

Module 3

Organometallic Reagents

Lecture 20

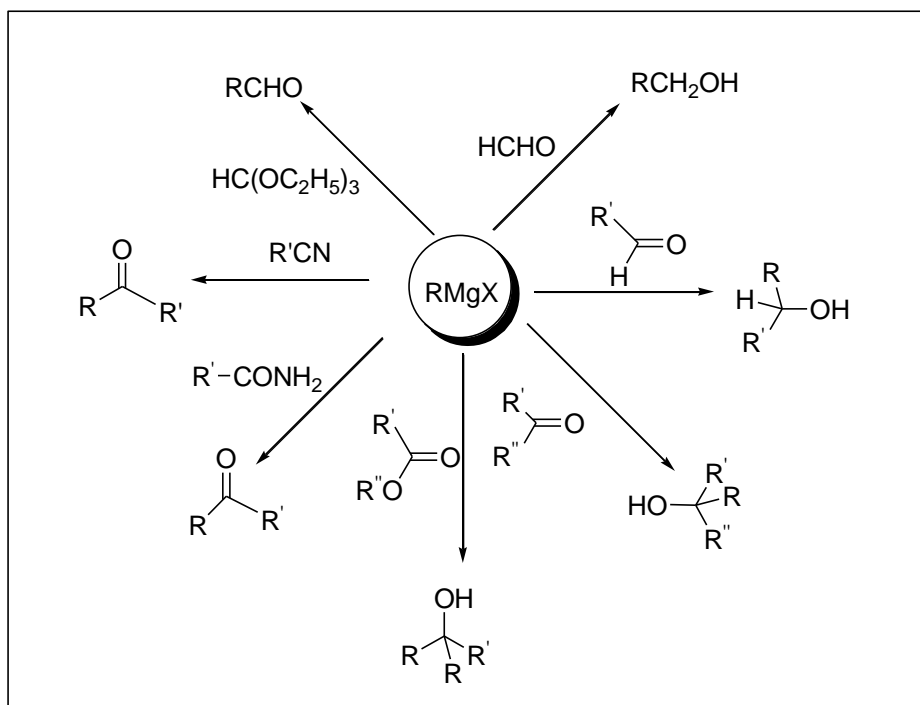
3.1.1 Organomagnesium Reagents

The organomagnesium halides (RMgX), known as Grignard reagents, are useful synthetic intermediates in organic chemistry for carbon-carbon bond formation. They may be regarded as polar compounds and are sources of nucleophilic carbanions.

The organomagnesium halides are prepared by the action of magnesium on alkyl, aryl or vinyl halides in either dry ether or THF, and the resultant solution is used for the subsequent reactions. In case the reaction is sluggish, small amount of iodine is added to initiate the reaction. The rate of the formation of the organomagnesium halides can be significantly accelerated by sonication.

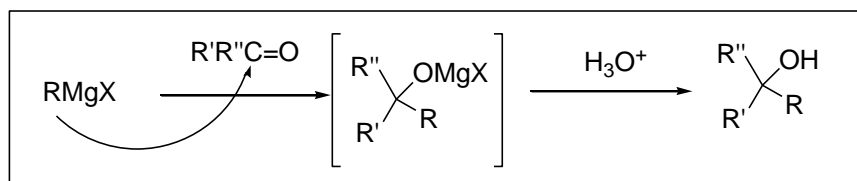
3.1.1.1 Reactions with Carbonyl Compounds

Being nucleophilic in nature, the organomagnesium halides undergo 1,2-addition to the carbonyl



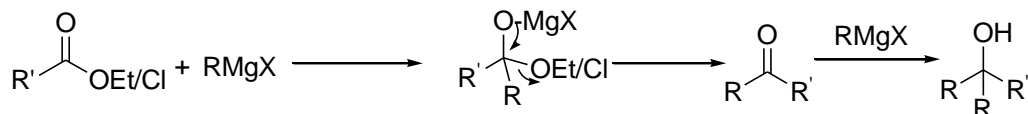
Scheme 1

group of aldehydes, ketones, esters, anhydrides, acid chlorides and amides (Scheme 1). In these reactions, the alkyl, aryl or vinyl group having carbanionic character become attached to the carbonyl carbon and the magnesium halide to the oxygen of the carbonyl group to give a complex (addition product). These addition products on decomposition with proton source give the corresponding alcohols (Scheme 2).



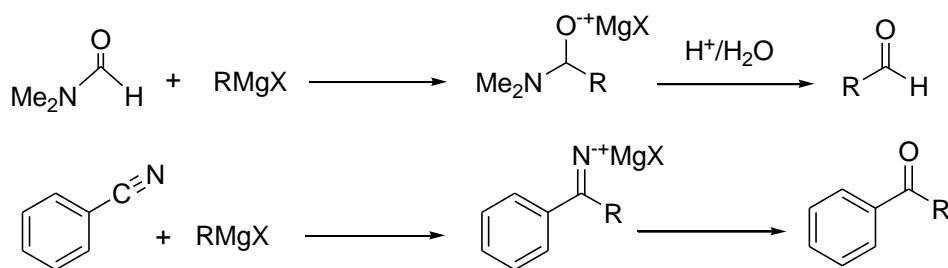
Scheme 2

If the carbonyl group is attached with a leaving group (i.e., if $R^1 = OR, Cl$) then the tetrahedral adduct can break down to regenerate a $C=O$ group that undergoes a fast second addition step (Scheme 3).



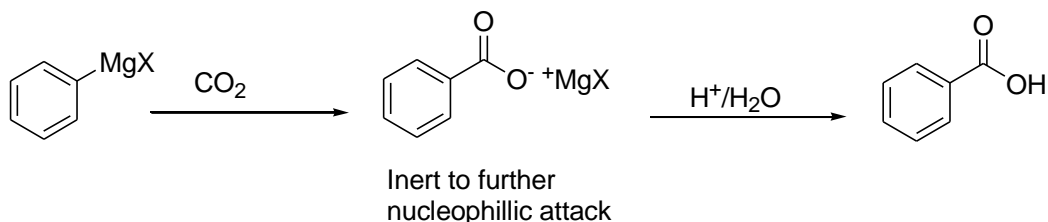
Scheme 3

However, a number of methods have been devised to stop the reaction at the aldehyde or ketone stage. Such protocols involve the formation of a masked carbonyl compound, which releases the desired compound on hydrolysis (Scheme 4).



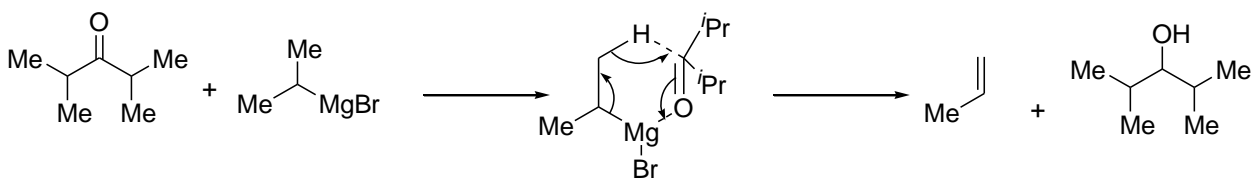
Scheme 4

In case of reaction of Grignard reaction with carbon dioxide, the reaction stops at the carboxylate (RCO_2^-) stage as it is resistant to further nucleophilic attack (Scheme 5)



Scheme 5

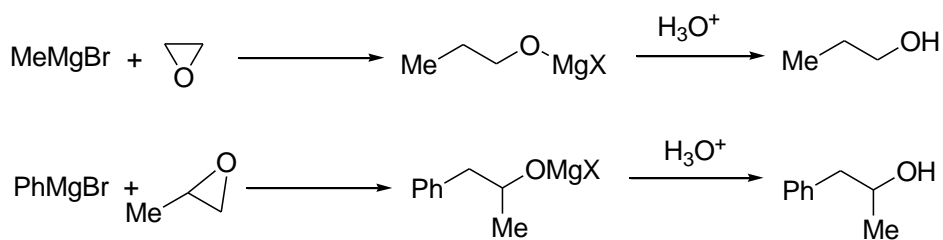
Grignard reactions are prone to undergo side reactions. The reaction of a sterically hindered ketone with a Grignard reagent having a β -H shows a tendency towards reduction of the carbonyl group (Scheme 6).



Scheme 6

3.1.1.2 Reactions with Epoxides

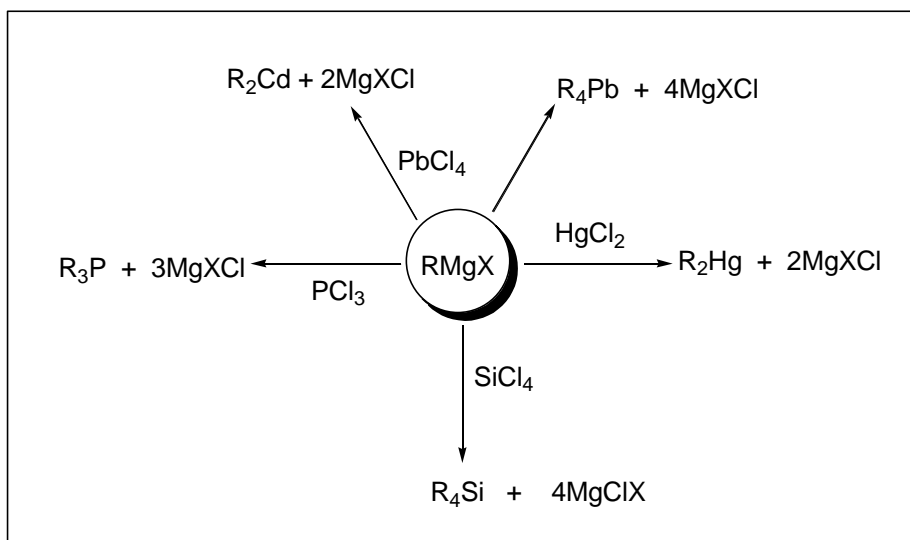
Epoxides react with organomagnesium halides to afford a primary alcohol with the lengthening of the carbon chain by two carbon atoms. However, in this case of substituted epoxides, the attack of the organomagnesium halide takes place from the less substituted ring carbon atom of the epoxides (Scheme 7).



Scheme 7

3.1.1.3 Reactions with some Inorganic Halides

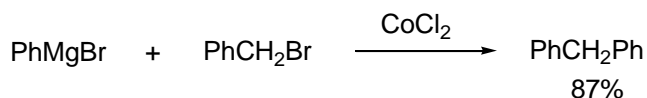
Organomagnesium halides react with inorganic halides to give organometallic compounds (Scheme 8).



Scheme 8

3.1.1.4 Reactions with Alkyl/Alenyl/Aryl Halides

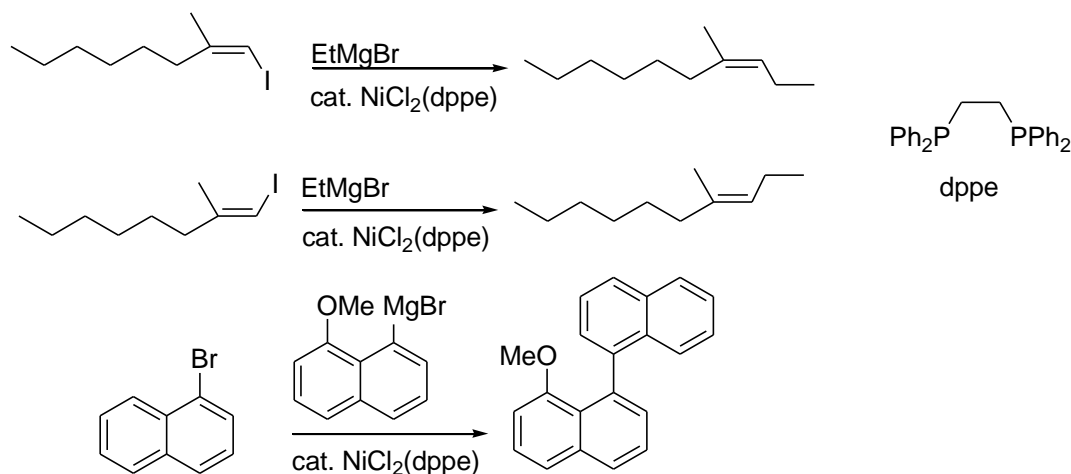
Alkyl, alkenyl as well as aryl triflates, bromides, and iodides can proceed substitution reactions with organomagnesium halides in the presence of transition metal catalysts. For examples, CoCl_2 catalyzes the cross-coupling of phenylmagnesium bromide with benzyl bromide in 87% yield (Scheme 9) (**Kharasch reaction**).



Scheme 9

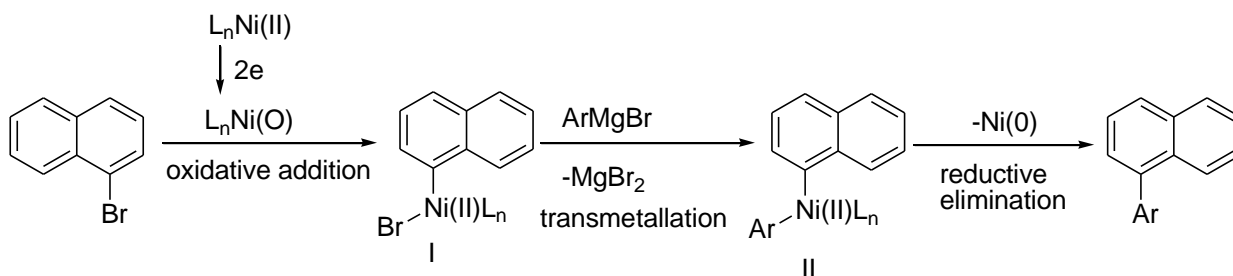
The coupling of alkenyl halides with organomagnesium halides can be successfully carried out in the presence of $\text{NiCl}_2(\text{dppe})$ in high yield. In these reactions the existing configuration of the stereogenic double bond is completely

retained (Scheme 10). These reaction conditions are also compatible for the cross-coupling aryl halides/triflates with arylmagnesium halides.



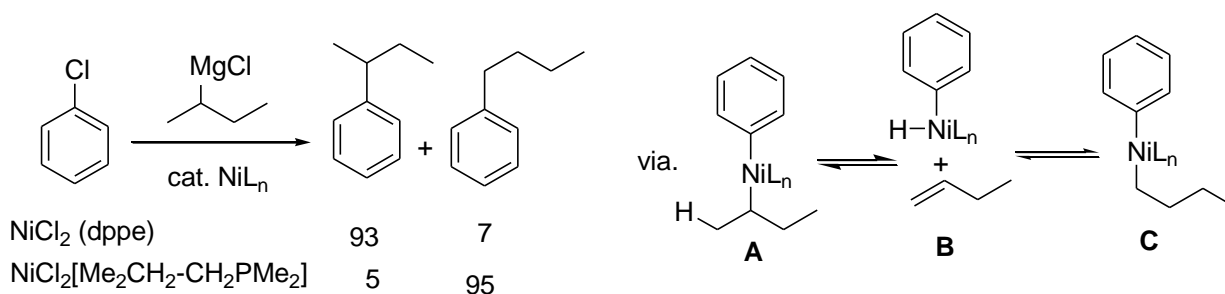
Scheme 10

Mechanism



ArBr can undergo coordination with in situ generated Ni(0) complex that could lead to oxidative addition to give the intermediate I. The latter may undergo reaction with ArMgBr to replace the bromide to give the intermediate II (transmetalation) that could complete the catalytic cycle by reductive elimination of the target biaryl product.

The C-C cross-coupling of secondary alkylmagnesium halide may occur in analogy to the reaction of the primary alkylmagnesium halide (Scheme 10), but they may also lead to the unexpected reactions depending on the catalytic system due to steric hindrance that could lead to isomerization of the C-C coupling (Scheme 11).

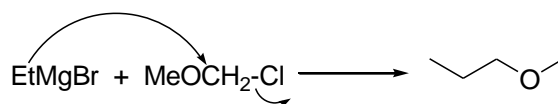


Scheme 11

3.1.1.5 Special Applications

Synthesis of Ethers

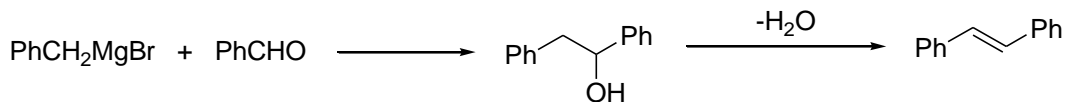
Organomagnesium halides with lower halogenated ethers produce higher ester (Scheme 12).



Scheme 12

Synthesis of Stilbene

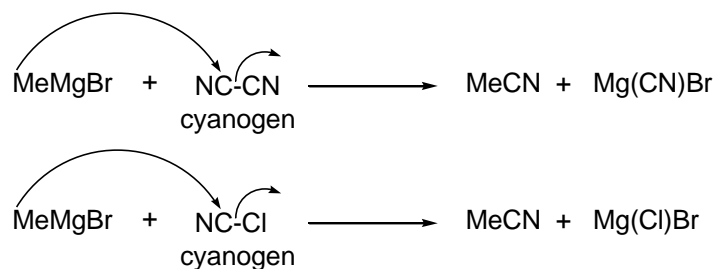
The synthesis of stilbene can be accomplished by the reaction of benzylmagnesium bromide with benzaldehyde, followed by dehydration (Scheme 13).



Scheme 13

Synthesis of Alkyl cyanide

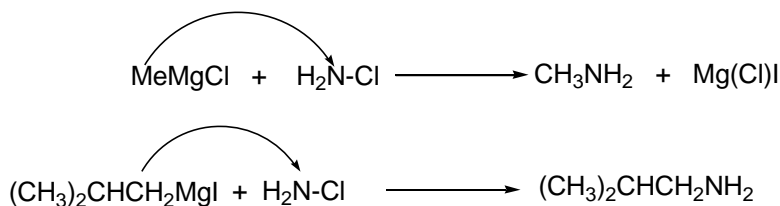
The reaction of alkylmagnesium halides with cyanogens or cyanogens chloride gives alkyl cyanides (Scheme 14).



Scheme 14

Synthesis of Primary Amines

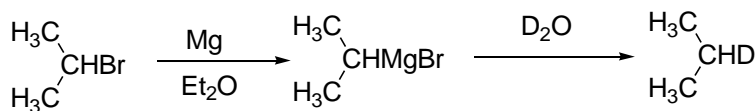
The reaction of chloramines with organomagnesium halides gives primary amines (Scheme 15).



Scheme 15

Synthesis of Deuterated Hydrocarbons

Deuterated hydrocarbons can be synthesized by the reaction of organomagnesium halides with D_2O (Scheme 16).

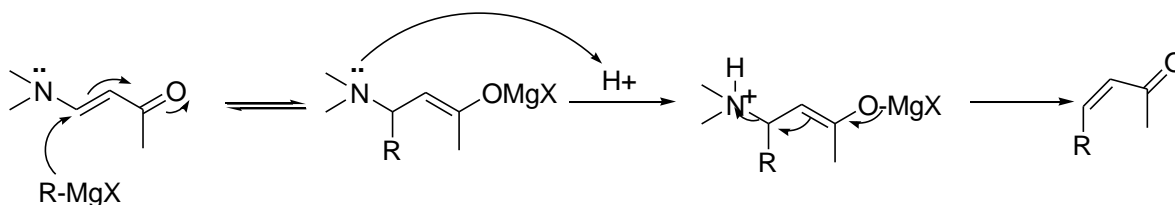


Scheme 16

There are several reactions employing organomagnesium halides that have their own names

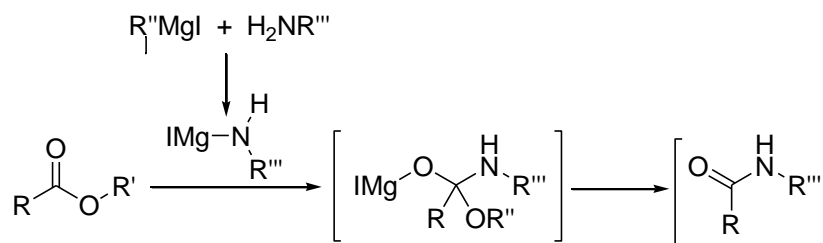
Benary Reaction

It provides an effective method for the synthesis of α,β -unsaturated carbonyl compounds from β -(*N,N*-dialkylamino)-vinyl ketone and Grignard reagent by 1,4-addition followed by hydrolysis and elimination of the dialkylated amine.



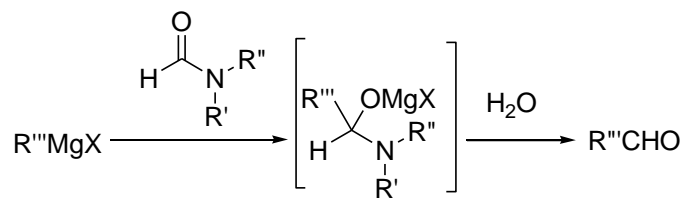
Bodrous Reaction

This reaction provides a method for the preparation of substituted amides from aliphatic or aromatic esters and an aminomagnesium halide which can be obtained from a primary or secondary amine and Grignard reagent at room temperature.



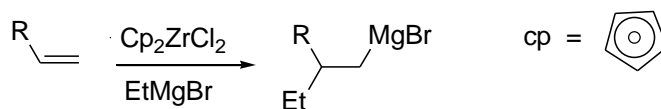
Bouveault Reaction

Primary alkyl halide can be converted into aldehydes with an additional carbon via the formation of Grignard reagent followed by reaction with *N,N*-disubstituted formamide and hydrolysis.



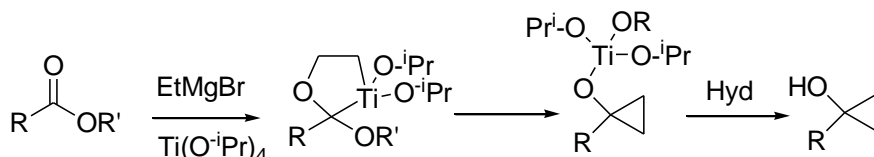
Dzheimilev Reaction

It involves the reaction of alkenes with Grignard reagent to give alkyl magnesium halide in the presence of Cp_2ZrCl_2 . This method had found wide application in organic and organometallic synthesis.



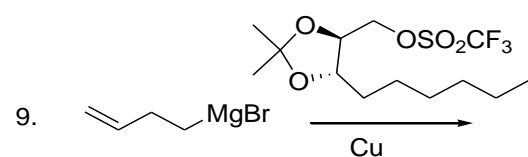
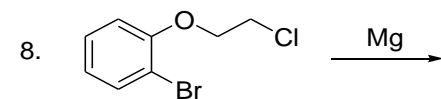
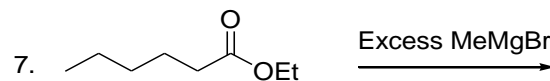
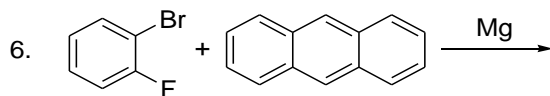
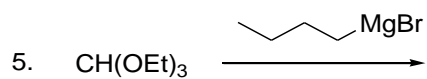
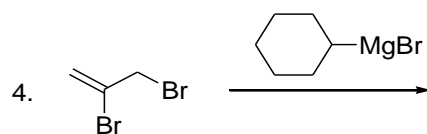
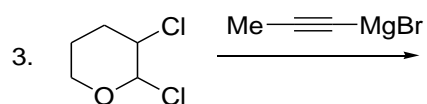
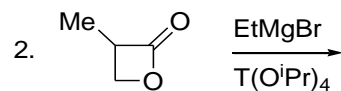
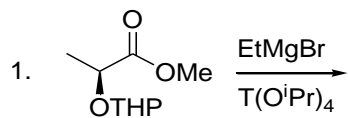
Kulinkovich Reaction

The reaction of esters with dialkyldialkoxytitanium reagents, generated *in situ* from Grignard reagents bearing hydrogen in β -position and titanium(IV) alkoxides such as titanium isopropoxide, gives cyclopropanols.



Problems:

Provide major products for the following reactions.



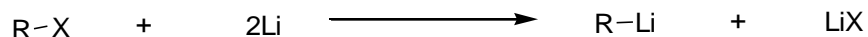
Text Book

M. B. Smith, *Organic Synthesis*, 2nd Ed., McGraw Hill, Singapore, 2004.

Lecture 21**3.1.2 Organolithium Reagents**

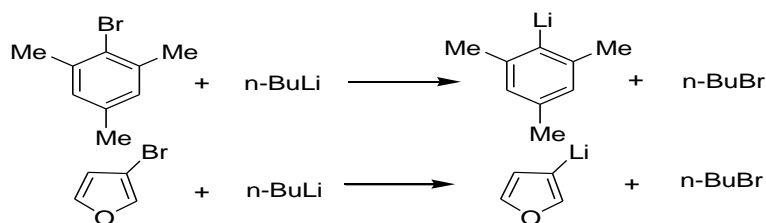
The organolithium reagents, characterized by a C-Li bond, are important in organic synthesis as organomagnesium halides. Lithium is less electronegative than carbon, and the C-Li bond is polarized as in organomagnesium halide. The organolithium reagents are more reactive than organomagnesium halides and are expected to behave both as a nucleophile and a base.

The reaction of lithium metal at low temperature with an alkyl halide in a hydrocarbon solvent gives alkyl lithium. The reaction proceeds smoothly in the presence of above 0.02% of sodium and the reactivity of the alkyl halides is $\text{RI} > \text{RBr} > \text{RCI}$.



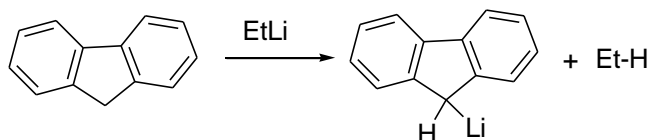
Scheme 1

Another route to the preparation of the organolithium compounds is the use of metal halogen exchange reactions. This method is useful for the preparation of organolithium reagents that cannot be obtained from alkyl halide and metal directly. In this method organic halide is treated with alkyl lithium. This process is best suited for the preparation of aryl lithium derivatives (Scheme 2).



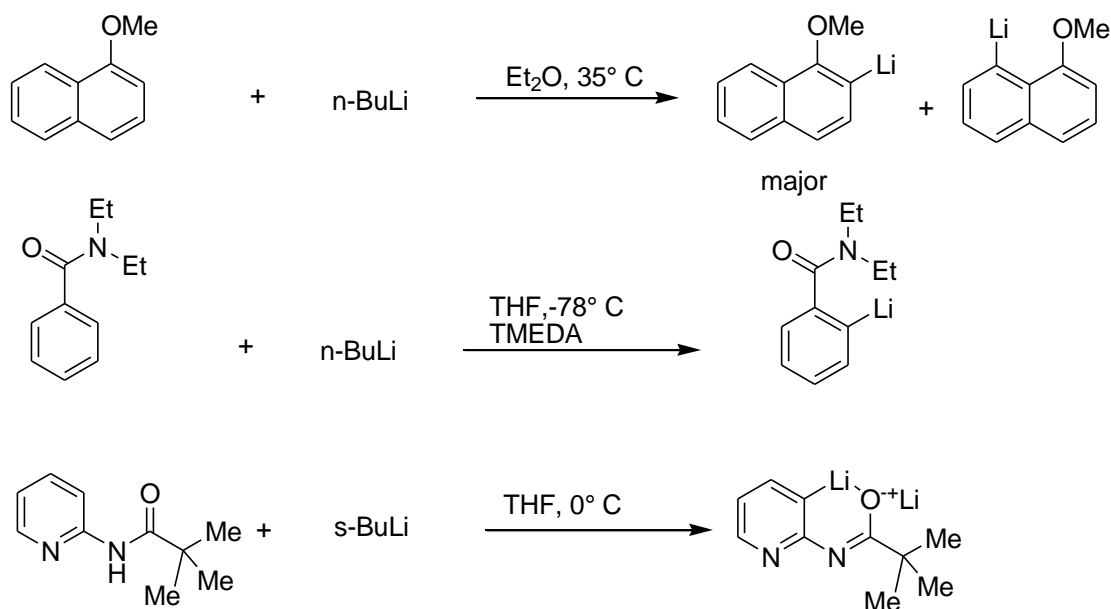
Scheme 2

In addition, compounds containing acidic hydrogen can be easily converted into organolithium compound by treatment with a suitable organolithium compound (Scheme 3).



Scheme 3

The replacement of a hydrogen by a lithium (known as lithiation) can also be used to generate organolithium species. This reaction is essentially an acid base reaction. However, in the case, where there is activation by a coordinating group, the reaction occurs with considerable ease. This type of activation is particularly helpful in introducing an *ortho* substituent to a preexisting coordinating group (Scheme 4).

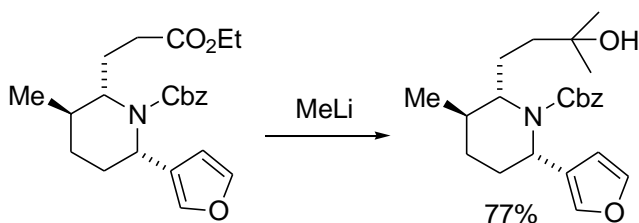


Scheme 4

The *ortho*-directing groups are usually arranged in the following order in order of their reactivity: $\text{SO}_2\text{NR}_2 > \text{SO}_2\text{Ar} > \text{CONR}_2 > \text{oxazoliny} > \text{CONHR} > \text{CSNHR}$, $\text{CH}_2\text{NR}_2 > \text{OR} > \text{NHAr} > \text{SR} > \text{CR}_2\text{O}^-$.

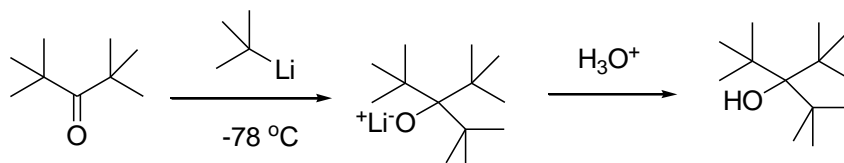
3.1.2.1 Reactions with Carbonyl Compounds

Organolithium reacts with aldehydes, ketones and esters to give alcohols as organomagnesium halides (Scheme 5).



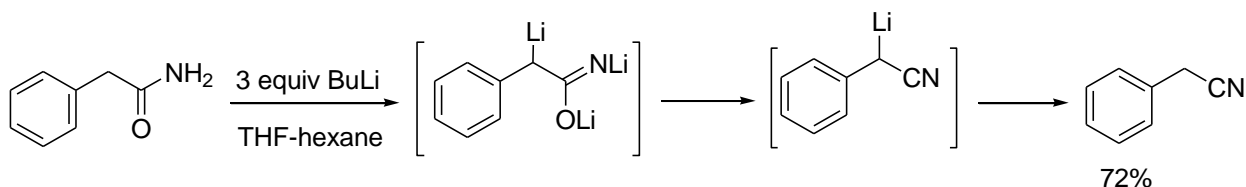
Scheme 5

In comparison to organomagnesium halides, organolithiums are less susceptible to steric factors and react with hindered ketones to give tertiary alcohols (Scheme 6).



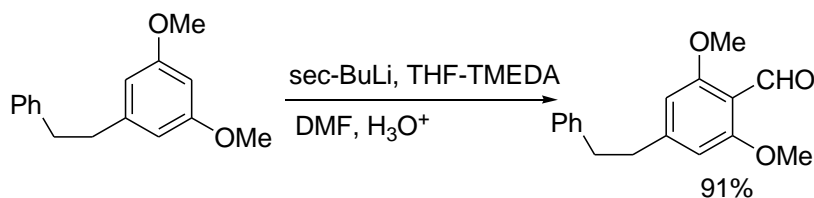
Scheme 6

Primary amides undergo reaction with excess organolithium to give a nitrile. For an example, phenylacetamide reacts with 3 equiv of butyllithium to give trillithiated species, which undergoes fragmentation to give intermediate that could be hydrolyzed to afford benzonitrile (Scheme 7).



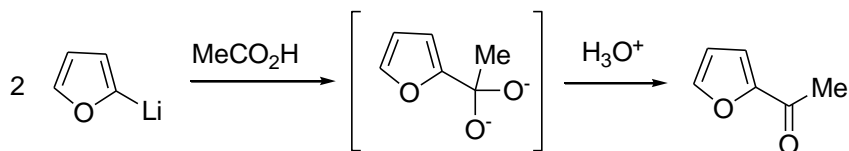
Scheme 7

Another useful reaction with amides is the reaction of organolithium reagents with DMF to give aldehydes (Scheme 8).



Scheme 8

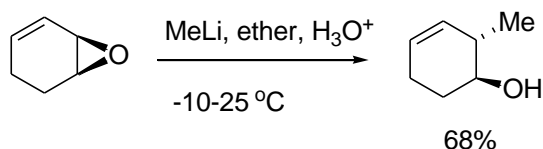
Reaction of carboxylic acid with organolithium reagent gives the expected carboxylate salt, but a second equiv can add to the lithium carboxylate to afford a ketone (Scheme 9).



Scheme 9

3.1.2.2 Reactions with Epoxides

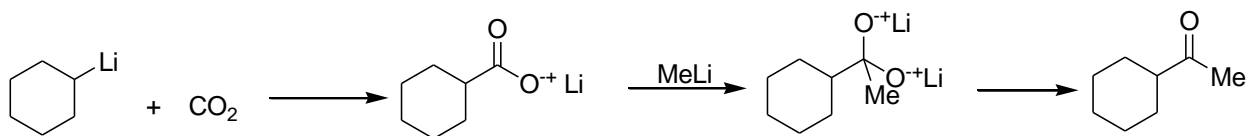
Epoxides react with organolithium reagents to give primary alcohols (as in the case of Grignard reagents) (Scheme 10). In general, the organolithium attacks the epoxides at the less sterically hindered carbon, as with any nucleophile.



Scheme 10

3.1.2.3 Reactions with Carbon Dioxide

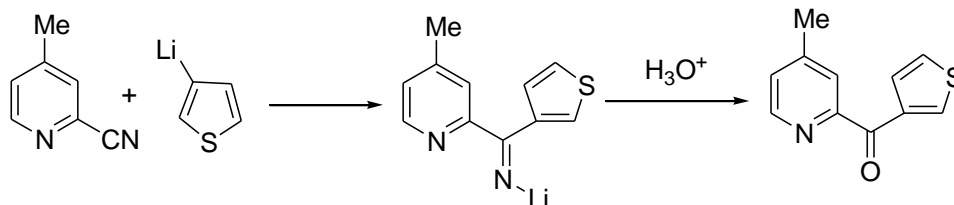
A major difference between the reactivity of organomagnesium halide and organolithium reagent is observed in their reactivity towards CO_2 . The reaction of organomagnesium halide with CO_2 stops at the carboxylate stage, while in case of organolithium reagents, the carboxylate ion formed reacts with another equiv of organolithium to generate a ketone (Scheme 11).



Scheme 11

3.1.2.4 Reactions with Aryl Cyanides

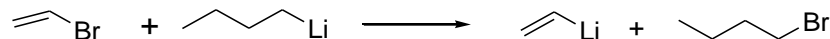
As in the case of organomagnesium halides, the reactions of organolithium reagents with aryl cyanides give imine salts, which undergo hydrolysis in the presence of water to give ketones (Scheme 12).



Scheme 12

3.1.2.5 Electrophilic Displacement

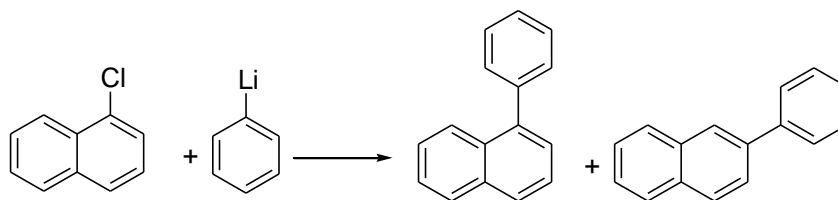
Reaction of an organic halide with an organometallic compound is known as metal-halogen exchange reaction is example for electrophilic displacement. This reaction is useful for the synthesis of vinyl- and phenyl lithium (Scheme 13).



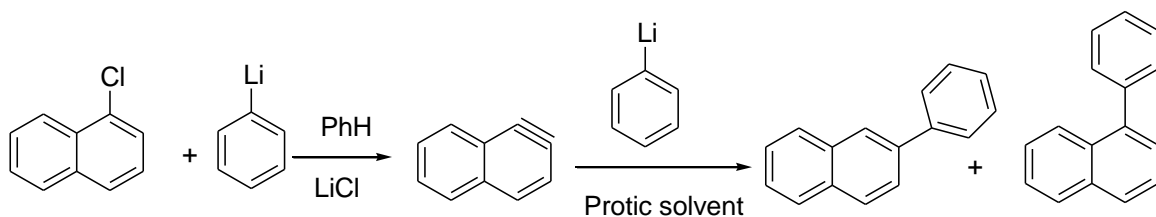
Scheme 13

3.1.2.6 Nucleophilic Displacement

Reactions of alkyl and aryl halides can be reacted with alkyl and aryl lithium reagents to give hydrocarbons. The reaction of alkyl halides with alkyl lithium takes place by $\text{S}_{\text{N}}2$ mechanism. While aryl halides react with aryl lithium via addition-elimination process (Scheme 14).



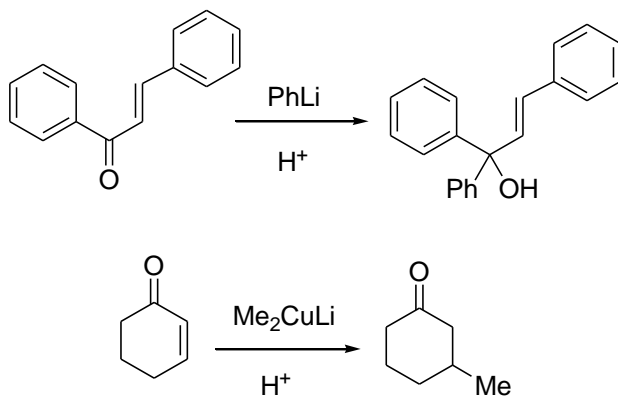
Mechanism



Scheme 14

3.1.2.7 Reactions with α,β -Unsaturated Carbonyl Compounds

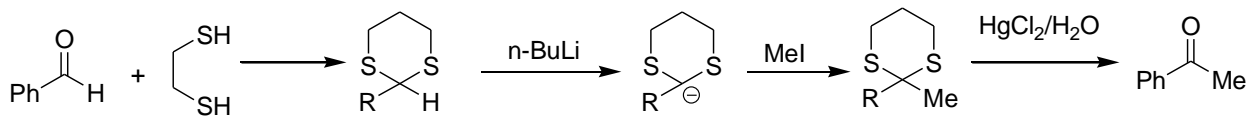
In the case of Grignard reagents, α,β -unsaturated carbonyl compounds undergo reaction either at 1,2- or 1,4-addition depending on the structure of the carbonyl compound. The main reason is steric hinderance. While the organolithium reagents undergo reaction exclusively to give 1,2-addition products (Scheme 15). Exclusive formation of 1,4-addition product, however, can be achieved using lithium dialkylcuprates.



Scheme 15

3.1.2.8 Deprotonation

The basic nature of organolithiums can also be put to good use in achieving umpolung at the carbonyl centre of an aldehyde. In this protocol a C=O function is first protected by 1,3-dithiane and then the proton is removed by an organolithium (Scheme 17).

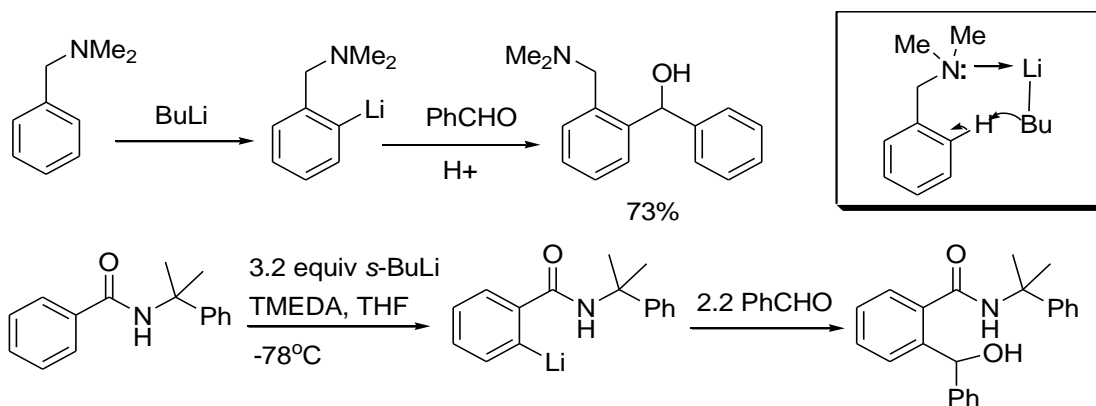


Scheme 16

The stereochemical outcome of the nucleophilic addition of organolithiums is similar to that of Grignard reaction. It can be predicted on the basis of Cram's rule.

3.1.2.9 Ortholithiation

The ortholithiation is useful reaction because the starting material does not need to have a halogen atom. For examples, in the case of benzyldimethylamine, the nitrogen atom directs attack of the butyllithium (Scheme 18). Likewise, *N*-cumylbenzamide with excess secondary butyllithium in the presence of TMEDA gives ortholithiated intermediate that could readily reacted with benzaldehyde with 80% yield.

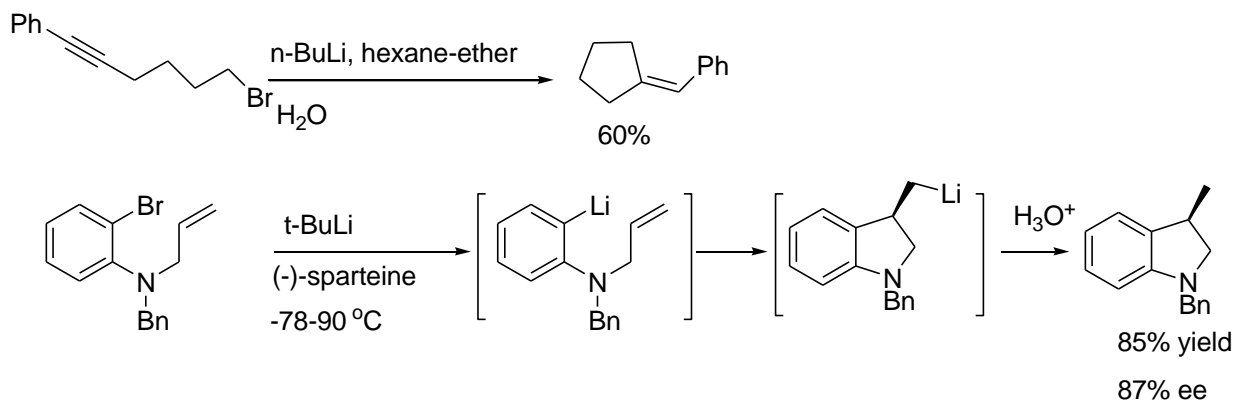


Scheme 17

3.1.2.10 Reactions with Alkenes and Alkynes

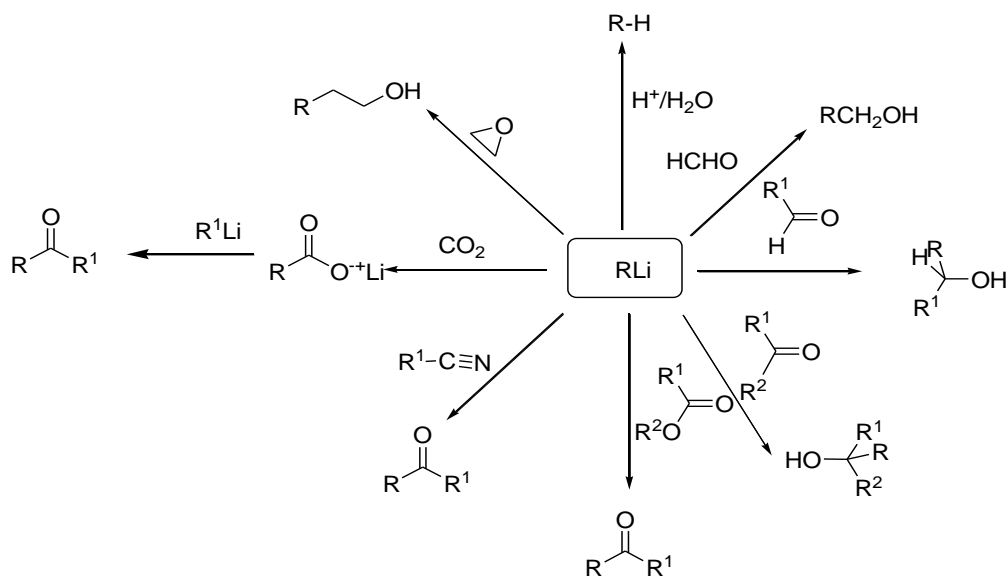
The organolithium reagents undergo addition with alkenes or alkynes in an intramolecular reaction. For examples, 1-(6-bromohex-1-ynyl)benzene in the presence of butyllithium gives alkylidene cyclopentane in 60% yield. The mechanism of the reaction is not well understood. While, *N*-allyl-*N*-benzyl-2-

bromobenzamine reacts with tertiary butyllithium in the presence of (-)-sparteine to afford 1-benzyl-3-methylindoline in 87% ee (Scheme 19).



Scheme 19

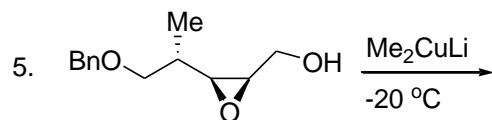
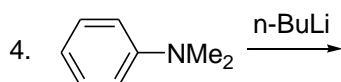
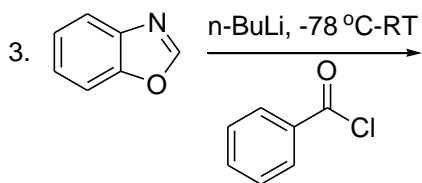
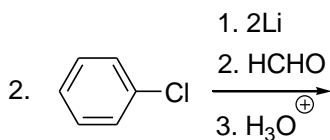
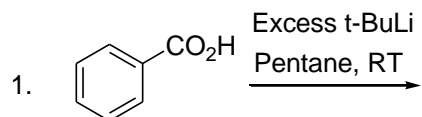
Summary of the Reactions of Organolithium Reagents



Scheme 19

Problems

Complete the following Reactions.



Text Book

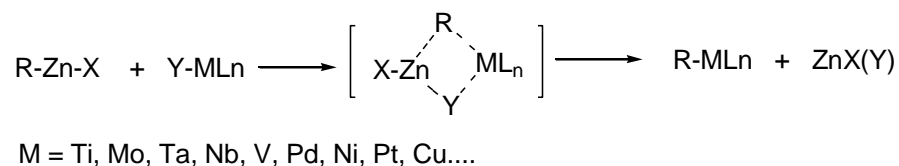
J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, 2001.

Lecture 22

3.2 Organozinc Reagents

Cyclopropanation

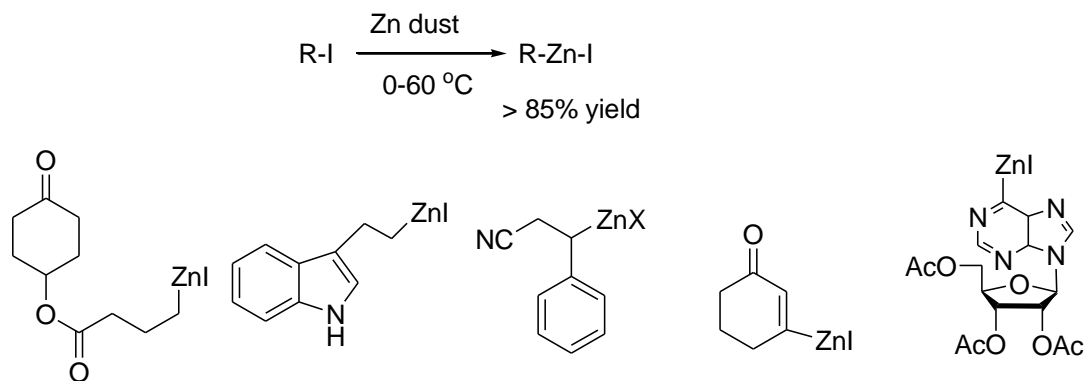
Organozinc reagents were the first organometallic compounds prepared in the laboratory. They are non-polar and soluble in organic solvents. Organozinc reagents are less reactive than the Grignard reagents. For example, organozinc reagents don't react with carbon dioxide and react slowly with ketones, esters and cyanides. However, organozinc reagents smoothly undergo transmetallation with a variety of transition metal salts or complexes leading to new transition metal complexes, thus allowing new reaction pathways not available to the main group metal zinc (Scheme 1).



Scheme 1

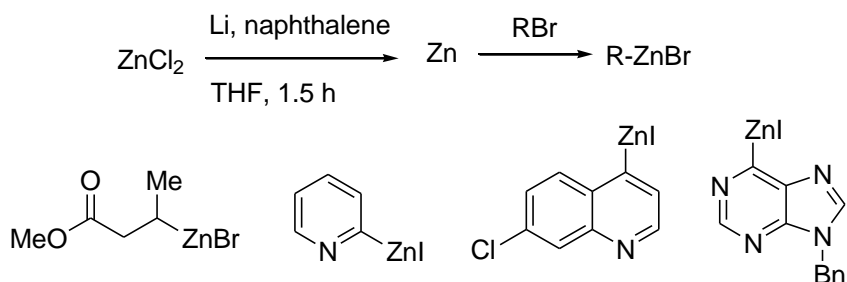
3.2.1 Preparation

Reaction of alkyl iodides with zinc dust gives organozinc halides. This method allows the preparation of organozinc iodides bearing almost all organic functionalities (Scheme 2). The zinc dust is treated with a few mol% of 1,2-dibromoethane and TMSI prior to the halide addition.



Scheme 2

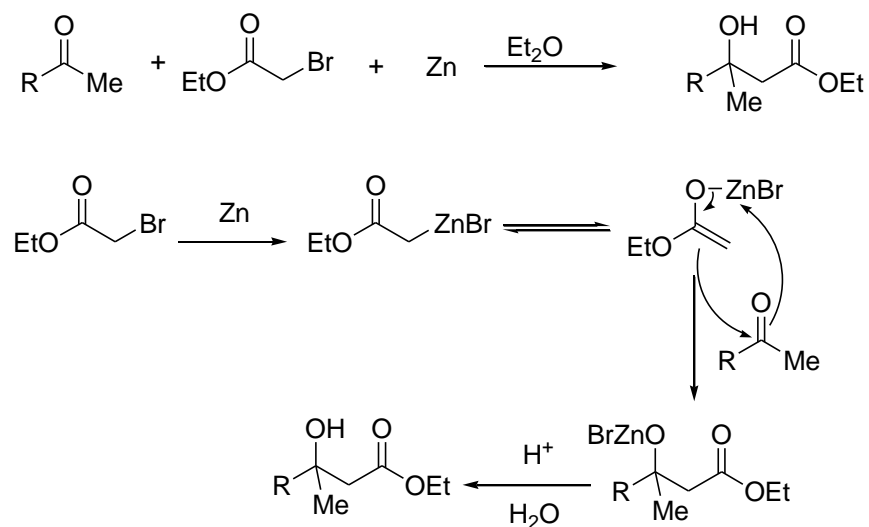
Alternatively, more activated zinc can be prepared by the reduction of ZnCl_2 that react even less reactive aryl iodides or bromides (Scheme 3). Using this procedure many heteroarylzinc reagents can be prepared.



Scheme 3

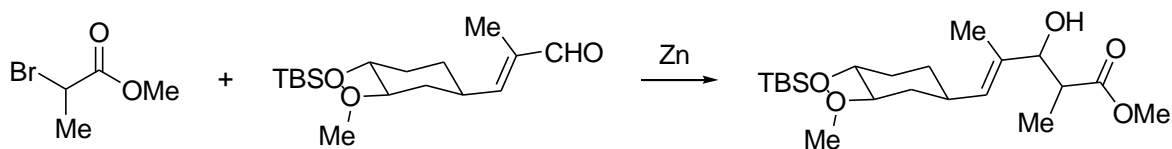
3.2.1 Nucleophilic Addition by Organozinc Reagents

Reformatsky reaction is one of the most important applications of organozinc reagent formed *in situ*. In this reaction zinc, α -haloester and a carbonyl compound react to give β -hydroxyester. The reaction involves the formation of a zinc enolate which attacks the carbonyl group (Scheme 4). As the zinc enolate is only weakly basic so the reaction works even in the presence of highly enolisable carbonyl partner. Sterically hindered ketones do not pose a problem for this reaction.



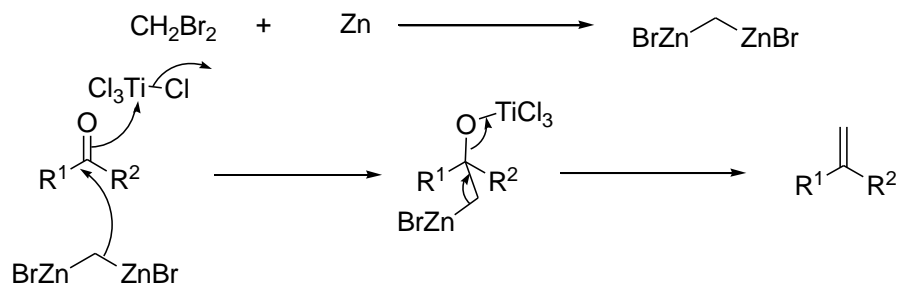
Scheme 4

In case of α,β -unsaturated carbonyl compound the addition takes place regioselectively in a 1,2 fashion (Scheme 5).



Scheme 5

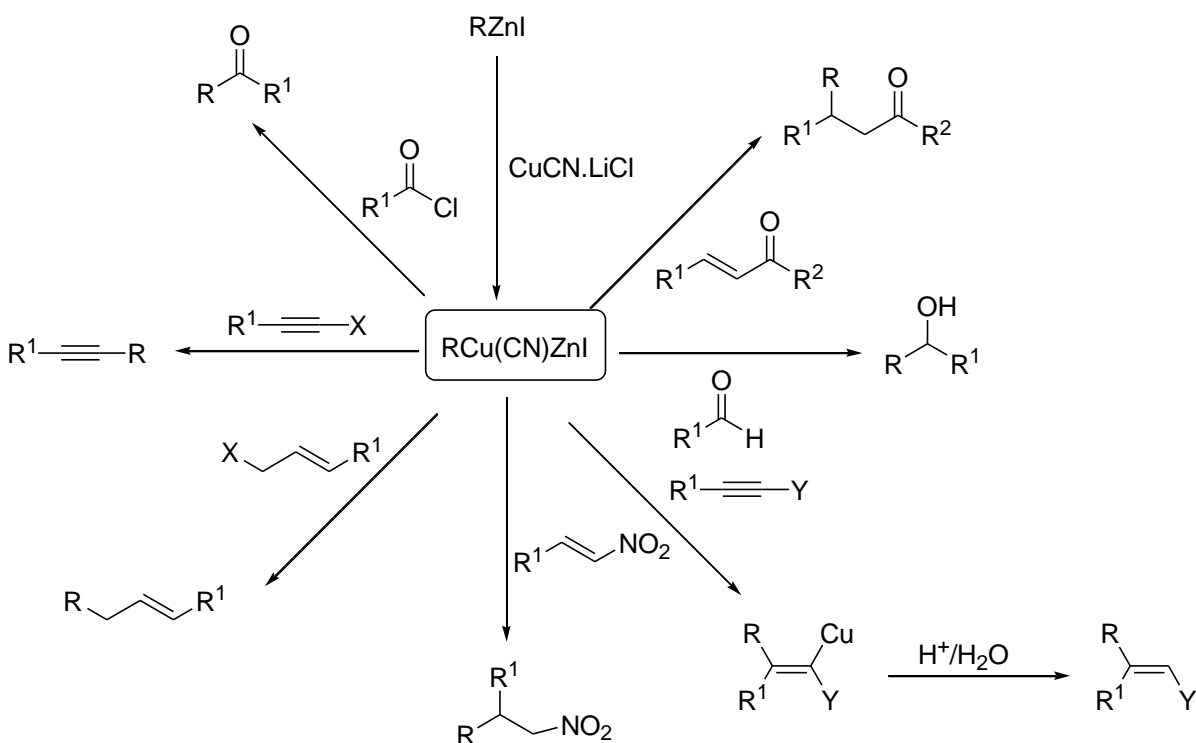
The combination of $Zn/CH_2Br_2/TiCl_4$ is known as **Lombardo reagent** which can convert ketones to methylene group. The reaction is believed to proceed through a dimetalated intermediate which adds to the ketone (Scheme 6).



Scheme 6

N. A. Petasis, J. P. Staszewski, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **3**, 1565.

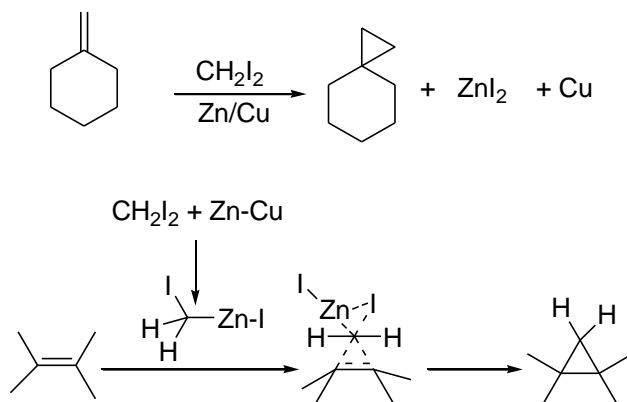
Organozinc reagents readily undergo transmetalation thereby making them suitable candidates to be used in conjunction with transition metal salts. Thus, RZnI reacts with THF soluble salt $\text{CuCN}\cdot\text{LiCl}$ to form new copper-zinc reagents which are usually formulated as RCu(CN)ZnI . The reactivity of this reagent is shown in Scheme 7.



Scheme 7

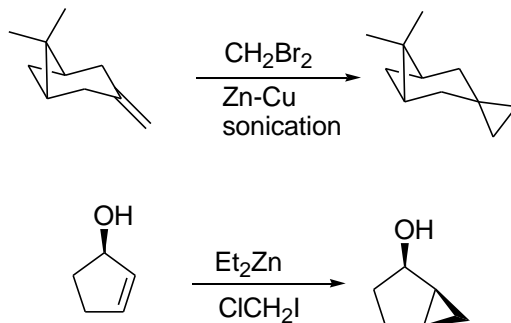
3.2.2 Cyclopropanation by Organozinc Reagents

Alkenes may be conveniently converted to cyclopropanes by treatment with methylene iodide and Zn/Cu couple. This reaction is known as Simmons-Smith cyclopropanation. The reactive species is iodomethylzinc iodide (Scheme 8).



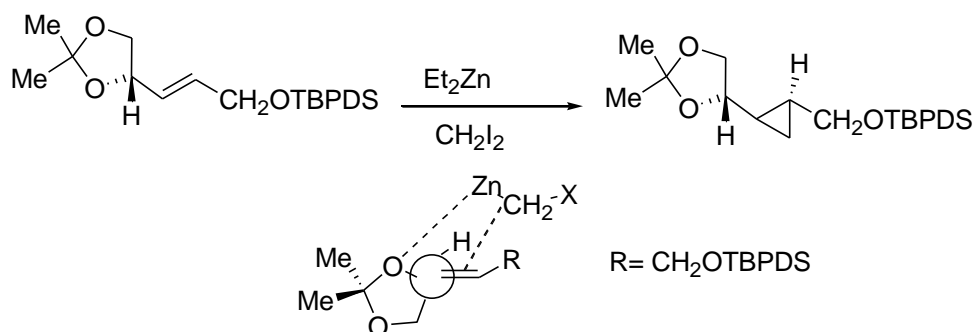
Scheme 8

Several modifications are available to allow the use of less reactive methylene group donors like chloriodomethane. Such methods employ the use of Lewis acids like TiCl_4 or organic reagents like acetyl chloride or trimethylsilyl chloride (Scheme 9). This reaction is also sensitive to the purity of zinc. Thus electrochemically prepared zinc is more effective than metallurgically prepared zinc.



Scheme 9

Simmons Smith reaction is highly stereospecific reaction as it does not involve a carbene intermediate ($:\text{CH}_2$). In case additional directing groups, the reaction exhibits considerable stereoselectivity. In Scheme 10, the stereoselectivity of the reaction is explained by the coordination of zinc to allylic oxygen in the transition state.



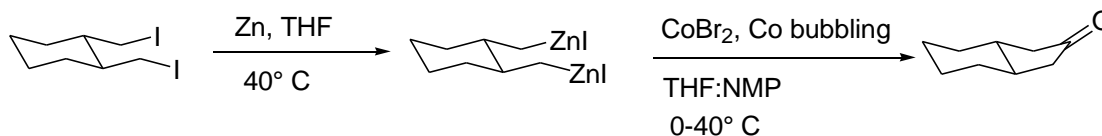
Scheme 10

Other reagents have been developed having aryloxy or acetoxy anions. These reagents are effective for cyclopropanation of unactivated alkenes. They are prepared by the reaction of diethyl zinc with a suitable oxyanion precursor such as trifluoroacetic acid followed by reaction with methylene iodide to generate reagents having formula ROZnCH₂I. The reactivity of the oxyanions are in the order CF₃COO⁻ > ArO⁻ > RO⁻.

3.3.3 Transition Metal Mediated Addition of Organozinc Reagents

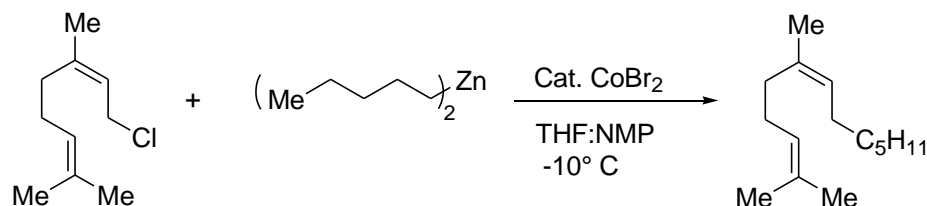
As mentioned earlier, organozinc reagents can be used in conjunction with various transition metal salts which may be added in either stoichiometric amount or catalytic amount. This transmetallation reaction has been already discussed in the previous section for copper salts. In this section we will see the effect of Pd, Ni, Fe and Co salts on the addition of organozinc reagents.

One of the most useful reactions using Co is the carbonylation reaction. Organozinc reagents when treated CoBr₂ generate organocobalt reagents which are stable for several hours at low temperature. Carbonylation is now possible by simply bubbling CO through such a solution (Scheme 11).



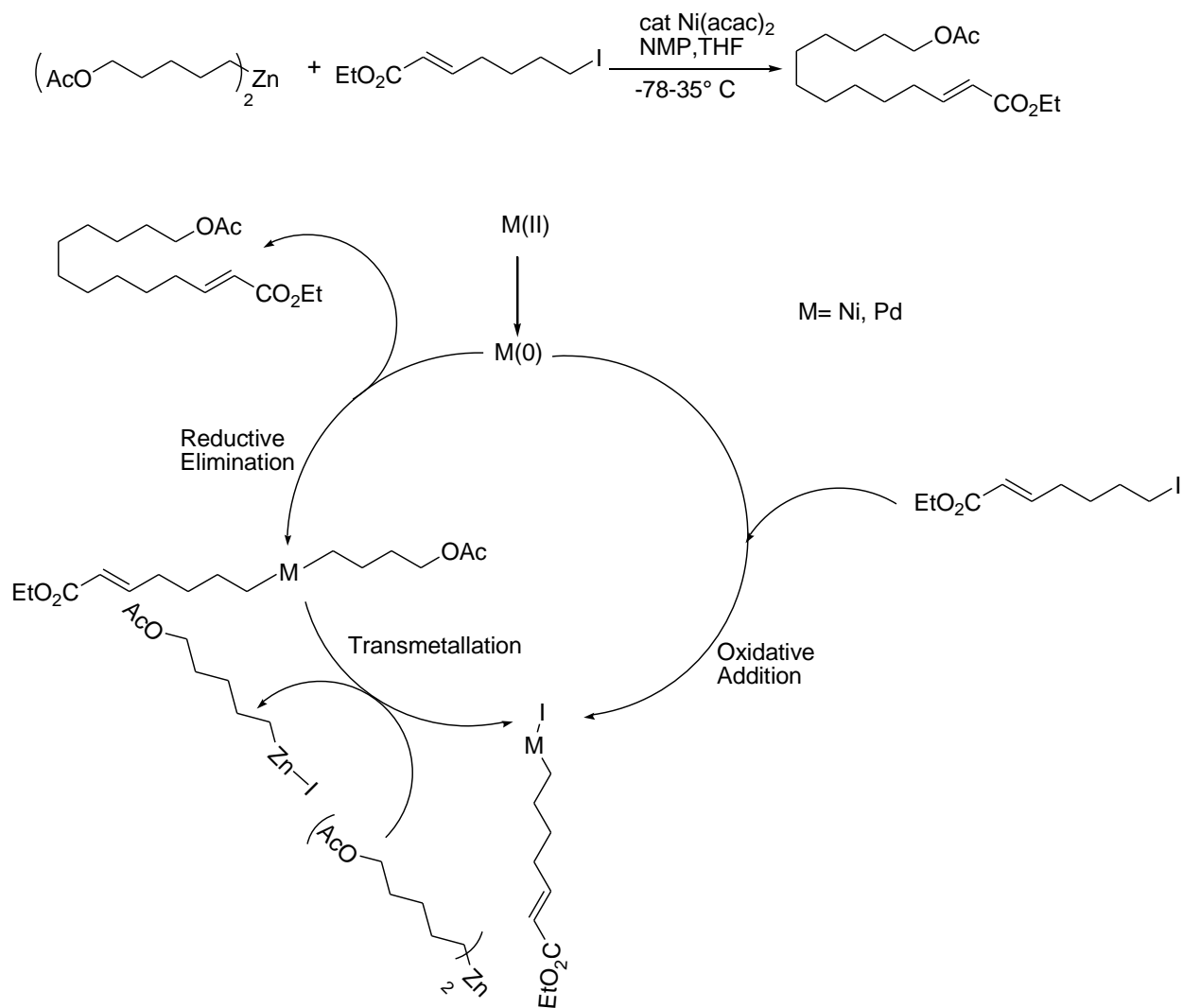
Scheme 11

Addition of cobalt salts in catalytic amount is known for acylation and allylation reaction of diorganozincs. The reaction occurs in a S_N^2 fashion thereby leading to a complete retention of double bond geometry (Scheme 12).

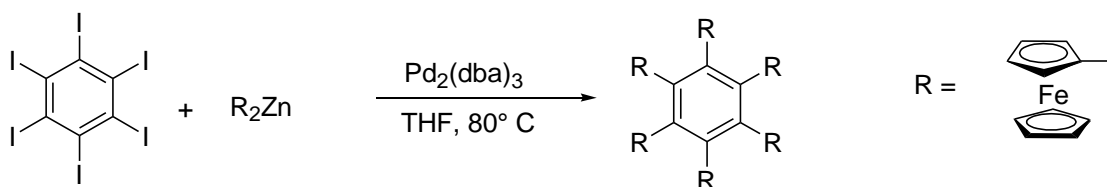


Scheme 12

The reaction between organozinc compound and an organic halide in the presence of $\text{Pd}(0)$ or $\text{Ni}(0)$ species is known as Negishi cross-coupling reaction which is one of the most widely used cross-coupling reactions. The mechanism of this reaction involves oxidative addition followed by transmetalation with the zinc compound and subsequent reductive elimination (Scheme 13). This reaction can be applied to highly substituted substrates. An interesting example of application of Negishi coupling is the synthesis of hexaferrocenyl benzene (Scheme 14).



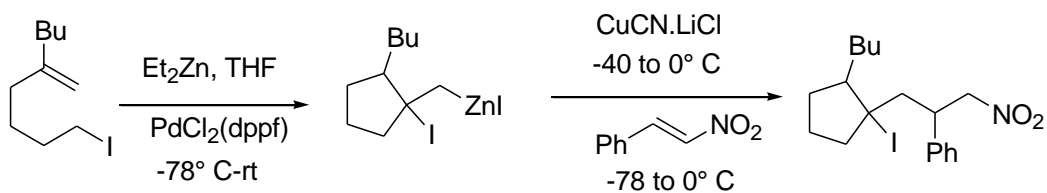
Scheme 13



Scheme 14

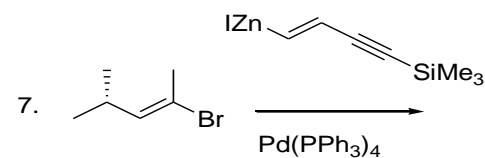
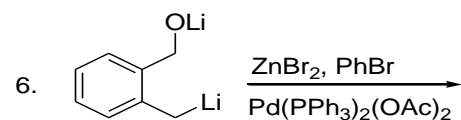
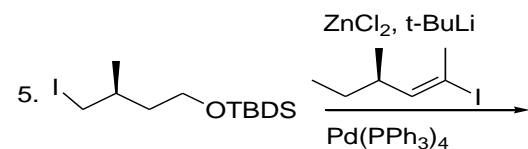
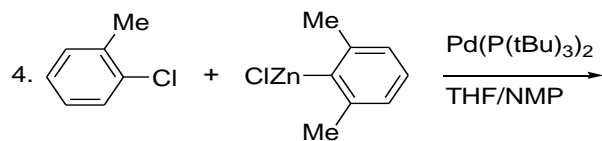
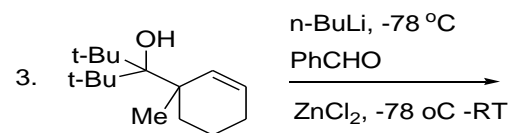
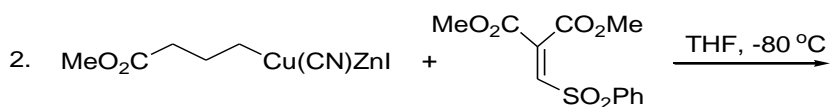
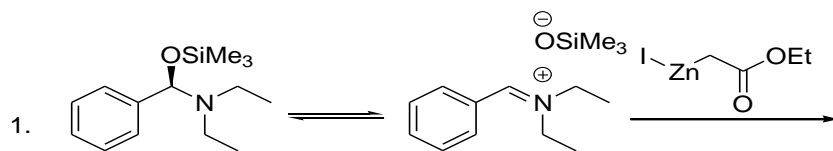
Besides Negishi cross-coupling, Ni and Pd salts are also known to catalyze the cyclization reactions of organozincs *via* a radical pathway. In these cases, an intermediate Ni(0) or Pd(0) is formed which initiates a radical chain providing a

new zinc derivative which can further undergo reaction with other electrophiles (Scheme 15).



Problems

What products would you expect in the following reactions.

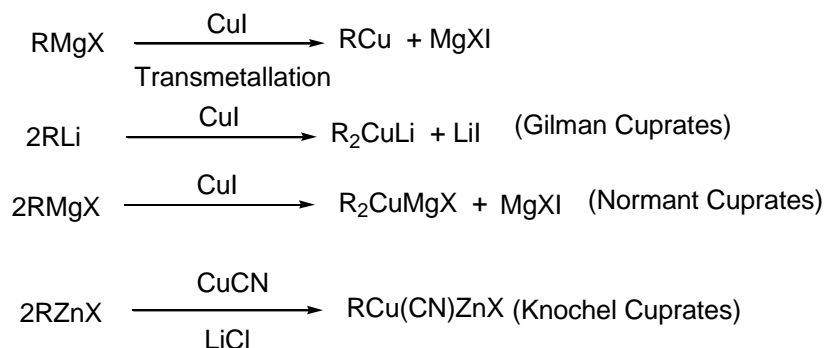
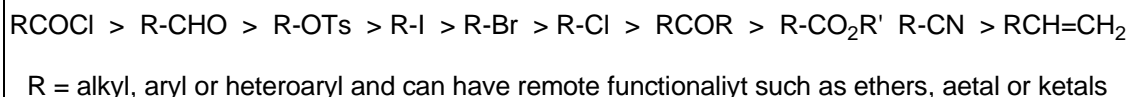


Text Book

J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, 2001.

Lecture 23**3.3 Organocopper Reagents**

Organocopper reagents are prepared by transmetallating the organomagnesium, organolithium or organozinc reagent with copper(I) salts (Scheme 1). There are two major reactions with organocuprates: (1) reaction with alkyl halides and (2) conjugate addition with α,β -unsaturated carbonyl compounds. The substitution reactions are promoted by the use of THF or ether-HMPA solvent, while the conjugate addition is facile when ether is employed as a solvent. The general reactivity of organocuprates with electrophiles follows the order:

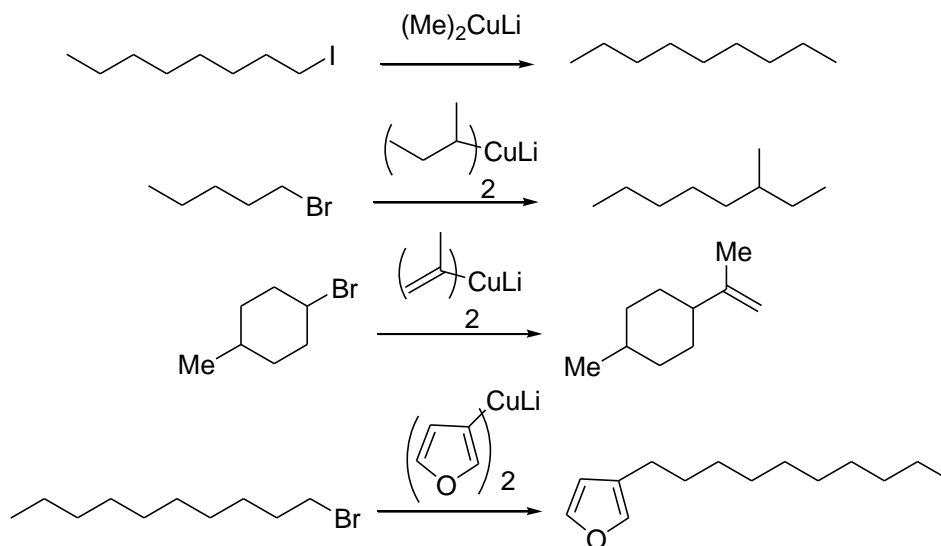


Scheme 1

3.3.1 Reactions with Dialkylcuprates (Gilman Reagent)

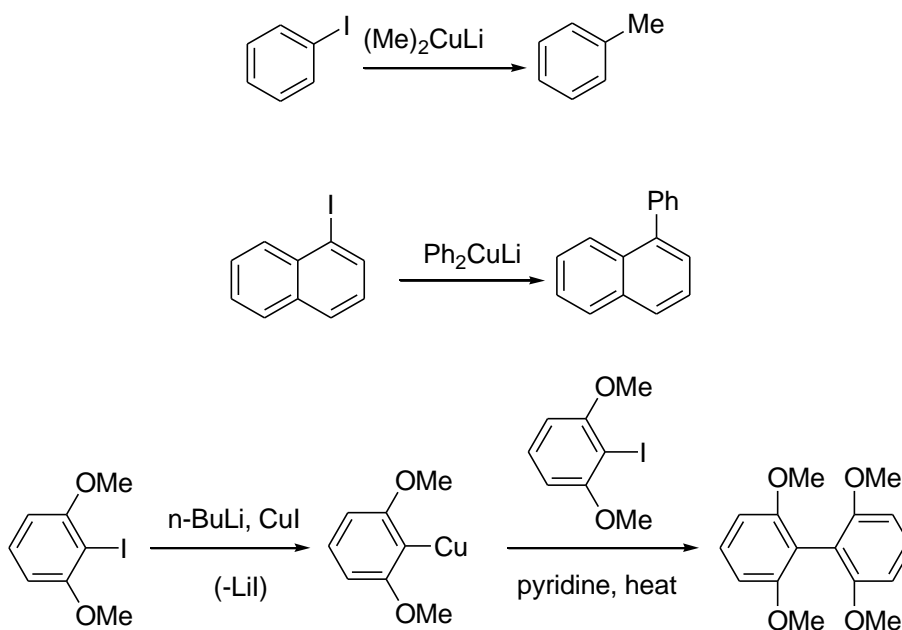
3.3.1.1 Coupling Reactions

Organocuprates can replace halide ion from primary and secondary alkyl halides to give cross-coupled products (Scheme 2). This method provides effective route for the construction C-C bond between two different alkyl halides, which is not possible by the well known Wurtz coupling reaction, in which a number of products are formed.



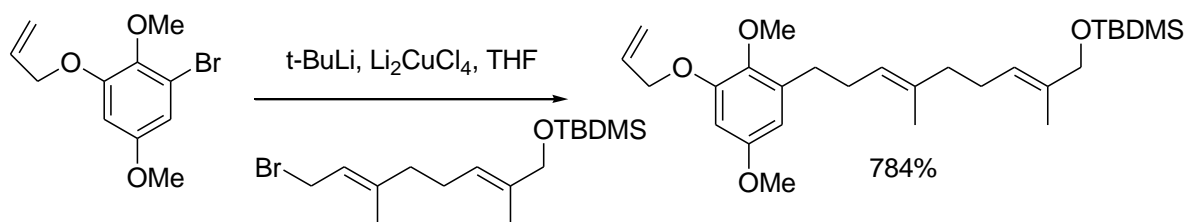
Scheme 2

Similar results are obtained from the reactions of aryl halides and organocuprates (Scheme 4).

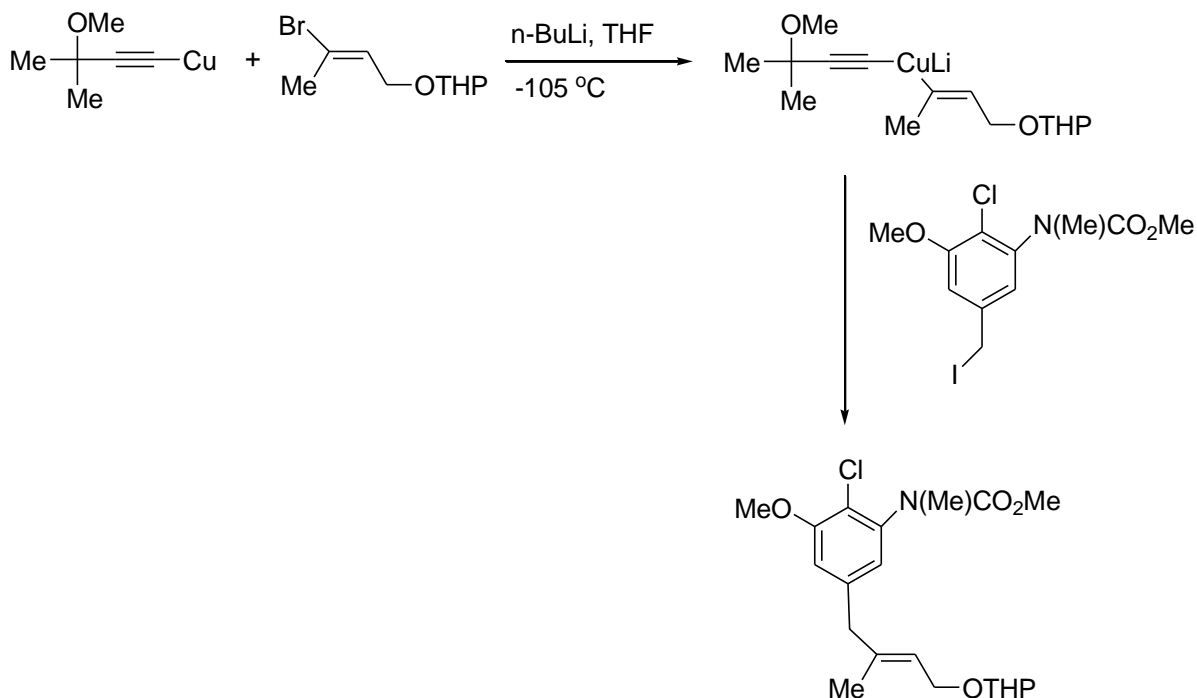


Scheme 4

Examples:



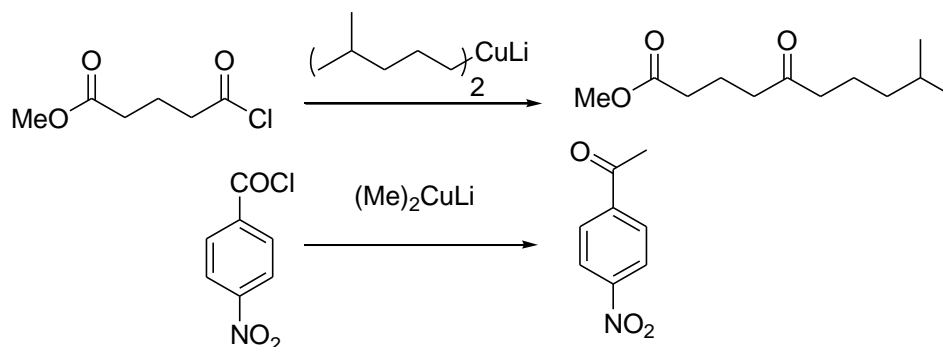
M. Bogenstatter, A. Lmberg, L. E. Overman, A. L. Tomasi, *J. Am. Chem. Soc.* **1999**, 121, 12206.

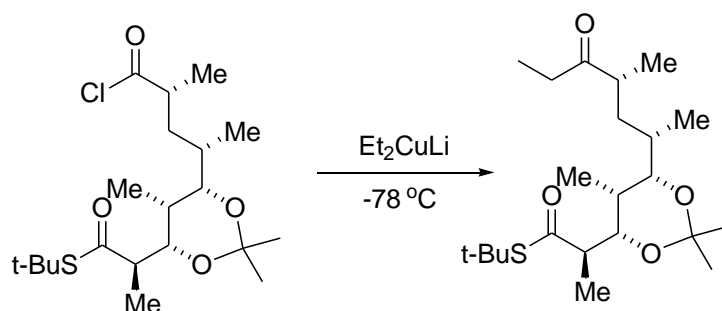


E. J. Corey, H. F. Wetter, A. P. Kozikowski, A. V. R. Rao, *Tetrahedron Lett.* **1977**, 777.

3.3.1.2 Reactions with Acid Chlorides

The reaction of a dialkyl cuprate and acid chloride is a preferred method to synthesize ketones (Scheme 5). Unlike in the case of Grignard reagents, the ketones formed do not react with organocopper reagent.



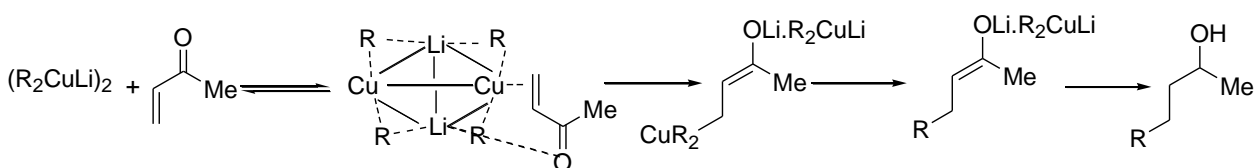


Scheme 5

3.3.1.3 Conjugate Addition

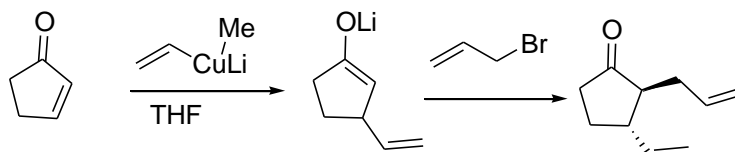
Conjugate addition is among the basic carbon-carbon bond forming reactions. Traditionally, organocopper reagents were choice to undergo this synthetic transformation. The organocopper reagents are softer than Grignard reagents (because copper is less electropositive than magnesium), and add in conjugate fashion to the softer C=C double bond.

The mechanism of the transfer of the alkyl group from the organocuprates to the β -position of the carbonyl compounds is uncertain. It is believed that initially a d- π^* complex between the organocopper(I) species and the enone is formed followed by the formation of a Cu(III) intermediate which may undergo reductive elimination to form the product (Scheme 6).



Scheme 6

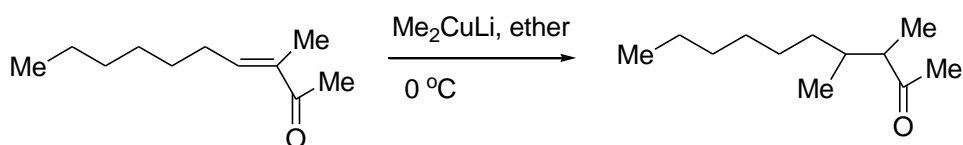
In the case of enones, consecutive addition of the organocopper reagent and alkyl halides, two different alkyl groups can be introduced in one operation (Scheme 7).



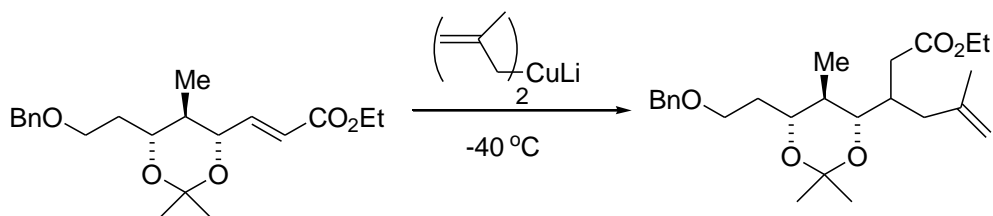
Scheme 7

In case of conjugated esters, greater reactivity observed when $\text{RCu}\cdot\text{BF}_3$ is as the organocopper reagent.

Examples:



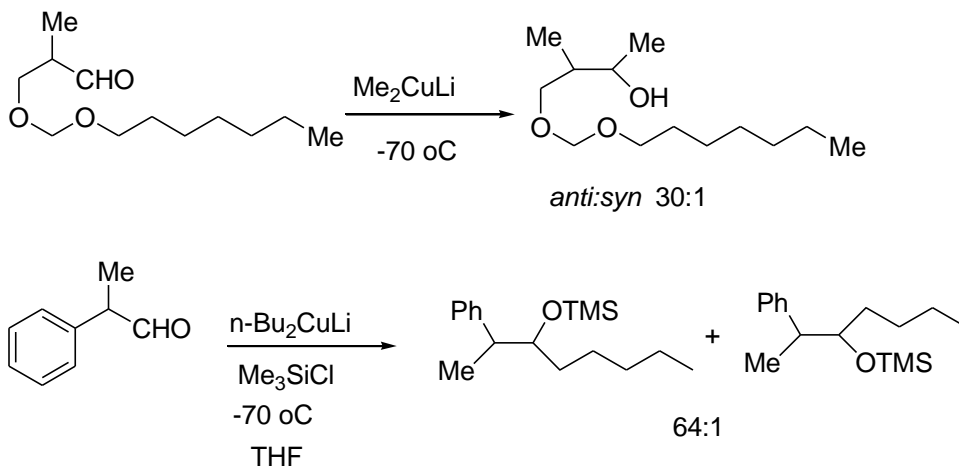
G. H. Posner, *Organic. React.* **1972**,19.



K. C. Nicolaou, M. R. Pavia, S. P. Seitz, *J. Am. Chem. Soc.* **1982**, 104, 2027.

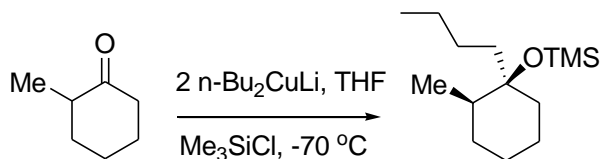
3.3.1.4 Reactions with Aldehydes and Ketones

Organocuprates react with aldehydes to give alcohols in high yield (Scheme 8). In the presence of chlorotrimethylsilane, the corresponding silylenol ethers can be obtained.



Scheme 8

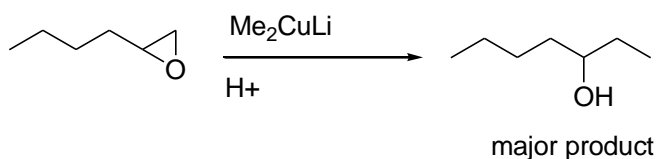
The reaction of ketones with organocuprates is very sluggish. However, the reaction takes place conveniently in the presence of chlorotrimethylsilane (Scheme 9).



Scheme 9

3.3.1.5 Reactions with Epoxides

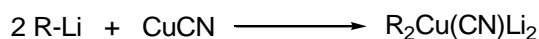
The epoxide is attacked by organocopper reagents at the least substituted carbon atom giving the corresponding alcohol (Scheme 10).



Scheme 10

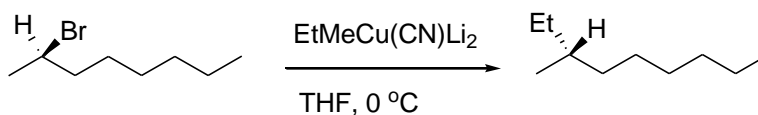
3.3.2 Higher Order Mixed Cuprates

Cuprates are useful but there are a few problems associated with them. To overcome these limitations, Lipshutz developed higher order mixed cuprates, $R_2Cu(CN)Li_2$, by the reaction of organolithium reagent with cuprous cyanide (Scheme 11).



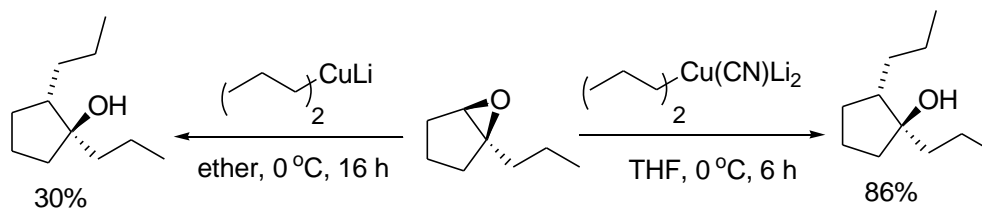
Scheme 11

Higher order cuprates show greater reactivity compared Gilman reagents with alkyl halides, even secondary halides. For example, (*S*)-2-bromooctane reacts with $EtMeCu(CN)Li_2$ at 0 °C to give (*R*)-3-methylnonane in 72% yield (Scheme 12).



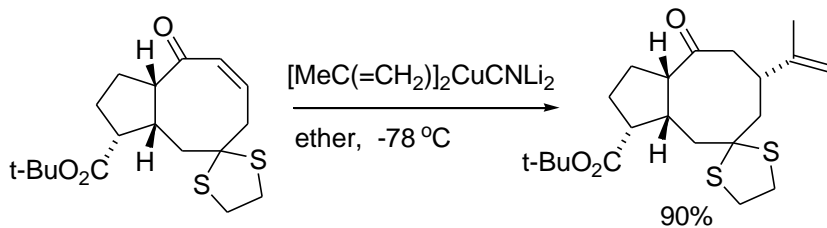
Scheme 12

Opening of epoxides ring is more efficient with the higher order cuprate than with Gilman reagents, and attack takes place at the less sterically hindered carbon (Scheme 13).



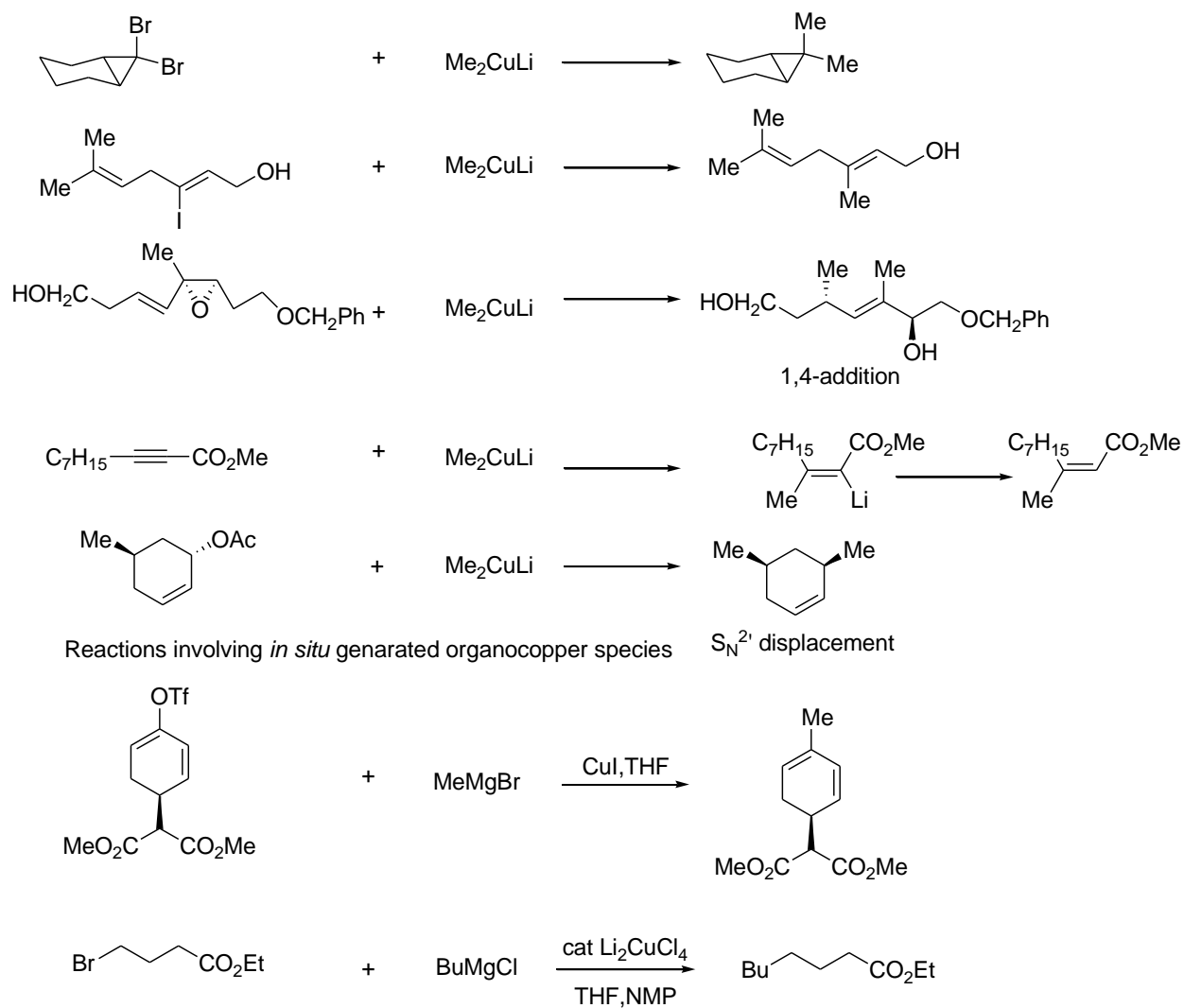
Scheme 13

Higher order cuprates react with α,β -unsaturated carbonyl compounds as Gilman reagent to afford the addition product in excellent yield (Scheme 14).



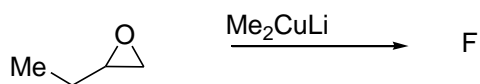
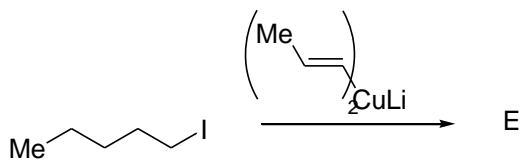
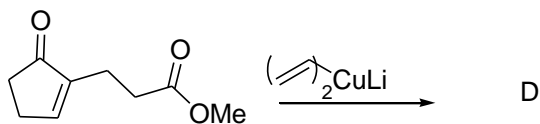
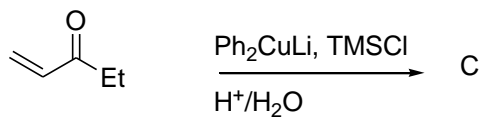
Scheme 14

Examples:



Problems

Predict the products of the following reactions



Text Book

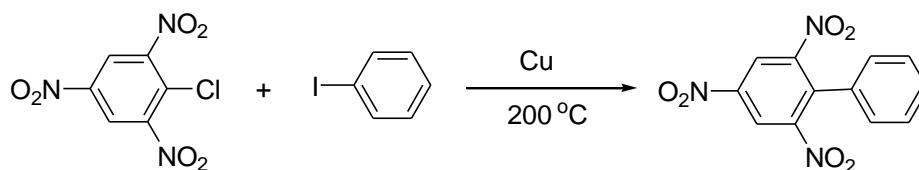
J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, 2001.

Lecture 24

3.3.4 Ullman Reaction

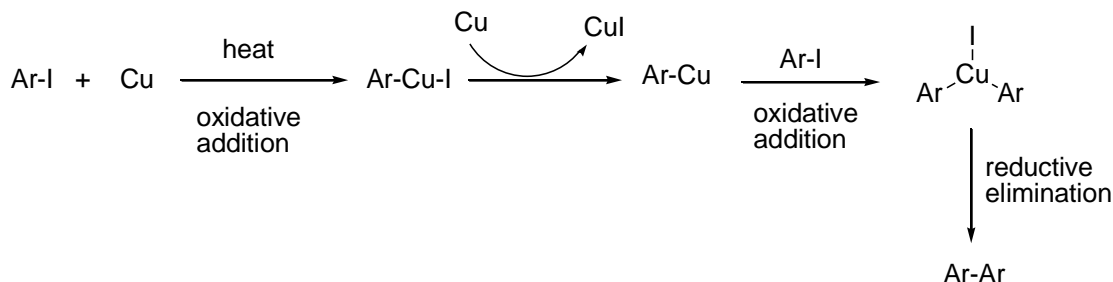
3.3.4.1 Biaryl Synthesis

The coupling of aryl halides to afford biaryls using copper source is called Ullman reaction. The order of reactivity of aryl halides follows the order: $\text{ArI} > \text{ArBr} > \text{ArCl}$. Aromatic ring having electron withdrawing groups at *ortho* position activate, the ring towards coupling reaction. Unsymmetrical biaryls can be prepared by taking two different aryl halides (Scheme 1). The byproducts can be minimized when one aryl halide is very reactive and the other is relatively unreactive. The reaction takes place via oxidative addition followed by reductive elimination.

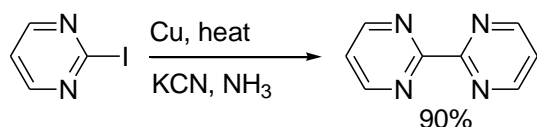


Scheme 1

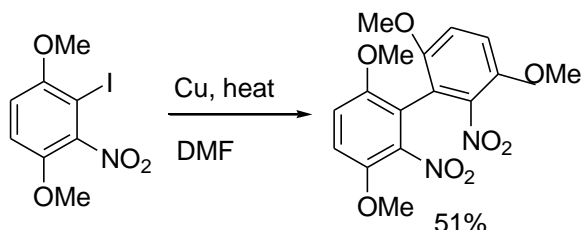
Proposed Mechanism



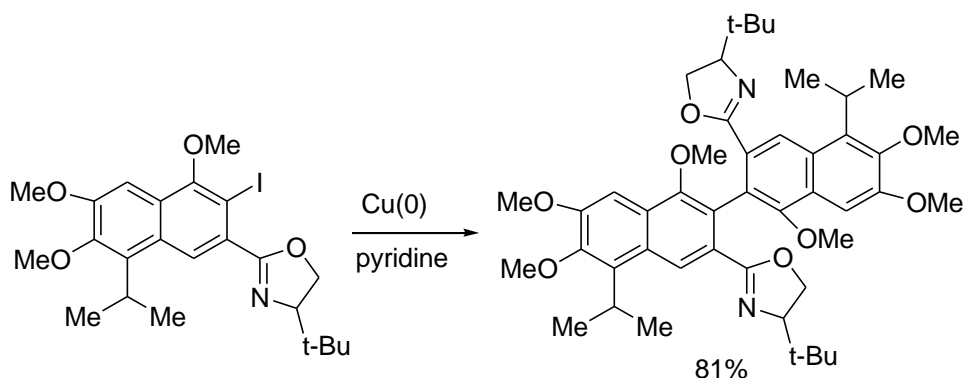
Examples:



G. Vlad, I. Horvath, *J. Org. Chem.* **2002**, 67, 6550.



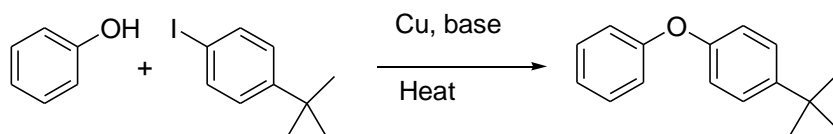
C. W. Lai, C. K. Lam, H. K. Lee, T. C. W. Mak, H. N. C. Wong, *Org. Lett.* **2003**, 5, 823.



A. I. Meyers, J. J. Willemsen, *Tetrahedron Lett.* **1996**, 37, 791.

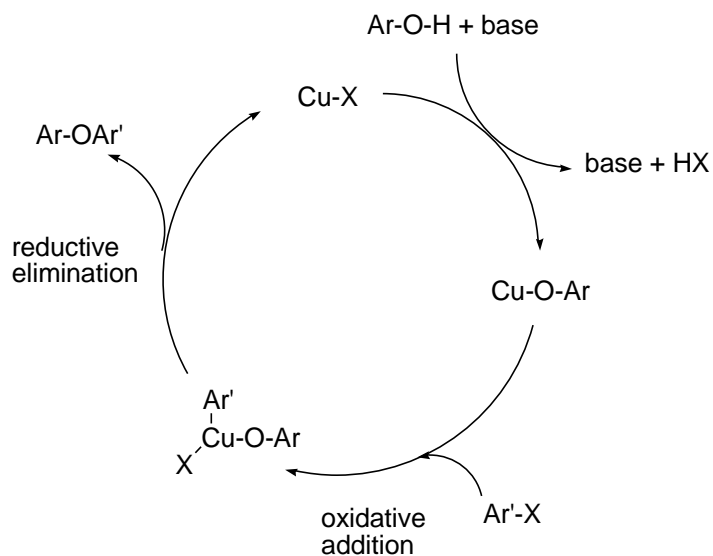
3.3.4.2 Biaryl Ether Synthesis

Diaryl ethers are important structural units present in many biologically active compounds. The coupling of aryl halides with phenols using copper source, known as Ullman ether synthesis, provides effective protocol for diaryl ether synthesis (Scheme 2). Both symmetrical and unsymmetrical ethers can be synthesized.



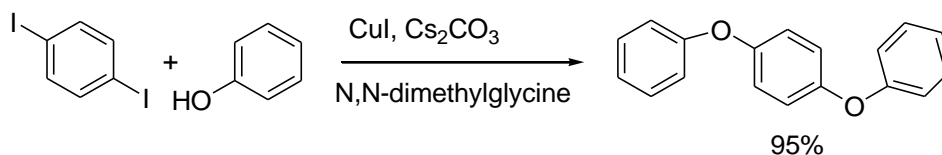
Scheme 2

Catalytic version of the reaction has been recently developed with copper(I) salts. The proposed mechanism involves oxidation addition followed by reductive elimination (Scheme 3).

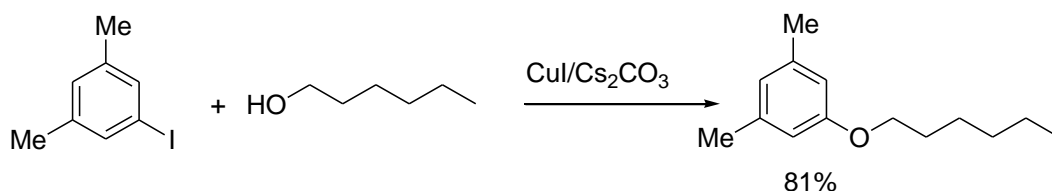


Scheme 3

Examples:



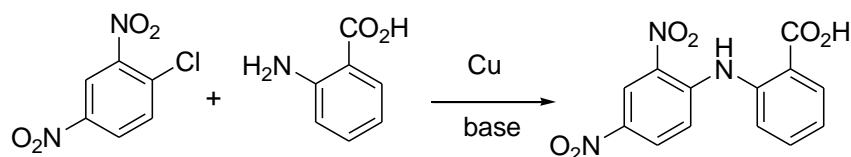
D. Ma, Q. Cai, *Org. Lett.* **2003**, 5, 3799.



M. Wolter, G. Nordmann, G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 973.

3.3.4.3 Amination

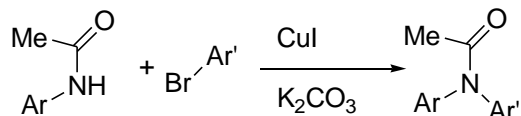
Ullman showed the C-N cross-coupling of anilines with aryl halides using copper source at elevated temperature ($\sim 200^\circ\text{C}$). Aryl halides having electron withdrawing groups show more reactivity with aryl amines substituted with electron donating groups. Catalytic version of the reaction has been developed during the recent years using copper(I) complex as a catalyst. The nature of the ligand plays a crucial role in the catalysis (Scheme 4). The proposed mechanism is similar to that proposed for the diaryl synthesis from aryl halides and phenols (Scheme 3).



Scheme 4

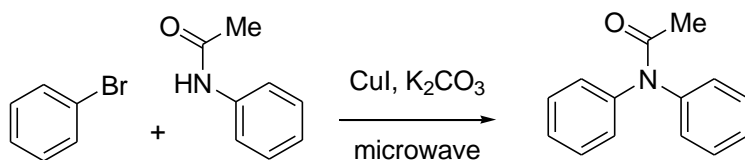
3.3.5 Goldberg Reaction

The C-N cross-coupling of amides with aryl halides using copper source is called Goldberg reaction (Scheme 5). The reaction becomes catalytic when we carry out in the presence of base. The traditional method involved elevated temperature ($\sim 200^\circ\text{C}$), however, the recent methods are effective at moderate temperature where copper (I) complexes are used as catalysts. The proposed mechanism is similar to that of diaryl synthesis (Scheme 3).



Scheme 5

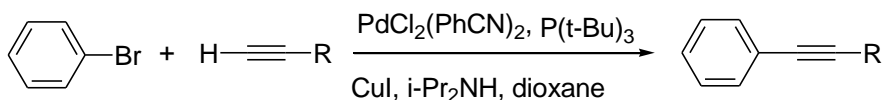
Examples:



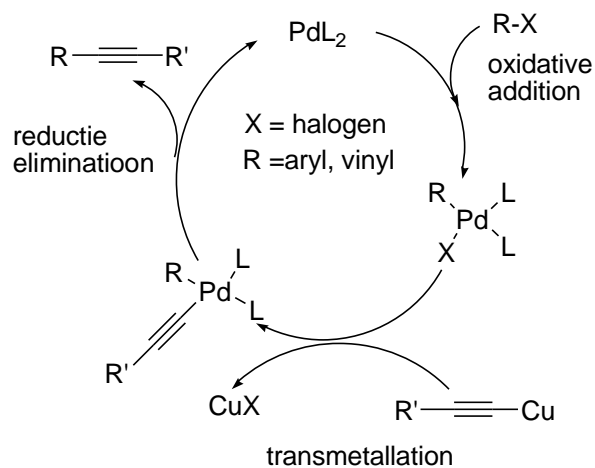
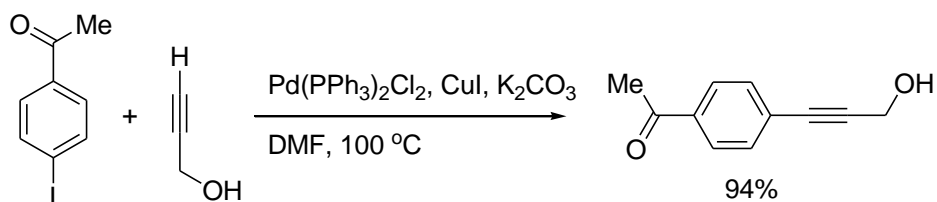
J. H.M. Lange, L. J. F. Hofmeyer, F. A. S. Hout, S. J. M. Osnabrug, P. C. Verveer, C. G. Kruse, R. W. Feenstra, *Tetrahedron Lett.* **2002**, 43, 1101.

3.3.6 Sonogashira Coupling

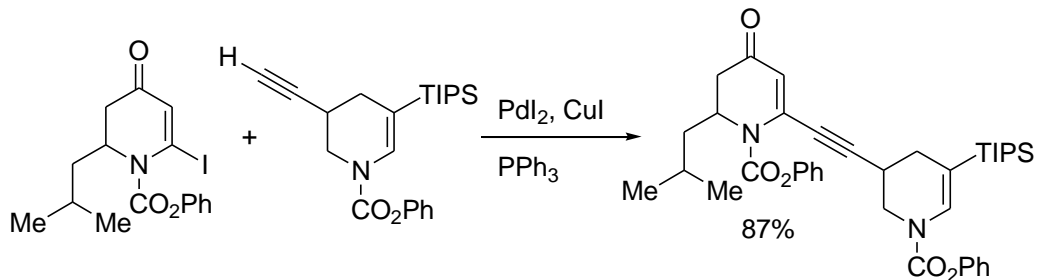
The C-C cross-coupling of aryl halides with alkynes using the combination of Pd and Cu complex is known as Sonogashira coupling reaction. The reactions are effective at moderate temperature with high yield (Scheme 6).



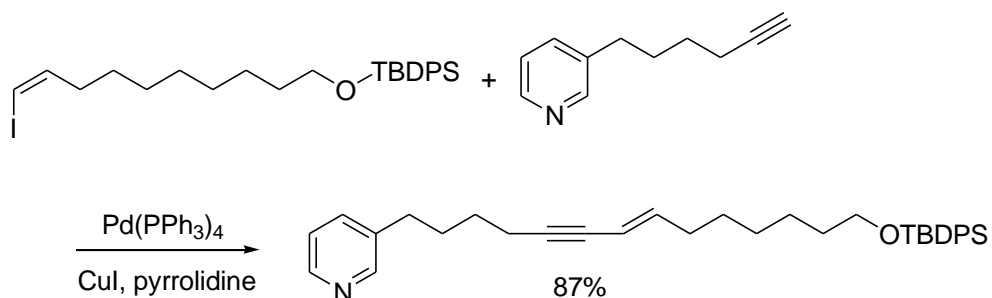
Scheme 6

Proposed Mechanism**Examples:**

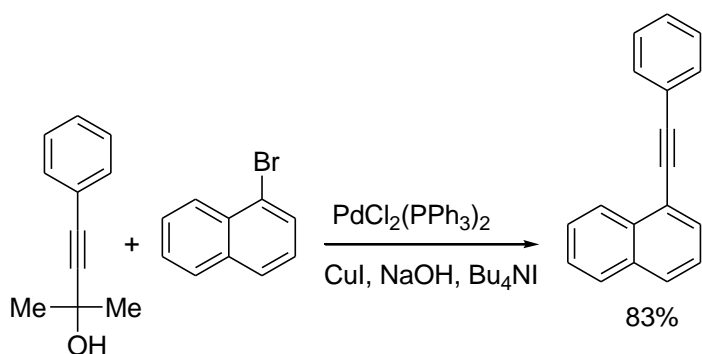
M. Feuerstein, H. Doucet, M. Santelli, *Tetrahedron Lett.* **2004**, 45, 1603.



D. L. Comins, A. L. Williams, *Org. Lett.* **2001**, 3, 3217.



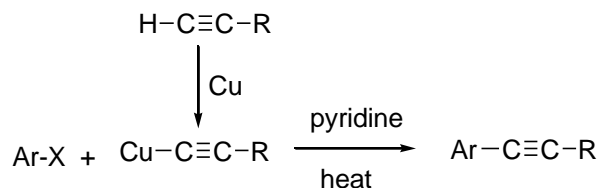
W. R. Goundry, J. E. Baldwin, V. Lee, *Tetrahedron* **2003**, 59, 1719.

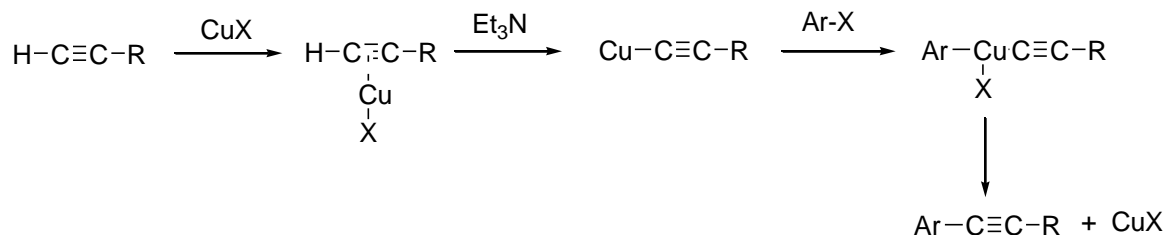
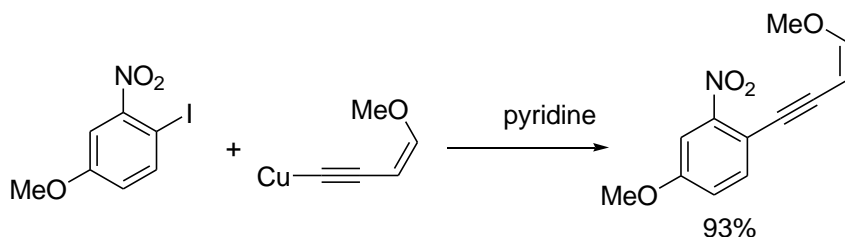


H.-F. Chow, C.-W. Wan, K.-H. Low, Y.-Y. Yeung, *J. Org. Chem.* **2001**, 66, 1910.

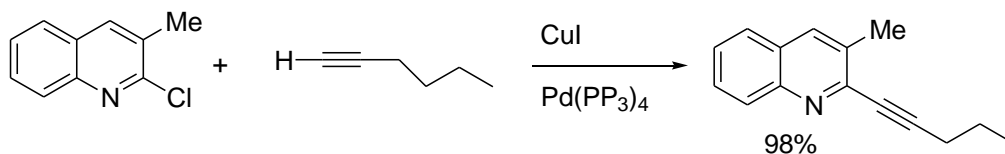
3.3.7 Castro-Stephens Coupling

The coupling of terminal alkynes and aryl halides using copper(I) salt is called Castro-Stephens coupling (Scheme 7).

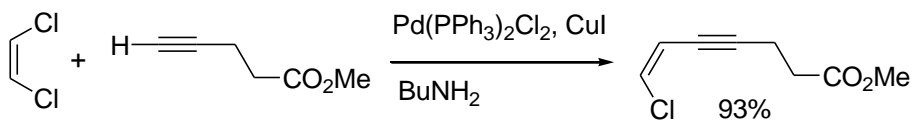


Proposed Mechanism**Examples:**

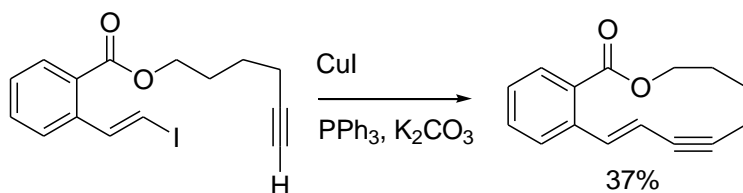
G. A. Krause, K. Frazier, *Tetrahedron Lett.* **1978**, 19, 3195.



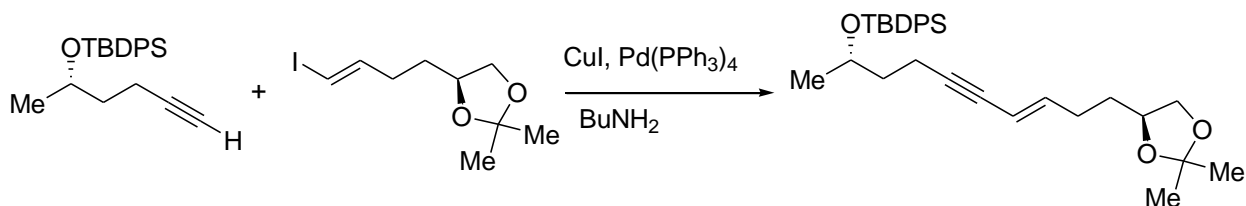
M. A. Ciufolini, J. W. Mitchell, F. R. Roschangar, *Tetrahedron Lett.* **1996**, 37, 8291.



D. Guillerme, G. Linstrumelle, *Tetrahedron Lett.* **1985**, 26, 3811.



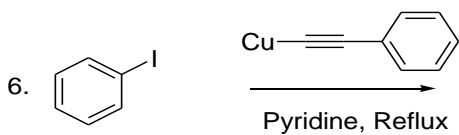
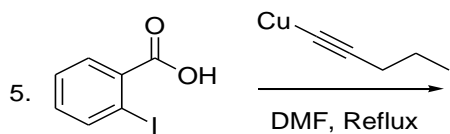
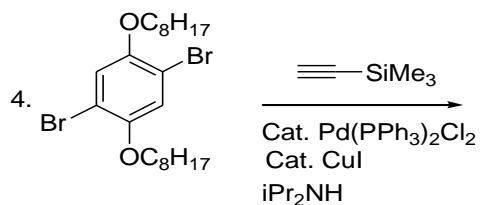
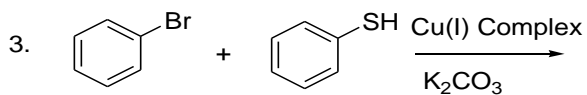
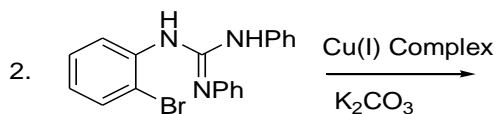
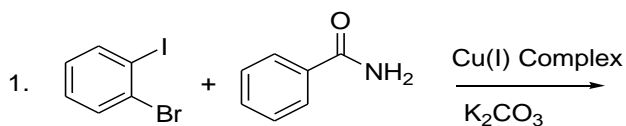
R. Garg, R. S. Coleman, *Org. Lett.* **2001**, 3, 3487.



J. Mulzer, M. Berger, *Tetrahedron Lett.* **1998**, 39, 803.

Problems:

Complete the following reactions.



Text Book

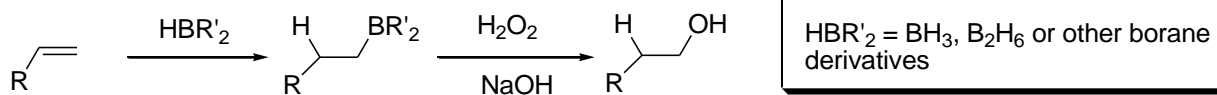
J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, 2001.

Lecture 25**3.4. Organoboranes**

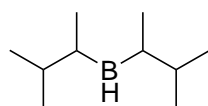
Borane (BH_3) exists as the gaseous diborane (B_2H_6). It is commercially available in the form of complexes generally with THF, Et_2O and Me_2S . It can also be prepared from the reaction of NaBH_4 with BF_3 . Organoboranes can be prepared rapidly by the addition reaction of borane to alkenes and alkynes.

3.5.1 Hydroboration of Alkenes

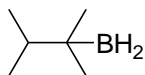
Boranes react with alkenes to form alkylboranes that could be oxidized in the presence of alkaline hydrogen peroxide to give alcohols. The result is a *cis*, anti-Markownikoff addition of water. The C-B bond is converted into a C-OH with retention of stereochemistry.



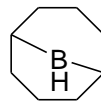
With hindered alkenes, it is more difficult to add three alkenes to borane. This becomes the basis for the development of unique borane derivatives. For examples, see:



Disiamylborane
Sia₂BH



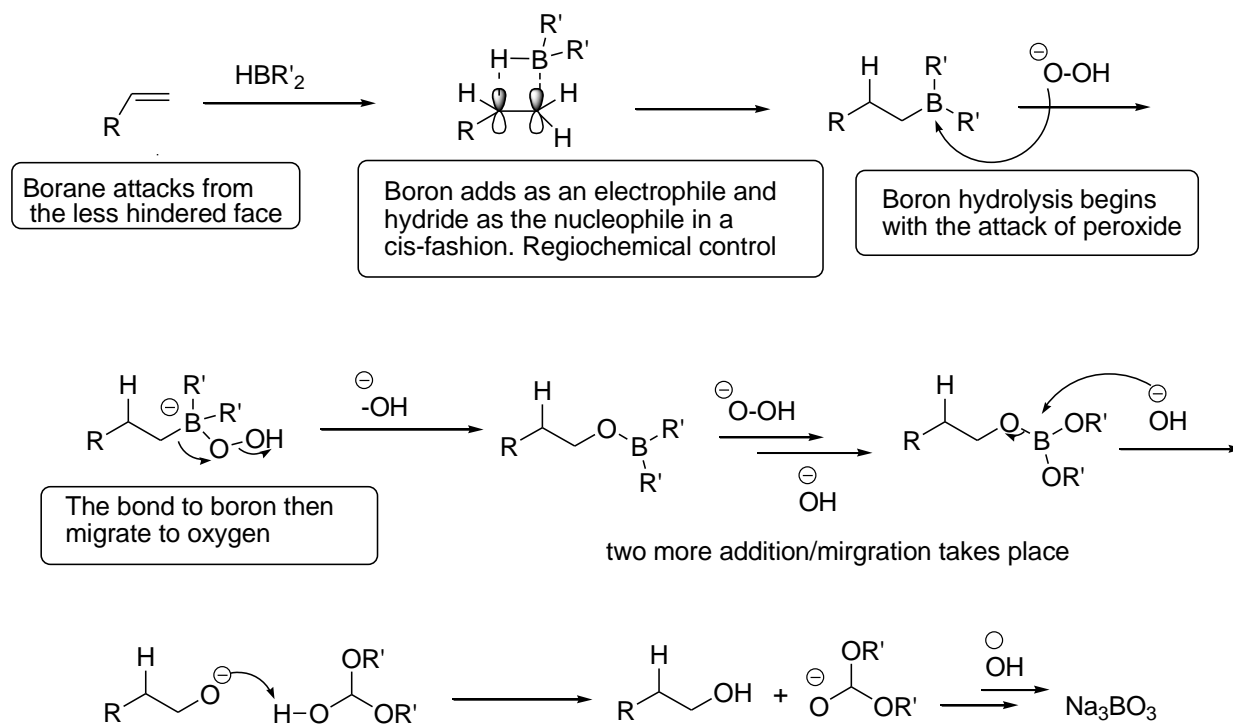
Thexylborane



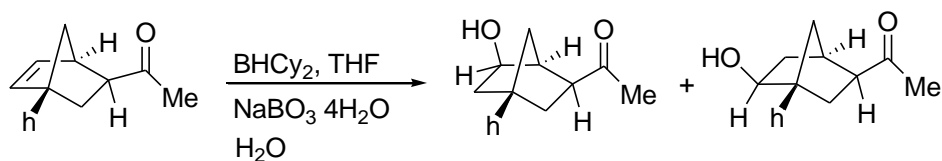
9-Borobicyclo[3.3.1]nonane
9-BBN

Proposed Mechanism

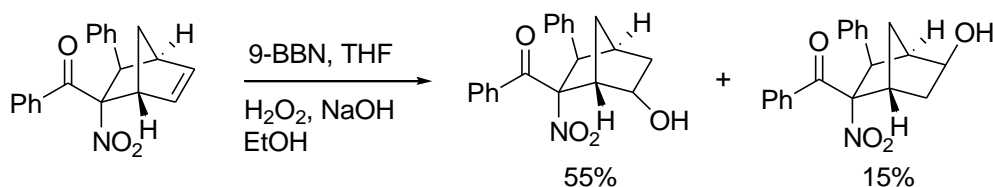
The hydroboration and oxidation reactions are regioselective and proceed by *cis* addition of hydrogen and boron, probably *via* a four-center transition state (Scheme 1).



Scheme 1

Examples:

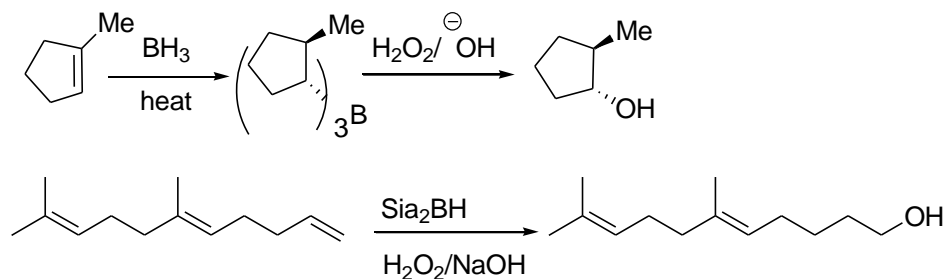
G. W. Kabalka, S. Yu, N.-S. Li, *Tetrahedron Lett.* **1997**, 38, 5455.



D.L. Gober, R. A. Lerner, B. F. Cravatt, *J. Org. Chem.* **1994**, 59, 5078.

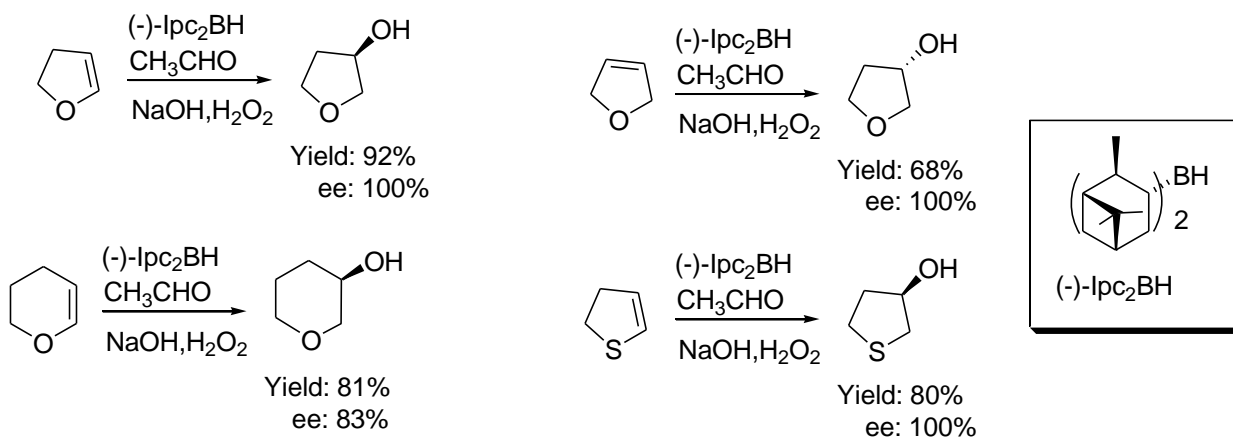
3.5.2 Reactions of Alkylboranes**3.5.2.1 Synthesis of Alcohols**

The transformation of alkenes to alcohols proceeds with complete retention of configuration at the boron-bearing carbon (Scheme 2).



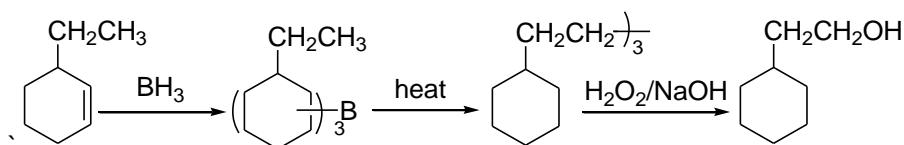
Scheme 2

Asymmetric hydroboration of alkenes can be carried out using chiral boranes with excellent enantioselectivity (Scheme 3).



Scheme 3

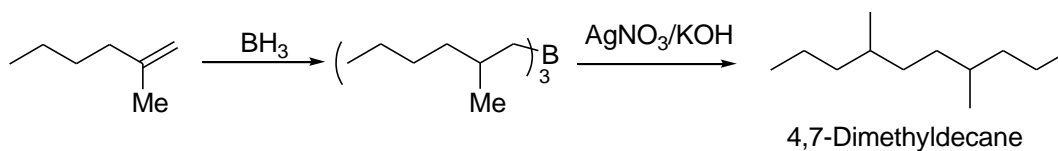
On heating, alkylboranes proceed isomerization to yield products that have the boron atom at the least hindered position of the alkyl chain (Scheme 4).



Scheme 4

3.5.2.2 Coupling

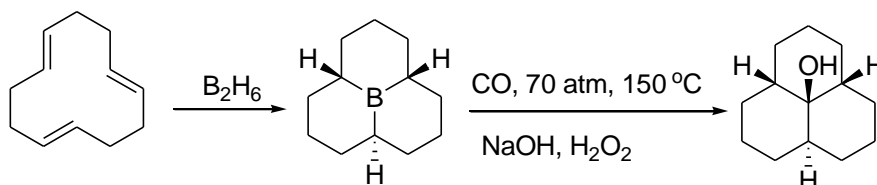
Alkylboranes on treatment with basic silver nitrate lead to coupling of the alkyl groups (Scheme 5). The reaction probably proceeds via an alkyl silver intermediate and affords a useful tool for the carbon-carbon bond formation.



Scheme 5

3.5.2.3 Carbonylation: Formation of Alcohols, Aldehydes and Ketones

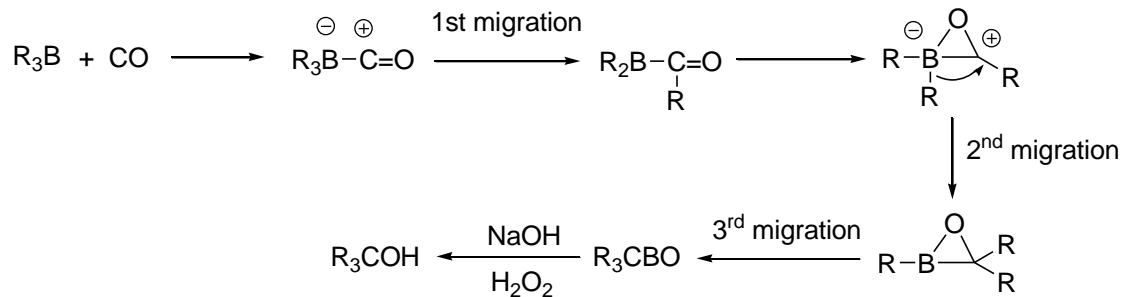
Alkylboranes can be transformed into alcohols, aldehydes and ketones on reaction with CO followed by oxidation. These reactions require high pressure and high temperature. For example, 1,5,9-cyclododecatriene proceeds reaction with B_2H_6 to give tricyclic borane that could be converted into tricyclic alcohol by carbonylation and oxidation (Scheme 6).



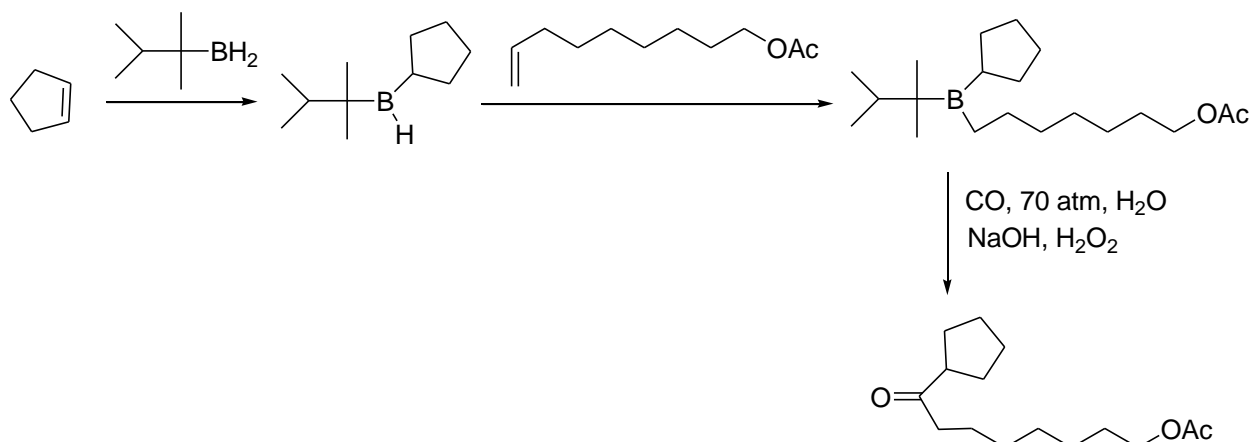
Scheme 6

Mechanism

The reaction involves an intramolecular migration of alkyl groups from boron to the carbon atom of CO.

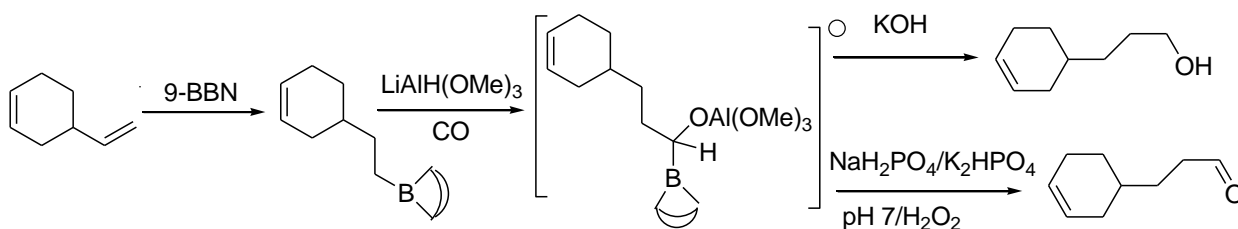


However, when carbonylation is carried out in presence of a small amount of water, migration of third alkyl group from boron to carbon is inhibited and resulting compound is dialkylketone and not trialkylcarbinol (Scheme 7).



Scheme 7

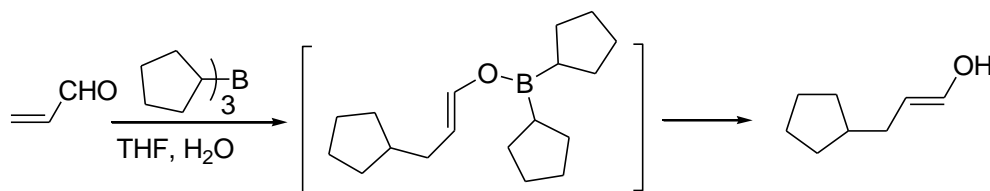
The carbonylation sequence can be modified to afford aldehydes as well as primary alcohols. For example, 4-vinylcyclohexene with 9-BBN gives the usual organoborane that can undergo carbonylation in the presence of lithium trimethoxyaluminum hydride [LiAlH(OMe)₃] to provide an α -boranyl alkoxyaluminate. The latter could be converted into alcohol by cleavage using hydroxide or can be oxidized to aldehyde using buffered hydrogen peroxide (Scheme 8).



Scheme 8

3.5.2.3 Conjugate Addition

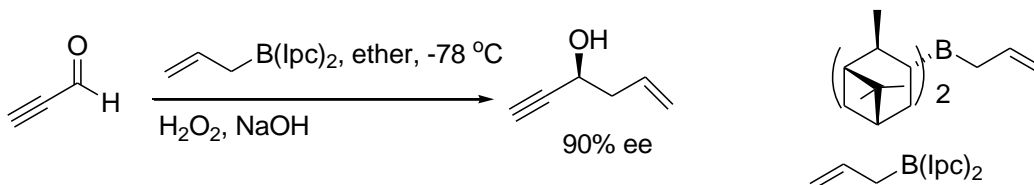
Trialkylboranes undergo conjugate addition with α,β -unsaturated aldehydes and ketones. In this reaction, alkyl group of the borane undergoes 1,4-addition and boron is transferred to the oxygen, giving a boron enolate that on hydrolysis gives the product (Scheme 9).



Scheme 9

3.5.2.3 Addition of Allylboranes to Carbonyl Compounds

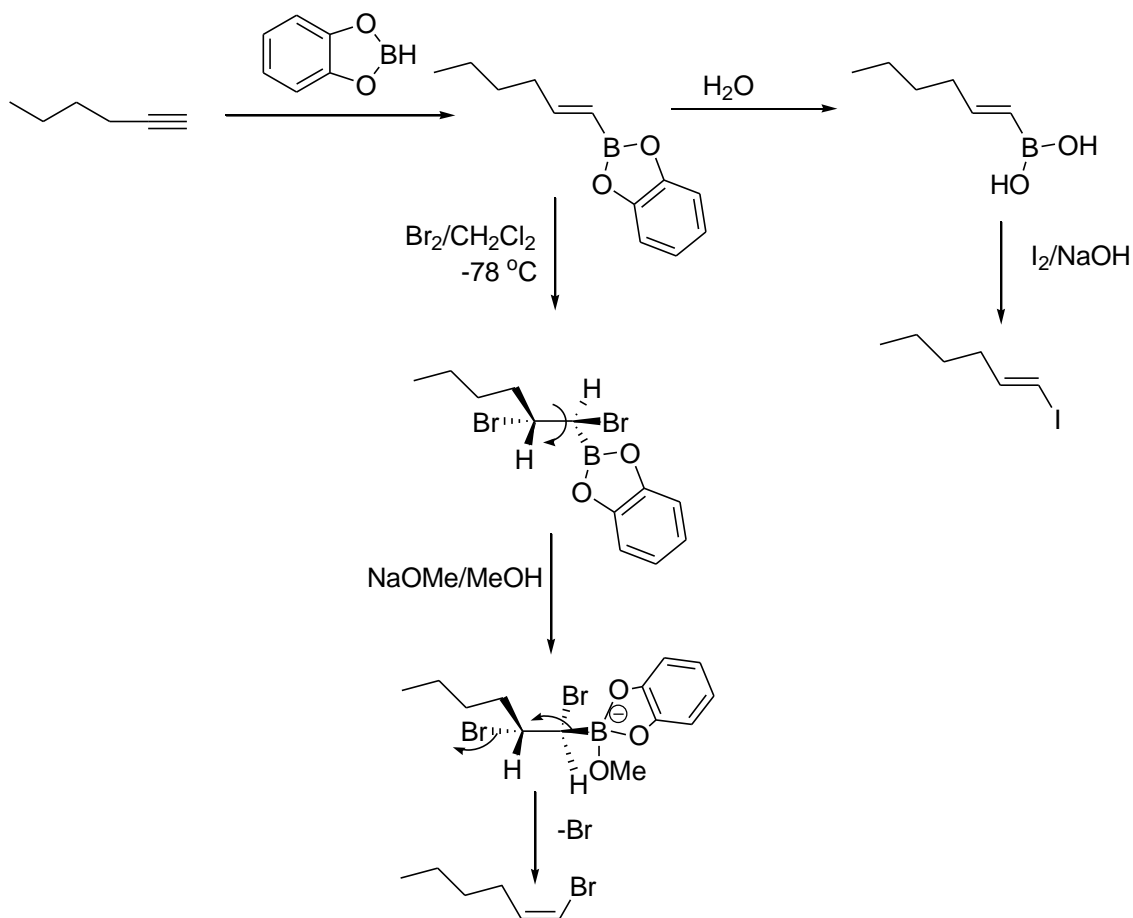
Carbonyl compounds react with allylboranes to give the corresponding alcohols. For an example, propionaldehyde could be transformed into hex-5-ene-1-yn-3-ol *via* 1,2-addition with (-)-B-allyl(diisopinocampheyl)borane followed by oxidation (Scheme 10).



Scheme 10

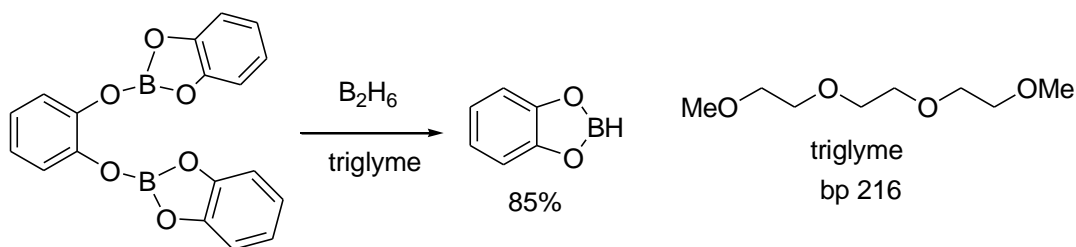
3.5.3 Hydroboration of Alkynes and Reactions of Vinylboranes

Hydroboration of alkynes gives vinylboranes that are versatile intermediates in organic synthesis. For example, 1-hexyne reacts with catcholborane to yield *trans*-1-alkenylborane, which on hydrolysis followed by reaction with I_2 in the presence of NaOH affords *trans*-vinyl iodide (Scheme 11). Both *trans*-1-alkenylboronic acid and *trans*-vinyl iodide are important substrate precursor for the palladium catalyzed C-C cross coupling reactions.



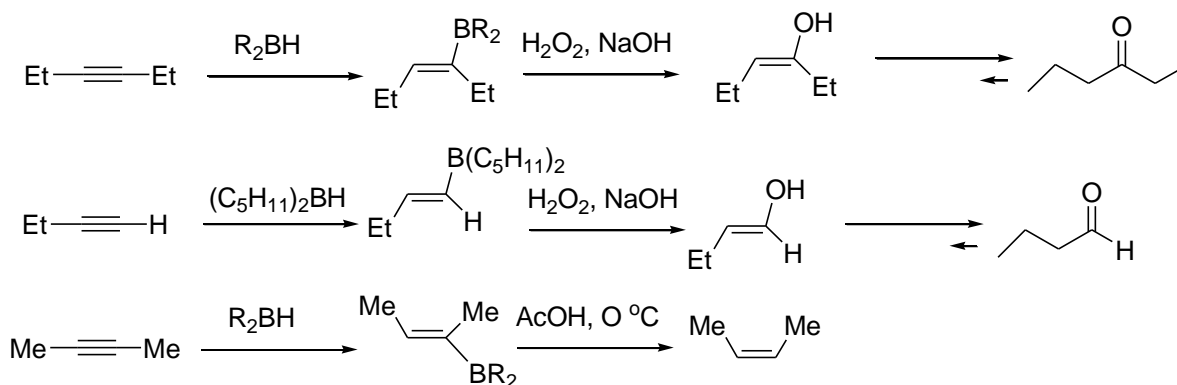
Scheme 11

Preparation of Catecholborane



M. S. VanNieuwenhez, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **2**, 1017.

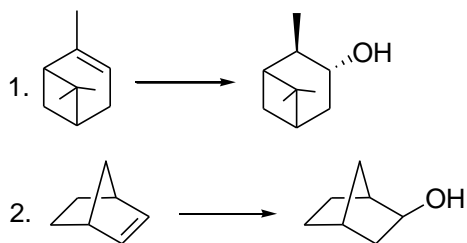
Alkynes on hydroboration with boranes give vinylboranes that could be readily transformed into a variety of synthetically useful compounds such as aldehydes, ketones or alkenes (Scheme 12). The reactivity and selectivity depend on the nature of organoboranes.



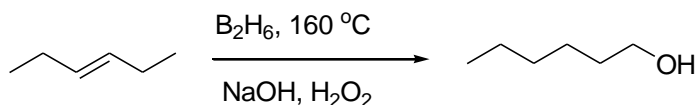
Scheme 12

Problems

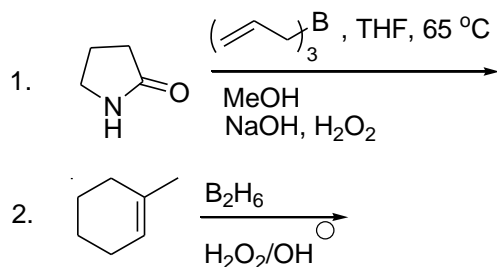
A. How will you carry out the following transformations.



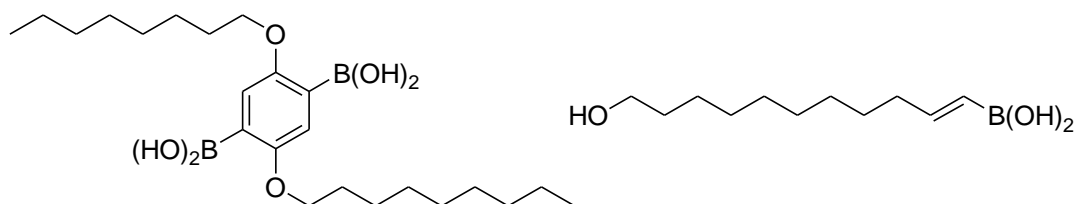
B. Provide a mechanistic rationale for the following transformation.



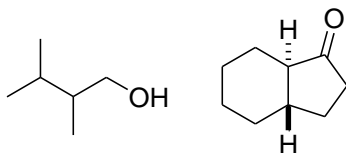
C. Give the major products for the following reactions.



D. How will you prepare the following organoboranes?



E. Show synthetic routes for the following compounds employing borane reagents.



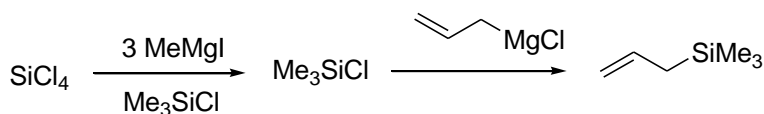
Text Book

J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, 2001.

Lecture 26

3.5 Organosilicon Compounds

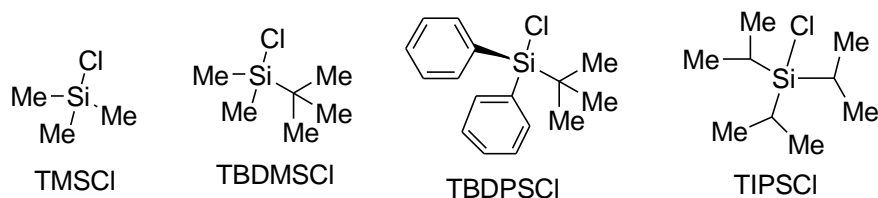
Organosilicon compounds can be prepared from metallic silicon and silicon halides. For examples, chlorotrimethylsilane is prepared by the reaction of methylmagnesium iodide with silicon chloride. Likewise, allylic silanes are prepared from chlorotrialkylsilanes and allylmagnesium halide (Scheme 1). The reactions involve nucleophilic displacement of halogen from silicon halides by organomagnesium halide.



Scheme 1

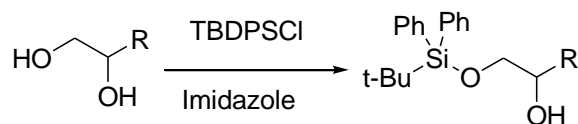
3.5.1 Formation of Silyl Ethers

Alcohols react with chlorotrialkylsilanes in the presence of amines to give silyl ethers which are useful having a number of applications. The silyl ethers can be easily removed by nucleophilic displacement with fluoride or oxygen nucleophiles and the rate of the removal depends mostly on the steric bulk for the silyl group. Some of the silicon based protecting groups follow:



A protecting group is useful only if it can be introduced and removed easily without affecting the rest of the molecule and survives during the reaction. For an

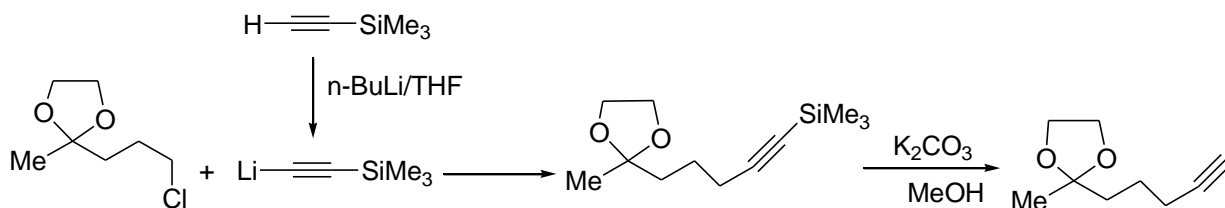
example, the extreme bulkiness of the TBDPS group makes it useful for the selective protection of unhindered primary alcohol in the presence of secondary alcohols (Scheme 1). In addition, it has excellent stability but can still be easily removed with fluoride.



Scheme 2

3.5.2 Formation of Alkynyl Silane

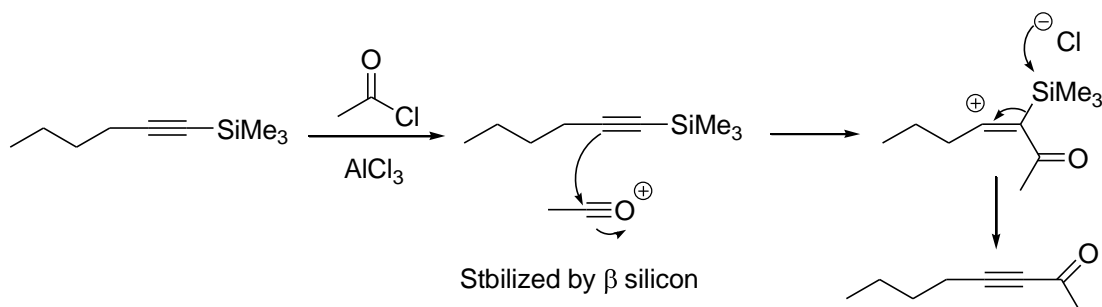
In some circumstances terminal alkynes having an acidic proton lead to unwanted side-reactions. To circumvent this problem, SiMe₃ is used for the protection of the terminus of alkyne during the reaction, which can be easily removed with fluoride or K₂CO₃ in MeOH (Scheme 3).



Scheme 3

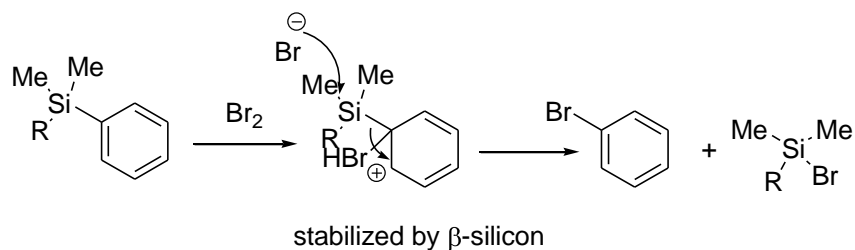
Silicon Stabilizes a Positive Charge on the β Carbon

In comparison to ordinary alkynes, silylated alkynes are nucleophilic towards electrophiles. The attack takes place only at the atom directly bonded to the silicon. This is because the intermediate β-carbocation is stabilized. This is useful for the synthesis of alkynyl ketones, which are otherwise difficult to prepare using conventional organometallic reagents (Scheme 4).



Scheme 4

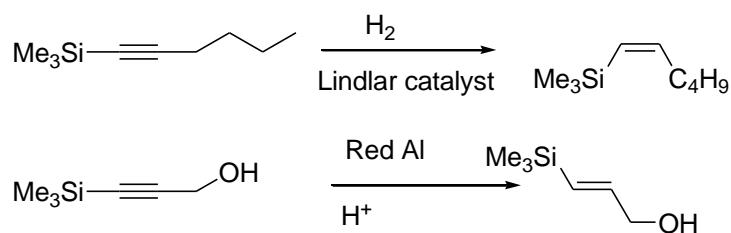
In case of aryl silanes ipso substitution is observed with electrophiles due to the stabilization of the cation β to silicon (Scheme 5).



Scheme 5

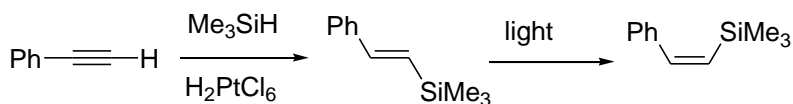
Synthesis of Vinyl Silanes

Controlled reduction of alkynyl silanes gives vinyl silanes and the method of reduction dictates the stereochemistry (Scheme 6)



Scheme 6

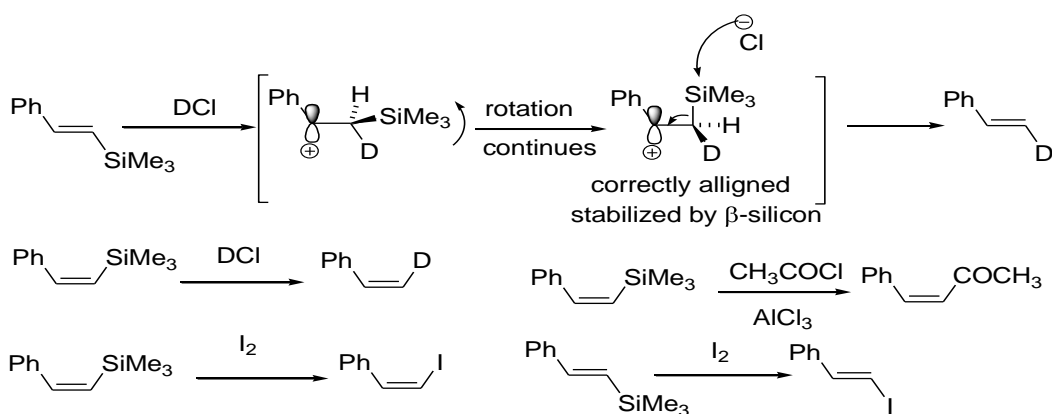
Alternatively, phenylacetylene can be reacted with Me_3SiH in the presence of H_2PtCl_6 to give vinyl silane (Scheme 7).



Scheme 7

Synthesis of Alkenes

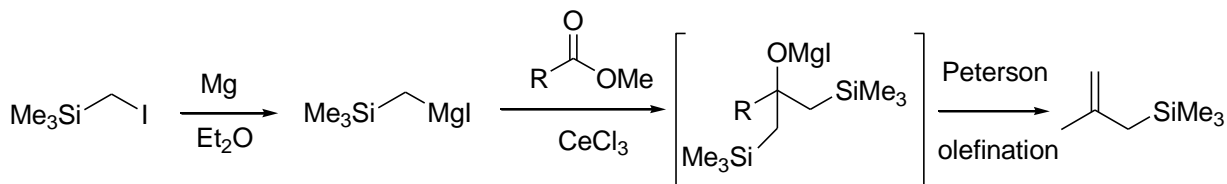
Vinyl silanes undergo *ipso* substitution with electrophiles to give alkenes. The reactions are regioselective and the exchange occurs with retention of geometry (Scheme 8).



Scheme 8

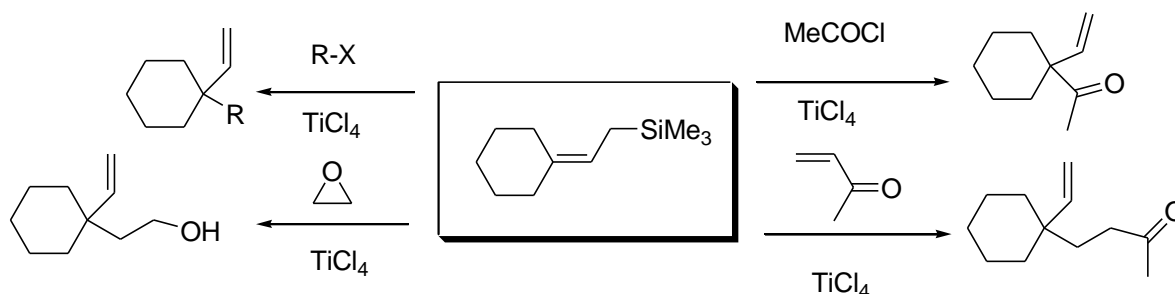
Synthesis and Reactions of Allyl Silanes

Peterson olefination is one of the methods used for the synthesis of allyl silanes (Scheme 9).



Scheme 9

Allyl silanes react with a wide variety of electrophiles in the presence of Lewis acids. Some of the examples are shown in Scheme 10.

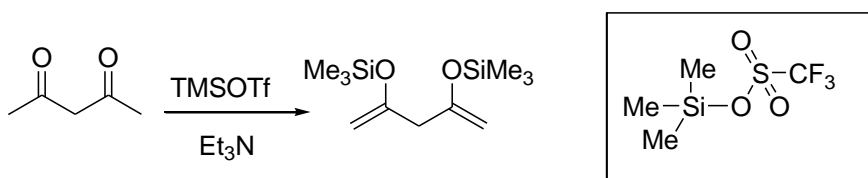


Scheme 10

3.5.3. Formation of Silyl Enol Ethers

Trialkylchlorosilane can trap the enolate ion, formed by the base treatment of ketones, to give silyl enol ethers that are useful intermediates for a variety of reactions. For examples, the silyl enol ether formed from aldehydes and ketone can proceed aldol condensation. The advantage of using pre-formed enolate reagent is that the coupling takes place on the desired site of an unsymmetrical ketone. This is known as directed aldol condensation.

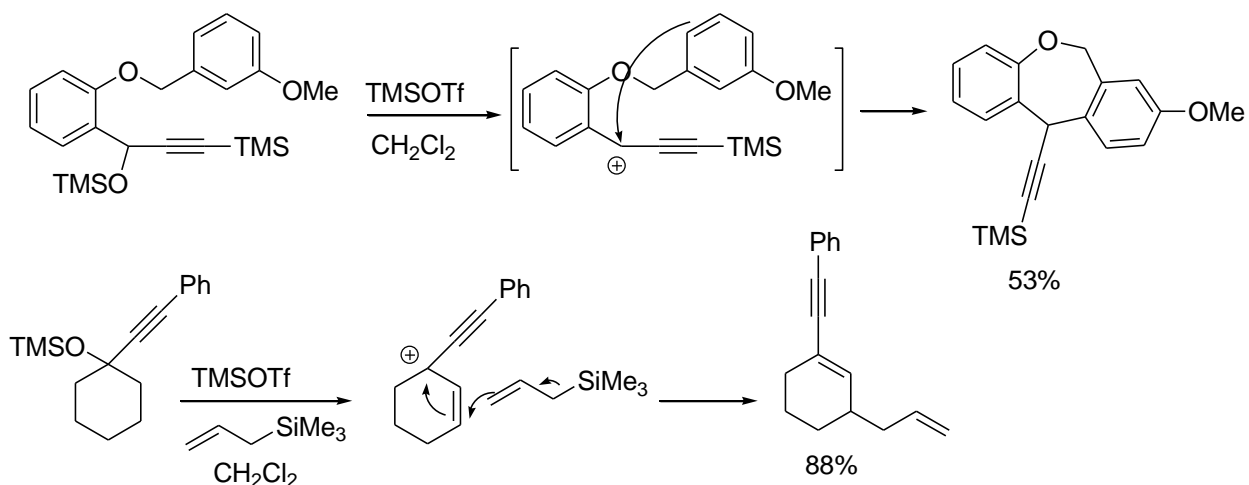
Alternatively, silyl enol ether can also be prepared from ketones using TMSOTf, which acts as a Lewis acid (Scheme 11).



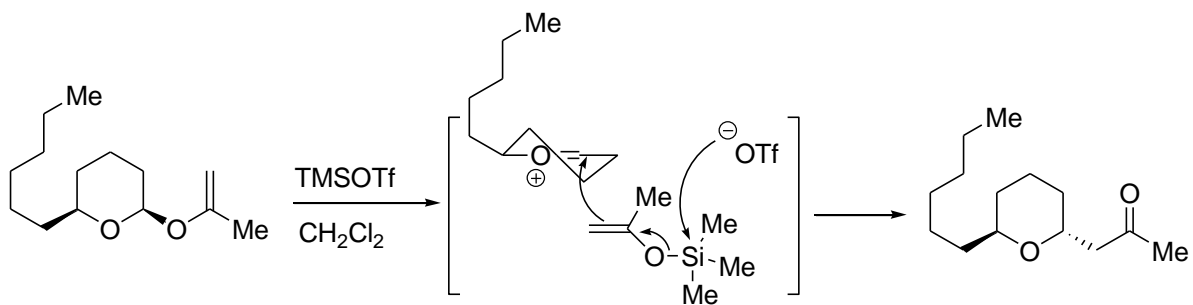
Scheme 11

J. J. Sweeny, G. Perkin, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **7**, 5315.

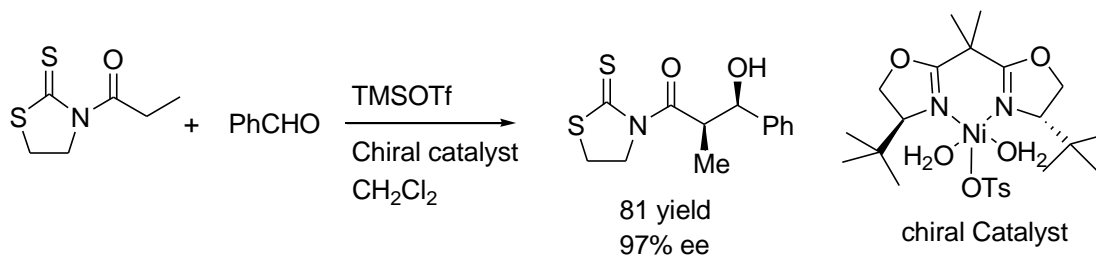
Examples:



T. Ishikawa, M. Okano, T. Aikawa, S. Saito, *J. Org. Chem.* **2001**, 66, 4635.

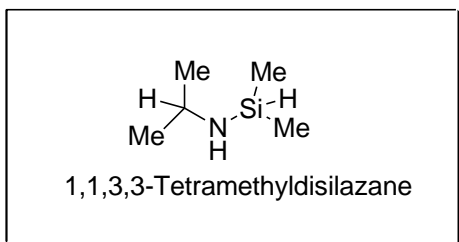


D. J. Dixon, S. V. Ley, E. W. Tate, *J. Chem. Soc., Perkin Trans 1* **1999**, 2665.

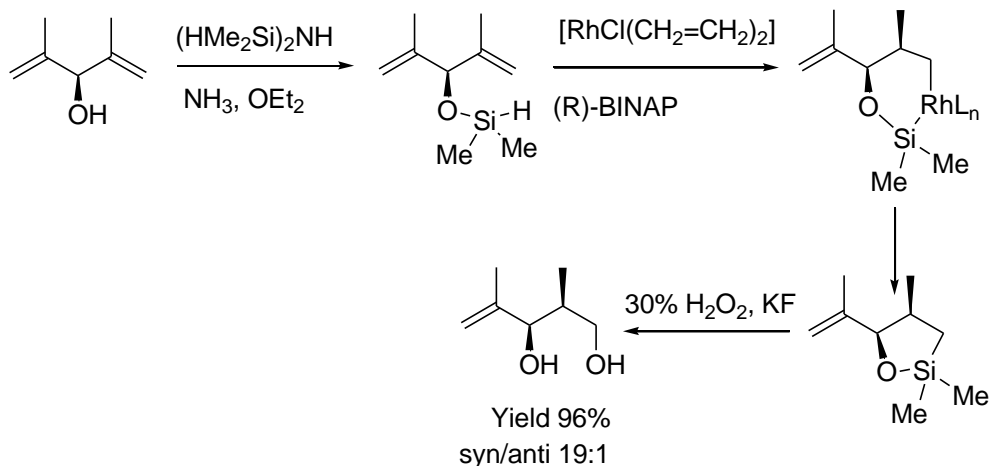


D. A. Evans, C. W. Downey, J. L. Hubbs, *J. Am. Chem. Soc.* **2003**, 125, 8706.

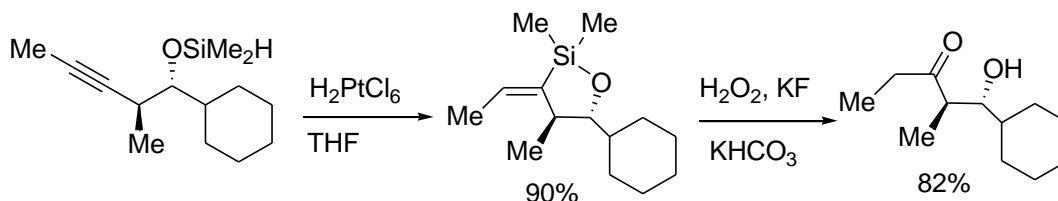
The application of 1,1,3,3-Tetramethyldisilazane for hydrosilylation of Alkenes



K. Tamao, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **7**, 4809.

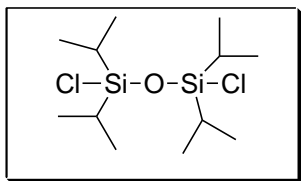


K. Tamao, T. Tanaka, T. Nakajima, R. Sumiya, H. Arai, Y. Ito, *Tetrahedron Lett.* **1990**, 31,7333.



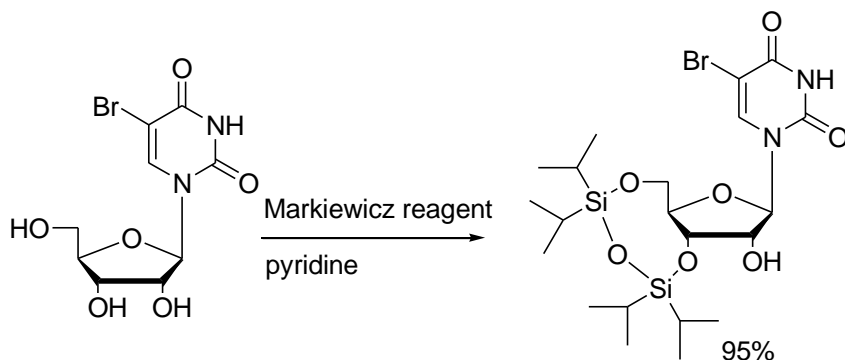
J. A. Marshall, M. M. Yanik, *Org. Lett.* **2000**, 2, 2173.

Application of 1,3-Dichloro-1,1,3,3-tetraisopropyl disiloxane (TIPSCI) for silyl ether formation (Markiewicz Reagent)



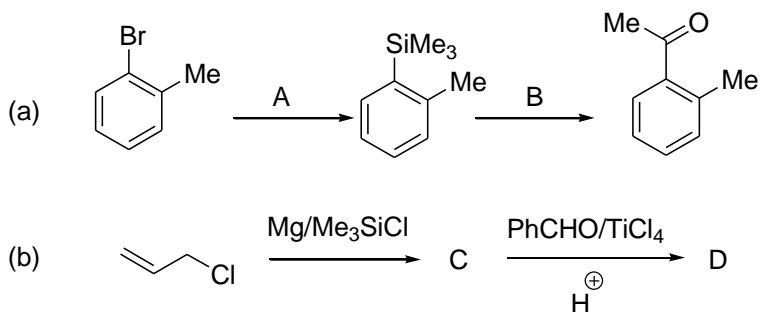
1,3-Dichloro-1,1,3,3-tetraisopropyl disiloxane (TIPSCI)

J. Slade, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **3**, 1730.

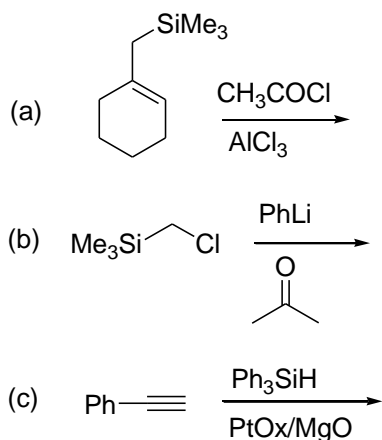


Problems:

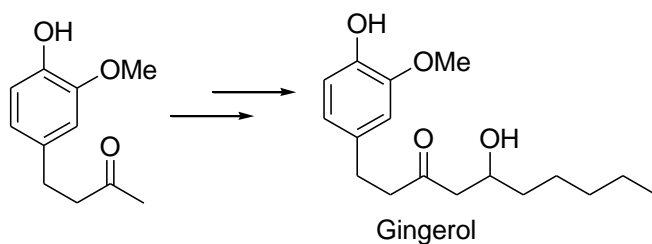
1. Complete the following reactions with suitable reagents or products.



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



3. How will you carry out the following conversion employing silicon reagents?



Text Book

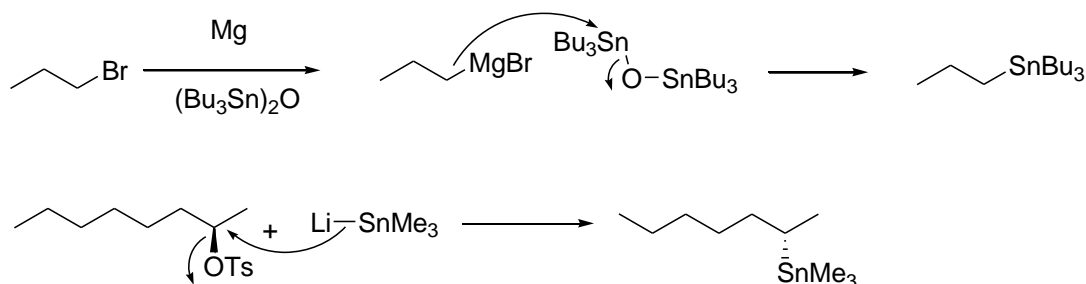
J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, 2001.

Lecture 27

3.6 Organotin Compounds

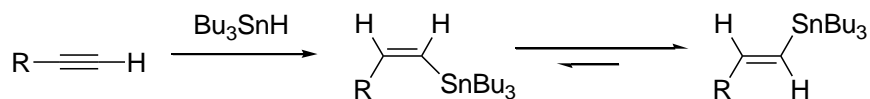
The preparation of organotin compounds is similar to that of organosilicones. Alkyl tributyltin can be prepared from alkyl Grignard reagent and bis(tributyltin) oxide. Alternatively, the polarity can be reversed and stannyl lithium can add to

organic electrophiles. The first reaction is S_N2 at tin and the second reaction is S_N2 at carbon (Scheme 1)

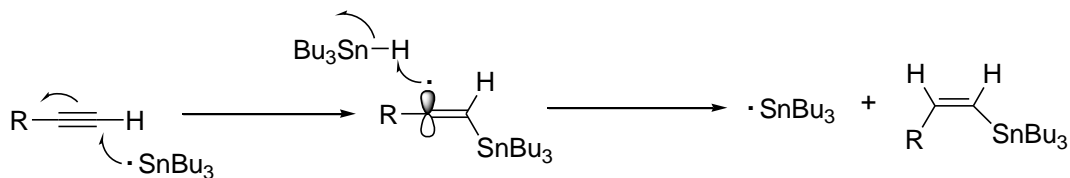


Scheme 1

The hydrostannylation of an alkyne with tin hydride can be radical-initiated to afford kinetically controlled vinyl stannane with Z-geometry. However, if there is an excess of tin hydride or sufficient radicals are present, isomerization can lead to the more stable E-isomer (Scheme 2).



Mechanism

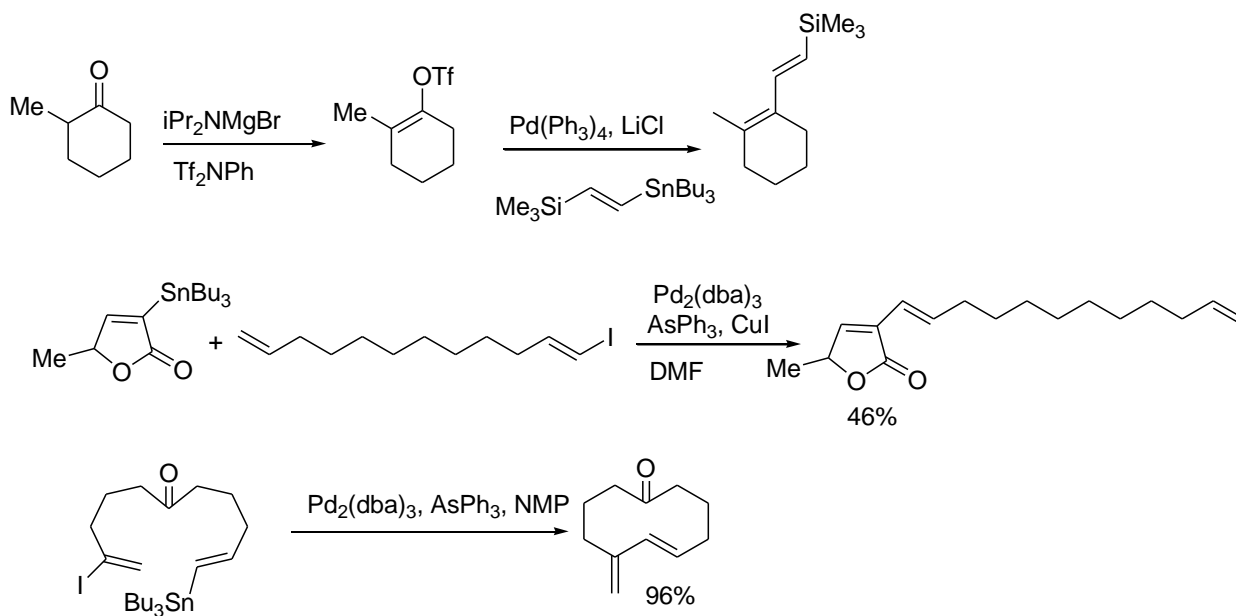


Scheme 2

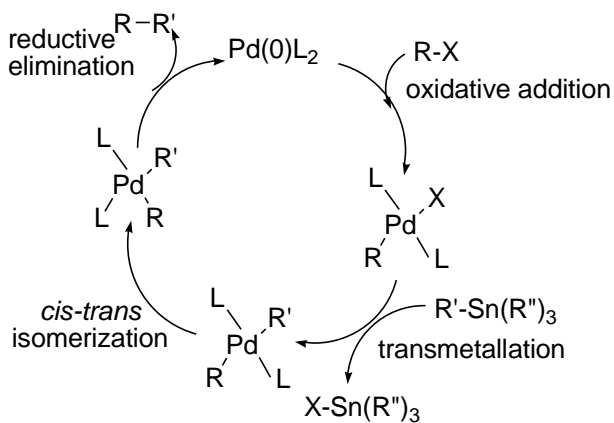
In this section we will see some important organostannane mediated organic transformations.

3.6.1 Reactions of Vinyl Stannanes (Stille Coupling)

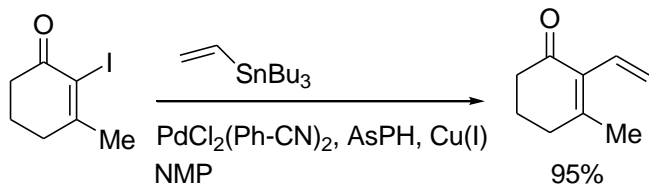
Vinyl stannanes react with vinyl halides or triflates in the presence of palladium catalyst to give dienes (Scheme 3). The reaction is compatible with a variety of functional groups and is run under relatively neutral conditions. Both inter- and intramolecular reactions have been explored and widely applied in the synthesis of complex molecules.



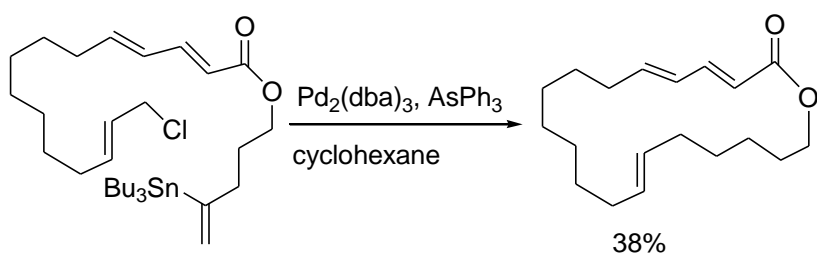
Proposed Mechanism



Scheme 3

Examples:

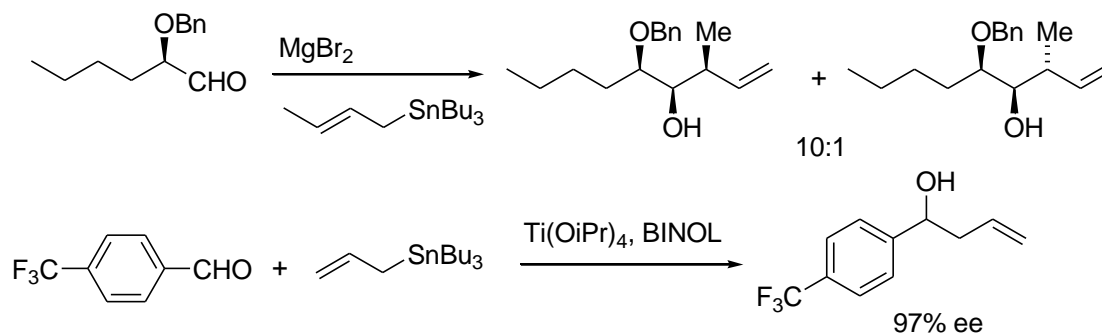
S. T. Handy, X. Zhang, *Org. Lett.* **2001**, 3, 233.



C. Boden, G. Pattenden, *Synlett* **1994**, 181.

3.6.2 Reactions of Allyl Stannanes

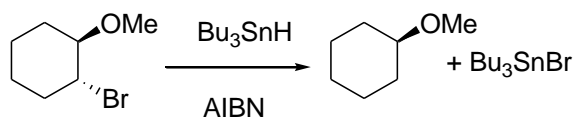
Allyl stannanes are important reagents in organic synthesis because they can be obtained with control over the double bond geometry and don't affect the presence of other functional groups. Asymmetric allylation of aldehydes with allyl stannanes has also been extensively explored with excellent stereocontrol in the presence of Lewis acids (Scheme 4).



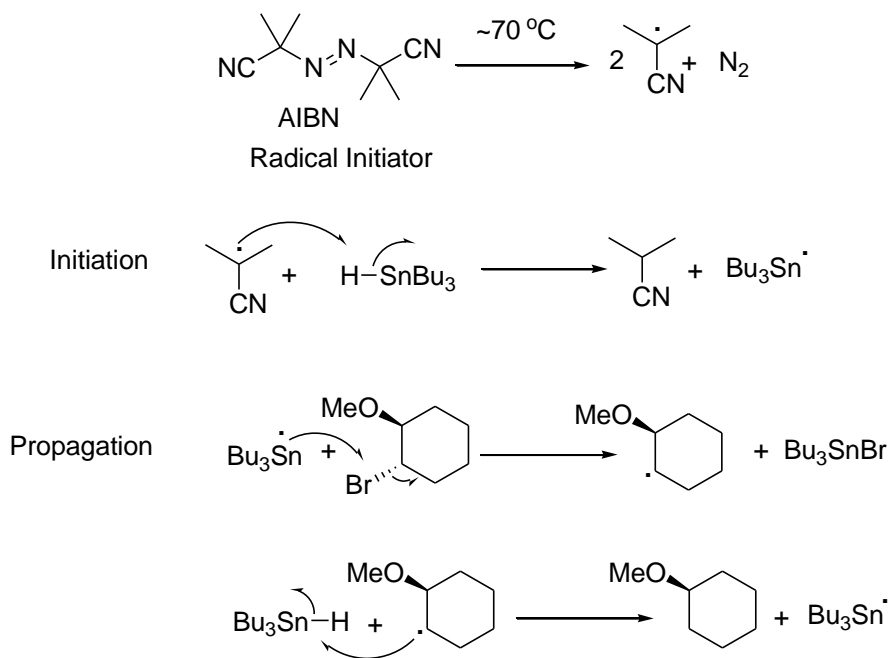
Scheme 4

3.6.2 Reactions of Tributyltinhydride

Tributyltinhydride (Bu_4SnH) is a useful reagent for the removal of halogen (I and Br) from alkyl halide by H (Scheme 5). The reaction is performed in the presence of light or radical initiator AIBN. The mechanism involves formation of an alkyl radical by abstraction of the halogen by $\text{Bu}_3\text{Sn}\cdot$. This alkyl radical abstracts H from Bu_3SnH .

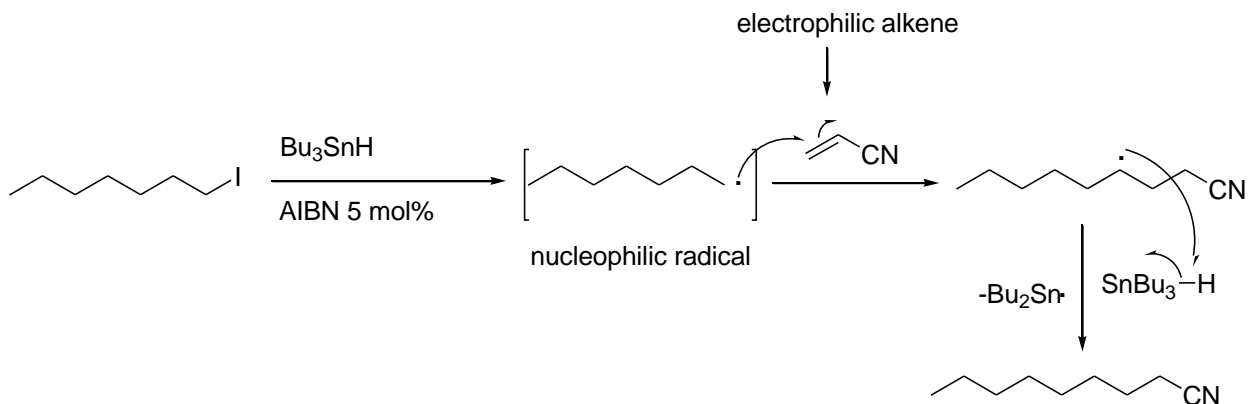


Mechanism



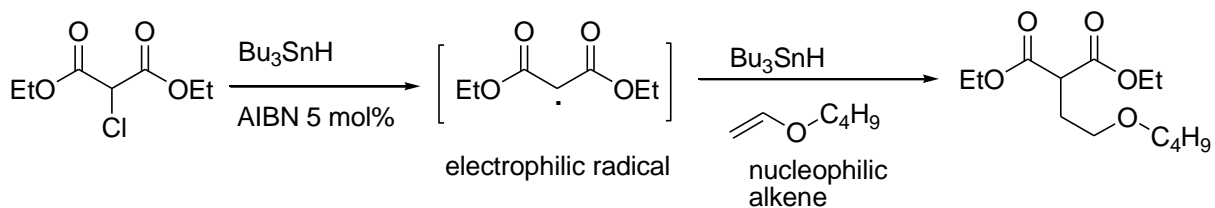
Scheme 5

The alkyl radical generated from alkyl halide undergoes reaction with alkenes to give alkane via the formation new carbon-carbon bond. Both inter- and intramolecular version of the reactions extensively studied. An example for the Bu_3SnH mediated addition of nucleophilic radical to electrophilic alkene is shown Scheme 6.



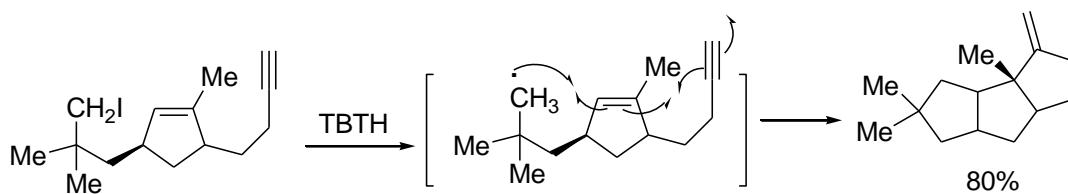
Scheme 6

An example for the Bu_3SnH mediated addition of electrophilic radical to nucleophilic alkene is shown in Scheme 7.

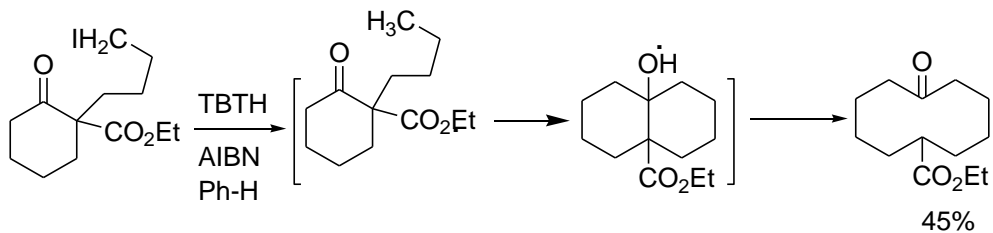


Scheme 7

Examples:



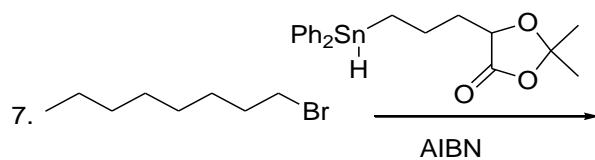
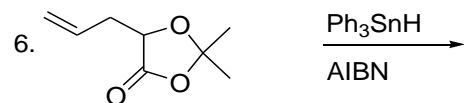
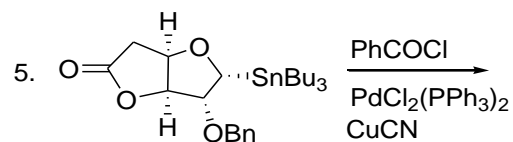
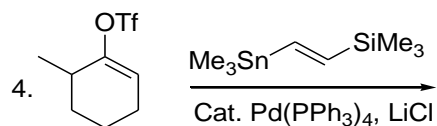
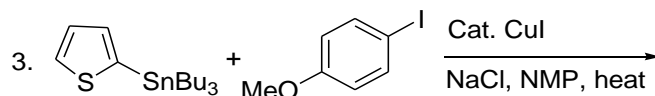
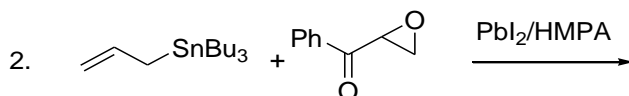
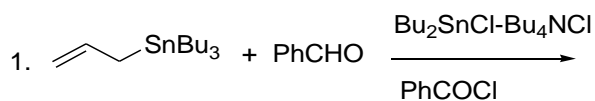
D. P. Curran, D. M. Rakiewicz, *Tetrahedron* **1985**, 41, 3943.



P. Dowd, S. C. Choi, *J. Am. Chem. Soc.* **1987**, 109, 6548.

Problems

A. Complete the following reactions.



Text Book

J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, 2001.

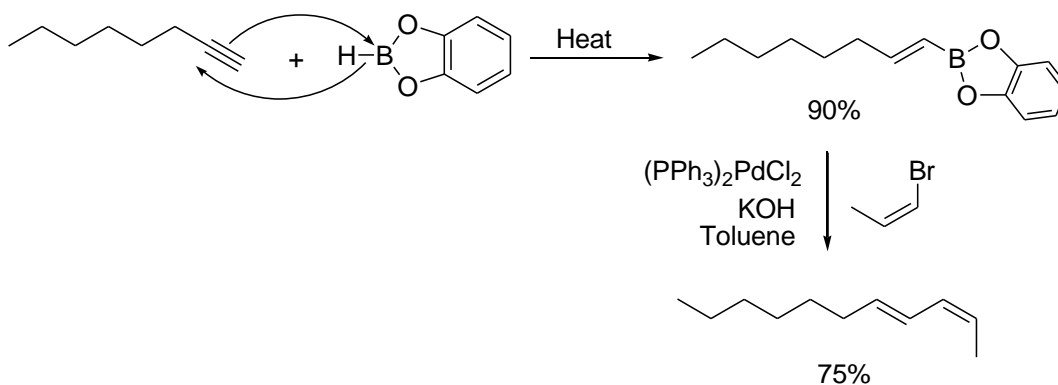
Lecture 28

3.7 Organopalladium Compounds

The organopalladium compounds are generated *in situ* for the synthesis. The importance organopalladium compounds lies in their ability to facilitate reactions that would not take under normal conditions. This section covers the palladium-catalyzed C-C bond formations.

3.7.1 Suzuki-Coupling

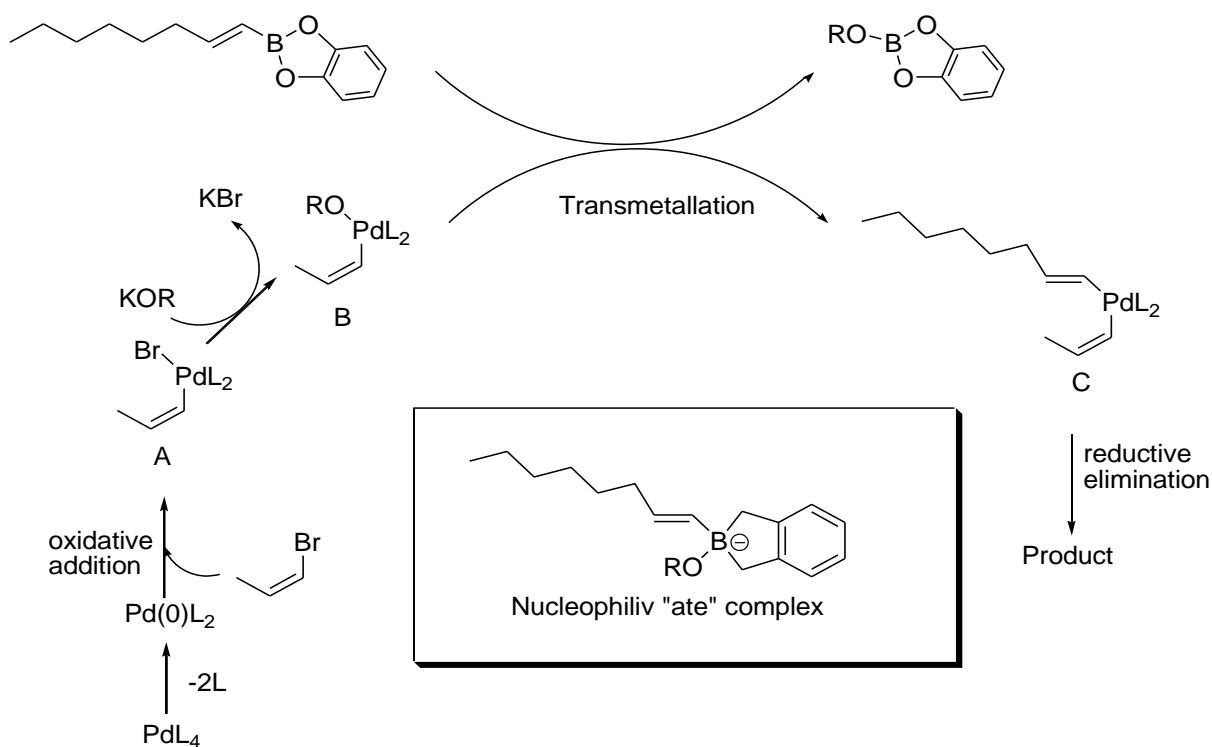
The palladium-catalyzed C-C cross-coupling of organoboranes, organoboronic acids, and organoboronic esters with organic halides is called 'Suzuki coupling'. This reaction has become extremely popular and covers about a quarter of all palladium-catalyzed coupling reactions (Scheme 1). The initial process consists of hydroboration of an alkyne with borane, followed by palladium(0)-catalyzed C-C cross-coupling of the organoborane with aryl halides. The hydroboration is usually regioselective for the less hindered position and addition of boron and hydrogen occurs *cis* stereospecifically



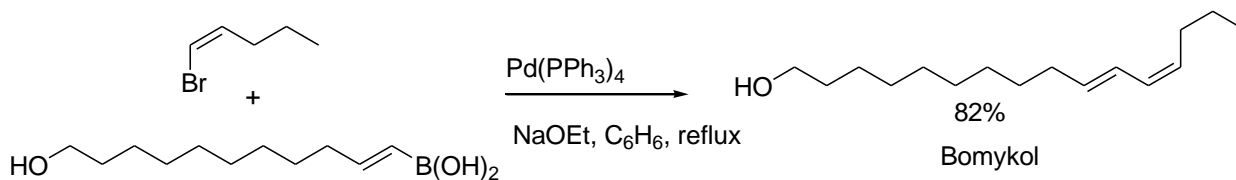
Scheme 1

Mechanism

The major difference of the Suzuki cross-coupling with the other cross-coupling reactions is the need of one equiv of a base due to the activation of the organopalladium halide complex A by conversion into the organopalladium alkoxide B. Due to the low nucleophilicity of the organoboron, the transmetallation takes place faster with B compared to A to give the intermediate C that can complete the catalytic cycle by reductive elimination (Scheme 2)



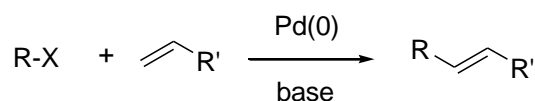
For an example, the synthesis of bombykol can be accomplished by C-C cross-coupling from vinyl boronic acid and vinyl bromide using $\text{Pd}(\text{PPh}_3)_4$ in the presence of NaOEt (Scheme 3). The reaction stereoselectively affords the product in 82% yield.



3.7.2 Heck Reaction

The palladium-catalyzed C-C cross-coupling of alkenes with alkenyl triflates (bromides, iodides) and aryl triflates (bromides, iodides) to give substituted alkenes in the presence of stoichiometric amount of triethylamine is called Heck Reaction (Scheme 4). The amine serves to reduce $\text{Pd}(\text{II})$ to the catalytically active $\text{Pd}(\text{0})$ complex. The amine also

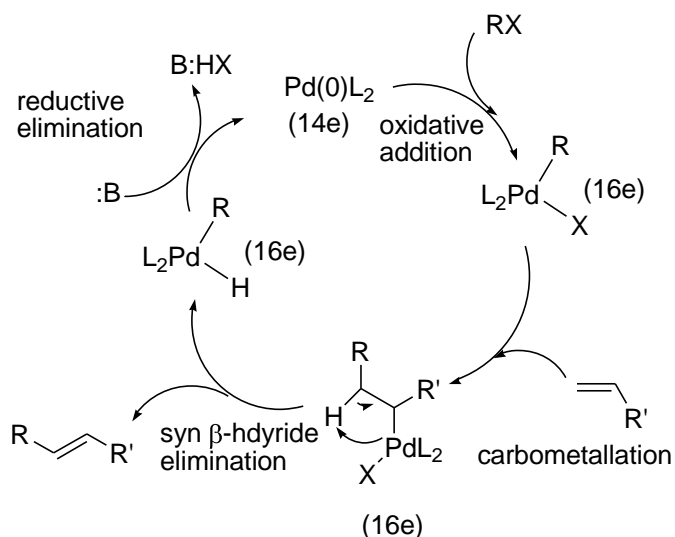
plays an important role in that it neutralizes the acid formed in the reaction (TfOH, HBr or HI).



Scheme 4

Mechanism

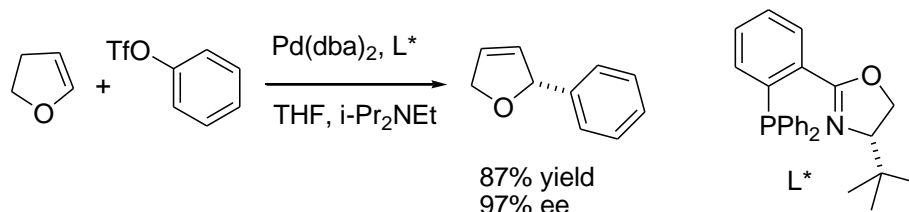
Pd(II) is reduced to active palladium(0) complex that undergoes oxidative addition with the alkenyl triflates to give organopalladium(II) complex. The latter proceeds *cis*-selective addition to the alkene double bond. This is a carbopalladiation of the double bond. The addition product is an alkyl-Pd(II) complex. The newly formed C-C bond undergoes rotation to bring an H-β atom and the PdL_x group into *syn* complex to occur β-hydride elimination. (Scheme 5). The base regenerates the catalyst.



Scheme 5

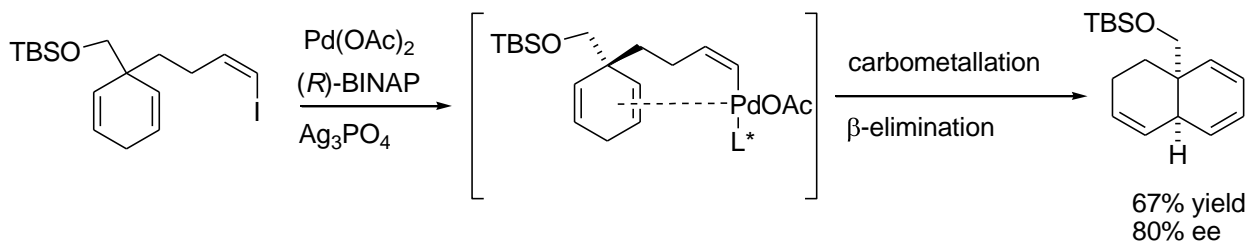
Asymmetric Reactions

Asymmetric Heck reaction has been extensively studied. For an example, the Heck reaction of phenyl triflate with dihydrofuran has been accomplished using the amino acid-derived phosphine ligand with high enantioselectivity (Scheme 6).



Scheme 6

Asymmetric intramolecular Heck reaction has been accomplished in the presence of (*R*)-BINAP for the synthesis of decalin derivative with good enantioselectivity (Scheme 7).

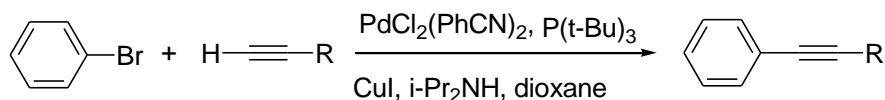


Scheme 7

3.7.3 Sonogashira Coupling

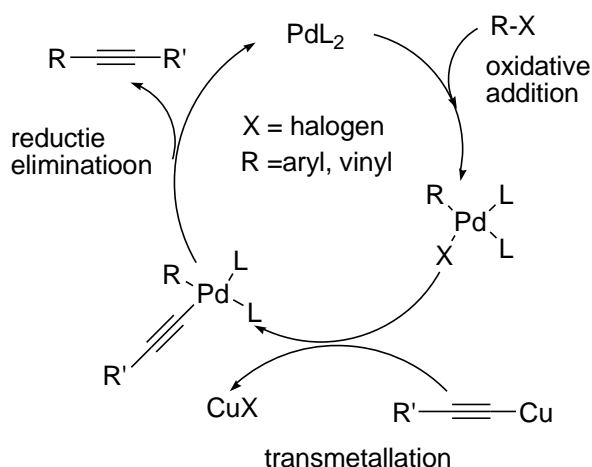
The C-C cross-coupling reaction of organocopper reagents with electrophiles is a well known method and does not require the presence of transition metals as catalyst. Nevertheless, it is found that palladium can accelerate the reaction. The palladium-catalyzed C-C cross-coupling of in situ generated alkynylcopper reagents with aryl as well as alkenyl halides is known as the Sonogashira Coupling (Scheme 8-9). The reaction takes place smoothly under mild conditions in the presence of catalytic amount of copper(I) iodide and tolerates a variety of functional groups in both coupling partners including hydroxo, carbonyl, amino, acyloxy, acetal, esters, amides etc. Thus, this

reaction has been extensively used to the synthesis of many natural products and pharmaceuticals and macromolecules.



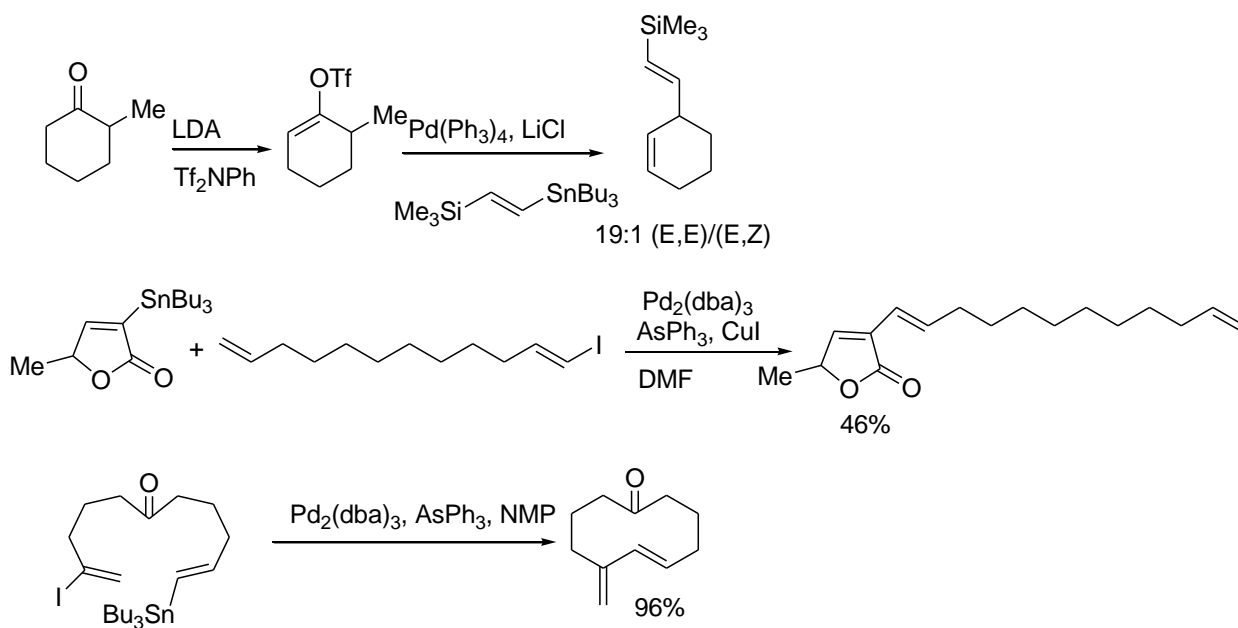
Scheme 8

Proposed Mechanism



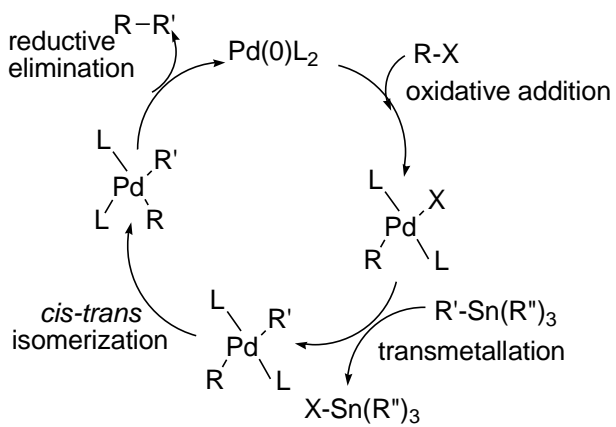
3.7.4 Stille Coupling

The palladium-catalyzed C-C cross-coupling reaction of organotin reagents with electrophiles to give dienes is called 'Stille Coupling' although Stille and Migita independently investigated this reaction (Scheme 3). The main advantage of this method is that a lot of functional groups like aldehydes, ketones, esters, nitriles, amines as well as alcohols are tolerated. In comparison to Suzuki coupling no base is needed. Therefore, organometallic compounds having tin as well as boron can be coupled selectively via tin. However, toxicity concerns are the major disadvantage of the cross-coupling of organostannanes. Both inter- and intramolecular reactions have been explored and widely applied in the synthesis of complex molecules.



Scheme 9

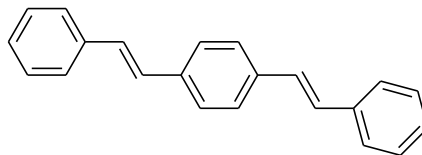
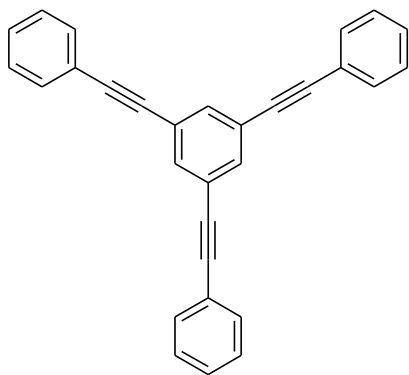
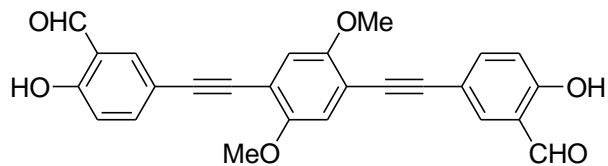
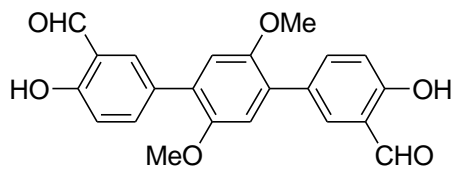
Proposed Mechanism



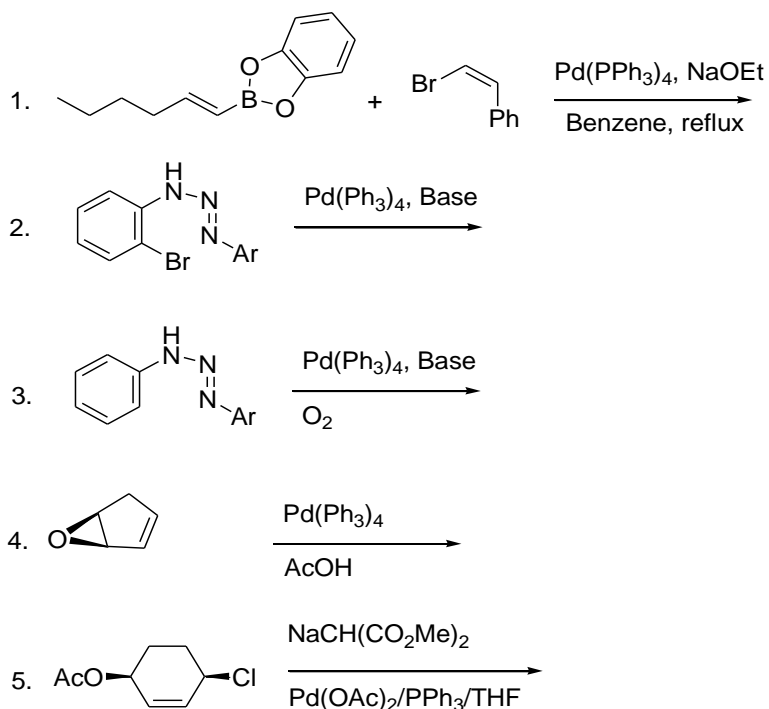
Scheme 10

Problems

A. Show effective synthetic routes for the synthesis of the following compounds using palladium-catalyzed C-C cross-coupling reactions.



B. What products would you expect in the following reactions?



Textbook

J. Clayden, N. Greeves, S. Warren, P. Wothers, Organic Chemistry, Oxford University Press, New York, 2001.

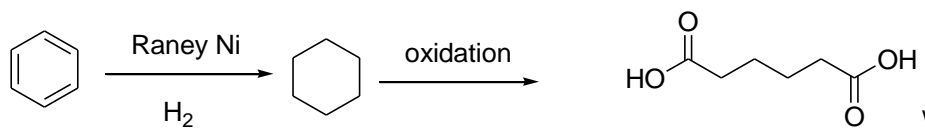
Lecture 29

3.8.1 Organonickel Compounds

Similar to organopalladium compounds, organonickel compounds are generated *in situ* for organic synthesis. Indeed the use of organonickel complexes for the construction of carbon-carbon bonds is synthetically older than the analogous organopalladium chemistry. Some of the important processes are here covered.

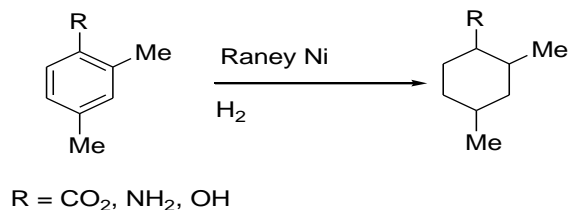
2.8.1.1 Hydrogenation

Raney nickel is one of the common catalysts used for the saturation of aromatic compounds. A practical example of the use of Raney nickel in industry is shown in Scheme 1, where benzene is reduced to cyclohexane. Similarly, naphthalene and anthracene are reduced to give *trans*-decalin and perhydroanthracene.



Scheme 1

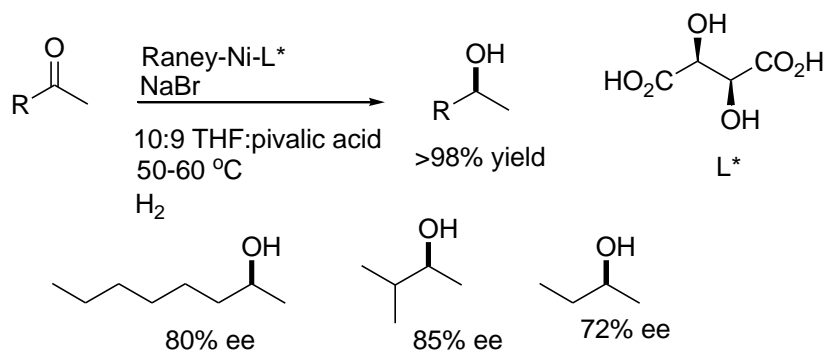
Under these conditions, substituted benzenes such as benzoic acids, phenols and anilines more easily undergo hydrogenation to give substituted cyclohexanes (Scheme 2).



Scheme 2

T. K. Yang, D. S. Lee, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 6, 4401.

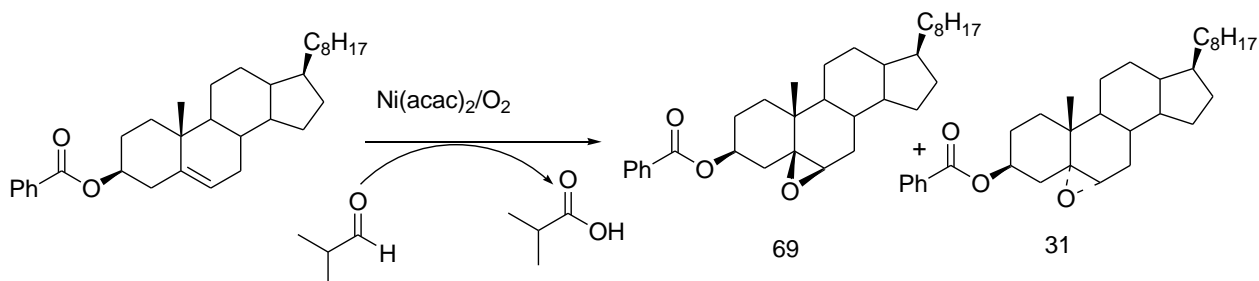
Heterogeneous Ni catalysts modified with tartaric acid and NaBr have been found to be effective catalyses for asymmetric hydrogenation of alkanones. For example, hydrogenation of 2-alkanones in the presence of the modified Raney Ni and an excess of pivalic acid gives 2-alkanols with up to 85% ee (Scheme 3).



Scheme 3

3.8.1.2 Epoxidation

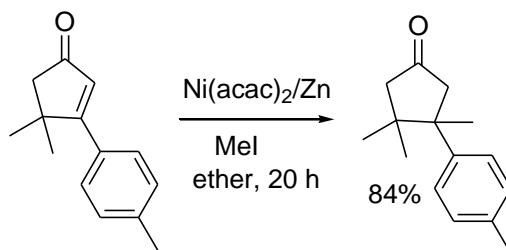
The aerobic epoxidation of functionalized alkenes can be accomplished using nickel(II) complex in the presence of aliphatic aldehydes as co-reductant. For an example, nickel(II)-1,3-diketonato complex catalyzes the epoxidation of cholesterol derivative to give a mixture of β and α epoxides in quantitative yield in the presence of 2-butanal under molecular oxygen (Scheme 4).



Scheme 4

3.8.1.3 Carbon-Carbon Bond Formation

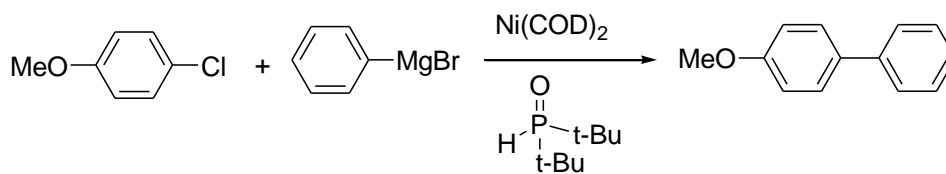
Carbon-carbon bond formation is heart of organic synthesis. Ni(0) generated *in situ* from Ni(acac)₂/Zn catalyzes the conjugate addition of alkyl aryl iodides to give α,β -conjugated carbonyl compounds under sonication. An interesting example is the methylation shown in Scheme 5, which fails to take place under other conditions.



Scheme 5

J. Doyon, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 6, 3689.

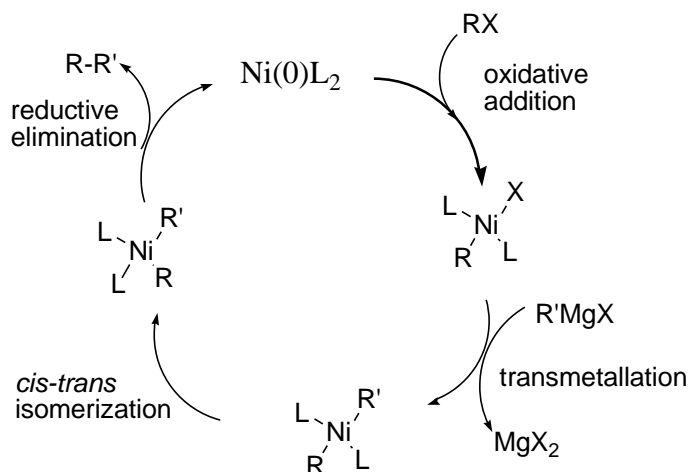
The nickel-catalyzed C-C cross-coupling of Grignard reagents with alkyl, vinyl or aryl halides provides an economic transformation, but the reaction is limited to halide partners that do not react with organomagnesium compounds. One example is in the industrial-scale production of styrene derivatives, and the Kumada coupling is the method of choice for the low-cost synthesis of unsymmetrical biaryls (Scheme 6).



Scheme 6

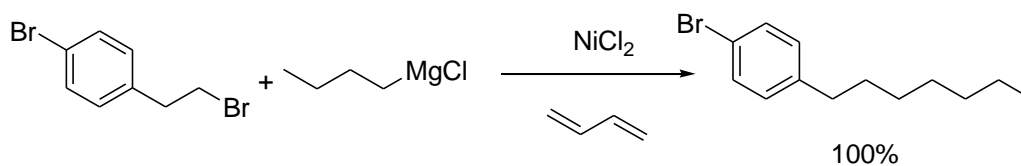
Mechanism

The proposed catalytic cycle involves oxidative addition followed by reductive elimination *via* transmetalation and *cis-trans* isomerization (Scheme 7).



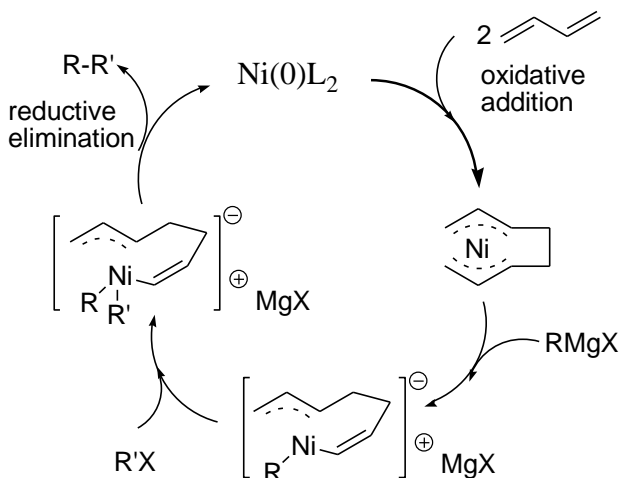
Scheme 7

In the cross-coupling of alkyl halide with alkyl magnesium chloride, an important influence of 1,3-butadiene on the reaction has been noted (Scheme 8).



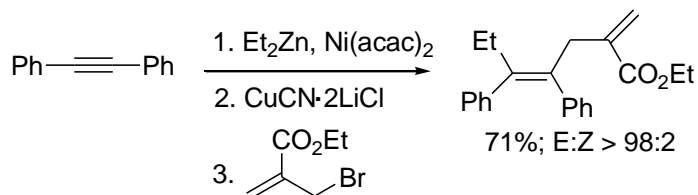
Scheme 8

The proposed mechanism for acceleration of the reaction with butadiene is shown in Scheme 9.



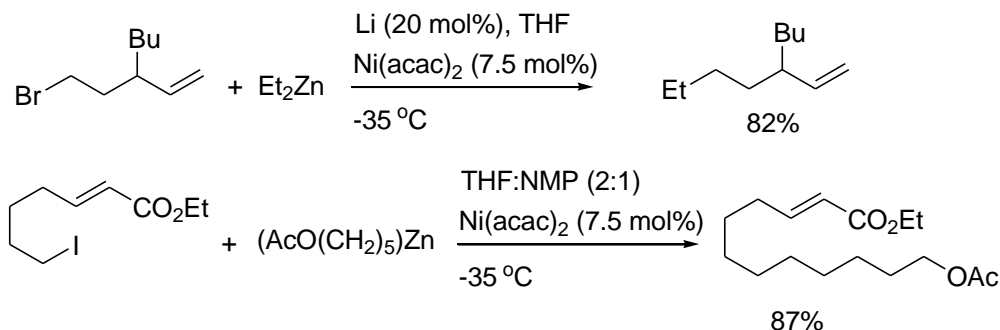
Scheme 9

In the presence of $\text{Ni}(\text{acac})_2$, organozinc adds to phenylacetylenes to give substituted alkenes with high stereoselectivity (> 99% *syn*-addition). The resulting organometallics can be trapped with electrophiles (Scheme 10).



Scheme 10

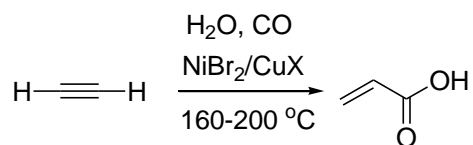
Unsaturated alkyl halides can be smoothly cross-coupled with Et_2Zn in the presence of $\text{Ni}(\text{acac})_2$ under mild conditions (Scheme 11). Using polar co-solvent N-methylpyrrolidinone, a variety of polyfunctional zinc organometallics can be coupled with alkyl iodides having remote double bonds. In these reactions, the double bond bounded to a metal center acts as a π -acceptor and therefore removes electron density from the metal center facilitating the reductive coupling reaction.



Scheme 11

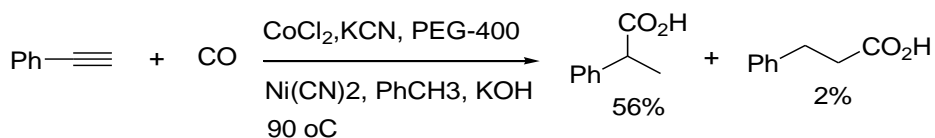
3.8.1.4 Carbonylation

Nickel-complexes catalyze the addition of carbon monoxide to alkynes. The industrial production of acrylic acid at one time consisted of combining acetylene, carbon monoxide and water at 40-55 atm and 160-200 °C with NiBr_2 and a copper halide (Scheme 12).



Scheme 12

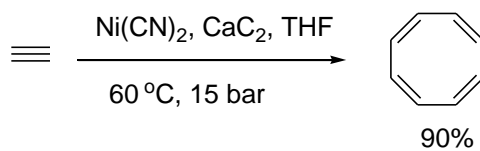
The direct regioselective hydrocarboxylation of alkynes to saturated carboxylic acids can be accomplished using CoCl_2 , KCN and $\text{Ni}(\text{CN})_2$, under phase transfer conditions (Scheme 13). Polyethylene glycol (PEG-400) is used as the phase-transfer agent and the branched saturated acids form as the major products.



Scheme 13

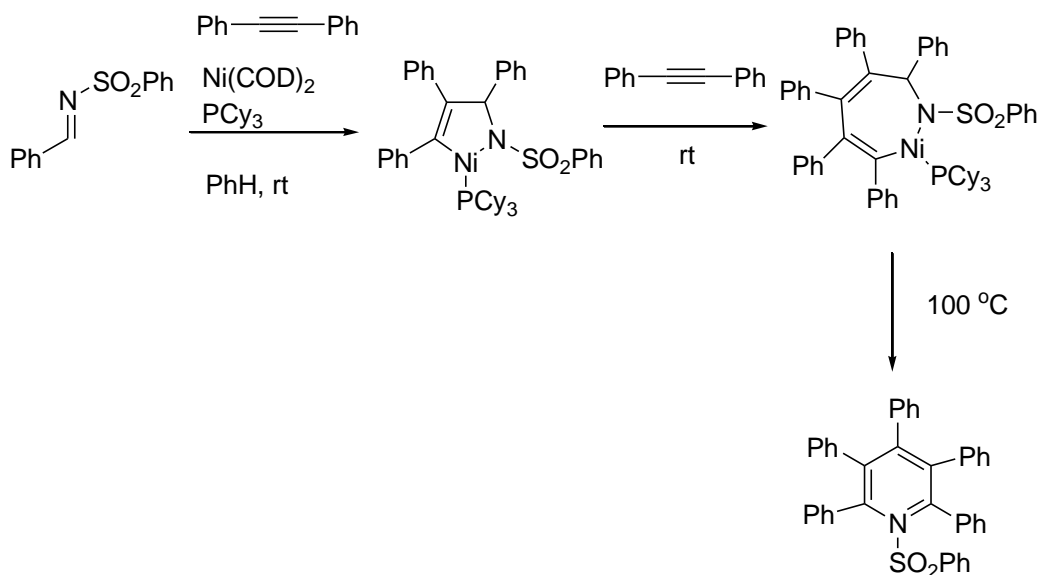
3.8.1.5 Alkene/Alkyne Oligomerization Reactions

Nickel catalysts have been extensively studied for the polymerization and dimerization of alkynes and alkenes. One practical implementation of alkyne oligomerization is the Reppe synthesis for example in the synthesis of cyclooctatetraene (Scheme 14).



Scheme 14

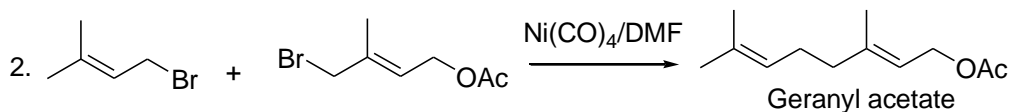
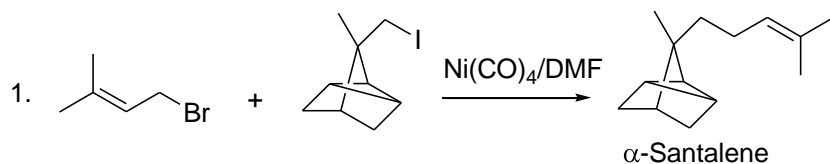
The formation of organonickel compounds have been revealed by a carefully designed experiment two such intermediates are formed quantitatively (Scheme 15).



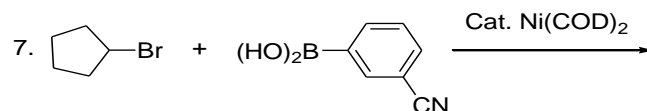
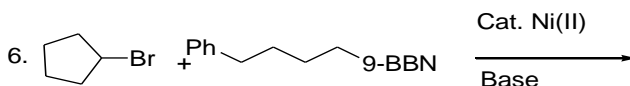
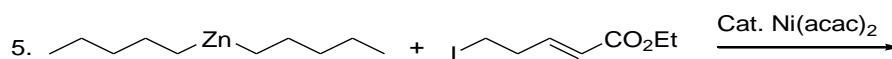
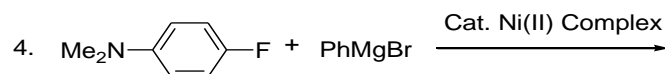
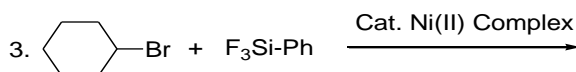
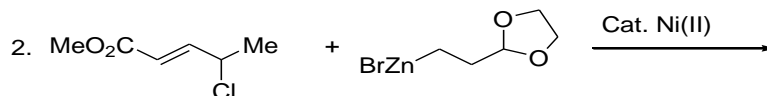
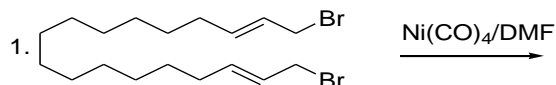
Scheme 15

Problems:

A. Rationalize the following reactions.



B. Write the major products for the following reactions.



Text Book

M. B. Smith, *Organic Synthesis*, 2nd Ed., McGraw Hill, New York, 2004.

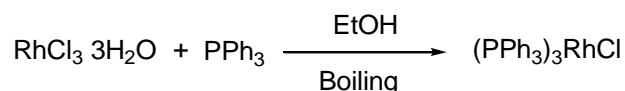
Lecture 30**3.8.2 Organorhodium Compounds**

Organorhodium compounds are used as soluble catalysts for effecting many useful organic transformations. This section covers some of the important processes.

3.8.2.1 Reactions of Alkenes

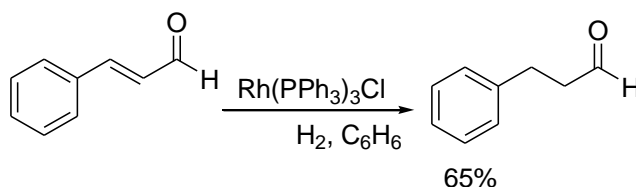
The addition of hydrogen to alkenes using transition metal catalysis occupies an important position in organic synthesis. Homogeneous hydrogenation processes offer distinct advantage over their heterogeneous counterparts, for example, superior chemo-, regio- and stereoselectivity.

One of the most versatile metal catalysts for double bond saturation in the homogeneous phase is Wilkinson's catalyst, $[\text{RhCl}(\text{PPh}_3)_3]$. It is prepared by the reaction of RhCl_3 with excess of PPh_3 in boiling EtOH (Scheme 1).



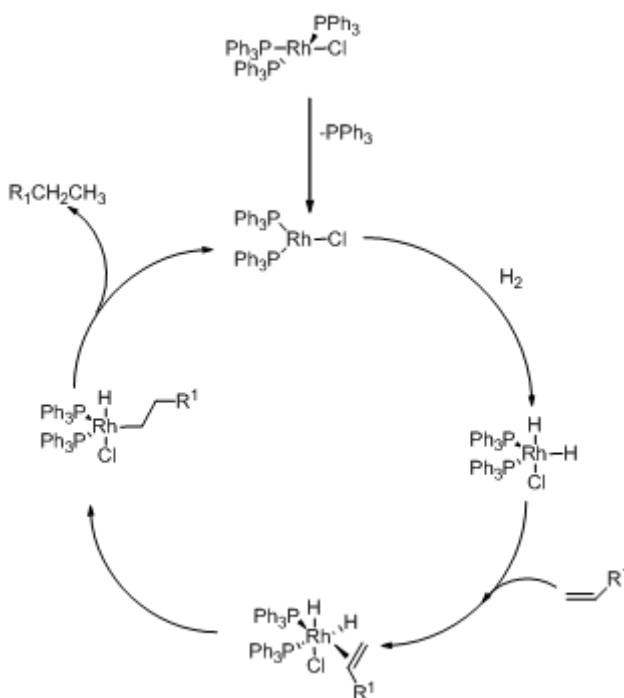
Scheme 1

Wilkinson's catalyst and its modified forms have been extensively used for the hydrogenation of alkenes (Scheme 2). Functional groups like oxo, cyano, nitro, choro and azo are compatible under ordinary temperature and pressure. If the functional groups are properly situated chelate on the active Rh and can thus direct hydrogenations providing high degree of selectivity.



Scheme 2

Mechanism

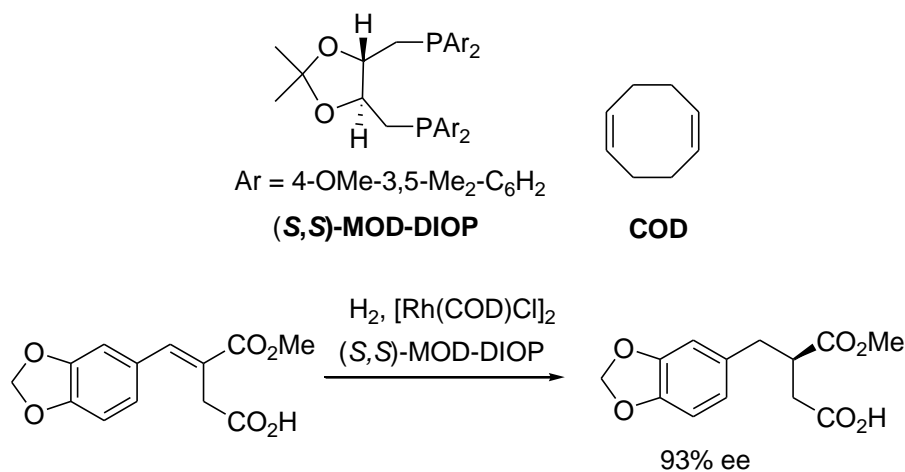


Scheme 3

The coordination complex is a square planar 16 electron complex whose stability is due to filled bonding molecular orbitals (Scheme 3). The complex loses a PPh_3

to form a 14 electron complex which coordinates with alkene and then undergoes oxidative addition with hydrogen. This is followed by transfer of a hydrogen to carbon from Rh to form alkyl Rh intermediate. Then, a second hydrogen migrates to carbon leading to reductive elimination of saturated product. In this step, rhodium is electrophilic and hydride transfer is nucleophilic. In some cases, however, an alternative reaction pathway seems to have been operating. This pathway first involves the addition of hydrogen to rhodium prior to the complexation of alkene. The evidence for this path comes from the fact that addition of hydrogen to the $[\text{RhCl}(\text{PPh}_3)_2(\eta\text{-C}_2\text{H}_4)]$ is not feasible.

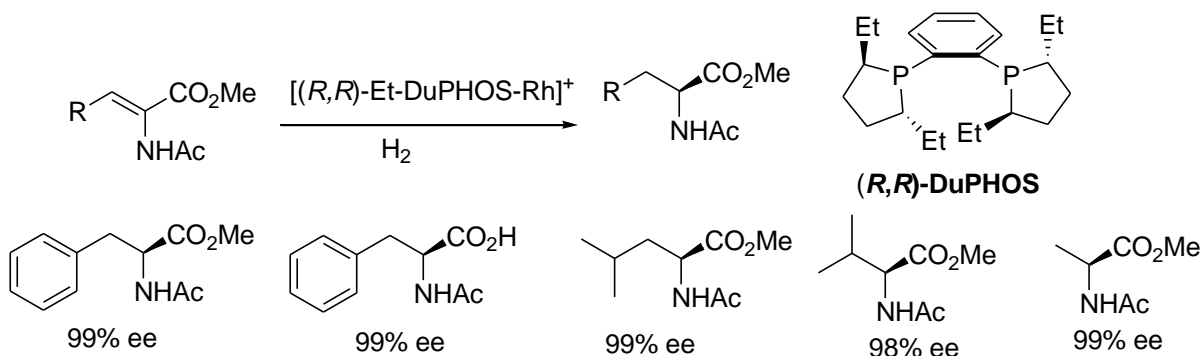
Subsequently, chiral rhodium(I)-phosphine complexes have been developed for asymmetric hydrogenation of alkenes. Among the vast number of chiral catalysts, Rh(I) diphosphine complexes revealed to be the most efficient for asymmetric reduction of functionalized alkenes. For examples, α -piperonylidene succinic acid half-ester with hydrogen in the presence of precatalyst prepared *in situ* by mixing of (S,S)-MOD-DIOP with $[\text{Rh}(\text{COD})\text{Cl}]_2$ affords the product in 93% ee (Scheme 4).



Scheme 4

A series of chiral rhodium(I)-diphosphine complexes have been explored for the hydrogenation of α -enamides to afford α -amino esters. For examples, *N*-acetyl-

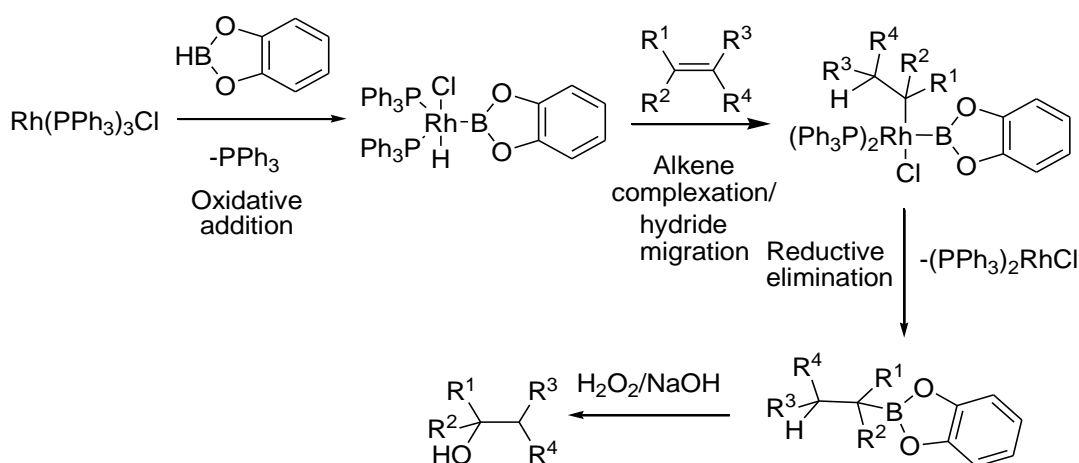
α -enamides with β -substituents can be reduced using the (*R,R*)-Et-DuPHOS-Rh complexes with excellent enantioselectivity (Scheme 5).



Scheme 5

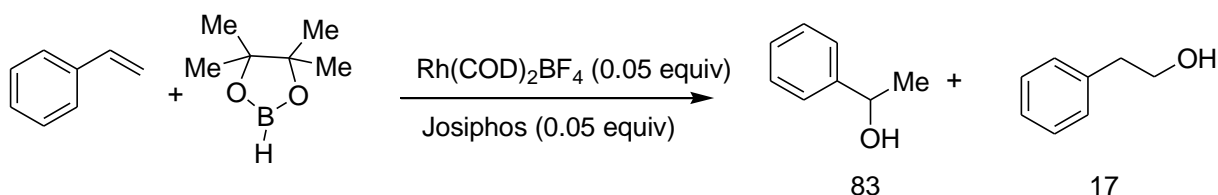
3.8.2.2 Hydroboration

Another interesting application of Wilkinson's catalyst is its use in the hydroboration of alkenes and alkynes. The reactions sensitive to steric effects, and afford diastereoselectivity that is complementary to the uncatalyzed hydroborations. Thus, it has been extensively used in natural product synthesis for the hydroboration of carbon-carbon multiple bonds. The proposed mechanism is analogy with that of the hydrogenation of alkenes (Scheme 6).



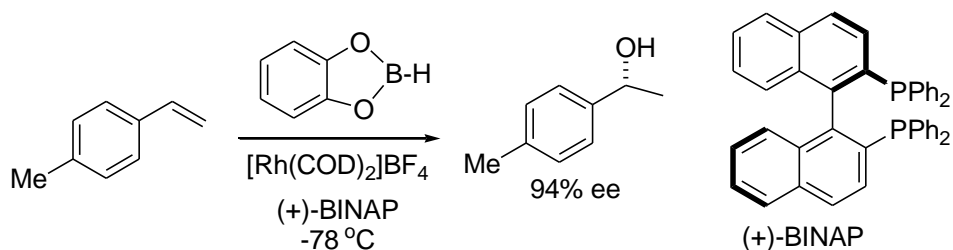
Scheme 6

Besides Wilkinson's catalyst, various other hydroboration catalysts based on rhodium have been used. The variation in ligand leads to changes in regio- and stereoselectivities. For an example, the hydroboration of styrene can be directed to the internal secondary borane by the use of $\text{Rh}(\text{COD})_2\text{BF}_4$ as a catalyst (Scheme 7).



Scheme 7

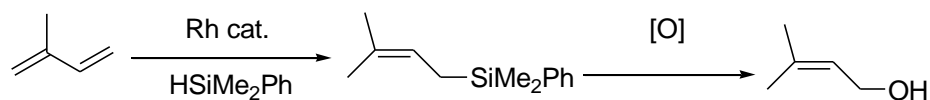
Several studies have subsequently focused on the development of boron hydrides and their application for asymmetric hydroboration with chiral rhodium complexes. For example, 4-methylstyrene reacts with catecholborane in the presence of cationic rhodium-BINAP complex with excellent enantioselectivity (Scheme 8).



Scheme 8

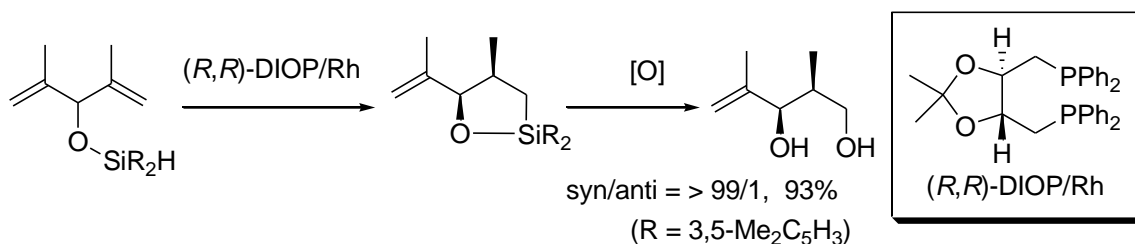
3.8.2.3 Hydrosilylation

Hydrosilylation of alkenes is not only of industrial importance, but also one of the most practical means that afford functionalized organosilicon compounds of synthetic applications. The rhodium(I)-catalyzed hydrosilylation of alkenes with anti-Markovnikov selectivity provides an effective route for the synthesis of 1-silylalkanes. The adducts can be subjected to an efficient oxidative cleavage of the silicon-carbon bond transforming into 1-alkanols (Scheme 9).



Scheme 9

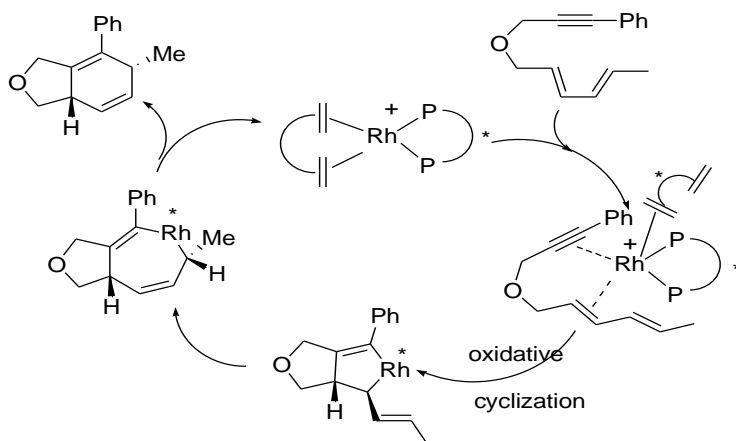
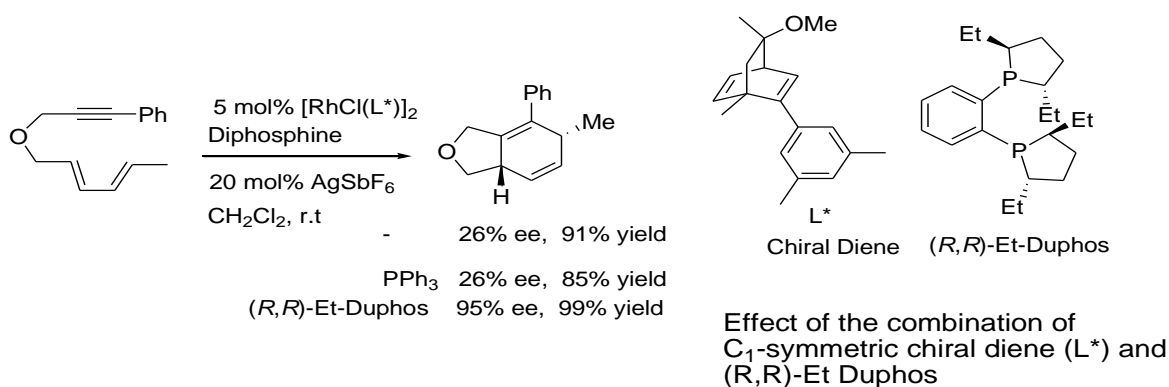
Asymmetric version of the reaction can be accomplished with high enantioselectivity (Scheme 10). For an example, Rh-BINAP complexes catalyze asymmetric intramolecular hydrosilylation of alkenes with high enantioselectivity.



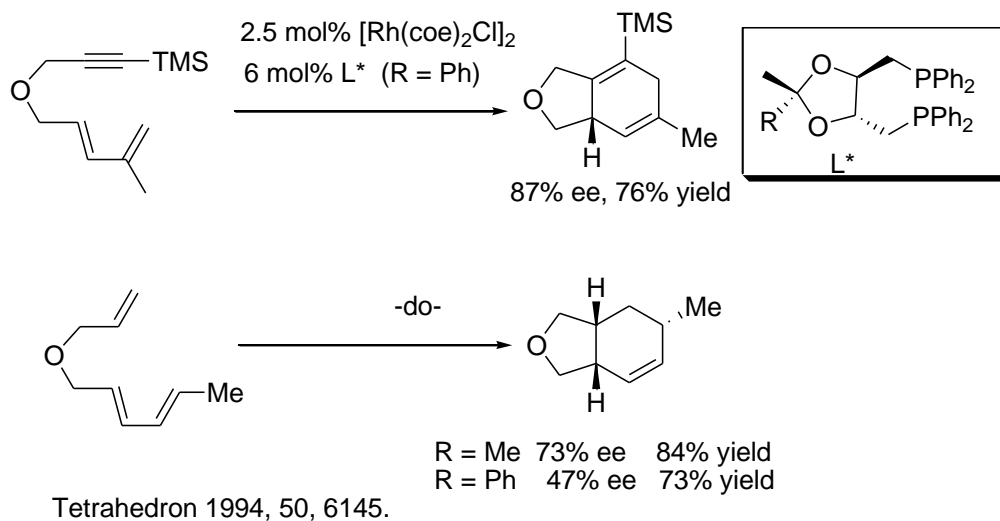
Scheme 10

3.8.2.4 Cycloaddition

Chiral rhodium-phosphine complexes can be employed as effective catalysts for cycloaddition reactions. For examples, rhodium(I)-complexes having diene and chiral bisphosphines catalyze intramolecular (4+2)-cycloadditions with excellent enantioselectivity (Scheme 11-12)



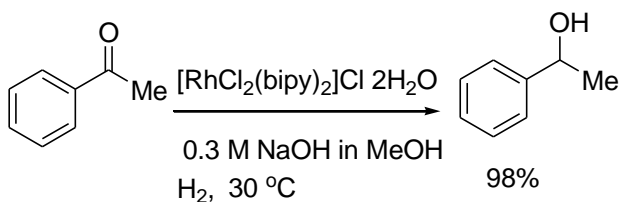
Scheme 11



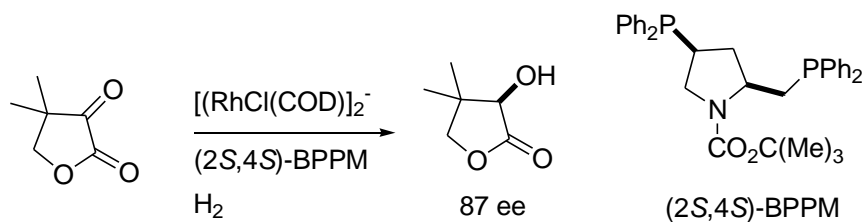
Scheme 12

3.8.2.5 Hydrogenation of Carbonyl Groups

Limited rhodium complexes have shown good catalytic activity towards the reduction of ketonic substrates possessing no functionality adjacent to the carbonyl group (Scheme 13). The asymmetric version of the reaction can be accomplished using chiral rhodium complex. For an example, chiral rhodium-phosphine complex is used for the hydrogenation of ketopantolactone with good enantioselectivity (Scheme 14).



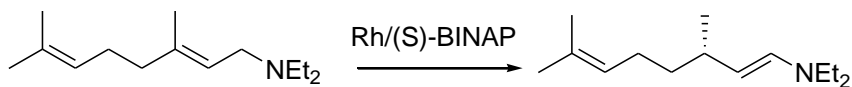
Scheme 13



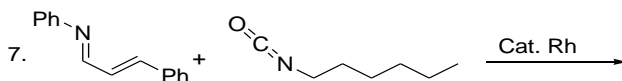
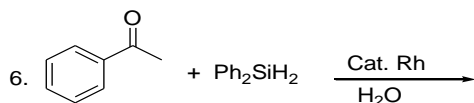
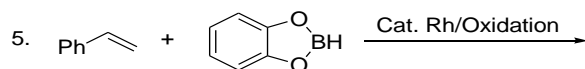
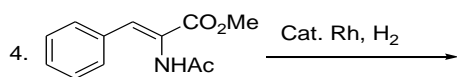
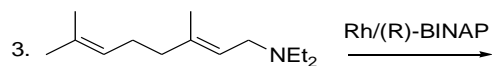
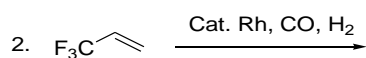
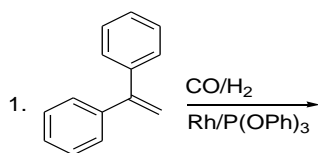
Scheme 14

Problems

A. Rationalize the following reaction.



B. Complete the following reactions.



Reference

Transition Metals for Organic Synthesis, Vol. I, Ed., M. Beller and C. Bolm, Wiley-VCH, New York, 1998.

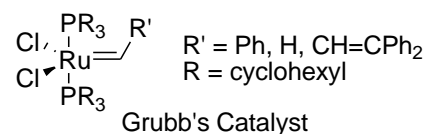
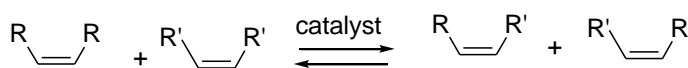
Lecture 31

3.8.3.1 Organoruthenium Compounds

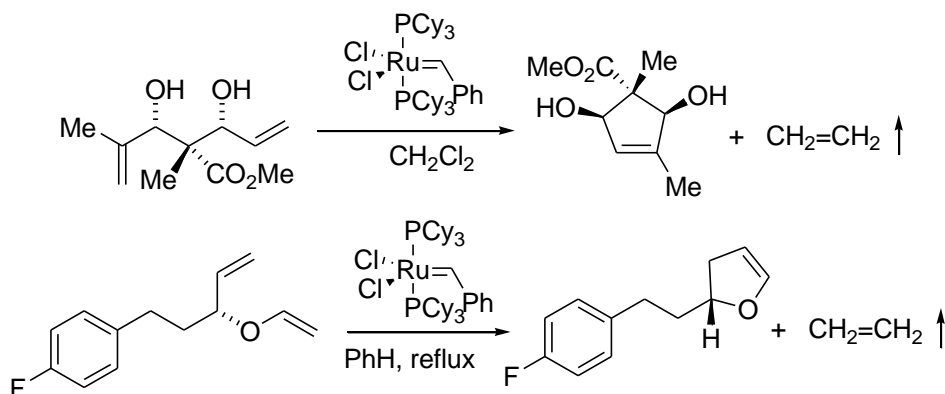
The organoruthenium compounds find extensive applications in organic synthesis. This section covers some of the important developments.

3.8.1.1 Alkene Metathesis

Ruthenium complexes have been the most common catalysts used for alkene metathesis (Scheme 1). The synthetic utilities of the reaction have increased with the development of the Grubb's catalysts, which are stable to Lewis acids, tolerant to an array of functional groups and allow the reactions to perform in aqueous and alcohol solution.

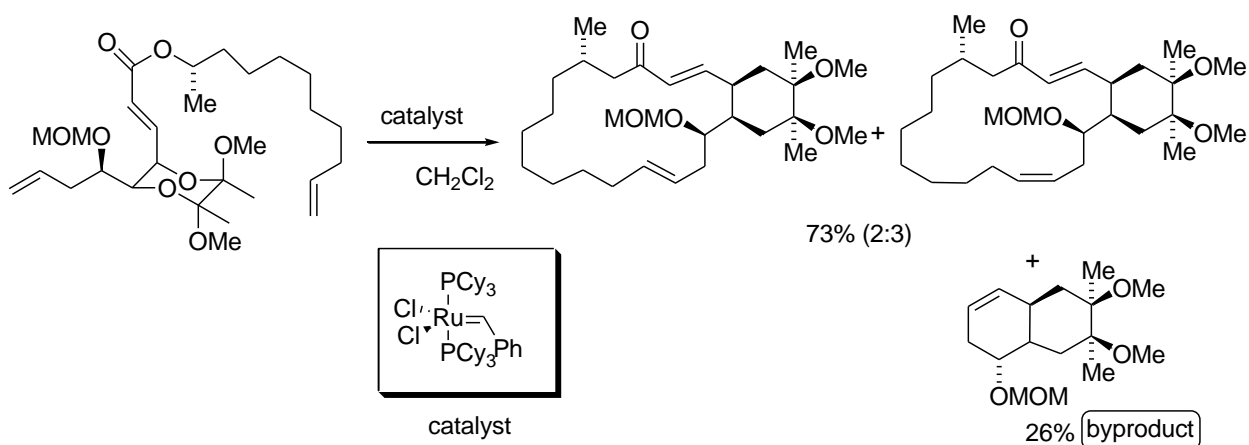


Scheme 1



Scheme 2

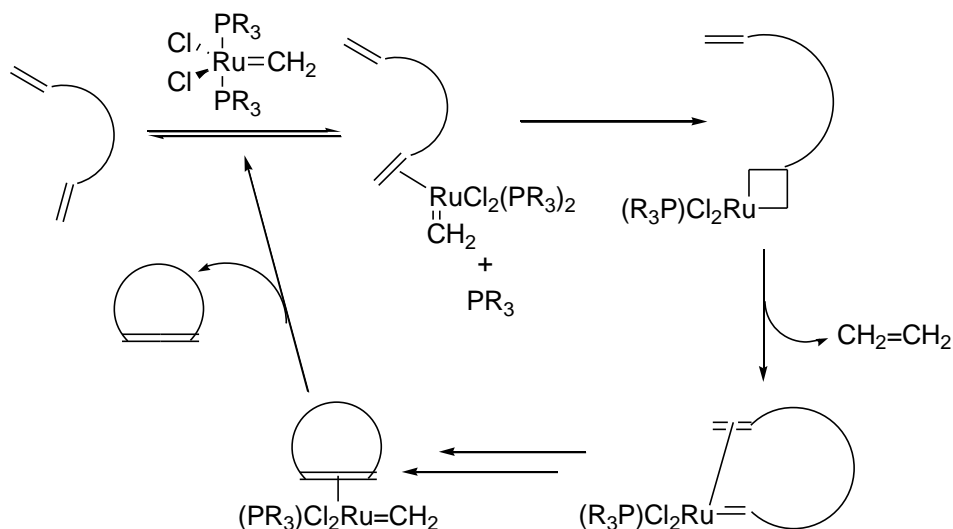
Among them, intramolecular processes dominate the synthetic applications and the alkenes having a $=\text{CH}_2$ unit are generally used so that one of the product is ethylene that can escape from the reaction medium and drives the equilibrium toward the desired cyclized product (Scheme 2). One of the more attractive features of this method is the ability to form macrocyclic compounds, which is otherwise difficult to accomplish (Scheme 3).



Scheme 3

Mechanism

The reaction proceeds *via* a metallacyclobutane intermediate (Scheme 4).

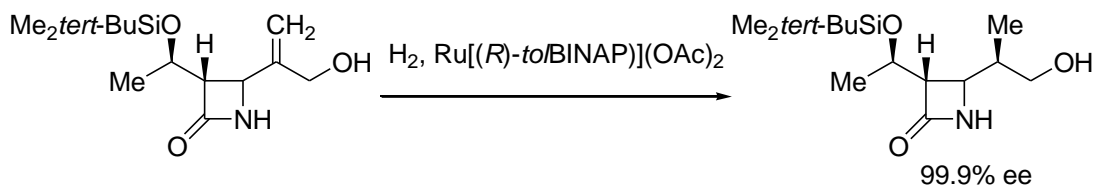
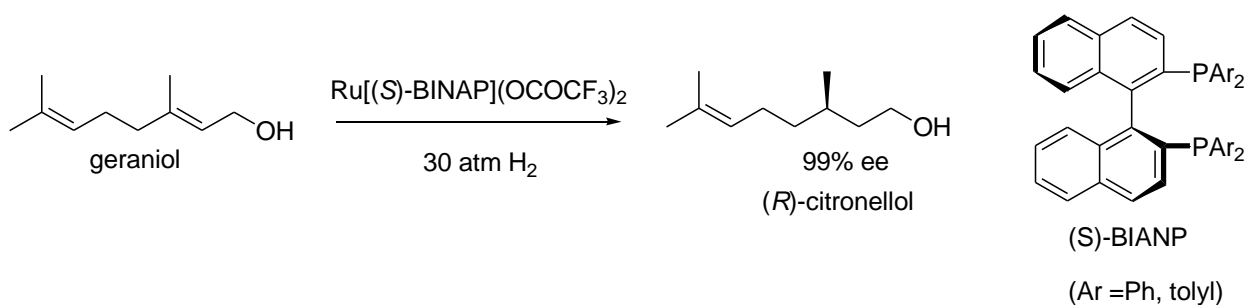


Scheme 4

3.8.1.2 Hydrogenation

Reactions with Alkenes

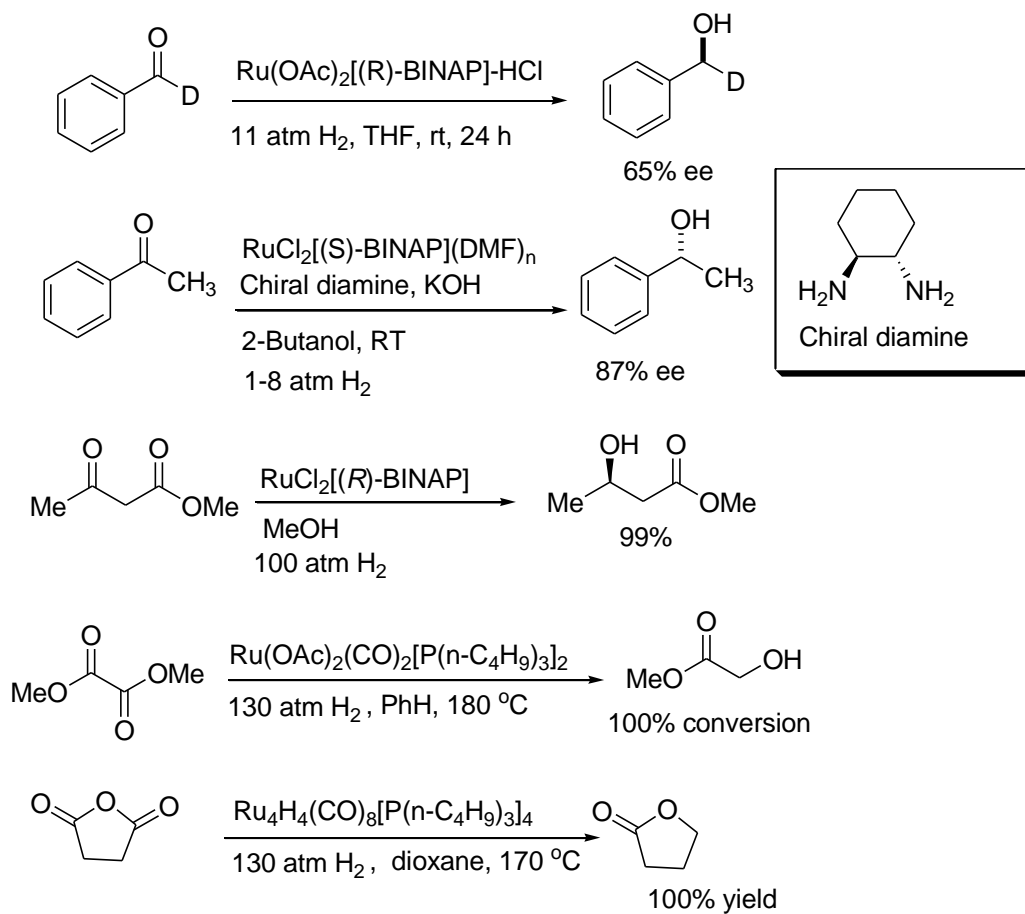
Alkene hydrogenation occupies an important place in transition metal mediated transformations. One of the most versatile catalysts for double bond reduction under homogeneous conditions is $\text{RuCl}_2(\text{PPh}_3)_2$. Its chiral version has also been found to be the most efficient for the asymmetric hydrogenation of double bonds. For examples, chiral Ru(II)-BINAP catalyzes the hydrogenation of a wide range of functionalized alkenes with excellent selectivity. Based on the substitution pattern of the substrate, the hydrogen pressure has to be applied in order to accomplish the high enantioface selection (Scheme 5).



Scheme 5

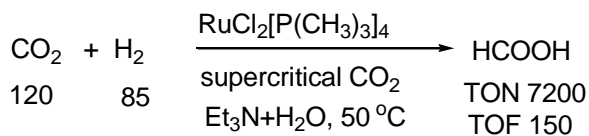
Reactions with Carbonyl Compounds

Hydrogenation of carbonyl compounds is among the most important synthetic transformations. Ruthenium phosphine based complexes in combination with molecular hydrogen have been excellent systems for hydrogenation a variety of carbonyl derivatives. Both asymmetric and non-asymmetric versions are well demonstrated. For examples, aldehydes, ketones, carboxylic acids and their derivatives can be efficiently hydrogenated (Scheme 6).



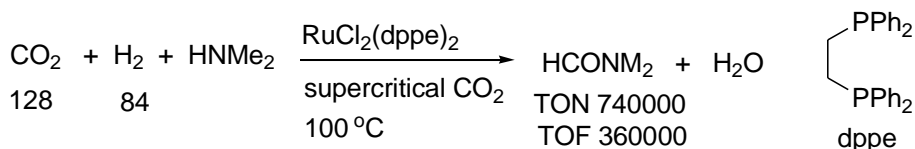
Scheme 6

CO₂ fixation is of great interest as a future technology. Ruthenium phosphine complexes have been found to be excellent catalysts for the hydrogenation of CO₂ to give formic acid (Scheme 7).



Scheme 7

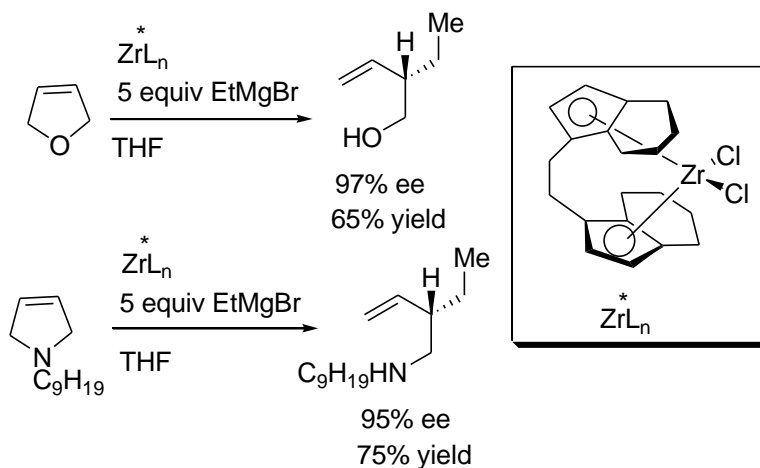
In the presence of amines, CO₂ can be transformed into formamides with high turnover number and turnover frequency (Scheme 8).



Scheme 8

3.8.3.2 Organozirconium Compounds

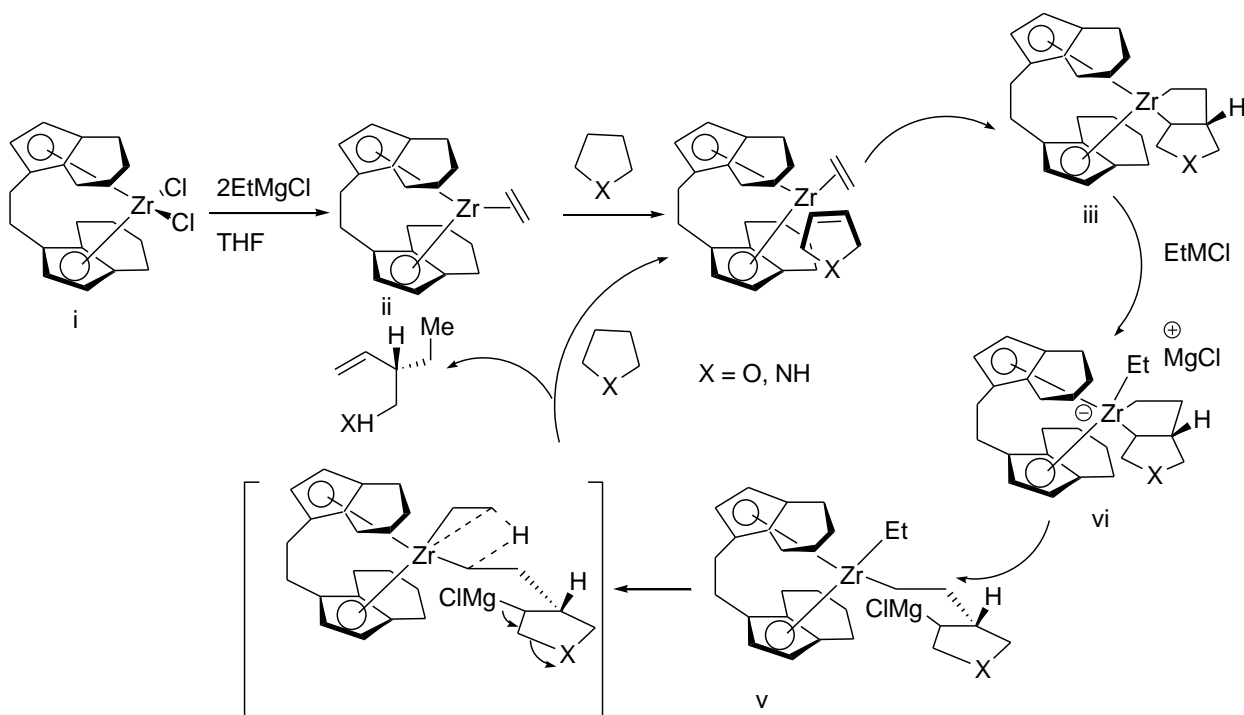
Carbon-carbon bond formation that proceeds under mild conditions in enantioselective fashion is an important process in chemical synthesis. Ethylene-bridged *bis*(tetrahydroindenyl)ZrCl₂ has been found to be effective catalyst for asymmetric ethylmagnesation of unsaturated heterocycles. The section covers the synthetic and mechanistic aspects of the reaction.



Scheme 9

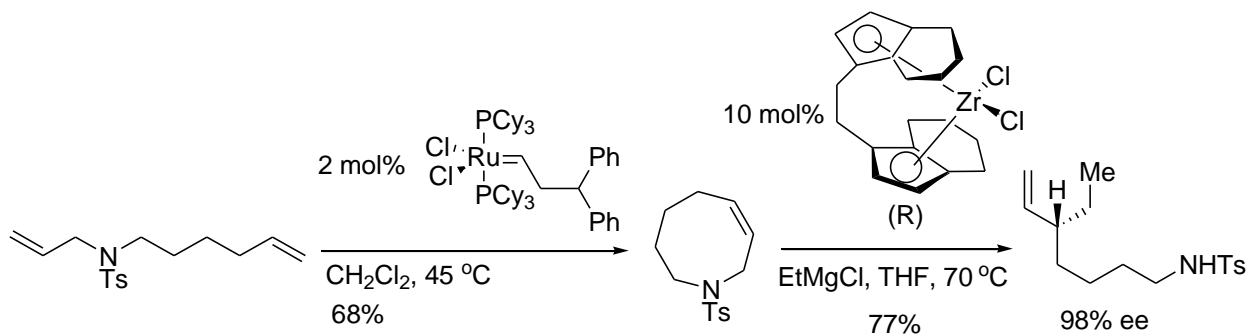
Reaction of the ethylene-bridged *bis*(tetrahydroindenyl)ZrCl₂ complex (i) with EtMgBr could generate zirconocene-ethylene complex (ii) that can couple with the unsaturated heterocycle to give metallocyclopentane intermediate (iii). Reaction of the intermediate (iii) with EtMgCl can give the intermediate (iv) that could undergo Zr-Mg ligand exchange to yield intermediate (v). The latter can

release the carbomagnesation product *via* β -hydride elimination to complete the catalytic cycle.



Scheme 10

The combination of Zr-catalyzed enantioselective alkylation with ruthenium catalyzed ring closing metathesis affords convenient tool for efficient synthesis of optically pure materials (Scheme 11).



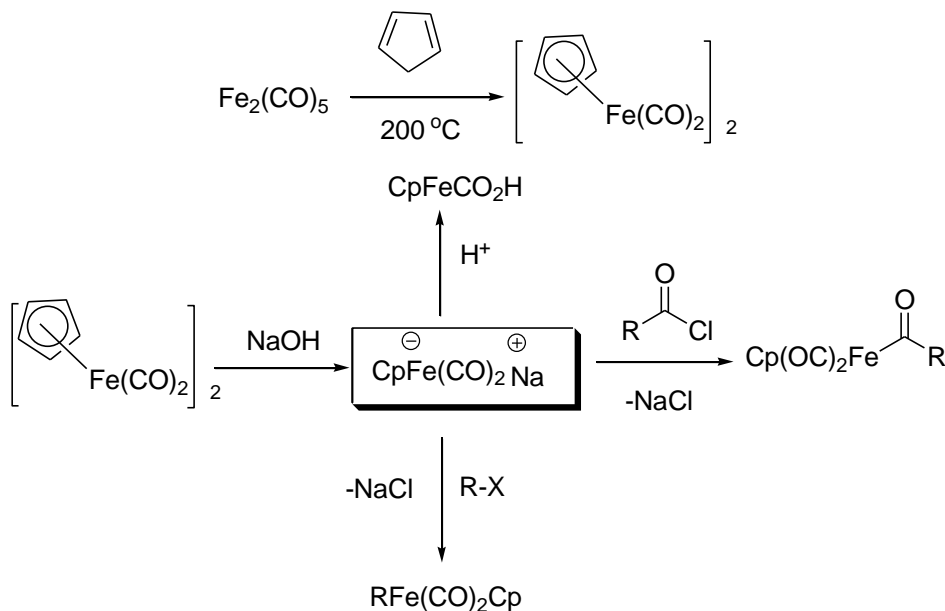
Scheme 11

3.8.3.3 Organoiron Compounds

A number of organoiron compounds have been developed. The Fe-C bond can be commonly cleaved by treatment with water, acid, alcohol or alkyl halide. Two most important organoiron reagents that are commonly used are cyclopentadienyliron dicarbonyl ($\text{CpFe}(\text{CO})_2$) and sodium tetracarbonyl ferrate ($\text{Na}_2\text{Fe}(\text{CO})_4$).

Cyclopentadienyliron carbonyl

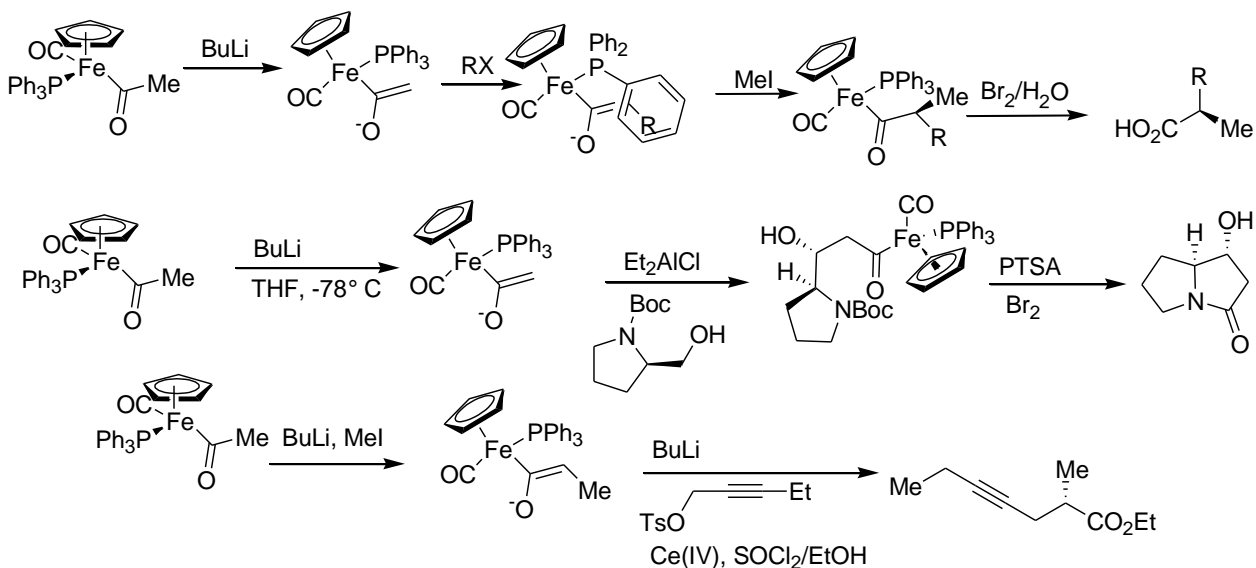
Reaction of $\text{Fe}(\text{CO})_5$ with cyclopentadiene gives the dimeric iron dicarbonyl complex that can be converted into the anionic $\text{CpFe}(\text{CO})_2\text{M}$ complex in the presence of base. The latter can be reacted with an array of acid chlorides, alkyl halides and acids to give the corresponding organoiron derivatives (Scheme 12).



Scheme 12

Chiral iron complexes have been developed for asymmetric synthesis. For example, (*S*)-aceto(carbonyl)(cyclopentadienyl)(triphenylphosphine)iron is a chiral enol equivalent which when deprotonated can react with a wide range of electrophiles to afford functionalized iron compounds. It can be alkylated with a high degree of enantioselectivity owing to the hindrance of attack by a phenyl

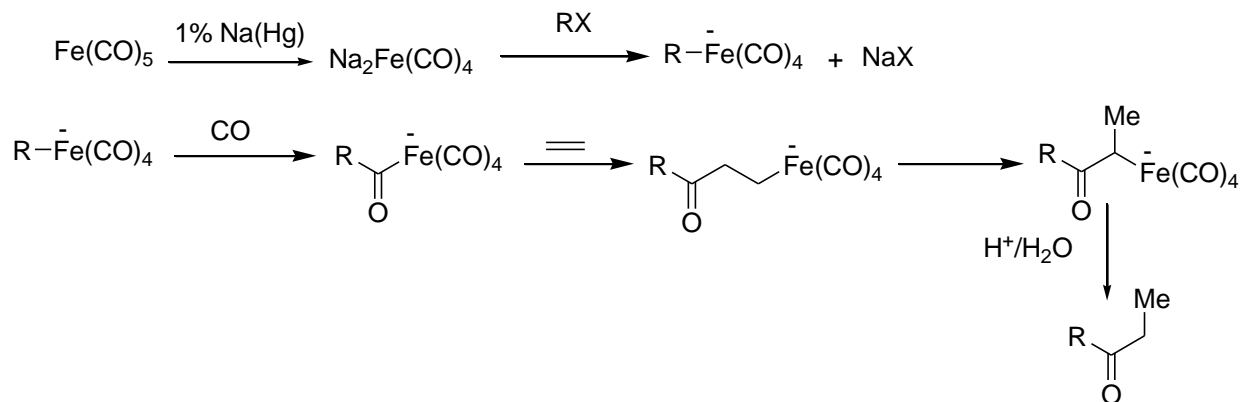
group on one face. A mild oxidation of this organoiron complex releases the enantiomerically pure product (Scheme 13).



Scheme 13

Sodium Tetracarbonyl Ferrate

It is known as Collman reagent and can be prepared by the reduction of iron pentacarbonyl. Using this reagent the synthesis of ketones, aldehydes, carboxylic acids, amides, esters can be accomplished (Scheme 14).

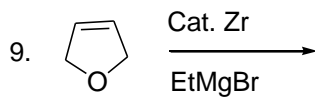
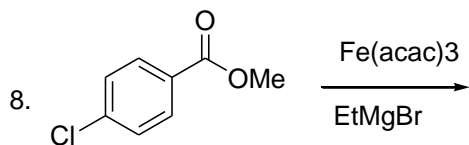
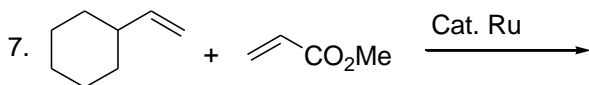
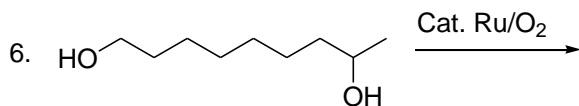
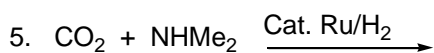
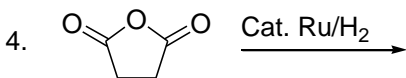
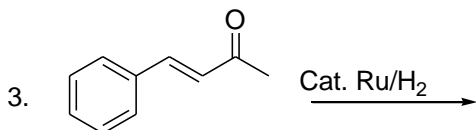
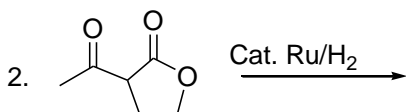
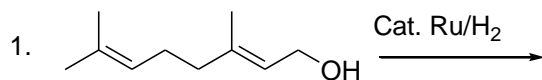


Scheme 14

R. D. Pike, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **4**, 2299.

Problems

What major products would you expect from the following reactions?



Reference

Transition Metals for Organic Synthesis, Vol. I, Eds., M. Beller and C. Bolm, Wiley-VCH, New York, 1998.

Lecture 32

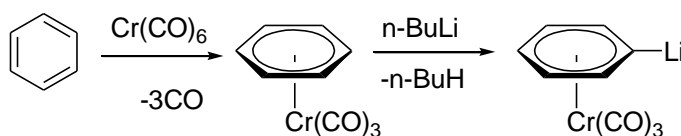
3.8.4 Organochromium Compounds

Organochromium based methods have been studied for a wide range of important organic transformations. This section covers the more significant methodological developments.

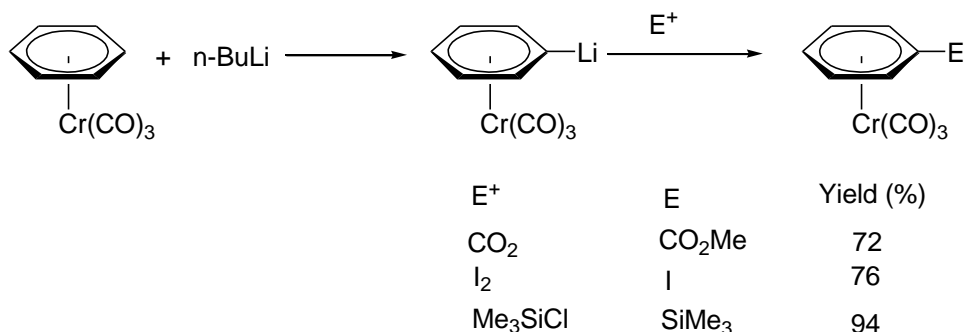
3.8.4.1 Reactions of Chromium-Arene Complex

Nucleophilic Substitution

Benzene and its derivatives react with chromium hexacarbonyl to give arylchromiumtricarbonyl complexes. In the complex, chromium resides in a position perpendicular to the plane of the ring, and the aryl ring is activated towards nucleophilic attack by metal complexes (Scheme 1). For example, arylchromiumtricarbonyl complexes can be used for the synthesis of alkyl substituted products by treatment with organolithium reagents, followed by treatment with electrophiles (Scheme 2).

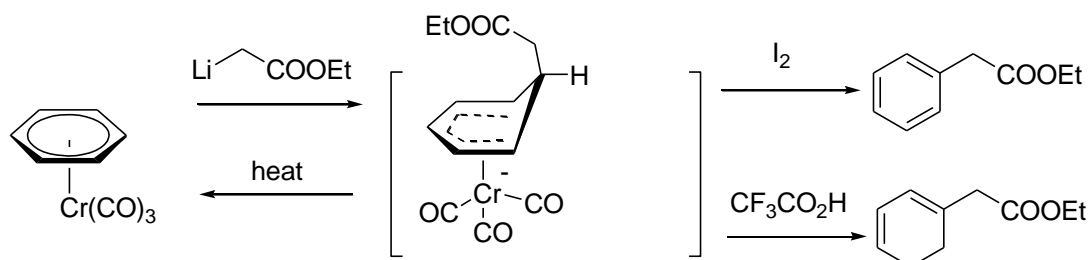


Scheme 1



Scheme 2

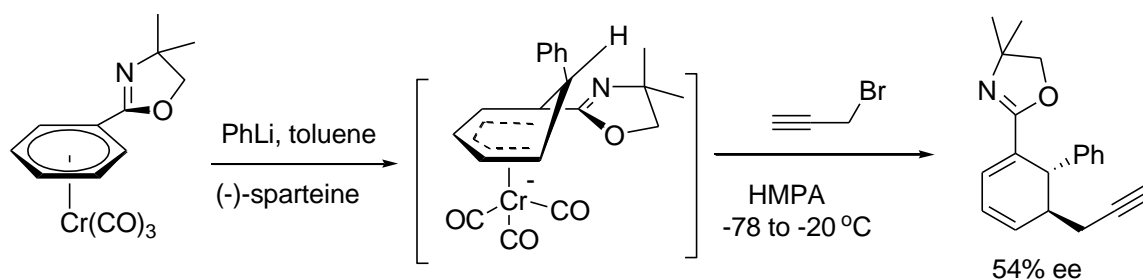
The arylchromiumtricarbonyl complex can also undergo nucleophilic aromatic substitution with carbon nucleophiles (Scheme 3). The mechanism involves the addition of nucleophile (R^-) to the aromatic ring to generate a chromium stabilized carbanionic complex. The metal stabilized anion intermediate can be decomposed by reaction with iodine or by protonolysis to give substituted products. However, the addition of nucleophile can also be reversed on heating the carbonionic arylchromiumtricarbonyl complex.



Scheme 3

When the benzene ring is functionalized, *ortho*, *meta* or *para* isomers are possible upon reaction of the chromiumtricarbonyl complex with nucleophiles.

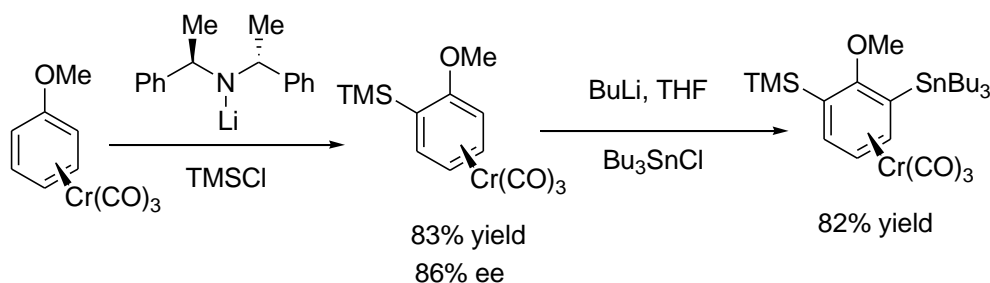
Asymmetric version of the reaction has been developed in the presence of chiral ligands. For an example, substituted arylchromiumtricarbonyl in the presence of (-)-sparteine undergoes reaction with PhLi , followed by propargyl bromide to give cyclohexadiene derivative in moderate enantioselectivity (Scheme 8).



Scheme 4

Ring Lithiation

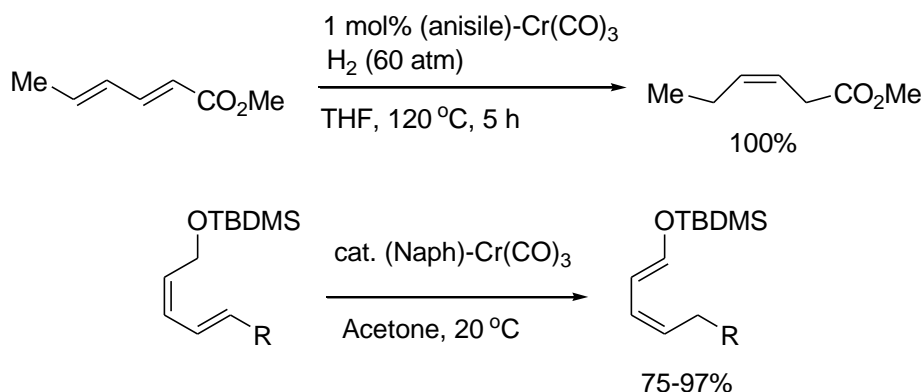
The ring deprotonation of arylchromiumtricarbonyl complex occurs to allow the regioselective preparation of a variety of alkylated complexes under mild conditions. Highly enantioselective deprotonation of prochiral substrates is possible in the presence of chiral bases (Scheme 5).



Scheme 5

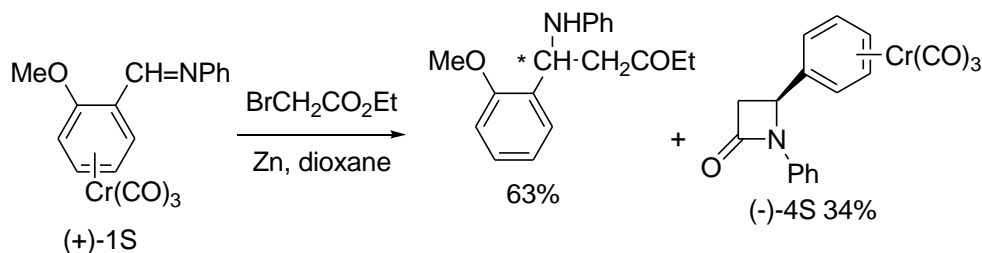
Catalysis

Arene- $\text{Cr}(\text{CO})_3$ is a good source for the generation of 'free' $\text{Cr}(\text{CO})_3$ unit that catalyzes useful organic transformations. For examples, the selective 1,4-hydrogenation of 1,3-dienes give Z-configured alkenes (Scheme 6). Only 1,3-dienes that can adopt a s-cisoid conformation is compatible, under these conditions isolated double bonds are not affected. While naphthalene- $\text{Cr}(\text{CO})_3$ complex catalyzes 1,5-hydrogenation.



Scheme 6

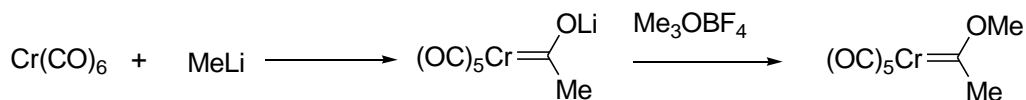
Arylchromiumtricarbonyl complexes have been employed in Zn-mediated Reformatsky-type alkylation reactions (Scheme 7). For an example, enantiomerically pure chromiumtricarbonyl complexes of benzaldimines react with bromoesters to afford stereoselectively (ee > 98%) β -aminoesters and β -lactams (Scheme 7)



Scheme 7

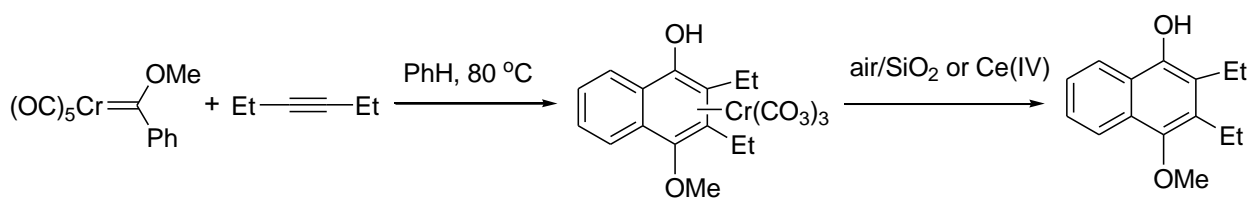
3.8.4.2 Chromium-Carbene Complex

Metal carbene complexes have received a great important in organic synthesis. Chromium forms Fischer-type carbene complexes. The usual method of synthesis involves the addition of an alkyl lithium to hexacarbonylchromium(0) followed by O-methylation (Scheme 8).



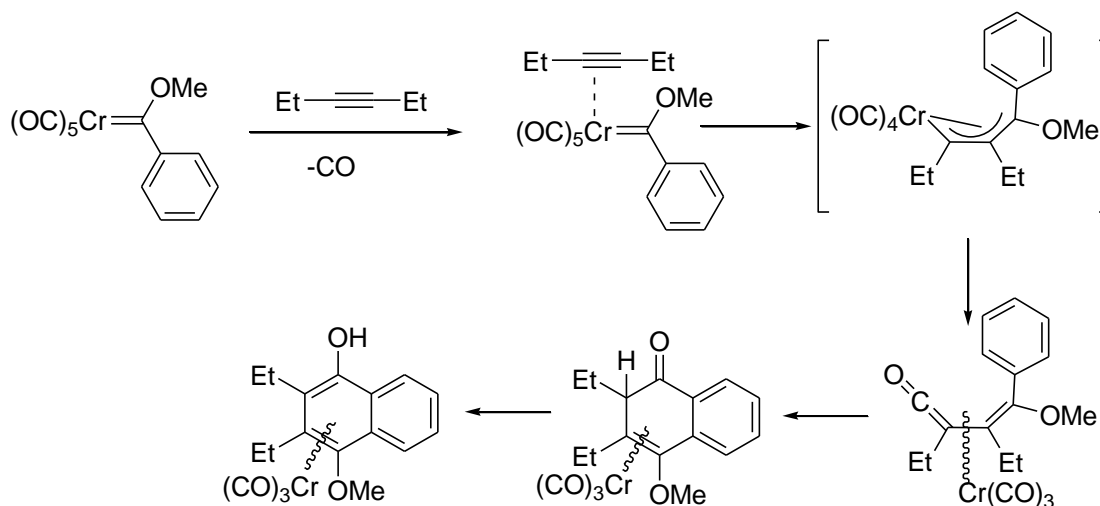
Scheme 8

These Fischer-type carbenes serve as reagents for various carbon-carbon bond formations such as Aldol and Micheal-addition, cycloaddition, benzannulation and cyclopropanation reactions. The reactions are believed to take place *via* insertion of an alkene or alkyne to the carbene to form a new carbene complex which undergoes further reaction. For an example, methoxycarbene chromium complexes bearing α,β -unsaturated carbene side chain react with alkyne under mild conditions to give $\text{Cr}(\text{CO}_3)$ -hydroquinones via a [3+2+1]-cycloaddition along with the $\text{Cr}(\text{CO}_3)$ fragment mediates the stepwise coupling of aryl carbene C_3 -synthon with an alkyne C_2 -unit and a carbonyl C_1 -building block (Scheme 9-10).



Scheme 9

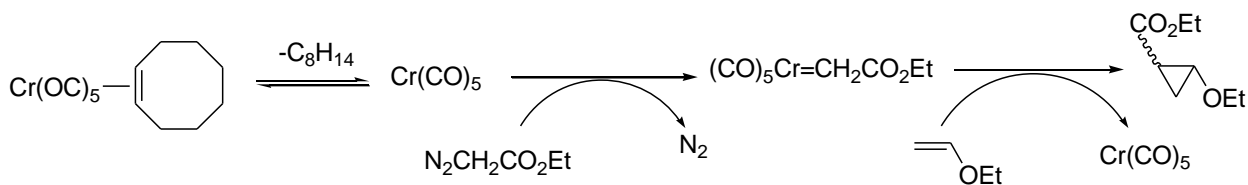
Mechanism



Scheme 10

Reaction of diazo compound with vinyl ethers in the presence of (cyclooctene)chromium(0) leads to cyclopropanes in moderate to good yields and stereoselectivities (Scheme 11). The reaction is catalytic and the results are

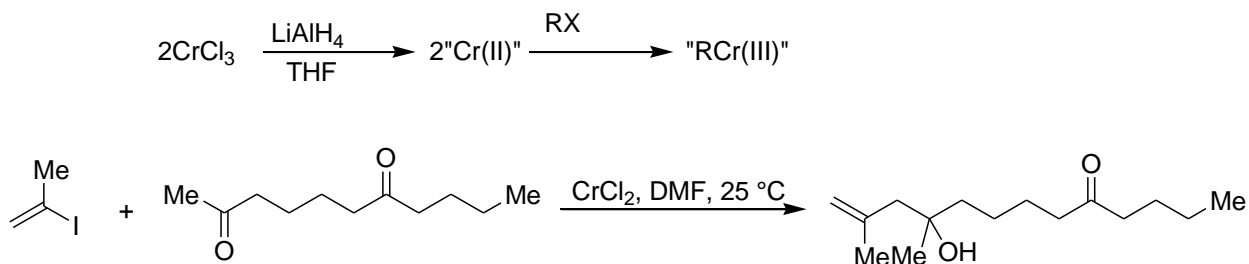
comparable to the rhodium-catalyzed cyclopropanation reactions. The carbene transfer occurs with retention of configuration.



Scheme 11

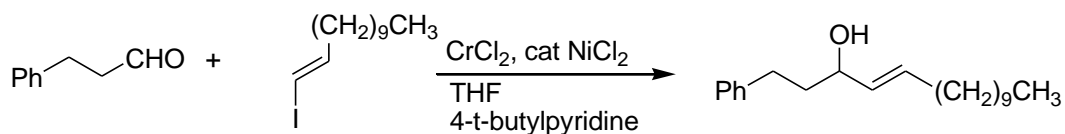
3.8.4.3 C-C Cross-Coupling Reaction

Organochromium species are useful in coupling an aldehyde to an allylic moiety where the more substituted carbon of the allylic moiety attaches to the carbonyl carbon. The organochromium species is formed by the oxidative addition of $\text{Cr}(\text{II})$ to allylic halides. This reaction is known as Nozaki-Hiyama coupling reaction (Scheme 12).



Scheme 12

A further modification of the protocol allows the coupling of vinyl halides and vinyl tosylates with aldehydes. This is known as Nozaki-Takai-Hiyama-Kishi coupling where the formation of organochromium derivatives is promoted by catalytic amount of $\text{Ni}(\text{II})$ salts (Scheme 13). The stereochemistry of the vinyl group is retained in the product.



Scheme 13

Problems

Provide the major products for the following reactions.

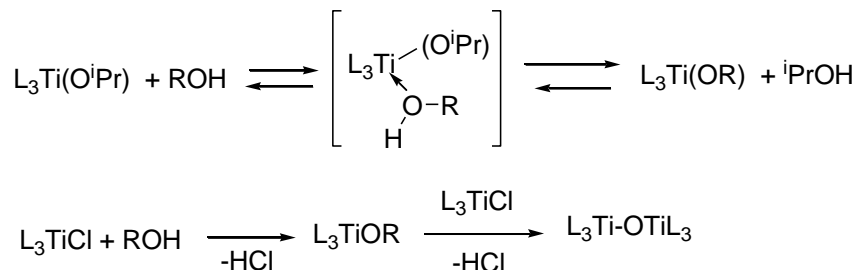
- $$(\text{OC})_5\text{Cr}=\text{C}(\text{OMe})\text{-C}_6\text{H}_5 \xrightarrow[\text{toluene, heat}]{\text{t-Bu-C}\equiv\text{C-H}}$$
- $$\text{MeO-C}_6\text{H}_3\text{(CH}_2\text{)}_2\text{CH}_2\text{-Cr(CO)}_3 \xrightarrow[\text{HCHO}]{\text{K}^t\text{OBu}}$$
- $$(\text{OC})_3\text{Cr-C}_6\text{H}_4\text{-[4-phenylcyclobutyl]-OH} \xrightarrow[\text{EtO}_2\text{C-CH=CH-CO}_2\text{Et}]{\text{i. BuLi}}$$
- $$(\text{OC})_3\text{Cr-C}_6\text{H}_4\text{-[2-phenylcyclohexyl]-C(=O)CH}_3 \xrightarrow[\text{ii. CF}_3\text{CO}_2\text{H, Et}_3\text{SiH}]{\text{i. MeLi}}$$
- $$\text{Me-CH=CH-CH=CH-CO}_2\text{Me} \xrightarrow[\text{H}_2]{\text{Cat. } (\text{OC})_3\text{Cr-C}_6\text{H}_4\text{-OMe}}$$
- $$\text{Me}_3\text{Si-CH=CH-CH}_2\text{-Br} \xrightarrow{\text{CrCl}_2, \text{ PhCHO}}$$
- $$\text{CH}_3\text{(CH}_2)_4\text{CHO} \xrightarrow[\text{Br}_2\text{CH}_2\text{SnBu}_3]{\text{CrCl}_2}$$

Reference

Transition Metals for Organic Synthesis, Vol. I, Ed., M. Beller and C. Bolm, Wiley-VCH, New York, 1998.

Lecture 33**3.8.5 Organotitanium Compounds**

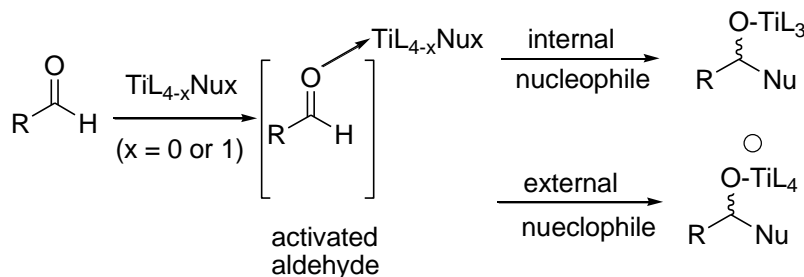
Titanium, an abundant and non-toxic transition metal, has been often used for the modification of organolithium and organomagnesium compounds. The preparation of individual titanium reagents is usually carried out by ligand exchange on, e.g. TiCl_4 , $\text{Ti}(\text{O}^i\text{Pr})_4$ or cyclopentadienyl-titanium trichloride (Scheme 1). Chloride ligands can be replaced by protonated (LH), silylated (LSiMe_3), stannylated (LSnR_3) or metalated (LM, $\text{M} = \text{Li}, \text{MgX}$) ligands. Volatiles such as HCl and Me_3SiCl can be removed by evaporation. Alkoxide ligands can be exchanged through adduct formation with alcohols. Many of the titanium compounds are moisture sensitive. The resulting hydroxo compounds are acidic and form μ -oxo dimers or trimers. With more water, complete hydrolysis occurs to give titanium dioxide. This section covers the recent developments on the use organotitanium compounds in organic synthesis.



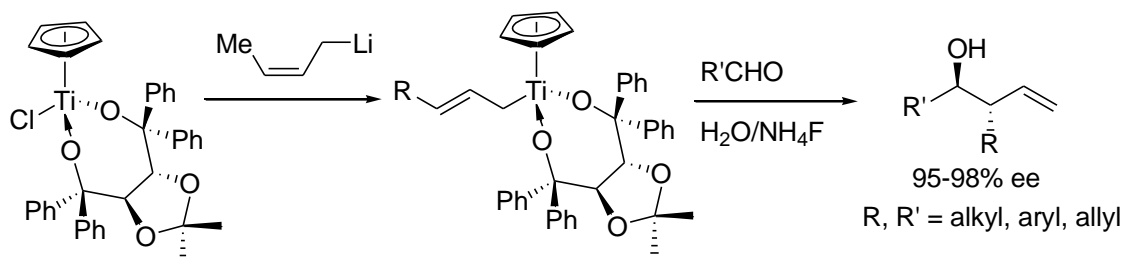
Scheme 1

3.8.5.1 Nucleophilic Addition to Aldehydes

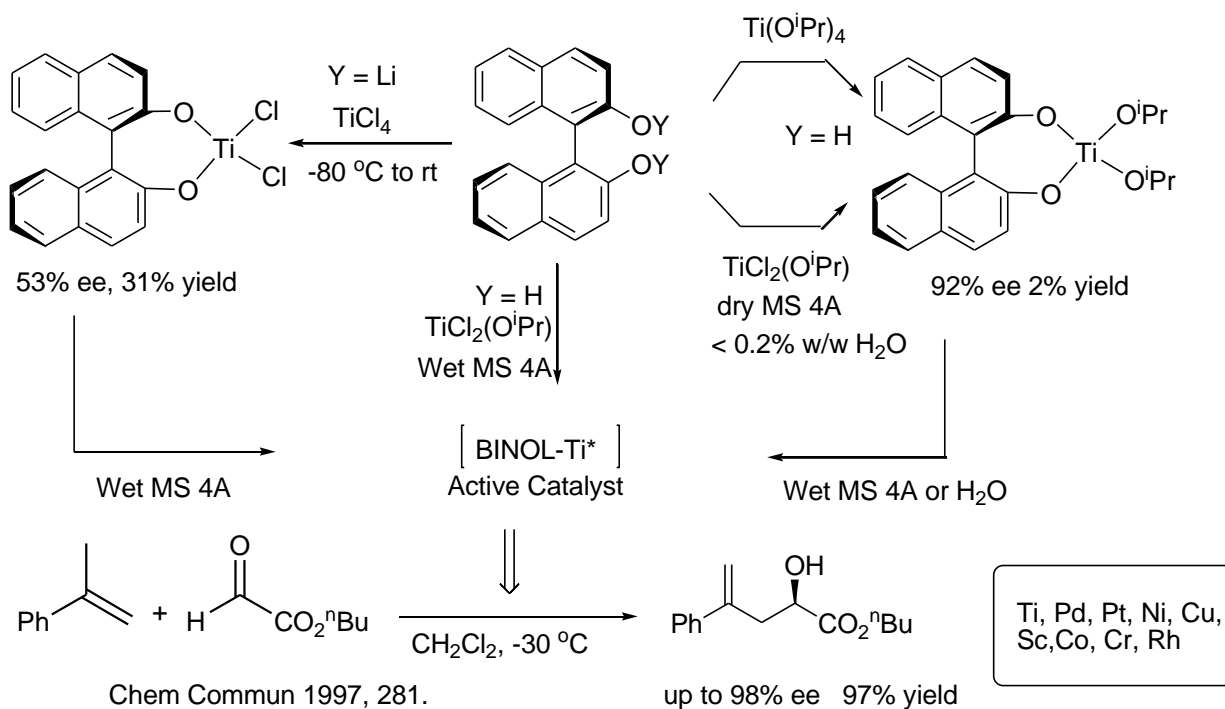
Titanium(IV)-mediated addition of nucleophiles to aldehydes exhibits excellent stereocontrol. The attacking nucleophile is either ligand of the activating titanium complex or an additional reagent. The stereoselectivity results from the bias of the titanium center (Scheme 2). For examples, asymmetric allylation of aldehydes and 'ene' reactions mediated by chiral titanium complexes provide the corresponding homoallylic alcohols with excellent enantioselectivity (Scheme 3-4).



Scheme 2

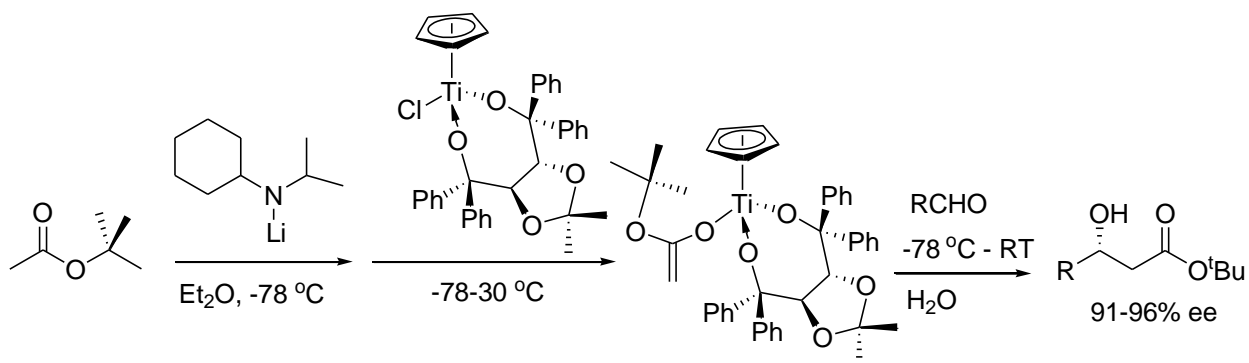


Scheme 3

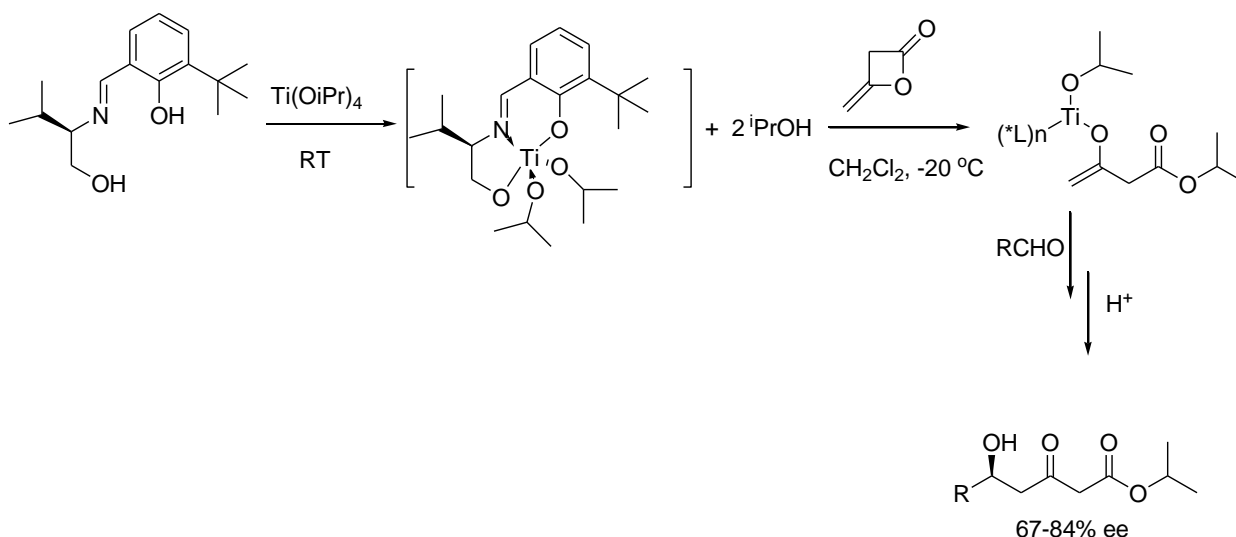


Scheme 3

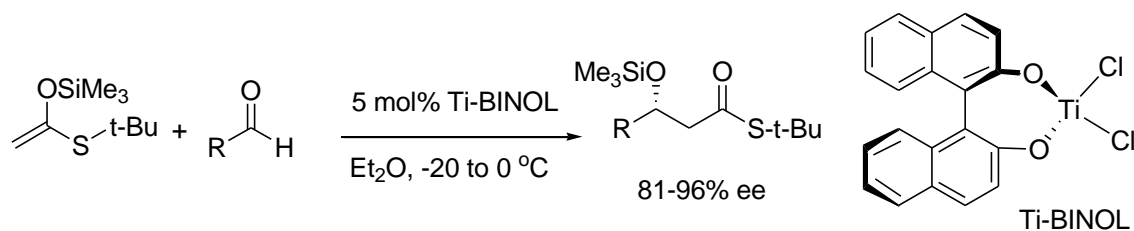
Similarly, aldol-type addition of enolates to aldehydes can be accomplished with excellent selectivity. For examples, the chiral cyclopentadienyltitanium complex derived from CpTiCl_3 and TADDOL has been used for highly enantio- and diastereoselective aldol reactions (Scheme 4). The products are obtained by transmetalating the Li-enolate with the Ti-TADDOL complex.



The addition of diketene to aldehydes can be accomplished using chiral titanium(IV) Schiff base complex to afford δ -hydroxy- β -ketoesters with reasonable enantioselectivity (Scheme 5). This reaction is too most probably proceeding *via* a Ti-enolate formed *in situ* from diketone and titanium(IV)-Schiff base complex. Catalytic version of this reaction can be carried out using Ti-BINOL complex. In this case a Mukaiyama-type aldol reaction between aldehydes and ketene silyl-acetal leads to provide silylated aldols with high optical purity (Scheme 6).

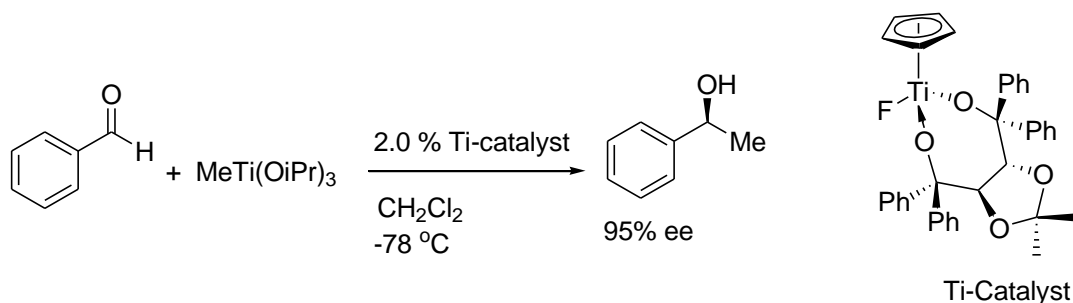


Scheme 5

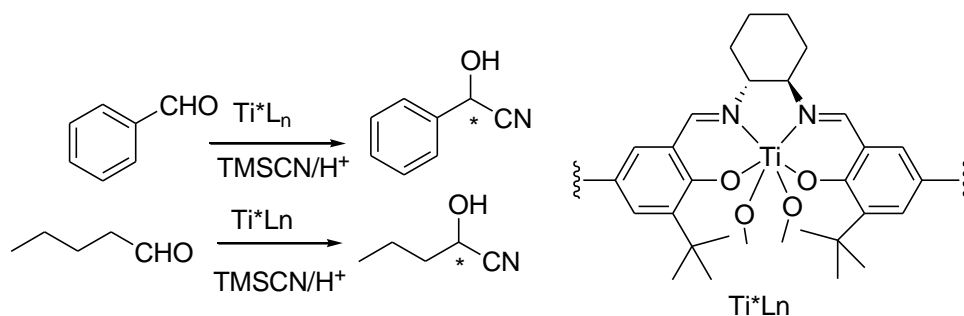


Scheme 6

The addition of alkyl nucleophile to aldehydes can be accomplished with high optical purity. For an example, the chiral cyclopentadienyltitanium fluoride complex catalyzes the addition of methyltitanium triisopropoxide to benzaldehyde with excellent enantioselectivity (Scheme 7).



Scheme 7



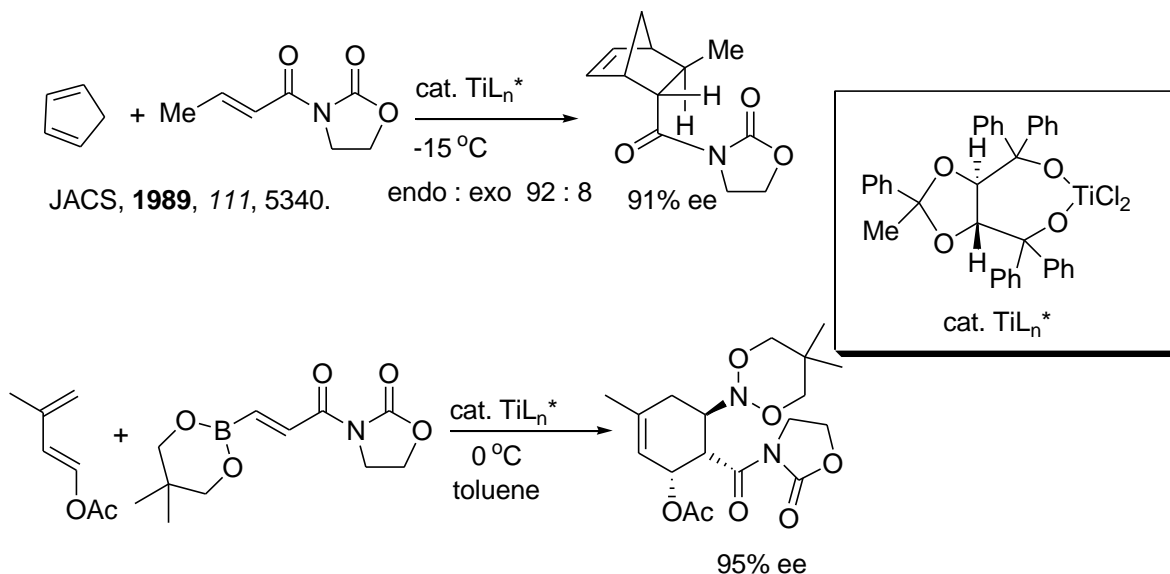
Scheme 8

The synthesis of cyanohydrins can be achieved with high optical purity using chiral titanium-polymer complex (Scheme 8). In these reactions, the catalyst catalyzes the reactions under homogeneous conditions, however, after completion, the catalyst can be precipitated from the reaction mixture and collected for recyclability without loss of activity and selectivity using MeOH. This catalytic system has the advantages of both homogeneous as well as heterogeneous processes.

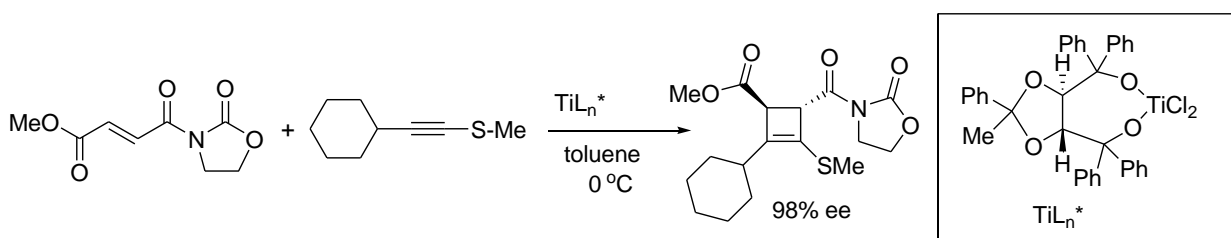
3.8.5.2 Cycloadditions

Chiral titanium(IV) complexes have been found to be excellent Lewis acid catalysts for cycloaddition reactions. For example, chiral titanium(IV) complex prepared from TADDOL and $\text{TiCl}_2(\text{O}^i\text{Pr})_2$ catalyzes Diels-Alder reactions of dienes with oxazolidinone derivatives of several α,β -unsaturated carboxylic acids with excellent optical purity (Scheme 9). These systems could also be used for [2+2]-cycloadditions between unsaturated N-acyl-oxazolidinones and electron-

rich alkenes. For example, fumarylol derivative reacts with alkynyl sulfide to give cyclobutene derivative with excellent yield and enantioselectivity (Scheme 10).



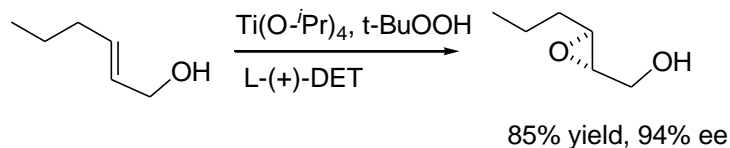
Scheme 9



Scheme 10

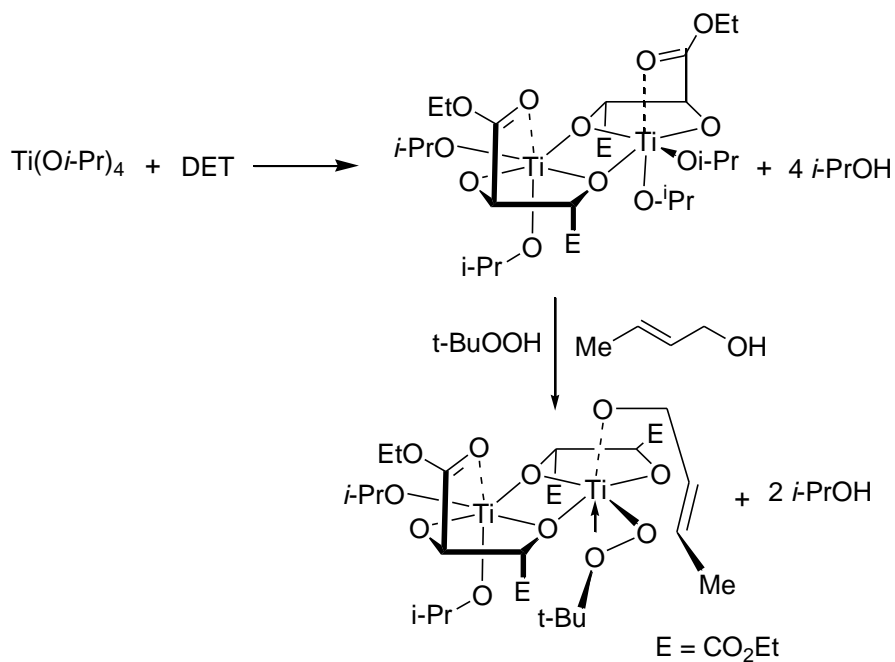
3.8.5.3 Asymmetric Epoxidation

Sharpless epoxidation of allylic alcohols is one of the important processes in asymmetric catalysis. It provides an effective route for the transformation of prochiral allylic alcohols to epoxy alcohols in the presence of $\text{Ti}(\text{O}i\text{-Pr})_4$, *t*-BuOOH and (*R,R*) or (*S,S*)-diethyltartarate (Scheme 11).

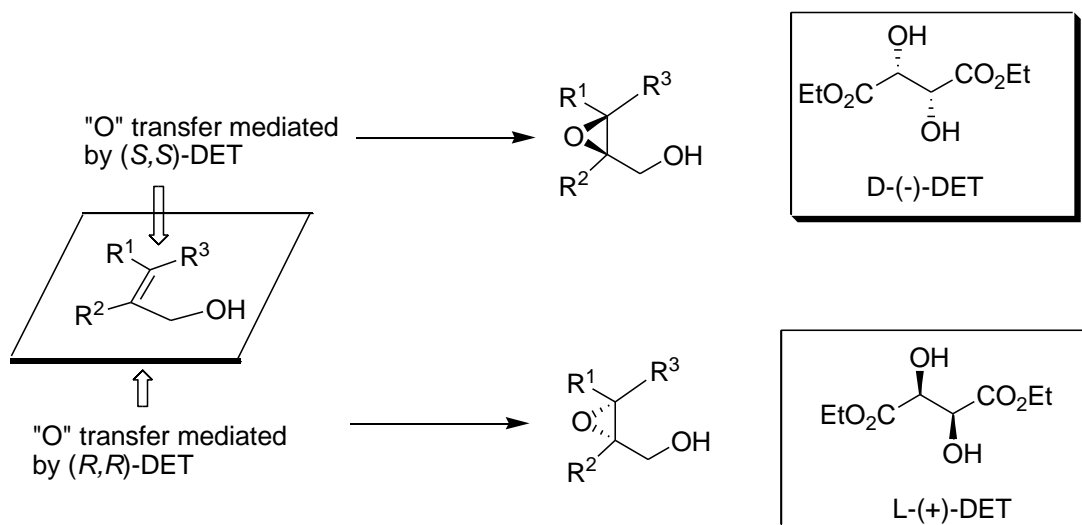


Scheme 11

The reaction proceeds through a dimeric complex having two titanium centers (Scheme 12). The allylic hydroxyl group coordinates with the metal thereby allowing the transfer of oxygen atom from one face only.



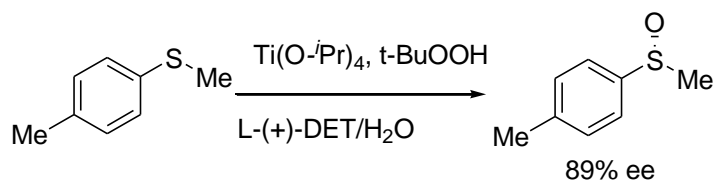
Scheme 12



Scheme 13

The absolute configuration of the epoxy alcohol can be predicted by the following mnemonic model in which the hydroxymethylene group is positioned at the lower right. The epoxidation takes place from the upper face of the allyl alcohol when (+)-(R,R)-DET is used and vice versa (Scheme 13).

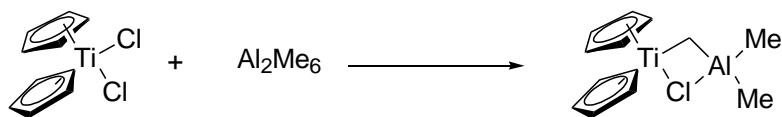
These reaction conditions, $\text{Ti}(\text{O}i\text{-Pr})_4$, $t\text{-BuOOH}$ and (R,R) or (S,S)-diethyltartarate, could also be used for asymmetric oxidation of aryl alkyl sulfides (Scheme 14).



Scheme 14

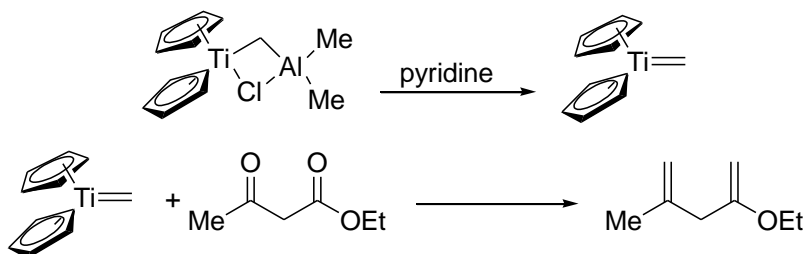
3.8.5.4 Olefination

Tebbe's reagent, $(\eta^5\text{-C}_5\text{H}_5)_2\text{TiCH}_2\text{ClAlMe}_2$, allows even less reactive carbonyl compounds to be transformed to the corresponding methylene compounds in the presence of pyridine. The reagent is prepared by the reaction of titanocene dichloride with trimethyl aluminium in toluene (Scheme 15).



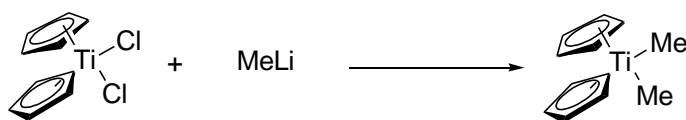
Scheme 15

In the presence of pyridine the reagent transforms into a Schrock carbene and reacts with the carbonyl group in a [2+2] cyclization which then undergoes ring opening metathesis to form the alkene (Scheme 16).



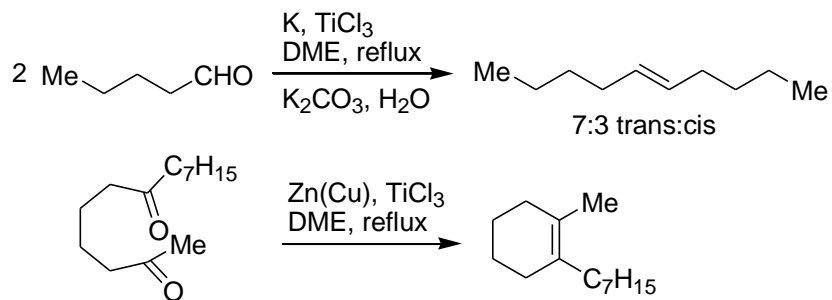
Scheme 16

Alternatively the same objective can be accomplished using Petasis reagent. It is synthesized by treating titanocene chloride with methyl lithium (Scheme 17). It shows reactivity similar to Tebbe's reagent. Petasis reagents can methylenate ketones, aldehydes and esters on thermolysis at 60 °C.



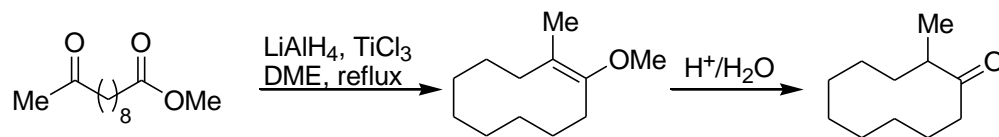
Scheme 17

McMurry reaction is used to synthesize alkenes from dicarbonyl compounds (Scheme 18). This reaction first generates an intermediate 1,2-diol which is then dehydrated on the surface of titanium to form alkene. However, the reaction is not stereospecific since the two the carbon-oxygen bonds do not break simultaneously. In case of cyclic 1,2-diols, a titanocycle has to be formed for this reaction to occur. Thus, *trans* diols are inert under these conditions.



Scheme 18

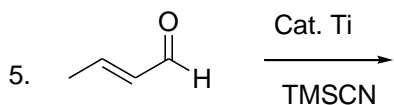
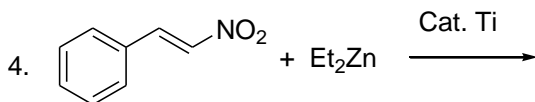
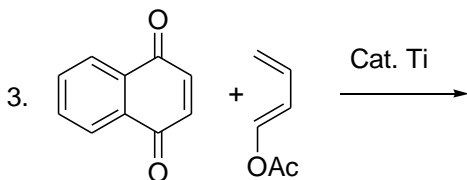
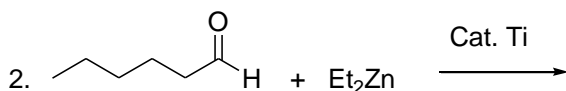
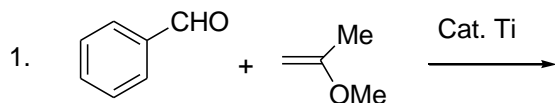
This methodology may be extended to ketoesters, where cyclic enol ether is formed which on hydrolysis forms the corresponding cycloalkanone (Scheme 19).



Scheme 19

Problems:

Complete the following reactions with mechanism.



Text Book

M. B. Smith, *Organic Synthesis*, McGraw Hill, Singapore, 2004.