CATALYTIC ASYMMETRIC SYNTHESIS

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Book: Catalytic Asymmetric Synthesis (Punniyamurthy)

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CHAPTER OVERVIEW

1: Reactions using Chiral Lewis Acids and Brønsted Acid

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.

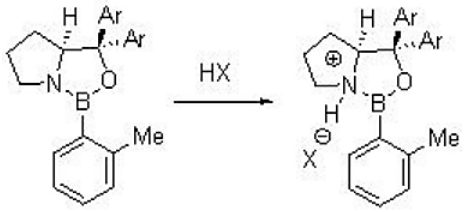
1.1: Brønsted Acid-Assisted Lewis Acid (BLA)

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.

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:

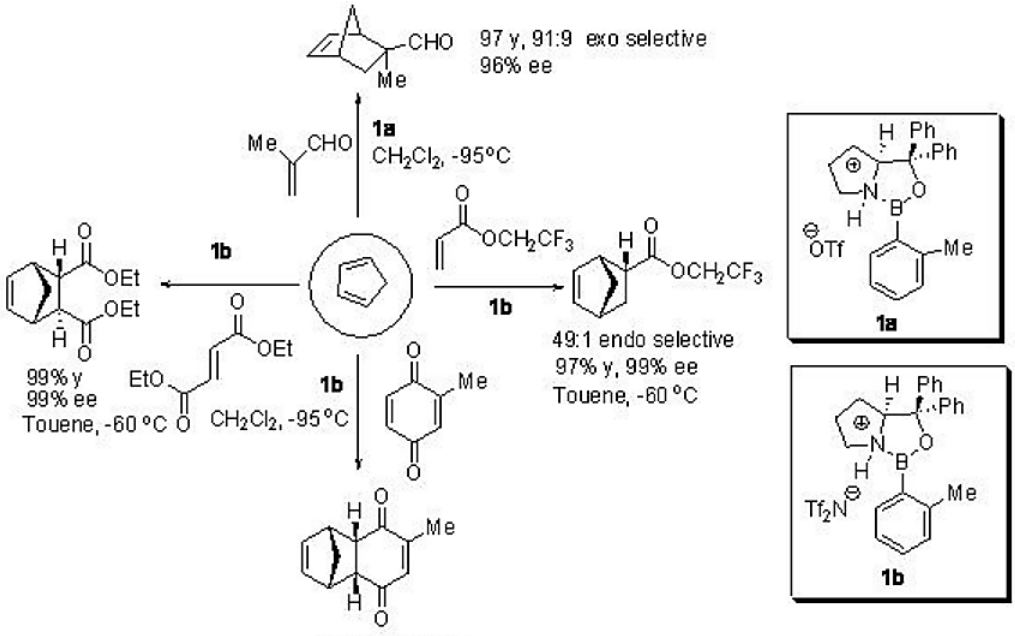
1.1.1: Diels Alder Reaction

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 (Tf_2 NH) (Scheme 1.1.1).

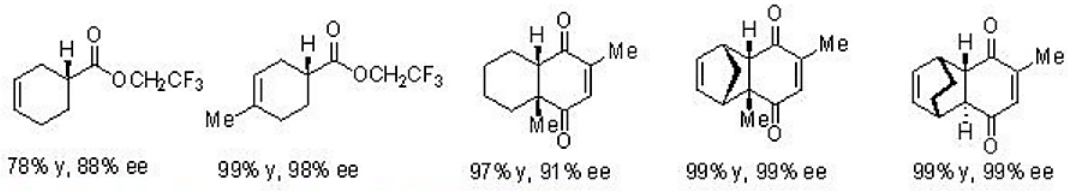


Scheme 1.1.1

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 1.1.2). The stereochemical outcome can be predicted using the transition state assemblies shown in Scheme 1.1.3. The face selectivity of α -substituted α,β -unsaturated enals is found to be opposite to α,β -unsaturated ketones, esters, and acrylic acids.

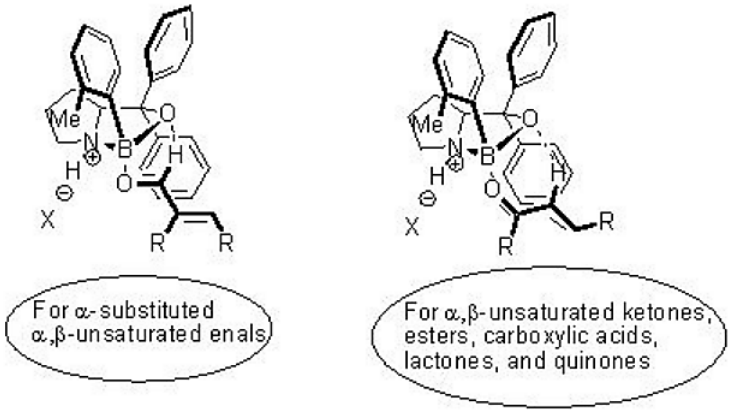


*Examples using **1b** :*

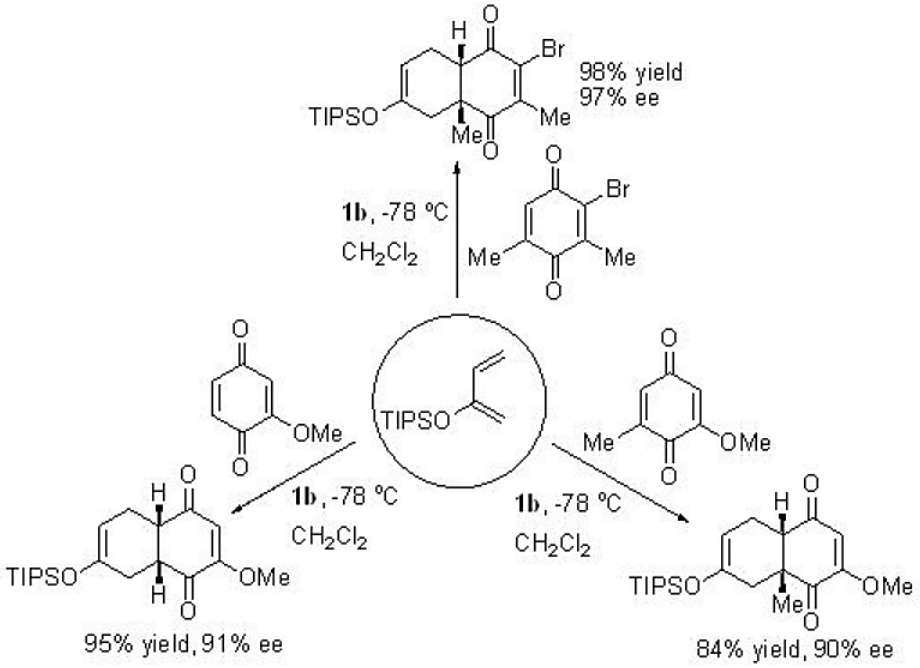


D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 6388.

Scheme 1.1.2



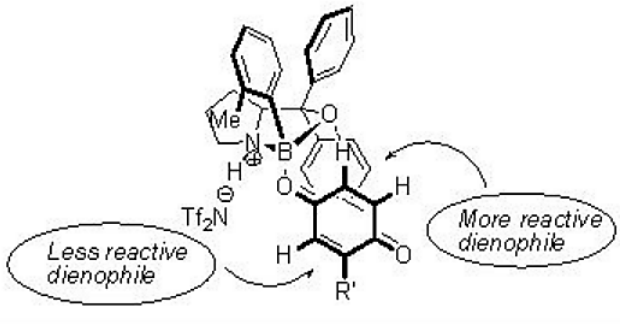
Scheme 1.1.3



Scheme 1.1.4

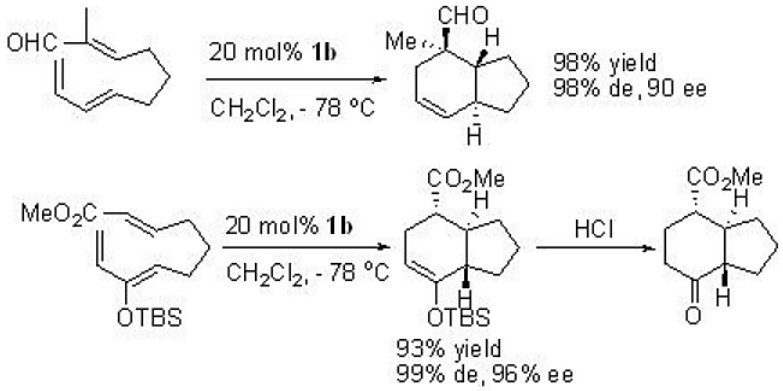
The chiral BLAs having counteranion triflimide (Tf_2N^-) provides remarkable catalytic stability compared to that bearing trilfate ($CF_3SO_3^-$). In addition, BLAs with triflimide are found to be versatile catalysts for wide range of Diels-Alder reactions. For examples, the reactions of the challenging unsymmetrical benzoquinones with 2-triisopropyloxy-1,3-butadiene has been shown with excellent enantio- and regioselectivities (Scheme 1.1.4).

The observed results suggest that the BLA coordination to the oxygen of unsymmetrical quinones takes place as shown in Scheme 1.1.5. The coordination predominately takes place with the more basic oxygen of the quinones.



Scheme 1.1.5

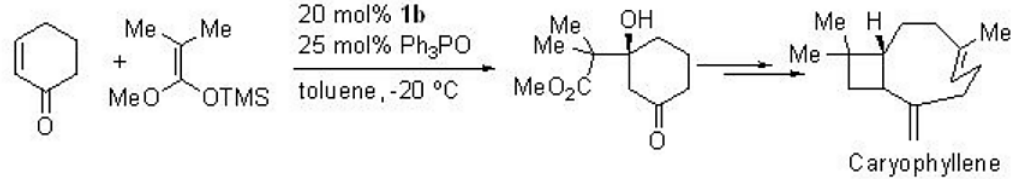
The catalytic system is also effective for intramolecular reactions to afford *trans* -fuzed bicyclic structures with excellent enantioselectivity (Scheme 1.1.6).



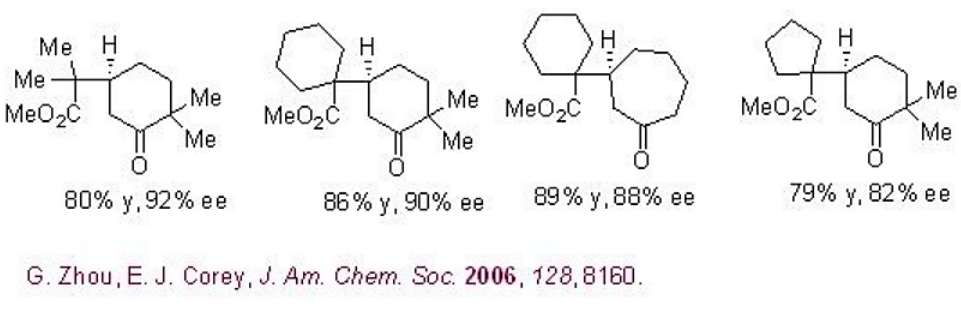
Scheme 1.1.6

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 cyclo hexenone with silyl ketene acetal to afford key intermediate for the enantioselective synthesis of caryophyllene (Scheme 1.1.7). The absolute stereochemical course of the reaction can be rationalized by the above proposed transition states.



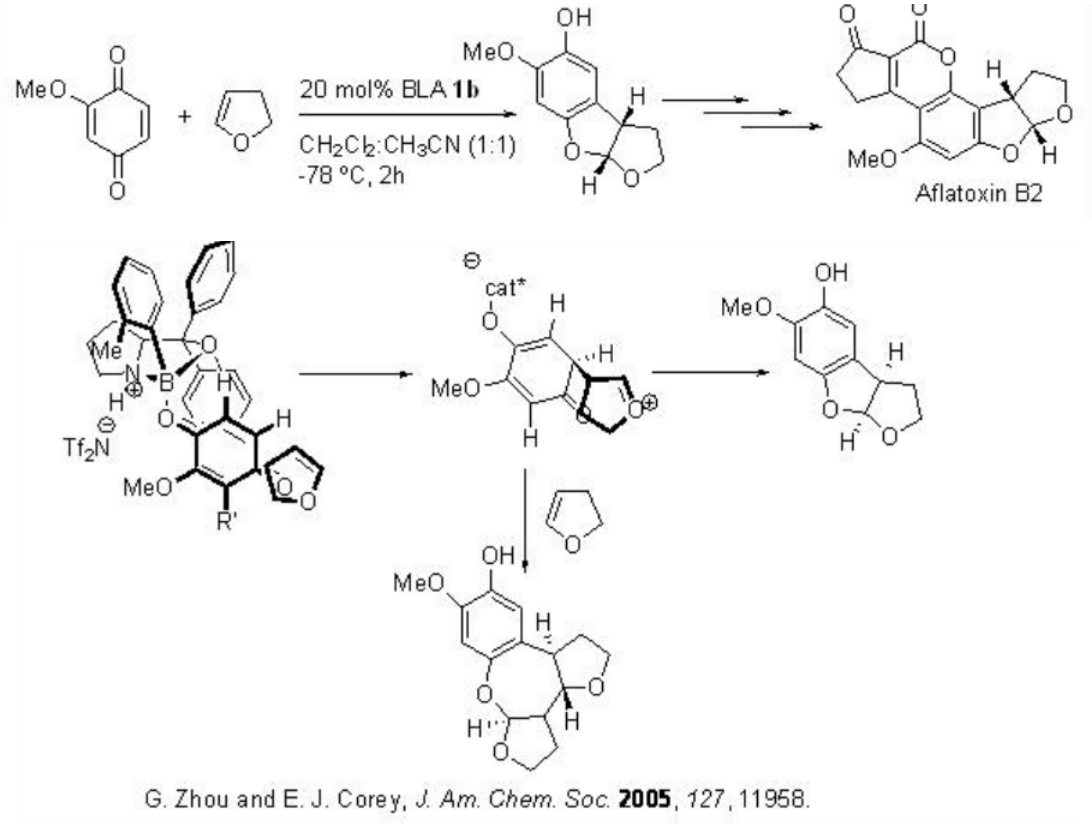
Examples:



***Scheme* 1.1.7**

[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 1.1.8).

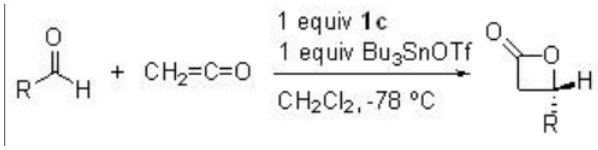


G. Zhou and E. J. Corey, *J. Am. Chem. Soc.* **2005**, *127*, 11958.

Scheme 1.1.8

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 1.1.9).



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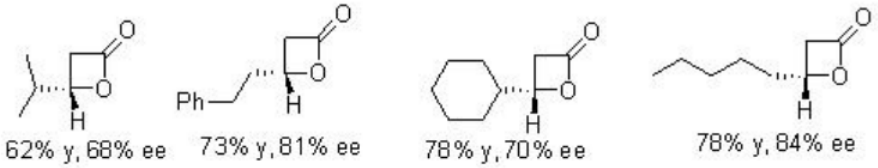
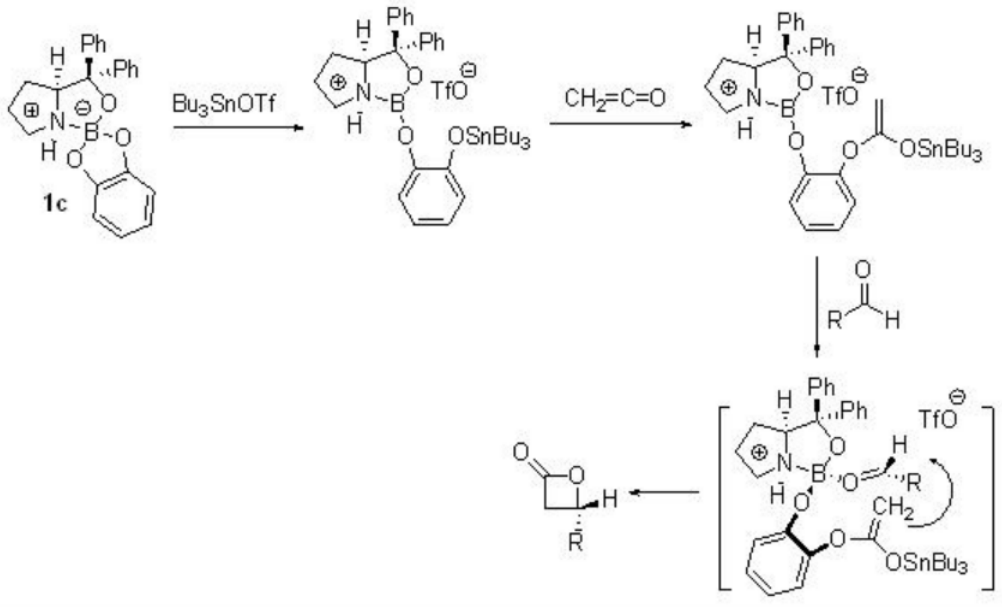


V. Gnanadesikin and E. J. Corey, *Org. Lett.* **2006**, *8*, 4943.

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 -

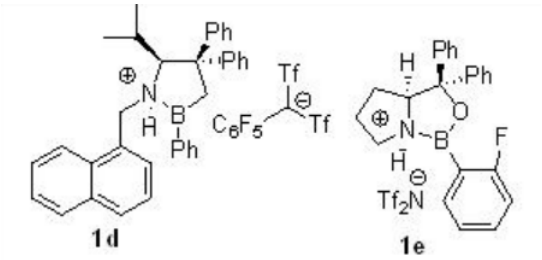
branched aldehydes has been demonstrated for the first time.



Scheme 1.1.9

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.

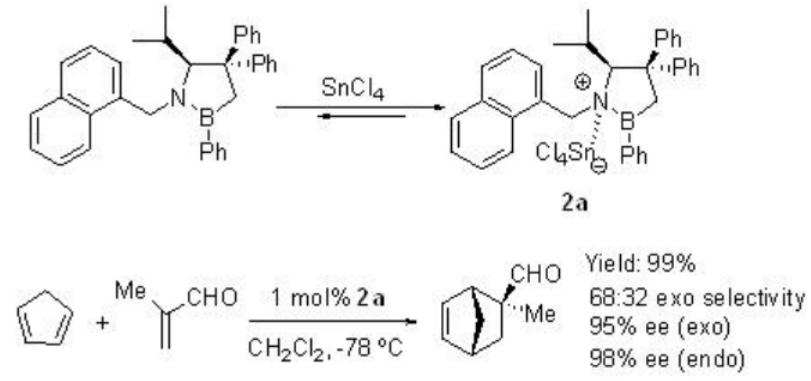


1.2: Lewis Acid-Assisted Lewis Acid (LLA)

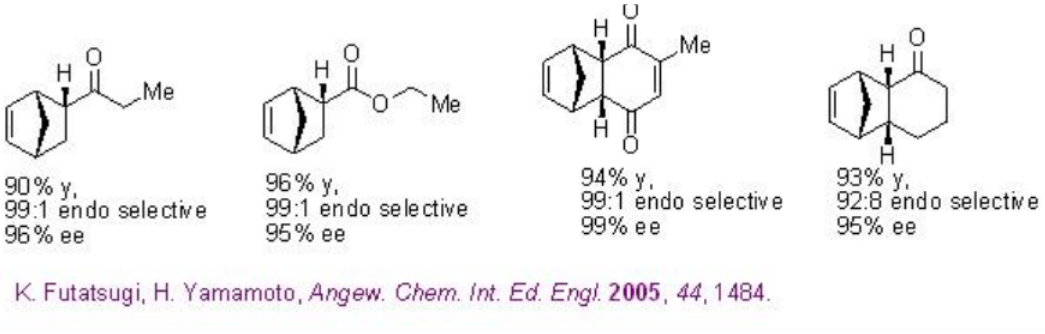
In Lewis acid assisted chiral Lewis acids (LLAs), achiral Lewis acid is added to activate chiral Lewis acid via complex formation. The reactivity of LLA is much greater compared to that of achiral Lewis acid, and thus, the latter's presence does not affect the selectivity of the reaction.

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 the for Diels-Alder reaction of wide range of substrates (Scheme 1.2.1). 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 $SnCl_4$.

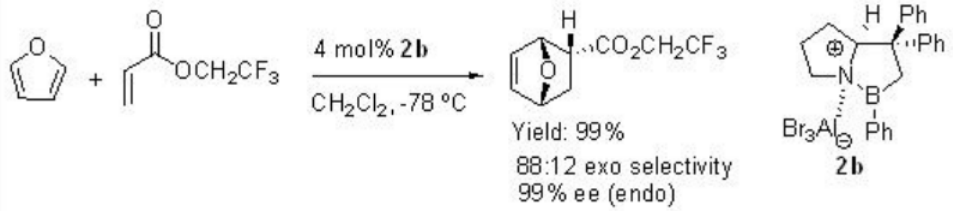


Additional examples:



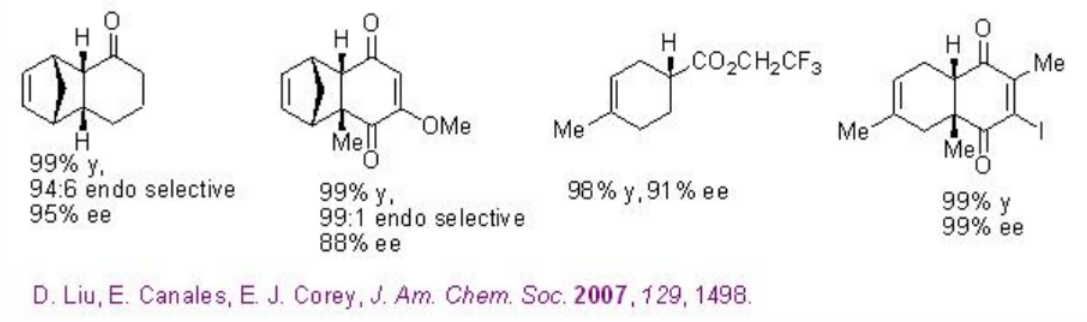
Scheme 1.2.1

The LLA **2b** , derived from the complexation of $AlBr_3$ with chiral oxazaborolidine, has been shown as useful catalyst for Diels-Alder reaction (Scheme 1.2.2). The observed results suggest that LLA **2b** is considerably is more efficient catalyst than the corresponding BLA **1a** or **1b** since 10-20 mol% of BLA is usually needed for the optimum results.



Scheme 1.2.2

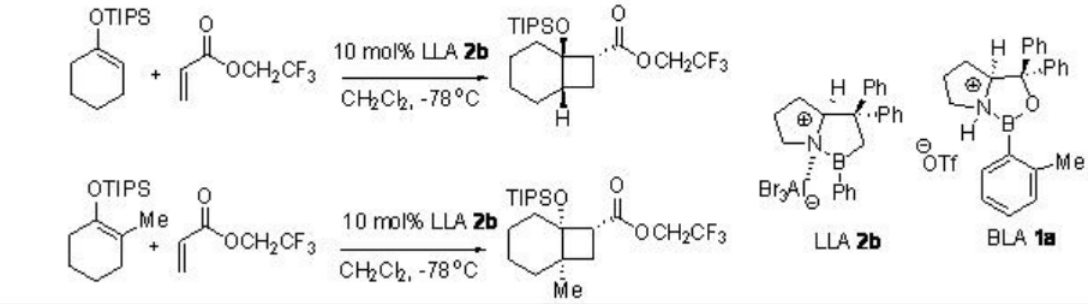
Additional examples:



Scheme 1.2.3

[2+2]-Cycloaddition

The utility of LLA **2b** has been further extended to [2+2]-cycloaddition reactions of trifluoroethyl acrylate with enol ethers (Scheme 1.1.1). The protonated BLA **1a** was found to 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 1.1.3, Lecture 1.



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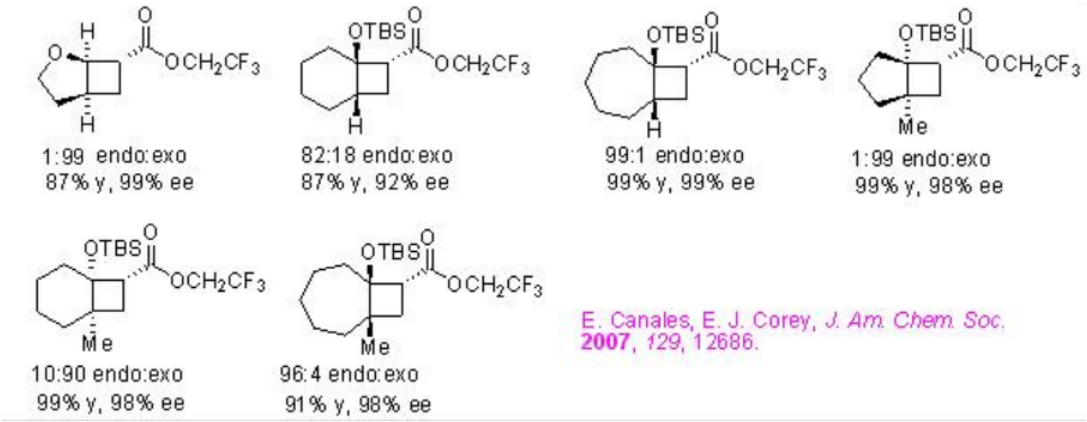
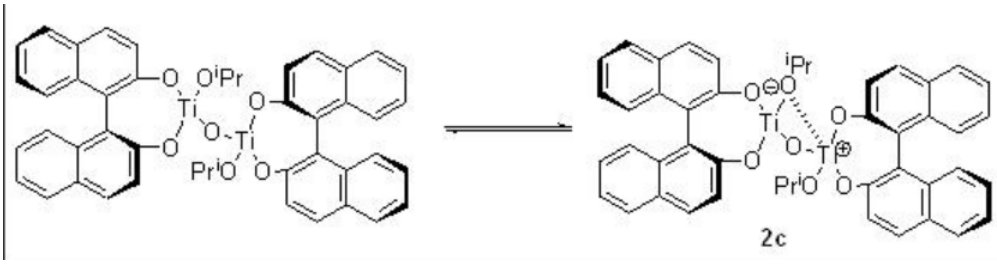
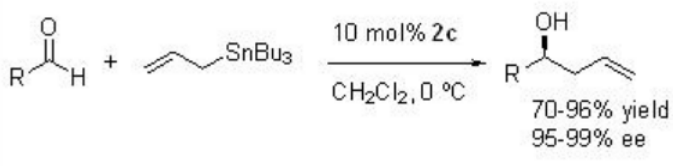


Scheme 1.2.4

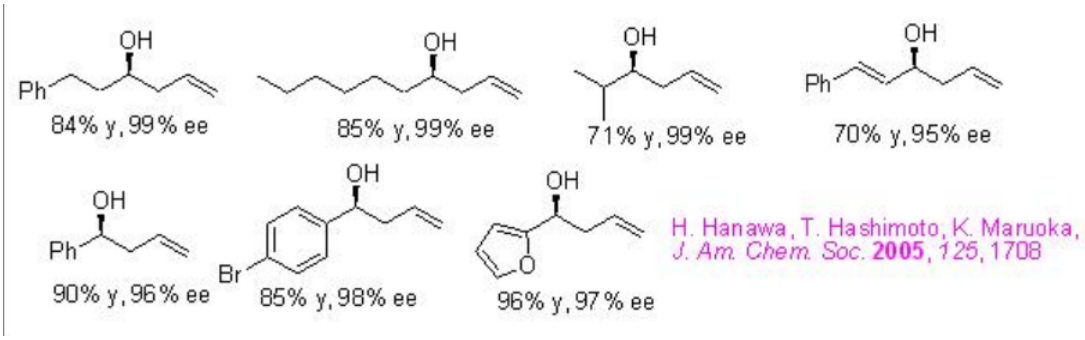
Allylation

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 1.2.5).



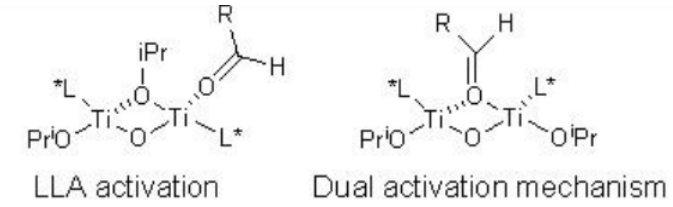


Examples:



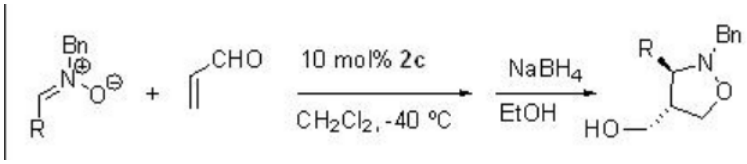
Scheme 1.2.5

For the high reactivity of the catalyst **2c** , two different transition states are proposed (Scheme 1.2.6). 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 1.2.6

The catalyst **2c** has also been found to effective for 1,3-dipolar cycloaddition reaction between diazoacetates and α -substituted acroleins to give 2-pyrazolines with a quaternary carbon centre (Scheme 1.2.7).



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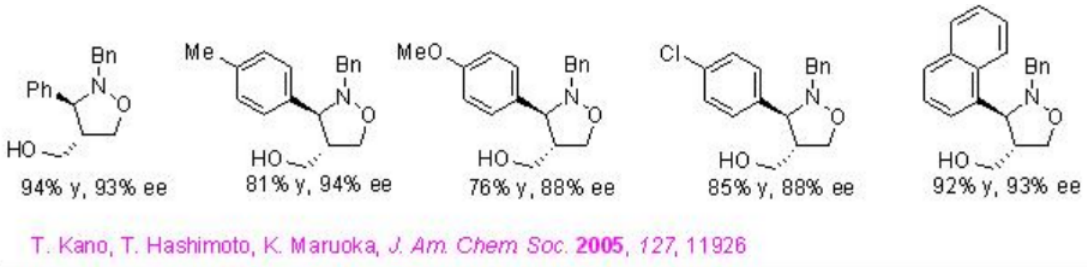
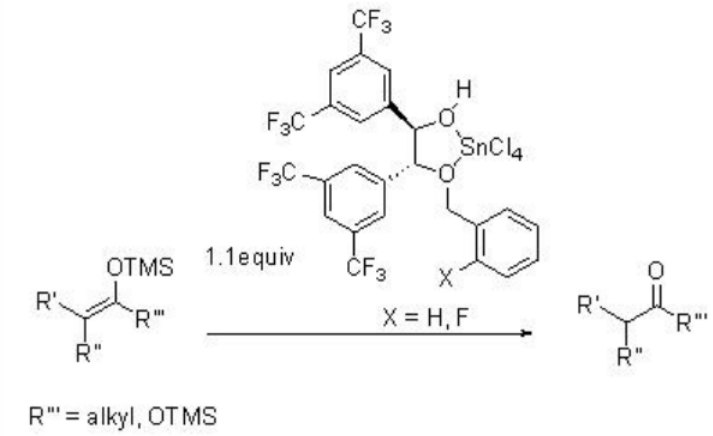


T. Kano, T. Hashimoto, K. Maruoka, *J. Am. Chem Soc.* **2005**, *127*, 11926

Scheme 1.2.7

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-diaryl ethane- 1,2-diol and $SnCl_4$, has been found to be an effective catalyst for the enantioselective protonation of silyl enol ethers and ketene disilyl acetals (Scheme 1.3.1).



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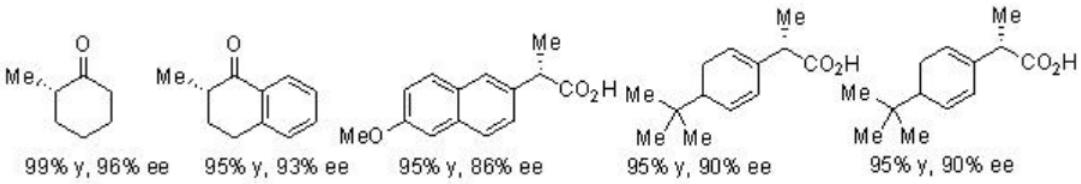
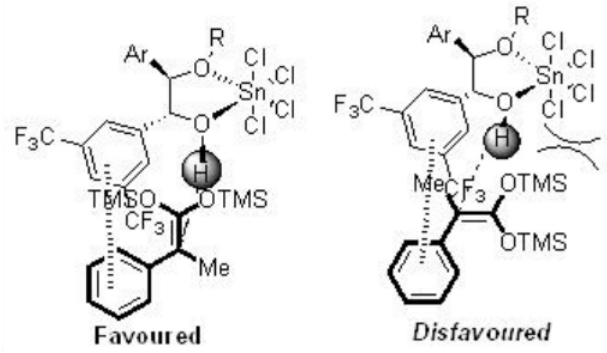


K. Ishihara et al., *J. Am. Chem. Soc.* **2003**, 123, 24.

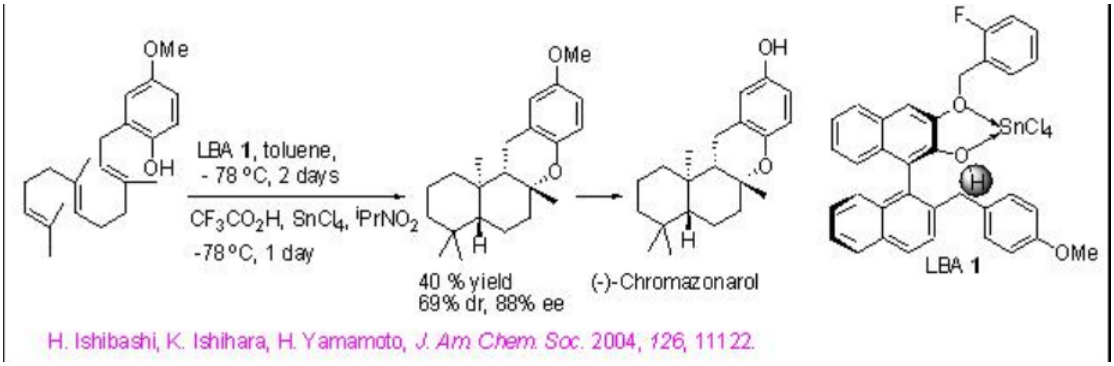
Scheme 1.3.1

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 1.3.2).

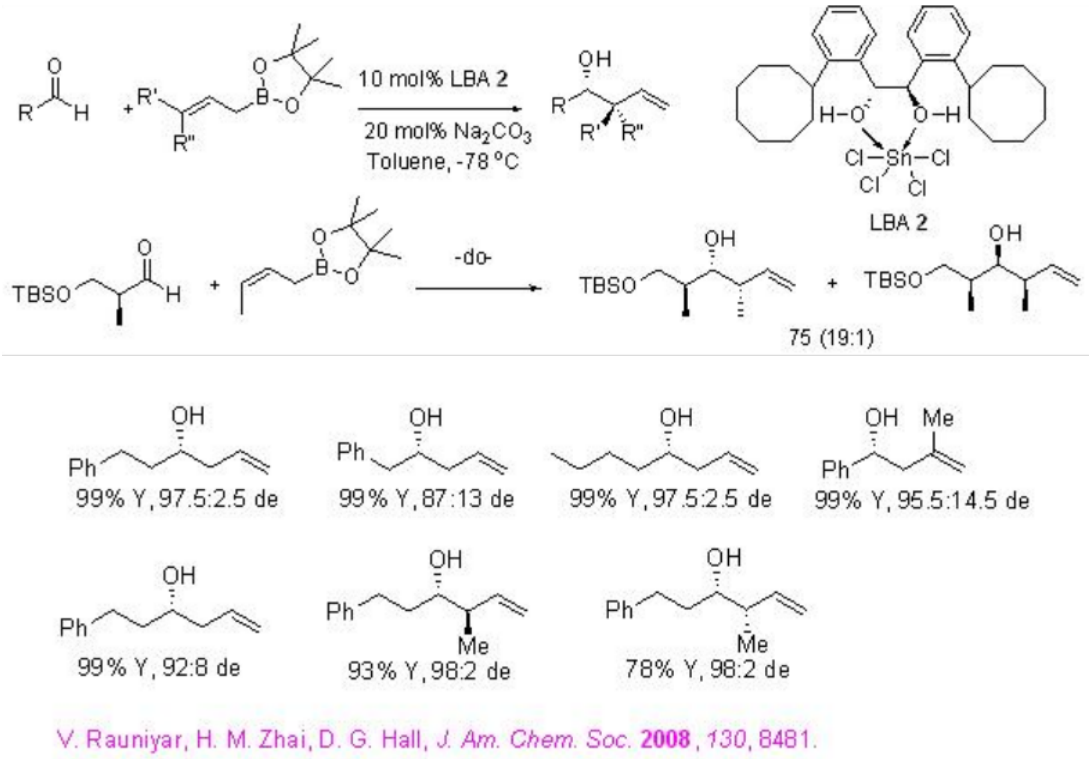


Scheme 1.3.2

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 1.3.3).



Scheme 1.3.3



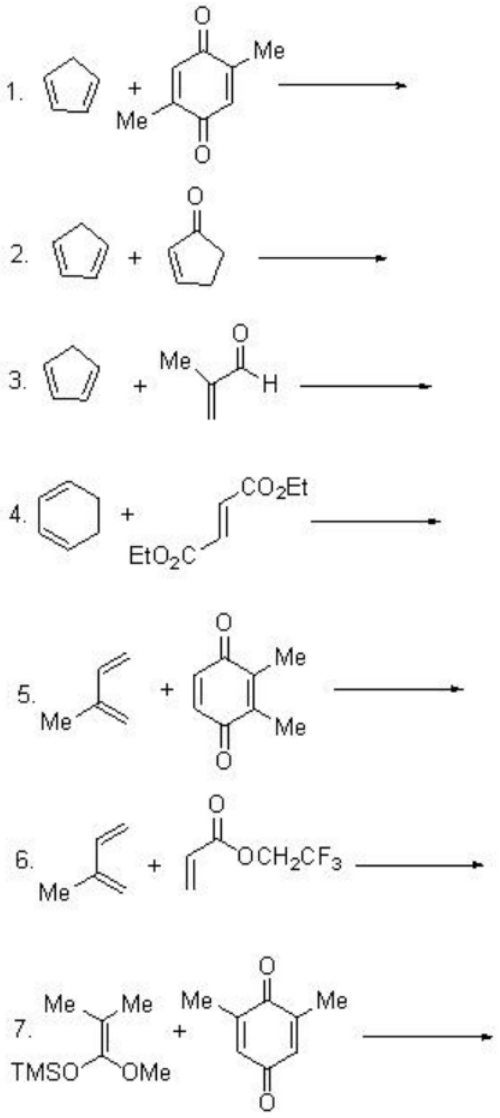
Scheme 1.3.4

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 diasterofacial selectivity (Scheme 1.3.4).

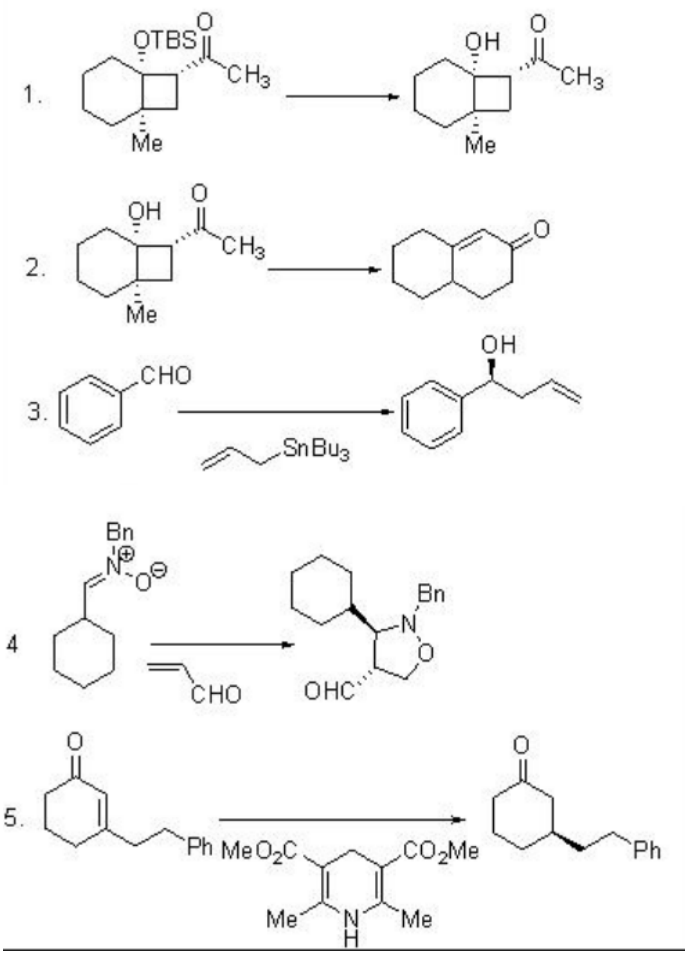
1.4: Problems + Reference

Problems:

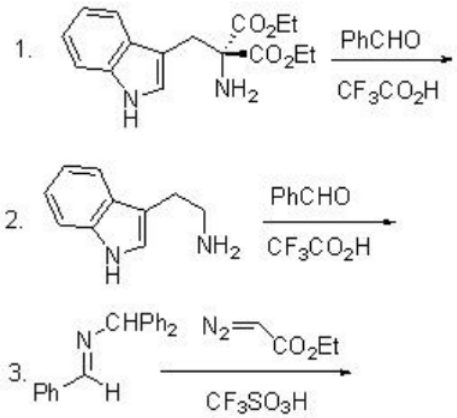
What products would expect from the following reactions using BLA **1b** as a catalyst?



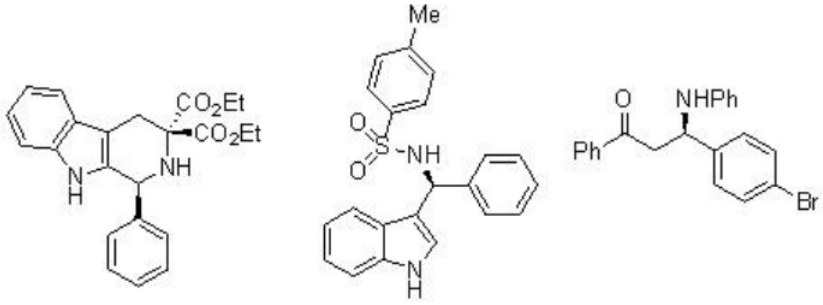
Provide suitable catalysts/reagents for the following conversions.



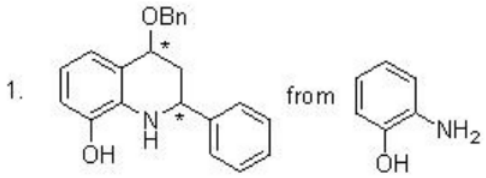
A. What major products would you expect from the following reactions?

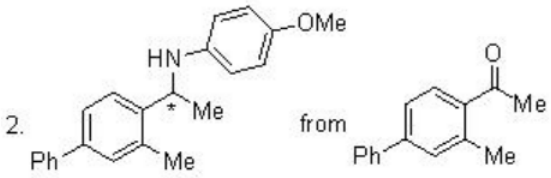


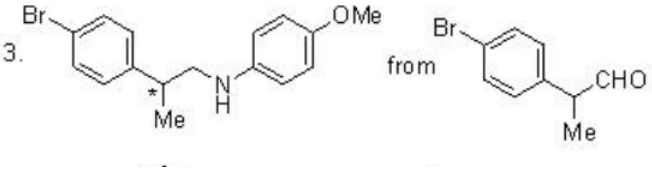
B. Write synthetic routes for the following compounds using chiral phosphoric acid catalysts.

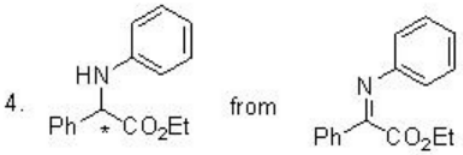


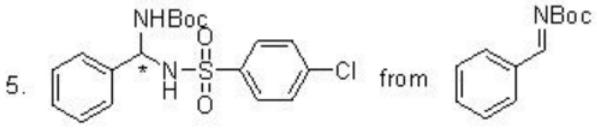
How would you employ chiral phosphoric acids in the synthesis of the following?

1. 

2. 

3. 

4. 

5. 

Reference/Text Book

1. I. Ojima, *Catalytic Asymmetric Synthesis* , 3 rd ed., Wiley, New Jersey, 2010.

2. M. B. Smith, *Organic Synthesis* , 2 nd edition, McGraw Hill, New Delhi, 2004.

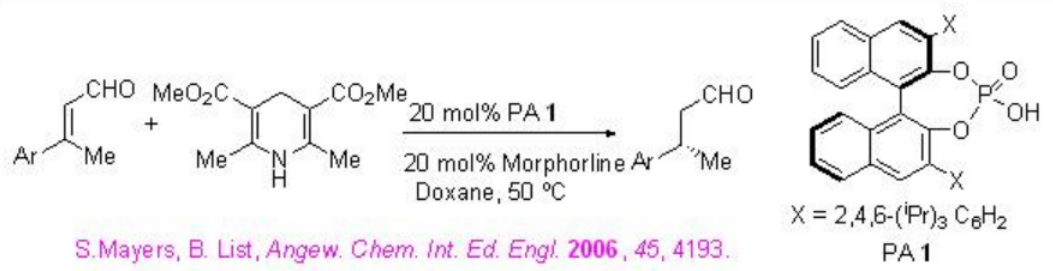
I. Ojima, *Catalytic Asymmetric Synthesis*, John Wiley & Sons, New Jersey, 2010.

1.5: 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 stereoinduction by controlling the structural and electronic properties.

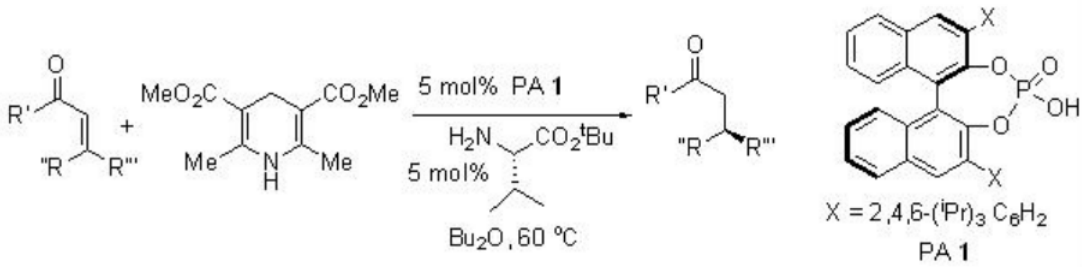
Asymmetric Counterion Directed Catalysis (ACDC)

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 1.5.1). 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 1.5.1

This method has been subsequently utilized for the reduction of α,β -unsaturated ketones (Scheme 1.5.2). In which both cation and anion are chiral that catalyze with high enantioselectivity.



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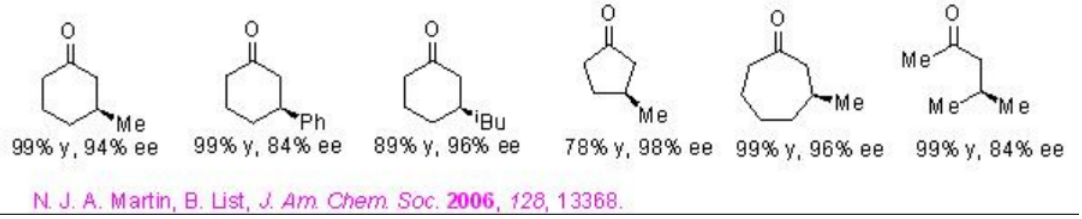
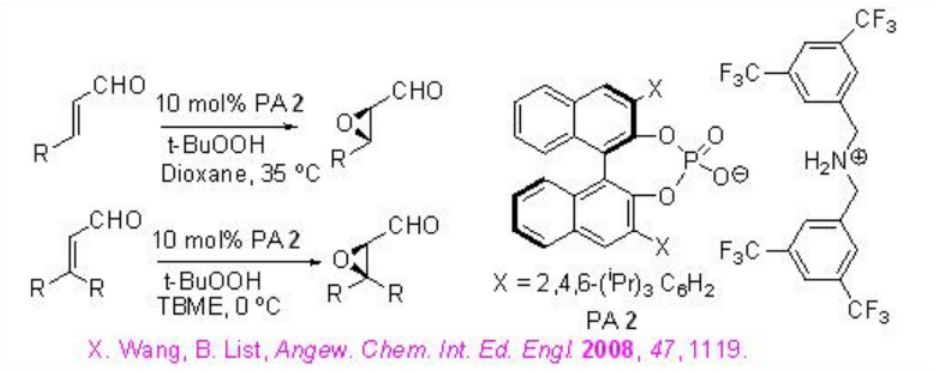


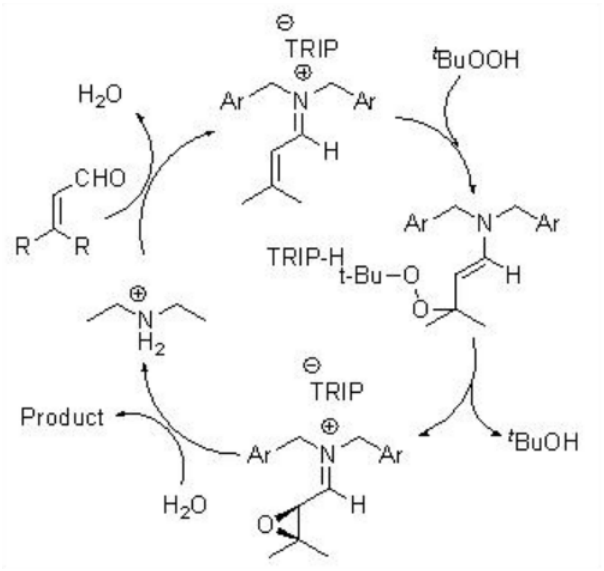
Scheme 1.5.2

The PA **2** has been further utilized for the asymmetric epoxidation of α,β -unsaturated aldehydes in the presence of t-BuOOH (Scheme 1.5.3). 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.

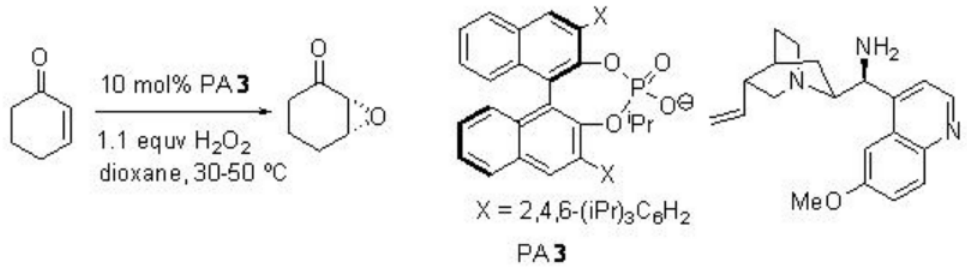


Scheme 1.5.3

This methodology has been further extended for the epoxidation of α,β -unsaturated ketones (Scheme 1.5.5). 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 1.5.6.



Scheme 1.5.4



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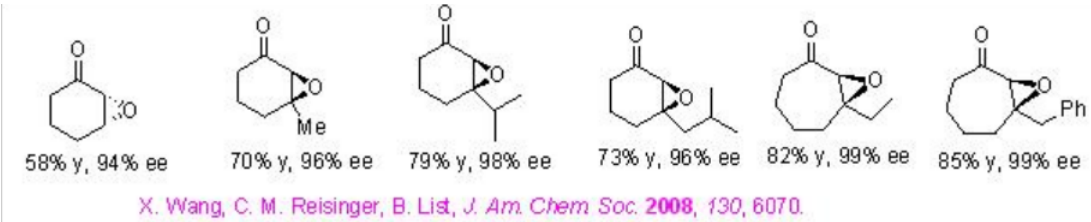
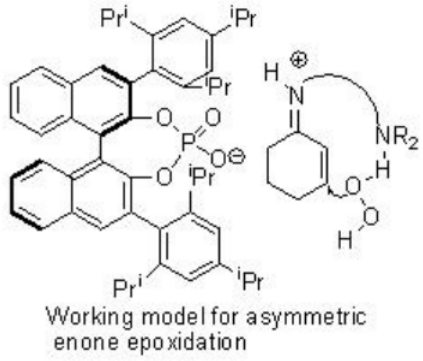
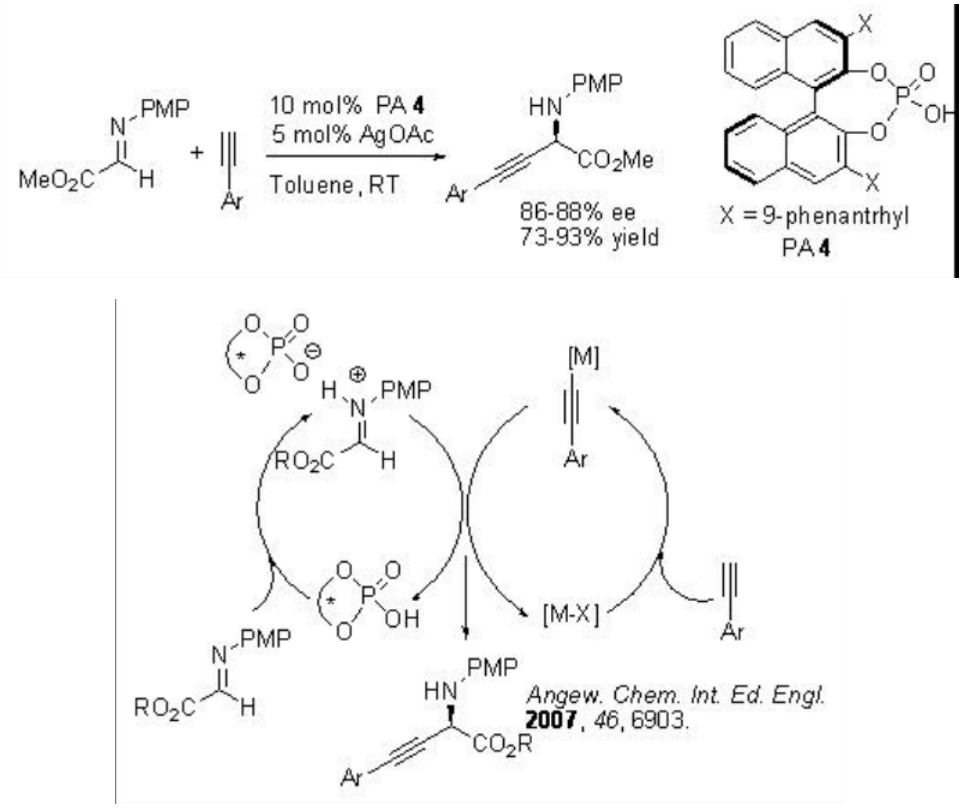


Scheme 1.5.5



Scheme 1.5.6

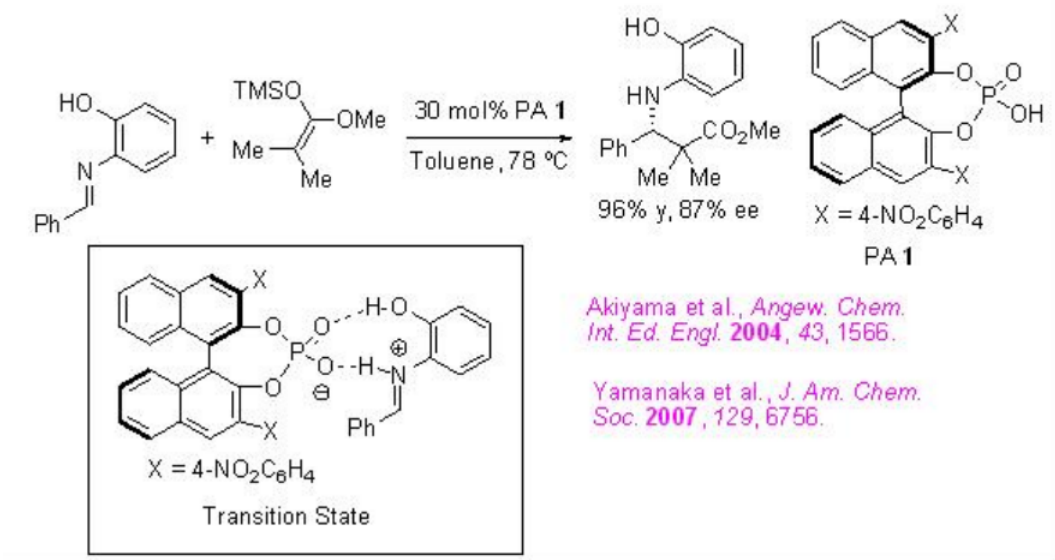
A dual catalytic procedure has been developed for the enantioselective activation of imines by a Brønsted acid combined with BINOL phosphate complex that results in a new metal catalyzed reaction in which the chiral counterion induces the enantioselectivity (Scheme 15).



Scheme 1.5.7

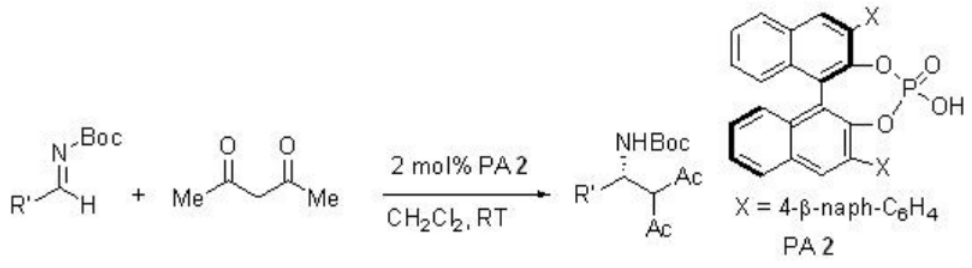
Nucleophilic Additions of Aldimines

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 1.5.8). Based on DFT calculations a nine-membered zwitterionic transition state has been proposed to explain the stereoinduction.



Scheme 1.5.8

The reaction of acetylacetone with *N* -boc-protected imines has been subsequently reported employing 2 mol% PA **2** with excellent yield and enantioselectivites (Scheme 1.5.9). The procedure is compatible with a series of substrates to afford target products in high enantioselectivities.



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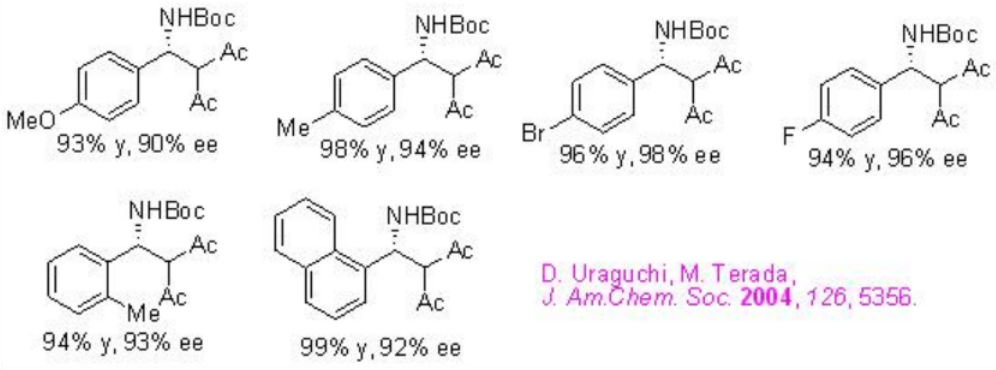
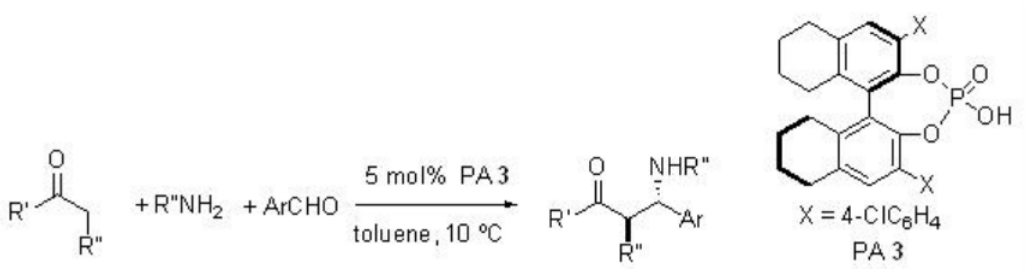


Scheme 1.5.9

Phosphoric acid PA **3** derived from H_8-BINOL derivative has been further studied for the direct Mannich reactions between *in situ* generated *N* -aryl imines and ketones (Scheme 1.5.10). The authors have proposed TS-1 for the acid-promoted enolization of the ketone and its addition to the protonated aldimine.



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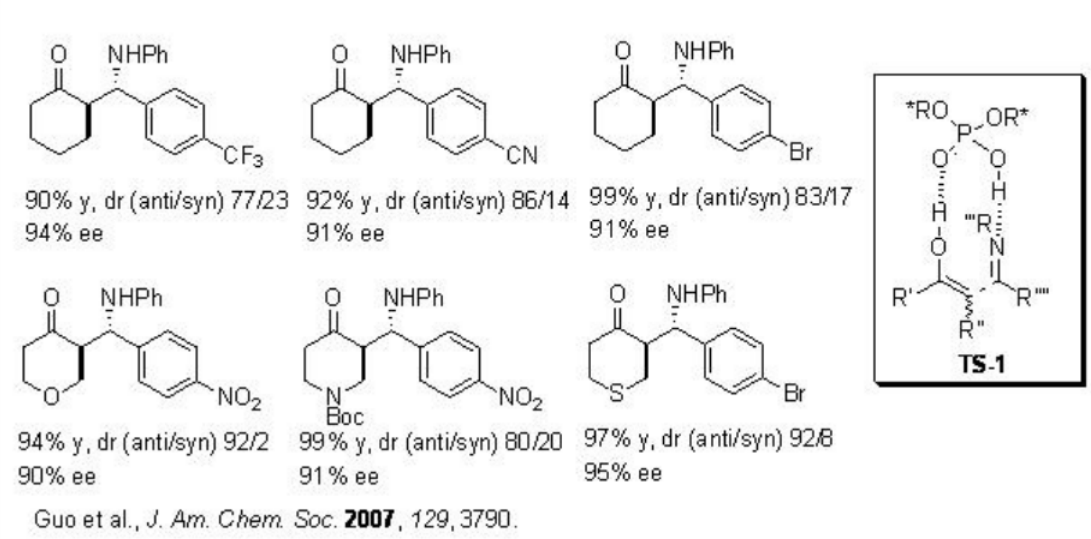
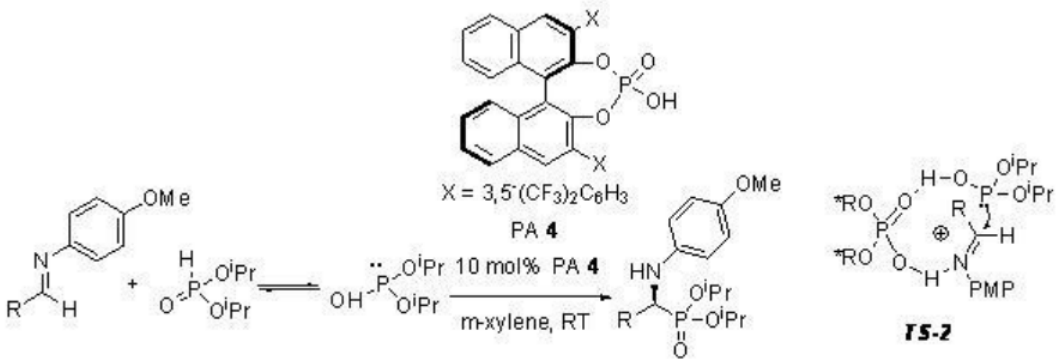


Guo et al., *J. Am. Chem. Soc.* **2007**, *129*, 3790.

Scheme 1.5.10

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 1.5.11). 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.



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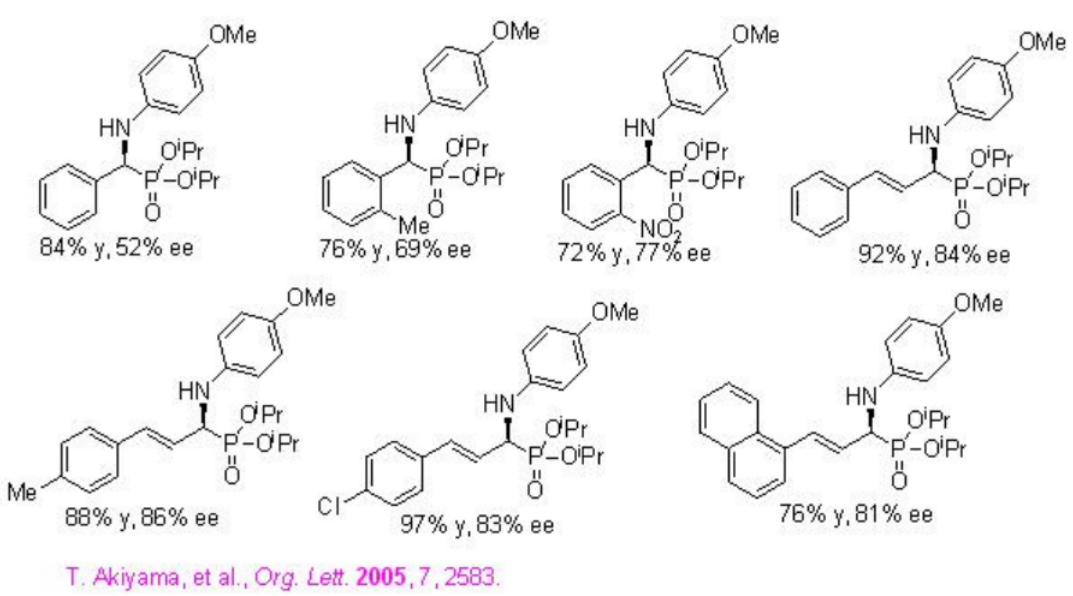
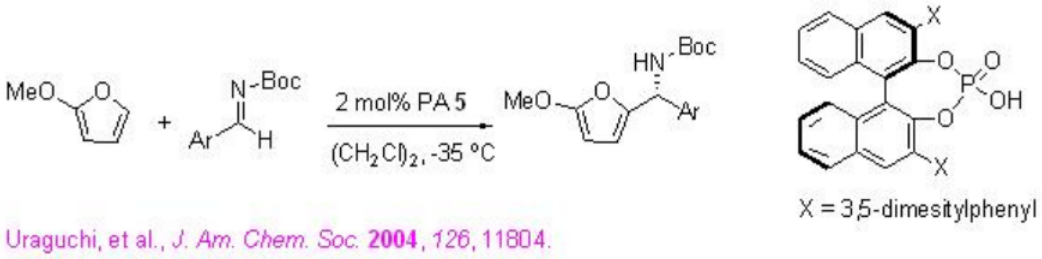


Scheme 1.5.11

Aza-Friedel-Crafts Reactions

The first organocatalytic aza-Friedel-Crafts reaction of aldimines has been accomplished using PA **5** (Scheme 1.5.12). 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.



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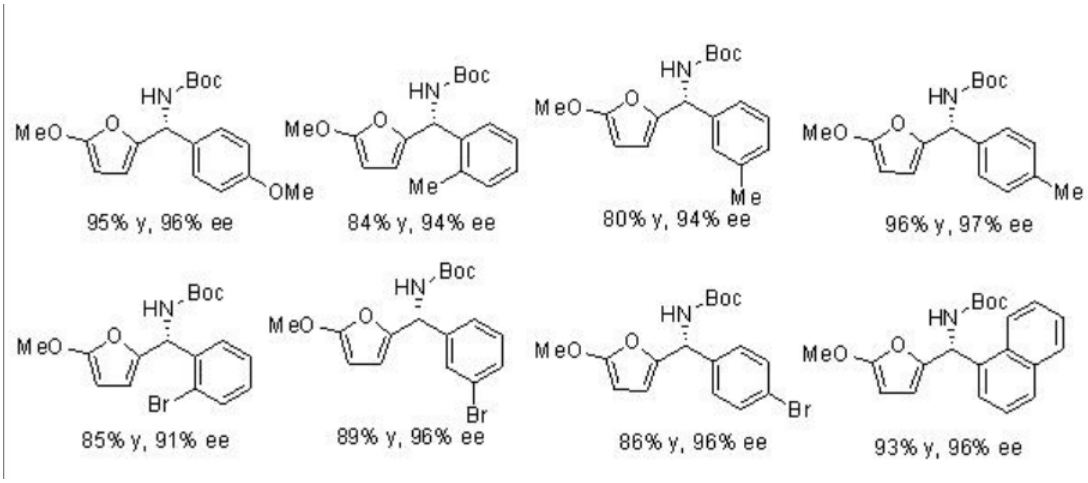
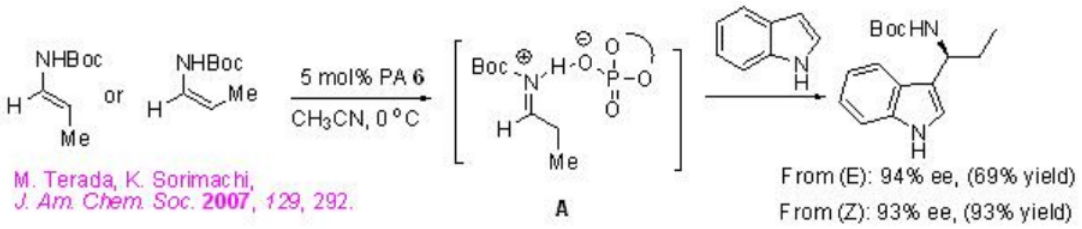


Scheme 1.5.12

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



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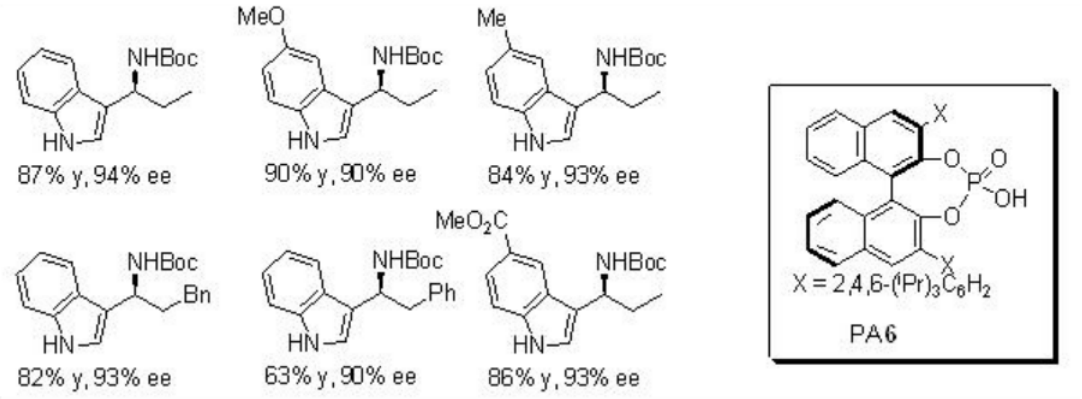
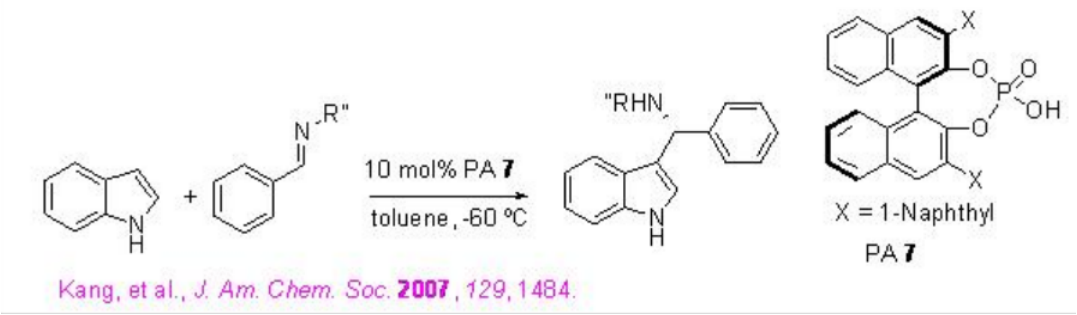


Scheme 1.5.13

of PA **6** (Scheme 1.5.13). Use of either pure regioisomers (E) or (Z)-enecarbamate gives the same product with similar enantioselectivities. Thus, the reaction is believed to takes 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 1.5.14).



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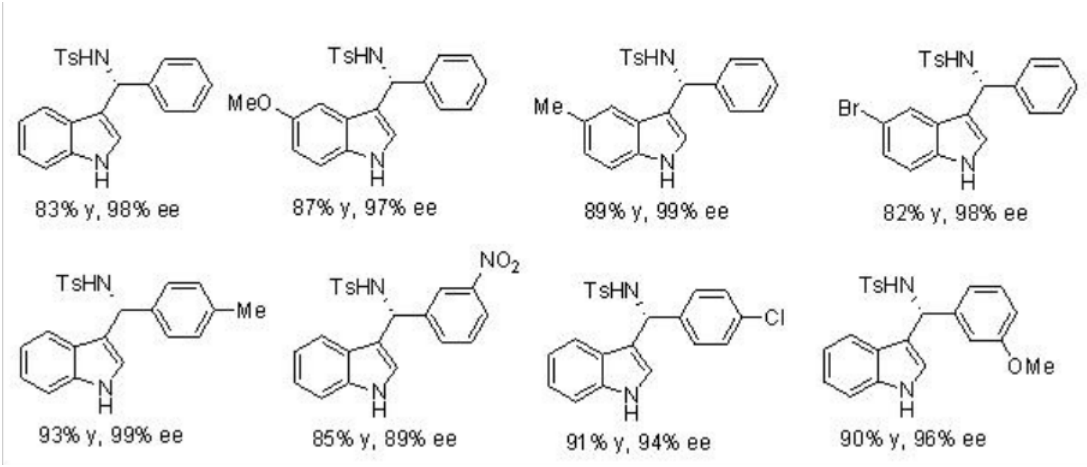
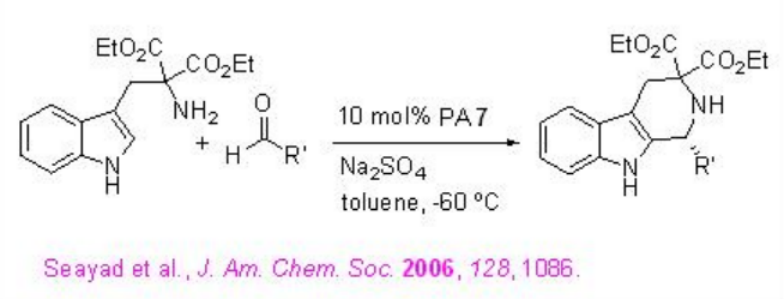


Scheme 1.5.14

The Pictet-Spengler reaction of *N*-tritylsulfenyl tryptamines with various alphatic and aromatic aldehydes has been accomplished using PA **7** (Scheme 1.5.15). The sulfenyl substituent stabilizes the intermediate iminium ion and favours the Pictet-Spengler cyclization compared to the undesired enamine formation.



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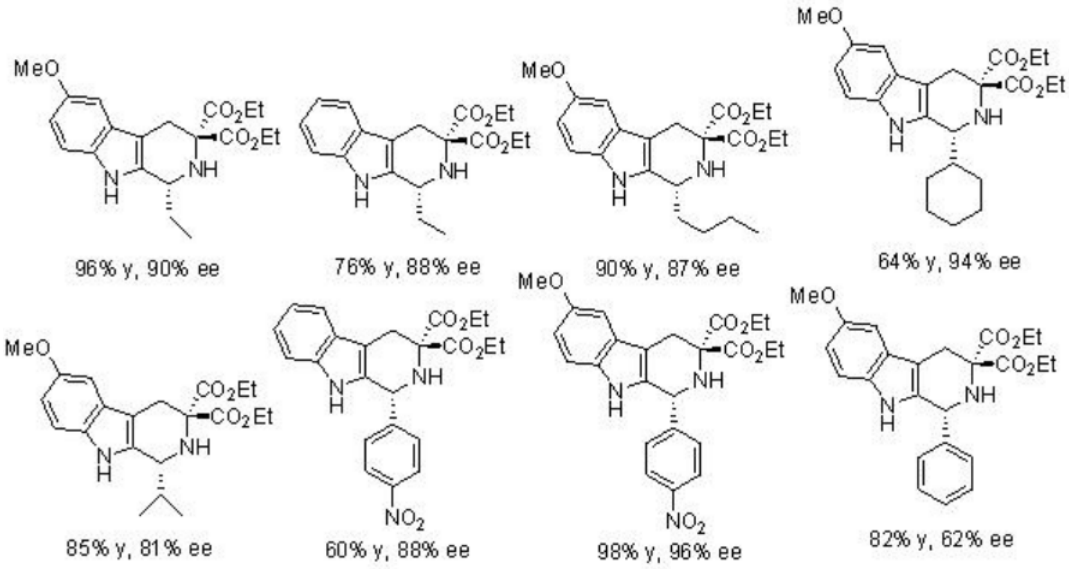
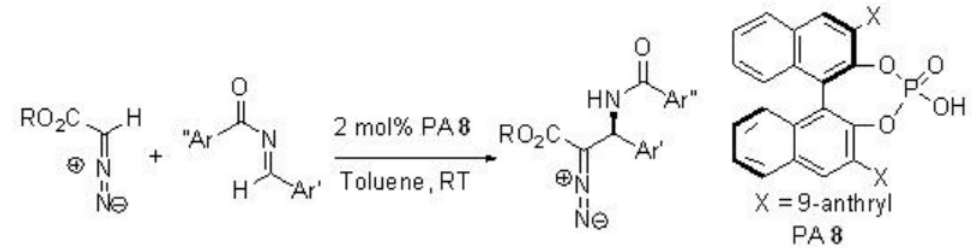


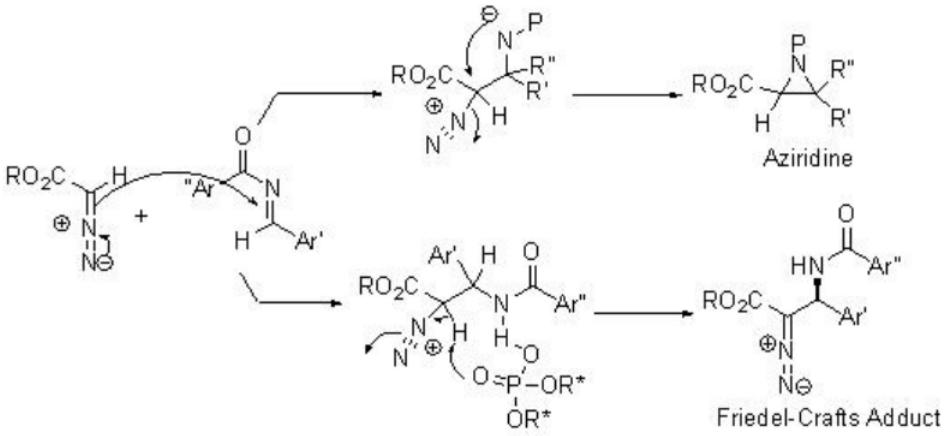
Scheme 1.5.15

The quite interesting alkylation of α -diazoesters with *N* -acyl imines has been shown using PA **8** with high enantioselectivities (Scheme 1.5.16). 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.



A.L. Williams, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 1612.



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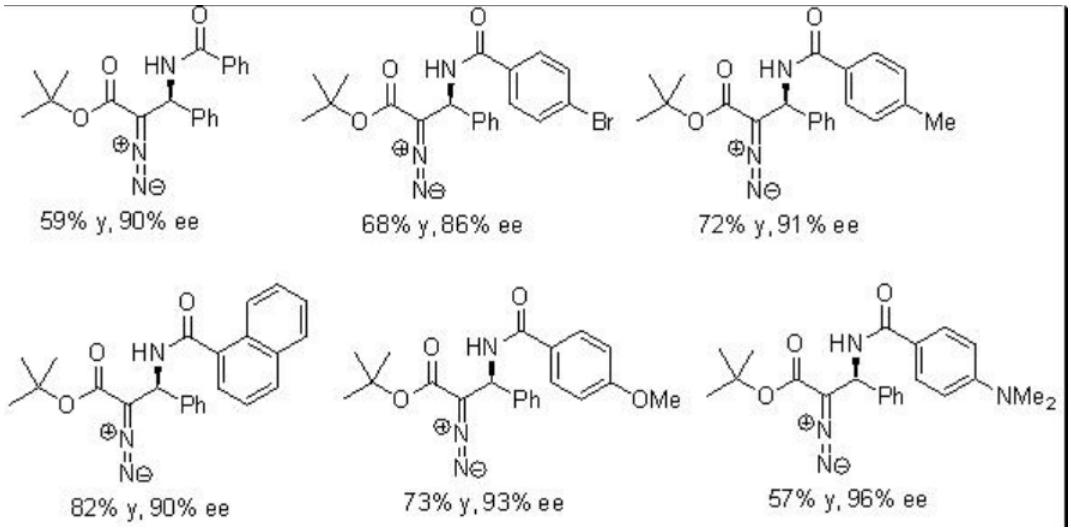
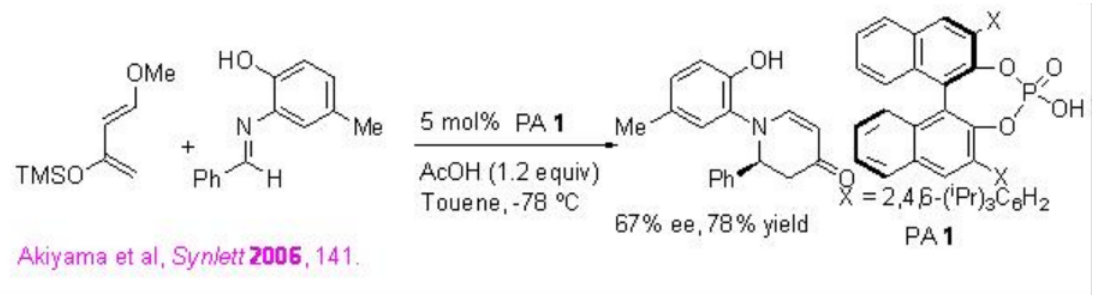


Scheme 1.5.16

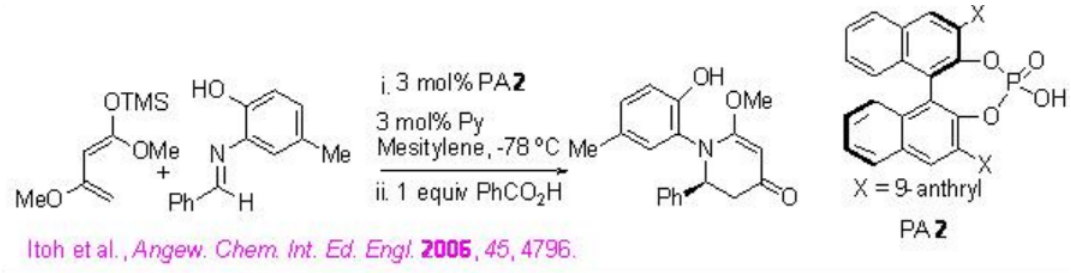
1.4.4: Diels-Alder Reaction

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 1.5.17). The addition of acetic acid leads to increase significantly the yield and enantioselectivities.



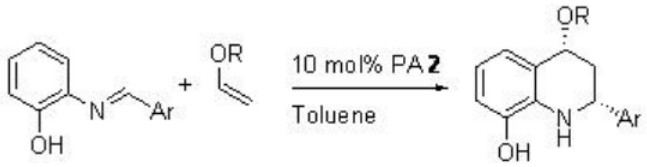
Scheme 1.5.17

Although the aza- Diels Alder reaction of Brassard's diene using a Brønsted acid is rare due to the labilitiy 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 1.5.18). The yield of the product could be improved using the pyridinium salt of the phosphoric acid as catalyst.



Scheme 1.5.18

The PA **2** has also been found to effective for the inverse electron-demand aza -Diels Alder reaction of electron-rich alkenes with 2-aza dienes with excellent enantioselectivities (Scheme 1.5.19). The presence of OH group is crucial for the *cis* selectivity in the products.



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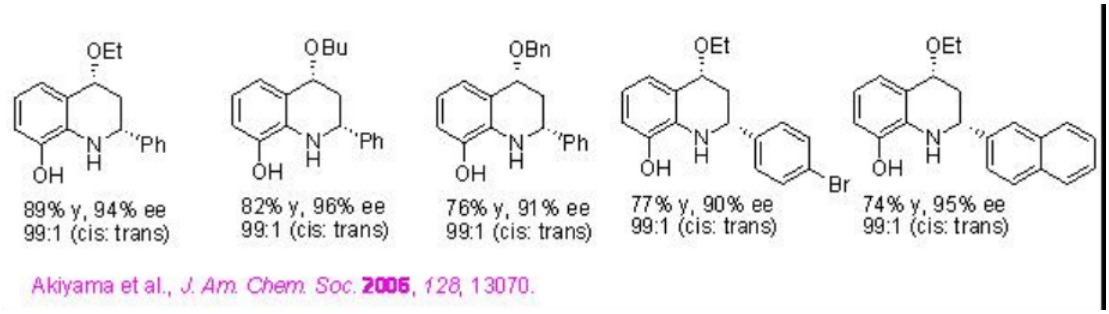
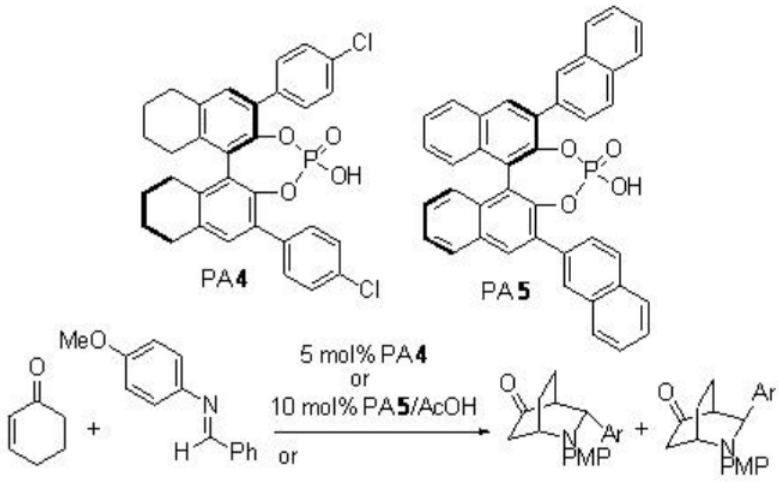


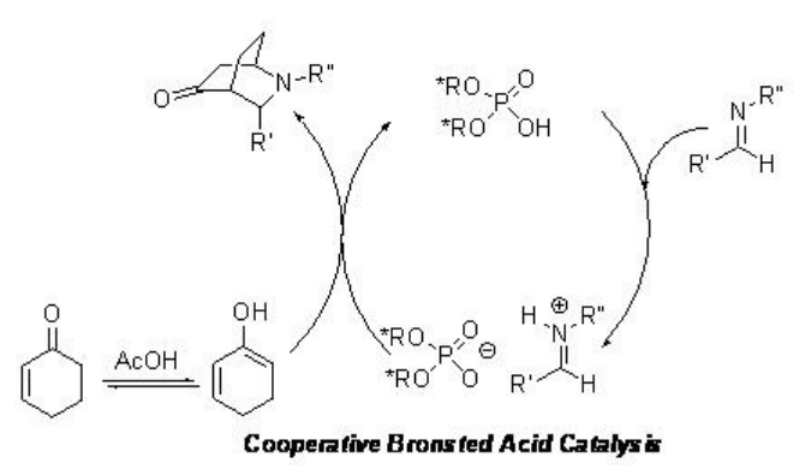
Scheme 1.5.19



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

Scheme 1.5.20

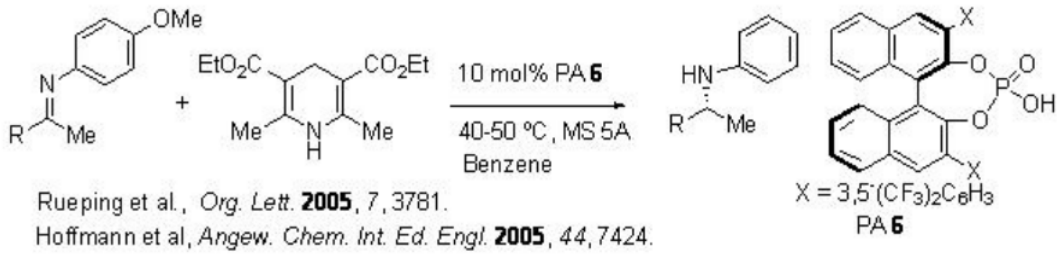
The aza- Diels Alder reaction of aldimines with cyclohexenone has been accomplished using either PA **4** or PA **5** /AcOH (Scheme 1.5.20). A cooperative catalytic is proposed for the reaction using PA **5** /AcOH, where both the activation of an electrophile and a nucleophile takes place cooperatively (Scheme 1.5.21).



Scheme 1.5.21

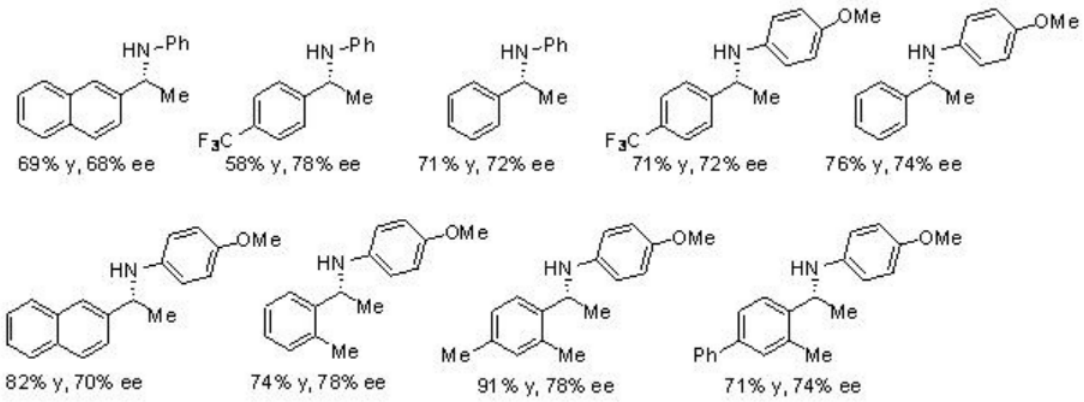
Transfer Hydrogenation

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 1.5.22). PA **1** bearing bulky 2,4,6-(i-Pr)$_3$ C_6 H_3 at the 3,3'-positions of BINOL is found to superior to PA **6** for this purpose.



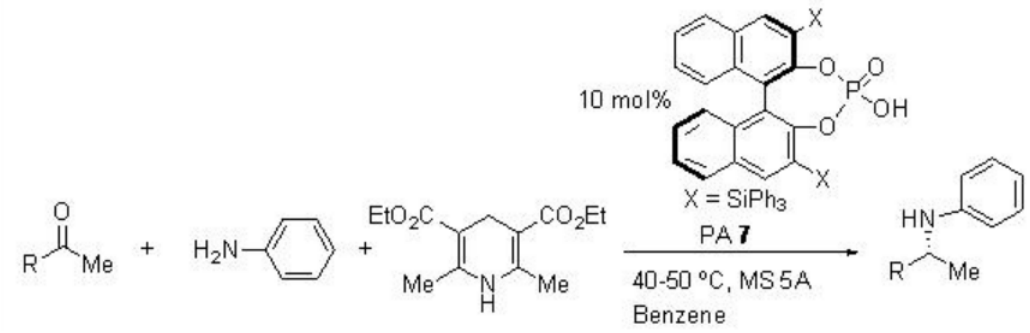
Rueping et al., *Org. Lett.* **2005**, *7*, 3781.
Hoffmann et al, *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 7424.

Examples:



Scheme 1.5.22

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 1.5.23). This method is also compatible for the reactions of methyl phenyl ketones as well as methyl alkyl ketones.



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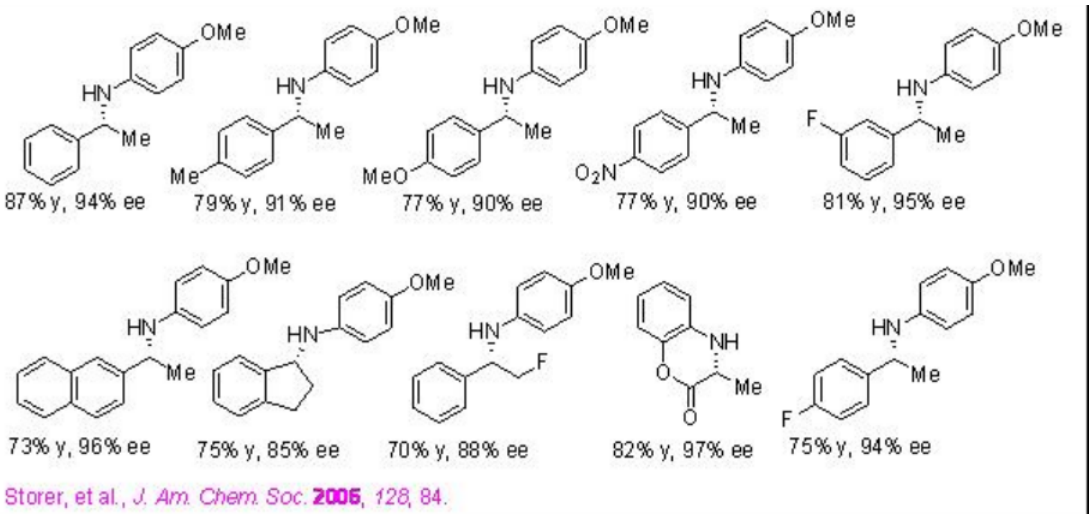
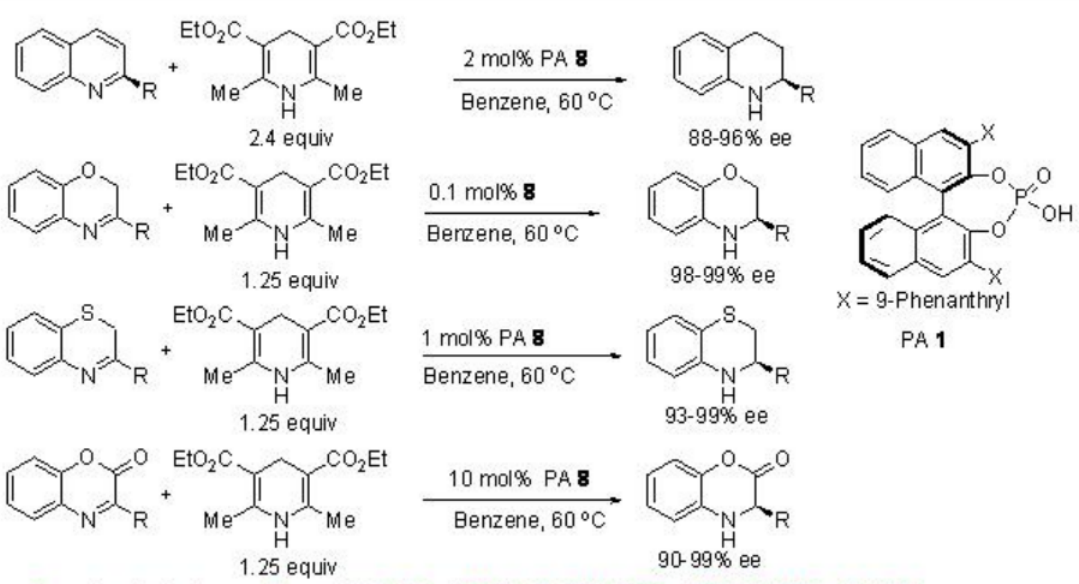


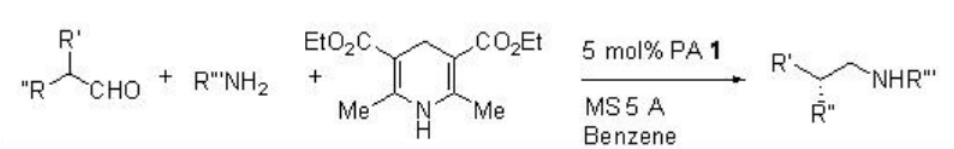
Scheme 1.5.23



Scheme 1.5.24

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 1.5.24).

Asymmetric reductive amination of α -branched aldehydes and *p* -anisidine with Hantzch ester can be performed employing PA **1** with high enantioselectivities (Scheme 1.5.25). The observed results suggest that the reaction proceeds via a dynamic kinetic resolution (Scheme 1.5.26).



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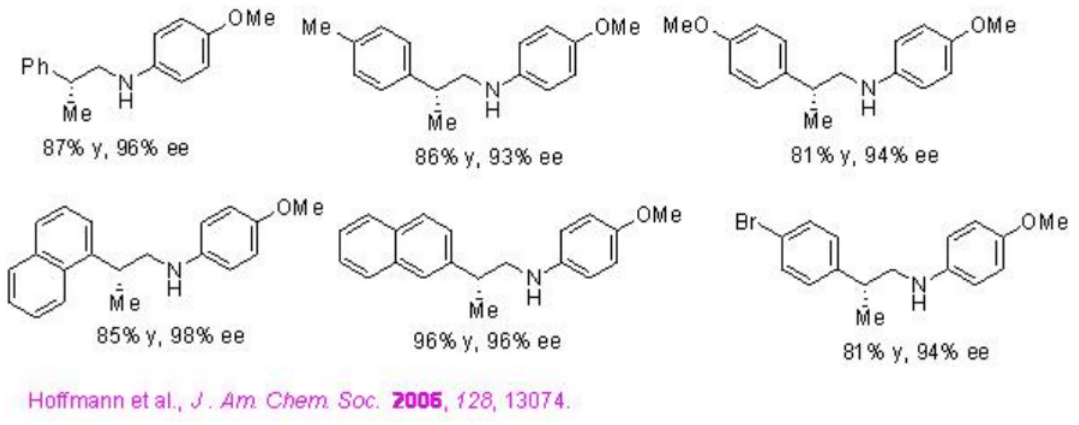
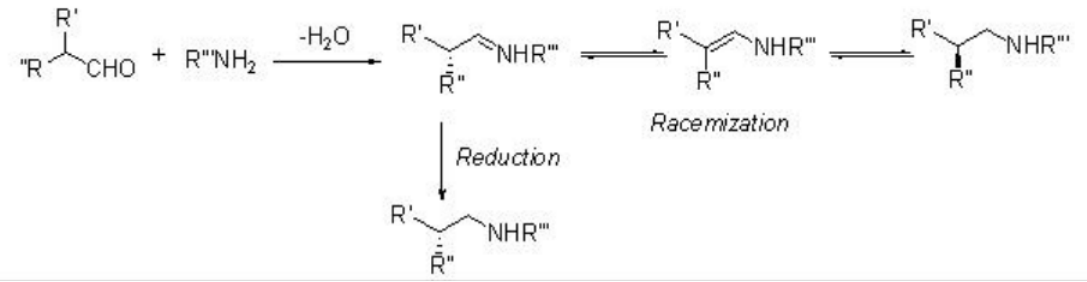


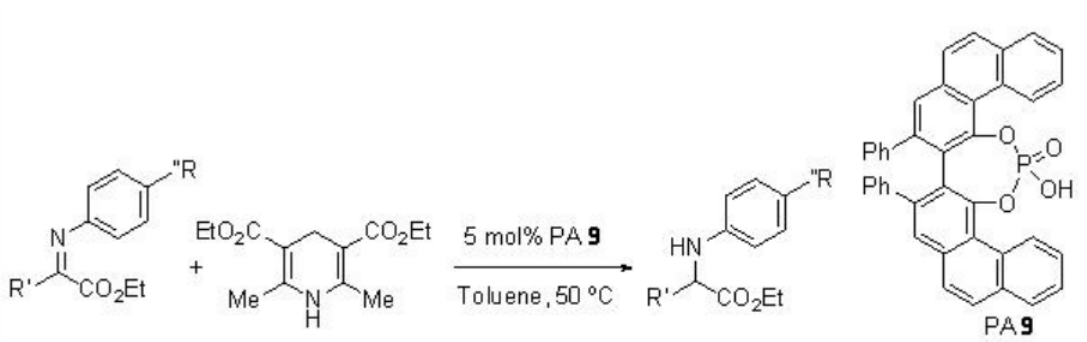
Scheme 1.5.25

Proposed Mechanism

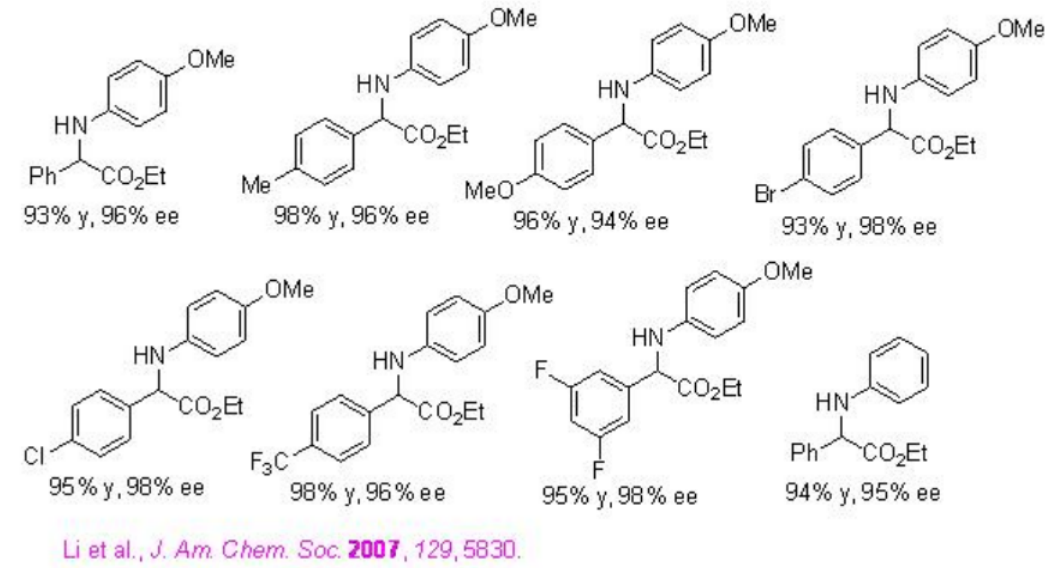


Scheme 1.5.26

Chiral phosphoric acid PA **9** derived from (*S*)-VAPOL is found to superior to PAs derived from BINOL for the reduction of α -imino esters using Hantzsh ester to afford α -amino esters with higher enantioselectivities (Scheme 1.5.27).



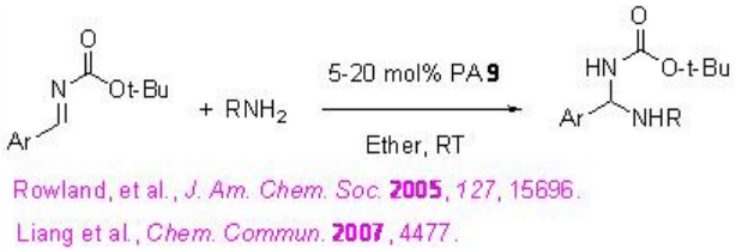
Examples:



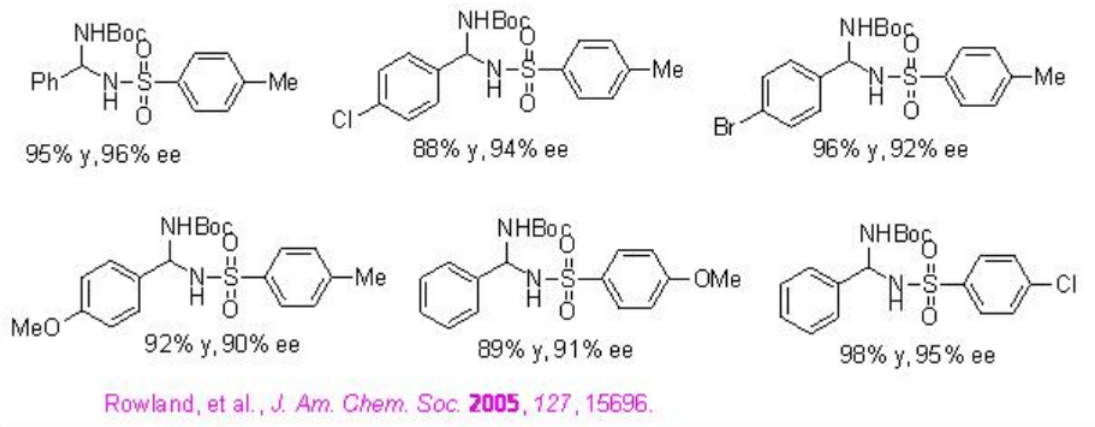
Scheme 1.5.27

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 aminals (Scheme 1.5.28). The procedure has wide substrate scope to give the target products in 73-99% ee and 80-99% yield.



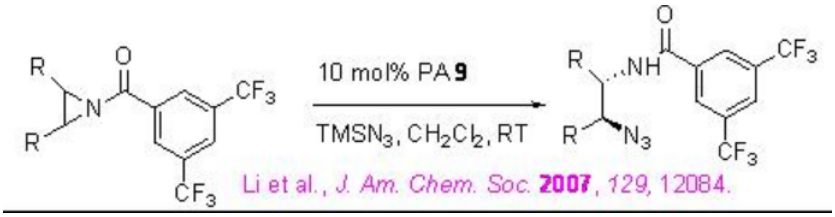
Examples:



Scheme 1.5.28

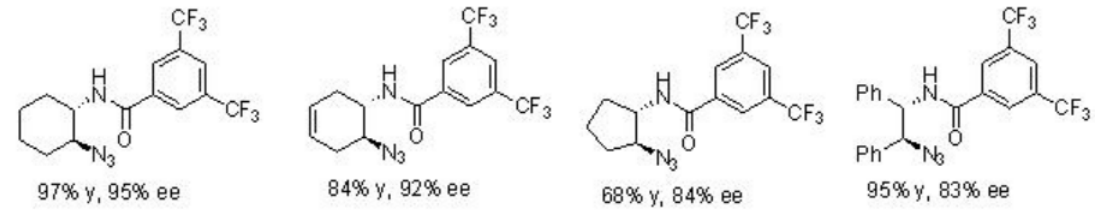
Asymmetric Desymmetrization of meso-Aziridines

The application of PA **9** has been further extended to ring opening of *meso* -pyridines. This is the first example of organocatalyic 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 1.5.29).



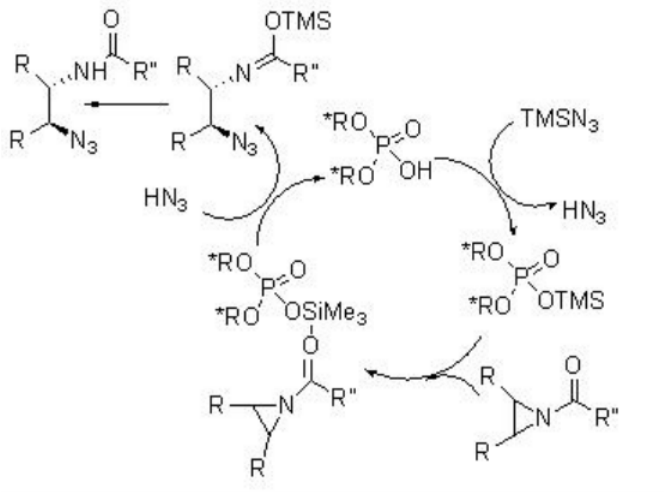
Scheme 1.5.29

Examples:



Proposed Mechanism

The phosphoric acid first reacts with TMSN 3 to give silylated phosphoric acid as the active catalyst (Scheme 1.5.30). 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 1.5.30

CHAPTER OVERVIEW

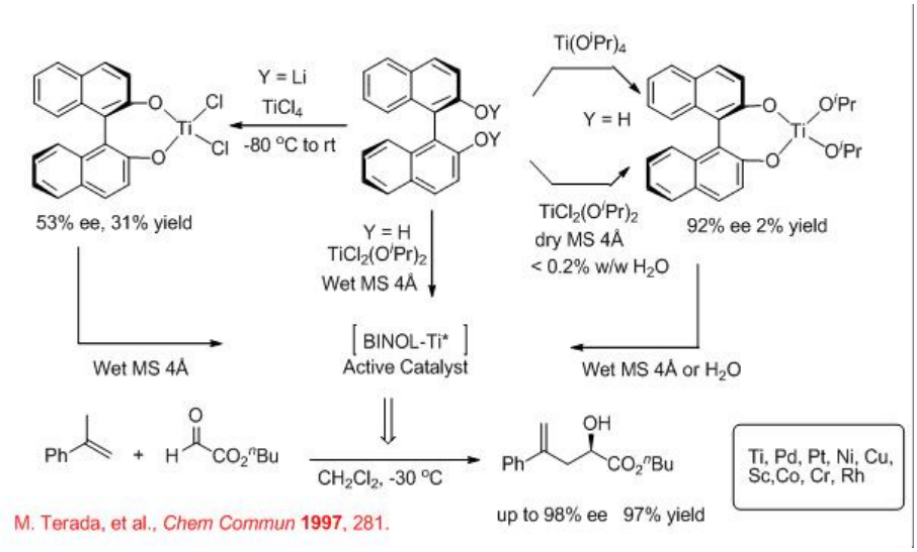
2: Asymmetric Carbon-Carbon Bond Forming Reactions

2.1: Enantioselective Ene and Cycloaddition Reactions

Alder-ene and Diels-Alder reactions are six electron pericyclic processes between a “diene” or an alkene bearing an allylic hydrogen and an electron-deficient multiple bond to form two bonds σ with migration of the π bond. The lecture covers the examples of recent developments in enantioselective intermolecular Alder-ene glyoxylates with alkenes.

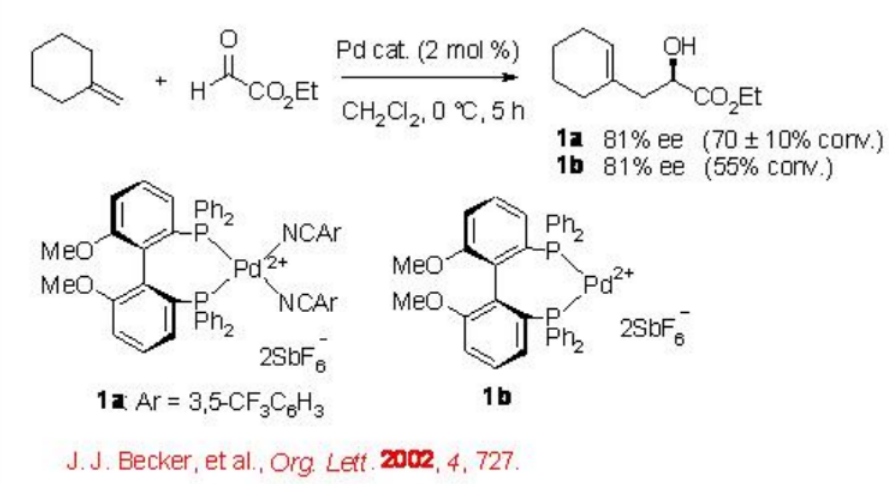
Carbonyl-Ene Reaction

Chiral Lewis acid catalyzed enantioselective ene reaction is one of the efficient methods for atom economical carbon-carbon bond formation. For example, Ti-BINOL prepared *in situ* catalyzes efficiently the carbonyl-ene reaction of glyoxylate with α -methylstyrene in the presence of molecular sieves with high enantioselectivity (Scheme 2.1.1).



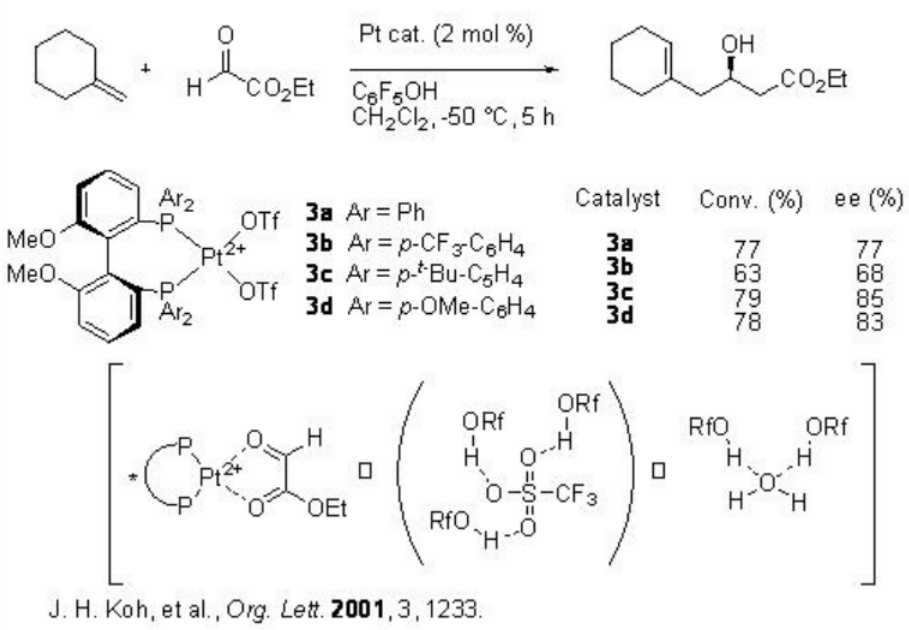
Scheme 2.1.1

Besides the early transition metal based Lewis acid catalysts, square planar dicationic late transition metal complexes bearing C_2-symmetric diphosphine ligands have also been considerably studied as chiral Lewis acids for carbonyl-ene reactions. For example, the isolated MeO-BIPHEP-Pd complex **1a** bearing electron withdrawing benzonitrile as the labile, stabilizing ligands has been used for the ene reaction of ethyl glyoxylate with up to 81% ee (Scheme 2.1.2). The isolated **1a** exhibits more catalytic activity compared to that **1b** which is *in situ* generated although both offer similar enantioselectivity.



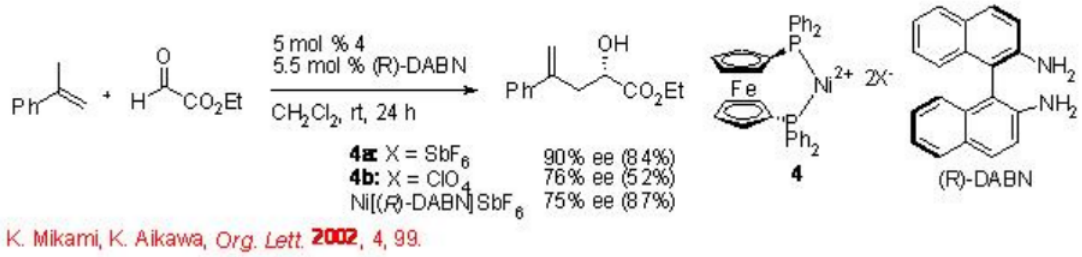
Scheme 2.1.2

MeO-BIPHEPs-Pt complexes **3** with OTf - as counter anion also exhibit similar catalytic activity and selectivity in the asymmetric glyoxylate ene reaction (Scheme 3). The addition of phenol facilitates the reaction by trapping the OTf anion and traces of water.



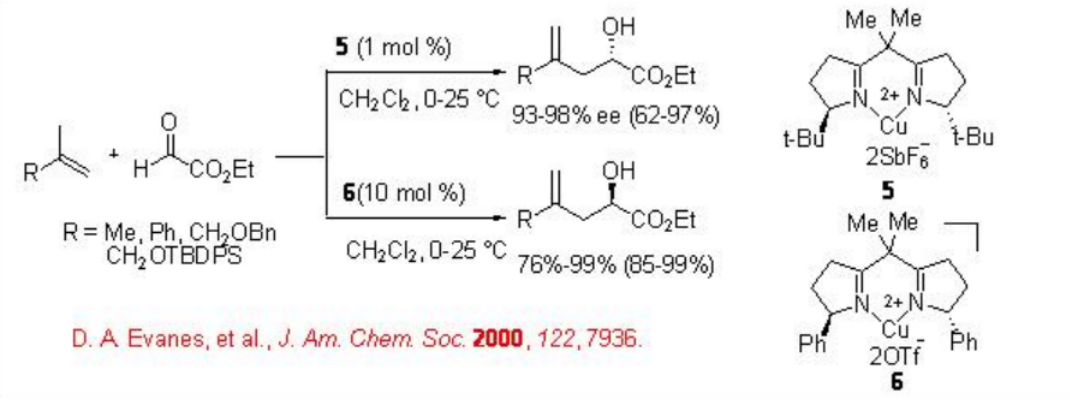
Scheme 2.1.3

The glyoxylate ene reaction is also effective using tropox dicationic DPPF-Ni complex **4** with enantioselectivity up to 90% ee (Scheme 2.1.4).



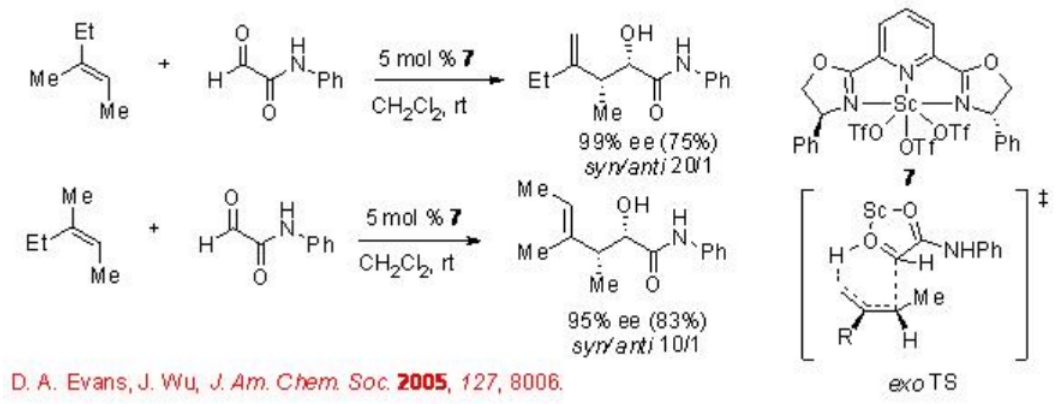
Scheme 2.1.4

The glyoxylate-ene reaction can also be carried out using chiral C_2-symmetric bisoxazolinyl copper(II) complexes **5** and **6** as Lewis acid catalysts (Scheme 2.1.5). The aqua complex is air and water stable and exhibits only slight decrease in the reaction rate compared to the anhydrous complex **6** . The sense of asymmetric induction depends on the oxazoline ring substituents, which can be rationalized by the tetrahedral and square-planer intermediates to account for the absolute configuration of the products.



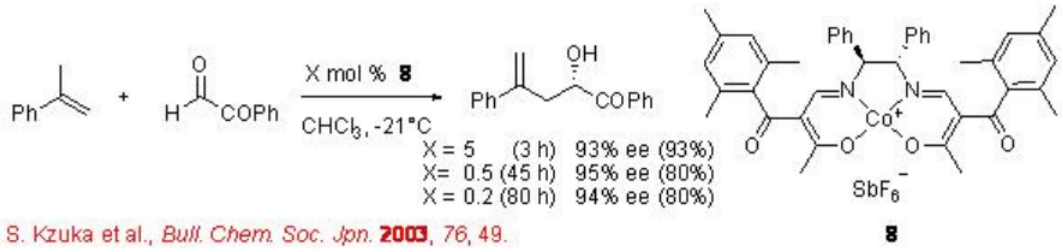
Scheme 2.1.5

In addition, chiral C_2-symmetric trivalent pybox-Sc complex **7** is studied for the carbonyl-ene reactions with *N* -phenyl glyoxamides (Scheme 2.1.6). The ene products are obtained with excellent diastereo- and enantioselectivity. Presumably, the products are formed *via* proton transfer from the β - *cis* substituent through an *exo* -transition state.



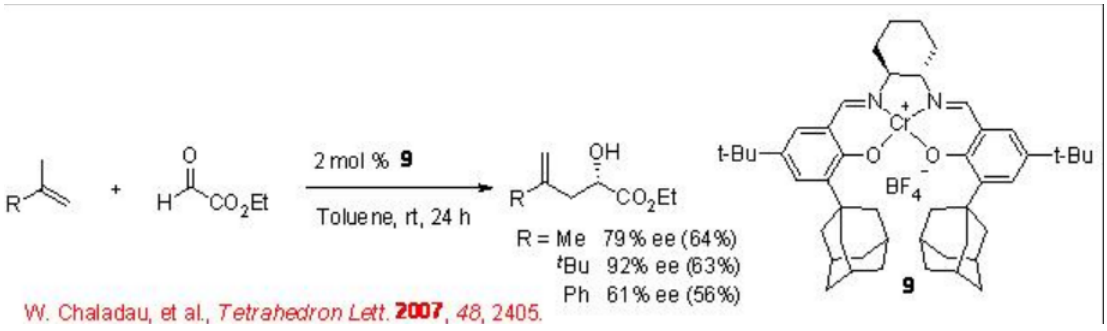
Scheme 2.1.6

Co and Cr-based chiral complexes have also been explored for the carbonyl-ene reaction with glyoxylates. For example, chiral β-ketoiminato complex **8** catalyzes efficiently the reaction of 1,1-disubstiuted alkene and glyoxyl derivative in high enantioselectivity (Scheme 2.1.7). Similar to the earlier described Pd, Pt and Ni-based catalysts, hexafluoroantimonate as a counter anion is found to be the most effective.



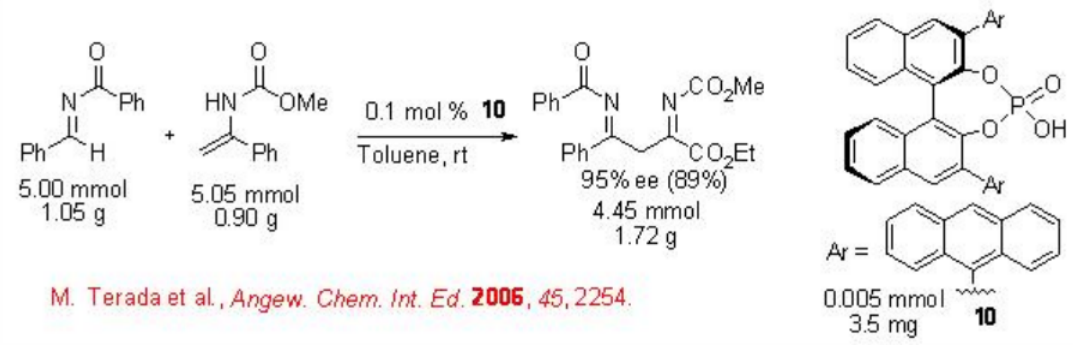
Scheme 2.1.7

Chiral Cr(III)-salen complex **9** bearing adamantyl group in the salen ligand has been used for the reaction of ethyl glyoxylate with 1,2-disubstituted alkenes (Scheme 2.1.8). The catalyst can be prepared in multigram scale and the ene products are obtained with up to 92% ee. The presence of adamantyl substituent essential for the enhancement in the enantioselectivity.



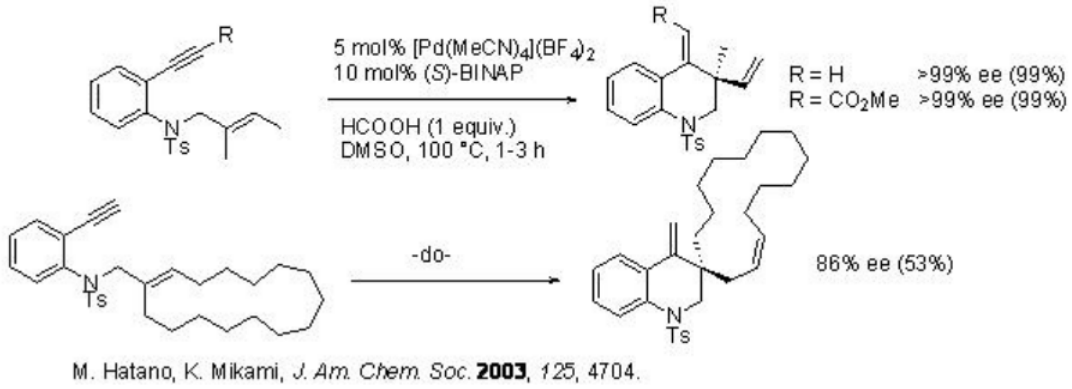
Scheme 2.1.8

Besides the metal based catalysts, chiral organocatalysts have also been considerably explored during the recent years for the carbonyl-ene reactions. For example, the chiral phosphoric acid **10** as a chiral Bronsted acid catalyzes readily the enantioselective aza-ene reaction of enamides to imines with excellent enantioselectivity even on a gram scale (Scheme 2.1.9).



Scheme 2.1.9

Besides the intermolecular reactions, intramolecular version of this reaction has also been well explored using chiral metal as well as chiral phosphoric acids as catalysts. For example, the palladium-phosphine complex catalyzed cyclization of 1,7-enyenes bearing benzene ring takes place efficiently to afford six membered quinoline derivatives with quaternary stereogenic centers as single enantiomer (Scheme 2.1.10).



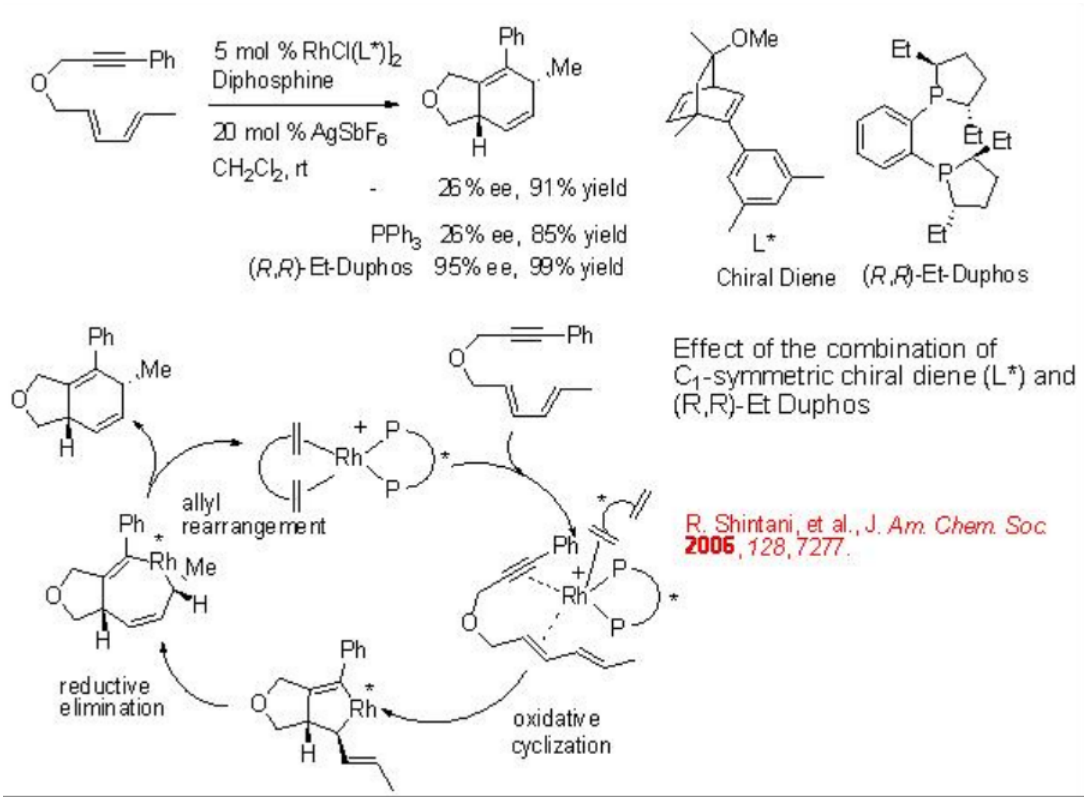
Scheme 2.1.10

Diels-Alder Type Reactions

Asymmetric intra- and intermolecular Diels-Alder reactions have made remarkable progress using chiral metal complexes as catalysts. Subsequently, several studies are focused on the use of chiral organocatalysis for this reaction. Since the organocatalysis based reactions are covered in module I, this lecture covers recent examples of the metal catalyzed reactions.

Intramolecular [4+2]-Cycloaddition

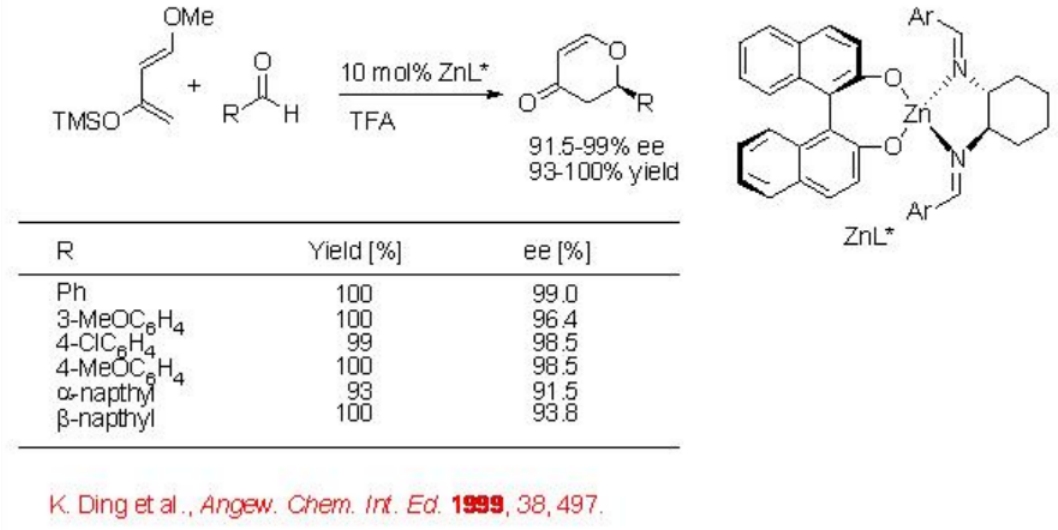
Intramolecular Diels-Alder reactions of unactivated dieneynes provide powerful tool to construct 5,6- or 6,6-fuzed rings. These fuzed rings can be inducted in the synthesis of many natural products. Therefore, a number of methods using transition metal catalysis have been developed over the past two decades. The chiral Rh complex bearing chiral diene and chiral phosphine has been shown to give better enantioselectivity compared to that bear achiral diene and chiral phosphine complex (Scheme 2.1.11).



Scheme 2.1.11

Intermolecular Diels-Alder Reactions

Intermolecular hetero Diels-Alder reactions have also been extensively explored using both chiral metal complexes as well as chiral organocompounds as catalysts. Since the use of chiral organocatalysis has been covered in module I, this section focuses on few examples using chiral metal complexes as the catalysts. The reaction of benzaldehyde with Danishefsky's diene proceeds in the presence of BINOL/diimine/Zn complex with excellent enantioselectivity and yield (Scheme 2.1.12).

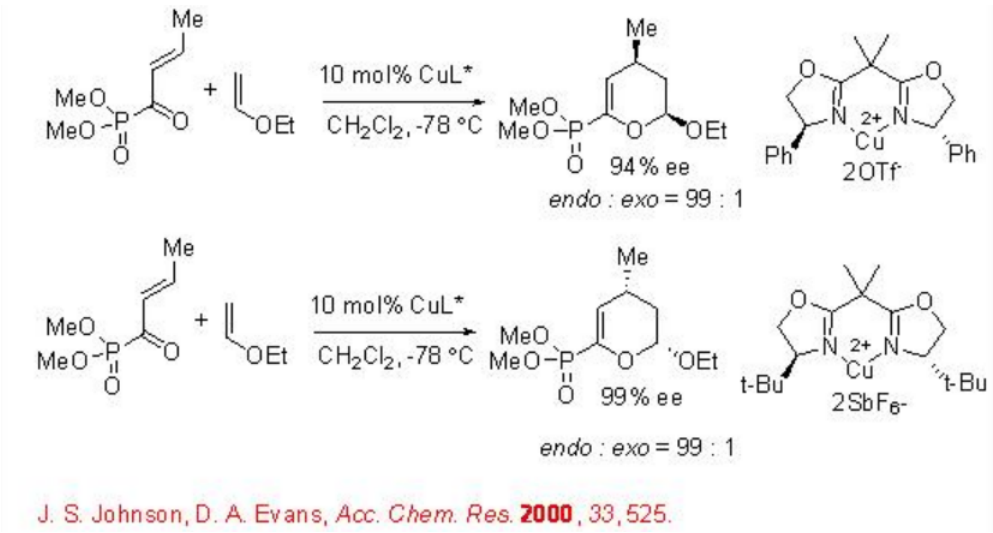


R	Yield [%]	ee [%]
Ph	100	99.0
3-MeOC$_6$H$_4$	100	96.4
4-ClC$_6$H$_4$	99	98.5
4-MeOC$_6$H$_4$	100	98.5
α-napthyl	93	91.5
β-napthyl	100	93.8

K. Ding et al., *Angew. Chem. Int. Ed.* **1999**, 38, 497.

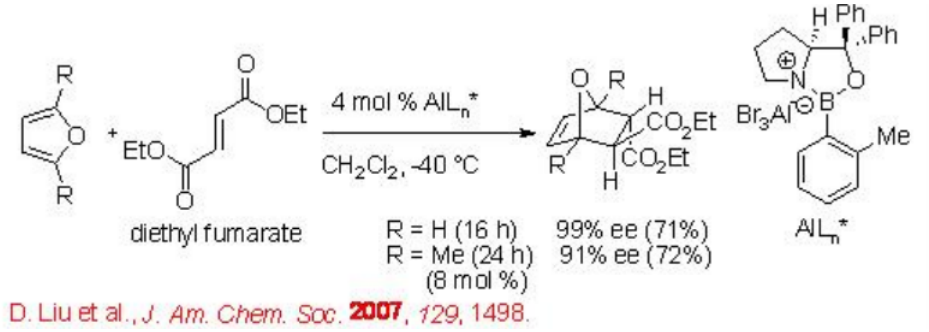
Scheme 2.1.12

Chiral box-Cu(II) complexes are found to be excellent catalysts for a variety of hetero Diels-Alder reactions (Scheme 2.1.13).



Scheme 2.1.13

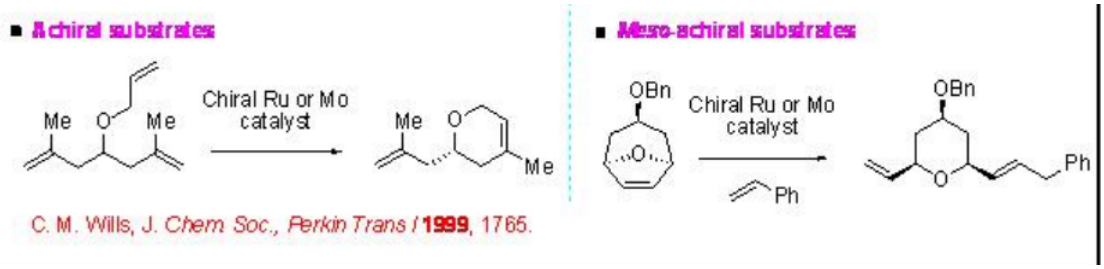
The readily accessible oxazaborolidine-aluminum bromide catalyst catalyzes the reaction of furan with diethyl fumarate with excellent enantioselectivity (Scheme 2.1.14).



***Scheme* 2.1.14**

2.2: Enantioselective Alkene Metathesis

Among the alkene metathesis catalysts, Mo and Ru-based complexes have emerged as powerful exhibiting complementary reactivity and functional group tolerance. The asymmetric alkene metathesis provides access to enantiomerically enriched molecules that can not be generally prepared through the commonly practiced strategy. Unlike most of the other enantioselective processes, alkene metathesis, which entails the formation and cleavage of carbon-carbon double bonds, does not involve the direct construction of *sp* 3 -hybridized stereogenic center. Instead, the stereochemistry is created indirectly, often by desymmetrization of an achiral substrate (Scheme 2.2.1), wherein the chiral catalyst has to discriminate between enaniotopic groups or sites of the molecule.

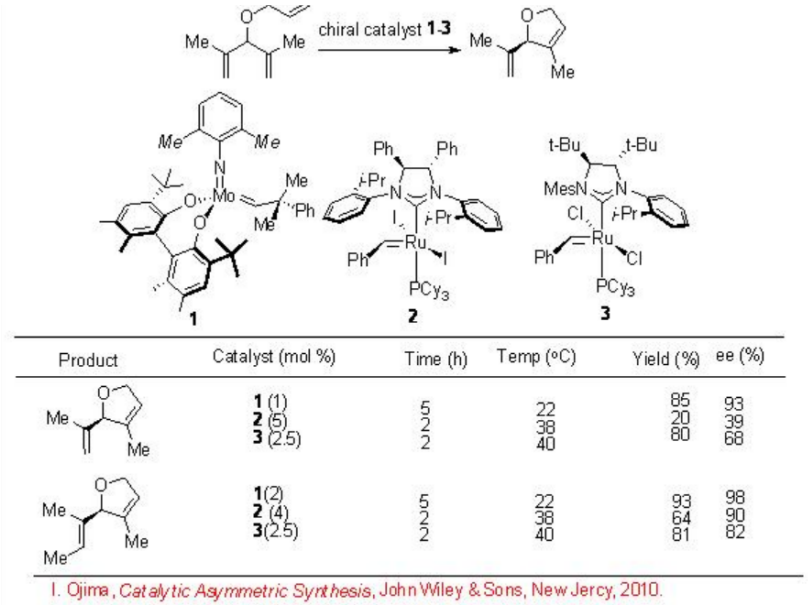


Scheme* 2.2.1*: Desymmetrization in catalytic enantioselective alkene metathesis .

Ring-Closing Metathesis (RCM) Reactions

2.2.1.1 Ru-Catalyzed Reactions

RCM is most commonly used in organic synthesis to construct cyclic systems, which are sometimes difficult to prepare by most of the other methods. During the past decade, several Ru and Mo-based chiral catalysts have been developed for the enantioselective RCM process and made remarkable progress. Scheme 2.2.2 summarizes examples for enantioselective RCM employing monodentate chiral NHC-Ru and chiral Mo-diolate complexes. The Ru-based catalysts are selective compared to Mo-based one, which catalyzes a wide range of substrates.



Product	Catalyst (mol %)	Time (h)	Temp (°C)	Yield (%)	ee (%)
	1 (1) **2** (5) **3** (2.5)	5 2 2	22 38 40	85 20 80	93 39 68
	1(2) **2** (4) **3**(2.5)	5 2 2	22 38 40	93 64 81	98 90 82

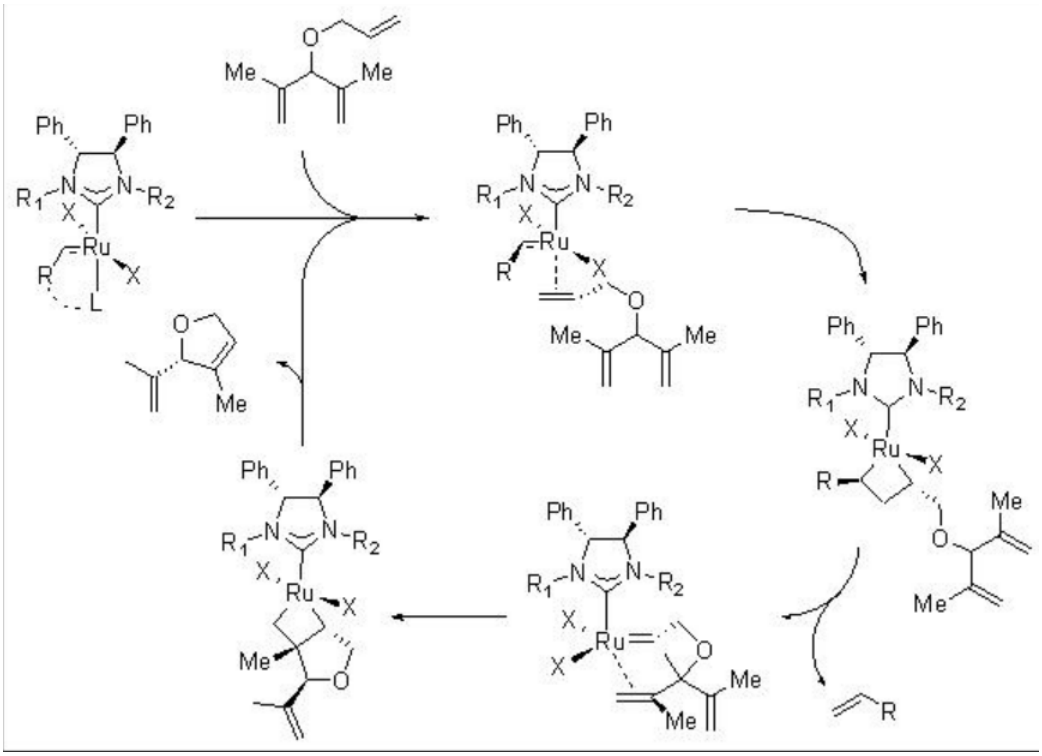
I. Ojima, *Catalytic Asymmetric Synthesis*, John Wiley & Sons, New Jercy, 2010.

Scheme 2.2.2: Comparison of Chiral Mo and Ru Catalysts in Enantioselective RCM

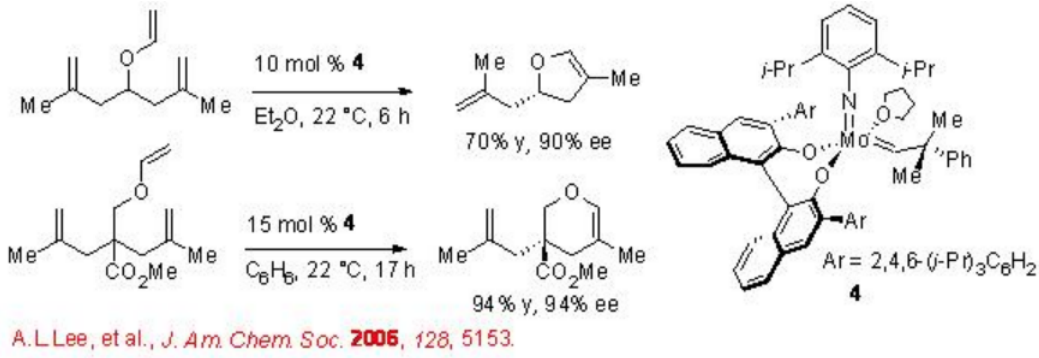
The mechanism of the Ru-catalyzed RCM is outlined in Scheme 2.2.3. Initiation of the reaction may take place *via* the dissociation of either the phosphine ligand or chelated etherate moiety. Subsequently, the less substituted alkene may make coordination to the Ru center, which could proceed [2+2]-cycloaddition, followed by cycloreversion and ruthenacyclobutane formation that could lead to the target product. The formation and cleavage of the cyclobutanes are crucial for the enantioselectivity of the products.

2.2.1.2 The Synthesis of Cyclic Enol Ethers using Mo-Catalyzed RCM

Mo-based RCM is found to be successful for the synthesis of furan and pyran products with up to 98% ee (Scheme 2.2.4). Although high catalyst loading is required, the products can be constructed with tertiary and quaternary stereogenic centers. In contrast, the Ru-based catalysts are not successful for this transformation.



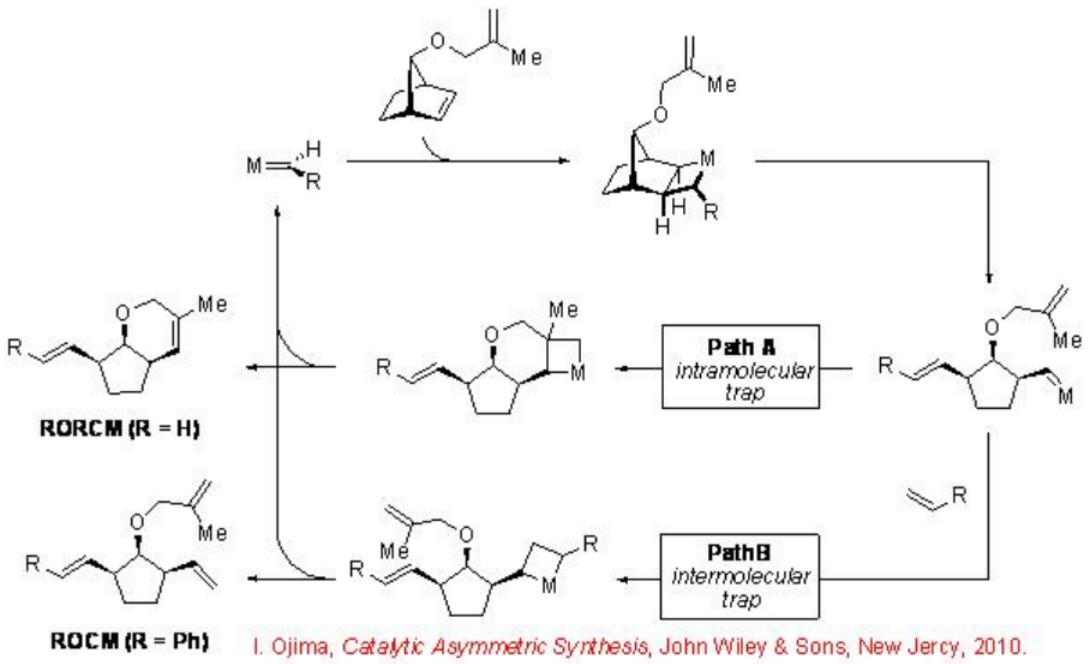
Scheme 2.2.3: Mechanism for Ru-catalyzed enantioselective RCM



Scheme 2.2.4: Synthesis of Cyclic Enol Ethers with Tertiary and Quaternary Stereogenic Centers

Ring-Opening/Ring-Closing Metathesis (RORCM) and Ring-Opening/Cross Metathesis (ROCM)

Following the ring opening, the resulting carbene intermediate can be traped intramolecularly by a pendant alkene (RORCM, Path A) or intermolecularly using a cross-partner (ROCM, Path B) (Scheme 2.2.5). These reaction pathways can be controlled by selection of the appropriate catalyst and cross partner, which can lead to a wide range of enantiomerically enriched products from common starting material. In the absence of intramolecular trap (ROCM process), a number of complex mixture of products can be generated.

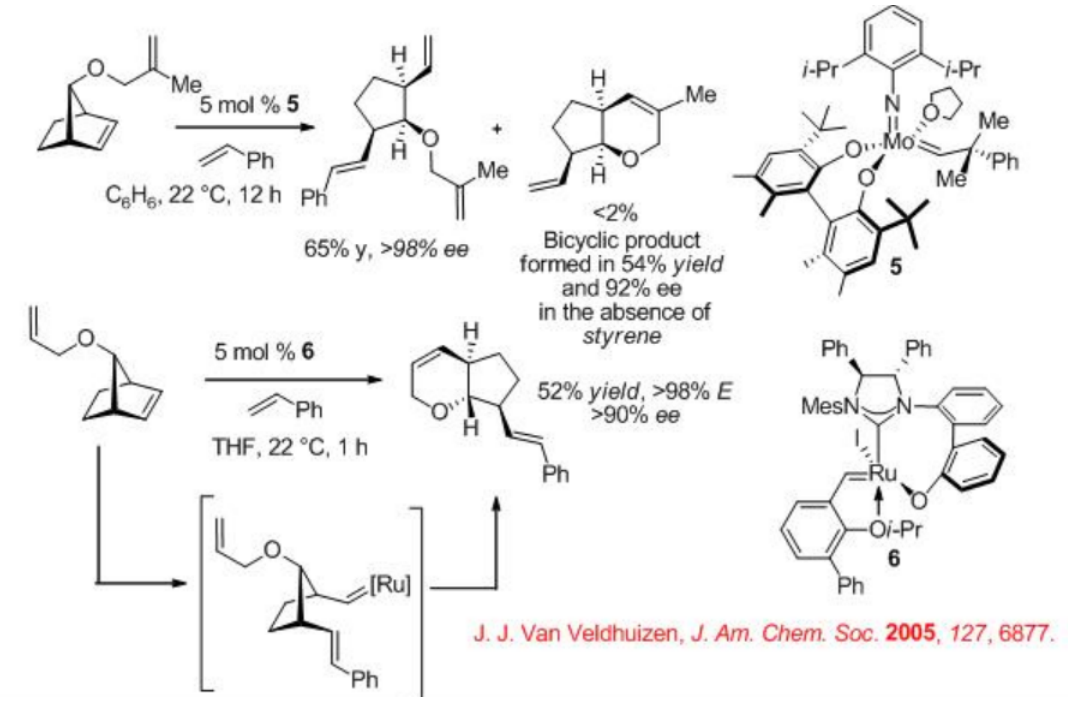


Scheme 2.2.5: Pathways for Enantioselective RORCM versus ROCM Products

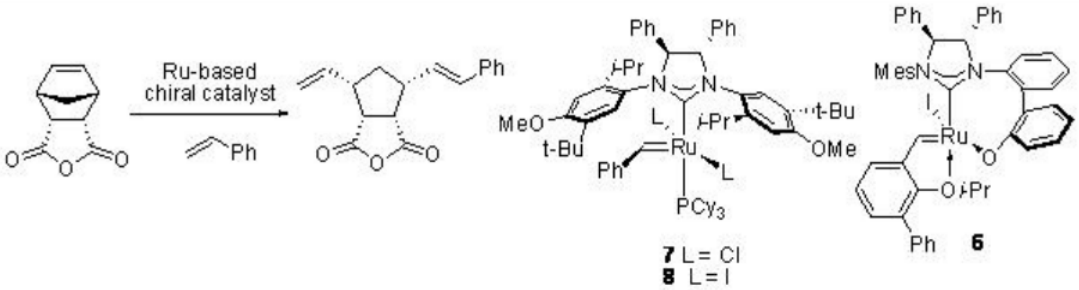
Scheme 2.2.6 presents examples for the Mo and Ru-catalyzed enantioselective ROCM processes. Norbornenes react with styrene *via* ROCM with high enantioselectivities. In both cases, *E* -alkenes are generated. In the absence of styrene, in the case of Mo-based system, RORCM product is formed with 92% ee. The substrate used for the Ru-catalyzed ROCM process, proceed polymerization in the presence of Mo-catalyst instead of ROCM process.

Scheme 2.2.7 shows the comparison of the Ru-catalyzed ROCM of norbornenes. The catalysts **7** and **8** bearing monodendate NHC ligands exhibit greater reactivity (i.e., lower catalyst loading) compared to the complex bearing bidendate NHC ligand **6** . But the systems using **7** and **8** produce poor *E* / *Z*selectivity, whereas the reaction using **6** gives exclusively *E* -isomer.

The synthesis of isoindole has been recently shown using chiral Ru-catalyzed RORCM with moderate enantioselectivity (Scheme 2.2.8). In this reaction the use of ethylene is to facilitate the release of the catalyst. The direct alkene metathesis product is unstable and thus it was isolated after hydrogenation.



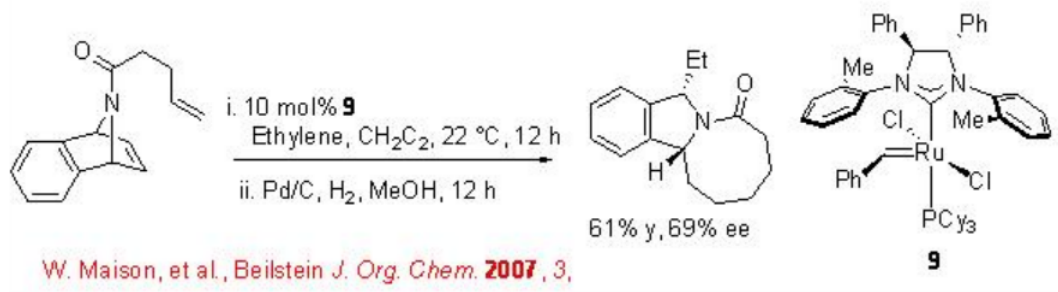
Scheme 2.2.6: Mo-and Ru-Catalyzed Enantioselective ROCM of Norbornenes.



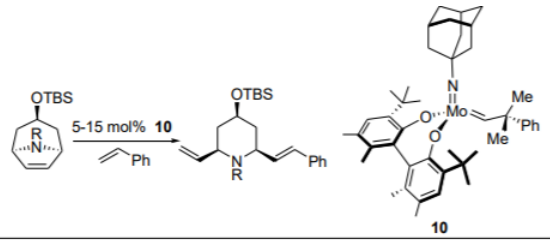
Catalyst (mol %)	Styrene (equiv)	Time	Temp. (°C)	Yield (%)	E/Z	ee(%)
7 (10)	1	10	22	95	1:1	76
8 (10)	3	10	22	96	1:1	80
6 (5)	5	5	22	50	98:2	90

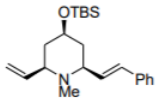
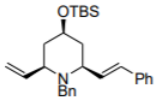
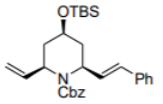
J. M. Berlin, et al., *Angew. Chem. Int. Ed.* **2006**, *45*, 7591.

Scheme 2.2.7: Comparison of the Activity of Chiral Ru Catalysts in ROCM of Norbornene



Scheme 2.2.8



Product	10 (mol%)	Time (h)	Yield (%)	ee (%)
	5	1	95	94
	5	1	85	21
	10	24	80	82

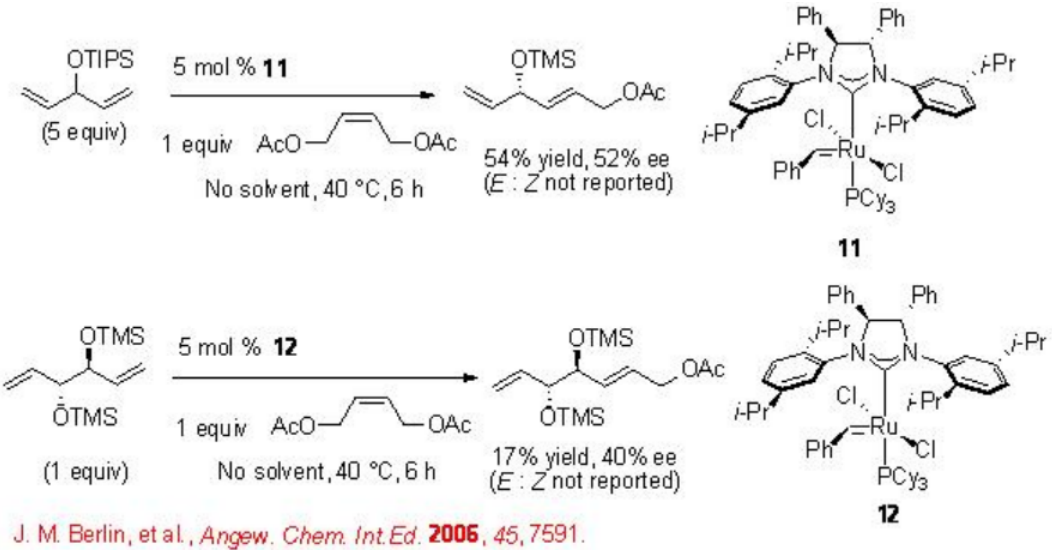
G. A. Cortez et al., *Org. Lett.* **2007**, 9, 2871.

Scheme 2.2.9: Enantioselective ROCM Reaction of *meso* -Azabicyles

2,6-Disubstituted piperidines are important structural unit present in medicinally significant compounds. Using the Mo-based enantioselective ROCM reactions, the synthesis of the *N* -protected 2,6-substituted piperidines can be accomplished from of *meso* -azabicycles with moderate to high enantioselectivities (Scheme 2.2.9).

Cross-Metathesis (CM)

Catalytic enantioselective CM is least developed in enantioselective alkene metathesis reactions. Unlike the ring-closing and ring-opening metatheses that are thermodynamically driven, there is minimal driving force for the CM. In addition, selectivity between two different cross partners leads to complex. Scheme 2.2.10 presents some examples of CM using chiral Ru complexes with moderate enantioselectivity. These substrates don't proceed RCM due to ring strain of the products.

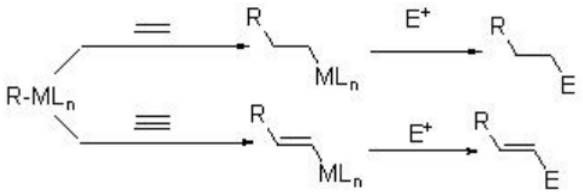


J. M. Berlin, et al., *Angew. Chem. Int. Ed.* **2006**, *45*, 7591.

Scheme 2.2.10: Catalytic enantioselective cross-metathesis reactions

2.3: Carbometallation and Carbocyclization Reactions

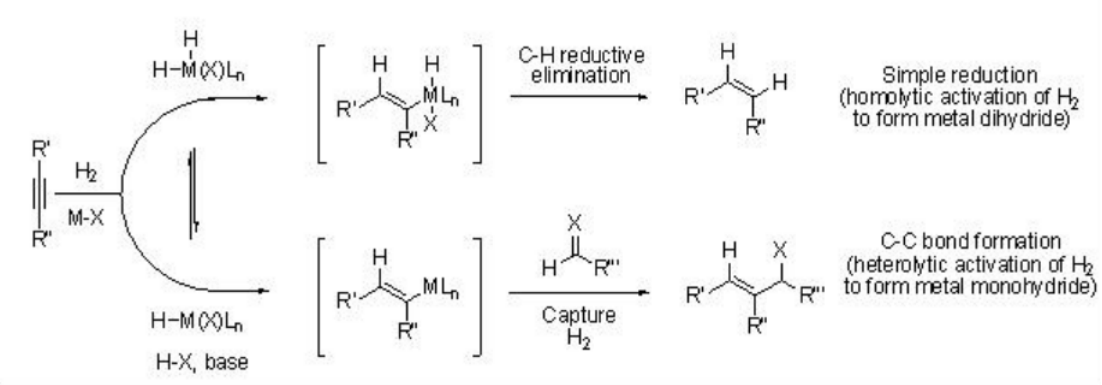
Organometallic compounds add to carbon-carbon multiple bonds to give a new organometallic species, which could be further modified to yield new carbon-carbon bonds. These processes are called as “carbometallation reactions”. It primarily refers to the relationship between the reactants and products (Scheme 2.3.1). This section covers some examples of the asymmetric carbometallation reactions using Rh, Cu and Pd-based systems.



Scheme 2.3.1

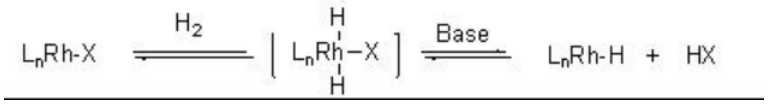
Rhodium-Catalyzed Reactions

Hydrogen-mediated carbon-carbon bond formation has emerged as powerful industrial process in chemical industries. For example, the hydroformylation and Fischer-Tropsch reactions are well known for the hydrogen-mediated carbon-carbon bond formation reactions. These processes require heterolytic activation of molecular hydrogen to give monohydride species, where the C-H reductive elimination pathway is disabled. Addition of a metal hydride to carbon-carbon multiples bonds (i.e., alkene and alkyne) give organometallic species that could be rapidly captured by an electrophile (i.e., aldehydes and imine) prior to its reaction with molecular hydrogen *via* oxidative addition or σ-bond metathesis of carbon-metal bond. Scheme 2.3.2 illustrates metal-dihydride route (leading to hydrogenation) and metal-monohydride route (leading to C-C bond formation) with an alkyne.



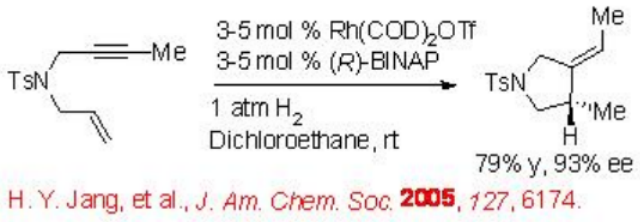
Scheme 2.3.2

Formation of the monohydride organometallic species depends on the choice of the catalytic system. For example, the heterolytic activation of molecular hydrogen is observed with cationic rhodium complexes in the presence of base. The reaction takes place *via* the oxidation addition of the molecular hydrogen with metal species followed by a base induced reductive elimination of HX (Scheme 2.3.3).



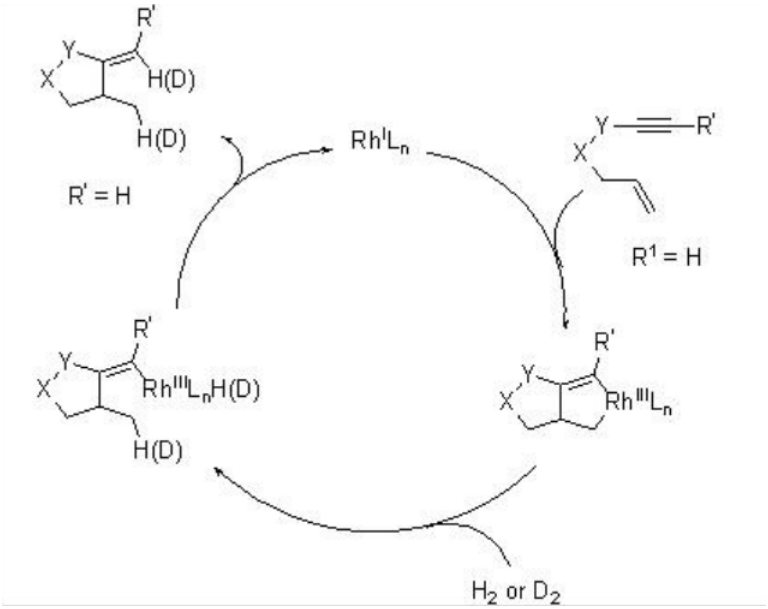
Scheme 2.3.3

For example, Scheme 2.3.4 presents enantioselective reductive cyclization of 1,6-enynes using Rh(COD)$_2$ OTf and (*R*)-BINAP in the presence of molecular hydrogen. This carbocyclization reaction is compatible with various functional groups, however, the yield and enantioselectivity of the product depends on the structure of 1,6-enynes and the ligands.



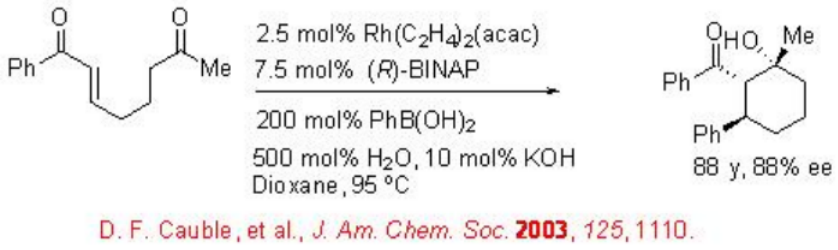
Scheme 2.3.4

A possible mechanism has been proposed for this reaction based on deuterium labeling control experiments (Scheme 2.3.5). The catalytic cycle starts with cycloaddition of RhL_n and 1,6-enyne forming rhodacyclopentene. Homolytic hydrogen activation *via* oxidative addition of molecular hydrogen or σ-bond metathesis may lead to the formation of vinyl-rhodium vinyl species that could afford cyclization product by reductive elimination to complete the catalytic cycle.



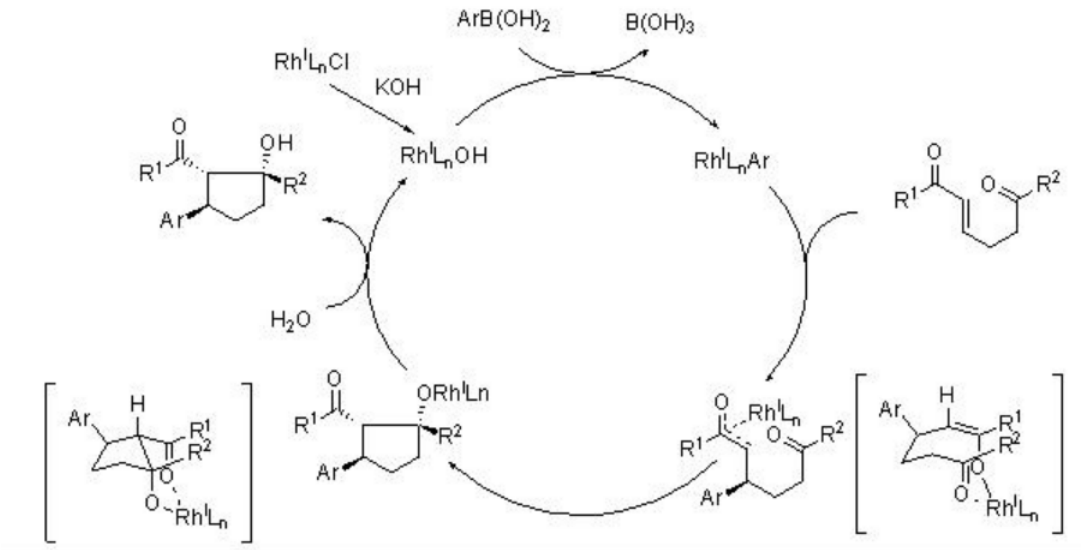
Scheme 2.3.5

1,4-Conjugate addition of organometallic reagents to α,β -unsaturated carbonyl compounds afford effective method for carbon-carbon bond formation. Much effort has been on the development of asymmetric version of the reaction using a series of catalytic systems. The first reductive aldol cyclization of keto-enone with phenylboronic acid has been shown utilizing $Rh[(COD)Cl]_2$ and (*R*)-BINAP with yield and enantioselectivity (Scheme 2.3.6).



Scheme 2.3.6

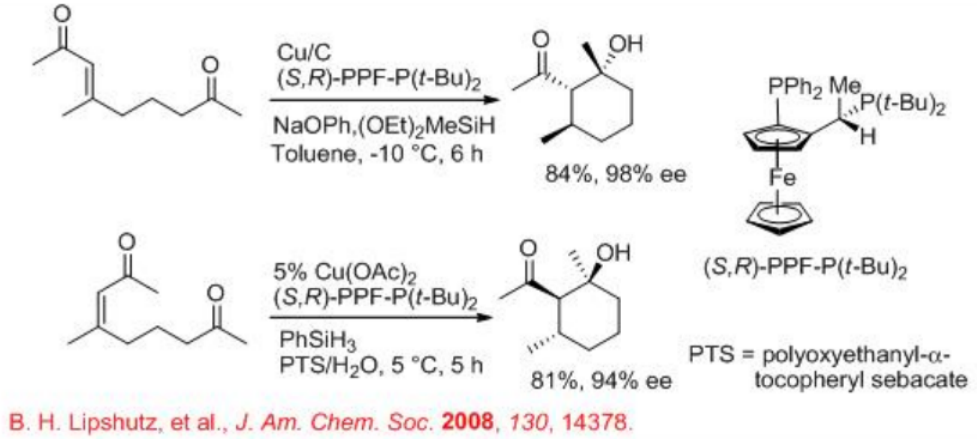
The mechanism of the reaction is presented in Scheme 7. The observed stereochemistry has been rationalized by assuming *Z* -enolate formation.



Scheme 2.3.7

Copper-Catalyzed Reactions

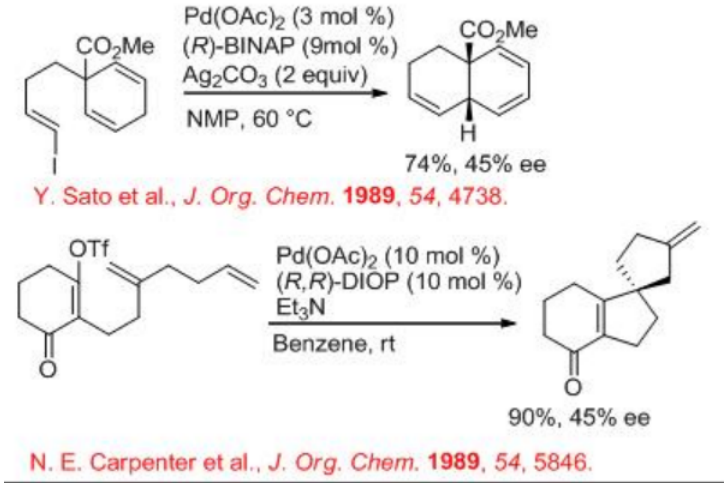
CuH is found to be highly efficient catalyst for the asymmetric reductive aldol cyclization of keto-enones to give the target product as a singly diastereoisomer with high enantiopuritiy (Scheme 2.3.8). These reactions use ferrocenylphosphines, (*S*, *R*)-PPE-P(*t* -Bu)$_2$, as effective chiral ligands in the presence of silane as a hydride source (Scheme 2.3.8). These reactions can also be carried out under heterogeneous as well as aqueous conditions with surfactant.



Scheme 2.3.8

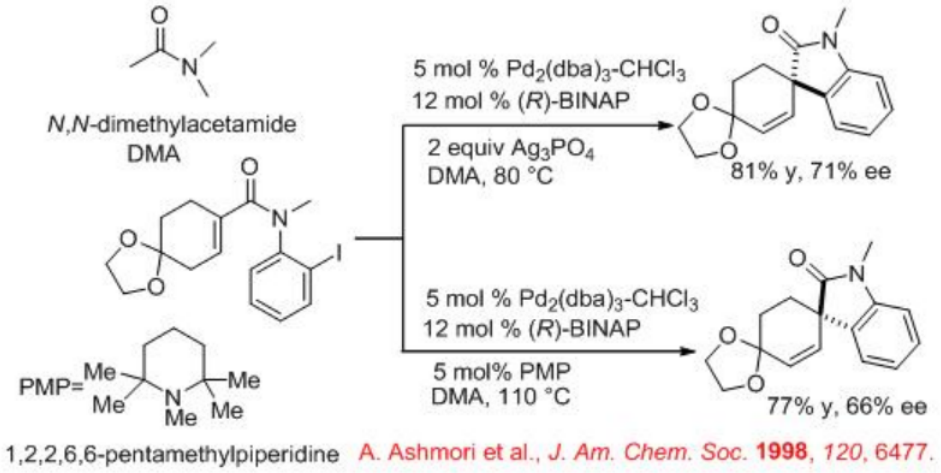
Palladium-Catalyzed Reactions

The palladium-catalyzed cross-coupling reactions of aryl or alkenyl halides with alkenes in the presence of base are among the powerful reactions in organic synthesis to construct carbon-carbon bonds. The asymmetric version of the reaction is also well explored. Scheme 2.3.9-2.3.12 illustrates some examples for the intramolecular and intermolecular Heck reactions. In 1970, the Heck reaction was discovered and, in 1989, the first example of asymmetric intramolecular Heck reactions appeared using Pd(OAc)$_2$ with (*R*)-BINAP with moderate enantioselectivity (Scheme 2.3.9).



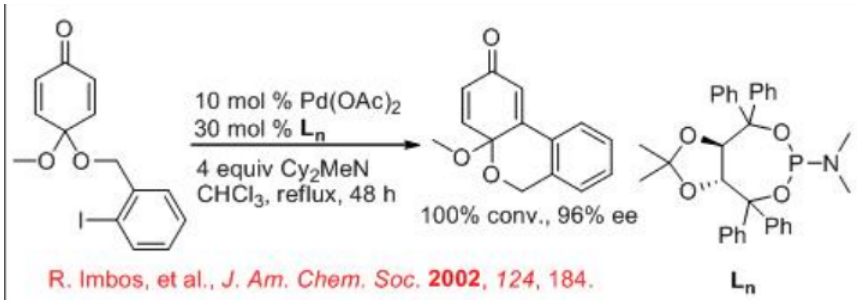
Scheme 2.3.9

The intramolecular Heck reaction finds wide applications in organic synthesis. Among those applications the synthesis of optically active oxindoles having a quaternary asymmetric center has been considerably explored. Because the oxindole moiety serves as useful synthetic intermediate in the synthesis of numerous natural products. For example, (*E*)- α,β -unsaturated-2-iodoanilide undergoes cyclization in the presence of Pd_2 $(dba)_3$-$CHCl_3$ and (*R*)-BINAP to give oxindoles with (*S*) or (*R*) configuration under cationic and neutral conditions, respectively. It is noteworthy that a dramatic switching in the direction of asymmetric induction has been observed between the two conditions even though the same chiral ligand (*R*)-BIANP is employed. In these reactions, $Ag_3PO_4$and PMP act as HI scavenger.



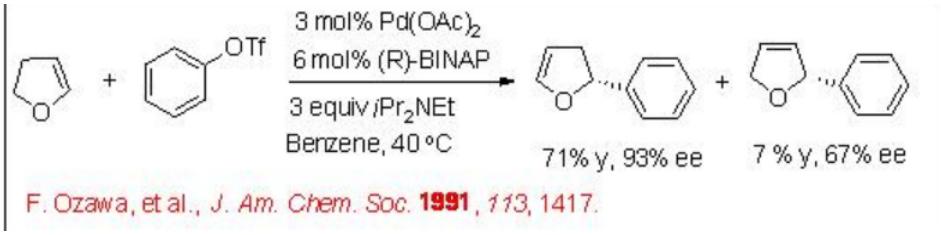
Scheme 2.3.10

The use of TADDOL-based monophosphoramide has been demonstrated instead of BINAP in the reaction of intramolecular cyclization of cyclohexadienone derivatives (Scheme 2.3.11). This reaction can be performed in the absence of silver salt.

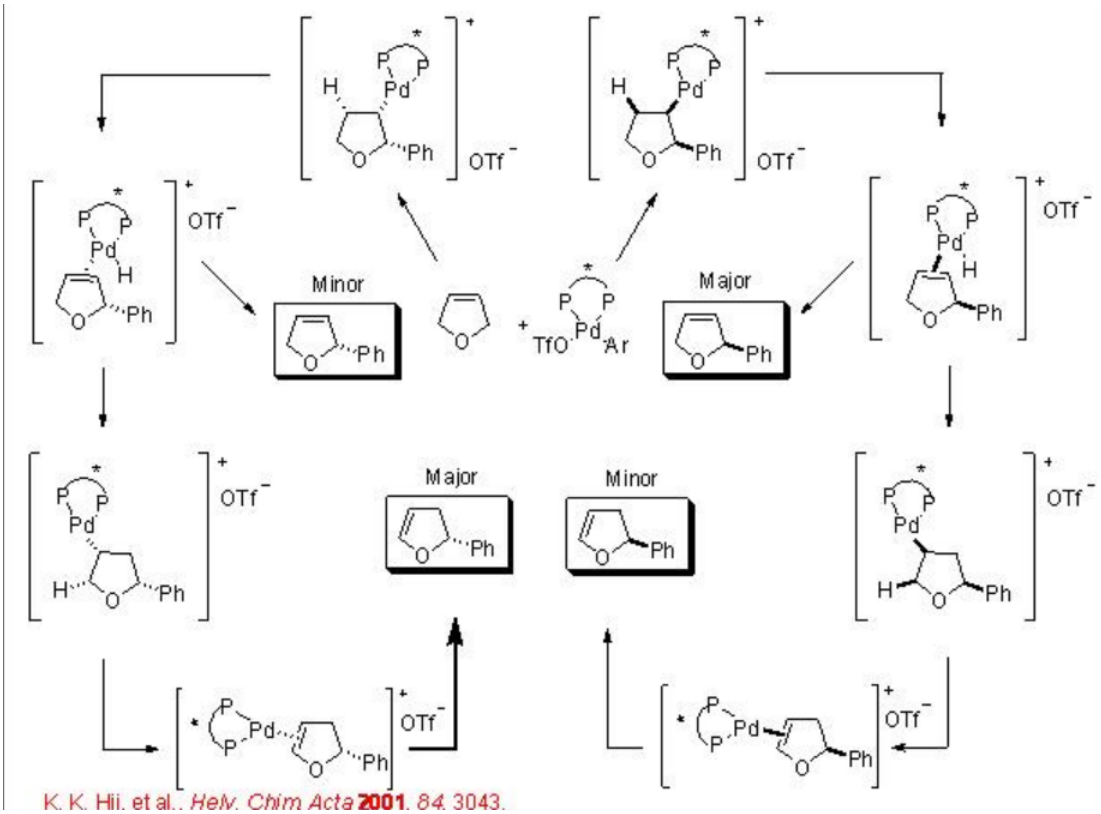


Scheme 2.3.11

Intermolecular Heck reaction is also well studied. For example, dihydrofuran reacts with phenyl triflate to give 2-phenyl-2,3-dihydrofuran along with small amount 2-phenyl-2,5-dihydrofuran in the presence of Pd-BINAP with excellent enantioselectivity (Scheme 2.3.12). A mechanism has been proposed to explain the high enantioselectivity of the major product and inversion configuration of the minor product (Scheme 2.3.13). It involves a kinetic resolution process that enhances the enantioselectivity of the major product.

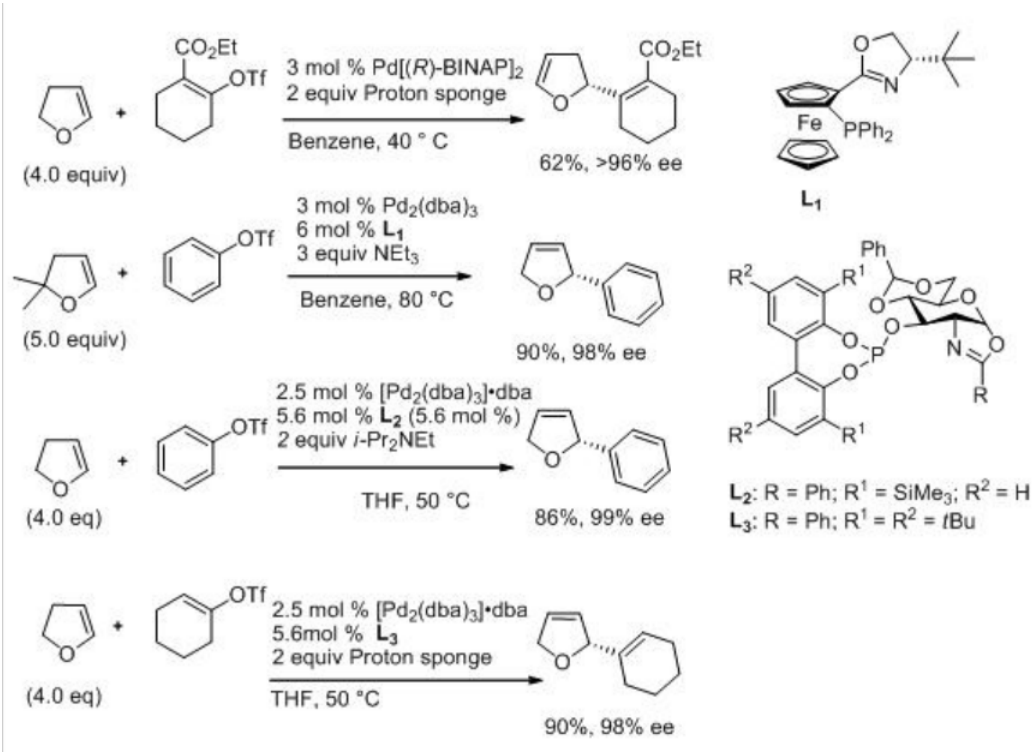


Scheme 2.3.12



Scheme 2.3.13

Scheme 2.3.14 exemplifies the reactions of 2,3-dihydrofuran and 2,2-dimethyl-2,3-dihydrofuran with phenyl triflate, 2-carbethoxy cyclohexenyl triflate and cyclohexenyl trilfate using palladium complexes with oxazoline based aminophosphine and (D-glucosamine)phosphiteoxazoline as the ligands. The reactions are effective affording the products with excellent enantioselectivity.



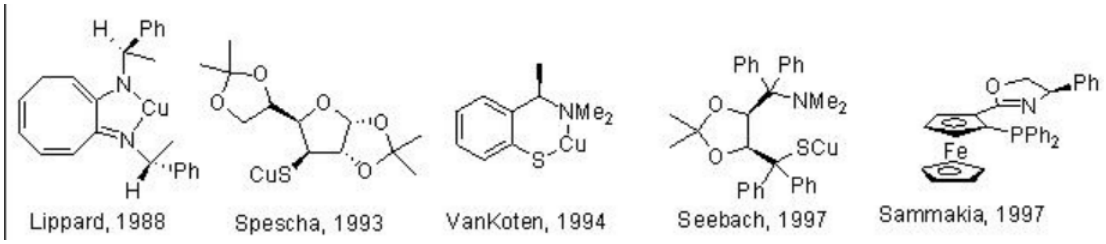
Scheme 2.3.14

2.4: Metal-Catalyzed Asymmetric Conjugate Addition Reactions

Asymmetric conjugate addition is one of the powerful tools for the construction carbon-carbon and carbon-heteroatom bonds in organic synthesis. This reaction finds extensive applications for the construction enantioenriched carbon skeletons for the total synthesis of numerous biologically active compounds. Sometimes possible to construct multiple stereocentres in single synthetic operation. This lecture covers some examples for the recent developments in the conjugate addition of Grignard, organozinc, organolithium, organocopper and organoborane reagents with activated alkenes in the presence of chiral ligand or chiral catalysts.

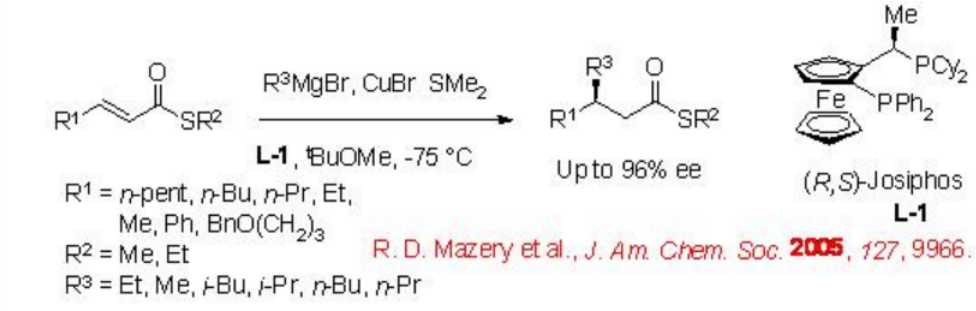
Reactions of Grignard Reagents

The conjugated addition of Grignard reagents with electrophilically activated alkenes is well explored. Some of the chiral ligands developed for the conjugate addition reactions of Grignard reagents with α,β -unsaturated carbonyl compounds are shown in Scheme 2.4.1.



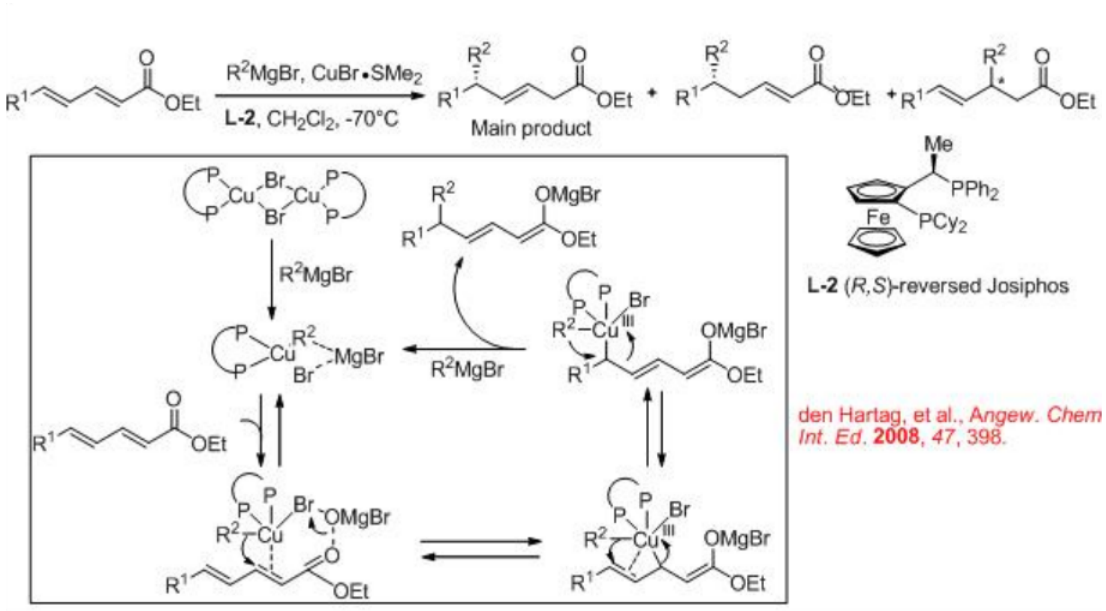
Scheme 2.4.1

One of the recent examples is the addition of alkyl magnesium bromide to α,β -unsaturated thioesters using Josiphos ligand **L-1** (Scheme 2.4.2). The reactions of a series of examples can be accomplished with up to 96% enantioselectivity.



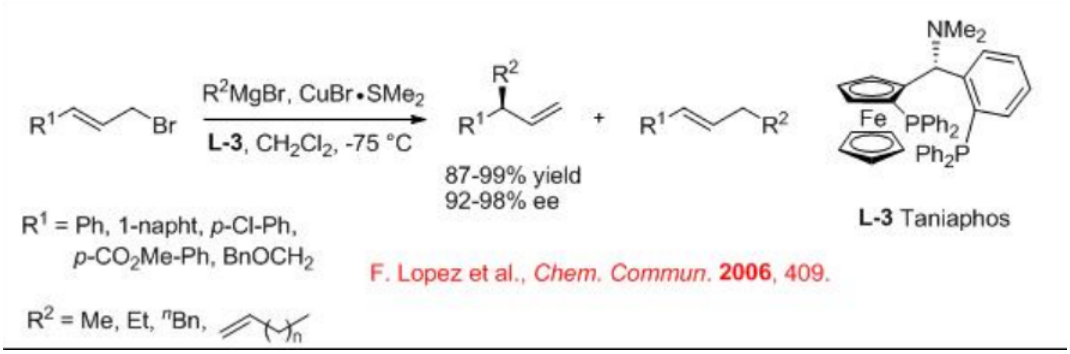
Scheme 2.4.2

Compared to the 1,4-conjugate addition reaction, the reactions with extended Michael acceptors needs additional control of the regioselectivity. For example, using the (*R*,*S*)-reversed Josiphos ligand **L-2** , 1,6-asymmetric conjugate addition to α,β,γ,δ -unsaturated esters has been developed (Scheme 2.4.3).



Scheme 2.4.3

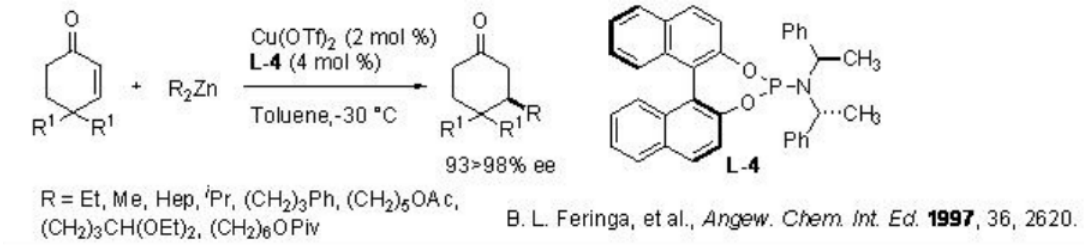
Besides the ferrocenyl ligands **L1-2** , taniaphos **L-3** with $CuBr{\cdot}SMe_2$ is also highly effective for the conjugate addition of allylic electrophiles with Grignard reagents (Scheme 2.4.4). In this reaction, aliphatic allylic bromides have been found to be excellent substrates.



Scheme 2.4.4

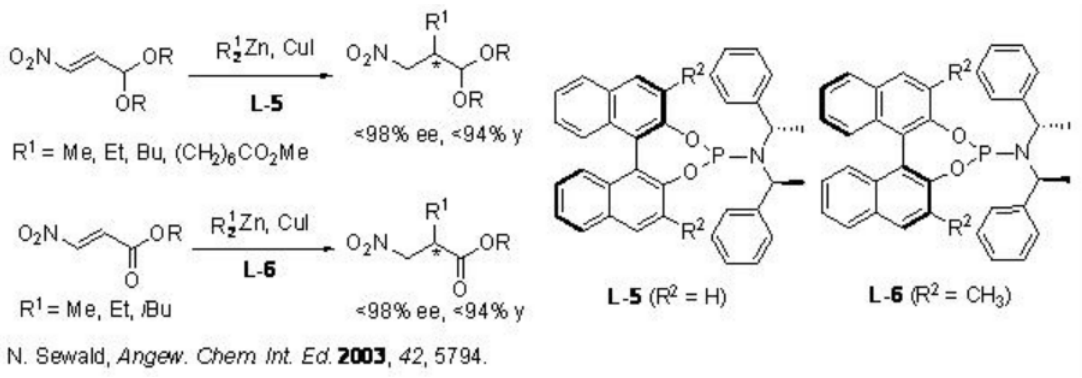
Reactions of Organozinc Reagents

The asymmetric conjugate addition of dialkylzinc to prochiral α,β -unsaturated compounds is one of the powerful methods for carbon-carbon bond formation in organic synthesis. Much attention has been made on the development of new ligands for this reaction. Phosphoramidite ligand from BINOL **L-4** has been found to be effective for the conjugate addition to cyclic substrates with up to 98% ee (Scheme 2.4.5).



Scheme 2.4.5

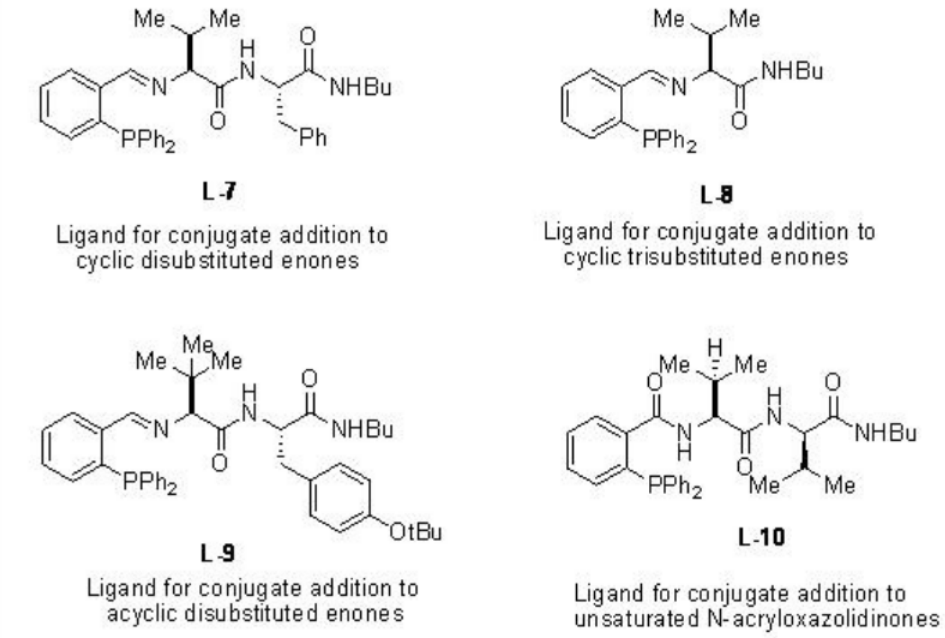
Subsequently, copper(I)-catalyzed enantioselective addition of dialkylzinc to 3-nitroacrolein derivatives has been demonstrated using phosphoramidite ligands **L-5** and **L-6** with up to 98% ee (Scheme 2.4.6).

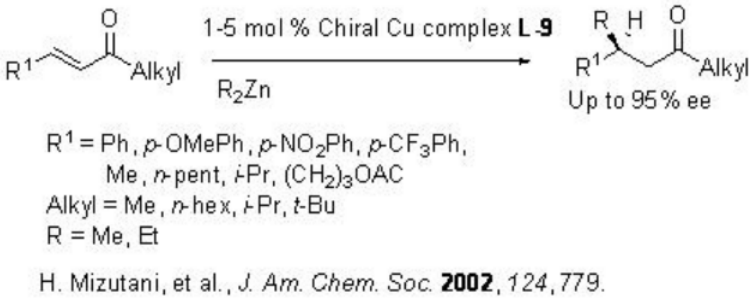


N. Sewald, *Angew. Chem. Int. Ed.* **2003**, *42*, 5794.

Scheme 2.4.6

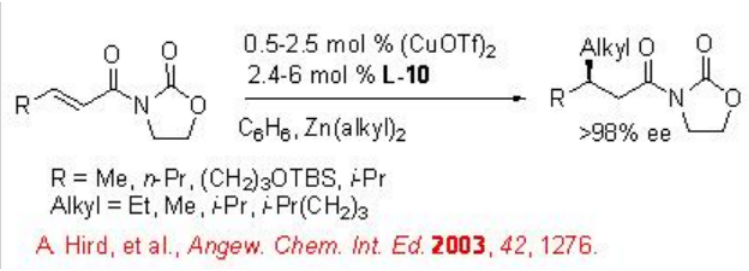
Scheme 2.4.7 summarizes some of the peptide based ligands for the dialkylzinc addition to α,β -unsaturated compounds. For example, the copper-catalyzed conjugate addition of dialkylzinc reagents to acyclic aliphatic α,β -unsaturated ketones proceed in the presence of **L-9** with up to 94% ee, while the reaction using **L-10** gives up to 98% ee (Scheme 2.4.8).





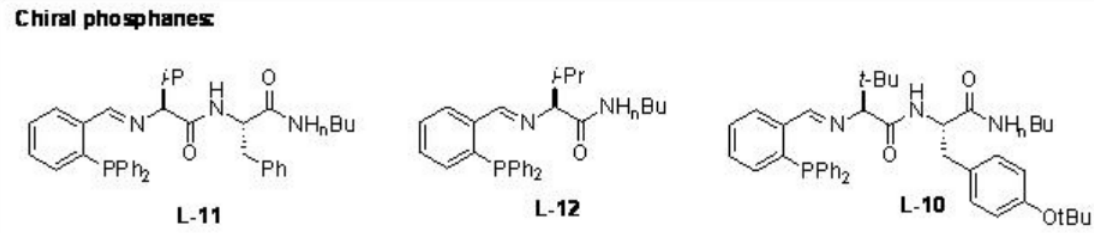
H. Mizutani, et al., *J. Am. Chem. Soc.* **2002**, *124*, 779.

Scheme 2.4.7

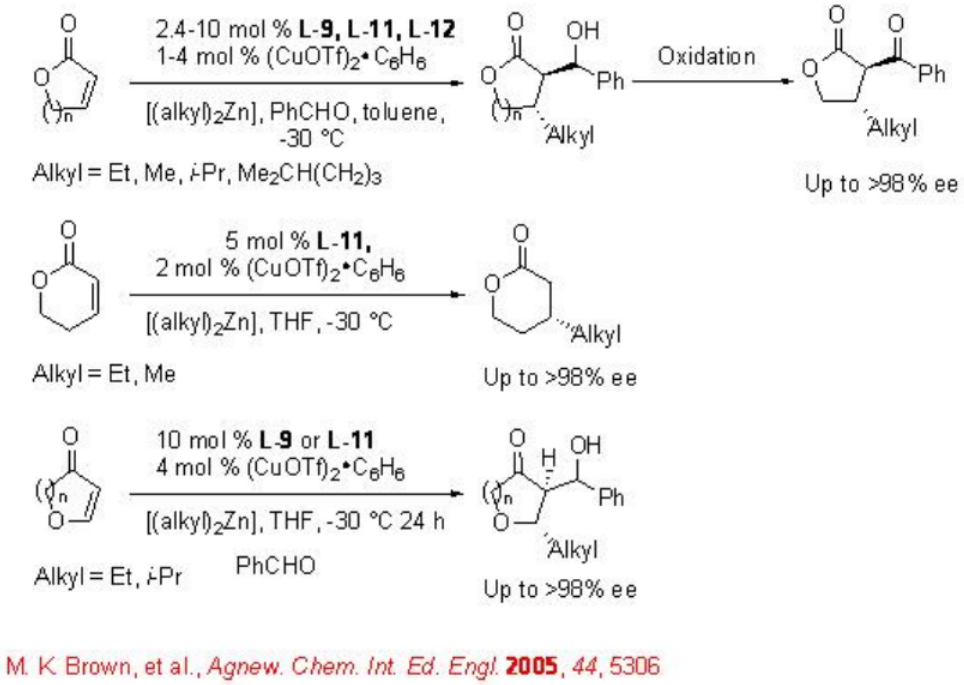


Scheme 2.4.8

Later, the chiral ligands **L-10** to **L-12** have been studied for the reactions of dialkylzinic reagents to heterocyclic enones such as furanones, pyranones and their derivatives (Scheme 2.4.9-2.4.10).



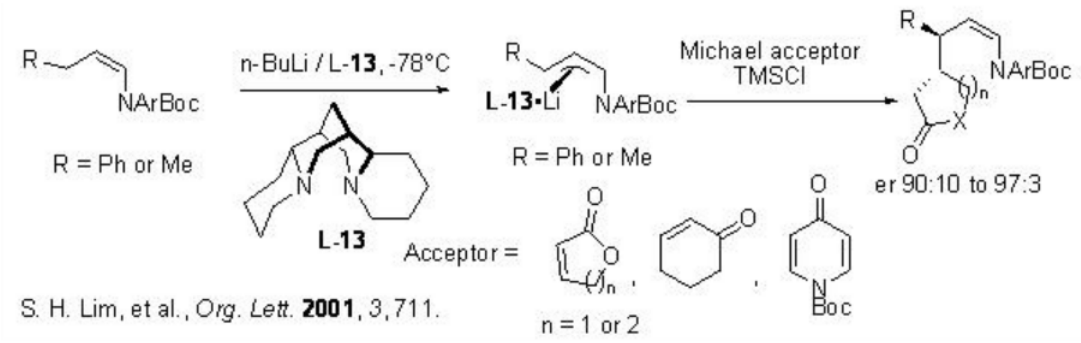
Scheme 2.4.9



Scheme 2.4.10

Reactions of Organolithium Reagents

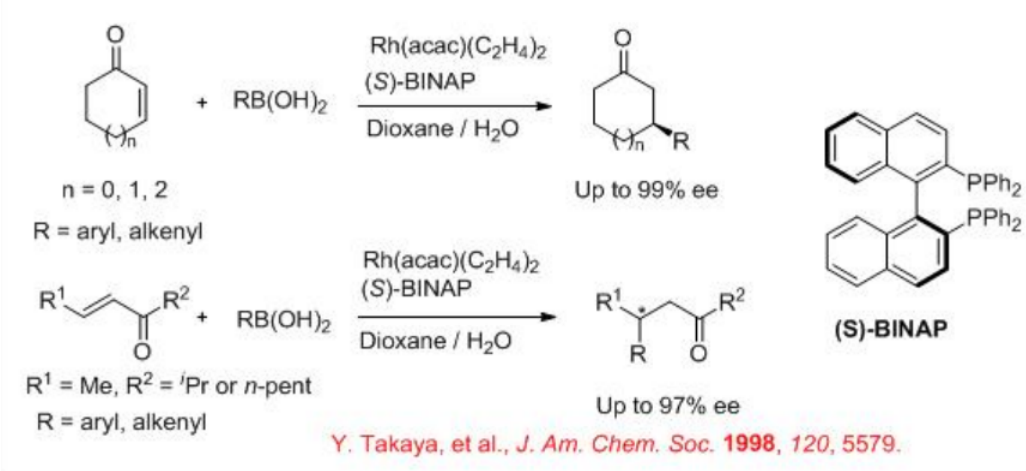
Organolithium reagents are highly reactive species and their conjugate addition reactions with α,β-unsaturated carbonyl compounds are of great interests. One of the recent examples is the reaction of configurationally stable organolithium to α,β -unsaturated cyclic carbonyl compounds using (-)-sparteine that can be performed with high enantioselectivity (Scheme 2.4.11).



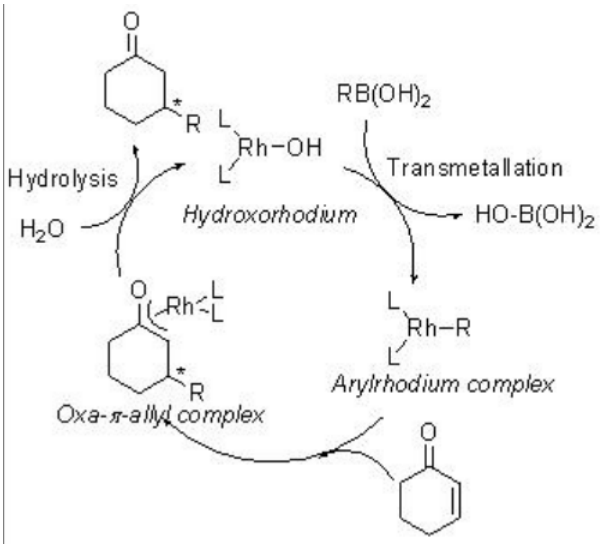
Scheme 2.4.11

Reactions of Organoboranes

The asymmetric conjugate addition of organoboranes using chiral rhodium phosphine complex is a successful process. For example, arylboronic and alkenylboronic acids undergo reaction with cyclic and acyclic α,β -unsaturated ketones in the presence of chiral rhodium complex bearing (*S*)-BINAP with high enantioselectivity (Scheme 2.4.12). The reaction proceeds *via* phenylrhodium, oxa- π -allylrhodium and hydroxorhodium intermediates (Scheme 2.4.13).

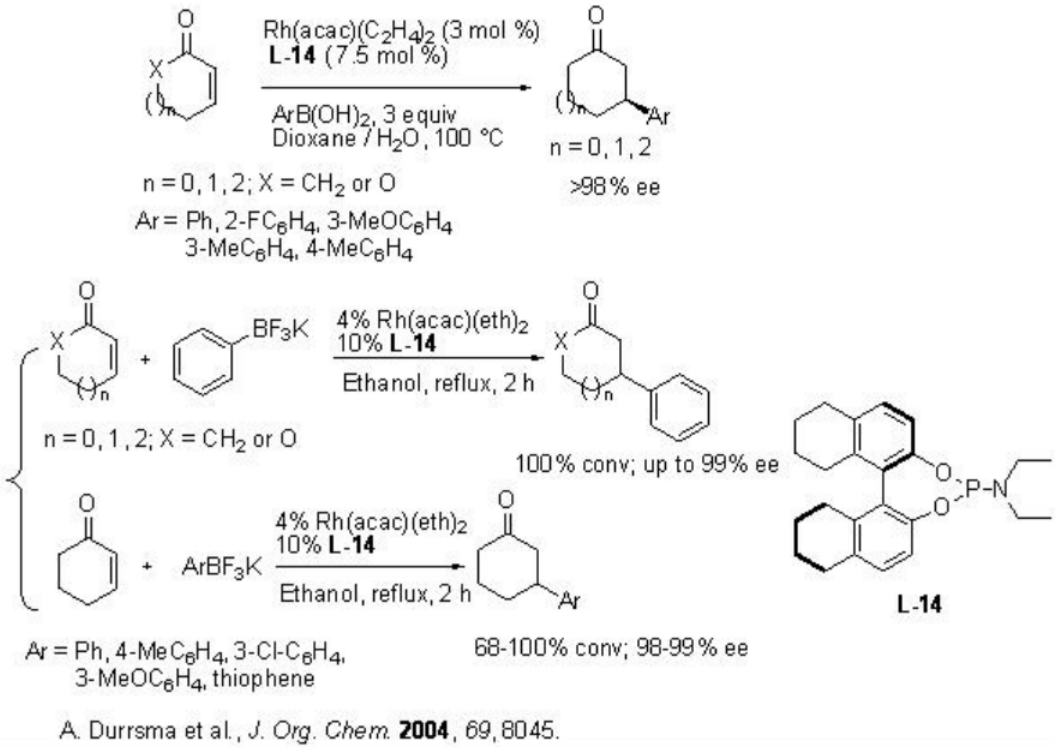


Scheme 2.4.12



Scheme 2.4.13

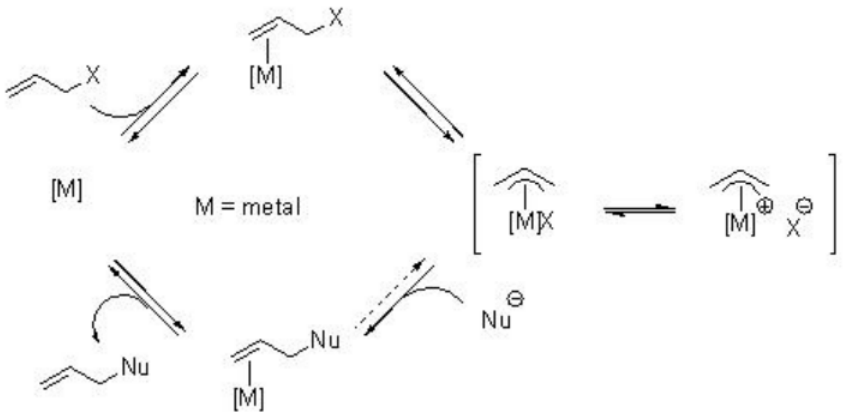
Besides chiral biphosphines, chiral dienes and chiral phosphoramidite ligands are also effective for the rhodium catalyzed conjugate addition of organoboranes. For example, the rhodium catalyzed conjugate addition of boronic acids and potassium trifluoroborates to enones occurs with high enantioselectivity (Scheme 2.4.14).



Scheme 2.4.14

2.5: Allylic Substitution with Carbon Nucleophiles

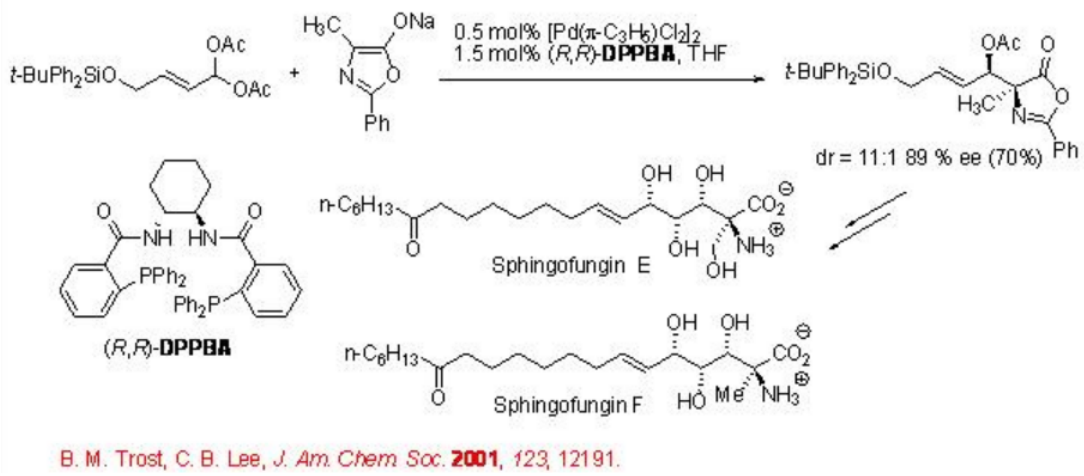
The metal-catalyzed allylic substitution is one most of the important processes in organic synthesis. Scheme 1 represents the catalytic cycle of a transition metal based allylic substitution reaction. The reaction begins with the coordination of the low valent metal complex to the double bond of an allylic system. Subsequent oxidative addition by removal of the leaving group X gives a π -allyl complex as intermediate. The intermediate could be a neutral or cationic species, depending on the nature of the ligands and the counter ion X. The nucleophile typically adds to the terminal carbon with inversion of configuration rather than *via* the metal cation with retention (Scheme 2.5.1).



Scheme 2.5.1

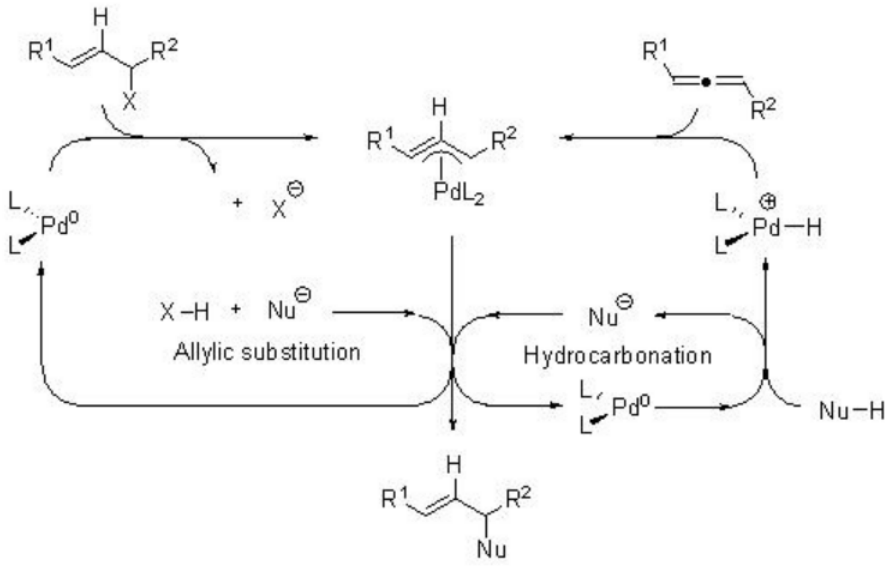
Palladium-Catalyzed Reactions

The palladium catalyzed allylic substitution reaction is a very powerful process. This section covers some recent examples on the palladium catalyzed enantioselective allylic substitution with carbon nucleophiles. The use of azlactones as a soft stabilized pronucleophile is particularly important because they give rise to amino acids as products. Scheme 2.5.2 presents Trost's synthesis of spingofungins *via* alkylation of a geminal diacetate with an azlactone. The product is formed with good diastereo- and enantioselectivity.



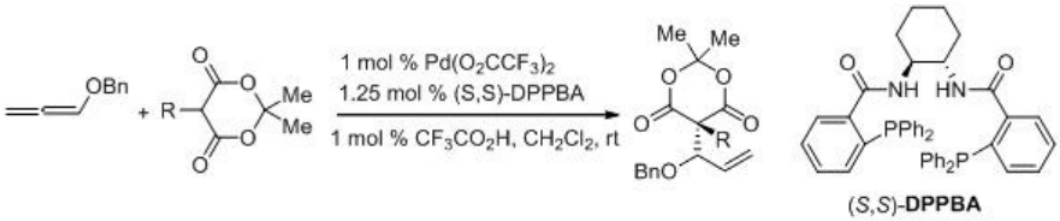
Scheme 2.5.2

Atom economical method to obtain (π -allyl)Pd intermediates from allenes by addition of hydrido-Pd complexes has been demonstrated (Scheme 2.5.3). This method affords the same products as that of the standard alkylation of allylic substrates. The pronucleophile are sufficiently acidic to produce $HPdL_2$ species (Scheme 2.5.4).



B. M. Trost et al., *J. Am. Chem. Soc.* **2003**, *125*, 4438.

Scheme 2.5.3: . Allylic alkylation and hydrocarbonation

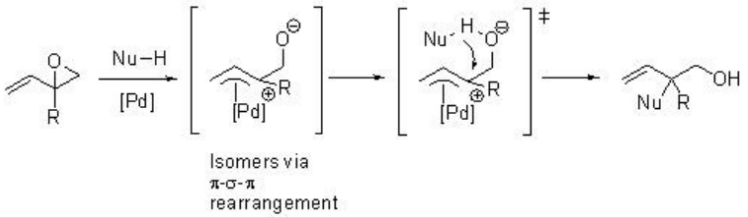


R	Yield [%]	ee [%]
CH_3	75	99
$(CH_3)_2CHCH_2$	61	88
$CH_2=CHCH_2$	82	96
$PhCH_2$	90	91
$2\text{-}C_4H_3OCH_2$	81	94
OH	63	82

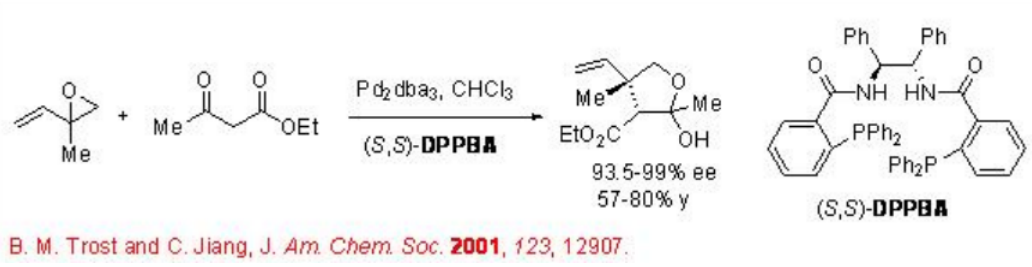
B. M. Trost et al., *J. Am. Chem. Soc.* **2003**, *125*, 4438.

Scheme 2.5.4

The palladium catalyzed reaction of vinyl epoxide with nucleophiles provides branched products (Scheme 2.5.5). This is due to interaction of the nucleophile with an alkoxy or OH moiety produced by reaction with the Pd(0) species. For example, the reaction of isoprene monoepoxide with β-keto esters preferentially gives the branched alkylation products in the form of the hemiacetals (Scheme 2.5.6). The nature of the β-ketoester and optimization of the reaction conditions are crucial for the success of this process.



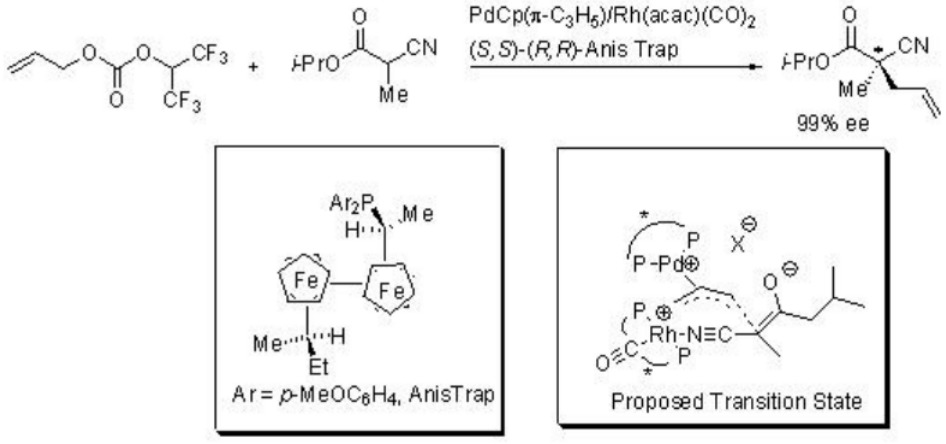
Scheme 2.5.5



B. M. Trost and C. Jiang, J. *Am. Chem. Soc.* **2001**, *123*, 12907.

Scheme 2.5.6

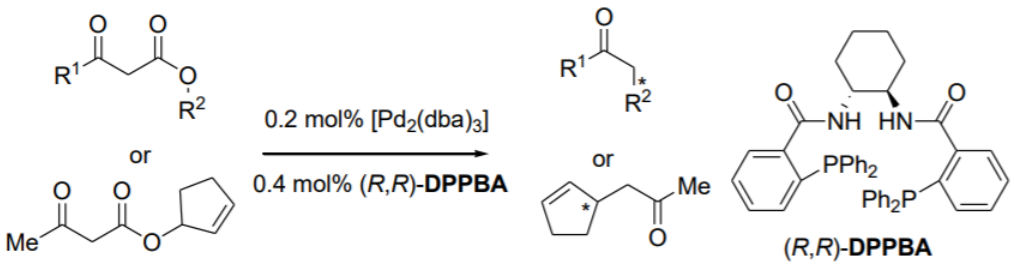
Bimetallic system having $Rh(acac)(CO)_2$, $Pd(Cp)(\pi\text{-}C_3H_5)$ and the ligand Anis Trap has been used for the allylic alkylation with α -cyanopropionic acid derivative as pronucleophile (Scheme 2.5.7). The control of the stereochemistry is believed to take place *via* the nucleophile with a chiral Rh complex coordinating to the cyano group.

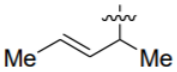
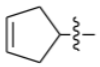
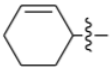
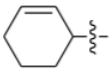
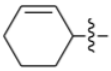
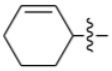


M. Sawamura, et al., *J. Am. Chem. Soc.* **1995**, *118*, 3309.

Scheme 2.5.7

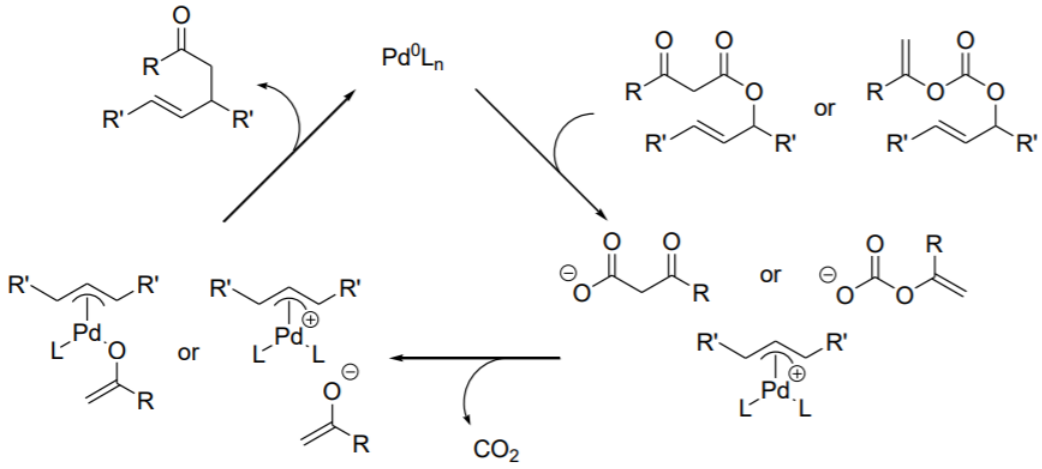
Recently, allylic alkylation has been realized by enolate generated *in situ* by decarboxylation (Scheme 2.5.8). Both allylic β -keto carboxylates and allyic enol carbonates undergo facile decarboxylation after oxidative addition of a Pd(0) species (Scheme 2.5.9).



R^1	R^2	Yield [%]	ee [%]
Me		82	86
Me		85	86
Me		75	94
PhCH2		71	90
i-Pr		94	80
Ph		69	92

E. C. Burger, J. A. Tunge, *Org. Lett.* **2004**, *6*, 4113.

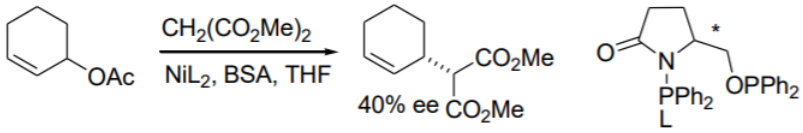
Scheme 2.5.8



Scheme 2.5.9

Nickel-Catalyzed Reactions

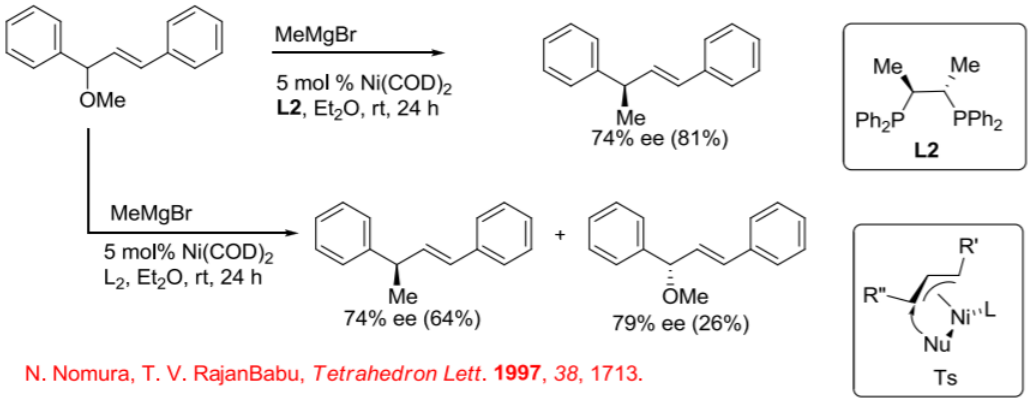
In comparison to the palladium catalyzed reactions, the nickel based chemistry is less explored. In addition, the nickel based chemistry less popular with the reactions of soft nucleophiles and few examples only so far investigated. For example, the reaction of allylic acetates has been studied with soft nucleophiles such as dimethyl malonate using a wide range of phosphine ligands (Scheme 2.5.10). Linear allylic substrates give a mixture of regioisomers, whereas in cyclohexenyl acetate, the regioselectivity does not play any role affording the alkylated product with moderate enantioselectivity in the presence of chiral phosphine L1.



H. Bricout et al., *Tetrahedron Lett.* **1996**, *37*, 6105.

Scheme 2.5.10

However, the nickel based systems are very popular with the reactions of hard nucleophiles such as boronic acids, borates and Grignard reagents. For example, the reaction of 1,3-disubstituted allyl ethers with Grignard reagents can be accomplished using nickel phosphine complex with good enantioselectivity (Scheme 2.5.11). The reaction of methyl ether gave better results compared to phenyl ethers. In this reaction, if the reaction is quenched before complete consumption of the staring material, a significant kinetic resolution is observed.

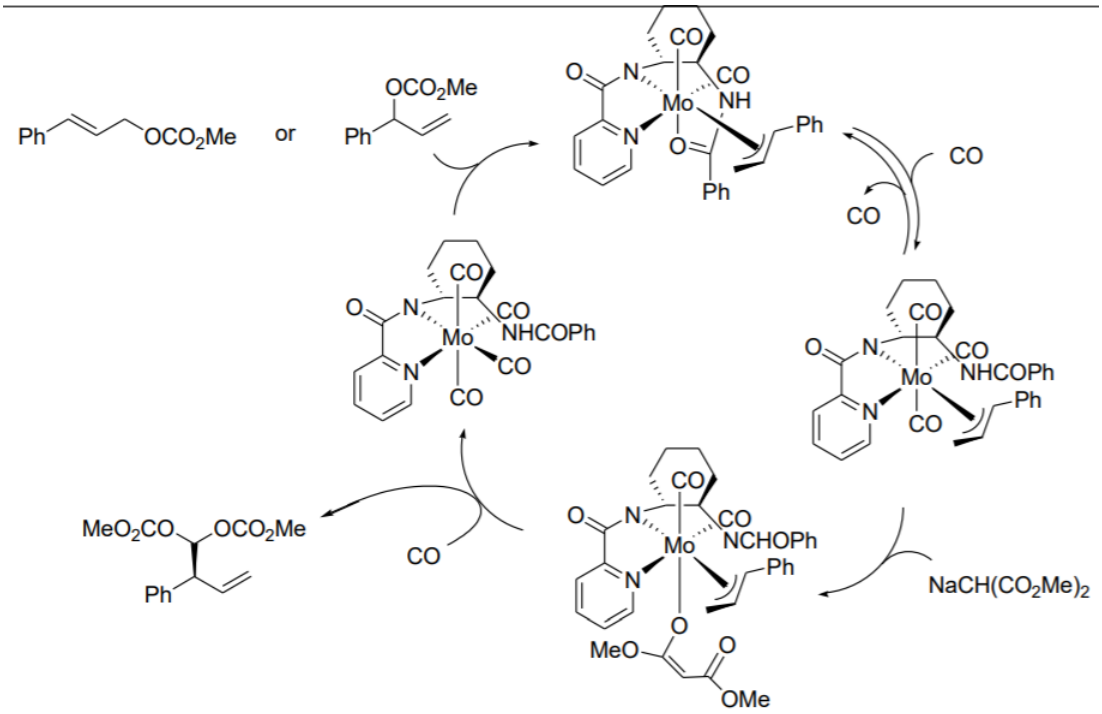


N. Nomura, T. V. RajanBabu, *Tetrahedron Lett.* **1997**, *38*, 1713.

Scheme 2.5.11

Molybdenum-Catalyzed Reactions

Although the palladium catalyzed systems dominate in π-allyl chemistry, analogues Mo-catalyzed reactions have also emerged as powerful reactions in organic synthesis. The Mo-based reactions are the one first showed different regioselectivity compared to the palladium catalyzed systems. Scheme 2.5.12 illustrates the mechanism for the asymmetric Mo-catalyzed allylic alkylation.

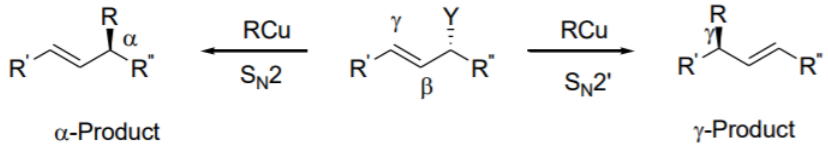


D. L. Huges, et al., *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5379.

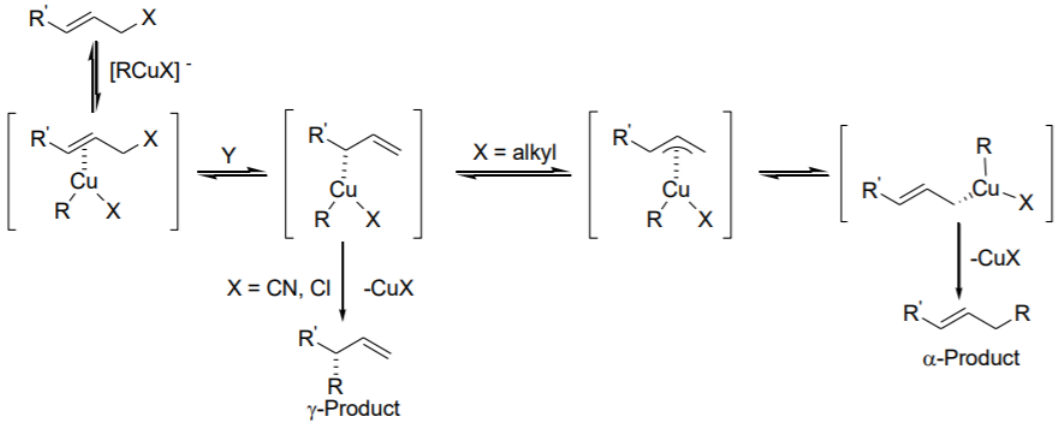
Scheme 2.5.12

Copper-Catalyzed Reactions

In case of the nonsymmetrical allylic substrates, the palladium catalyzed allylic alkylation reactions show poor regioselectivity. In this context, the copper based chemistry is an interesting alternative and lots of efforts have been made on this topic during last years. The copper based systems tolerate a wide range of hard and nonstabilized nucleophiles. Scheme 2.5.13 presents the regioselectivity in copper-catalyzed allylation reactions. In unsymmetrical substrates, nucleophile may attack directly at the leaving group (SN2) or at the allylic position (SN2') under migration of the double bond depending on the reaction parameters as well as the substrate and nucleophile.



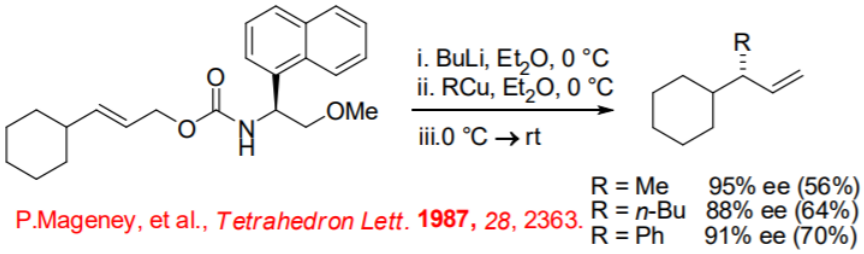
Scheme 2.5.13



E. S. M. Persson et al., *Chem. Eur. J.* **1995**, 1, 351.

Scheme 2.5.14

The observed results suggest that the regioselectivity and stereoselectivity are established at different stages (Scheme 2.5.14). For example, the reaction of chiral carbamates with achiral copper reagent gives SN2' product with excellent enantioselectivity (Scheme 2.5.15).

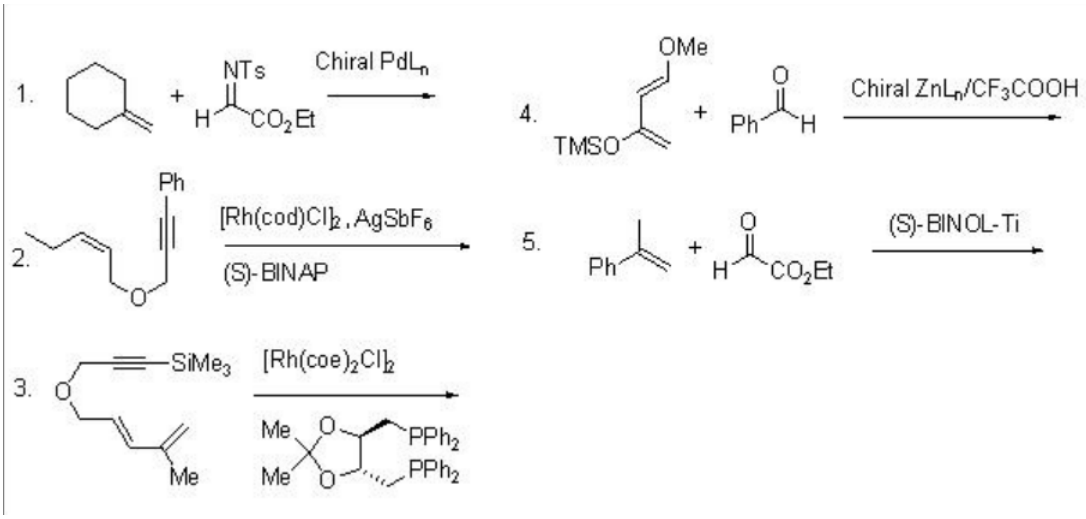


Scheme 2.5.15

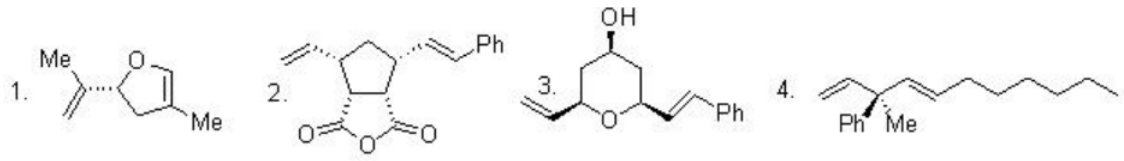
2.6: Problems and Reference

Problems:

Complete the following reactions.

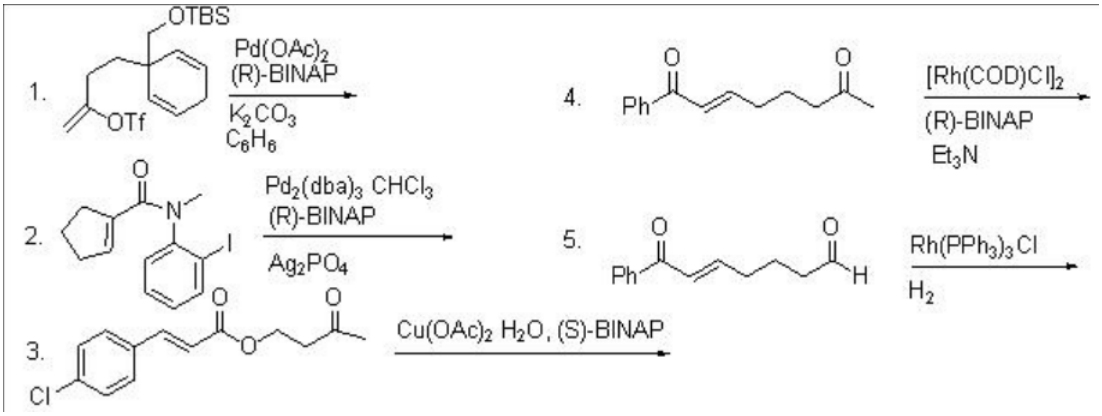


How will you synthesis the following compounds using alkene metathesis?



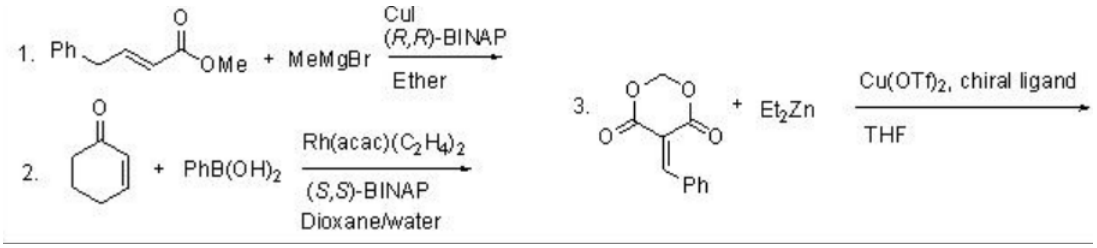
Give some examples of chiral Zr-catalyzed carbometallation reactions.

Complete the following reactions.

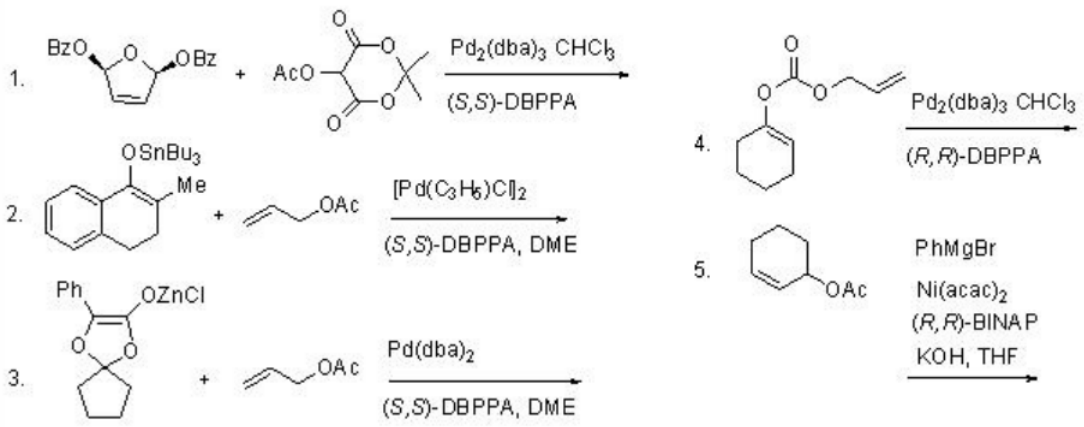


Describe conjugate addition reactions using organocatalysis.

Complete the following reactions.



Predict the major product for the following reactions.



Describe the chiral Fe, Ru, Ir and Rh-catalyzed asymmetric allylic alkylation reactions.

Reference /Text Book

• I. Ojima, *Catalytic Asymmetric Synthesis* , 3 rd ed., Wiley, New Jersey, 2010.

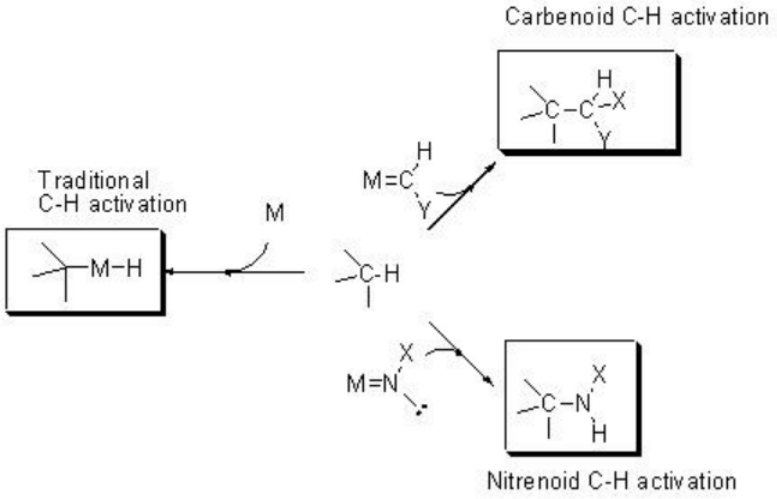
• M. B. Smith, *Organic Synthesis* , 2 nd edition, McGraw Hill, New Delhi, 2004.

CHAPTER OVERVIEW

3: Synthesis via C-H Activation

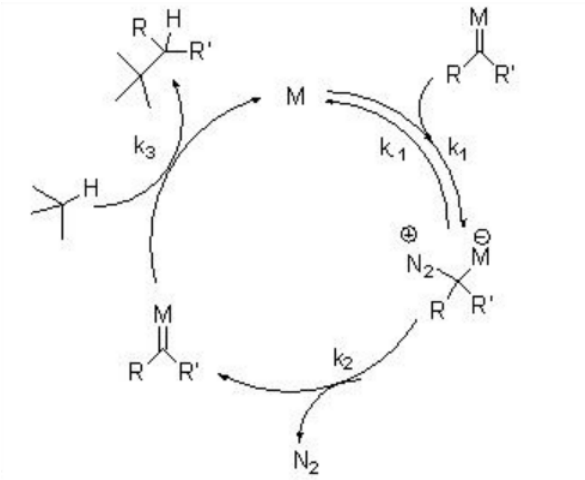
3.1: Reactions with Metal Carbenoid

Functionalization of C-H bonds constitutes an attractive approach for the direct synthesis of complex organic molecules such as pharmaceuticals, natural products, and other industrially relevant targets. Thus, much effort has been devoted to achieve practical, catalytic and selective methods for the C-H functionalization. Scheme 3.1.1 presents the two major directions evolved for the C-H functionalization process: (i) direct C-H activation involving oxidative addition to the C-H bond onto an active metal center, and (ii) insertion of transition metal-coordinated carbenes or nitrenes into the C-H bond to give functionalized products.



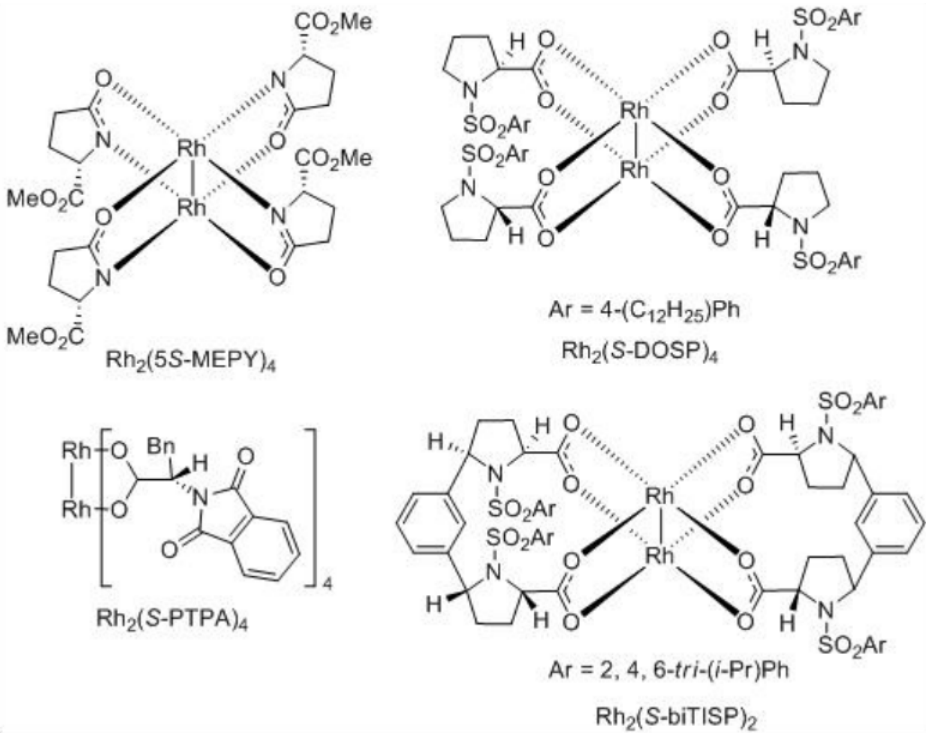
Scheme 3.1.1: Modes of C-H Activation

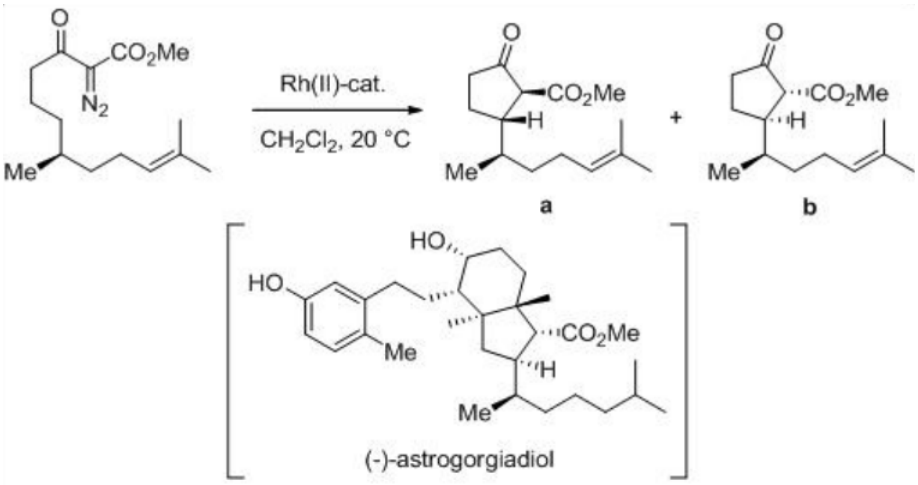
Metal carbenes generally produced from diazo compound by metal-catalyzed nitrogen extrusion. Alternative carbene precursors include iodonium, sulfonium, sulfoxonium, thiophenium and phosphonium ylides, but their synthetic application is less explored. The general mechanism for the generation of carbene via dirhodium complexes is shown in Scheme 3.1.2. In the presence of suitable metal complex, the diazo compound can coordinate reversibly and undergo rate limiting extrusion of nitrogen to give reactive metal carbenoid intermediate. The latter will react with a suitable trapping agent present in the reaction mixture.



Scheme 3.1.2: Carbenoid C-H Insertion

For example, chiral dirhodium complexes catalyze the intramolecular C-H insertion of α -diazo -β -ketoester to give the intermediate for the total synthesis of the marine secosteroid (-)-astrogorgiadiol (Scheme 3.1.3). Up to 58% de is observed with moderate yield of 38% employing Rh_2(*S* -biTISP)$_2$ as the catalyst. The reaction using Rh_2 (S-PTPA)$_2$ afforded excellent yield but with lower diastereoselectivity.



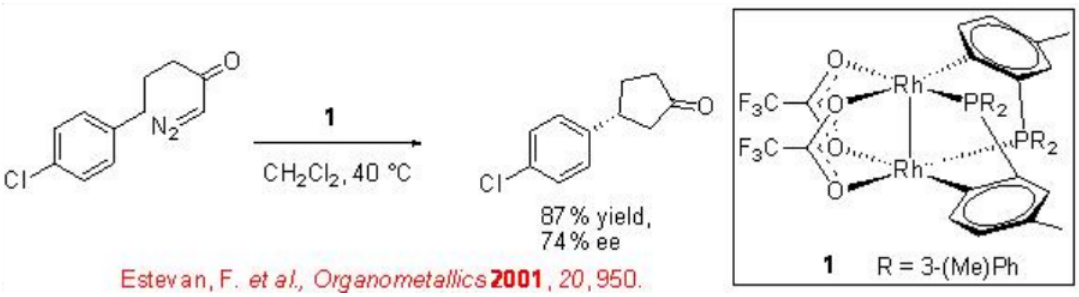


Catalyst	d.r. a : b	Yield (%)
Rh_2(*S*-PTPA)$_4$	26:74	98
Rh_2(5*S*-MEPY)$_4$	43:57	66
Rh_2(*S*-DOSP)$_4$	36:64	94
Rh_2(*S*-biTISP)$_2$	21:79	38

Taber, D. F. *et al.*, *J. Org. Chem.* **2001**, *66*, 944.

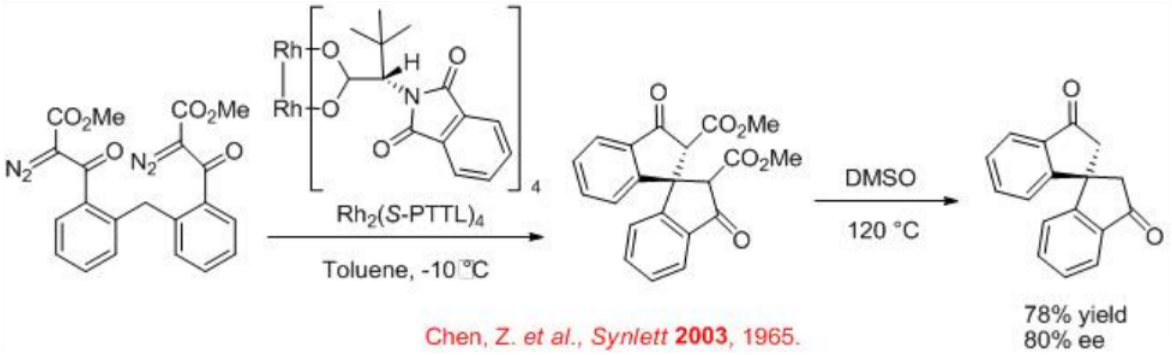
Scheme 3.1.3: Synthetic Studies toward (-)-Astrogorgiadiol

ortho -Metallated arylphosphine dirhodium(II) complexes are found to be effective catalysts for intramolecular C-H insertions of certain diazoketones (Scheme 3.1.4). One of the examples is the use of dirhodium complex **1** for the reaction of chloro-substituted system to afford cyclophentanone in 74% ee and 87% yield. This system works well with the aryl portion having electron withdrawing group.



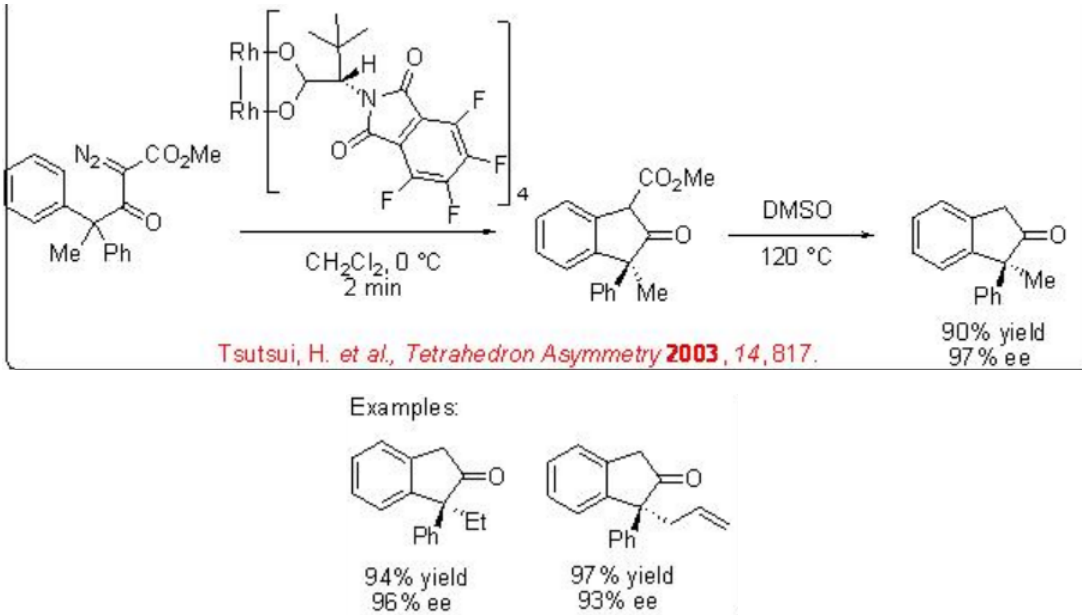
Scheme 3.1.4

Scheme 3.1.5 illustrates an example for the stereocontrolled formation of quaternary stereocenter using chiral Rh_2 (S-PTTL)$_4$ catalyzed carbenoid C-H insertion process.



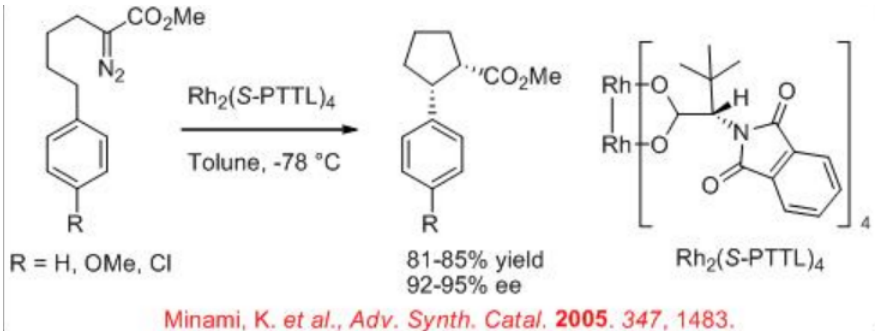
Scheme 3.1.5

The above catalytic system is also effective for the desymmetrization of aryl-substituted diazo ketoesters (Scheme 3.1.6). This reaction proceeds via electrophilic aromatic substitution and turnover numbers of up to 98000 have been achieved.

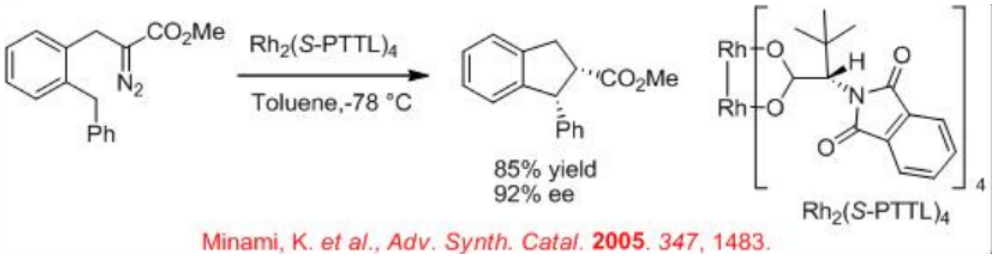


Scheme 3.1.6

Furthermore, the construction of *cis* -cyclopentanones from diazoester can be achieved via exclusive insertion (Scheme 3.1.7). In addition, the construction of disubstituted *cis* -indane can be accomplished with 85% yield and 92% ee (Scheme 3.1.8). These examples illustrate that the choice of the reaction conditions and catalysts for carbenoid transformation are crucial for selectivity.

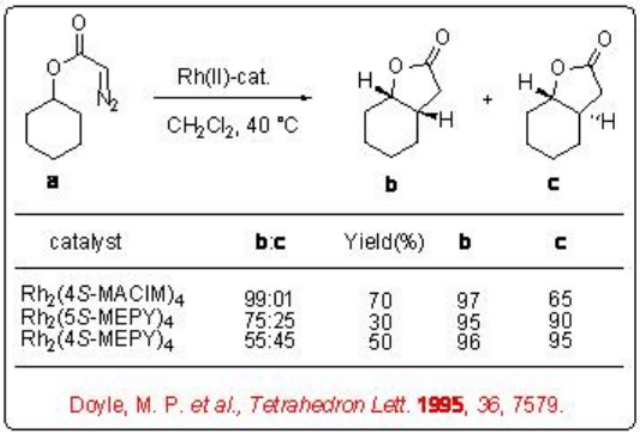


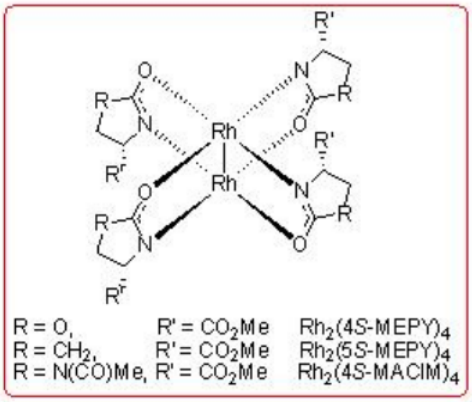
Scheme 3.1.7



Scheme 3.1.8

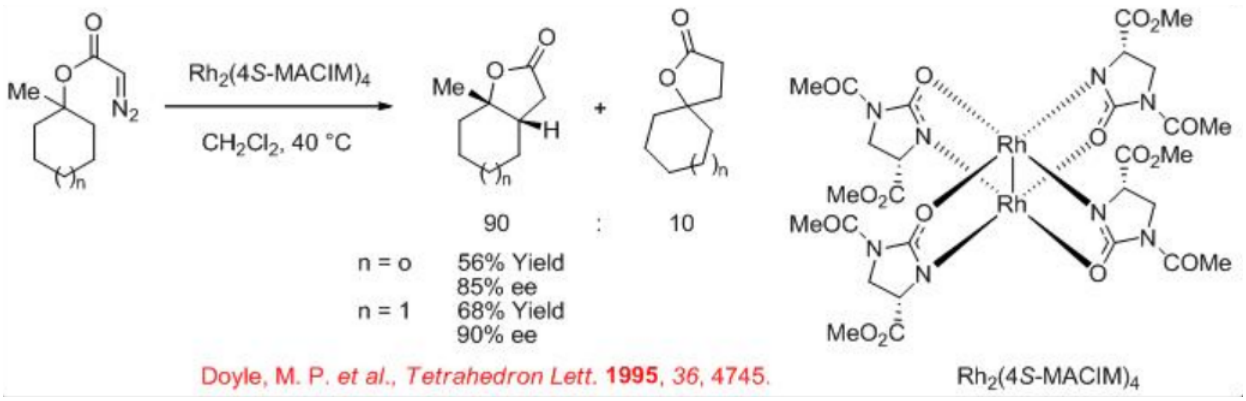
Both the first ($Rh_2(MEOX)_4$ and Rh_2 $(MEPY)_4$) and second (Rh_2(4S-MACIM)$_4$) generation carboxamidate catalysts show very good enantiocontrol for the desymmetrization reaction of cyclohexyl diazoacetate (Scheme 3.1.9). In terms diastereoselectivity, the latter gives the best results of 99:1 which is attributed to the *N* -substituent that control the carbenoid orientation.



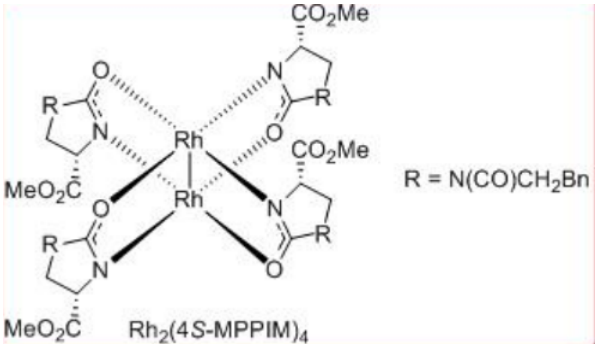


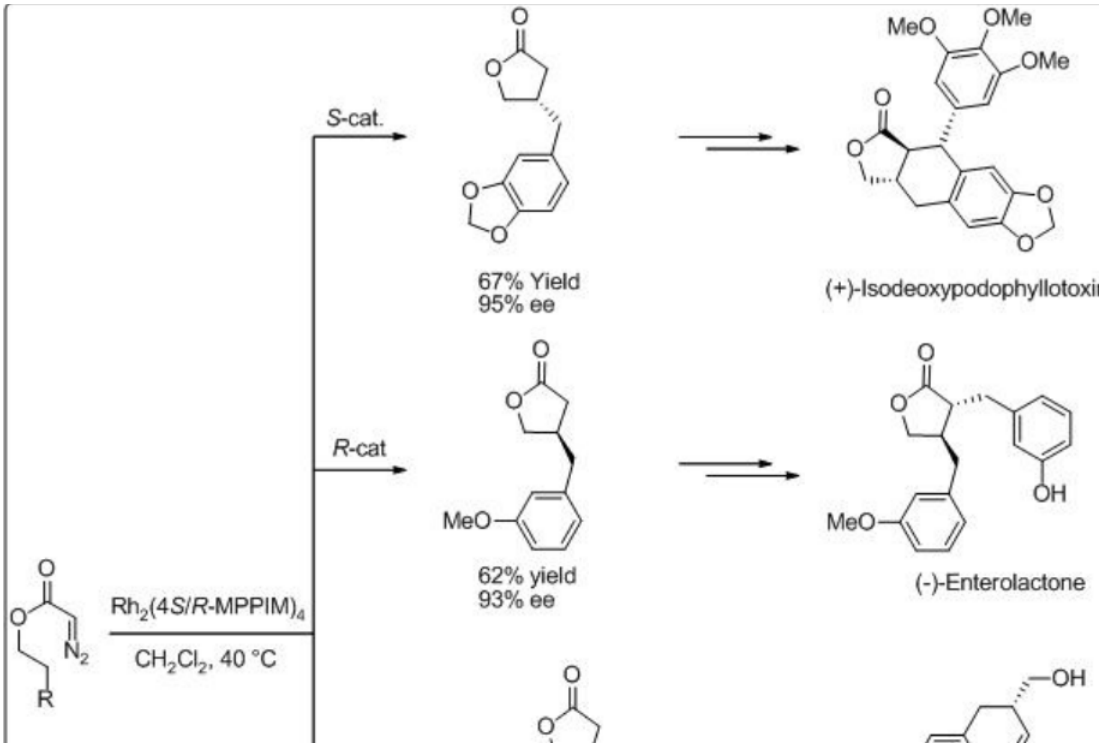
Scheme 3.1.9

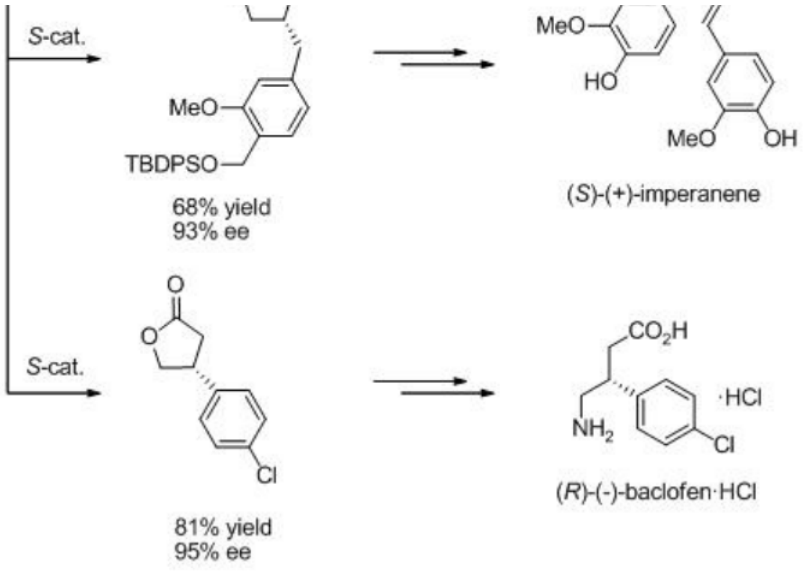
In case of cyclohexyl diazoacetate having the tertiary system, a mixture of the expected insertion into methylene group and insertion into the methyl group has been observed in the presence of Rh_2(4S-MACIM)$_4$ (Scheme 3.1.10). Cyclopentane system also provides similar results with somewhat lower yield and enantioselectivity.


Rh2(4S-MACIM)4
CH2Cl2, 40 °C
90 : 10
n = o 56% Yield 85% ee
n = 1 68% Yield 90% ee
Doyle, M. P. et al., Tetrahedron Lett. 1995, 36, 4745.
Rh2(4S-MACIM)4

Scheme 3.1.10


R = N(CO)CH2Bn
Rh2(4S-MPPIM)4


S-cat.
R-cat
Rh2(4S/R-MPPIM)4
CH2Cl2, 40 °C
67% Yield
95% ee
62% yield
93% ee
(+)-Isodeoxypodophyllotoxi
(-)-Enterolactone

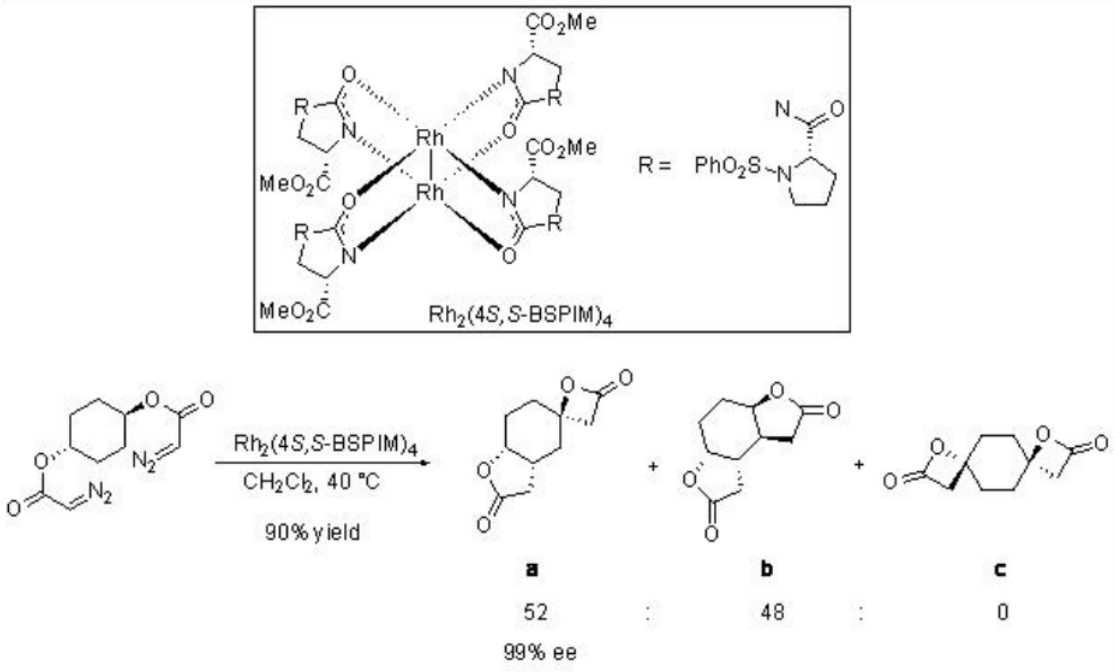


Bode, J. W. *et al.*, *J. Org. Chem.* **1996**, *61*, 9146.
Doyle, M. P. *et al.*, *J. Org. Chem.* **2002**, *67*, 2954.

Scheme 3.1.11

The construction of γ -lactone has been demonstrated *via* intramolecular C-H insertion of diazoacetates that find wide applications in the synthesis of natural products and pharmaceutical agents. For example, the synthesis of (+)-isodeoxypodophyllotoxin, (-)-enterolactone, (S)-(+)-imperanene and (R)-(-)-baclofen have been accomplished with the lactone formation as a key step in the presence of Rh_2 (4S/R-MPPIM)$_4$ (Scheme 3.1.11).

The carbenoid insertion reactions have also been used for amplification of asymmetric induction. For example, sequential intramolecular C-H insertions have been carried out on *meso* -cyclohexyl diazoacetate (Scheme 3.1.12). The formation of a 1:1 mixture of **a** and **b** is observed using Rh_2(4 *S,S* -BSPIM)$_4$ with over 90% yield and 99% enantioselectivity.

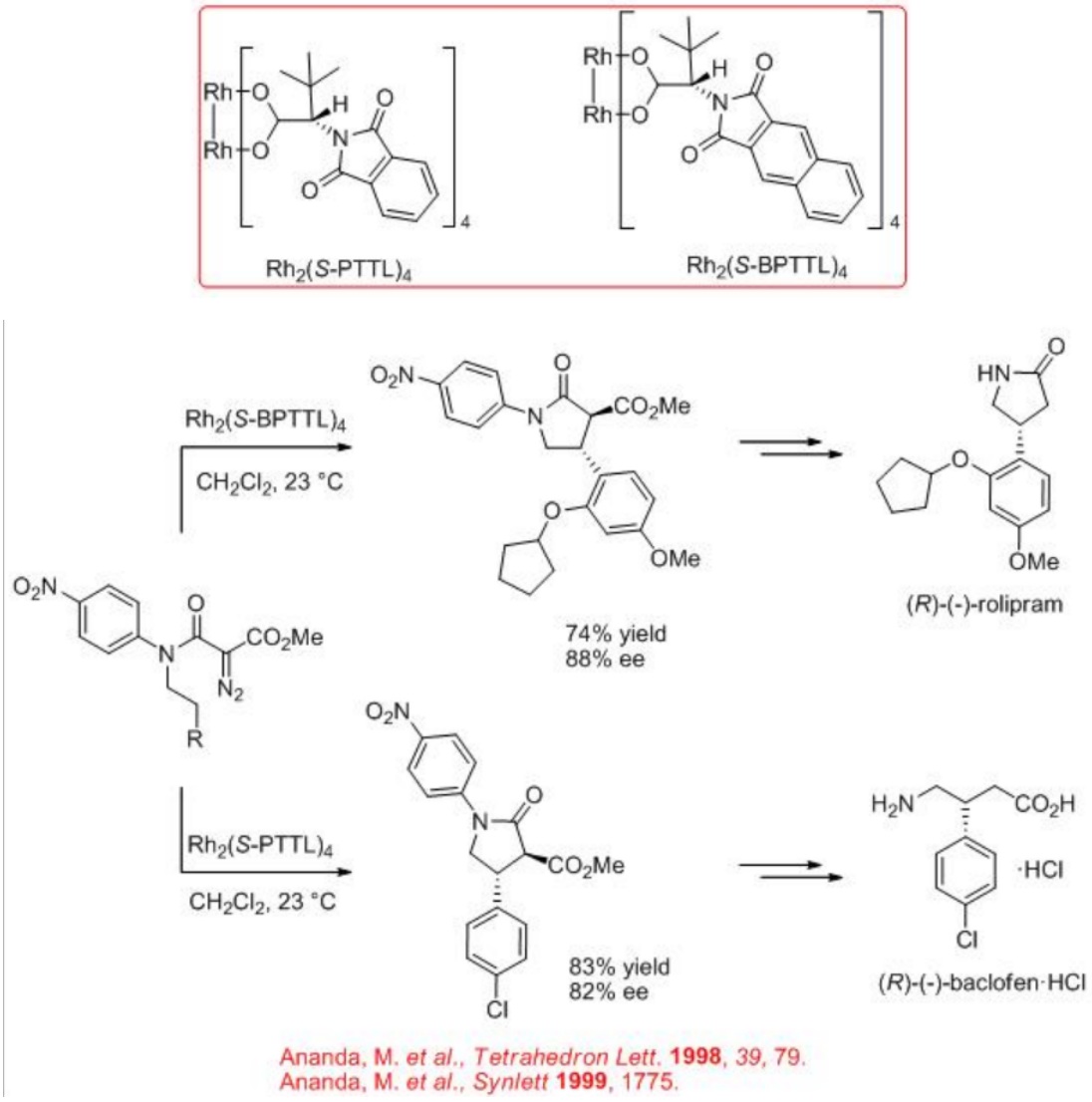


Doyle, M, P. *et al.*, *Org. Lett.* **2005**, 7, 5035.

Scheme 3.1.12: Kinetic amplification in double C-H insertion

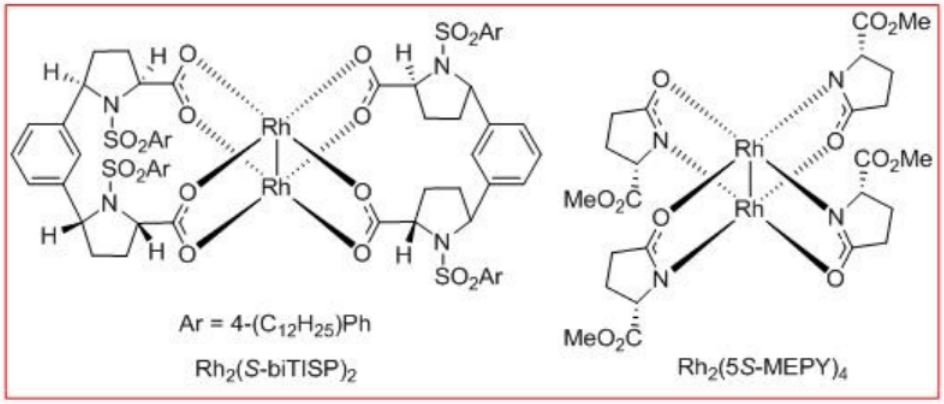
Synthetic application of the dirhodium catalyzed carbenoid C-H insertion chemistry has been demonstrated as key step for the site controlled γ -lactam formation to the syntheses of (*R*)-(-)-baclofen, GABAB receptor agonist and (*R*)-(-)-rolipram (Scheme 3.1.13).

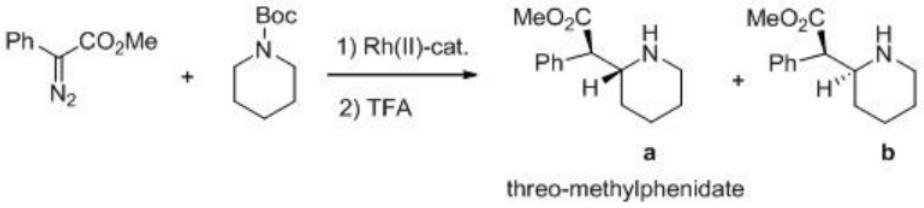
Rh_2 (*S*-BPTTL) is found to be the optimal catalyst for the synthesis of the intermediate for (*R*)-(-)-rolipram with 74% yield and 88% ee, while Rh_2 (*S*-BPTTL) is effective for the synthesis of the intermediate to (*R*)-(-)-baclofen with 83% yield and 82% ee.



Scheme 3.1.13

So far we have seen intramolecular carbenoid C-H insertion reactions. Intermolecular carbenoid C-H insertion reactions have been recently explored. Scheme 6 illustrates the reaction N-Boc piperidine with methylphenyldiazoacetate in the presence of Rh_2(*S*-biDOSP)$_2$ at ambient temperature. Two diastereomers in a 71:29 ratio is formed in overall 73% yield and up to 86% ee. The racemic *threo* -methylphenidate is currently marketed drug for treatment of attention hyperactivity disorder. Seven and eight member nitrogen heterocycles afford higher selectivity. The use of dirhodium carboxamidate Rh_2(5R-MEPY)$_4$ for this chemistry shows improved diastereoselectivity but with low yield and enantioselectivity.





Catalyst	T (°C)	Ratio a : b	yield (%)	ee (%) a	ee (%) b
Rh_2(*S*-biDOSP)$_2$	25	71:29	73	86	65
Rh_2(5*R*-MEPY)$_4$	50	82:18	22	53	-

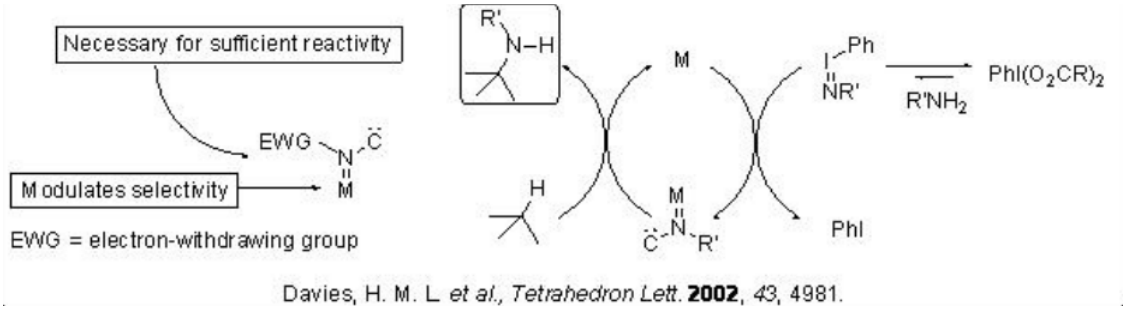
Davies, H. M. L. *et al.*, *J. Am. Chem. Soc.* **1999**, *121*, 6509.

Scheme 3.1.14

3.2: Reactions With Metal Nitrenoid and Direct C-H Oxidation

3.2.1 Reactions with Metal Nitrenoid

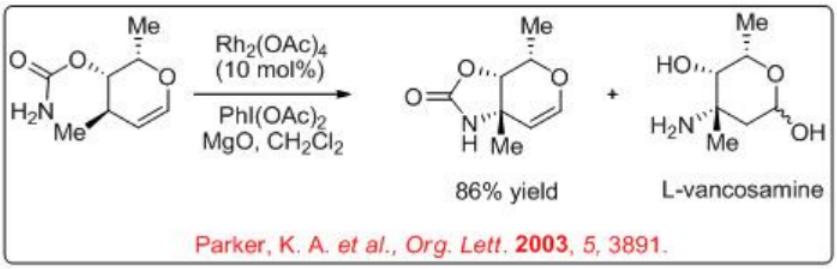
The amine functional group is an important component of many biologically active compounds. The nitrene insertion into C-H bonds provides powerful tool for the direct introduction of C-N bond from C-H bonds. The mechanism of metal nitrenoid formation is believed to take place via an in situ-formed iodonium ylide that produces the reactive metal nitrenoid intermediate in the presence of suitable metal (Scheme 3.2.1). The major intrinsic factors controls the selectivity are (i) the catalyst and (ii) the electron withdrawing group.



Scheme 3.2.1

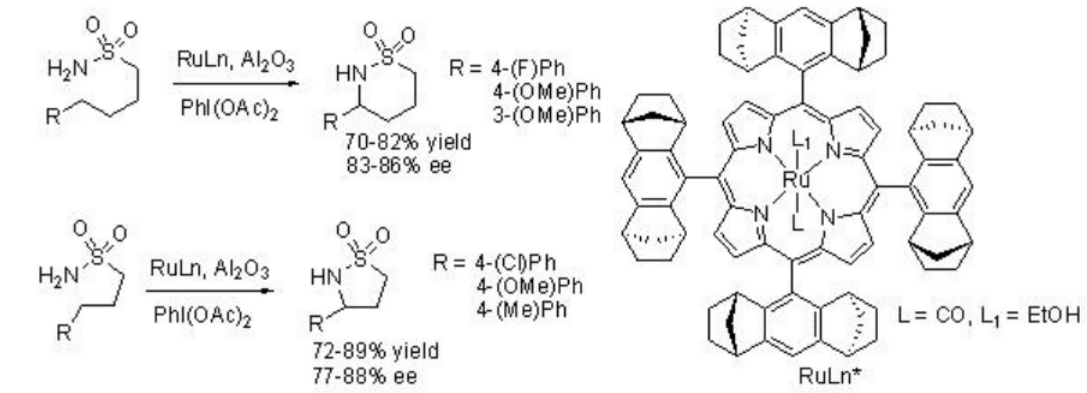
3.2.1.1 Intramolecular Reactions

3-Amino glycol derivatives serve as intermediates for the synthesis of 2-oxygenated sugars, 2-deoxysugars and antibiotics. Dirhodium-catalyzed nitrene transfer has been utilized as a key step in the synthesis of carbamate-protected 3-aminoglycols. For example, Scheme 3.2.2 illustrates the selective transformation of carbamate into oxazolidinone via nitrene insertion with 86% yield. The resulting oxazolidinone can be converted into L-vancosamine. This method has been employed for the synthesis of protected glycols of L-daunosamine, D-saccharosamine and L-ristosamine.



Scheme 3.2.2

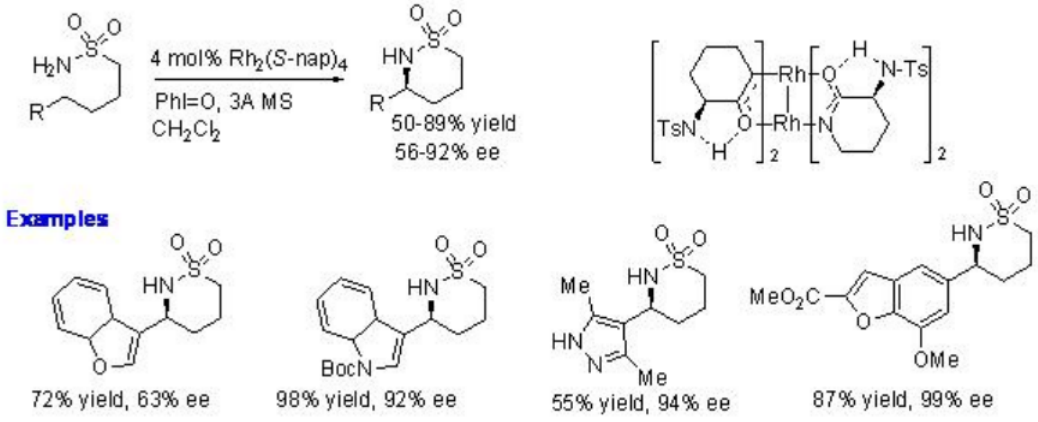
Chiral Ru(II) porphyrin complex catalyzes the C-H amination of prochiral sulfonamides with good enantioselectivity (Scheme 3.2.3). This procedure can be used for the synthesis of both five and six membered cyclic sulfamidates.



Liang, et al., *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 3465.

Scheme 3.2.3

Chiral dirhodium has been shown effective catalyst for the cyclization of sulfonamides (Scheme 3.2.4). This procedure is an example for the highly enantioselective amination process catalyzing the reactions of heteroaromatic substituents with up to 99% ee.

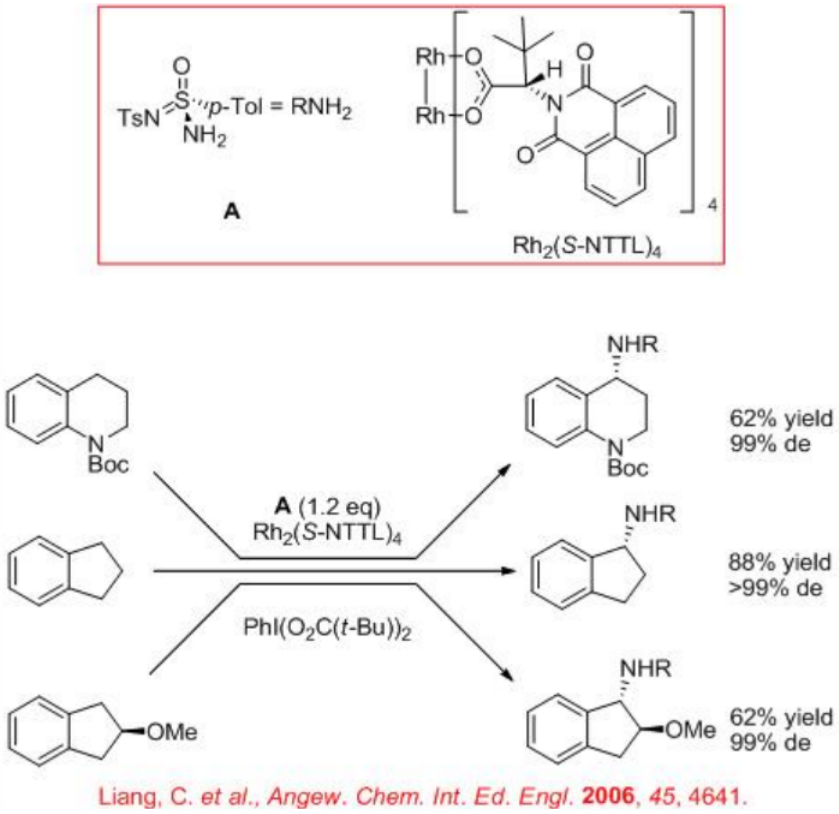


Zalatan, et al., *J. Am. Chem. Soc.* **2008**, *130*, 9220.

Scheme 3.2.4

3.2.1.2 Intermolecular Reaction

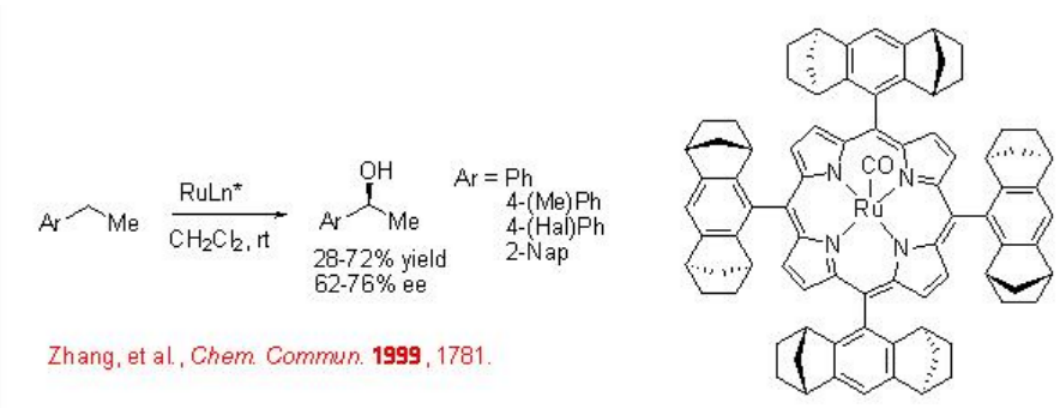
Intermolecular amination of benzylic C-H bonds can be accomplished using the chiral tosylsulfonylimidamide as a nitrene precursor in the presence of chiral dirhodium carboxylate Rh_2(S-NTTL)$_4$ with excellent diastereoselectivity (Scheme 3.2.5).



Scheme 3.2.5

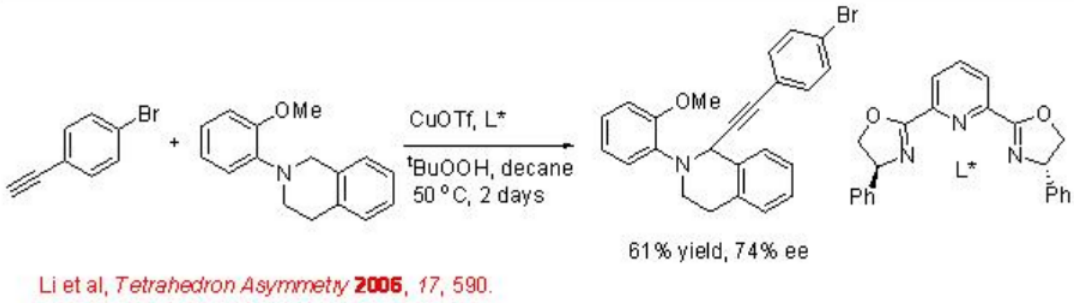
3.2.2 C-H Activation via Direct C-H Oxidation

Chiral Ru-porphyrin complex has been shown to catalyze benzylic C-H hydroxylation with moderate enantioselectivity (Scheme 3.2.6).



Scheme 3.2.6

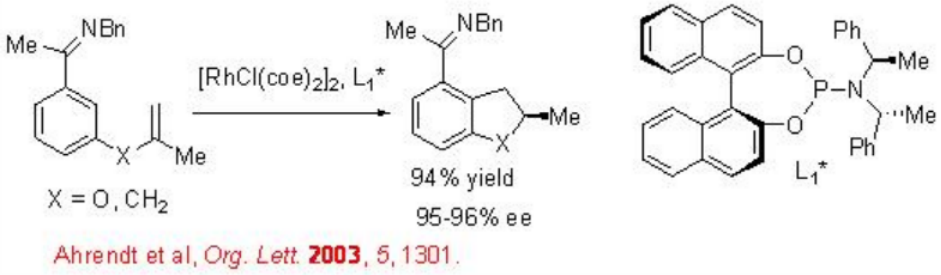
C-H functionalization via insertion of a reactive metal complex is one of the emerging areas for the development of practical C-H activation. The synthesis of alkynyl tetrahydroisoquinoline has been shown by double C-H activation in the presence of copper-pyBox at moderate temperature (Scheme 3.2.7). The reaction of series of alkynes and aryl substituents is demonstrated. However, the presence of *ortho* methoxy substituent is essential for the success of the reaction.



Li et al, *Tetrahedron Asymmetry* **2006**, *17*, 590.

Scheme 3.2.7

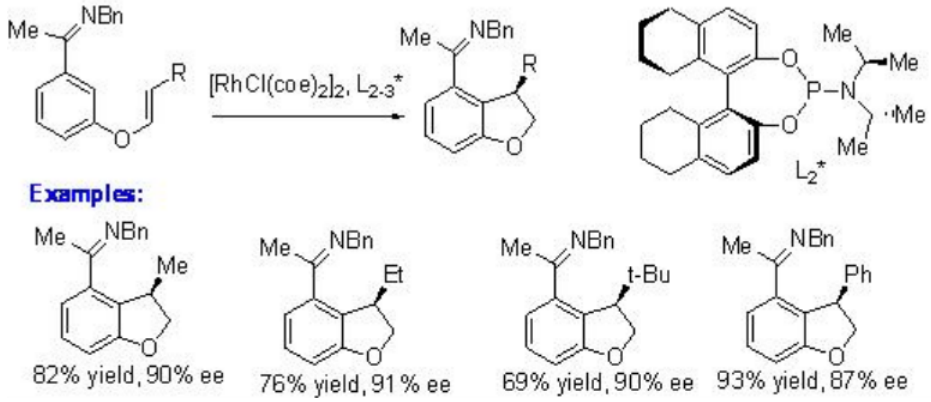
Intramolecular alkylation of ketimines has been shown using chiral rhodium complex bearing chiral phosphoramidite L_1* (Scheme 3.2.8). The observed results suggest that the reaction involves substrate directed oxidative addition of rhodium into the arene C-H bond. This approach provides a new cyclization strategy for the construction of five and six membered cyclic system.

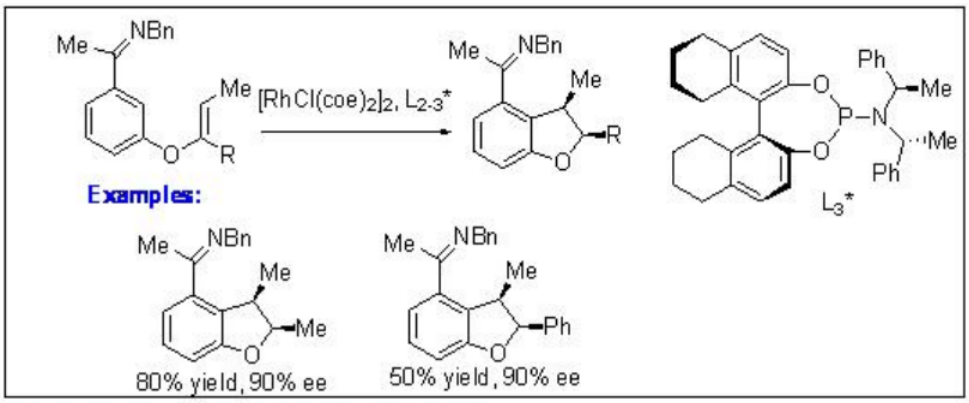


Ahrendt et al, *Org. Lett.* **2003**, *5*, 1301.

Scheme 3.2.8

The scope of the above procedure has been expanded for the reactions of 1,2-disbstituted and 1,1,2-trisubstituted alkenes to give chiral indane, dihydrobenzofuran and dihydropyrroloindole with high enantioselectivity (Scheme 3.2.9). The formation of *syn* - products is observed regardless the configuration of the starting alkenes. Thus, a mixture of E and Z alkenes may be used as starting material.



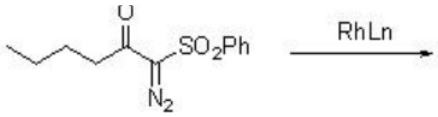


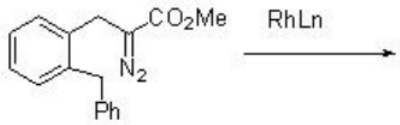
Harada et al., *J. Org. Chem.* **2008**, 73, 6772.

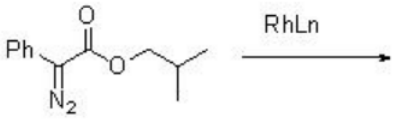
Scheme 3.2.9

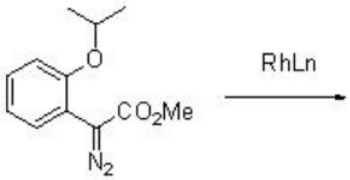
3.3: Problems and Reference

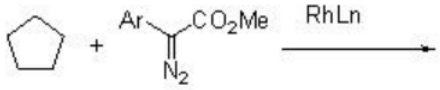
Complete the following reactions.

1. 

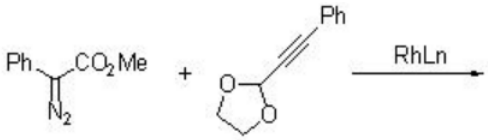
2. 

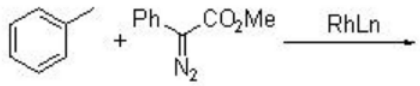
3. 

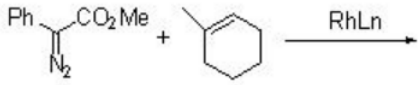
4. 

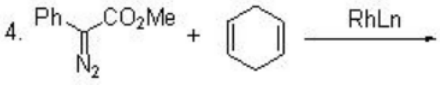
5. 

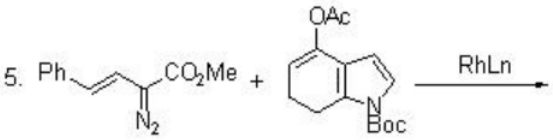
What product would you expect from the following reactions?

1. 

2. 

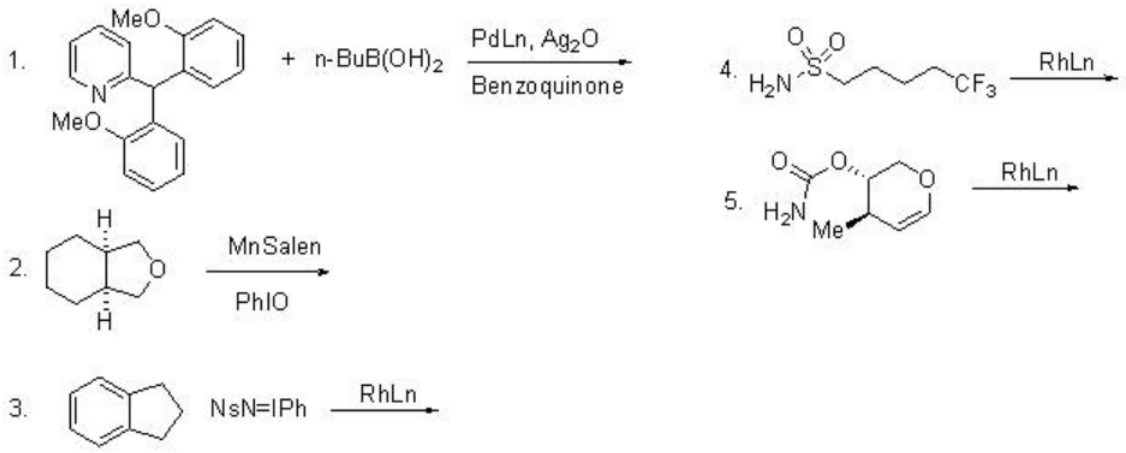
3. 

4. 

5. 

Describe rhodium catalyzed combined C-H activation and cope rearrangement reactions.

Predict the major product for the following reactions.



Reference/Text Book

• I. Ojima, *Catalytic Asymmetric Synthesis* , 3 rd ed., Wiley, New Jersey, 2010.

• M. B. Smith, *Organic Synthesis* , 2 nd edition, McGraw Hill, New Delhi, 2004.

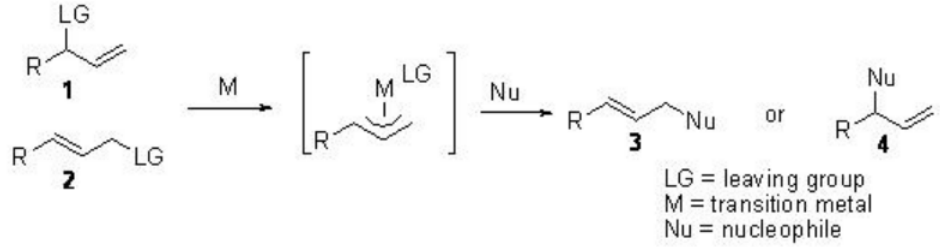
CHAPTER OVERVIEW

4: Carbon-Heteroatom Bond-Forming Reactions

Asymmetric carbon-heteroatom bond formation is among the fundamentally important reactions. This module covers the carbon-heteroatom bond-forming reactions using transition-metal-complex as well as the chiral Lewis acid catalyzed protocols.

4.1: Allylic Substitution Reactions

Much effort has been devoted on controlling the regioselectivity and enantioselectivity in allylic substitution of substrates **1** or **2** (Scheme 4.1.1). The palladium-catalyzed allylic substitution is versatile, however, the (*E*)-linear product **3** is often formed. Thus, the control of regioselectivity has been recently the main focus to provide product **4**.

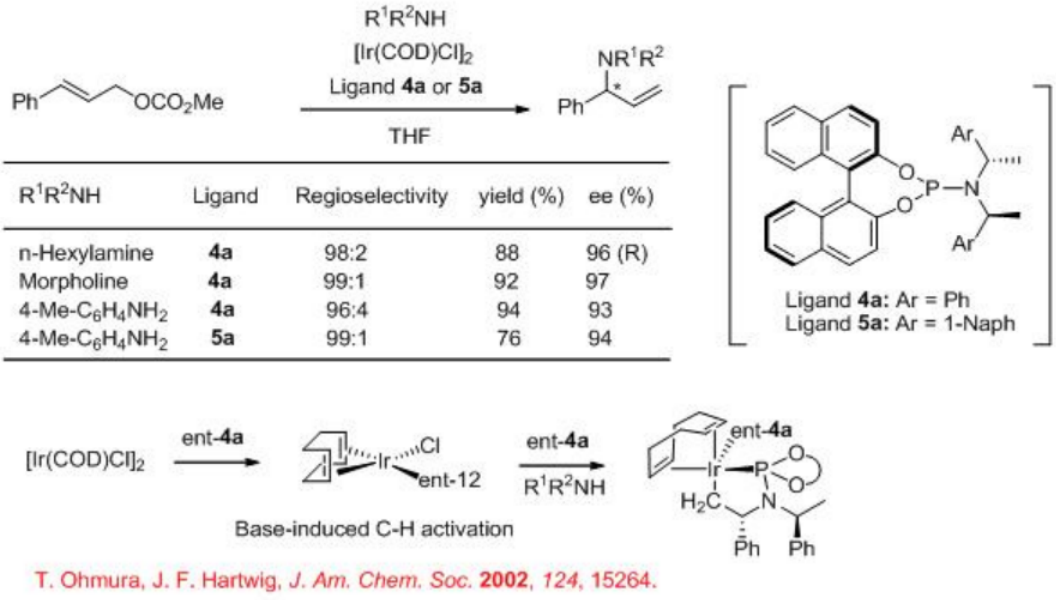


Scheme 4.1.1

4.1.1 Allylic Amination and Etherification of Allylic Alcohol Derivatives

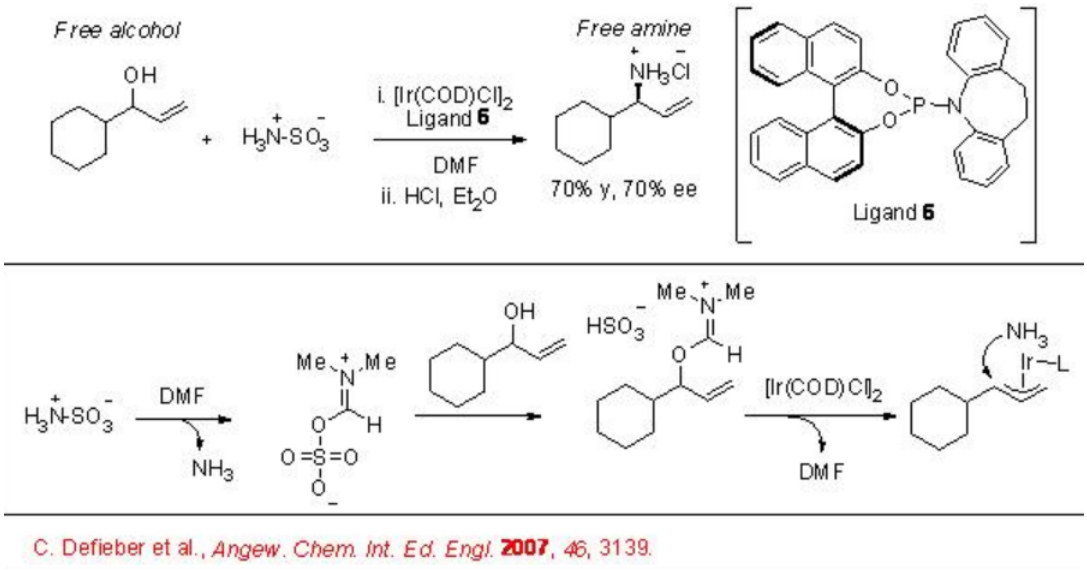
Chiral iridium complex having phosphoramidate **4a** or **5a** has been shown to catalyze the allylic amination of carbonate to give branched product with excellent enantioselectivity (Scheme 4.1.2). An activated form of the iridium complex by *in situ* C-H activation at CH_3 group of a hindered ligand **4a** has been identified.

The direct reaction of allylic alcohols has been studied to give allylic amines in the presence of chiral iridium complex derived from $[Ir(COD)Cl]_2$ and ligand **6** (Scheme 4.1.3). In this reaction, sulfamic acid serves not only as a nitrogen source but also as an *in situ* activator of the hydroxyl group of the allylic alcohol.



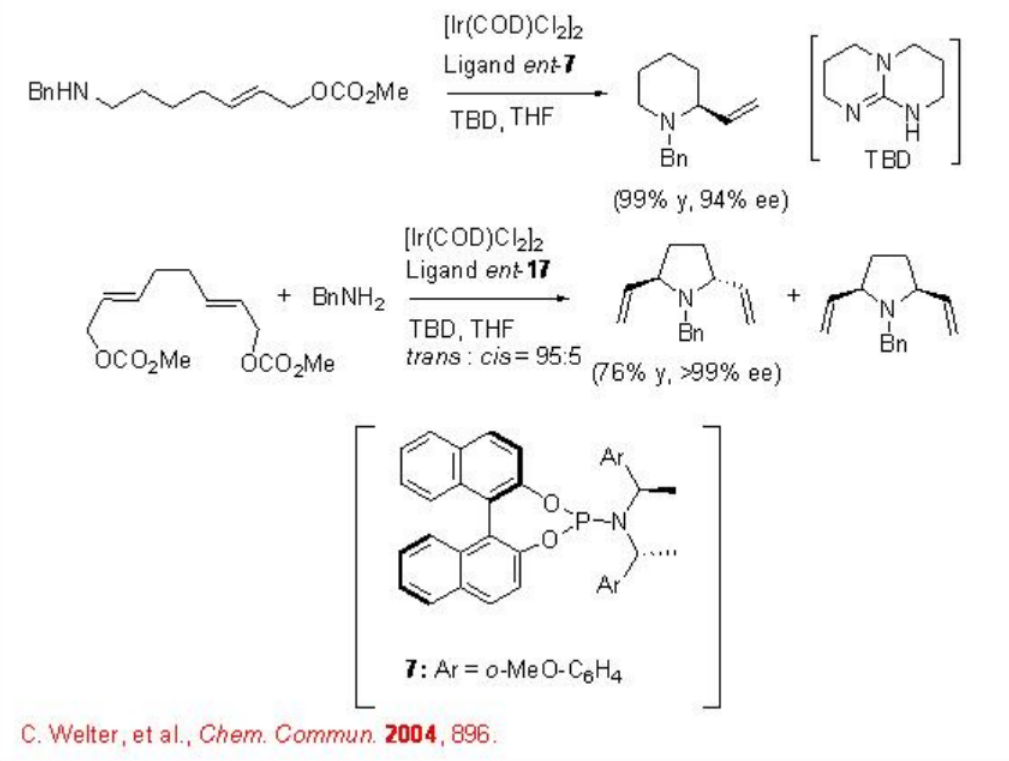
T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15264.

Scheme 4.1.2



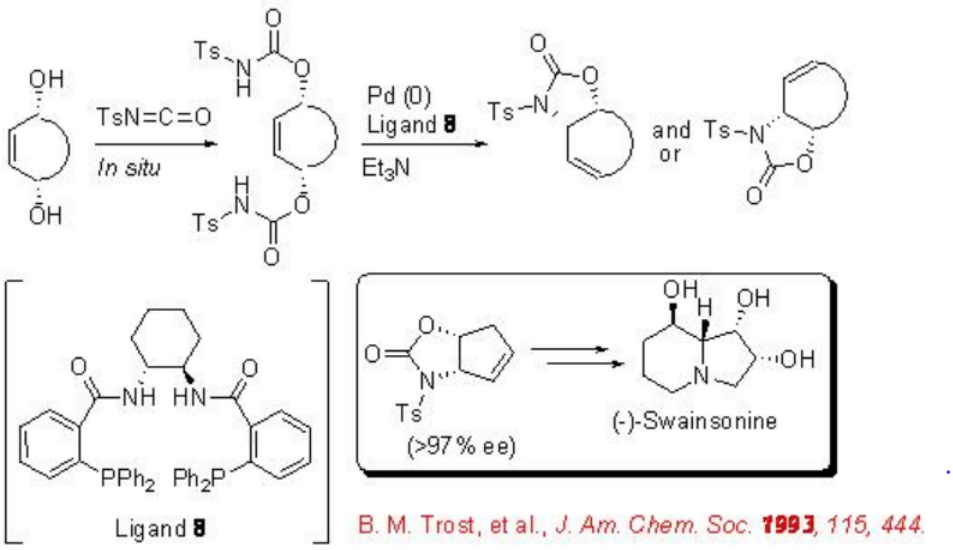
Scheme 4.1.3

Allylic amination is important for the construction of nitrogen-based heterocyclic compounds (Scheme 4.1.4). The enantioselective intramolecular allylic amination has been accomplished using chiral iridium complex derived from $[Ir(CDD)Cl_2]_2$ and ligand **7**. Good enantioselectivity has been obtained upon activation using 1,5,7-triazabicylo[4.4.0]undec-5-ene (TBD) as base. The catalytic system has also been used for the sequential aminations of *bis* -allylic carbonate *via* an inter- followed by an intramolecular reactions.



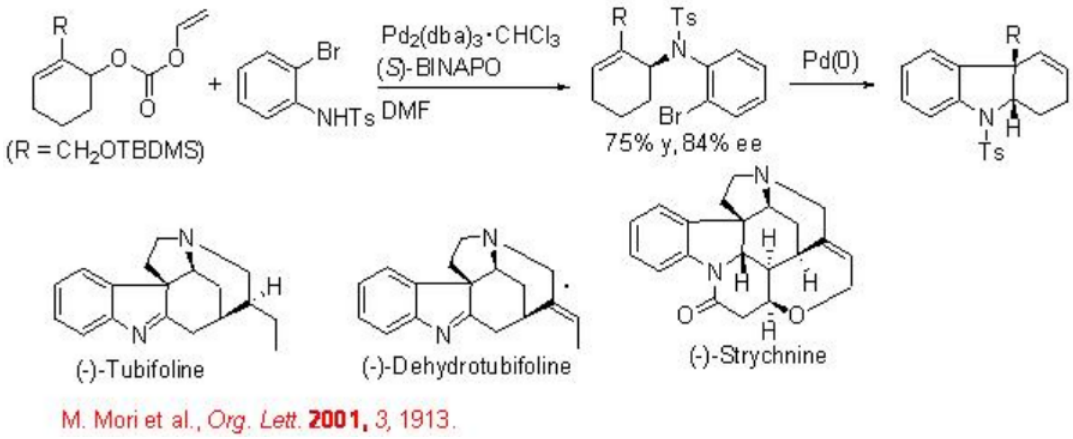
Scheme 4.1.4

Enantioselective allylic amination is also a powerful tool for the construction of natural products. For example, asymmetric desymmetrization of *meso* -diol with *p* -tosylisocyanate using chiral palladium complex gives easy access to chiral nitrogen-substituted heterocycles which are precursor for the synthesis of (-)-swainsonine (Scheme 4.1.5).



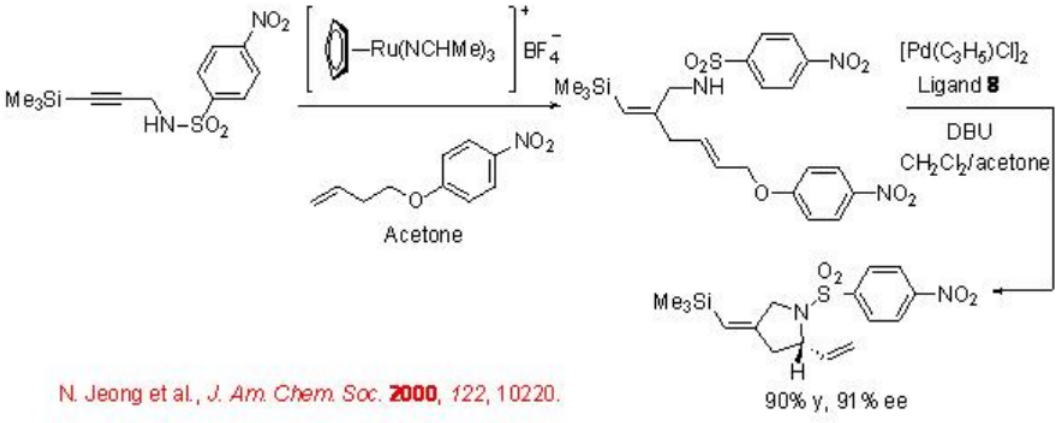
Scheme 4.1.5

The chiral palladium catalyzed enantioselective allylic amination has also been utilized for the total synthesis of (-)-tubifoline, (-)-dehydrotubifoline and (-)-strychnine (Scheme 4.1.6).



Scheme 4.1.6

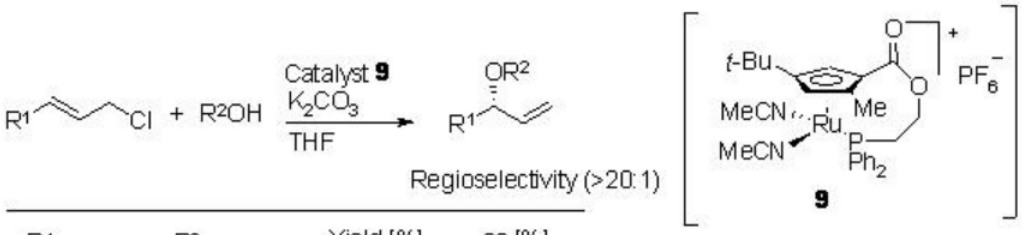
The one-pot enantioselective synthesis of azacycle has been shown using a ruthenium-catalyzed ene-yne addition followed by a palladium-catalyzed asymmetric allylic amination (Scheme 4.1.7).



N. Jeong et al., *J. Am. Chem. Soc.* **2000**, *122*, 10220.

Scheme 4.1.7

The regio- and enantioselective allylic etherification has been studied using chiral ruthenium complex. For example, planar-chiral cyclopentadienyl ruthenium complex **9** catalyzes efficiently the reaction of cinnamoyl chloride with 3-methylphenol with high enantioselectivity and yield (Scheme 4.1.8).

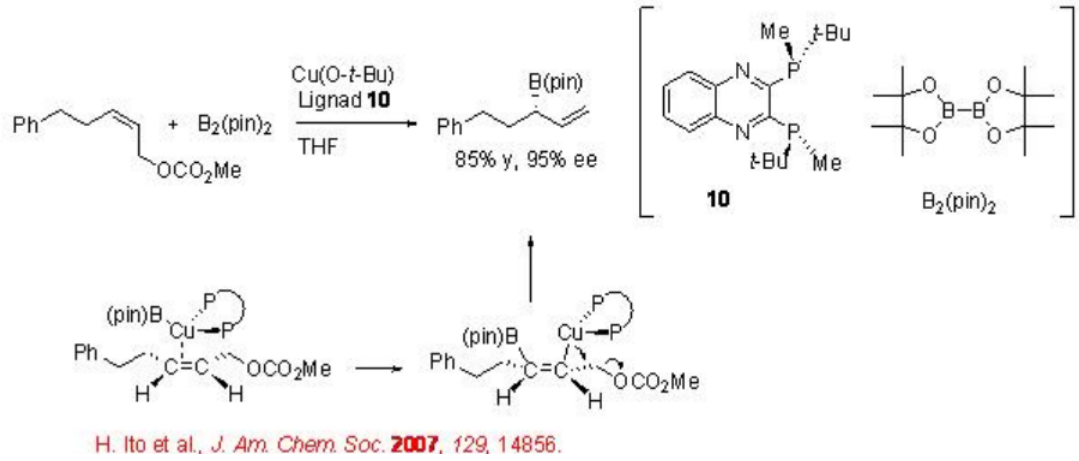


R1	R2	Yield [%]	ee [%]
Ph	Ph	99	92
Ph	4-$CF_3C_6H_4$	99	91
Ph	4-ClC_6H_4	98	93
4-$CF_3C_6H_4$	Ph	90	94
4-ClC_6H_4	Ph	96	86
Me	Ph	36	80
1-napthyl	Ph	98	82

K. Onitsuka, *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 1454.

Scheme 4.1.8

Enantioselective allylic substitutions of carbonates with a diboron using copper(I)-based catalysts has been demonstrated. For example, Cu(I)-phosphine complex generated *in situ* from Cu(O-t-Bu) with ligand **10** has been shown to catalyze the reaction of allylboronate with carbonate in excellent regioselectivity and enantioselectivity (Scheme 4.1.9). Addition-elimination mechanism having the generation of Cu-alkene π -complex and borylalkylcopper intermediate has been suggested.



H. Ito et al., *J. Am. Chem. Soc.* **2007**, *129*, 14856.

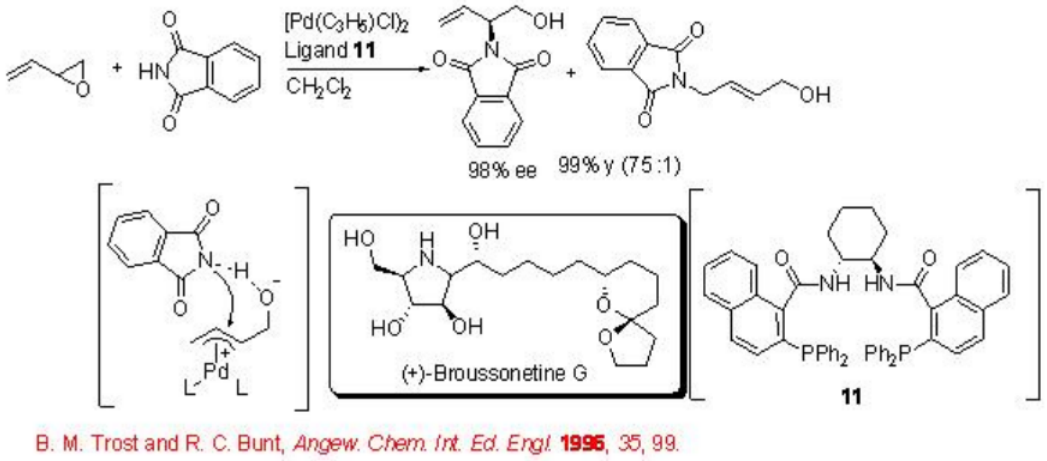
Scheme 4.1.9

4.1.2 Reaction of π -Allyl Intermediates

Nucleophilic attack of an amine to a π -allyl intermediate can afford an allylic amine derivative. For example, palladium complex derived from $[Pd(C_3H_5)Cl]_2$ and ligand **11** catalyzes the reaction of racemic vinyloxirane with phthalimide in nearly quantitative yield (Scheme 4.1.10). Involvement of the hydrogen bond of the nucleophile to the oxygen leaving group is proposed to deliver the nucleophile to the adjacent carbon to provide the target molecule. The process has been utilized for the synthesis of (+)-broussonetine G.

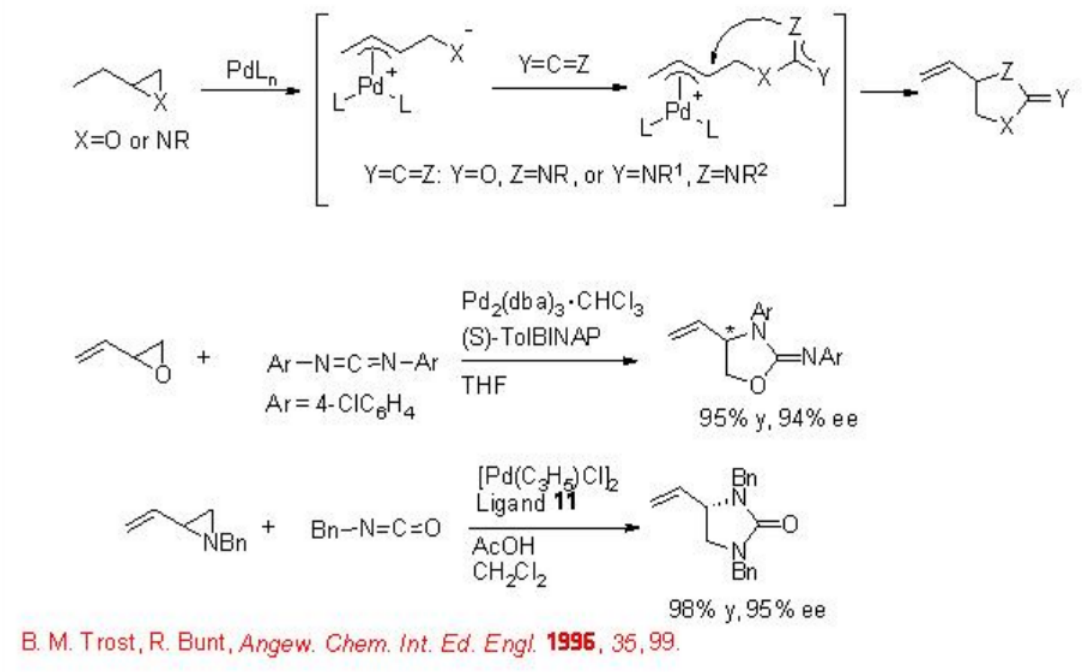
Palladium based systems has also been utilized for the cycloaddition reaction of epoxides and aziridines with heterocumulenes (Scheme 4.1.11).

Enantioselective copper(I)-catalyzed substitution reactions of propargylic acetates with amines has been explored. For examples, copper complexes derived from copper(I) salts and ligands **12** and **13** catalyze the reaction of propargylic amination with 85% ee (Scheme 4.1.12).

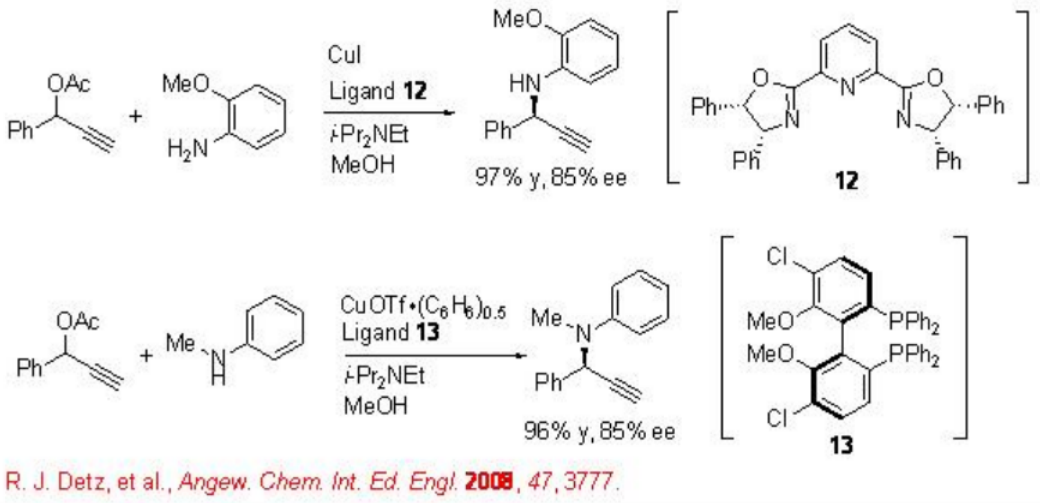


B. M. Trost and R. C. Bunt, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 99.

Scheme 4.1.10



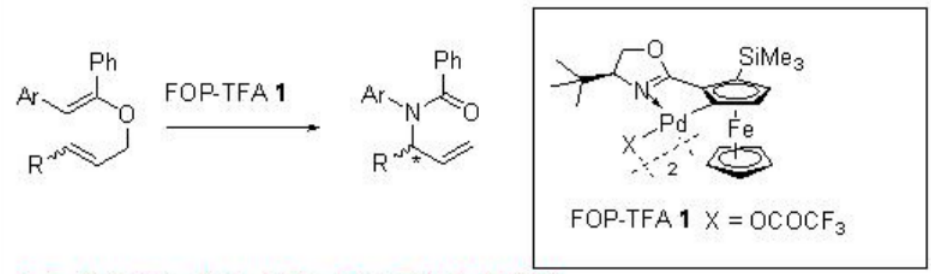
Scheme 4.1.11



Scheme 4.1.12

4.2: Aza-Claisen Rearrangement and Related Reactions

Aza-Claisen rearrangement, known as the Overman rearrangement, has been extensively studied that allows us to synthesize chiral allylic amines from achiral allylic imidates with excellent enantioselectivity. For example, prochiral *N* -arylbenzimidates can be converted into chiral *N*- a rylbenzamides in the presence of ferrocenyloxazoline palladacycle , FOP-TFA, (Scheme 4.2.1).

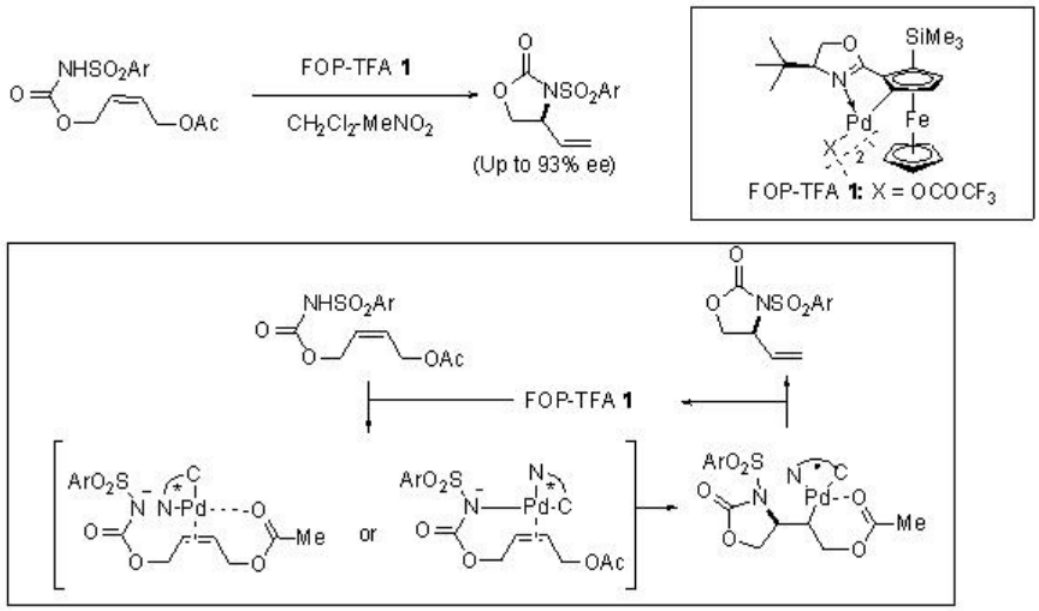


C. E. Anderson, et al., *J. Org. Chem.* **2005**, *70*, 648.

Scheme 4.2.1

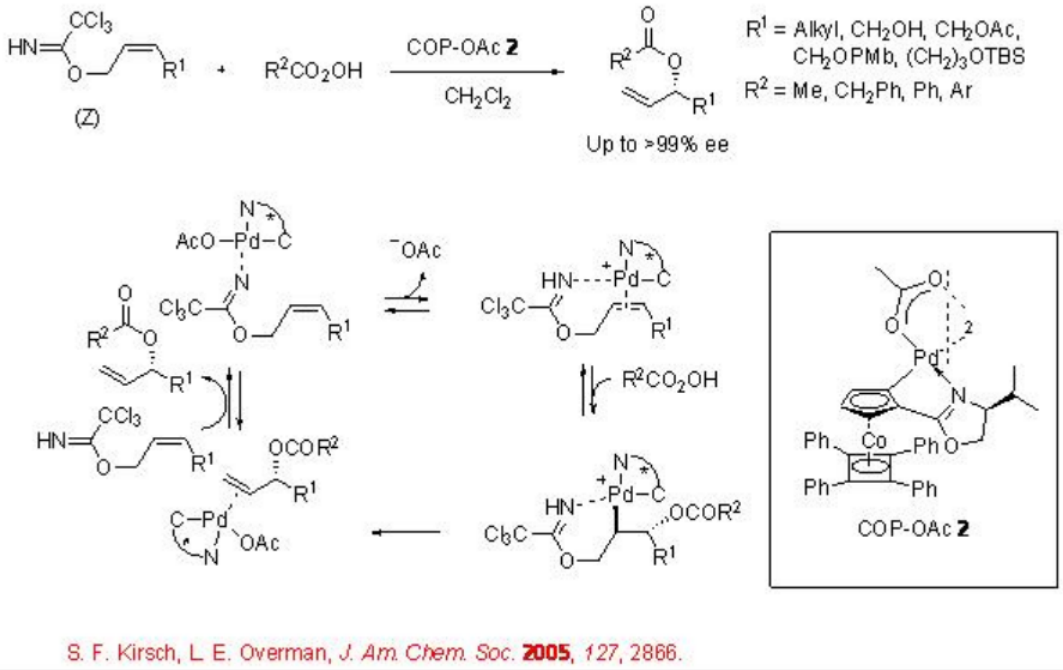
This catalytic system has also been shown to promote the cyclization of allylic *N* -arylsulfonyl carbamates to give five-membered nitrogen containing heterocycles (Scheme 2). An involvement of aminopalladation of the alkene followed by insertion of the alkene into the Pd-N has been proposed.

This procedure has also been extended for the allylic etherification reaction. For example, the reaction of (*Z*)-allylic trichloroacetimidates with carboxylic acids in the presence of COP-OAc **2** gives chiral allylic esters in high enantiopurity (Scheme 4.2.3). Under these reaction conditions, *E* -stereoisomer show inferior results. In these reactions, the COP-OAc activates the carbon-carbon double bond for attack by external oxygen nucleophile and the trichloroacetimidate group serves as a leaving group along with templating the catalyst to the double bond.



L. E. Overman, T. P. Remarchuk, *J. Am. Chem. Soc.* **2002**, *124*, 12.

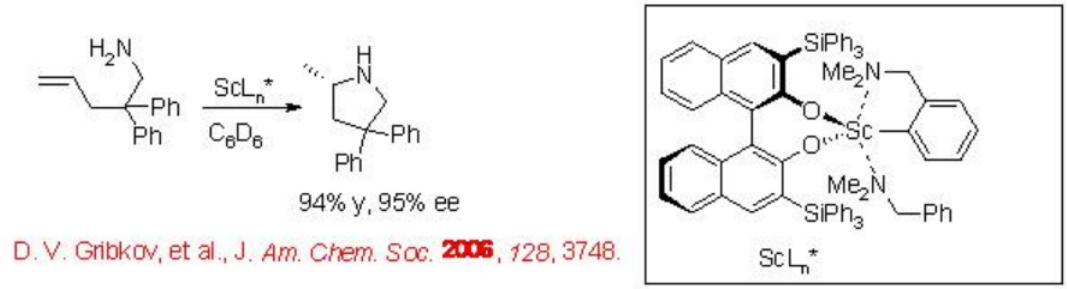
Scheme 4.2.2



Scheme 4.2.3

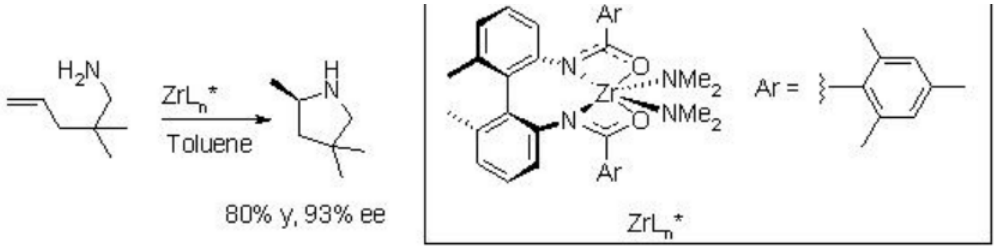
4.3: Hydroamination of Alkenes

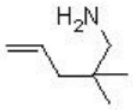
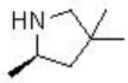
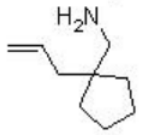
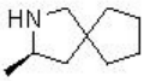
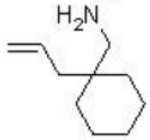
Scandium 3,3'-tris(phenylsilyl)binaphtholate can be used as a highly active catalyst for the synthesis of pyrrolidine *via* intramolecular hydroamination (Scheme 4.3.1).



Scheme 4.3.1

Chiral neutral zirconium amidate has been used for hydroamination of primary aminoalkenes with 93% ee (Scheme 4.3.1).



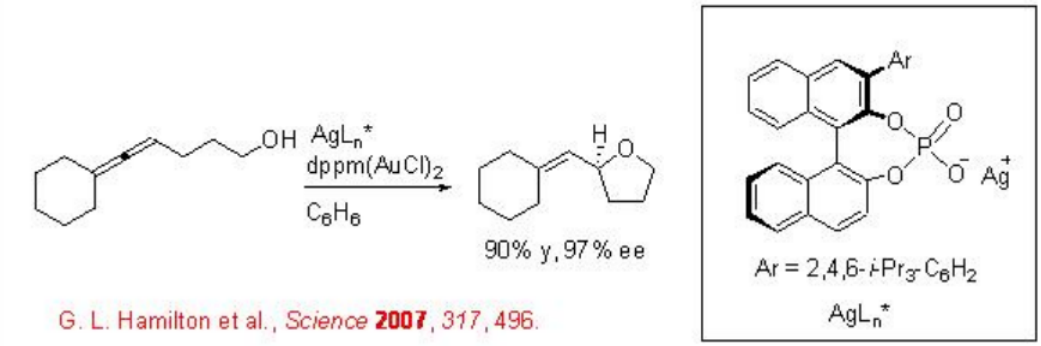
Aminoalkene	Product	Yield [%]	ee [%]
		80	93
		91	88
		96	82

M. C. Wood, et al., *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 354.

Scheme 4.3.2

4.4: Hydroalkoxylation of Allenes

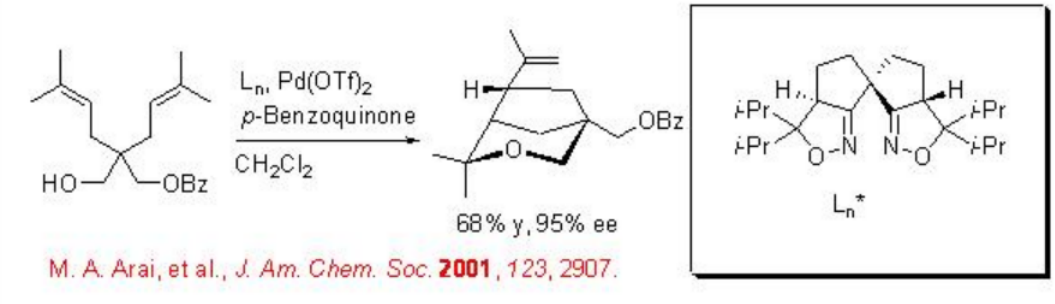
Hydroalkoxylation of allenes has been accomplished using 1:2 mixture of the dppm$(AuCl)_2$ and chiral silver phosphonate to give furan with 97% ee (Scheme 4.4.1).



Scheme 4.4.1

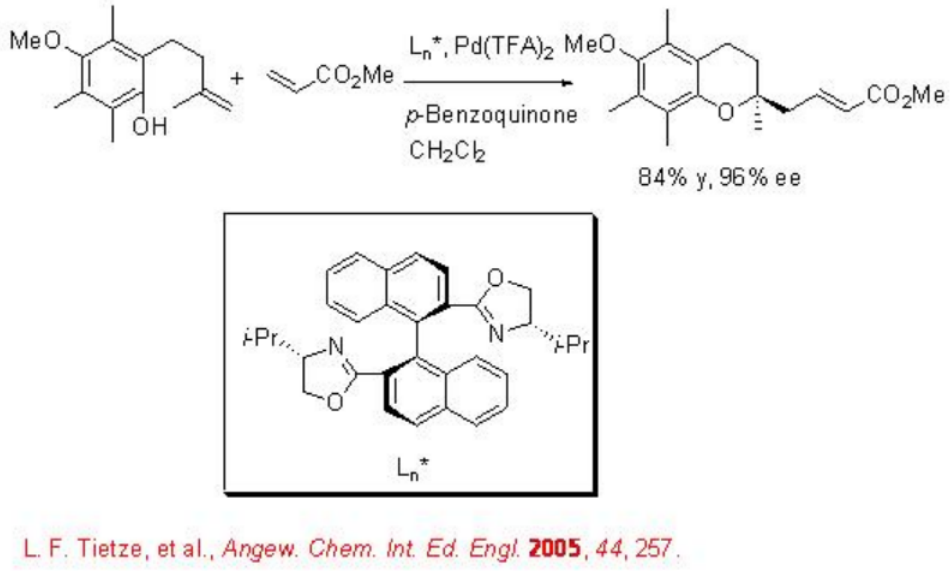
4.5: Oxidation Reactions

Wacker-type tandem cyclization reaction of alkenyl alcohol is reported using chiral palladium(II)-spirobis(isoxazoline) with excellent enantioselectivity (Scheme 4.5.1). In this reaction, benzoquinone reoxidizes the reduced palladium(0) to palladium(II) species to complete the catalytic cycle.



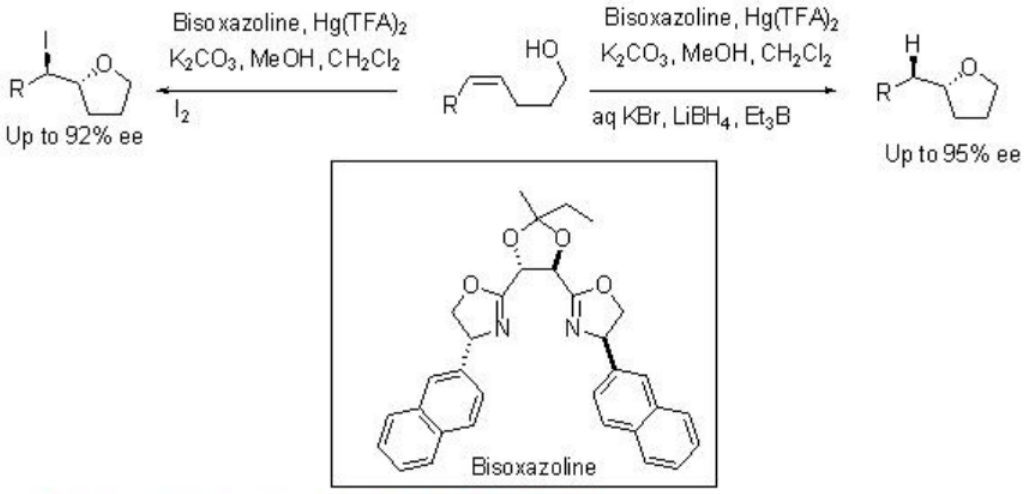
Scheme 4.5.1

Palladium complex derived from $Pd(TFA)_2$ and (*S*,*S*)-BOXAX has been found to be effective for the synthesis of chiral chroman framework in the presence of benzoquinone (Scheme 4.5.2).



Scheme 4.5.2

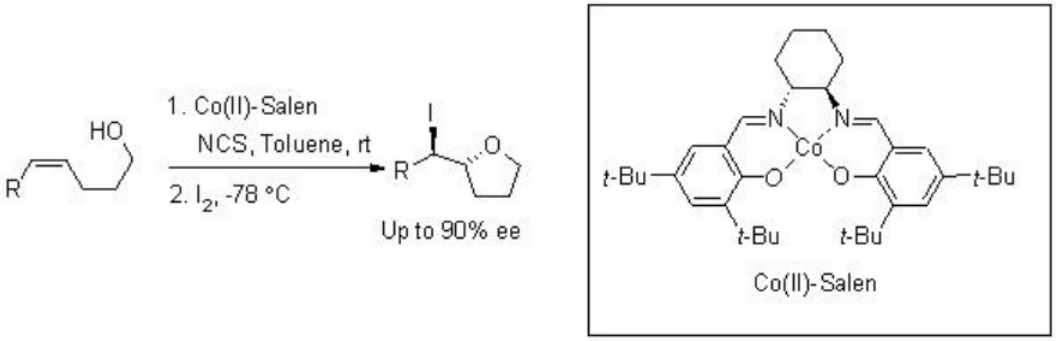
The mercury(II) complex derived from $Hg(TFA)_2$ and bisoxazoline has been used for the mercuriocyclization with high enantioselectivity (Scheme 4.5.3).



S. H. Kang, M. Kim, *J. Am. Chem. Soc.* **2003**, *125*, 4684.

Scheme 4.5.3

Chiral cobalt(II)-salen has been used for the enantioselective intramolecular iodoetherification to procure 2-substituted tetrahydrofurans with up to 90% ee (Scheme 4.5.4).



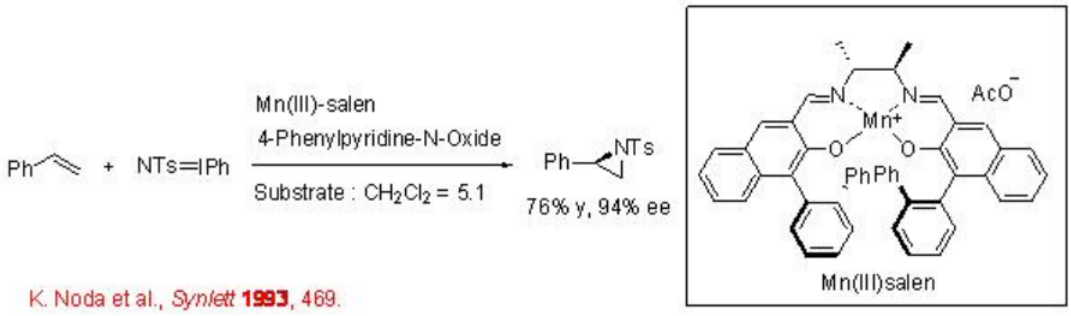
R	Yield [%]	ee [%]
$(CH_2)_3Ph$	94	84
Me	96	67
Et	89	82
n-Pr	85	85
i-Pr	83	73
$(CH_2)_3OTr$	89	90

S. H. Kang, et al., *J. Am. Chem. Soc.* **2003**, *125*, 15748.

Scheme 4.5.4

4.6: Aziridination of Alkenes

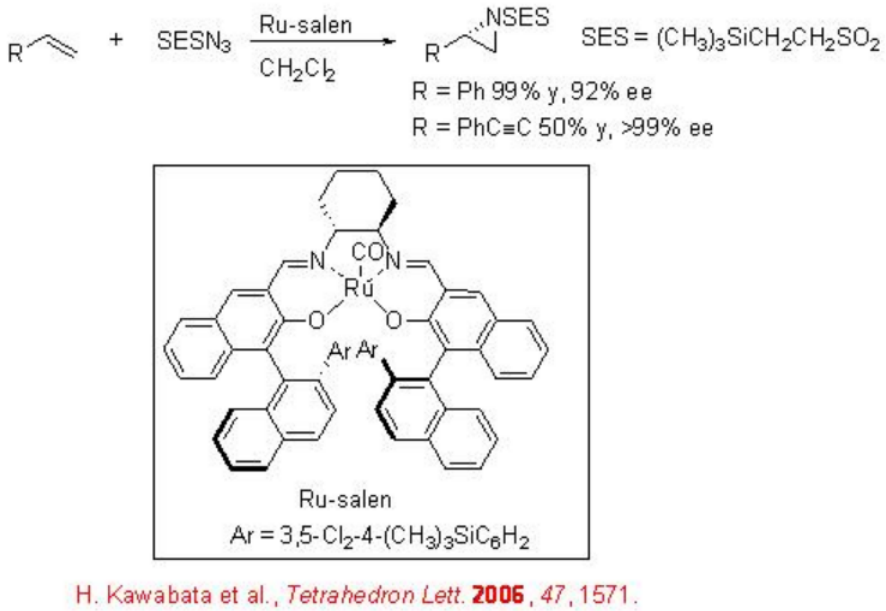
The aziridination of alkenes has been successfully accomplished using chiral Mn-salen with 94% ee. The presence of catalytic amount of 4-phenylpyridine- *N* -oxide leads to enhancement in the enantioselectivity (Scheme 4.6.1).



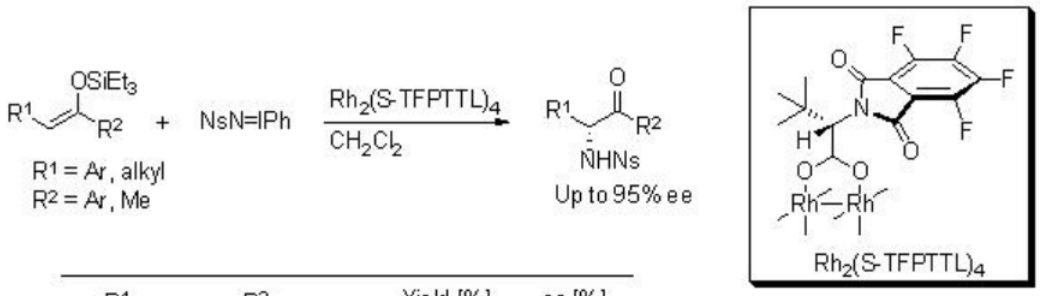
Scheme 4.6.1

Chiral Ru(salen)(CO) can be utilized for the aziridination using 2-(trimethylsilyl)ethanesulfonyl (SES) group as a nitrene precursor, because the SES group is an easily removable *N* -protecting group under milder conditions (Scheme 4.6.2). These reaction conditions are compatible for the reactions of conjugated alkenes with high enantioselectivity.

Although the aziridination of alkenes has been explored well, the reaction of enols remains elusive. The aziridination of enols generally lead to α -amino ketones via the ring opening process of the aziridine intermediates. The chiral dirhodium complex, Rh_2(*S* -TFPTTL)$_4$, catalyses efficiently the amination of enol ethers employing NsN=IPh as a nitrogen source (Scheme 4.6.3). The use of the *N*-2-nitrophenylsulfonyl (Ns) group is synthetically valuable, because the alkylation and deprotection of *N* -monosubstituted Ns-amide takes under milder conditions. The application of this protocol has been shown in the formal synthesis of (-)-metazocine.



Scheme 4.6.2

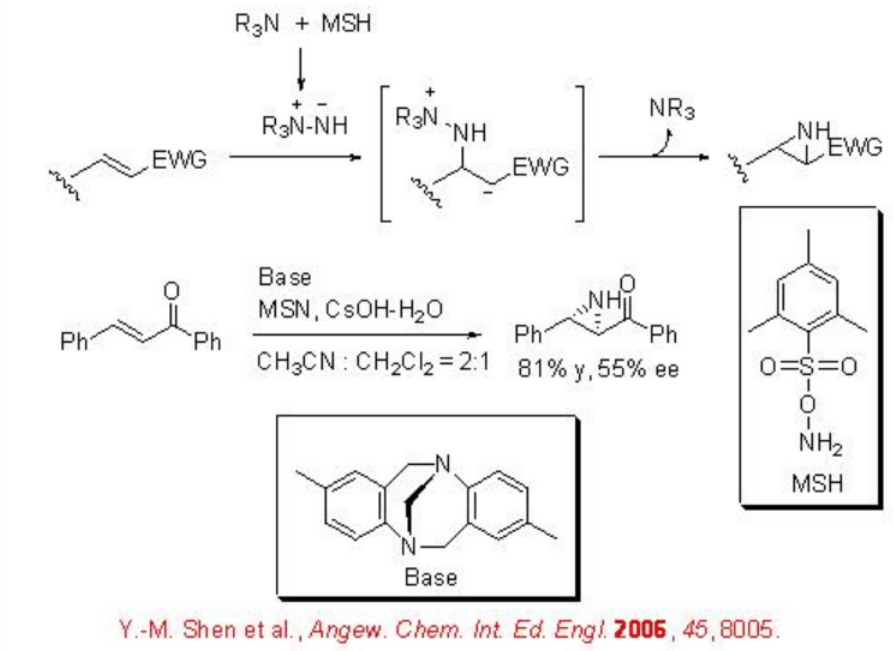


R^1	R^2	Yield [%]	ee [%]
Ph	Me	94	95
4-ClC_6H_4	Me	95	84
4-$MeOC_6H_4$	Me	91	78
$CH_3(CH_2)_3$	Me	81	47
Me	Ph	97	93
Me	4-ClC_6H_4	94	90
Me	4-$MeOC_6H_4$	98	95

M. Anada et al., *Org. Lett.* **2007**, *9*, 4559.

Scheme 4.6.3

The use of chiral amine has been demonstrated for the reaction of electron deficient alkenes. For example, the use of aminimide as an effective NH-transfer reagent for the aziridination of electron deficient alkenes is reported (Scheme 4.6.4). In this reaction, in situ generation of a hydrazinium salt from tertiary amine and O-mesitylenesulfonylhydroxylamine (MSH), deprotonation of the hydrazinium salt to form an aminimide, and subsequent aziridination is involved.

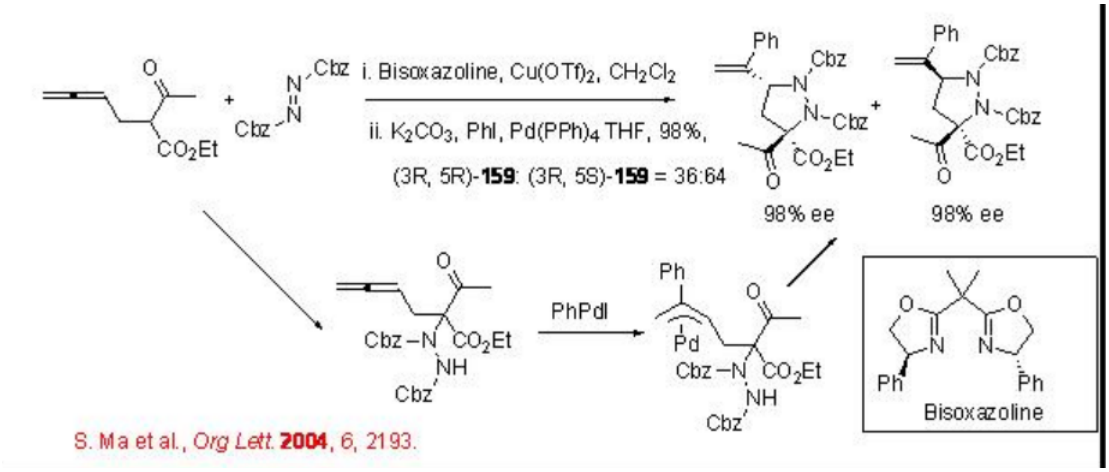


Y.-M. Shen et al., *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 8005.

Scheme 4.6.4

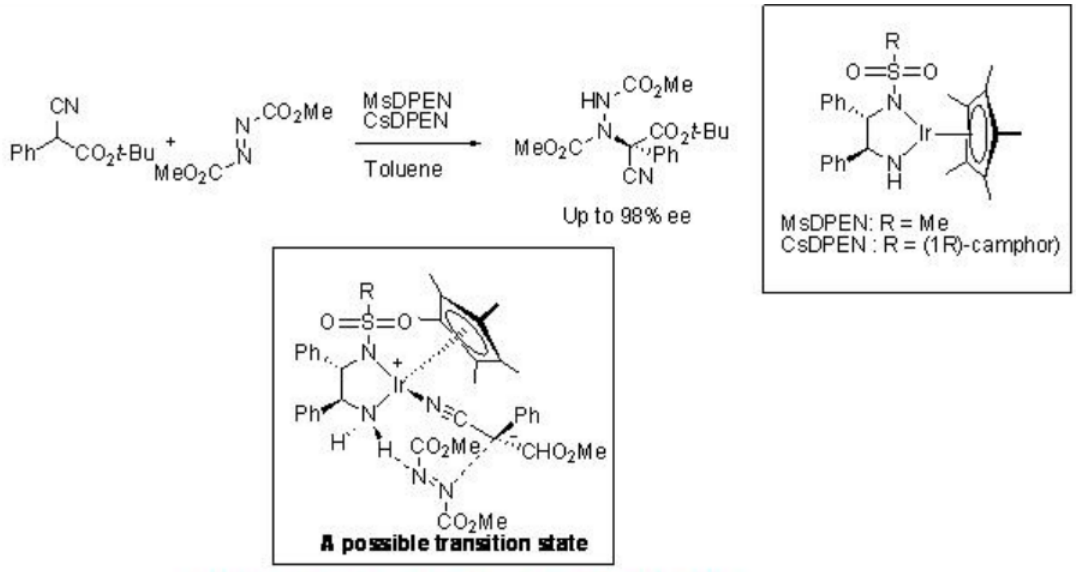
4.7: Amination of Carbonyl Compounds

The electrophilic amination reaction is useful technology for the introduction of an amine functionality next to carbonyl carbon. Asymmetric version of this process has been considerably explored. Recently, the use of the combination of copper and palladium based catalytic system has been demonstrated for the asymmetric one-pot tandem addition-cyclization reaction of 2-(2',3'-dienyl)-β-keto esters, aryl halides, and dibenzylazodicarboxylate to afford pyrazolidine (Scheme 4.7.1). An involvement of π -allylpalladium intermediate *via* the carbopalladation of allene has been proposed.



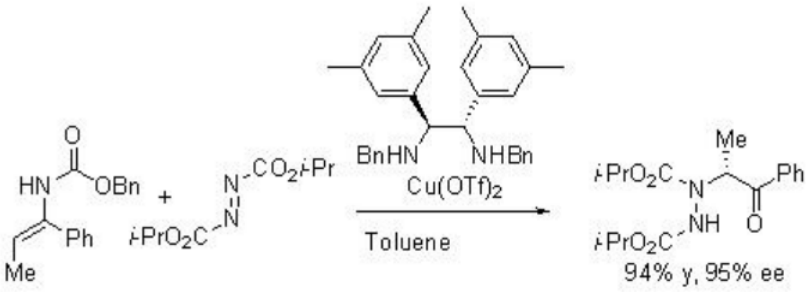
Scheme 4.7.1

The use of bifunctional chiral amide iridium complex for the direct amination of α -substituted α -cyanoacetate with azodicarboyxlate has been demonstrated with excellent enantioselectivity (Scheme 4.7.2). In this reaction, the chiral amide complexmay be involved in the deprotonation of cyanoacetate that would lead to the formation of *N* -bound nitrile complex; thus, cyanoacetate and azodicarboxylate are activated sequentially by the bifunctional catalyst that could facilitate the transformation.



Scheme 4.7.2

Using chiral diamine-copper(II) the amination of enecarbamates can be accomplished with excellent enantioselectivities (Scheme 4.7.3). Under these conditions, the changing the enecarbamate geometry from *Z* to *E* resulted in a dramatic improvement of the reactivity.

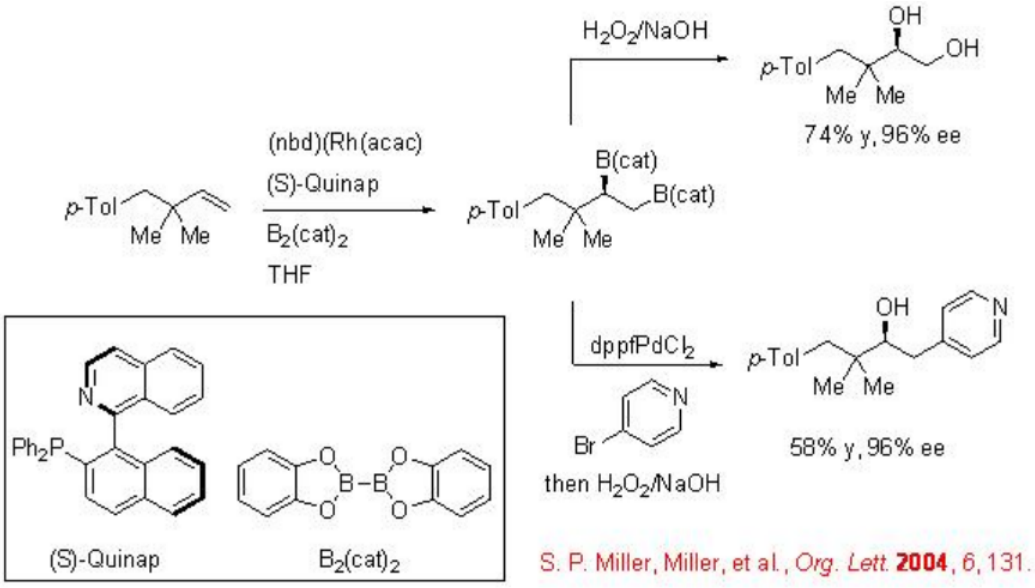


R. Matsubara, S. Kobayashi, *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 7993.

Scheme 4.7.3

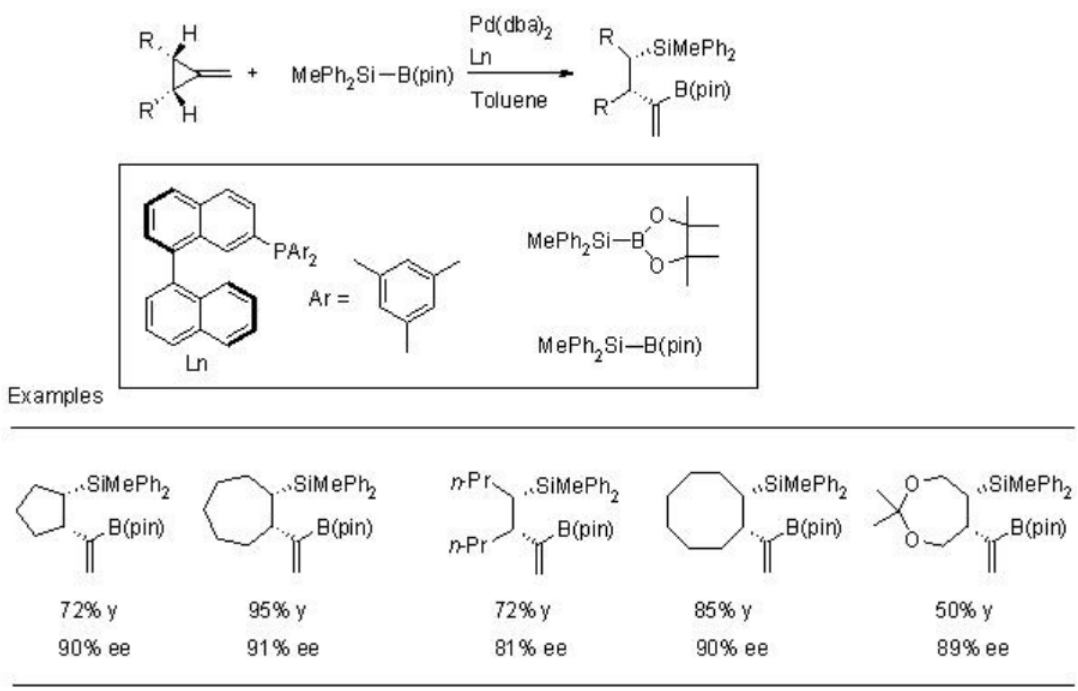
4.8: Boration of Alkenes

Organoboranes are useful reagents for organic synthesis. Recently, catalytic methods have been developed for enantioselective boration of unsaturated substrates. For example, the diboration of alkenes with bis(catecholato)diboron using rhodium(I) salt and (*S*)-quinap can be accomplished (Scheme 4.8.1). Oxidation of the diborane derivatives can lead to chiral 1,2-diols. Furthermore, tandem diboration, Suzuki cross-coupling and oxidation reaction can lead to carbohydroxylation with similar enantioselectivity.

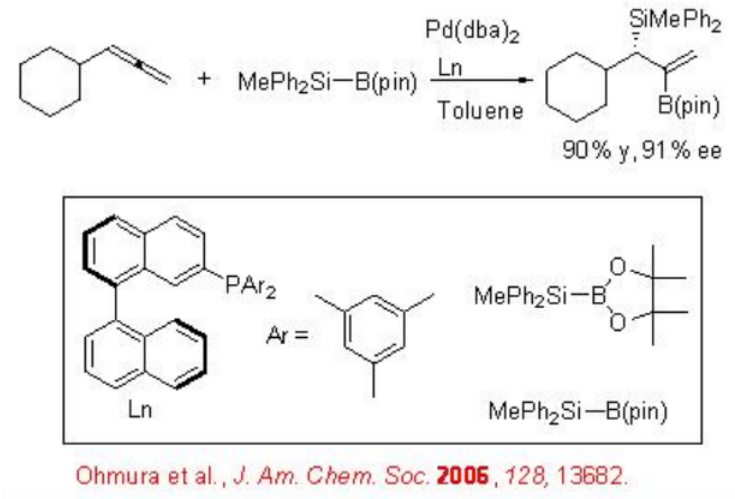


Scheme 4.8.1

The asymmetric silaboration of symmetrically substituted *meso* -methylcyclopropanes can be accomplished *via* carbon-carbon bond cleavage employing chiral palladium-catalyzed boration withMe_2PhSiB(pin) as the silylboron reagent (Scheme 4.8.2). The catalytic system is also effective for the silaboration of mono-substituted allene to give allylsilane with good enantioselectivity (Scheme 4.8.3).

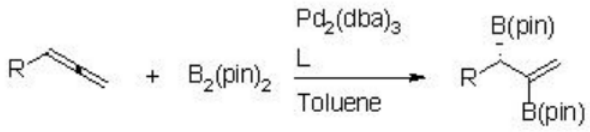


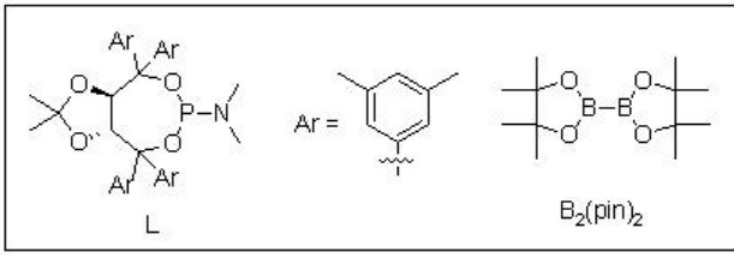
Scheme 4.8.2



Scheme 4.8.3

The diboration of terminal allenes is also demonstrated using palladium complex derived from $Pd(dba)_2$ and a chiral phosphoramidite to give 1,2-bis(boronate)ester with high enantioselectivity (Scheme 4.8.4). The rate determining step involves the oxidative addition of the diboron to Pd, which is followed by the transfer of both boron groups to the unsaturated substrate *via* a π -allyl complex.





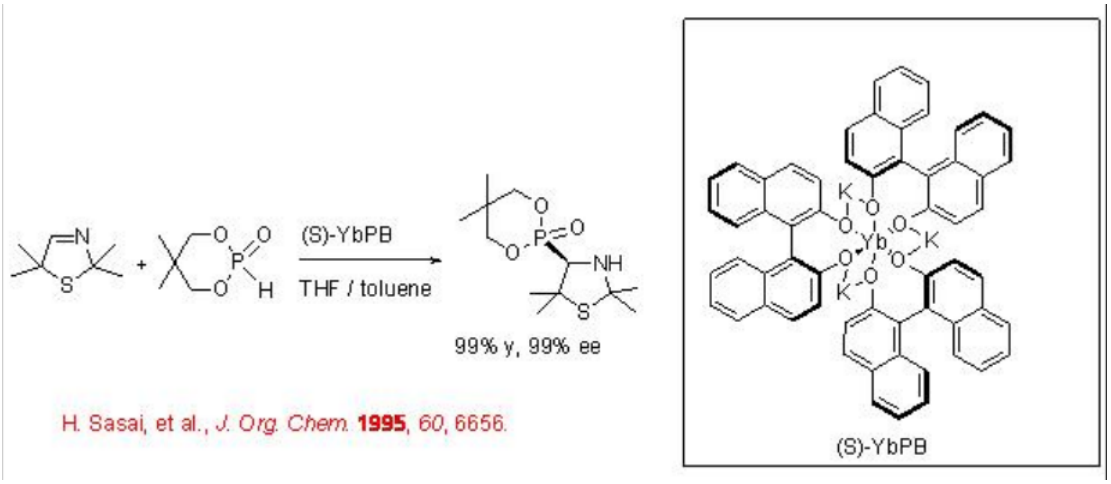
R	Yield [%]	ee [%]
$C_{10}H_{21}$	72	98
CH_3	77	95
C_6H_{11}	92	93
Ph	71	97
4-$MeOC_6H_4$	68	94

H. E. Burks, et al., *J. Am. Chem. Soc.* **2007**, *129*, 8766.

Scheme 4.8.4

4.9: Hydrophosphonylation of Imines

The hydrophosphonylation of aldehydes and imines affords an effective route for the formation of C-P bonds. Recently, the reaction of cyclic phosphate with cyclic imines has been shown employing bimetallic chiral (*S*)-YbPB with excellent enantioselectivity (Scheme 4.9.1).

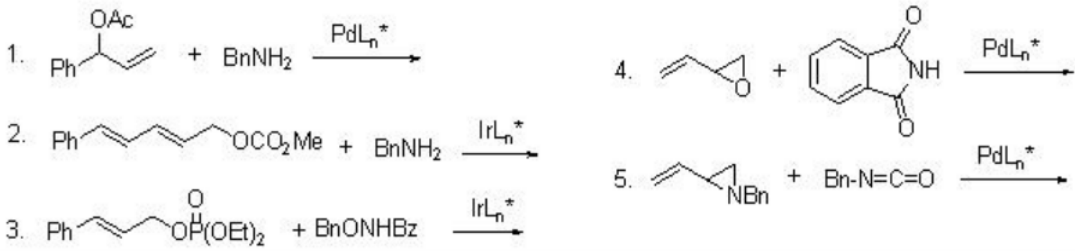


Scheme 4.9.1

4.10: Problems and Reference

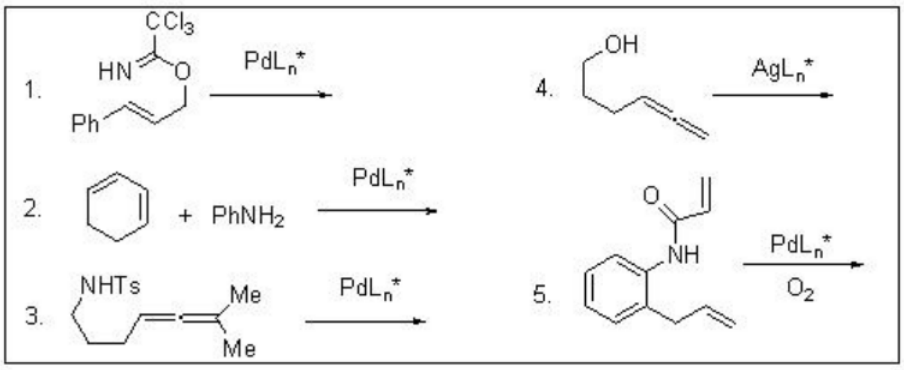
Problems:

What major products would you expect from the following reactions?



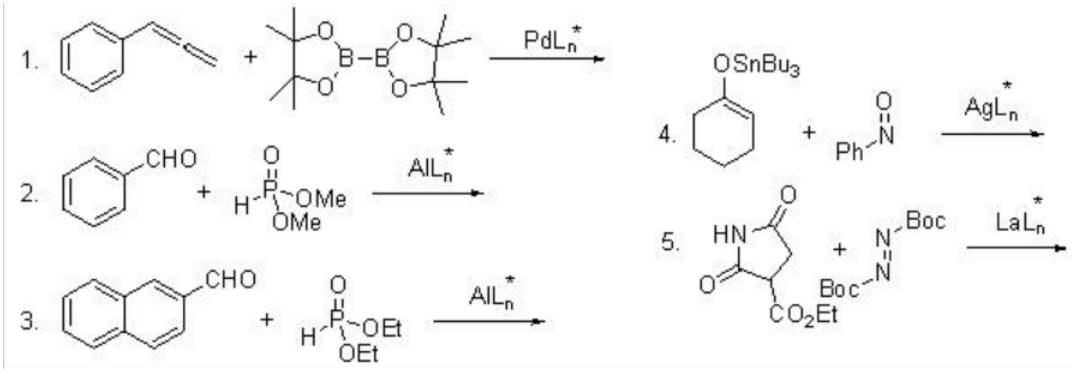
Describe Rh-catalyzed allylic substitution.

Complete the following reactions.



Provide some examples for the chiral Y and Au-catalyzed hydroamination reactions.

Predict the major product for the following reactions.



Describe asymmetric oxygenation of carbonyl compounds.

Reference /Text Book

• I. Ojima, *Catalytic Asymmetric Synthesis* , 3 rd ed., Wiley, New Jersey, 2010.

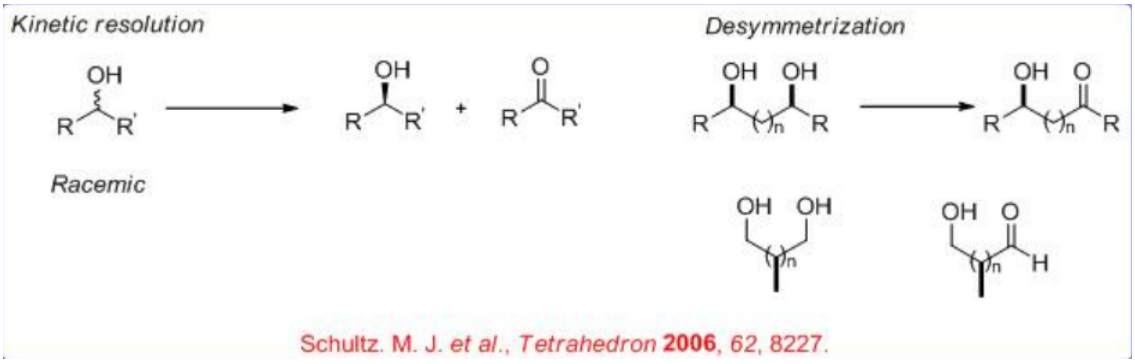
• M. B. Smith, *Organic Synthesis* , 2 nd ed., McGraw Hill, New Delhi, 2004.

CHAPTER OVERVIEW

5: Oxidation Reactions

5.1: Oxidation of Alcohols

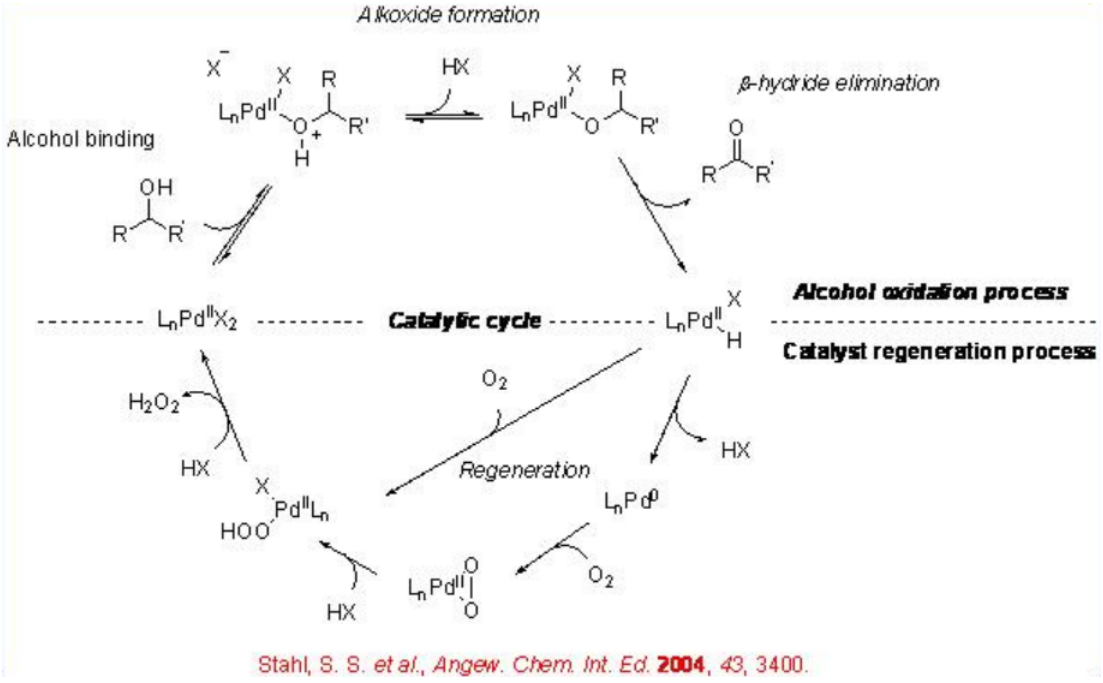
Oxidation of alcohols to carbonyl compounds is a pivotal process in organic chemistry. In particular, the oxidations that use readily available molecular oxygen, especially ambient air, as the stoichiometric oxidant are the most preferable. During the recent years, asymmetric version of the process has been developed using molecular catalysis, which can be divided into kinetic resolution of secondary alcohols and desymmetrization of *meso* - or prochiral diols (Scheme 5.1.1).



Scheme 5.1.1

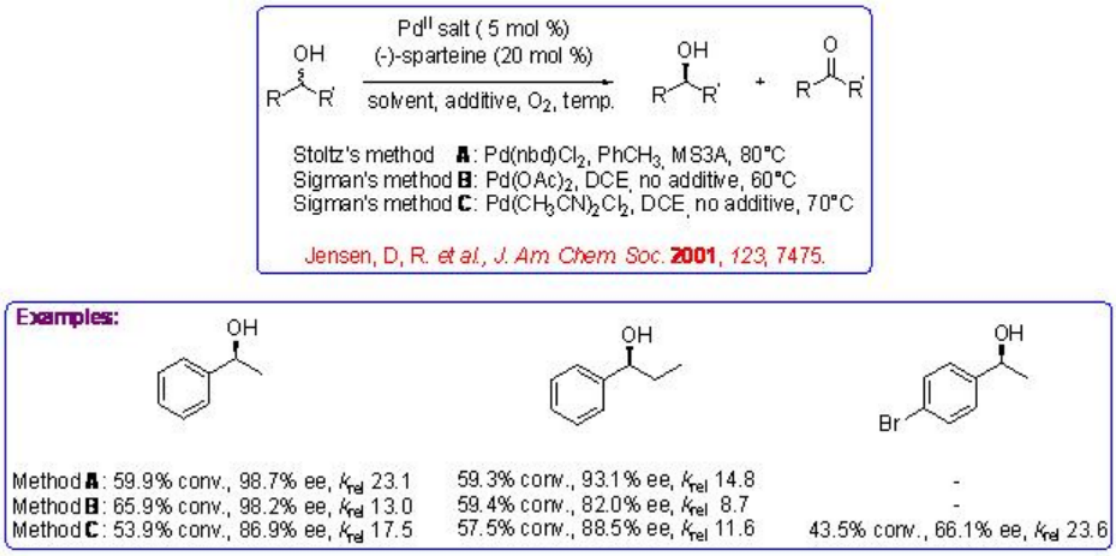
5.1.1 Palladium Catalyst

The palladium catalyzed aerobic oxidation of alcohols to carbonyl compounds has received much attention in recent years and the catalytic cycle for this process is presented in Scheme 5.1.2. The cycle consists two separate processes: the oxidation of alcohols and the regeneration of the catalyst. In the oxidation of alcohols palladium alkoxide is generated after the coordination of the alcohol, and then β -hydride elimination occurs to afford the carbonyl compounds. The resultant palladium hydride reacts with molecular oxygen to generate palladium hydroperoxo complex and the subsequent ligand exchange reproduce the catalyst.



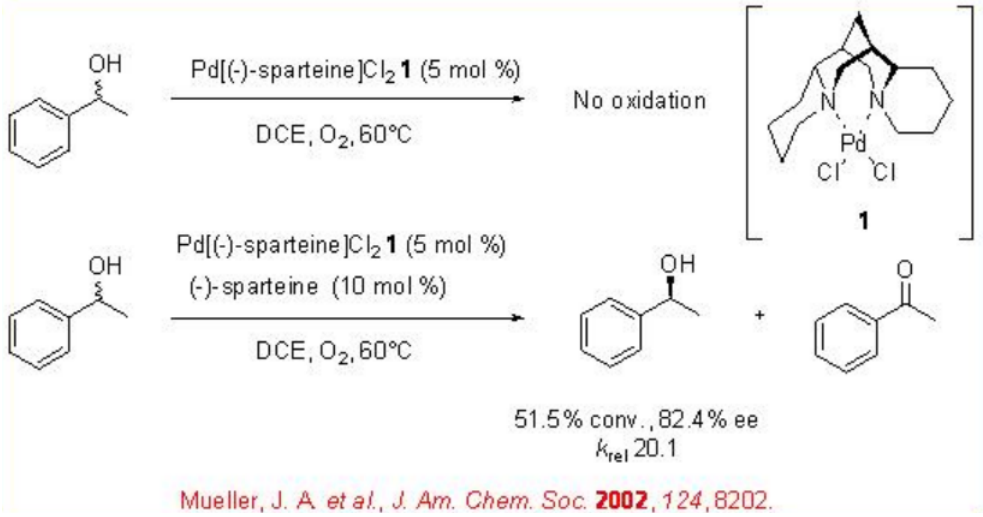
Scheme 5.1.2

A series of experiments by three research groups have carried out using palladium complex bearing naturally occurring diamine, (-)-sparteine, to catalyzes the oxidation of aliphatic, benzylic and allylic alcohols with moderate to good k_{rel} values (Scheme 5.1.3).



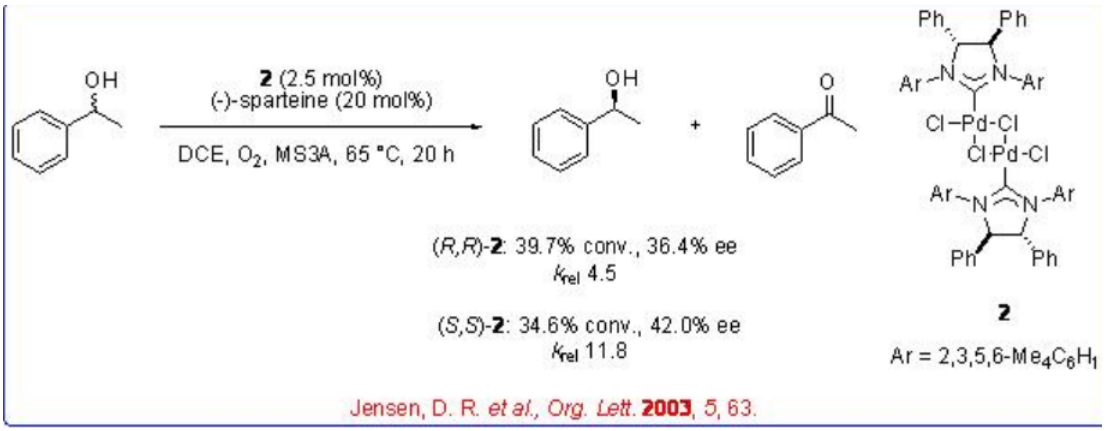
Scheme 5.1.3

However, the isolated palladium-sparteine complex shows no catalytic activity and the reaction is effective employing additional (-)-sparteine (Scheme 5.1.4). This result suggest that the additional (-)-sparteine serves as base to abstract a proton to a palladium bound alcohol in the alkoxide formation process.



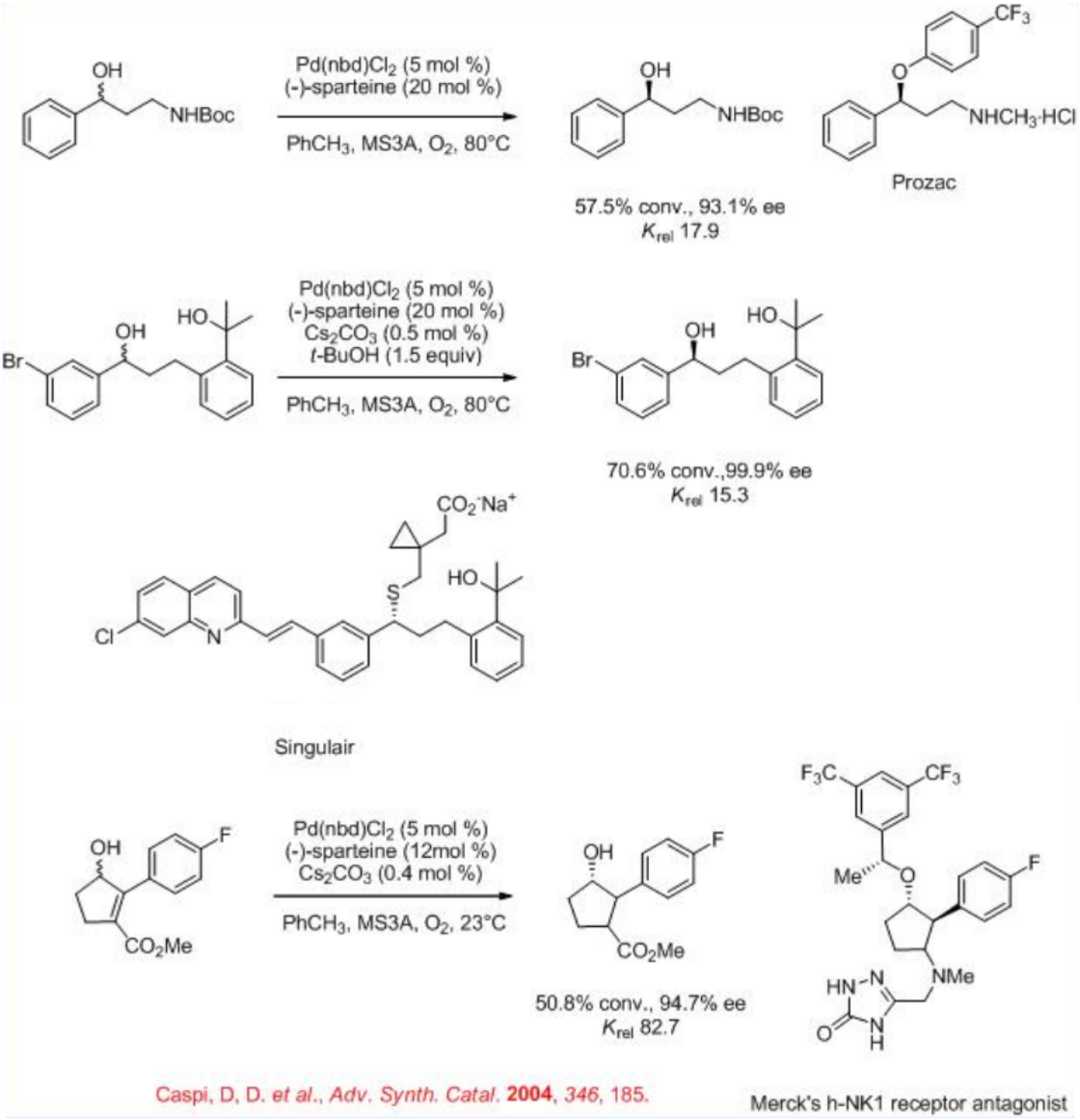
Scheme 5.1.4

Subsequently, the combination of palladium complexes bearing chiral and achiral N-heterocyclic carbene lignads with (-)-sparteine has been used for the kinetic resolution of secondary alcohols with high selectivity (Scheme 5.1.5).



Scheme 5.1.5

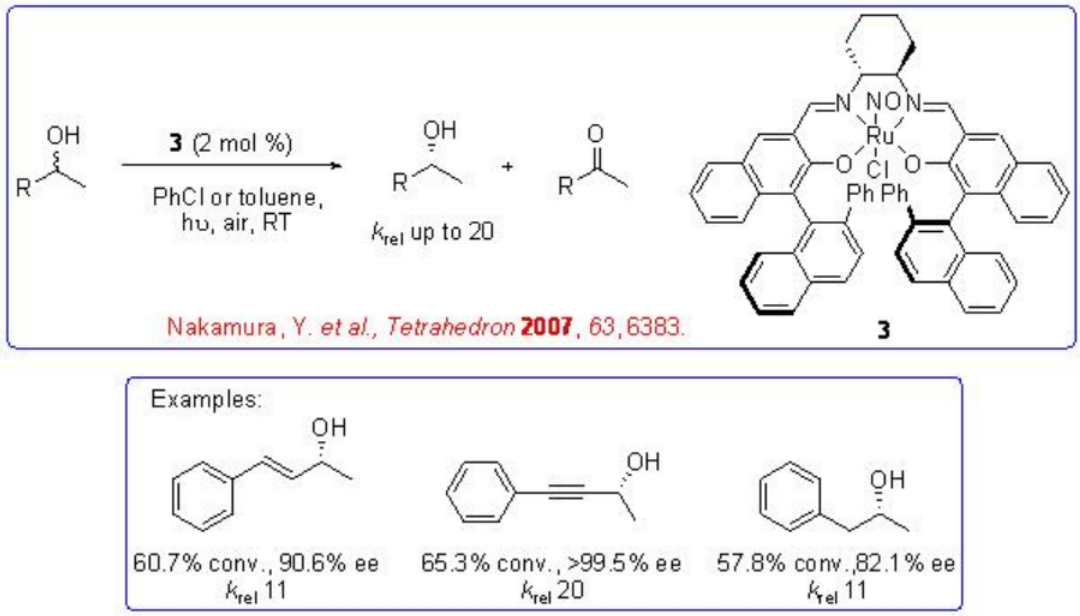
The reaction is found to be accelerated in the presence of Cs_2CO_3 under ambient air (Scheme 5.1.6). The procedure is found to be useful for the synthesis of several pharmaceutically important substances including Prozac®, Singlair®, and Merck's h-NK1 receptor antagonist.



Scheme 5.1.6

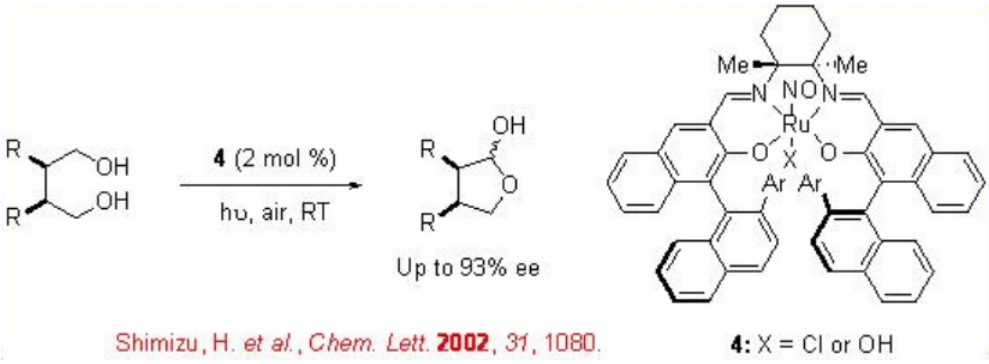
5.1.2 Ruthenium Catalyst

Chiral Ru-salen complex **3** having nitrosyl ligand has been found to be effective catalyst for the oxidative kinetic resolution of secondary alcohols under ambient air as oxidant under visible light (Scheme 5.1.7). The irradiation of the visible light promotes dissociation of the nitrosyl ligand and generates a catalytically active ruthenium species. Kinetic resolution of aryl, alkynyl and alkyl alcohols has been observed with k_{rel} up to 30.



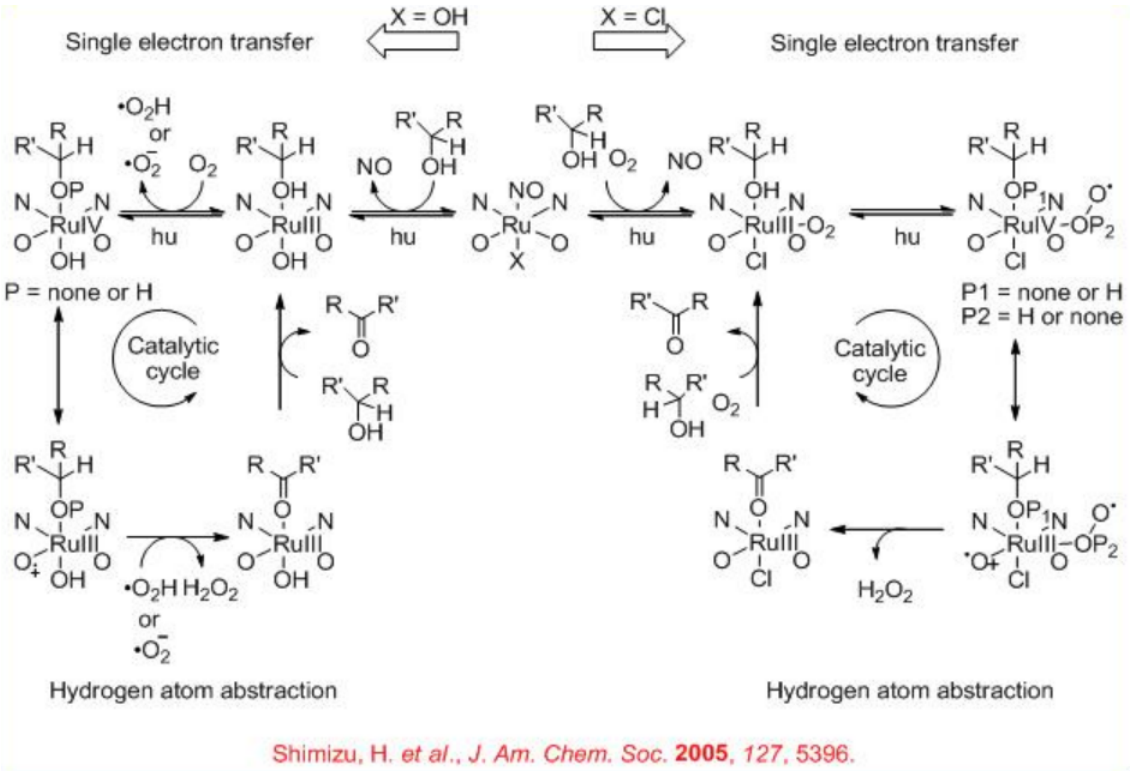
***Scheme* 5.1.7**

The chiral ruthenium based complex **4** is also effective for the oxidative desymmetrization of 1,4- *meso* -diols (Scheme 5.1.8).



Scheme 5.1.8

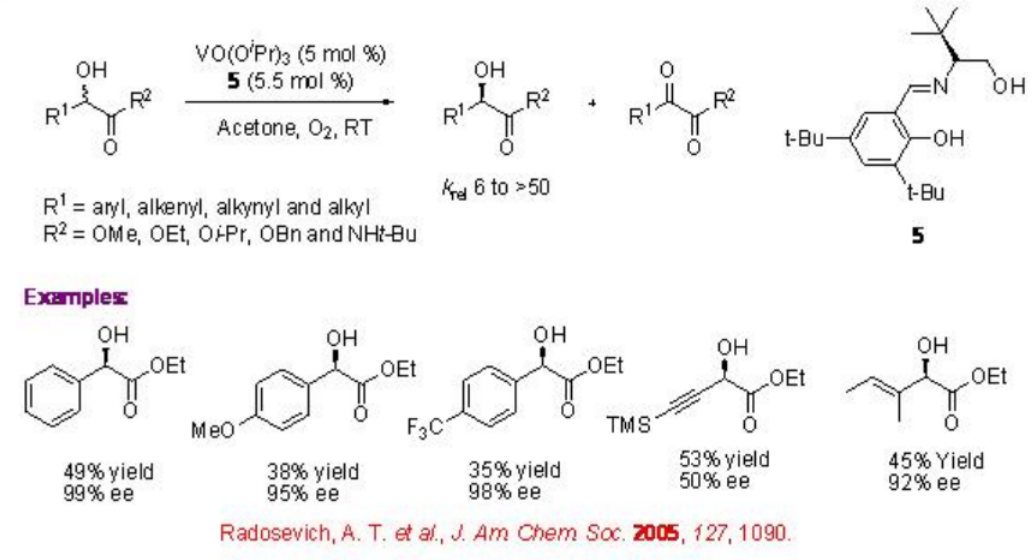
Scheme 5.1.9 shows the proposed mechanism for the Ru-catalyzed aerobic oxidation of alcohols which is similar to the galactose oxidase system.



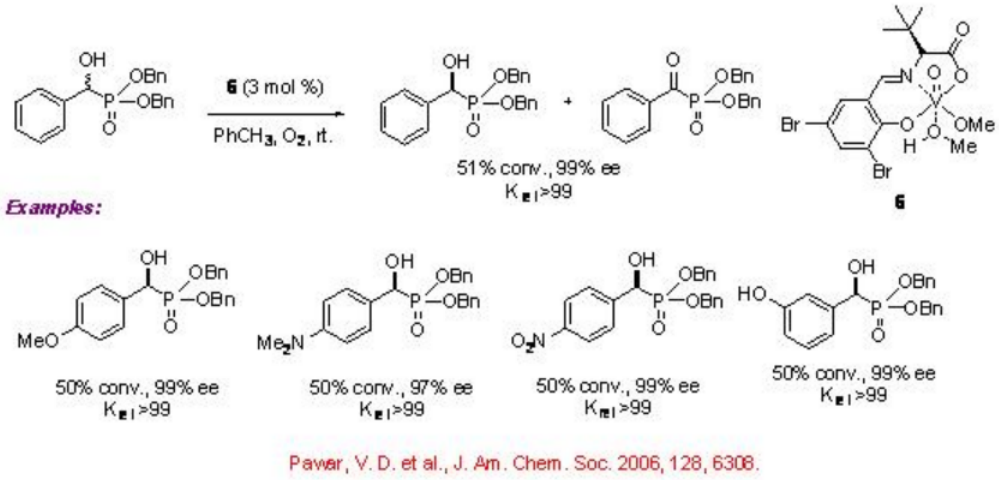
Scheme 5.1.9

5.1.3 Vanadium Catalyst

Vanadium complexes having chiral tridentate Schiff base ligand **5** derived from optically active amino alcohol and benzaldehyde derivative catalyze efficiently the kinetic resolution of α -hydroxy carbonyl compounds (Scheme 5.1.10). The reactions of α -hydroxy esters can be accomplished with k_{rel}ranging from 6 to 50. Subsequently, the chiral tridentate Schiff base ligand **6** derived from optically active α -amino acids and aldehydes have also been found to be effective for the vanadium catalyzed aerobic kinetic solution of hydroxy compounds (Scheme 5.1.11). For example, the reaction of α -hydroxyphosphonic acids can be accomplished with excellent selectivity (k_{rel} 99). The observed experimental results suggest that these oxidation reactions don't involve radical process.



Scheme 5.1.10

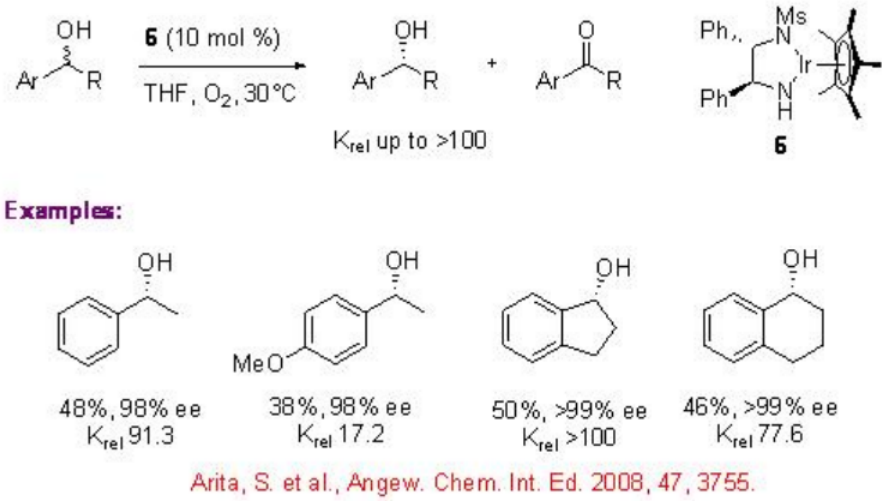


Pawar, V. D. et al., J. Am. Chem. Soc. 2006, 128, 6308.

Scheme 5.1.11

5.1.4 Iridium Catalyst

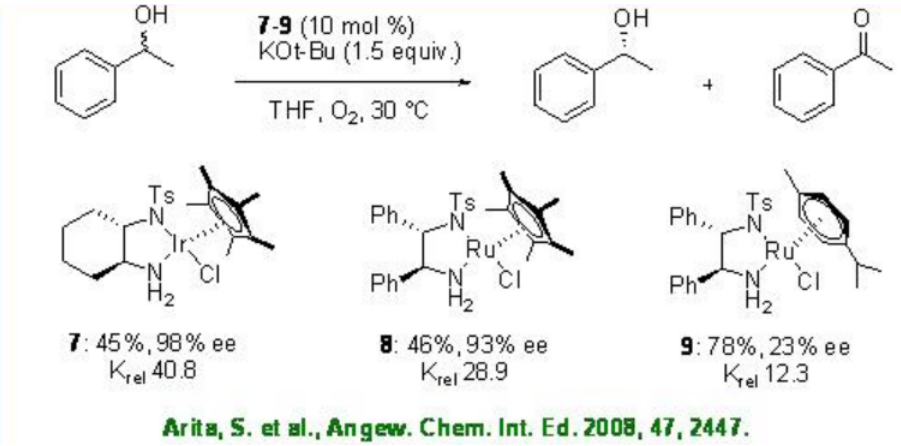
Few studies are focused on the use of chiral iridium complexes for the oxidative kinetic resolution of racemic secondary alcohols. Chiral iridium complex **6** has been shown to catalyze the oxidation benzylic alcohols with high k_{rel} under air. Using these reaction conditions, the oxidation of 1-indanol is reported with enantioselectivity of up to 99% and 50 yield.



Arita, S. et al., Angew. Chem. Int. Ed. 2008, 47, 3755.

Scheme 5.1.12

Iridium chloride complex **7** has been used for the oxidation of racemic secondary alcohols with k_{rel}as high as 48.8 (Scheme 5.1.13). The Rh analogue **8** exhibits high catalytic activity in the presence of base, while the related Ru complex **9** gives diminished result.



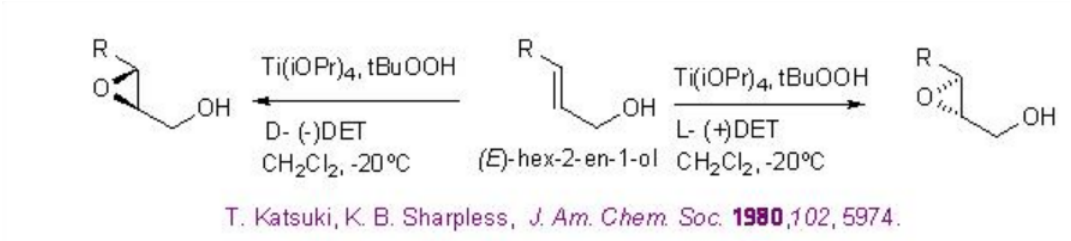
Scheme 5.1.13

5.2: Epoxidation of Allylic Alcohols

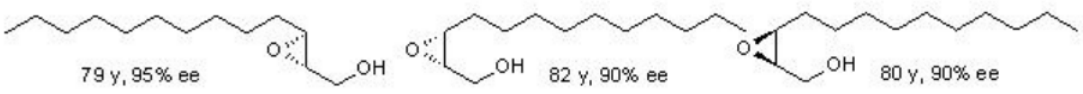
Epoxidation of allylic alcohols is a well developed practical process in asymmetric catalysis.

Titanium-Catalyzed Epoxidation

The Sharpless asymmetric epoxidation of allylic alcohol provides a powerful tool for the synthesis of optically active epoxy alcohol. For example, hexe-2-en-1-ol undergoes epoxidation to give chiral epoxy alcohols with 94% ee and 85% yield in presence of 5-10 mol% of $Ti(O^iPr)_4$, L-(+)-DET and *t* -BuOOH (Scheme 5.2.1). Using D-(-)-DET as chiral source the opposite enantiomer can be obtained with similar yield and enantioselectivity.

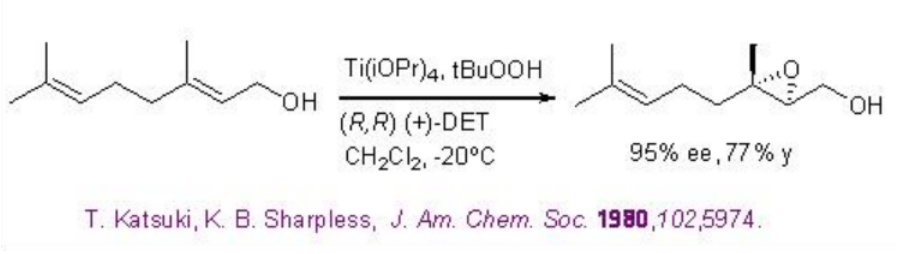


Examples:



Scheme 5.2.1

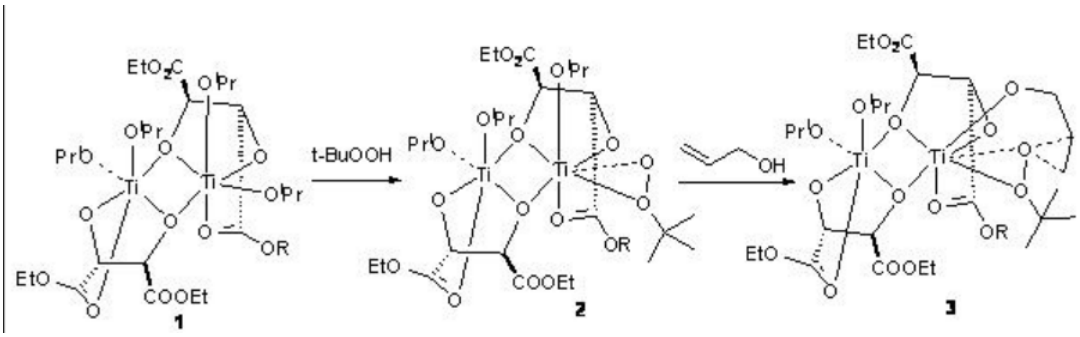
In case the substrates having more double bonds, the allylic double bond can be oxidized. For example, the allylic double bond of geraniol can be selectively oxidized with 95% ee (Scheme 5.2.2).



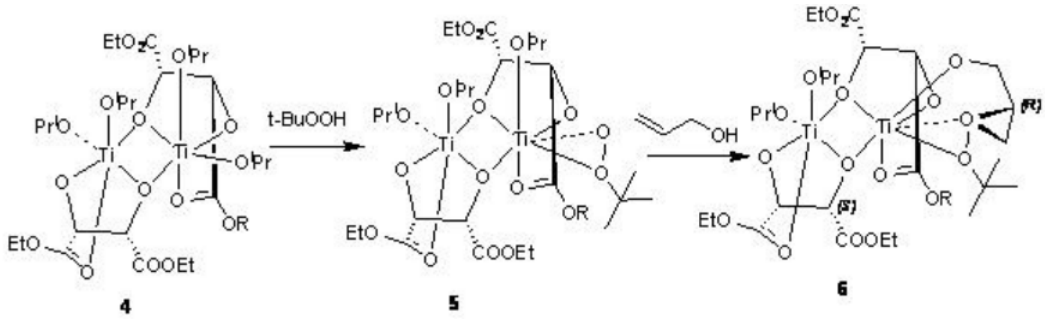
Scheme 5.2.2

Mechanism

The reaction of titanium alkoxide with tartrate ligands leads to the formation of the dimers **1** and **4** that in the presence of *t* -BuOOH are converted into the intermediates **2** and **5**, respectively, by displacement of the isopropoxide and tartrate carbonyl groups (Scheme 5.2.3-5.2.4). Reaction of **2** and **5** with allylic alcohol give the intermediates **3** and **6**, respectively. The stereochemistry of the epoxide is determined by the diastereomer of the chiral tartrate diester.

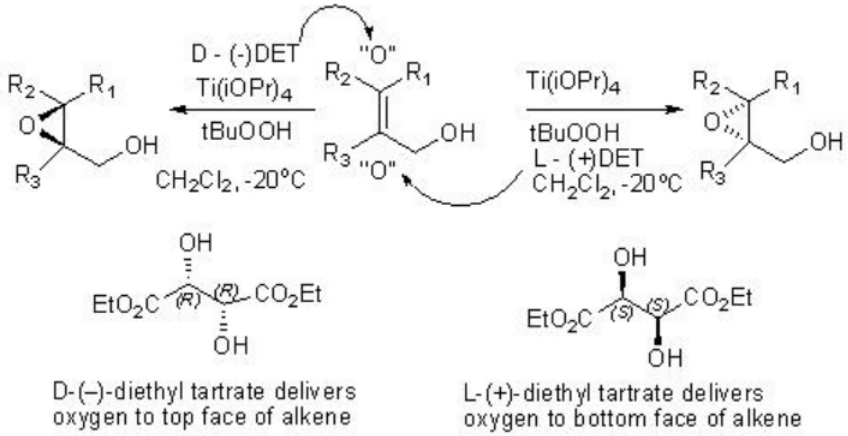


Scheme 5.2.3



Scheme 5.2.4

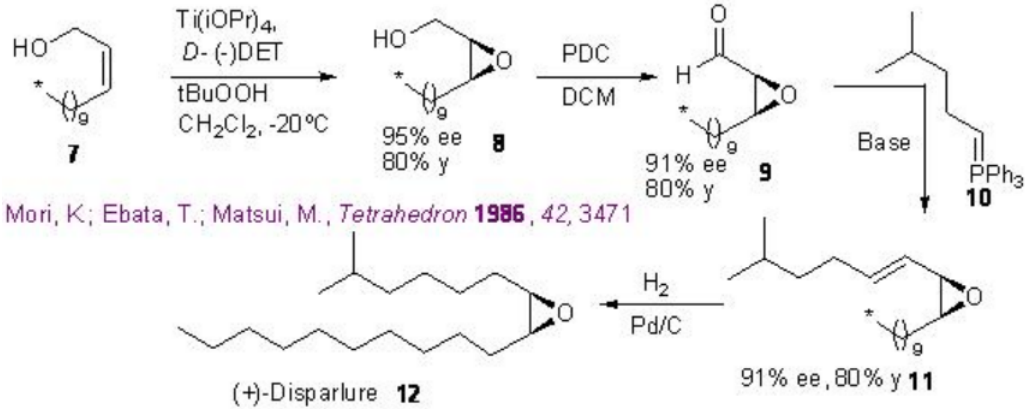
The product stereochemistry can be predicted using the model shown in Scheme 5.2.5.



Scheme 5.2.5

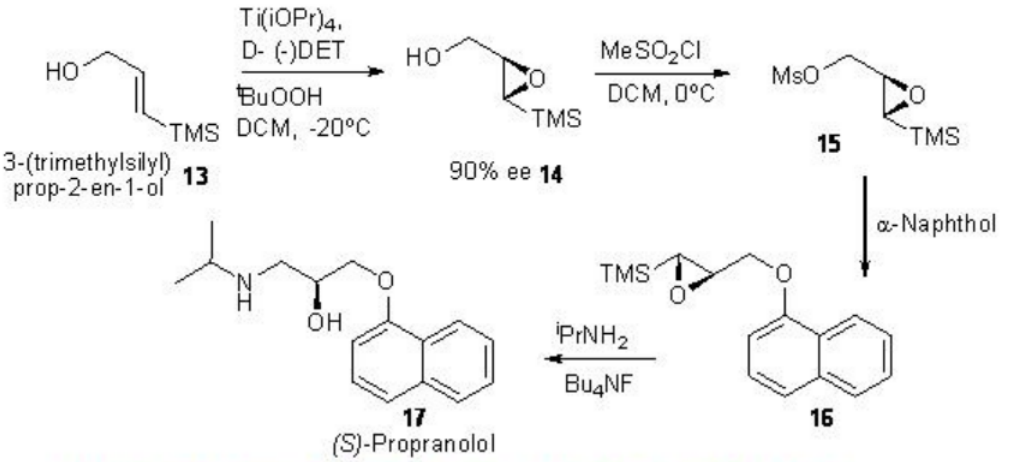
Application

The reaction has been applied for the synthesis of a number of natural products, antibiotics and pharmaceuticals. For examples, the synthesis of the sex pheromone of gypsy moth (*Lymantria dispar*) (+)-disparlure **12** has been accomplished (Scheme 5.2.6). The epoxidation of allyl alcohol **7** by Sharpless procedure affords optically active epoxy alchohol **8** with 95% ee that in presence of pyridinium dichlorochromate (PDC) gives chiral aldehyde **9** . The latter with Wittig salt **10** affords *trans* -alkene **11** that could be reduced using Pd/C to give the target (+)-disparlure **12** .



Scheme 5.2.6

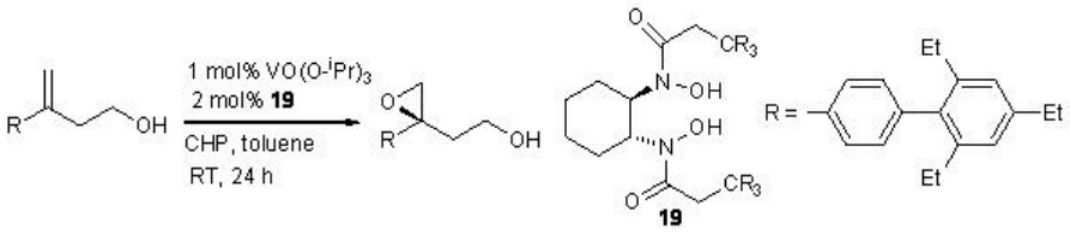
The Scheme 5.2.7 shows the use of the Sharpless asymmetric epoxidation for the synthesis of gastric inhibitor *(S)* -propanolol. The epoxidation of 3-(trimethylsilyl) prop-2-en-1-ol **13** affords epoxy alcohol **14** with 90% ee that could be converted into **16** by mesylation **15** followed by coupling with 1-naphthol. Opening of the epoxide **16** with isopropylamine leads to the formation of the target *(S)* -propanolol **17** .



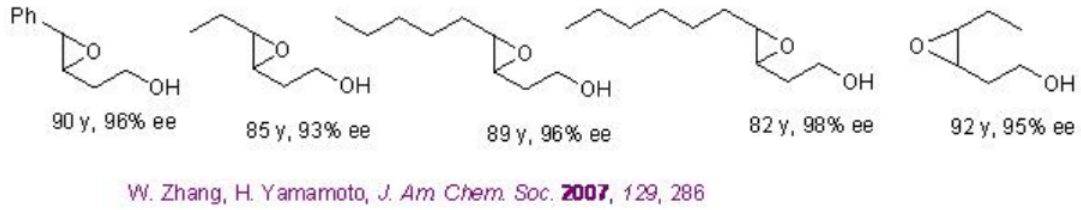
Scheme 5.2.7

Vanadium-Catalyzed Epoxidation

Few Studies are focused on chiral vanadium catalyzed the epoxidation of allylic alcohols. The epoxidation of homoallylic alcohol has been found to be successful (Scheme 5.2.8).



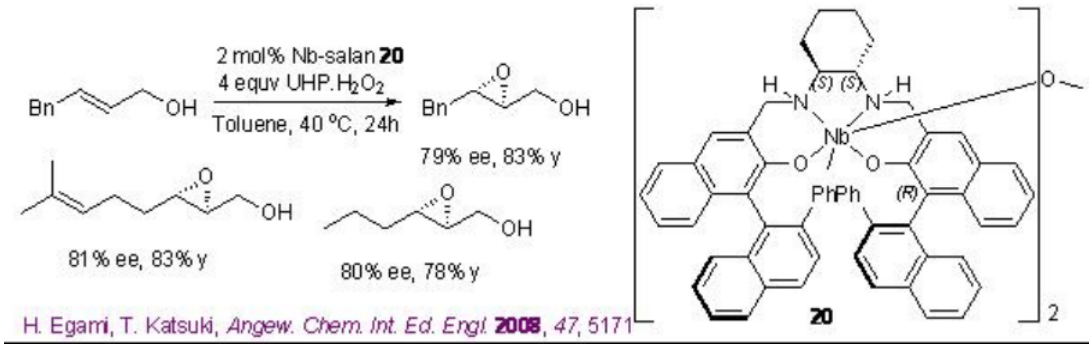
Examples:



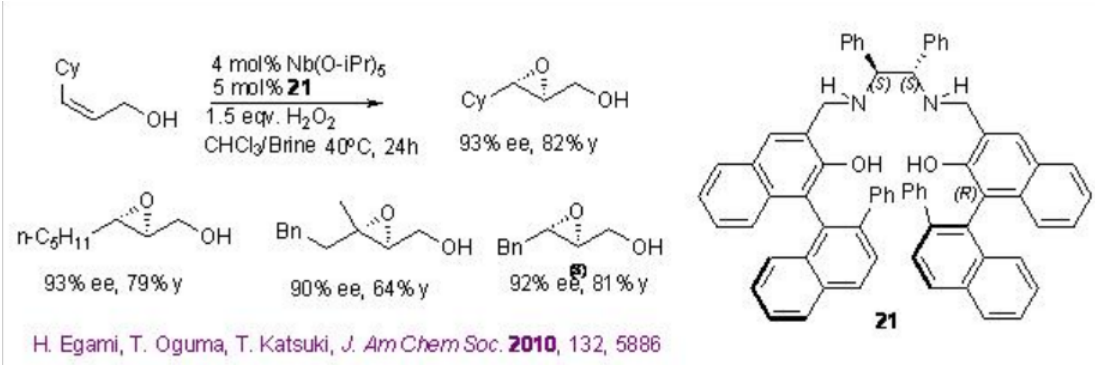
Scheme 5.2.8

Niobium-Catalyzed Epoxidation

Chiral niobium-complexes catalyze the epoxidation of allylic alcohols in the presence of hydrogen peroxide (H_2O_2) or urea hydrogen peroxide (UHP). From environmental and economic standpoint, this process is more attractive because it is atom economical and generates water as by-product. For example, [(μ-oxo){Nb(salan)}$_2$] **20** catalyzes the epoxidation of allylic alcohols in the presence of UHP at ambient conditions (Scheme 5.2.9-5.2.10).

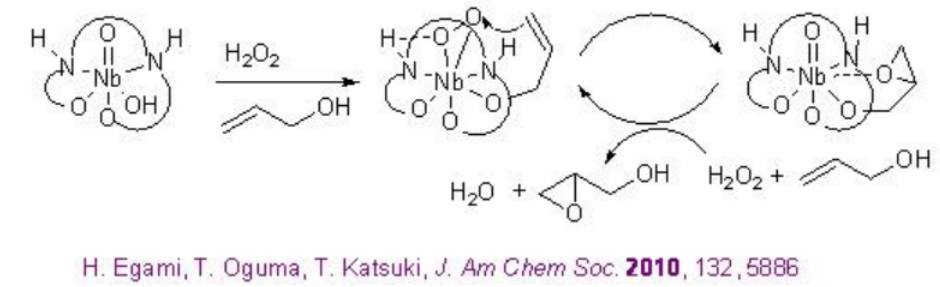


Scheme 5.2.9



Scheme 5.2.10

In this protocol, the μ-oxo dimer dissociates into a monomeric species that catalyzes the reaction (Scheme 5.2.11). Moreover, monomeric Nb(salan) complexes prepared *in situ* from $Nb(O^iPr)_5$ and salan ligands followed by water treatment are found to catalyze the epoxidation better using aq. $H_2O_2$with enantioselectivity ranging from 83 to 95% ee. This is the first example of the enantioselective epoxidation of allylic alcohols using aq. H_2O_2 as terminal oxidant.



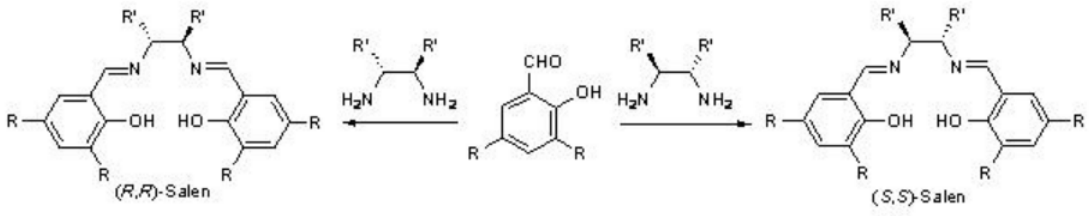
Scheme 5.2.11

5.3: Epoxidation of Unfunctionalized Alkenes

Asymmetric epoxidation of unfunctionalized alkenes affords an appealing strategy for the synthesis optically active organic compounds. This section covers some of the recent developments on this protocol.

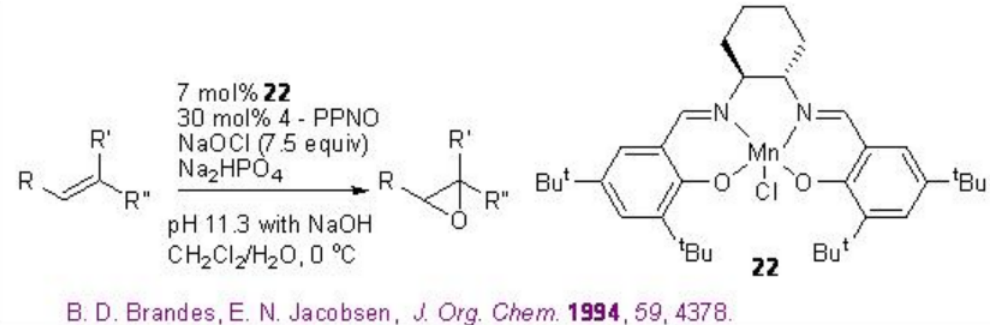
5.3.1 Manganese-Catalyzed Reactions

In 1990, Jacoben and Katsuki groups independently reported the chiral Mn-catalzyed asymmetric epoxidation of unfunctionalized alkenes. The catalysts can readily be synthesized by the reaction of $Mn(OAc)_2$ with Schiff base derived from chiral 1,2-diamines and 2-hydroxybenzaldehyde derivatives (Scheme 5.3.1). Reaction with $Mn(OAc)_2$ in the presence of air gives the Mn(III) complex that may be isolated as the chloro derivative after the addition of lithium chloride.

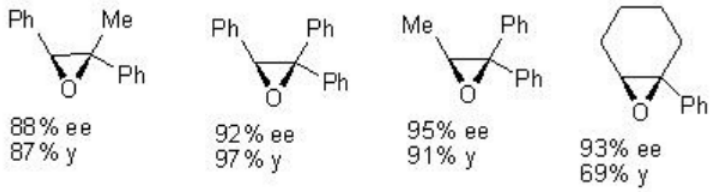


Scheme 5.3.1

For example, chiral Mn-salen **22** catalyzes the epoxidation of trisubstituted unfunctionalized alkenes with 88-95% ee (Scheme 5.3.2).



Examples:



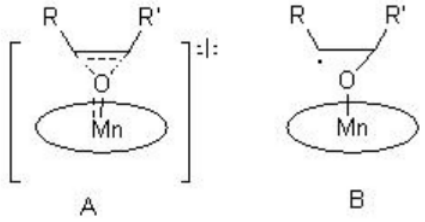
Scheme 5.3.2

Styrene derivatives can be successfully epoxidized using **23a-b** with good enantioselectivity (Scheme 5.3.3). The reaction is effective using the combination of *N* -morpholine oxide and *m* -chloroperbenzoic acid.

Scheme 5.3.3

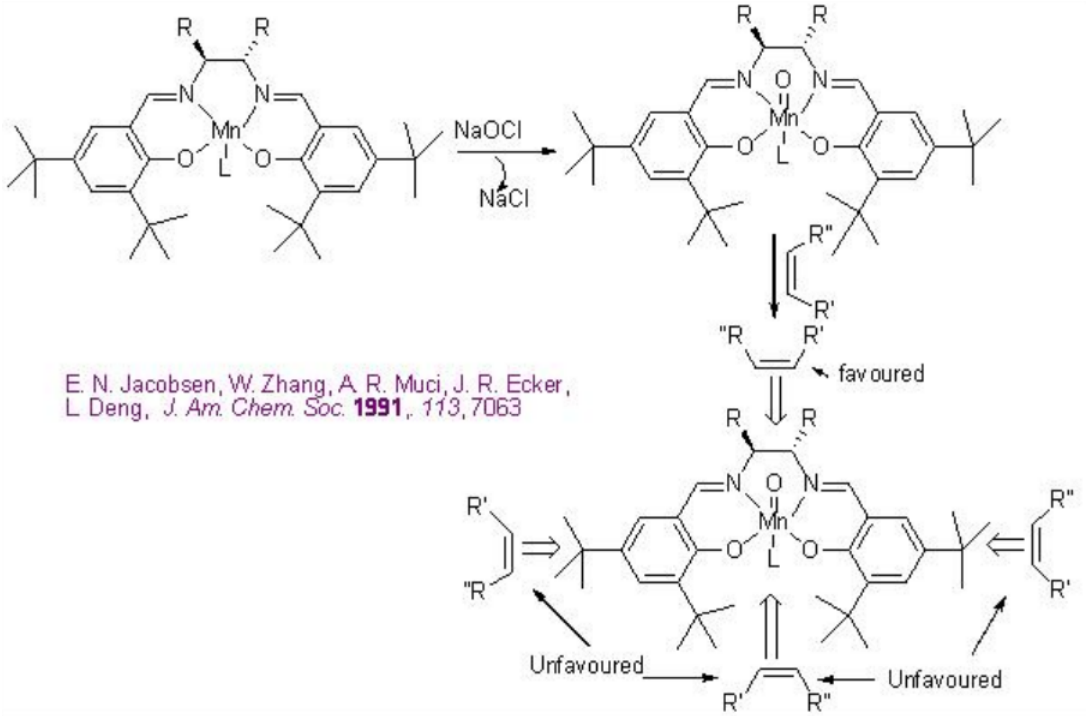
Mechanism

The epoxidation may proceed via a concerted (A) or radical-mediated (B) stepwise manner that depends on the electronic and oxidation state of the *oxo species* (Scheme 5.3.4).

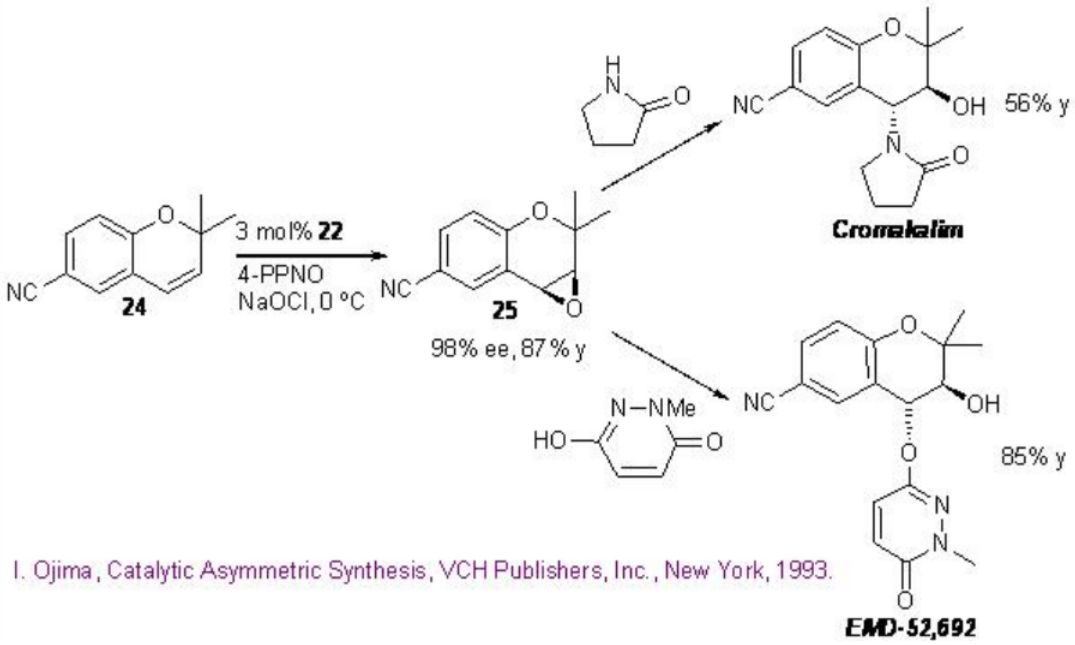


Scheme 5.3.4

To account the degree and sense of the enantioselectivity, side-on perpendicular approach of the alkene to the high valent metal-oxo intermediate has been invoked (Scheme 5.3.5).



Scheme 5.3.5

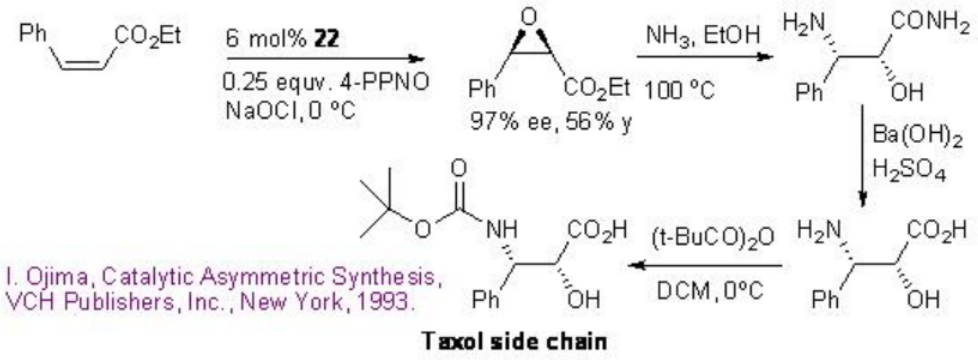


Scheme* 5.3.6*: Construction of Anti-hypertensive Agents.

Applications

The epoxidation of 6-cyano - 2,2-dimethylchormene **24** with **22** affords **25** that can be converted into *anti-hypertensive agents* cromakalim and EMD-52692 by reaction with appropriate nitrogen nucleophiles (Scheme 5.3.6).

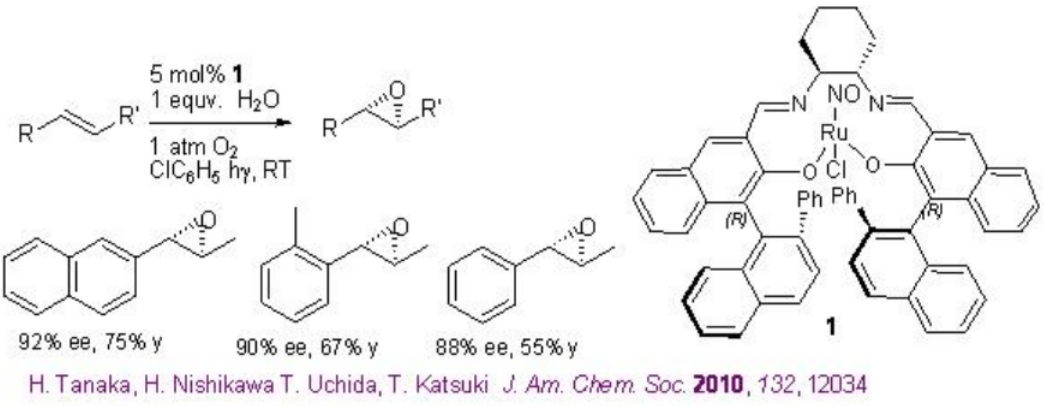
The catalyst **22** has been further utilized for the epoxidation of *cis* -cinnamic ester in 97% ee and 56% yield that can be converted into taxol side chain by opening of the epoxide with ammonia followed by hydrolysis and protection using $(t\text{-BuCO})_2O$ (Scheme 5.3.7).



Scheme 5.3.7

5.3.2 Ruthenium-Catalyzed Aerobic Epoxidation

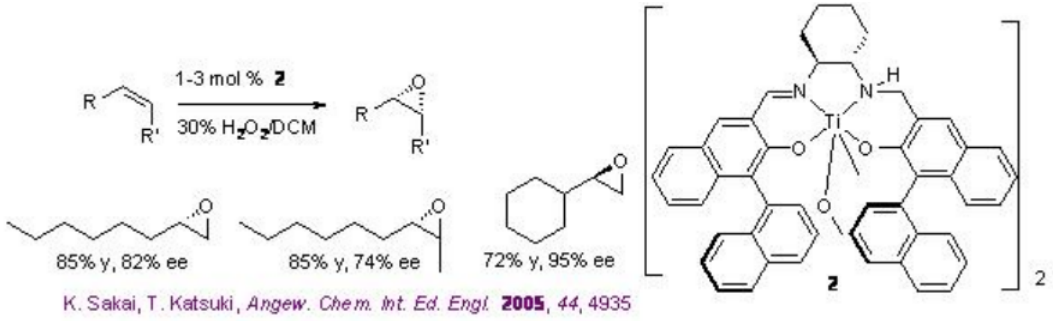
Chiral Ru(NO)-salen complexes has been found to catalyze the aerobic epoxidation of alkenes in presence of water under visible light irradiation at room temperature (Scheme 5.3.8). This method is attractive from environmental and economic standpoint. The observed preliminary experimental results suggest that an aqua ligand coordinated with the ruthenium ion acts as a proton transfer agent for the oxygen activation process.



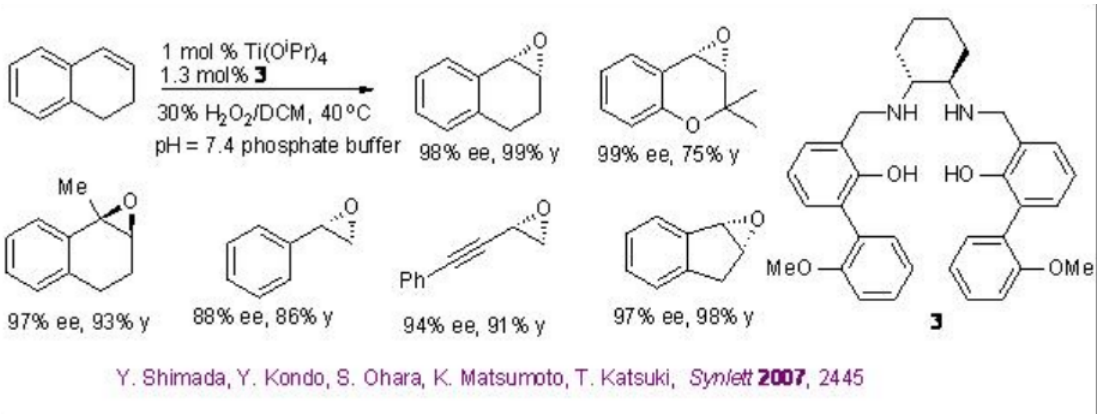
Scheme 5.3.8

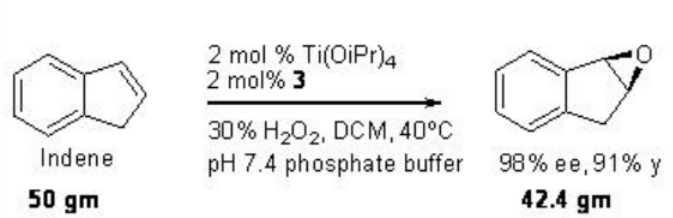
5.3.3 Titanium-Catalyzed Epoxidation with Hydrogen Peroxides

The use of Ti(salan) for the epoxidation of alkenes has been demonstrated in the presence of aqueous H_2O_2. The reaction is stereospecific and decomposition of H_2O_2 has not been observed. The most striking feature of this system is aliphatic alkenes that are one of the most challenging substrates for asymmetric epoxidation can be successfully oxidized with high enantioselectivity (Scheme 5.3.9). Furthermore, the in situ generated titanium complex derived from **3** (SALANEL) and $Ti(O^iPr)_4$ in CH_2 Cl_2 catalyzes the epoxidation of alkenes in the presence of phosphate buffer with excellent enantioselectivity (Scheme 5.3.10).



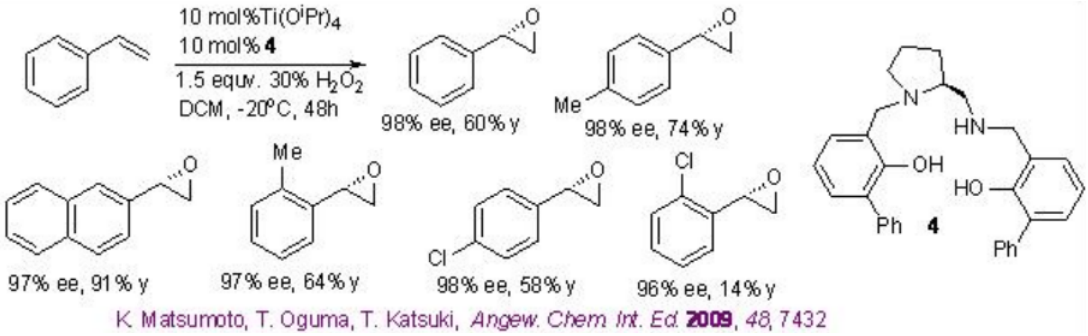
Scheme 5.3.9





Scheme 5.3.10

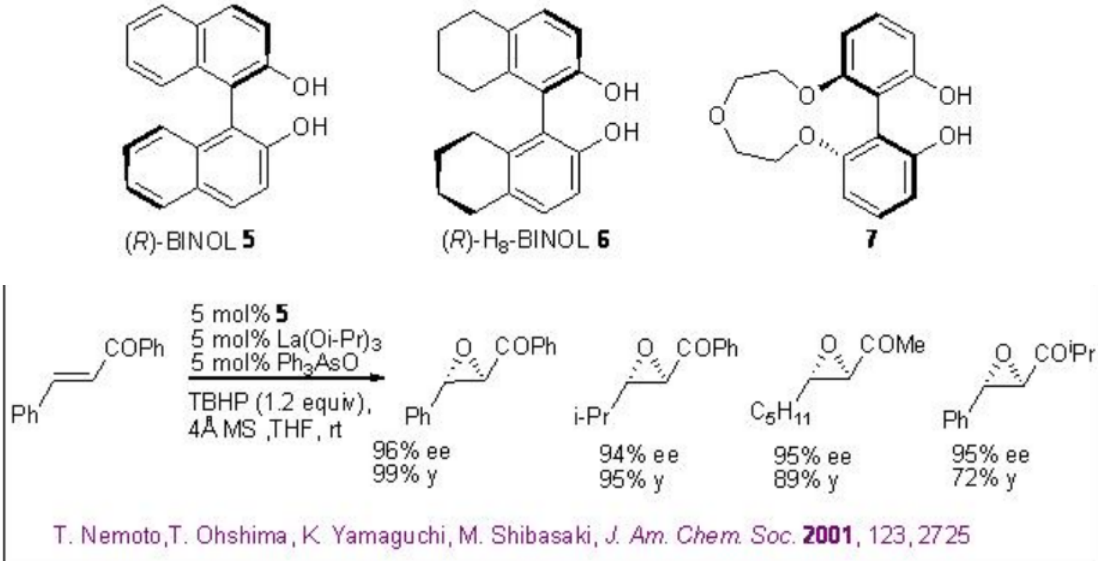
This epoxidation protocol has been successfully applied to a multigram scale synthesis of indene oxide. While the proline-based C_1 -symmetric Ti-(salan) from **4** and $Ti(O^iPr)_4$ has been found to be excellent catalyst for the epoxidation of styrene derivatives (Scheme 5.3.11).



Scheme 5.3.11

5.3.4 Lanthanoid-Catalyzed Epoxidation

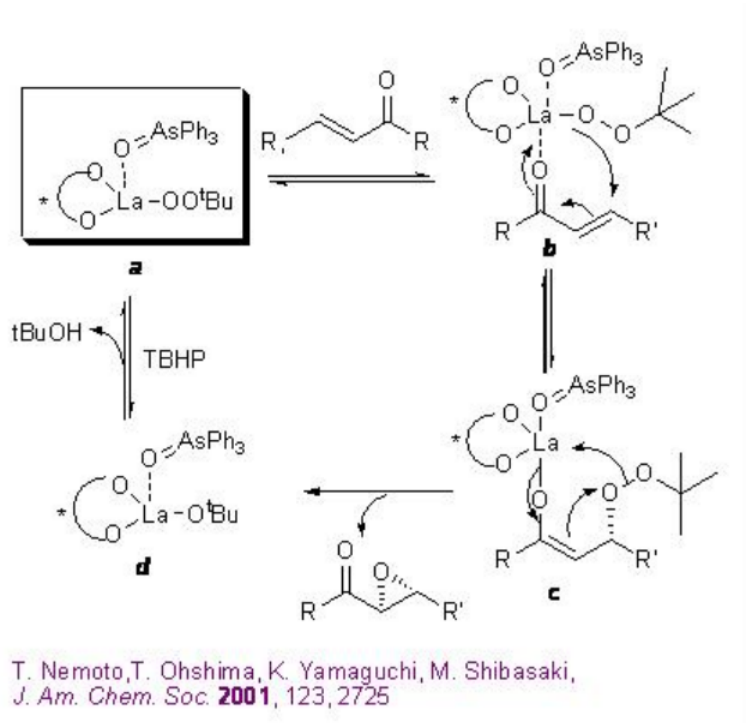
Nucleophilic epoxidation methods represent a viable alternative to electrophilic methods, many of which do not epoxidize electron-poor double bonds. The lanthanide based catalysts derived from chiral ligands **5-7** have been found to be effective in the epoxidation of α,β-unsaturated ketones (Scheme 5.3.12). It is mainly nucleophilic epoxidation of electron-deficient double bonds through the action of nucleophilic oxidants.



Scheme 5.3.12

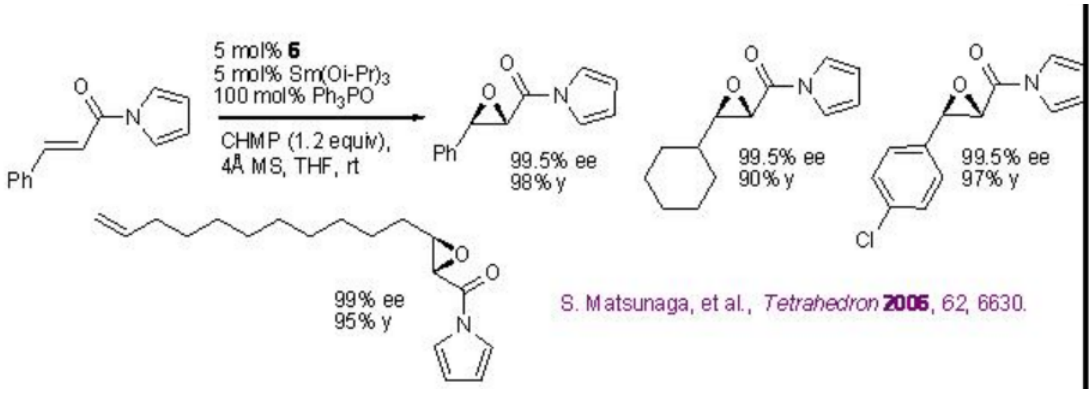
Proposed Mechanism

A 1:1:1 mixture of $La(O^iPr)_3$, BINOL and $Ph_3As{=}O$ may afford the active complex **a** in the reaction medium (Scheme 5.3.13). Activation of the enone ***b*** by coordination to lanthanum metal followed by 1,4-addition of lanthanum peroxide may lead to the formation of enolate ***c*** that could provide the epoxide and intermediate ***d*** . The latter with TBHP can provide the active complex ***a*** to regenerate the catalytic cycle.



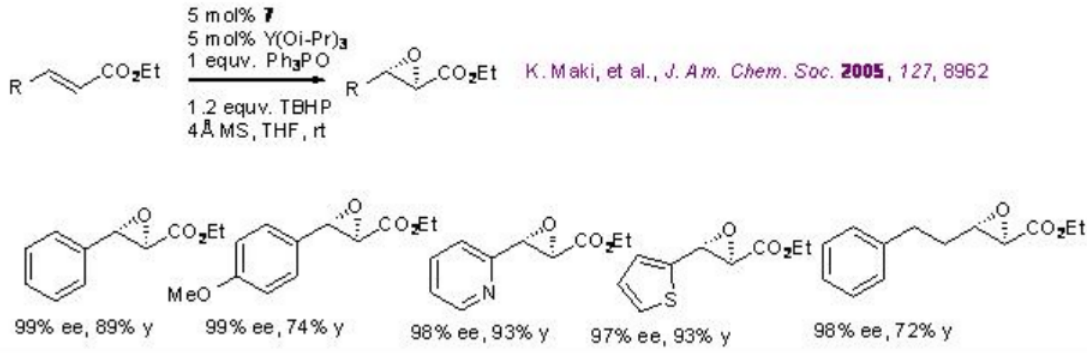
Scheme 5.3.13

Replacement of La(O^iPr)$_3$ by Sm(Oi-Pr)$_3$, (*R*)-BINOL **5** by (*R*)-H_8-BINOL **6,** Ph_3As=O by Ph_3P=O and TBHP by CHMP greatly enhances the yield and enantiomeric purity under similar condition for alkenes bearing amides (Scheme 5.3.14).



Scheme 5.3.14

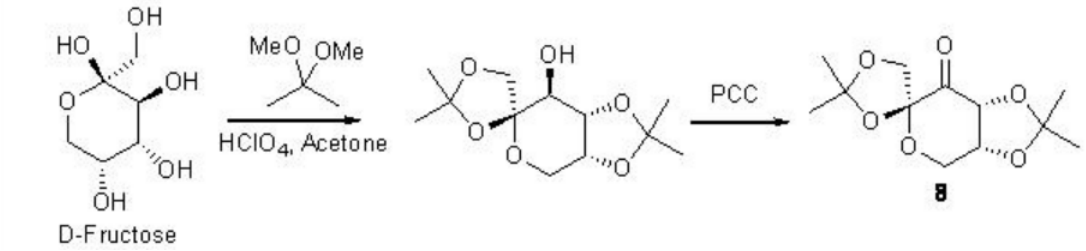
The catalyst derived from **7** and Y(O^iPr)$_3$ catalyzes the epoxidation of α,β -unsaturated esters with excellent enantioselectivity (Scheme 5.3.15). The system is compatible with alkenes bearing heteroaromatic rings.



Scheme 5.3.15

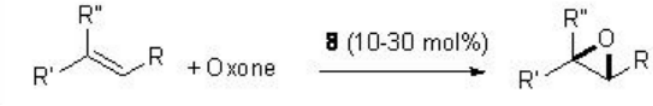
5.3.5 Organocatalysis

Remarkable progress has been made on the asymmetric epoxidation of alkenes using organo catalysis. Chiral ketones are among the some of the most developed epoxidation catalysts. Active dioxirane is generated from ketone and oxone (potassium peroxomonosulfate) or hydrogen peroxide under milder reaction conditions. Among the many useful chiral ketones reported, fructose derived ketone developed by Shi group is the most reliable catalyst with respect to high enantioselectivity and broad substrate scope (Scheme 5.3.16).

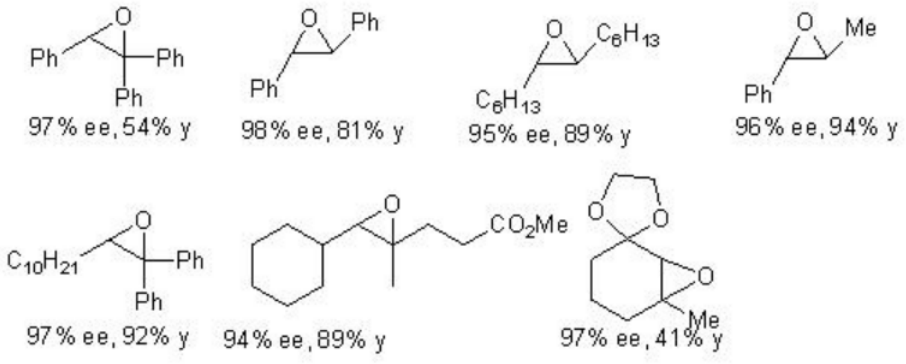


Scheme 5.3.16

For example, in presence of **8** (typically 20-30 mol%), a variety of trisubstituted alkenes proceed reaction with excellent enantioselectivity (Scheme 5.3.17).



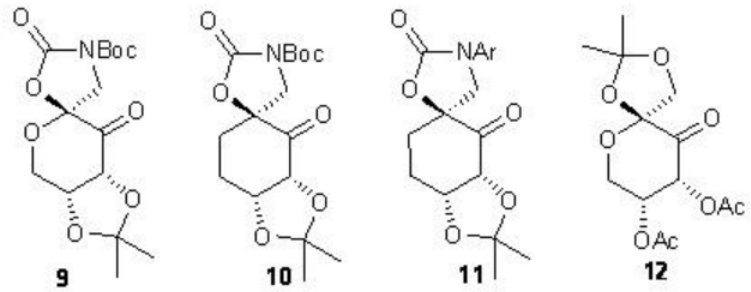
Examples:



Wang et al., *J. Am. Chem. Soc.* **1997**, *119*, 11224

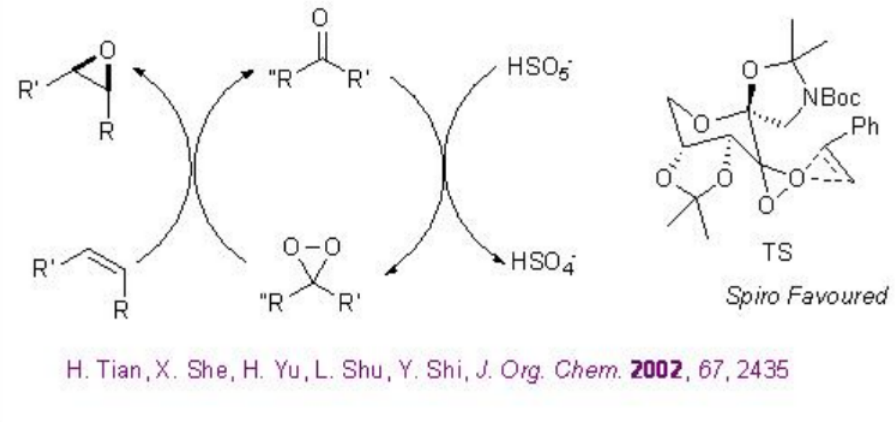
Scheme 5.3.17

In case of *cis* and terminal alkenes, the glucose-derived ketone **9** with *N* -Boc oxazolidinone provides high enantioselectivity. A carbocyclic analogue **10** and *N* -aryl substituted variants **11** have also been introduced for the epoxidation of styrene derivatives and *cis* -disubstituted alkenes. Furthermore, the chiral ketone **12** with electron-withdrawing acetate has been found to catalyze the epoxidation of α,β -unsaturated ester with high enantioselectivies.



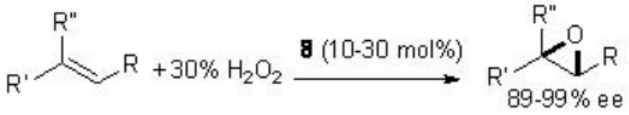
Proposed Mechanism

Scheme 5.3.18 shows the proposed catalytic cycle and the most favored transition state for the chiral ketone based epoxidations in the presence of oxone as terminal oxidant.



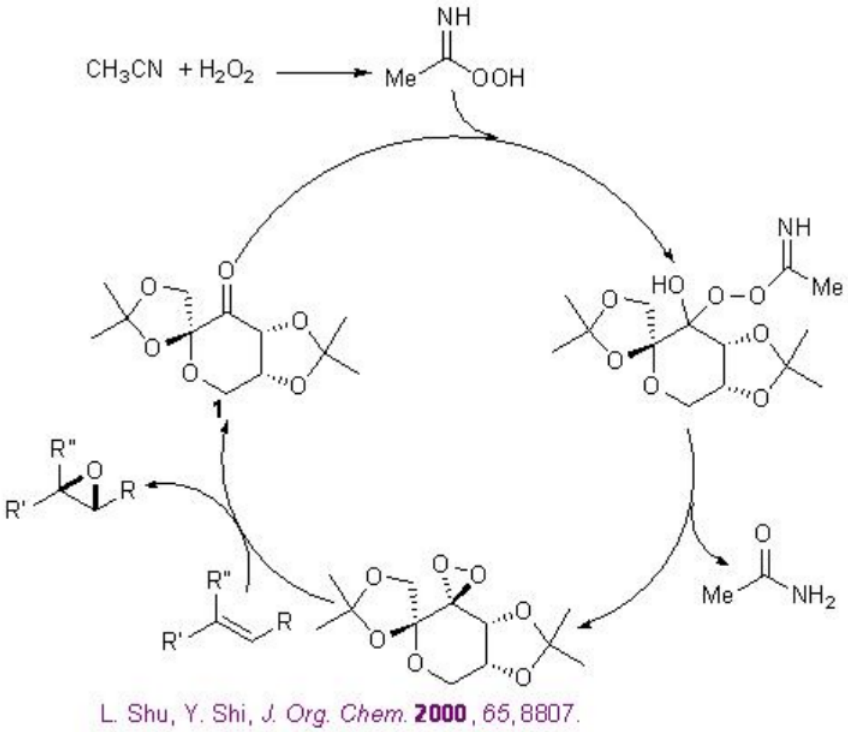
Scheme 5.3.18

The chiral ketone-catalyzed epoxidation has been subsequently found to be effective using the combination of hydrogen peroxide and acetonitrile as an alternative oxidant. For example, chiral ketone **8** has been used for the epoxidation of a variety of alkenes with comparable yields and enantioselectivity (Scheme 5.3.19).



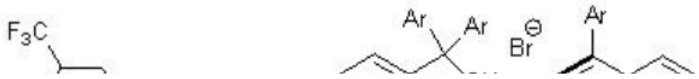
Proposed Mechanism

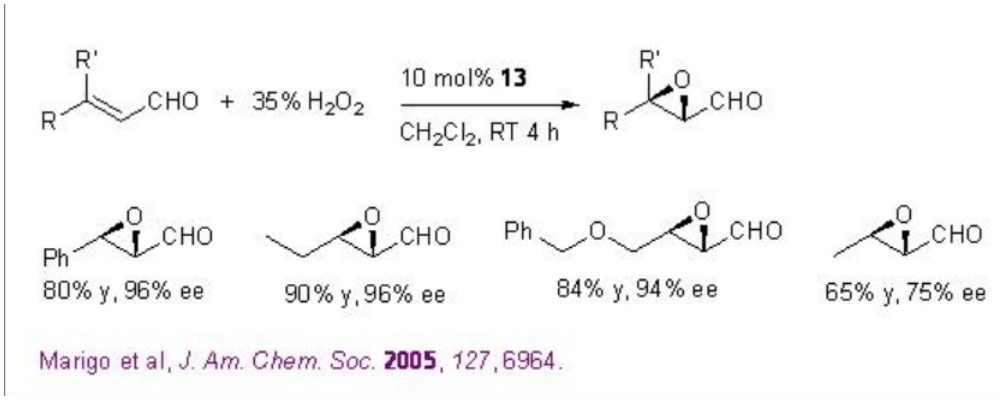
In this protocol, acetonitrile reacts with hydrogen peroxide to generate peroxyimidic acid and then reacts with the ketone to give the active dioxirane. Under these conditions, a stoichiometric amount of the amide is generated as a product.



Scheme 5.3.19

Besides the chiral ketones, chiral amine based catalysts **13** and **14** have been explored for the epoxidation of unfunctionalized alkenes. For example, chiral pyrrolidine **15** has been used for the α,β -unsaturated aldehydes with excellent enantioselectivity in the presence of 35% H_2O_2 (Scheme 5.3.20). α,β -Unsaturated aldehydes containing an aromatic substituent at the β -position are good substrates affording the epoxides with high diastereo- and enantioselectivities.



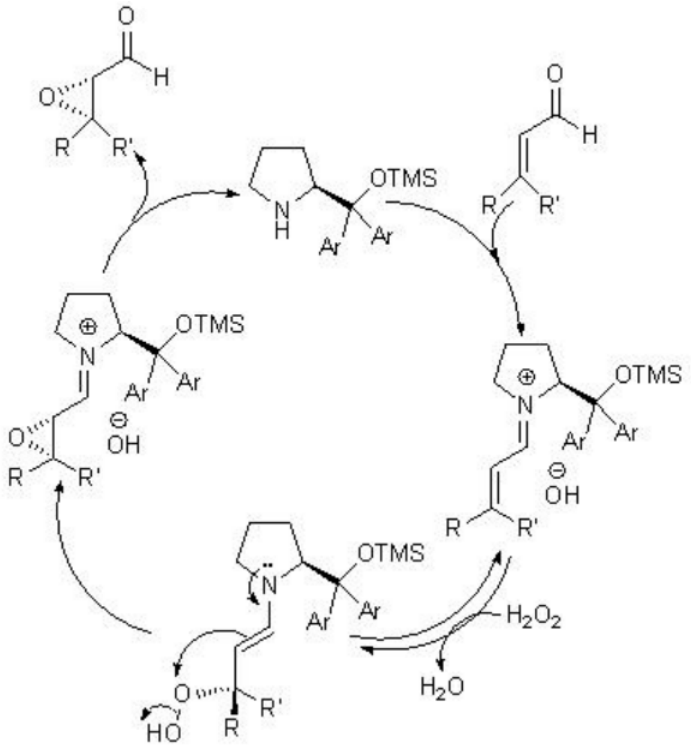


Scheme 5.3.20

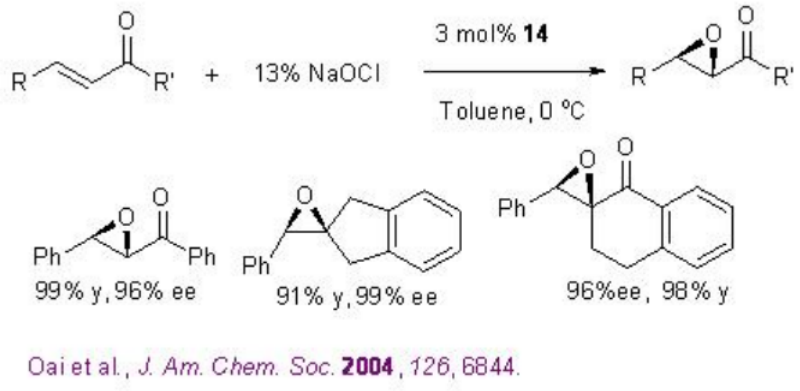
Proposed Mechanism

The proposed mechanism states that the reaction takes place through the Weitz-Scheffer mechanism (Scheme 5.3.22). The addition of hydrogen peroxide to the β -carbon atom of the electrophilic iminium ion is reversible and the attack on the electrophilic oxygen atom by the nucleophilic enamine determines the product stereochemistry.

While chiral *N* -spiro ammonium salt **14** bearing an axially chiral binaphthyl unit functions as phase transfer catalyst for the epoxidation of enones with high enantioselectivity (Scheme 5.3.22). The hydroxyl groups are appropriately bonded to recognize and activate the enone substrate by hydrogen bonding.



Scheme 5.3.22

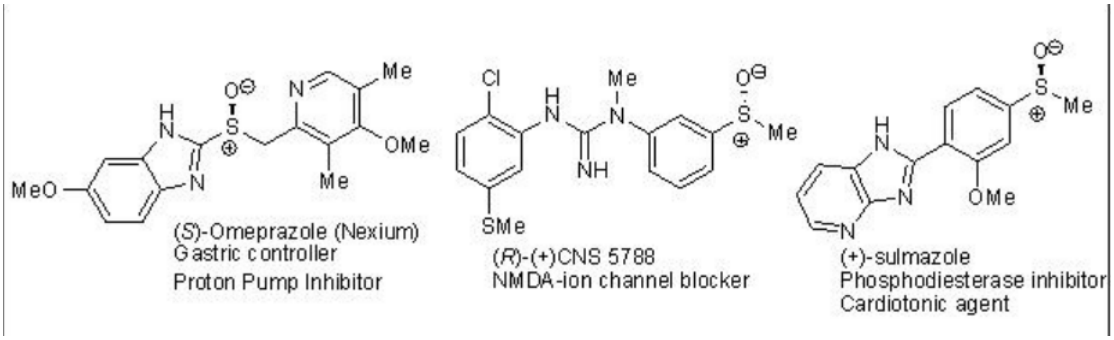


Oai et al., *J. Am. Chem. Soc.* **2004**, *126*, 6844.

Scheme 5.3.23

5.4: Enantioselective Sulfoxidation

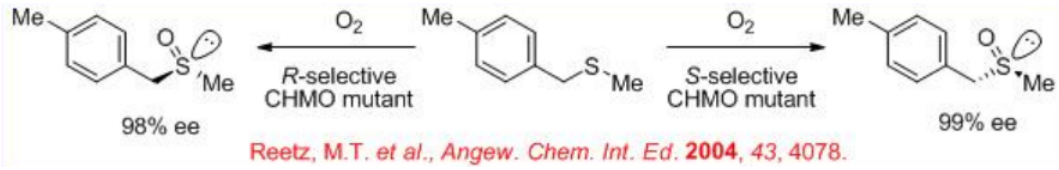
Enantiopure sulfoxides serve as chiral auxiliary as well as intermediates for the synthesis of optically active compounds. Optically active sulfoxide structural unit is also present in many compounds that exhibit interesting biological properties (Scheme 5.4.1). Development of methods for the asymmetric sulfoxidation has thus been active topic in asymmetric catalysis. This lecture covers the common methods that are used for the synthesis of optically active sulfoxides.



Scheme 5.4.1: Some Examples of Chiral Sulfoxide Based Drugs

5.4.1 Enzyme-Catalyzed Reactions

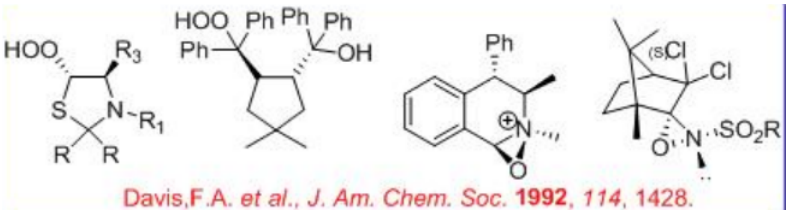
Enzyme catalyzed asymmetric oxidation of sulfides provides effective methods for the synthesis of optically active sulfoxides. For example, cyclohexanone monooxygenase (CHMO), a bacterial flavoenzyme, catalyzes the oxidation of prochiral thioethers with excellent enantioselectivity (Scheme 5.4.2).



Scheme 5.4.2

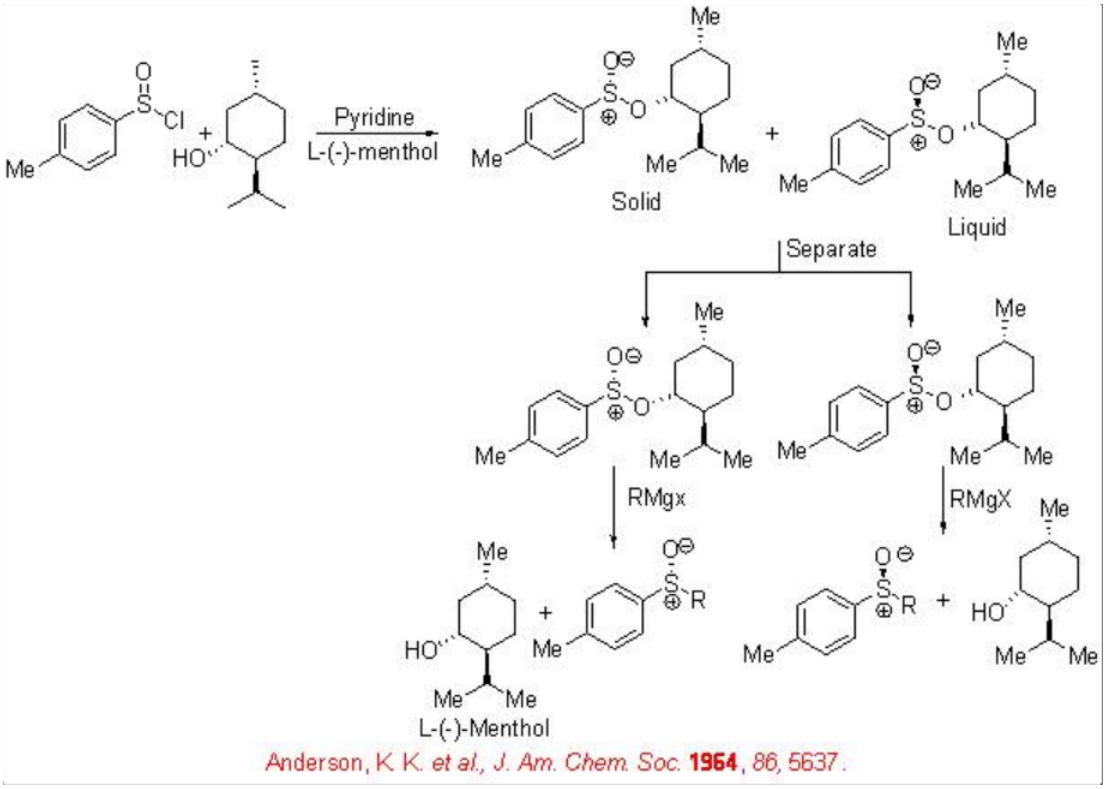
5.4.2 Chiral Reagents Based Reactions

Chiral reagents have been used for the oxidation of prochiral sulfides. For example, chiral hydroperoxides, *N* -sulfonyl oxaziridines and chiral oxaziridines can oxidize prochiral sulfides to optically active sulfoxides with moderate to good enantioselectivity (Scheme 5.4.3).



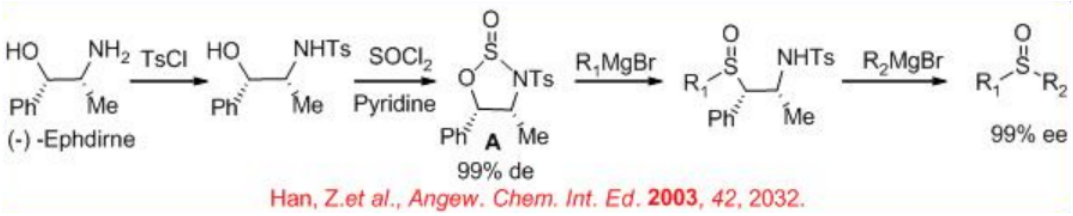
Scheme 5.4.3

In addition, chiral sulfinates are precursors of chiral sulfoxides (Scheme 5.4.4). This approach is of preparative interest to provide the sulfoxides with high enantioselectivity. The important issue is need to prepare the menthyl- *p* -tolylsulfinates from L-(-)-menthol and then to separate them.



Scheme 5.4.4

Furthermore, *N* -tosyl-norephedrine can be reacted with thionyl chloride to afford heterocyclic compound A, which could be reacted *via* the sequential addition of R_1MgX and R_2MgX, in a one-pot procedure to give sulfoxides in >99% ee (Scheme 5.4.5). The configuration depends on the order of introduction of the two Grignard reagents.



Scheme 5.4.5

5.4.3 Metal-Catalyzed Reactions

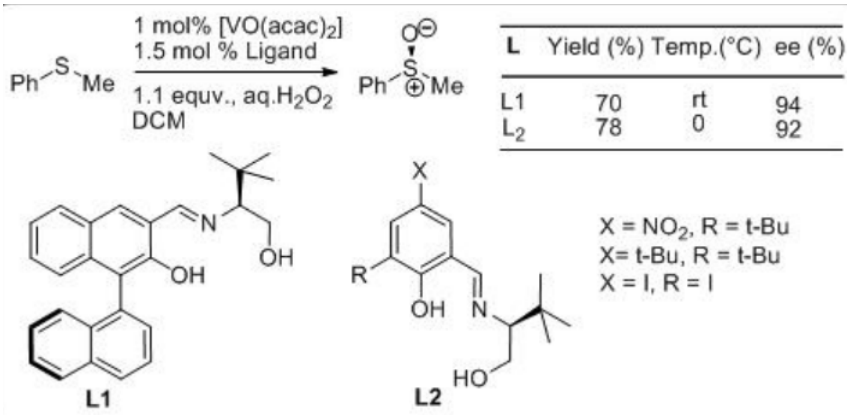
5.4.3.1 Reactions with Diethyl Tartrates

In the middle of 1980, Kagan and Modena groups independently modified the conditions that were employed by Sharpless group for the asymmetric epoxidation of allylic alcohols, and used for the oxidation of sulfides. The modified conditions involve the combination of $Ti(O^iPr)_4$, (*R,R)*- diethyl tartrate (DET) and *t* -BuOOH (TBHP) in water (Scheme 5.4.6). The replacement of TBHP with cumyl hydroperoxide (CHP) led to improvement in the enantioselectivity of the sulfoxide.

Scheme 5.4.6

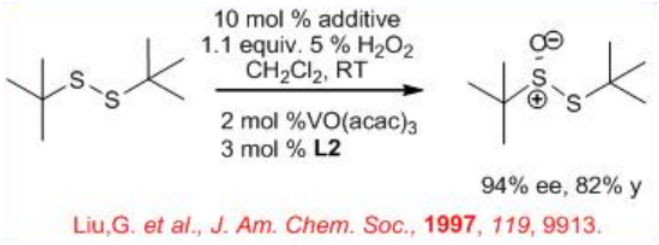
5.4.3.2 Reactions with Tridentate Ligands

In the middle of 1990, vanadium complexes having the tridentate Schiff base ligands L1-2 derived from optically active amino alcohols and aryl aldehydes have been studied for the oxidation of sulfides in the presence of aq. H_2O_2 as terminal oxidant (Scheme 5.4.7). The catalysts are prepared *in situ* and the effect of series Schiff base ligands is studied.



Scheme 5.4.7

In case of di- *tert* -butyldisulfide, monoxidation occurs selectively with up to > 90% ee (Scheme 5.4.8).



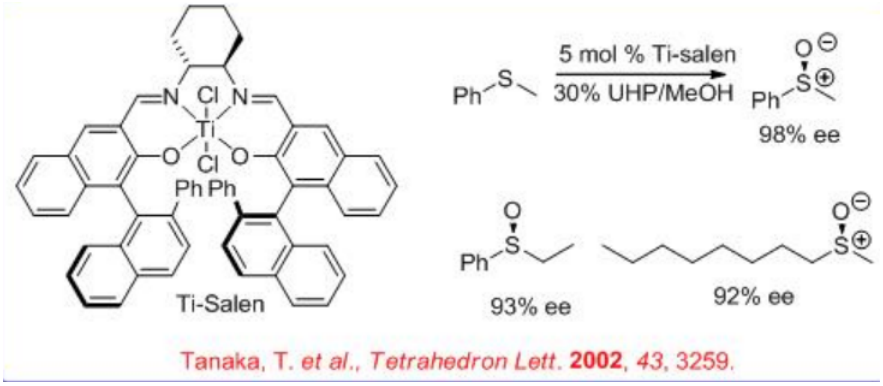
Scheme 5.4.8

Subsequently, the reaction has also been found to be effective with $Fe(acac)_3$ in the presence of additive such as *p-methoxybenzoic acid* (Scheme 5.4.9). For example, the oxidation of *p* -chlorophenyl methyl sulfide can be accomplished with 92% ee and 60% yield. In some cases, kinetic resolution is observed.

Scheme 5.4.9

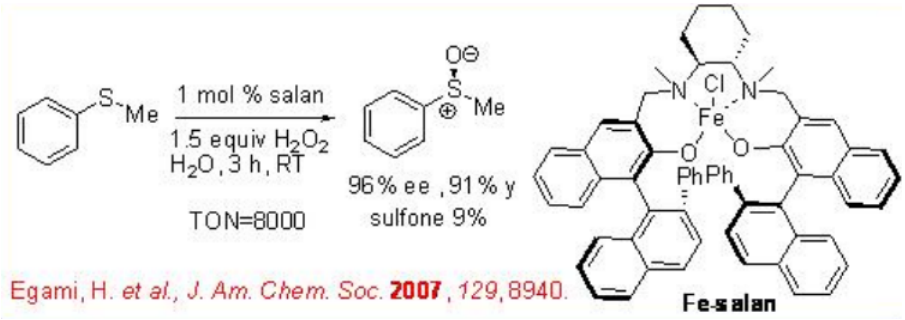
5.4.3.3 Reactions with Salen Based Ligands

Chiral Ti-salen has been found to be effective catalyst for the oxidation of sulfides in the presence of urea hydrogen peroxide (UHP) or aqueous H_2O_2 . First, Ti-salen is converted into *cis* - μ -dioxo Ti-dimer that reacts with H_2O_2 to give peroxo species. The latter can oxidize the sulfide to sulfoxide (Scheme 5.4.10). The oxidation of several alkyl aryl sulfides can be accomplished with 92–99% ee.



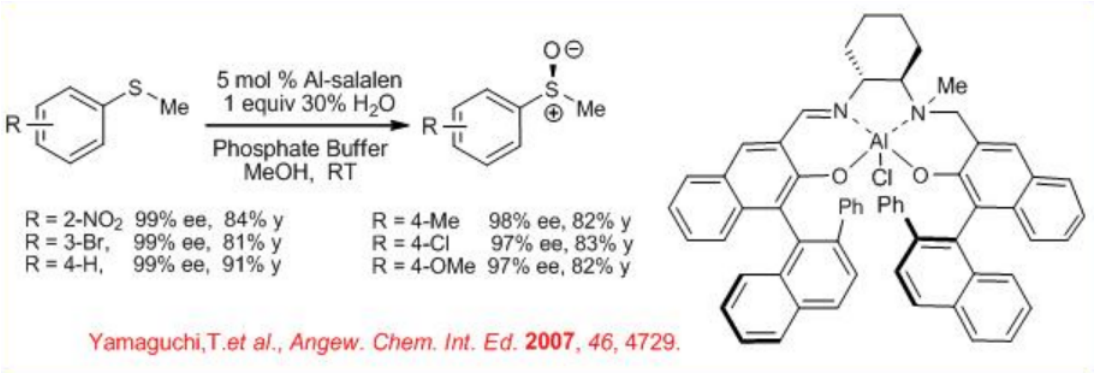
Scheme 5.4.10

Subsequently, Fe(salan) has been found to catalyze the oxidation of sulfides in the presence of a queous H_2O_2 in water (Scheme 5.4.11). This procedure has the advantages of high catalytic turnover number (TON) of 8000 as well as the use of water as reaction medium.



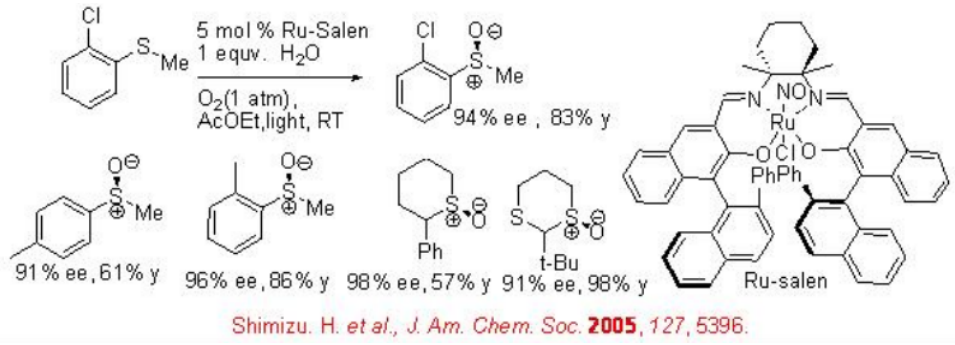
Scheme 5.4.11

Furthermore, Al(salalen), which is compatible in water, catalyzes the oxidation of sulfides with aqueous H_2O_2 at room temperature in phosphate buffer condition (Scheme 5.4.12). The reactions of a variety of sulfides have been demonstrated with high enantioselectivity.



Scheme 5.4.12

Meanwhile, chiral Ru(NO)-salen has been found to catalyze the sulfoxidation under aerobic conditions in the presence of water under visible light irradiation at room temperature (Scheme 5.4.13). Unlike biological oxygen atom transfer reactions that need a proton and electron transfer system, this aerobic oxygen atom transfer reaction requires neither such a system nor a sacrificial reductant.



Shimizu. H. *et al., J. Am. Chem. Soc.* **2005**, *127*, 5396.

Scheme 5.4.13

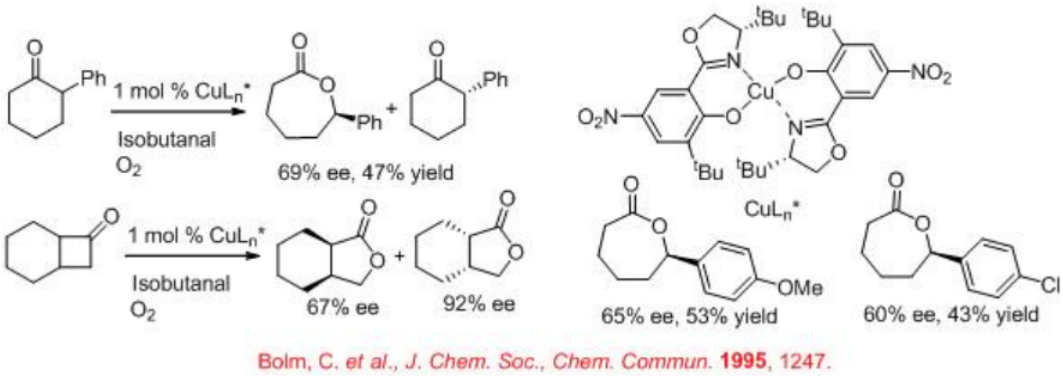
Although the mechanism of this oxidation has not been completely clarified, some experimental results support the notion that an aqua ligand coordinated with the ruthenium ion serves as a proton transfer agent for the oxygen activation process, and it is recycled and used as the proton transfer mediator during the process.

5.5: Baeyer-Villiger Oxidation (BVO)

Insertion of oxygen atom in between the ketone carbonyl and an adjacent carbon yielding the expanded ester is called as Baeyer-Villiger oxidation (BVO). Under the influence of a chiral reagent, this oxidation can be carried out asymmetrically. In case of a racemic ketone, a chiral catalyst has the potential of performing a kinetic resolution. A century after its discovery, the catalytic asymmetric BVO remains as one of the most powerful methods to convert a ketone into an ester proceeding by insertion of an oxygen atom into a bond.

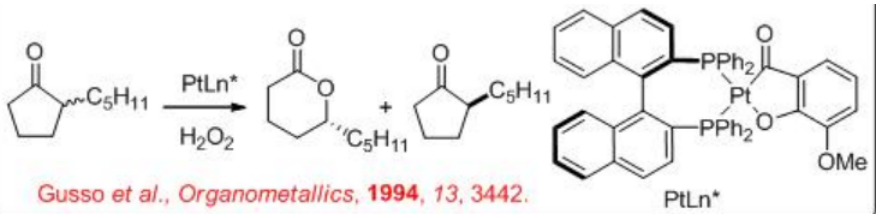
Metal-Catalyzed Reactions

Copper(II) complexes with oxazoline-based ligands are studied for the oxidation of substituted cyclic ketones to give lactones with high enantioselectivity (Scheme 5.5.1). These reactions employ isobutanal as co-reductant under aerobic conditions. During the reaction isobutanal is oxidized to the corresponding carboxylic acid.



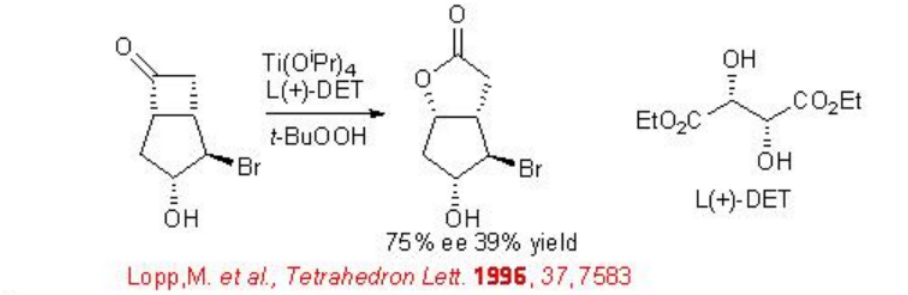
Scheme 5.5.1

Platinum complexes bearing chiral phosphines catalyze oxidation of substituted cyclic ketones in the presence of hydrogen peroxide (Scheme 5.5.2). Coordination of Pt and peroxide to the carbonyl leads to the formation of a metallocycle that could be decomposed into the target lactone. Chiral ligands associated with Pt allow for diastereomeric transition states, which discriminate between the two possible migrating carbon atoms resulting in enantioselectivity.



Scheme 5.5.2

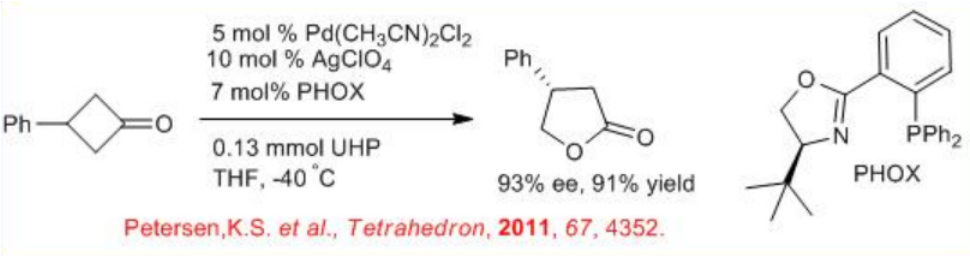
The reaction conditions used for the enantioselective epoxidation of allylic alcohols (Sharpless epoxidation) is also effective for the oxidation of substituted cyclobutanones to give lactones with moderate to good enantioselectivity (Scheme 5.5.3).



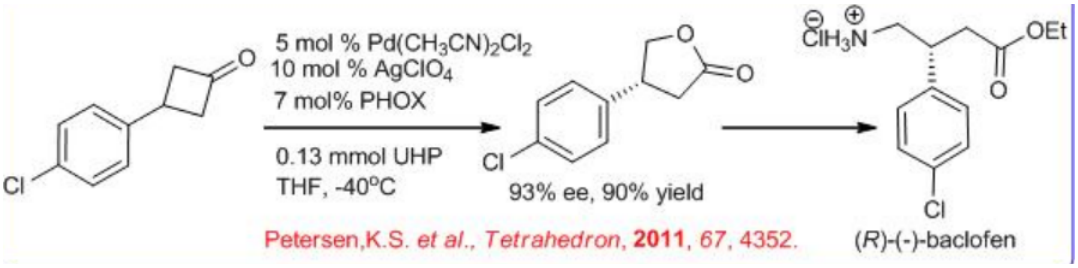
Scheme 5.5.3

The oxidation of symmetrical cyclobutanones is effective using chiral palladium complex bearing phosphinooxazoline (PHOX) in the presence of urea hydrogen peroxide. For example, prochiral 3-substituted cyclobutanones undergoes oxidation to give γ -lactones, which can be recrystallized to obtain the target products with 93% ee and 91% yield. This procedure has been utilized for

the synthesis of GABA-B receptor agonist *(R)* -(_)-baclofen (Scheme 5.5.5). The racemic form of baclofen is commercially available to treat spasticity and alcoholism; however, the (*R*) - isomer has been shown to be predominantly responsible for the molecule's bioactivity. The molecule has been the target of many asymmetric syntheses. Several of these strategies start from enantioenriched lactone using enzymatic BVO or from an enantioselective C-H insertion.

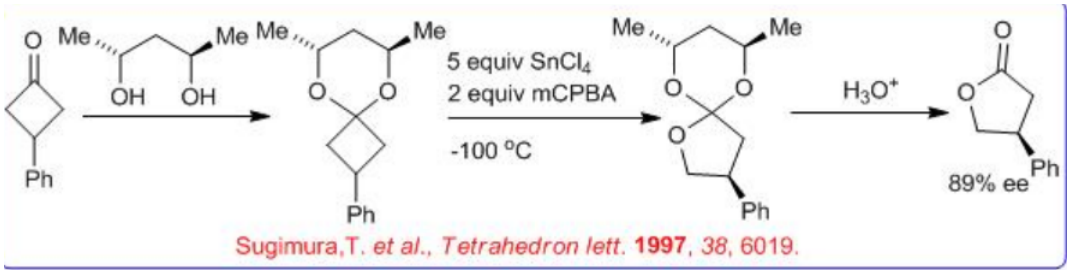


Scheme 5.5.4



Scheme 5.5.5

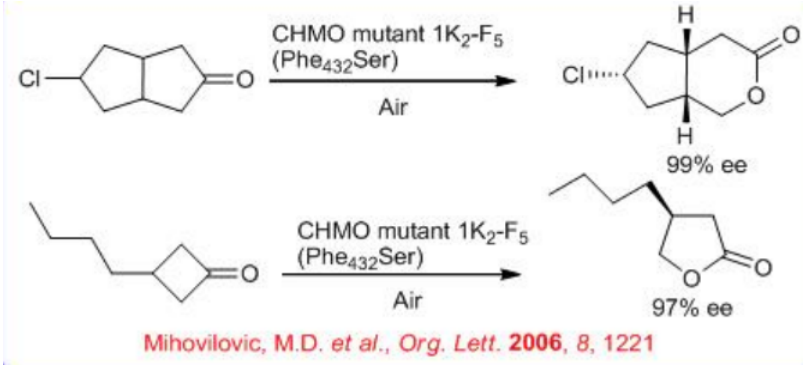
In addition to the metal-catalyzed BVOs, chiral auxiliary approach is also followed to synthesis lactone with good enantioselectivity (Scheme 5.5.6). For example, reaction of optically active 1,3-diol with an achiral cyclobutanone can give chiral ketal. The latter can be reacted with *m* CPBA and $SnCl_4$ to give an orthoester, which upon acidic work-up affords the lactone.



Scheme 5.5.6

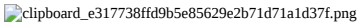
Enzyme Catalyzed Reactions

Baeyer-Villiger monooxygenases are enzymes that catalyze the insertion of an oxygen atom in a ketone, next to the carbonyl carbon atom. So far, only a limited number of BVMO have been identified from bacteria and fungi. These enzymes typically contain FAD or FMN as a cofactor and catalyze highly regio- and stereoselective oxygenations at the expense of NAD(P)H and molecular oxygen. Bio-catalyzed BVO proceeds with high levels of enantioselectivity. For example, cyclohexanone monooxygenase (CHMO), a bacterial flavoenzyme, carries out an oxygen insertion reaction on cyclohexanone to form a seven-membered cyclic product, ε-caprolactone (Scheme 5.5.7). This reaction involves the four-electron reduction of O_2 at the expense of a two-electron oxidation of NADPH and a two-electron oxidation of cyclohexanone to form ε-caprolactone. The CHMO has been employed successfully for the oxidative desymmetrization of cyclobutanone and cyclopentanone rings with high enantioselectivity. CHMO mutant $1K_2$ -F_5 (Phe_{432} Ser) has been used with air as the oxidant in a whole-cell process. Mutant Phe_{432} Ser also tested for oxidative desymmetrization of a set of 4-substituted cyclohexanone derivatives (methyl, ethyl, methoxy, chloro, bromo, iodo) and in all cases enantioselective transformations are observed with up to 99% ee.



Scheme 5.5.7

Similarly, PAMO mutant Gln_{93} Asn/ Pro_{94} Asp is tested for the asymmetric desymmetrization of 4-substituted cyclohexanone derivatives to give chiral lactones with high enantioselectivity (Scheme 5.5.8). It is interesting to note that the absolute configuration of the lactone products is opposite to what is observed with the thermolabile cyclohexanone monooxygenase (CHMO) as the catalyst.



Scheme 5.5.8

Reactions using Organocatalysis

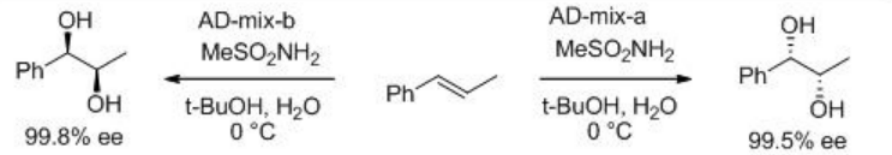
Readily available glucose-derived oxazolidinone containing ketone can be employed for BVO of a variety of benzylidenecyclopropanes in the presence of oxone (Scheme 5.5.9). Optically active *α* -aryl- *γ*-butyrolactones and *α* -aryl- *γ* -methyl- *γ*-butyrolactones can be obtained in reasonable yields and enantioselectivities. The reaction works *via in situ* epoxide rearrangement and BVO. Chiral cyclobutanones can also be obtained by suppressing BVO with more ketone catalyst and less oxone.

Scheme 5.5.9

5.6: Dihydroxylation, Aminohydroxylation and Aziridination Reactions

5.6.1 Dihydroxylation Reaction

In 1980, the first attempt for enantioselective *cis* -dihydroxylation of alkenes with osmium tetroxide was appeared. Subsequent continuous efforts led to improve the reaction yield and enantioselectivity in the presence of osmium-cinchona alkaloid complexes (Scheme 5.6.1). The reactions can be performed at ambient conditions in liquid-liquid biphase system having water and t-BuOH employing secondary oxidant such as $K_3Fe(CN)_6$ to afford the target 1,2- *cis* diols with high enantioselectivity. Please see Module I, Reagents and Organic Reactions, for the mechanism.



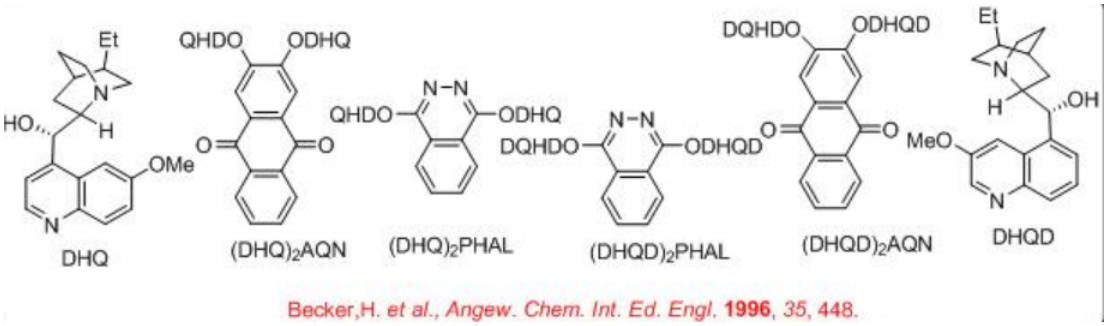
AD-mix-a = $K_3Fe(CN)_6$ (3 mmol) + K_2CO_3 (3 mmol) + $(DHQ)_2PHAL$ (0.01 mmol) + $K_2OsO_2(OH)_4$ (0.002 mmol)

AD-mix-b = $K_3Fe(CN)_6$ (3 mmol) + K_2CO_3 (3 mmol) + $(DHQD)_2PHAL$ (0.01 mmol) + $K_2OsO_2(OH)_4$ (0.002 mmol)

Jacobsen, E. N. *et al., J. Am. Chem. Soc.* **1988**, *110*, 1968.

Scheme 5.6.1

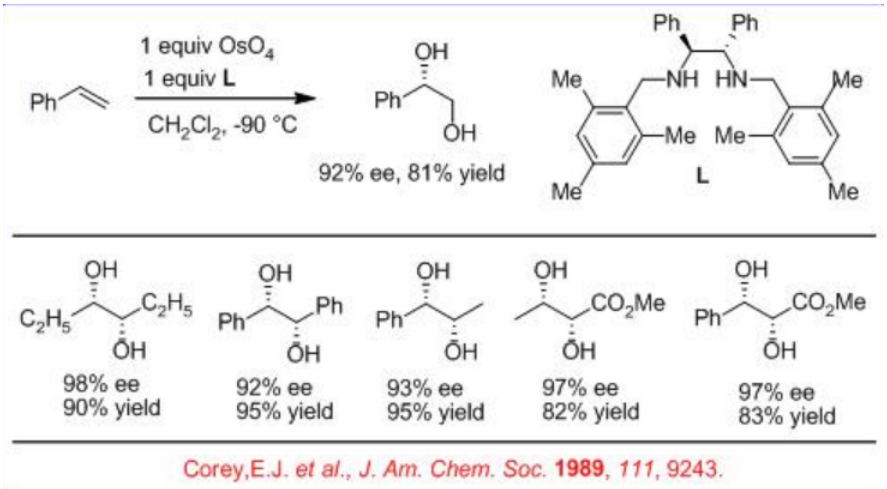
$K_3Fe(CN)_6$ is used as a oxidant to reoxidize the Os(VI) after each catalytic cycle. Since OsO_4 is volatile and toxic, the osmium is usually added as K_2OsO_2 $(OH)_4$, which forms OsO_4 in the reaction mixture. K_2CO_3 and methanesulfonamide ($MeSO_2$ NH_2) are used as additive to enhance the rate of the reaction. Scheme 2 summarizes some of the successful cinchona alkaloid based ligands for the asymmetric dihydroxylation reactions. The approach of hydroxyl group is directed to either the top face or the bottom face of the alkene which depends on the nature of the ligands, DHQD or DHQ, are used.



Becker,H. *et al., Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448.

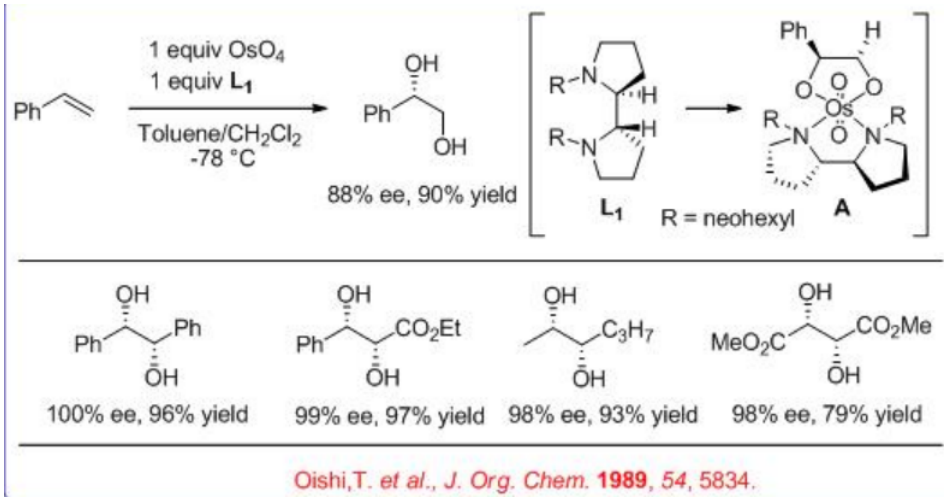
Scheme 5.6.2

In parallel to the above described catalytic processes, the use of optically active bidentate 1,2-diamine based ligand **L** has been demonstrated in place of alkaloid as a chiral source for the asymmetric dihydroxylation of alkenes using OsO_4 (Scheme 5.6.3). The reactions of a series of alkenes can be accomplished with good to excellent yield and enantioselectivity.



Scheme 5.6.3

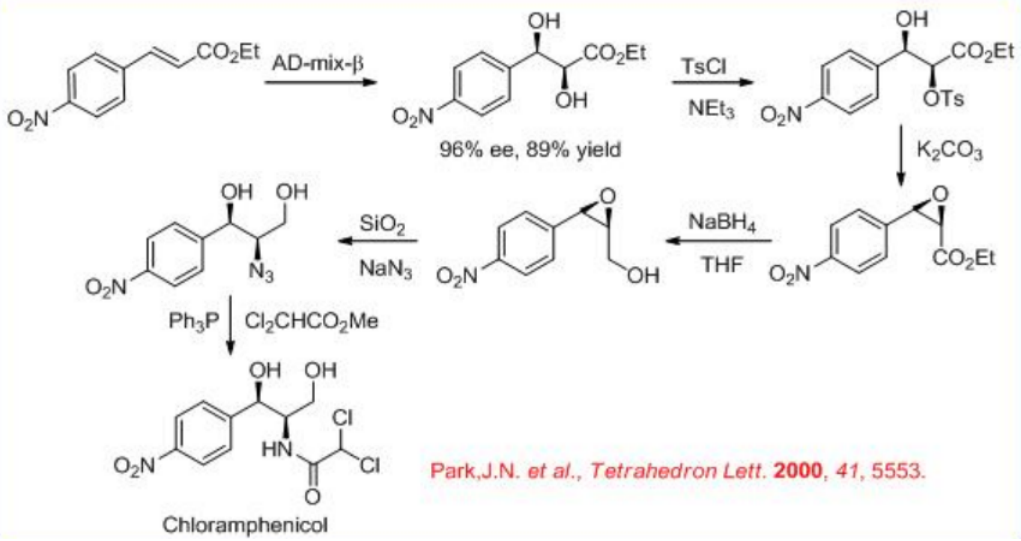
In addition, the bidentate ligand **L 1** is found to effective for the OsO_4 -mediated dihydroxylation of *trans* -disubstituted and monosubstituted alkenes (Scheme5.6.4). The reaction is believed to involve intermediate A and the products are obtained with high yield and enantioselectivity.



Scheme 5.6.4

5.6.1.1 Synthesis of Biologically Important Molecules

The Os-catalyzed enantioselective dihydroxylation is used as a key step in the highly expeditious synthesis of the antibacterial agent (–)-chloramphenicol (Scheme 5.6.5).

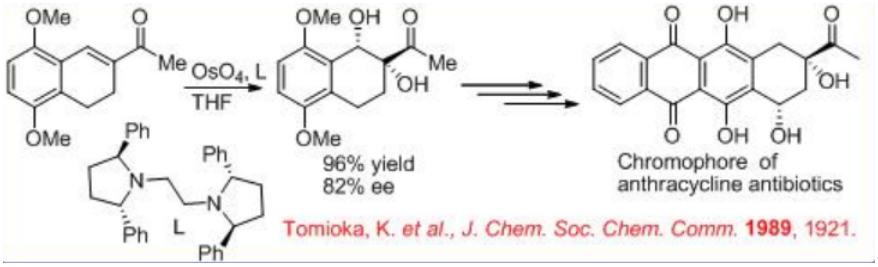


Scheme 5.6.5: Synthesis of Chloramphenicol

The synthesis of the β -receptor-blocking drug (S) - propranolol has been demonstrated employing osmium-catalyzed dihydroxylation as a key step (Scheme 5.6.6). Reaction of α - naphthol with allylic bromide gives allyl naphthyl ether that could be dihydroxylated using AD-mix - β with 91% ee. The diol derivative could be converted into (S) - propranolol by classical methods.

Scheme 5.6.6: Synthesis of *(S)*- Propranolol

The synthesis of chromophore of anthracycline antibiotic uses chiral osmium complex bearing chiral diamine L for asymmetric dihydroxylation with good enantioselectivity (Scheme 5.6.7). The resultant 1,2-diol could be subsequently converted into the desired chromophore of anthracycline antibiotic in good yield.



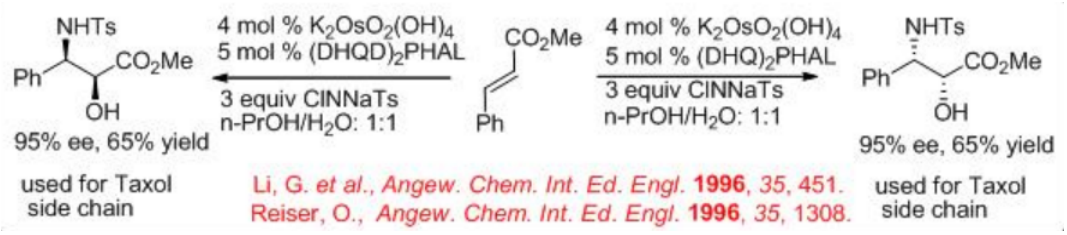
Scheme 5.6.7: Synthesis of Chromophore of Anthracycline Antibiotic

5.6.2 Asymmetric Aminohydroxylation

The chiral β-amino alcohol structural unit is a key motif in many biologically important molecules. It is difficult to imagine a more efficient means of creating this functionality than by the direct addition of the two heteroatom substituents to an alkene, especially if this transformation could be achieved in regioselective and enantioselective fashion. In parallel to allylic epoxidation and dihydroxylation of alkenes; Sharpless group has developed asymmetric aminohydroxylation of alkenes using osmium based catalysis.

Synthesis of chiral α -sulfonamido hydroxy compounds can be obtained when the alkene substrates are subjected to the aminohydroxylation reaction using chloramine-T (TsNClNa) as the nitrogen source and H_2O as the oxygen source. The reaction is found to be successful in the presence of osmium complex bearing $(DHQ)_2$ PHAL or $(DHQD)_2$ PHAL. The α -sulfonamido hydroxy compounds can be isolated with high yield and enantiomeric purity. Better results are obtained with chloramine-T (oxidant) salts bearing smaller organic substituents on the sulfur. This reagent could be prepared separately and added to the reaction mixture as the stable anhydrous salt or it can be generated *in situ* (Scheme 5.6.8). The methyl (E)-cinnamate can be

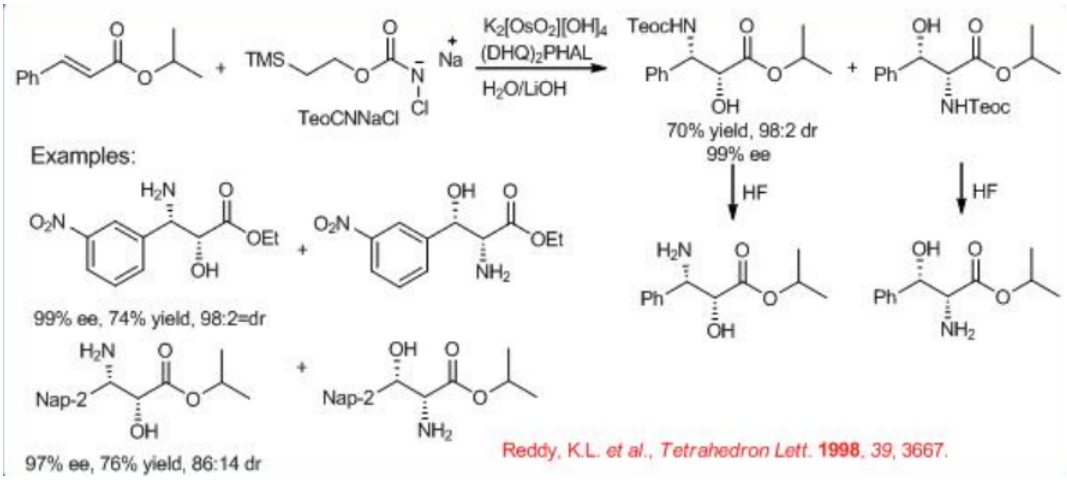
successfully converted into α-hydroxy- β-amino product with high enantioselectivity. The resultant product is used to construct the taxol side chain, and this process establishes the shortest and the most efficient route to the side chain of this pharmaceutically important agent.



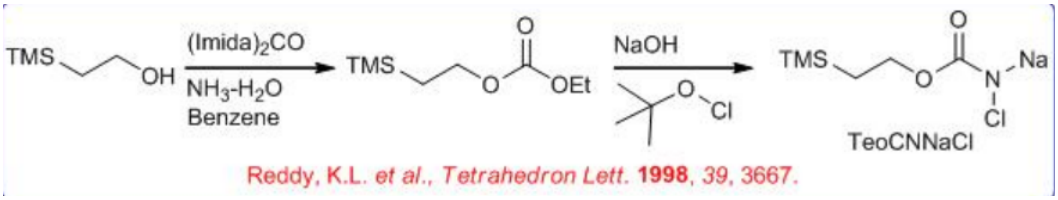
Scheme 5.6.8

The key issue is the regioselectivity of the reaction. Replacement of sulfonamide in chloramine-T with alkyl carbamates like BnO_2CNH_2 , EtO_2CNH_2, and t-BuO_2CNH_2 or amides greatly improves the reaction scope of the substrate and selectivity up to 99% ee and 80% yield. Also carbamate product could be easily converted into free amino alcohol. *t* -Butyl carbamate is superior to ethyl carbamate in terms of yield, enantioselectivity, and ease of removal of the *N* -protecting group.

Nitrogen source 2-trimethylsilylethyl *N* -chloro- *N* -sodiocarbamate (TeoCNClNa) could be synthesized by reacting NaOH and *t* -BuOCl with 2-(trimethylsilyl)ethyl carbamate, which can be prepared by successively adding carbonyl diimidazole and ammonia to 2-trimethylsilylethanol in benzene (Scheme 5.6.9-5.6.10). The TeoC group can be cleaved by fluoride under very mild conditions, yielding the free amino alcohol with high enantiomeric purity.

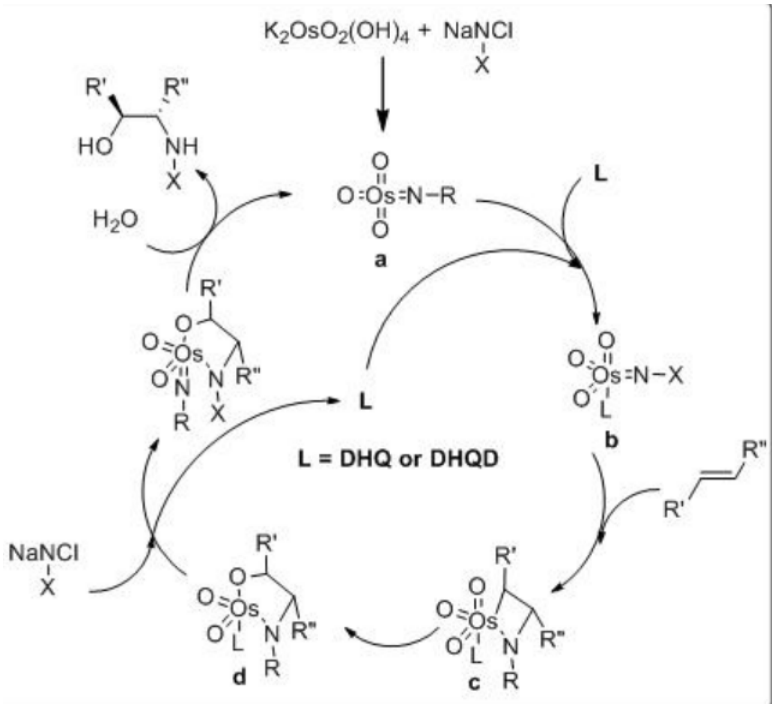


Scheme 5.6.9: Aminohydroxylation using TeoCNNaCl as the Nitrogen Source



Scheme 5.6.10: Synthesis of TeoCNNaCl

The mechanism of the reaction is shown in Scheme 5.6.11. The Os(VI) azaglycolate is reoxidized by the *N* -chloroamide substrate and releases the target product after hydrolysis. The reoxidized metallacycle undergoes a second cycloaddition leading to an Os(VI) bis(azaglycolate). Conducting the reaction in an aqueous medium under more dilute conditions favors the hydrolysis.

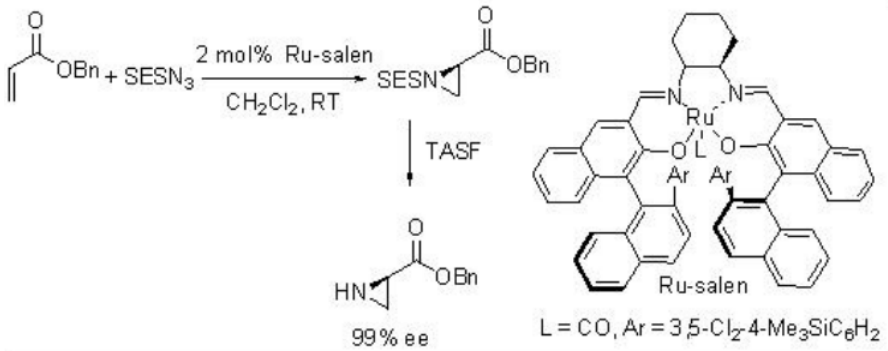


Scheme 5.6.11: Mechanism of Sharpless Aminodihydroxylation

5.6.3 Asymmetric Aziridination

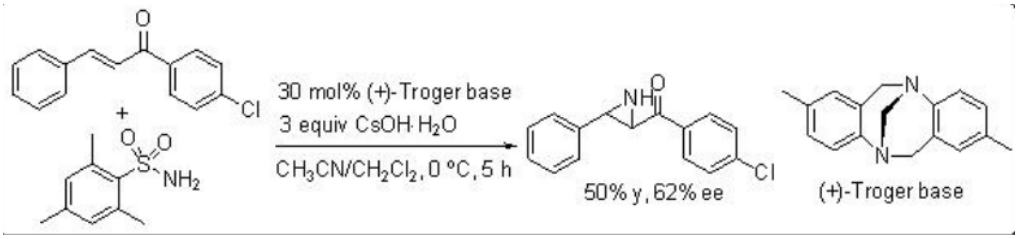
Aziridines are versatile building blocks in organic synthesis. Considerable progress has been made in the area of asymmetric aziridination employing copper based systems. Mn(porphyrin) and Mn-salen complexes have been shown as effective catalysts for this reaction. The reactions proceed via active nitrenoid species and most of the methods use a hypervalent iodine reagent such as PhI=NTs as nitrenoid source. The deprotection of N-sulfonyl groups require harsh reaction conditions, development of new methods has thus been focused without protecting group or with a readily removable group. In this context, the use of azide compounds as nitrogen source has been recently demonstrated.

Ru-salen is found to be effective catalyst for the aziridination of alkenes with TsN_3 at room temperature with excellent enantioselectivity (Scheme 5.6.12). *p* -Nitro and *o* -nitrobenzenesulfonyl azide and 2-(trimethylsilyl)ethanesulfonyl azide ($SESN_3$) are also effective for this reaction affording the aziridine with high enantioselectivity. Furthermore, less nucleophilic α, β -unsaturated esters proceed aziridination with high enantioselectivity.

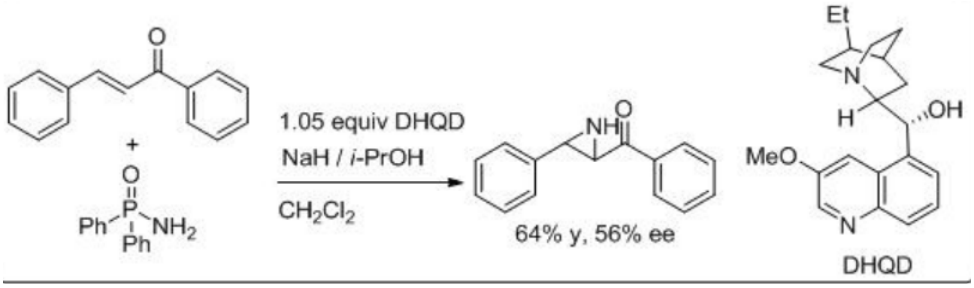


Scheme 5.6.12

An aminimide that is generated by deprotonation of the corresponding aminimine undergoes aziridination of chalcone via conjugate addition and ring closure by N-N bond cleavage. For example, O-mesitylenesulfonylhydroxylamine proceeds reaction in the presence of (+)-Troger base and $CsOH{\cdot}H_2O$ with moderate enantioselectivity (Scheme 5.6.13). Soon after the use of quiniclidine for the reaction of *O* -(diphenylphosphinyl)hydroxylamine with chalcone is shown with 56% ee (Scheme 5.6.14).



Scheme 5.6.13

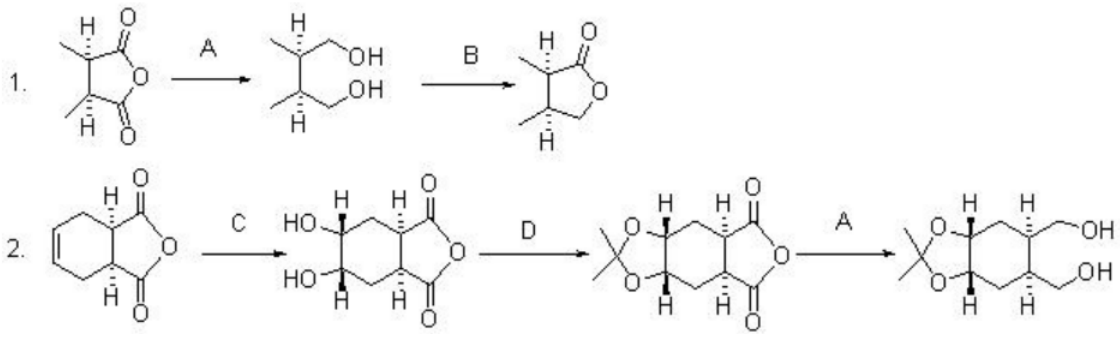


Scheme 5.6.14

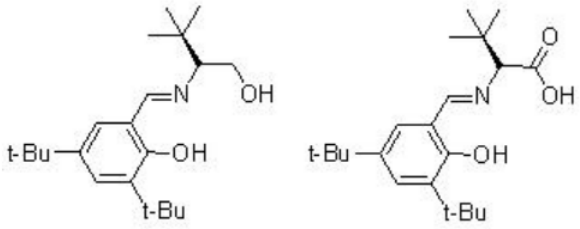
5.7: Problems and Reference

Problems:

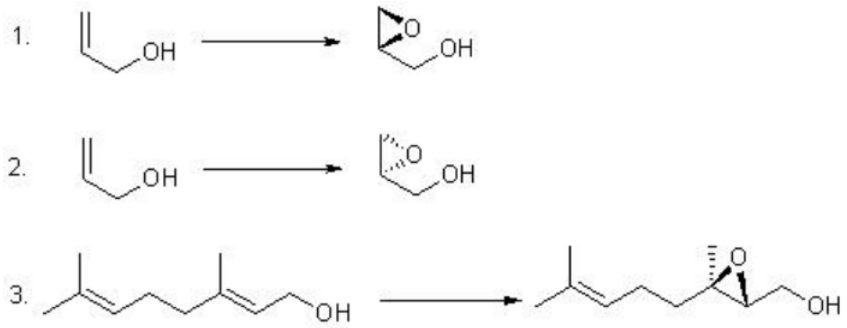
Complete the following transformations.



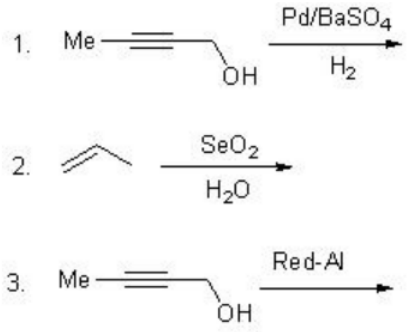
How will you prepare the following chiral ligands?



Complete the following reactions.



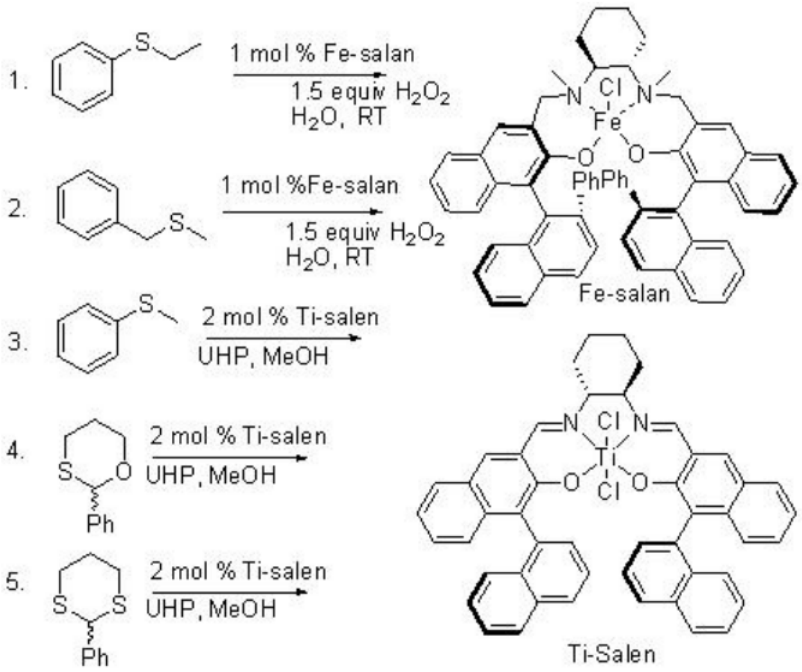
Predict the major products for the following reactions.



List three effective organo catalysts for the epoxidation of α,β -unsaturated ketones. Provide mechanism.

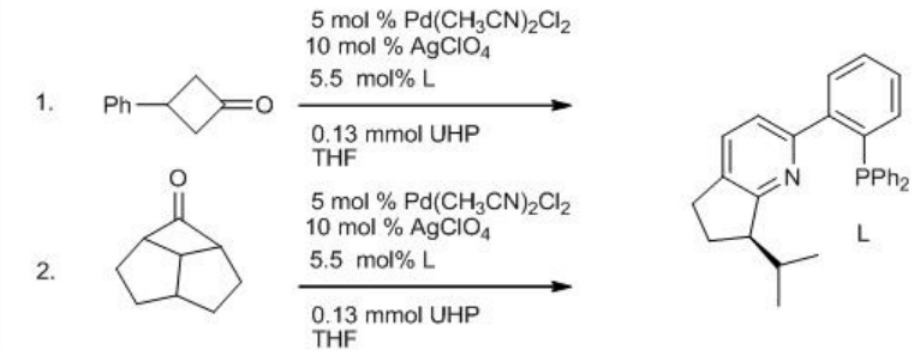
List three effective organo catalysts for the epoxidation of α,β -unsaturated aldehydes. Provide mechanism.

Complete the following reactions.

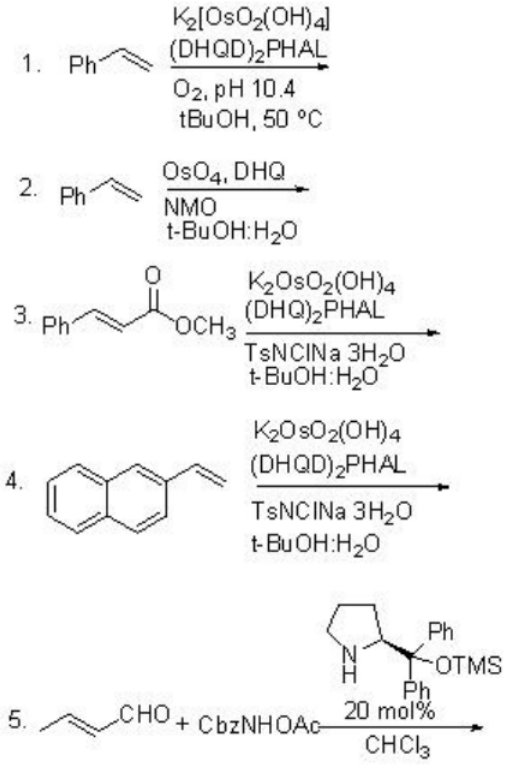


Describe chiral phosphoric acid catalyzed asymmetric Baeyer-Villiger oxidation.

Complete the following reactions.



What product(s) would you expect from the following reactions?



Reference/Text Book

1. I. Ojima, *Catalytic Asymmetric Synthesis* , 3 rd ed., Wiley, New Jersey, 2010.

2. M. B. Smith, *Organic Synthesis* , 2 nd edition, McGraw Hill, New Delhi, 2004.

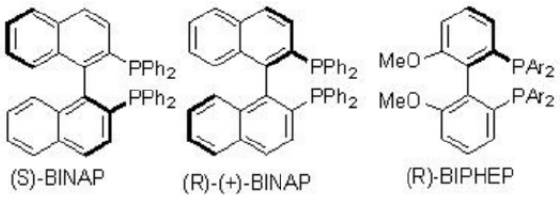
• Ojima, Catalytic Asymmetric Synthesis, VCH Publishers, Inc., New York 1993.

CHAPTER OVERVIEW

6: Hydrogenation Reactions

6.1: Reactions Carbon-Carbon Double Bonds

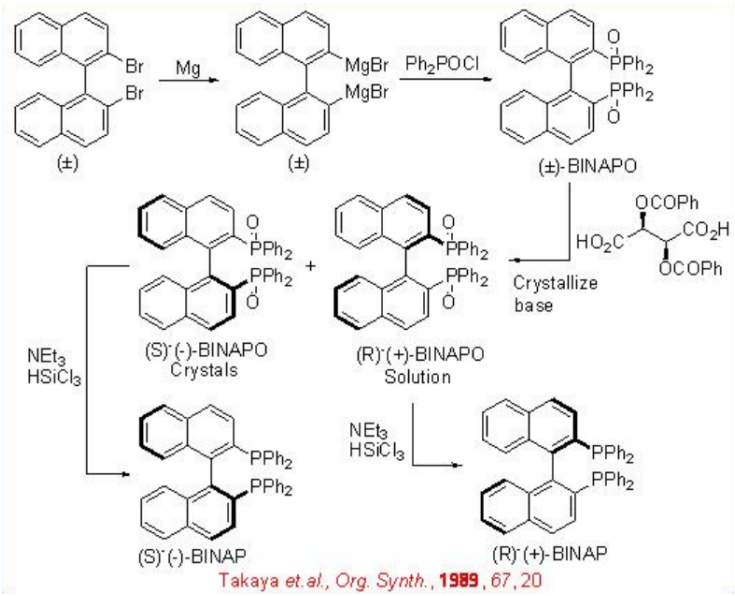
Enantioselective reduction of C=C double bond has important application in the synthesis of many natural products and pharmaceutically important compounds. Scheme 6.1.1 summarizes some of the common successful phosphine based chiral ligands developed for the catalytic asymmetric hydrogenation of alkenes.



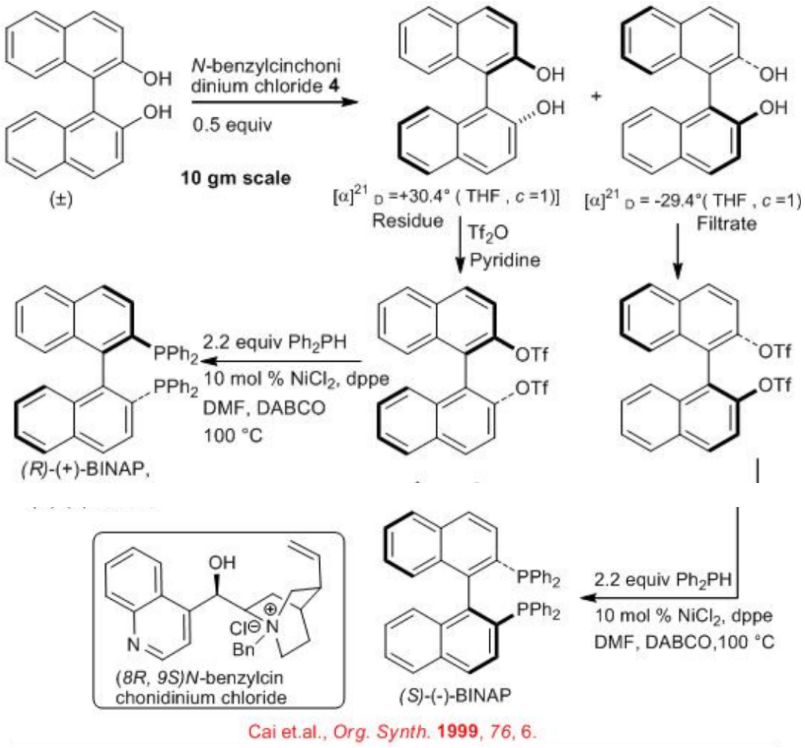
Scheme 6.1.1

BINAP based ligands play an important role for asymmetric hydrogenation of alkenes. Both *(S)*- BINAP and *(R)*- BINAP could be synthesized by resolution methods using *(1S,2S)*- tartaric acid as well as *(8R,9S)*- *N* - benzylcinchonidinium chloride as the chiral sources . Synthesis of *(S)*- BINAPcould be performed from racemic 2,2'-dibromo BINAP (Scheme 6.1.2). Resolution of the corresponding phosphine oxide with *(1S,2S)*- tartaric acid and subsequent reduction with $HSiCl_3$ can afford *(S)*- BINAP in gram scale.

Alternatively, *(S)*- BINAP and *(R)*- BINAP can be synthesized by resolution of racemic BINOL using *(8R,9S)*- *N* - benzylcinchonidinium chloride (Scheme 6.1.3) . Converting them into triflate derivative and subsequent cross-coupling with Ph_2 PH using $NiCl_2$ to afford *(S)*- BINAP and (*R*) - BINAP in gram scale. *(S)*- BINAP ; light brown solid, mp 205°C , 99 % ee, $[\alpha]^{21}_D$= −29.4° (THF , *c* =1). *(R)*- BINAP; white crystalline solid, mp 207°C , 99% ee, $[\alpha]^{21}_D$ = 26.2 - 30.9° (THF , *c* 1).



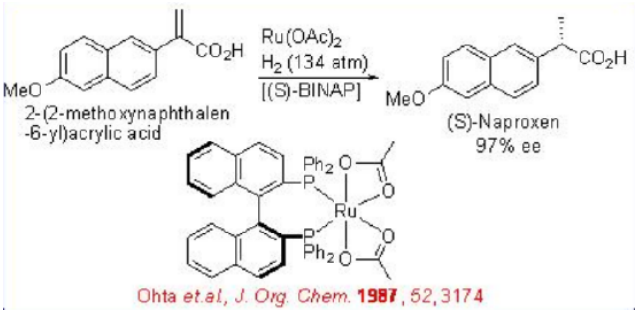
Scheme 6.1.2: Gram Scale Synthesis of *(S)*- BINAP and *(R)*- BINAP



Scheme 6.1.3: Alternative Synthesis of Chiral *(S)*- BINAP *and (R)*- BINAP

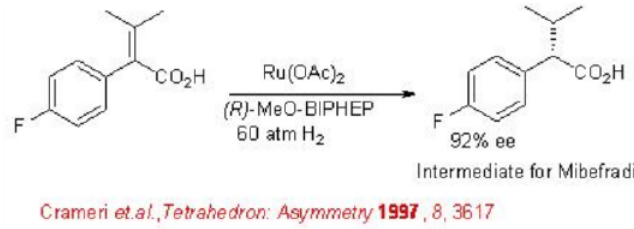
6.1.1 Reduction of *α,β* -Unsaturated Carboxylic acids

Chiral Ru(II)-BINAP catalyzes the hydrogenation of *α,β*- unsaturated carboxylic acids. For example, the hydrogenation of naphthacrylic acid can be performed using a Ru-(*S*)-BINAP with 134 atm H_2pressure (Scheme 6.1.4). The reaction affords chiral (*S*)-naproxen with 98% ee, which is a nonsteroidal anti-inflammatory drug.



Scheme 6.1.4: Synthesis of *(S)*- Naproxen by Chiral Reduction of *α,β*- Unsaturated Carboxylic Acids

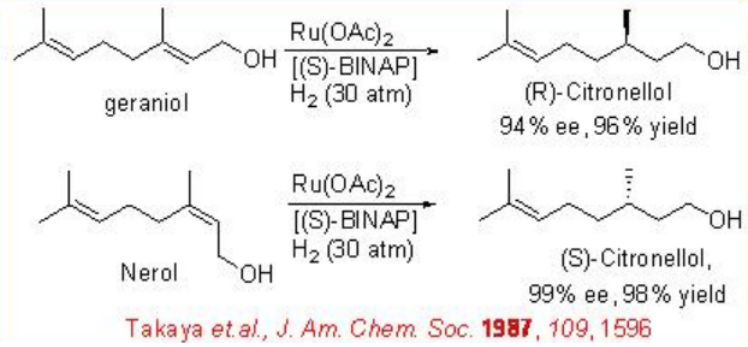
Hydrogenation has been explored for the synthesis of intermediate of *(S)*- mibefradil. For this reaction chiral Ru-complex bearing (*R*)-MeO-BIPHEP is found to be effective affording the target intermediate with 92% ee (Scheme 6.1.5).



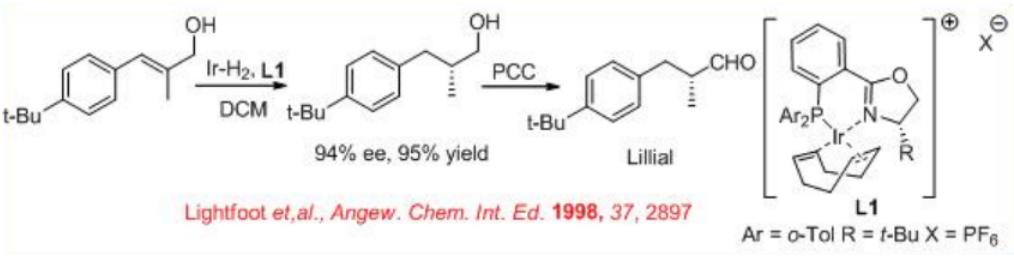
Scheme 6.1.5: Synthesis of Intermediate for *(S)*- Mibefradil

6.1.2 Reduction of Allylic alcohol

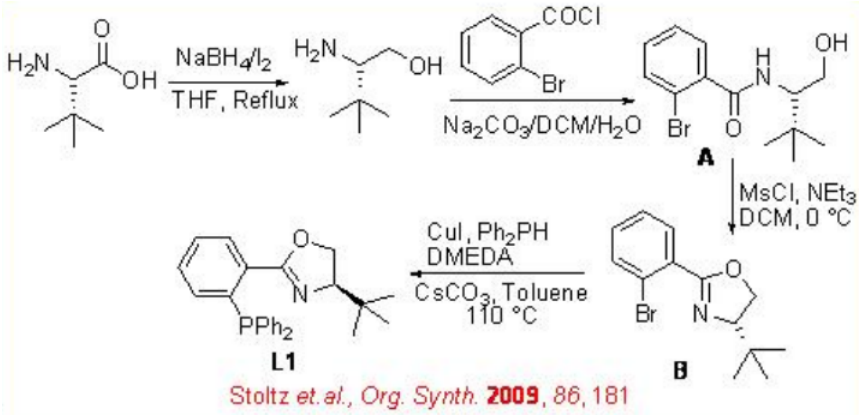
Allylic alcohols can be reduced with high selectivity using chiral Ru-(*S*)-BINAP as a catalyst. For example, the reduction of geraniol can be accomplished with 94% ee (Scheme 6.1.6). The reduced product is used for the large scale synthesis of L-(+)-menthol. Under these conditions, nerol undergoes reduction to give (*S*)-citronellol in 99% ee. Chiral iridium-based catalytic systems have also been subsequently explored for the asymmetric reduction of allylic alcohols. For example, the complex bearing chiral phosphanodihydrooxazole L_1 catalyzes asymmetric reduction of an allyl alcohol, which is used as a key step in the synthesis of lillial (Scheme 6.1.7). Scheme 6.1.8 illustrates the synthesis of chiral phosphanodihydrooxazole L_1.



Scheme 6.1.6: Synthesis of *(S)* and *(R)*- Citronellol by Chiral Reduction of Geraniol and Nerol



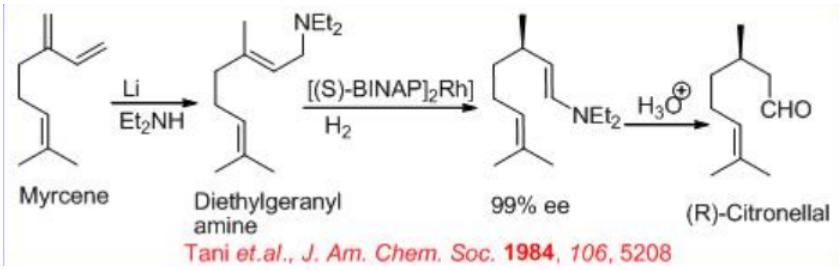
Scheme 6.1.7: Asymmetric Synthesis of Lillial.



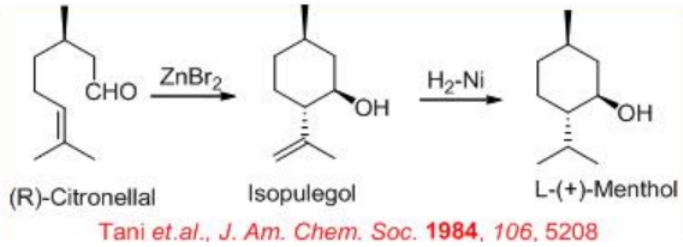
Scheme 6.1.8: Synthesis of Phosphanodihydrooxazole L_1

6.1.3 Reduction of Allylic Amines

In parallel to the reduction of allylic alcohol, Rh-(*S*)-BINAP system has been used for the reduction of allylic amine. For example, the synthesis of *(R)*- citronellal can be accomplished via reduction of allylic amine (Scheme 6.1.9). The key step is the isomerization of geranyl diethylamine forming (*R*)-citronellal enamine . The Rh-complex performs the rearrangement of this allylic amine to the enamine creating a new chiral centre with >98% ee, which upon hydrolysis gives (*R*)-citronellal in 96–99% ee. The latter serves as substrate precursor for the synthesis of L-(+)-menthol *via* intramolecular ene reaction followed by hydrogenation (Scheme 6.1.10).



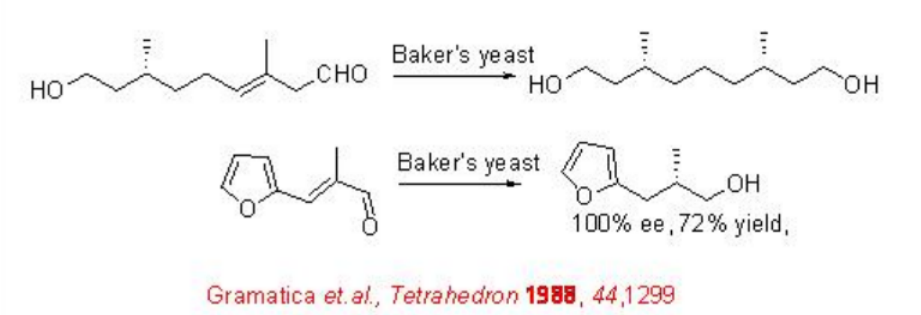
Scheme 6.1.9: Chiral Reduction of Allylic Amine to Synthesize (*R*)-Citronellal



Scheme 6.1.10: Industrial preparation of L-(+)-Menthol by Chiral Reduction of Allylic Amine

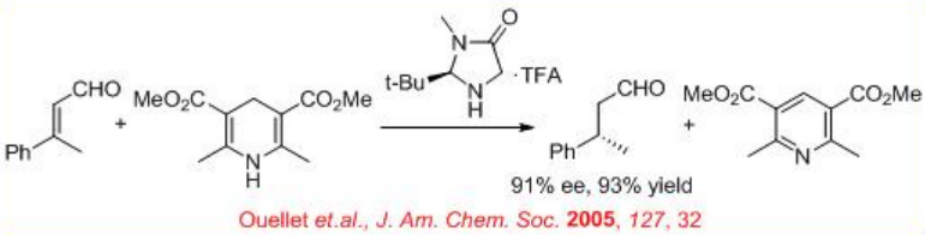
6.1.4 Reduction of α, β-Unsaturated Aldehydes

Asymmetric reduction of α, β -unsaturated aldehydes with transition metal catalysts has not yet proven ready for wide spread industrial application. In comparison to CBS catalyst, the Baker's yeast is most useful, since the precursor (*R*)-proline used to synthesize CBS is expensive. The chiral reduction of enals to chiral alcohols using Baker's yeast has been known for over 30 years. Scheme 6.1.11 summarizes some of the examples for the Baker yeast catalyzed reduction of C=C of α, β -unsaturated aldehydes.



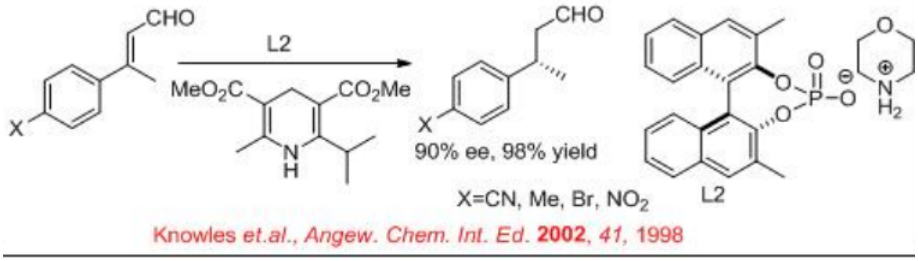
Scheme 6.1.11: Baker's yeast cell for Reduction of α, β -Unsaturated Aldehydes

Subsequently, organocatalysis has been found be effective for the asymmetric reduction. A recent interesting development is the organocatalytic hydride transfer reductions of α, β -unsaturated aldehydes to chiral aldehyde. Hantzsch ester acts as a good NADH mimic in the hydride transfer to an iminium ion, formed when the *α,β* -unsaturated aldehyde reacts with the amine of the organocatalyst (Scheme 6.1.12).



Scheme 6.1.12: Organocatalytic Reduction of an Unsaturated Aldehyde

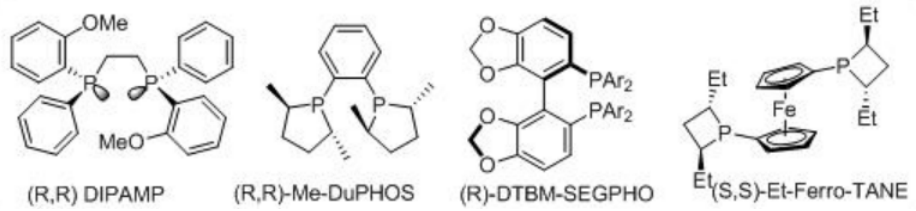
Similarly, chiral phosphoric acid L2 catalyses the reduction of C=C of α, β -unsaturated aldehyde with 90% ee and 98% yield in the presence of Hantzsch ester (Scheme 6.1.13).



Scheme 6.1.13: Organocatalytic Reduction of an α, β -Unsaturated Aldehyde

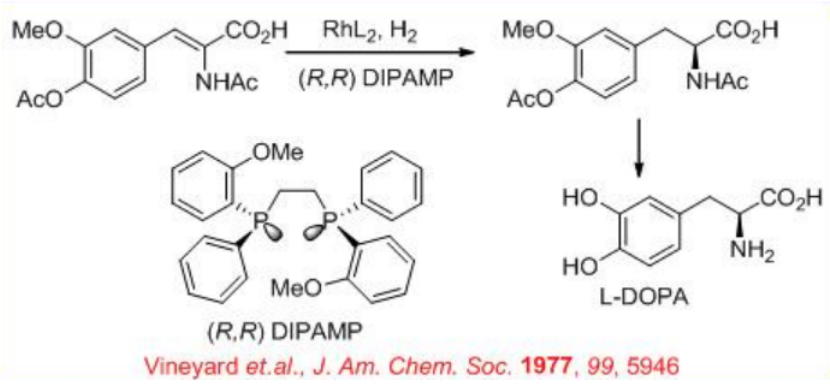
6.1.5 Reduction of α, β-Unsaturated α-Amino Acid

Asymmetric reduction of α, β -unsaturated α-amino acid has wide application in organic synthesis. Chiral biphosphines in combination with Rh acts as the best combination for the reduction α, β-unsaturated *α* -amino acids. Scheme 6.1.14 summarizes some of the successful chiral phosphines for the Rh-catalyzed reactions.



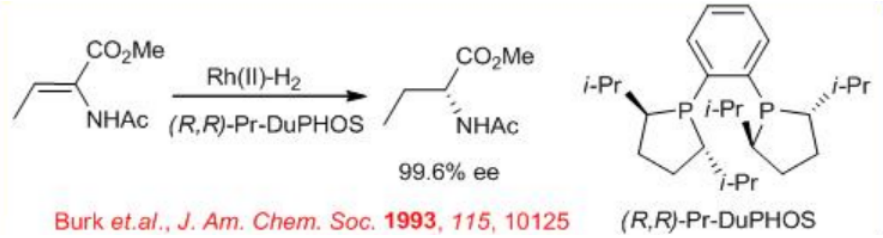
Scheme 6.1.14: Ligands used for Chiral Reduction of α, β-Unsaturated *α* -Amino acid

Rh-DIPAMP has been explored for the reduction of α, β-unsaturated α-amino acids. For example, L-DOPA, a chiral drug for treating *Parkinson's* disease, is synthesized using Rh-(*R,R*)-DIPAMP catalyzed reduction of α, β-unsaturated *α* -amino acid as a key step (Scheme 6.1.15).



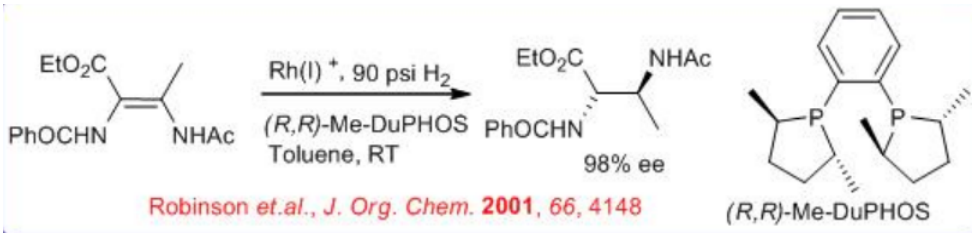
Scheme 6.1.15: Key Step for Industrial Synthesis of L-DOPA

Rh -*(R,R)*- DuPHOS can be used for the reduction of α, β-unsaturated α-amino acid to give chiral amino acid (Scheme 6.1.16). Using this procedure many of the unnatural α-amino acids can be obtained directly with enantioselectivity approaching 100% ee and S/C ratio 10000-50000. The rhodium-catalyzed hydrogenation of the *E*- and *Z* -isomers, with BINAP in THF, affords products with opposite absolute configurations. Remarkably, the *(R,R)*- DuPHOS system provides excellent enantioselectivity for both isomeric substrates with the same absolute configuration, irrespective of the *E*/*Z* -geometry. This result is particularly important for the construction of alkyl dehydroamino acid derivatives, which are difficult to prepare in enantiomerically pure form.

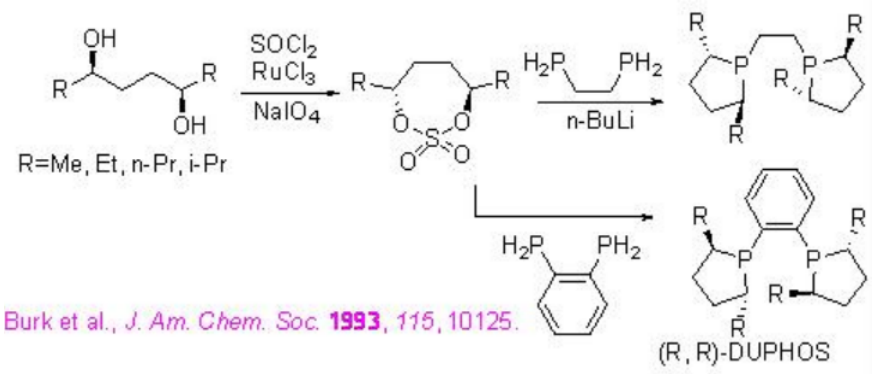


Scheme 6.1.16: Reduction of α, β-Unsaturated α-Amino Ester

The hydrogenation of the (*E*)- or (*Z*)- isomer of β-(acetylamino)- β-methyl- α-dehydroamino acids with Rh(I)-Me-DuPHOS provides either diastereomers of the *N*, *N* -protected 2,3-diaminobutanoic acid derivatives with 98% ee (Scheme 6.1.17-6.1.18).

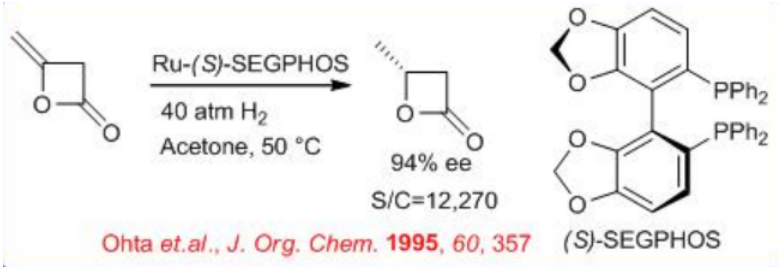


Scheme 6.1.17: Reduction of α, β-Unsaturated α-Amino β-ester



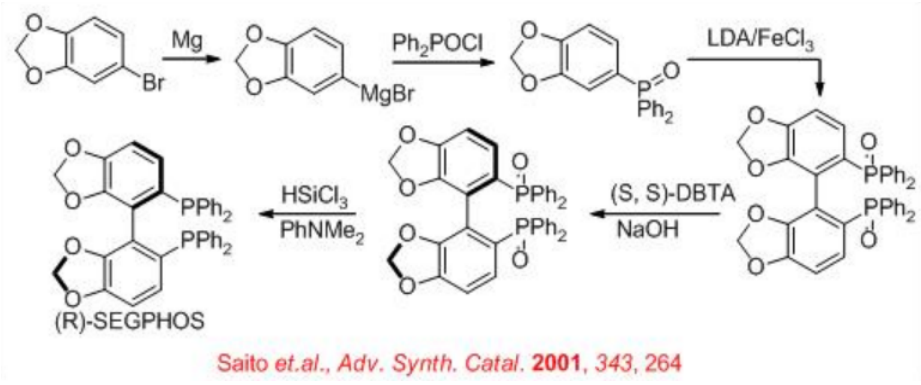
Scheme 6.1.18: Synthesis of 1,2-Bis(phospholano) (DuPHOS) Ligands

(S)- SEGPHOS and its analogous provide superior results in Ru-catalyzed hydrogenation of four and five-membered cyclic lactones or carbonates bearing an exocyclic methylene group. For example, the reduction of the four membered lactone can be achieved with excellent enantioselectivity using S/C=12270 (Scheme 6.1.19).



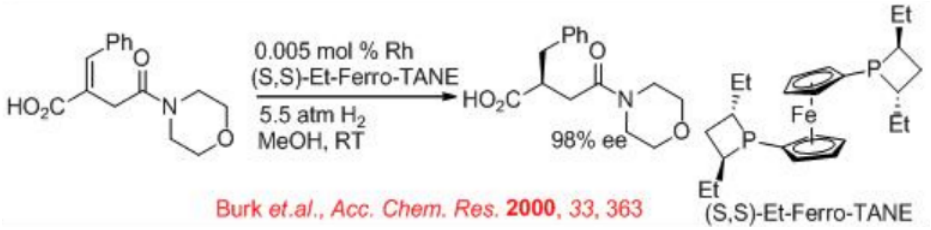
Scheme 6.1.19: Reduction of *α,β* -Unsaturated Lactone using *(S)*- SEGPHOS

Scheme 6.1.20 describes the synthesis of SEGPHOS. The key step is the resolution of racemic phosphine oxide with *(S,S)*- DBTA (di-benzoyl-tartaric acid) to provide chiral phosphine oxide. Subsequent reduction with $HSiCl_3$ affords the target SEGPHOS in good yield.



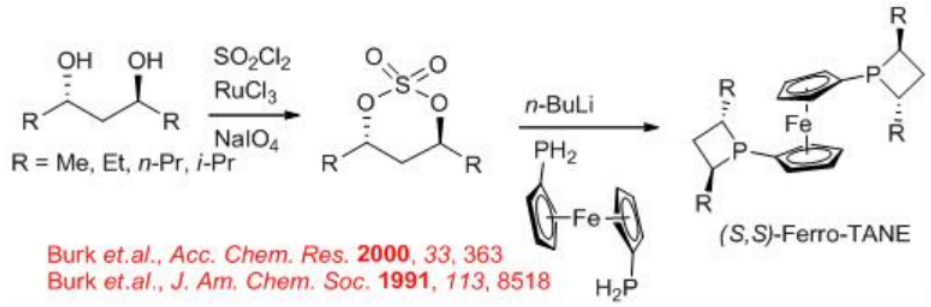
Scheme 6.1.20: Synthesis of *(R)*- SEGPHOS Ligands

Moreover, chiral 1,10-diphosphetanylferrocene Et-FerroTANE serves as an effective ligand for the rhodium-catalyzed hydrogenation of β -aryl- and β -alkyl-substituted monoamido *itaconate* (Scheme 6.1.21). For example, Et-DuPHOS–Rh is utilized for the asymmetric hydrogenation of the trisubstituted alkene to afford the reduced product, which is used for synthesis of intermediate of the drug *candoxatril* in 99% *ee* . *Candoxatril* is the orally active prodrug of candoxatril (UK-73967) human neutral endopeptidase (Neprilysin).



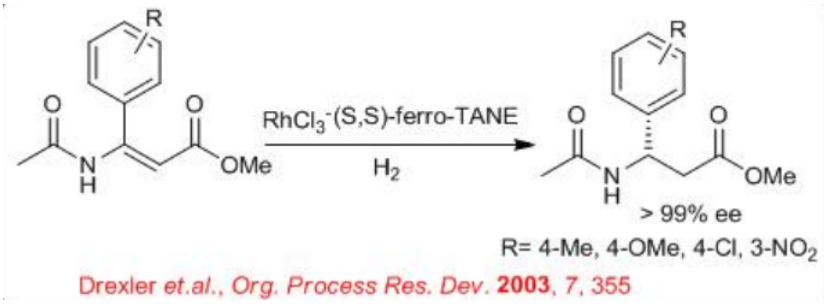
Scheme 6.1.21 Reduction of *α,β*-Unsaturated Carboxylic using Et-Ferro TANE

The above described alkyl/aryl-ferro-TANE family ligands could be synthesized from optically active diols (Scheme 6.1.22). Cyclization with SO_2Cl_2 in presence of $RuCl_3$ and $NaIO_4$ affords chiral cyclized sulfonate, which reacts with ferro-phosphine in the presence of n-BuLi to give the target chiral alkyl/aryl-Ferro-TANE family in good yield.



Scheme 6.1.22: Synthesis of Chiral Et-Ferro TANE Ligands

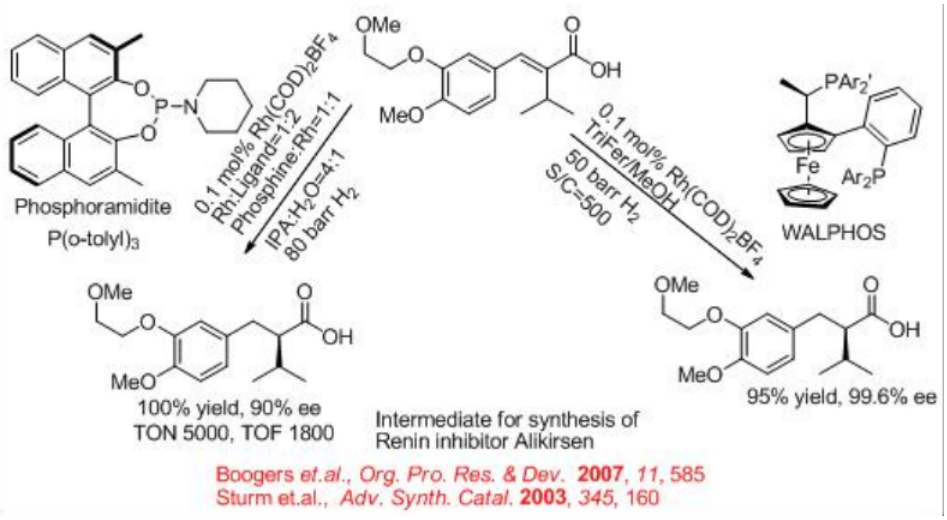
Similarly, the reduction of α,α -disubstituted α, β-unsaturated ester can be carried out using chiral Ru-Et-Ferro TANE (Scheme 6.1.23). The reaction is compatible with different electron donating and withdrawing groups attached to benzene ring.



Scheme 6.1.23: Chiral Reduction of *α,α* -Disubstituted *α,β*-Unsaturated Ester.

6.1.6 Reduction of *α* -Alkyl Substituted Acids

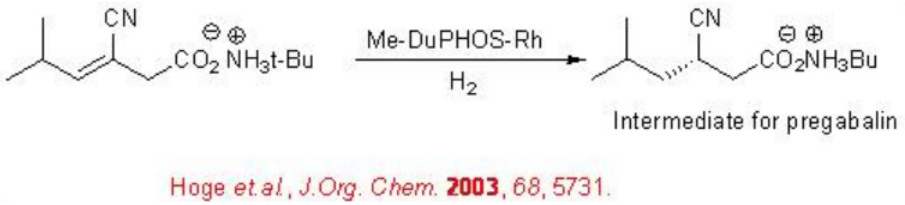
Another important chiral acid is the *α* -alkyl substituted acid which is used in the synthesis of *aliskiren* (the active ingredient of Tekturna1) (Scheme 6.1.24). The key step for the synthesis requires the hydrogenation of cinnamic acid derivative in the presence of Rh-phosphoramidite . The reduction also affords 97% ee using Rh-WALPHOS.



Scheme 6.1.24 Key Step for Synthesis of Renin Inhibitors *Aliskiren*

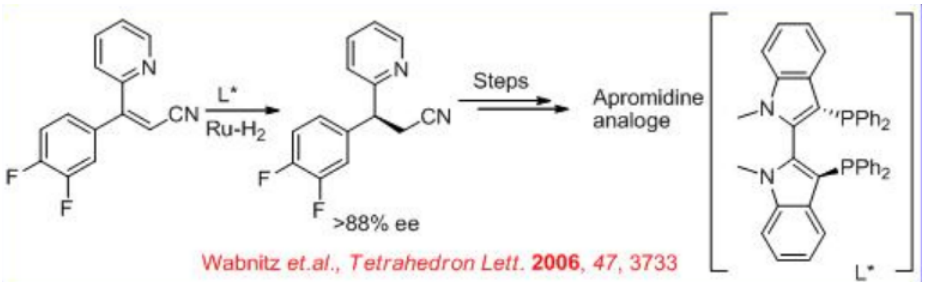
6.1.7 Reduction of α, β-Unsaturated Nitriles

The asymmetric reduction of unsaturated nitriles is a very useful process for the synthesis of many pharmaceutical intermediates. An important application of this strategy involves the further reduction of the nitrile group to yield chiral amines. For example, chiral Rh-phosphine catalyzes the asymmetric hydrogenation of an unsaturated nitrile (Scheme 6.1.25). The reduced product is used for the synthesis of the *Pregabalin*.



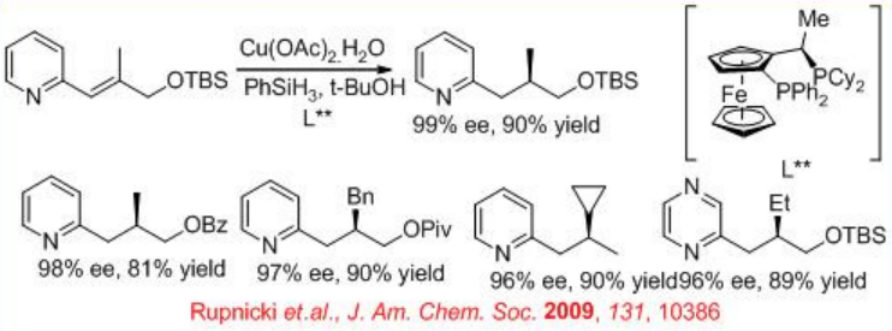
Scheme 6.1.25: Pfizer *Pregabalin* Intermediate Synthesis

A more challenging example of an unsaturated nitrile reduction that lacks the carboxylate functional group is the asymmetric reduction of the nitrile shown in Scheme 6.1.26. The reduced product is used for the synthesis of chiral 3,3-diarylpropylamine, which is an intermediate for the synthesis of the *Arpromidines*. The arpromidines analogues are the most potent histamine H_2 receptor agonists known and are promising positive inotropic vasodilators for the treatment of severe congestive heart failure.



Scheme 6.1.26: Hydrogenation of Diaryl-substituted *α,β*-Unsaturated nitriles.

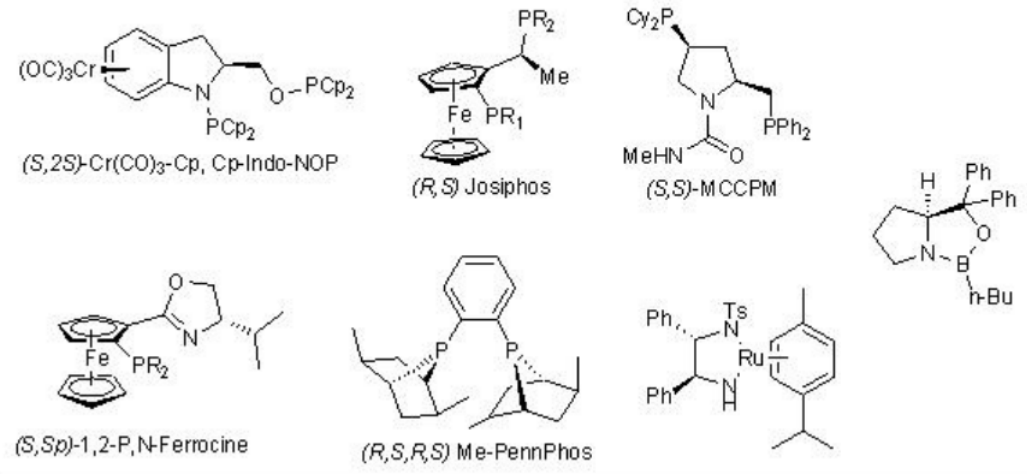
In parallel to Ru, Rh and Ir-based catalytic systems, chiral copper hydride catalysis have been demonstrated for enantioselective 1,4-reductions of 2-alkenyl heteroarenes. Both azoles and azines serve as efficient activating groups for this process (Scheme 6.1.27).



Scheme 6.1.27: Enantioselective Hydrogenation of Protected Allylic Alcohol

6.2: Reactions of Ketones

Enantioselective reduction of C=O double bond in organic synthesis has important application in synthesis of many natural products as well as pharmaceutical products. The lecture covers the representative examples of metal catalyzed reactions. The reactions using CBS and enzymes are covered in the other modules of this course. The frequently used chiral ligands for the metal catalyzed enantioselective reduction reactions of ketones are listed in Scheme 6.2.1.



Scheme 6.2.1

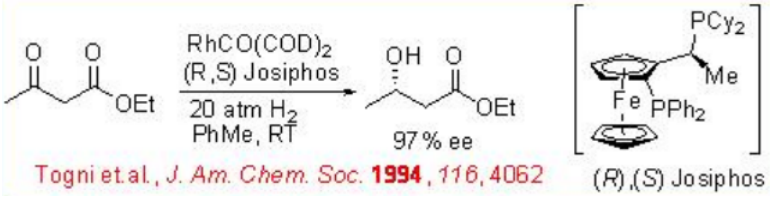
6.2.1 Reactions of α-Keto Amides

Asymmetric hydrogenation of α -keto esters has been studied with several rhodium catalysts. Neutral rhodium catalysts with chiral ligands such as $Cr(CO)_3$-Cp,Cp-Indo-NOP demonstrate excellent enantioselectivity and reactivity in the hydrogenation of amides (Scheme 6.2.2).

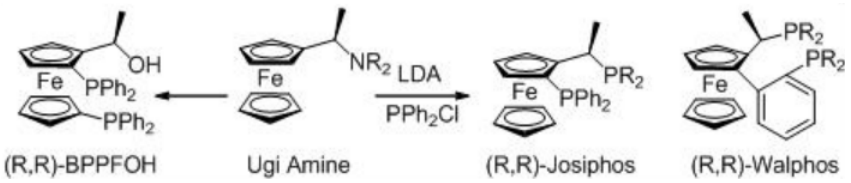
Scheme 6.2.2: Enantioselective Hydrogenation of *α* -Keto Amide

6.2.2 Reactions of β - Keto Esters

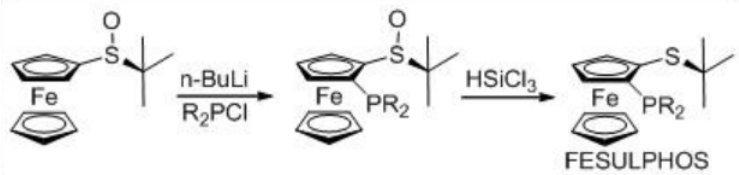
Asymmetric hydrogenation of β -keto esters has been extensively studied using chiral ruthenium catalysts. However, only handful of examples analogous to rhodium-catalyzed reaction are explored (Scheme 3). The Rh-(*R,S*)-Josiphos complex provides an effective catalyst for the asymmetric hydrogenation of ethyl 3-oxobutanoate affording the corresponding β -hydroxy ester in 97% ee. The above ligands *Josiphos* family such as chiral Walphos, Joshiphos, BPPFOH, TRAP and PIGIPHOS ligands could be easily synthesized from commercially available *Ugi* amine (Scheme 6.2.4-6.2.6).



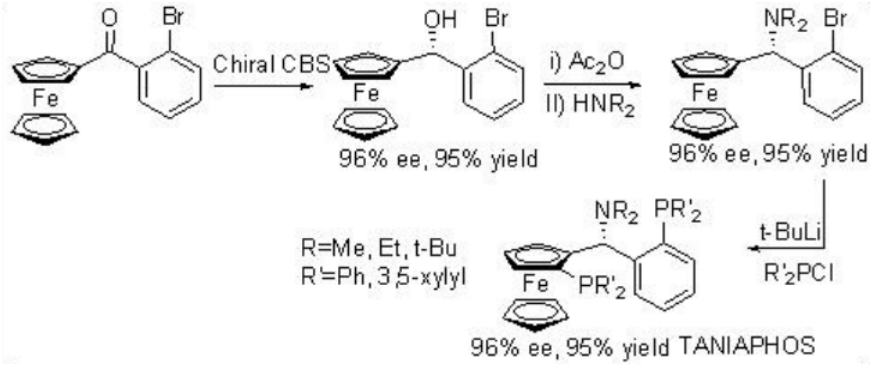
Scheme 6.2.3: Enantioselective Hydrogenation of β -Keto ester



Scheme 6.2.4: Synthesis of *Josiphos* Type Ligands

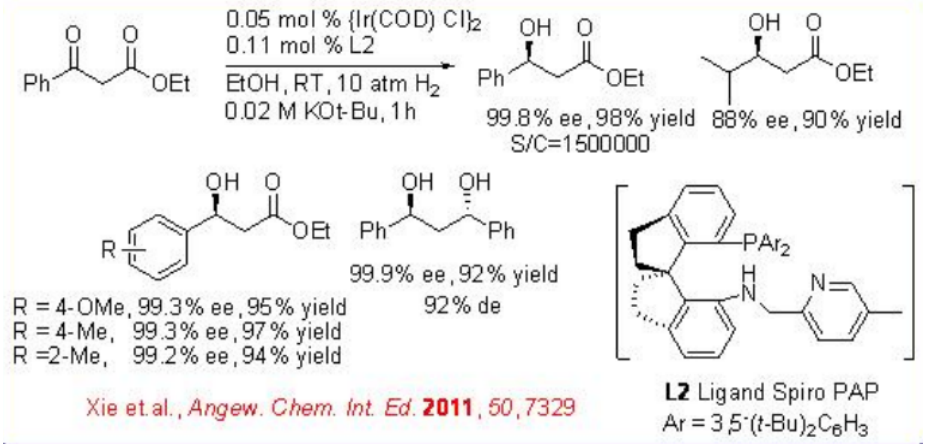


Scheme 6.2.5: Synthesis of *Feluphos*



Scheme 6.2.6: Synthesis of *Taniaphos*

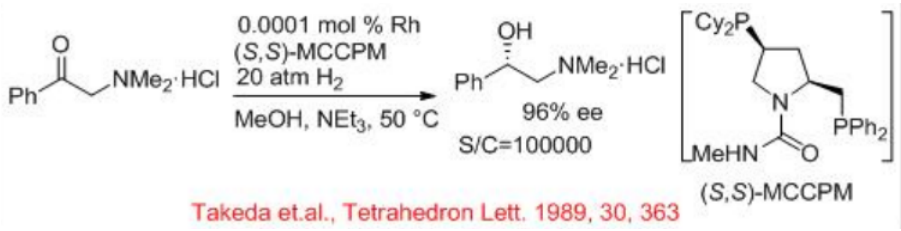
Iridium/spiro PAP has been used as effective catalyst for the asymmetric hydrogenation of β-aryl β-ketoesters (Scheme 6.2.7). The reaction provides a readily accessible method for the synthesis of β-hydroxy esters in high enantioselectivity up to 99.8% ee and high TONs up to 1230000.



Scheme 6.2.7: Enantioselective hydrogenation of β- ketoesters

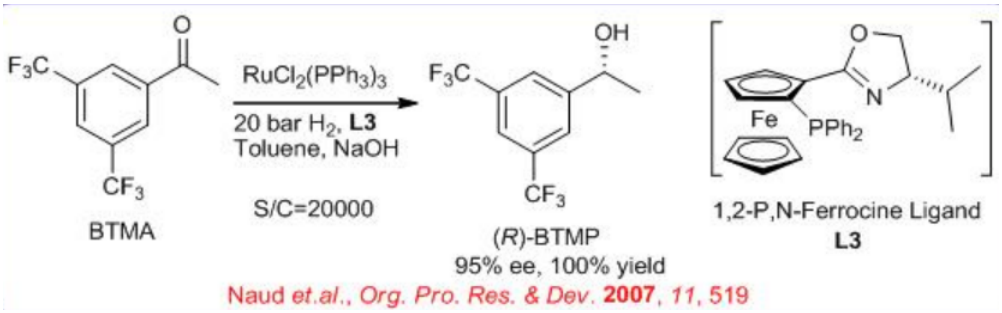
6.2.3 Reactions of Aromatic Ketones

Amino ketones and their hydrochloride salts can be effectively hydrogenated with chiral rhodium catalysts (Scheme 6.2.8). The rhodium precatalysts, combined with chiral phosphorous ligands *(S,S)*- MCCPM provide excellent enantioselectivity and reactivity for the asymmetric hydrogenation of *α*, *β*, and *γ* -alkyl amino ketone hydrochloride salts with S/C=100000.

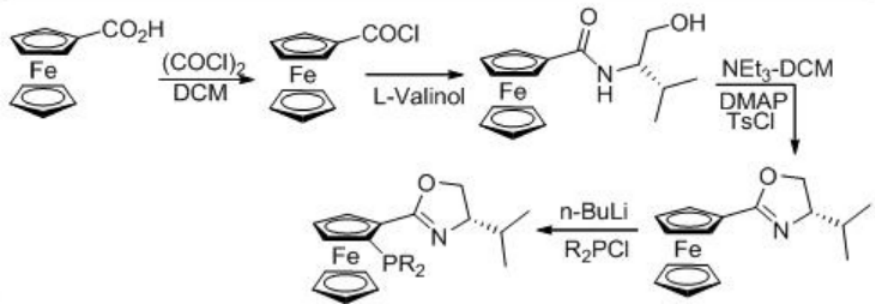


Scheme 6.2.8: Enantioselective Hydrogenation of α -Aryl Amino Ketone

The enantioselective hydrogenation of 3,5-bistrifluoromethyl acetophenone (BTMA) can be carried out using a Ru/phosphine-oxazoline complex (Scheme 6.2.9) . The reaction is compatible with 140-kg scale at 20 bar and 25°C with S/C ratios of 20,000. The synthesis of the ligand is shown in Scheme 6.2.10.

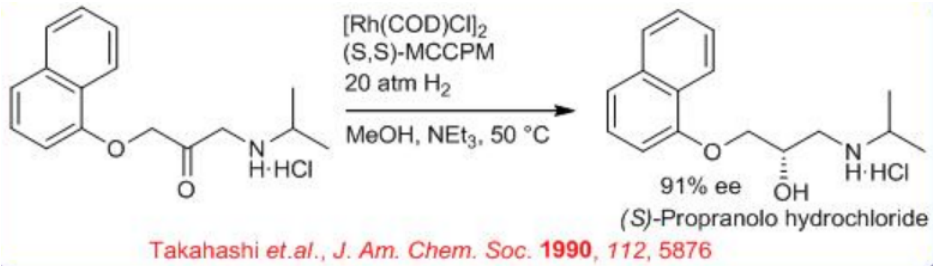


Scheme 6.2.9: Hydrogenation of α -Aryl Ketone

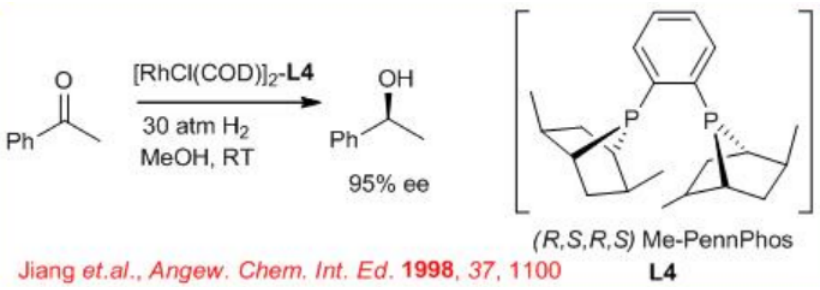


Scheme 6.2.10: Synthesis of *(S,Sp)*- 1,2-P,N-Ferrocine

The enantioselective hydrogenation of amino ketones has been applied extensively to the synthesis of chiral drugs and pharmaceuticals (Scheme 6.2.11). For example, direct enantioselective hydrogenation of 3-aryloxy-2-oxo-1-propylamine leads to 1-amino-3-aryloxy-2-propanol using 0.01 mol % of the neutral Rh-(*S*, *S*)-MCCPM complex. The chiral product 1-amino-3-aryloxy-2-propanol serves as β-adrenergic blocking agents. (*S*)-Propranolol is obtained in 90.8% *ee* from the corresponding α-amino ketone.



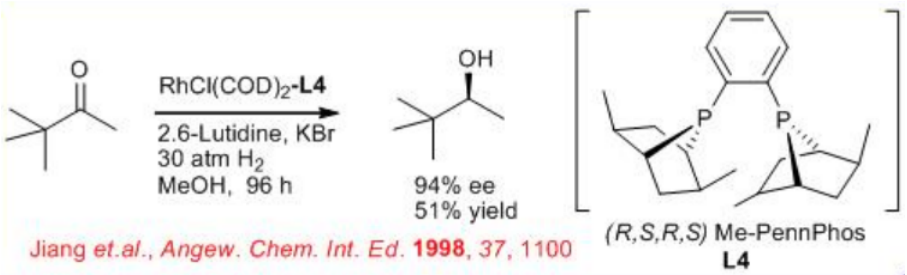
Scheme 6.2.11: Key step for the Direct Synthesis of *(S)*- Propranolol



Scheme 6.2.12: Asymmetric Reduction of Acetophenone

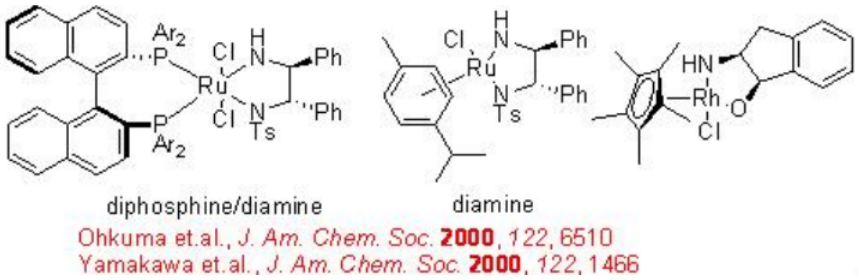
6.2.4 Reactions of Aliphatic Ketones

The asymmetric hydrogenation of simple aliphatic ketones remains still a challenging problem. This is due to the difficulty to design the appropriate chiral catalyst that will easily differentiate between the two-alkyl substituents of the ketone. Promising results have been obtained in asymmetric hydrogenation of aliphatic ketones using the (*R*,*S*,*R*,*S*)-PennPhos- Rh complex in combination with 2,6-lutidine and KBr. For example, the reaction of *tert* -butyl methyl ketone takes place with 94% *ee* . Similarly, isopropyl-, *n* -butyl- and cyclohexyl methyl ketones can be reduced with 85% *ee* , 75% *ee* and 92% *ee*, respectively.

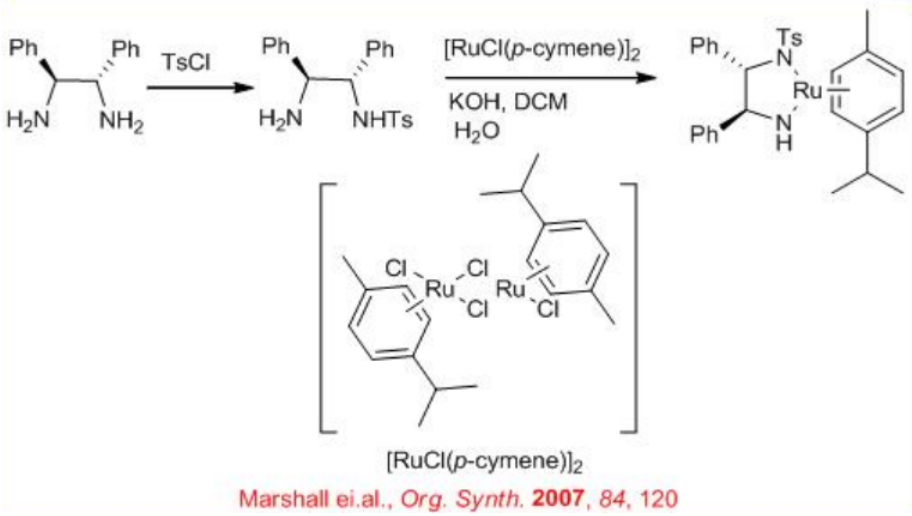


Scheme 6.2.13

The chiral Ru-diphosphine/diamine derived from chiral BINAP, DPEN (diphenylethylene diamine) and indanol effect enantioselective hydrogenation of certain amino or amido ketones *via* a non-chelate mechanism without interaction between Ru and nitrogen or oxygen (Scheme 6.2.14). The diamine catalyst can be synthesized from chiral 1,2- diphenylethylene diamine (Scheme 6.2.15).

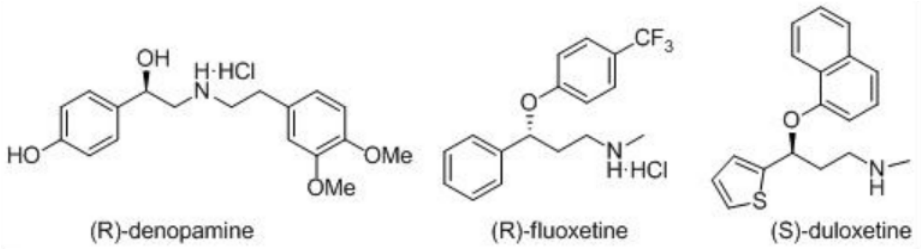


Scheme 6.2.14



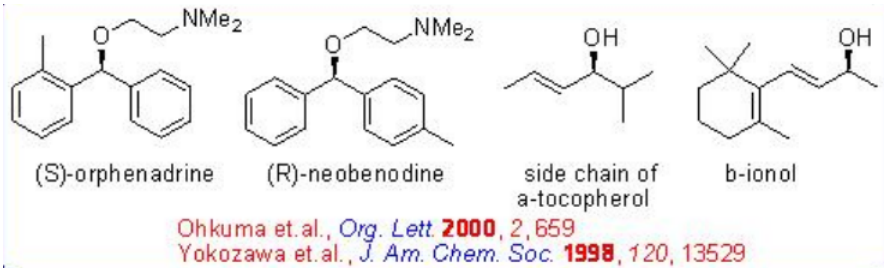
Scheme 6.2.15

These catalysts have been employed for the asymmetric synthesis of various important pharmaceuticals, including (*R*)-denopamine, a β 1-receptor agonist, the *anti* -depressant (*R*)-fluoxetine, the *anti* -psychotic BMS 181100 and (*S*)-duloxetine (Scheme 6.2.16).



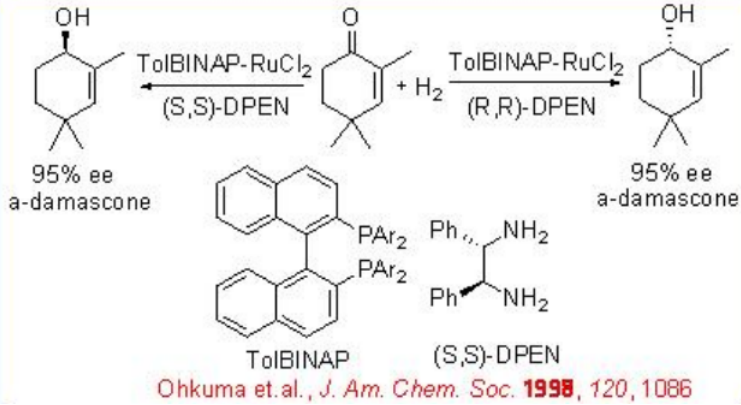
Scheme 6.2.16

Unsymmetric benzophenones could also be hydrogenated with high *S/C* ratio of up to 20000 without over-reduction (Scheme 6.2.17). Enantioselective hydrogenation of certain *ortho* -substituted benzophenones leads to the unsymmetrically substituted benzhydrols, allowing convenient synthesis of the *anti*- cholinergic and *anti* -histaminic (*S*)-orphenadrine and antihistaminic (*R*)-neobenodine.



Scheme 6.2.17: Asymmetric Synthesis of Some of the Important Pharmaceuticals

The asymmetric hydrogenation of simple ketone is generally achieved by the combined use of an (*S*)-BINAP and an (*S*)-1,2-diphenylethylenediamine. However, the reaction of 2,4,4-trimethyl-2-cyclohexenone can be effectively done with racemic $RuCl_2$ [-tol-BINAP]- and chiral DPEN with up to >95% ee (Scheme 6.2.18).

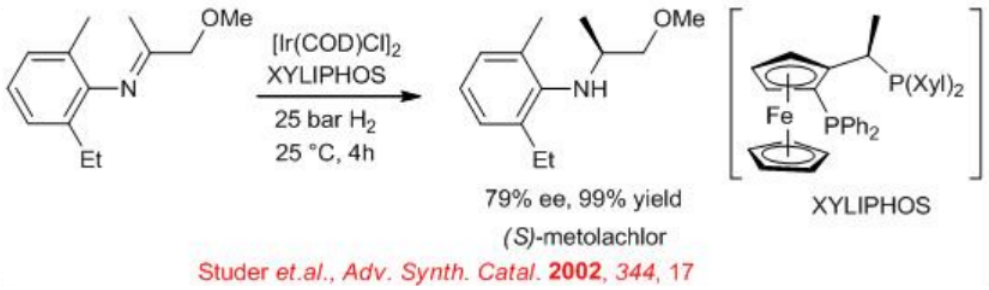


Scheme 6.2.18

6.3: Reactions of Imines (C=N)

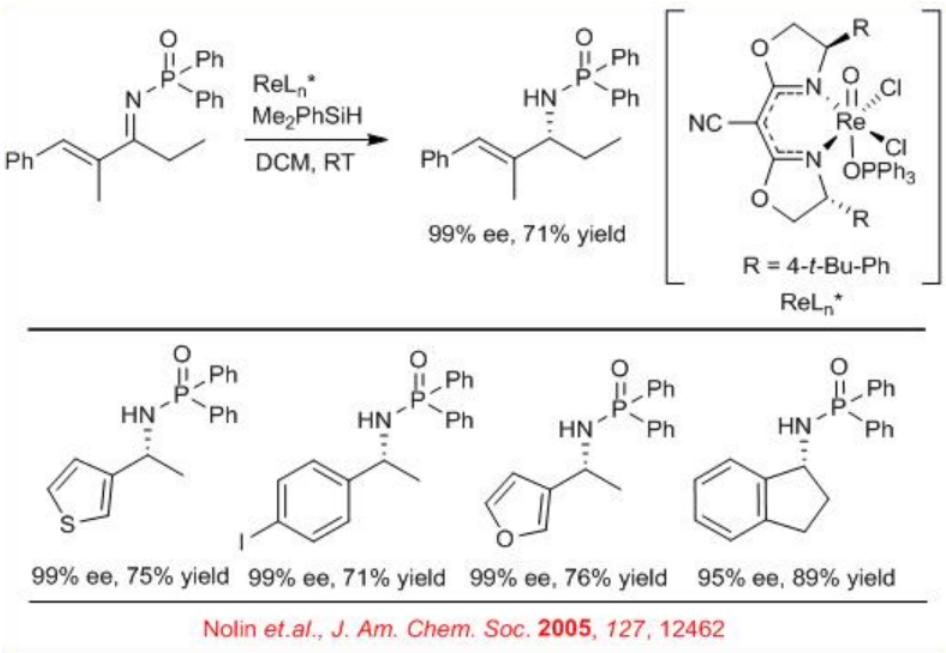
An important field of investigation for new industrial catalysts is the development of improved catalysts for the reduction of imines to obtain the corresponding chiral amines. These chiral amines are used as key components in many active pharmaceutical intermediates.

Synthesis of (*S*)-metolachlor (widely used as an herbicide) has been achieved by enantioselective hydrogenation of imine in presence of a catalyst generated *in situ* from $[Ir(COD)Cl]_2$ and (*R*, *S*)-PPF–P(3,5-Xyl)$_2$ (xyliphos) (Scheme 6.3.1). This catalyst shows a high catalytic activity with TOF=396 h^{-1} and enantioselectivity of 79% ee.



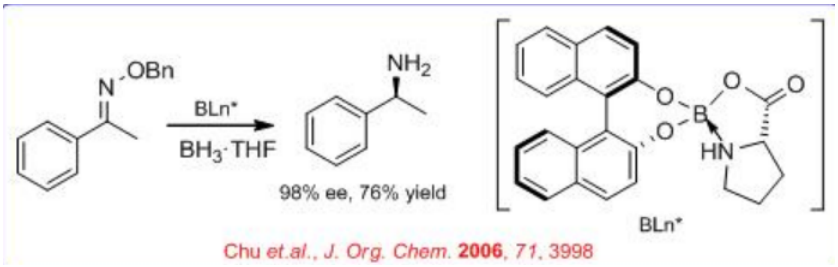
Scheme 6.3.1: Preparation of (*S*)- *Metolachlor* by Enantioselective Hydrogenation

Subsequently, an air- and moisture-tolerant enantioselective reduction of *N* -phosphinyl imines has been performed with (CNbox)Re(O)Cl_2 ($OPPh_3$) (Scheme 6.3.2). A wide range of aromatic imines, including cyclic, acyclic and heteroaromatic, *α* -iminoesters, and *α*,*β* -unsaturated imines undergo reaction with good to excellent enantioselectivity.



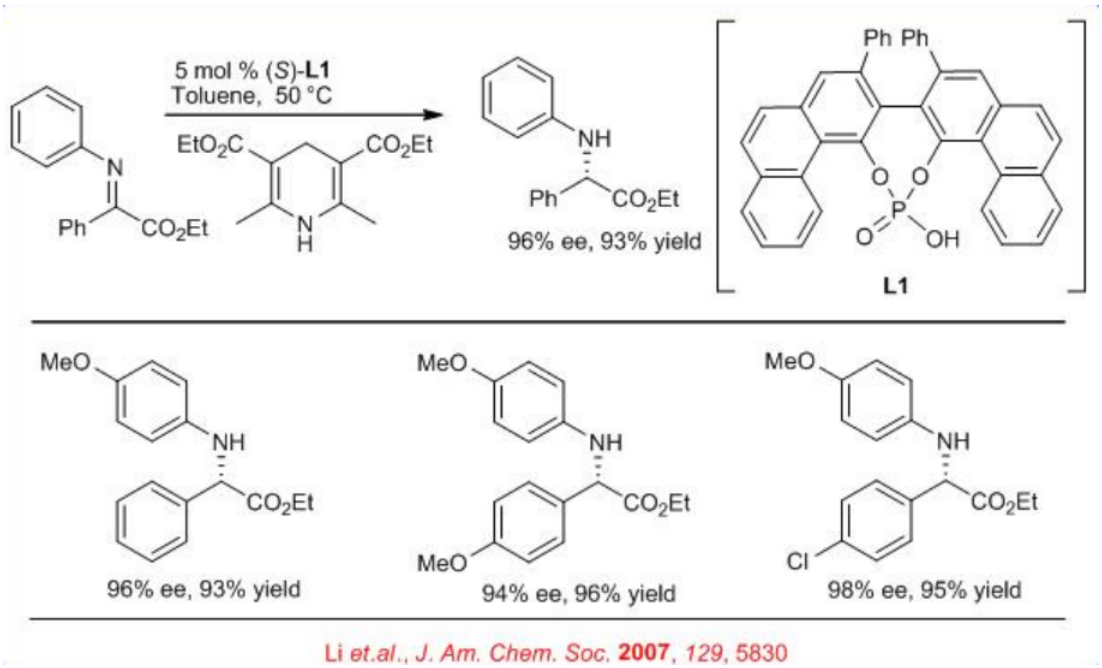
Scheme 6.3.2: Enantioselective Reduction of Imines Catalyzed by Rhenium(V)-oxo Complex

The use of modified CBS-type catalysts has been extended to the reduction of oximes into chiral amines (Scheme 6.3.3). The BINOL-proline-borate complex reduces acetophenone oxime into chiral 1-phenylethylamine with 98% ee, but the ee drops when the borate complex is used catalytically.



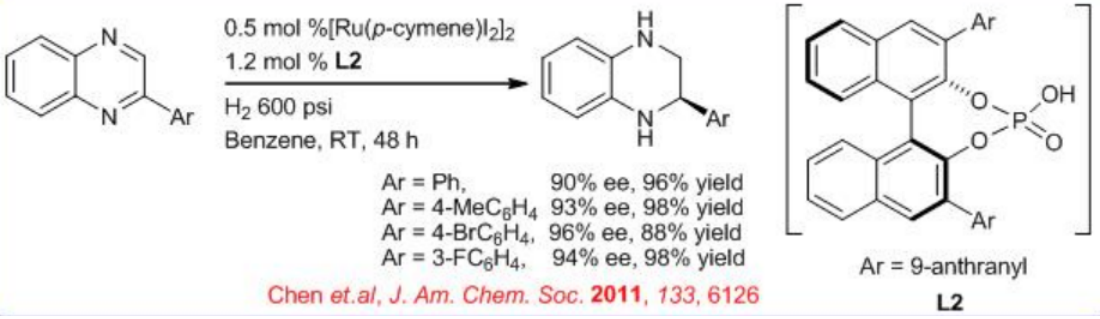
Scheme 6.3.3: Modified CBS catalyst for Enantioselective Reduction of Imines

A new method for the reduction of α -imino esters using Hantzsch ester is reported with chiral phosphoric acid (Scheme 4). A series of α -imino esters could be reduced to the corresponding α-amino esters in excellent yield with up to 94% ee.



Scheme 6.3.4: Chiral Biaryl Phosphoric Acid-Catalyzed Reduction of α-Imino Esters

An efficient metal/brønsted acid relay catalysis has been shown for the highly enantioselective hydrogenation of quinoxalines through convergent disproportionation of dihydroquinoxalines with up to 94% (Scheme 6.3.5).



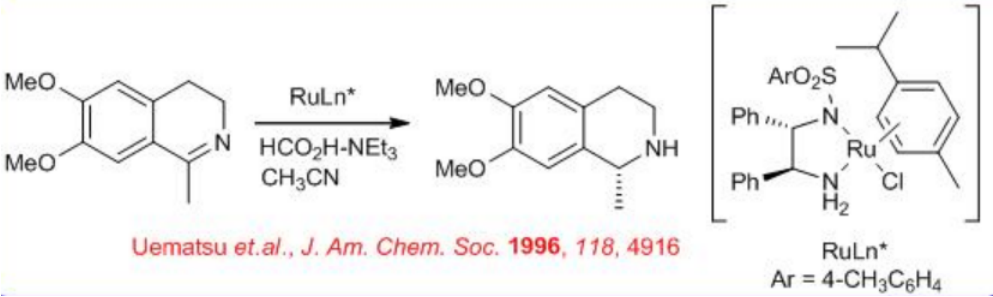
Scheme 6.3.5: Metal/Brønsted Acid Catalysis for Enantioselective Reduction of Quinoxalines

Employing hydrogen gas as the reductant makes this convergent disproportionation an ideal atom-economical process. A dramatic reversal of enantioselectivity is observed for the hydrogenation relative to the transfer hydrogenation of quinoxalines promoted by chiral phosphoric acids L2**.**

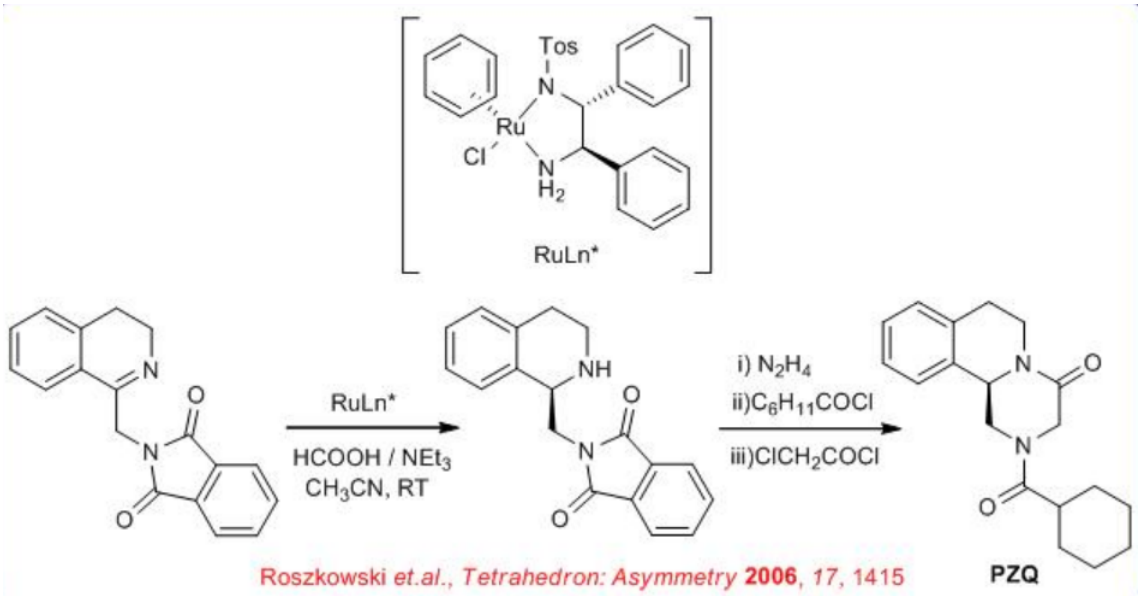
Asymmetric Transfer Hydrogenation Reactions (ATHRs)

Another field where asymmetric transfer hydrogenation (ATH) catalysts have made an industrial impact is in the area of chiral amine synthesis by stereo controlled reduction of imines. The reduction of cyclic imines to yield chiral amines is proved to be a

highly versatile and successful strategy for the synthesis of chiral tetrahydroisoquinolines and related compounds (Scheme 6.3.6).



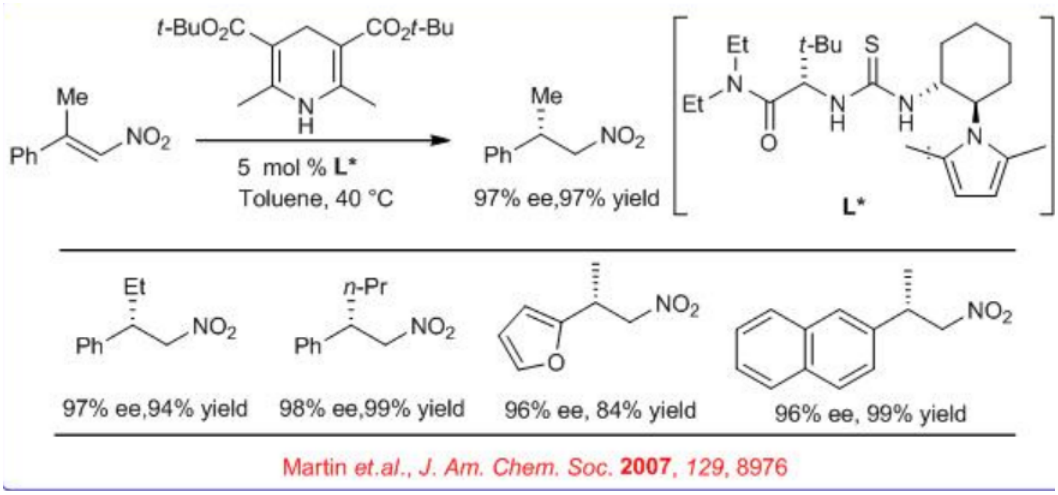
Scheme 6.3.6: Catalytic enantioselective conjugate reduction of imines



Scheme 6.3.7: Enantioselective Synthesis of *(R)* - Praziquantel (PZQ)

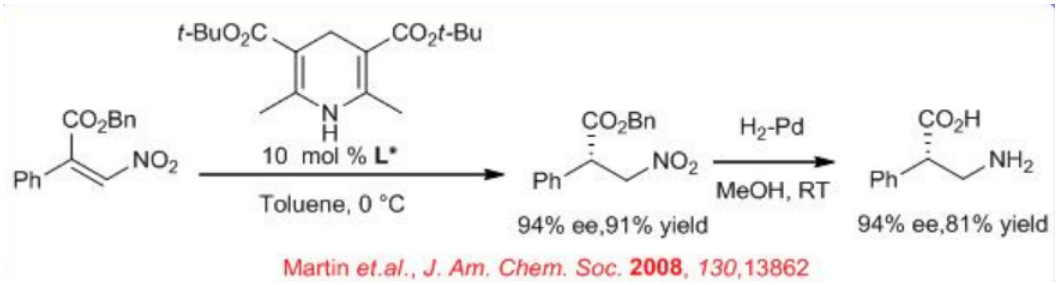
The enantioselective preparation of *Praziquantel* (PZQ) a pharmaceutical for the treatment of schistosomiasis and soil-transmitted helminthiasis has been accomplished. The synthesis is completed from staring chiral reduction of imine which could be synthesized from readily available phenyl ethyl amine, phthalic anhydride and glycine (Scheme 6.3.7).

In parallel to metal catalysis, organo catalyst like chiral thiourea and chiral imidazoilidines have been used for the asymmetric hydrogen transfer (ATS) reaction in presence of Hantzsch ester. For example, enantioselective Hantzsch ester mediated conjugate transfer hydrogenation of α,β -disubstituted nitro-alkenes has been shown using chiral thiourea (Scheme 6.3.8). A broad range of substrates including β,β -unsaturated aldehydes and ketones, ketimines and aldimines, α -keto esters, and now nitro alkenes are successfully employed for hydrogenation.



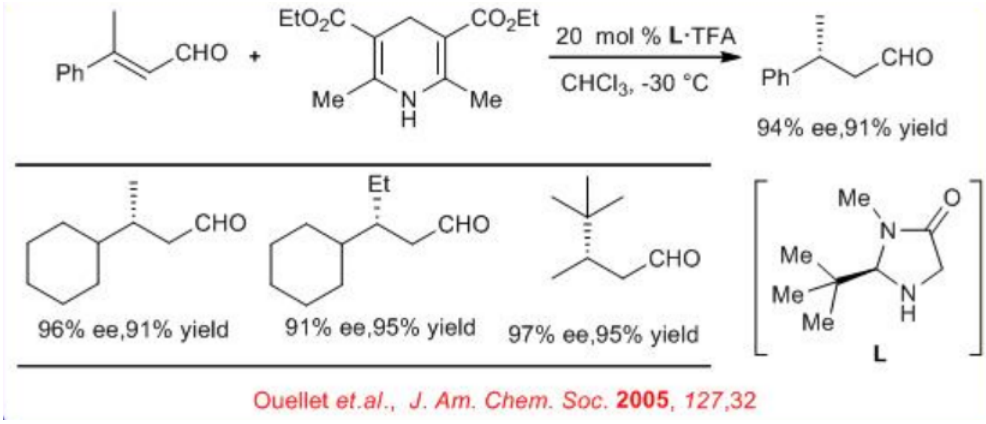
Scheme 6.3.8: Transfer Hydrogenation of Nitro Styrene by Chiral Thiourea Catalyst

The above catalyst is also used for enantioselective Hantzsch ester mediated conjugate reduction of β -nitroacrylates (Scheme 6.3.9). After subsequent reduction with Pd-H_2-MeOH, chiral β -amino acids can be synthesized with high yield and ee. This provides a key step in a new route to optically active β^2-amino acids.



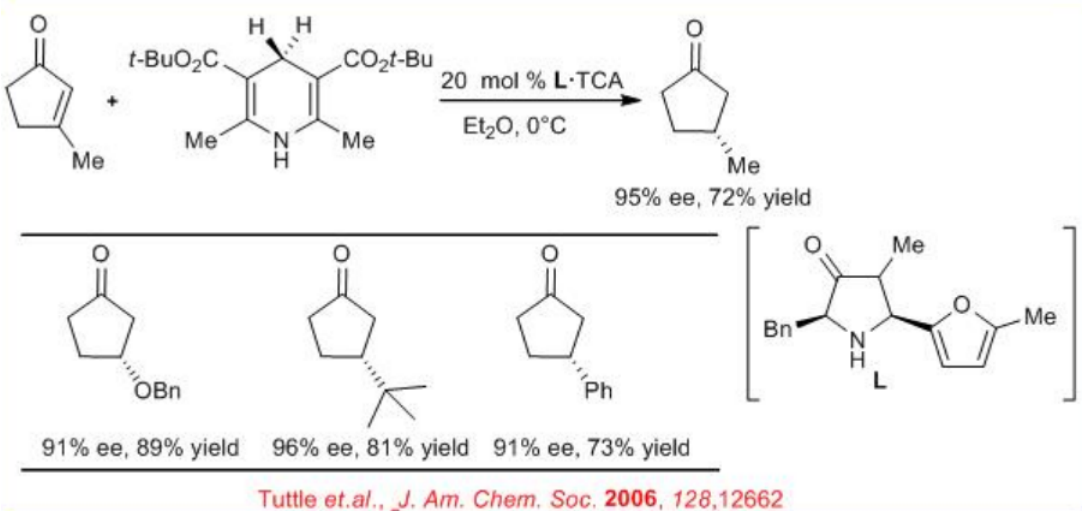
Scheme 6.3.9: Transfer Hydrogenation of Nitro Styrene by Chiral Thiourea Catalyst

In parallel to the chiral thiourea catalyst, the use of iminium catalysis for the enantioselective reduction of β, β -substituted α, β -unsaturated aldehydes to generate β -stereogenic aldehydes has been shown (Scheme 6.3.10). The capacity of the catalyst to accelerate (*E)-(Z)* isomerization prior to selective (*E)* -alkene reduction allows the implementation of geometrically impure enals in this operationally simple protocol.



Scheme 6.3.10: Transfer Hydrogenation of α , β -Unsaturated Aldehydes by Chiral Imidazolidinone

The above catalytic system is used for transfer hydrogenation of cyclic enones (Scheme 6.3.11). Cycloalkenones with 5-, 6-, and 7-membered ring systems undergo reaction with high stereoselectivity.

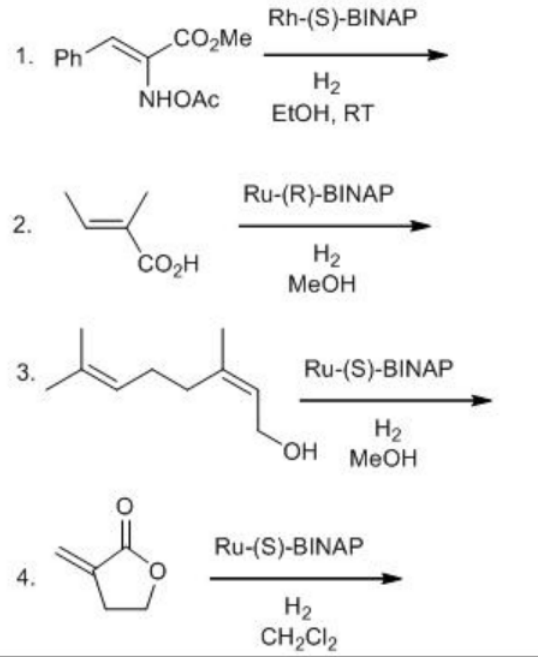


Scheme 6.3.11: Transfer Hydrogenation of Cyclic Enones by Imidazolidinone

6.4: Problems and Reference

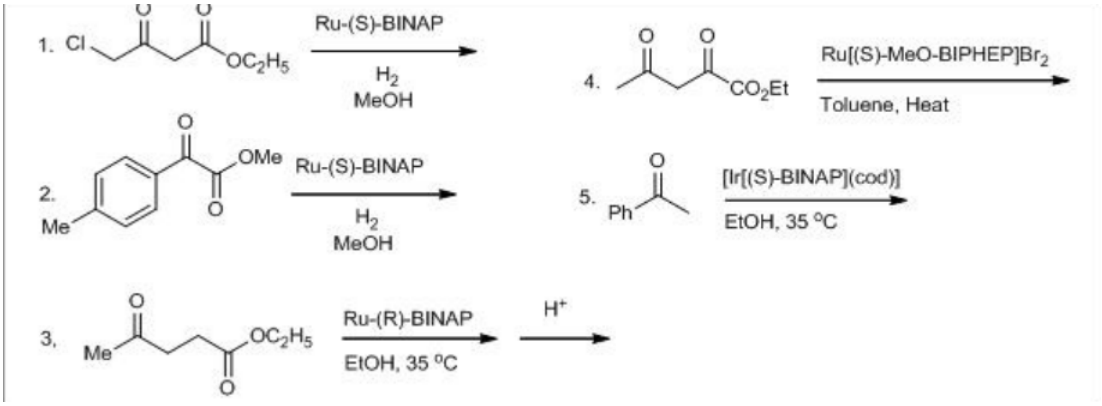
Problems

Predict the major product of the following reactions.

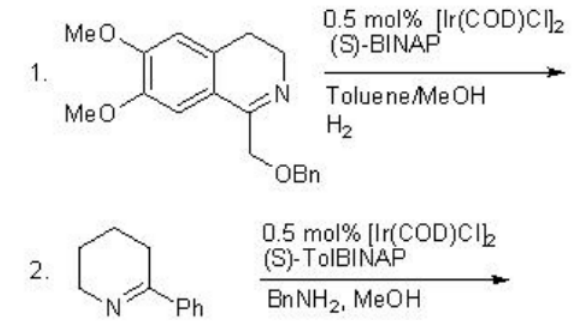


List the phosphine ligands for the asymmetric hydrogenation of carbon-carbon double bonds.

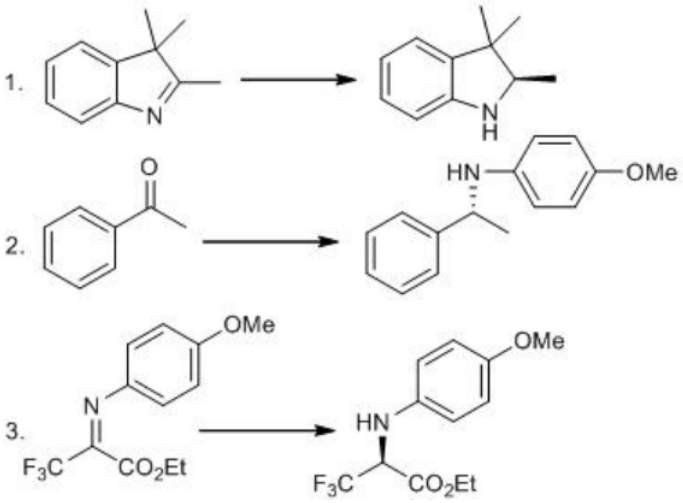
Complete the following reactions.



Complete the following reactions.



How will you carry out the following hydrogenation reactions?



Reference/Text Book

• I. Ojima, *Catalytic Asymmetric Synthesis* , 3 rd ed., Wiley, New Jersey, 2010.

• M. B. Smith, *Organic Synthesis* , 2 nd edition, McGraw Hill, New Delhi, 200

CHAPTER OVERVIEW

7: Reactions in Nonconventional Conditions

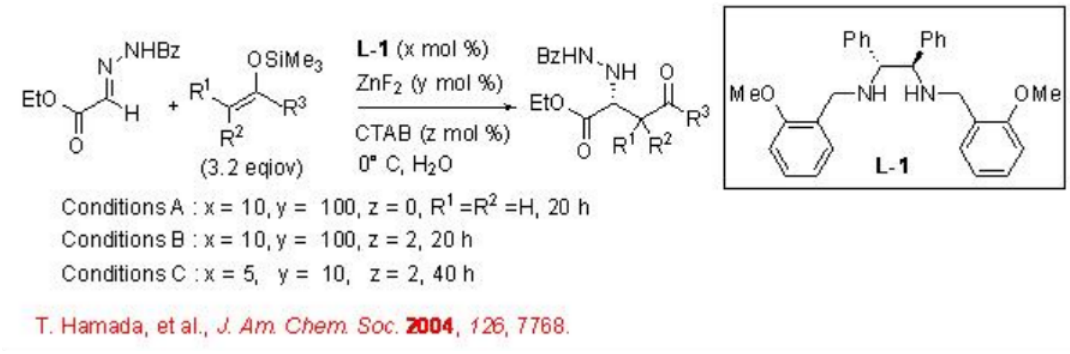
7.1: Reactions in Water

Many of the organic solvents are volatile, flammable, sometimes explosive and have damaging effect to human health or on the environment. Thus, effort has been made to use nonconventional solvents which are not only attractive from economical aspects, they can provide advantages of recovery and recyclability of the catalysts. The section covers the use of water, fluorous solvents, supercritical fluids and ionic liquids as nonconventional solvents.

The use of water as a reaction medium for organic synthesis has attracted much interest in recent years. Because water is the most abundant liquid on the planet, cheap, readily available, non-toxic and non-flammable. This section covers some of the recent developments in asymmetric catalysis that have been performed in water as reaction medium.

Mannich Reaction

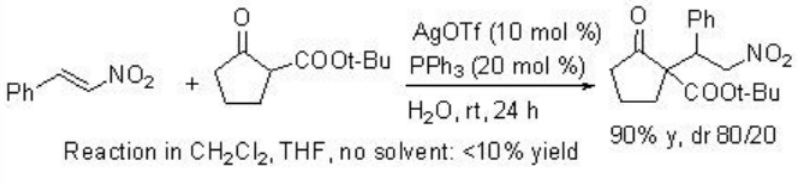
Mannich reaction affords useful route for the synthesis of β -amino ketones and esters that serve as building blocks for the construction of nitrogen containing compounds. The asymmetric version of the reaction has been shown from α -hydrazono ester and silicon enoate using chiral ZnF_2 - **L-1** complex in aqueous medium (Scheme 7.1.1). The reaction proceeds without any organic solvents or additives and the presence of cetyltrimethyl ammonium bromide (CTAB) is necessary to accelerate the reaction.



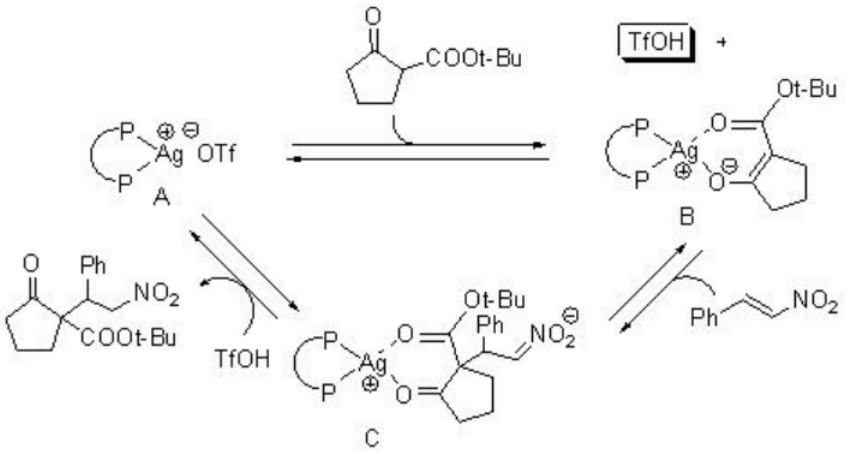
Scheme 7.1.1

Michel Reaction

Michel addition of β -ketoesters to nitroalkanes using AgOTf-PPh_3 proceeds efficiently in water but not in organic solvents (Scheme 7.1.2). Regarding the mechanism, the reaction in water becomes heterogeneous, and the metal enolate stays in organic phase, while TfOH is excluded into water phase because of the difference between their hydrophobicity (Scheme 7.1.3). Thus, the metal enolate B does not have the contact with TfOH, and the reverse reaction from B to A is suppressed. In contrast, in normal organic solvent, the reaction mixture becomes homogeneous and the reverse reaction from B to A is fast.

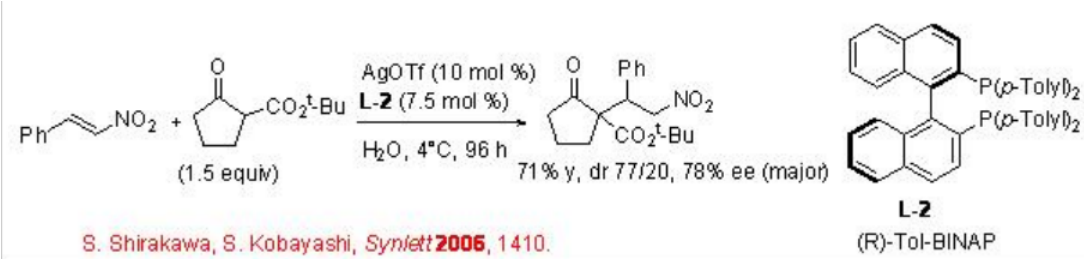


Scheme 7.1.2



Scheme 7.1.3

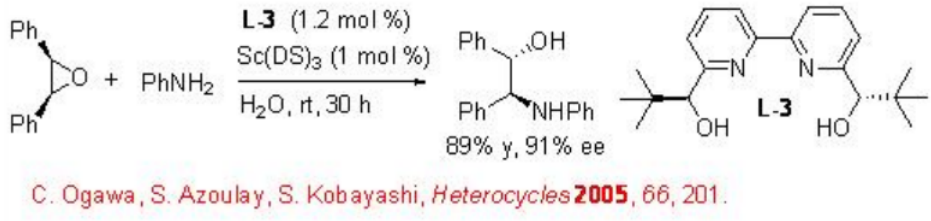
This reaction has been applied for the asymmetric version employing **L-2** as chiral source to afford the target products with up to 78% ee (Scheme 7.1.4).



Scheme 7.1.4

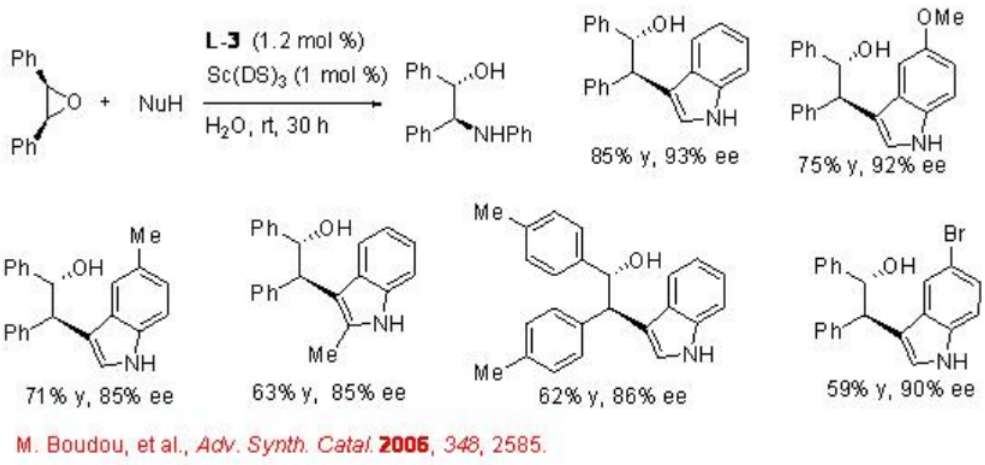
Desymmetrization of Epoxides

This reaction condition has been subsequently used for the asymmetric desymmetrization of epoxides with nitrogen nucleophiles using **L-3** as chiral source (Scheme 7.1.5). The reaction proceeds with high enantioselectivity and no diol formation has been observed.



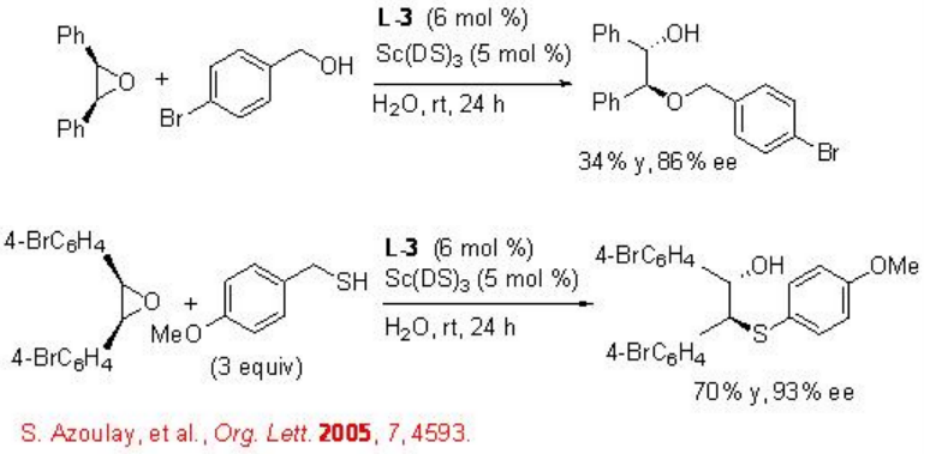
Scheme 7.1.5

The asymmetric desymmetrization of the epoxides is also successful with indoles, alcohols and thiols with high enantioselectivities (Schemes 7.1.6 and 7.1.7).



M. Boudou, et al., *Adv. Synth. Catal.* **2006**, *348*, 2585.

Scheme 7.1.6

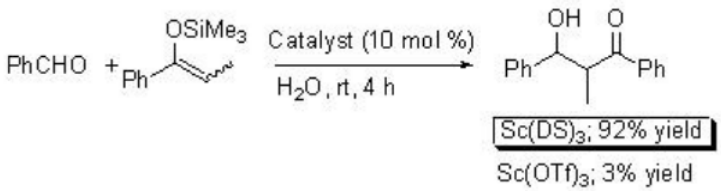


S. Azoulay, et al., *Org. Lett.* **2005**, *7*, 4593.

Scheme 7.1.7

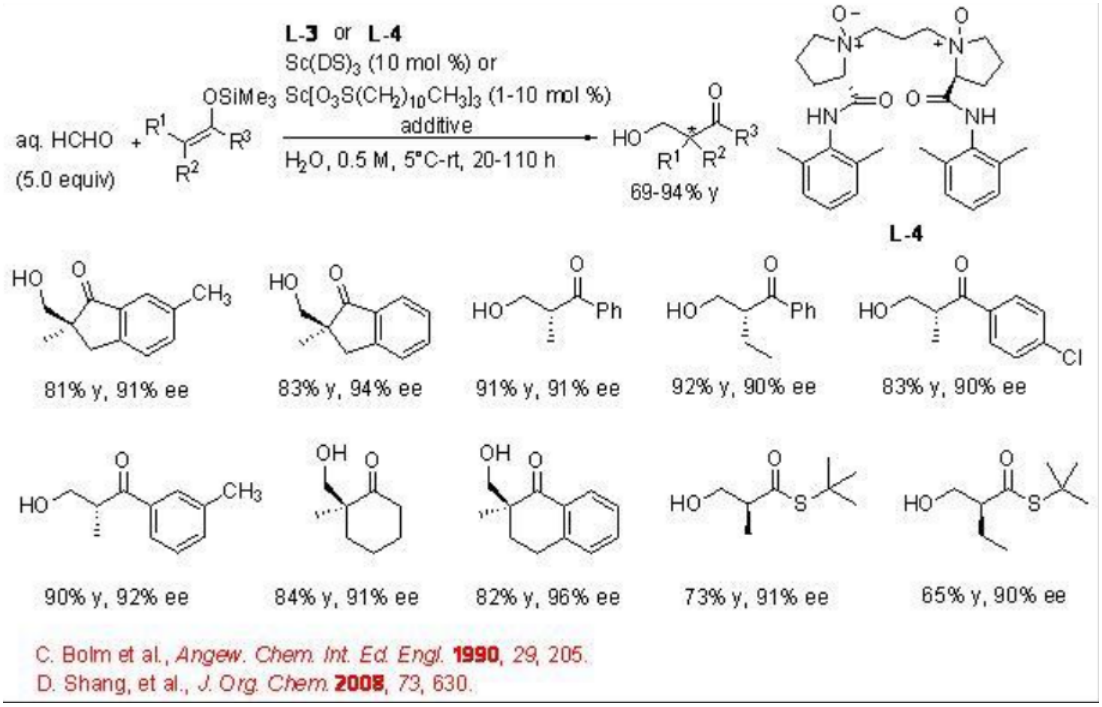
Aldol Reaction

The reaction of silyl enol ethers with aldehydes has been demonstrated using scandium trisdodecylsulfate ($Sc(DS)_3$) as a Lewis acid as well as surfactant in water (Scheme 7.1.8). The reaction is sluggish when $Sc(OTf)_3$ is used as a catalyst. In this process, the formation of stable emulsions takes place.



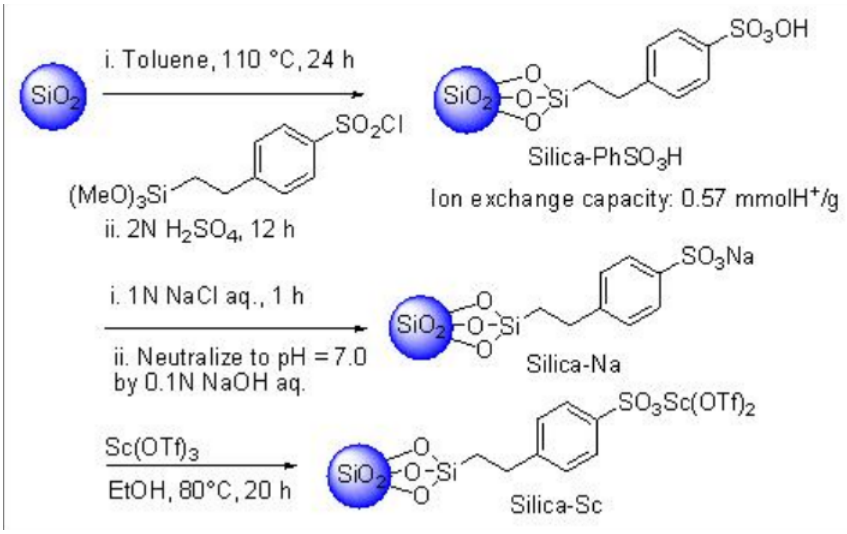
Scheme 7.1.8

The reaction condition has also been further demonstrated for the hydroxymethylation using aq HCHO with excellent enantioselectivity (Scheme 7.1.9).

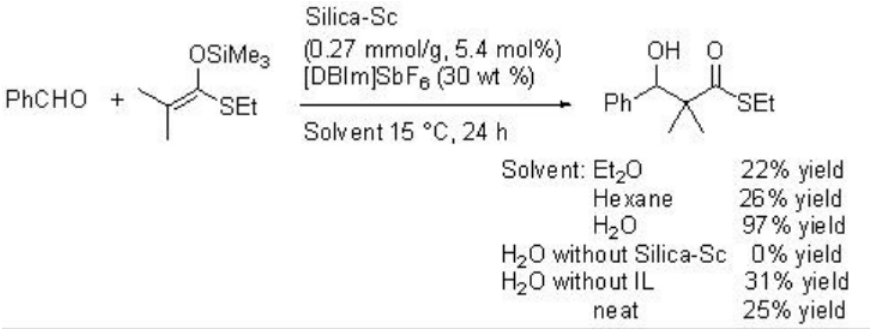


Scheme 7.1.9

Silica gel-supported scandium (Silica-Sc) with ionic liquid, [DBIm]SBF_6, is a heterogeneous catalytic system works efficiently in Mukaiyama aldol reaction in water (Schemes 7.1.10 and 7.1.11). The reaction proceeds efficiently in water medium compared to that in organic solvents, without solvent or in the absence of ionic liquid (IL).

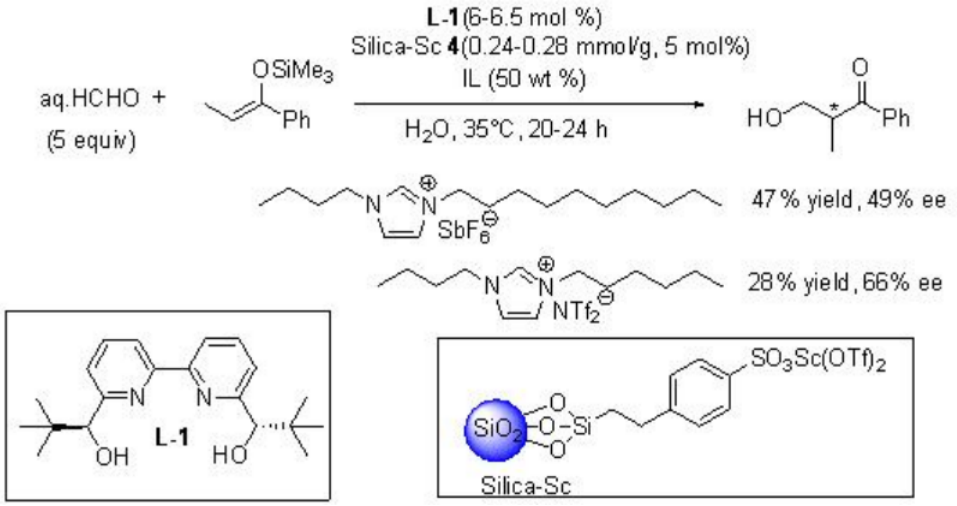


Scheme 7.1.10



Scheme 7.1.11

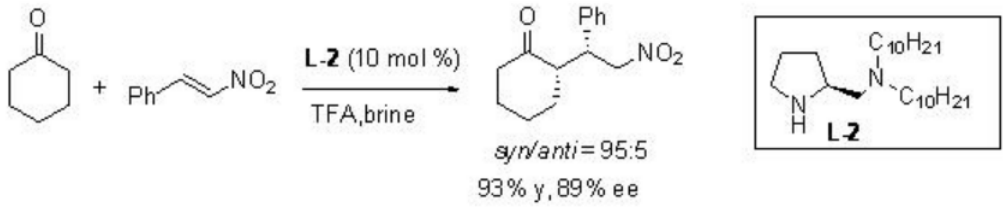
Asymmetric version of the reaction has been subsequently developed employing **L-1** as chiral source with moderate enantioselectivity (Scheme 7.1.12).



Scheme 7.1.12

Michael Reaction

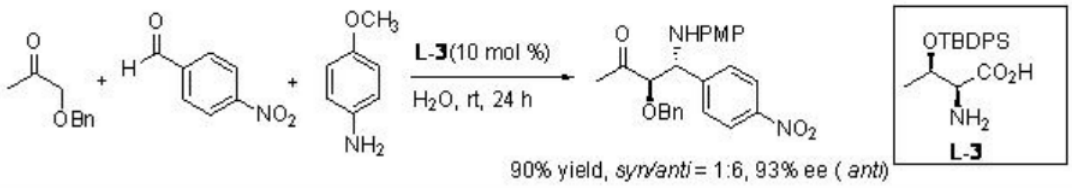
Asymmetric Michael reaction of ketones with β -nitrostyrene has been studied using proline derivative **L-2** in brine with good enantioselectivity (Scheme 7.1.13).



Scheme 7.1.13

Mannich Reaction

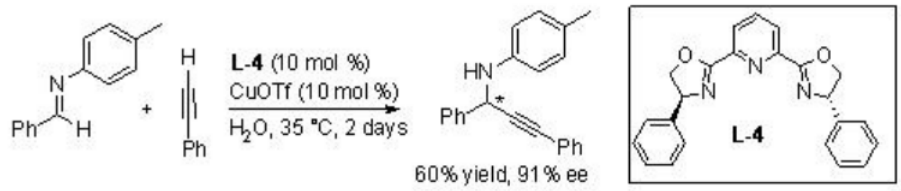
Asymmetirc Mannich reaction of aryl aldehydes, aryl amines and aliphatic ketones occurs in water in the presence of threonine derivative **L-3** with excellent diastereoselectivity (Scheme 7.1.14).

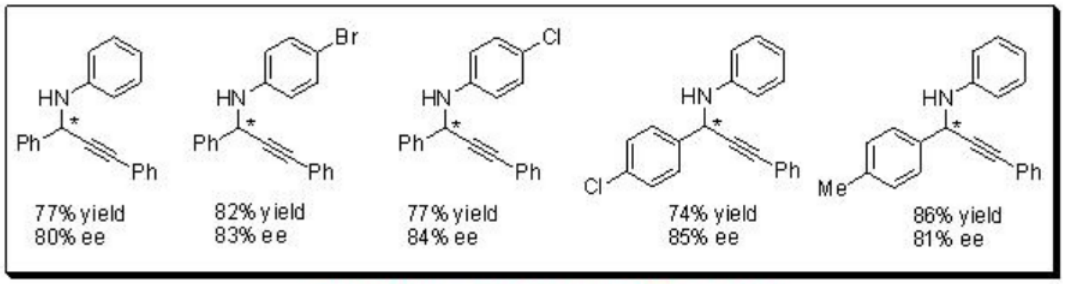


Scheme 7.1.14

Addition Reactions of Alkynes

Propargylamines are important synthetic intermediates for the synthesis of nitrogen containing compounds in organic synthesis. The direct alkyne-imine addition can be accomplished employing chiral CuOTf- **L-4** complex (Scheme 7.1.15). The method is simple and affords a diverse range of propargylic amines with high enantioselectivity.



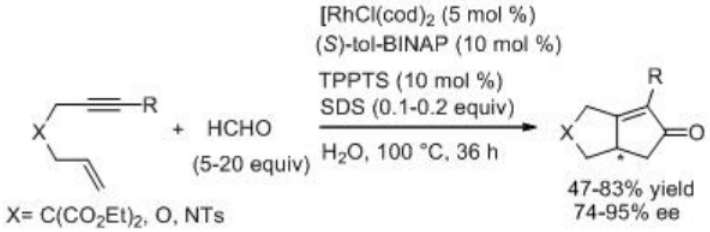


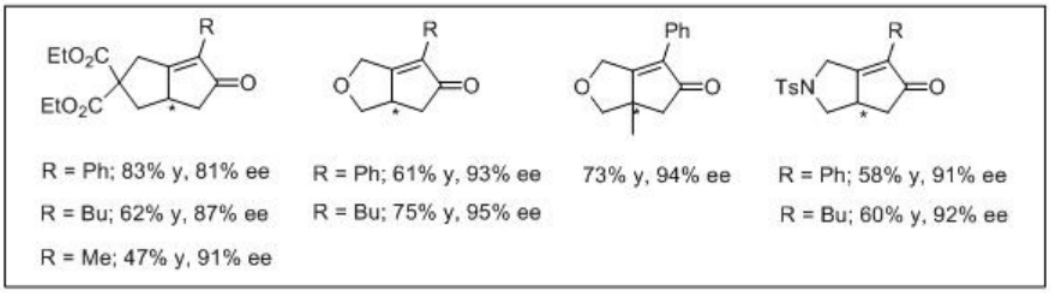
C. Wei, et al., *J. Am. Chem. Soc.* **2002**, *124*, 5638.

Scheme 7.1.15

Pauson-Khand Reaction

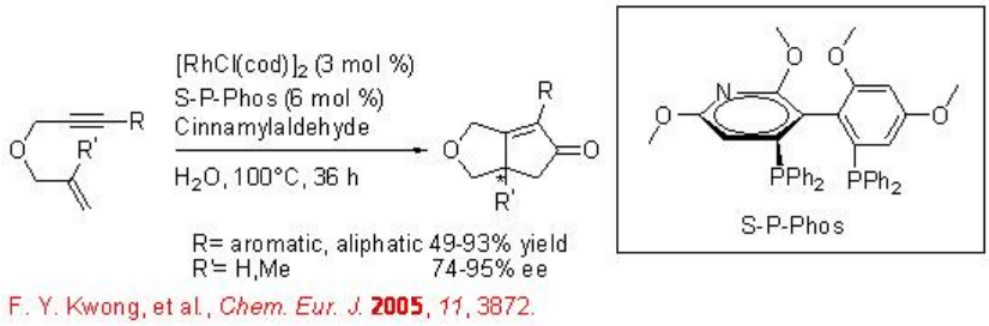
Asymmetric Pauson-Khand reaction can be performed using chiral Rh complexes in water. The complex derived from $[RhCl(cod)]_2$ and (S)-tol-BINAP has been found to be effective for the Pauson-Khand reaction employing HCHO as CO source with good enantioselectivity (Scheme 7.1.16). Chiral rhodium complex derived from $[RhCl(cod)]_2$ and S-P-Phos has also been used for the Pauson-Khand reaction with similar enantioselectivity (Scheme 7.1.17).





K. Fuji et al., *Tetrahedron Lett.* **2004**, *45*, 9163.

Scheme 7.1.16



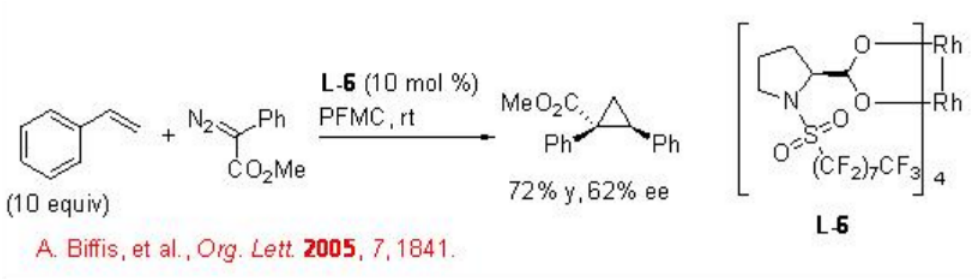
F. Y. Kwong, et al., *Chem. Eur. J.* **2005**, *11*, 3872.

7.2: Reactions in Fluorous Solvents

Fluorous solvents having suitable boiling and melting points can be used as solvent. Importantly, the fluorous solvents are different from the corresponding hydrocarbons and form two layers with conventional organic solvents. Thus, some catalysts can be immobilized in fluorous solvents in biphase system and can be recovered and recycled. In addition, in some combination, the fluorous and organic solvents on heating are miscible at elevated temperature leading to a homogeneous mixture, which, after the reaction, on cooling to room temperature lead to the formation of a biphase system. The products stay in organic phase and the catalysts move to fluorous phase that can be recovered and recycled.

7.2.1 Cyclopropanation

Fluorous complex tetrakis-dirhodium(II)-(*S*)-N-(n-perfluorooctylsulfonyl) pollinate **L-6** exhibits good chemo- and diastereoselectivity in cyclopropanation of styrene (Scheme 7.2.1). The advantage of the protocol is that the catalyst can be separated from the reaction mixture and recycled.



Scheme 7.2.1

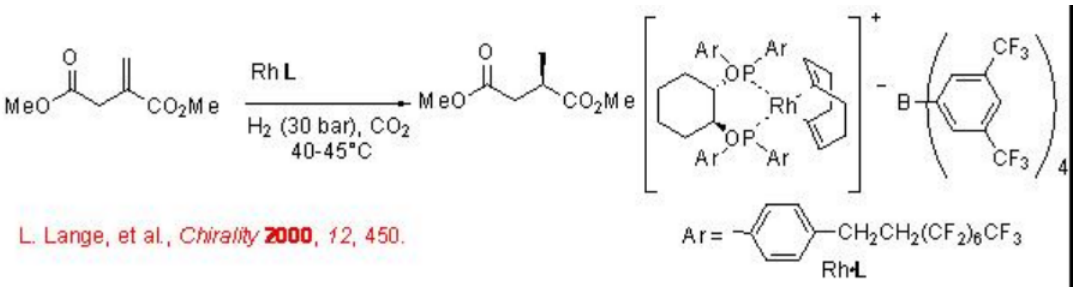
7.3: Reactions in Supercritical Fluids (SCFs)

SCF is a substance above its critical temperature (*Tc*) and pressure (*Pc*), but below the pressure condensation leads to a solid. At the critical point, high temperature and pressure, the substance can exit both as a vapor and a liquid in equilibrium. Thus, in a closed system, as both the temperature and pressure increase, the liquid becomes less dense due to thermal expansion, and the gas becomes dense as the pressure rises. Thus, the densities of both the phases converge until they become identical at the critical point. At this point, both the phases become indistinguishable and SCF is formed. In such SCF, a high reactivity and selectivity are sometime observed.

Supercritical carbon dioxide ($scCO_2$) offers the advantages that simple depressurization leads to removal of the residual $scCO_2$, and thus, no hazardous solvent is produced, providing effective route for the separation of the products. Thus the synthesis of organic compounds can be accomplished under solvent-free conditions that find wide applications in pharmaceutical, food and cosmetic industries.

7.3.1 Hydrogenation of Alkenes

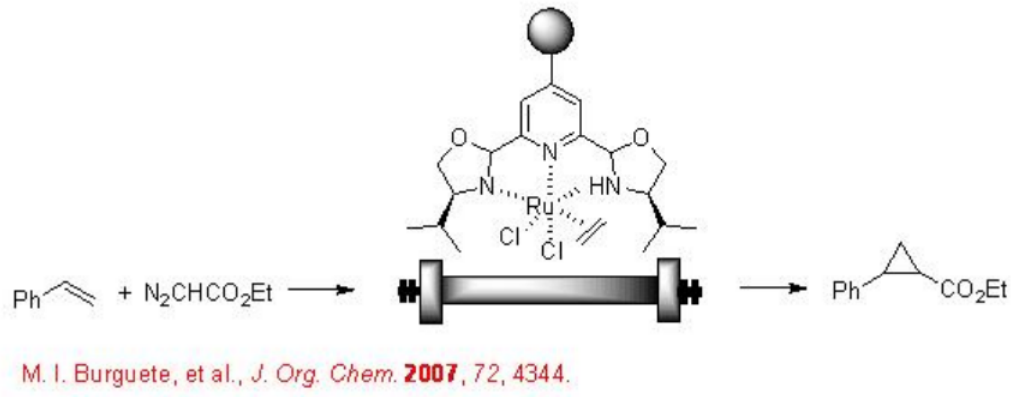
Asymmetric hydrogenation of alkenes can be carried out in $scCO_2$ using chiral Rh complex with good enantioselectivity (Scheme 7.3.1). The catalyst is dissolved in $scCO_2$ during the reaction making the process homogeneous.



Scheme 7.3.1

7.3.2 Cyclopropanation

The continuous flow of $scCO_2$ has been used for the asymmetric cyclopropanation using an immobilized chiral Ru complex (Scheme 7.3.2). The reaction has been reported 7.7 fold more efficient compared to that within dichloromethane solvent. In addition, easy product separation and environmental friendliness makes the process more attractive.



Scheme 7.3.2

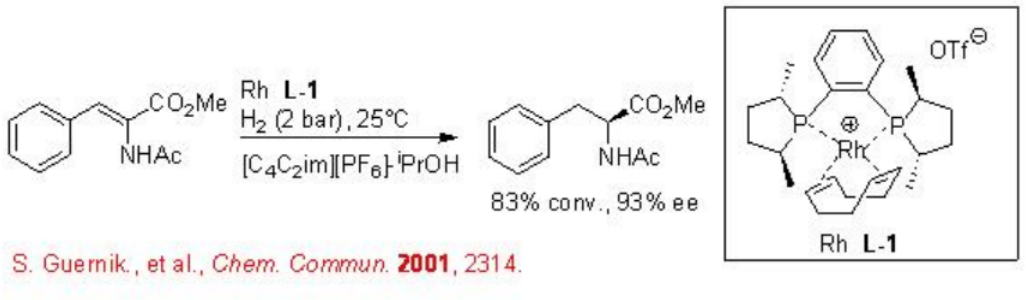
7.4: Reactions in Ionic Liquids (IL)

Ionic liquids are composed of ions having melting points below 100°C. They are nonvolatile and facilitate the recovery and recyclability of the catalysts. Scheme 7.4.1 presents some the typical ILs.

Scheme 7.4.1

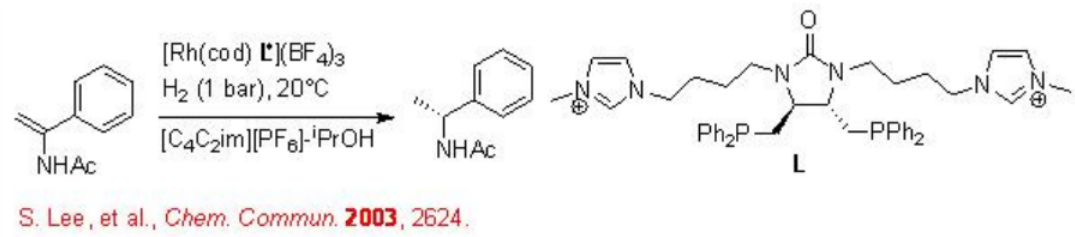
7.4.1 Hydrogenation of Alkenes

Asymmetric hydrogenation of alkenes using molecular hydrogen as hydrogen source is one of the useful chemical transformation. For example, the chiral rhodium complex Rh **L-1** catalyses the hydrogenation of α -acetoamide cinnamic acid and related enamides with high enantioselectivity in IL [C_4C_2 im][PF_6]. The catalyst can be reused and IL can suppress the catalyst aging in some cases.



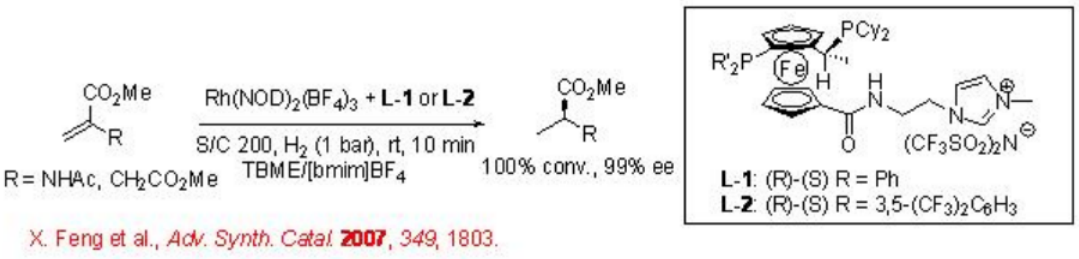
Scheme 7.4.2

The modified rhodium complex bearing chiral diphosphine with imidazolium moieties has been used as effective catalyst for hydrogen reaction in IL (Scheme 7.4.3). The catalyst can be recovered and recycled without loss of activity and selectivity.



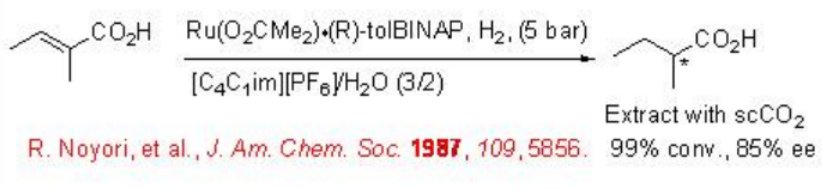
Scheme 7.4.3

The asymmetric hydrogenation of methyl acetamidiacrylate can be accomplished in biphasic cosolvent/IL combination in the presence of chiral rhodium complex bearing Josephose with imidazolium tag in *tert* -butyl methyl ether/[bmim]BF_4 (Scheme 7.4.4). The presence of imidazolium tag in the Josephose ligand enhances the affinity of the Rh complex for the IL and suppresses the catalyst leaching. The catalyst can be recycled without loss of activity.



Scheme 7.4.4

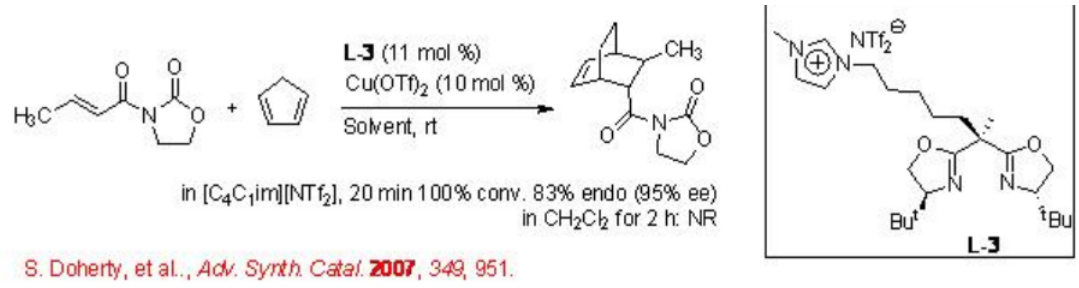
The hydrogenation of tiglic acid has been successible using Ru-BINAP in [bimm]PF_6 /H_2O with good enantioselectivity (Scheme 7.4.5). The enantioselectivity depends on the pressure of the reaction. At high pressure the presence of water increases the enantioselectivity, but low pressure show no effect.



Scheme 7.4.5

7.4.2 Diels-Alder Reaction

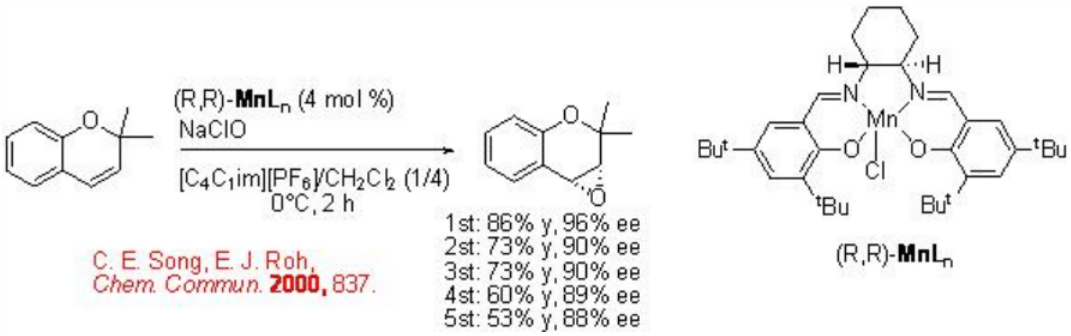
Copper(II) bisoxazoline complex having imidazolium tag can catalyze the Diels-Alder reaction of *N* -crotonyloxazolidinones with cyclopentadienes in [C_4C_1 im][NTf_2] (Scheme 7.4.6). The catalyst can be recovered and recycled without loss of activity and enantioselectivity at least 10 times. The presence of imidazolium tag to bisoxazoline considerably enhances the recovery and reuse of the catalyst from the IL.



Scheme 7.4.6

7.4.3 Epoxidation

The epoxidation of alkenes using chiral Mn(III) salen has been successful in a mixture of [C_4C_1 im][PF_6]/CH_2Cl_2 (Scheme 7.4.7). Since IL is solidified at 0°C, the reaction requires CH_2Cl_2 to form homogeneous solution. The catalyst and IL can be recycled with slight drop in the enantioselectivity.

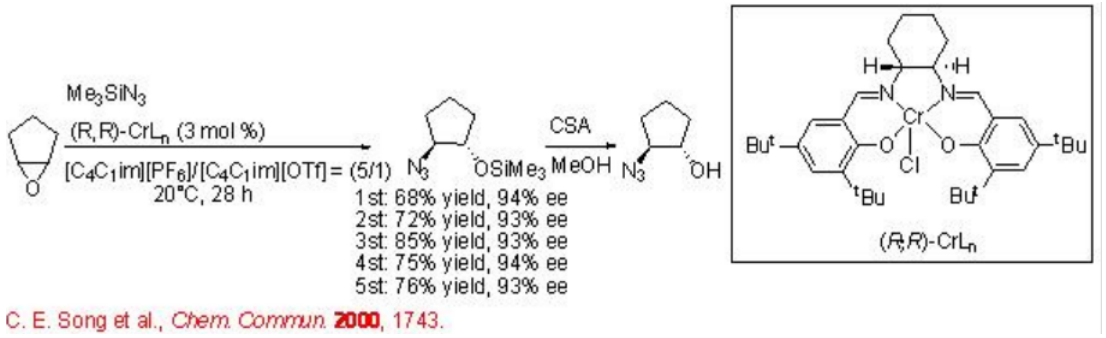


Scheme 7.4.7

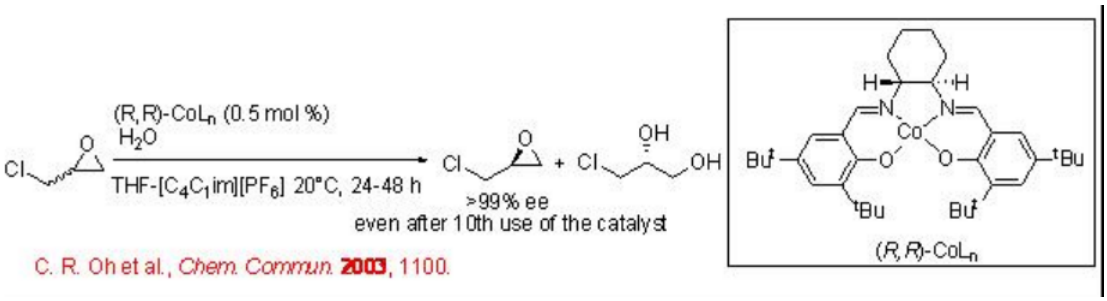
The ring opening of epoxides with $TMSN_3$ can be pursued using chiral Cr(III)salen complex in $[C_4C_1im][OTf]$ and $[C_4C_1\ im][PF_6]$ at ambient temperature (Scheme 7.4.8). The catalyst can be recycled up to five times without loss of activity.

7.4.4 Epoxide Opening

Hydrolytic resolution of racemic epoxides is effective using chiral Co(II)salen complex in THF and $[C_4C_1\ im][PF_6]$ with excellent enantioselectivity (Scheme 7.4.9). In this reaction, Co(II) is oxidized to Co(III) catalyzes the reaction. The catalyst can be recycled 10 times without loss of activity and selectivity.



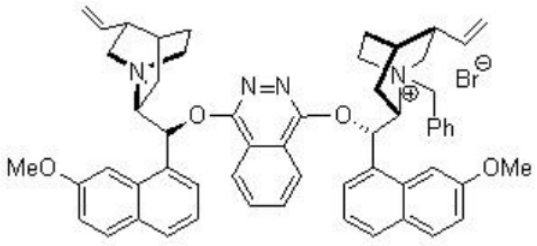
Scheme 7.4.8



Scheme 7.4.9

7.4.5 Dihydroxylation Reaction

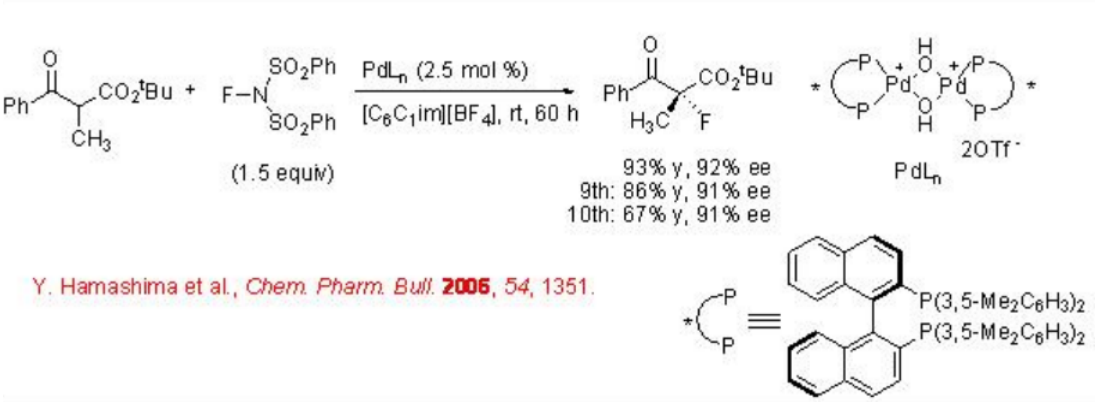
The asymmetric dihydroxylation of *trans* -stilbene has been done using OsO_4 (1.5 mol%) and **L-3** (2 mol%) in the presence of *N* -methylmorpholine *N* -oxide (NMO) (2.6 mol%) and $[C_4\ C_1\ im][PF_6]$ (2 mL) in acetone-water (v/v, 10/1) at °C. The catalyst can be recovered in IL and recycled up to three times without significant loss of activity and with a small amount of OsO_4 leaching from the IL to organic phase.



L-27

7.4.6 Fluorination

Fluorination of β -ketoester can be accomplished employing chiral Pd-BINAP in $[C_4\ C_1\ im][BF_4]$. (Scheme 7.4.10). The reaction proceeds smoothly with good enantioselectivity and the catalyst can be recycled up to 10 times without slight loss of activity.



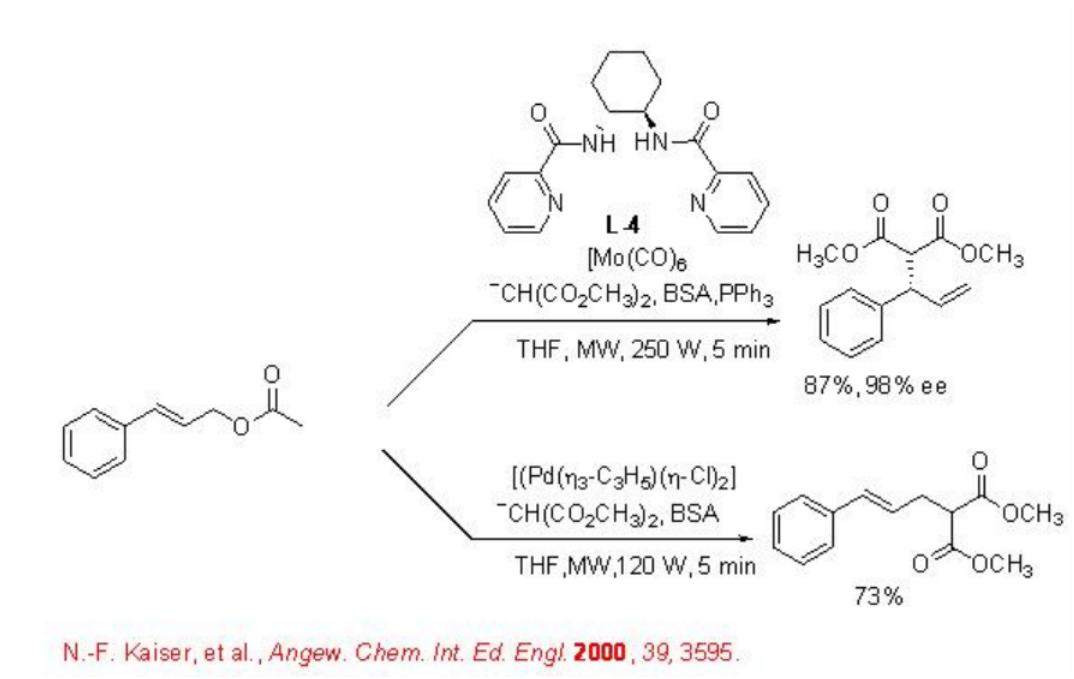
Y. Hamashima et al., *Chem. Pharm. Bull.* **2006**, *54*, 1351.

Scheme 7.4.10

7.5: Microwave-Assisted Reactions

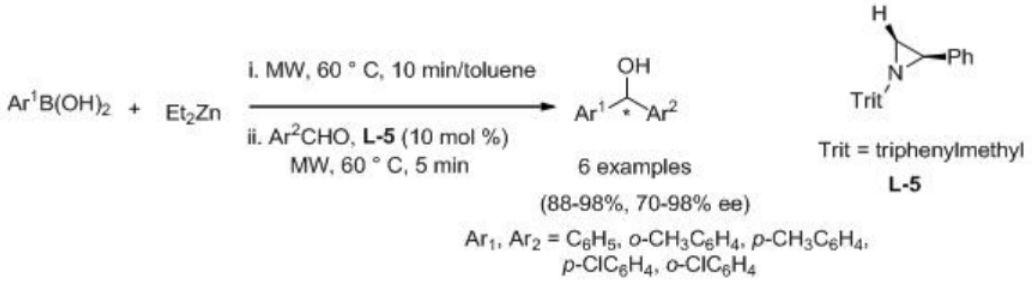
The use of microwave irradiation can reduce the reaction time compared to the conventional heating. Thus, sometimes, the side reactions can be minimized with increase of the product yield. Thus, microwave assisted organic synthesis has been widely accepted in academia as well as pharmaceutical industries.

Asymmetric allylic alkyaltions can be effective using chiral molybdenum complex under microwave irradiation in THF (Scheme 7.5.1). For example, carbonate reacts with dimethyl malonate with high enantioselectivity. Under these conditions, palladium based system gives different regioisomer.



Scheme 7.5.1

Microwave irradiation has also been found to be effective for the arylation of aromatic aldehydes with high enantioselectivity (Scheme 7.5.2). For example, the reaction of arylboronic acid with aryl aldehydes in the presence of diethylzinc and aziridine based ligand **L5** gives arylated product with up to 98% ee. The reaction time can be decreased from 1 h to 15 min by changing conventional heating to microwave irradiation.



Ar^1	Ar^2	Yield [%]	ee [%]
Ph	o-ClC_6H_4	88	98
Ph	o-MeC_6H_4	98	93
Ph	p-ClC_6H_4	93	93
Ph	p-MeC_6H_4	97	98
p-ClC_6H_4	Ph	90	89
p-MeC_6H_4	Ph	96	70

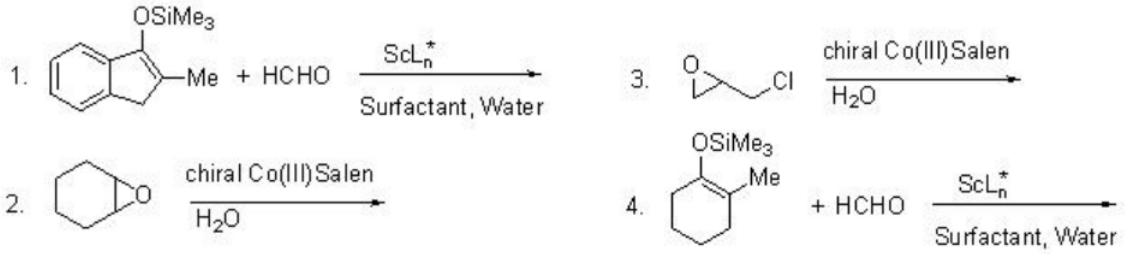
A. Braga, et al., *J. Org. Chem.* **2008**, *73*, 2879.

Scheme 7.5.2

7.6: Problems and Reference

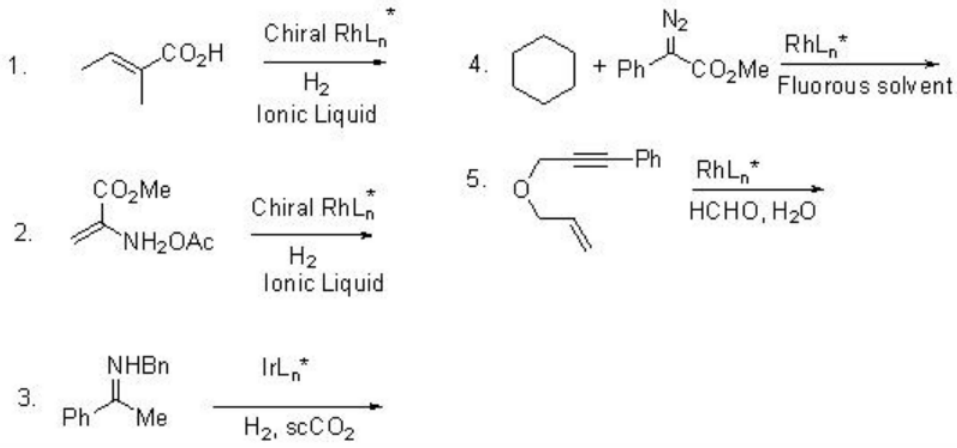
Problems:

Complete the following reactions.



Describe chiral Fe, Ti and Co-catalyzed asymmetric oxidations in water medium.

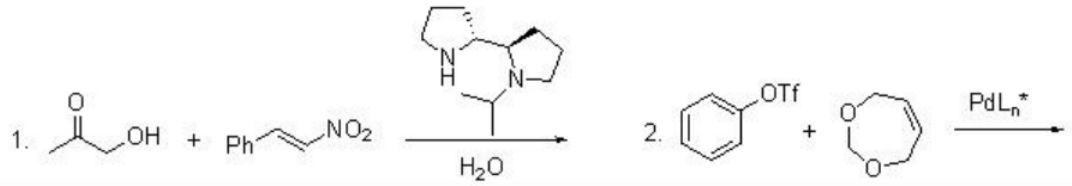
Write the major product for the following reactions.



Provide some examples for asymmetric Heck reaction in water.

Describe asymmetric organocatalysis in water.

Complete the following reactions.



Reference/Text Book

• I. Ojima, *Catalytic Asymmetric Synthesis* , 3 rd ed., Wiley, New Jersey, 2010.

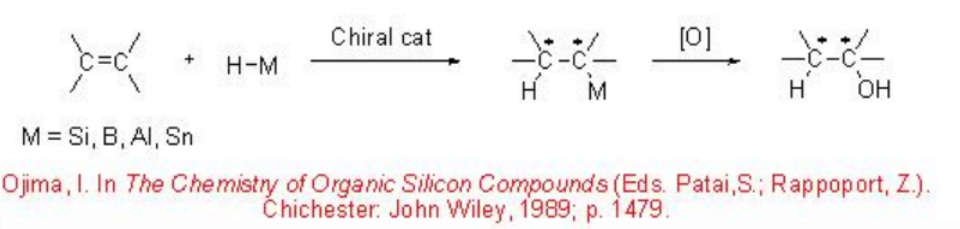
• M. B. Smith, *Organic Synthesis* , 2 nd edition, McGraw Hill, New Delhi, 2004.

CHAPTER OVERVIEW

8: Asymmetric Hydrosilylation and Related Reactions

8.1: Hydrosilylation of Alkenes

Asymmetric hydrosilylation and hydroboration of carbon-carbon double bonds followed by oxidative cleavage of the C-Si and C-B bonds give effective methods for the construction of optically active alcohols (Scheme 8.1.1).

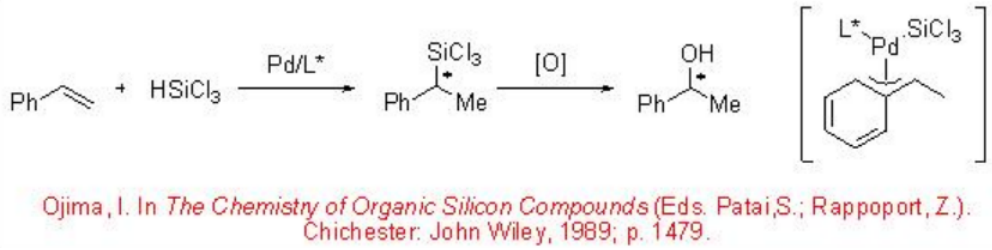


Scheme 8.1.1

Asymmetric hydrosilylation of carbon-carbon unsaturated substrates provides effective methods for the synthesis of optically active organosilanes, which are versatile intermediates in organic synthesis. Chiral alkyl and aryl silanes can be converted into optically active alcohols with retention configuration by oxidative cleavage of a carbon-silicon bond into carbon-oxygen bond, while the diastereoselective reaction of chiral allyl- and allenyl silanes with C=O bond can give homoallylic and homopropargylic alcohols.

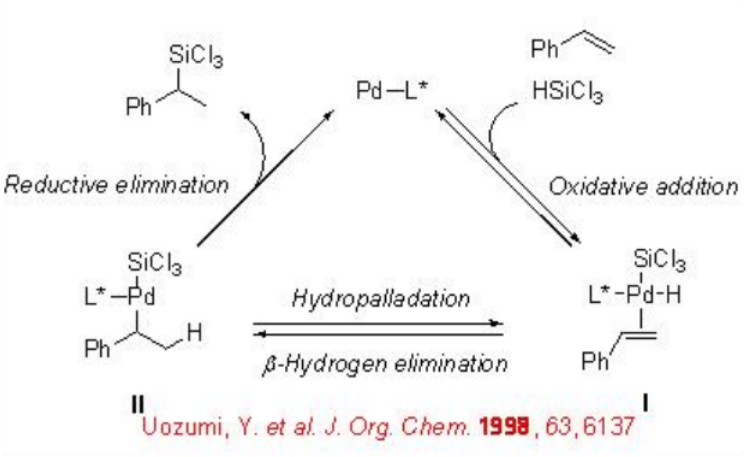
8.1.1 Reactions of Styrene and its Derivatives

Chiral Palladium-catalyzed asymmetric hydrosilylation of styrene with trichlorosilane has been extensively studied. The reaction proceeds with excellent regioselectivity to give 1-phenyl-1-silylethane *via* a stable π -benzyl palladium intermediate (Scheme 8.1.2).



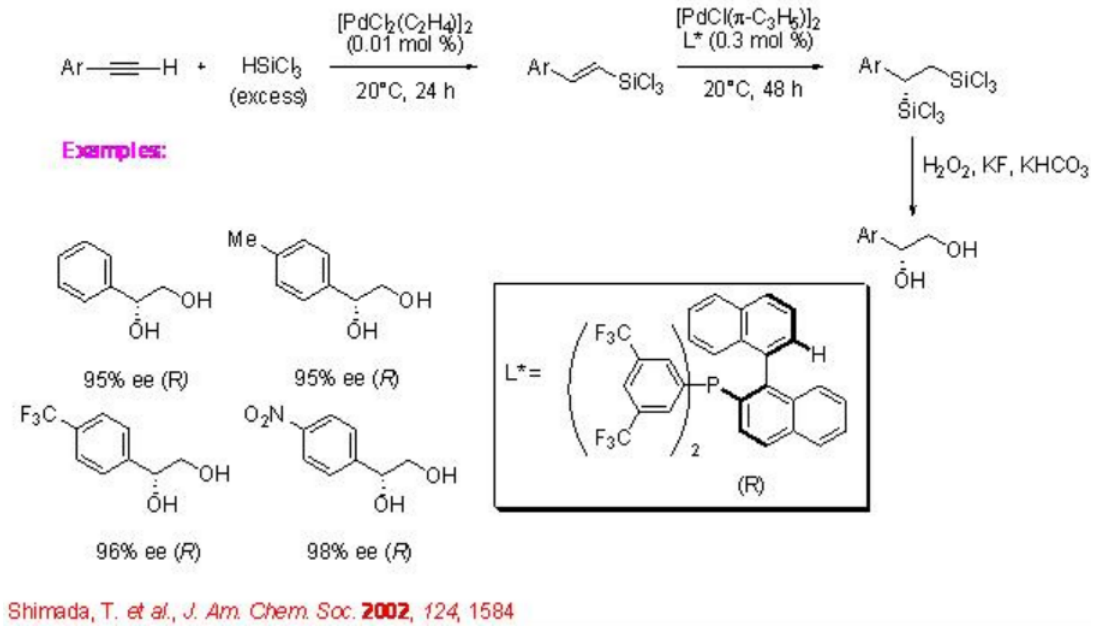
Scheme 8.1.2

Scheme 8.1.3 illustrates the possible mechanism. Deuterium-labeling studies suggest that the β -hydrogen elimination is found to be much faster compared to the reductive elimination from the intermediate **II** . The involvement hydropalladation in the catalytic cycle has been revealed by the side product analysis from the reaction of *o* -allylstyrene.



Scheme 8.1.3

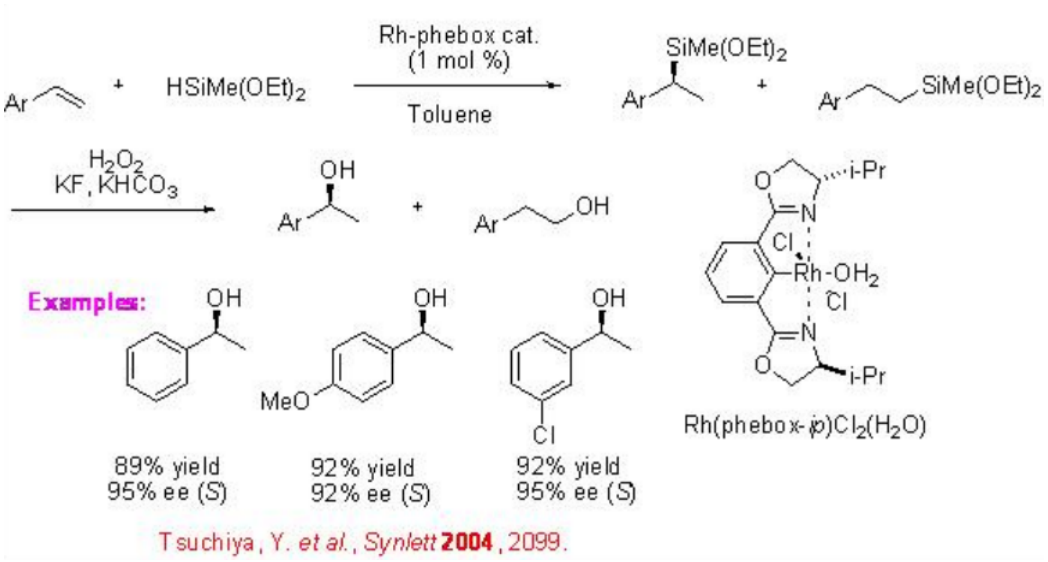
The reaction has been utilized in the synthesis of 1-aryl-1,2-diols from arylacetylenes (Scheme 8.1.4). Platinum-catalyzed hydrosilylation of arylacetylene gives (*E*)-1-aryl-2-(trichlorosilyl)ethanes that could be further reacted with trichlorosilane in the presence of chiral palladium complex to afford optically active 1-aryl-1,2-bis(trichlorosilyl)ethanes. The latter could be transformed into optically active 1,2-diol via oxidative cleavage of the carbon-silicon bond into carbon oxygen bond.



Shimada, T. *et al.*, *J. Am. Chem. Soc.* **2002**, *124*, 1584

Scheme 8.1.4

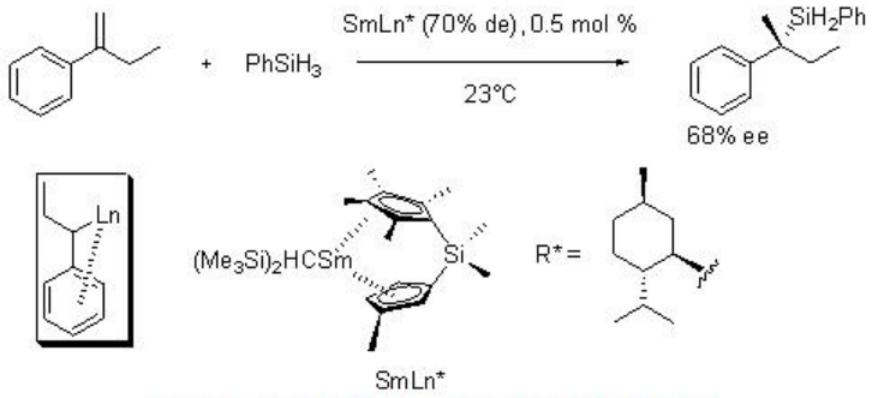
Other chiral catalysts have also been employed for the asymmetric hydrosilylation of alkenes. The chiral *bis* (oxazolinyl)phenylrhodium complex catalyzes the asymmetric hydrosilylation of styrenes with hydro(alkoxy)silanes in high enantioselectivity, although the regioselectivity is found to be somewhat moderate (Scheme 8.1.5).



Tsuchiya, Y. *et al.*, *Synlett* **2004**, 2099.

Scheme 8.1.5

α -Substituted styrenes proceed reaction with phenylsilane to afford benzylic *tert* -alkylsilanes in the presence chiral organolanthanide as catalyst in moderate enantioselectivity (Scheme 8.1.6).

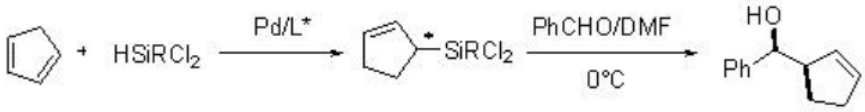


Molander, G. A. *et al.*, *Organometallics* **1998**, *17*, 3754.

Scheme 8.1.6

8.1.2 Reactions of 1,3-Dienes

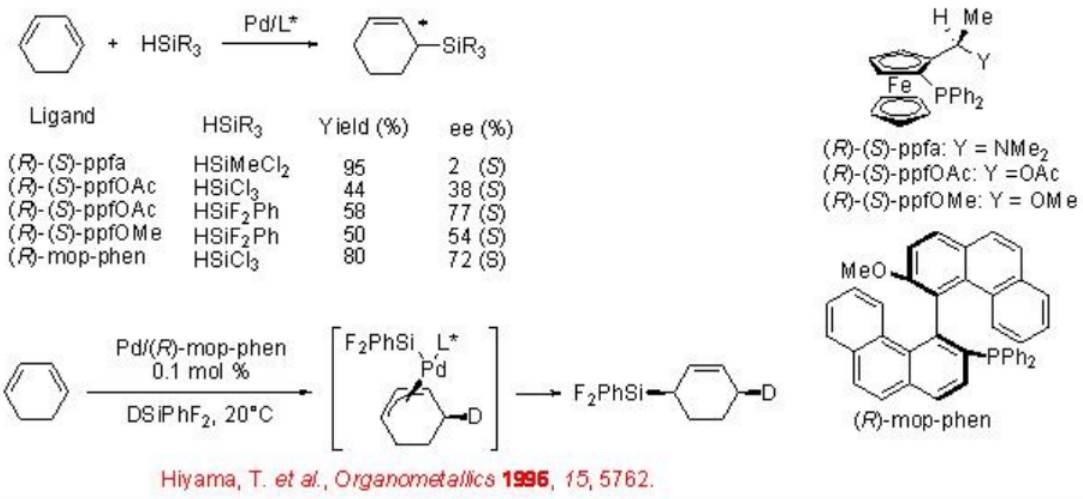
The reaction of 1,3-dienes with hydrosilanes having electron-withdrawing groups on silicon affords synthetically useful optically active silanes in the presence of chiral palladium complex (Scheme 8.1.7). The reaction proceeds in a 1,4-fashion providing chiral allylsilanes that could be converted into homoallylic alcohols on the reaction with aldehydes.



Masse, C. E. *et al.*, *Chem. Rev.* **1995**, *95*, 1293.

Scheme 8.1.7

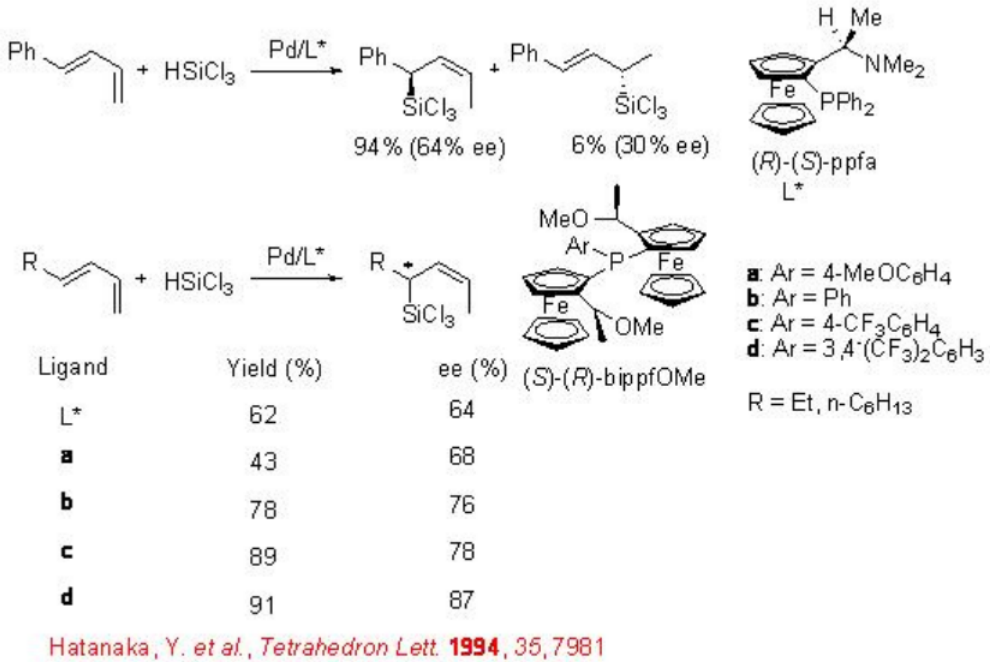
The use of ferrocenylphosphine and mop-phen ligands has been demonstrated for the hydrosilylation of cyclo-1,3-hexadiene in the presence of palladium salts (Scheme 8.1.8). The reaction with phenyldifluorosilane afforded the highest enantioselectivity compared to that with trichlorsilane or methyldichlorosilane. Based on the reaction of with deuterium-labeled silane the involvement of π-allylpalladium intermediate and 1,4-*cis*-addition has been proposed.



Hiyama, T. *et al.*, *Organometallics* **1996**, *15*, 5762.

Scheme 8.1.8

In case of linear 1,3-dienes, the regioselectivity has become an issue. In the reaction of 1-phenyl-1,3-butadiene using ferrocenyl ligand, (*R*)-(*S*)-ppfa, the formation of a mixture of regioisomeric allylsilanes is observed (Scheme 8.1.9). However, in the reaction of alkyl substituted 1,3-dienes, 1,3-hexadiene and 1,3-decadiene, a single regioisomer is obtained with moderate enantioselectivity. Improvement in the enantioselectivity is observed employing the *bis* (ferrocenyl)monophophine ligands **a-d** having two planar chiral ferrocenyl moieties on phosphorus atom.

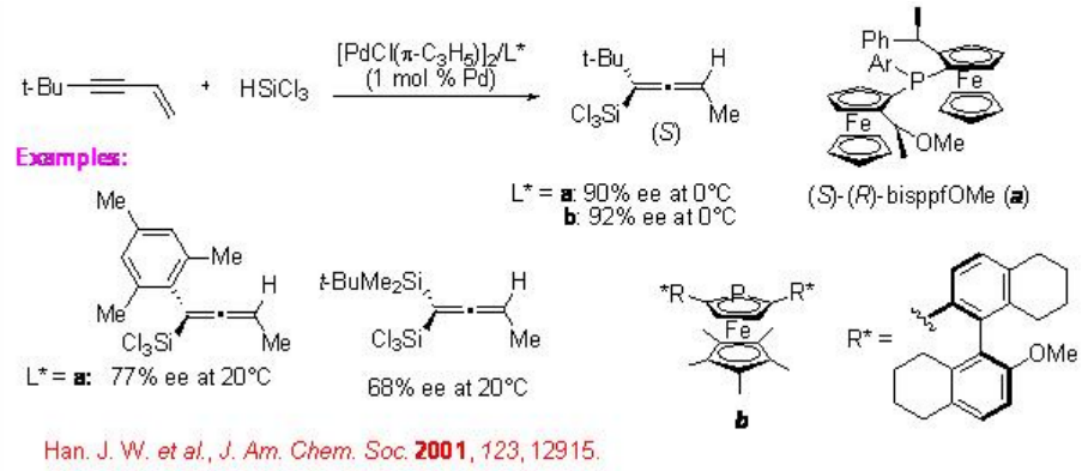


Ligand	Yield (%)	ee (%)
L*	62	64
a	43	68
b	78	76
c	89	78
d	91	87

Hatanaka, Y. *et al.*, *Tetrahedron Lett.* **1994**, *35*, 7981

Scheme 8.1.9

The reaction of 1-buten-3-ynes substituted with bulky groups at the alkyne terminus affords enantiomerically enriched allenylsilanes in the presence of palladium complex (Scheme 8.1.10). For example, the reaction of 5,5-dimethyl-1-hexen-3-yne using (*S*)-(*R*)-bisppfOMe ***a*** proceeds in a 1,4-fashion to give allenyl(trichloro)silanes in high regio- and enantioselectivity. Further enhancement in the enantioselectivity is shown employing chiral phosphametallocene ***b*** having a sterically demanding η^5 -C_5 Me_5 moiety.



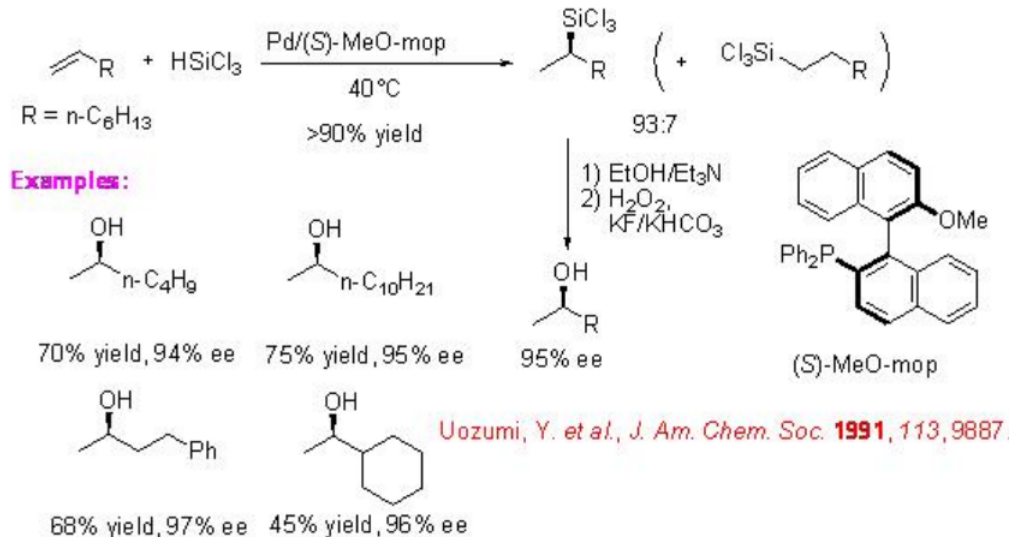
Han. J. W. *et al.*, *J. Am. Chem. Soc.* **2001**, *123*, 12915.

Scheme 8.1.10

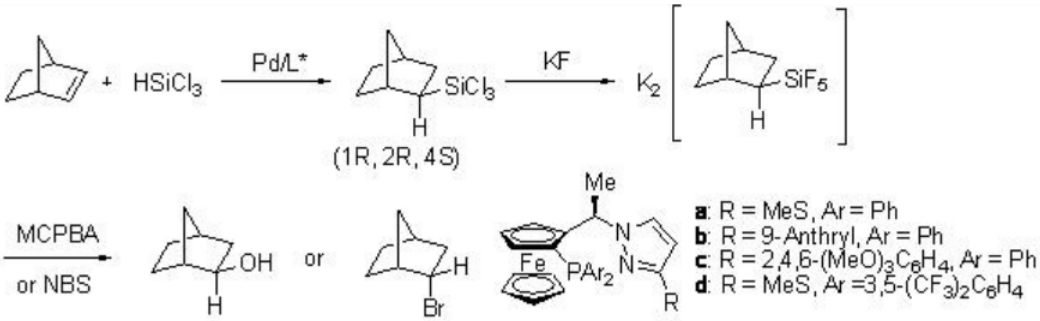
8.1.3 Reactions of Alkyl Substituted Alkenes

Hydrosilylation of simple terminal alkenes give branched products with high regioselectivity. The palladium systems show exceptional catalytic system compared to Pt, Ni and Rh based systems. For example, the hydrosilylation of 1-octene with trichlorosilane using palladium-(S)—MeO-mop gives a 93:7 mixture of 1-octylsilane and 2-octylsilane with 95% ee (Scheme 8.1.11).

The above catalytic system is also effective for the hydrosilylation of cyclic alkenes, such as norbornene and bicyclo[2.2.2]octane, 2,5-dihydrofuran and norbornadiene. For example, the reaction of norbornene gives *exo* adduct exclusively (Scheme 8.1.12). The hydrosilylated product can be transformed into *exo* -2-norbornanol or *endo* -2-bromonorbornane via the corresponding pentafluorosilicate. In addition, chiral ferrocenylmonophosphines **a-d** are too found to be effective for this process with excellent enantioselectivity.



Scheme 8.1.11

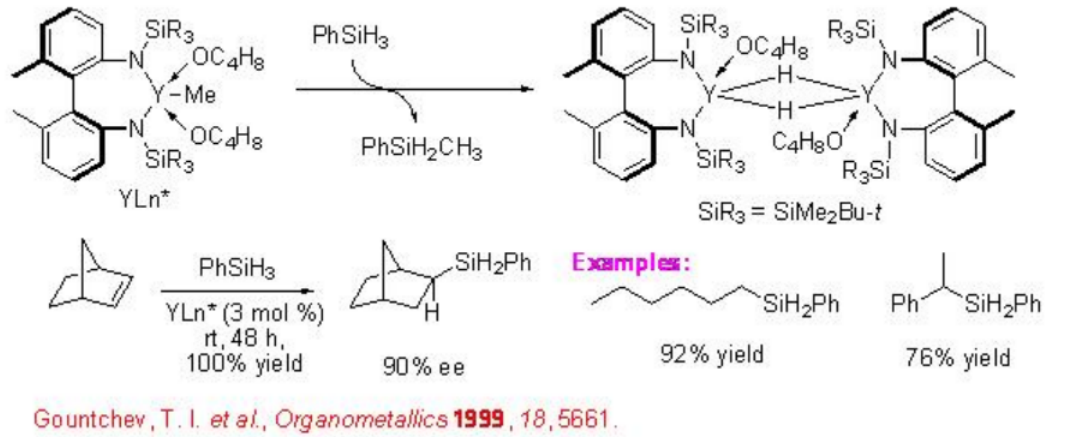


Ligand	Yield (%)	ee (%)
(*R*)-Meo-mop	99	96
a	56	91
b	54	81
c	30	92
d	59	99.5

Uozumi, Y. *et al.*, *Tetrahedron Lett.* **1992**, *33*, 7185.

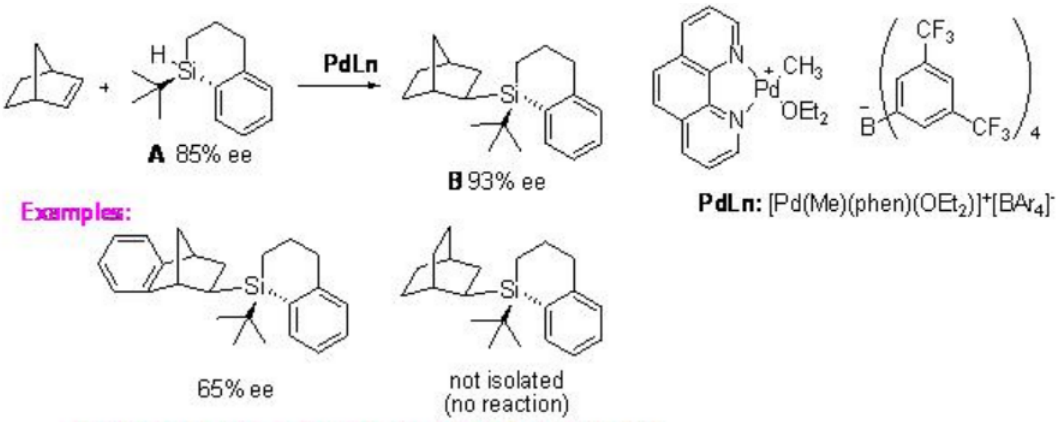
Scheme 8.1.12

Chiral yttrium hydride complex (d^0 metal complex) bearing non-Cp ligand catalyzes the hydrosilylation of norbornene with phenylsilane to produce *exo* -adduct with 90% ee (Scheme 8.1.13). More recently, the first chirality transfer from silicon to carbon in a reagent-controlled reaction of norbornene is reported in the presence of achiral palladium complex. The hydrosilylation of norbornene with chiral silane A having 85% ee is found to form the hydrosilylated product B with 93% ee exhibiting asymmetric amplification (Scheme 8.1.14).



Gountchev, T. I. *et al.*, *Organometallics* **1999**, *18*, 5661.

Scheme 8.1.13

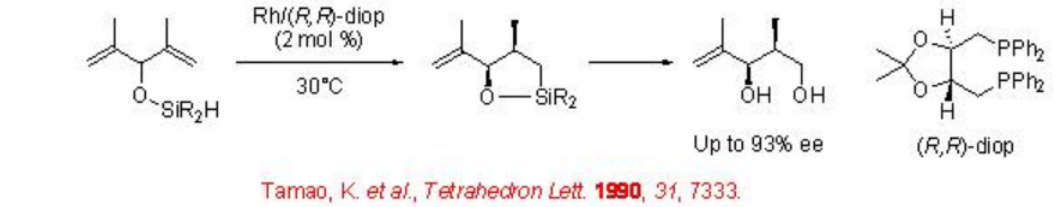


Oestreich, M. *et al.*, *Angew. Chem. Int. Ed.* **2005**, *44*, 1661.

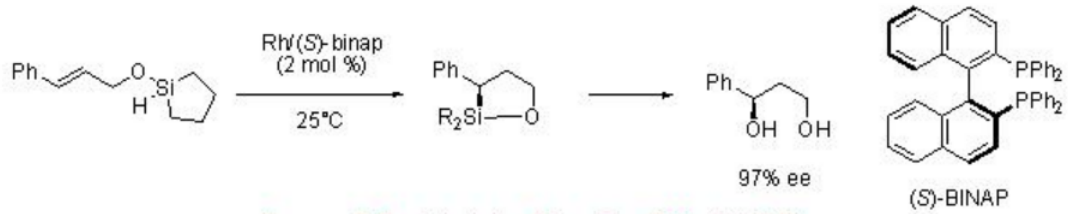
Scheme 8.1.14

8.1.4 Intramolecular Hydrosilylation

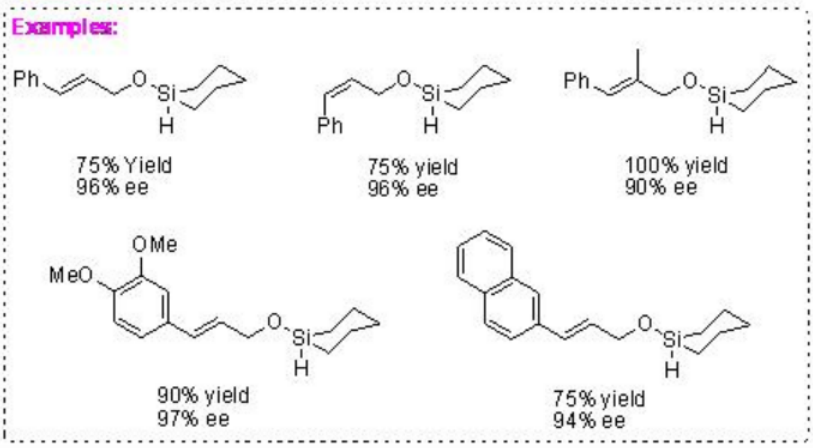
Synthesis of optically active polyols from allylic alcohols can be achieved using chiral Rh-catalyzed intramolecular hydrosilylation followed by oxidation of allyloxy hydrosilanes (Scheme 8.1.15). For example, hydrosilyl ether of di(2-propenyl)methanol can be converted into optically active 1,3-diol using intramolecular hydrosilylation in the presence of chiral rhodium-(R,R)-diop followed by oxidation. Rh-BINAP is also found to be effective catalyst for the intramolecular hydrosilylation of hydrosilyl ethers of allyl alcohols.



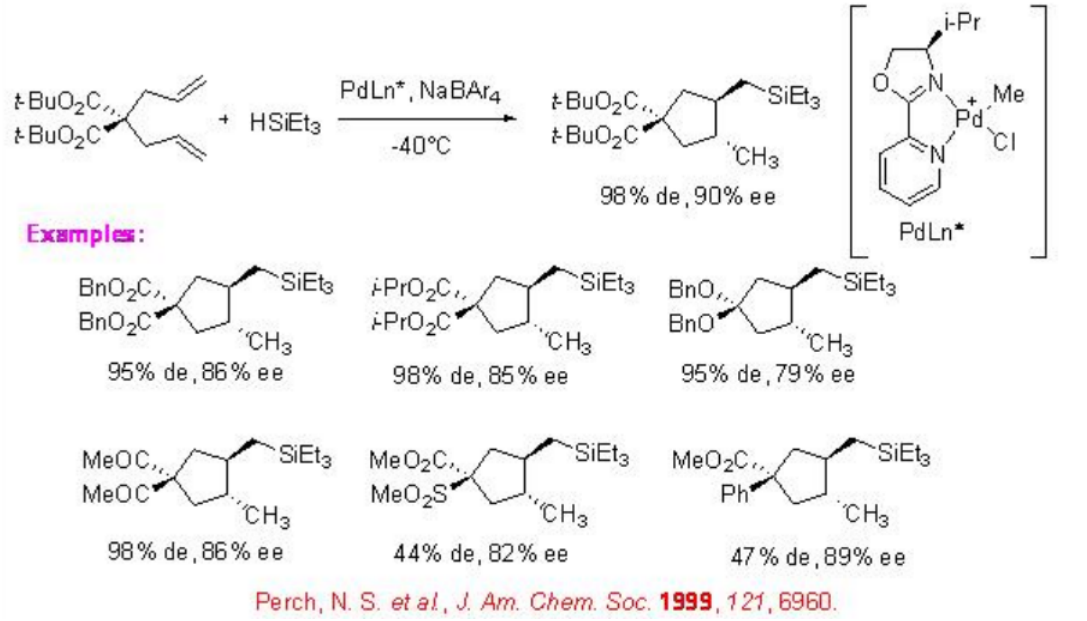
Tamao, K. *et al.*, *Tetrahedron Lett.* **1990**, *31*, 7333.



Bergens, S. E. *et al.*, *J. Am. Chem. Soc.* **1992**, *114*, 2121



Scheme 8.1.15

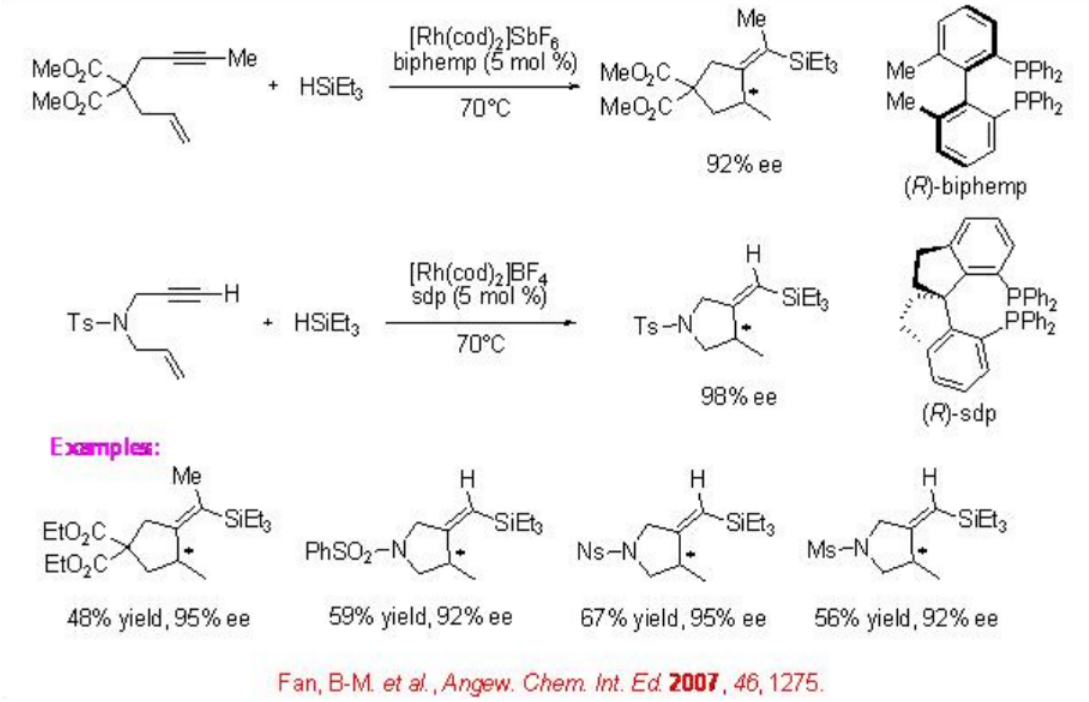


Scheme 8.1.16

8.1.5 Cyclization/Hydrosilylation

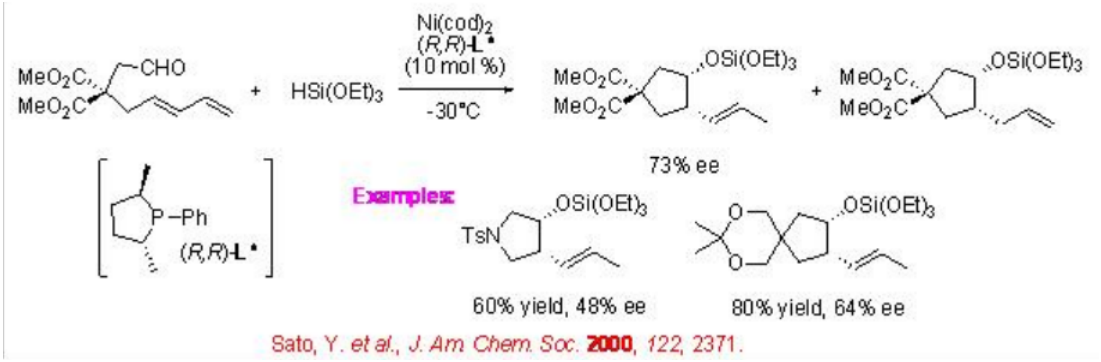
Asymmetric cyclization and hydrosilylation of a ,ω-diunsaturated compounds such as 1,6-dienes and 1,6-enynes affords powerful tool for the construction of optically active functionalized carbocycles. For example, the tandem reaction of diallylmalonate in the presence of cationic Pd complex bearing a chiral pyridine-oxazoline proceeds with high diastereoselectivity to yield the corresponding trans-substituted cyclopentane with 90% ee (Scheme 8.1.16).

The reactions of 1,6-diynes using cationic Rh complexes bearing chiral bisphosphine gives the hydrosilylated alkylidenecyclopentanes with high enantioselectivity. For example, the 1,6-enyne proceeds reaction with triethylsilane in the presence of cationic Rh and (*R*)-biphemp to give hydrosilylated alkylidene cyclopentane in 92% ee (Scheme 8.1.17). Subsequently, chiral Rh complex containing spiro diphosphine (*R*)-sdp is found to be effective for this process.



Scheme 8.1.17

The synthesis of carbocycles can also be accomplished by the cyclization of ω-formyl-1,3-dienes in the presence of hydrosilanes and chiral nickel complex (Scheme 8.1.18). For example, zerovalent nickel complex of (2 *R* ,5 *R*)-2,5-dimethyl-1-phenylphospholane catalyzes the cyclization of 1,3-dienes with a tethered formyl group in the presence of triethoxysilane to give five-membered carbocycle with 73% ee.

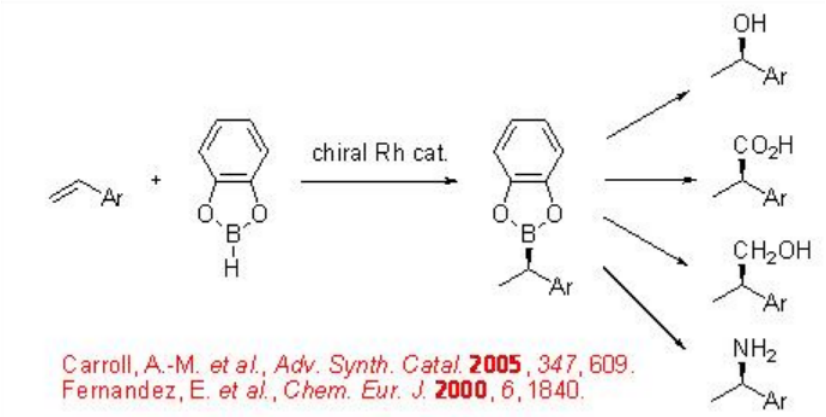


Scheme 8.1.18

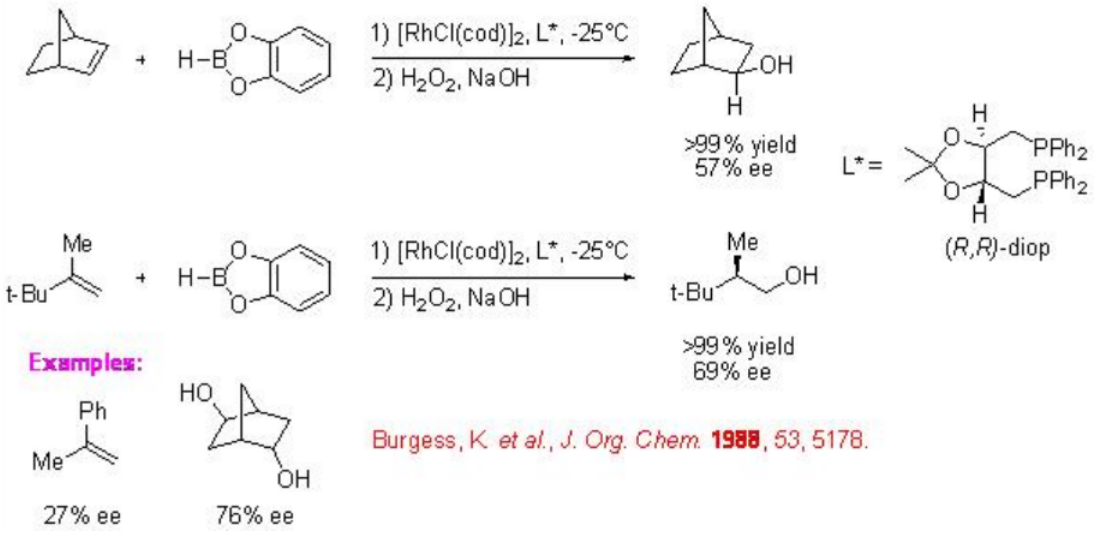
8.2: Hydroboration, Hydroalumination and Hydrostannation of Alkenes

8.2.1 Hydroboration of Alkenes

Chiral Rh catalyzed hydroboration of alkenes provides effective method for the synthesis of optically active organoboranes, which are versatile intermediates in organic synthesis. The carbon-boron bond can be converted into several functional group by subsequent carbon-carbon, carbon-oxygen, boron-carbon or carbon-nitrogen bond-forming reactions with retention of stereochemistry (Scheme 8.2.1).



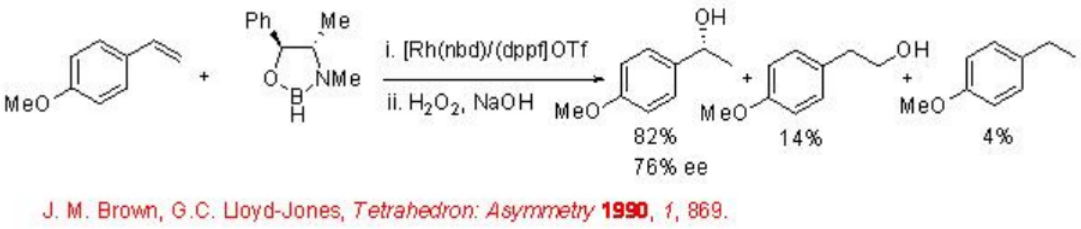
Scheme 8.2.1



Scheme 8.2.2

The first catalytic asymmetric hydroboration of norbornene and 2-*tert*-butylpropene with catecholborane appeared in the presence of Rh-(*R*, *R*)-diop complex (Scheme 2). The products, 2-hydroxynorbornane and 2,3,3-trimethylbutanol are obtained after the treatment with alkaline hydrogen peroxide solution.

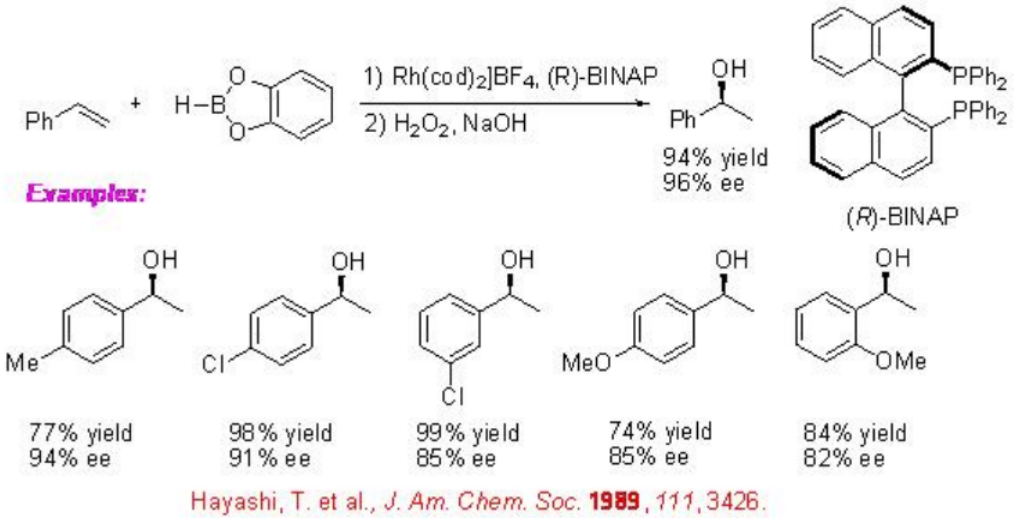
The use of the combination of chiral borane and achiral catalyst has been demonstrated for the asymmetric hydroboration. For example, the hydroboration of 4-methoxystyrene proceeds with chiral borane derived from pseudoephedrine in the presence of achiral rhodium complex to the corresponding secondary alcohol with 76% ee after the oxidation (Scheme 8.2.3).



J. M. Brown, G.C. Lloyd-Jones, *Tetrahedron: Asymmetry* **1990**, *1*, 869.

Scheme 8.2.3

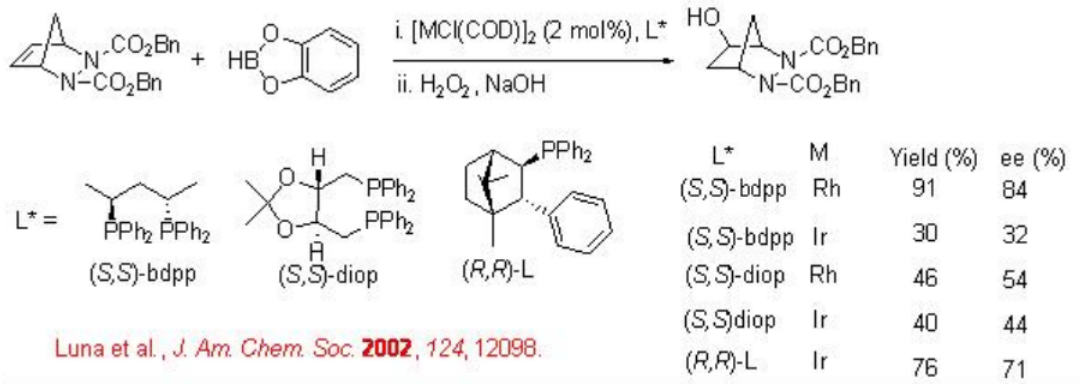
The reaction of vinylarenes with catecholborane has been extensively studied using chiral Rh complex. For example, the cationic Rh-(*R*)-BIANP catalyzes the hydroboration of styrene with complete branch selectivity to afford 1-phenylethanol with 96% ee after oxidation. The regioselectivity is opposite to that observed with uncatalyzed reactions (Scheme 8.2.4).



Hayashi, T. et al., *J. Am. Chem. Soc.* **1989**, *111*, 3426.

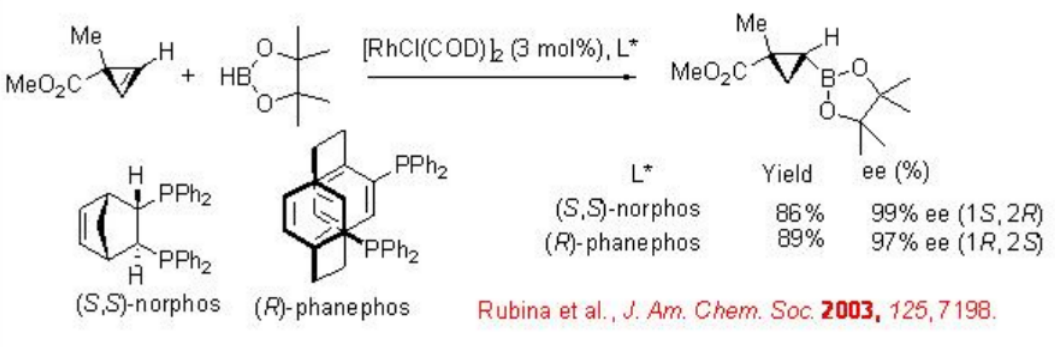
Scheme 8.2.4

Asymmetric desymmetrization of *meso* -bicyclic hydrazines has been shown with catecholborane using chiral Rh and Ir-based complexes (Scheme 8.2.5). A reversal of enantioselectivity is observed between the Rh and Ir catalysts.

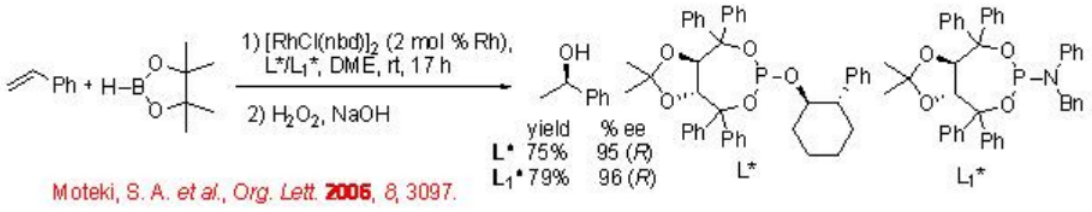


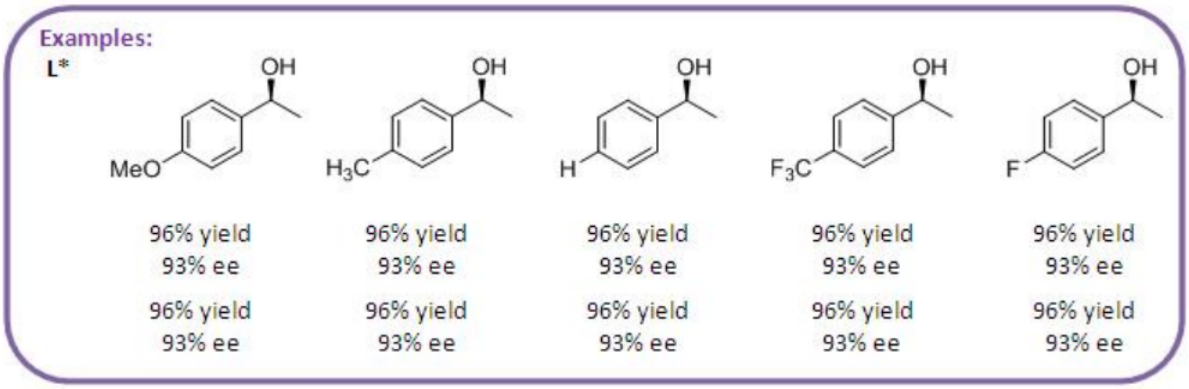
Luna et al., *J. Am. Chem. Soc.* **2002**, *124*, 12098.

Scheme 8.2.5



Scheme 8.2.6



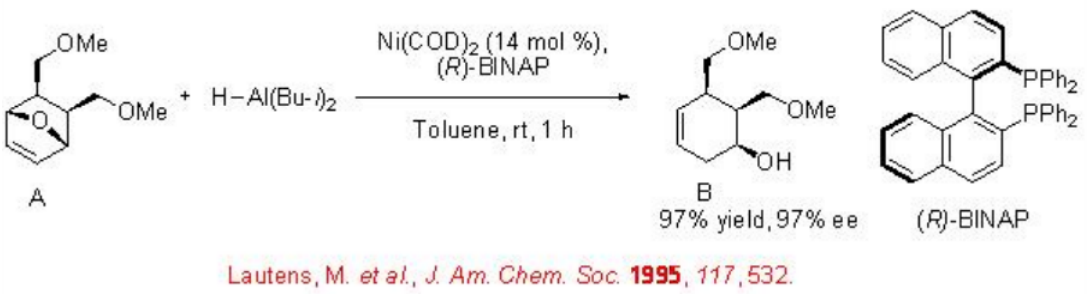


Scheme 8.2.7

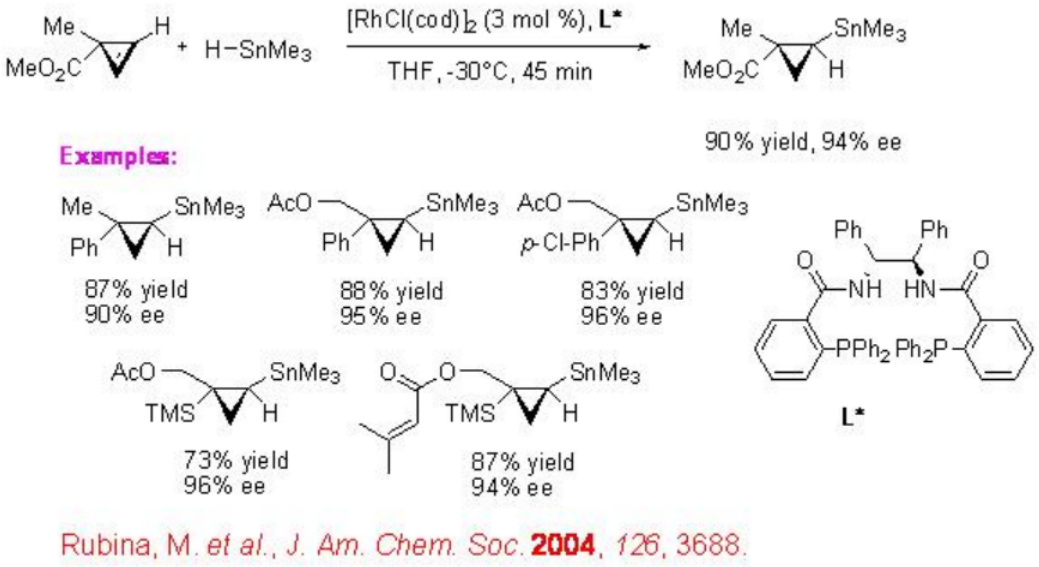
The reaction of cyclopropene is studied with pinacolborane as a new hydroborating agent in the presence of a series of chiral Rh phosphine complexes (Scheme 8.2.6). The reaction using pinacolborane showed enhanced selectivity compared to that with catecholborane due to steric control between the substrates and the hydroborating agent.

Rh complexes with chiral monodentate phosphate and phosphoramidite derived from taddol are studied for the hydroboration of vinylarenes with pinacolborane (Scheme 8.2.7). The reactions of a series of vinylarenes having electron withdrawing- and donating substituted proceed with high enantioselectivity.

8.2.2 Hydroalumination and Hydrostannation of Alkenes



Scheme 8.2.8



Rubina, M. *et al.*, *J. Am. Chem. Soc.* **2004**, *126*, 3688.

Scheme 8.2.9

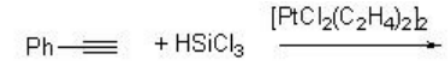
While the catalytic asymmetric hydrosilylation and hydroboration reactions are well known, the catalytic hydroalumination and hydrostannation of alkenes are rare. Chiral nickel complex is used for the asymmetric hydroalumination of oxabicyclic alkenes. For example, Ni-(*R*)-BINAP catalyzes the reaction of A with *iso* -Bu_2 AlH to give B with 97% ee (Scheme 8.2.8).

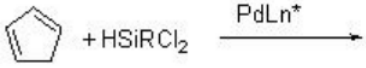
The first example for the asymmetric hydrostannation of cyclopropenes is appeared using Rh-complex bearing chiral diphenylphosphinobenzoic acid-derived L* (Scheme 8.2.9). The product *trans*- cyclopropylstannane is obtained with 94% ee. The procedure is general and the reaction a series of substituted cyclopropenes is demonstrated.

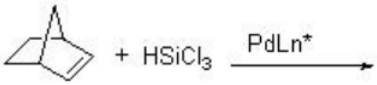
8.3: Problems and Reference

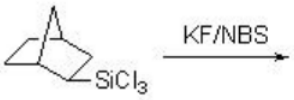
Problems

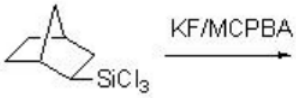
Write the major products for the following reactions.

1. 

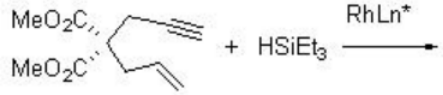
2. 

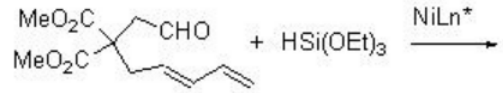
3. 

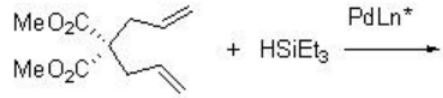
4. 

5. 

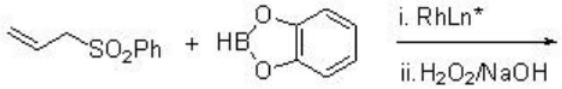
Complete the following reactions.

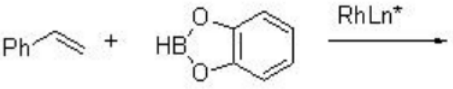
1. 

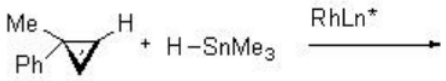
2. 

3. 

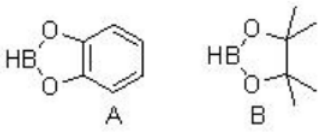
Predict the major product for the following reactions.

1. 

2. 

3. 

How will you prepare the following hydroborating agents?



Reference/Text Book

• I. Ojima, *Catalytic Asymmetric Synthesis* , 3 rd ed., Wiley, New Jersey, 2010.

• M. B. Smith, *Organic Synthesis* , 2 nd edition, McGraw Hill, New Delhi, 2004

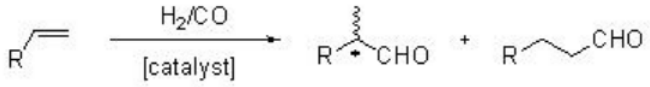
CHAPTER OVERVIEW

9: Carbonylation Reactions

9.1: Hydroformylation Reaction

Carbonylation of the unsaturated substrates using transition metal catalysis provides powerful tool to produce fine chemical intermediates. The asymmetric carbonylation is among the most challenging homogeneous process and their potential is yet to be made. The Rh-catalyzed hydroformylation of alkenes together with the Pd-catalyzed hydroxy and alkoxycarbonylation of alkenes are the most famous examples for the asymmetric carbonylation reactions. The important difference between these reactions is the Rh-catalyzed hydroformylation is of greater industrial interest than the palladium based carbonylation process.

The conversion of alkenes to aldehydes is the largest volume homogeneous transition metal-catalyzed reaction. This process has been extensively explored and a number of methods and catalysts have been developed to control the regioselectivity in internal and terminal aldehydes (Scheme 9.1.1).

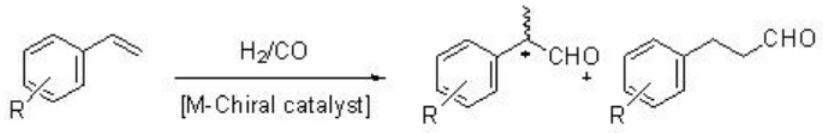


van Leeuwen, P. W. N. M. Claver, C. *Rhodium Catalysed Hydroformylation*. Dordrecht: Kluwer Academic Press, 2000.

Scheme 9.1.1

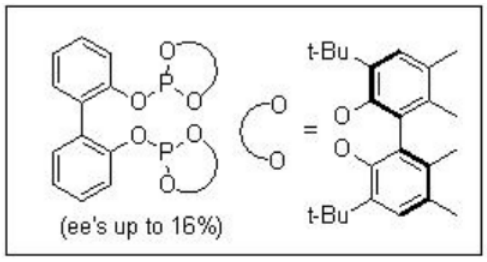
9.1.1 Reaction of Vinyl Arenes

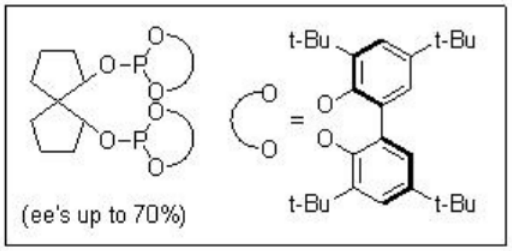
The asymmetric hydroformylation of vinyl arenes is an attractive route to afford optically active aldehydes, which are substrate precursors for the synthesis of high-value pharmaceuticals, agrochemicals, biodegradeful polymers and liquid crystals (Scheme 9.1.2). Since the beginning of 1970, chiral Rh-diphosphine complexes have been used as catalysts for this transformation with moderate enantioselectivity (below 60%). From beginning of 1990, the use of bisphophacyclic ligands, diphosphites and phosphine-phosphite, has emerged as alternative for this reaction. Scheme 9.1.3 summarizes some of the new diphosphite ligands developed with biaryl, spiro, pyranoside, mannitol and macrocyclic backbones for the asymmetric hydroformylation of vinyl arenes with low to moderate success (ee's from 16% to 76%).

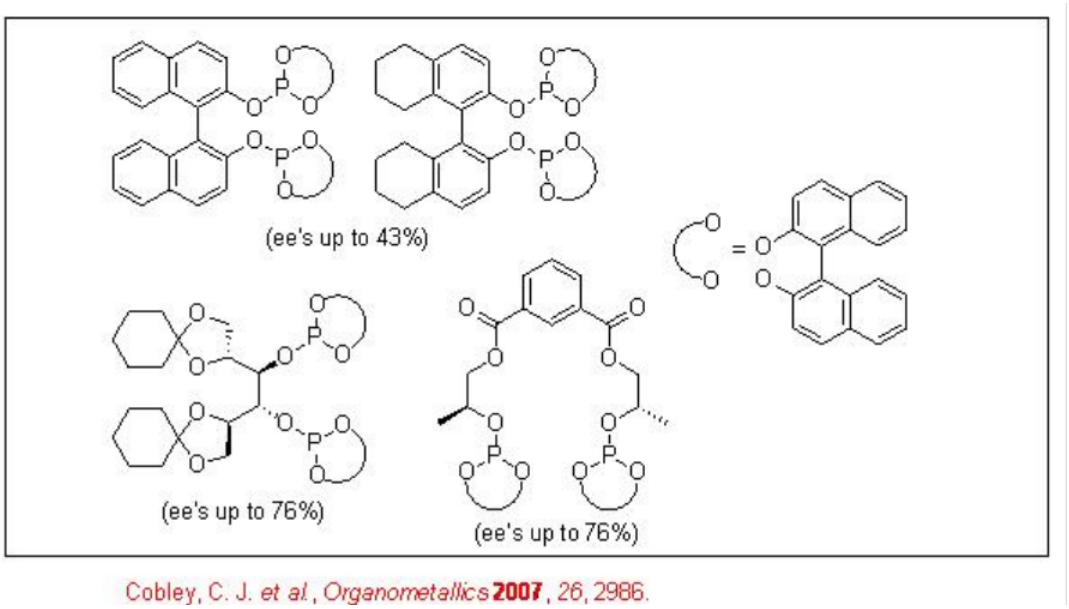


Rampf, F. *et al*., *J. Organomet. Chem.* **2000**, *601*, 138.

Scheme 9.1.2



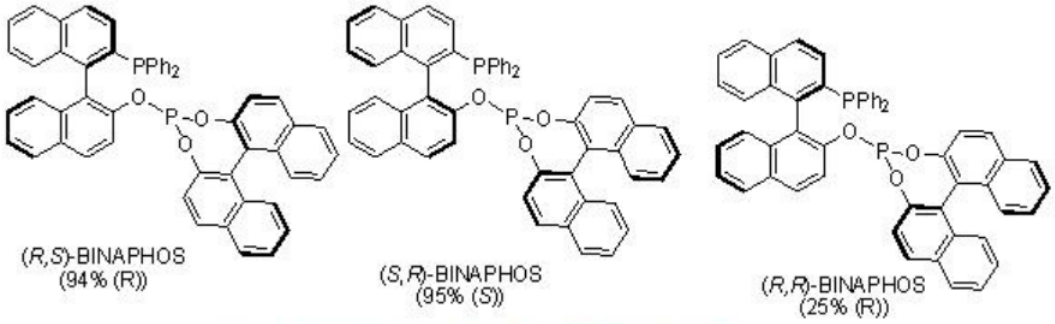




Cobley, C. J. *et al.*, *Organometallics* **2007**, *26*, 2986.

Scheme 9.1.3: Diphosphite Ligands for Hydroformylation

Scheme 9.1.4 summarizes some of successful phosphine-phosphite ligands for the asymmetric hydroformylation of vinyl arene. The enantioselectivity depends on the configuration of both the binaphthyl moieties. The best enantioselectivity is observed when the configurations of the two binaphthyl moieties are opposite.

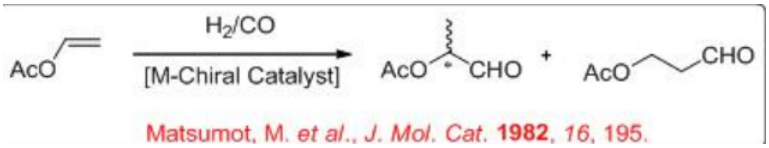


Nozaki, K. *et al.*, *J. Am. Chem. Soc.* **1997**, *119*, 4413.

Scheme 9.1.4: Rh-Catalyzed Asymmetric Hydroformylation of Styrene. Enantioselectivities obtained at 100 bar of syn gas and 60°C are shown in brackets.

9.1.2 Reaction of Vinyl Acetate

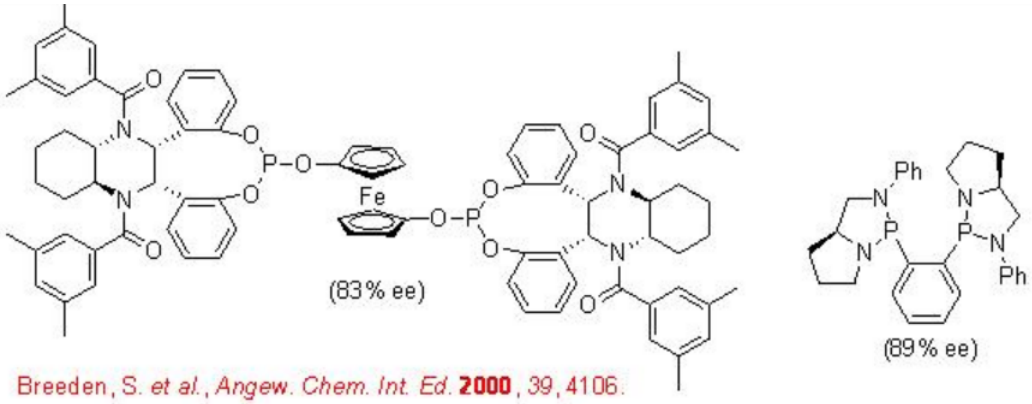
The reaction of vinyl acetate is more challenging compared to that of vinylarenes. This process affords 2- and 3- acetoxy propanals with high selectivity (Scheme 9.1.5). Ethyl acetate and acetic acid are produced as by-products.



Matsumot, M. *et al.*, *J. Mol. Cat.* **1982**, *16*, 195.

Scheme 9.1.5

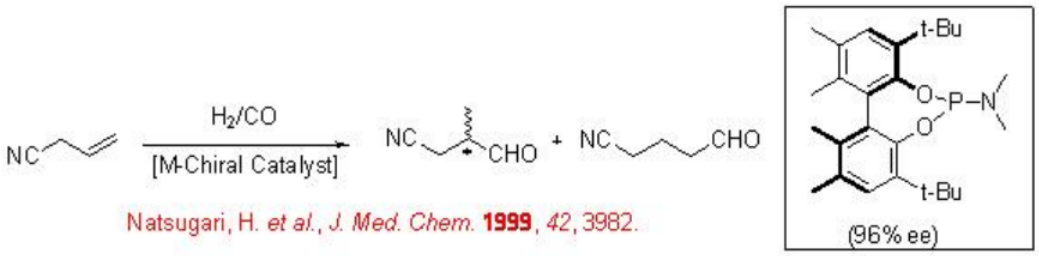
Scheme 9.1.6 illustrates some of the successful ligands for the Rh-catalyzed hydroformylation of vinyl acetate. The enantioselectivity of the reactions are shown in the brackets.



Scheme 9.1.6

9.1.3 Reaction of Allyl Cyanide

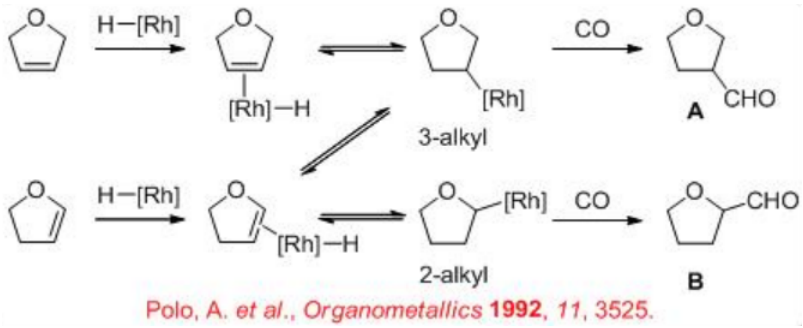
The asymmetric hydroformylation of allyl cyanide is of great interest because the iso-aldehyde derivative can be converted into 2-methyl-4-butanol, which is intermediate, for the asymmetric synthesis of tachikinin, a novel NK1 receptor agonist (Scheme 9.1.7). The reaction has been studied using diphosphite, phosphine-phosphite, bis-phosphacyclic and phosphoroamidite ligands with up to 96% ee.



Scheme 9.1.7

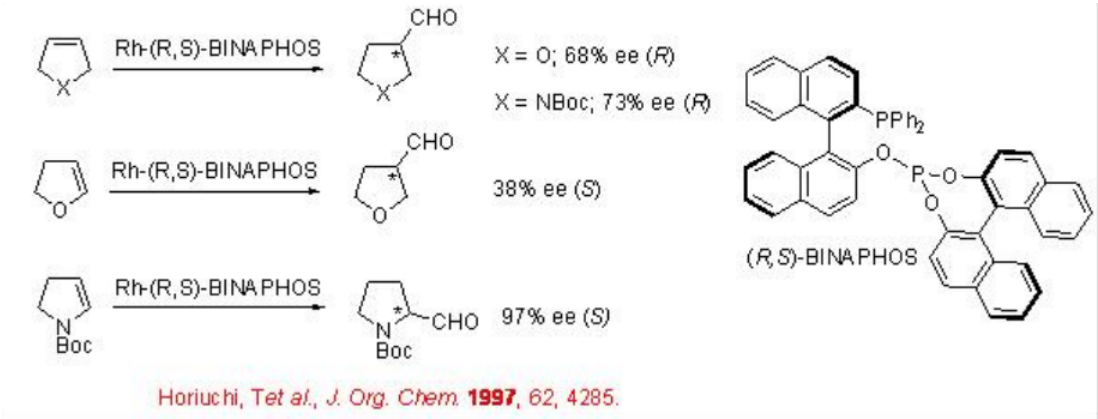
9.1.4 Reaction of Heterocyclic Alkenes

Few studies are focused on the hydroformylation of heterocyclic alkenes. For these substrates, the regioselectivity is of special interest because it is different from that of the acyclic alkenes. For example, the hydroformylation of 2,5-dihydrofuran can lead to the formation of both the tetrahydrofuran-3-carbaldehyde **A** (expected product) and tetrahydrofuran-2-carbaldehyde **B** (could be formed via an isomerization process). The regioselectivity is to be controlled by the modification of the ligands and reaction conditions.



Scheme 9.1.8

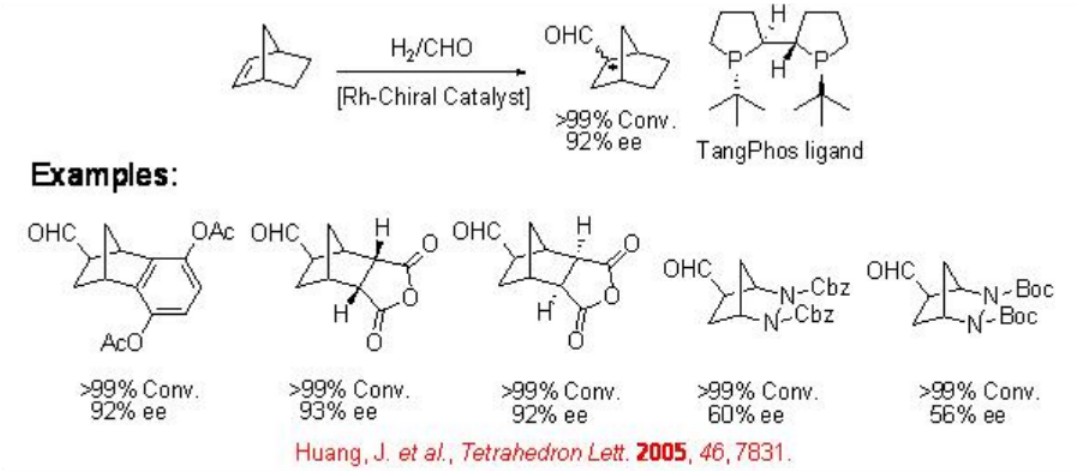
Scheme 9.1.9 summarizes the reaction of 2,5-dihdyrofuran, 3-pyrroline derivative and 4,7-dihdyro-1,3-dioxepin derive using chiral Rh-complex bearing R,S-BINAPHOS. The optically active aldehydes are obtained as single products with enantioselectivities between 64-97%. In case of 2,5-dihydrofuran, up to 64% regioselectivity is observed for the formation of tetrahydrofuran-3-carbaldehyde **A** , while the reaction of 2,3-dihyrofuran led to the formation of a mixture of **A** and **B** (1:1) with an ee of 38% in **A**.



Scheme 9.1.9

9.1.5 Reaction of Bicyclic Alk*enes*

The asymmetric hydroformylation of bicyclic alkenes has received little attention. This reaction is interesting because of the following features: (i) the reaction can lead to the formation of three chiral centers upon one C-C bond formation; (ii) there is no regioselectivity problem; (iii) functional groups located opposite to the carbon-carbon double bond could be versatile. Scheme 9.1.10 summarizes some of the examples for the asymmetric hydroformylation of bicyclic alkenes employing Rh-TangPhos.



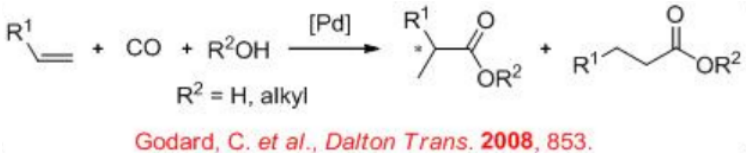
Scheme 9.1.10

9.2: Asymmetric Alkoxycarbonylation and Related Reactions

Reaction of Vinylarenes

From academic and industrial standpoint, the Pd-catalyzed asymmetric hydroxy- and alkoxycarbonylation reactions are attractive processes. However, they are less successful compared to the Rh-catalyzed hydroformylation reactions. This is because of the difficulty in getting simultaneously both high regio- and enantioselectivities.

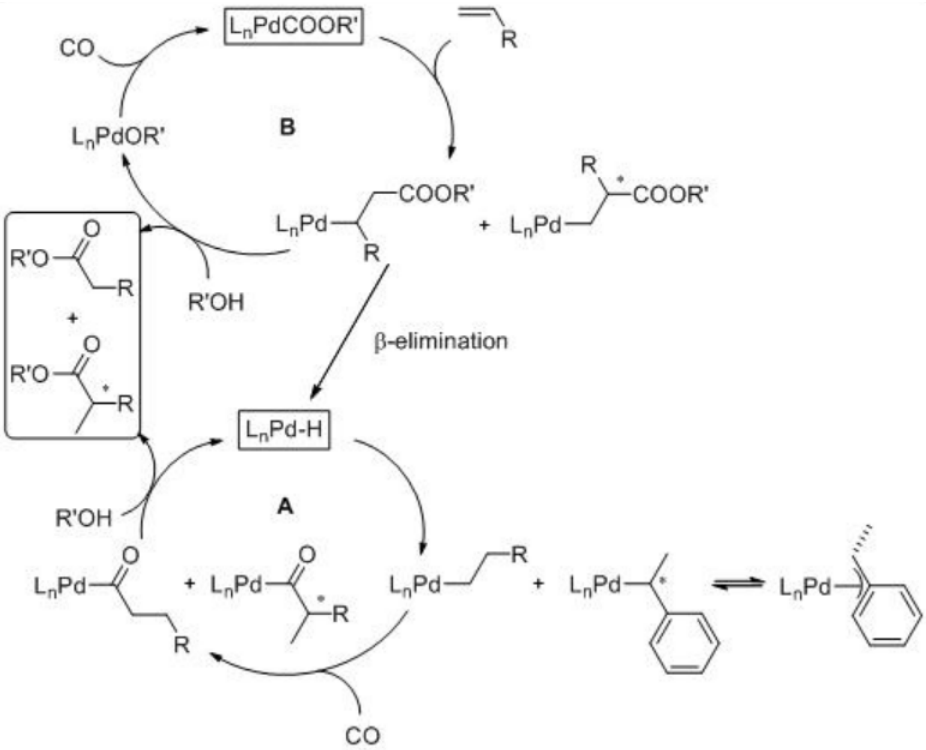
The alkoxycarbonylation of vinylarenes is an important process and the resulting products (2-arylpropanoic acids and derivatives) serve as substrate precursors for nonsteroidal anti-inflammatory drugs, particularly ibuprofen and naproxen (Scheme 9.2.1).



Godard, C. *et al.*, *Dalton Trans.* **2008**, 853.

Scheme 9.2.1

The coexistence of two catalytic cycles has been suggested for the alkoxycarbonylation reaction (Scheme 9.2.2). In the hydrido-palladium complex cycle A, the insertion of the alkene to the Pd-H bond can give alkyl palladium complex that could react with CO via coordination and migratory insertion to yield Pd-acyl complex. Alcoholysis of the Pd-acyl complex can regenerate the Pd-H species and yield the ester. In the alkoxycarbonyl cycle B, the alkene inserts into the palladium-carbon bond of alkoxycarbonyl-palladium complex and the resulting product on alcoholysis gives an alkoxy-palladium complex and the ester. The alkoxy-palladium complex then reacts with CO via coordination and migratory insertion to regenerate the alkoxycarbonyl-palladium complex. The formation of the Pd-H species may also take place from the complexes formed in the catalytic cycle B via β -elimination of an unsaturated ester after the alkene insertion. In case of vinylarene, the branched alkyl intermediate could be stabilized through the formation of π -benzylic species.



Kanawa, M. *et al.*, *J. Organomet. Chem.* **1997**, *542*, 185.

Scheme 9.2.2

In case of asymmetric synthesis, the regioselectivity of these reactions is of critical importance due to the branched products only contain the chiral center. Figure 9.2.1 summarizes the some of the diphosphine ligands used for the palladium catalyzed hydroxy-

and alkoxycarbonylation of vinylarenes. Although the enantioselectivity is found to be moderate to good (up to 98%), in most of the methods, the regioselectivity is found to be low.

Bidentate pyridine-phosphine ligands have also been studied for palladium catalyzed asymmetric ethoxycarbonylation of styrene (Figure 9.2.2). The regioselectivity of branched products is to be good but the enantioselectivity is found to be low (l/b = linear/branched).

Figure 9.2.3 summarizes the selective monodentate ligands studied for the palladium catalyzed asymmetric methoxycarbonylation of vinaylarenes. The ligand **18** is found to be effective for the hydroxycarbonylation of 2-vinyl-6-methoxynaphthalene under 1 atm of a mixture of CO and O_2 in the presence of $PdCl_2$ -$CuCl_2$ at room temperature affording the target product with 91% ee and 100% regioselectivity.

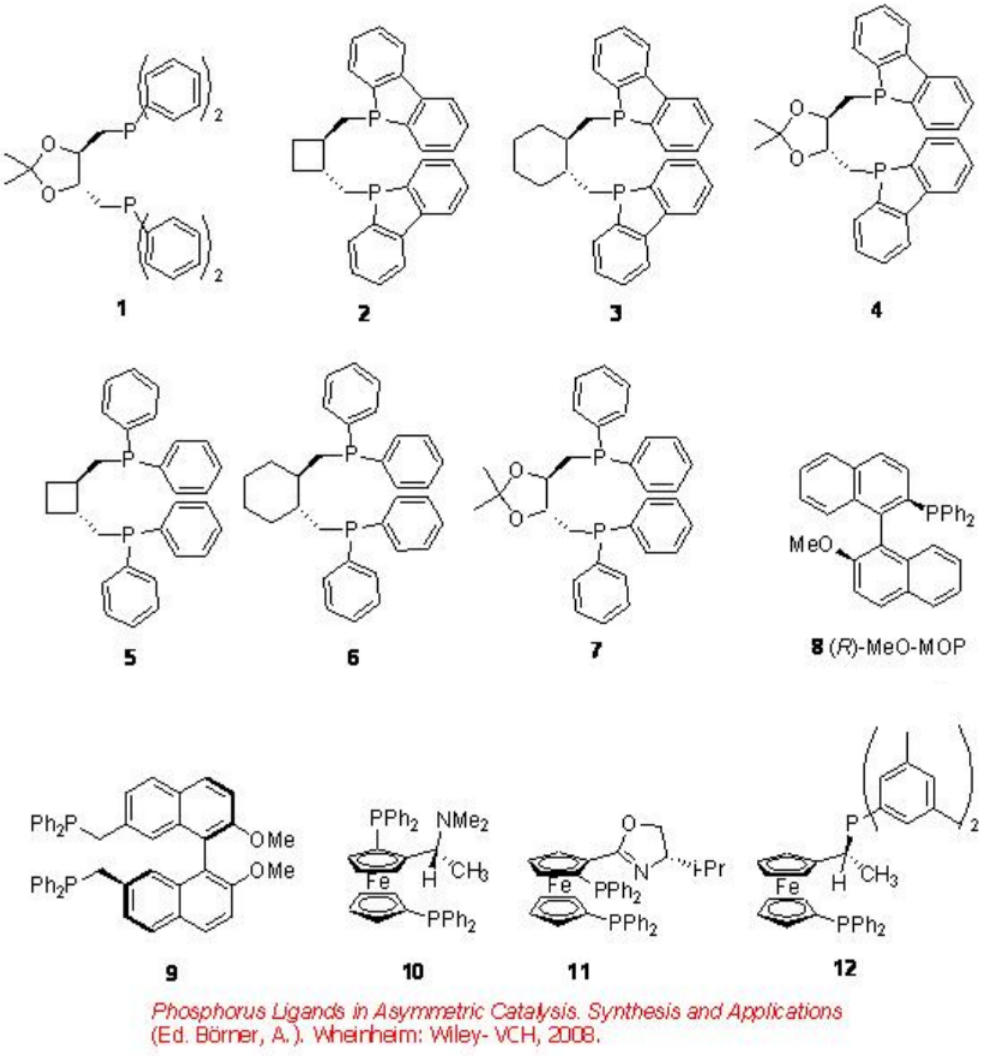


Figure* 9.2.1*: Diphosphine Ligands used in the Asymmetric Hydroxy- and Alkoxycarbonylation of Vinylarenes.

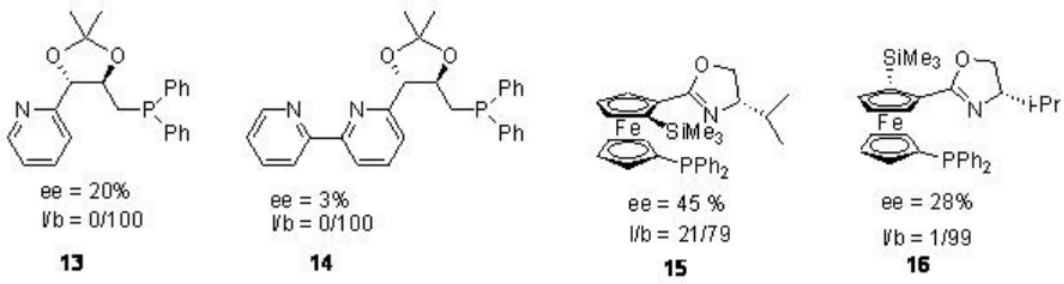


***Figure* 9.2.2:** P-N Ligands used for Alkoxycarbonylation Reactions.

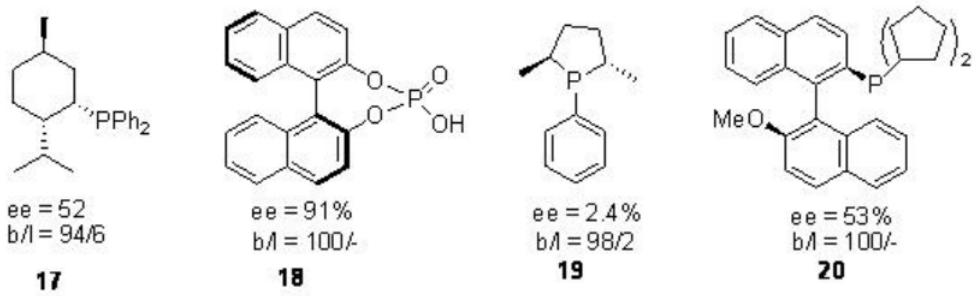
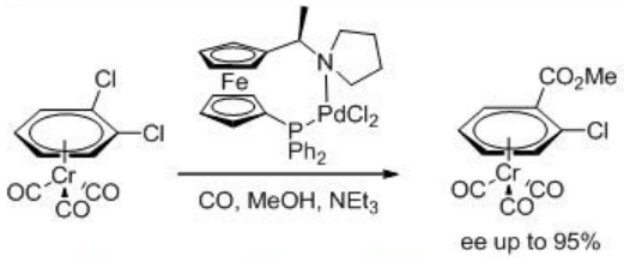


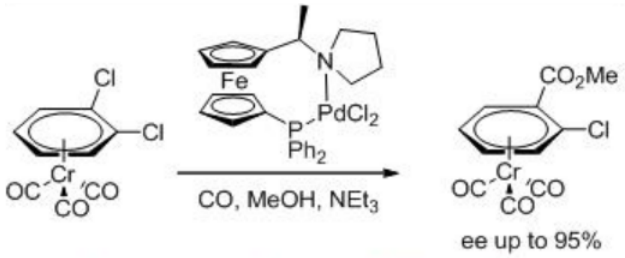
***Figure* 9.2.3:** Monodentate Phosphine Ligands used for methoxcarbonylation of vinylarenes.



Gotov, N. *et al*., *Org. Lett*. **2001**, *3*, 1753.

9.2.2 Reaction of Other Substrate

The methoxycarbonylation of 1,2-dichlorobenzene-$Cr(CO)_3$ has been studied using palladium complex bearing chiral ferrocenyl (*R*,*S*)-PPF-pyrrolidine system to introduce planar chirality in p -complexes (Scheme 9.2.3). The reaction provides up to 95% ee in the presence 1 atm of CO at 60°C in the presence of triethylamine.



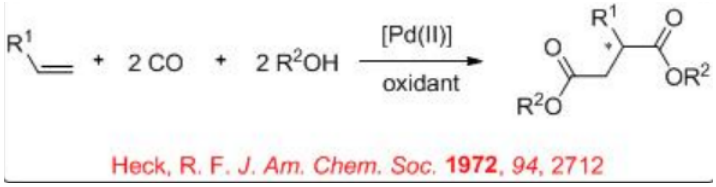
Gotov, N. *et al*., *Org. Lett*. **2001**, *3*, 1753.

Scheme 9.2.3

Bis-Alkoxycarbonylation of Vinylarenes

Optically active butanedioic acid derivatives are important class compounds that can be used as intermediates for the synthesis of pharmaceuticals and building blocks for the construction of inhibitors. Palladium-catalyzed bis-alkoxycarbonylation of alkenes provides effective methods for the construction of these compounds. In 1970, Heck reported the first example of the reaction and its asymmetric version appeared after nearly 20 years. Figure 9.2.4 summarizes some of the ligands employed for the bis-alkoxycarbonylation reactions. Chiral bidentate phosphine, P-N and S,N-ligands have been screened and high enantioselectivity

(92%) is reported in the bis-methoxycarbonylation of styrene with moderate chemoselectivity (50%) employing **21** as the ligand. In case of propene, 60% ee is observed as the highest enantioselectivity with poor chemoselectivity and conversion (13% and 23%, respectively), while the reaction of 4-methyl-1-pentene afforded good chemoselectivity (79%) but with lower enantioselectivity (14% ee).



Scheme 9.2.4

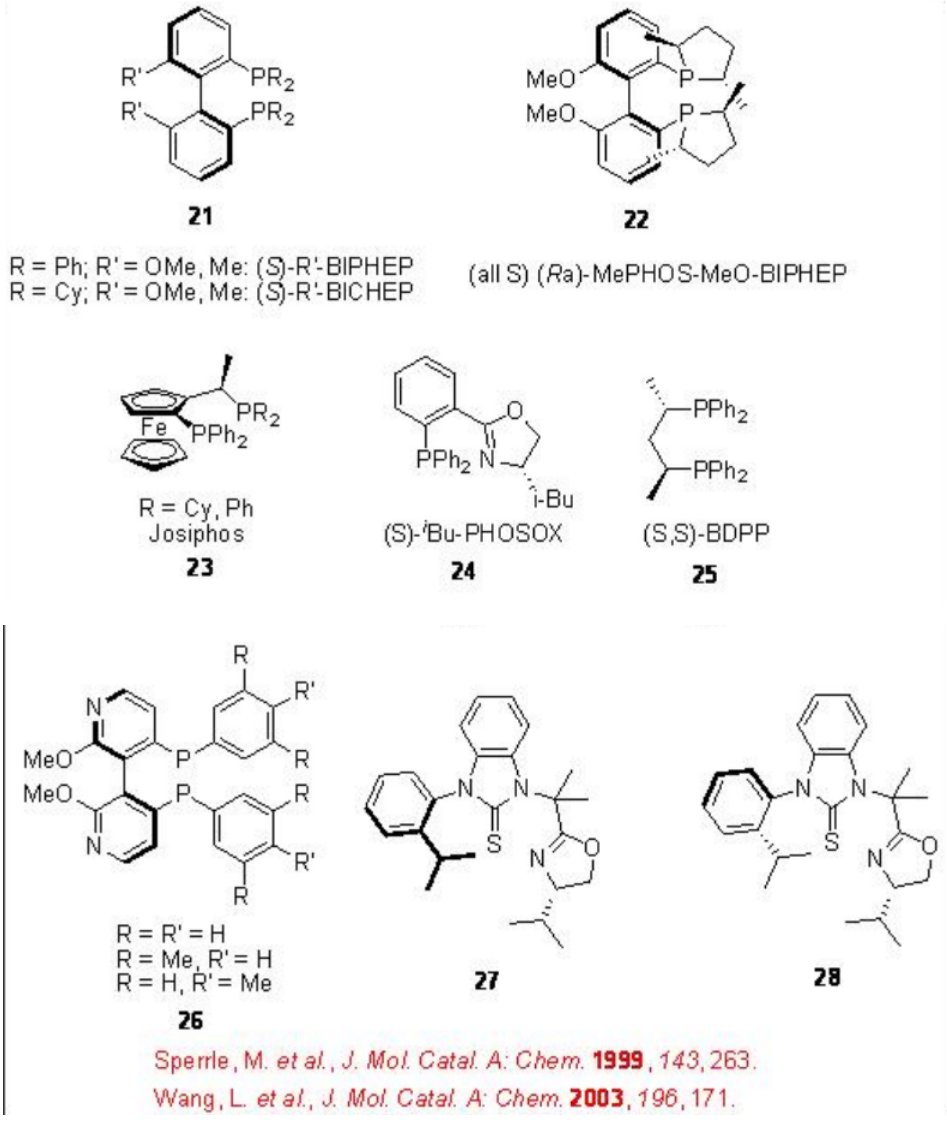
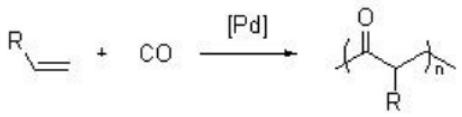


Figure* 9.2.4*: Ligands used in Asymmetric Bis-alkoxycarbonylation of Alkenes

9.3: Co- and Terpolymerization of Alkenes with Carbon Monoxide

The catalytic copolymerization of alkenes with carbon monoxide to afford polyketones is of the industrial interest (Scheme 9.3.1). Polyketones represent low-cost thermoplastics whose synthesis, properties and applications are thus the object of intense fundamental and applied research. The properties of polyketones can be modified by changing the nature or number of monomers, which makes them superior to polyalkenes, polyamides and polyacetals.

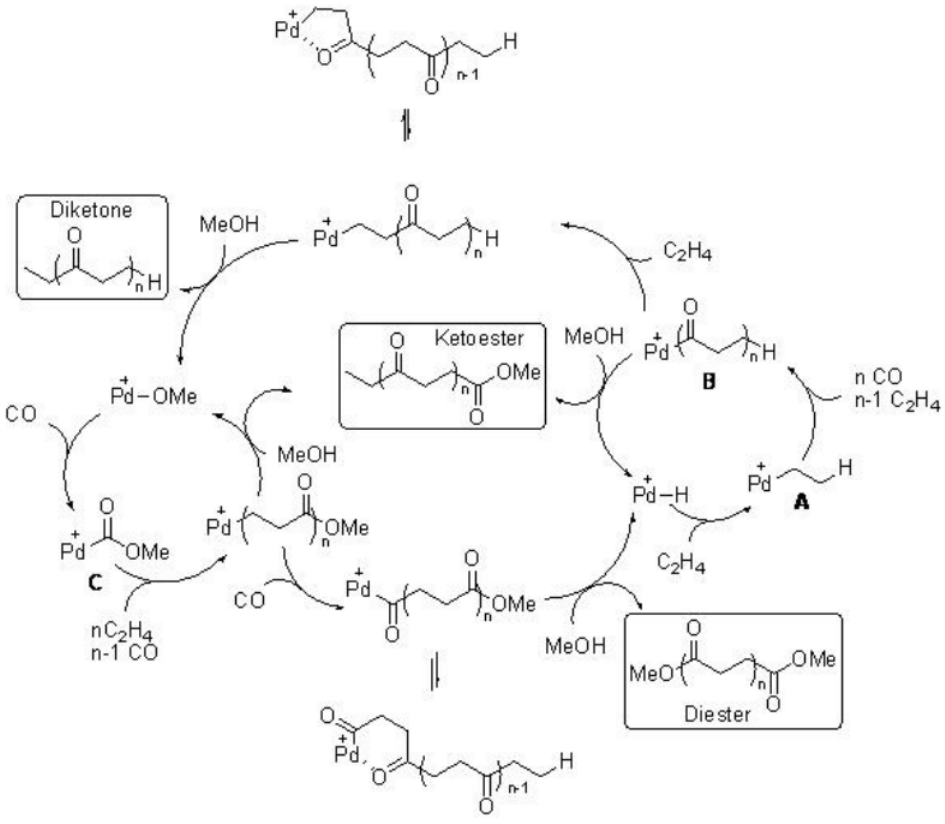


Ash, C. E. *Int. J. Polym. Mater.* **1995**, *30*, 1.

Scheme 9.3.1

The reaction involves two competing catalytic cycles (Scheme 9.3.2). One of the cycles initiates via a Pd-H species, in which, rapid insertion with ethylene with Pd-H leads to the formation of Pd-alkyl species **A** that reacts with CO to give Pd-acyl complex **B** . The latter irreversibly can insert with second ethylene molecule. Thus, the chain propagation occurs through alternating ethylene and CO insertions. Depending on the termination path, the catalytic cycle gives diketones or ketoesters. For example, methanolysis can lead to the formation of ketoester, while protonolysis can give diketones. While the second catalytic cycle initiates via a Pd-OMe species, in which, CO reacts with the Pd-OMe species to a form a Pd-carbomethoxy complex **C** . By this cycle ketoester is also produced along with copolymer diester that is produced via methanolysis of a Pd-acyl complex. Thus, the methonolysis is the main terminating step of the reaction and the ethylene insertion is the rate determining step of the reaction.

With respect to the CO/vinylarene copolymerization, the main features of the catalytic cycle are comparable to that of the CO/ethylene copolymerization. In particular, the chain propagation step is similar, although, the termination and initiation steps will depend on the nature of the alkenes.



Drent, E. *et al.*, *Chem Rev.* **1996**, *96*, 663

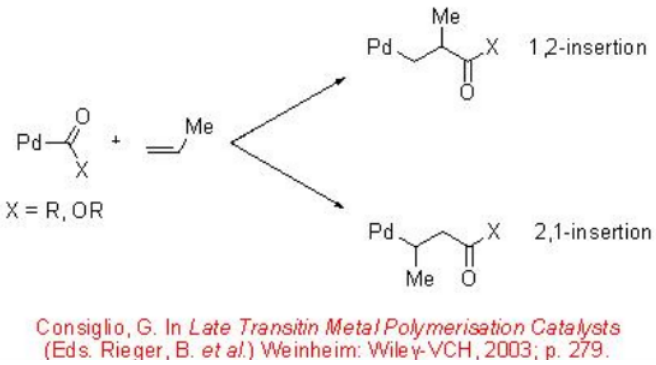
Scheme 9.3.2

9.3.1 Asymmetric Copolymerization of CO with Aliphatic Alkenes

Unlike the reaction with ethylene, the CO/propene copolymerization can afford stereoregular copolymers. The mode of insertion of the propene into the Pd-acyl or Pd-carbomethoxy bond in a 1,2 or 2,1-fashion governs the regiochemistry (Scheme 9.3.3). The stereochemistry of the reaction can lead to the formation of isotactic, syndiotactic or atactic structure (Scheme 9.3.4).

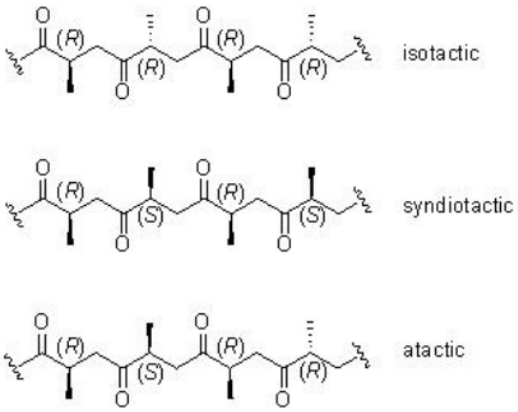
The best results are obtained utilizing catalyst containing bidentate phosphine ligands. The steric and electronic properties of the ligands control the activity of the catalyst and selectivity of the products. Scheme 9.3.5 summarizes some of the active ligands for the CO/propene copolymerization process that provide highly regio- and stereoselective co-polymers.

These catalysts are also effective for the copolymerization of CO with higher aliphatic 1-alkenes but slightly lower activity is observed compared to that with the reaction of propene. However, the regio- and stereoselectivities are found to be similar to that of propene reaction.

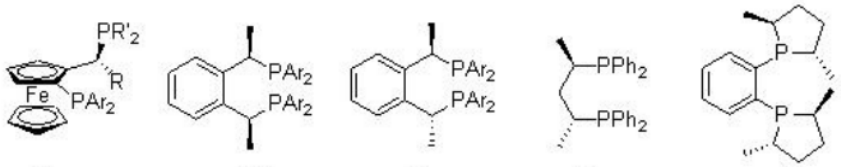


Consiglio, G. In *Late Transitin Metal Polymerisation Catalysts* (Eds. Rieger, B. *et al.*) Weinheim: Wiley-VCH, 2003; p. 279.

Scheme 9.3.3



Scheme 9.3.4

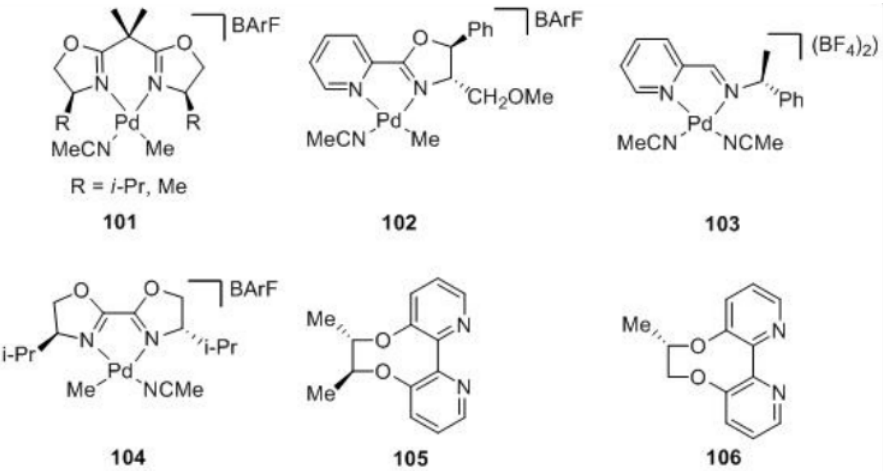


Nozaki, K. *et al.*, *Polyhedron* **1998**, *17*, 1159.
Gambs, C. *et al.*, *Angew. Chem. Int. Ed.* **2000**, *39*, 2486.

Scheme 9.3.5: Examples of Chiral ligands used in CO/Propene Copolymerization

9.3.2 Asymmetric Copolymerization of CO with Vinylarenes

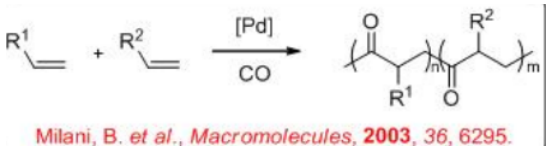
Unlike the CO/propene polymerization process that employs phosphine based ligands, the copolymerization of styrene with CO is generally found to be successful with dinitrogen ligands. Scheme 6 summarizes some of the successful dinitrogen based chiral ligands and chiral Pd-complexes for the CO/styrene copolymerization process.



Scheme 9.3.6: Ligands and Catalysts used in Pd-Catalyzed CO/Styrene Copolymerization

9.3.3 Asymmetric CO/Alkenes Terpolymerization

The CO/alkene copolymer is packed in orderly that makes highly crystalline and very fragile. One of the ways to somewhat disturb the orderly crystal packing in the copolymer is the introduction two different kinds of alkenes so that they can have two types of units: CO/alkene$_1$ and CO alkene$_2$(Scheme 9.3.7). Both chiral phosphines and chiral diamine ligands are found to be effective for these reactions.



Scheme 9.3.7

9.4: Problems and Reference

Problems

How does the product formation differ from cyclic alkenes compared to that of acyclic alkenes?

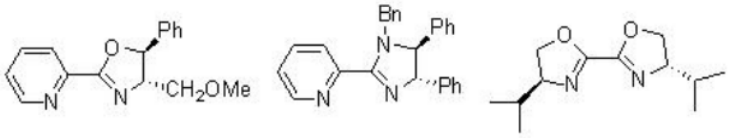
Write a mechanism for the Rh-catalyzed hydroformylation of alkenes.

What is the major difference between the Rh-catalyzed hydroformylation and the Pd-catalyzed hydroxy- and alkoxycarbonylation reactions?

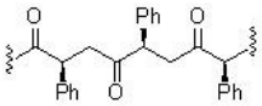
What is the role of benzoquinone in the palladium-catalyzed bis-alkoxycarbonylation of alkenes?

Complete the following reactions.

Propose synthetic routes for the preparation of the following chiral ligands.



How will you prepare the following syndiotactic copolymer.



Reference

I. Ojima, *Catalytic Asymmetric Synthesis* , 3 rd ed., Wiley, New Jersey, 2010.

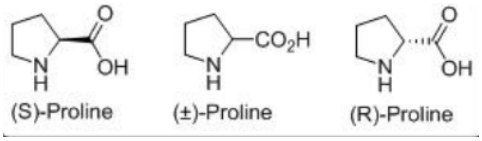
CHAPTER OVERVIEW

10: Organocatalysis

10.1: Chiral Proline Based Reactions

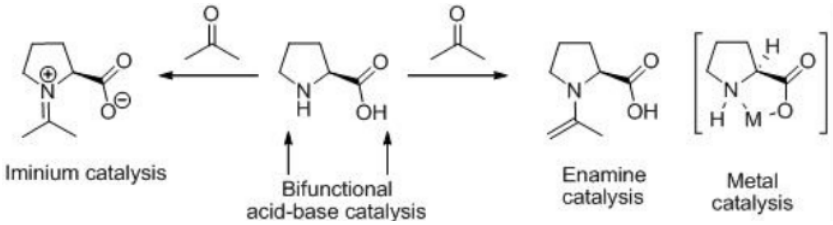
Enantioselective organocatalysis has emerged as a powerful synthetic method complementary to the metal- and enzyme-catalyzed reactions. The low toxicity associated with organocatalysis and operational simplicity makes it an attractive method to synthesize complex structures. Among the organocatalysts, small molecules like chiral proline, chiral thiourea, chiral TADDOL and chiral alkaloids have special reactivity in the asymmetric synthesis.

Chiral proline is termed as the simplest bifunctional organocatalysts (Scheme 10.1.1). This amino acid is called as “simplest enzyme” due to its ability to catalyze reactions with high stereoselectivity.



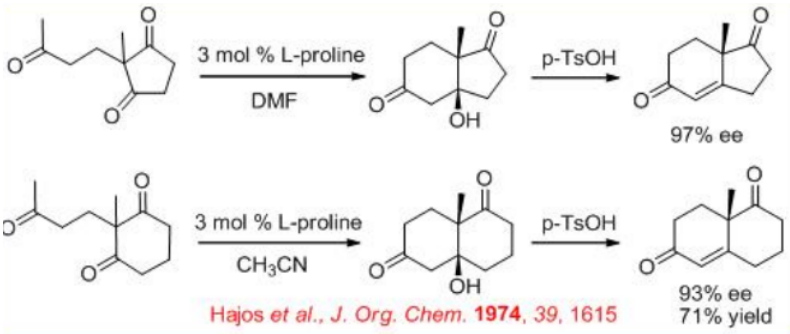
Scheme 10.1.1: Forms of Proline Available

L-Proline is a small molecule, non-toxic, inexpensive, readily available in both enantiomeric forms having bifunctional acid-base sites (Scheme 10.1.2). The reaction may proceed through either iminium catalysis, or enamine catalysis or bifunctional acid–base catalysis.

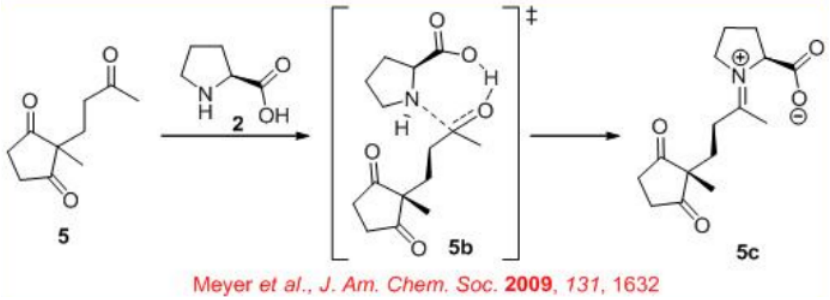


Scheme 10.1.2: Reactivity Modes of L-Proline

In the early 1970, the first L-proline-catalyzed aldol cyclization was appeared (Scheme 10.1.3). After nearly 25 years, the expected transition state for the reaction has been illustrated (Scheme 10.1.4).



Scheme 10.1.3: L -Proline-Catalyzed Robinson Annulation Through Aldol Reaction

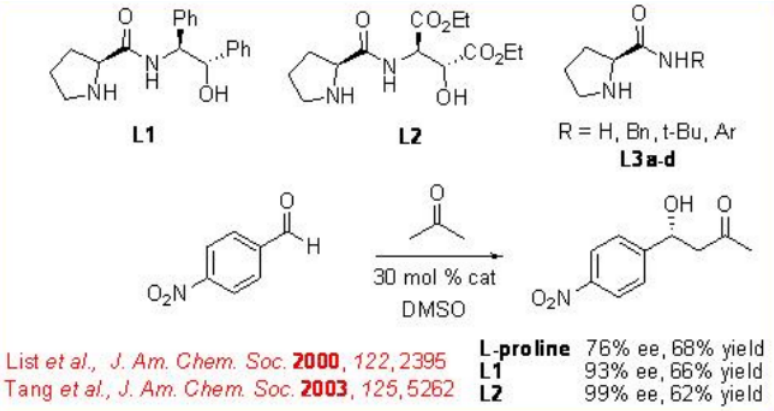


Scheme 10.1.4: Expected Transition State

Intermolecular Aldol Reaction

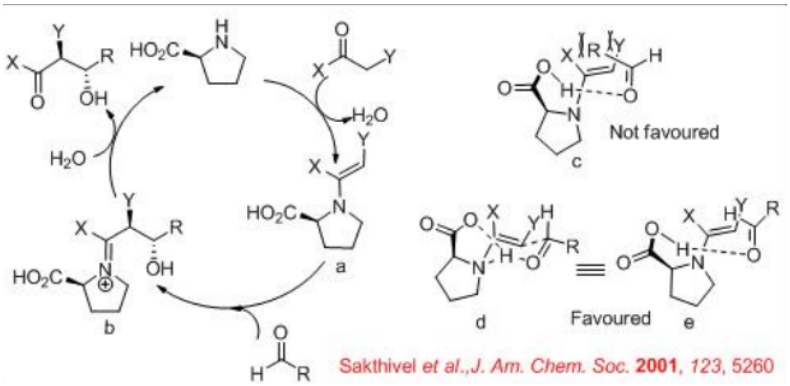
The enantioselective aldol reaction is one of the most powerful methods for the construction of chiral polyol. The first intermolecular direct enantioselective aldol reaction catalyzed by L-proline appeared employing acetone and 4-nitrobenzaldehyde

as the substrates (Scheme 10.1.5). This result sparked high interest from several groups in further investigating proline-catalyzed direct asymmetric aldol reactions. Subsequently, modified chiral proline derived catalysts **L1-3** has been developed to enhance the selectivity of the reaction.



Scheme 10.1.5: First L-Proline Catalyzed Direct Aldol Reaction

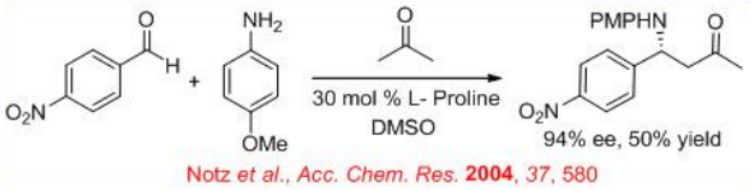
For the mechanism, reaction of pyrrolidine with the carbonyl donor can give enamine **a** that could proceed reaction with the *re* -face of the aldehydes to give the iminium ion **b** (Scheme 10.1.6). The latter can undergo hydrolysis to afford chiral β-hydroxyketone. The proposed transition state illustrates that enamine attack occurs on the *re* -face of the aldehyde **d** and **e**. This facial selectivity of attack by the enamine is dictated by minimizing steric interactions between the aldehyde substituent and the enamine substituent. The attack of the enamine on the *si* -face of the aldehyde leads to the unfavorable transition state **c** .



Scheme 10.1.6: Mechanism for Proline Catalyzed Aldol Reaction

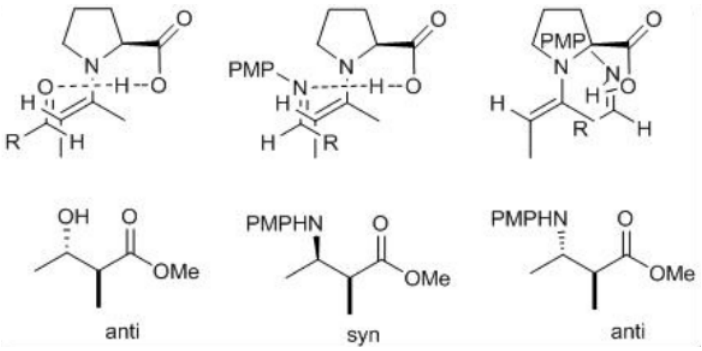
Mannich Reaction

Parallel to the aldol reaction, enantioselective *Mannich* reaction of aldehyde, acetone and *p* -anisidine as the substrates has been explored with 50% yield and 94% ee (Scheme 10.1.7).



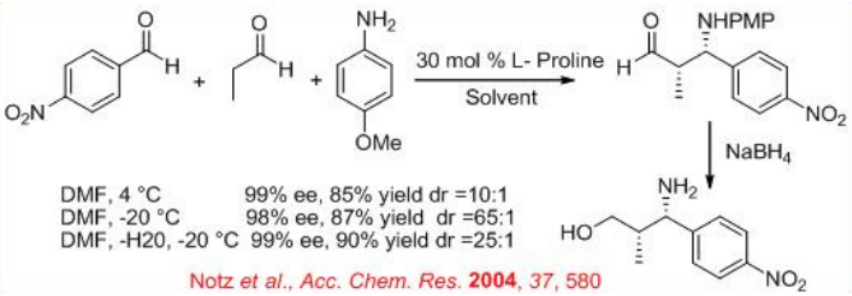
Scheme 10.1.7: L-Proline-Promoted One-Pot Three-Component Mannich-Type Reaction

The mechanism is analogous to that of the aldol reactions (Scheme 10.1.8). The reaction of proline with aldehyde or ketone can give *enamine* that could undergo reaction with the imine to form new stereocenters as iminium product. The latter on hydrolysis can give the target *Mannich* product. The reaction of (*E*)-aldimine with the enamine on its *si* -face can give the *syn* product. Because of the *re* -face is blocked by steric interactions between the aromatic ring of the *p* -methoxyphenyl group and the ring of proline.



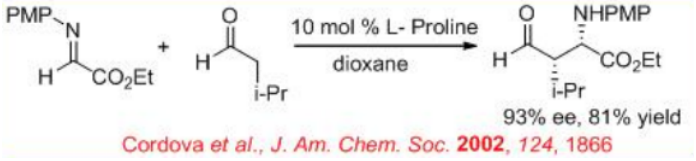
Scheme 10.1.8: Proposed Transition States and Products for the *Mannich* Reactions

The proline-catalyzed *Mannich* reactions of *N* -PMP-protected α-imino ethyl glyoxylate with a variety of ketones afford functionalized α-amino acids (Scheme 9). These reactions can generate two adjacent stereogenic centers simultaneously upon C-C bond formation with complete *syn* -stereocontrol and can be performed in a gram scale with operational simplicity.



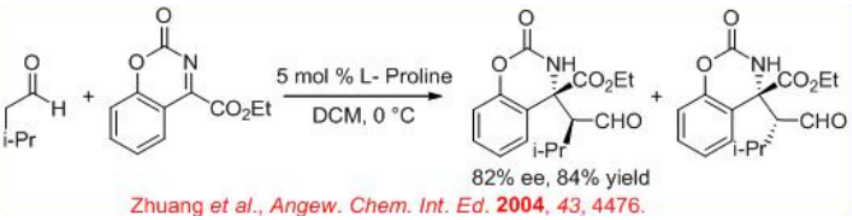
Scheme 10.1.9: One-Pot Three-Component Mannich-Type Reaction

The proline-catalyzed reaction of *N* -PMP-protected α-imino ethyl glyoxylate with aliphatic aldehydes provides a general method for synthesis of β-amino and α-amino acid derivatives (Scheme 10.1.10). The diastereoselectivity depends on the bulkiness of the substituents of the aldehyde donor. In most of cases high *syn* stereoselectivity can be achieved.



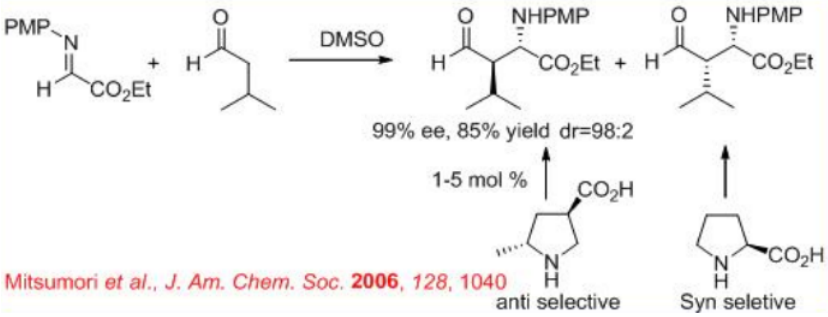
Scheme 10.1.10: Mannich Reactions of Unmodified Aldehydes with Preformed Aldimines

The synthesis of chiral quaternary amino acid derivatives can be accomplished using proline based catalysis (Scheme 10.1.11). The nitrogen is tethered to the α -aryl amine in order to increase the reactivity through ring strain and the products are obtained with high enantioselectivity.



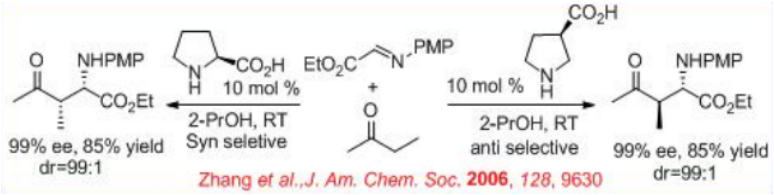
Scheme 10.1.11: Mannich Reaction of Unmodified Aldehyde with Ketimines

(*S*)-Proline-catalyzed Mannich-type reaction of aldehydes with α-imino ethyl glyoxylate affords *syn* -products, while the reaction utilizing (3*R*, 5*R*)-5-methyl-3-pyrrolidinecarboxylic acid gives *anti* -selective product (Scheme 10.1.12).



Scheme 10.1.12: Anti and *Syn* Selectivity in Mannich reaction

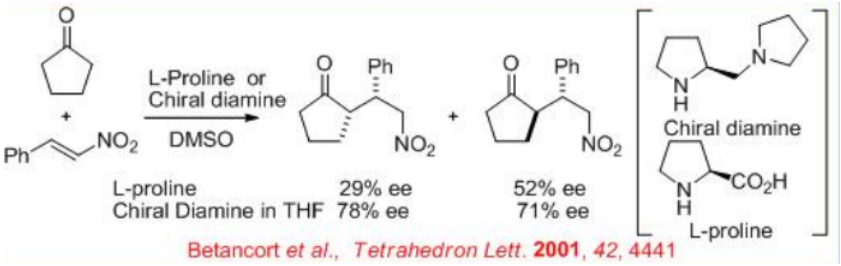
In addition , *(R*)-3-pyrrolidinecarboxylic acid catalyzes the Mannich-type reactions of ketones with α-imino ethyl glyoxylate to give *anti* -products, while *(S)*- proline based reactions give *syn* -products (Scheme 10.1.13). Thus, the position of the carboxylic acid group on the pyrrolidine ring directs the stereoselection of the catalyzed reaction providing either *syn* - or *anti* -Mannich products.



Scheme 10.1.13: Anti and *syn* Mannich-type Reactions of Ketones

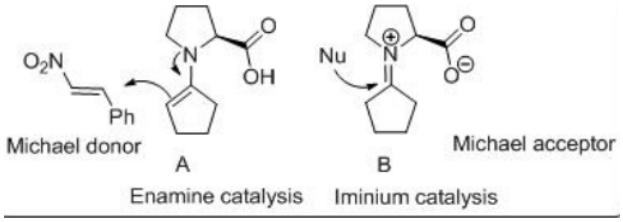
Michael Reaction

In 2001, the first example for a direct asymmetric Michael reaction employing an enamine-activated donor appeared. The proline-catalyzed reaction of acetone and cyclopentanone with benzalmalonate and nitrostyrene affords the Michael product with low enantiomeric excess. However, the use of chiral diamine improves the *ee* significantly with both nitrostyrene and alkylidene malonates as acceptors and ketone donors (Scheme 10.1.14).



Scheme 10.1.14

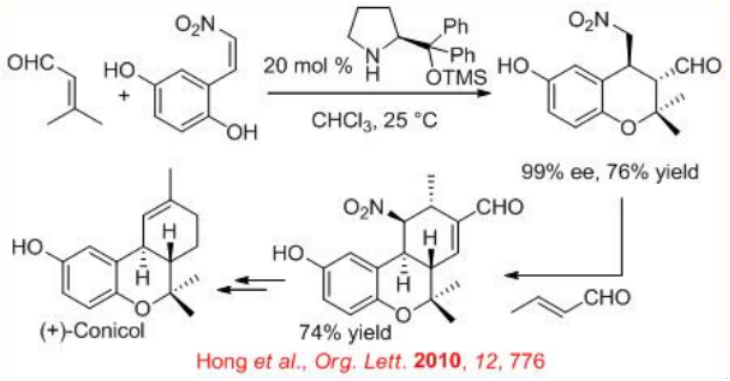
Possible stereochemical result has been accounted by assuming acyclic transition states **A** and **B** . These Michael reactions constituted the first direct catalytic asymmetric reactions of any type s involving aldehyde donors and encouraged the development of aldehyde-based reactions with a range of electrophiles (Scheme 10.1.15).



Scheme 10.1.15: Mode of Action in Chiral Michael Reaction

The iminium-enamine activation mode can be envisaged to explain the domino oxa-Michael–Michael reaction occurring between 3-methylbut-2-enal and (*E*)-2-(2-nitrovinyl)-benzene-1,4-diol upon catalysis with chiral diphenyl prolinol silyl ether, which afford the corresponding enantiopure oxa-Michael–Michael cycloadduct in 76% yield and 99% ee (Scheme 10.1.16). The latter can be further implicated in a Michael–aldol sequence through the reaction with crotonaldehyde to afford corresponding hexahydro-6H-

benzo-chromene in 74% yield. These two domino reactions have constituted the key steps of the first asymmetric total synthesis of the natural biologically active product (+)-conicol.



Scheme 10.1.16: Domino oxa-Michael–Michael Reaction in the Synthesis of (+)-Conicol

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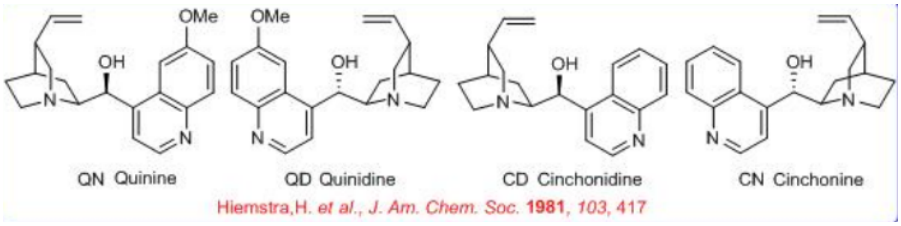
10.2: Alkaloid Based Reactions

Conjugate Addition Reactions

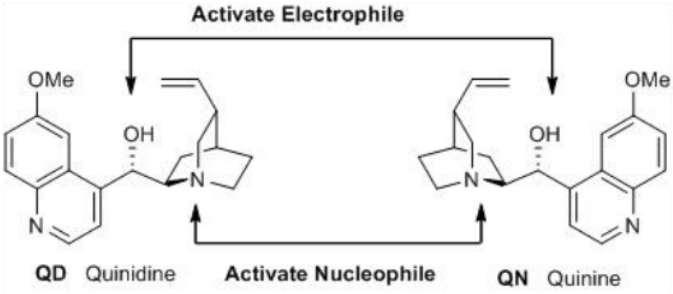
Cinchona alkaloids are a large class of compounds extracted from the bark of homonym trees cultivated in equatorial climatic zones, between Bolivian and Venezuelan Andes, and Indonesia. In the extract of the bark are present more than 30 alkaloids (5-15% w/w). Four of them represent 50% of all the alkaloids such as quinine (QN), quinidine (QD), cinchonidine (CD) and cinchonine (CN) (Scheme 10.2.1).



Scheme 10.2.1: Bifunctional Alkaloid Based Organocatalysts

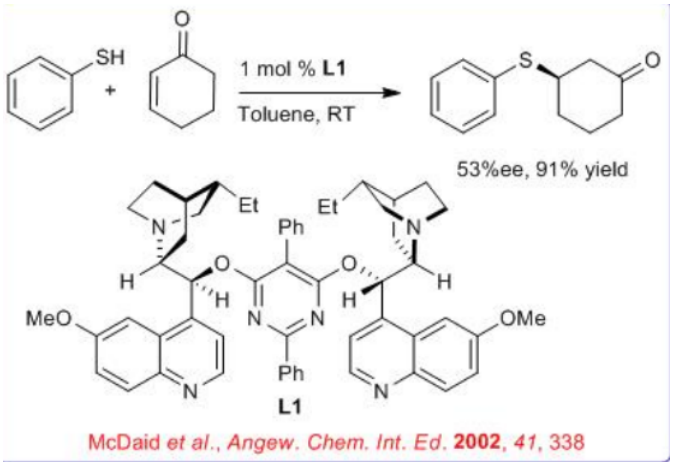
QN is the most well known alkaloid and used as the anti-malarial drug of choice for over 400 years until chloroquine discovered, while QD is used as an anti-arrhythmic agent. In chemistry, all these compounds (QN , QD , CD and CN) are used as cheap chiral source. These molecules activate the nucleophile by enamine and carbanion formation, and electrophile via hydrogen bond.

These compounds are diastereomers having five stereogenic centers and the chiral quinuclidinyl nitrogen is the most important as it is responsible of the direct transfer of chirality during catalysis. Quinine *vs* quinidine and cinchonidine *vs* cinchonine have opposite absolute configuration this means that very often these pairs of diastereomers act as enantiomers at C-9 position. Furthermore, the C-9 OH group acts as Brønsted acid. So acid and base coexist in these molecules, and thus, it is possible to activate both the nucleophile and the electrophile simultaneously to use as *bifunctional organocatalysts* (Scheme 10.2.2).



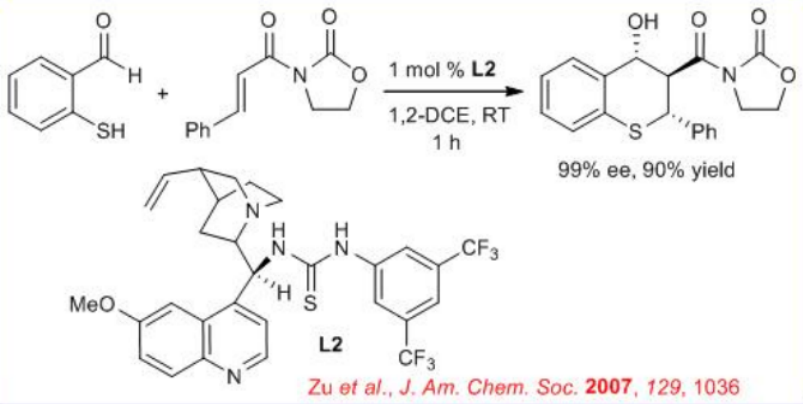
Scheme 10.2.2:Dual Activation Modes by Bifunctional Basic QD and QN Organocatalysts

The catalytic asymmetric 1,4-addition of thiols to cyclic enones with modified cinchona alkaloid has been demonstrated (Scheme 10.2.3). The Michael products can be isolated with high yield and enantioselectivity for a range of substances.



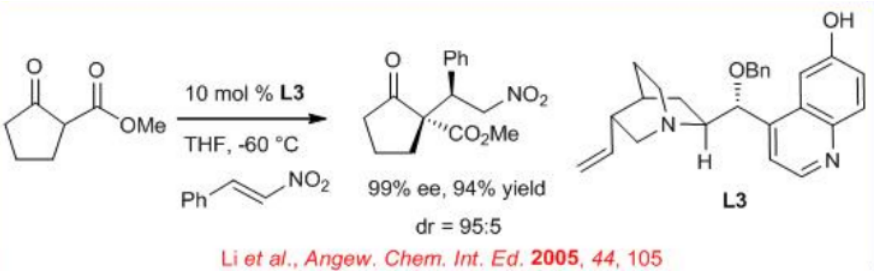
Scheme 10.2.3: Enantioselective Michael Addition of Thiophenols to Enones

Later, tandem Michael-aldol reactions have been developed for the preparation of medicinally important chiral thiochromanes (Scheme 10.2.4). This new one-pot process proceeds with 1 mol % of the cinchona alkaloid derived thiourea catalyst **L2** , which synergistically activates both the Michael donor and acceptor.



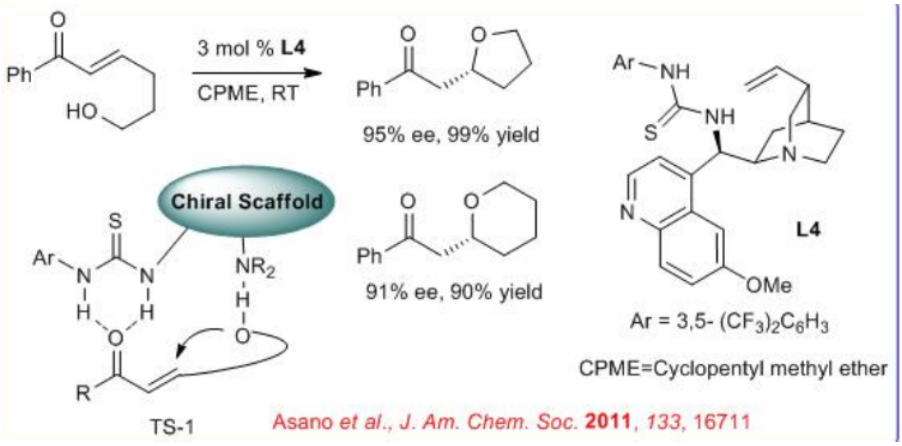
Scheme 10.2.4: Reaction of 2-Mercaptobenzaldehyde with α,β -Unsaturated oxazolidinone

Similarly, the conjugate addition has been reported with catalyst **L3** for a direct, stereocontrolled construction of adjacent carbon- or heteroatom-substituted quaternary and tertiary stereocenters from readily available starting β -ketoester (Scheme 10.2.5).



Scheme 10.2.5: Asymmetric Michael Addition Reaction

Chiral oxacyclic structures such as tetrahydrofuran rings are commonly found in many bioactive compounds. Cinchona-alkaloid-thiourea **L4** catalyzes the cycloetherification of ε-hydroxy-α,β-unsaturated ketones with excellent enantioselectivity, even with low catalyst loadings at room temperature. The probable activation intermediate might go through TS-1.

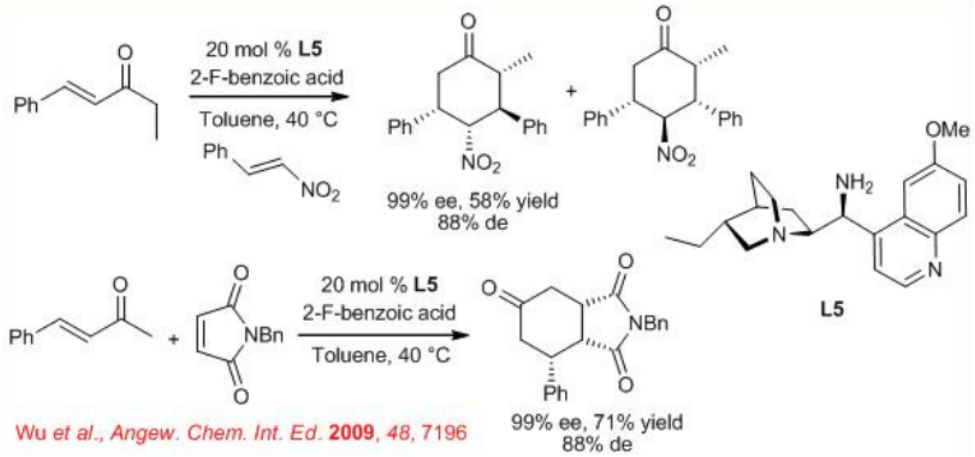


Scheme 10.2.6: Cycloetherification via intramolecular oxy-Michael addition reaction

The catalyst **L4** can also catalyze the domino aza-Michael–Michael reactions of anilines with nitroolefin enoates to afford chiral 4-aminobenzopyrans bearing two consecutive stereogenic centers and one quaternary stereocenter (Scheme 10.2.7). The products can be isolated with high yield and enantioselectivity.

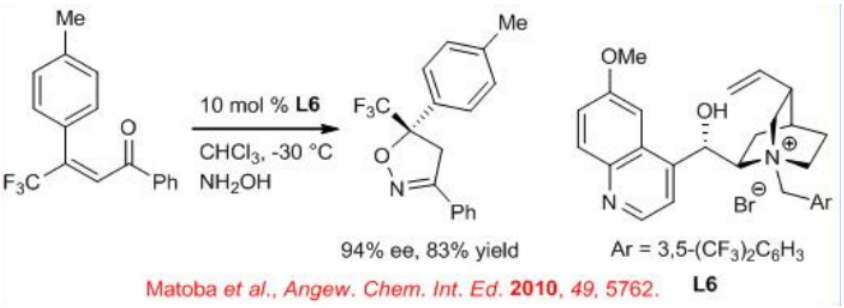
Scheme 10.2.7: Domino aza-Michael–Michael Reactions

Chiral amine **L5** has been used to activate α,β -unsaturated enones with nitro alkenes toward a well-defined enamine-iminium activation mode in presence of 2-fluorobenzoic acid as an additive. The reaction affords the Diels–Alder adduct bearing three or four stereogenic centers with high enantioselectivity (Scheme 10.2.8). The extension of this process to other Michael acceptors such as *N* -benzyl maleimide leads to the formation of cyclohexanones with up to >99% ee



Scheme 10.2.8: Asymmetric Domino Michael–Michael Reactions

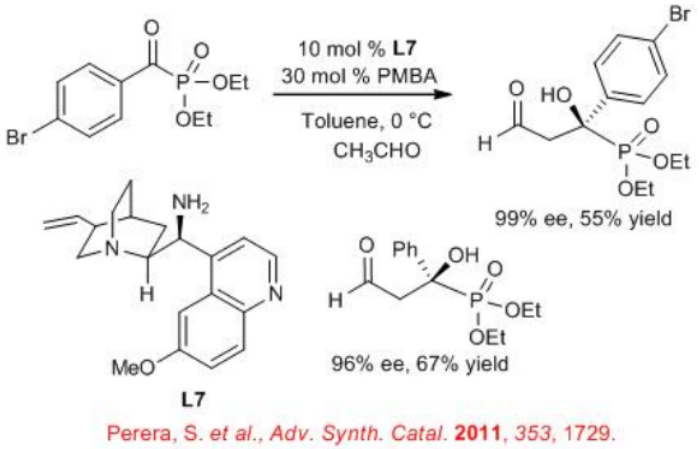
The synthesis of trifluoromethyl-substituted 2-isoxazolines can be accomplished by a domino Michael–cyclization–dehydration reaction of hydroxylamine (NH_2OH) with a range of *(E)*- trifluoromethylated enone derivatives in the presence of *N* -3,5-bis(trifluoromethyl benzyl) quinidinium bromide **L6** as a chiral phase transfer catalyst (Scheme 10.2.9).



Scheme 10.2.9: Synthesis of Trifluoromethyl Substituted 2-Isoxazolines

Aldol Reaction

The cross-aldol reaction between enolizable aldehydes and α -ketophosphonates can be achieved using 9-amino-9-deoxy- *epi* -quinine **L7** (Scheme 10). The reaction works especially well with acetaldehyde, which is a tough substrate for organocatalyzed cross-aldol reaction.

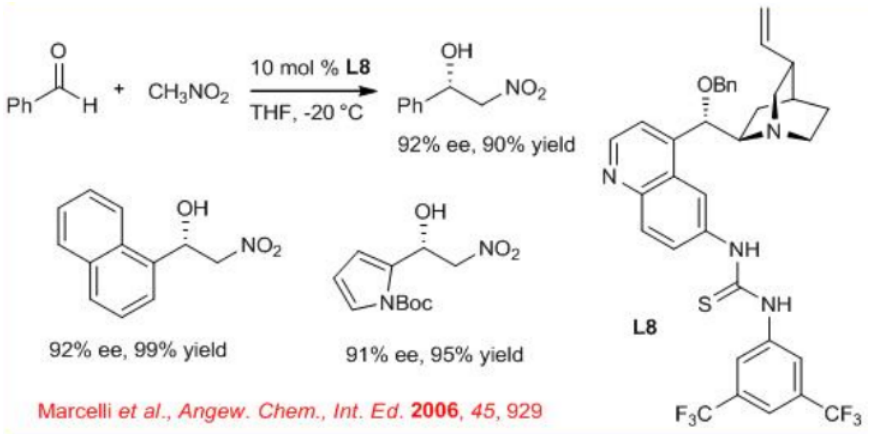


Perera, S. *et al., Adv. Synth. Catal.* **2011**, *353*, 1729.

Scheme 10.2.10

10.2.3 Henry Reaction

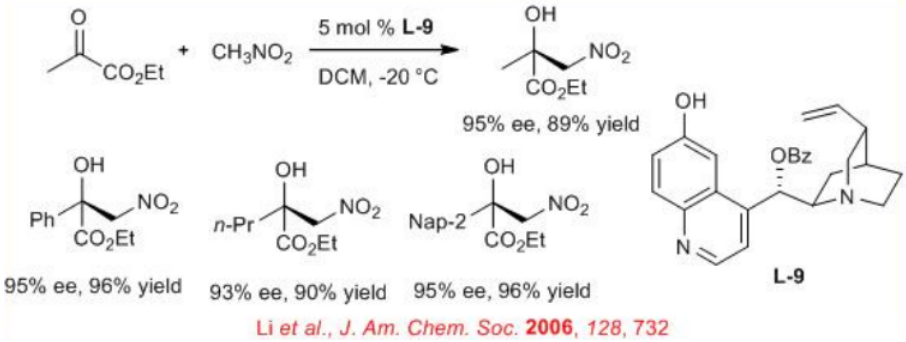
Henry reaction is a classical carbon-carbon bond forming reaction in organic synthesis. Aryl aldehydes react with nitromethane in the presence of 6'-thioureasubstituted cinchona alkaloid **L8**with high enantioselectivity (Scheme 10.2.11). Hydrogen-bond donor at the C6′ of **L8** has been found to induce preferential formation of one enantiomer.



Marcelli *et al., Angew. Chem., Int. Ed.* **2006**, *45*, 929

Scheme 10.2.11

The 6'-OH cinchona alkaloid **L-9** is an excellent catalyst for the reaction of α- ketoesters with nitromethane (Scheme 10.2.12). The highly enantioenriched products from the Henry reaction could be elaborated to aziridines, *β*- lactams and α -alkylcysteines. This reaction is operationally simple and affords high enantioselectivity as well as good to excellent yield for a broad range of α-ketoesters .

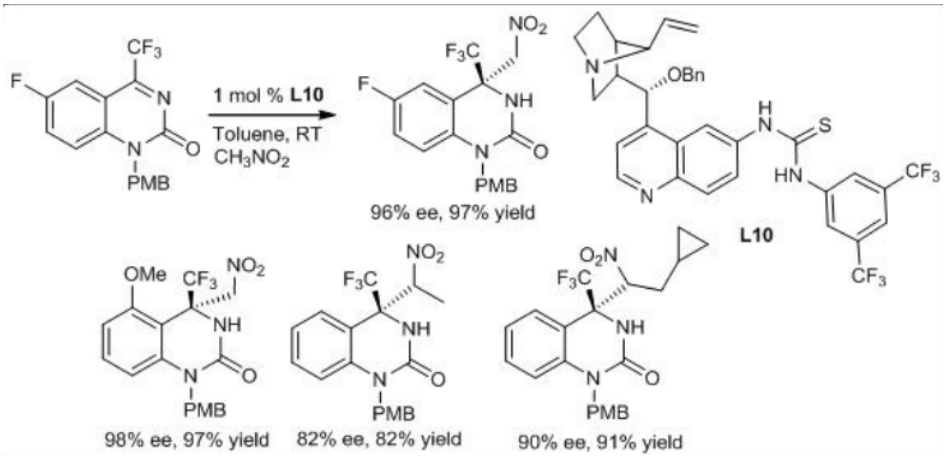


Li *et al., J. Am. Chem. Soc.* **2006**, *128*, 732

Scheme 10.2.12: Cinchona-Catalyzed in Henry Reaction

Bifunctional cinchona alkaloid-thiourea **L10** can catalyze efficiently the aza-Henry reaction of cyclic trifluoromethyl ketimines with nitromethanes (Scheme 10.2.13). The title reaction can provide biologically interesting chiral trifluoromethyl

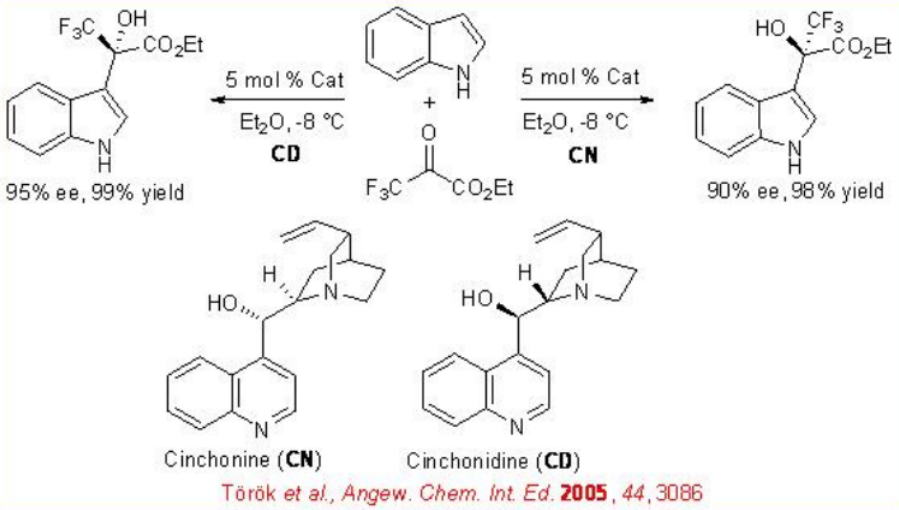
dihydroquinazolinone frameworks with high yield and enantioselectivity.



Scheme 10.2.13: Cinchona-Catalyzed in Henry Reaction

Hydroxyalkylation Reaction

The readily available cinchonidine (CD) and cinchonine (CN) can be used for the catalysis of the hydroxyalkylation of heteroaromatics. For example, the hydroxyalkylation of indoles with ethyl-3,3,3-trifluropyruvate occurs to afford corresponding 3-substituted products in high yields and ee values (Scheme 10.2.14) .

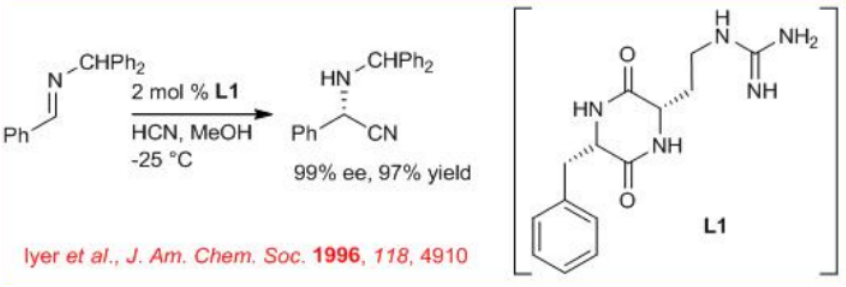


Scheme 10.2.14: Hydroxyalkylation of Indoles with Ethyl-3,3,3-trifluropyruvate

10.3: Thiourea Based Catalysis

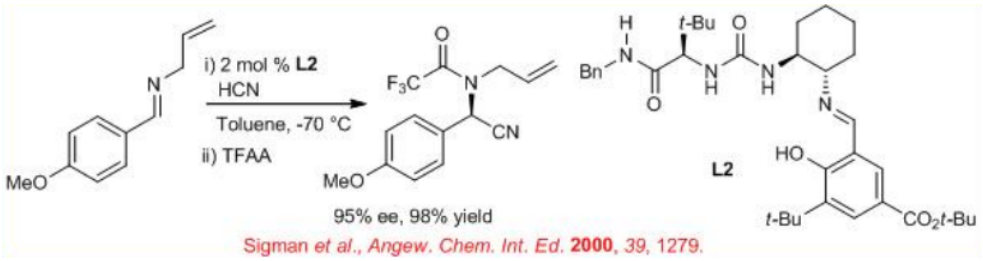
Strecker Synthesis

In 1996 the first asymmetric organocatalytic *Strecker* synthesis appeared employing **L1** as a catalyst (Scheme 10.3.1). The reaction involves the addition of *HCN* to imines in the presence of diketopiperazine derivative with up to >99% ee.



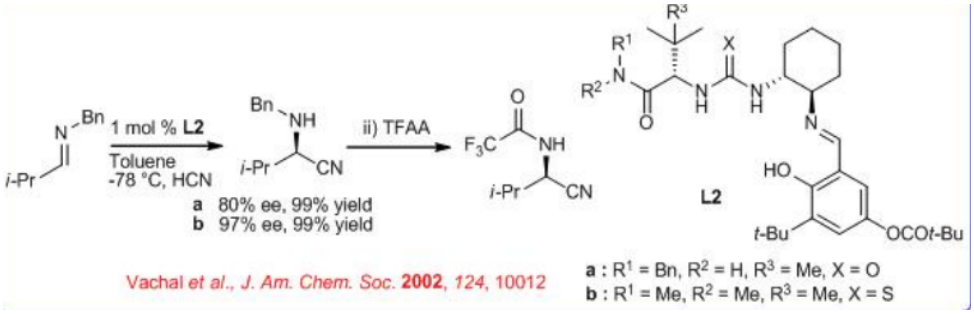
Scheme 10.3.1

Subsequently, chiral thiourea derivative **L2** has been used for this reaction to afford the cyanohydrins with 98% ee (Scheme 10.3.2).



Scheme 10.3.2

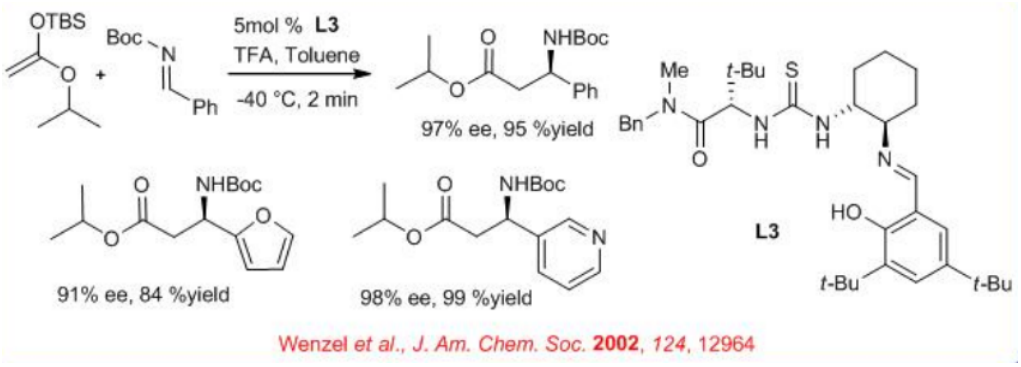
Further improvement in this reaction has been made employing thiourea derivative **L3** (Scheme 10.3.3). The active site of the catalyst, the relevant stereoisomer of the imine substrate and the solution structure of the imine−catalyst complex are elucidated using kinetics, structural activity and NMR experiments. An unusual bridging interaction between the imine and the urea hydrogens of the catalyst is identified.



Scheme 10.3.3: Improved Asymmetric Addition of HCN to Imines

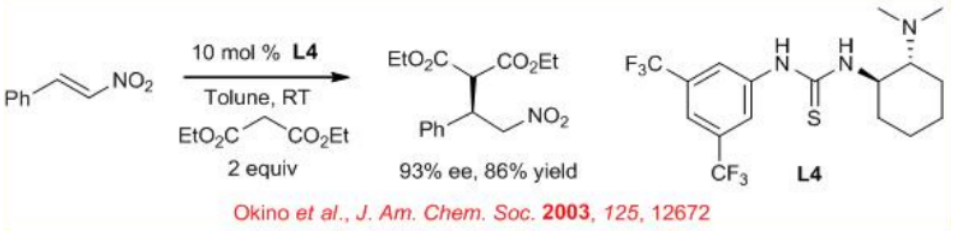
Mannich Reaction

In parallel to Strecker reaction, the Mannich reaction of a wide variety of N -Boc aryl imines is studied in the presence of thiourea derivative **L3** with high enantioselectivity (Scheme 10.3.4). The catalyst **L3** is as highly effective for the asymmetric addition of silyl ketene acetal derivatives to aldimines. From a steric and electronic standpoint, the *N* -Boc imine substrates utilized in this reaction are fundamentally different from the *N* -alkyl derivatives employed in the Strecker reaction.



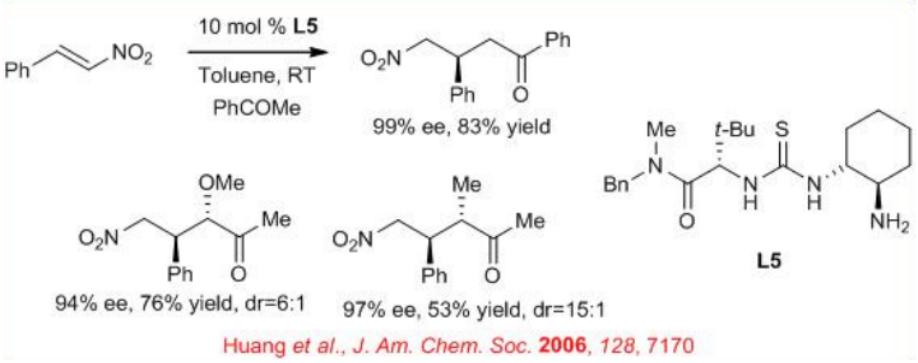
Scheme 10.3.4

Bifunctional thiourea derivative **L4** can catalyze the Michael reaction of malonates with various nitro olefins in high enantioselectivity (Scheme 10.3.5). The catalyst activates nucleophile by general base catalysis and electrophile by H-bonding to the nitro group. This methodology has been applied for enantioselective additions of substituted keto ester and double Michael additions of α,β -unsaturated ketoesters.



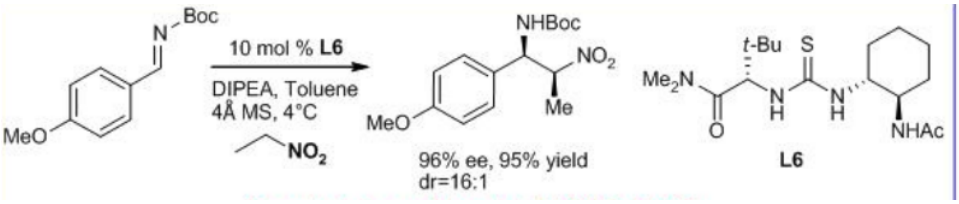
Scheme \PageIndex{5}

Chiral primary amine - thiourea **L5** is effective for the direct conjugate addition of ketones to nitroalkenes (Scheme 10.3.6) . The observed *anti* diastereoselectivity suggests the participation of a (*Z*) -enamine intermediate which is complementary to the diastereoselectivity obtained in analogous reactions involving (*E*) -enamines generated from secondary amine catalysts.



Scheme 10.3.6

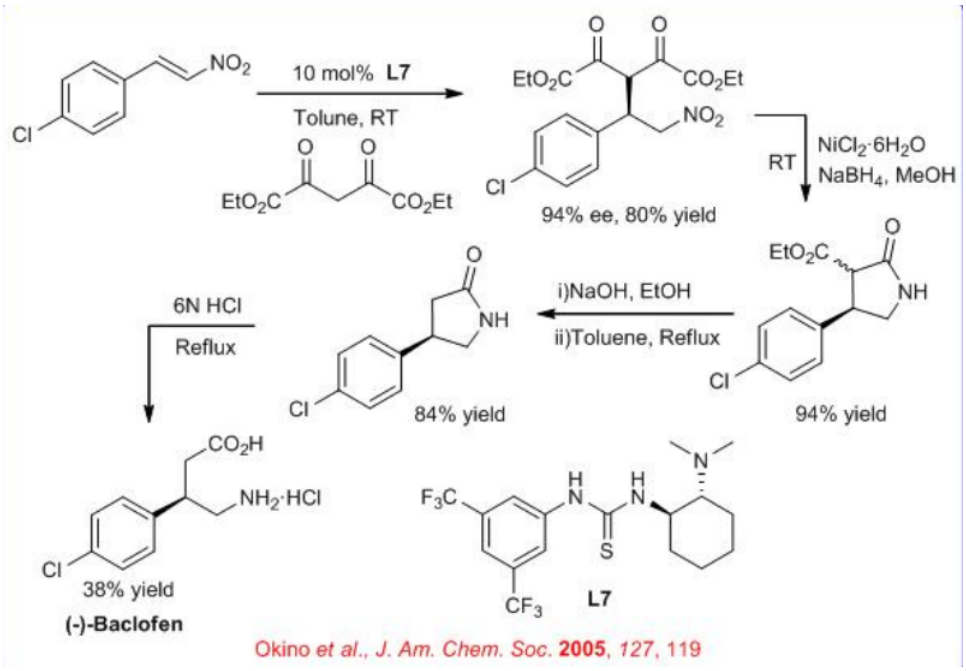
Likewise, the addition of a range of nitroalkanes to aromatic *N* -Boc imines has been shown using the thiourea derivative **L6** with mostly *anti* diastereoselectivity (Scheme 10.3.7).



Scheme 10.3.7

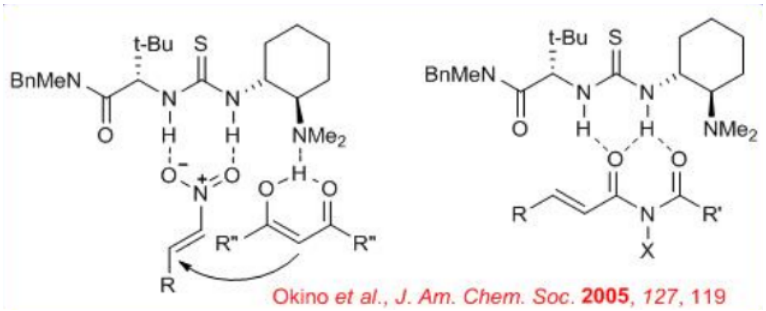
The thiourea catalyst **L7** bearing 3,5-bis(trifluoromethyl) benzene and dimethylamino groups has been revealed to be efficient for the asymmetric Michael reaction of 1,3-dicarbonyl compounds to nitroolefins (Scheme 10.3.8). This methodology has been applied for the total synthesis of (*R*)-(−)-baclofen. Reaction of 4-chloronitrostyrene and 1,3-dicarbonyl compound generates quaternary

carbon center with 94% ee. Reduction of the nitro gruop to amine and subsequent cyclization, esterification and ring opening provides (*R*)-(−)-baclofen in 38% yield.



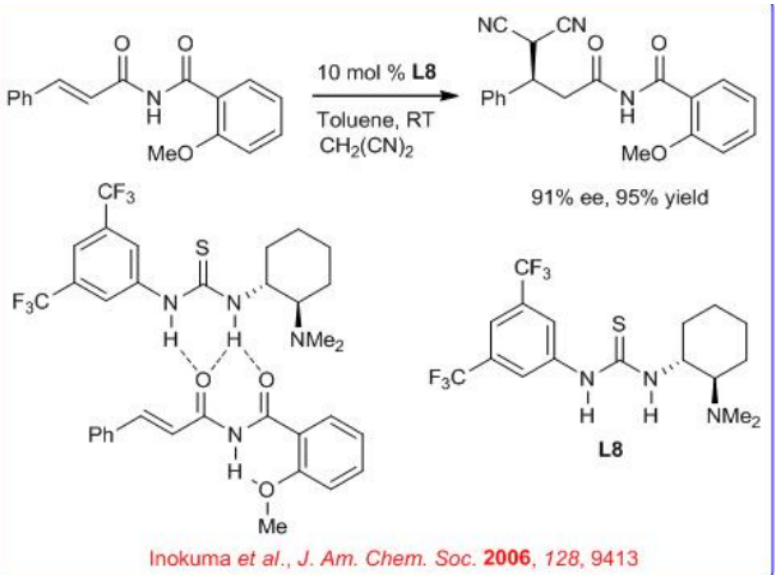
Scheme 10.3.8: Total Synthesis of (*R*)-(−)-Baclofen

The mechanism of above enantioselective Michael addition of acetyl acetone to a nitroolefin catalyzed by a thiourea-based chiral bifunctional organocatalyst has been investigated using density functional theory calculations and the results suggests that both substrates coordinate preferentially via bidentate hydrogen bonds (H-bond) (Scheme 10.3.9). The deprotonation of the enol form of acetylacetone by the amine of the catalyst is found to occur easily, leading to an ion pair characterized by multiple H-bonds involving the thiourea unit as well. Two distinct reaction pathways have been explored toward the formation of the Michael product that differs in the mode of electrophile activation. Both reaction channels are shown to be consistent with the notion of non-covalent organocatalysis in that the transition states leading to the Michael adduct are stabilized by extensive H-bonded networks.



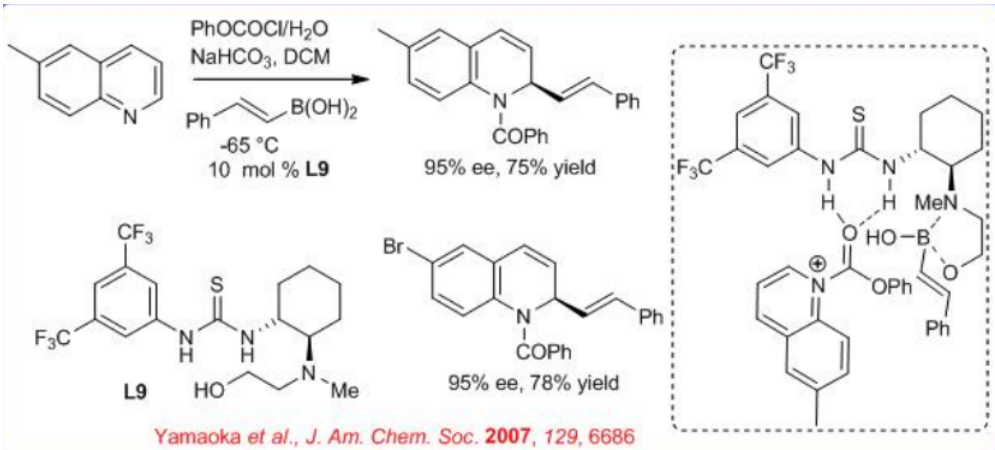
Scheme 10.3.9

A thiourea-catalyzed asymmetric Michael addition of activated methylene compounds to α,β- unsaturated imides have been developed (Scheme 10.3.10). *N* -Alkenoyl-2-methoxybenzamide is the best substrate among the corresponding benzamide derivatives bearing different substituents on the aromatic ring and react with several activated methylene compounds such as malononitrile, methyl α -cyanoacetate, and nitromethane with up to 93% ee. The reactivity can be attributed to the intramolecular H-bonding interaction between the N-H of the imide and the methoxy group of the benzamide moiety.



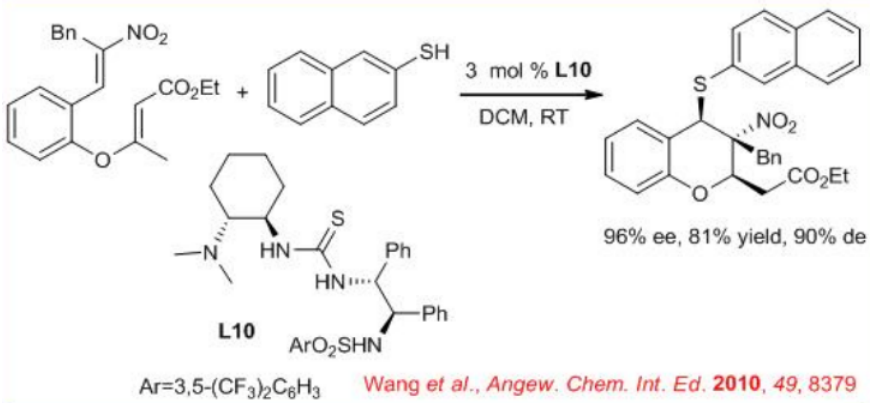
Scheme 10.3.10: Dual-activation of *N* -Alkenoyl-2-methoxybenzamide

Thiourea catalyst **L9** has been explored for the activation of quinoline with organoboronic acids to facilitate stereocontrol in the Petasis transformation even at low temperatures (Scheme 10.3.11). The quinoline gets activated by formation of N-COBz with PhCOCl and a high degree of stereo control can be achieved using a combination of H_2O and $NaHCO_3$ as additives.



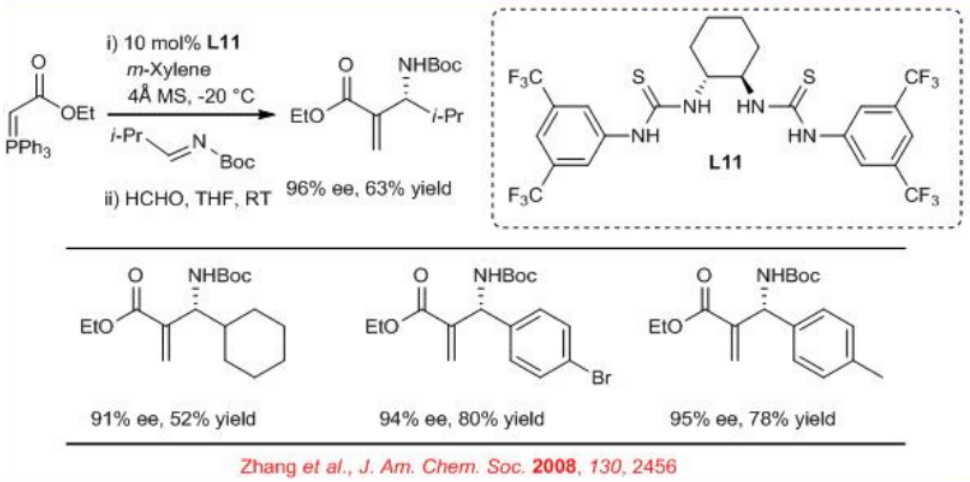
Scheme 10.3.11

The domino thia-Michael–Michael reaction of thiols with nitro olefin enoates provides polyfunctionalized chroman derivatives in a highly stereoselective manner in the presence of thiourea **L10** . Three consecutive stereogenic centers including one quaternary stereocenter can be generated with high enantioselectivity (Scheme 10.3.12). The catalyst **L10** activates nitroolefin enoates through H-bonding activation, and its tertiary amino moiety activates the nucleophilic thiols, forming an intermediate which undergo the intermolecular thia-Michael addition.



Scheme 10.3.12

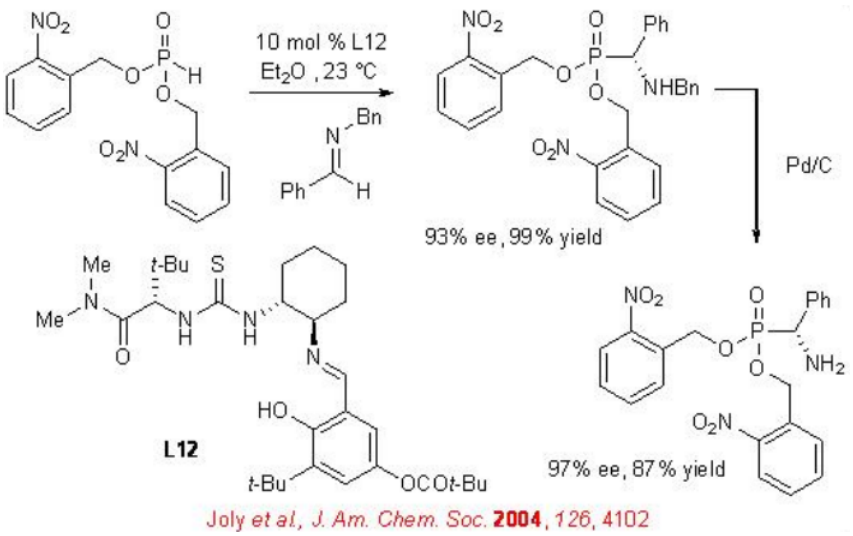
The synthesis of chiral N-Boc- β-Amino- α -methylene carboxylic esters can be performed by reaction of stabilized phosphorus ylides and Boc-protected aldimines in presence of readily available bisthiourea **L11** (Scheme 10.3.13). Subsequent reaction with formaldehyde provides a facile access to chiral *N* -Boc- β-amino- α -methylene carboxylic esters. The catalyst has been found to be recyclable.



Scheme 10.3.13: Mannich-type Reaction of Phosphorus Ylides

Hydrophosphonylation Reactions

Chiral thiourea catalyst **L12** has been used for highly enantioselective hydrophosphonylation of a wide range of *N* -benzyl imines (Scheme 10.3.14). The hydrophosphonylated products can be readily deprotected by hydrogenolysis using Pd/C to provide chiral α-amino phosphonic acids with high enantioselectivity. This methodology provides general and convenient access for the synthesis of optically active α -amino phosphonates.



Scheme 10.3.14: Thiourea-Catalyzed Enantioselective Hydrophosphonylation of Imines: Practical Access to Enantiomerically Enriched α -Amino Phosphonic Acids

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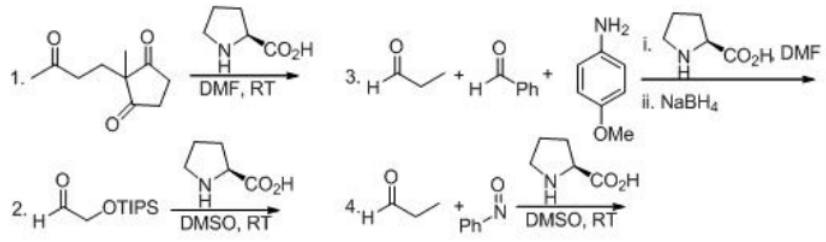
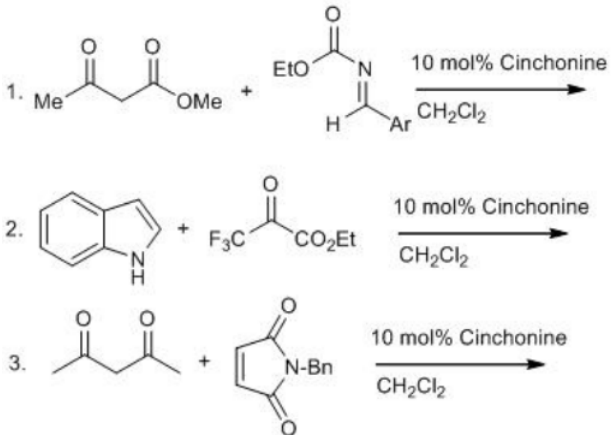
10.4: Problems and Reference

Problems

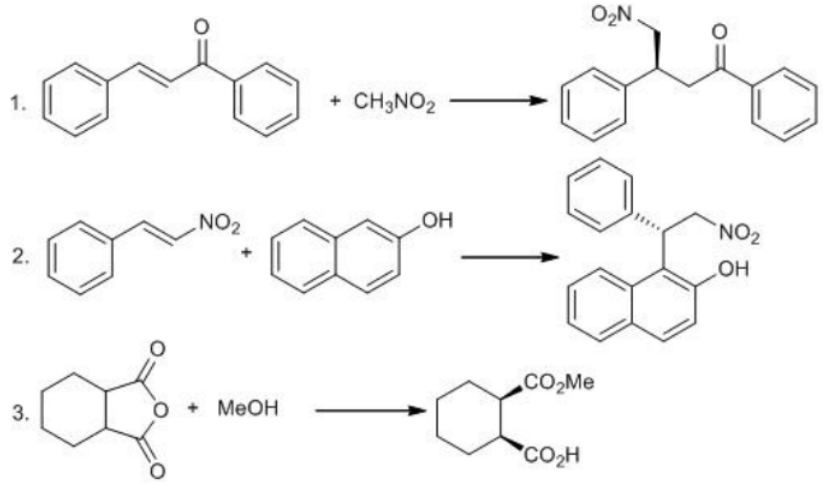
Complete the following reactions.



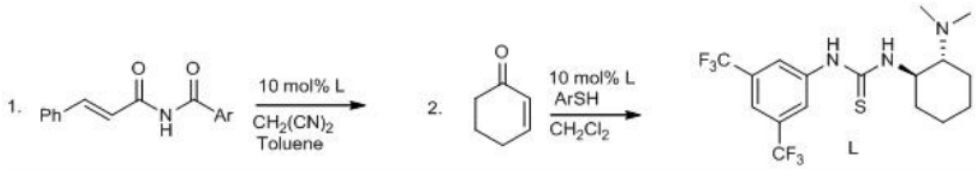
Complete the following reactions.



How will you carry out the following using thiourea based organocatalysis?



Complete the following reactions.



Reference/Text Book

• I. Ojima, *Catalytic Asymmetric Synthesis* , 3 rd ed., Wiley, New Jersey, 2010.

• M. B. Smith, *Organic Synthesis* , 2 nd edition, McGraw Hill, New Delhi, 2004.

CHAPTER OVERVIEW

11: Enzyme-Catalyzed Asymmetric Reactions

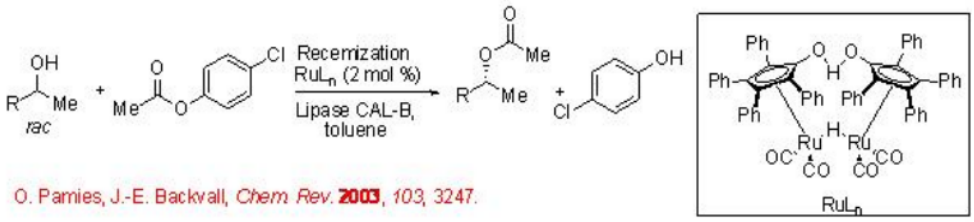
11.1: Acylation of Alcohols and Amines

Biocatalysis is a highly efficient and a powerful tool for organic chemists to prepare optically pure molecules. A broad range of biocatalytic methods has been already in use for large-scale manufacture of drug intermediates. This module covers some of the recent developments in the enzyme catalysis.

The enzymatic resolution of alcohols and amines affords an effective method to access optically active alcohols and amines from racemic or prochiral substrates.

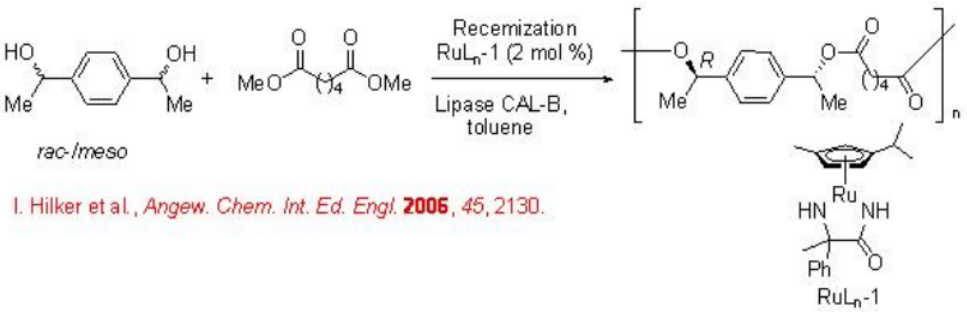
Reactions with Alcohols

The use of lipase for the resolution of racemic alcohols is a widely known technology. However, this method gives the product with maximum up to 50% yield. This limitation can be overcome by coupling the lipase-catalyzed enantioselective resolution with a racemization of the alcohol substrate, thus obtaining a dynamic kinetic resolution process. The latter process can be pursued employing a nonchiral metal complex as a catalyst. For example, using the combination of Ru complex and CAL-B, the acylation of racemic alcohol can be accomplished with 78-92% yield and 99% ee (Scheme 11.1.1).



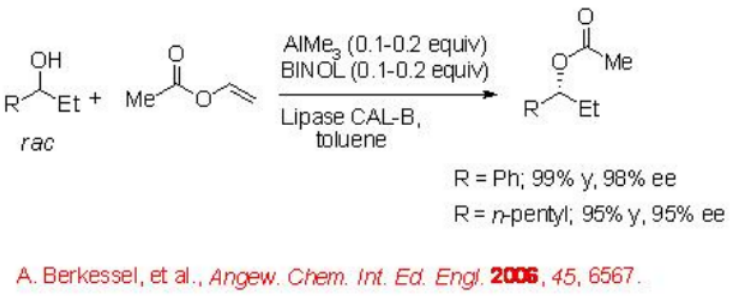
Scheme 11.1.1

This methodology has been subsequently utilized for the enantio- and diastereoselective synthesis of chiral polymers. For example, dimethyl adipate reacts with a mixture of racemic and *meso* -alcohols to give chiral polyester (Scheme 11.1.2). Ru complex acts as a racemization catalyst in combination with lipase CAL-B as biocatalyst for the resolution.



Scheme 11.1.2

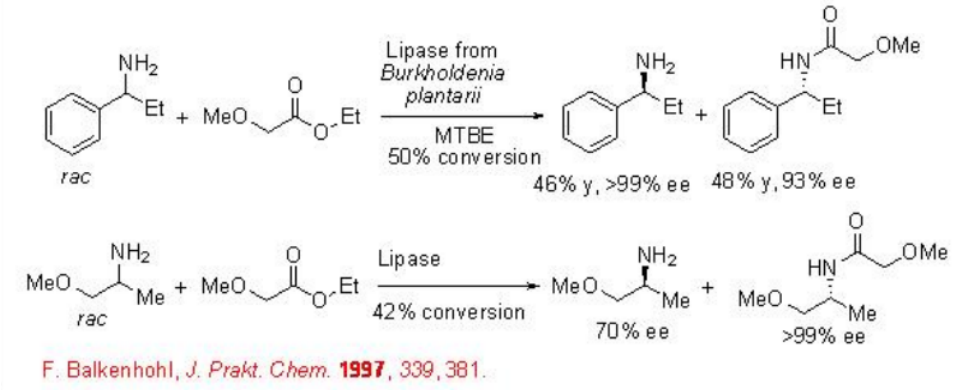
Furthermore, the transformation has been demonstrated employing a cheap and readily available aluminium complex prepared from $AlMe_3$ and BINOL as the racemization catalyst. For example, racemic 1-phenyl-1-propanol can be acylated with 99% yield and 98% ee (Scheme 11.1.3).



Scheme 11.1.3

11.1.2 Reactions with Amines

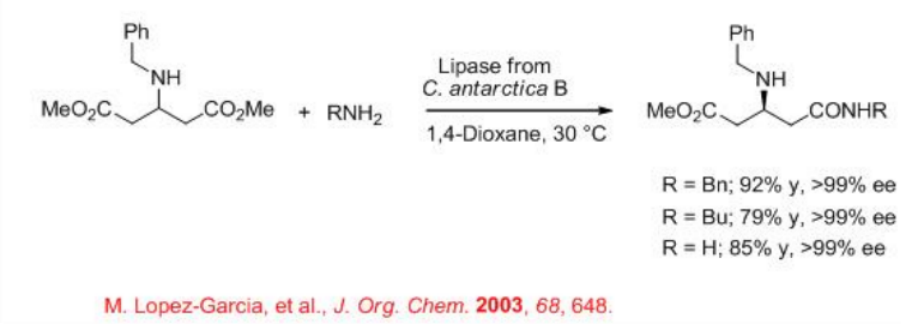
Optically pure amines serve as versatile intermediates in the manufacture of pharmaceuticals and agrochemicals. The lipase-catalyzed acylation of amines proceeds efficiently with excellent enantioselectivity (Scheme 11.1.4). In this reaction, one of the enantiomer is converted into amide and the remaining amine enantiomer can be obtained in enantiomerically enriched form. The reaction functions in organic medium, MTBE as solvent, and E value exceeds 2000 (E = environmentally impact of the process.



Scheme 11.1.4

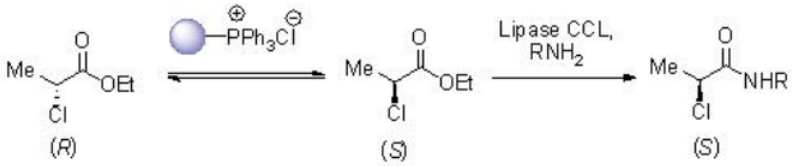
11.1.3 Other Acylations

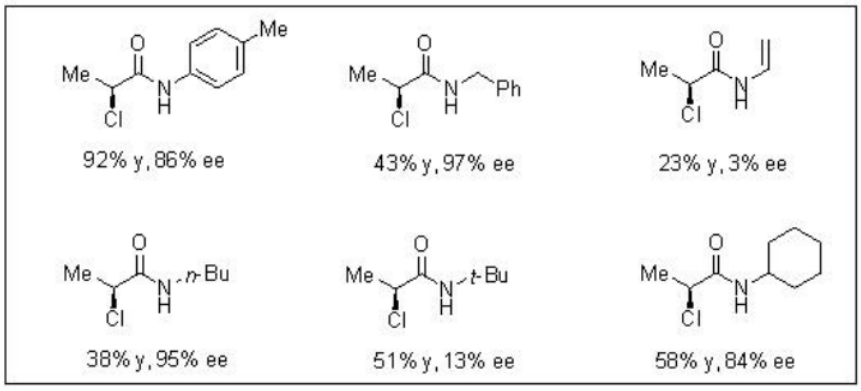
Enzymatic catalytic transformation of achiral amines and racemic acid components known as aminolysis affords elegant approach for the synthesis of enantioenriched acids. An interesting example is the reaction of dimethyl 3-(benzylamino)glutarate to give monoamides with excellent enantioselectivity (Scheme 11.1.5). The monoamides are intermediates for the synthesis of unnatural β -amino acids.



Scheme 11.1.5

A dynamic kinetic resolution with enzymatic aminolysis provides effective route towards the access of enantiomerically enriched acids. For example, in the presence of an immobilized phosphonium chloride for racemization of ethyl 2-chloropropionate and lipase, aminolysis can be carried out to give amides with up to 92% yield and 86% ee (Scheme 11.1.6).





J. D. Bodjic, et al., *Org. Lett.* **2001**, 3, 2025.

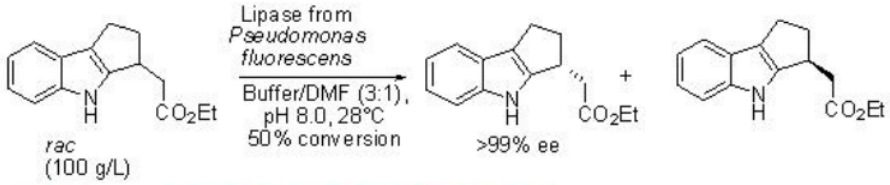
Scheme 11.1.6

Hydrolytic Reactions

The enzymatic hydrolysis of racemic esters, amides, nitriles and epoxides affords effective methods for the synthesis of optically pure carboxylic acids, amines, amides, esters and alcohols. The reactions of a broad range of substrates have been well explored.

Ester Hydrolysis

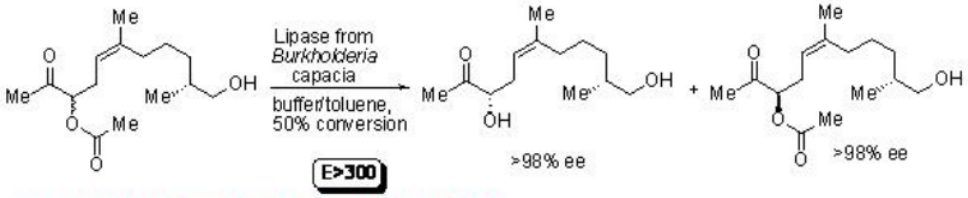
Hydrolysis of racemic or prochiral ester using enzymes such as lipase, esterase and protease provides effective method for the resolution of broad range of substrates. Recently, the hydrolysis of indole ethyl ester has been shown using a lipase from Pseudomonas fluoresens (Scheme 11.1.7). The process runs at a high substrate concentrate 100g/L and turned out to be technically feasible to perform successfully on a 40-kg scale.



M. D. Truppo, et al., *Org. Proc. Res. Dev.* **2006**, *10*, 592.

Scheme 11.1.7

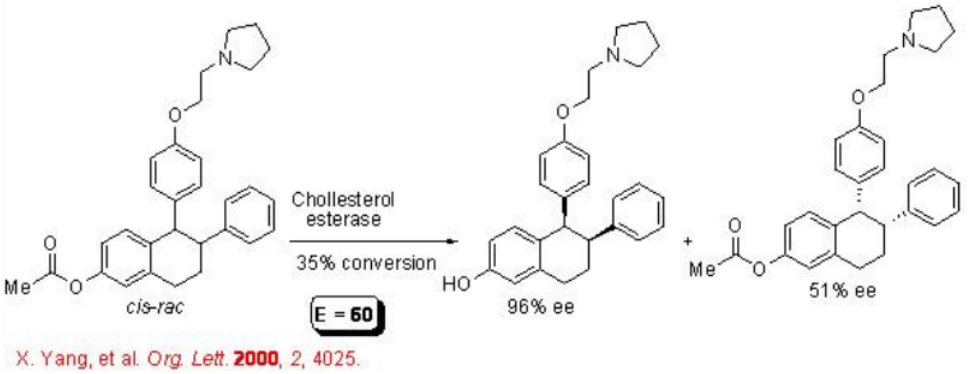
Lipases are also suitable for the resolution of complex molecules having more than one additional functional group. For example, acyloin acetate can be hydrolyzed with E > 300 leading to diol in excellent enantioselectivity (Scheme 11.1.8).



G. Scheid et al., *Tetrahedron Asymmetry* **2004**, *15*, 2861.

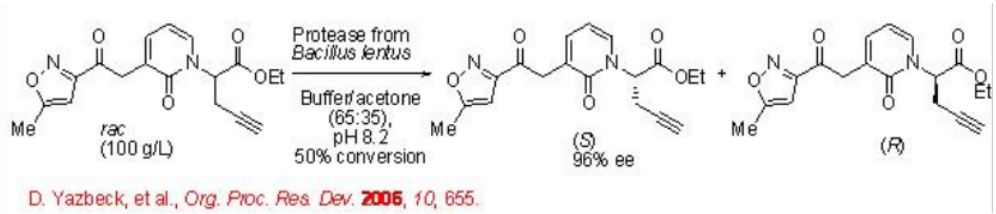
Scheme 11.1.8

Hydrolases can also recognize “remote chiral centers”. For example, ester group separated from the stereogenic center by an aromatic group proceeds hydrolysis with enantioselectivity having the E value of 60 (Scheme 11.1.9). The product, Lasofoxifene (*cis*), is a potent and selective estrogen receptor modulator.



Scheme 11.1.9

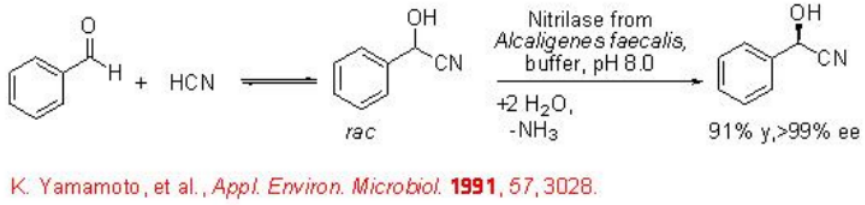
The synthesis of an intermediate for a rhinovirus protease inhibitor has been accomplished by an impressive resolution employing a protease from Bacillus lentus (Scheme 11.1.10).



Scheme 11.1.10

Nitrile Hydrolysis

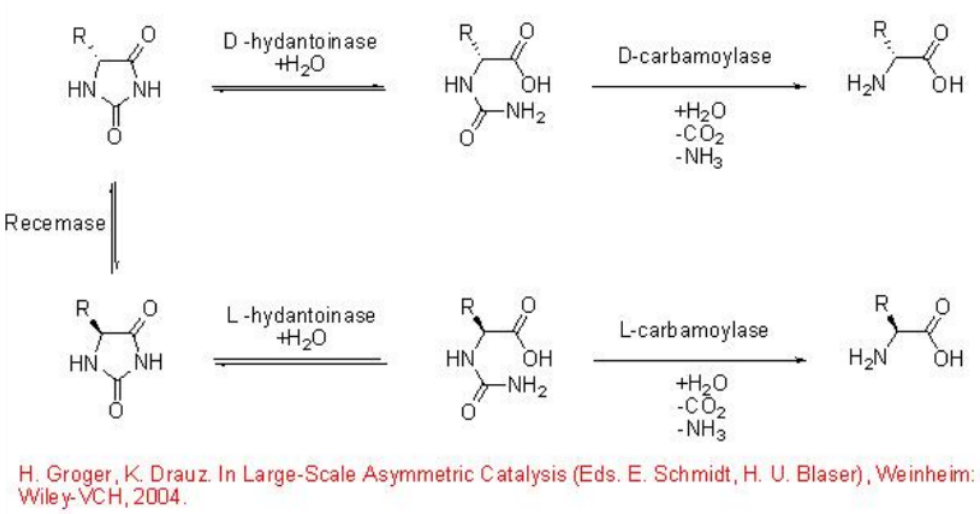
Nitrilases are used for the hydrolysis of racemic or prochiral nitriles to give carboxylic acids. For example, nitrilase from *A. faecalis* catalyzes the hydrolysis of α -hydroxy nitriles to give (*R*)-mandelic acid with excellent enantioselectivity (Scheme 11.1.11).



Scheme 11.1.11

11.2.3 Hydantoin Hydrolysis

Hydantoinases and carbamoylases hydrolyses racemic hydantoins to give optically pure α -amino acids (Scheme 11.1.12). In the beginning, the hydantoinase catalyzes the hydrolytic ring opening of the hydantoin to give an *N* -carbamoyl amino acid that proceeds cleavage to give the desired α -amino acid.

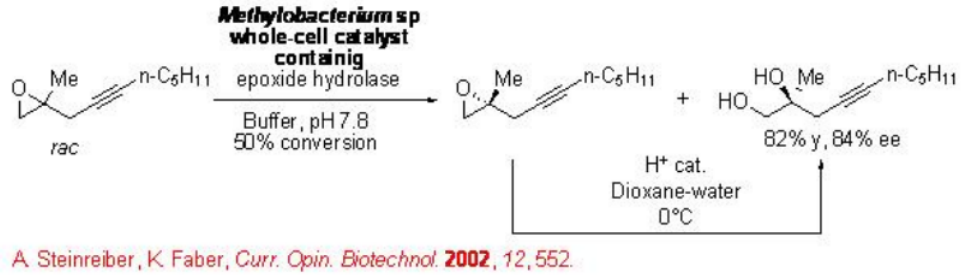


H. Groger, K. Drauz. In Large-Scale Asymmetric Catalysis (Eds. E. Schmidt, H. U. Blaser), Weinheim: Wiley-VCH, 2004.

Scheme 11.1.12

11.2.4 Epoxide Hydrolysis

Hydrolysis of racemic epoxide using epoxide hydrolase proceeds with high enantioselectivity. For example, the resolution of aliphatic epoxide having functional group can be accomplished using *Methylobacterium* sp. with good enantioselectivity (Scheme 11.1.13).



A. Steinreiber, K. Faber, *Curr. Opin. Biotechnol.* **2002**, *12*, 552.

Scheme 11.1.13

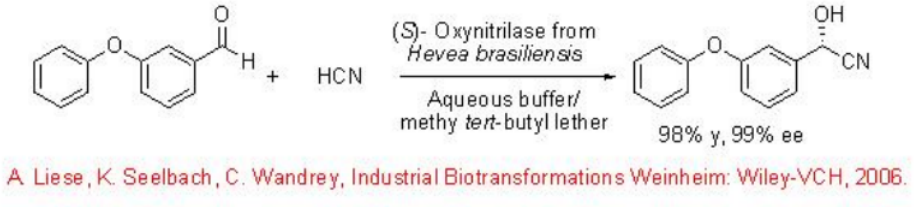
11.2: Formation of Carbon-Carbon Bonds

Biocatalysts are turned out to be versatile catalysts for carbon-carbon bond forming and reduction reactions in organic synthesis.

Carbon-carbon bond formation belongs to the heart of organic synthesis. The biocatalyzed route provides effective tool for the construction of carbon-carbon with excellent enantioselectivity.

Hydrocyanation of Aldehydes

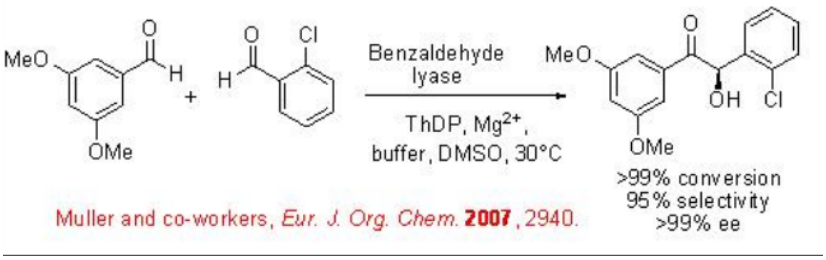
The biocatalytic hydrocyanation of aldehydes is one of the oldest methods in organic synthesis. One of the well-established technologies for the large-scale hydrocyanation of aldehydes is the oxynitrilase (Griengl process) catalyzed production of (*S*)-phenoxybenzaldehyde cyanohydrins, which is an important intermediate for the industrial pyrethroid manufacture (Scheme 11.2.1). This method is turned out to be useful for the reactions of numerous aldehydes.



Scheme 11.2.1

Benzoin Condensation

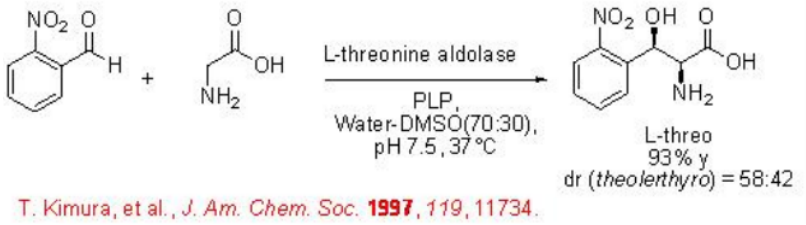
The development of an asymmetric cross-benzoin condensation *via* enzymatic cross-coupling reactions is a synthetically useful process. Highly enantiomerically enriched mixed benzoins can be obtained from two different substituted benzaldehdyes using benzaldehyde lyase as a catalyst (Scheme 11.2.2). One of the aldehydes acts as acceptor, whereas the other one acts as donor.



Scheme 11.2.2

Aldol Reaction

The biocatalytic aldol reactions are highly specific with respect to donor component, whereas a broad substrate scope is observed for the acceptor molecules. One of the examples is the reaction of glycine (donor) with substituted benzaldehyde (acceptor) employing threonine aldolases to give α-amino β -hydroxy acids with excellent enantioselectivity (Scheme 11.2.3).

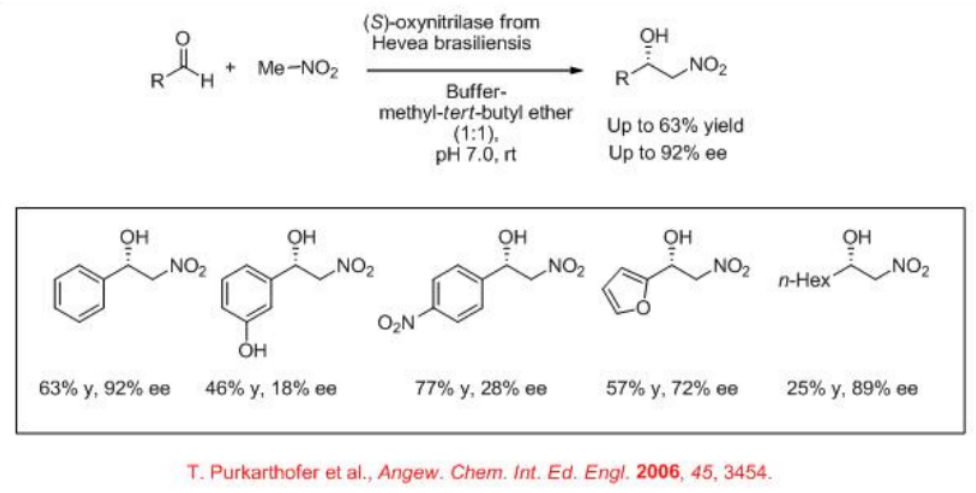


Scheme 11.2.3

Nitroaldol Reaction

Enzymes are also useful for the non-natural reactions. For example, using (*S*)-oxynitrilase the reaction of nitromethane with a broad range of aldehydes can be accomplished with excellent enantioselectivity (Scheme 11.2.4). Nitroalkane acts donor, whereas the

aldehydes are acceptors.



T. Purkarthofer et al., *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 3454.

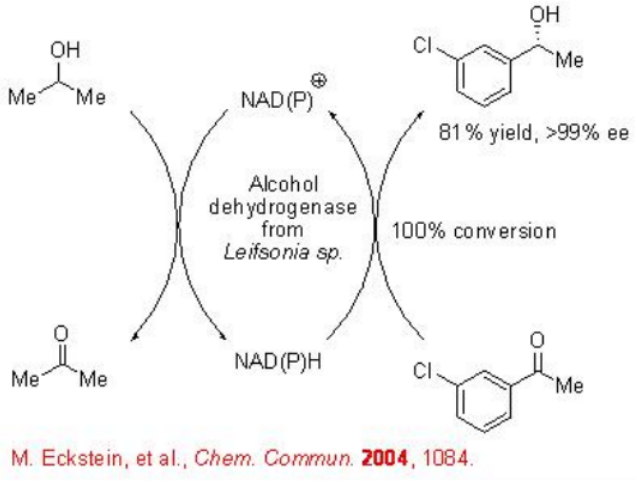
Scheme 11.2.4

11.3: Reduction Reactions

The enantioselective reduction of C=X double bonds (X = O, NR, C) to C-XH single bonds plays a major role in asymmetric synthesis.

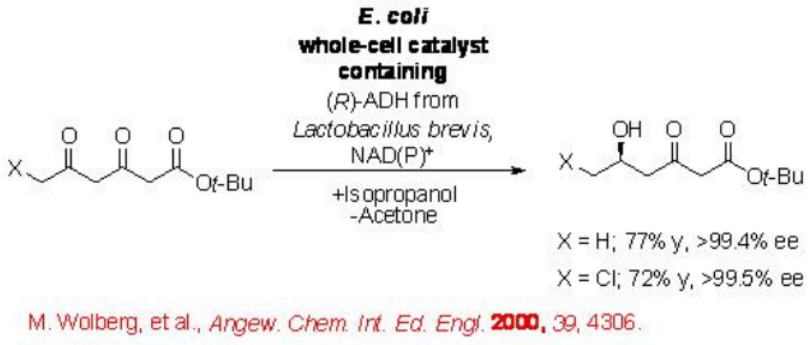
Reduction of Ketones

The enantioselective reduction of ketones represents an atom-economical approach towards optically active alcohols. The biocatalytic reduction of ketones is based on the use of an alcohol dehydrogenase (ADH) as a catalyst, and a cofactor as a reducing agent. For example, ADH from *Leifsonia* sp. catalyses the reduction of substituted acetophenone to give secondary alcohols with high enantioselectivity (Scheme 11.3.1). In this process, 2-propanol acts as a reducing agent oxidizing into acetone.



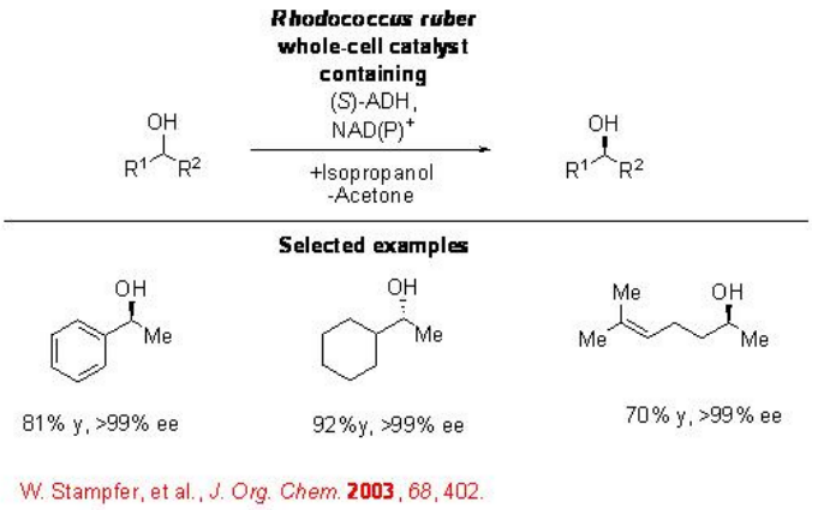
Scheme 11.3.1

The keto group of 2,5-diketo ester can be selectively reduced with excellent regio- and enantioselectivity using *E. coli* cells with overexpressed ADH from *Lactobacillus brevis* (Scheme 11.3.2). In this process 2-propanol acts as a reducing agent oxidizing into acetone.



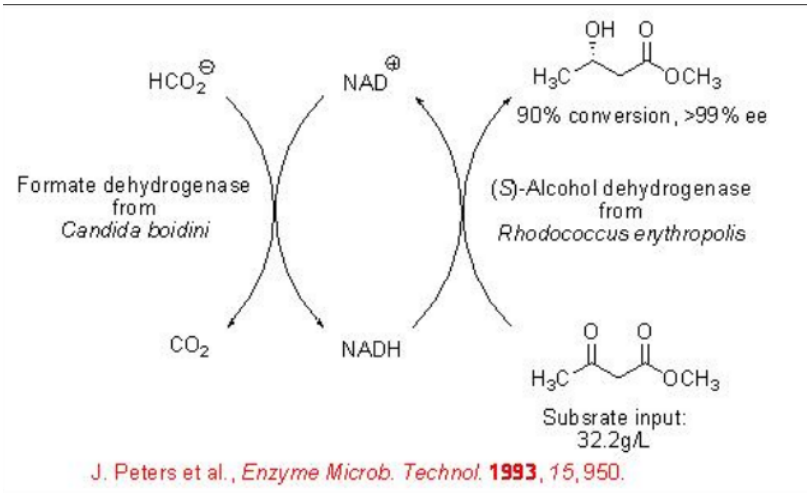
Scheme 11.3.2

The reduction of a wide range of aliphatic and aromatic ketones can be accomplished employing *R. ruber* ADH to give the corresponding alcohols with excellent enantioselectivity in 2-propanol (Scheme 11.3.7).



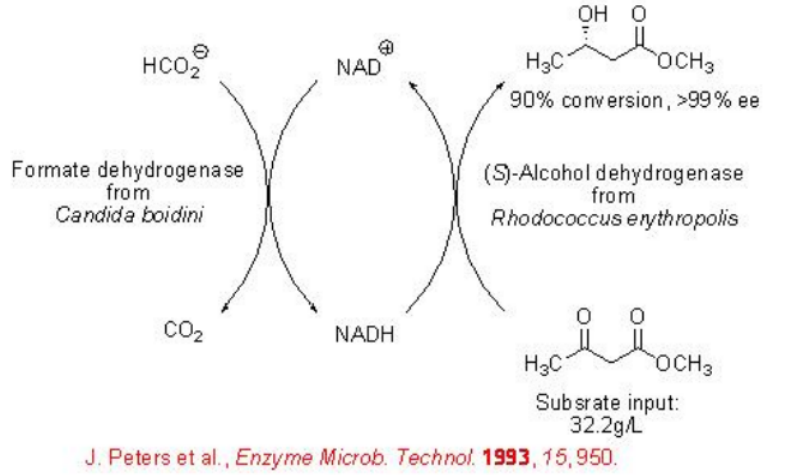
Scheme 11.3.3

Whereas formate dehydrogenase (FDH) from *C. boidinii* catalyzes selectively the reduction of keto group of β -keto esters with high enantioselectivity. In this reaction, formate is oxidized into carbon dioxide (Scheme 11.3.4).



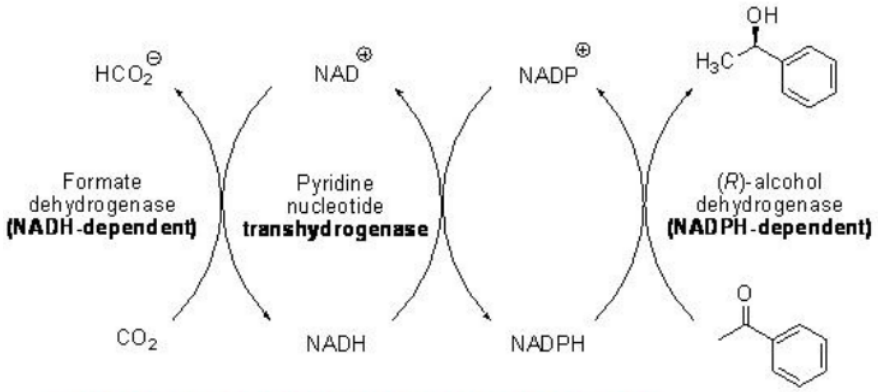
Scheme 11.3.4

The FDH-based whole-cell can be used for the reduction of ethyl 4-chloro-3-oxobutanoate with 99% ee (Scheme 11.3.5).



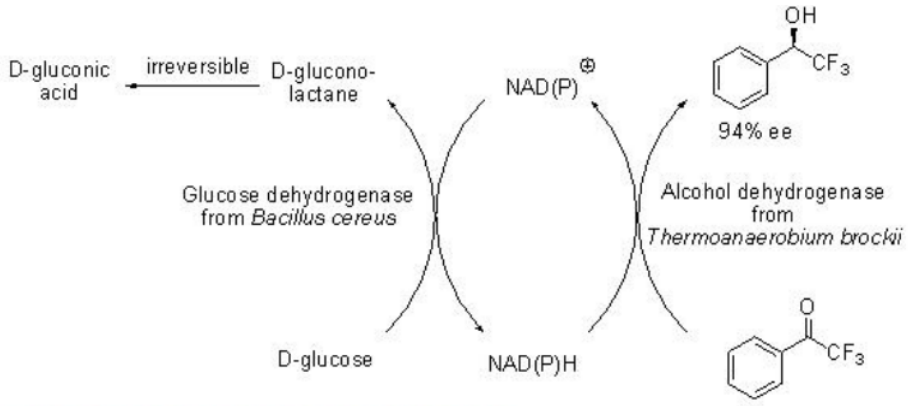
Scheme 11.3.5

The use of FDH from *C. boidinii* has limitation due to its inability to regenerate $NADP^+$. This has been overcome by expanding the application range of FDH-based cofactor regeneration to $NADP^+$ -dependent ADHs (Scheme 11.3.6). This involves the integration of an additional enzymatic step within the cofactor-regeneration cycle that is exemplified in the reduction of acetophenone to (*R*)-phenylethanol. In this process, the pyridine nucleotide transhydrogenase (PNT)-catalyzes regeneration of NADPH from $NADP^+$ under consumption of NADH forming NAD^+.



A. Weckbecker, W. Hummel., *Biotechnol. Lett.* **2004**, *26*, 1739.

Scheme 11.3.6

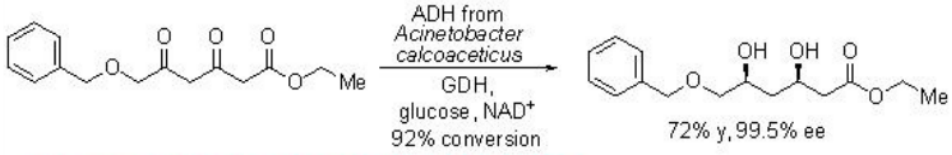


C.-H. Wong et al., *J. Am. Chem. Soc.* **1985**, *107*, 4028.

Scheme 11.3.7

Further, for recycling the cofactor NAD(P)H, the use of a glucose dehydrogenase (GDH) has been demonstrated. In this system, D-glucose is oxidized to D-gluconolactone, while the oxidized cofactor $NAD(P^+)$ is reduced to NAD(P)H. Since D-gluconolactone is then hydrolyzed into D-gluconic acid, the reaction is irreversible shifting the whole process towards the desired alcohol product formation. This GDH coupled cofactor-regeneration process has been used for the reduction of ketone to alcohol with high enantioselectivity (Scheme 11.3.7).

This principle has been recently used for the reduction of ethyl 6-benzyloxy-3,5-dioxohexanoate to afford ethyl (3 *R*,5 *S*)-6-benzyloxy-3,5-dihydroxyhexanoate with 99% ee employing ADH from *Acinetobacter calcoaceticus* in combination with a GDH and glucose (Scheme 11.3.8).

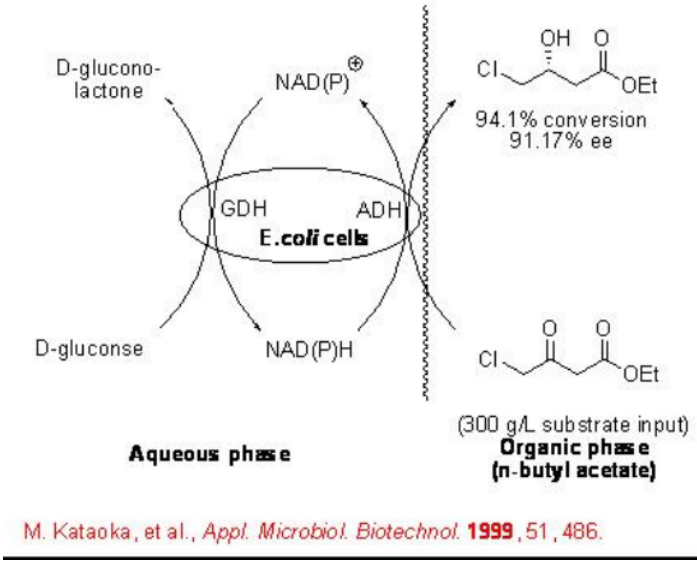


R. N. Patel., et al., *Enzyme Microb. Technol.* **1993**, *15*, 1014.

Scheme 11.3.8

Reduction of Ketones

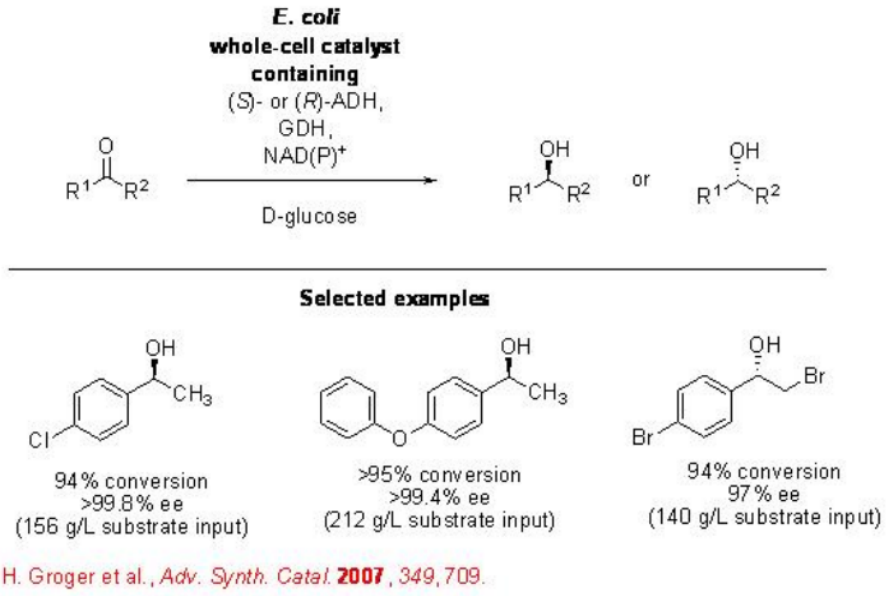
Recombinant whole-cell catalytic system having *E. coli* , co-expressing both the ADH from *S. salmonicolor* and the GDH from *B. megaterium* , has been developed for the asymmetric reduction of 4-chloro-3-oxobutanoate in a mixture of *n* -butyl acetate/water (Scheme 11.3.9). It is an elegant approach toward tailor-made biocatalysts containing both of the desired enzymes, ADH and GDH, in overexpressed form (Scheme 11.3.9).



M. Kataoka, et al., *Appl. Microbiol. Biotechnol.* **1999**, 51, 486.

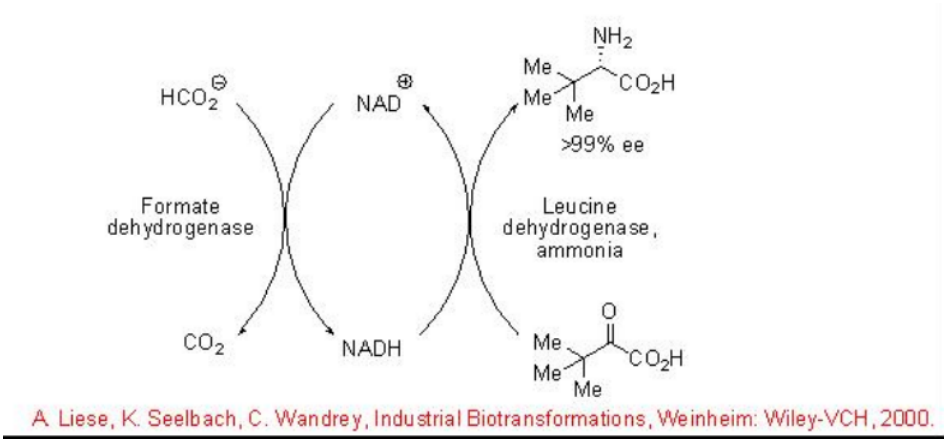
Scheme 11.3.9

The application of recombinant whole-cell biocatalytic system has been further demonstrated in pure aqueous media without the need of addition of external amount of cofactor (Scheme 11.3.10). This method is economical and simple, and finds applications for the reduction of a wide range of ketones (Scheme 11.3.10).



H. Groger et al., *Adv. Synth. Catal.* **2007**, 349, 709.

Scheme 11.3.10

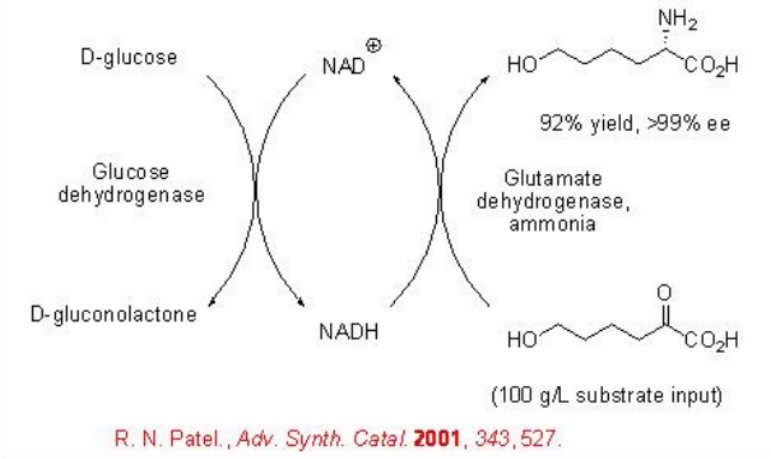


Scheme 11.3.11

Reductive Amination of α -Keto Acids

Enzyme catalyzed asymmetric reductive amination of α -keto acids represents a straightforward method to access optically active α -amino acids. For example, L- *tert*- leucine, which serves as building block for the pharmaceutical industry, is obtained with high conversion and enantioselectivity using a leucine dehydrogenase for the reductive amination and an FDH from *C.boidinii* (Scheme 11.3.11). The latter is required for an *in situ* recycling of the cofactor NADH.

Similarly, the synthesis of L-6-hydroxynorleucine can be accomplished from α -keto acid with complete conversion and >99% enantioselectivity (Scheme 11.3.12). In this reaction, a beef liver glutamate dehydrogenase has been used as L-amino acid dehydrogenase and a GDH from *B. megaterium* has been used for the cofactor regeneration.

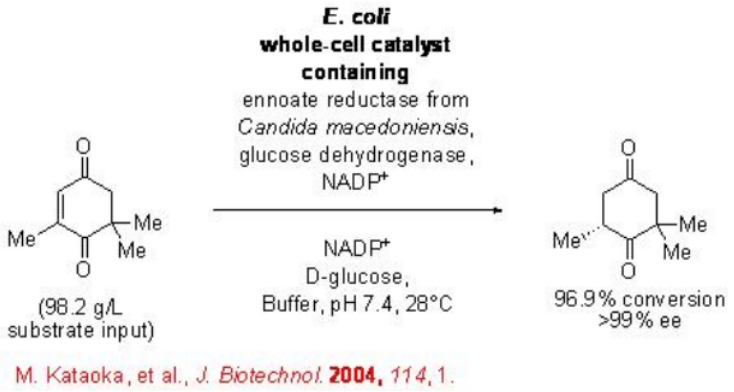


Scheme 11.3.12

However, the need for the addition of expensive cofactor NAD^+ as well as the isolation and cost of the enzymes make these approaches are limited. Thus, efforts have been made to address these aspects by employing a whole-cell catalyst, having both an amino acid dehydrogenase and FDH in overexpressed form. For example, the synthesis of L-allysine ethylene acetal has been shown using a whole-cell catalyst, *Pichia pastoris* cells having a phenylalanine dehydrogenase from *Thermoactinomyces intermedius* and an FDH from *P. pastoris* (Scheme 11.3.13).

Reduction of Activated Carbon-Carbon Double Bonds

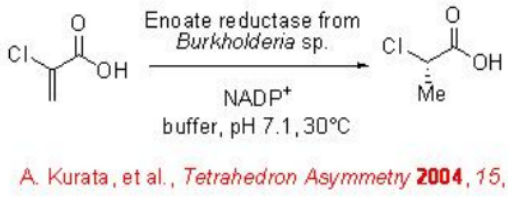
The reduction of carbon-carbon double bonds using the biocatalytic systems has high potential in organic chemistry. However, this process is less explored compared to the C=O reduction of ketones and keto esters. The reduction of the carbon-carbon double bond in ketoisophorone has been accomplished using whole-cell catalyst overexpressing an enolate reductase from *Candida macedoniensis* and a GDH (Scheme 11.3.13). This study can be regarded as one of the pioneering works in the reduction of carbon-carbon double bonds using biocatalytic systems.



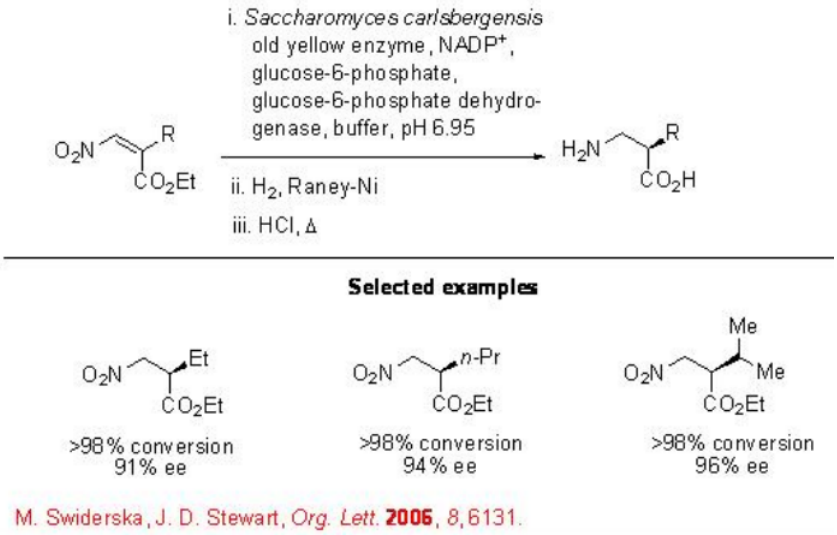
Scheme 11.3.13

α,β -Unsaturated carboxylic acids can also be used as substrates. For example, α -chloroacrylic acid can be converted into α -chloropropionate using an enolate reductase from *Burkholderia sp* ., in high enantioselectivity (Scheme 11.3.14).

Besides, enone and α,β -unsaturated carboxylic acid, nitroalkanes are also suitable substrates for enoate reductase. For example, the reduction of carbon-carbon double bond in *Z* -nitroalkenes proceed reaction to give 2-substituted 3-nitropropanoates with high conversion and in most cases with high enantioselectivity (Scheme 11.3.15).



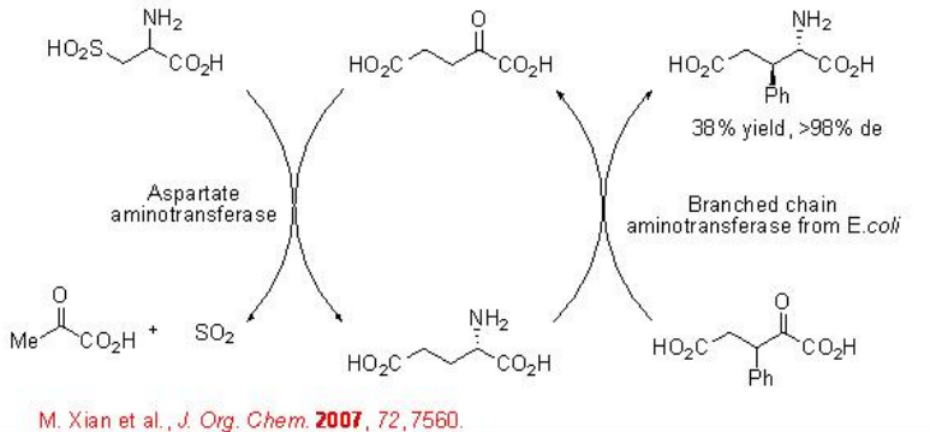
Scheme 11.3.14



Scheme 11.3.15

Transamination11.3.1

Depending on the nature of the transaminase, α -keto acids and ketones proceed reaction to give α-amino acids and amines with a stereogenic center in α -position, respectively. For example, a coupling of the transaminase process with an irreversible aspartate aminotransferase-catalyzed transamination process using cysteine sulfinic acid as an amino donor has been used for the synthesis of various types of non-natural 3- or 4-substituted glutamic acid analogues (Scheme 11.3.16).



Scheme 11.3.16

Furthermore, the highly efficient synthesis (*S*)-methoxyisopropylamine has been accomplished using a recombinant whole-cell catalyst overexpressing a transaminase. A key feature in this process is the high substrate concentration and the desired target molecule can be obtained with excellent enantioselectivity (Scheme 11.3.17).

Scheme 11.3.17

11.4: Enantioselective Oxidations

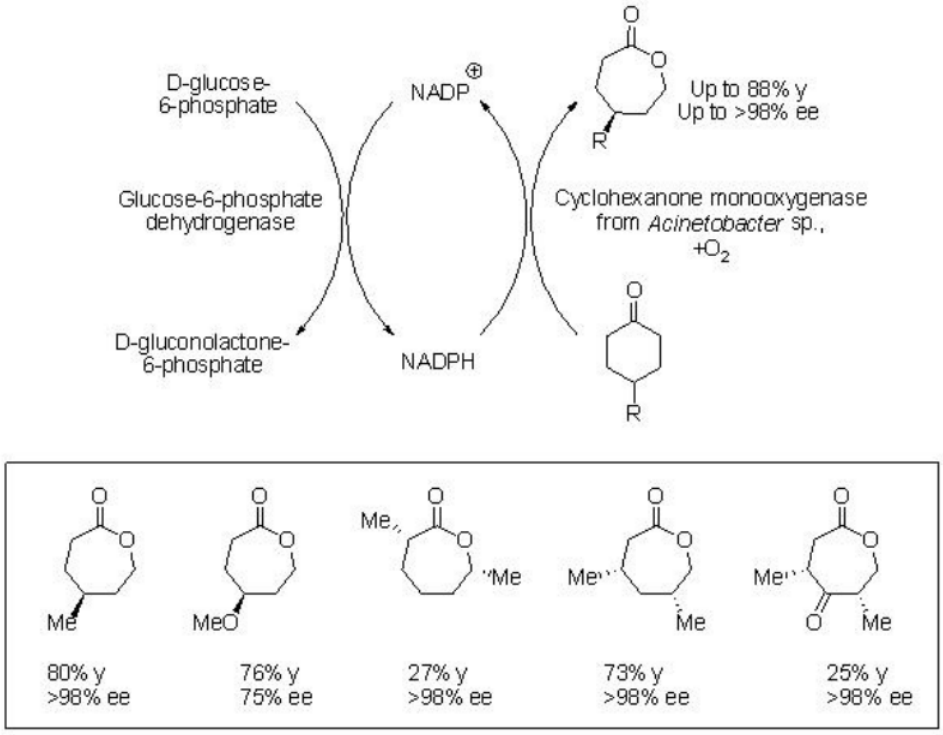
Biocatalysts are also turned to be useful for asymmetric oxidations. A wide range of asymmetric oxidations using biocatalytic systems has been explored.

Baeyer-Villiger Oxidation

Baeyer-Villiger reaction is known for more than 100 years. However, the asymmetric version of this reaction remains as challenge for organic chemists. Depending on the nature of ketones the reaction can be carried out as a resolution of racemic ketones as well as an asymmetric desymmetrization reaction from prochiral ketones. The enzymes used for this reaction is known

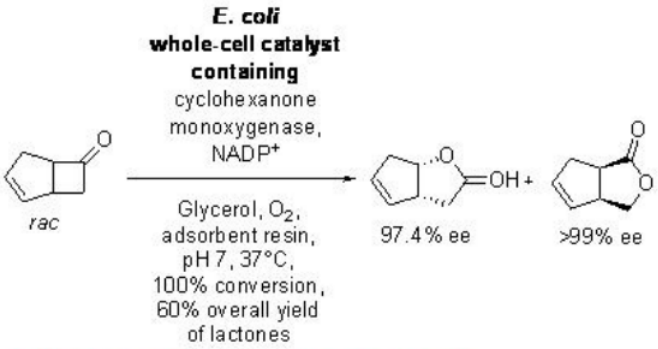
as Baeyer-Villiger monooxygenases. These enzymes are cofactor dependant and are generally obtained from microbial sources. For example, 4-substituted monocyclic cyclohexanones can be oxidized into the lactones in good yield and with high enantioselectivities (Scheme 11.4.1). In this process, the reduced form of the cofactor (NADPH) is needed under the formation of $NADP^+$ that is *in situ* recycled using an enzymatic coupled cofactor reproduction.

The scale up of the process has also been explored. For example, the racemic bicyclo[3.2.0]hept-2-enone with input of 25g/L proceeds oxidation in the presence of a recombinant whole-cell biocatalyst to afford regioisomeric lactones with high enantioselectivity (Scheme 11.4.2).



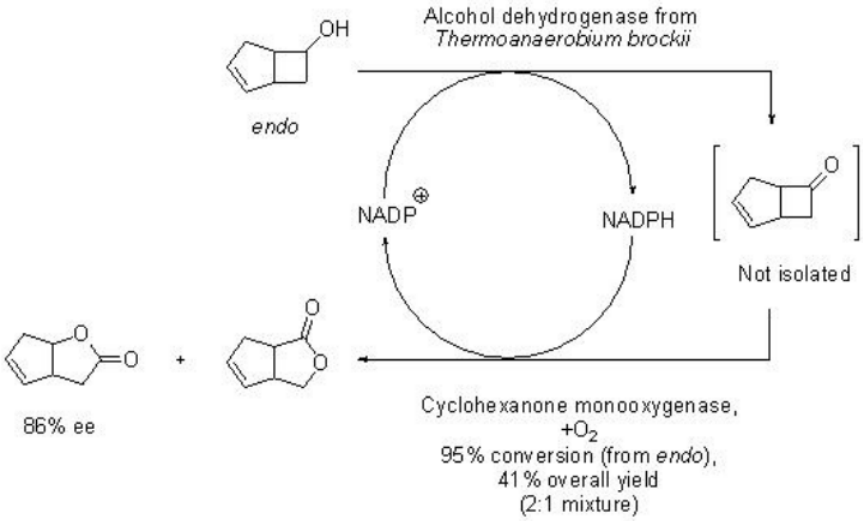
M. J. Taschner, D. J. Black, *J. Am. Chem. Soc.* **1988**, *110*, 6892.

Scheme 11.4.1



I. Hilker et al., *Biotechnol. Bioeng.* **2005**, *92*, 702.

Scheme 11.4.2



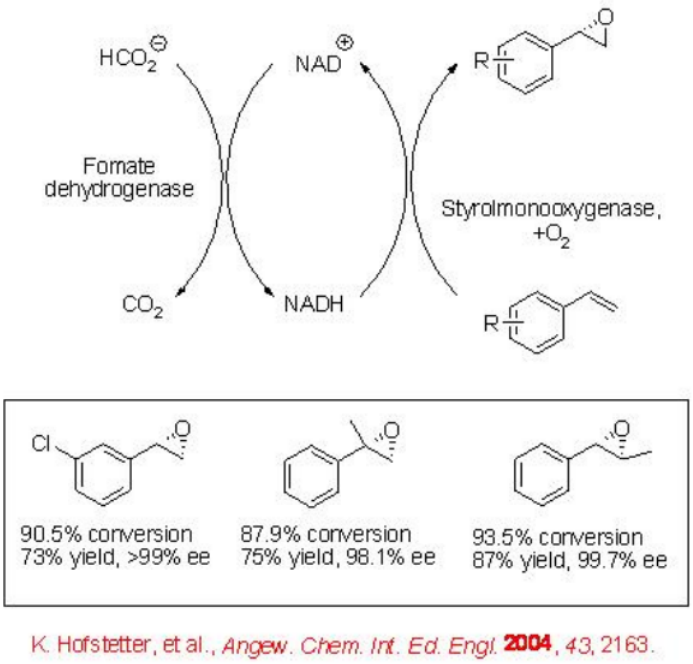
A. J. Willetts, et al., *J. Chem. Soc. Perkin Trans I* **1991**, 1608.

Scheme 11.4.3

A further process improvement is the coupling of a cyclohexanone monooxygenase with an ADH from *T. brockii* , a cosubstrate-free “double oxidation” of an alcohol into lactones (Scheme 11.4.3). In this system, the oxidized form of the cofactor ($NADP^+$) is consumed in the initial ADH-catalyzed step, while the reduced form of the cofactor (NADPH) is then needed for the second, monooxygenase-catalyzed oxidation step. In the second step, the oxidized form of the cofactor ($NADP^+$), which is then needed for the first step, is produced again.

Epoxidation

Optically active epoxides serve as versatile building blocks in organic synthesis. Besides metal and organocatalysts, cofactor dependent monooxygenase turned out to be valuable catalyst for the epoxidation of alkenes. For example, the epoxidation of styrene has been shown using a stable recombinant FAD/NADH-dependent styrene monooxygenase in aqueous-organic emulsions (Scheme 11.4.4). The reaction condition is also effective for the oxidation of other styrene derivatives.

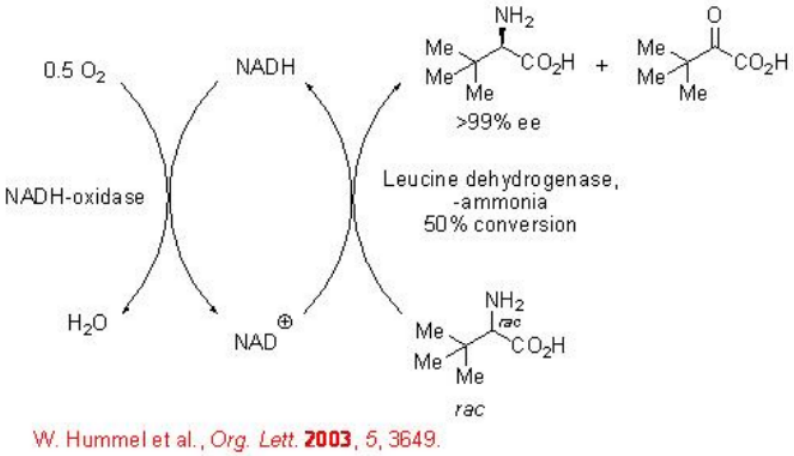


K. Hofstetter, et al., *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 2163.

Scheme 11.4.4

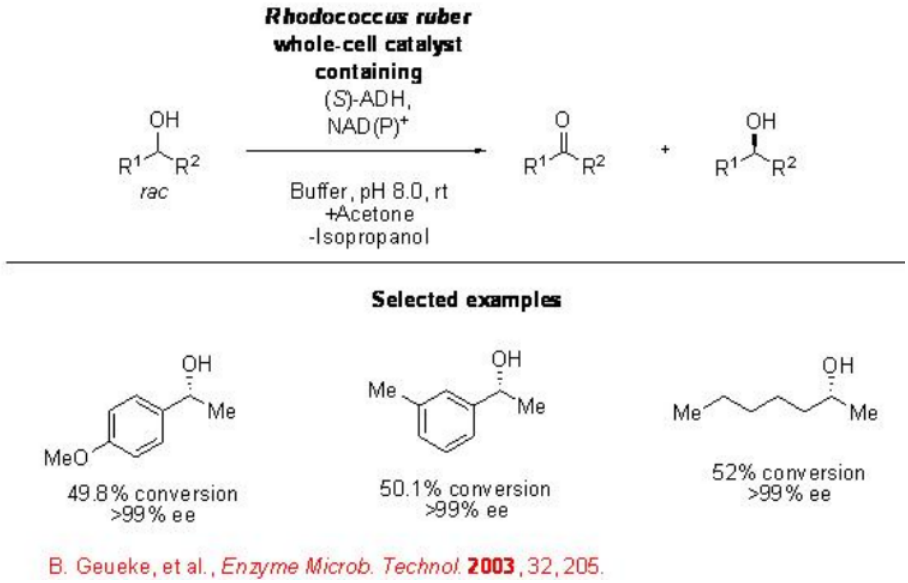
Oxidation of Amino Acids

The asymmetric oxidation of amine group in amino acids provides effective method for the synthesis unnatural amino acid which is important in drug synthesis. For example, racemic *tert* -leucine can be oxidized to D- *tert* -leucine using a leucine amino dehydrogenase and an NADH-oxidase from *E-coli* with excellent enantioselectivity (Scheme 11.4.5).



W. Hummel et al., *Org. Lett.* **2003**, *5*, 3649.

Scheme 11.4.5



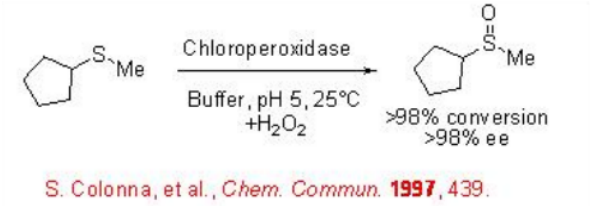
Scheme 11.4.6

Oxidation of Alcohols

The oxidation of secondary alcohols into ketones has also been investigated using biocatalytic systems. For example, the oxidation of racemic secondary alcohols proceeds in the presence of an ADH from *R. ruber* (Scheme 11.4.6). The recycling of the cofactor NADPH is carried out *in situ* using acetone, which is reduced into 2-propanol under the formation of $NADP^+$.

Sulfoxidation

Optically active sulfoxides play important role in organic synthesis as chiral auxiliary as well as intermediates for the construction of optically active molecules. Optically active sulfoxide is also present as structural unit in many biologically active compounds. The enzymatic oxidation of sulfides provides an effective method for the synthesis optically active sulfoxides. For example, cyclopentyl methyl sulfide undergoes oxidation in the presence of chloroperoxidase with excellent conversion and enantioselectivity.

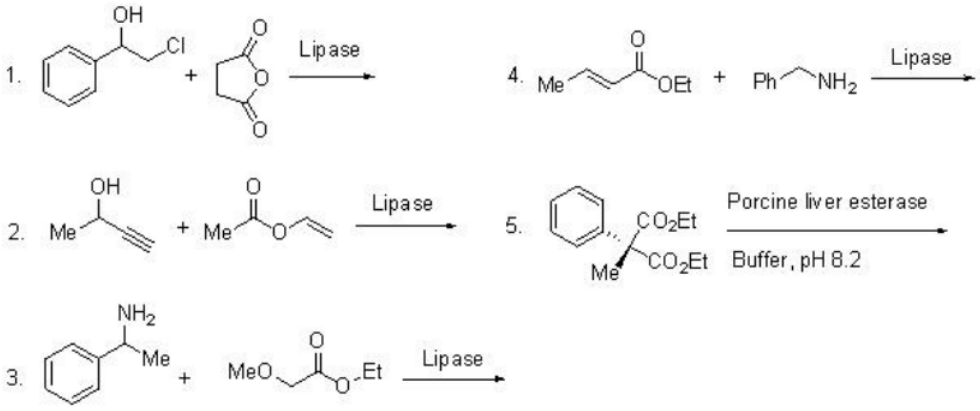


Scheme 11.4.7

11.5: Problems and Reference

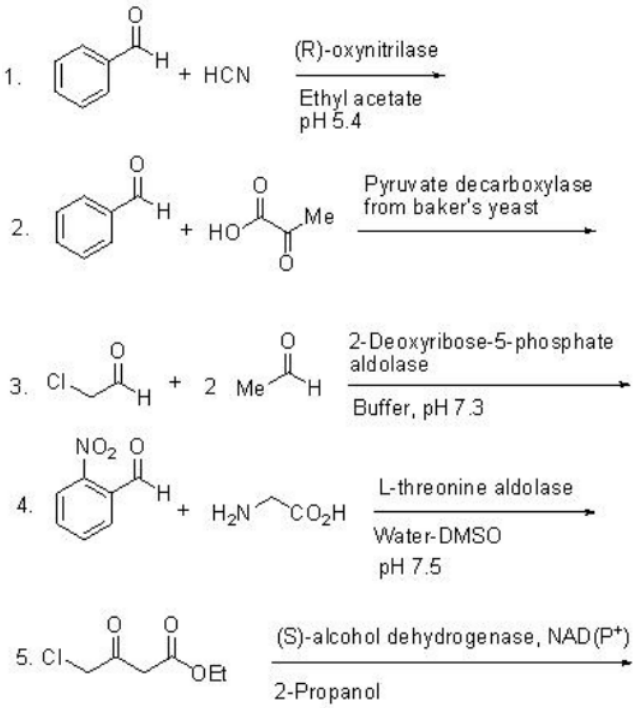
Problems:

Complete the following reactions.

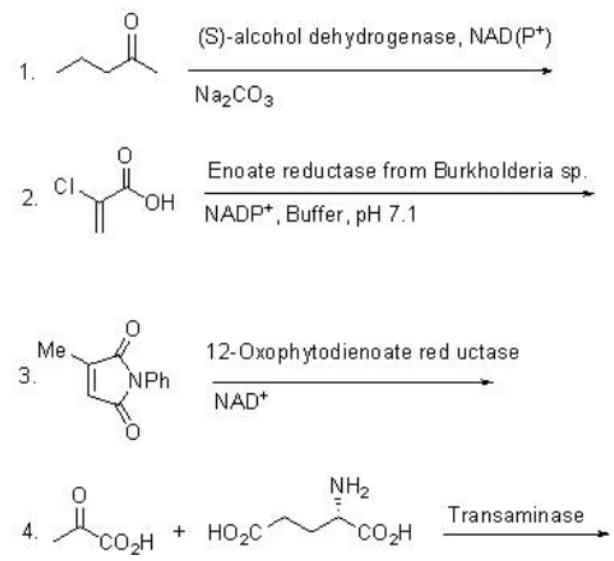


Describe enzyme-catalyzed amide hydrolysis

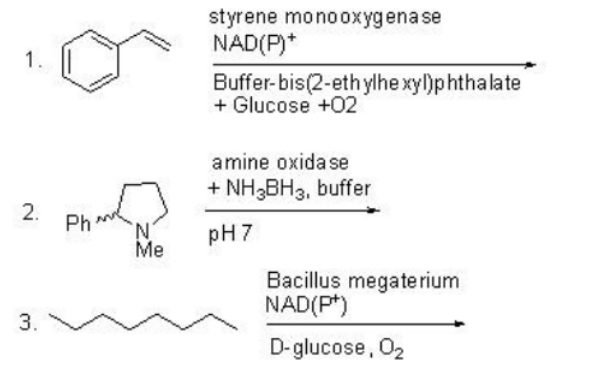
Complete the following reactions.



Complete the following reactions.



Complete the following reactions.



Describe enzyme catalyzed hydroxylation of alkanes and oxidation of amines.

Reference/Text Book

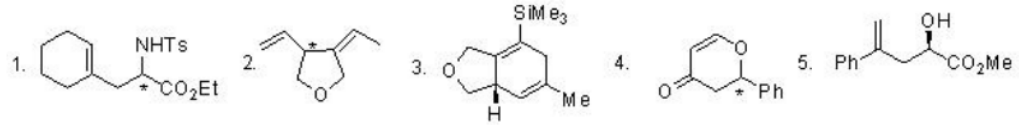
• I. Ojima, *Catalytic Asymmetric Synthesis* , 3 rd ed., Wiley, New Jersey, 2010.

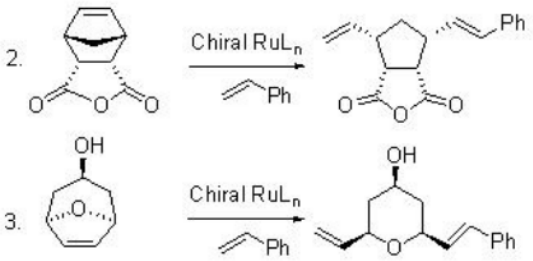
• M. B. Smith, *Organic Synthesis* , 2 nd edition, McGraw Hill, New Delhi, 2004.

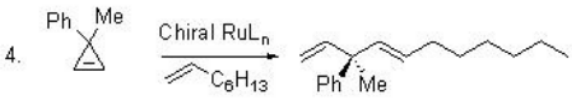
CHAPTER OVERVIEW

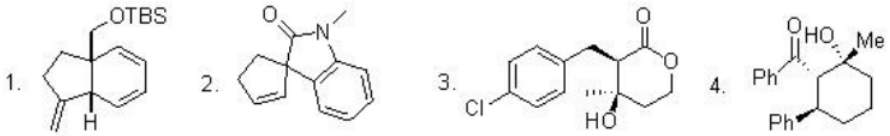
12: Solutions

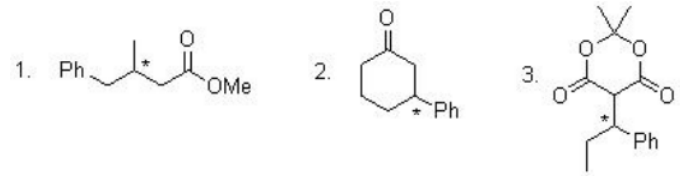
12.1: Asymmetric Carbon-Carbon Bond Forming Reactions

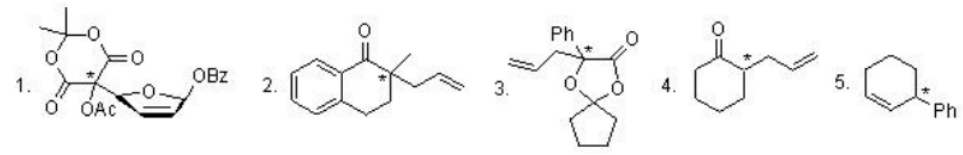




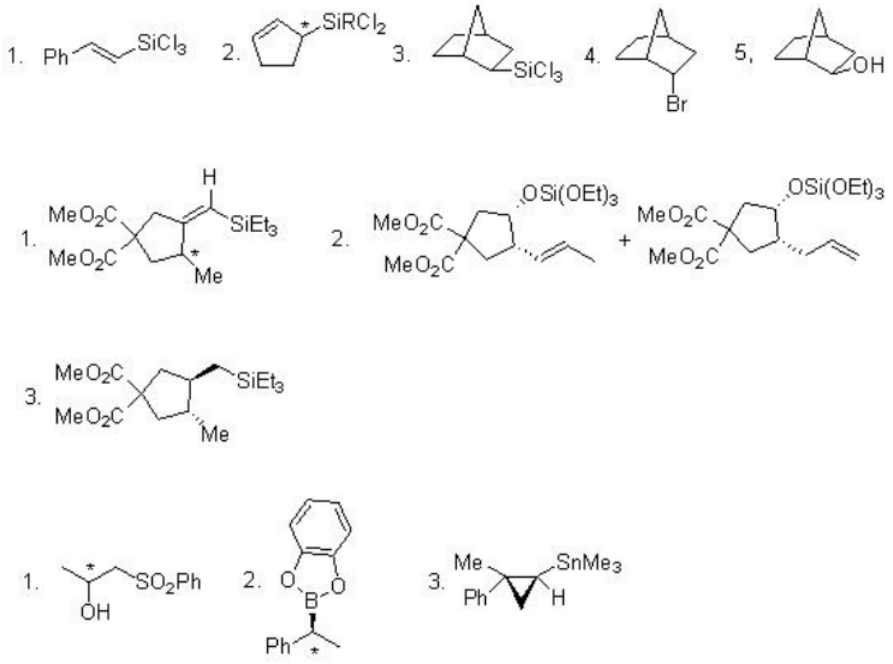




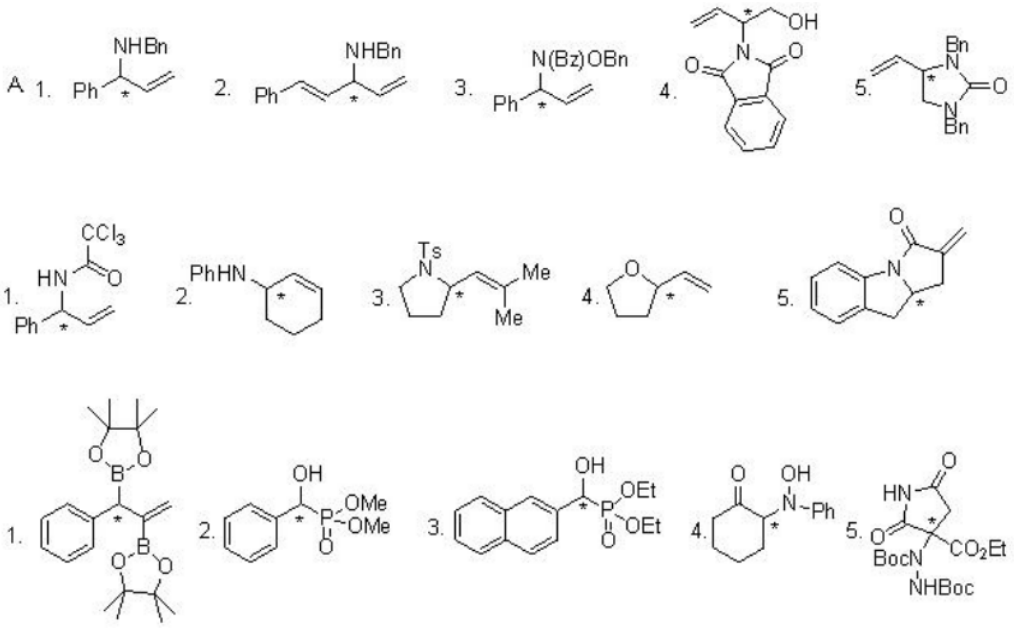




12.2: Asymmetric Hydrosilylation and Related Reactions



12.3: Carbon-Heteroatom Bond-Forming Reactions



12.4: Carbonylation Reactions

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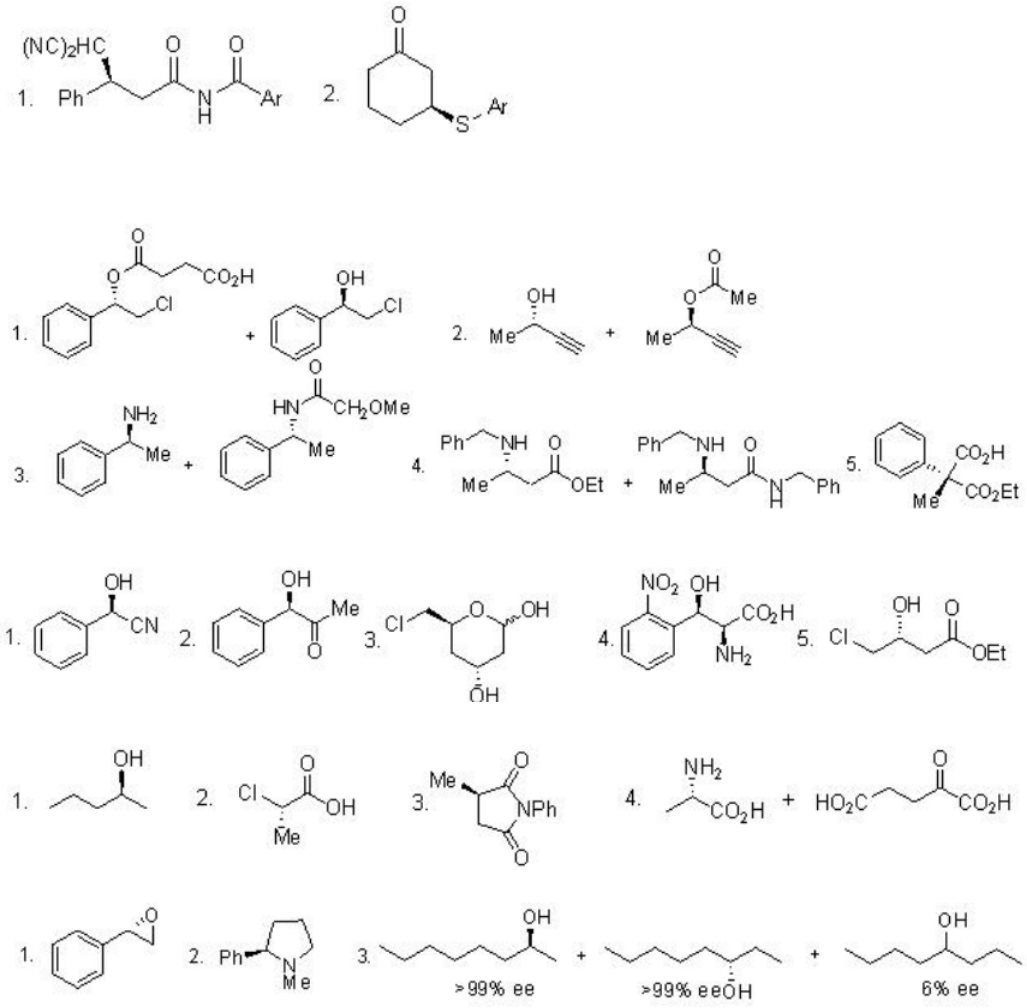
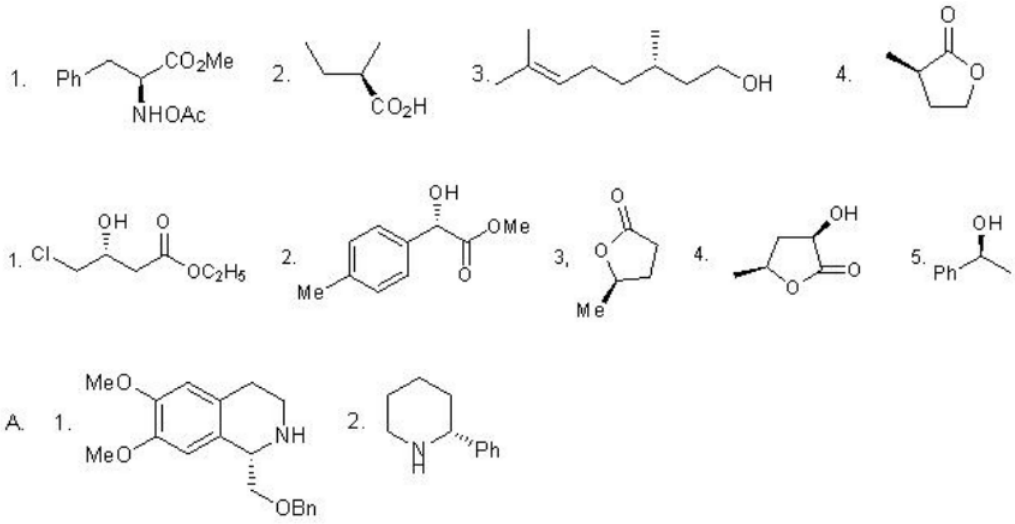
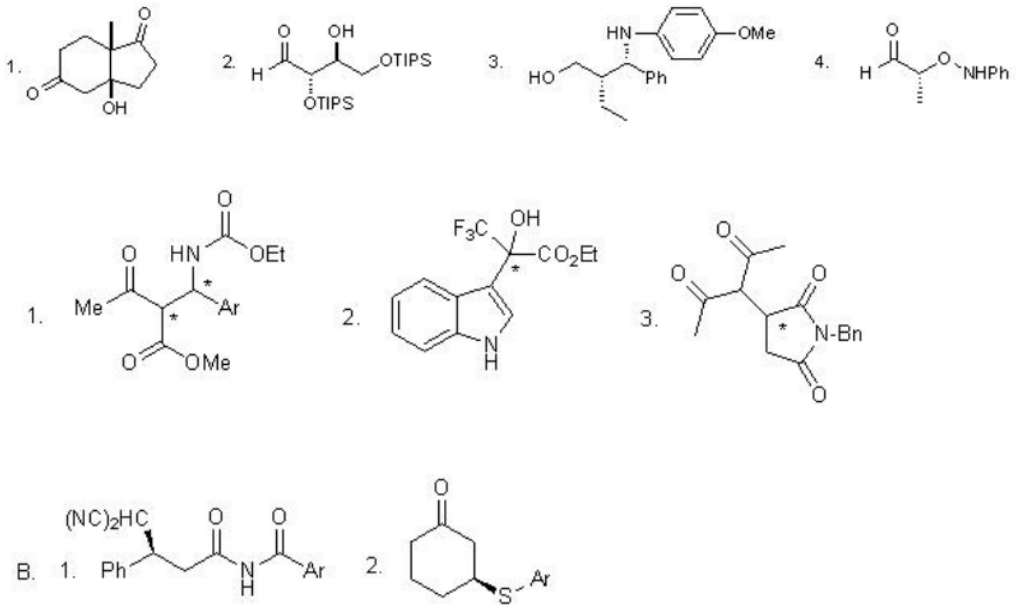
12.5: Enzyme-Catalyzed Asymmetric Reactions



12.6: Hydrogenation Reactions



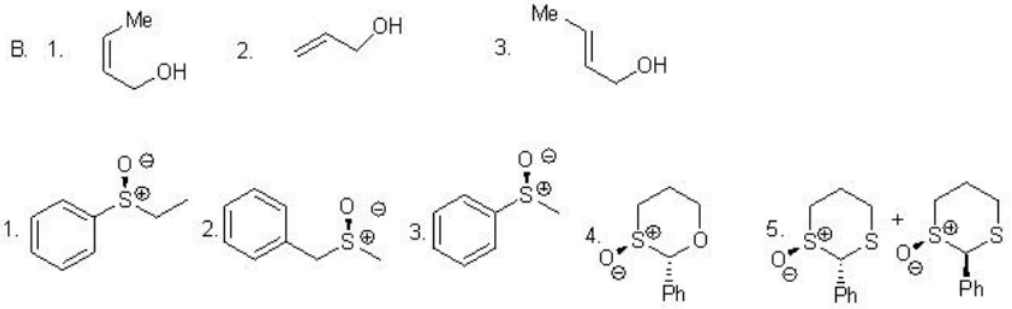
12.7: Organocatalysis

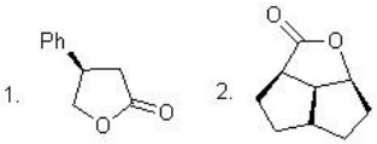


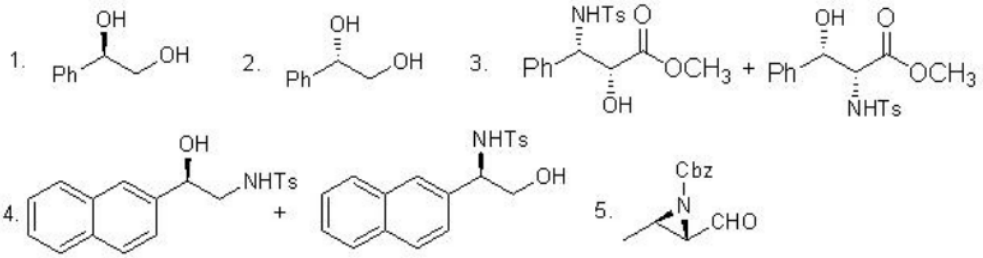
12.8: Oxidation Reactions

A. $LiAlH_4$ B. Chiral RuSalen/air C. OSO_4 D. Acetone, H^+

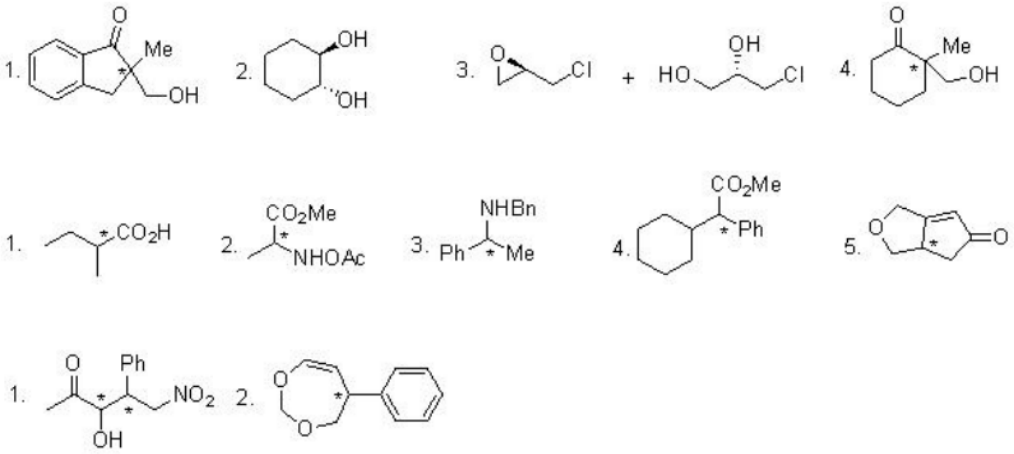
A. 1. $Ti(OiPr)_4$, (-)-DET, TBHP 2. $Ti(OiPr)_4$, (+)-DET, TBHP 3. $Ti(OiPr)_4$, (-)-DET, TBHP



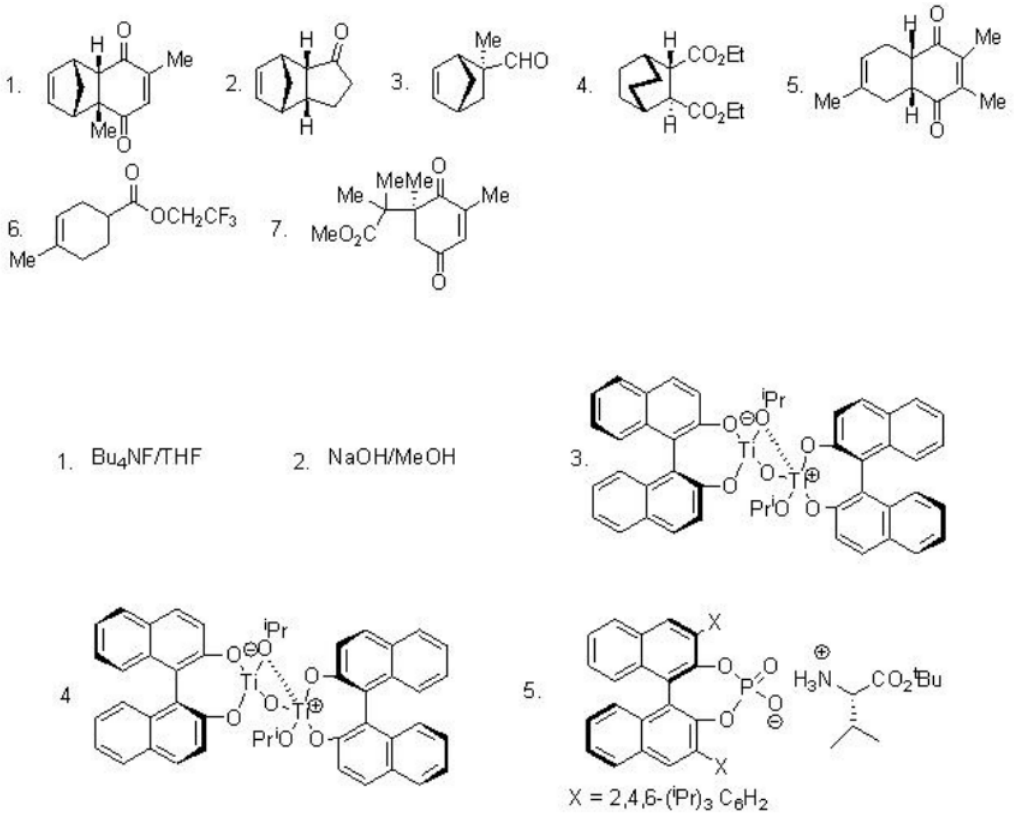


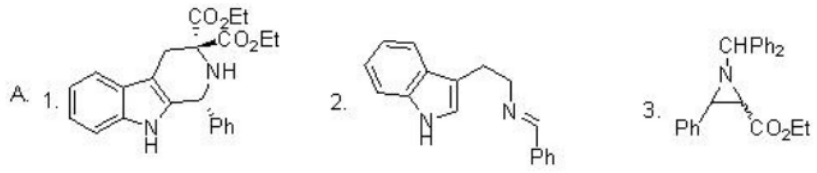


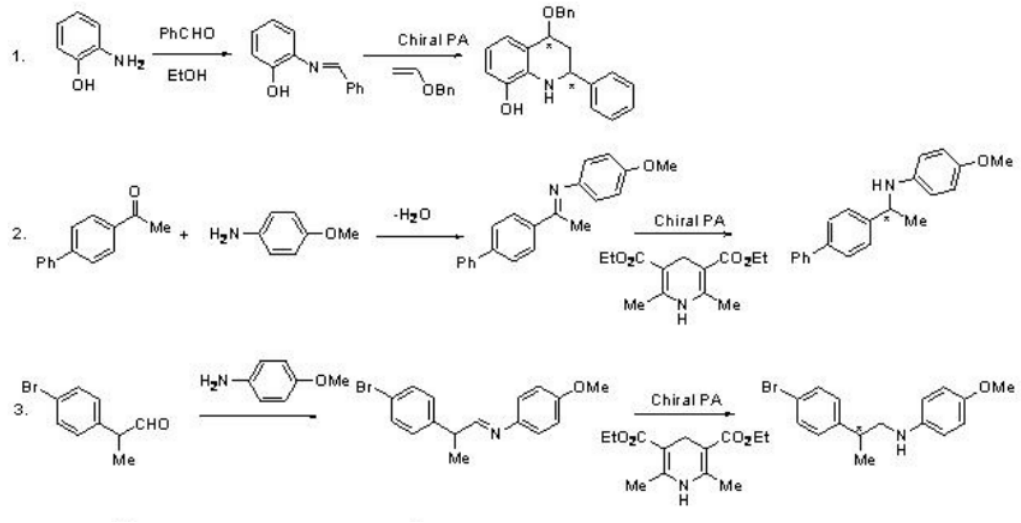
12.9: Reactions in Nonconventional Conditions

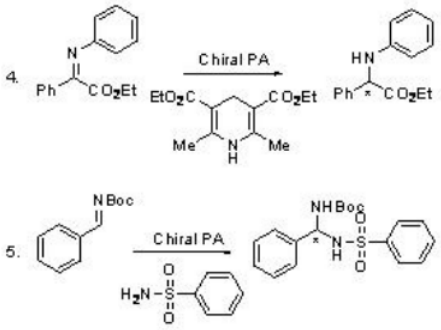


12.10: Reactions Using Chiral Lewis and Brønsted Acids

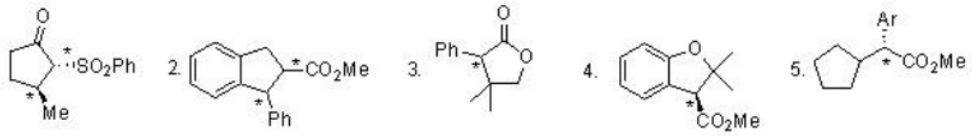


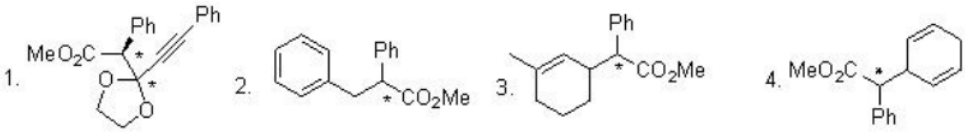


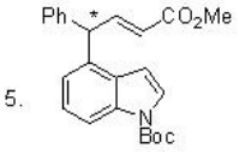


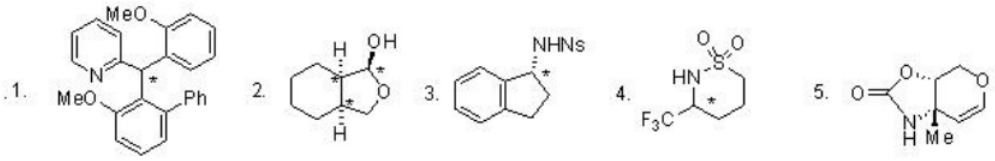


12.11: Synthesis via C-H Activation









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