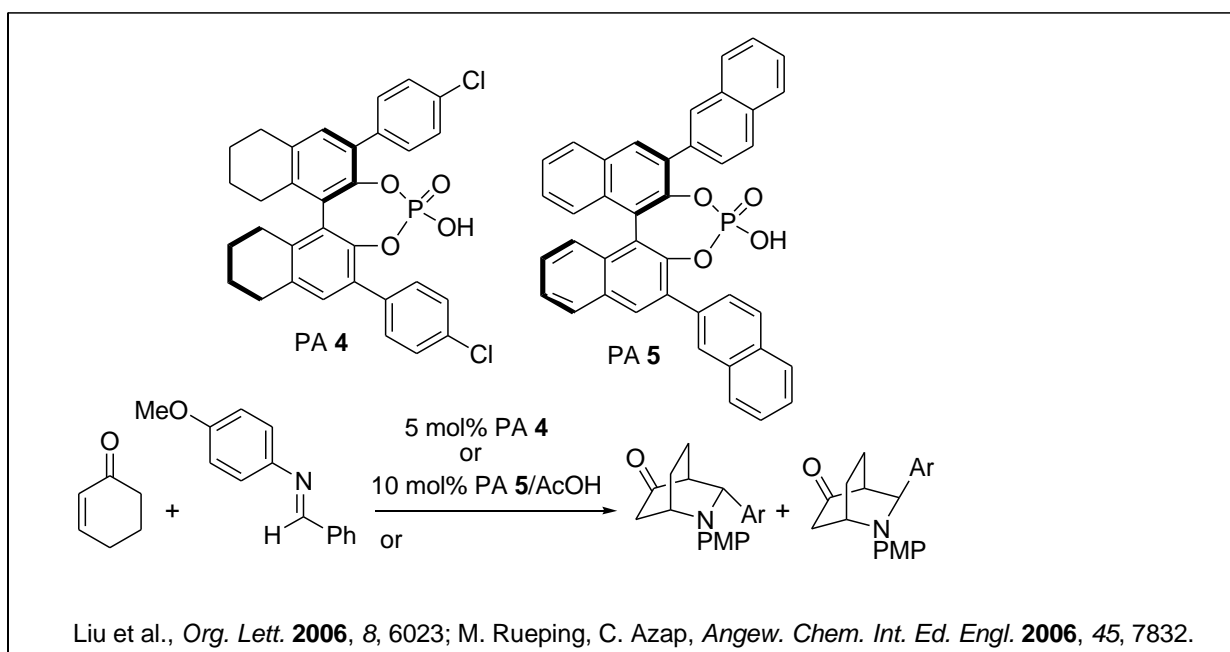
The PA **2** has also been found to be effective for the inverse electron-demand aza-Diels-Alder reaction of electron-rich alkenes with 2-aza dienes with excellent enantioselectivities (Scheme 3). The presence of OH group is crucial for the *cis* selectivity in the products.



Examples:



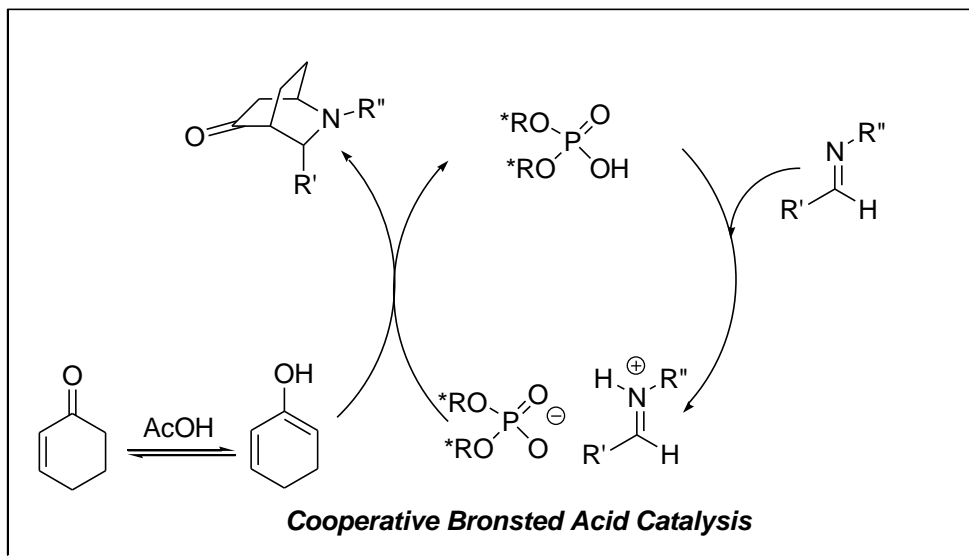
Scheme 3



Liu et al., *Org. Lett.* **2006**, *8*, 6023; M. Rueping, C. Azap, *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 7832.

Scheme 4

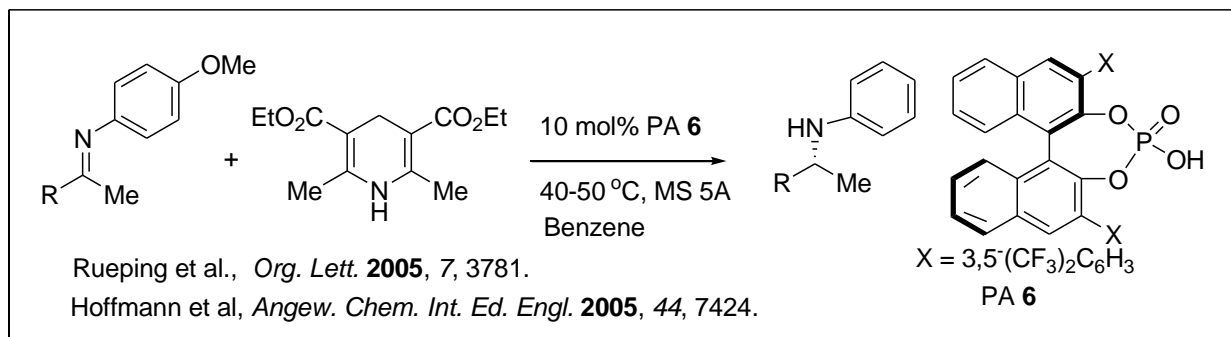
The aza-Diels Alder reaction of aldimines with cyclohexenone has been accomplished using either PA **4** or PA **5**/AcOH (Scheme 4). A cooperative catalytic is proposed for the reaction using PA **5**/AcOH, where both the activation of an electrophile and a nucleophile takes place cooperatively (Scheme 5)



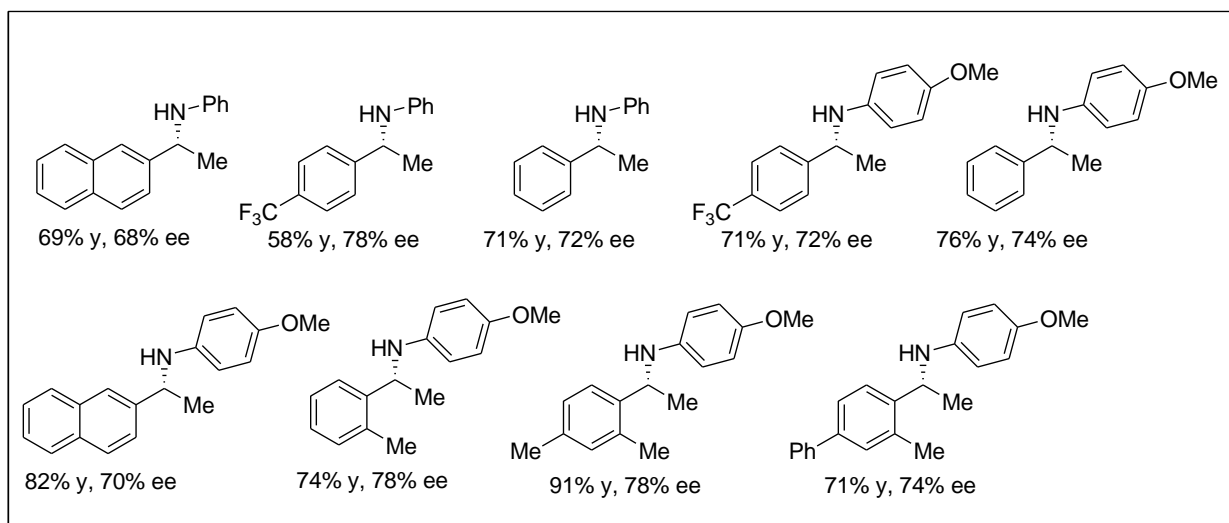
Scheme 5

1.4.5 Transfer Hydrogenation

Chiral phosphoric acids (PAs) are effective catalysts for the biomimetic hydrogenation using Hantzsch ester as a hydride source. For examples, the reduction of ketimines using Hantzsch ester can be accomplished using PA **6** with good yield and enantioselectivities (Scheme 6). PA **1** bearing bulky 2,4,6-(i-Pr)₃C₆H₃ at the 3,3'-positions of BINOL is found to superior to PA **6** for this purpose.

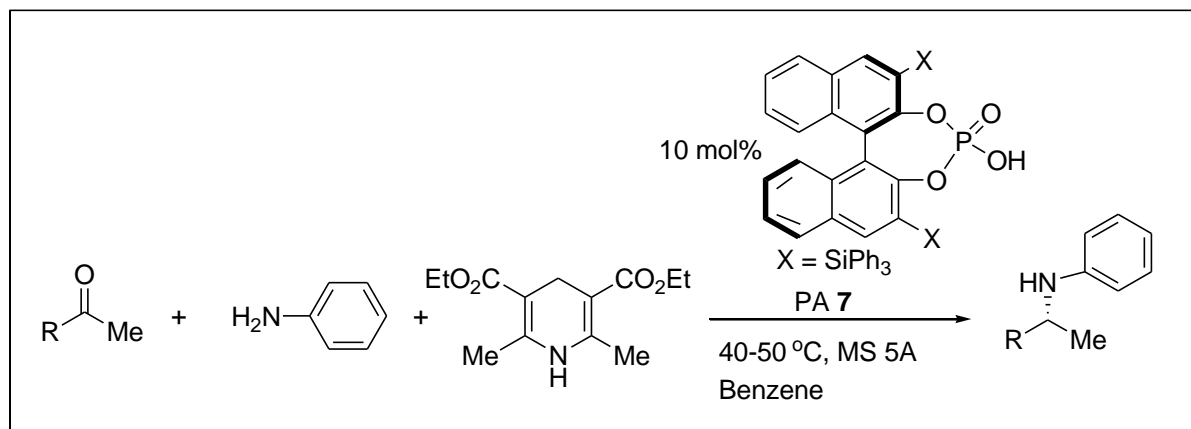


Examples:

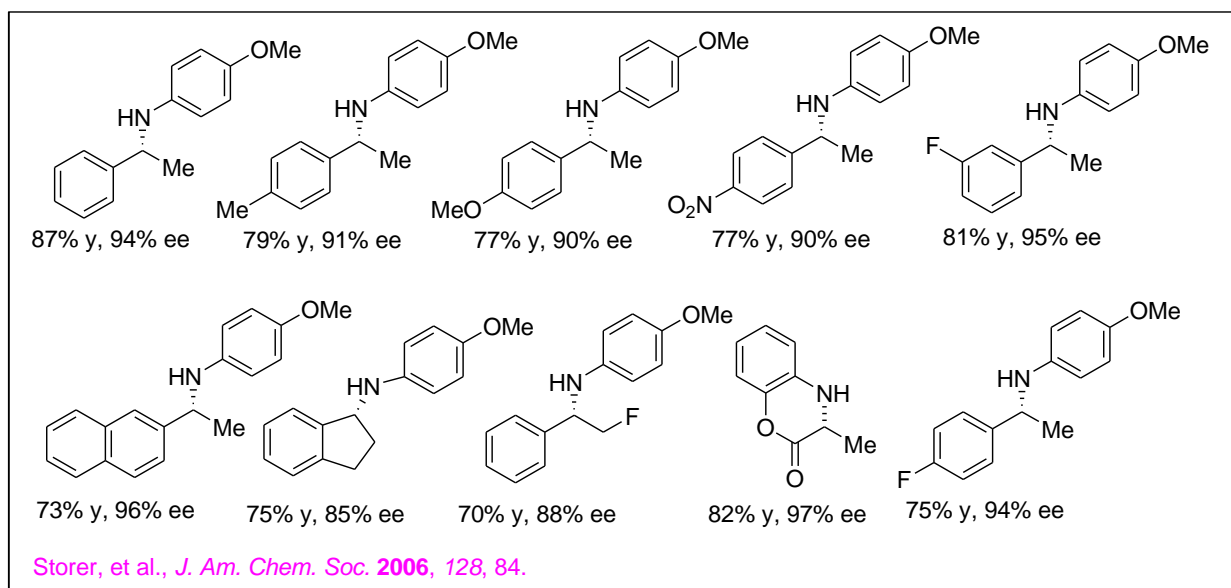


Scheme 6

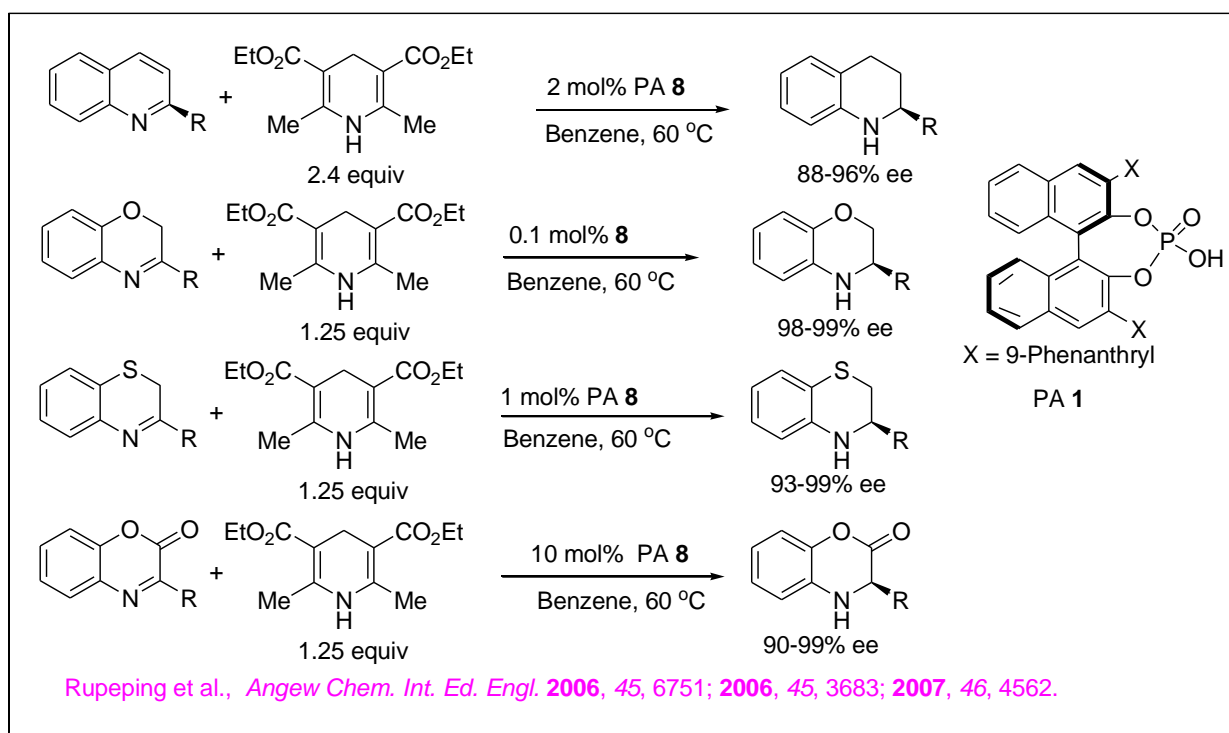
A three-component reductive amination reactions starting from ketones, amines and Hantzsch ester can be accomplished using PA 7 with excellent yield and enantioselectivities (Scheme 7). This method is also compatible for the reactions of methyl phenyl ketones as well as methyl alkyl ketones.



Examples:



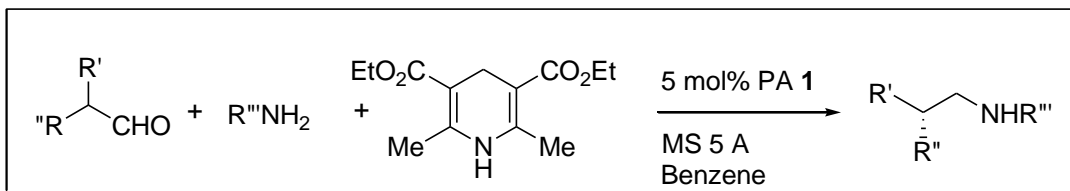
Scheme 7



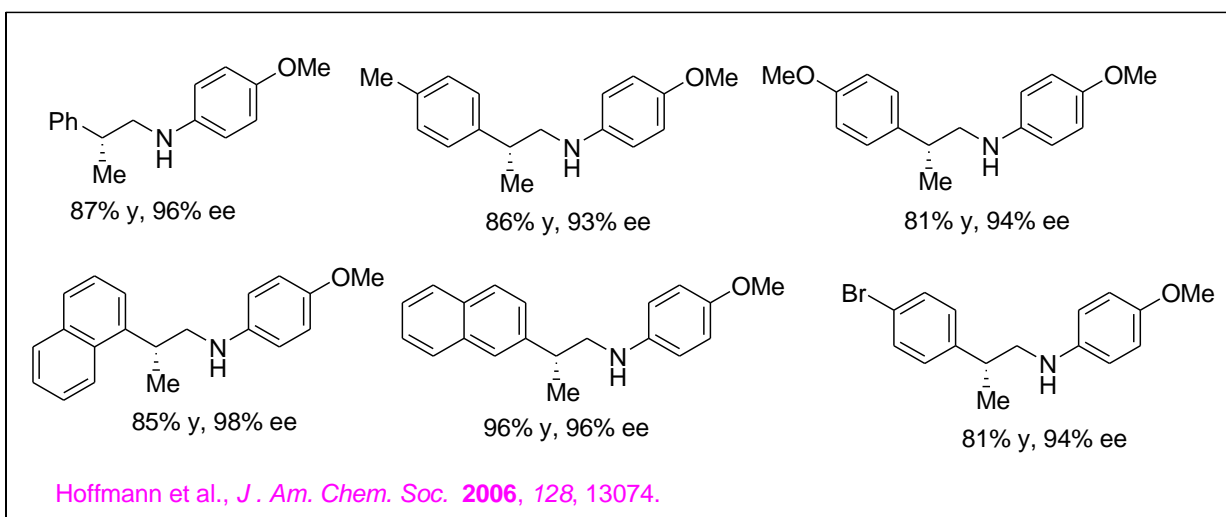
Scheme 8

Following these initial studies, the reduction of wide of range of heterocycles has been explored. For examples, the reduction of a series of substituted quinonlines, benzoxazines, benzothiazines and benzoxazinones can be accomplished using PA **8** with excellent enantioselectivities (Scheme 8)

Asymmetric reductive amination of α -branched aldehydes and *p*-anisidine with Hantzsch ester can be performed employing PA **1** with high enantioselectivities (Scheme 9). The observed results suggest that the reaction proceeds via a dynamic kinetic resolution (Scheme 10).

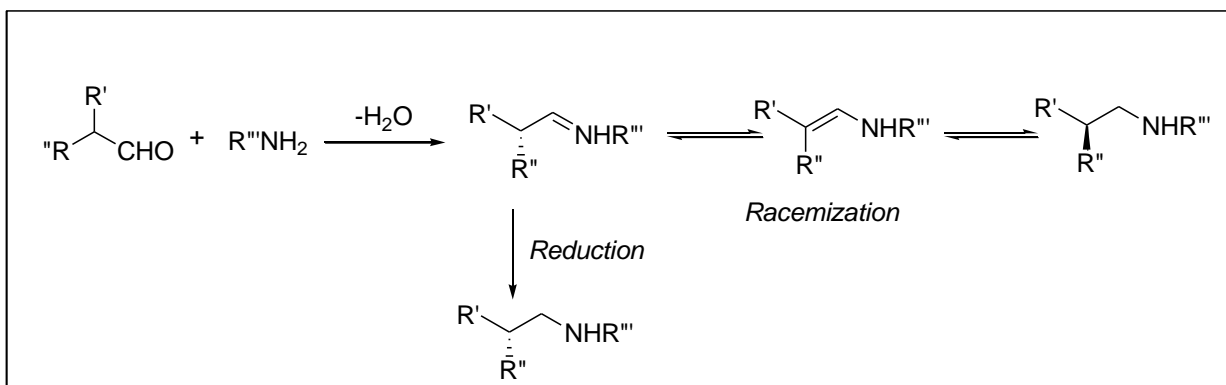


Examples:



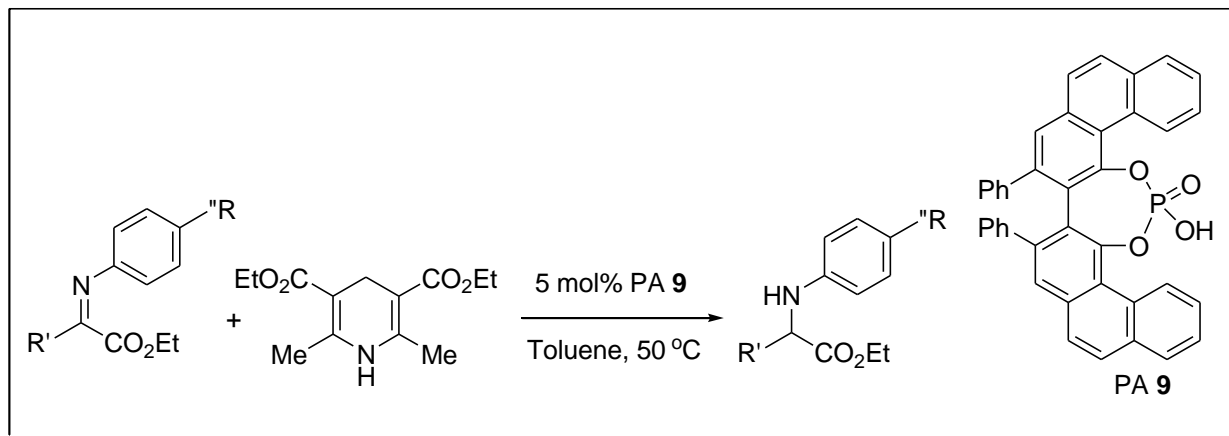
Scheme 9

Proposed Mechanism

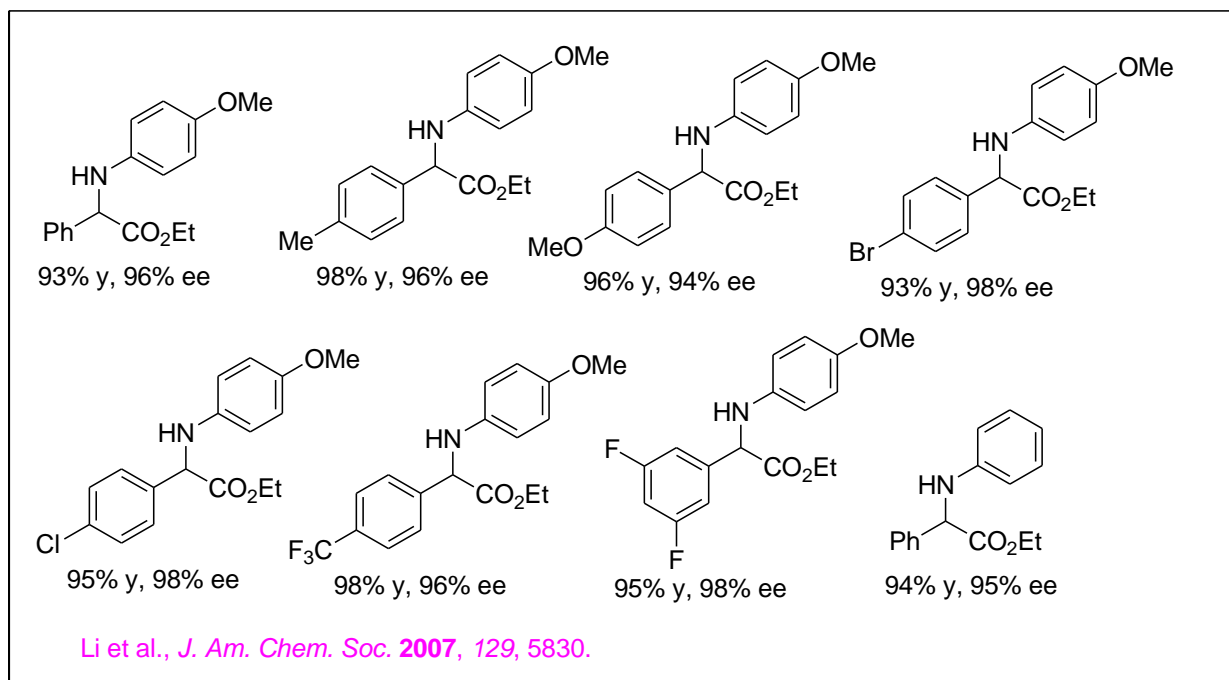


Scheme 10

Chiral phosphoric acid PA **9** derived from (*S*)-VAPOL is found to be superior to PAs derived from BINOL for the reduction of α -imino esters using Hantzsch ester to afford α -amino esters with higher enantioselectivities (Scheme 11).



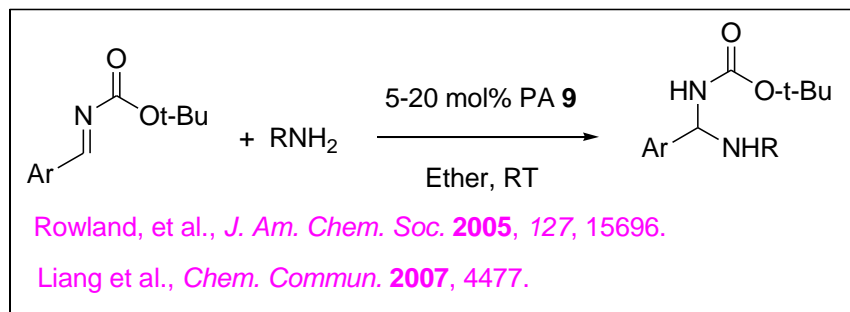
Examples:



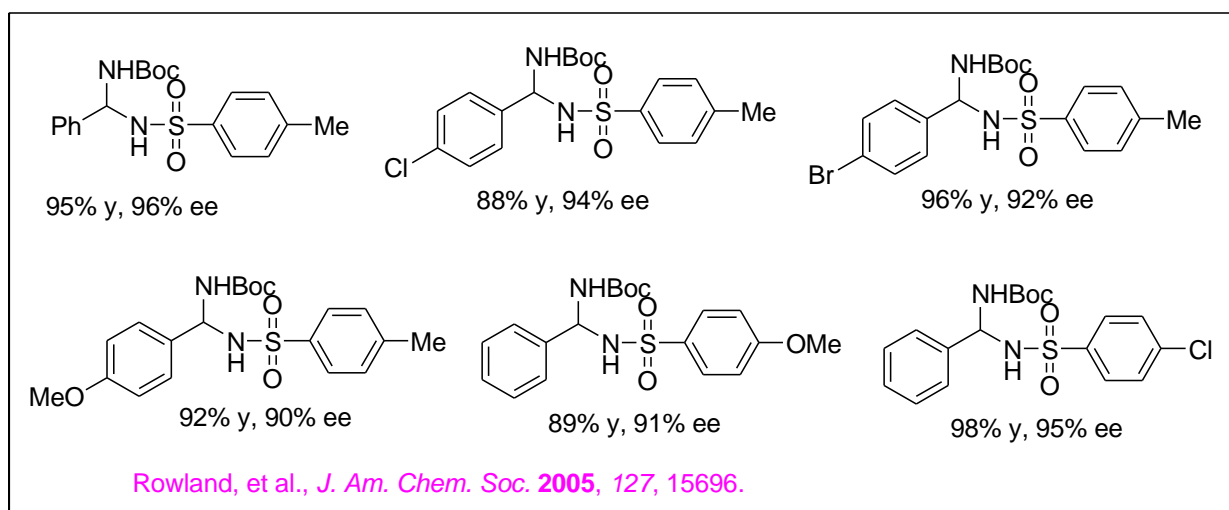
Scheme 11

1.4.6 Mannich-type Reaction

The utility of PA **9** has been further extended as excellent catalyst for the addition of nitrogen nucleophiles such as sulfonamides and imides to imines to give protected amins (Scheme 12). The procedure has wide substrate scope to give the target products in 73-99% ee and 80-99% yield.



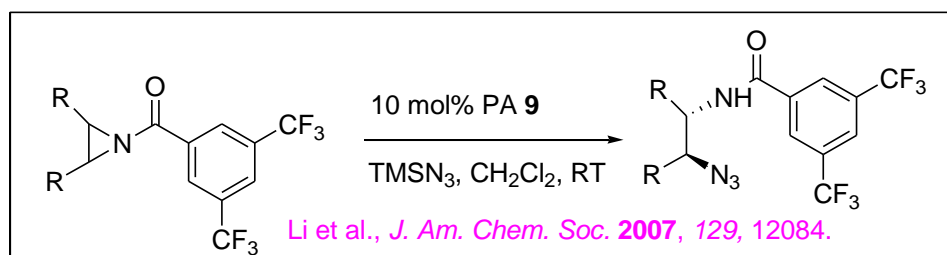
Examples:



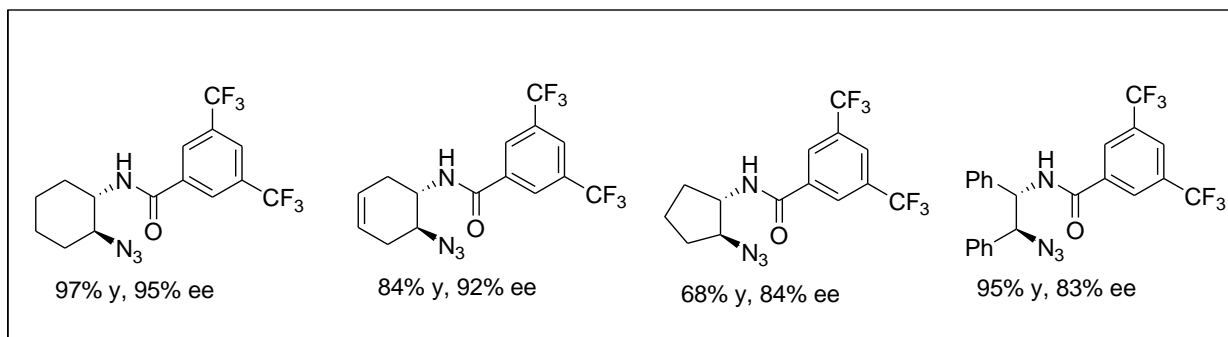
Scheme 12

1.4.7 Asymmetric Desymmetrization of meso-Aziridines

The application of PA **9** has been further extended to ring opening of *meso*-pyridines. This is the first example of organocatalytic desymmetrization of *meso*-aziridines. The substrates having electron-withdrawing protecting groups on the nitrogen proceed reaction with enhanced yields and enantioselectivity of the products (Scheme 13).



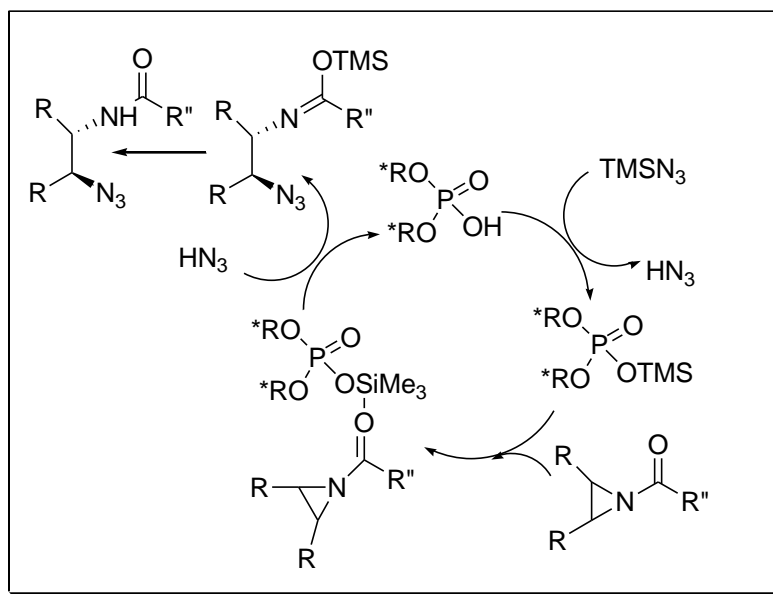
Examples:



Scheme 13

Proposed Mechanism

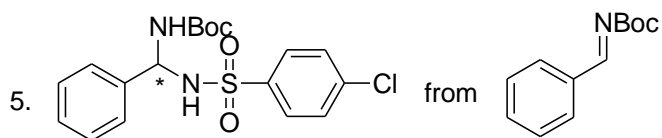
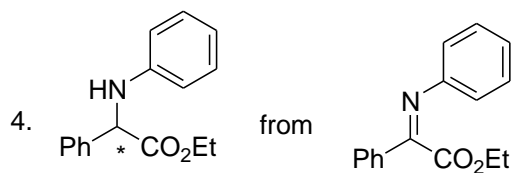
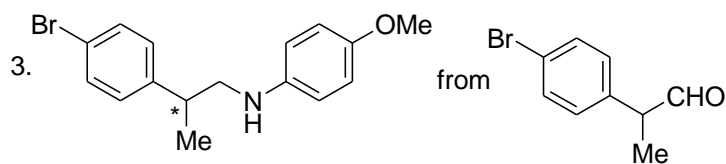
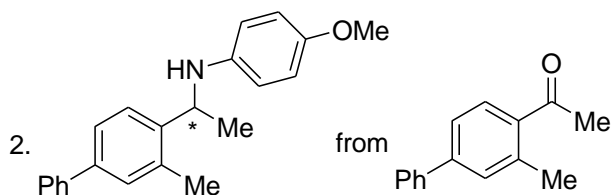
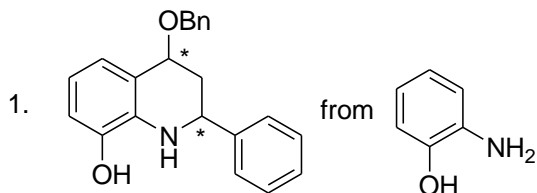
The phosphoric acid first reacts with TMSN_3 to give silylated phosphoric acid as the active catalyst (Scheme 14). The latter activates the aziridine by coordination of its carbonyl group, and subsequent attack of azide affords the precursor of the product and regeneration of the phosphoric acid.



Scheme 14

Problems

How would you employ chiral phosphoric acids in the synthesis of the following?



Reference

- I. Ojima, *Catalytic Asymmetric Synthesis*, John Wiley & Sons, New Jersey, 2010.