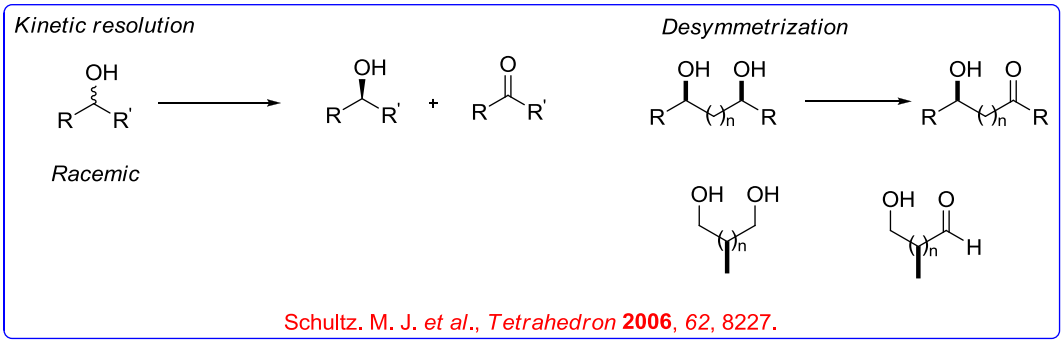
Module 5 Oxidation Reactions
Lecture 16

5.1 Oxidation of Alcohols

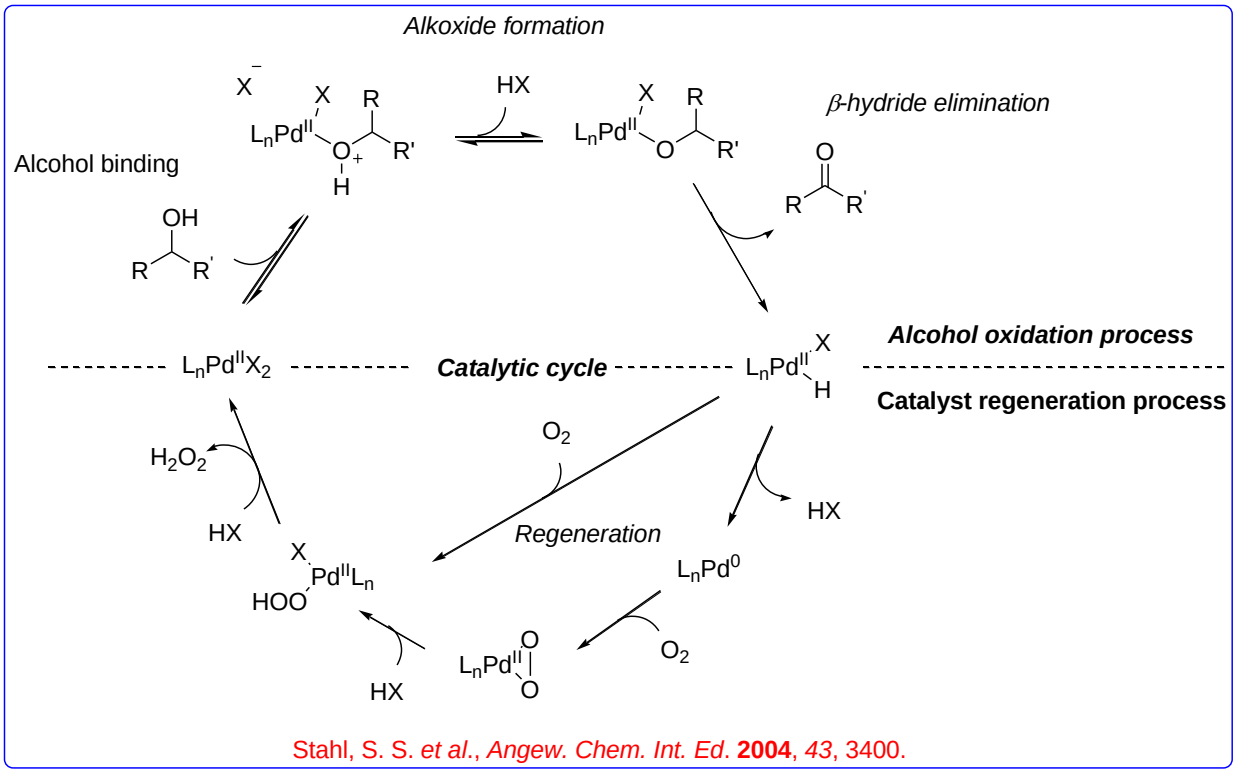
Oxidation of alcohols to carbonyl compounds is a pivotal process in organic chemistry. In particular, the oxidations that use readily available molecular oxygen, especially ambient air, as the stoichiometric oxidant are the most preferable. During the recent years, asymmetric version of the process has been developed using molecular catalysis, which can be divided into kinetic resolution of secondary alcohols and desymmetrization of *meso*- or prochiral diols (Scheme 1).



Scheme 1

5.1.1 Palladium Catalyst

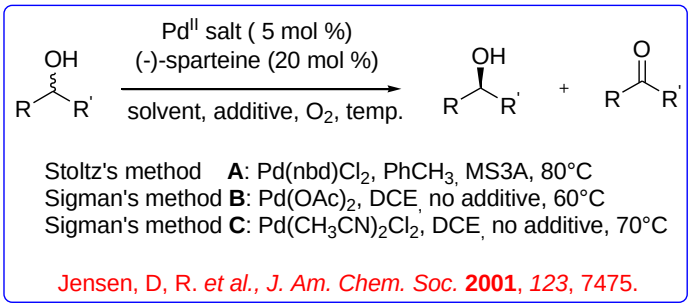
The palladium catalyzed aerobic oxidation of alcohols to carbonyl compounds has received much attention in recent years and the catalytic cycle for this process is presented in Scheme 2. The cycle consists two separate processes: the oxidation of alcohols and the regeneration of the catalyst. In the 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.

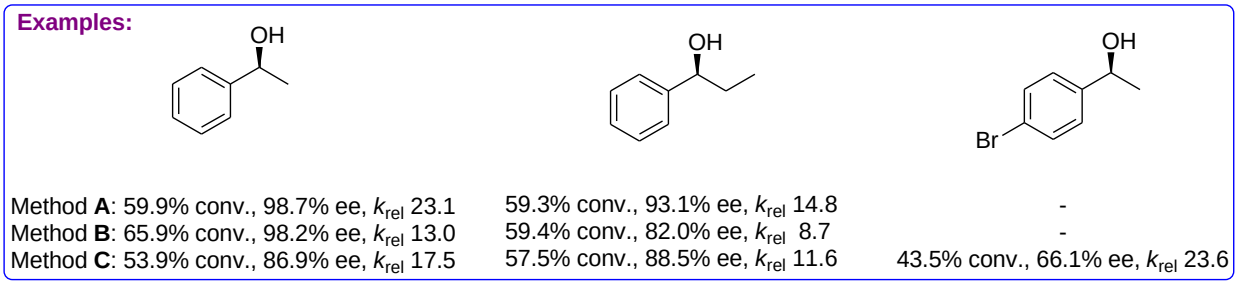


Stahl, S. S. *et al*., *Angew. Chem. Int. Ed*. **2004**, *43*, 3400.

Scheme 2

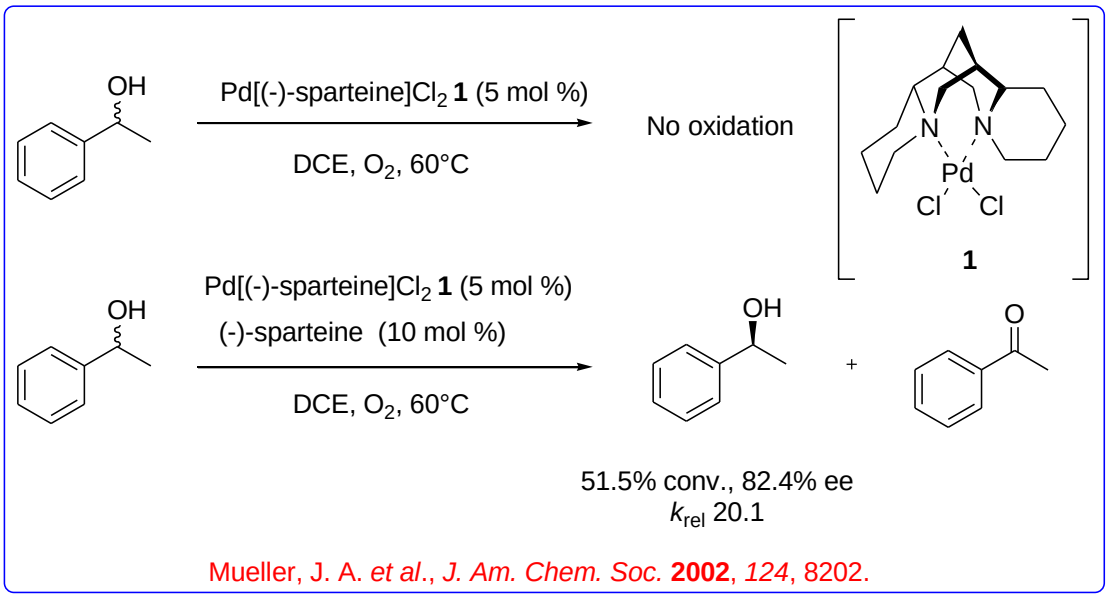
A series of experiments by three research groups have carried out using palladium complex bearing naturally occurring diamine, (-)-sparteine, to catalyzes the oxidation of aliphatic, benzylic and allylic alcohols with moderate to good k_{rel} values (Scheme 3).





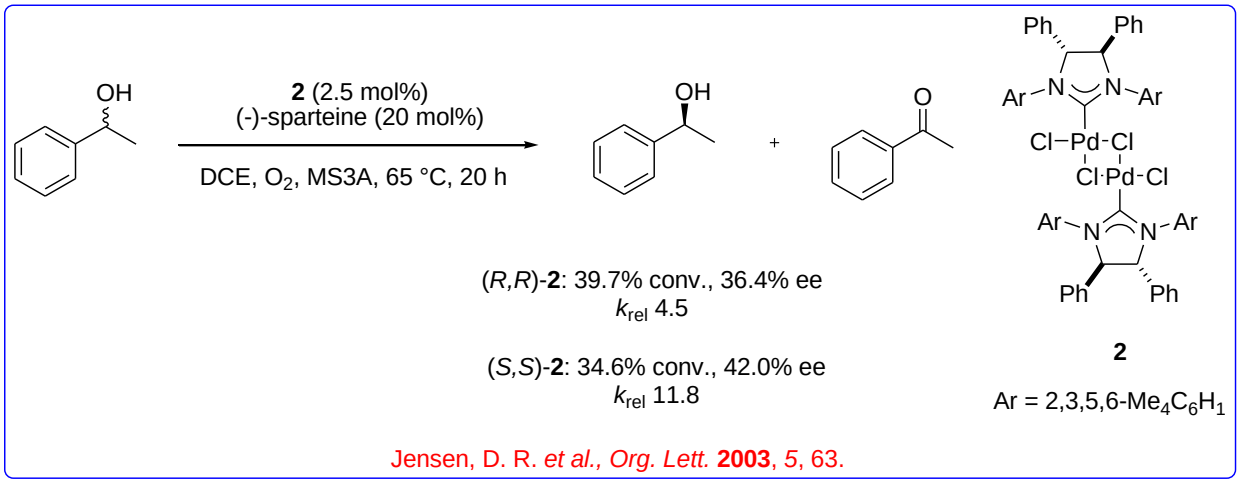
Scheme 3

However, the isolated palladium-sparteine complex shows no catalytic activity and the reaction is effective employing additional (-)-sparteine (Scheme 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.



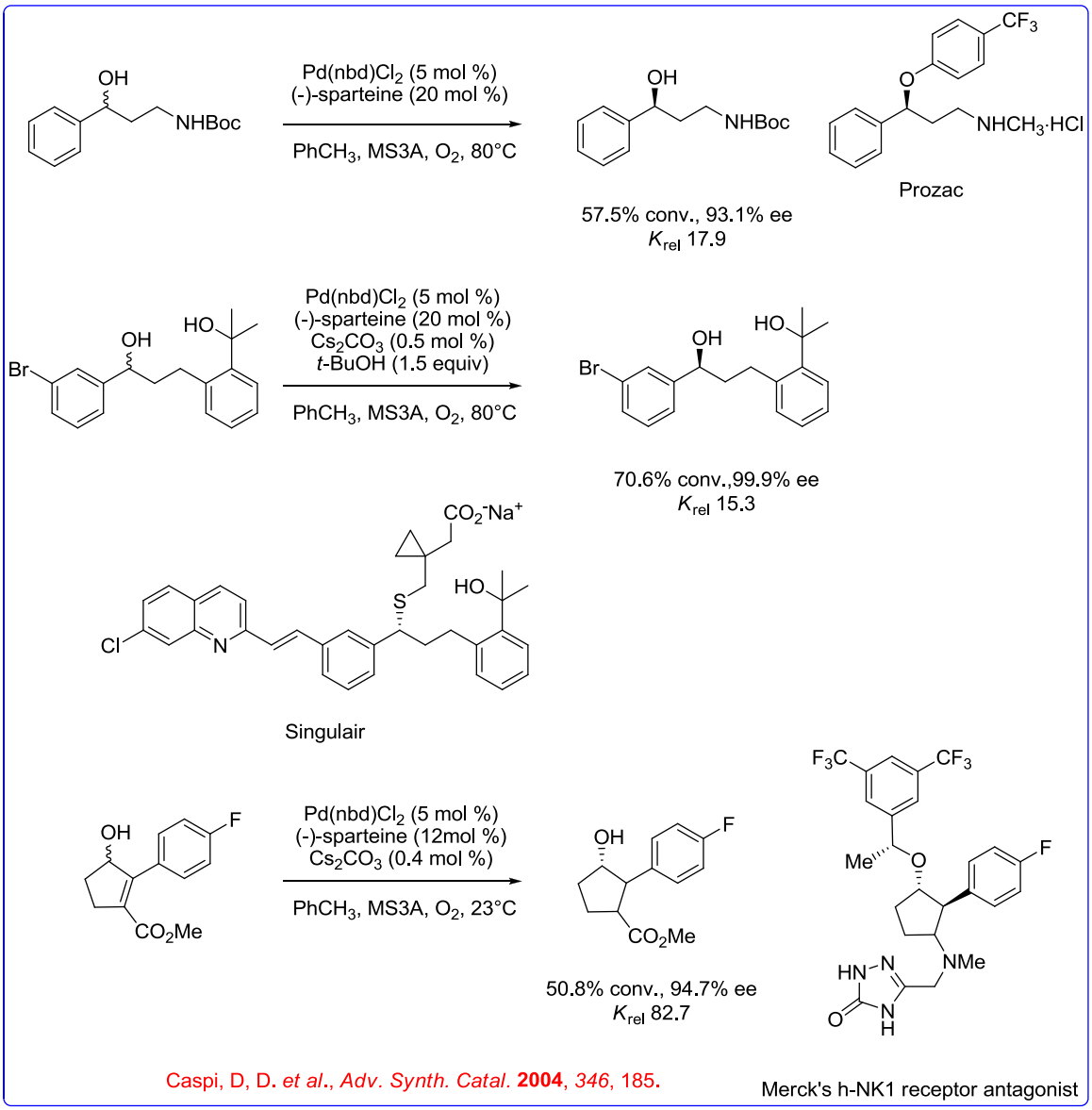
Scheme 4

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).



Scheme 5

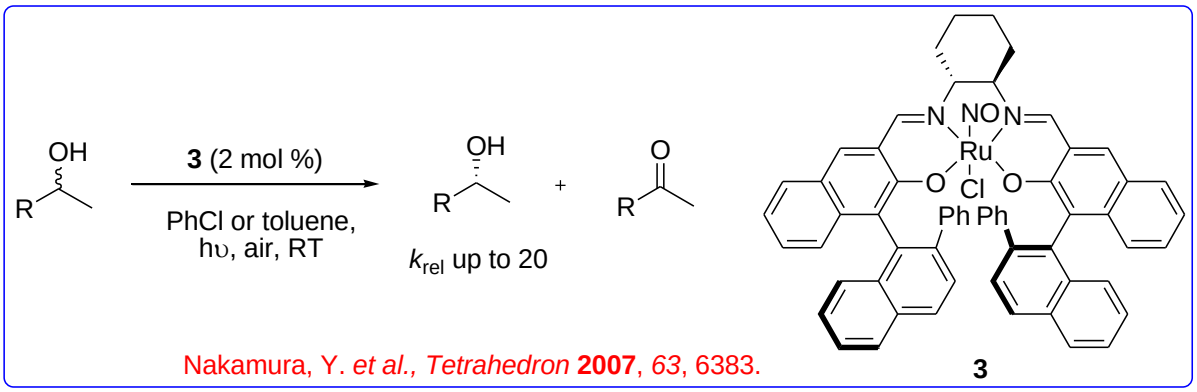
The reaction is found to be accelerated in the presence of Cs_2CO_3 under ambient air (Scheme 6). The procedure is found to be useful for the synthesis of several pharmaceutically important substances including Prozac®, Singlair®, and Merck's h-NK1 receptor antagonist.

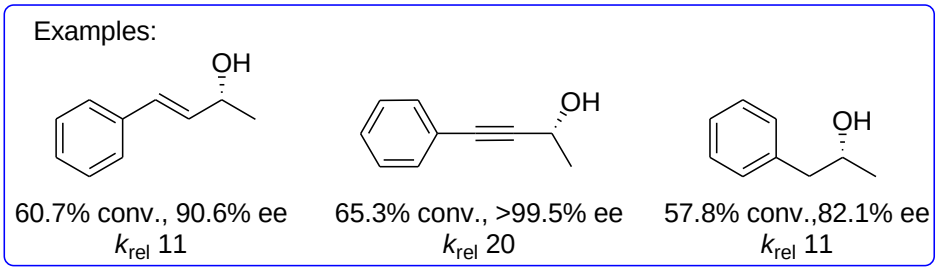


Scheme 6

5.1.2 Ruthenium Catalyst

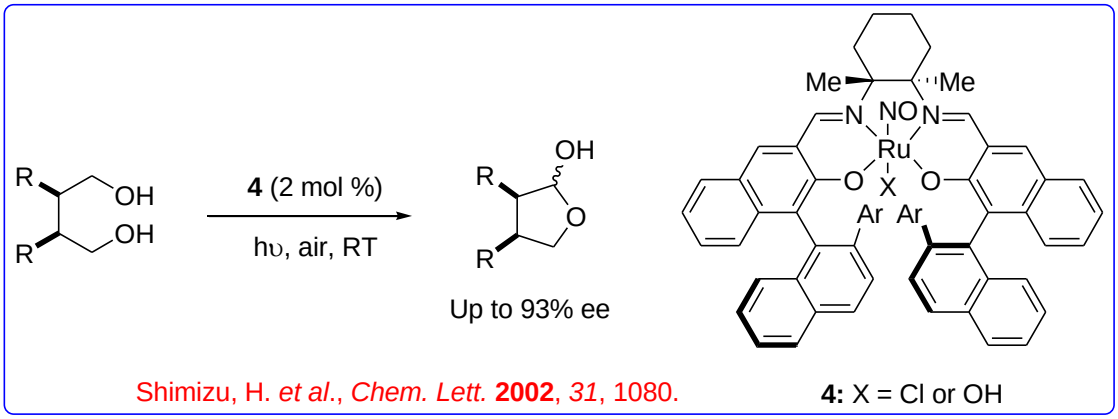
Chiral Ru-salen complex **3** having nitrosyl ligand has been found to be effective catalyst for the oxidative kinetic resolution of secondary alcohols under ambient air as oxidant under visible light (Scheme 7). The irradiation of the visible light promotes dissociation of the nitrosyl ligand and generates a catalytically active ruthenium species. Kinetic resolution of aryl, alkynyl and alkyl alcohols has been observed with k_{rel} up to 30.





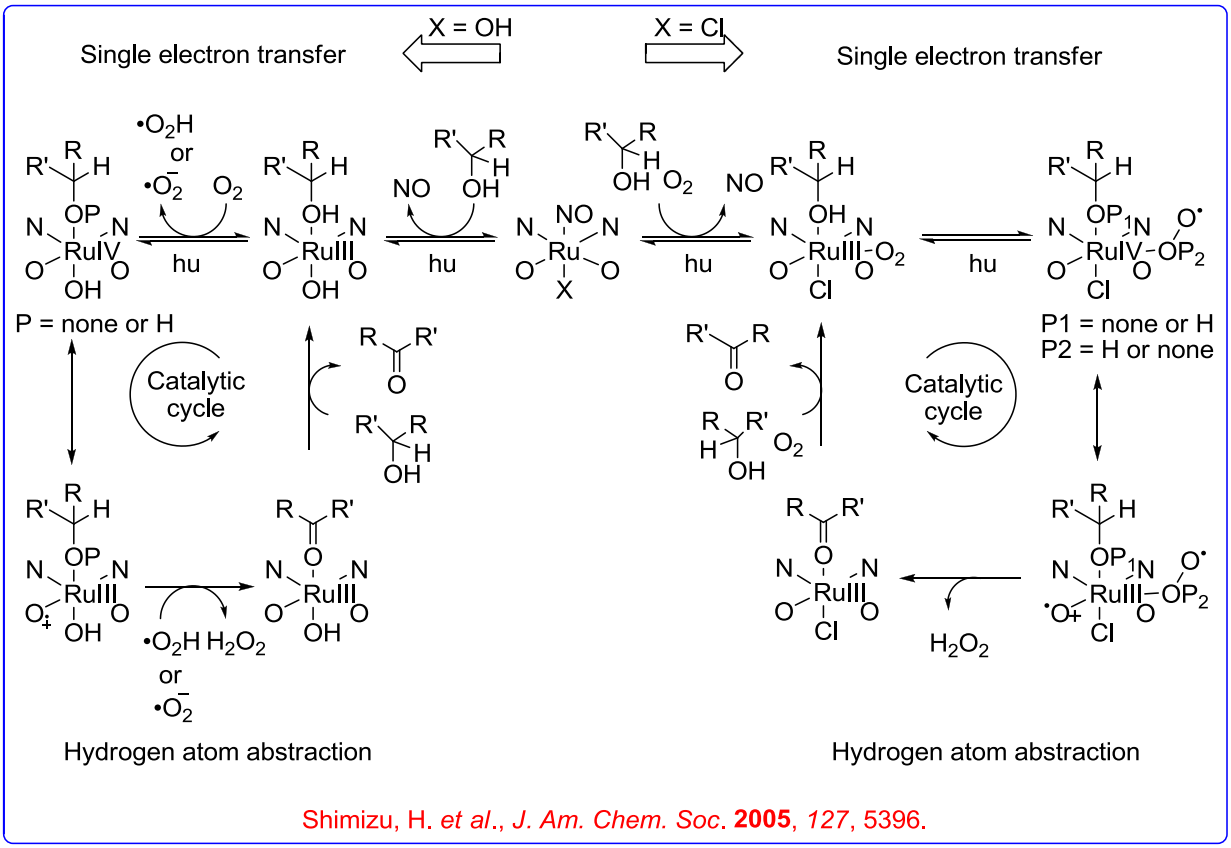
Scheme 7

The chiral ruthenium based complex **4** is also effective for the oxidative desymmetrization of 1,4-*meso*-diols (Scheme 8).



Scheme 8

Scheme 9 shows the proposed mechanism for the Ru-catalyzed aerobic oxidation of alcohols which is similar to the galactose oxidase system.

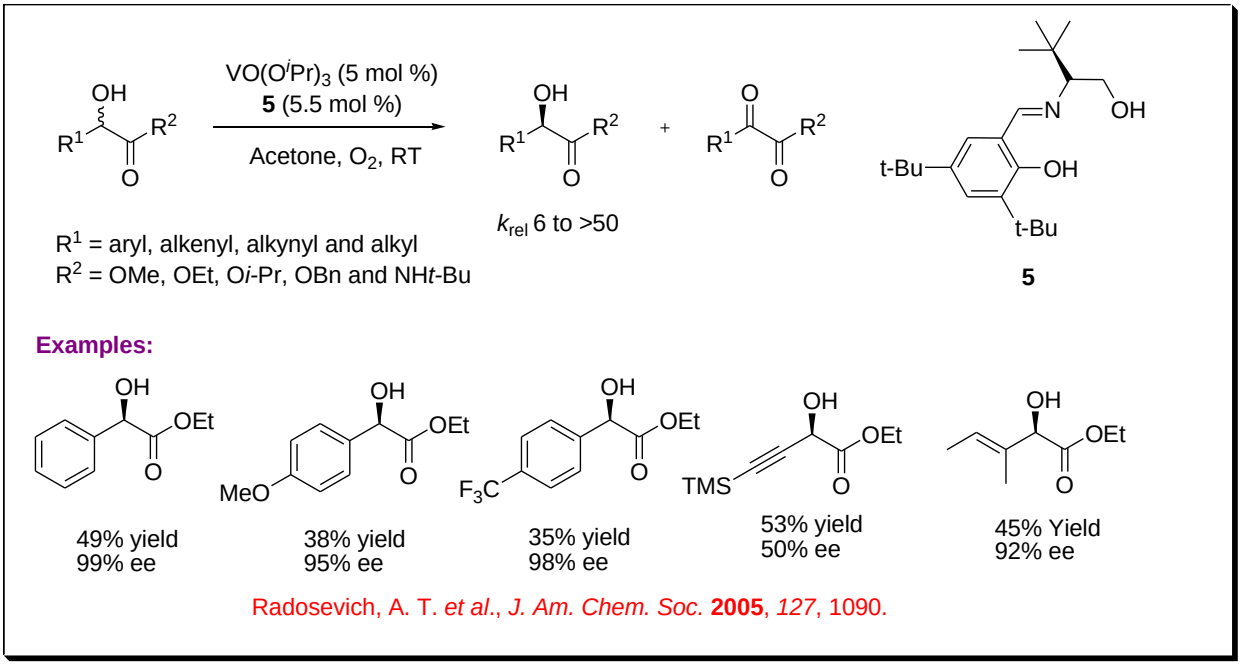


Shimizu, H. *et al*., *J. Am. Chem. Soc*. **2005**, *127*, 5396.

Scheme 9

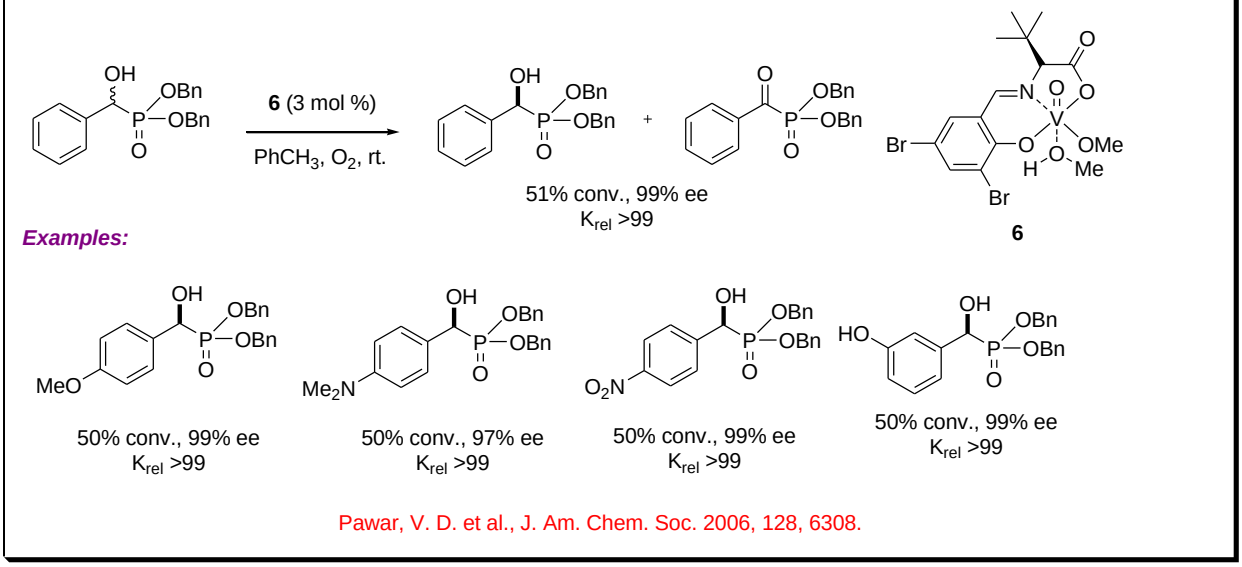
5.1.3 Vanadium Catalyst

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 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 11). For example, the reaction of □-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.



Radosevich, A. T. *et al*., *J. Am. Chem. Soc.* **2005**, *127*, 1090.

Scheme 10

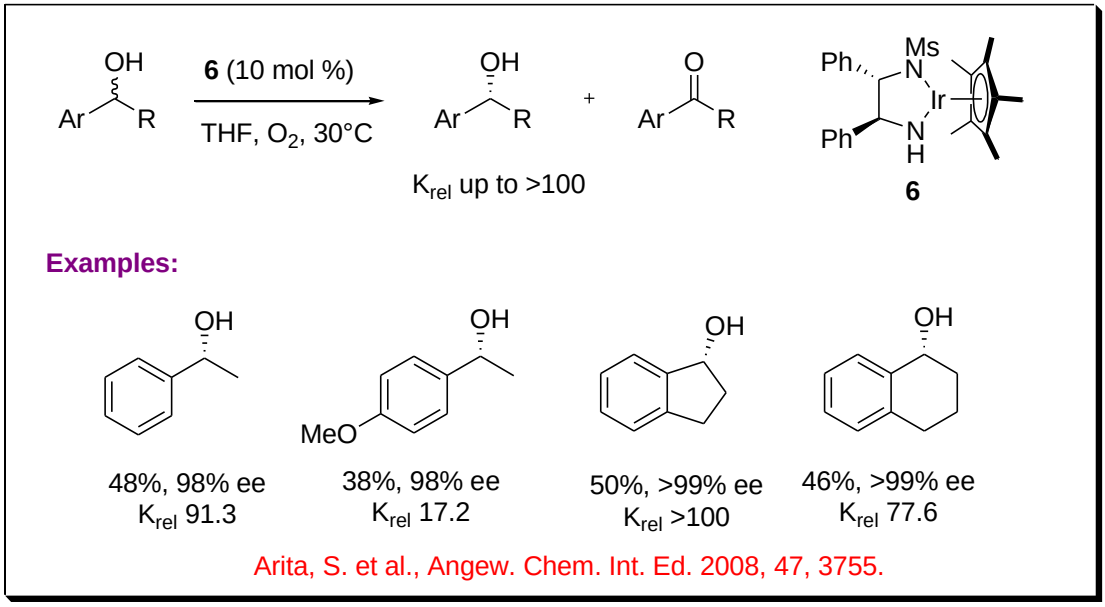


Pawar, V. D. et al., J. Am. Chem. Soc. 2006, 128, 6308.

Scheme 11

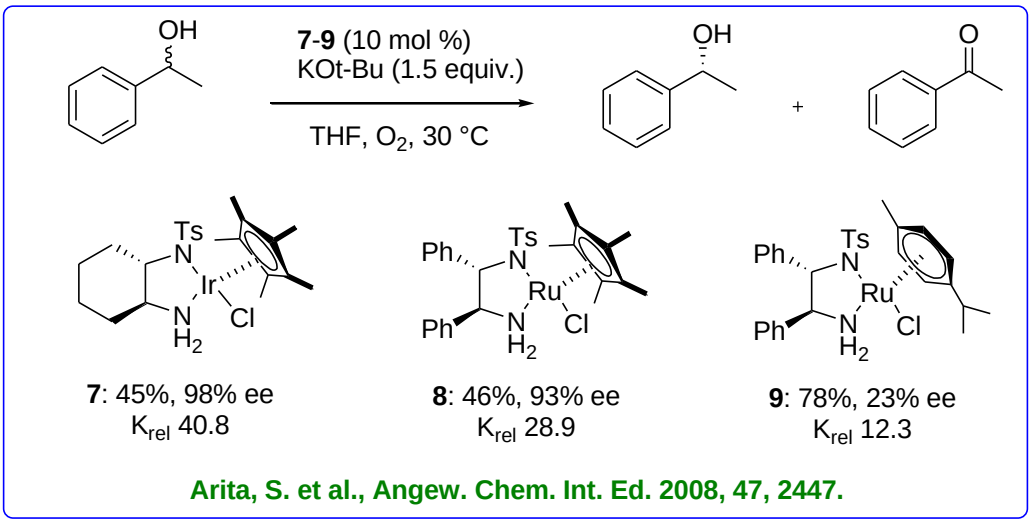
5.1.4 Iridium Catalyst

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.



Scheme 12

Iridium chloride complex **7** has been used for the oxidation of racemic secondary alcohols with k_{rel} as high as 48.8 (Scheme 13). The Rh analogue **8** exhibits high catalytic activity in the presence of base, while the related Ru complex **9** gives diminished result.

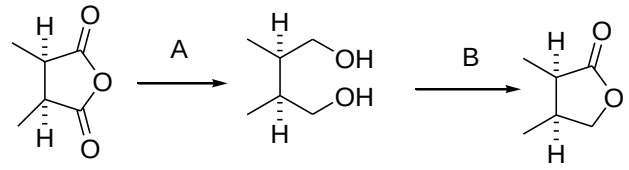


Scheme 13

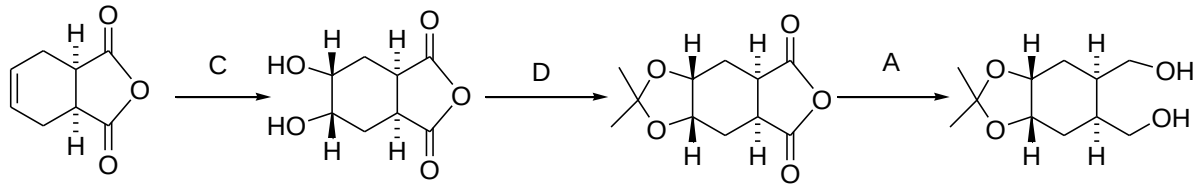
Problems

A. Complete the following transformations.

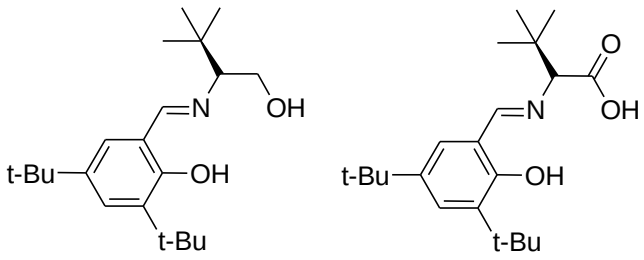
1.



2.



B. How will you prepare the following chiral ligands?



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.

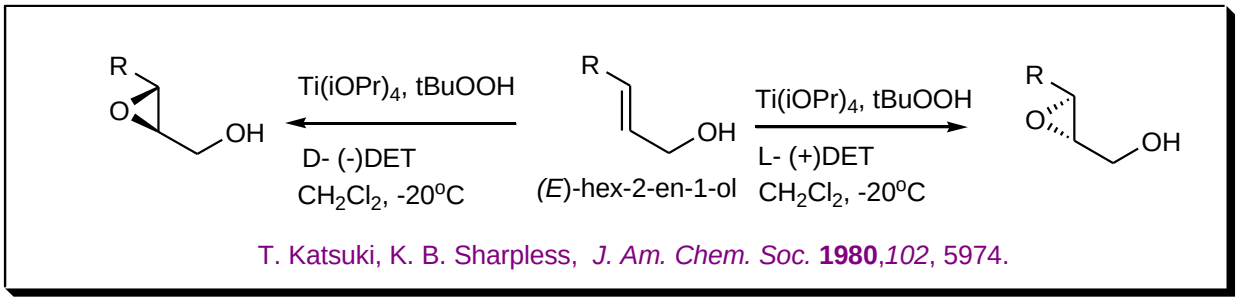
Lecture 17: Epoxidation I

5.3 Epoxidation of Allylic Alcohols

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

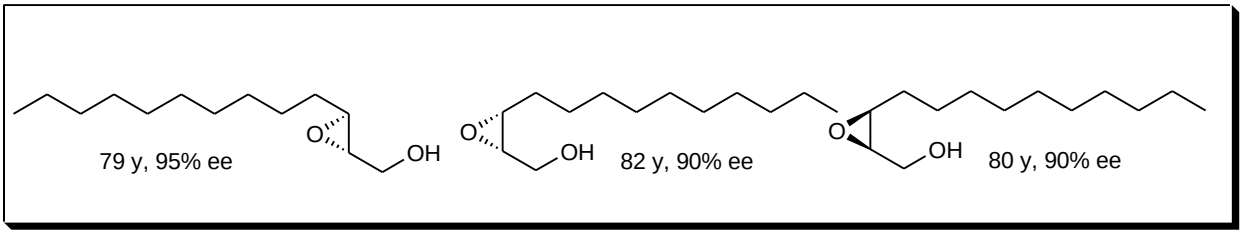
5.3.1 Titanium-Catalyzed Epoxidation

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 alcohol with 94% ee and 85% yield in presence of 5-10 mol% of $Ti(O^iPr)_4$, L-(+)-DET and *t*-BuOOH (Scheme 1). Using D-(-)-DET as chiral source the opposite enantiomer can be obtained with similar yield and enantioselectivity.



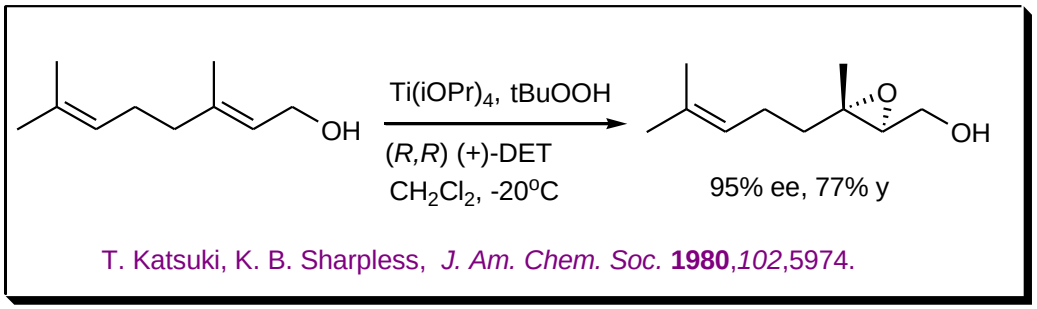
T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**,*102*, 5974.

Examples:



Scheme 1

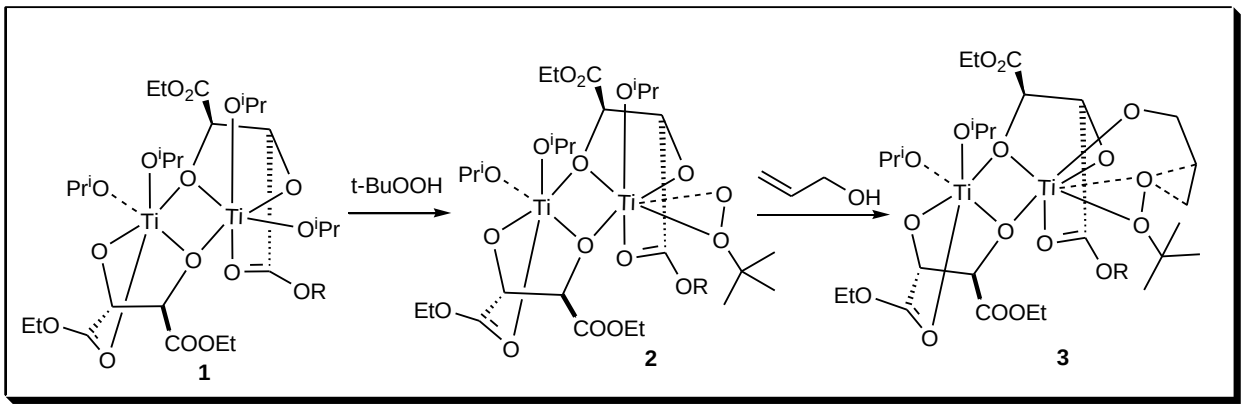
In case the substrates having more double bonds, the allylic double bond can be oxidized. For example, the allylic double bond of geraniol can be selectively oxidized with 95% ee (Scheme 2).



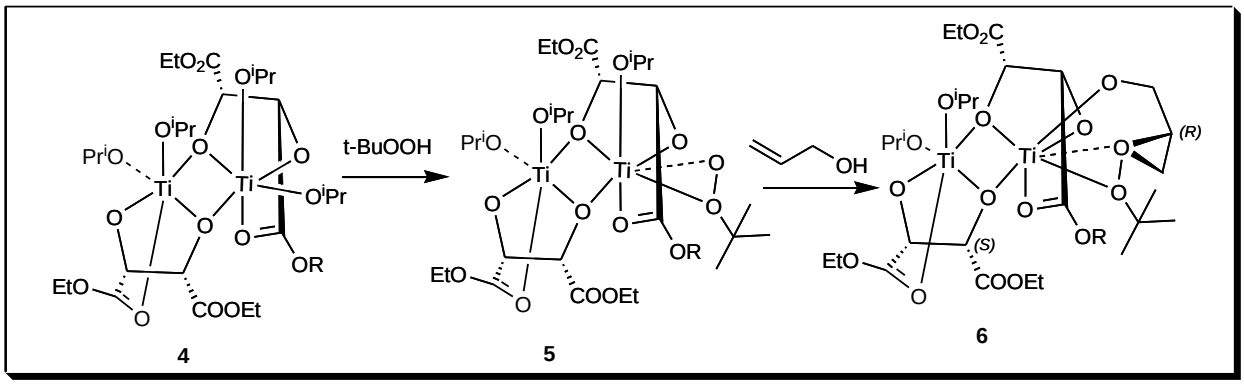
Scheme 2

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 3-4). 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.

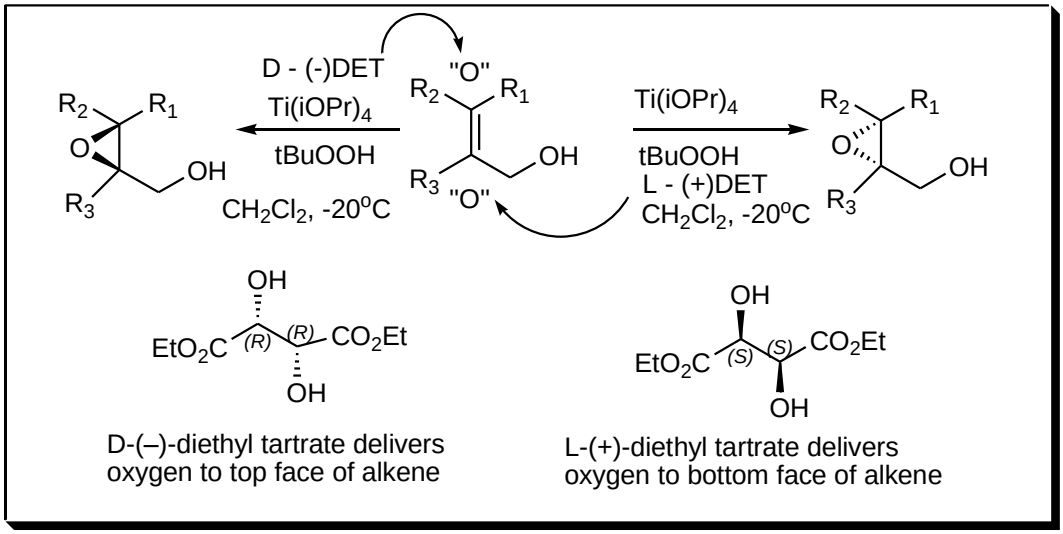


Scheme 3



Scheme 4

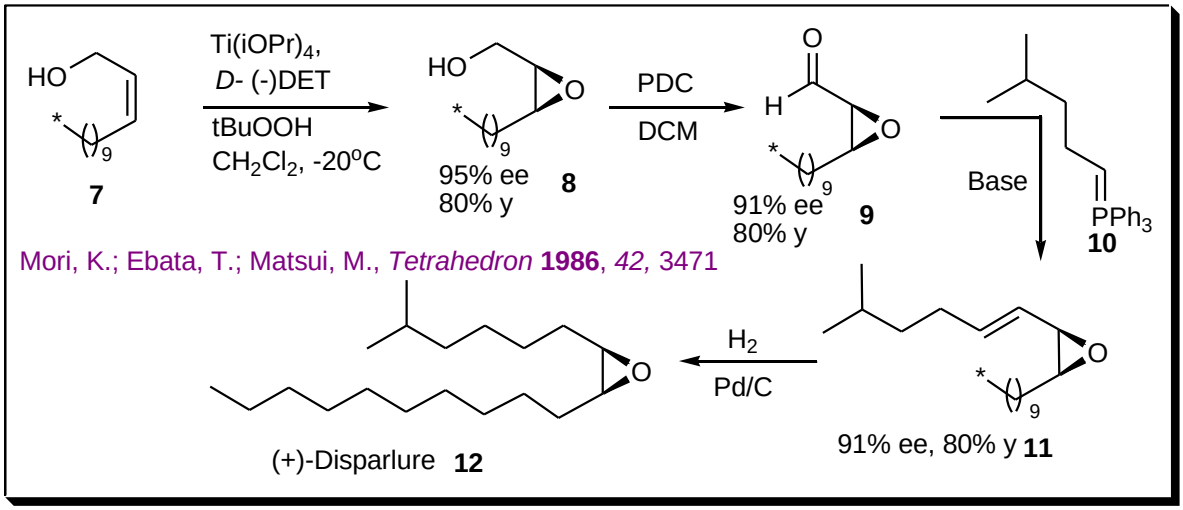
The product stereochemistry can be predicted using the model shown in Scheme 5.



Scheme 5

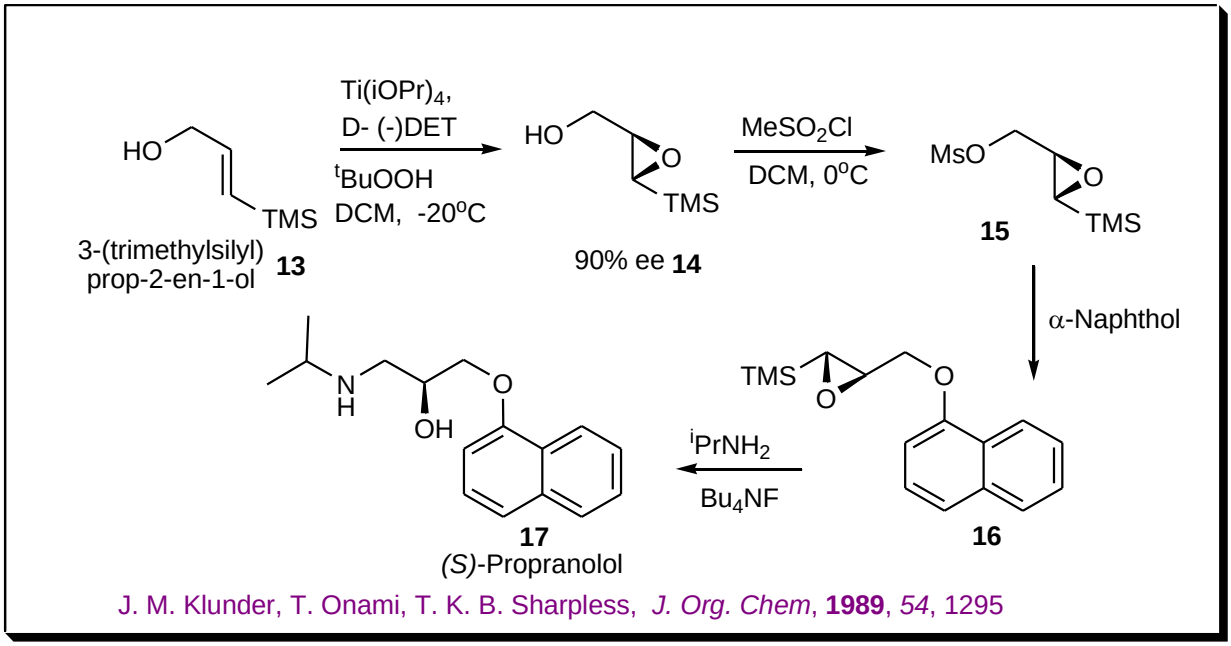
Application

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 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 6

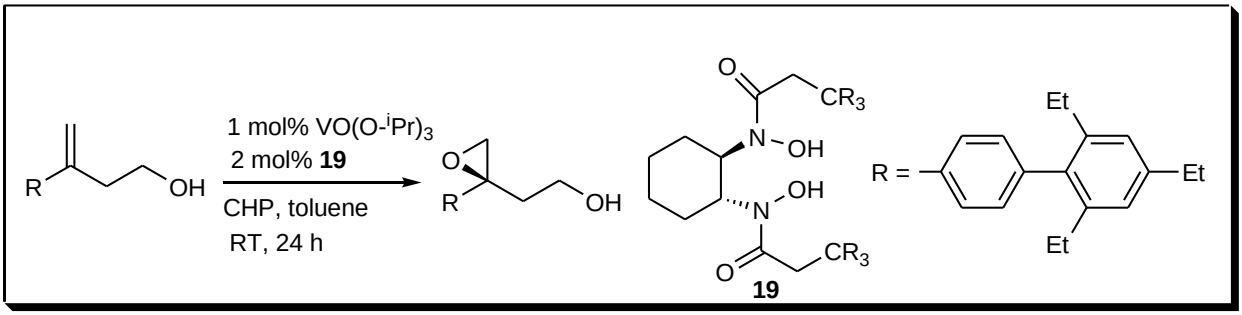
The Scheme 7 shows the use of the Sharpless asymmetric epoxidation for the synthesis of gastric inhibitor *(S)*-propanolol. The epoxidation of 3-(trimethylsilyl) prop-2-en-1-ol **13** affords epoxy alcohol **14** with 90% ee that could be converted into **16** by mesylation **15** followed by coupling with 1-naphthol. Opening of the epoxide **16** with isopropylamine leads to the formation of the target *(S)*-propanolol **17**.



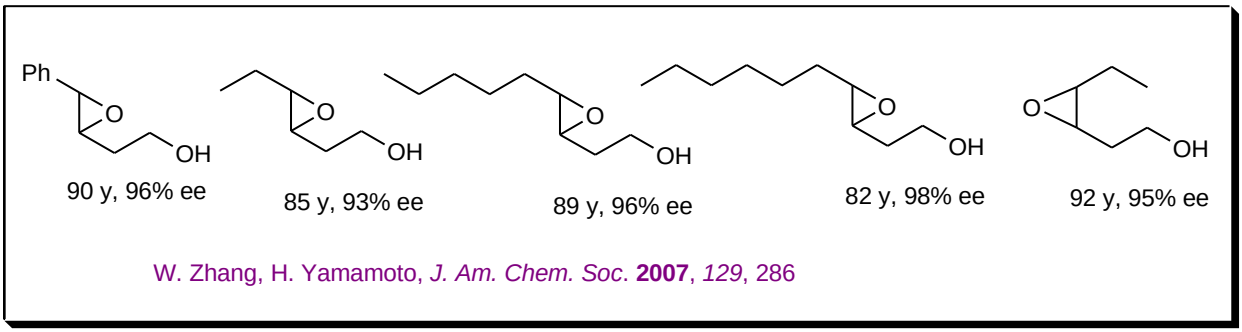
Scheme 7

5.3.2 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 8).



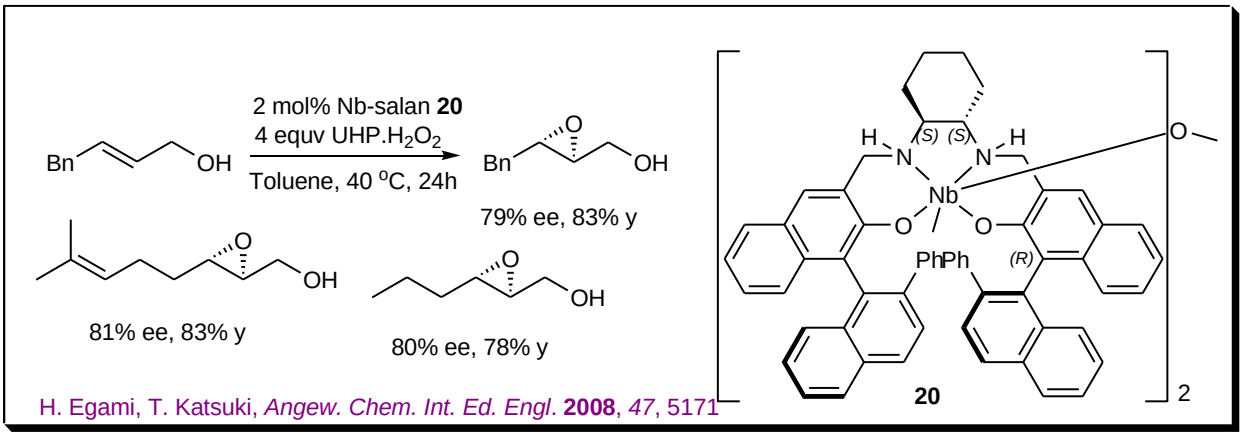
Examples:



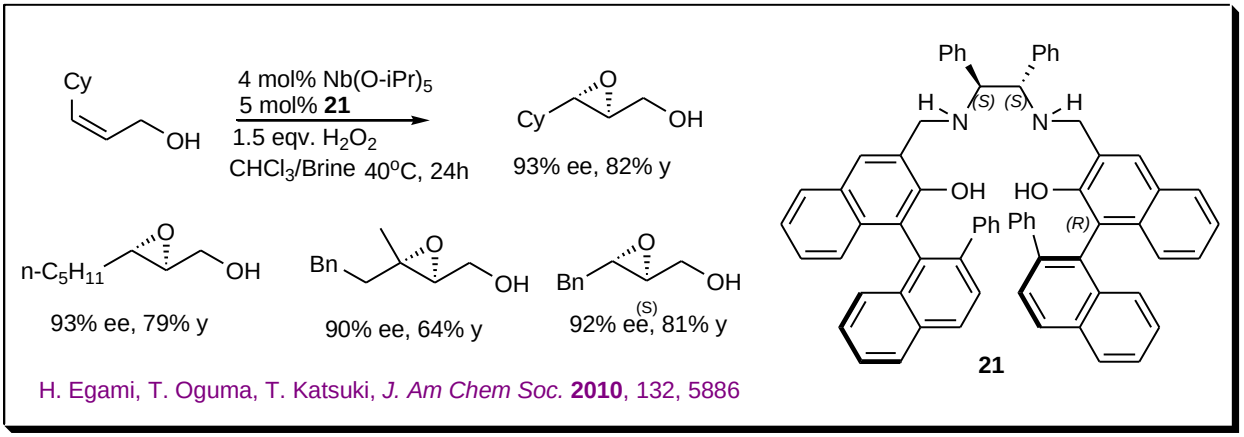
Scheme 8

5.3.3 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 9-10).



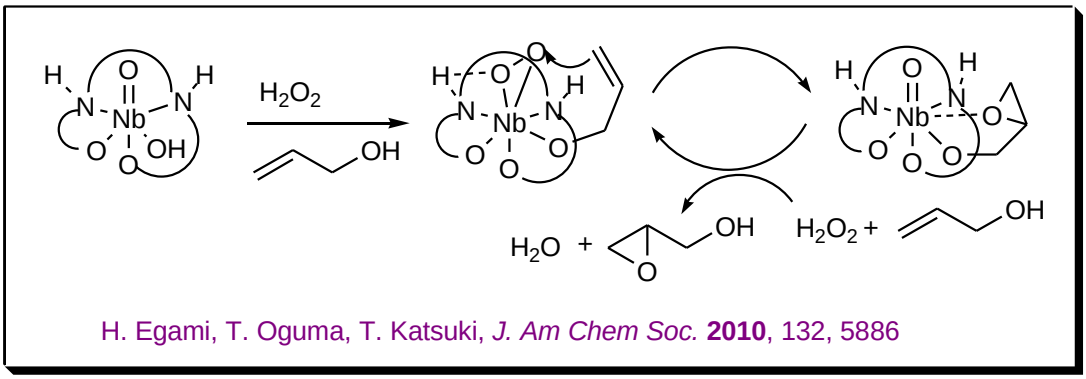
Scheme 9



Scheme 10

In this protocol, the μ-oxo dimer dissociates into a monomeric species that catalyzes the reaction (Scheme 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.



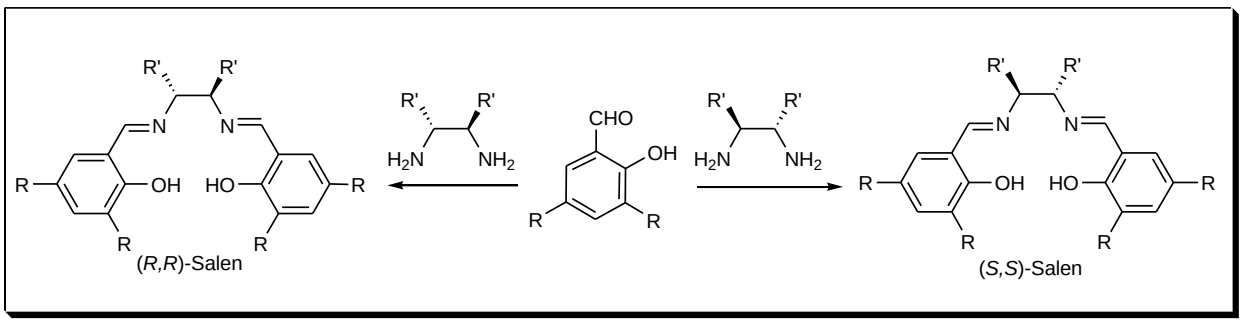
Scheme 11

5.4 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.

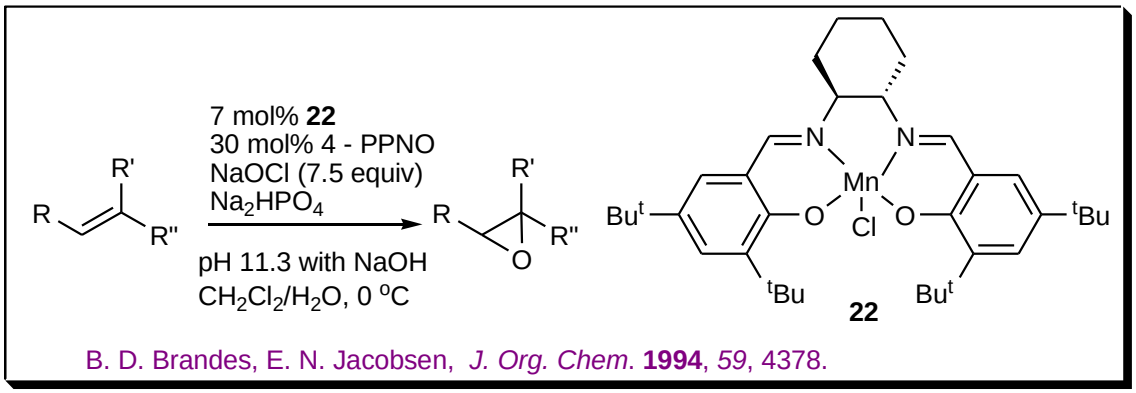
5.4.1 Manganese-Catalyzed Reactions

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 12). 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.



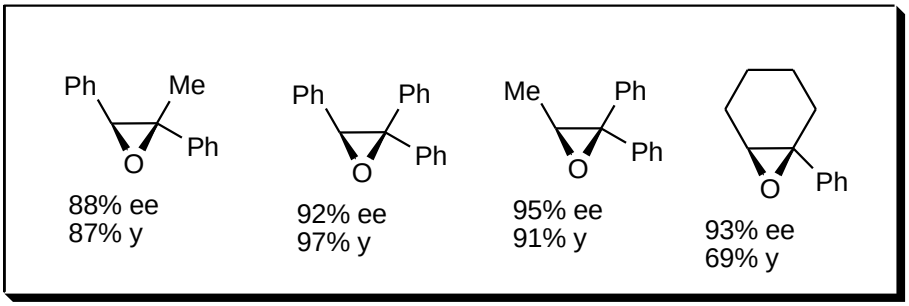
Scheme 12

For example, chiral Mn-salen **22** catalyzes the epoxidation of trisubstituted unfunctionalized alkenes with 88-95% ee (Scheme 13).



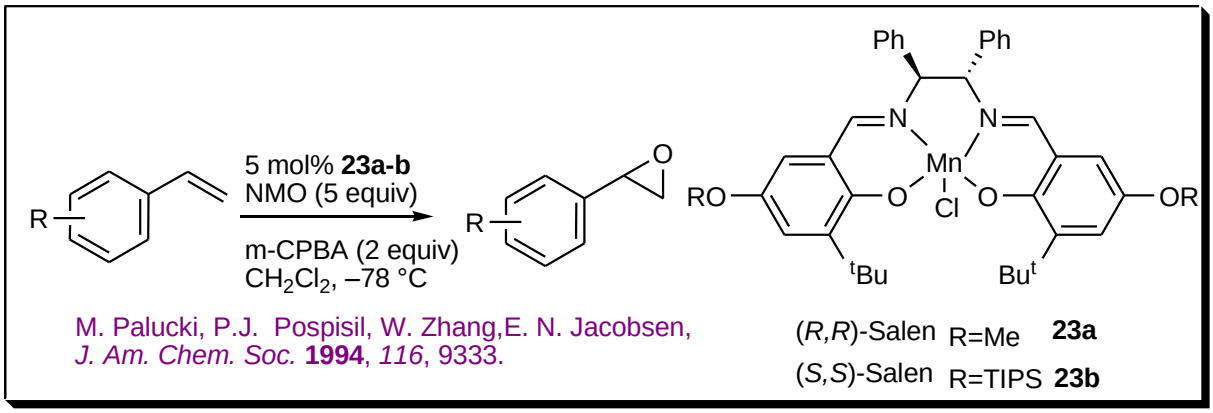
B. D. Brandes, E. N. Jacobsen, *J. Org. Chem*. **1994**, *59*, 4378.

Examples:

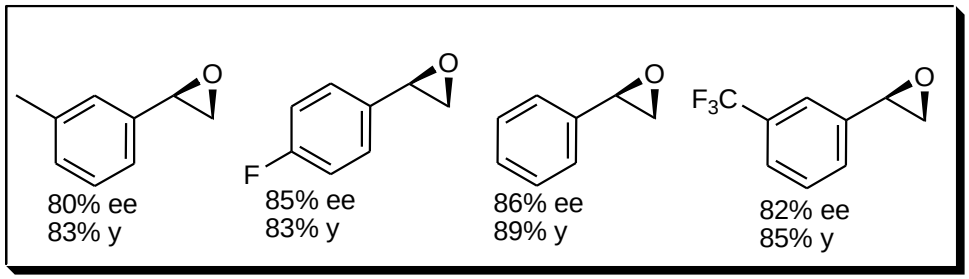


Scheme 13

Styrene derivatives can be successfully epoxidized using **23a-b** with good enantioselectivity (Scheme 14). The reaction is effective using the combination of *N*-morpholine oxide and *m*-chloroperbenzoic acid.



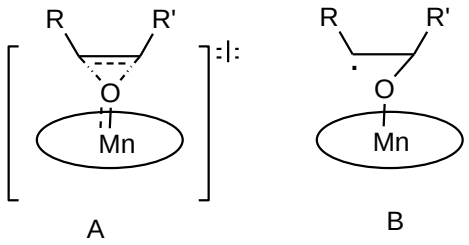
Examples:



Scheme 14

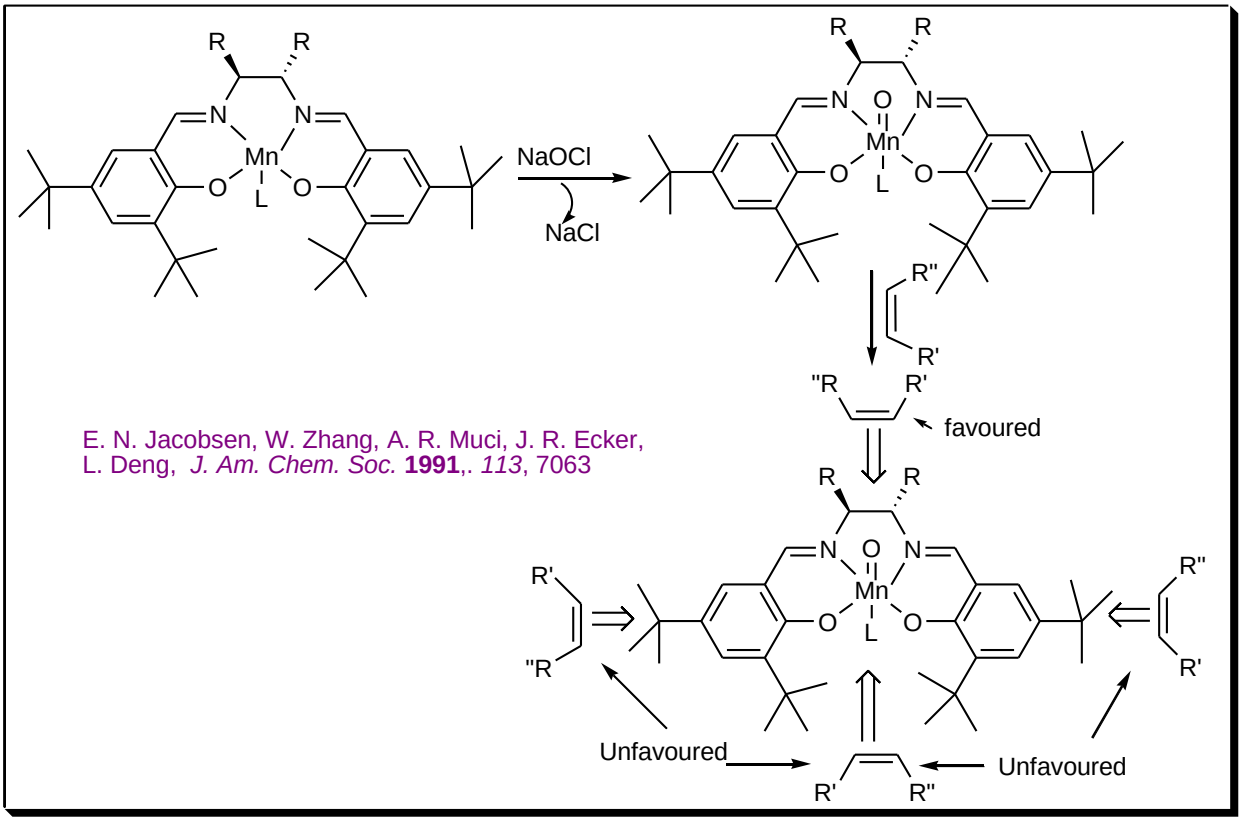
Mechanism

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 15).

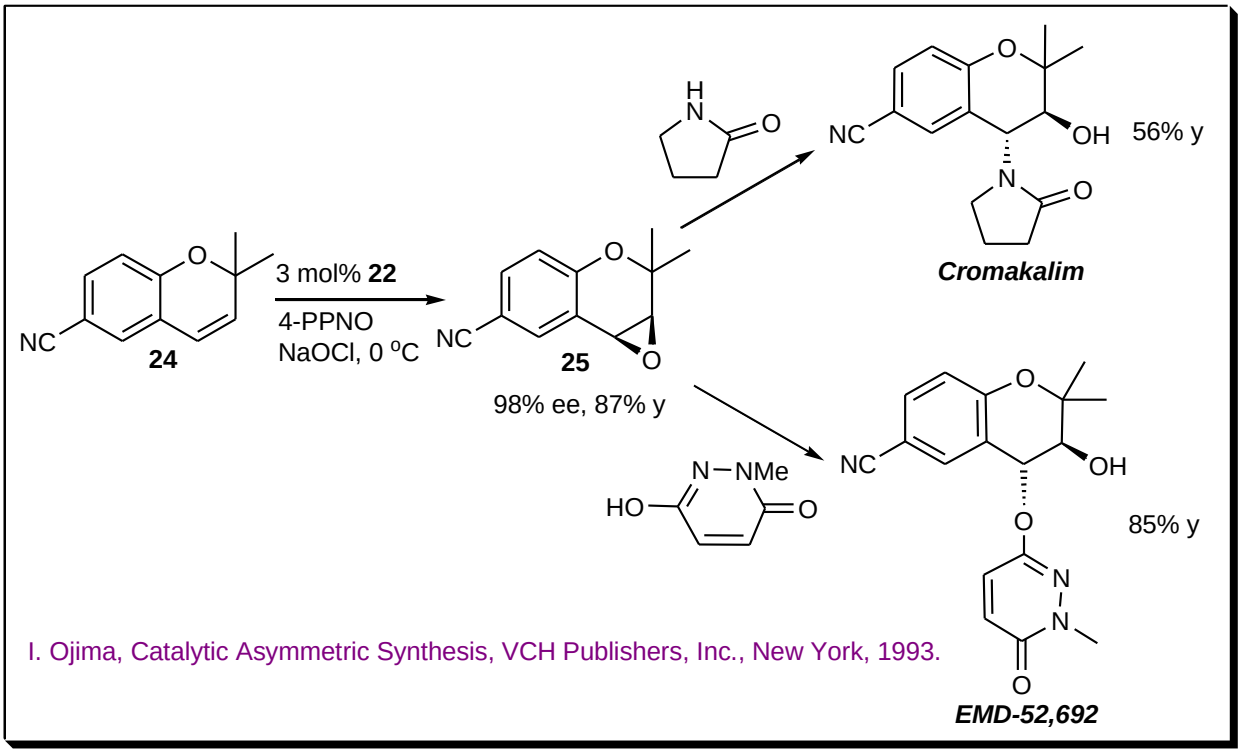


Scheme 15

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 16).



Scheme 16

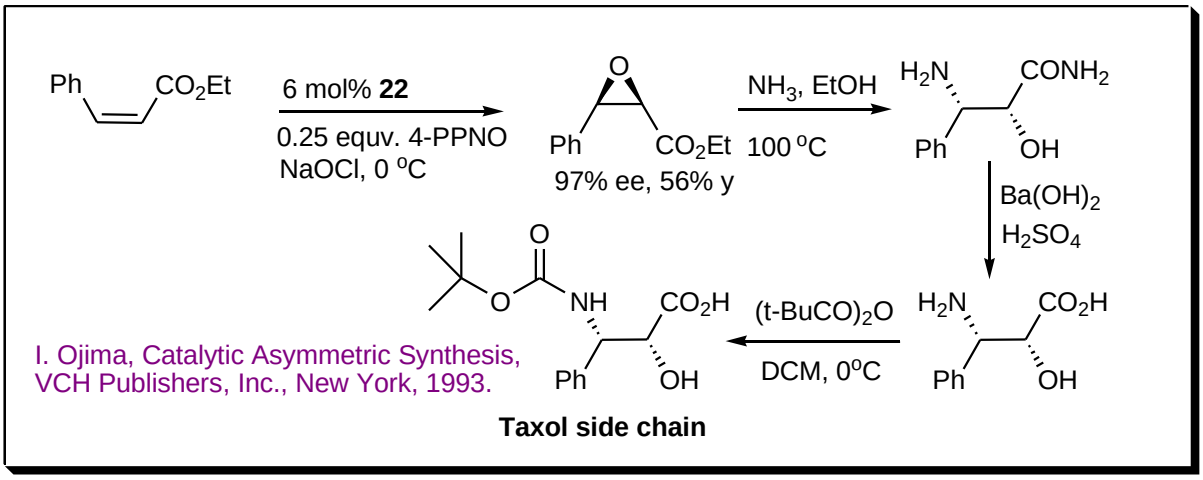


Scheme 17. Construction of Anti-hypertensive Agents.

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 17).

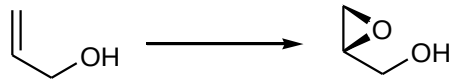
The catalyst **22** has been further utilized for the epoxidation of *cis*-cinnamic ester in 97% ee and 56% yield that can be converted into taxol side chain by opening of the epoxide with ammonia followed by hydrolysis and protection using $(t\text{-}BuCO)_2O$ (Scheme 18).

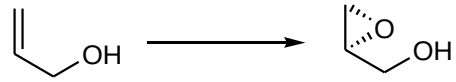


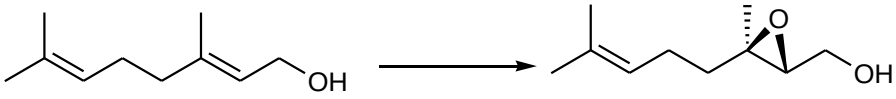
Scheme 18

Problems:

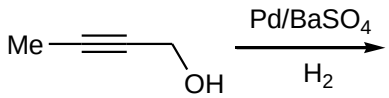
A. Complete the following reactions.

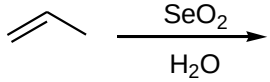
1. 

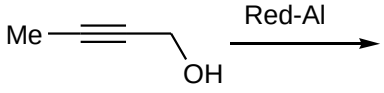
2. 

3. 

B. Predict the major products for the following reactions.

1. 

2. 

3. 

Reference

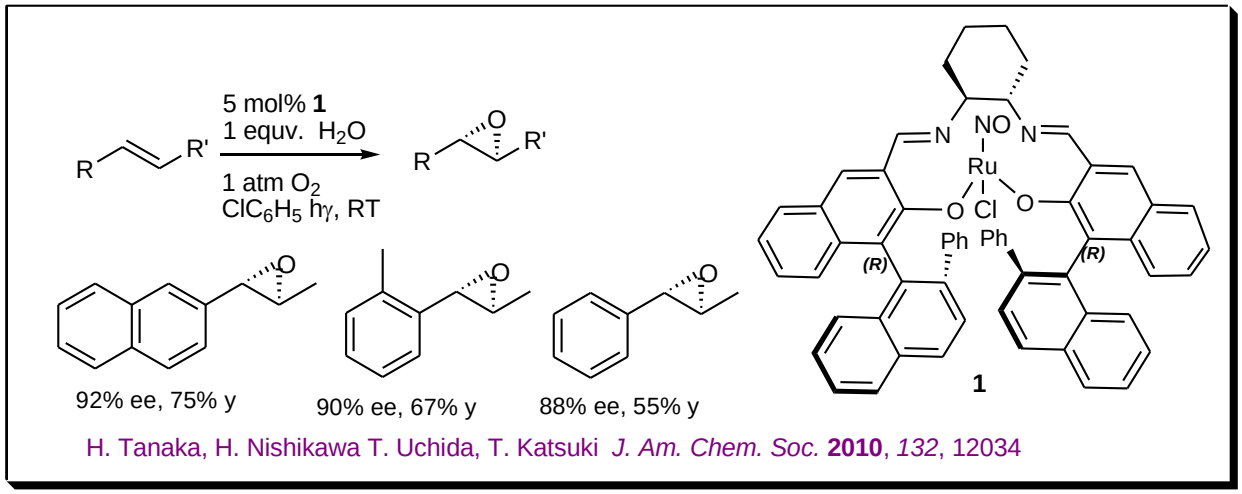
I. Ojima, Catalytic Asymmetric Synthesis, VCH Publishers, Inc., New York 1993.

Lecture 18

Epoxidation II

5.4.2 Ruthenium-Catalyzed Aerobic Epoxidation

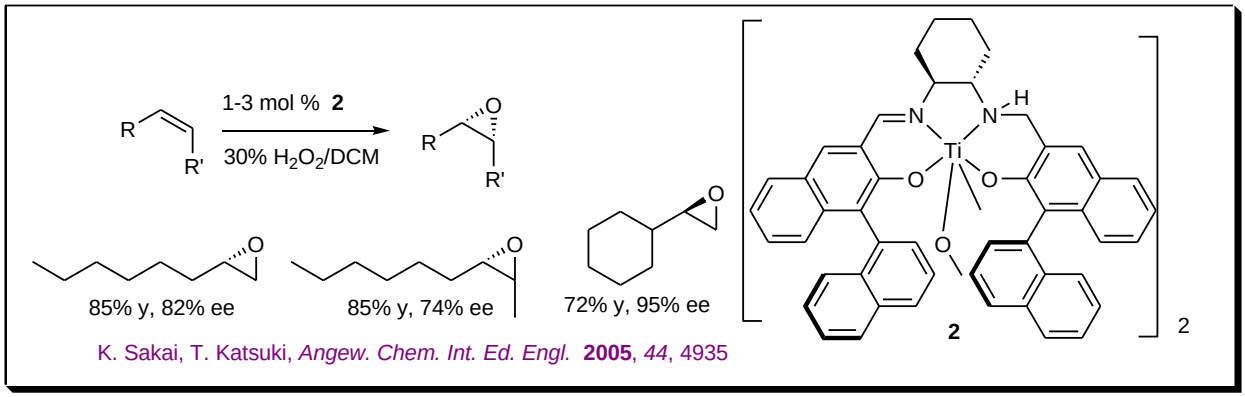
Chiral Ru(NO)-salen complexes has been found to catalyze the aerobic epoxidation of alkenes in presence of water under visible light irradiation at room temperature (Scheme 1). This method is attractive from environmental and economic standpoint. The observed preliminary experimental results suggest that an aqua ligand coordinated with the ruthenium ion acts as a proton transfer agent for the oxygen activation process.



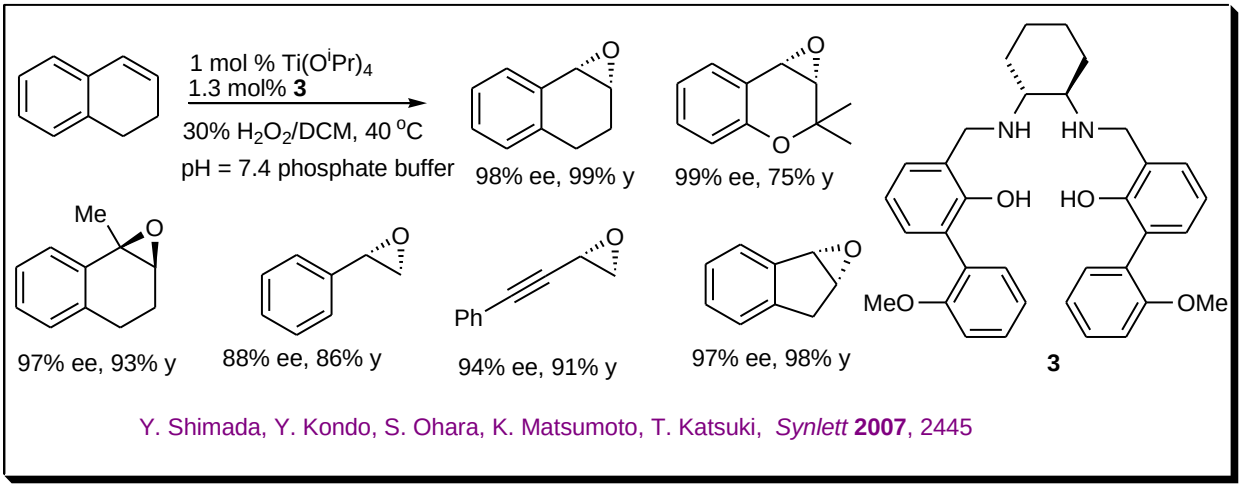
Scheme 1

5.4.3 Titanium-Catalyzed Epoxidation with Hydrogen Peroxides

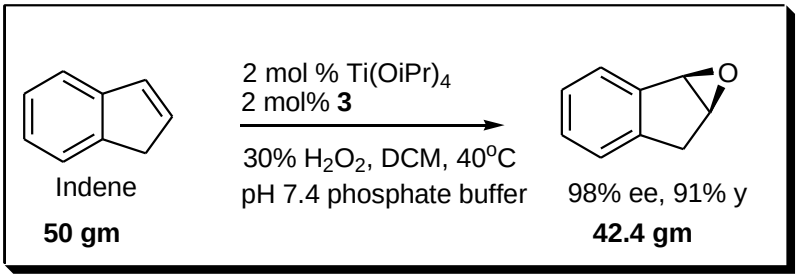
The use of Ti(salan) for the epoxidation of alkenes has been demonstrated in the presence of aqueous H_2O_2. The reaction is stereospecific and decomposition of H_2O_2 has not been observed. The most striking feature of this system is aliphatic alkenes that are one of the most challenging substrates for asymmetric epoxidation can be successfully oxidized with high enantioselectivity (Scheme 2). Furthermore, the in situ generated titanium complex derived from **3** (SALANEL) and $Ti(O^iPr)_4$ in CH_2Cl_2 catalyzes the epoxidation of alkenes in the presence of phosphate buffer with excellent enantioselectivity (Scheme 3).



Scheme 2

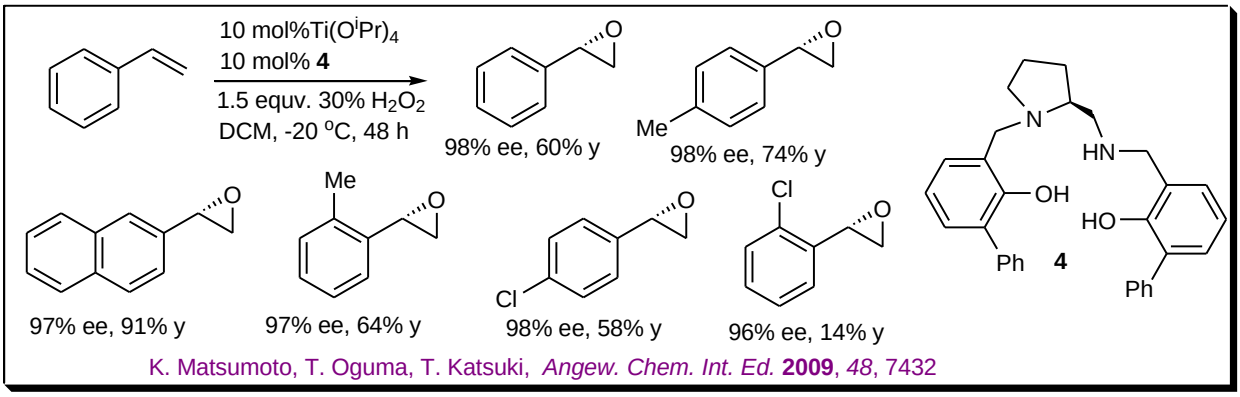


This epoxidation protocol has been successfully applied to a multigram scale synthesis of indene oxide



Scheme 3

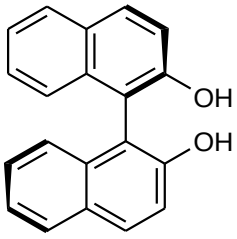
While the proline-based C_1-symmetric Ti-(salan) from **4** and Ti(O^iPr)$_4$ has been found to be excellent catalyst for the epoxidation of styrene derivatives (Scheme 4).



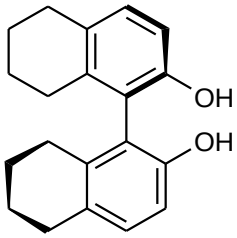
Scheme 4

5.4.4 Lanthanoid-Catalyzed Epoxidation

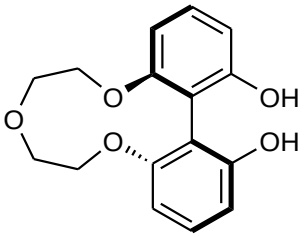
Nucleophilic epoxidation methods represent a viable alternative to electrophilic methods, many of which do not epoxidize electron-poor double bonds. The lanthanide based catalysts derived from chiral ligands **5-7** have been found to be effective in the epoxidation of α,β-unsaturated ketones (Scheme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



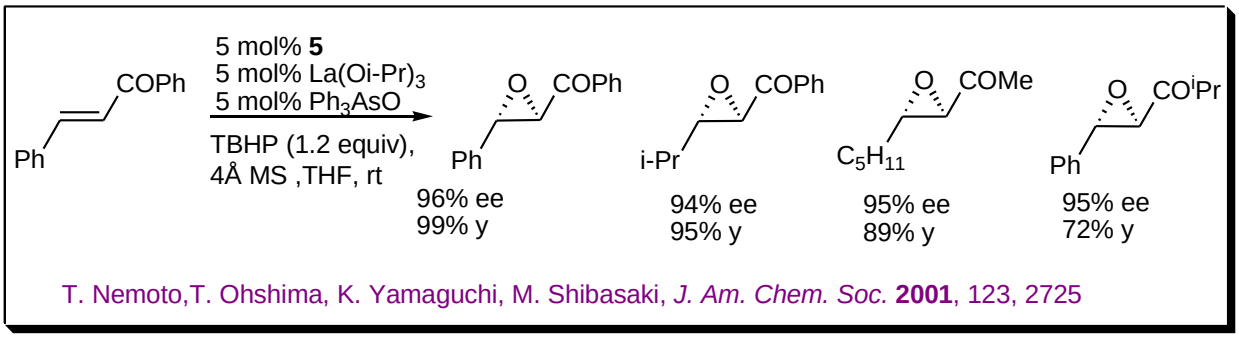
(*R*)-BINOL **5**



(*R*)-H_8-BINOL **6**



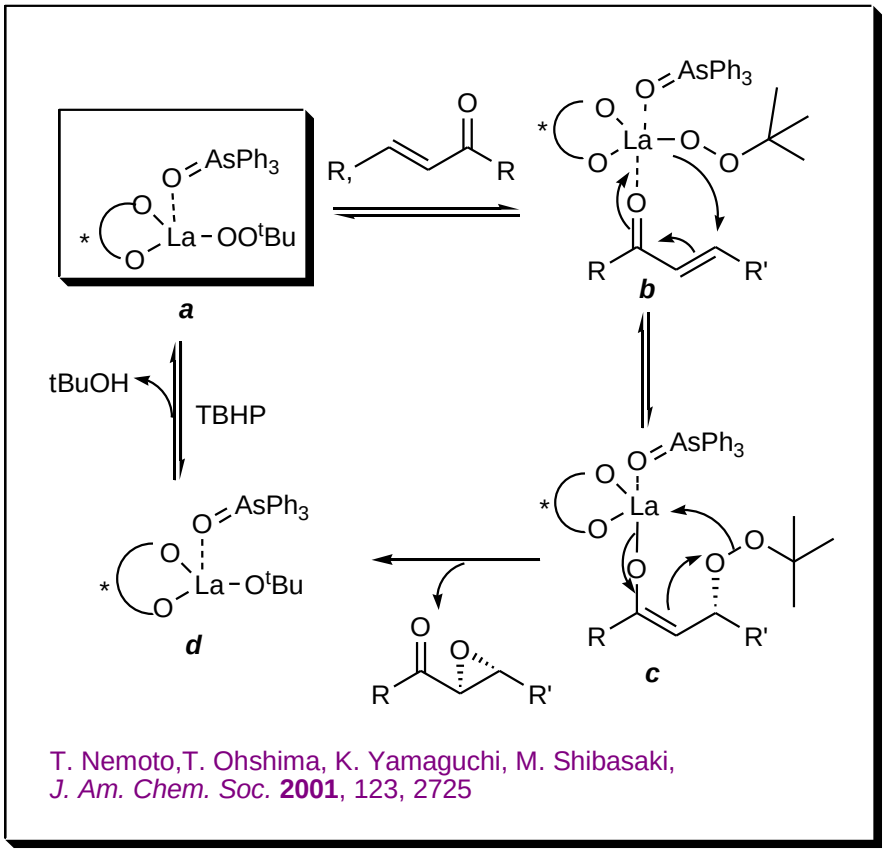
7



Scheme 5

Proposed Mechanism

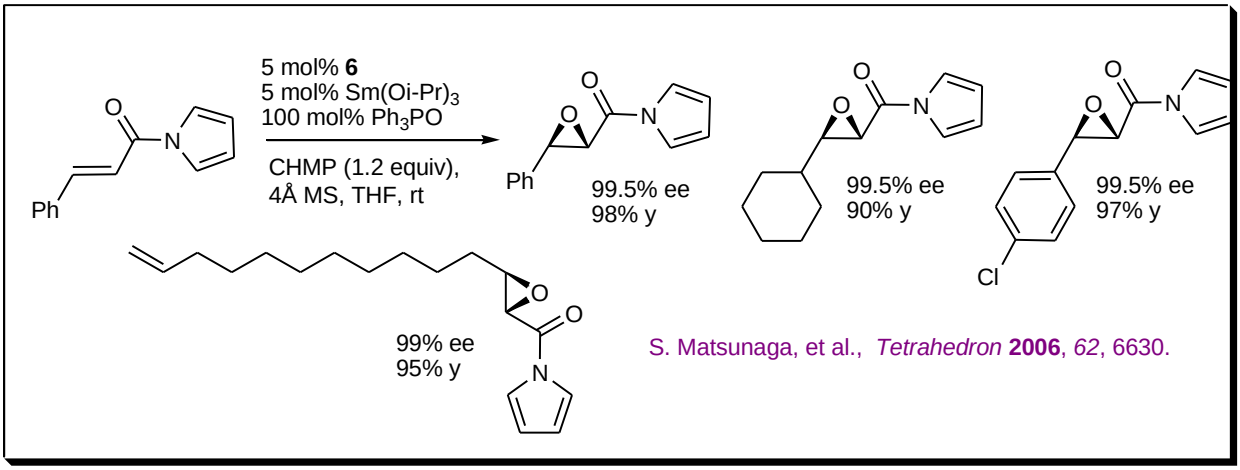
A 1:1:1 mixture of La(O^iPr)$_3$, BINOL and Ph_3As=O may afford the active complex **a** in the reaction medium (Scheme 6). Activation of the enone ***b*** by coordination to lanthanum metal followed by 1,4-addition of lanthanum peroxide may lead to the formation of enolate ***c*** that could provide the epoxide and intermediate ***d***. The latter with TBHP can provide the active complex ***a*** to regenerate the catalytic cycle.



T. Nemoto,T. Ohshima, K. Yamaguchi, M. Shibasaki,
J. Am. Chem. Soc. **2001**, 123, 2725

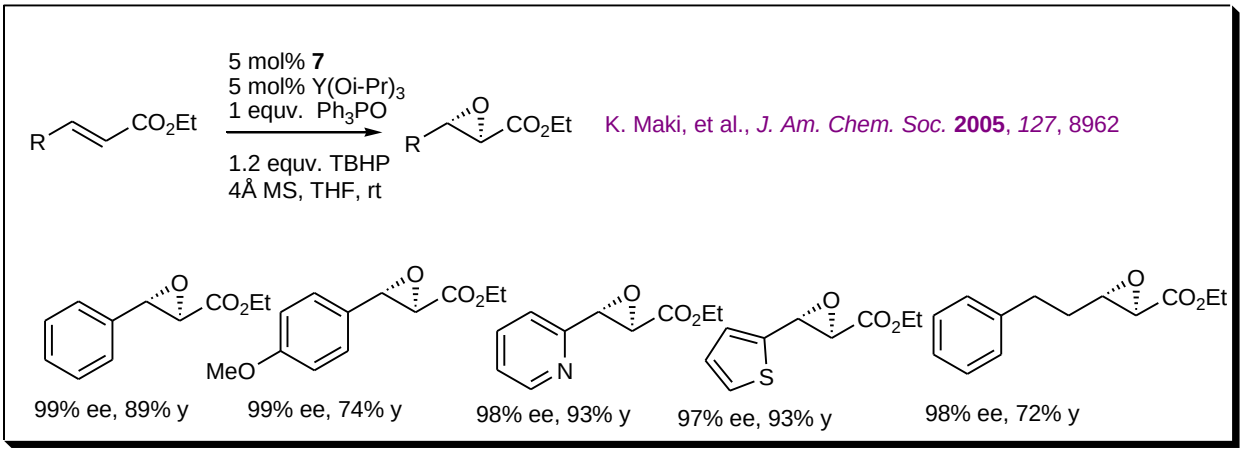
Scheme 6

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 7).



Scheme 7

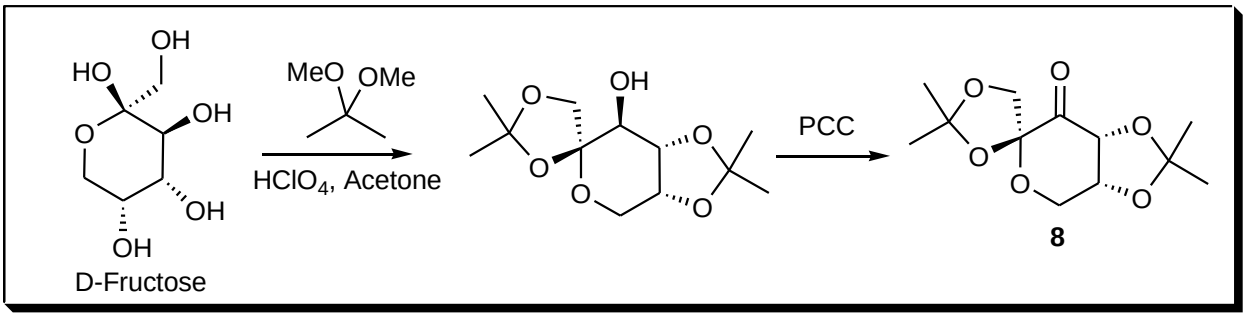
The catalyst derived from **7** and $Y(O^iPr)_3$ catalyzes the epoxidation of α,β-unsaturated esters with excellent enantioselectivity (Scheme 8). The system is compatible with alkenes bearing heteroaromatic rings.



Scheme 8

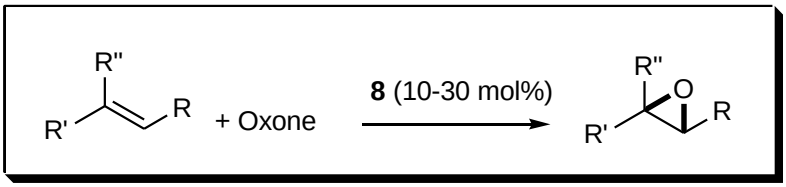
5.4.5 Organocatalysis

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 9).

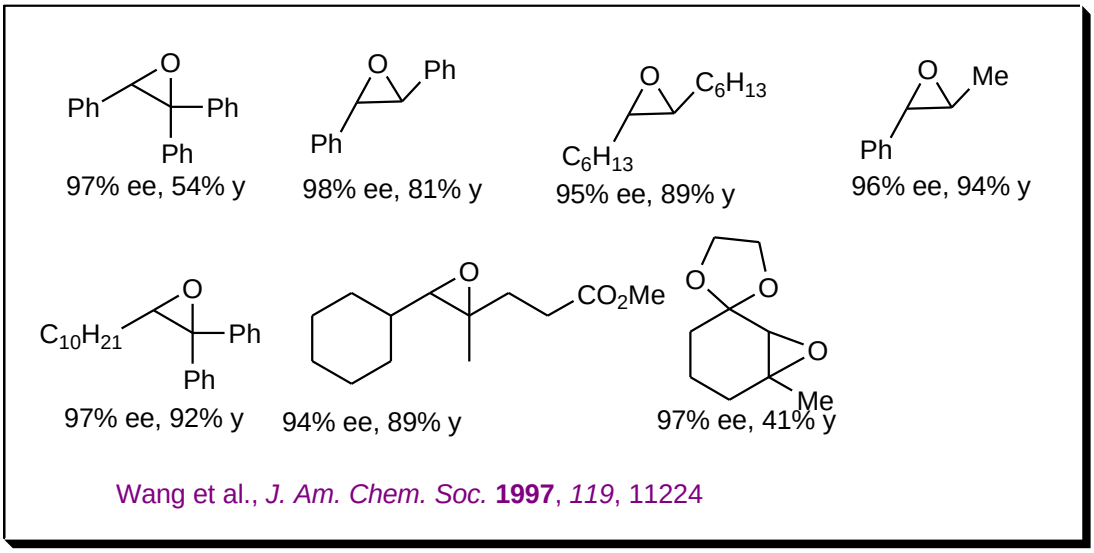


Scheme 9

For example, in presence of **8** (typically 20-30 mol%), a variety of trisubstituted alkenes proceed reaction with excellent enantioselectivity (Scheme 10).



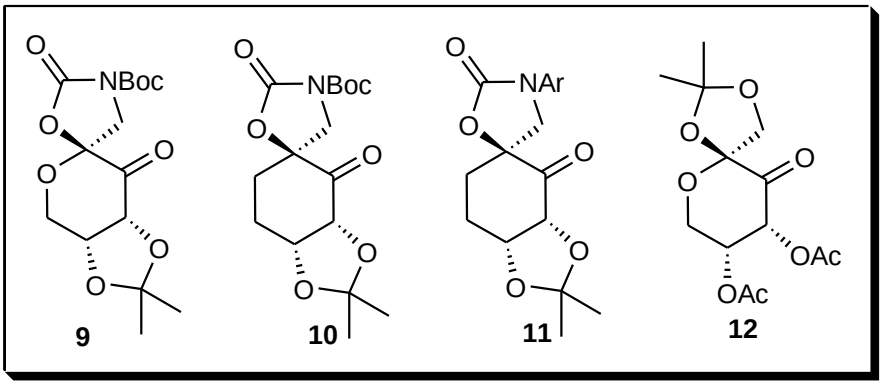
Examples:



Scheme 10

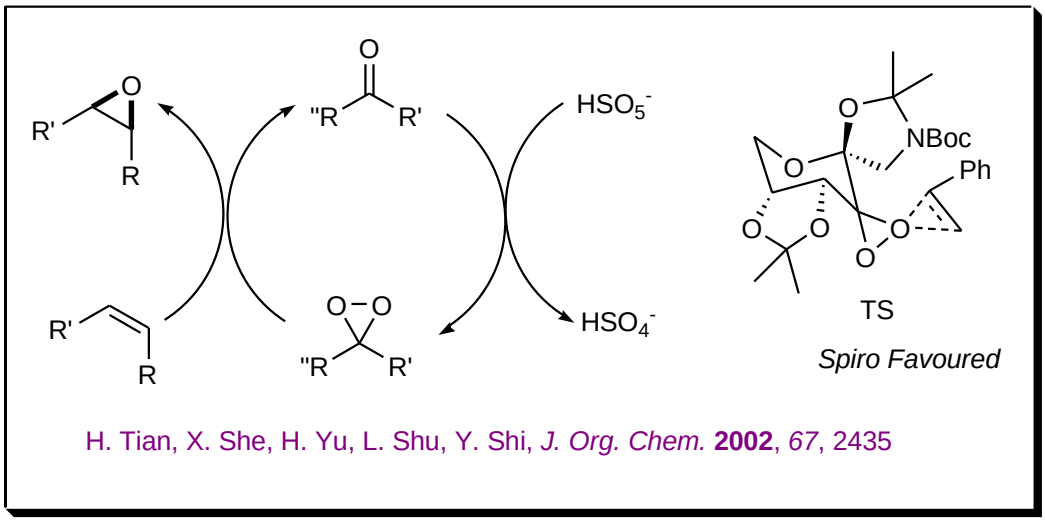
In case of *cis* and terminal alkenes, the glucose-derived ketone **9** with *N*-Boc oxazolidinone provides high enantioselectivity. A carbocyclic analogue **10** and *N*-aryl substituted variants **11** have also been introduced for the epoxidation of styrene derivatives and *cis*-disubstituted alkenes. Furthermore, the chiral ketone **12** with

electron-withdrawing acetate has been found to catalyze the epoxidation of α,β-unsaturated ester with high enantioselectivies.



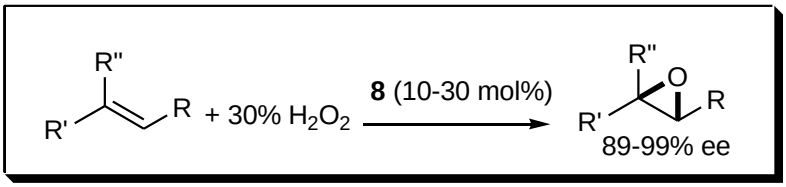
Proposed Mechanism

Scheme 11 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.



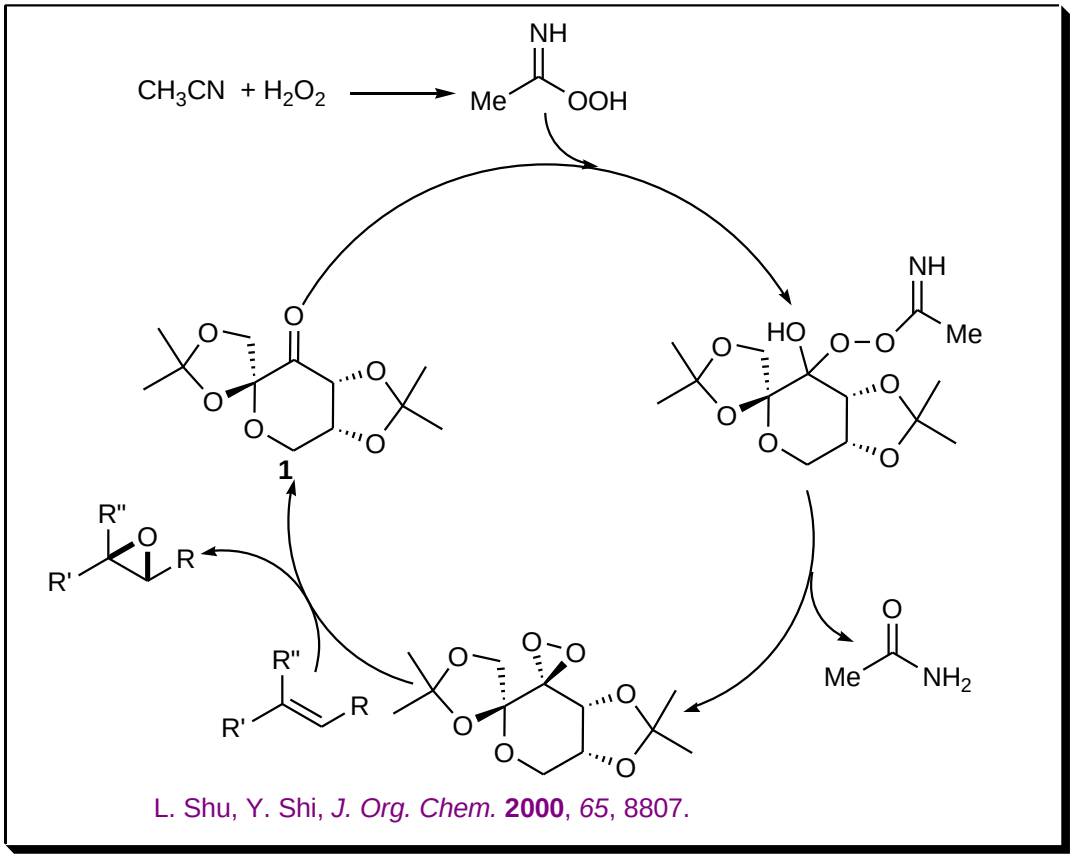
Scheme 11

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 12).



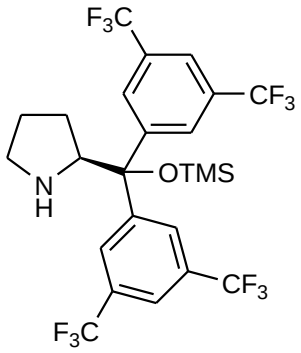
Proposed Mechanism

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.

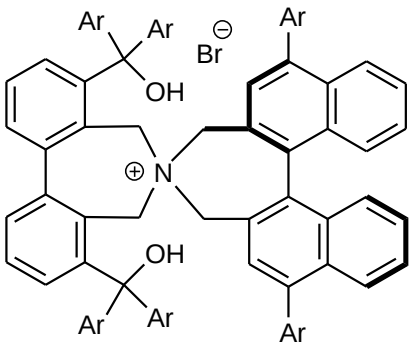


Scheme 12

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 13). α,β-Unsaturated aldehydes containing an aromatic substituent at the β-position are good substrates affording the epoxides with high diastereo- and enantioselectivities.

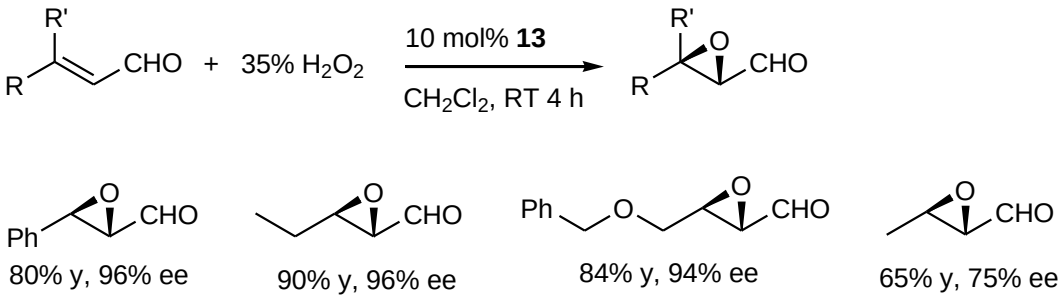


13



Ar = 3,5-Ph_2-C_6H_5

14

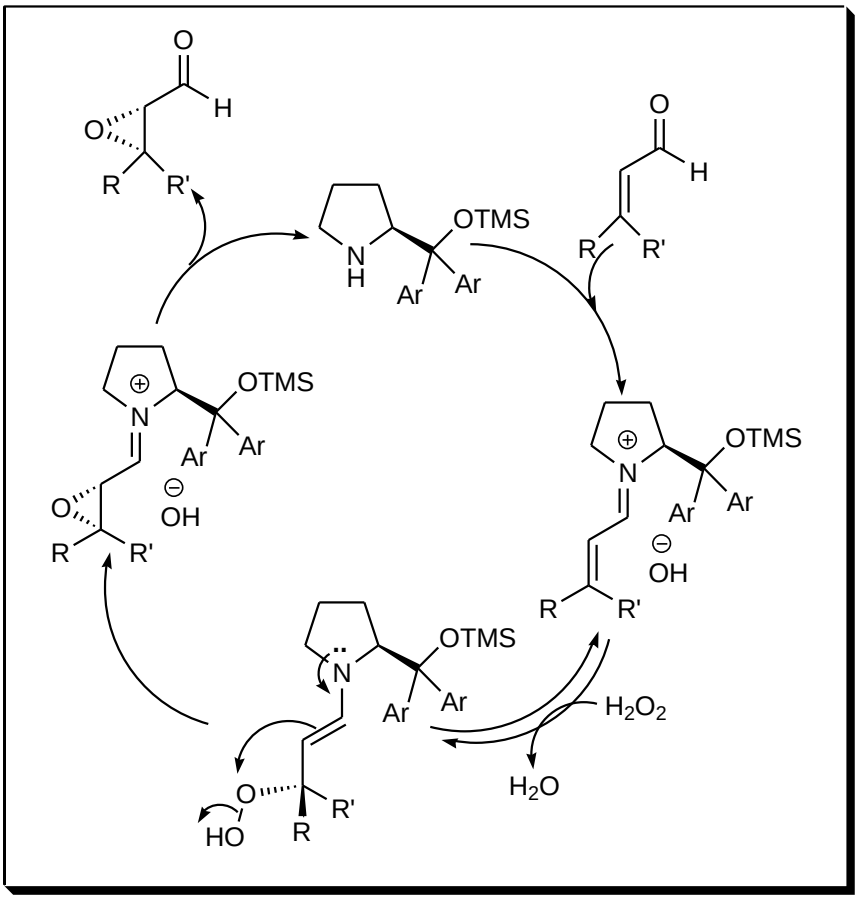


Scheme 13

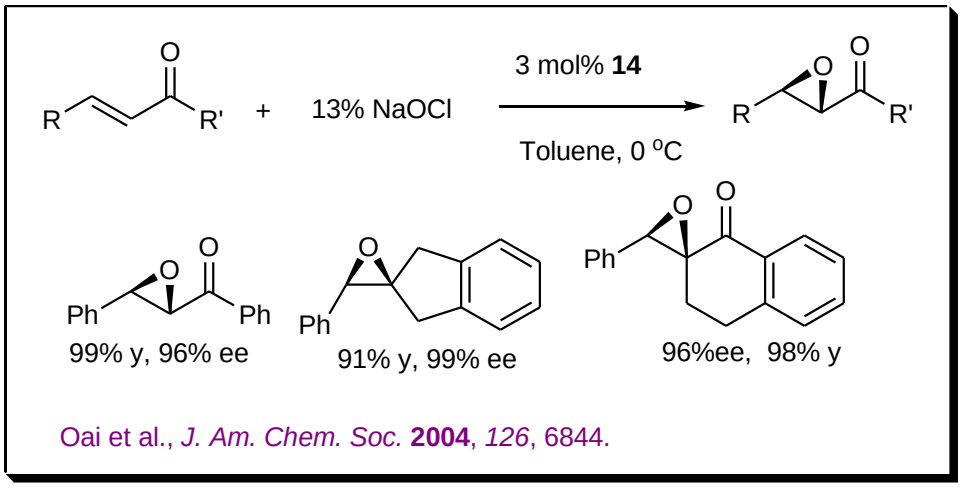
Proposed Mechanism

The proposed mechanism states that the reaction takes place through the Weitz-Scheffer mechanism (Scheme 14). 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 14). The hydroxyl groups are appropriately bonded to recognize and activate the enone substrate by hydrogen bonding.



Scheme 14



Scheme 15

Problems:

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

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

Reference/Text Book

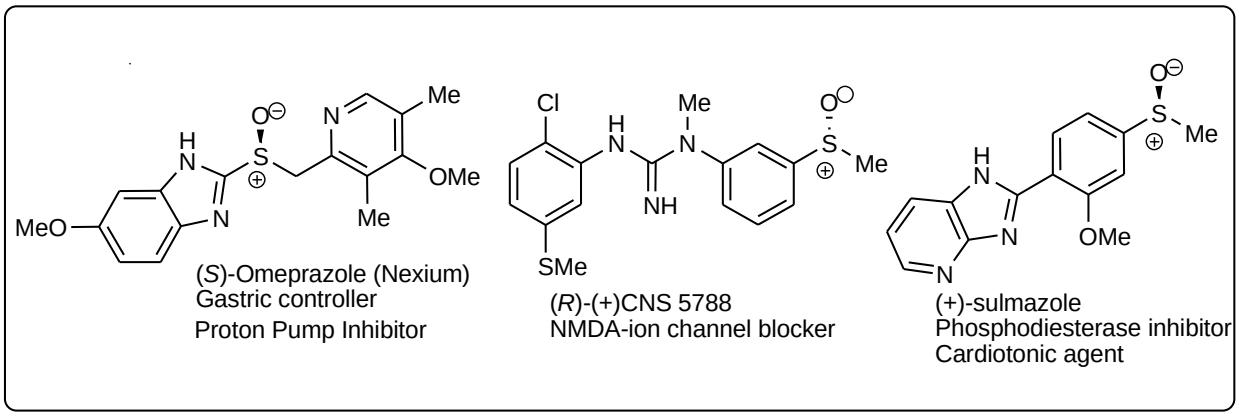
3. I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., Wiley, New Jersey, 2010.

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

Lecture 19

5.3 Enantioselective Sulfoxidation

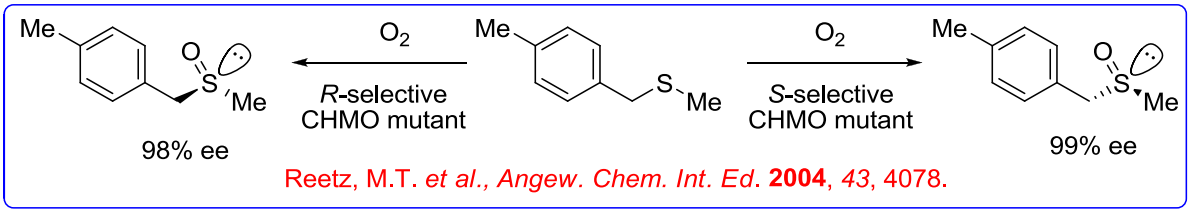
Enantiopure sulfoxides serve as chiral auxiliary as well as intermediates for the synthesis of optically active compounds. Optically active sulfoxide structural unit is also present in many compounds that exhibit interesting biological properties (Scheme 1). Development of methods for the asymmetric 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 1. Some Examples of Chiral Sulfoxide Based Drugs

5.3.1 Enzyme-Catalyzed Reactions

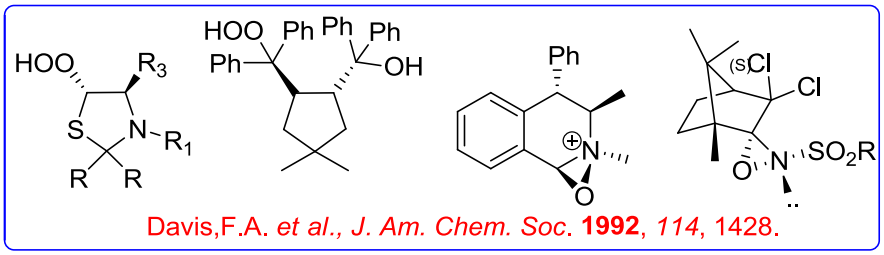
Enzyme catalyzed asymmetric oxidation of sulfides provides effective methods for the synthesis of optically active sulfoxides. For example, cyclohexanone monooxygenase (CHMO), a bacterial flavoenzyme, catalyzes the oxidation of prochiral thioethers with excellent enantioselectivity (Scheme 2).



Scheme 2

5.3.2 Chiral Reagents Based Reactions

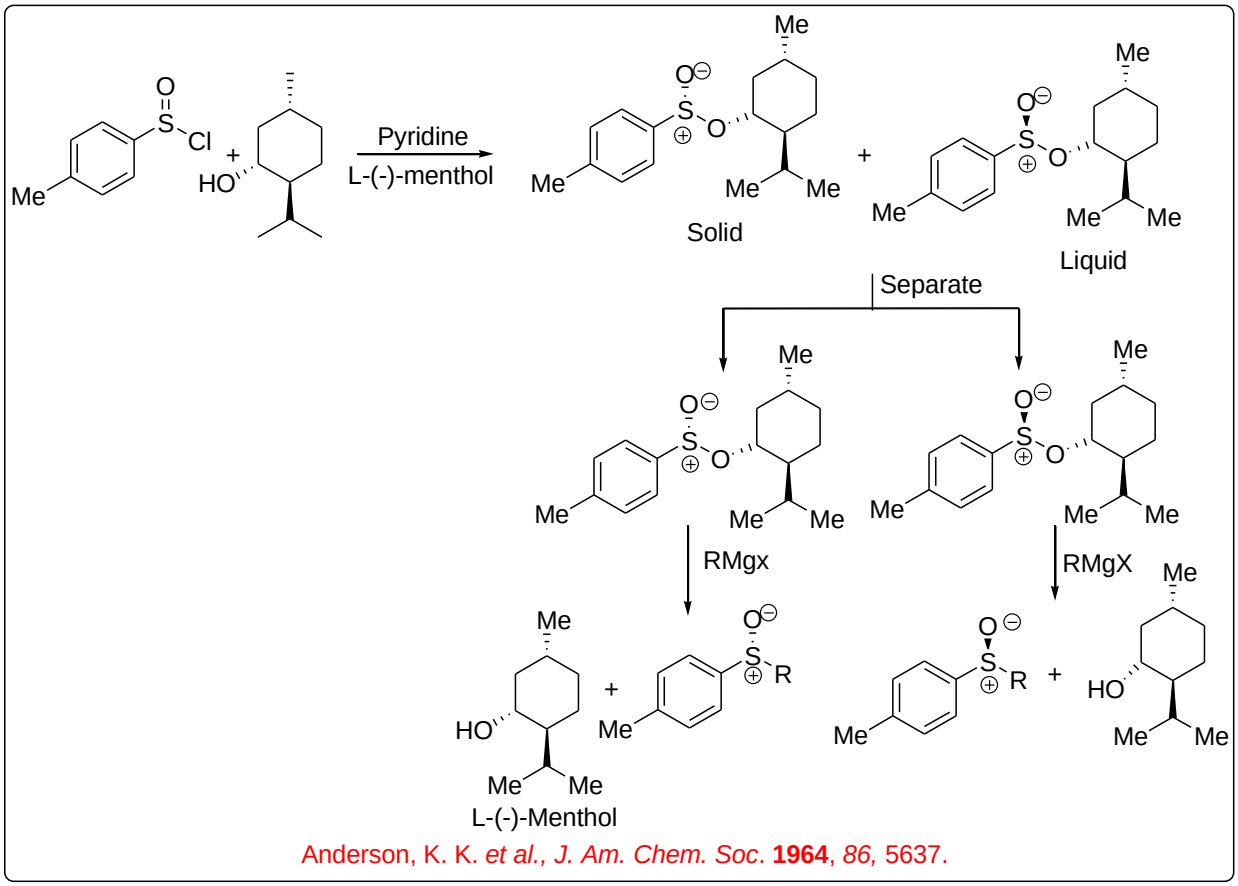
Chiral reagents have been used for the oxidation of prochiral sulfides. For example, chiral hydroperoxides, *N*-sulfonyl oxaziridines and chiral oxaziridines can oxidize prochiral sulfides to optically active sulfoxides with moderate to good enantioselectivity (Scheme 3).



Davis,F.A. *et al., J. Am. Chem. Soc*. **1992**, *114*, 1428.

Scheme 3

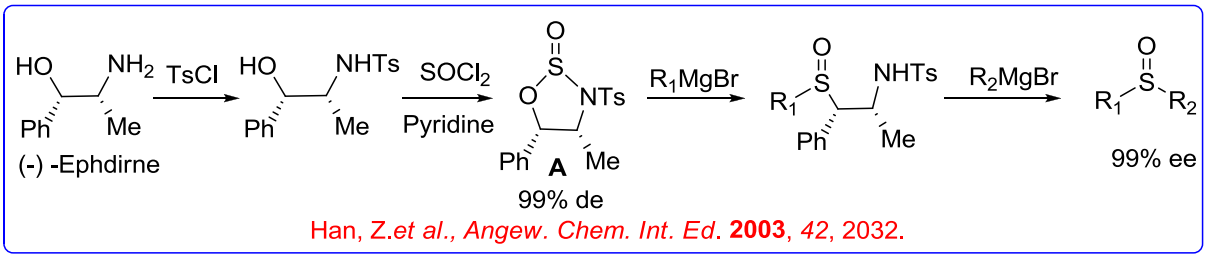
In addition, chiral sulfinates are precursors of chiral sulfoxides (Scheme 4). This approach is of preparative interest to provide the sulfoxides with high enantioselectivity. The important issue is need to prepare the menthyl-*p*-tolylsulfinates from L-(-)-menthol and then to separate them.



Anderson, K. K. *et al., J. Am. Chem. Soc*. **1964**, *86,* 5637.

Scheme 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). The configuration depends on the order of introduction of the two Grignard reagents.

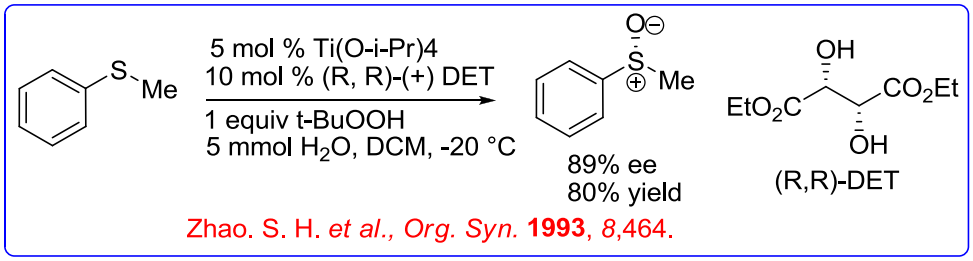


Scheme 5

5.3.3 Metal-Catalyzed Reactions

5.3.3.1 Reactions with Diethyl Tartrates

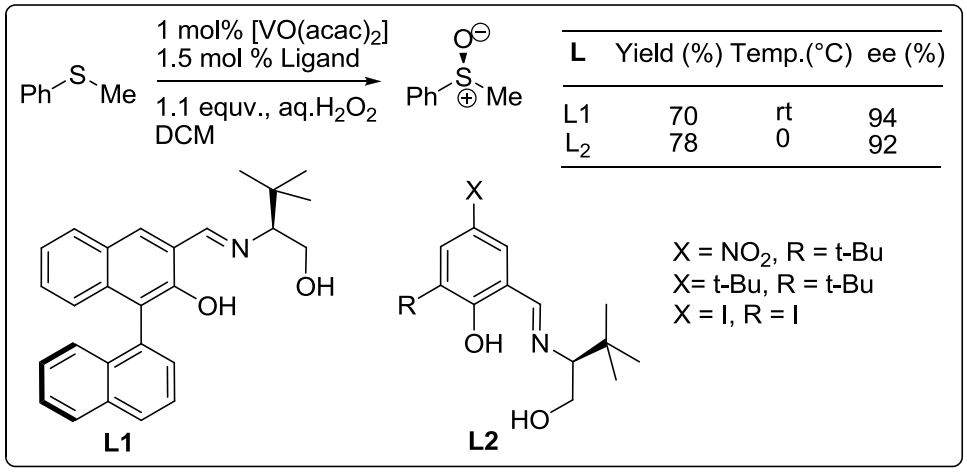
In the middle of 1980, Kagan and Modena groups independently modified the conditions that were employed by Sharpless group for the asymmetric epoxidation of allylic alcohols, and used for the oxidation of sulfides. The modified conditions involve the combination of $Ti(O^iPr)_4$, (*R,R)*-diethyl tartrate (DET) and *t*-BuOOH (TBHP) in water (Scheme 6). The replacement of TBHP with cumyl hydroperoxide (CHP) led to improvement in the enantioselectivity of the sulfoxide.



Scheme 6

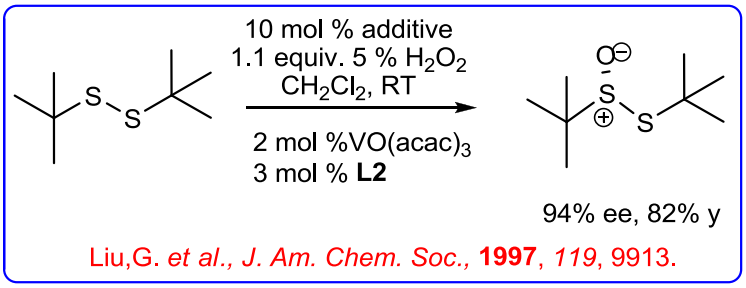
5.3.3.1 Reactions with Tridentate Ligands

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 7). The catalysts are prepared *in situ* and the effect of series Schiff base ligands is studied.



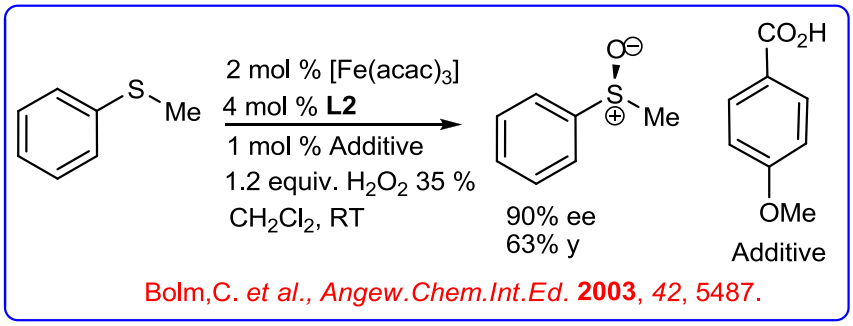
Scheme 7

In case of di-*tert*-butyldisulfide, monoxidation occurs selectively with up to > 90% ee (Scheme 8).



Scheme 8

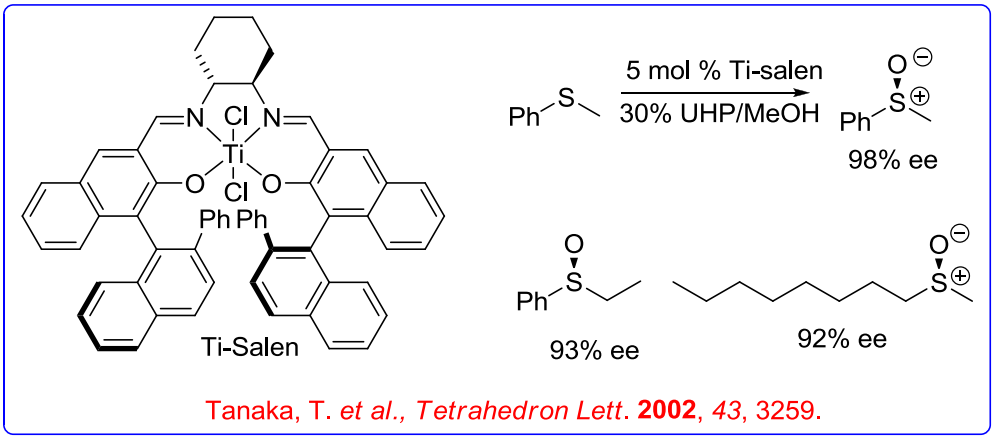
Subsequently, the reaction has also been found to be effective with $Fe(acac)_3$ in the presence of additive such as *p-methoxybenzoic acid* (Scheme 9). For example, the oxidation of *p*-chlorophenyl methyl sulfide can be accomplished with 92% ee and 60% yield. In some cases, kinetic resolution is observed.



Scheme 9

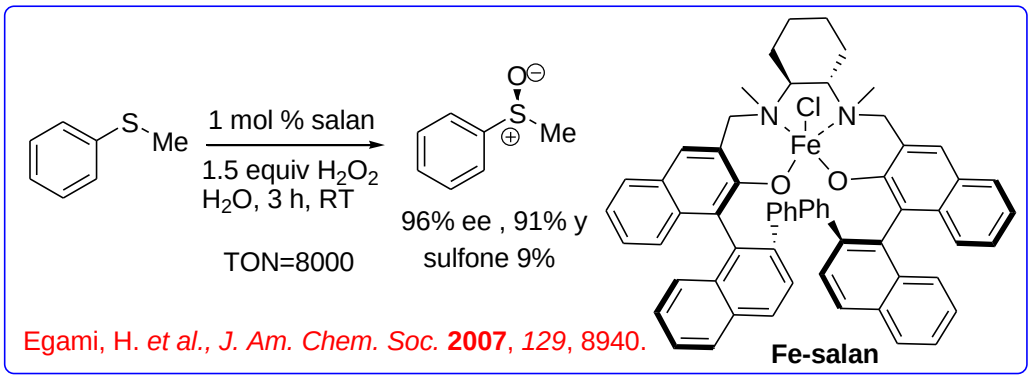
5.3.3.1 Reactions with Salen Based Ligands

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 10). The oxidation of several alkyl aryl sulfides can be accomplished with 92–99% ee.



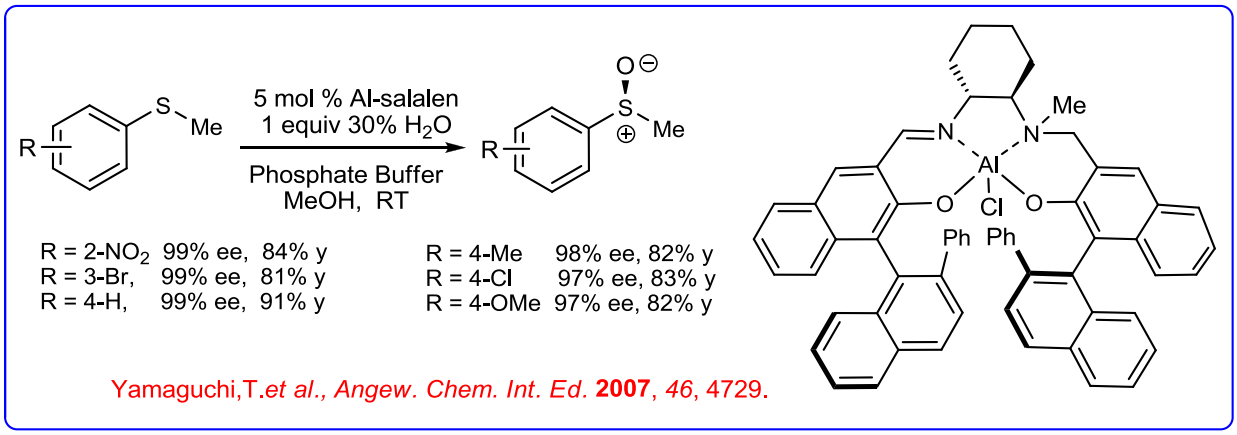
Scheme 10

Subsequently, Fe(salan) has been found to catalyze the oxidation of sulfides in the presence of aqueous H_2O_2 in water (Scheme 11). This procedure has the advantages of high catalytic turnover number (TON) of 8000 as well as the use of water as reaction medium.



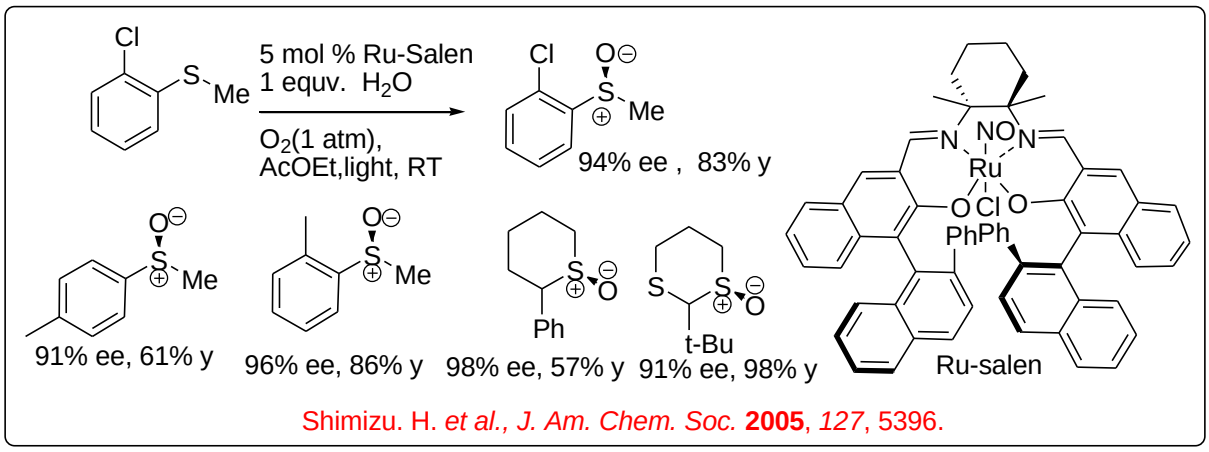
Scheme 11

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 12). The reactions of a variety of sulfides have been demonstrated with high enantioselectivity.



Scheme 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 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



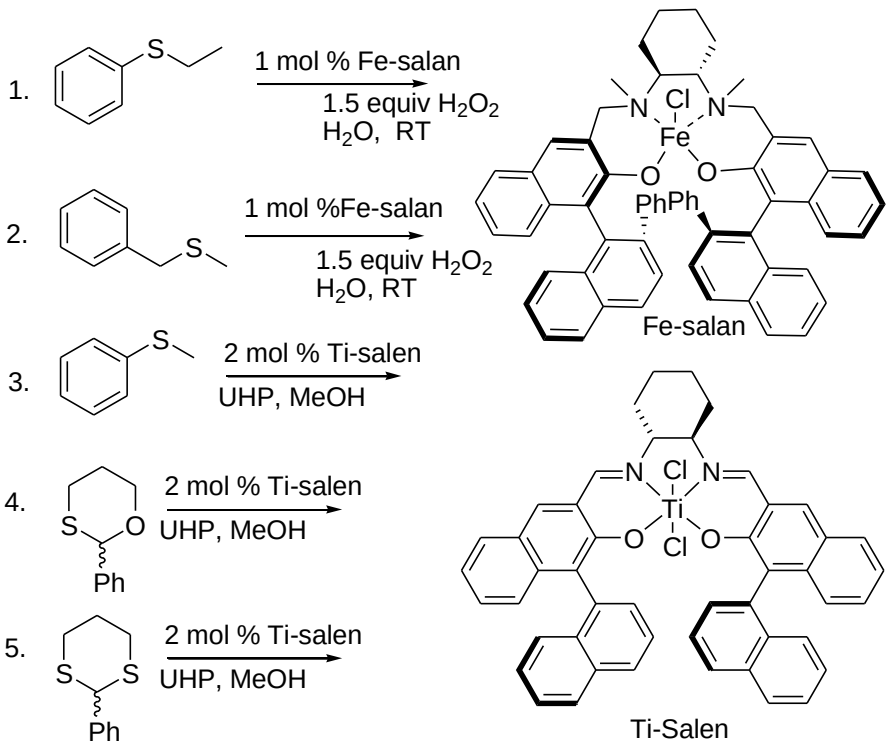
Scheme 13

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.

Problems

Complete the following 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.

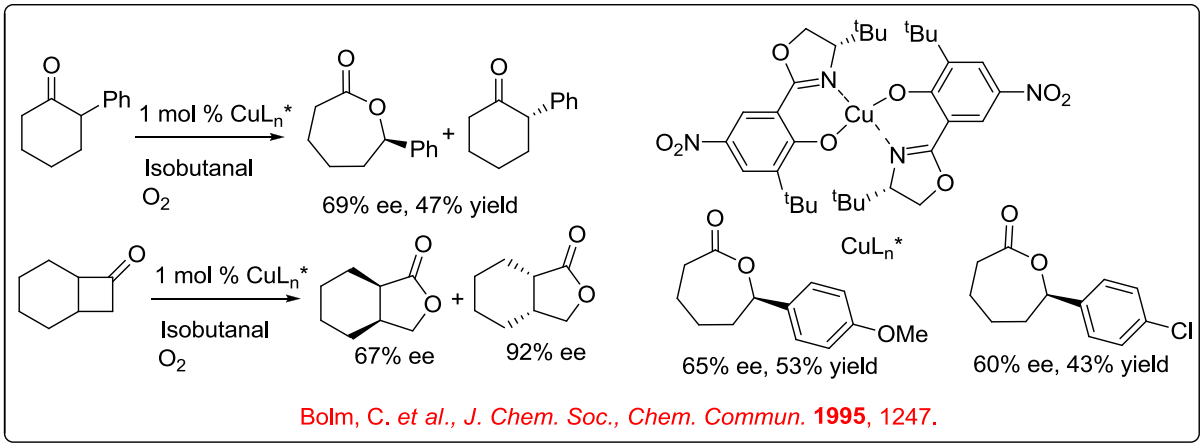
Lecture 20

5.4 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.

5.4.1 Metal-Catalyzed Reactions

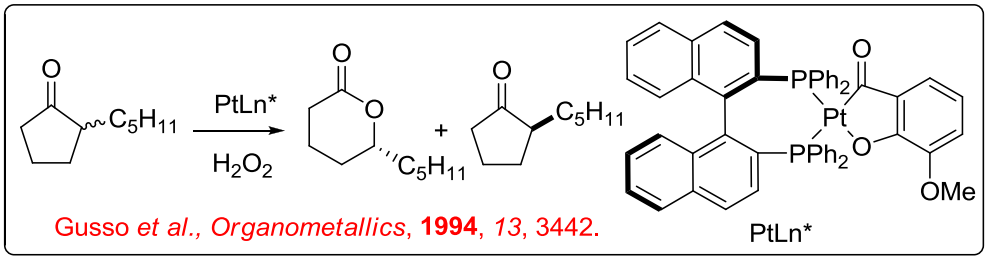
Copper(II) complexes with oxazoline-based ligands are studied for the oxidation of substituted cyclic ketones to give lactones with high enantioselectivity (Scheme 1). These reactions employ isobutanal as co-reductant under aerobic conditions. During the reaction isobutanal is oxidized to the corresponding carboxylic acid.



Scheme 1

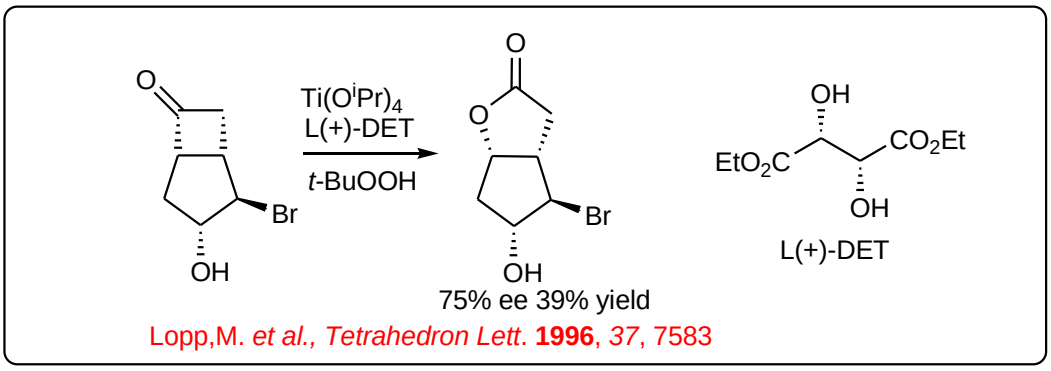
Platinum complexes bearing chiral phosphines catalyze oxidation of substituted cyclic ketones in the presence of hydrogen peroxide (Scheme 2). Coordination of Pt and

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 2

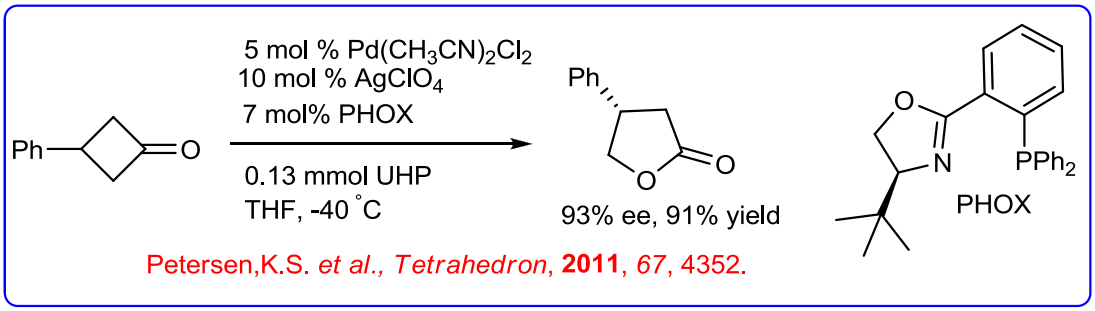
The reaction conditions used for the enantioselective epoxidation of allylic alcohols (Sharpless epoxidation) is also effective for the oxidation of substituted cyclobutanones to give lactones with moderate to good enantioselectivity (Scheme 3).



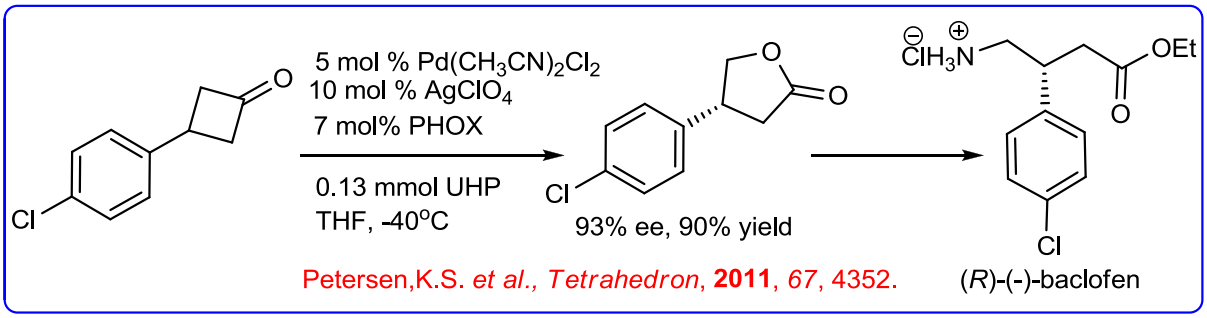
Scheme 3

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 □-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). 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.

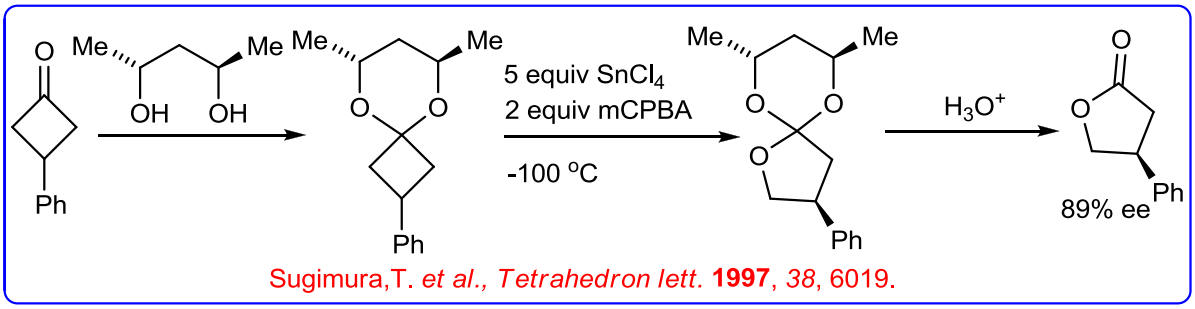


Scheme 4



Scheme 5

In addition to the metal-catalyzed BVOs, chiral auxiliary approach is also followed to synthesis lactone with good enantioselectivity (Scheme 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.

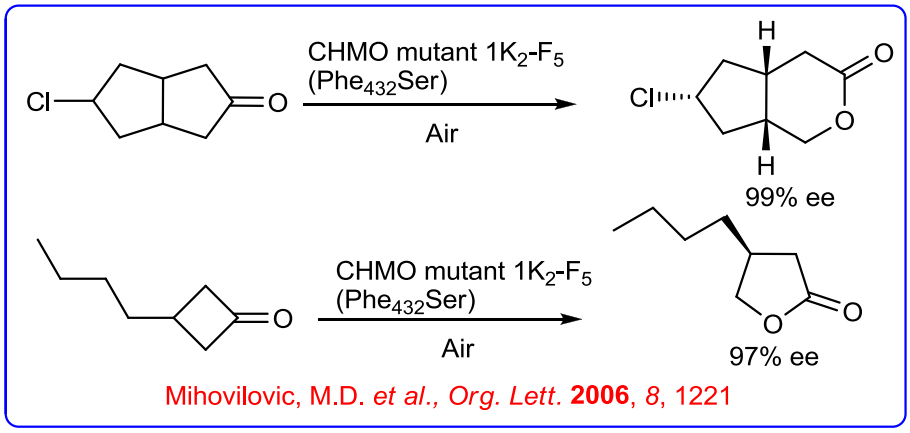


Scheme 6

5.4.2 Enzyme Catalyzed Reactions

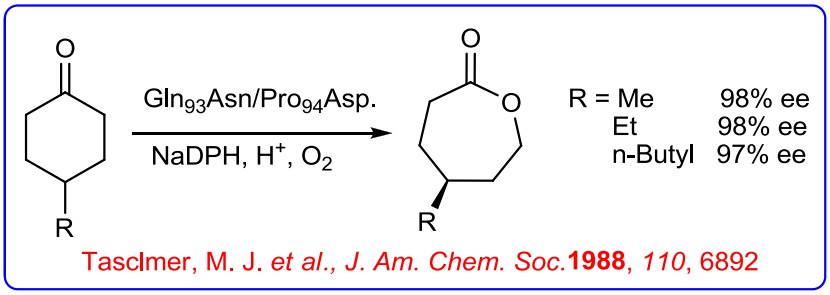
Baeyer-Villiger monooxygenases are enzymes that catalyze the insertion of an oxygen atom in a ketone, next to the carbonyl carbon atom. So far, only a limited number of

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 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 7

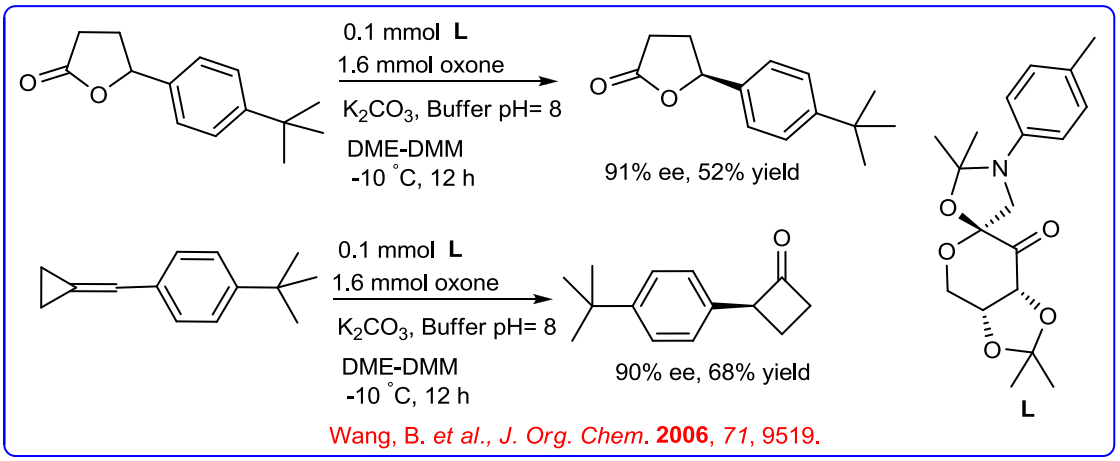
Similarly, PAMO mutant $Gln_{93}Asn$/ $Pro_{94}Asp$ is tested for the asymmetric desymmetrization of 4-substituted cyclohexanone derivatives to give chiral lactones with high enantioselectivity (Scheme 8). It is interesting to note that the absolute configuration of the lactone products is opposite to what is observed with the thermolabile cyclohexanone monooxygenase (CHMO) as the catalyst.



Scheme 8

5.4.3 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 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.

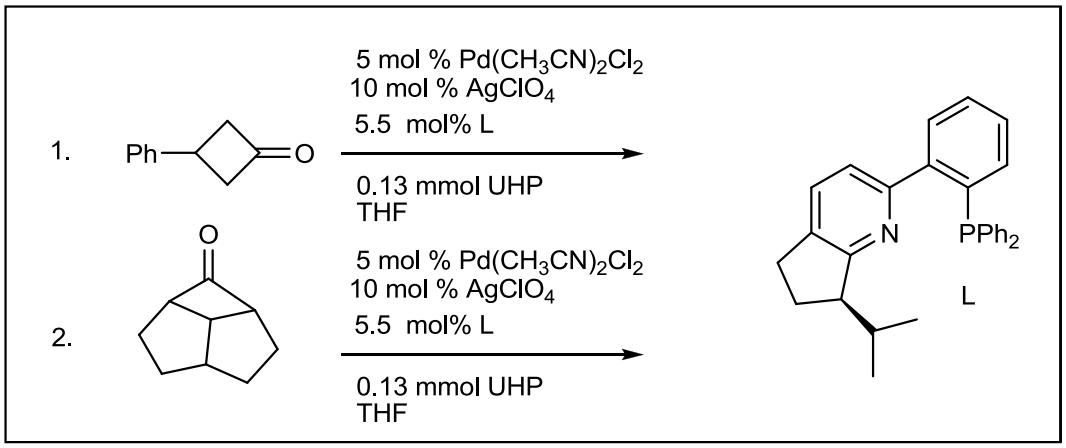


Scheme 9

Problems

A. Describe chiral phosphoric acid catalyzed asymmetric Baeyer-Villiger oxidation.

B. Complete the following reactions.



Reference/Text Book

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

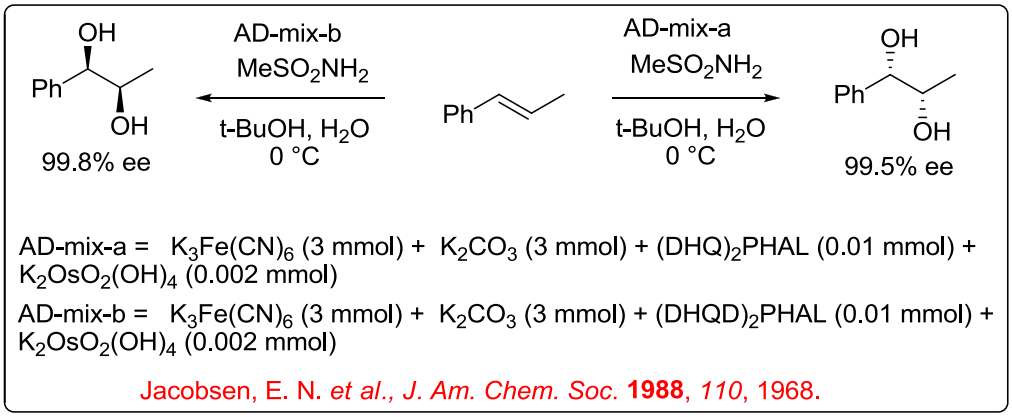
8. M. B. Smith, *Organic Synthesis*, 2nd edition, McGraw Hill, New Delhi, 2004.

Lecture 21

5.6 Dihydroxylation, Aminohydroxylation and Aziridination Reactions

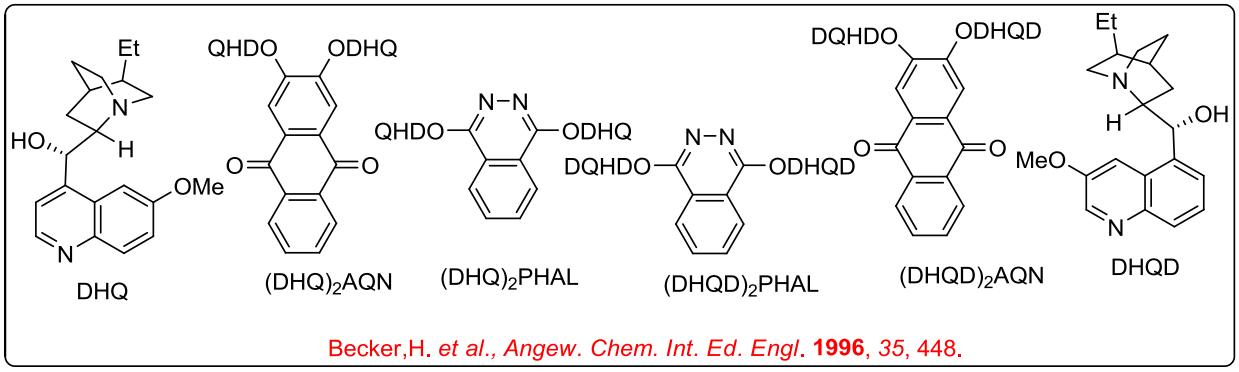
5.6.1 Dihydroxylation Reaction

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 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.



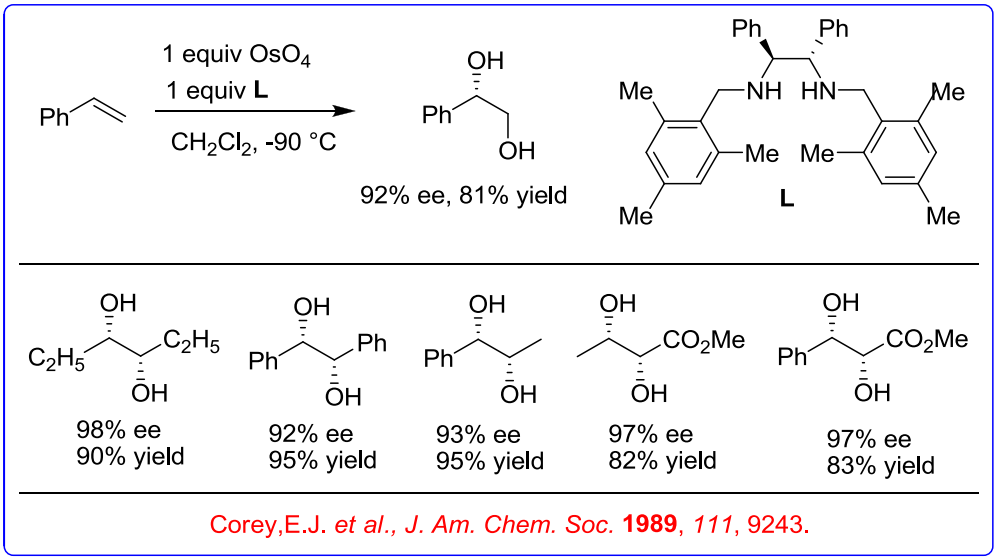
Scheme 1

$K_3Fe(CN)_6$ 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 ($MeSO_2NH_2$) 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.



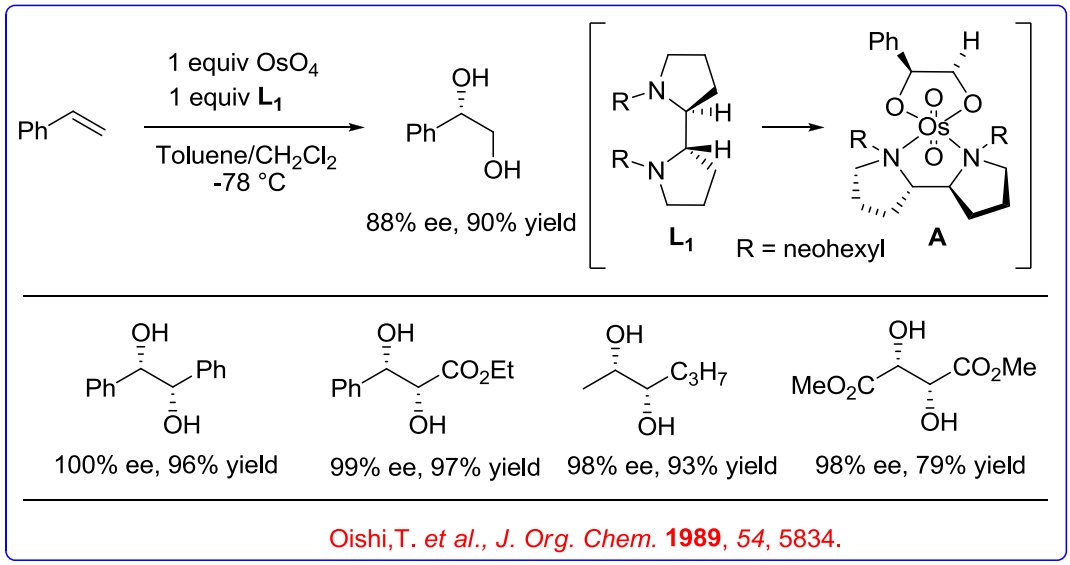
Scheme 2

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 3). The reactions of a series of alkenes can be accomplished with good to excellent yield and enantioselectivity.



Scheme 3

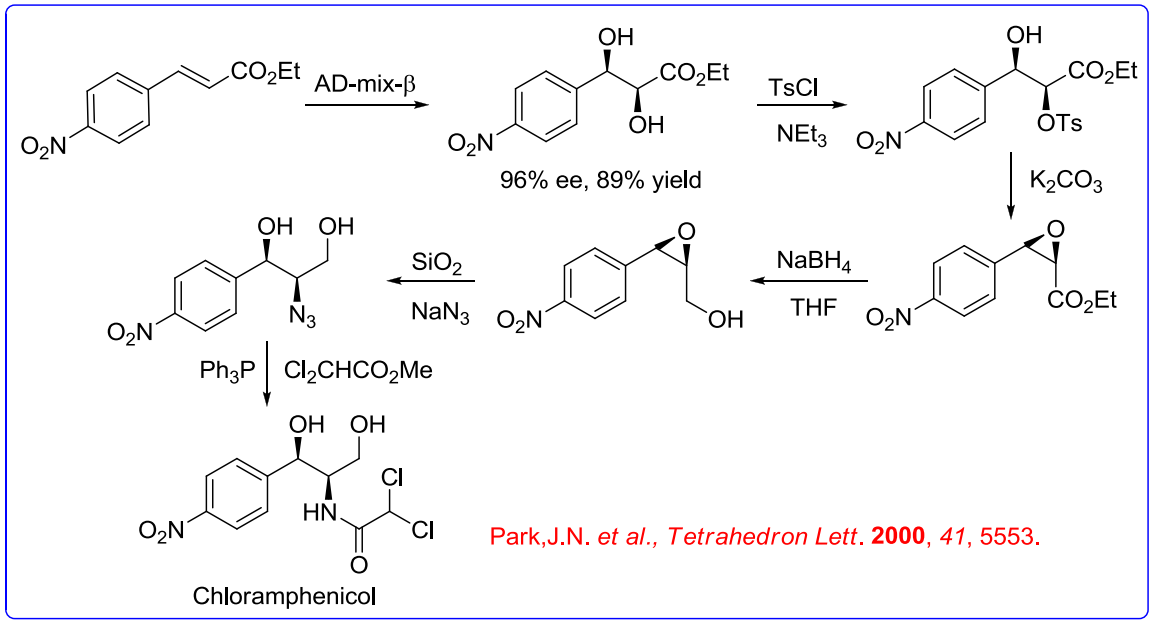
In addition, the bidentate ligand $\mathbf{L_1}$ is found to effective for the OsO_4-mediated dihydroxylation of *trans*-disubstituted and monosubstituted alkenes (Scheme 4). The reaction is believed to involve intermediate A and the products are obtained with high yield and enantioselectivity.



Scheme 4

5.6.1.1 Synthesis of Biologically Important Molecules

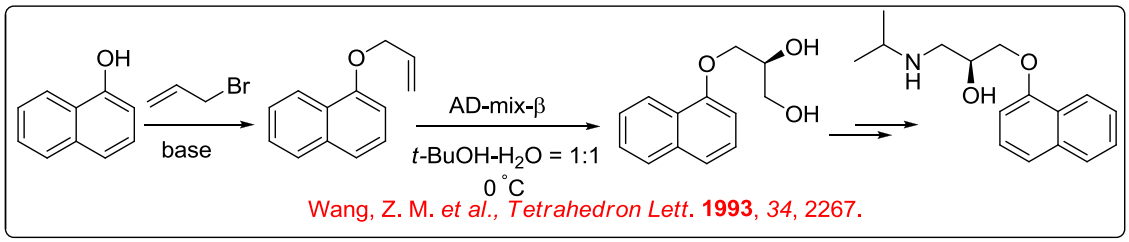
The Os-catalyzed enantioselective dihydroxylation is used as a key step in the highly expeditious synthesis of the antibacterial agent (–)-chloramphenicol (Scheme 5).



Scheme 5. Synthesis of Chloramphenicol

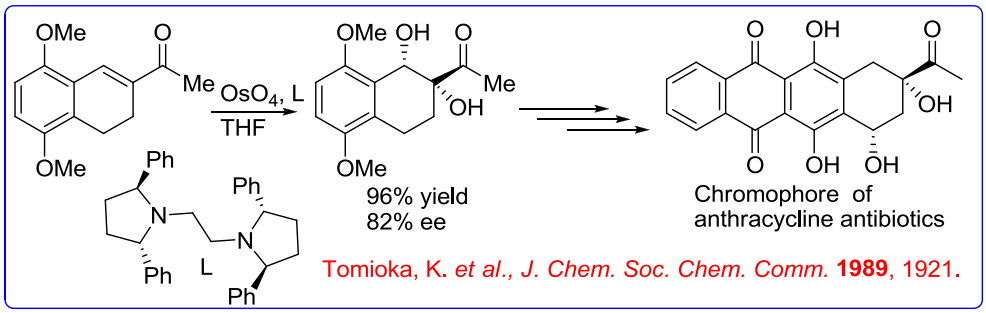
The synthesis of the *β*-receptor-blocking drug (*S*)-propranolol has been demonstrated employing osmium-catalyzed dihydroxylation as a key step (Scheme 6). Reaction

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 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 7). The resultant 1,2-diol could be subsequently converted into the desired chromophore of anthracycline antibiotic in good yield.



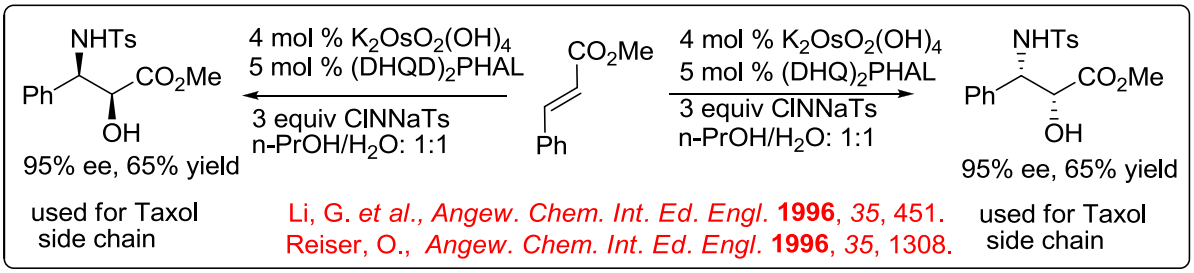
Scheme 7. Synthesis of Chromophore of Anthracycline Antibiotic

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.

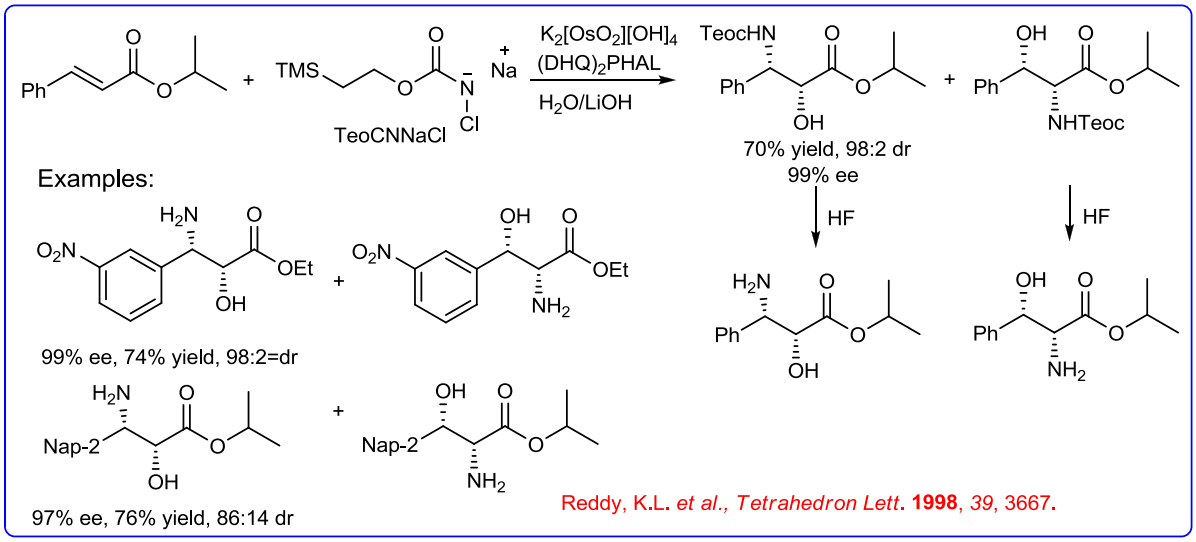
Synthesis of chiral α-sulfonamido hydroxy compounds can be obtained when the alkene substrates are subjected to the aminohydroxylation reaction using chloramine-T (TsNClNa) as the nitrogen source and H_2O as the oxygen source. The reaction is found to be successful in the presence of osmium complex bearing $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$. The □-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 8). The methyl (*E*)-cinnamate can be successfully converted into □-hydroxy-□-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.



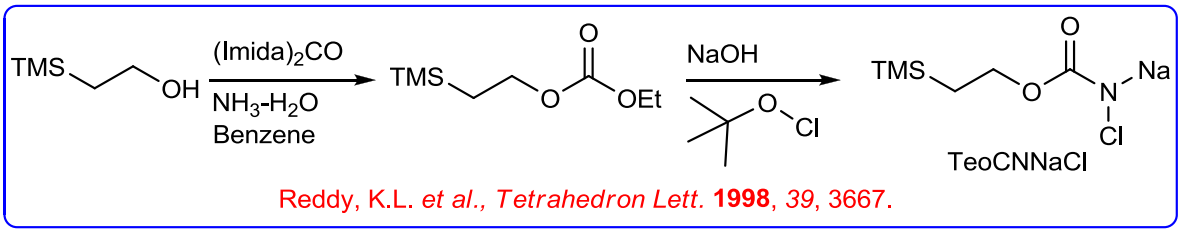
Scheme 8

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 9-10). The TeoC group can be cleaved by fluoride under very mild conditions, yielding the free amino alcohol with high enantiomeric purity.

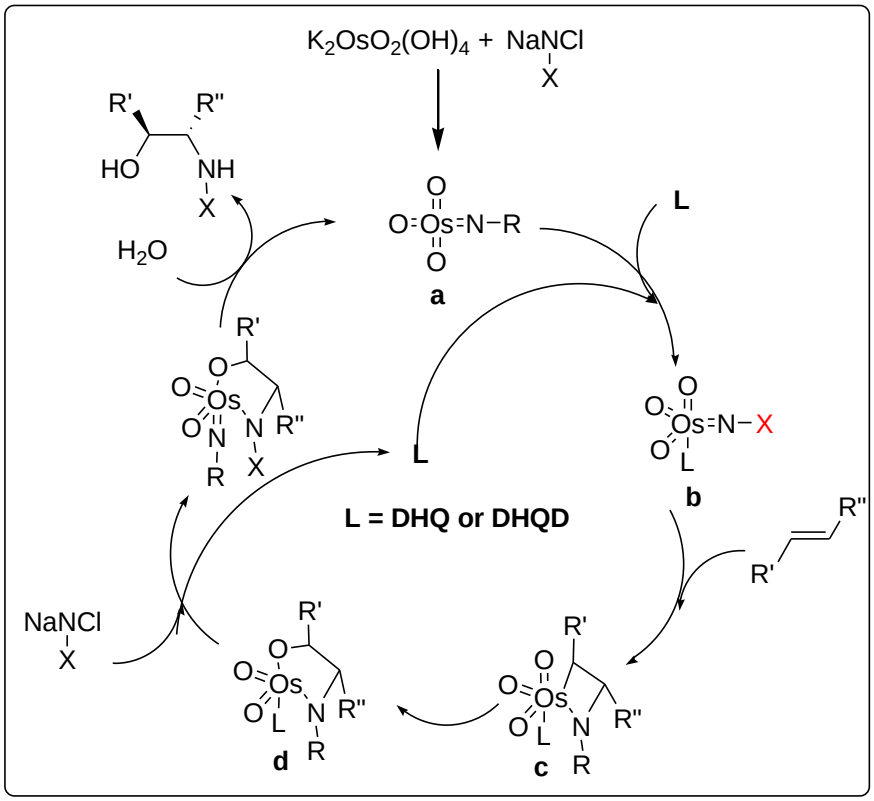


Scheme 9. Aminohydroxylation using TeoCNNaCl as the Nitrogen Source



Scheme 10. Synthesis of TeoCNNaCl

The mechanism of the reaction is shown in Scheme 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.

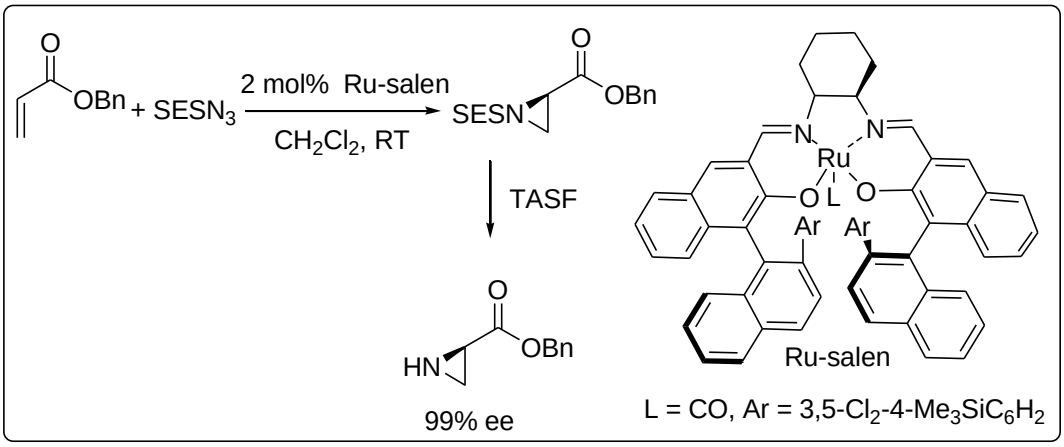


Scheme 11. Mechanism of Sharpless Aminodihydroxylation

5.6.2 Asymmetric Aziridination

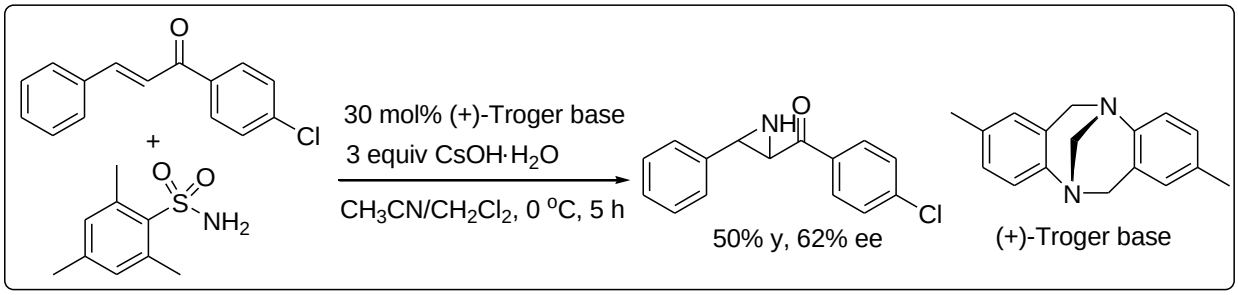
Aziridines are versatile building blocks in organic synthesis. Considerable progress has been made in the area of asymmetric aziridination employing copper based systems. Mn(porphyrin) and Mn-salen complexes have been shown as effective catalysts for this reaction. The reactions proceed via active nitrenoid 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 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 □□□-unsaturated esters proceed aziridination with high enantioselectivity.

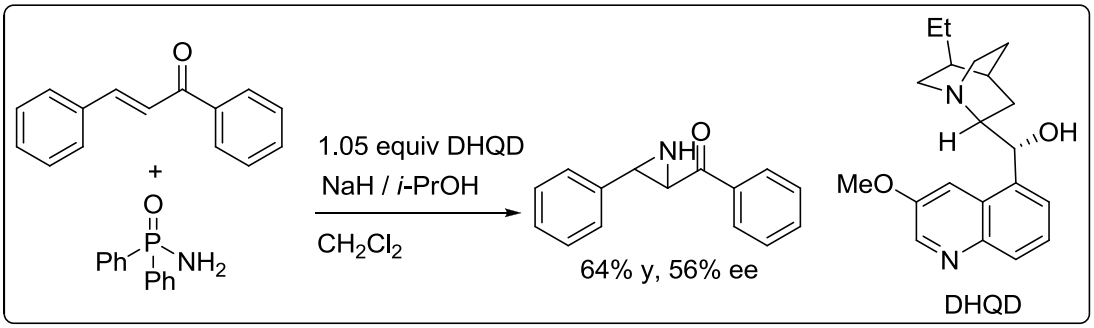


Scheme 12

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 13). Soon after the use of quiniclidine for the reaction of *O*-(diphenylphosphinyl)hydroxylamine with chalcone is shown with 56% ee (Scheme 14).



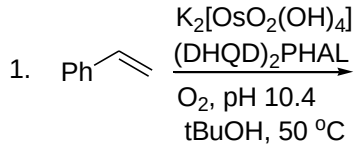
Scheme 13

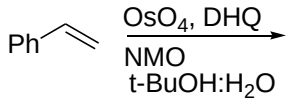


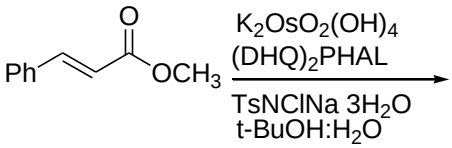
Scheme 14

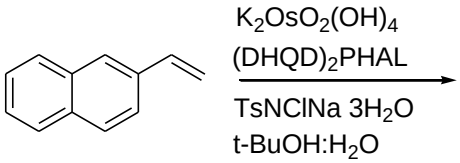
Problems

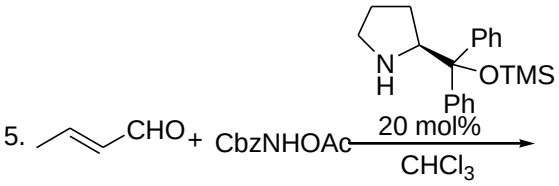
What product(s) would you expect from the following reactions?

1. 

2. 

3. 

4. 

5. 

Reference/Text Book

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

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