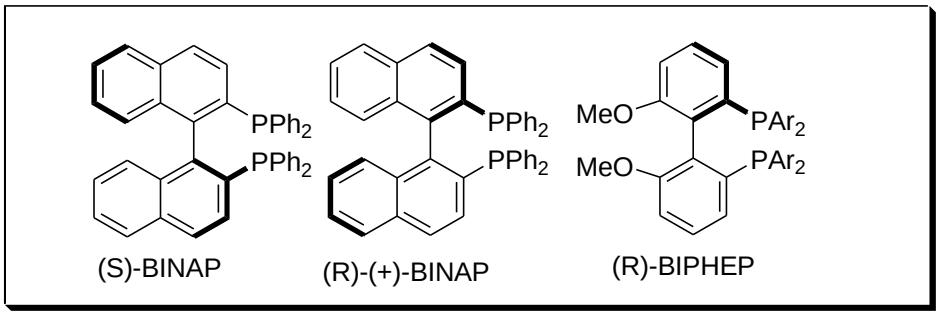
Module 6 Hydrogenation Reactions
Lecture 22

6.1 Reaction Carbon-Carbon Double Bonds

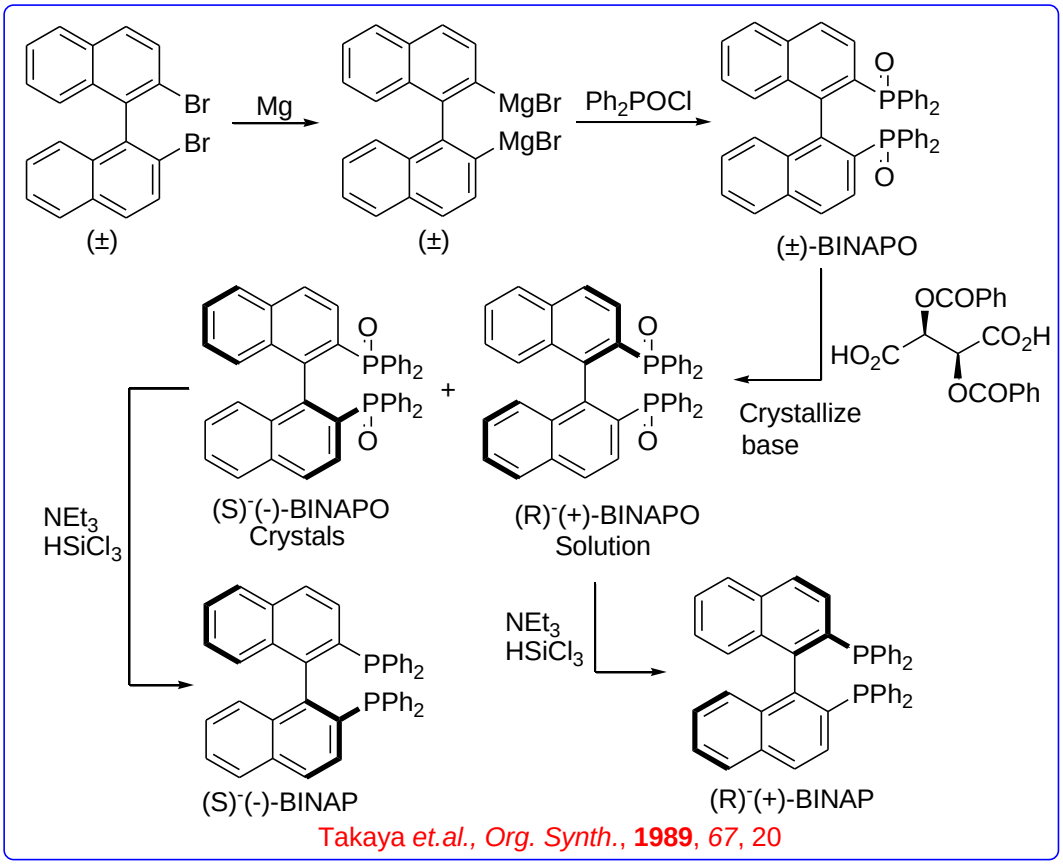
Enantioselective reduction of C=C double bond has important application in the synthesis of many natural products and pharmaceutically important compounds. Scheme 1 summarizes some of the common successful phosphine based chiral ligands developed for the catalytic asymmetric hydrogenation of alkenes.



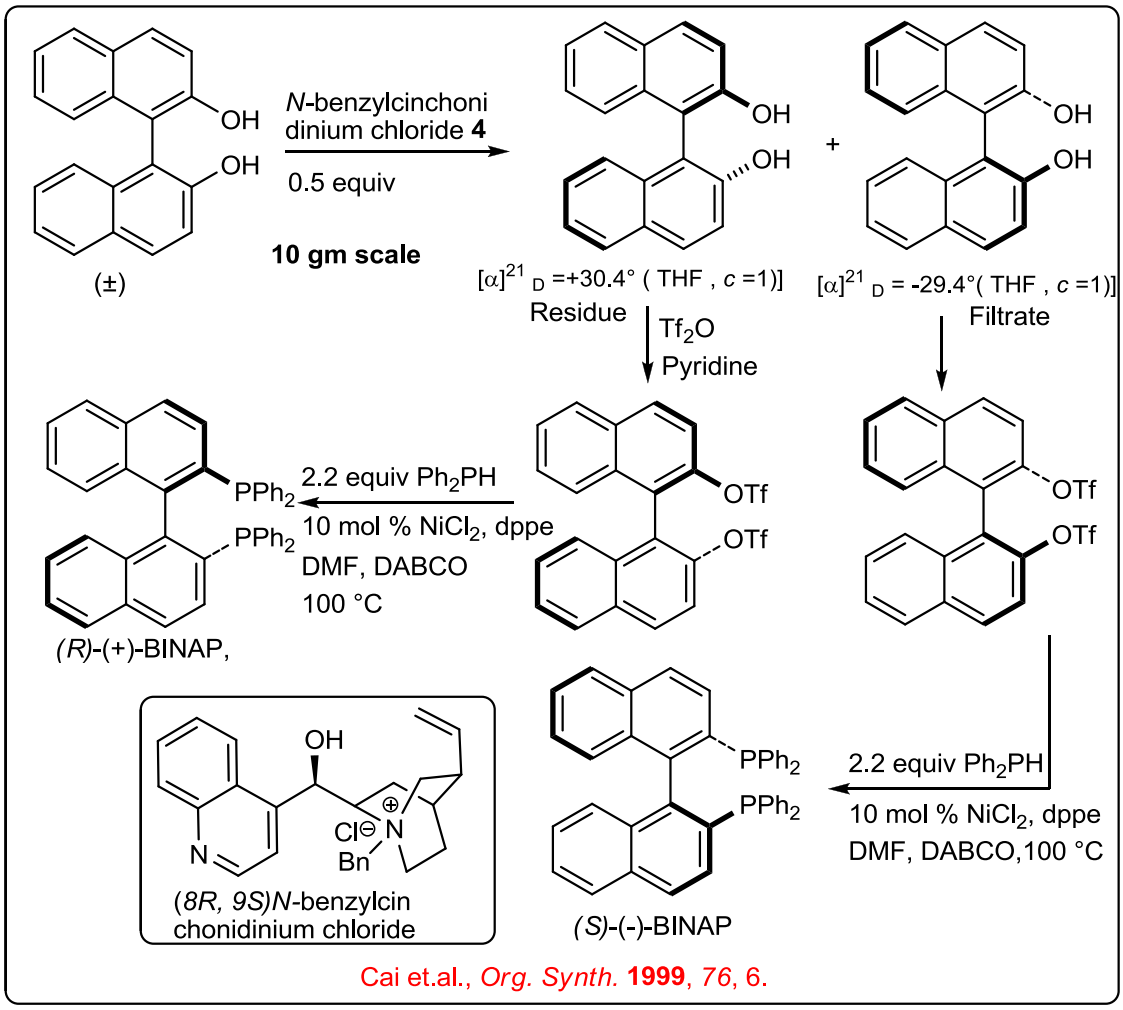
Scheme 1

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)*-BINAP could be performed from racemic 2,2'-dibromo BINAP (Scheme 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 3). Converting them into triflate derivative and subsequent cross-coupling with Ph_2PH 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).



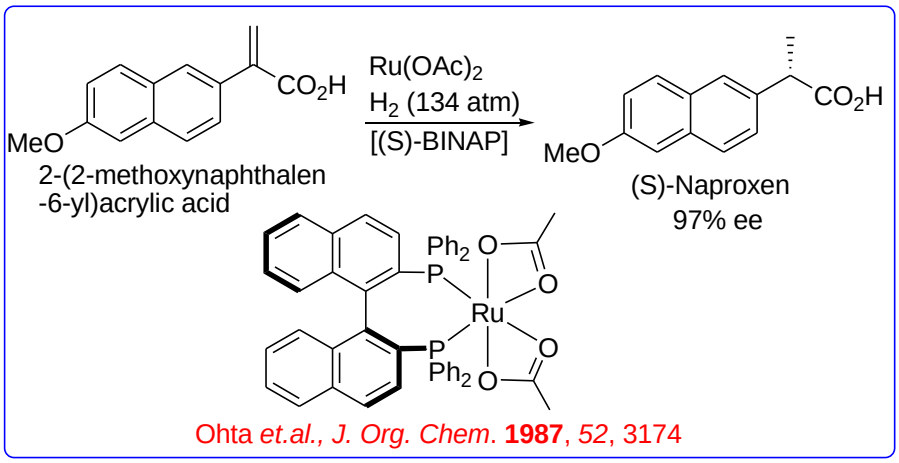
Scheme 2. Gram Scale Synthesis of *(S)*-BINAP and *(R)*-BINAP



Scheme 3. Alternative Synthesis of Chiral *(S)*-BINAP *and (R)*-BINAP

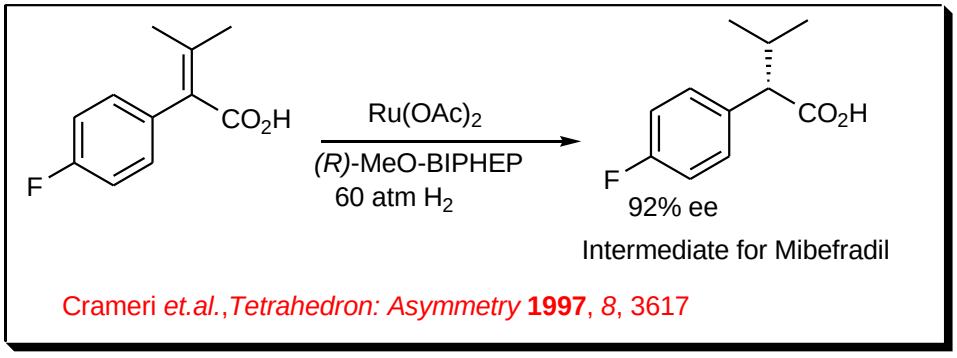
6.1.1 Reduction of α,β-Unsaturated Carboxylic acids

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_2 pressure (Scheme 4). The reaction affords chiral (*S*)-naproxen with 98% ee, which is a nonsteroidal anti-inflammatory drug.



Scheme 4. Synthesis of *(S)*-Naproxen by Chiral Reduction of □□□-Unsaturated Carboxylic Acids

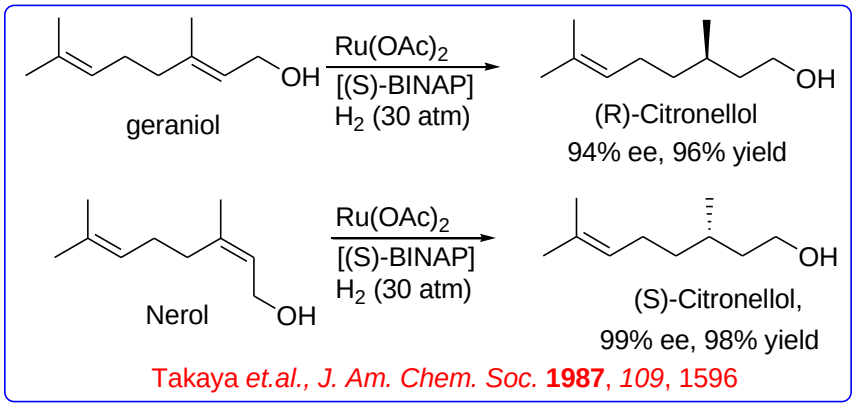
Hydrogenation has been explored for the synthesis of intermediate of *(S)*-mibefradil. For this reaction chiral Ru-complex bearing (*R*)-MeO-BIPHEP is found to be effective affording the target intermediate with 92% ee (Scheme 5).



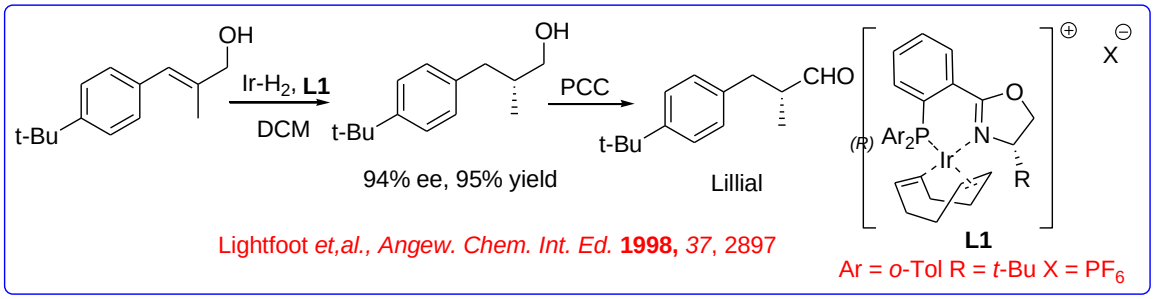
Scheme 5. Synthesis of Intermediate for *(S)*-Mibefradil

6.1.2 Reduction of Allylic alcohol

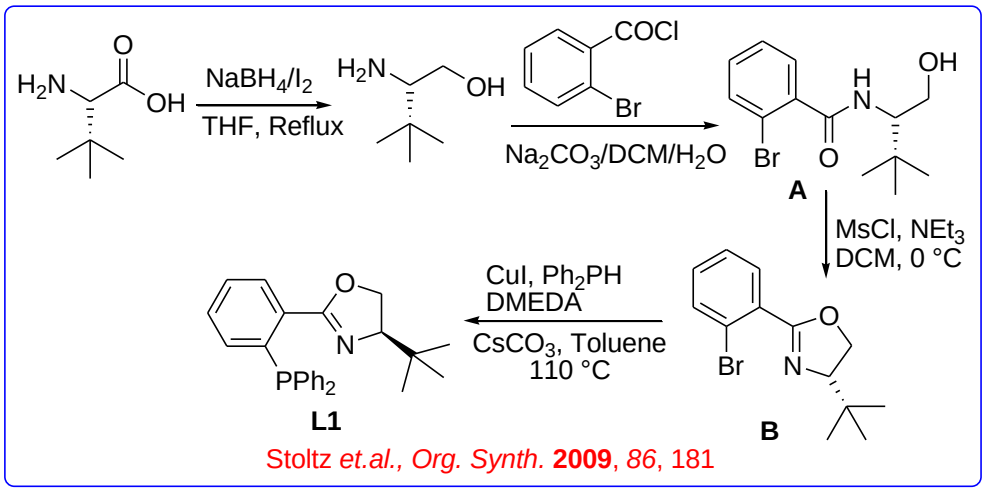
Allylic alcohols can be reduced with high selectivity using chiral Ru-(*S*)-BINAP as a catalyst. For example, the reduction of geraniol can be accomplished with 94% ee (Scheme 6). The reduced product is used for the large scale synthesis of L-(+)-menthol. Under these conditions, nerol undergoes reduction 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 7). Scheme 8 illustrates the synthesis of chiral phosphanodihydrooxazole L_1.



Scheme 6. Synthesis of *(S)* and *(R)*-Citronellol by Chiral Reduction of Geraniol and Nerol



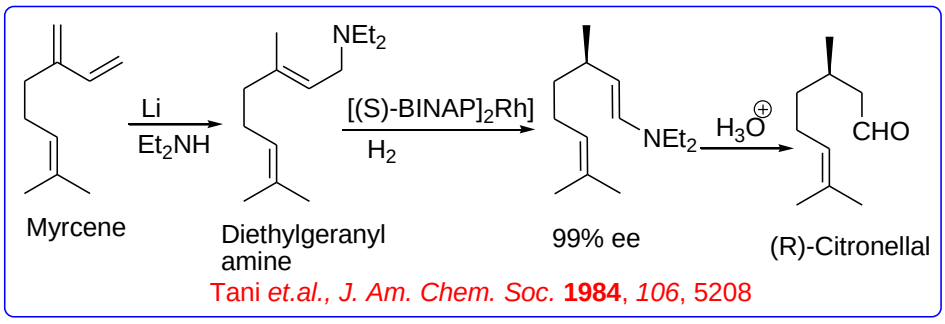
Scheme 7. Asymmetric Synthesis of Lillial.



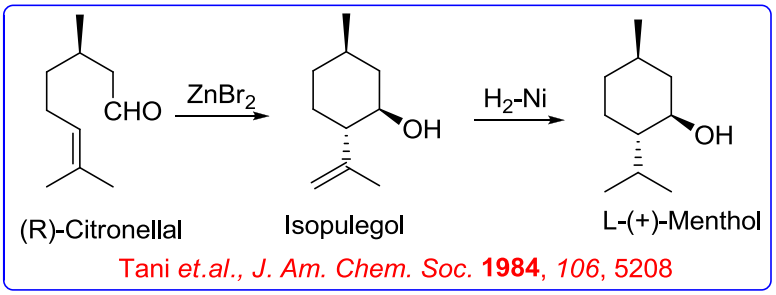
Scheme 8. Synthesis of Phosphanodihydrooxazole L_1

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 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 10).



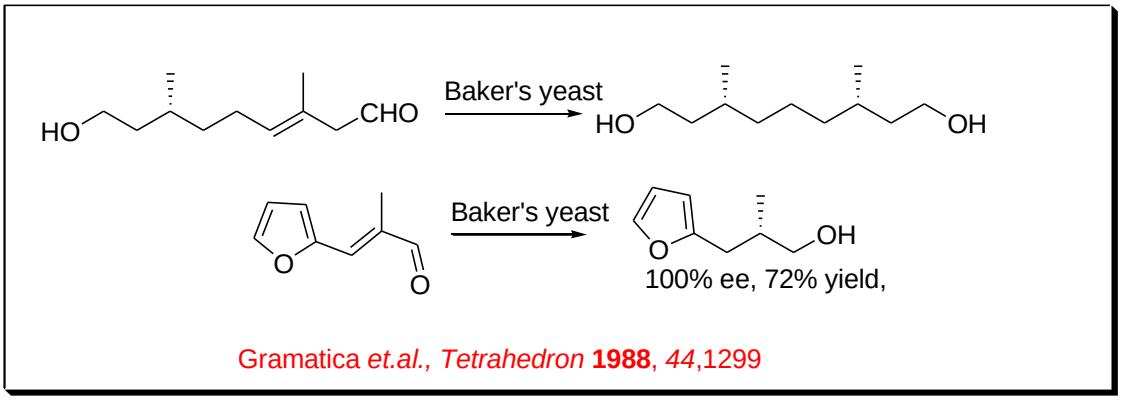
Scheme 9. Chiral Reduction of Allylic Amine to Synthesize (*R*)-Citronellal



Scheme 10. Industrial preparation of L-(+)-Menthol by Chiral Reduction of Allylic Amine

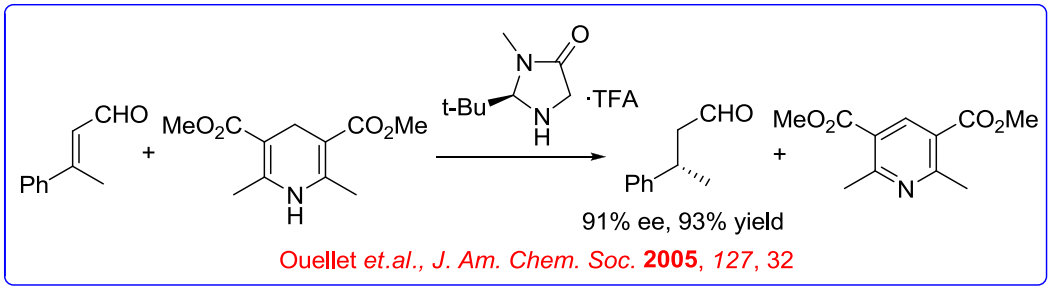
6.1.4 Reduction of α,β-Unsaturated Aldehydes

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 11 summarizes some of the examples for the Baker yeast catalyzed reduction of C=C of α,β-unsaturated aldehydes.



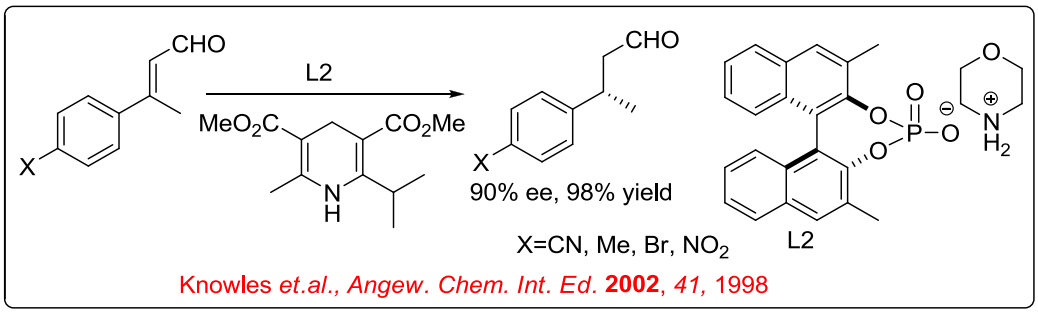
Scheme 11. Baker's yeast cell for Reduction of α,β-Unsaturated Aldehydes

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 12).



Scheme 12. Organocatalytic Reduction of an Unsaturated Aldehyde

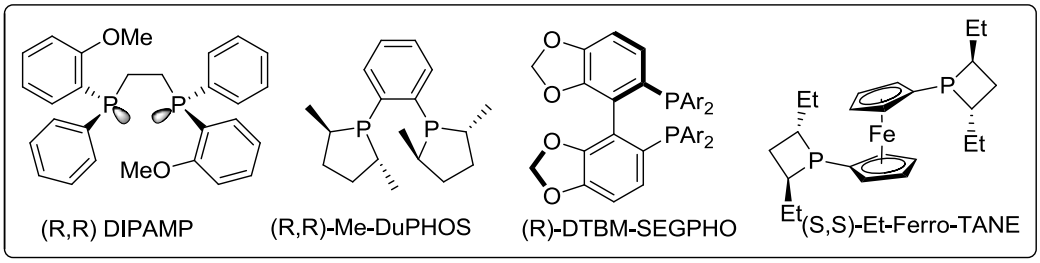
Similarly, chiral phosphoric acid L2 catalyses the reduction of C=C of *α,β*-unsaturated aldehyde with 90% ee and 98% yield in the presence of Hantzsch ester (Scheme 13).



Scheme 13. Organocatalytic Reduction of an α,β-Unsaturated Aldehyde

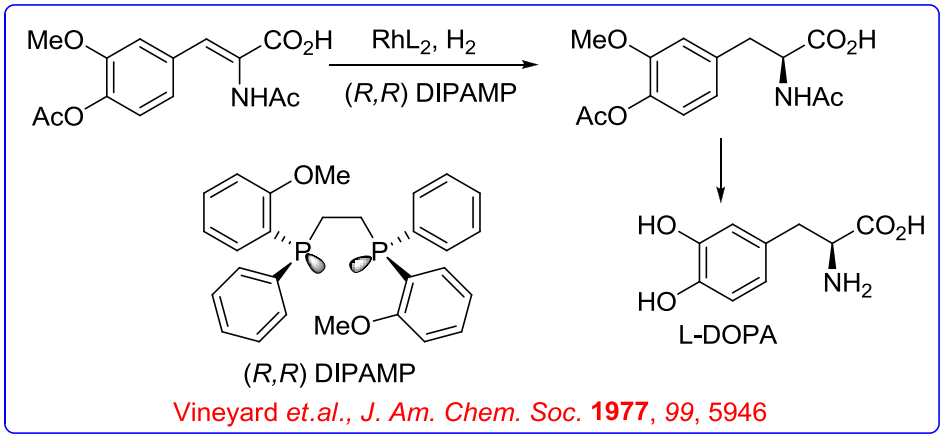
6.1.5 Reduction of α,β-Unsaturated α-Amino Acid

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 14 summarizes some of the successful chiral phosphines for the Rh-catalyzed reactions.



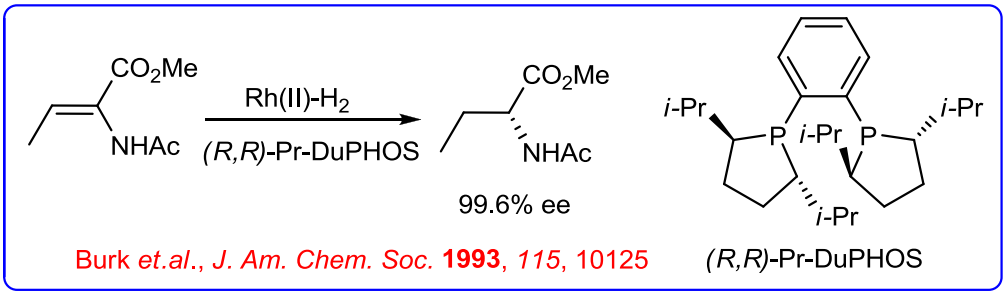
Scheme 14. Ligands used for Chiral Reduction of *α,β*-Unsaturated *α*-Amino acid

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 15).



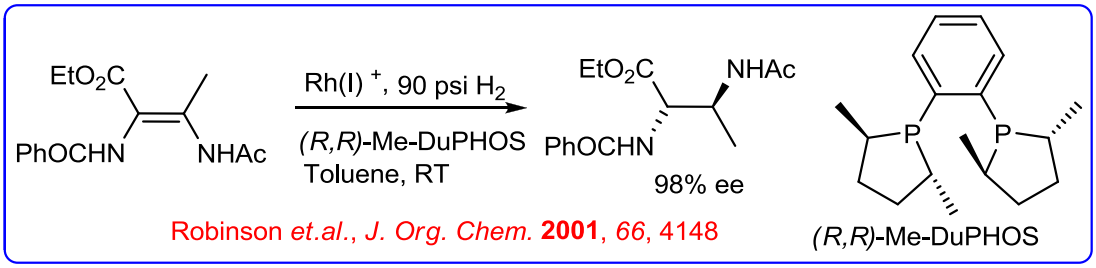
Scheme 15. Key Step for Industrial Synthesis of L-DOPA

Rh-*(R,R)*-DuPHOS can be used for the reduction of *α,β*-unsaturated *α*-amino acid to give chiral amino acid (Scheme 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.

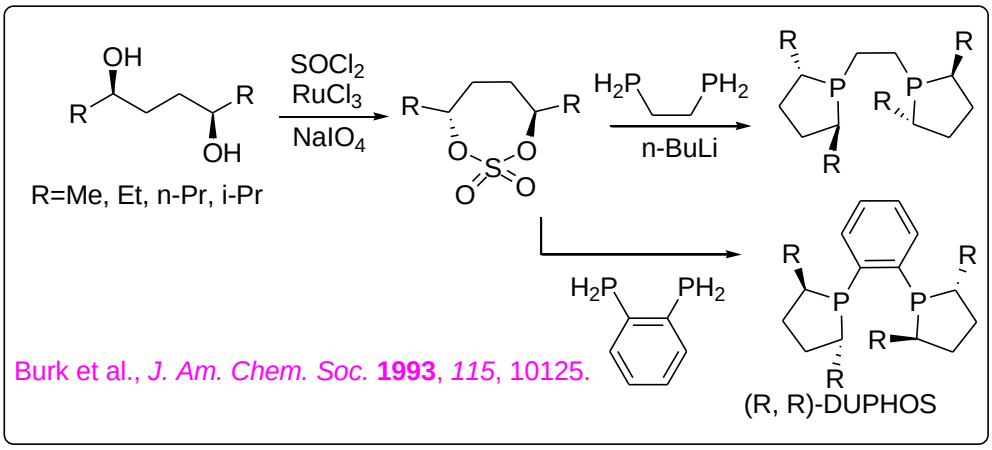


Scheme 16. Reduction of *α,β*-Unsaturated *α*-Amino Ester

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 17-18).

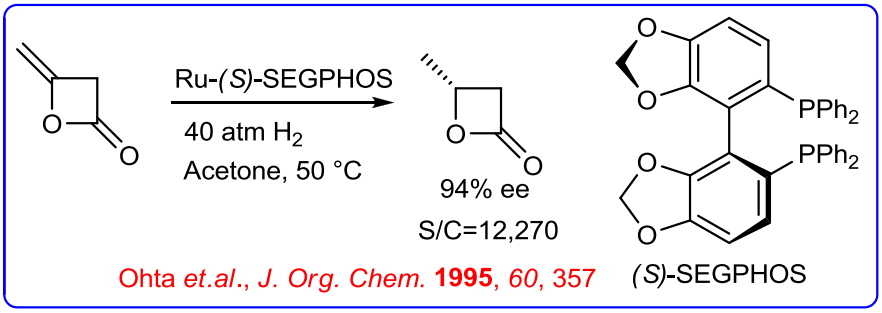


Scheme 17. Reduction of *α,β*-Unsaturated *α*-Amino *β*-ester



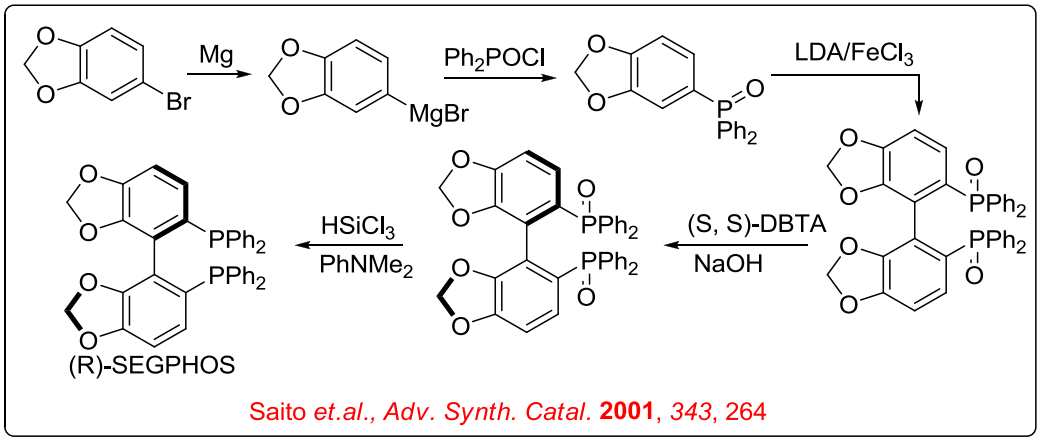
Scheme 18. Synthesis of 1,2-Bis(phospholano) (DuPHOS) Ligands

(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 19).



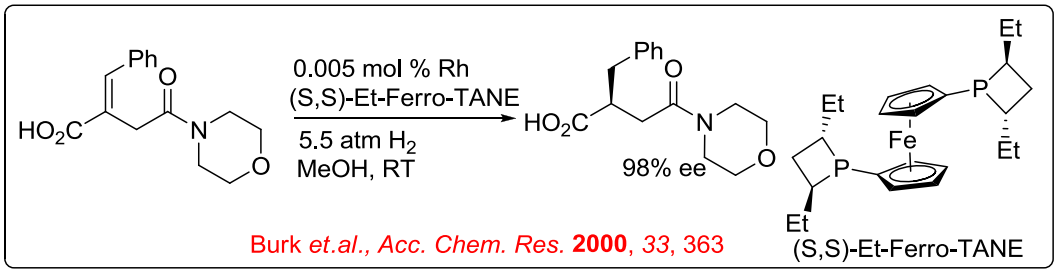
Scheme 19. Reduction of *α,β*-Unsaturated Lactone using *(S)*-SEGPHOS

Scheme 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.



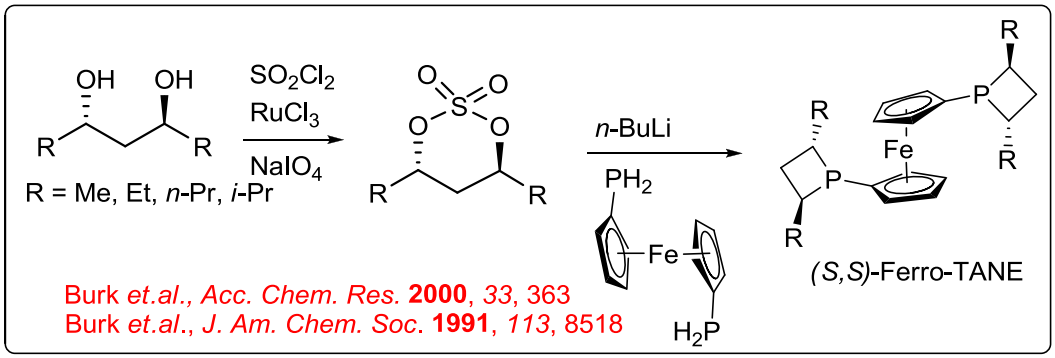
Scheme 20. Synthesis of *(R)*-SEGPHOS Ligands

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 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).



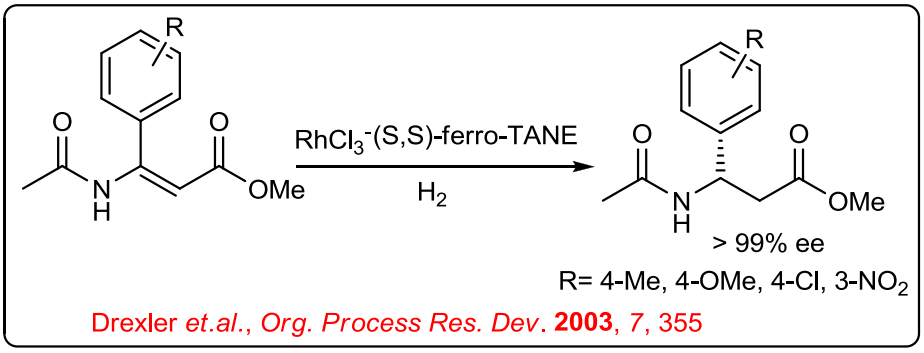
Scheme 21. Reduction of *α,β*-Unsaturated Carboxylic using Et-Ferro TANE

The above described alkyl/aryl-ferro-TANE family ligands could be synthesized from optically active diols (Scheme 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 22. Synthesis of Chiral Et-Ferro TANE Ligands

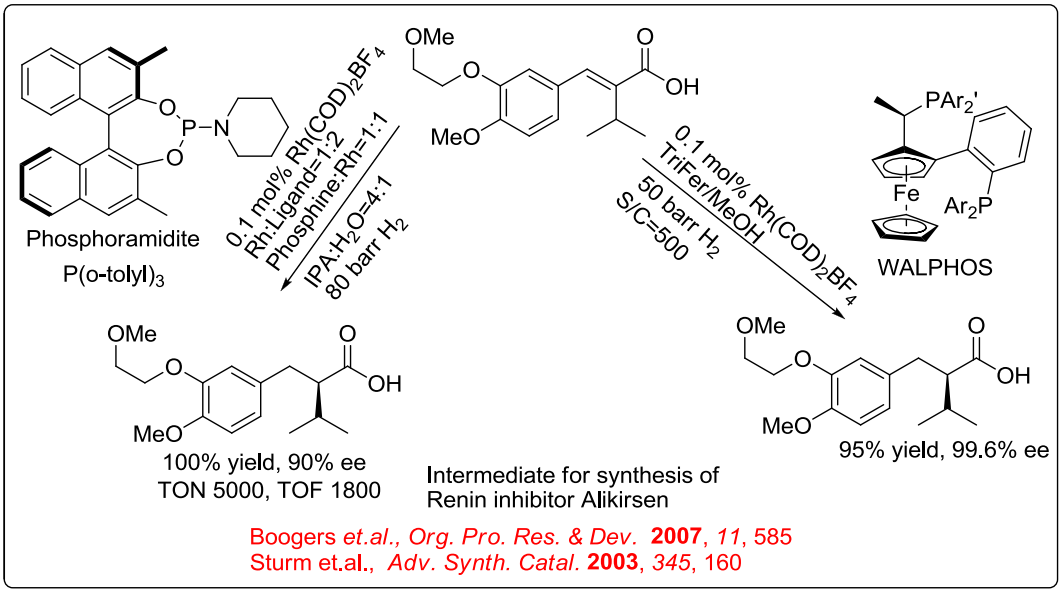
Similarly, the reduction of α,α-disubstituted α,β-unsaturated ester can be carried out using chiral Ru-Et-Ferro TANE (Scheme 23). The reaction is compatible with different electron donating and withdrawing groups attached to benzene ring.



Scheme 23. Chiral Reduction of α,α-Disubstituted α,β-Unsaturated Ester.

6.1.6 Reduction of α-Alkyl Substituted Acids

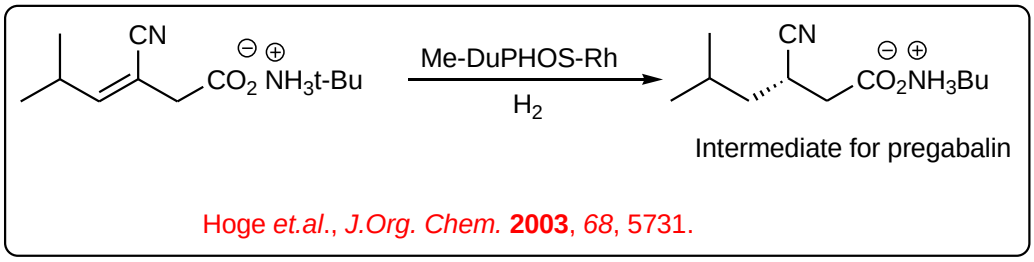
Another important chiral acid is the *α*-alkyl substituted acid which is used in the synthesis of *aliskiren* (the active ingredient of Tekturna1) (Scheme 24). The key step for the synthesis requires the hydrogenation of cinnamic acid derivative in the presence of Rh-phosphoramidite**.** The reduction also affords 97% ee using Rh-WALPHOS.



Scheme 24. Key Step for Synthesis of Renin Inhibitors *Aliskiren*

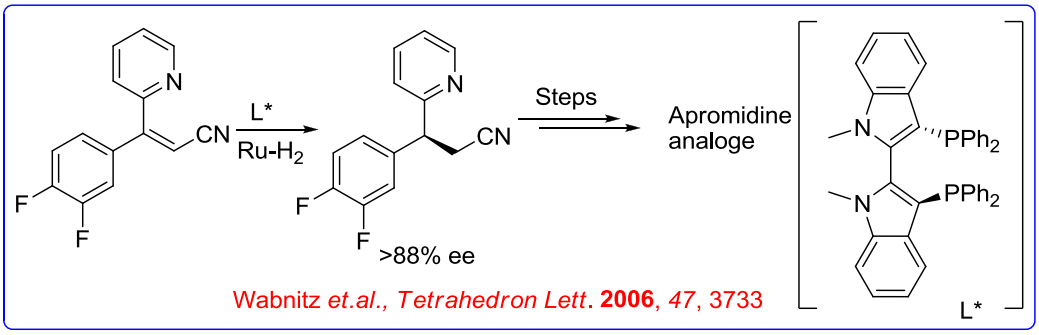
6.1.7 Reduction of α,β-Unsaturated Nitriles

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 25). The reduced product is used for the synthesis of the *Pregabalin.*



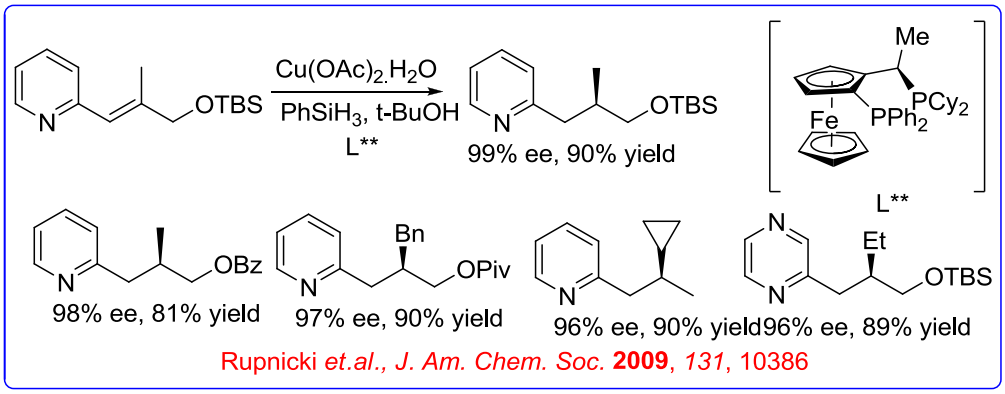
Scheme 25. Pfizer *Pregabalin* Intermediate Synthesis

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 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 26. Hydrogenation of Diaryl-substituted *α,β*-Unsaturated nitriles.

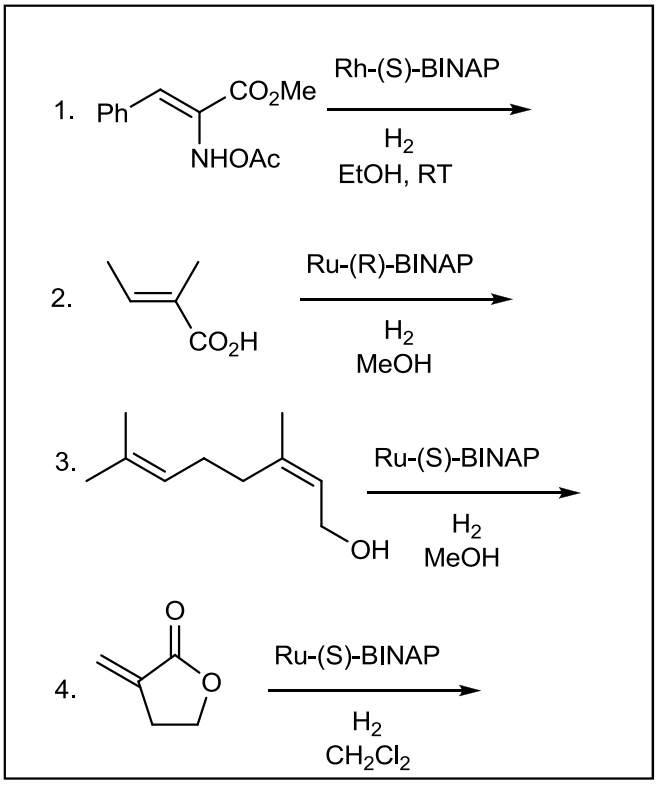
In parallel to Ru, Rh and Ir-based catalytic systems, chiral copper hydride catalysis have been demonstrated for enantioselective 1,4-reductions of 2-alkenyl heteroarenes. Both azoles and azines serve as efficient activating groups for this process (Scheme 27).



Scheme 27. Enantioselective Hydrogenation of Protected Allylic Alcohol

Problems

A. Predict the major product of the following reactions.



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

Reference/Text Book

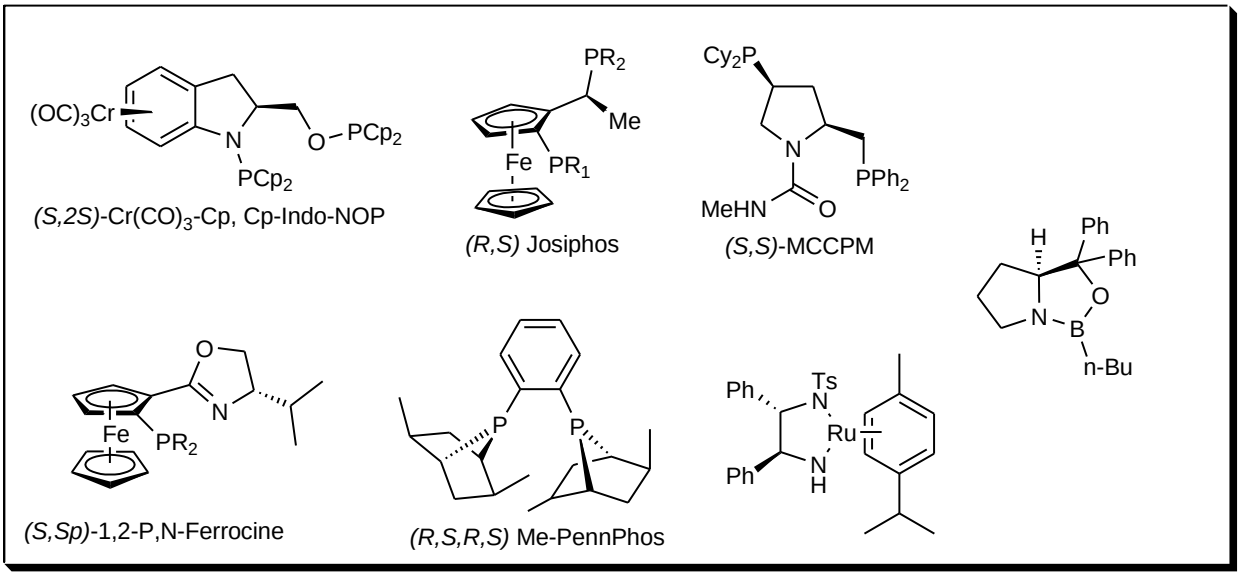
1. I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., Wiley, New Jersey, 2010.

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

Lecture 23

6.2 Reactions of Ketones

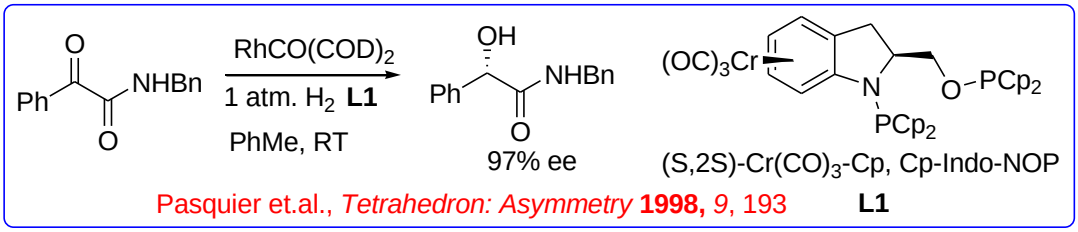
Enantioselective reduction of C=O double bond in organic synthesis has important application in synthesis of many natural products as well as pharmaceutical products. The lecture covers the representative examples of metal catalyzed reactions. The reactions using CBS and enzymes are covered in the other modules of this course. The frequently used chiral ligands for the metal catalyzed enantioselective reduction reactions of ketones are listed in Scheme 1.



Scheme 1

6.2.1 Reactions of α-Keto Amides

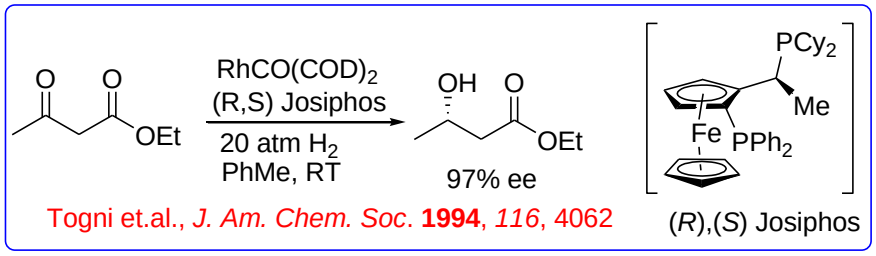
Asymmetric hydrogenation of *α*-keto esters has been studied with several rhodium catalysts. Neutral rhodium catalysts with chiral ligands such as $Cr(CO)_3$-Cp,Cp-Indo-NOP demonstrate excellent enantioselectivity and reactivity in the hydrogenation of amides (Scheme 2).



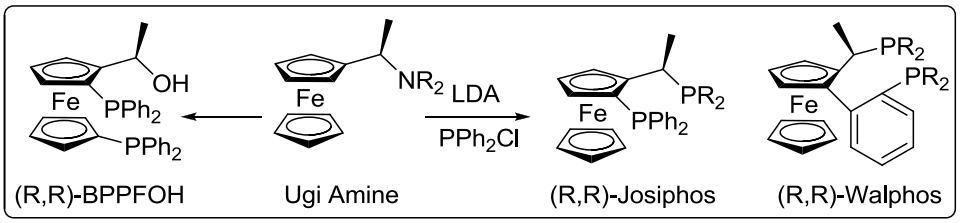
Scheme 2. Enantioselective Hydrogenation of *α*-Keto Amide

6.2.2 Reactions of β-Keto Esters

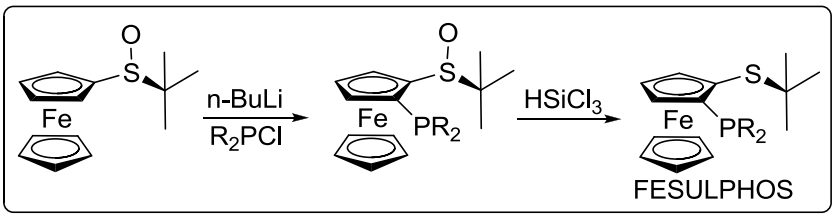
Asymmetric hydrogenation of *β*-keto esters has been extensively studied using chiral ruthenium catalysts. However, only handful of examples analogous to rhodium-catalyzed reaction are explored (Scheme 3). The Rh-(*R,S*)-Josiphos complex provides an effective catalyst for the asymmetric hydrogenation 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 4-6).



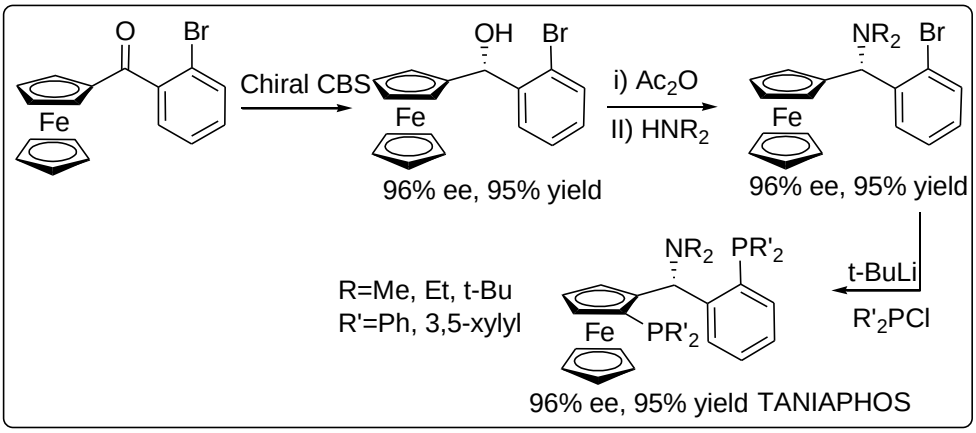
Scheme 3. Enantioselective Hydrogenation of *β*-Keto ester



Scheme 4. Synthesis of *Josiphos* Type Ligands

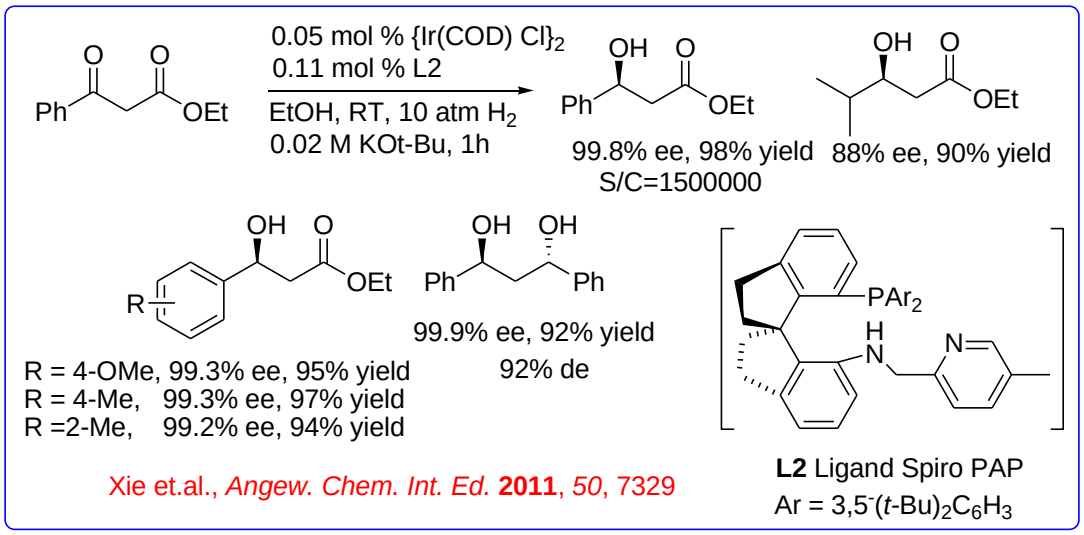


Scheme 5. Synthesis of *Feluphos*



Scheme 6. Synthesis of *Taniaphos*

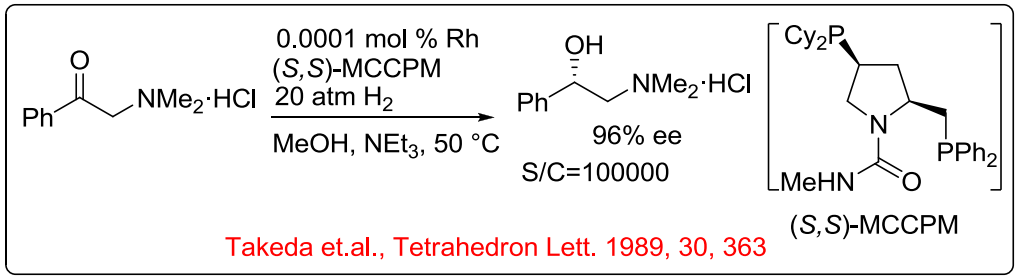
Iridium/spiro PAP has been used as effective catalyst for the asymmetric hydrogenation of *β*-aryl *β*-ketoesters (Scheme 7). The reaction provides a readily accessible method for the synthesis of *β*-hydroxy esters in high enantioselectivity up to 99.8% ee and high TONs up to 1230000.



Scheme 7. Enantioselective hydrogenation of *β*-ketoesters

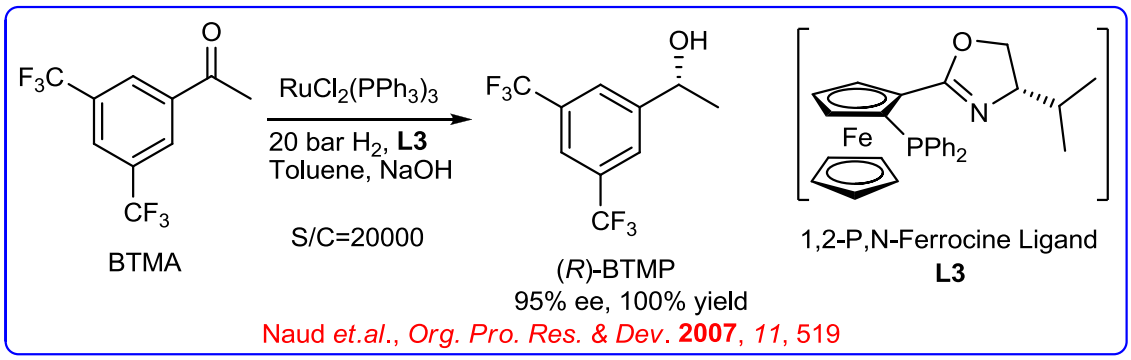
6.2. 3 Reactions of Aromatic Ketones

Amino ketones and their hydrochloride salts can be effectively hydrogenated with chiral rhodium catalysts (Scheme 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.

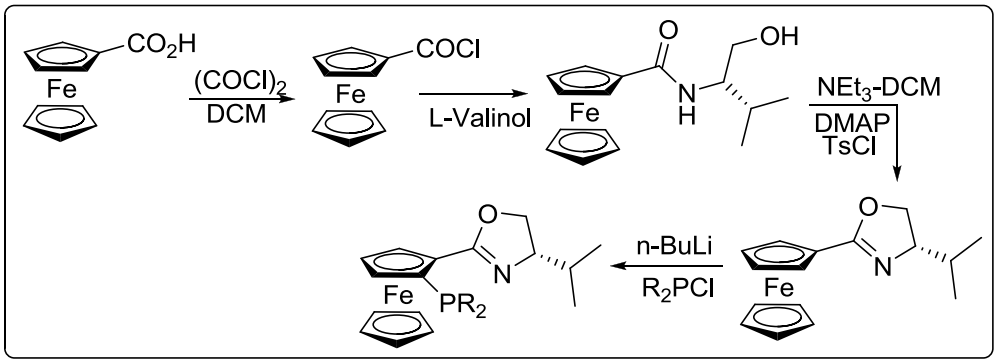


Scheme 8. Enantioselective Hydrogenation of α-Aryl Amino Ketone

The enantioselective hydrogenation of 3,5-bistrifluoromethyl acetophenone (BTMA) can be carried out using a Ru/phosphine-oxazoline complex (Scheme 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 10.

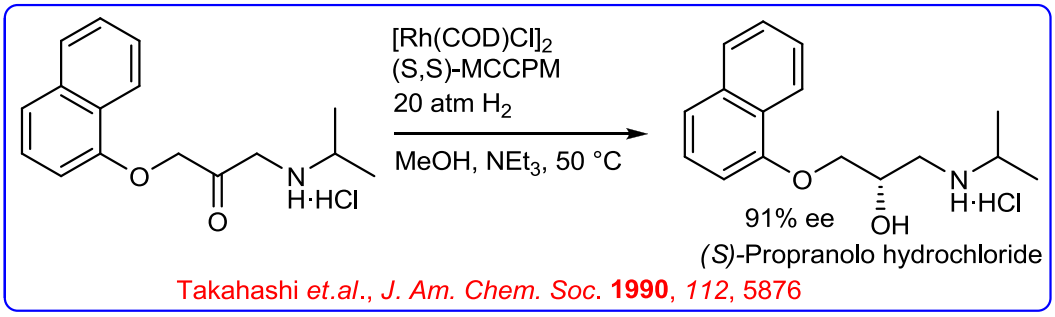


Scheme 9. Hydrogenation of α-Aryl Ketone



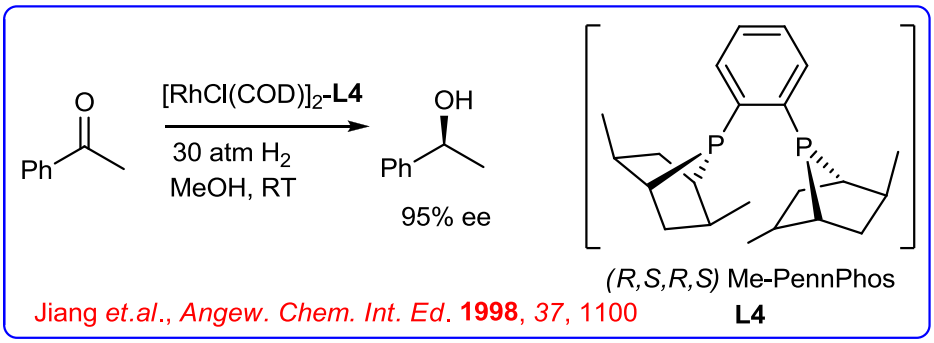
Scheme 10. Synthesis of *(S,Sp)*-1,2-P,N-Ferrocine

The enantioselective hydrogenation of amino ketones has been applied extensively to the synthesis of chiral drugs and pharmaceuticals (Scheme 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 11. Key step for the Direct Synthesis of *(S)*-Propranolol

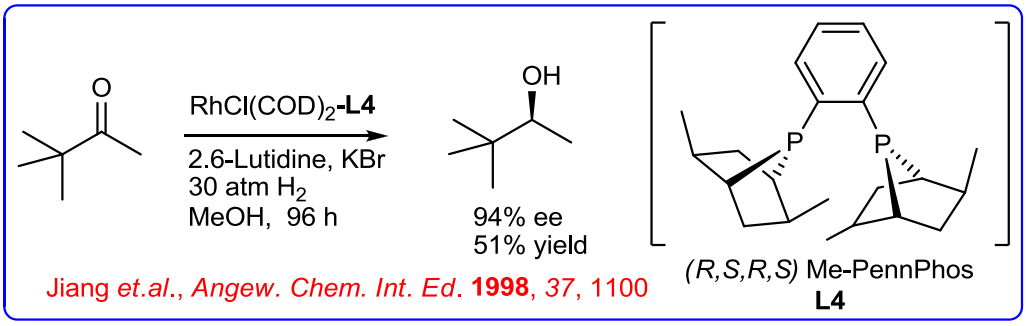
The hydrogenation of acetophenone can be performed using (*R*,*S*,*R*,*S*)-Me-PennPhos–Rh with enantioselectivity of up to 96% *ee* (Scheme 12). Interestingly, the additives 2,6-lutidine and KBr are found to be crucial for optimum selectivity, although their specific role is to be determined.



Scheme 12. Asymmetric Reduction of Acetophenone

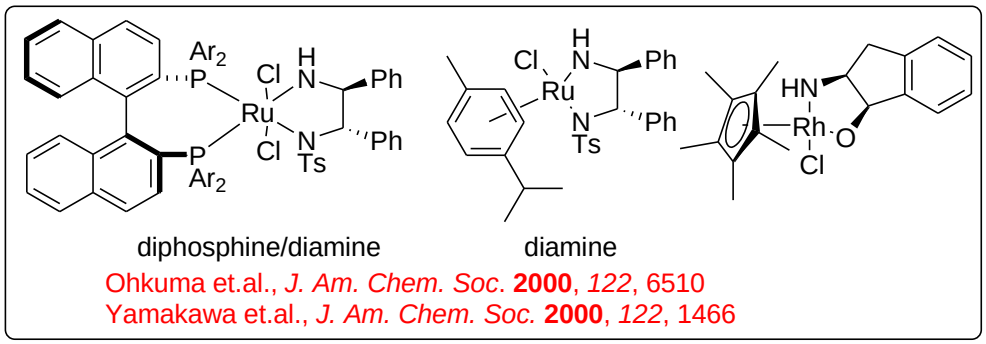
6.2.4 Reactions of Aliphatic Ketones

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.

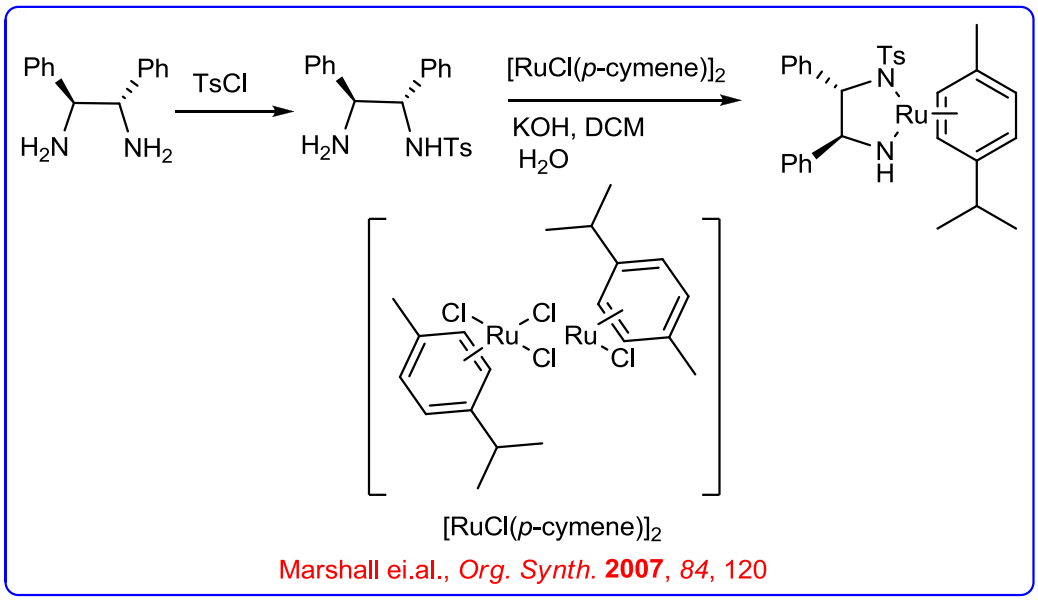


Scheme 13

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 14). The diamine catalyst can be synthesized from chiral 1,2-diphenylethylene diamine (Scheme 15).

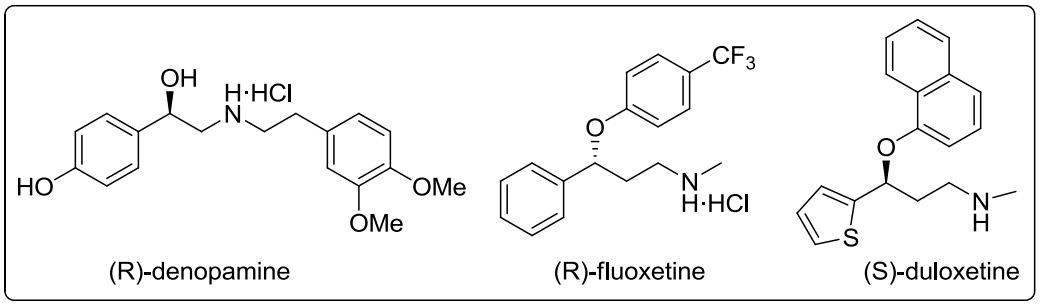


Scheme 14



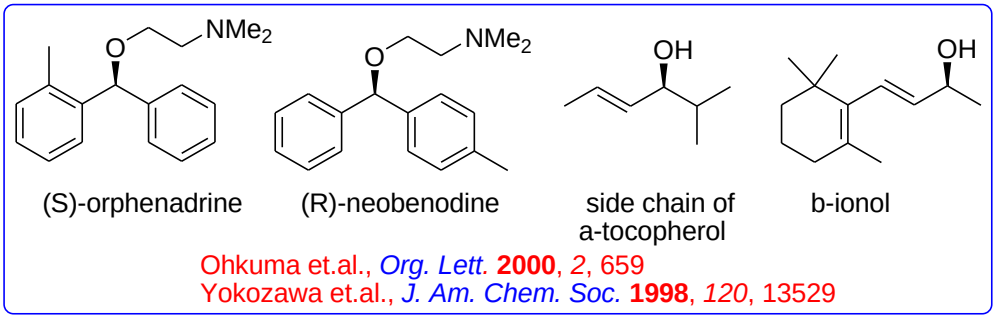
Scheme 15

These catalysts have been employed for the asymmetric synthesis of various important pharmaceuticals, including (*R*)-denopamine, a β1-receptor agonist, the *anti*-depressant (*R*)-fluoxetine, the *anti*-psychotic BMS 181100 and (*S*)-duloxetine (Scheme 16).



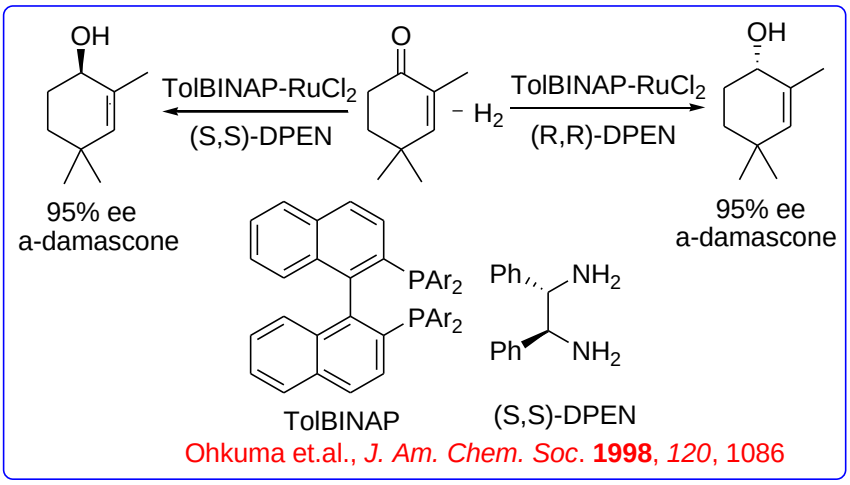
Scheme 16

Unsymmetric benzophenones could also be hydrogenated with high *S/C* ratio of up to 20000 without over-reduction (Scheme 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 17. Asymmetric Synthesis of Some of the Important Pharmaceuticals

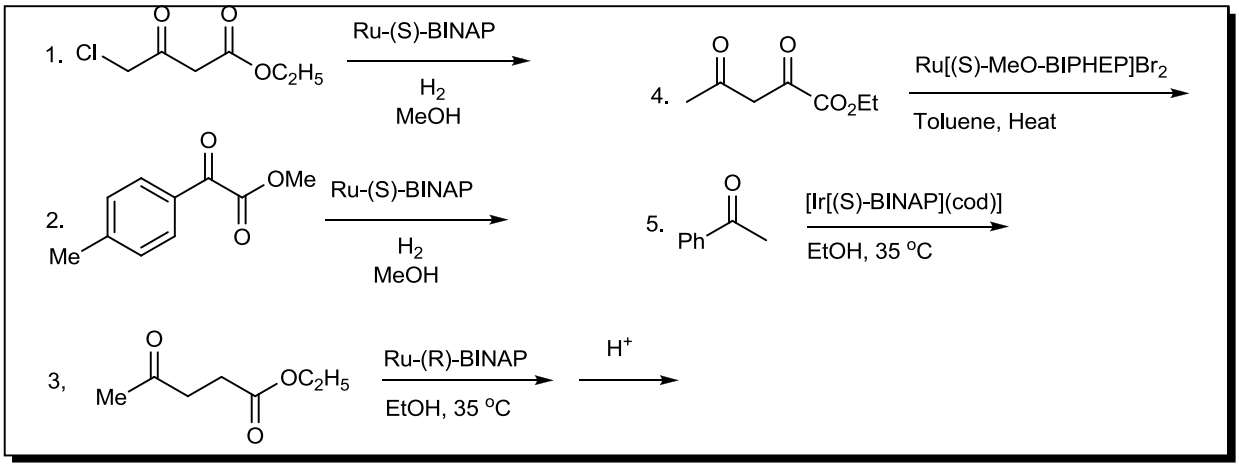
The asymmetric hydrogenation of simple ketone is generally achieved by the combined use of an (*S*)-BINAP and an (*S*)-1,2-diphenylethylenediamine. However, the reaction of 2,4,4-trimethyl-2-cyclohexenone can be effectively done with racemic $RuCl_2$[-tol-BINAP]- and chiral DPEN with up to >95% ee (Scheme 18).



Scheme 18

Problems

C. Complete the following reactions.



Reference/Text Book

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

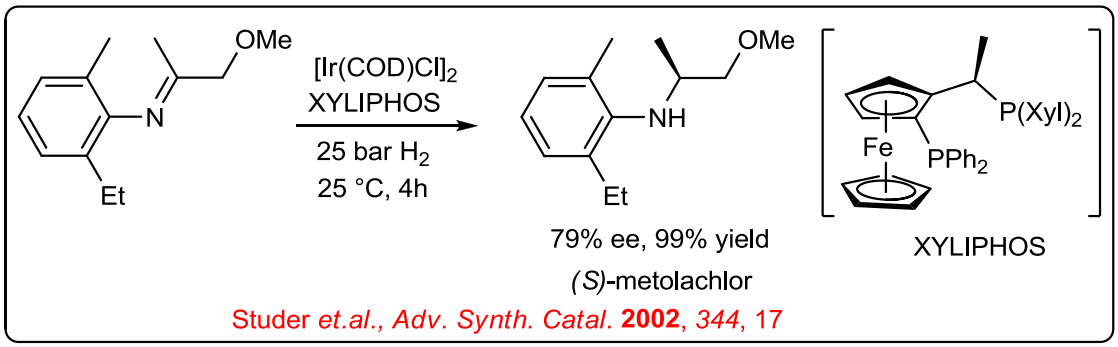
4. M. B. Smith, *Organic Synthesis*, 2nd edition, McGraw Hill, New Delhi, 2004.

Lecture 24

6.3 Reactions of Imines (C=N)

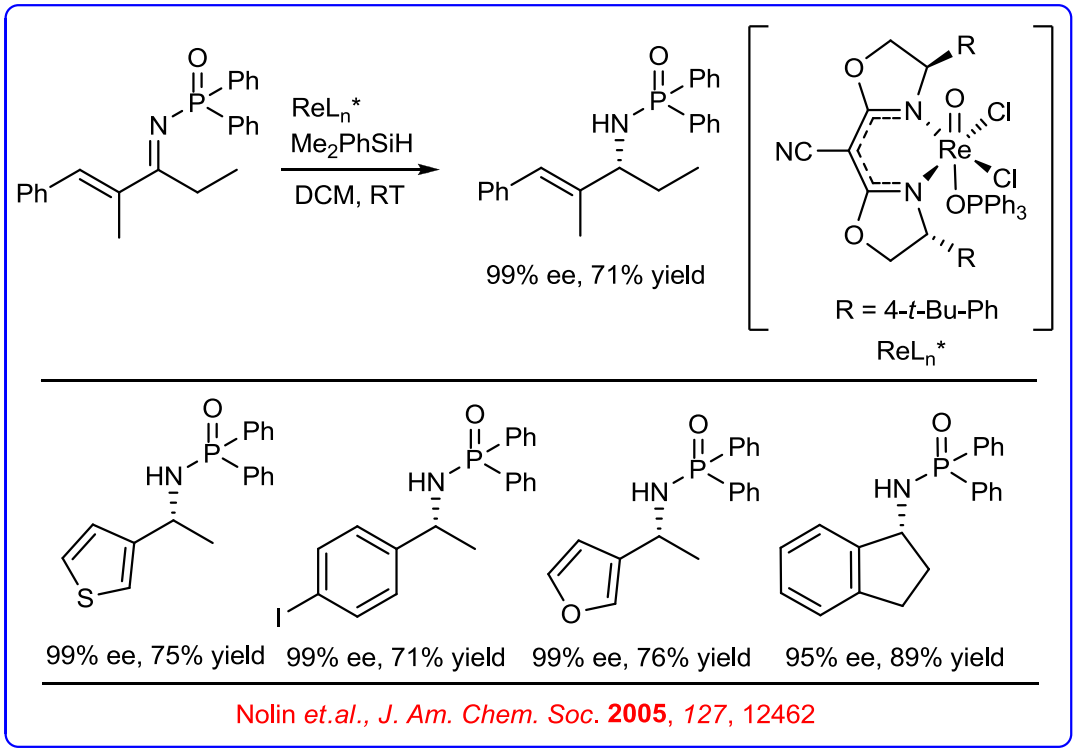
An important field of investigation for new industrial catalysts is the development of improved catalysts for the reduction of imines to obtain the corresponding chiral amines. These chiral amines are used as key components in many active pharmaceutical intermediates.

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 1). This catalyst shows a high catalytic activity with TOF=396 h^{-1} and enantioselectivity of 79% ee.



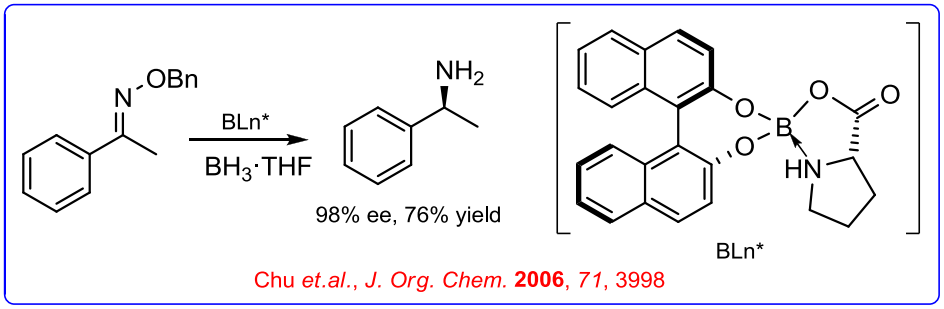
Scheme 1. Preparation of (*S*)-*Metolachlor* by Enantioselective Hydrogenation

Subsequently, an air- and moisture-tolerant enantioselective reduction of *N*-phosphinyl imines has been performed with (CNbox)Re(O)Cl_2($OPPh_3$) (Scheme 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.



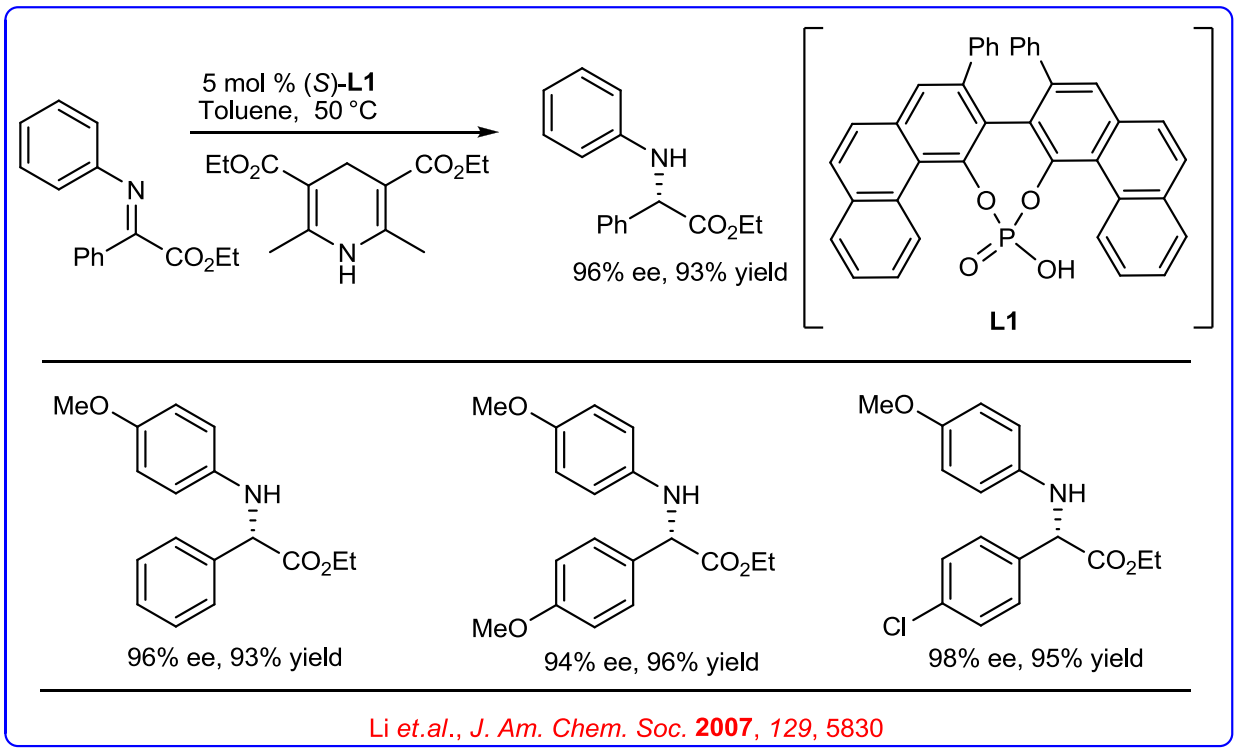
Scheme 2. Enantioselective Reduction of Imines Catalyzed by Rhenium(V)-oxo Complex

The use of modified CBS-type catalysts has been extended to the reduction of oximes into chiral amines (Scheme 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.



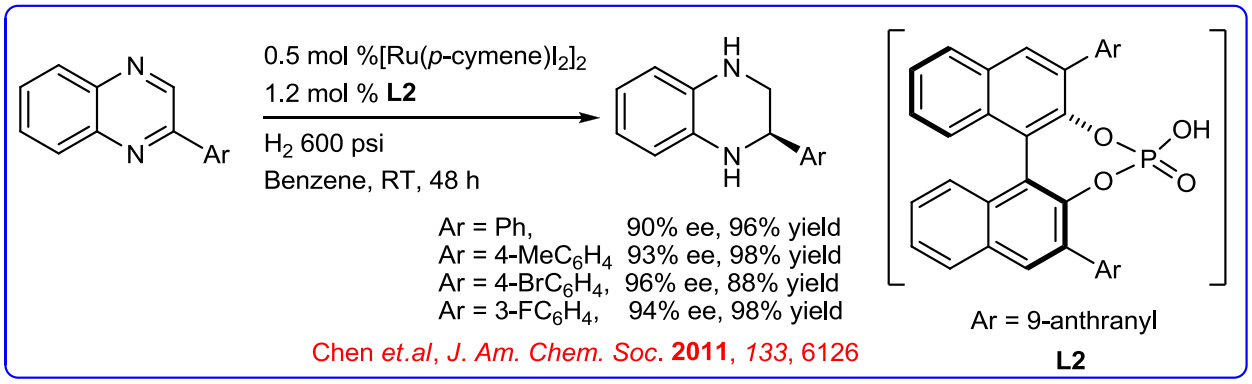
Scheme 3. Modified CBS catalyst for Enantioselective Reduction of Imines

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 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 5).

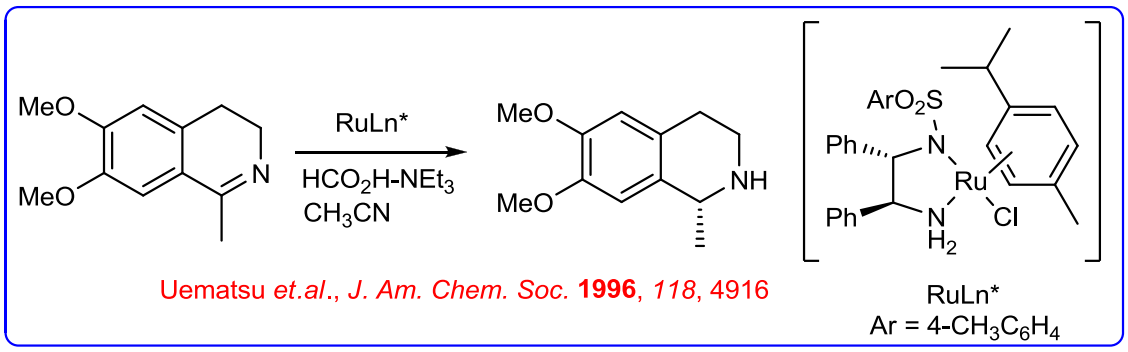


Scheme 5. Metal/Brønsted Acid Catalysis for Enantioselective Reduction of Quinoxalines

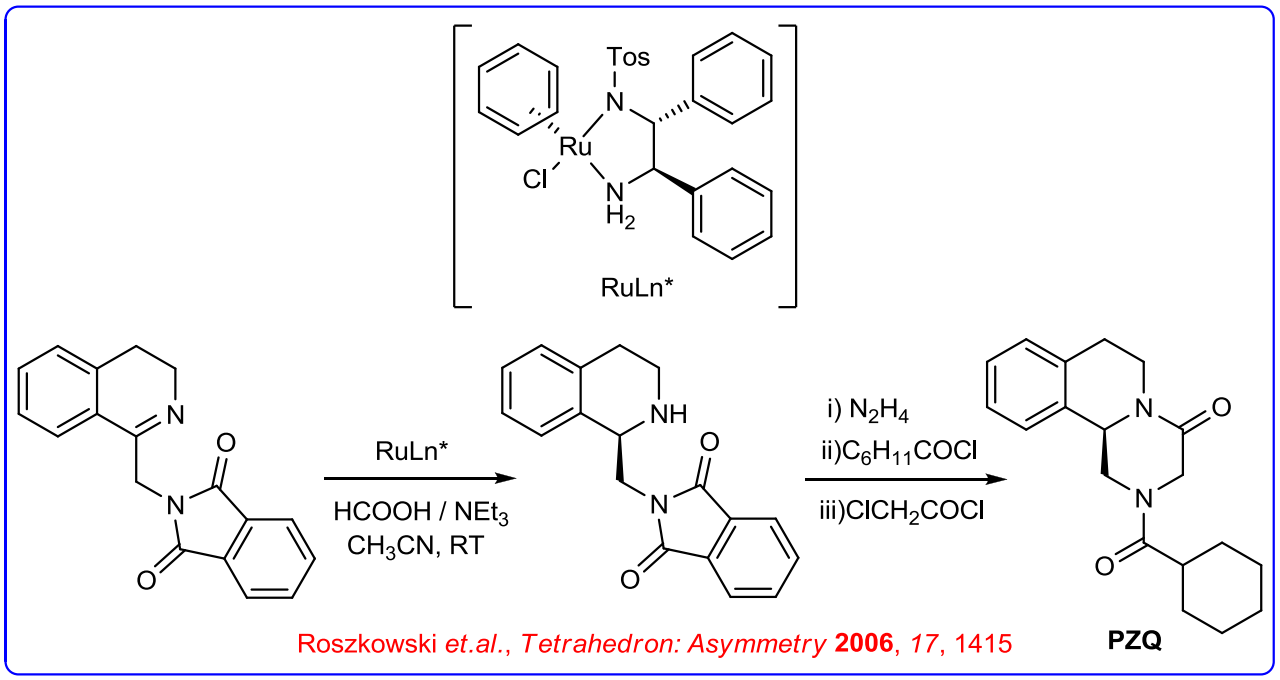
Employing hydrogen gas as the reductant makes this convergent disproportionation an ideal atom-economical process. A dramatic reversal of enantioselectivity is observed for the hydrogenation relative to the transfer hydrogenation of quinoxalines promoted by chiral phosphoric acids L2**.**

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).



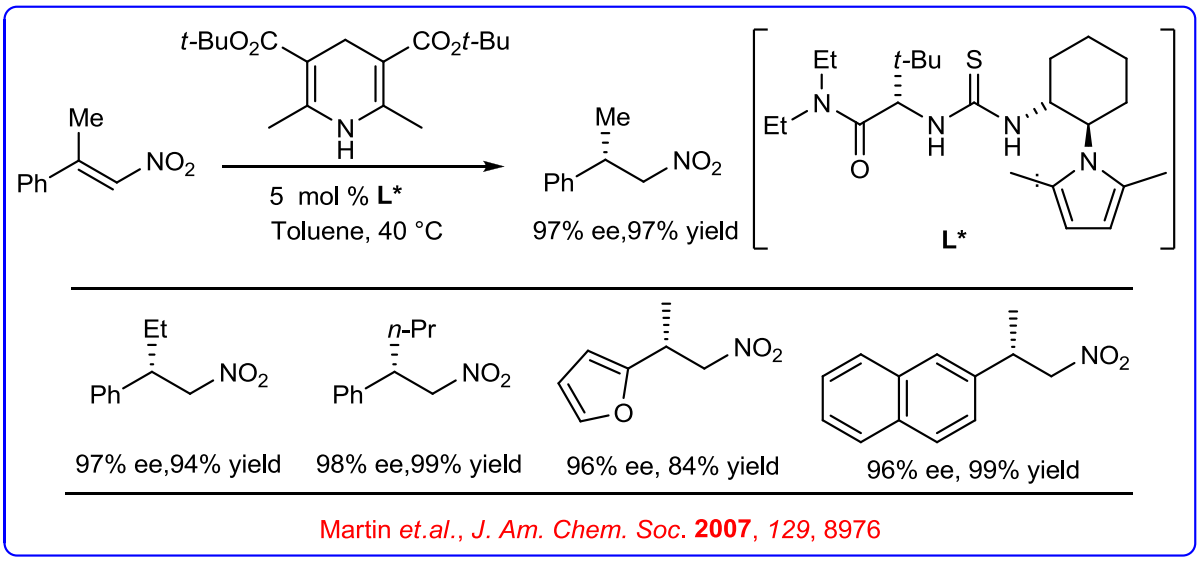
Scheme 6. Catalytic enantioselective conjugate reduction of imines



Scheme 7. Enantioselective Synthesis of *(R)*-Praziquantel (PZQ)

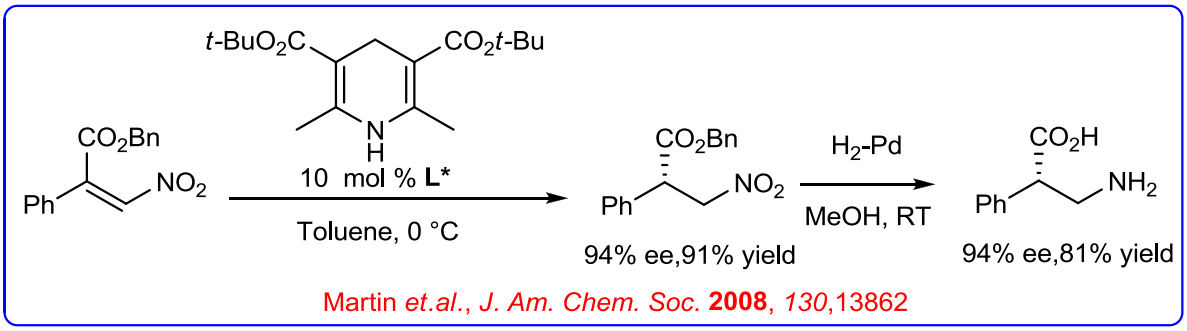
The enantioselective preparation of *Praziquantel* (PZQ) a pharmaceutical for the treatment of schistosomiasis and soil-transmitted helminthiasis has been accomplished. The synthesis is completed from staring chiral reduction of imine which could be synthesized from readily available phenyl ethyl amine,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



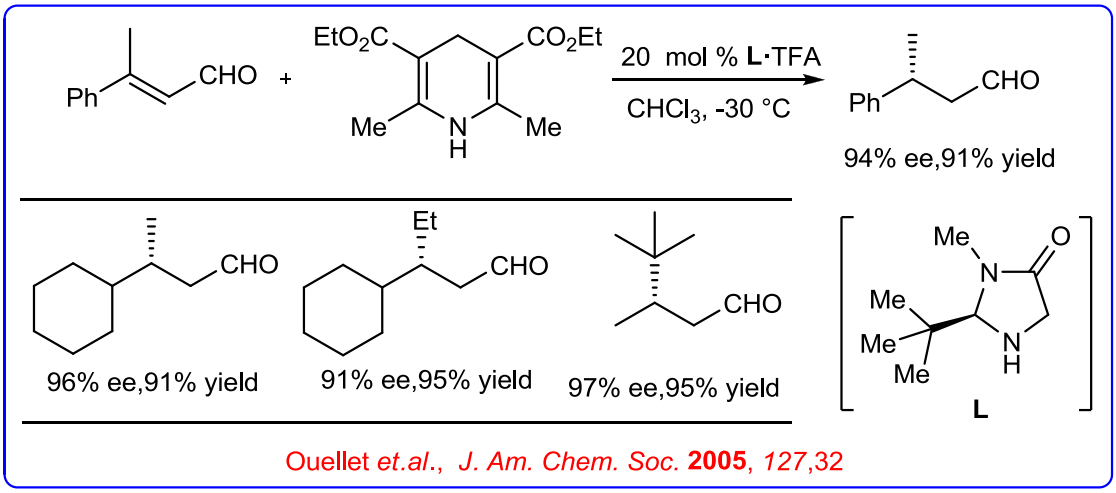
Scheme 8. Transfer Hydrogenation of Nitro Styrene by Chiral Thiourea Catalyst

The above catalyst is also used for enantioselective Hantzsch ester mediated conjugate reduction of β-nitroacrylates (Scheme 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.



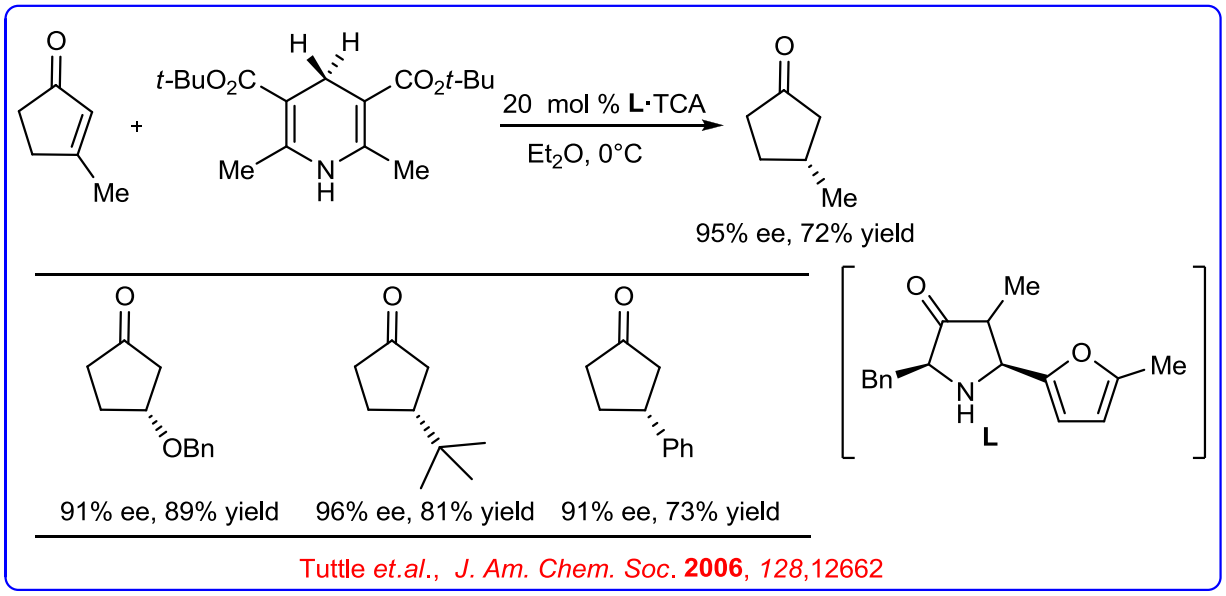
Scheme 9. Transfer Hydrogenation of Nitro Styrene by Chiral Thiourea Catalyst

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 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 10. Transfer Hydrogenation of α,β-Unsaturated Aldehydes by Chiral Imidazolidinone

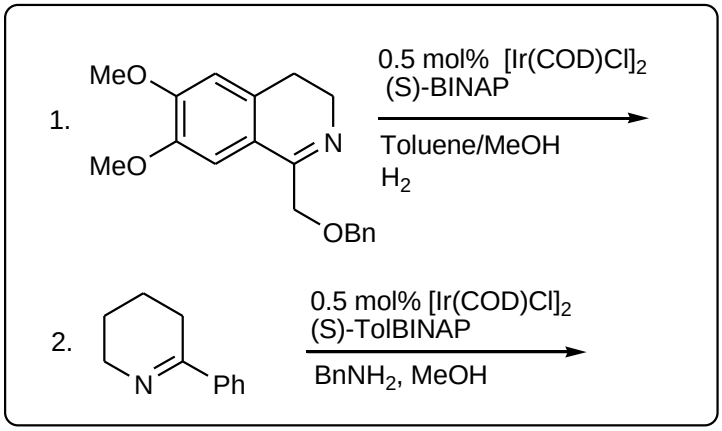
The above catalytic system is used for transfer hydrogenation of cyclic enones (Scheme 11). Cycloalkenones with 5-, 6-, and 7-membered ring systems undergo reaction with high stereoselectivity.



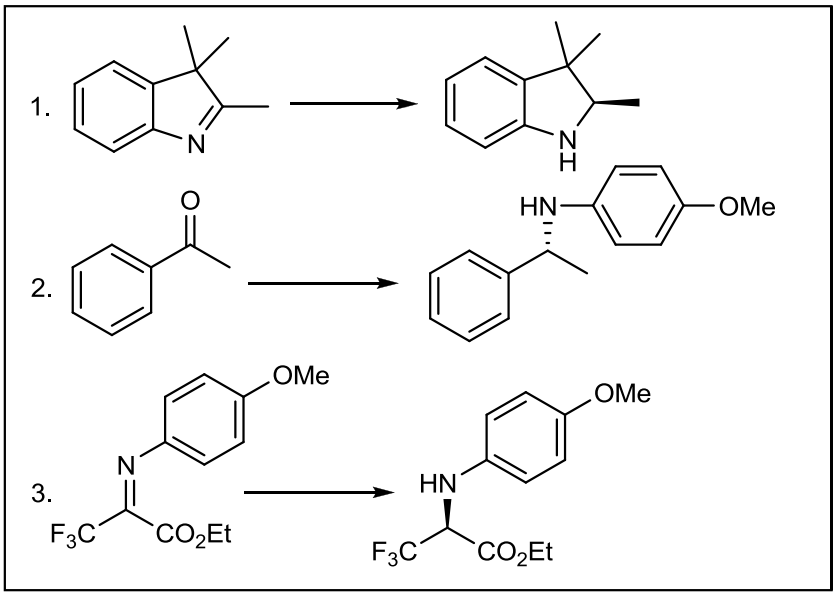
Scheme 11. Transfer Hydrogenation of Cyclic Enones by Imidazolidinone

Problems

D. Complete the following reactions.



E. How will you carry out the following hydrogenation reactions?



Reference/Text Book

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

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