

## Lecture 28

### 3.6.1 Introduction

Transition metals can be defined as an element whose atoms have an incomplete *d*-shell or which can give rise to cations with an incomplete shell. Due to incompletely filled *d*-orbitals it can exhibit a large number of oxidation states. The lower oxidation states can act as reducing agent while the higher oxidation states act as oxidizing agents. Some transition metals exhibit a pair of oxidation states in which the process of redox reaction is very facile. Pd(0)/Pd(II), Cu(I)/Cu(II) and Ni(II)/Ni(IV) are examples of such oxidation states. As such, these oxidation states may support catalytic cycles.

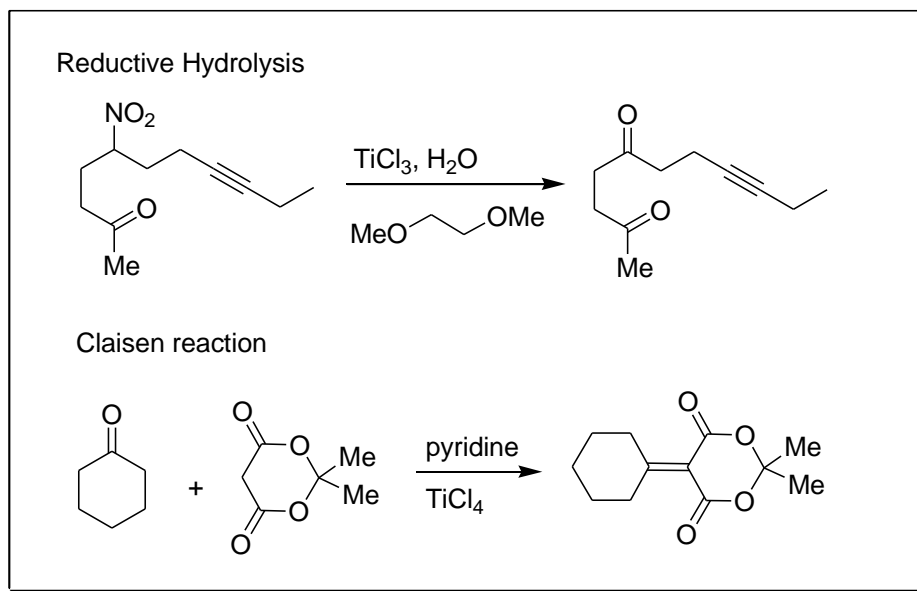
Transition metals can also bind to an organic ligand thus forming a metal-carbon bond. The metal-carbon bond may have  $\sigma$ -character or  $\pi$ -character or both. In case of a bond formation between a *d*-orbital of the metal with a *s*-containing hybrid orbital of carbon it gives rise to a  $\sigma$ -organometallic compound. Similarly, if the bond is formed between a *d*-orbital of a metal with  $\pi$ -orbitals of ligand then it gives rise to  $\pi$ -organometallic compound. In the latter case, bonding is provided by both donation from a filled  $\pi$ -orbital of the ligand to the empty orbital of metal and by the interaction of an unfilled  $\pi^*$ -orbital of the ligand with the filled metal *d*-orbital. Gilman's reagent is an example of the former type of organometallic compounds while Zeise complex is an example of the latter variety.

### 3.6.1 Titanium Catalysts

Titanium is a 3d series transition element belonging to Group IV. Thus, it has a low valence shell electron density compared to other transition metals belonging to other group. Since the valence shell electrons are strongly attracted by the nucleus, titanium has a high ionization potential. However, once ionized, Ti can attain up to +IV oxidation state. The cationic species are strong Lewis acids and, therefore, they have found application in a wide variety of Lewis acid catalyzed reactions.

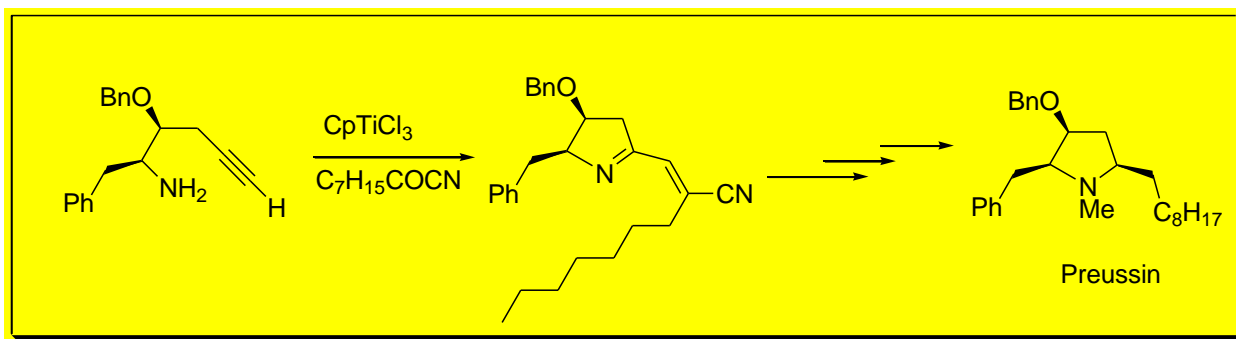
## 3.6.1.1 Lewis Acid Catalysis

The Lewis acidity of  $\text{TiCl}_4$  is applied in case of aldol reaction, Micheal addition, Claisen condensation and reductive hydrolysis among many other reactions. Some examples of these are exemplified in Scheme 1.



Scheme 1

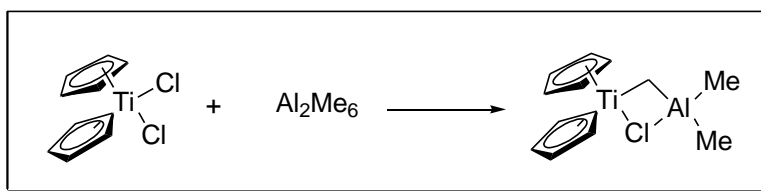
Regioselective intramolecular amination of alkynes has been accomplished using  $\text{CpTiCl}_3$  which is key step for the total synthesis of the antifungal agent (+)-preussin (Scheme 2).



Scheme 2

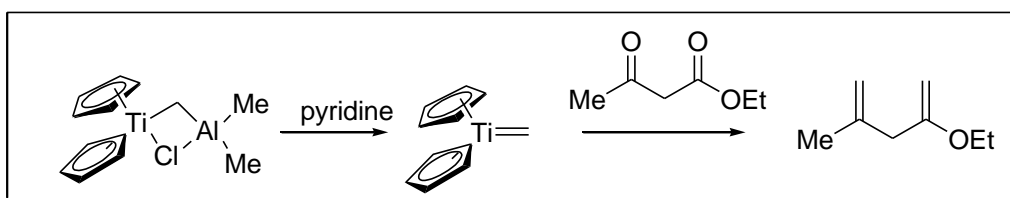
## 3.6.1.2 Olefination

Titanium metallocenes alone do not serve much to the organic synthesis but when they are used in conjunction with trimethyl aluminium they form interesting reagents for the synthesis of terminal alkenes from carbonyl compounds. Tebbe's reagent having the formula  $(\eta^5\text{-C}_5\text{H}_5)_2\text{Ti CH}_2\text{ClAlMe}_2$  perform the same task as Wittig's reagent but the higher reactivity of Tebbe's reagent allows even less reactive carbonyl compounds to be transformed to the corresponding methylene compounds. It is prepared by the reaction of titanocene dichloride with trimethyl aluminium in toluene (Scheme 3).



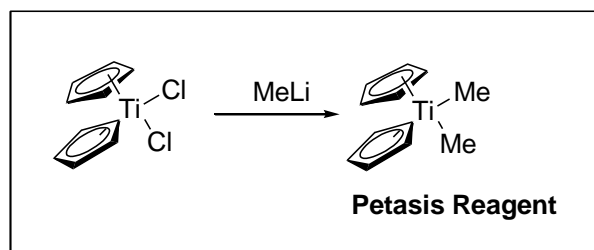
Scheme 3

Tebbe's reagent as shown above is not the active reagent. The active reagent, a Schrock carbene, is formed by treating it with a mild Lewis base like pyridine. This then reacts with the carbonyl group in a [2+2] cyclization which then undergoes ring opening metathesis to form the alkene (Scheme 4).

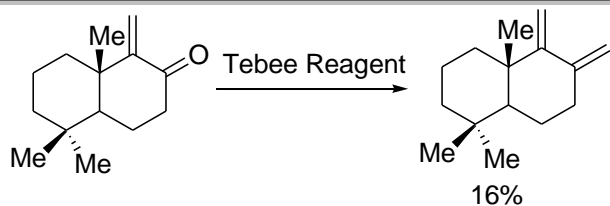


Scheme 4

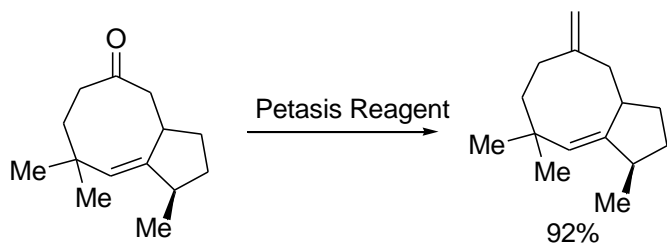
The same transformation can also be accomplished with Petasis reagent that can methylenate ketones, aldehydes and esters on thermolysis at 60 °C (Scheme 5).



Scheme 5

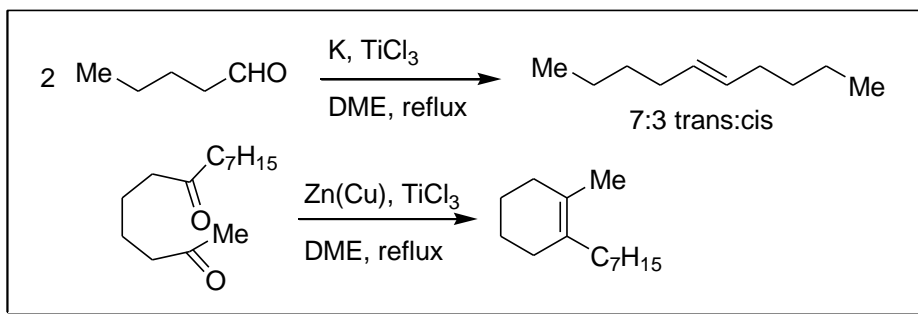
**Examples:**


M. Cortes, J. A. Valderrama, M. Cuellar, V. Armstrong, M. Preite, *J. Nat. Prod.* **2001**, *64*, 348.



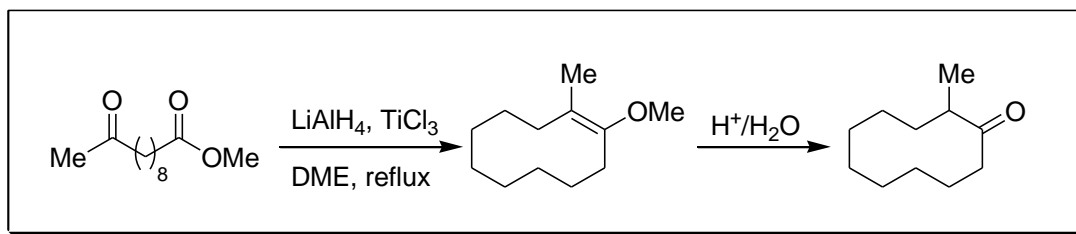
N. A. Petasis, M. A. Patane, *Tetrahedron Lett.* **1990**, *31*, 6799.

McMurry reaction is also used to synthesize alkenes from dicarbonyl compounds using Ti(0) generated *in situ*. The reduction may be carried out by a variety of reagents like Zn-Cu couple, LiAlH<sub>4</sub> and alkali metals Li, Na and K (Scheme 6). This reaction first produces 1,2-diol which is then dehydrated on the surface of titanium into an alkene. The reaction is not stereospecific since the two the carbon-oxygen bonds do not break simultaneously.



Scheme 6

This methodology can be extended to ketoesters, where a cyclic enol ether is produced which on hydrolysis gives cycloalkanone (Scheme 7).



Scheme 7

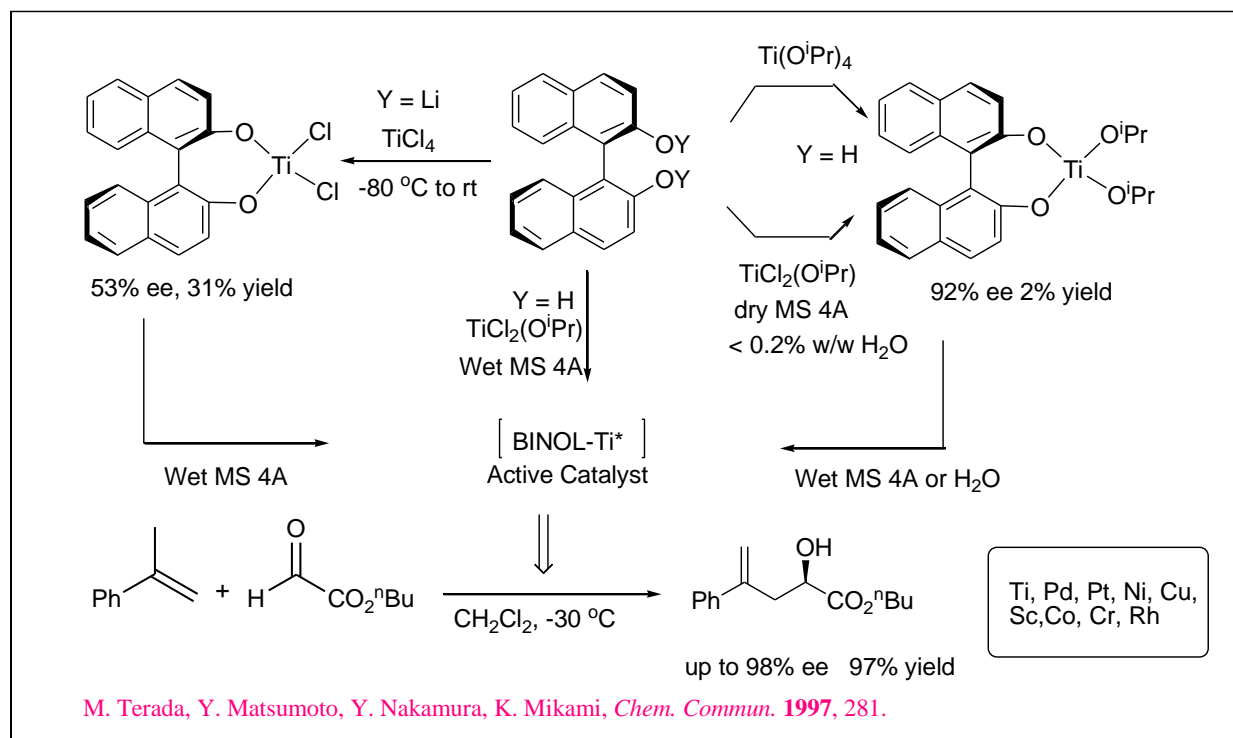
### 3.6.1.3 Polymerization

Perhaps the most famous titanium catalyst is a mixture of  $\text{TiCl}_4$  and  $\text{AlMe}_3$  which is known as Ziegler-Natta catalyst. Today, a great variety of catalysts having a Ti, Zr or Hf centre along with Mg or Al co-catalyst are known by this generic name. The polymerization of alkenes carried out by these catalysts can be highly stereoregular by suitable tailoring of the catalyst. This has been widely used for the polymerization of high density polyethylene, polypropylene and polybutadiene among other alkenes. Ziegler-Natta catalysts can be classified into 3 classes.

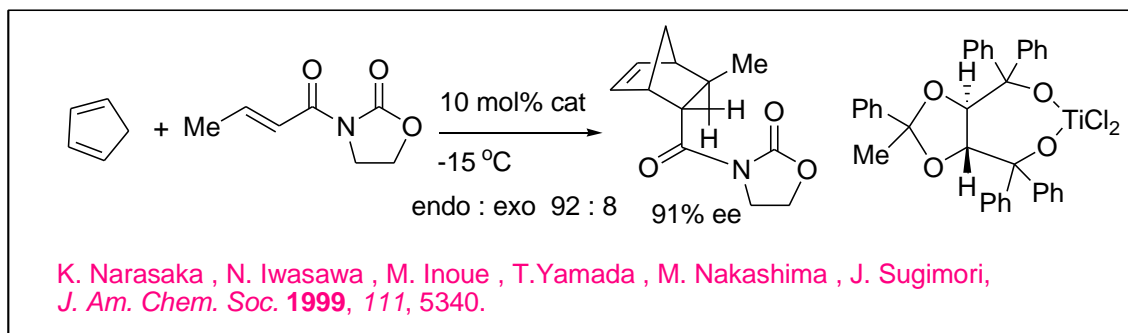
- Titanium chloride based catalysts. The catalysts are usually supported on silica supports and can be used for homopolymerization as well as polymerization of isotactic 1-alkenes.
- Metallocene based catalysts. Early transition metal metallocenes along with methylalkoxyaluminium compounds as co-catalyst have been used for the polymerization of alkenes. The metallocene complexes are usually bent sandwich complexes with formula  $\text{Cp}_2\text{MCl}_2$  ( $\text{M} = \text{Ti}, \text{Zr}, \text{Hf}$ ).
- Coordination complexes as catalysts. A variety of coordination complexes of different metals in conjunction with alkoxyaluminium as co-catalysts are known to polymerize alkenes.

### 1.6.1.4 Asymmetric Catalysis

The Lewis acidity of titanium has been used in asymmetric catalysis. Due to its strong Lewis acidity, it can easily coordinate with heteroatoms like oxygen and nitrogen. Now if the environment of the titanium centre is so modified such that the heteroatom containing substrate can find stereoselectively, then asymmetric induction is possible. This is achieved by attaching suitable chiral ligands to titanium centre which also tailors the Lewis acidity of titanium. For examples, asymmetric ene and Diels-Alder reactions have been demonstrated with excellent enantioselectivity in the presence of chiral titanium complexes as chiral Lewis acid catalysts (Scheme 8-9).

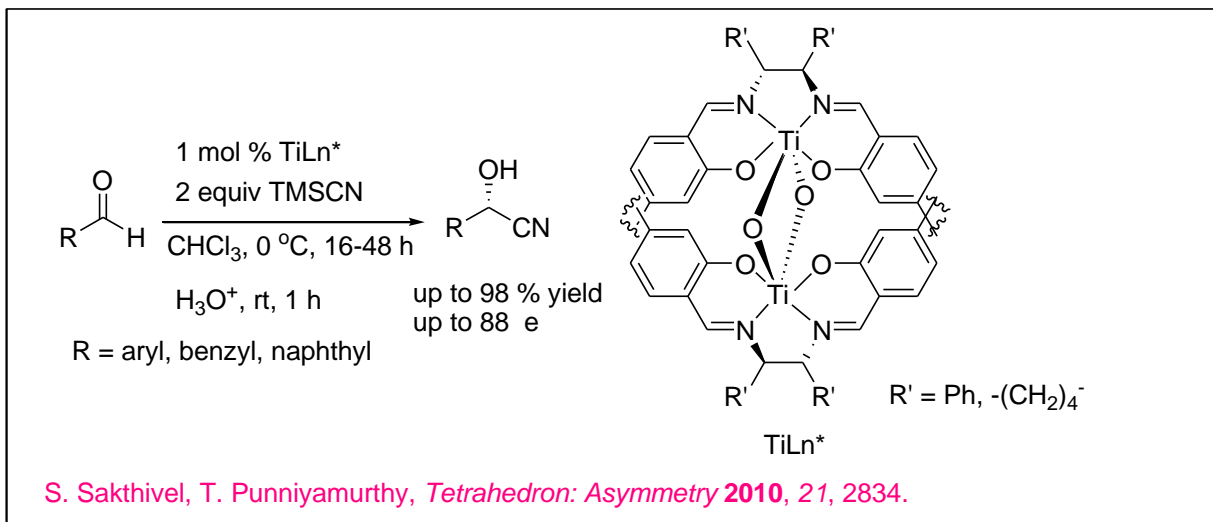


Scheme 8



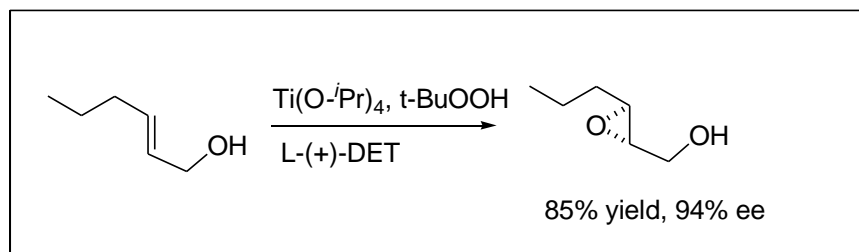
Scheme 9

Chiral titanium-polymer complex has been used as recyclable catalyst for cyanohydrin synthesis with high enantioselectivity (Scheme 10). The advantage of this protocol, the catalyst can be recovered and recycled without loss of activity and selectivity.

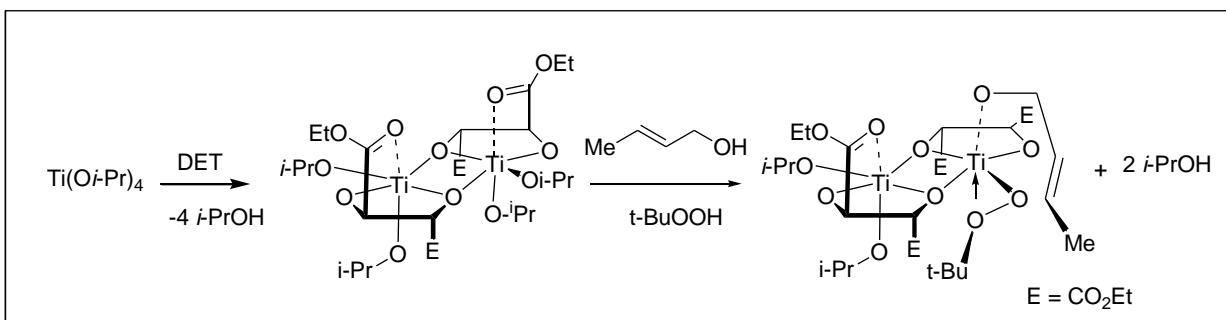


Scheme 10

Sharpless asymmetric epoxidation is one of the most famous examples of an asymmetric reaction using titanium alkoxides. In this method, prochiral allylic alcohols are stereoselectively oxidized to the corresponding epoxides using  $Ti(Oi-Pr)_4$ ,  $t-BuOOH$  and ( $R,R$ ) or ( $S,S$ )-diethyltartarate (Scheme 11).

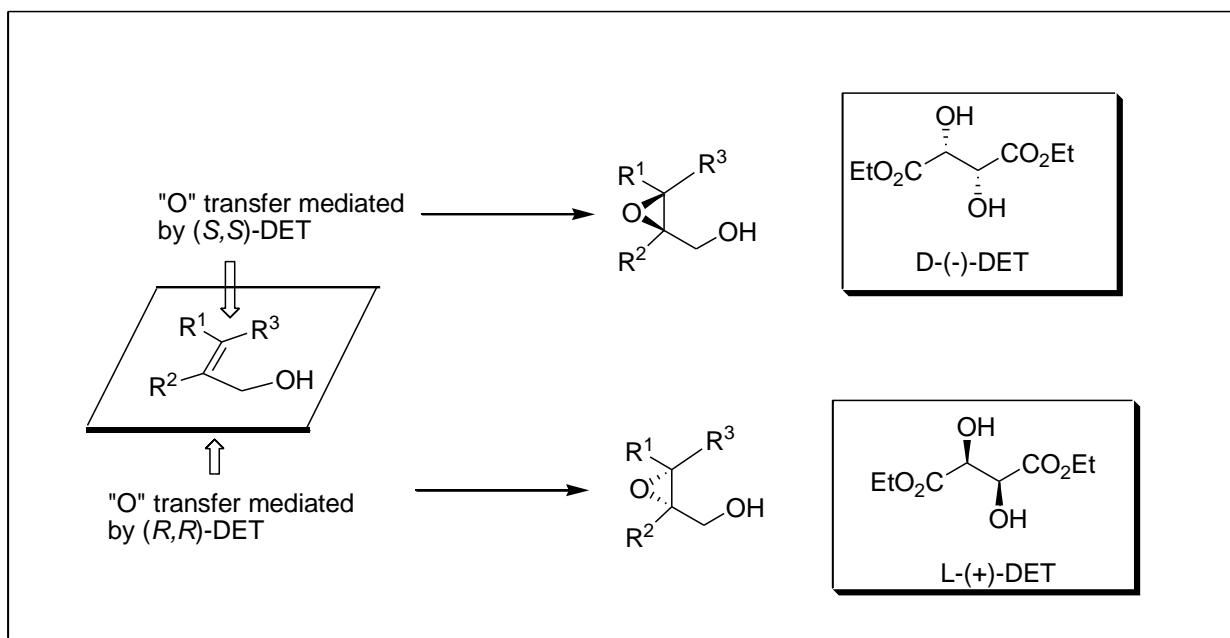


Scheme 11



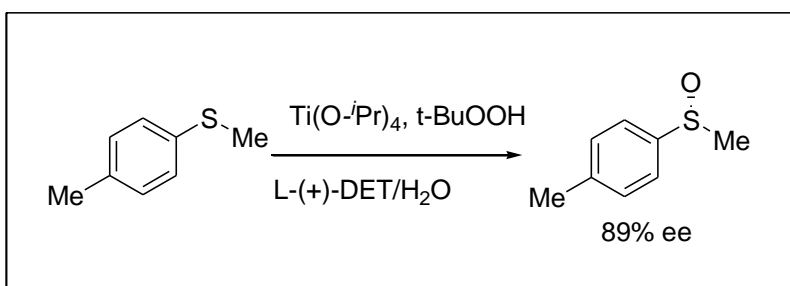
Scheme 12

The reaction is believed to proceed through a dimeric complex having two titanium centres (Scheme 12). The presence of the allylic hydroxyl group is necessary as it coordinates with the metal thereby allowing the transfer of oxygen atom from one face only. 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).



Scheme 13

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

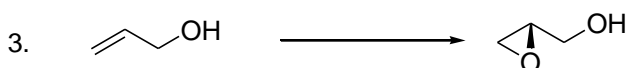
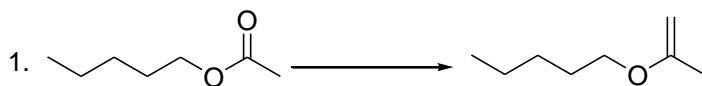


Scheme 14

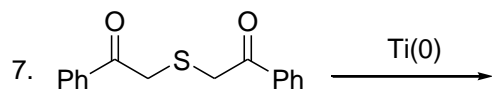
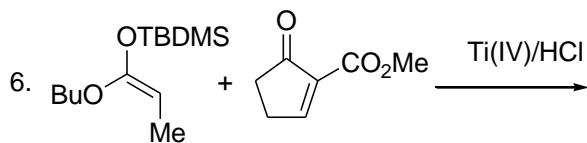
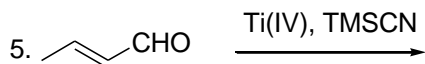
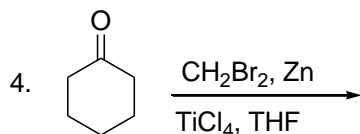
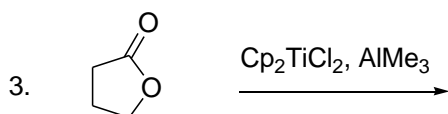
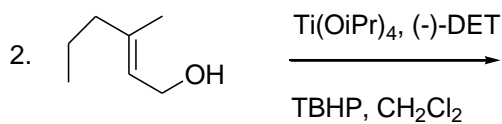
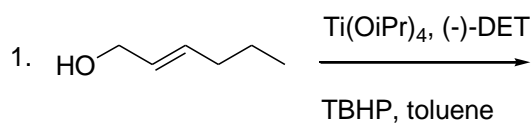


**Problems**

A. Provide suitable catalytic system for the following transformations.



B. Complete the following reactions.



**Text Book**

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

## Lecture 29

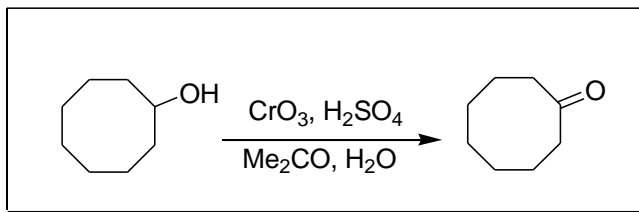
### 3.6.3 Chromium Reagents/Catalysts

Chromium can exist in a variety of oxidation states, Cr(III) and Cr(VI) being the most common of them. These two oxidation states form a redox couple with standard reduction potential of 1.33 V. Thus, Cr(VI) reagents are very strong oxidizing agents.

#### 3.6.1 Oxidation of Alcohols

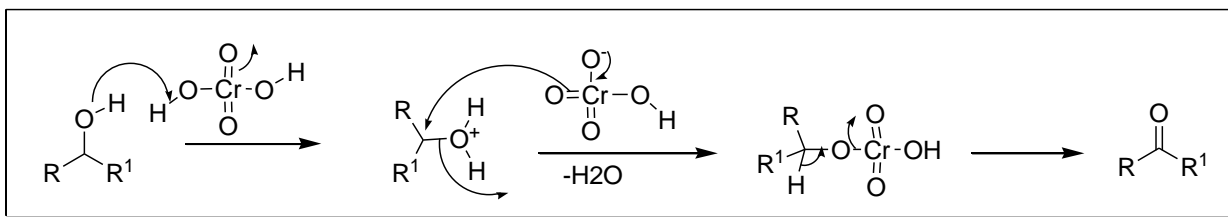
Chromium(VI) oxide is a very powerful oxidizing agent whose oxidizing power can be tailored by using it in conjunction of a Lewis base like pyridine. CrO<sub>3</sub> when dissolved in H<sub>2</sub>SO<sub>4</sub> forms a

F. Freeman, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 2, 1261.



Scheme 1

#### Mechanism

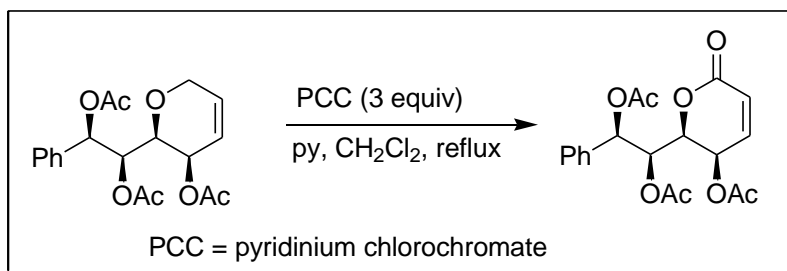


Scheme 2

mixture of various chromic acids (Jones Reagent). It is a very powerful oxidizing agent capable of oxidizing primary alcohols to carboxylic acids and secondary alcohols to ketones (Scheme 1-2).

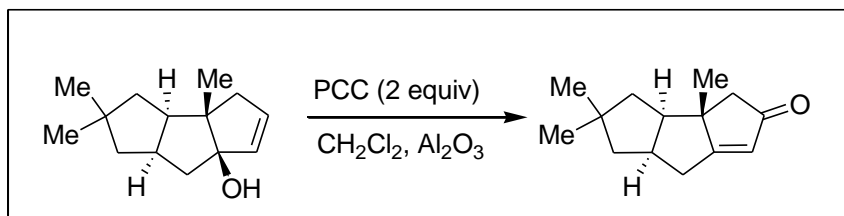
In the presence of pyridine, the oxidizing property of Cr(VI) is lowered and now it can be used to selectively oxidize primary alcohols to the corresponding aldehydes. The chromium trioxide-pyridine complexes,  $\text{CrO}_3 \cdot \text{py}_2$  (Collins reagent) and  $\text{pyH}^+\text{CrO}_3\text{Cl}^-$  (Sarrett reagent), are also known to oxidize allylic methylene group (Scheme 3).

F. Freeman, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 5, 2272.



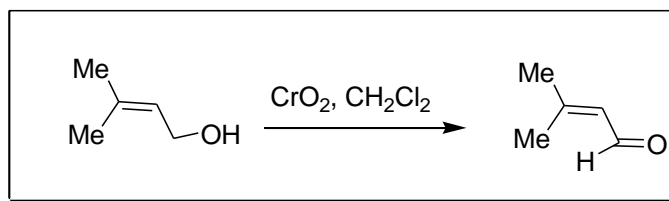
Scheme 3

Another useful application of PCC is in the conversion of allylic tertiary alcohols to their transposed  $\alpha,\beta$ -unsaturated ketones. The reaction is thought to proceed by rearrangement of the chromate ester of the allylic alcohol to give a new allyl chromate ester that is oxidized to the ketone (Scheme 4).

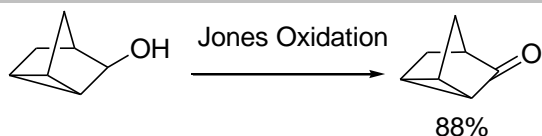


Scheme 4

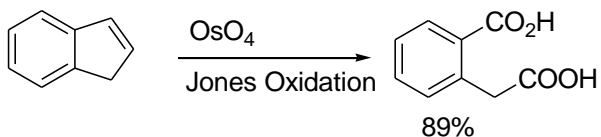
Despite its wide applicability as an oxidizing agent, chromium is not environmentally benign due to its high toxicity. Thus, the use of chromium reagents for bulk scale productions has not attained much popularity. However, methods have been developed to bypass this problem, one of them being the use of magnetic chromium(IV) oxide, which can oxidize allylic and benzylic alcohols (Scheme 5). After the reaction is completed, the CrO<sub>2</sub> particles can be separated from the solution by a magnet.



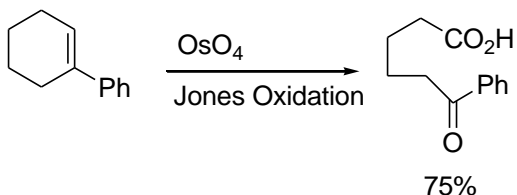
Scheme 5

**Examples:**


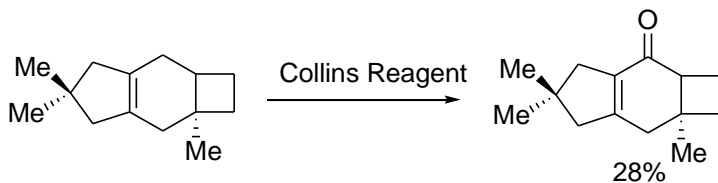
J. Meinwald, J. Crandall, W. E. Hymans, *Org. Synth.* CV5, 866.



J. R. Henry, S. M. Weinreb, *J. Org. Chem.* **1993**, 58, 4145.

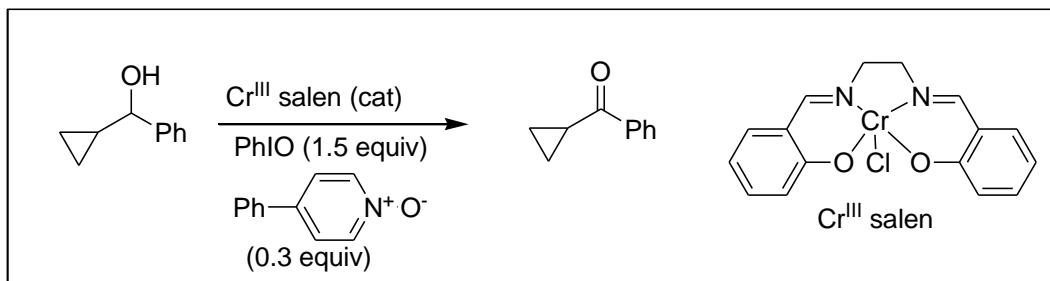


J. R. Henry, S. M. Weinreb, *J. Org. Chem.* **1993**, 58, 4145.



M. Harmata, G. J. Bohnert, *Org. Lett.* **2003**, 5, 59.

Another way to increase the E-factor is to use catalytic amount of chromium reagents for oxidation. Thus, Cr(III)-salen complexes have been used for oxidation of alcohols. The combination of Cr(III)-salen along with terminal oxidant PhIO is selective for allylic, benzylic and cyclopropyl alcohols (Scheme 6).

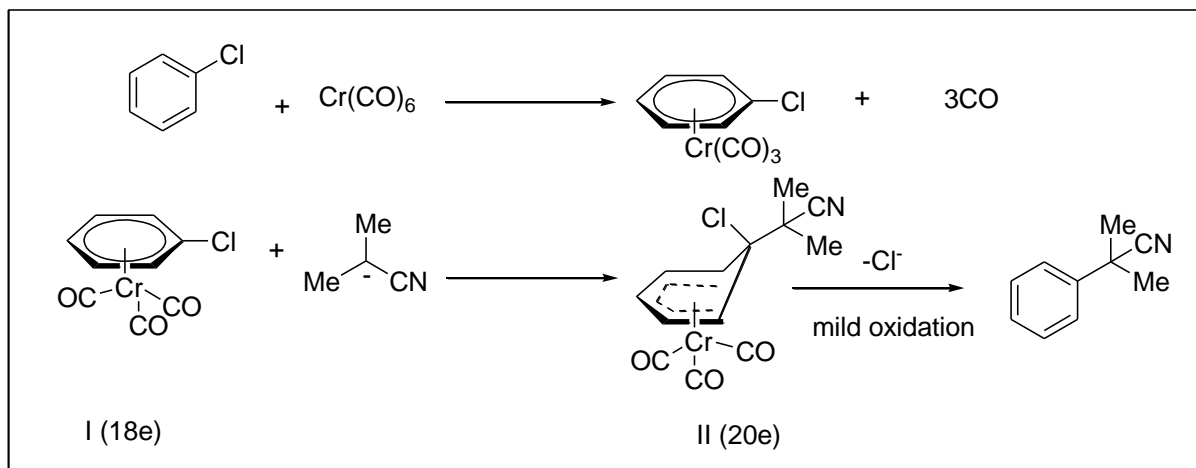


Scheme 6

### 3.6.2 Reactions of Chromium-Arene Complex

#### 3.6.2.1 Nucleophilic Addition

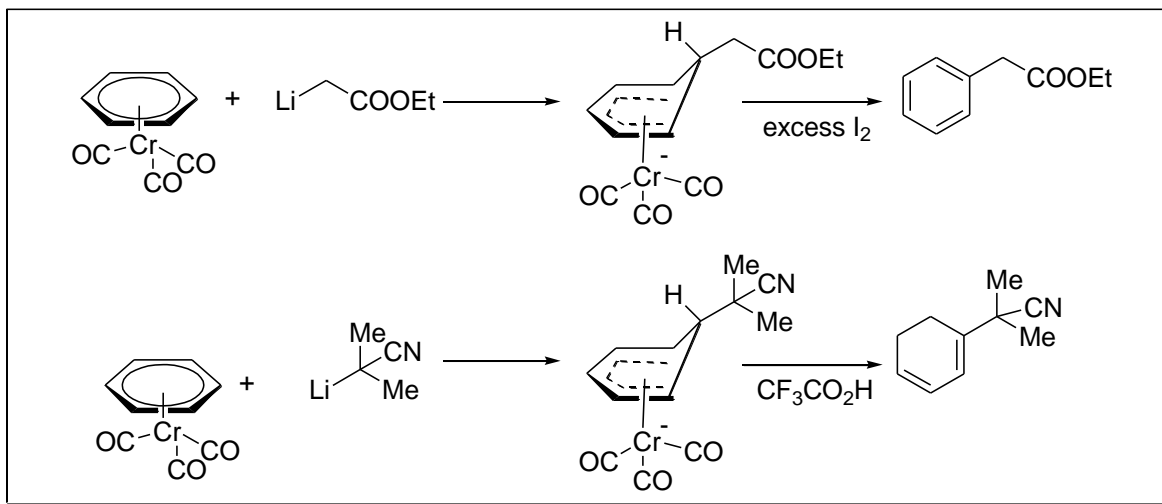
Arylchromium complexes prepared by heating Cr(CO)<sub>6</sub> with arene have found use as a source of preparation of arene derivatives by attack of a nucleophile (Scheme 6). The rationale for this lies in the fact that arylchromiumtricarbonyl complexes follow 18 electron complexes and as such



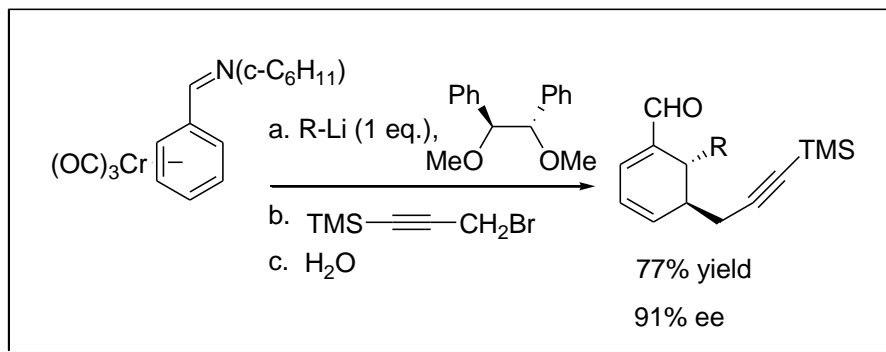
Scheme 7

they have a tendency to preserve the 18e structure. For example, ( $\eta^6$ -chlorophenyl)tri-carbonylchromium(0) has 18e which on addition of nucleophile generates intermediate II with 20e that loses 2 electrons by losing chloride to regain its 18e structure.

If there is no leaving group present on the arene, then the intermediate cyclohexadienyl anion can be oxidized by a suitable oxidant or it may be trapped by an electrophile (Scheme 8). In the former case it leads to re-aromatization along with alkylation while in the latter case it leads to formation of a cyclohexadiene derivative.



Scheme 8

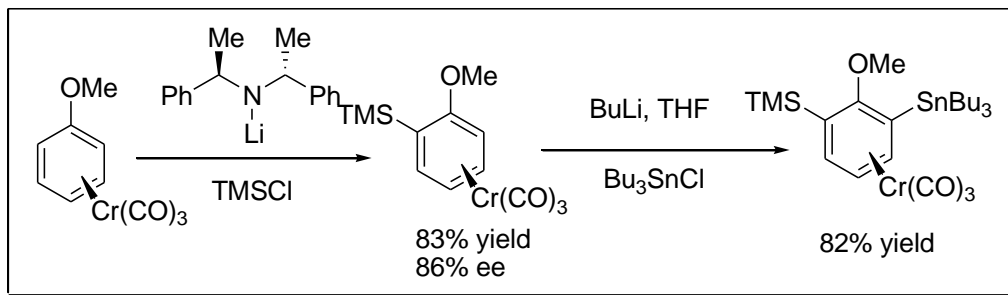


Scheme 9

Asymmetric version of the reaction has been developed for the synthesis of functionalized cyclohexadienes from benzaldimine complexes and the conversion of *ortho*-substituted anisole complexes to give cyclohexanones (Scheme 9).

### 3.6.2.2 Ring Lithiation

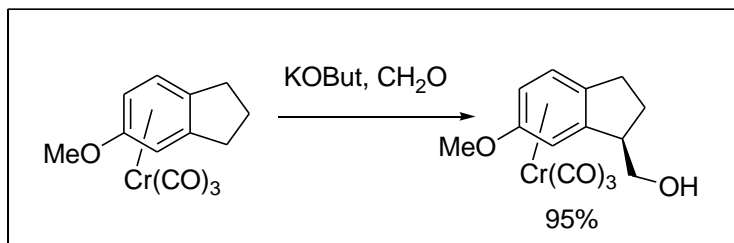
The ring deprotonation of  $\text{Cr}(\text{CO})_3$ -complexed arene leads to the regioselective preparation of alkylated complexes. Using chiral bases enantioselective deprotonation of prochiral substrates can be accomplished (Scheme 10).



Scheme 10

### 3.6.2.2 Side-Chain Activation

The  $\text{Cr}(\text{CO})_3$  group strongly stabilizes the negative charge at the  $\alpha$ -position of alkyl side chains facilitating benzylic deprotonation. In case of substrates having two competing benzylic positions the regiochemistry can be controlled by electronic effects (Scheme 11).

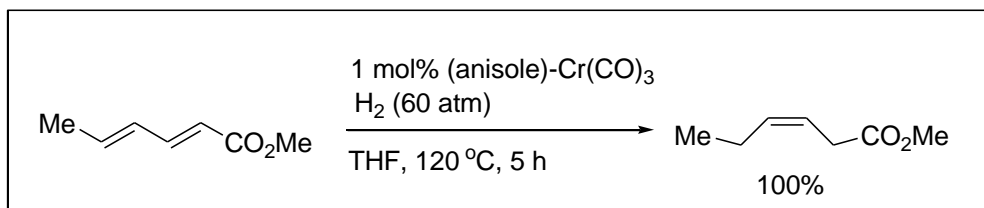


Scheme 11



### 3.6.2.3 As Catalysts

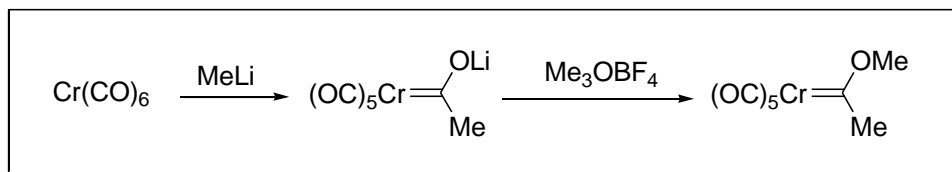
Arene-Cr(CO)<sub>3</sub> complexes are a good source for the ‘free’ Cr(CO)<sub>3</sub> unit that catalyzes a number of useful transformations. For example, the 1,4-hydrogenation of 1,3-dienes gives *Z*-configured alkenes (Scheme 12). 1,3-Dienes that can adopt a *s*-cisoid conformation proceed the reaction, whereas isolated double bonds are not affected.



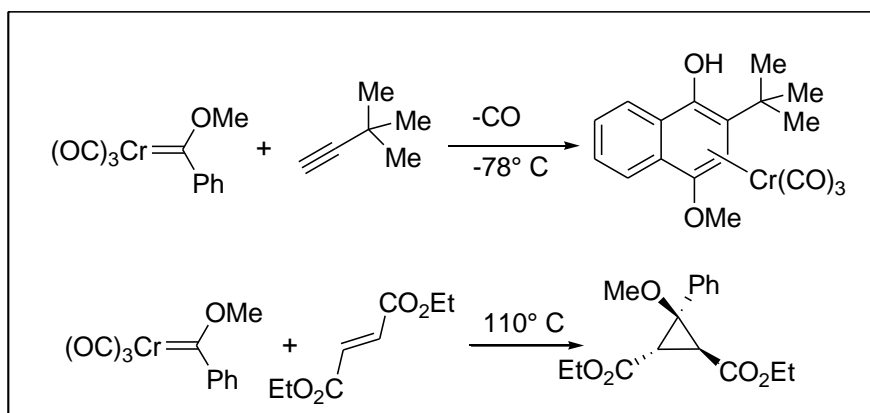
Scheme 12

### 3.6.3 Chromium-Carbene Complex

Chromium forms Fischer carbene complexes that serve as reagents for various cyclization reactions like benzannulation and cyclopropanation reactions. These 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 (Scheme 13-14).



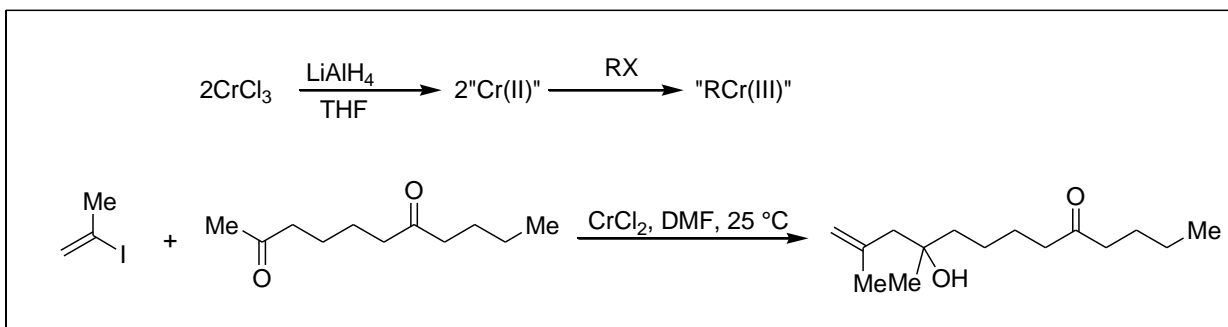
Scheme 13



Scheme 14

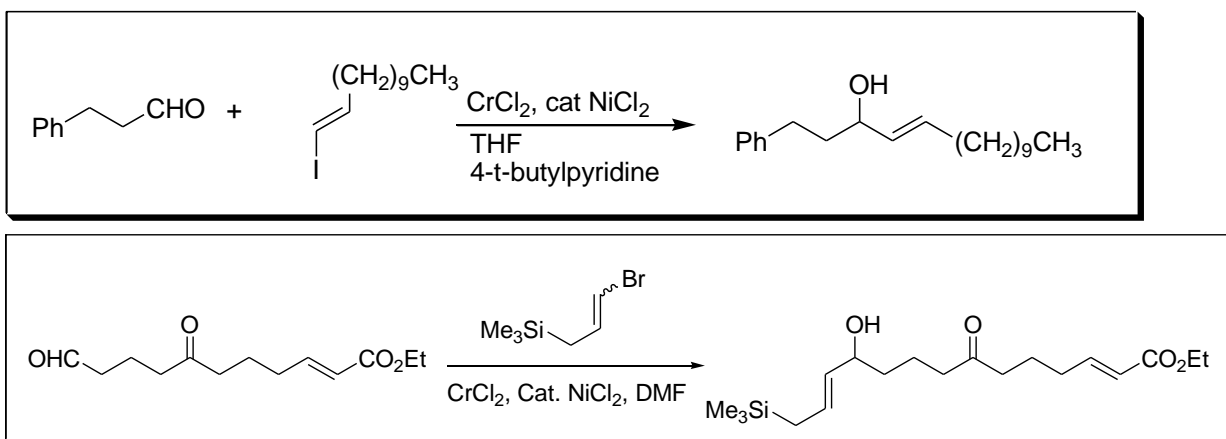
### 3.6.4 Nozaki-Hiyama-Kishi Reaction

Much of the carbon-carbon bond forming reactions using chromium(II)-based protocols can be summarized as involving the coupling of an organic halide (or equivalent) with a carbonyl compound (Scheme 15).



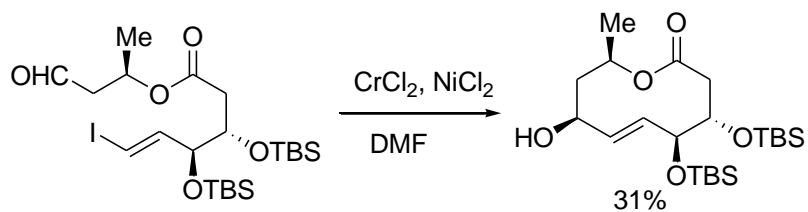
Scheme 15

Subsequent modification of the protocol have led to the coupling of vinyl halides and vinyl tosylates with aldehydes. This is known as Nozaki-Hiyama-Kishi coupling where the formation of organochromium derivatives is promoted by catalytic amount of Ni(II) salts (Scheme 16). The stereochemistry of the vinyl group is retained in the product.

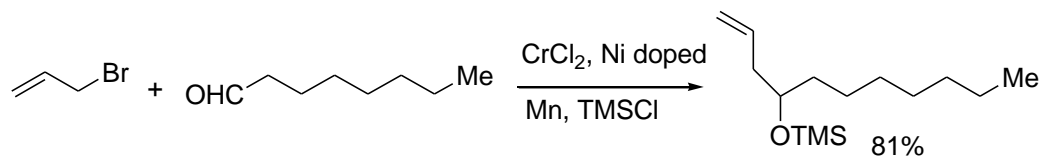


Scheme 16

**Examples**



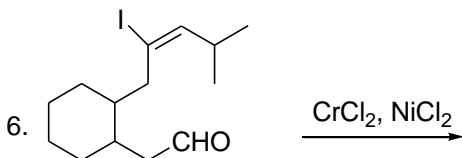
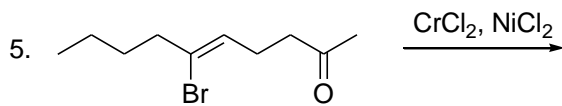
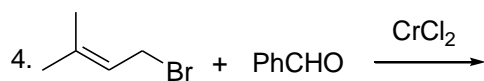
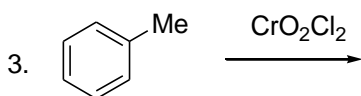
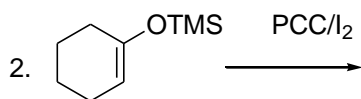
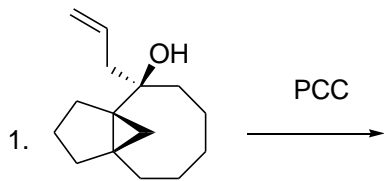
R. A. Pilli, M. M. Victor, *Tetrahedron Lett.* **2002**, *43*, 2815



A. Furstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 12349.

**Problems**

Predict the major product for the following reactions.



**Reference**

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

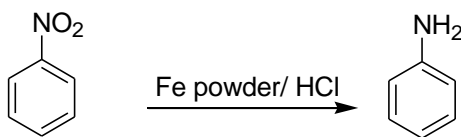
## Lecture 30

### 3.6.4 Iron Catalysts

Iron is 3d-series transition element belonging to Group 8. It is present in haemoglobin and myoglobin and so it is one of the most important metals in biology. It exists in +2 and +3 oxidation states mainly. In +3 oxidation state it is a strong Lewis acid while metallic iron may behave as a single electron donor under suitable conditions.

#### 3.6.4.1 Reduction of Nitro Group

Aromatic nitro compounds can be reduced to the corresponding aromatic amines in presence of iron powder under acidic conditions. The reaction proceeds through single electron transfer in similar lines to Clemensen reduction (Scheme 1).

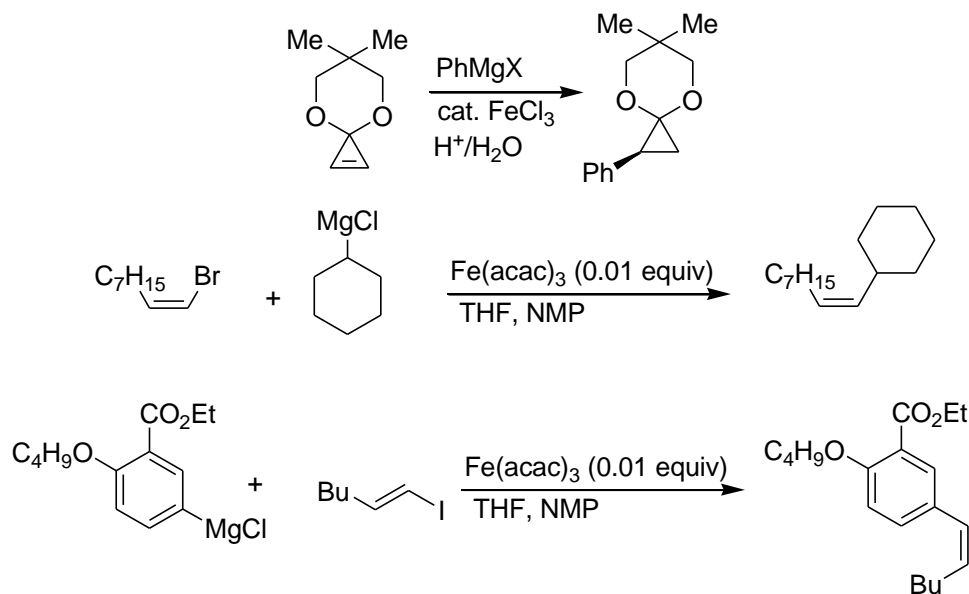


Scheme 1

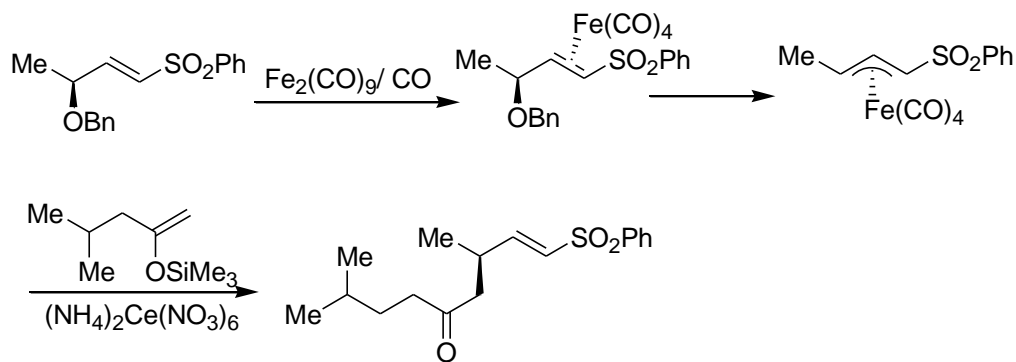
#### 3.6.4.2 C-C Bond Formation

The Lewis acidity of iron(III) has been utilized for several reactions. These reactions mostly involve activation by co-ordination with heteroatoms or  $\pi$ -bonds. Bromination of aromatic compounds can be carried out by bromine in the presence of iron powder. Similarly, addition of catalytic amount of iron(III) salts facilitates the addition of organometallic nucleophiles (Scheme 2).

Cationic  $[(\text{allyl})\text{Fe}(\text{CO})_4]^+$  is known to react with different types of nucleophiles regioselectively and stereoselectively. If the reaction is carried out at low temperature then the olefin geometry can be preserved during substitution as the  $\pi$ - $\sigma$ - $\pi$ -isomerization is slow in this case. If allyl substrates possess electron withdrawing group, then nucleophilic substitution of the leaving group proceeds regioselectively (Scheme 3).



Scheme 2

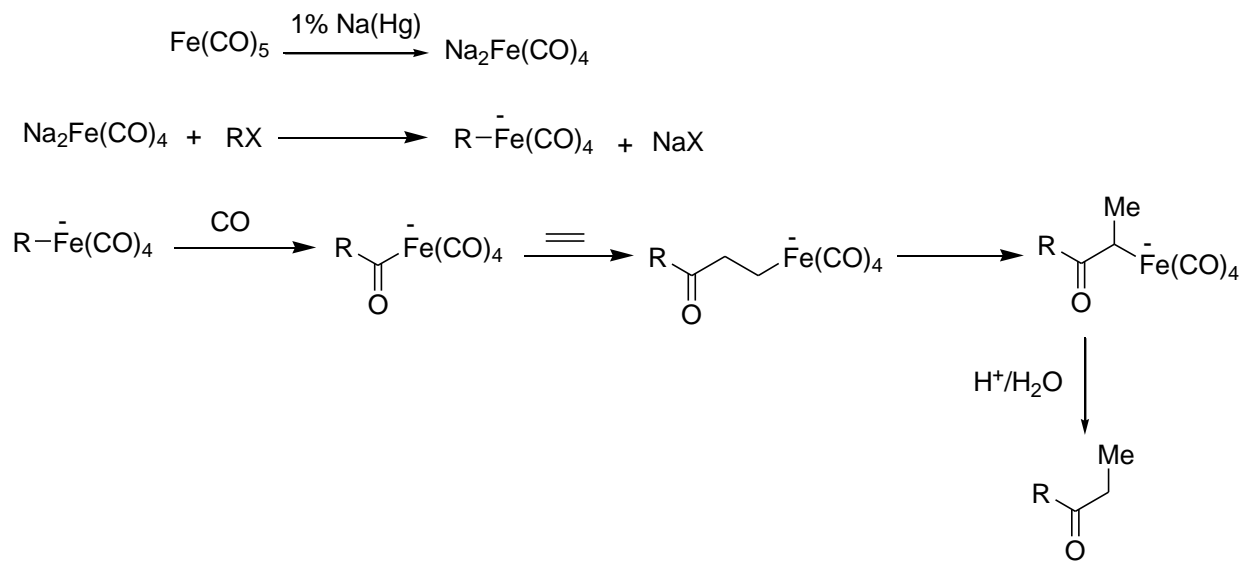


Scheme 3

### 3.6.4.3 Carbonylation

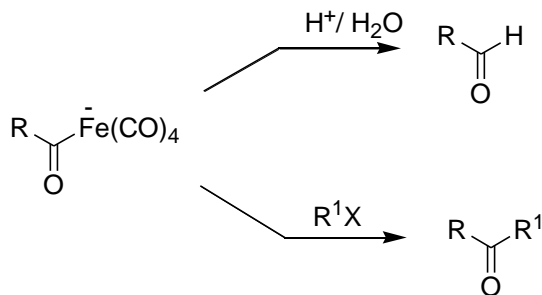
Iron carbonyl complexes have been used for various reactions, the most obvious of which is carbonylation. Collman's reagent prepared by the reduction of pentacarbonyliron(0) by sodium naphthalenide can be used for preparation of aldehydes and ketones. In this two step process, Collman's reagent ( $\text{Na}_2\text{Fe}(\text{CO})_4$ ) is first treated with an alkyl halide and subsequently with CO and an alkene to form a ketone (Scheme 4).

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



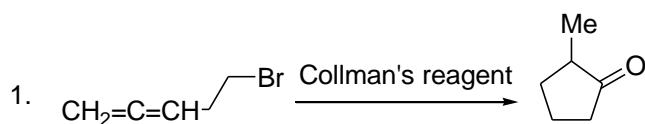
Scheme 4

An interesting fact to observe is that Collman's reagent causes umpolung at the carbonyl centre. Thus, a carbonyl compound may be generated by treating alkyl-iron complex with an electrophile (Scheme 5).

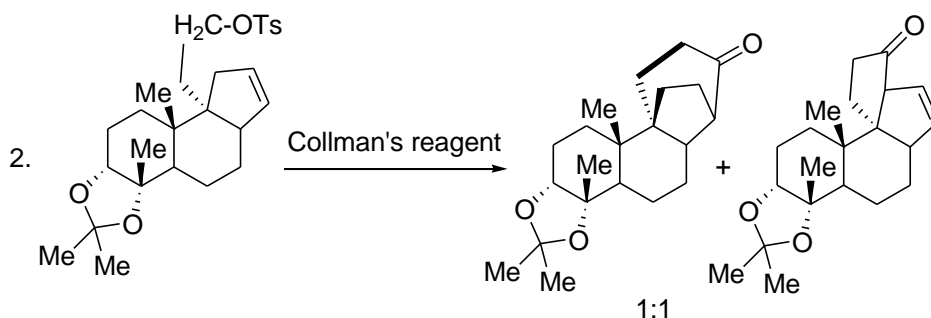


Scheme 5



**Examples:**

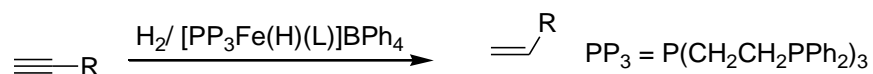
J. Y. Merour, J. L. Roustan, C. Charrier, J. Benaim, J. Collin, P. Cadiot, *J. Organomet. Chem.* **1979**, 168, 337.



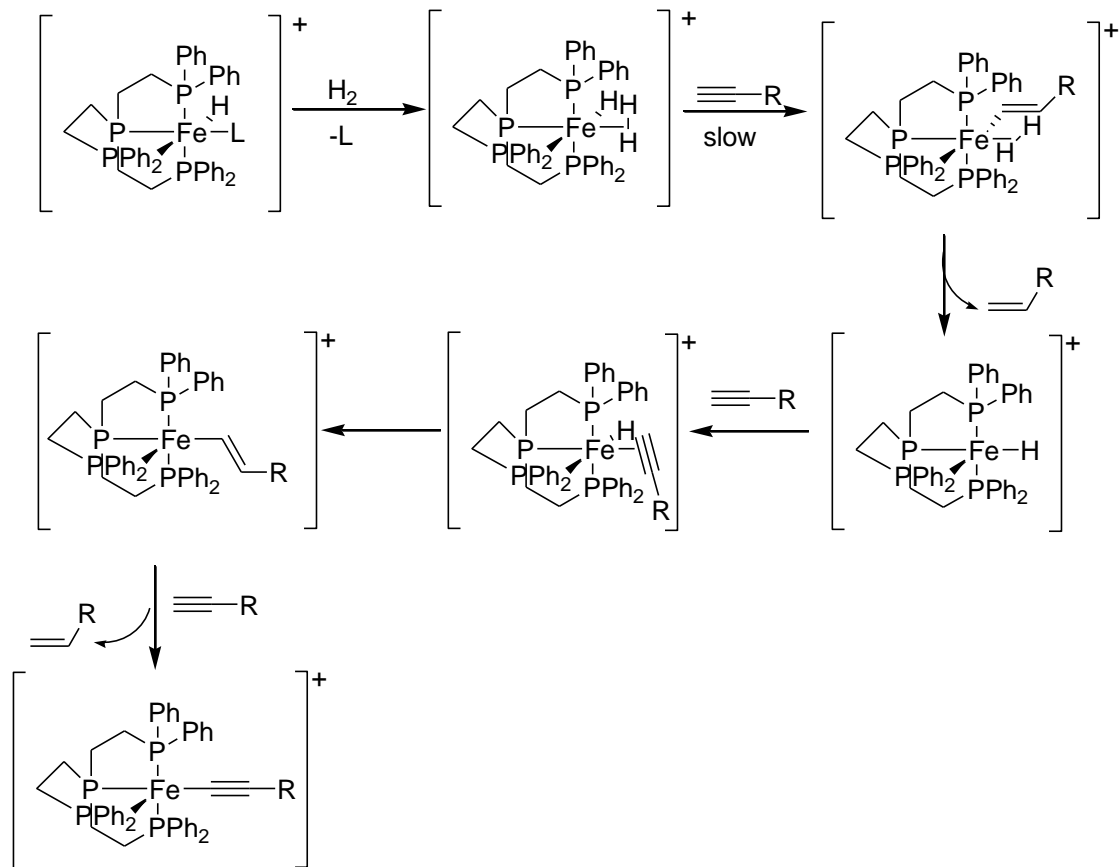
J. E. McMurry, A. Andrejs, G. M. Ksander, J. H. Musser, M. A. Johnson, *Tetrahedron* **1981**, 37, 319.

## 3.6.4.4 Hydrogenation of Alkyne

Iron phosphine catalysts, known as Bianchini catalysts, are known for selective hydrogenation of terminal alkynes to give alkenes (Scheme 6). The selectivity is explained by the reluctance of iron hydride complex to insert alkenes. The mechanism is depicted below in Scheme 7.



Scheme 6

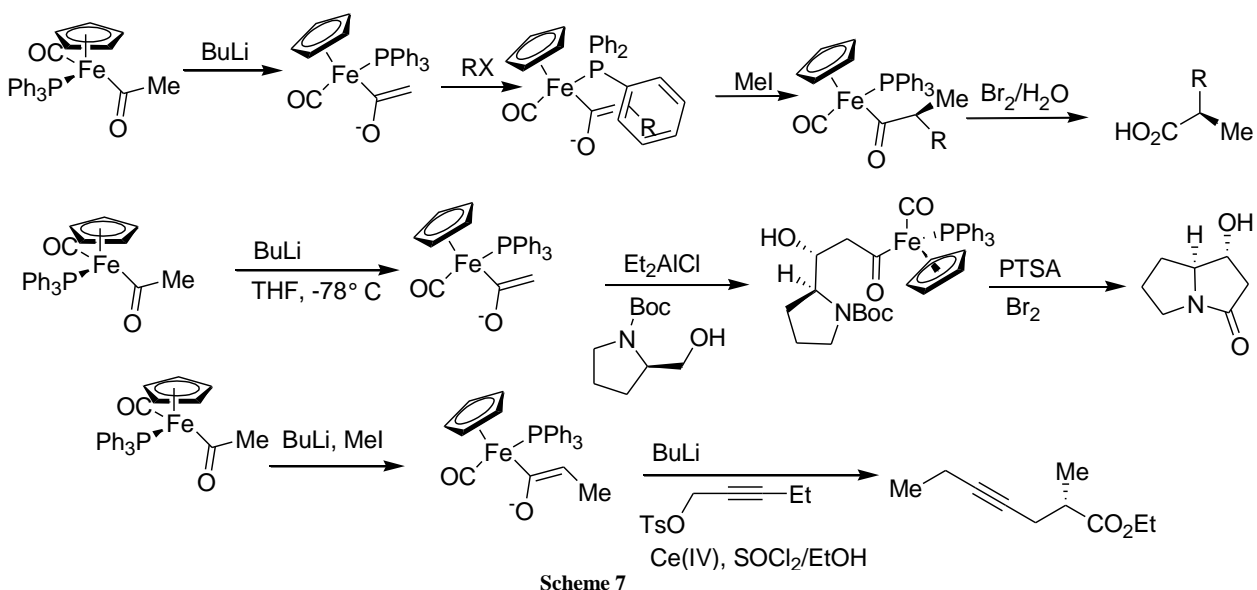


Scheme 7

## 3.6.4.5 Asymmetric Catalysis

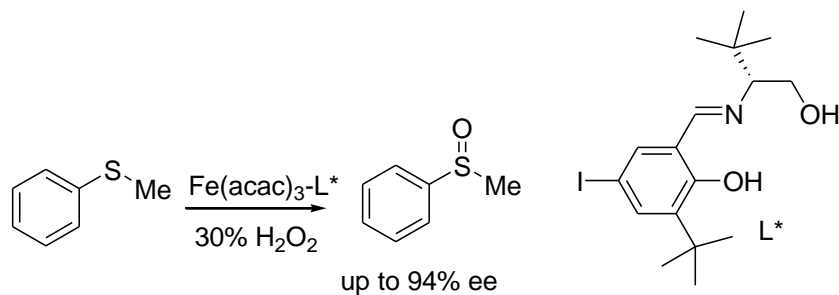
## 3.6.4.5.1 C-C Bond Formation

Chiral iron complexes are used for asymmetric catalysis. One of the most common and useful complex is *S*-aceto(carbonyl)(cyclopentadienyl)(triphenylphosphine)iron. It is a chiral enol equivalent which when deprotonated can react with a variety of electrophiles to generate a variety of functionalized iron compounds. Thus, 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 7).



## 3.6.4.5.2 Sulfoxidation

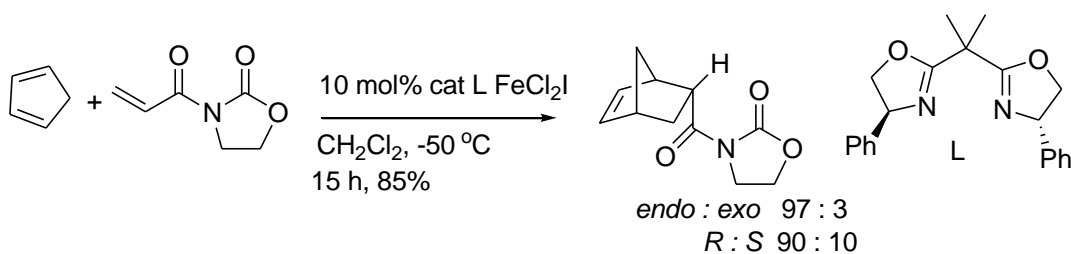
The oxidation of aryl alkyl sulfides has been accomplished using *in situ* generated Fe(III)-Schiff base complex in the presence of 30% H<sub>2</sub>O<sub>2</sub> as terminal oxidant (Scheme 8). Addition of benzoic acid as an additive enhances the enantioselectivity significantly.



Scheme 8

## 3.6.4.5.3 Cycloaddition

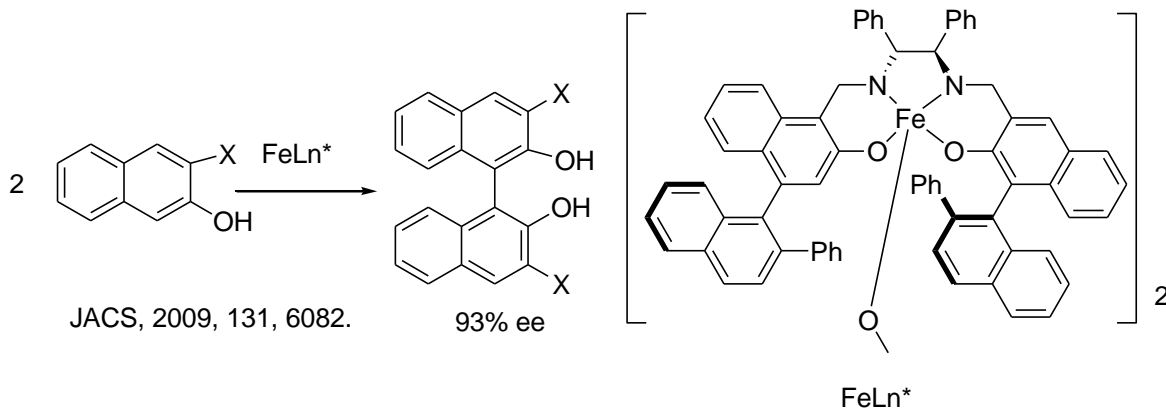
Chiral iron(III)-*bis*(oxazoline) has been used for the asymmetric (4+2)-cycloaddition reaction with good enantioselectivity (Scheme 9).



Scheme 9

## 3.6.4.5.4 Oxidative Coupling

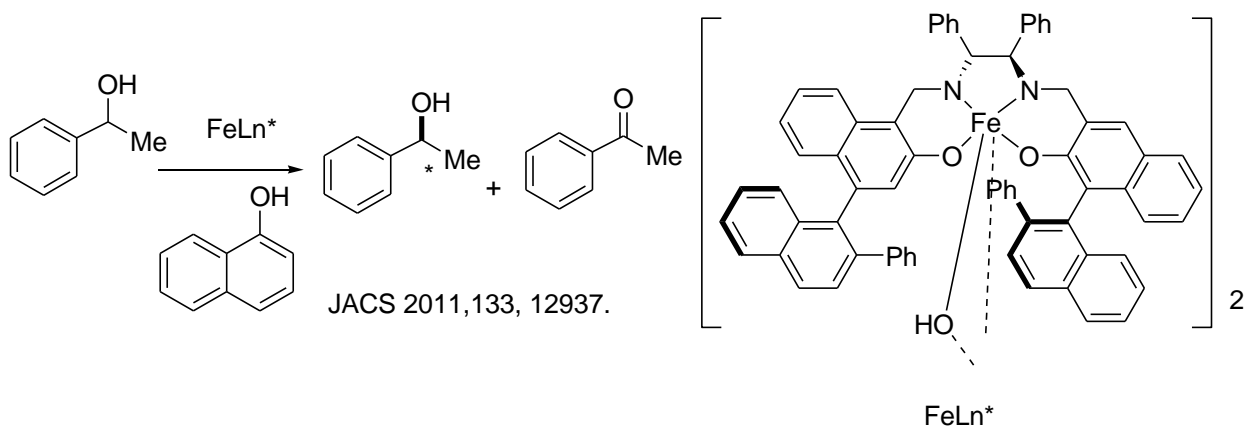
Aerobic oxidative coupling of 2-naphthols has been demonstrated using di- $\mu$ -hydroxo iron(salan) complex (Scheme 10). The substrates having substituents at 3-position exhibited the best enantioselectivity. Detailed kinetic and X-ray studies indicate that the reactions take place *via* a radical anion mechanism.



Scheme 10

## 3.6.4.5.4 Kinetic Resolution

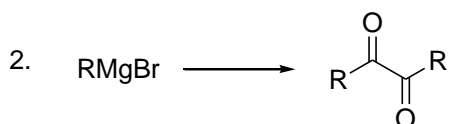
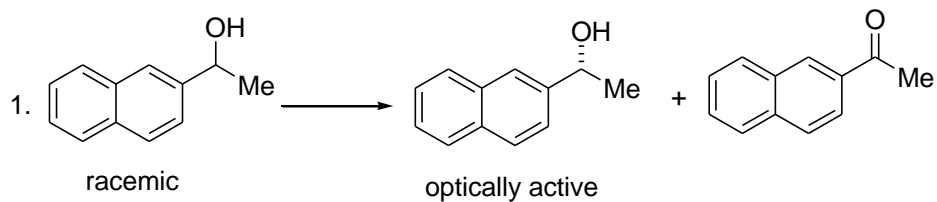
Aerobic oxidative kinetic resolution of secondary alcohols has been shown in the presence of naphthoxide bound iron(salan) complex with good selectivity ( $k_{\text{rel}} = 7-10$ ). Coordination of naphthoxide ion enhances the catalytic activity of the iron(salan) complex.



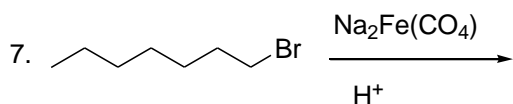
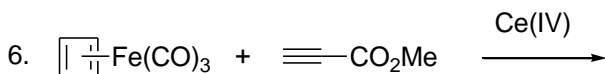
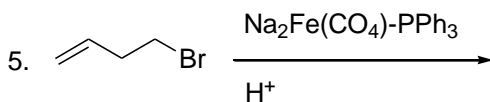
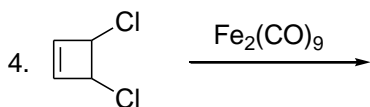
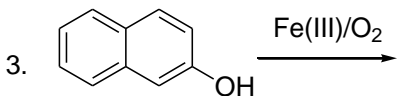
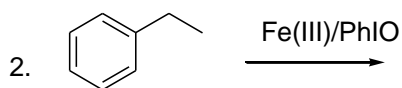
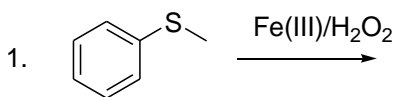
Scheme 11

**Problems**

A. Provide suitable reaction conditions for the following transformations.



B. Complete the following reactions.



**Reference**

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

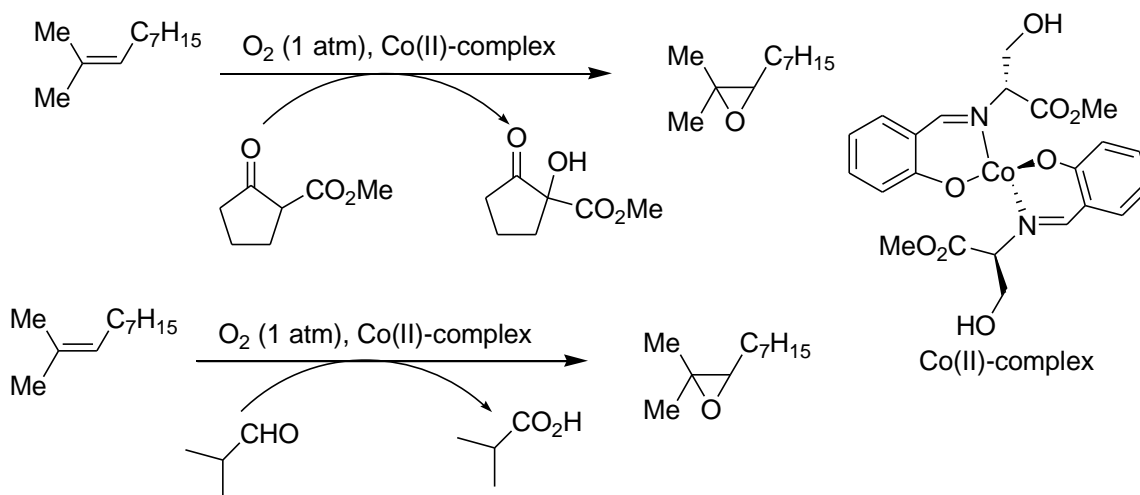
## Lecture 31

### 3.6.5 Cobalt Catalysts

Cobalt is present in various metalloenzymes like methylmalonyl coenzyme A mutase. It is also a key constituent of vitamin B<sub>12</sub> which plays an important role in normal functioning of the central nervous system. Cobalt exists mainly in two oxidation states. The standard electrode potential for Co(III)/Co(II) system is 1.82 V which shows that it is a very strong oxidant. Also, the existence of cobalt based redox systems in biological systems has intuited the exploration of similar bio-mimicking systems for redox reactions. Some of these reactions are illustrated below.

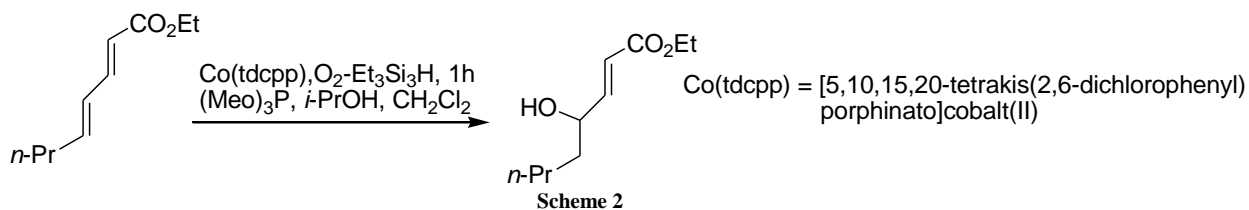
#### 3.6.5.1 Oxidation Reactions

Epoxidation of alkenes can be achieved by using cobalt(II)-Schiff base complex in the presence of reducing agent such as aldehydes,  $\beta$ -ketoester, acetal and triphenylphosphine under molecular oxygen (Scheme 1). A series of cobalt(II) complexes have been designed and developed for this purpose. The reactions are general, efficient and effective at ambient temperature.

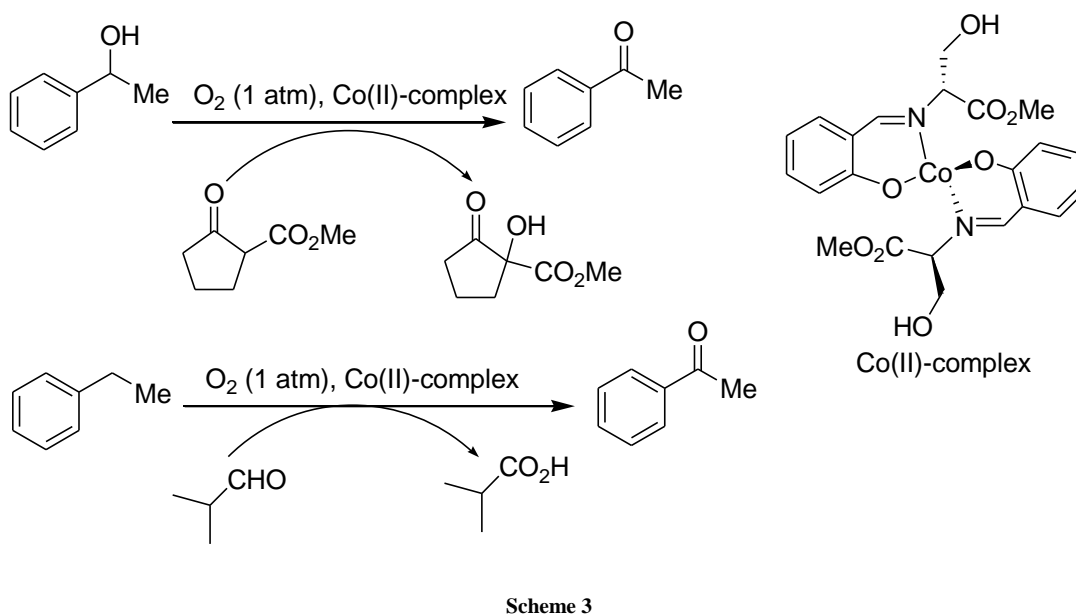




In the presence of  $\text{Et}_3\text{SiH}$ , hydration of alkenes can be accomplished using cobalt catalysts with high yield (Scheme 2). The reaction is general and provides effective route for the oxidation of alkenes to alcohols under mild conditions.

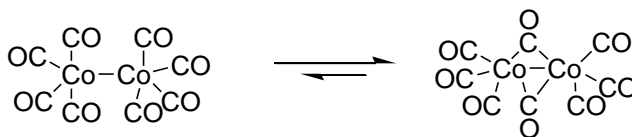


Cobalt(II)-complexes with aldehyde or  $\beta$ -ketoester have been found to be effective method for the oxidation of alcohols to give aldehydes or ketones under molecular oxygen (Scheme 3). The reaction conditions can be employed for the oxidation of alkanes to give alcohols and carbonyl compounds.



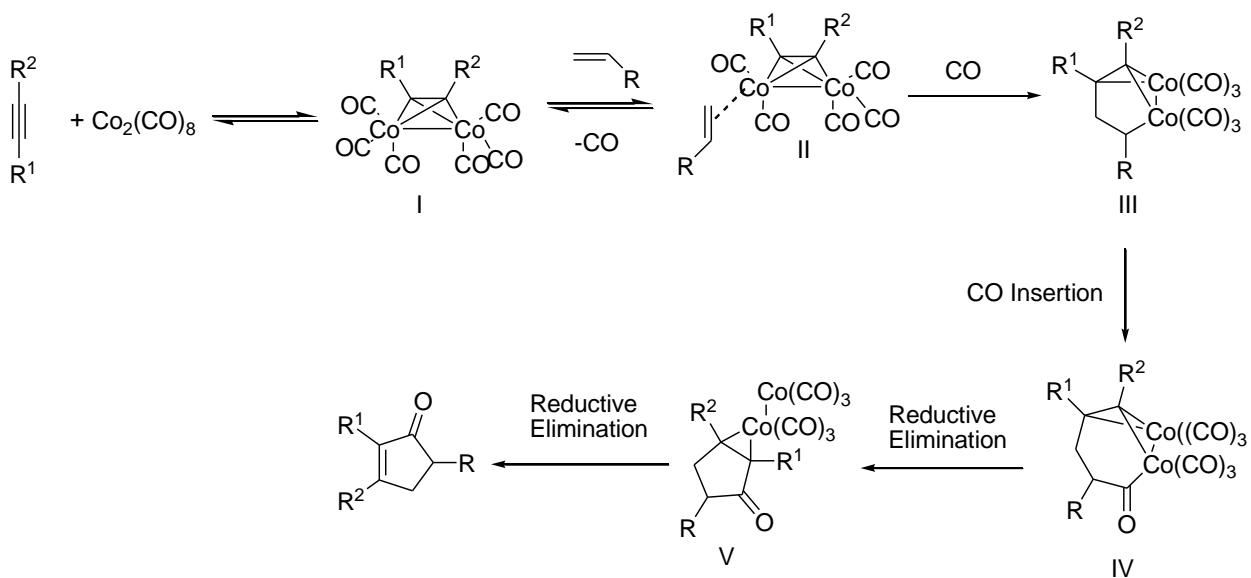
### 3.5.6.2 Pauson-Khand Reaction

Dicobalt octacarbonyl, the predominant cobalt carbonyl complex, has found wide applications in organic synthesis. It is prepared by the high pressure carbonylation of cobalt(II) salts. In solution it exists in equilibrium between two forms, both of which obey to the 18 electron rule (Scheme 4).

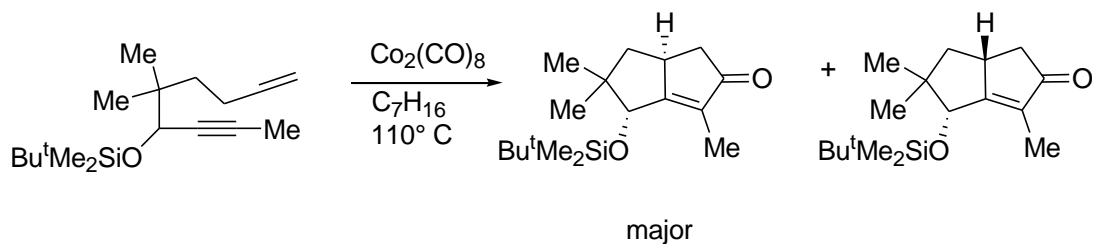


Scheme 4

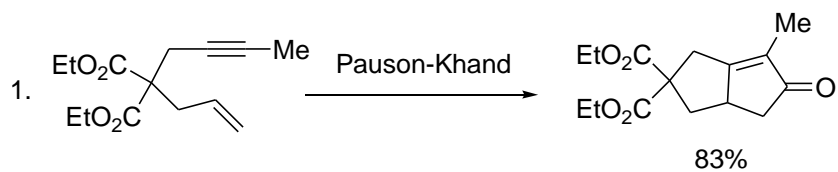
The reactions of dicobalt octacarbonyl involve insertion of CO into the substrate resulting in carbonylation as the overall result. The reaction of an alkyne with this complex result in the formation of stable organocobalt complex that exists as a tetrahedral cluster(I). This cluster can react with an alkene on heating to generate a cyclopentanone derivative *via* a [2+2+1] cycloaddition. This reaction is known as Pauson-Khand reaction. It is believed to involve loss of a CO molecule from the tetrahedral complex followed by coordination with the alkene which inserts itself in the Co-CO bond. This intermediate(III) undergoes insertion reaction where CO insertion takes place between the Co-alkene bond forming the intermediate(IV) which may undergo reductive elimination to give the product (Scheme 5).



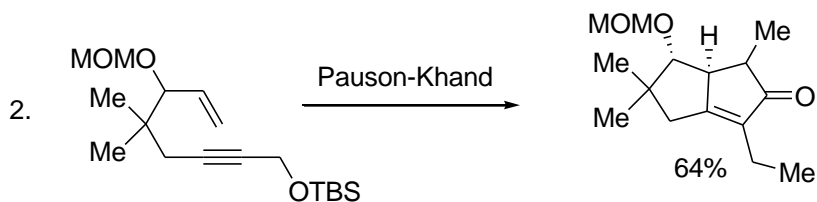
The reaction is completely regioselective with respect to the alkyne. The larger substituents always occupy the position adjacent to the carbonyl group in the product. However, the use of an unsymmetrical alkene usually leads to a mixture of regioisomers (Scheme 6).



**Examples:**



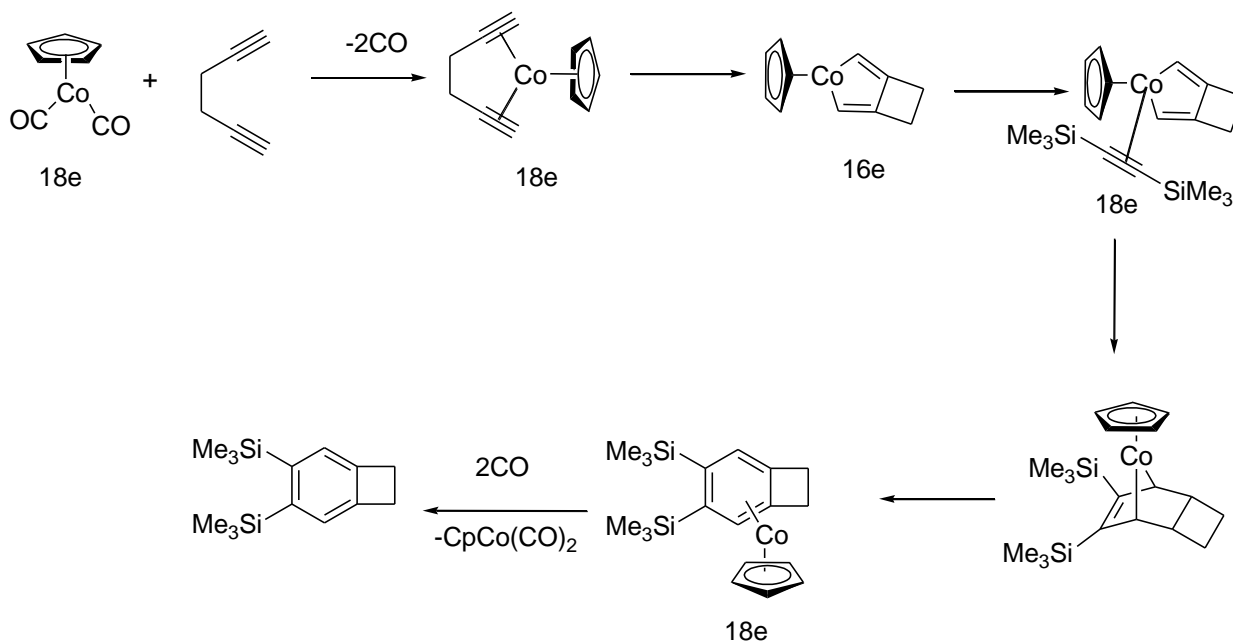
M. E. Krafft, J. A. Wright, L. V. R. Bonaga, *Tetrahedron Lett.* **2003**, *44*, 3417.



P. Magnus, M. J. Slater, L. M. Principe, *J. Org. Chem.* **1989**, *54*, 5148.

## 3.5.6.3 Cycloaddition

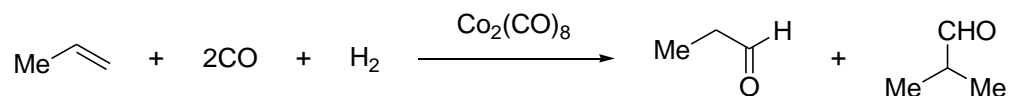
Dicobalt octacarbonyl can be converted into ( $\eta^5$ -cyclopentadienyl)dicarbonylcobalt(0) which is the catalyst for Volhardt cyclotrimerization reaction. This reaction is unique as it brings about the formation of a benzene ring in one step by [2+2+2] cycloaddition of a dialkyne with a monoalkyne (Scheme 7).



Scheme 7

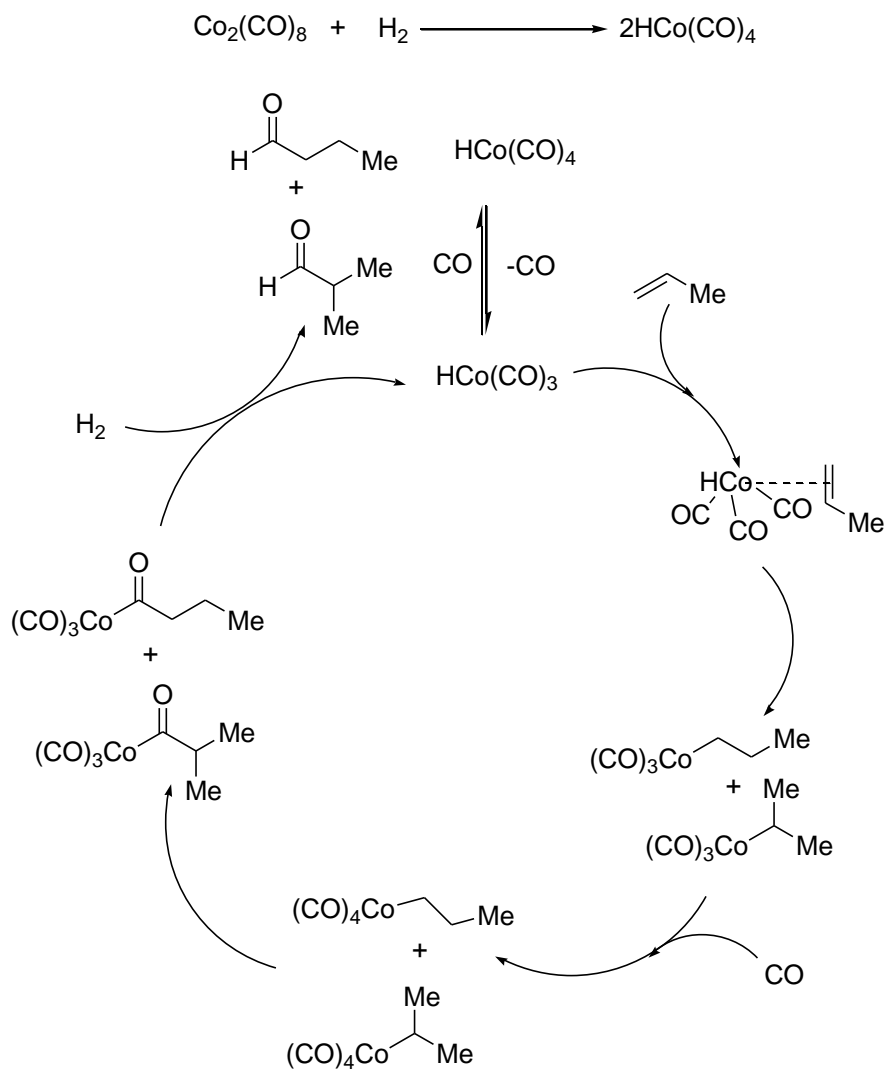
### 3.5.6.4 Hydroformylation

One of the most industrially important reactions using cobalt is definitely the hydroformylation. This reaction inserts a carbonyl group in an alkene thereby giving rise to aldehydes (Scheme 8). It is also known as the oxo process.



Scheme 8

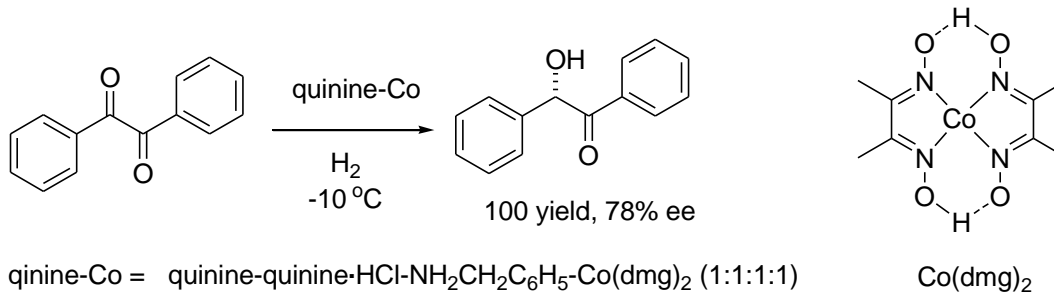
Both the linear isomer (usually referred as *n*-product) and the branched isomer (*iso*-product) are produced. The ratio of the two isomers is crucial for industry as the linear aldehydes are usually important from their perspective. The formation of the two isomers is outlined in the mechanism shown in Scheme 9. At a very high pressure (~ 100 bar), dicobalt octacarbonyl reacts with hydrogen gas to form tetracarbonylhydridocobalt(I). This complex loses one CO molecule to form a coordinatively unsaturated complex which then undergoes alkene insertion to give *n*-alkyl complex (Markwonikov addition) as well as a branched alkyl complex (anti-Markwonikov addition). Both these complexes now undergo migratory insertion of CO to generate acyl complexes which then undergo attack by hydrogen to yield the target aldehydes. The use of bulky ligands like  $\text{PBu}_3$  diminishes the extent of branched aldehyde formation and improves the *n*/*iso* ratio.



Scheme 9

## 3.5.6.5 Hydrogenation

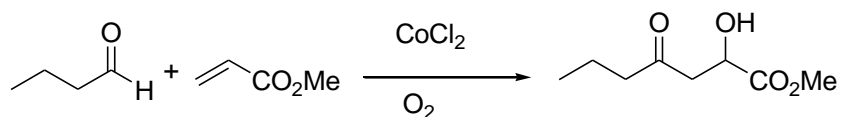
Homogeneous asymmetric hydrogenation of benzil has been accomplished using cobalt(II) complexes in combination with quinine under 1 atm of hydrogen. The reactions are efficient to give benzoin with good enantioselectivity (Scheme 10).



Scheme 10

## 3.5.6.6 Oxidative Addition

Cobalt(II) chloride has been shown as effective catalyst for the oxidative addition of acyl radical to electron deficient alkenes under molecular oxygen. The reactions of aliphatic aldehydes have been explored with methyl acrylate at ambient conditions (Scheme 11).



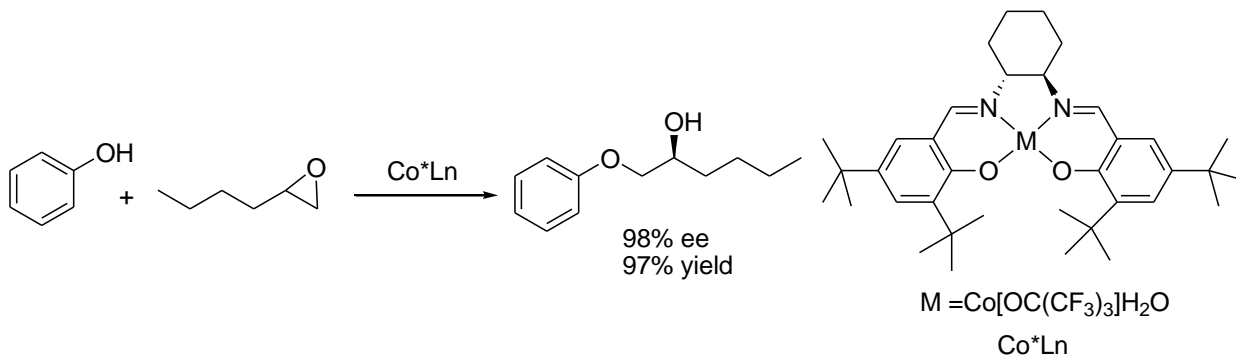
Scheme 11



### 3.5.6.7 Kinetic Resolution

Chiral cobalt(III) salen complexes have been studied for the kinetic resolution of terminal epoxides with nucleophiles such as water and phenols with excellent enantioselectivity.

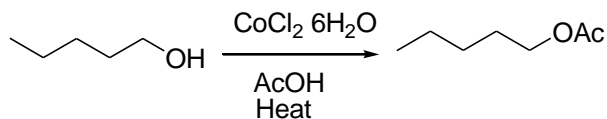
1,2-Epoxybutane with phenol gives  $\alpha$ -aryloxy alcohol in 98% ee (Scheme 12).



Scheme 12

### 3.5.6.7 Esterification

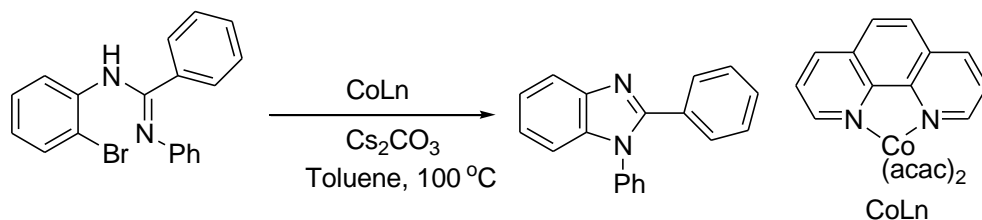
Cobalt(II) chloride has been considerably studied as Lewis acid for the acylation of alcohols and amines with acylating agents such as acid chloride, acetic anhydride and acetic acid. The acylation of alcohols with acetic acid is attractive where water is generated by-product (Scheme 13).



Scheme 13

### 3.5.6.7 Cross-Coupling Reaction

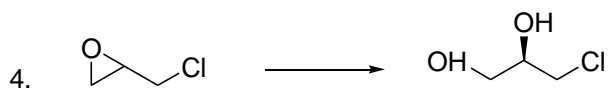
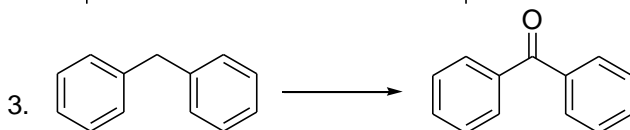
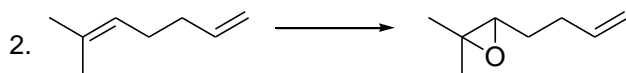
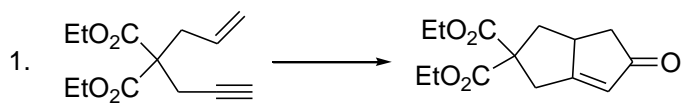
Cobalt(II)-1,10-phenanthroline has been recently used for intramolecular cyclization of amidines to give 2-aryl benzimidazoles in high yield (Scheme 14). The reaction is general, efficient and operates at moderate temperature.



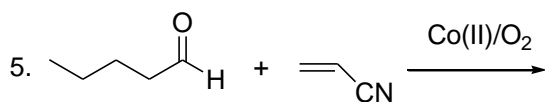
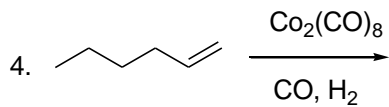
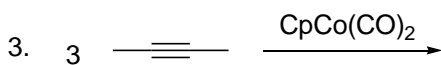
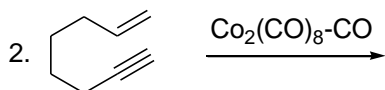
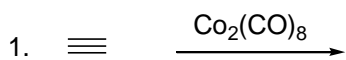
Scheme 14

**Problems**

A. Provide suitable reaction conditions for the following transformations.



B. What major product would you expect from the following?



**Reference**

*Transition Metals for Organic Synthesis*, Vol. I &2, Eds., M. Beller and C. Bolm, Wiley-VCH, New York, 1998.

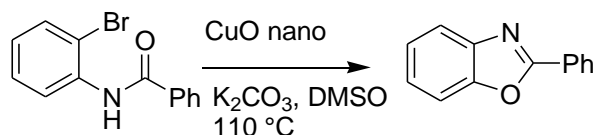
## Lecture 32

### 11.6 Copper Catalysts

Copper catalysts find extensive applications in organic synthesis. Since lectures 8 and 22 cover the common copper-based reactions, this lecture is devoted to some of the modern methods on the use of copper-catalysis for the synthesis of medicinally important heterocyclic compounds.

#### 11.6.1 Synthesis of Substituted Benzoxazoles

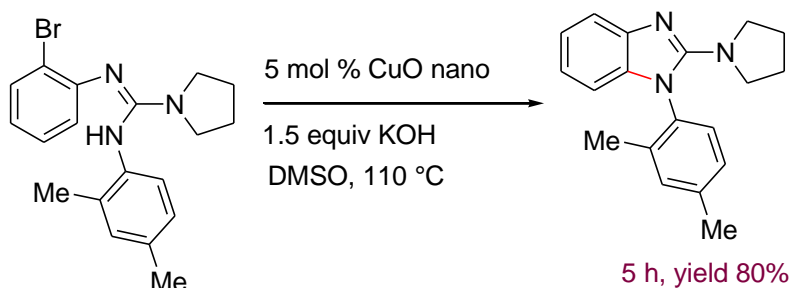
Benzoxazoles are important structural units present in numerous compounds that are important in medicinal chemistry. The copper-catalyzed intramolecular cyclization of 2-bromoanilides via intramolecular C-O cross-coupling reaction provides a straightforward route for the construction of 2-aryl and 2-alkylbenzoxazoles (Scheme 1).



Scheme 1

#### 11.6.2 Synthesis of Substituted Benzimidazoles

The above reaction conditions can be employed for the synthesis of substituted benzimidazoles and 2-aminobenzimidazoles from 2-bromoamidines and 2-bromoarylguanidines (Scheme 2). These processes involve intramolecular cyclization *via* C-N cross-coupling reactions.

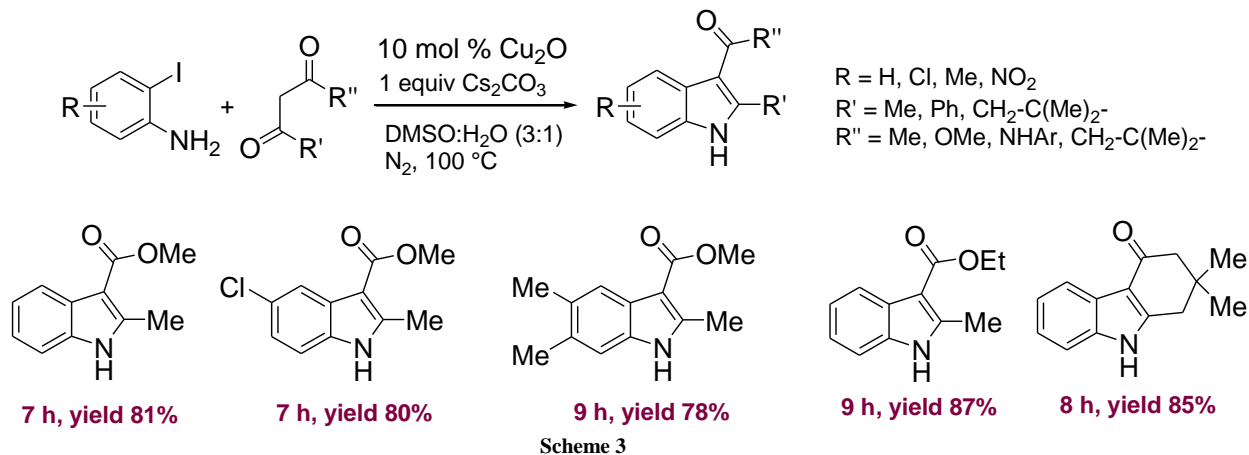


Scheme 2

## 11.6.2 Tandem Reactions

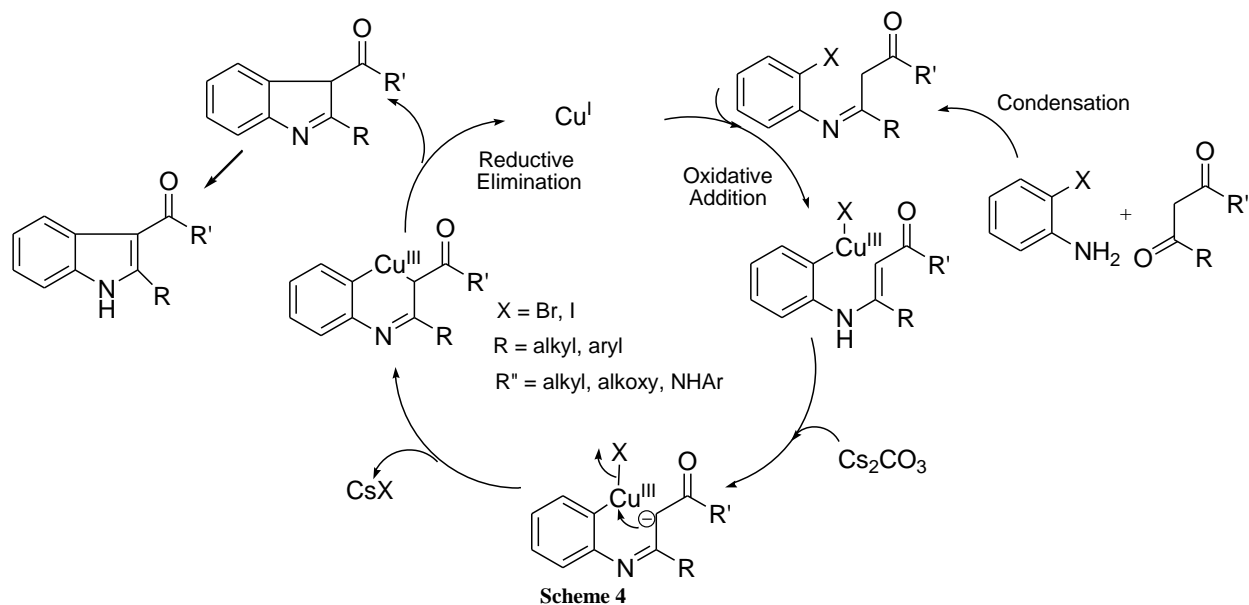
### 11.6.2.1 Synthesis of Substituted Indoles

Indoles are important structural motifs and found in several natural products and biologically active compounds. The domino synthesis of polysubstituted indoles has been shown using copper(I)-catalysis from 2-haloaniline and 1,3-dicarbonyl compounds (Scheme 3).



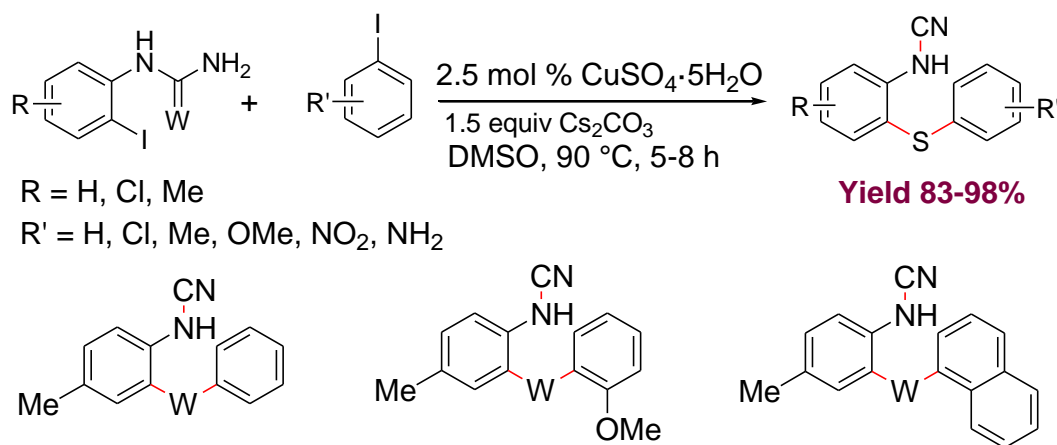
### Mechanism

This process involves condensation followed C-C cross-coupling reaction (Scheme 5).



### 11.6.2.2 Synthesis of Arylthioarylcyanamides and Arylselanylarylcyanamides

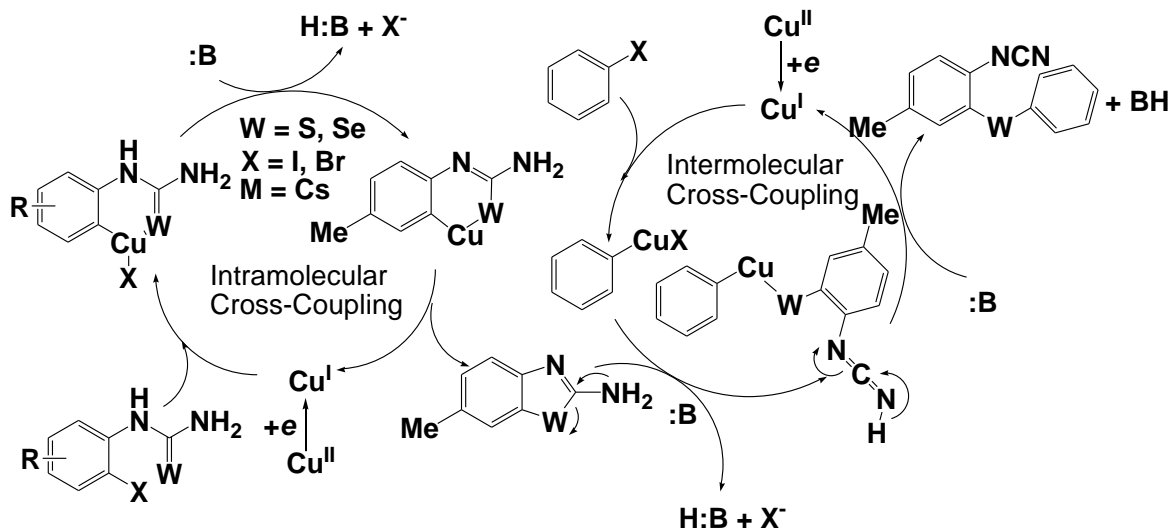
The cross-coupling of 2-haloarylthiourea and 2-haloarylselenourea with aryl halides take place in presence of copper catalysts to give 2-arylthioarylcyanamides and 2-arylselanylarylcyanamides *via* intra- followed by intermolecular C-S/C-Se cross-coupling reactions (Scheme 5). The C-S cross-coupling reactions are effective with Cu(I)/Cu(II), while the C-Se cross-coupling reactions give the best results with the complex derived from CuI and 1,10-phenanthroline.



Scheme 5

### Mechanism

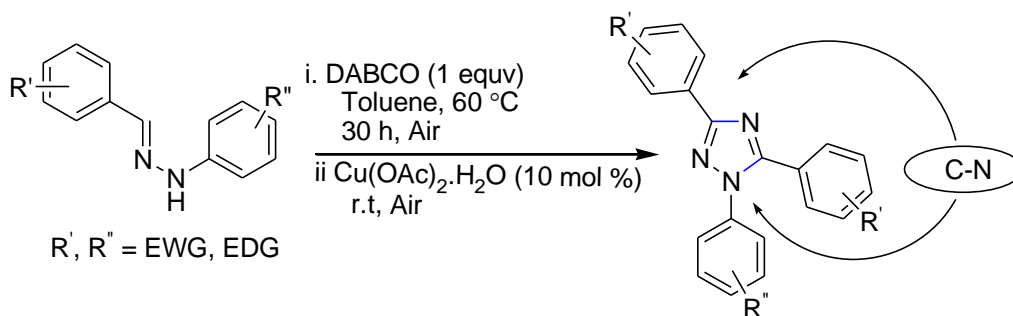
The proposed catalytic cycle involves intra- followed by intermolecular cross-coupling reactions (Scheme 6).



Scheme 6

#### 11.6.2.3 Synthesis of 1,3,5-Trisubstituted 1,2,4-Triazoles

Bisaryldiazones undergo reaction in the presence of DABCO and  $Cu(OAc)_2$  to afford 1,3,5-trisubstituted 1,2,4-triazoles (Scheme 7). This is the first example for room temperature copper-catalyzed C-H functionalization process.

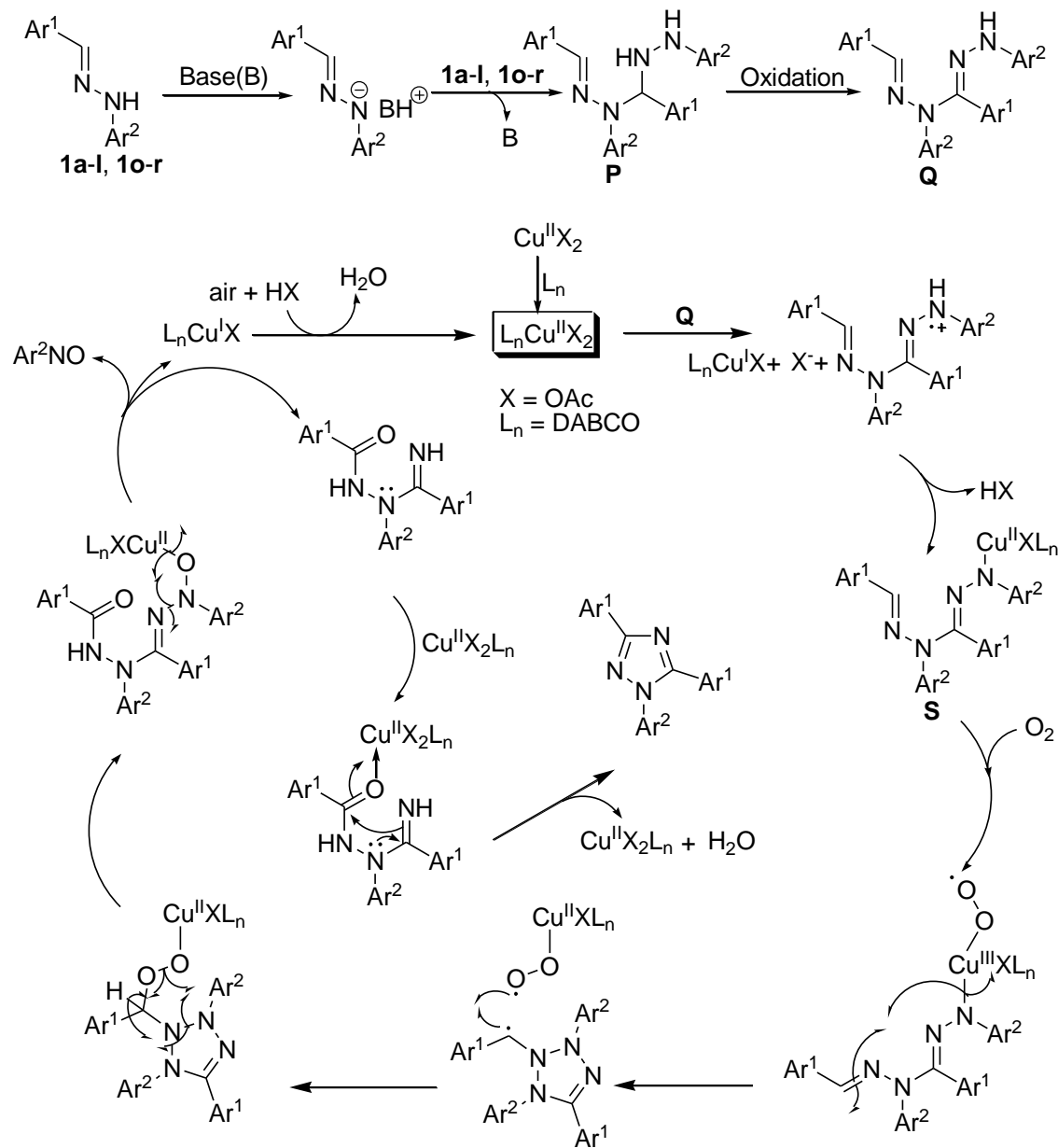


Scheme 7



## Mechanism

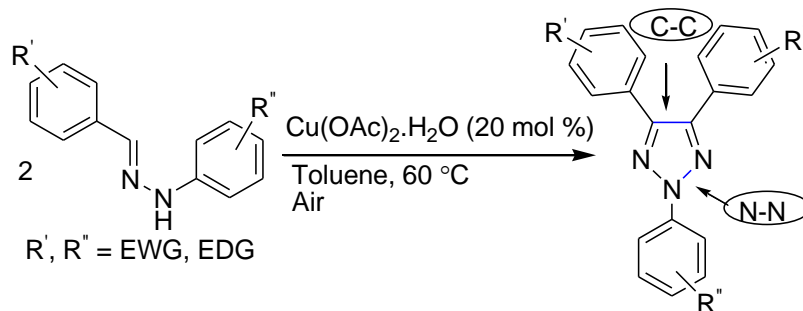
The detailed investigation suggests that DABCO acts as base as well as ligand for the copper-catalysis (Scheme 8).



Scheme 8

## 11.6.2.3 Synthesis of 2,4,5-Trisubstituted 1,2,3-Triazoles

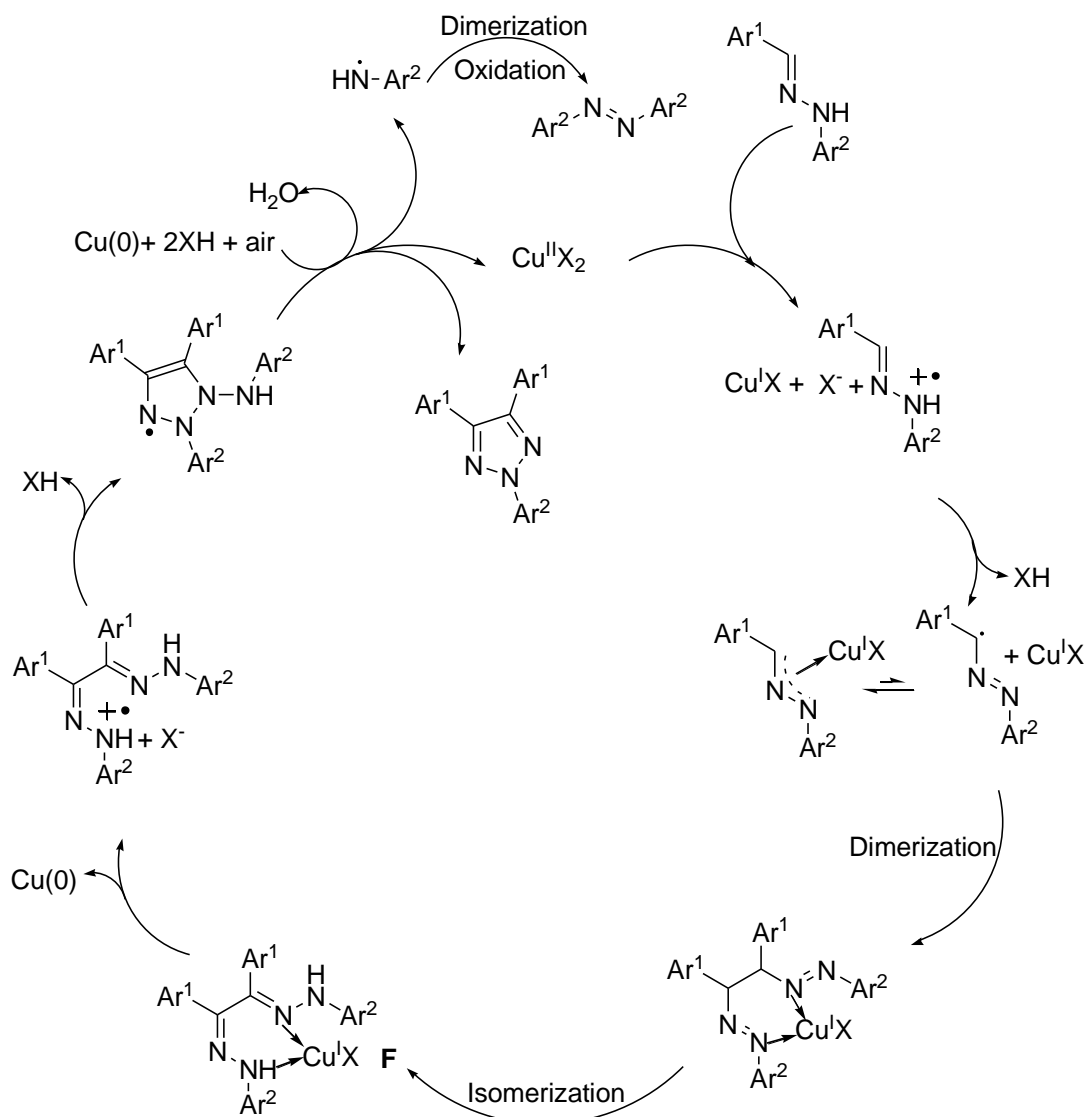
The above process, in the absence DABCO, affords 2,4,5-trisubstituted 1,2,3-triazoles (Scheme 9).



Scheme 9

### Mechanism

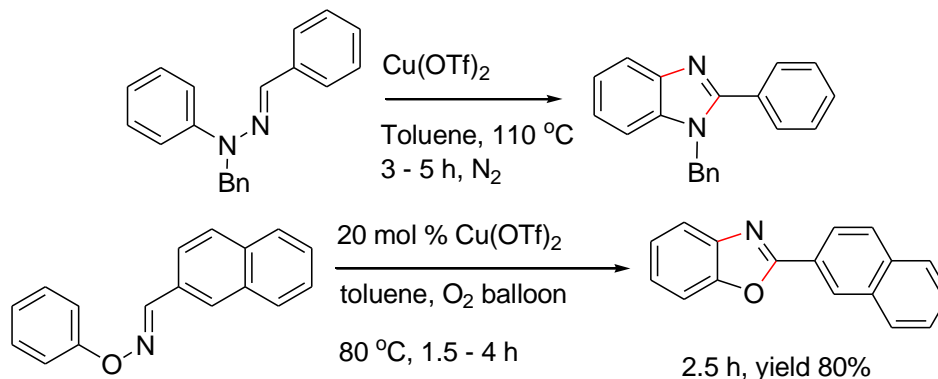
The reaction intermediates have been isolated and the proposed mechanism is shown in Scheme 10.



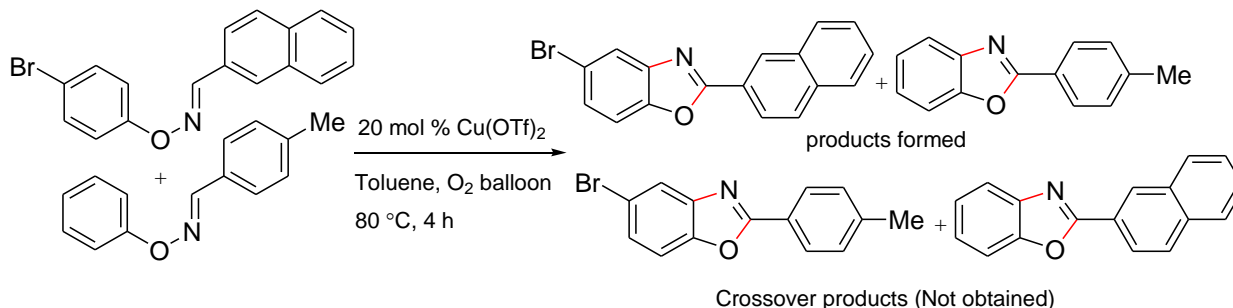
Scheme 10

## 11.6.2.4 Synthesis of Substituted Benzimidazoles and Benzoxazoles

Using  $\text{Cu}(\text{OTf})_2$ , N-protected bisarylhydrazones and bisaryloxime ethers can be converted into 2-arylbenzimidazoles and 2-arylbenzoxazoles under neutral conditions at moderate temperature (Scheme 11). The cross-over experiments with two different bisaryloxime ethers show that the protocol involves intramolecular process (Scheme 12).



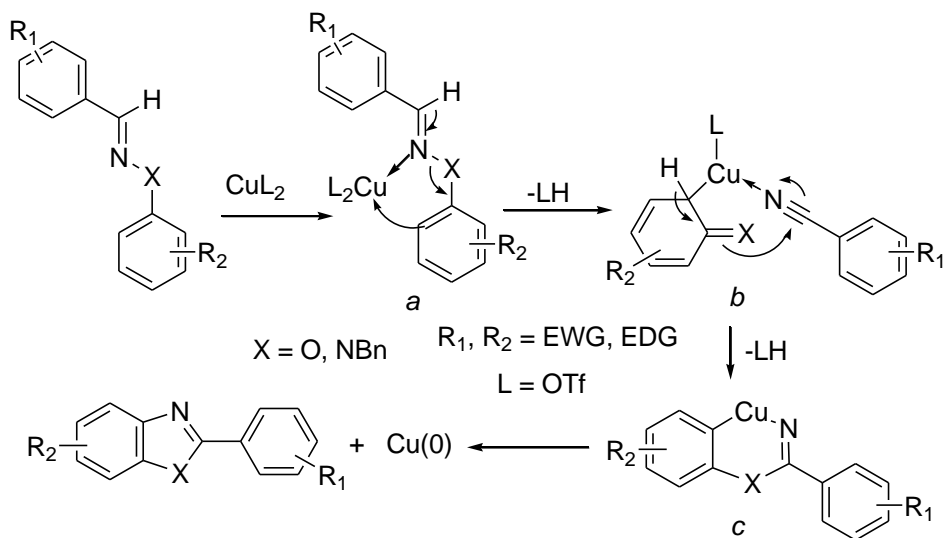
Scheme 11



Scheme 12

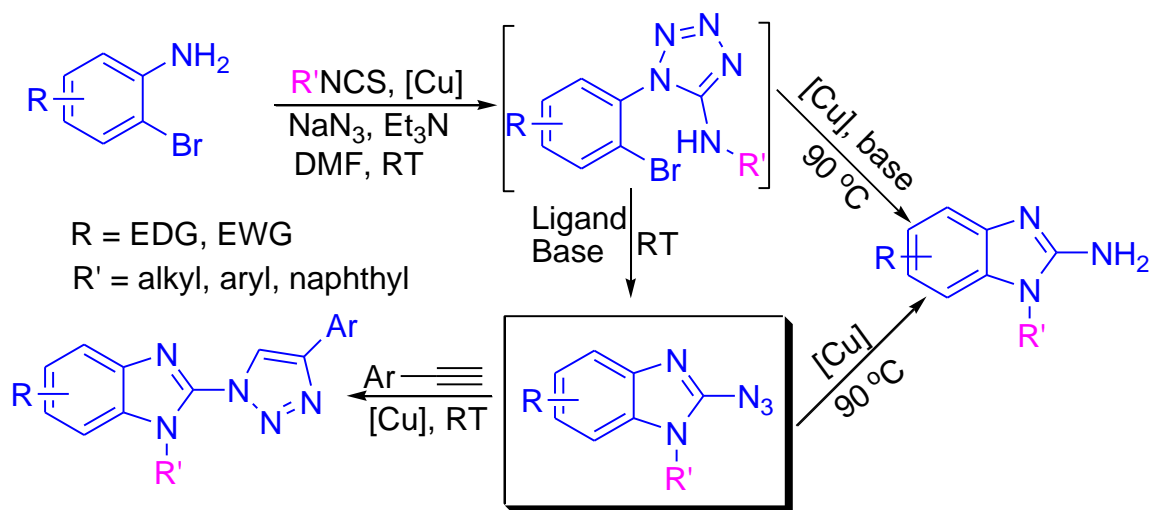
### Mechanism

Observed results suggest that the process involves a tandem C-H functionalization, C-O or C-N bonds formation (Scheme 13).



Scheme 13

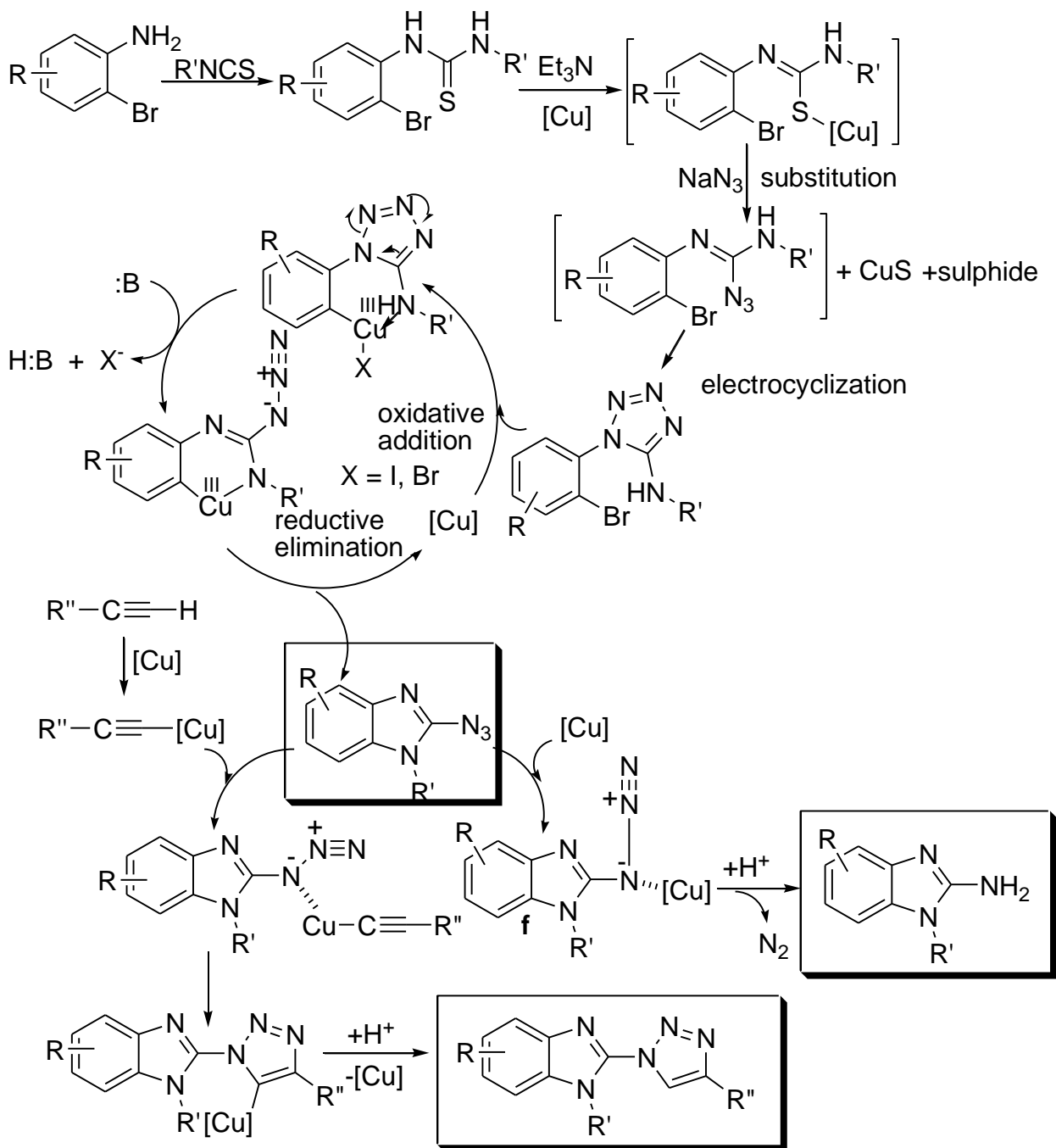
Three component syntheses of 2-aminobenzimidazoles and analogues can be accomplished from 2-haloaniline, sodium azide and isothiocyanate using copper-based systems (Scheme 14).



Scheme 14

### Mechanism

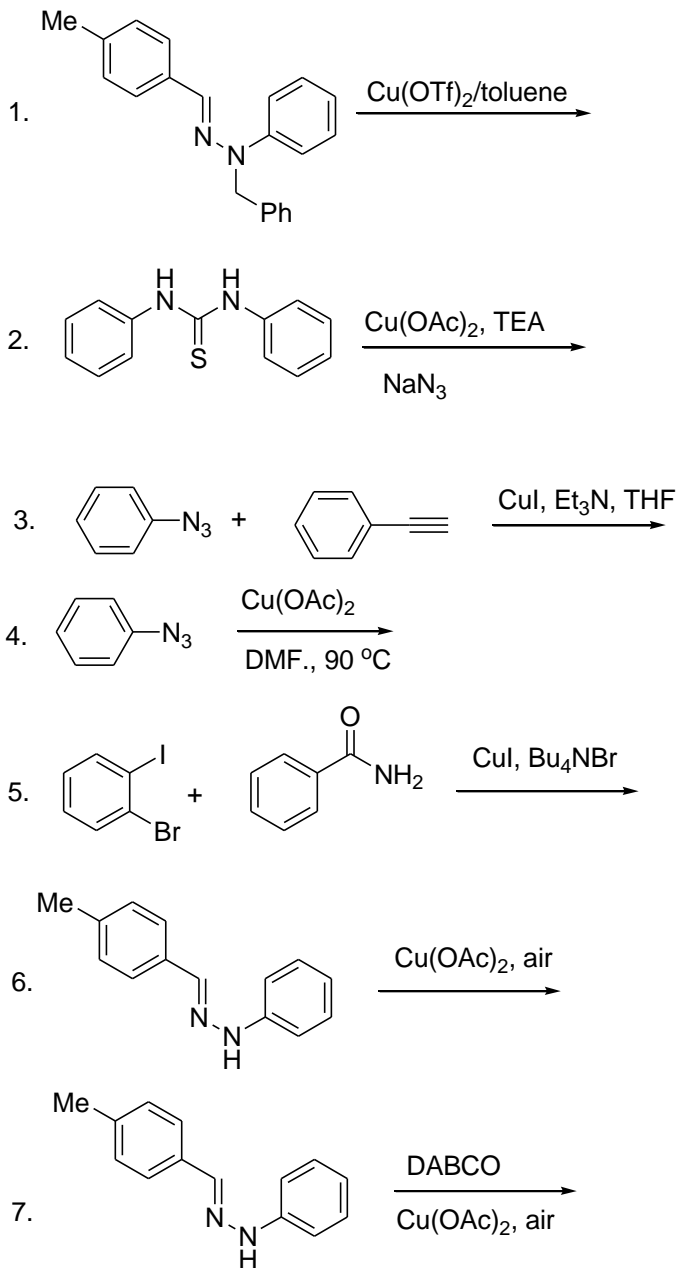
This reaction involves a tandem addition/substitution/electrocyclization/*N*-arylation/tautomerism processes (Scheme 15)



Scheme 15

**Problems**

Predict the major products for the following reactions.



**Reference**

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



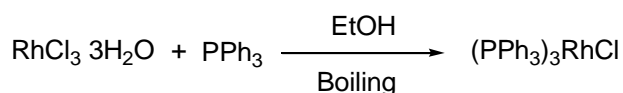
## Lecture 33

### 3.6.5 Rhodium Catalysts

Rhodium is a silvery white monoisotopic metal of platinum group metals belonging to the 4d series. Rhodium is used mainly in the three way catalytic converters of automobiles for oxidation of incompletely burnt hydrocarbons. It is also alloyed with platinum and palladium for use in high temperature surroundings. The most stable oxidation state of rhodium is +3 but it can show oxidation states ranging from 0 to +6.

#### 3.6.5.1 Hydrogenation

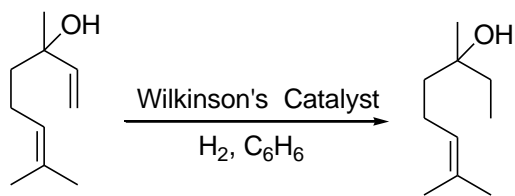
Transition metal catalyzed hydrogenation of alkenes and carbonyl compounds occupies an important position in organic synthesis. Wilkinson's complex,  $[\text{RhCl}(\text{PPh}_3)_3]$ , is one of the most versatile catalysts for the homogeneous hydrogenation process. It is obtained in the form of a red-violet crystalline solid from the reaction of  $\text{RhCl}_3$  with excess of  $\text{PPh}_3$  in boiling EtOH (Scheme 1).



Scheme 1

K. Burgess, W. A. van derDonk, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 2, 1253.

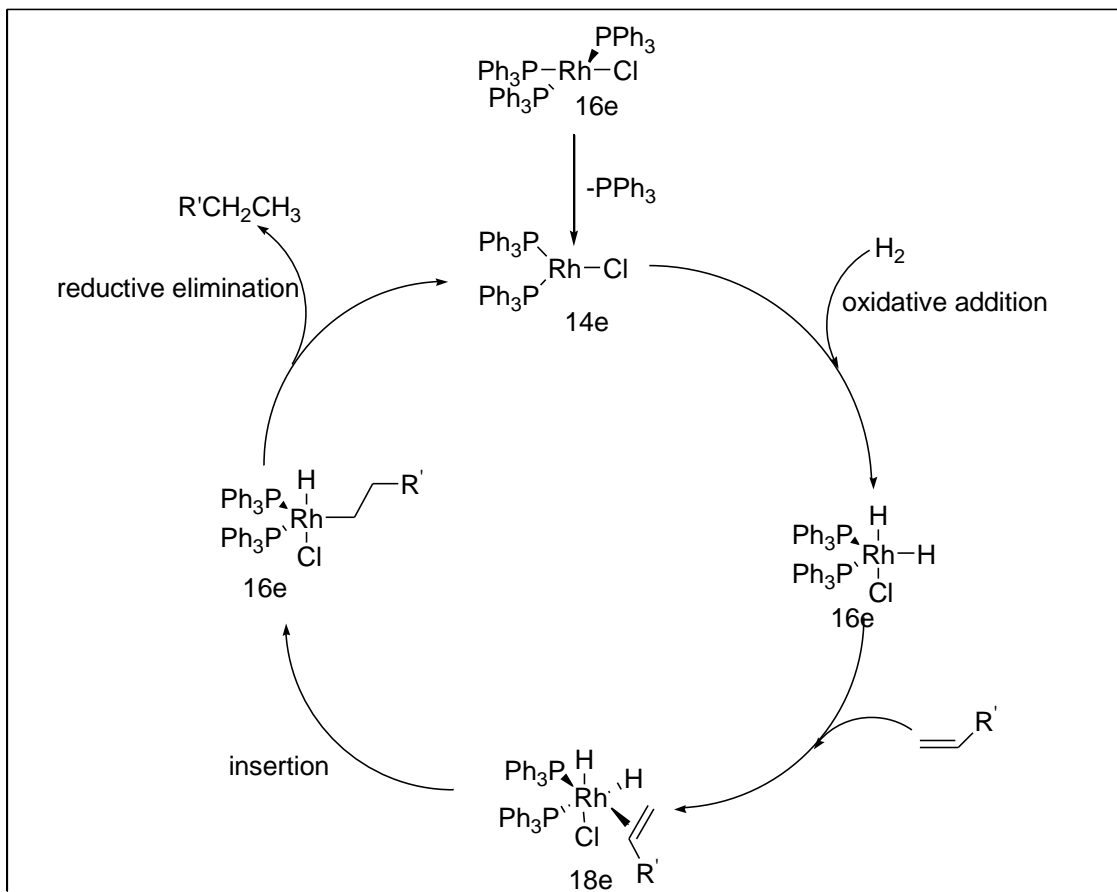
Rhodium-catalyzed hydrogenation is compatible with the substrates having functional groups such as oxo, cyano, nitro, choro and azo, and selectively reacts with the double bond (Scheme 2). Chelation of the functional group on the catalytically active Rh may lead to high degree of selectivity. The reduction takes place from the less-hindered face with a *cis*-stereochemistry.



Scheme 2

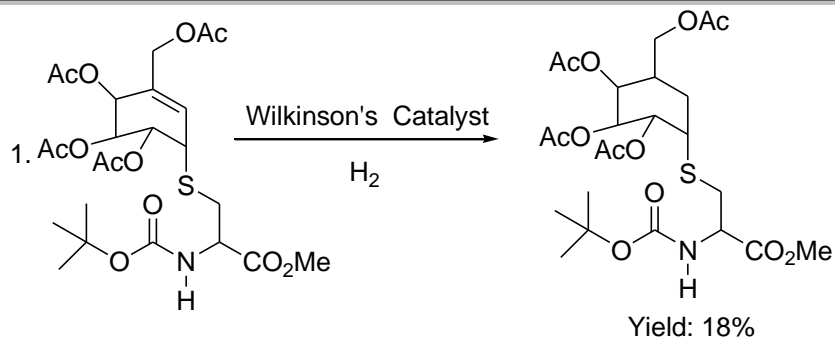
### Mechanism

The initial dissociation of a triphenylphosphine ligand leads to the formation of a 14-electron Rh complex that undergoes oxidative addition with  $H_2$  followed by  $\pi$ -complexation with alkene, intramolecular hydride transfer and reductive elimination of the target product (Scheme 3).

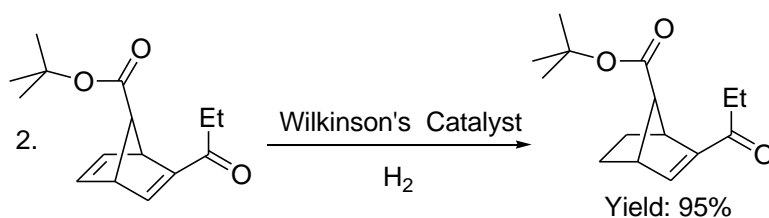


Scheme 3

**Examples:**

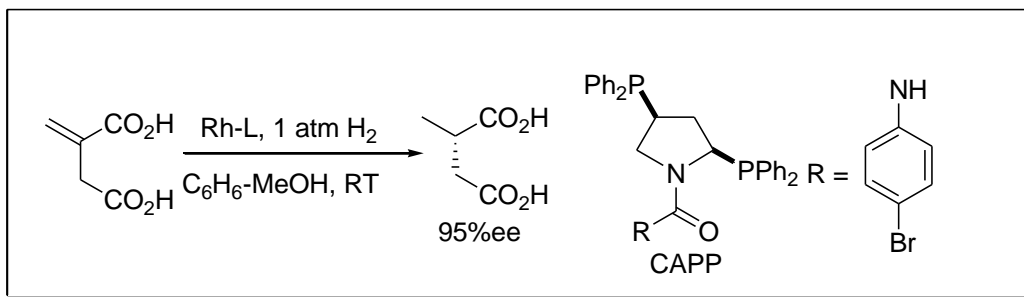


L. J. Whalen, R. L. *Org. Lett.* **2004**, *6*, 3221.



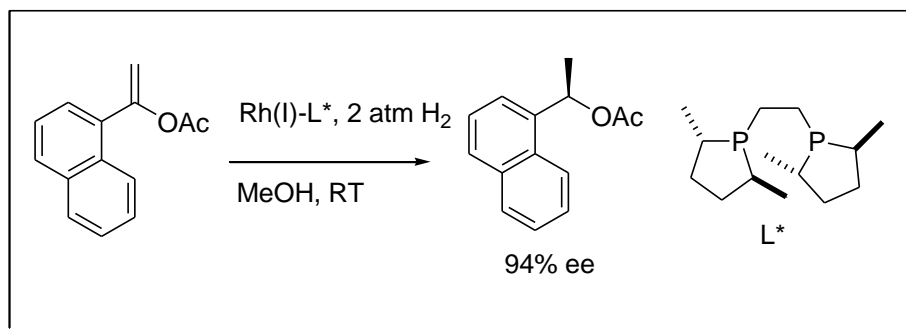
H. M. L. Davies, E. Saikali, N. J. S. Huby, V. J. Gilliatt, J. J. Matasi, T. Sexton, S. R. Childers, *J. Med. Chem.* **1994**, *37*, 1262.

When the triphenylphosphine ligands are replaced by chiral phosphines, the complex becomes chiral and converts prochiral alkenes into chiral alkanes with excellent enantioselectivity. For example, itaconic acid undergoes hydrogenation to give (S)-methylsuccinic acid with 95% ee in the presence of chiral CAPP-Rh(I) complex (Scheme 4).



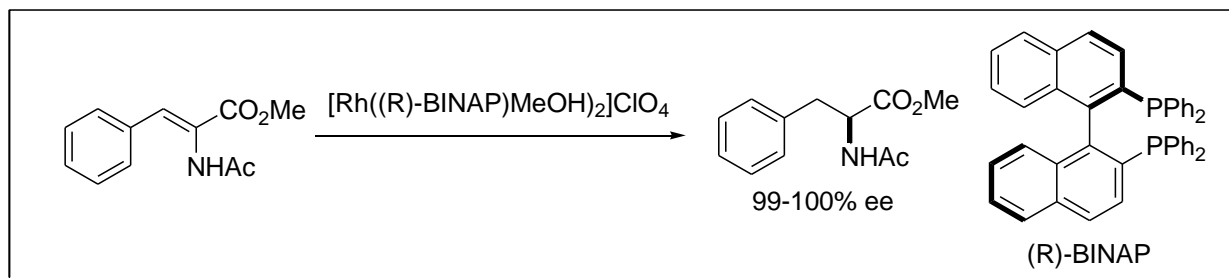
Scheme 4

Likewise, 1-naphthyl methyl ketone enol acetate can be hydrogenated using Rh-diphospholane with 94% ee (Scheme 5).



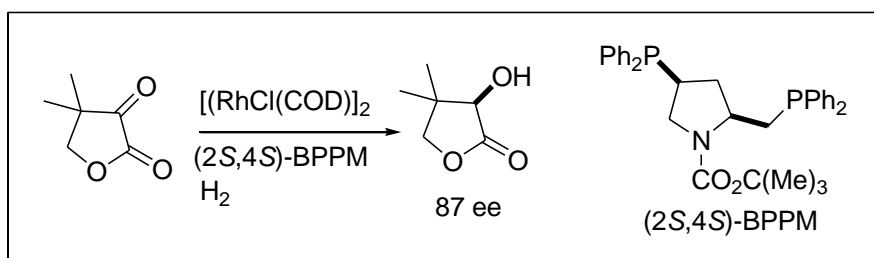
Scheme 5

A similar result is obtained with the hydrogenation of N-acylaminoacrylic acids utilizing Rh-BINAP complex (Scheme 6).



Scheme 6

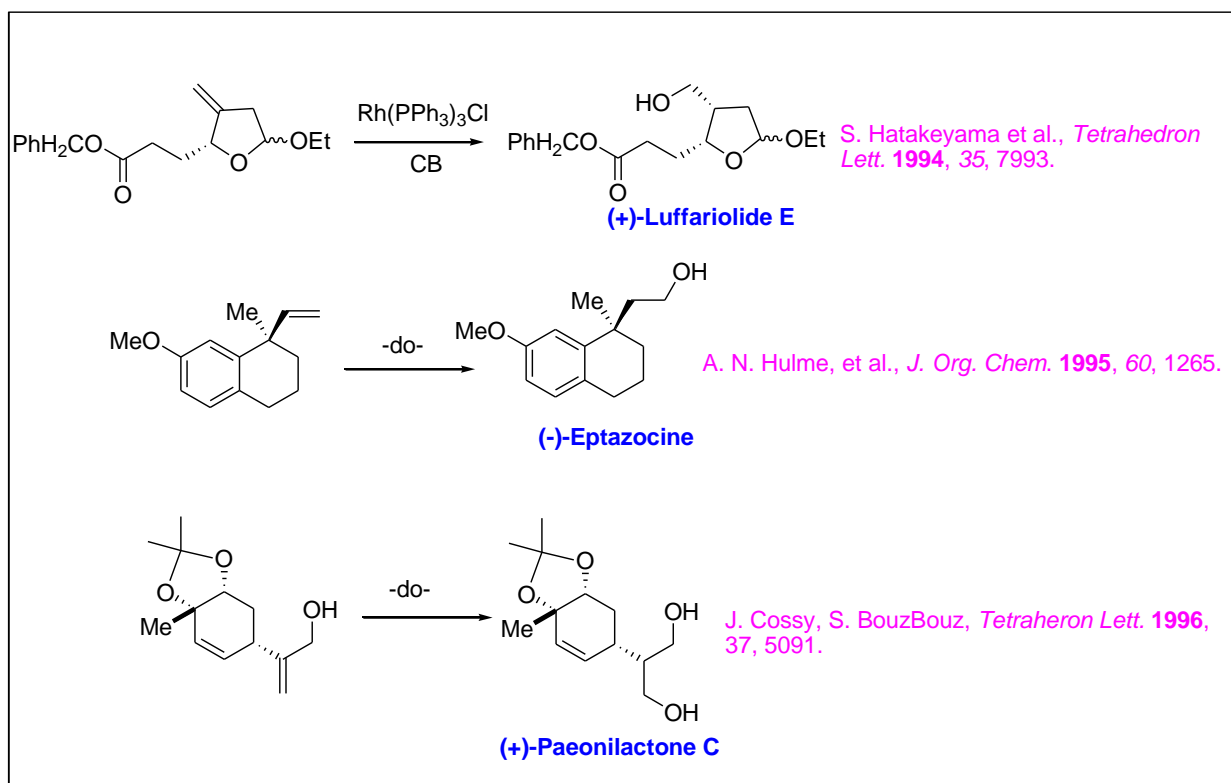
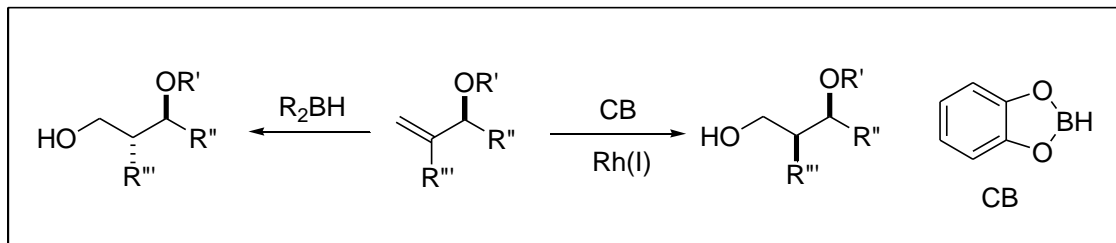
Likewise, the hydrogenation of ketopantolactone using Rh-(2S,4S)-BPPM can be accomplished with good enantioselectivity (Scheme 7).



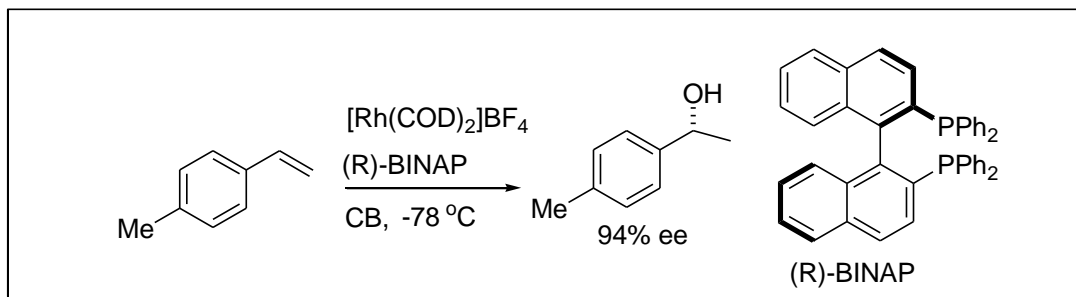
Scheme 7

## 3.6.5.2 Hydroboration

Wilkinson's complex serves as an effective catalyst for the addition of catecholborane (CB) to alkenes and alkynes. The Rh-catalyzed reaction is sensitive to steric effects, and can be diastereoselective which is complementary to uncatalyzed hydroborations (Scheme 8). This has been employed for the diastereoselective synthesis of several natural products. Scheme 9 presents some examples.



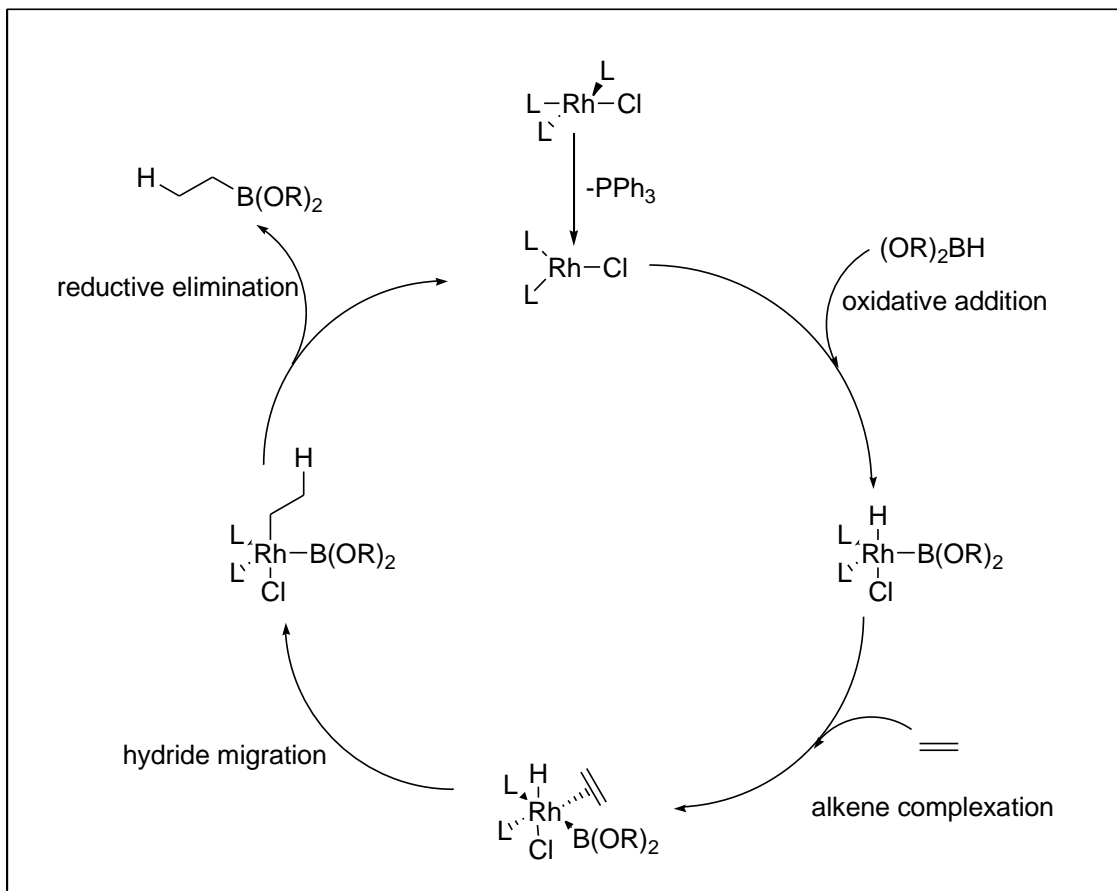
Asymmetric hydroboration of prochiral alkenes can be demonstrated using chiral Rh(I) complex with catecholborane with excellent enantioselectivity. For example, hydroboration of styrene with CB in the presence of Rh(I)-(*R*)-BINAP takes places with 94% ee (Scheme 10)



Scheme 10

### Mechanism

The reaction takes place via oxidative addition, alkene complexation, hydride migration and reductive elimination (Scheme 11).

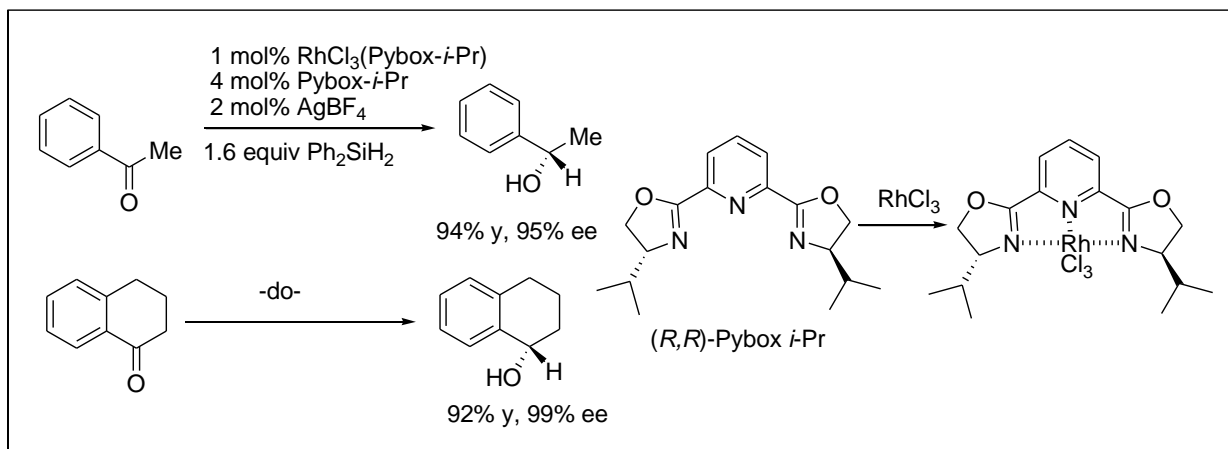


Scheme 11

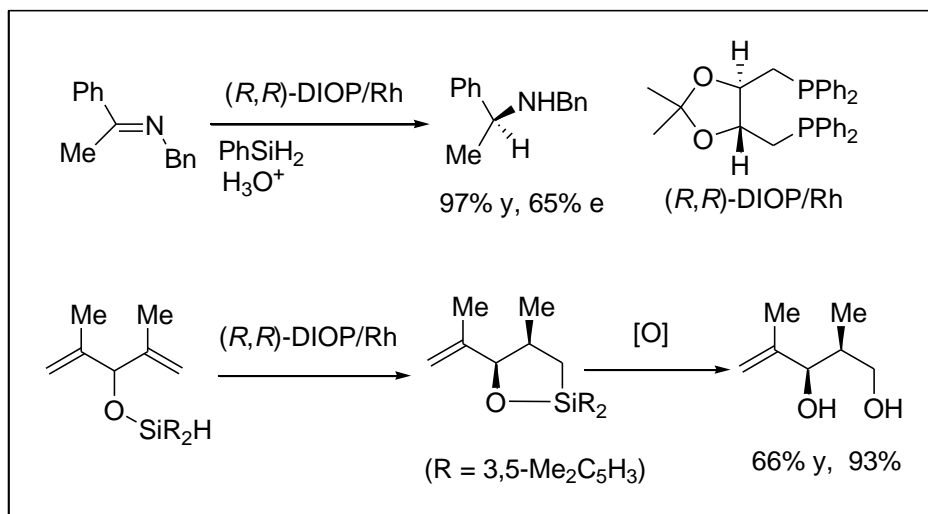


## 3.6.5.3 Hydrosilylation

Rhodium catalyzed hydrosilylation of ketones, imines and alkenes provides an effective route to alcohols, amines and alkanes. Subsequently, a number of chiral rhodium complexes are developed for asymmetric hydrosilylation. Scheme 12-13 shows some examples for chiral rhodium-phosphine catalyzed hydrosilylations.



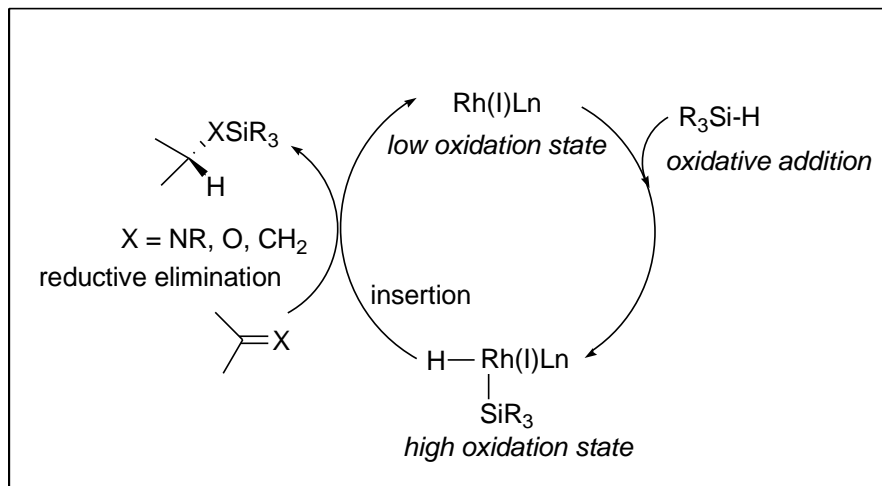
Scheme 12



Scheme 13

### Mechanism

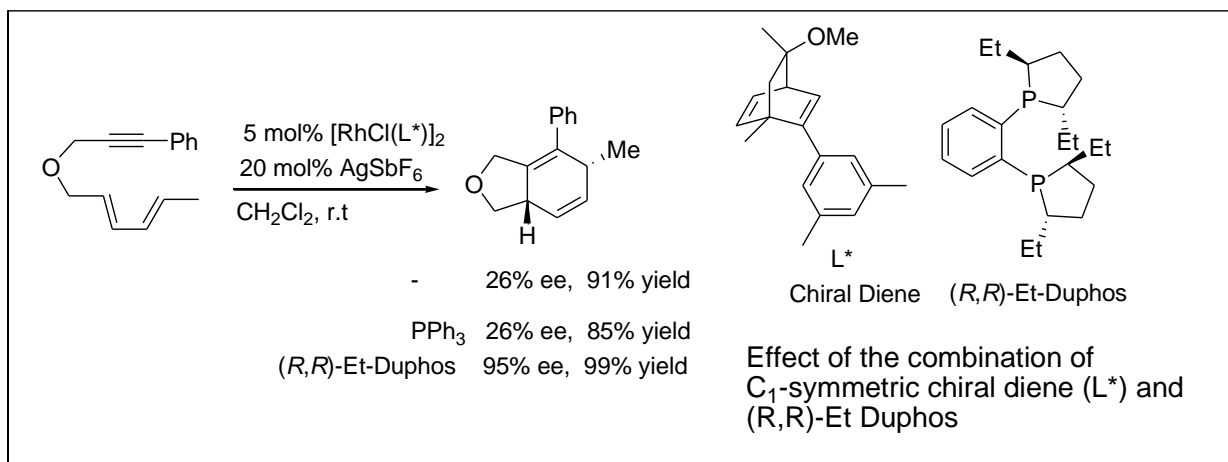
The reaction takes place via oxidative addition, insertion and reductive elimination (Scheme 14).



Scheme 14

### 3.6.5.4 Cycloaddition

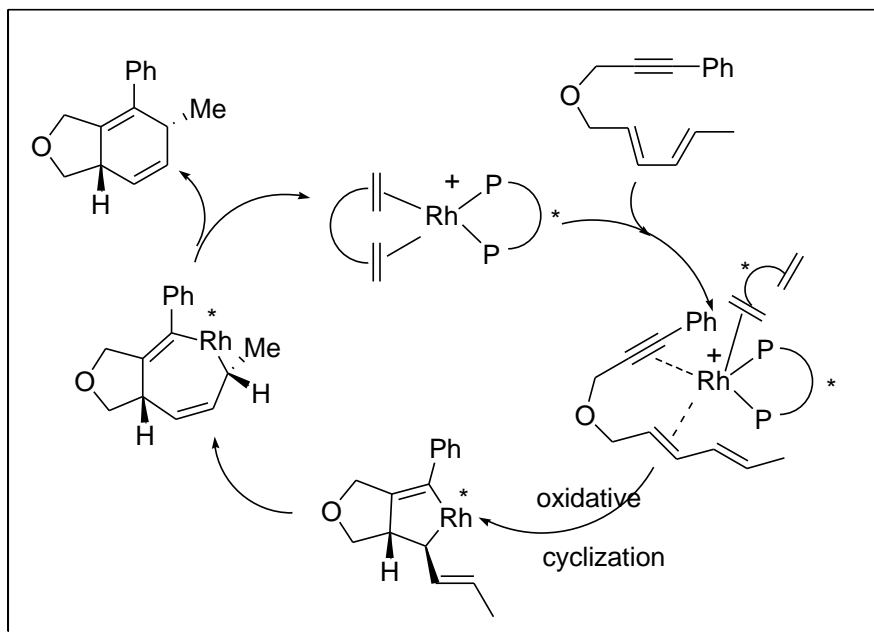
The cycloaddition reaction using chiral rhodium complexes finds wide applications in organic synthesis. Scheme 14 presents an example for chiral rhodium-catalyzed intramolecular [4+2]-cycloaddition reaction.



Scheme 15

## Mechanism

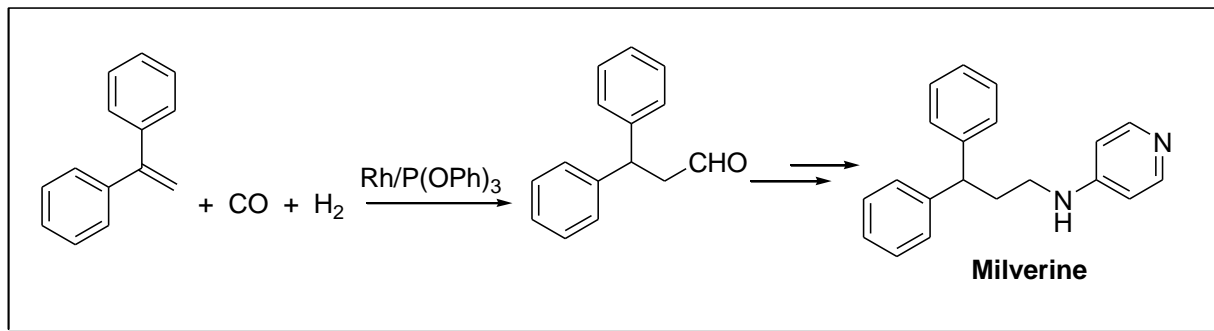
The reaction takes place via oxidative cyclization (Scheme 16).



Scheme 16

### 3.6.5.5 Hydroformylation

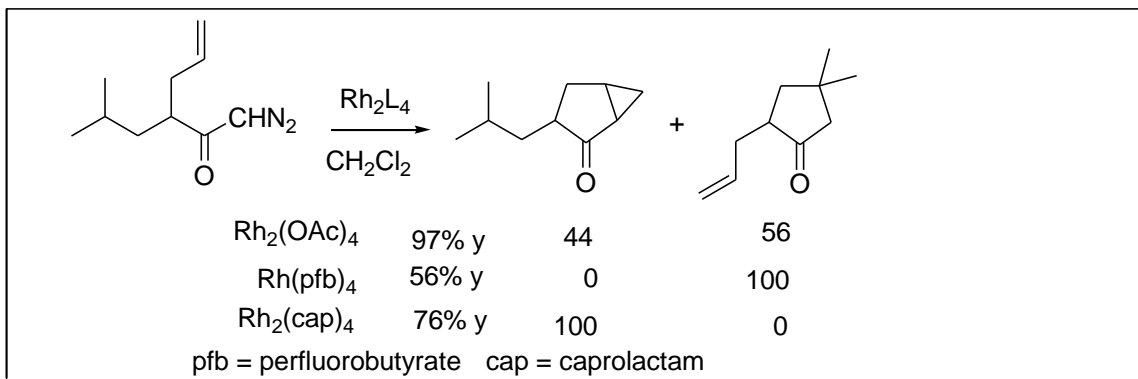
Transition metal catalyzed hydroformylation of alkenes with carbon monoxide and hydrogen is an important tool for organic synthesis. The reaction is generally carried out at temperature between 40 and 120 °C and total pressure between 10 and 100 atm, in the presence of catalytic amount of rhodium, cobalt or palladium catalysts (Scheme 17).



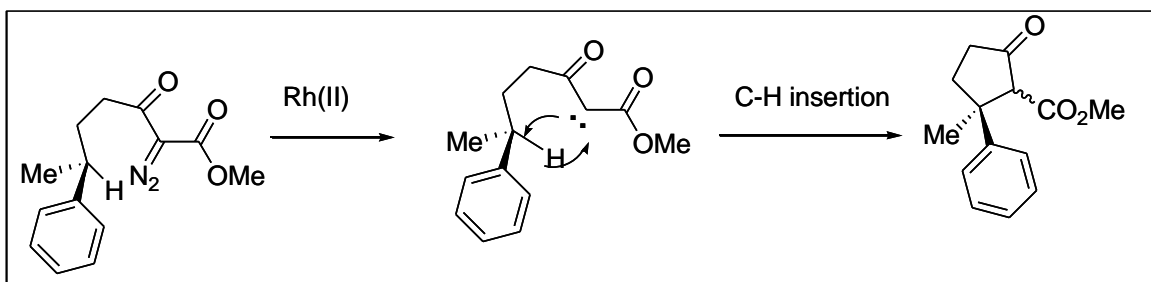
Scheme 17

### 3.6.5.5 Cyclopropanation and C-H Insertion

Rhodium(II) complexes are highly efficient and versatile catalysts for the extrusion of dinitrogen from diazo compound. Dirhodium(II) carboxylates, especially,  $\text{Rh}_2(\text{OAc})_2$ , are extensively used for cyclopropanation and C-H insertion. The nature of ligand plays a crucial role in the selectivity of the products (Scheme 18-19).

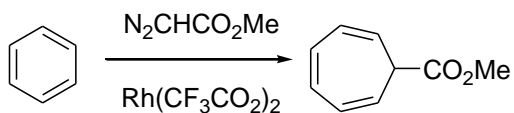


Scheme 18

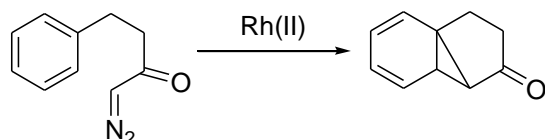


Scheme 19

#### Examples:



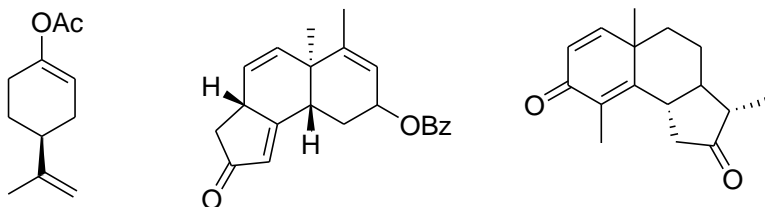
A. J. Anciaux, et al., *J. Org. Chem.* 1981, 46, 873.



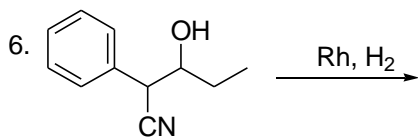
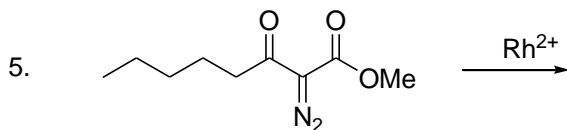
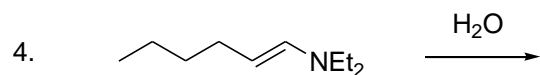
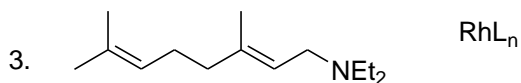
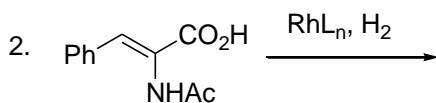
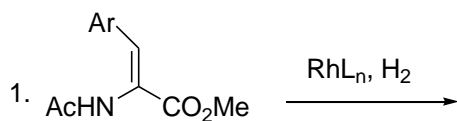
J.L. Kane et al., *Org. Lett.* 2001, 3, 1081.

**Problems**

A. Predict the major product of the following compounds with hydrogenation using Wilkinson-type complexes.



B. Complete the following reactions.



**Reference**

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

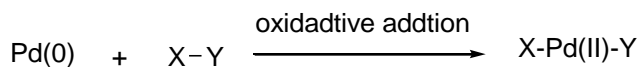
## Lecture 34

### 11.8 Palladium Catalysts

There are several features which make reactions involving Pd catalysts particularly useful and versatile among many transition metals used for organic synthesis. Most importantly, Pd catalysts offer an abundance of possibilities for carbon-carbon and carbon-heteroatom bonds formation in organic synthesis. The tolerance of Pd catalysts towards many functional groups such as carbonyl and hydroxyl groups is an important feature.

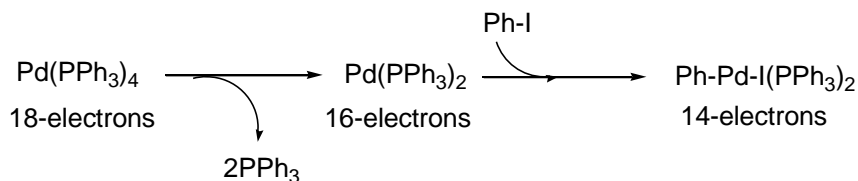
#### 11.8.1 Oxidative Addition

The “oxidative” addition is addition of a molecule X-Y to Pd(0) with cleavage of its covalent bond, forming two new bonds (Scheme 1). This process is similar to the formation of Grignard reagent from alkyl/aryl halide and Mg(0).



Scheme 1

The oxidative addition occurs with coordinative unsaturated complexes. As a typical example, the saturated Pd(0) complex undergoes reversible dissociation *in situ* in a solution to give the unsaturated 16-electrons species which is capable to undergo oxidative addition (Scheme 2).

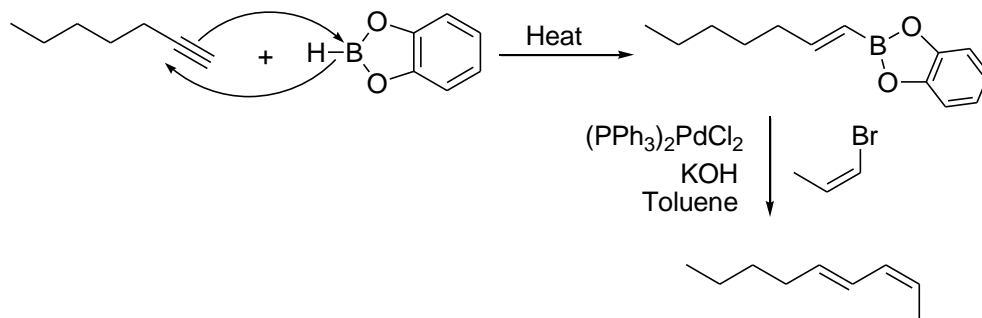


Scheme 2

Oxidative addition is facilitated by higher electron density of Pd, and in general,  $\sigma$  donor ligands such as  $\text{R}_3\text{P}$  attached to Pd facilitate the reaction. On the other hand,  $\pi$  acceptor ligands such as CO and alkenes tend to suppress oxidative addition.

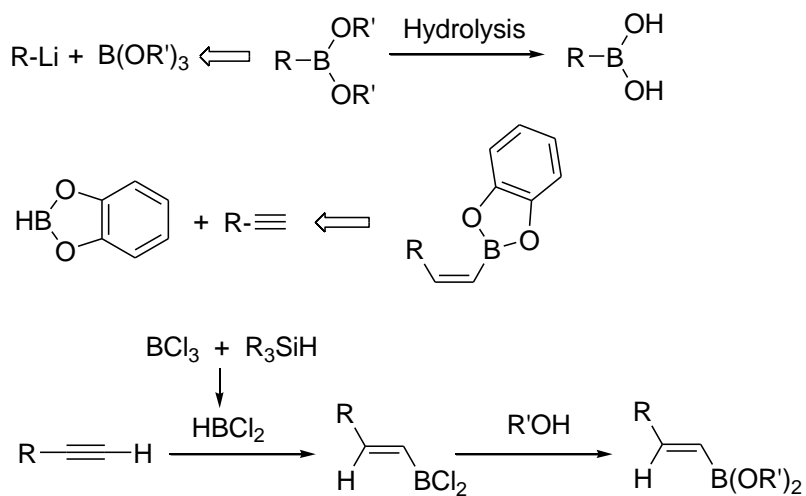
### 11.8.2 Suzuki-Coupling

The Suzuki coupling of a boronic acid with a halide or triflate has emerged into one of the most important cross-coupling reactions, covering about a quarter of all palladium-catalyzed coupling reactions (Scheme 3).



Scheme 3

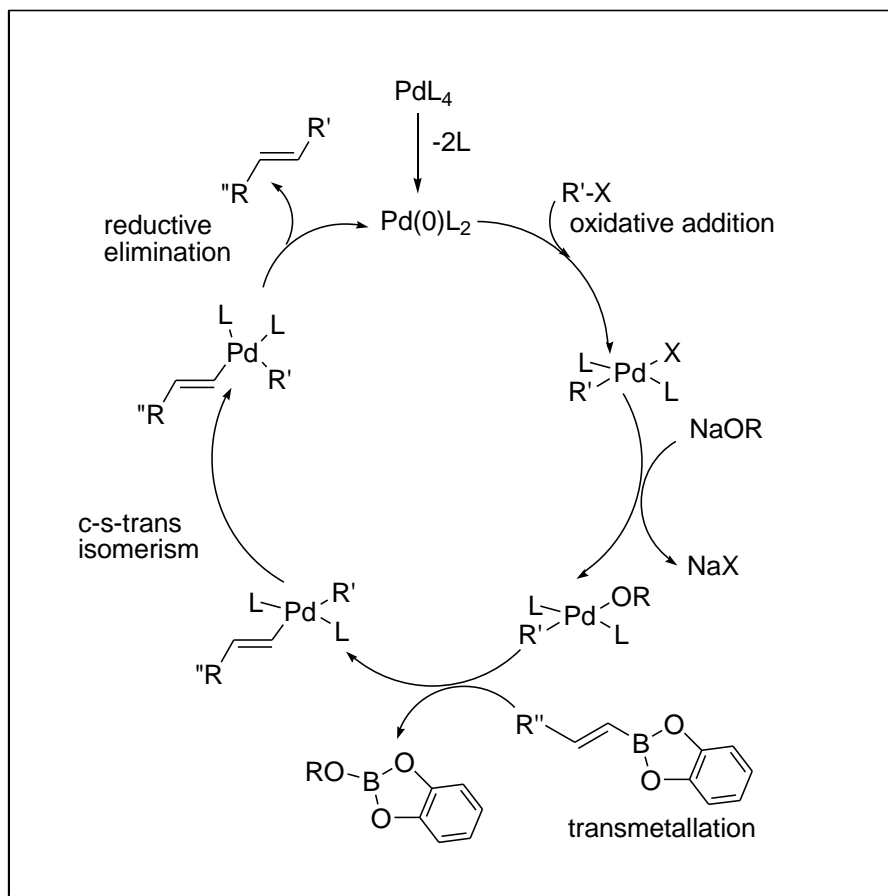
General source of common boron reagents:





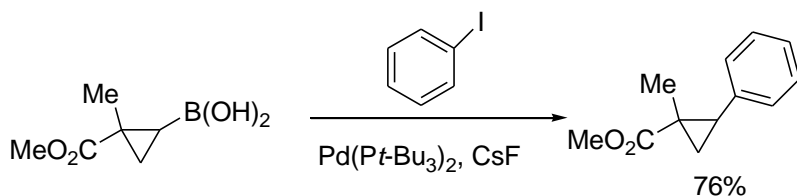
## Mechanism

Oxidative addition of the Pd(0) with vinyl halide leads to the formation of the intermediate A that with base gives organopalladium alkoxide B. Due to low nucleophilicity of the organoboron, the transmetalation takes place faster with B compared to A to afford the intermediate C that can complete the catalytic cycle by reductive elimination of the target product (Scheme 4).

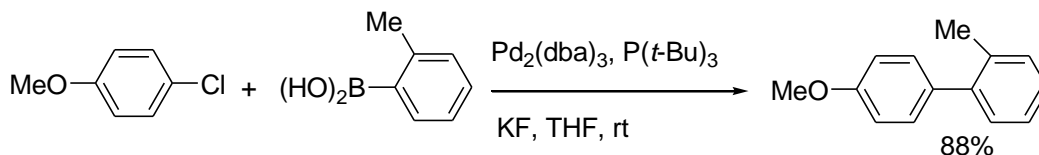


Scheme 4

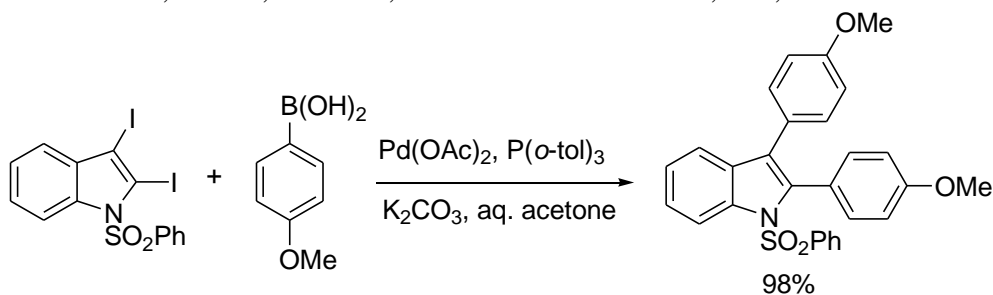
**Examples:**



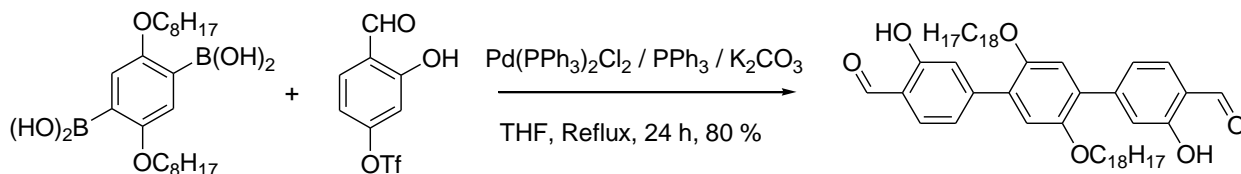
M. Rubina, M. Rubin, V. Geforgyan, *J. Am. Chem. Soc.* **2003**, *125*, 7198.



A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *127*, 4020.



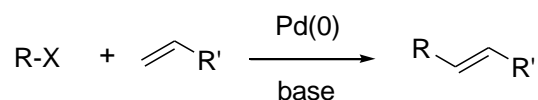
Y. Liu, G. W. Gribble, *Tetrahedron Lett.* **2000**, *41*, 8717.



S. Sakthivel, T. Punniyamurthy, *Tetrahedron: Asymmetry* **2012**, *23*, 101.

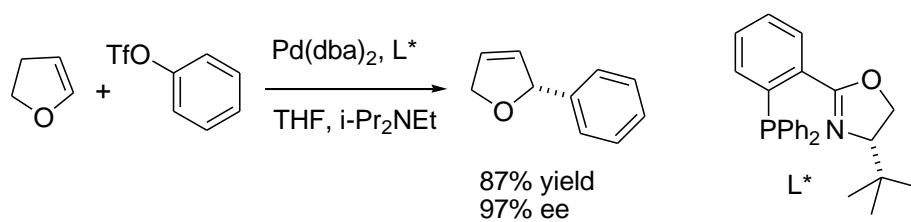
### 11.8.3 Heck Reaction

The Heck reaction, is one of the most synthetically important Pd-catalyzed C-C cross-coupling reactions, couples an alkene with a halide or triflate to form a new alkene (Scheme 6). The alkene can be mono- or disubstituted and can be electron-rich, poor or neutral.



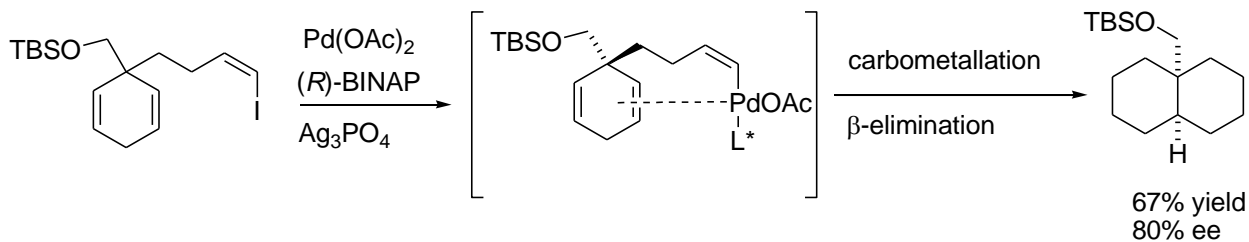
Scheme 6

Asymmetric version of this coupling reaction has also been explored. For example, the chiral palladium complex having amino acid-derived phosphine ligand catalyzes the reaction of phenyl triflate with dihydrofuran with excellent enantioselectivity (Scheme 7).



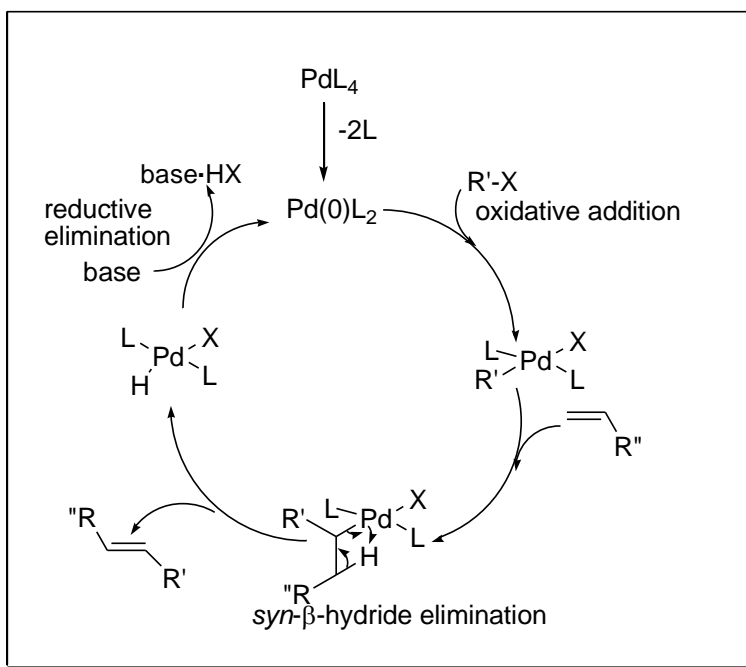
Scheme 7

Likewise, the intramolecular Heck reaction using (*R*)-BINAP affords decalin derivative with 80% ee (Scheme 8).

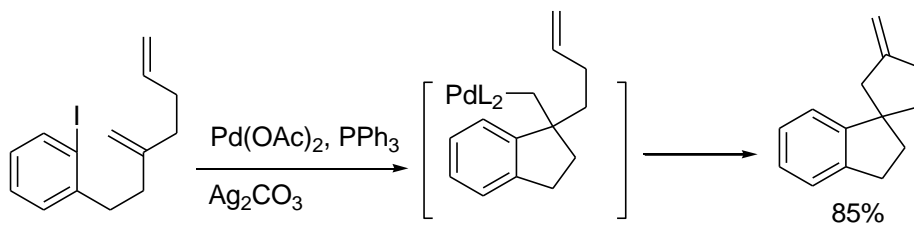


### Mechanism

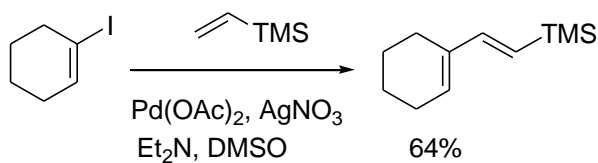
The mechanism involves the oxidative addition, carbometallation,  $\beta$ -hydride elimination and elimination of the target product (Scheme 9).



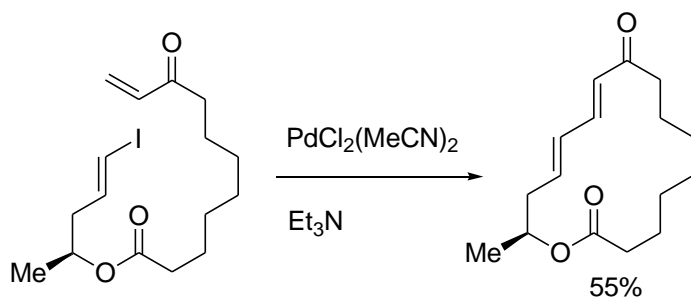
**Examples:**



M. M. Abelman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2338.



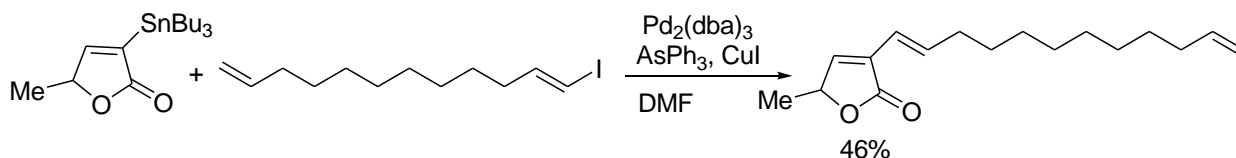
K. Karabelas, A. Hallber, *J. Org. Chem.* **1988**, *53*, 4909.



F. E. Ziegler, U. R. Chakroborty, R. B. Weisenfield, *Tetrahedron* **1981**, *37*, 4035.

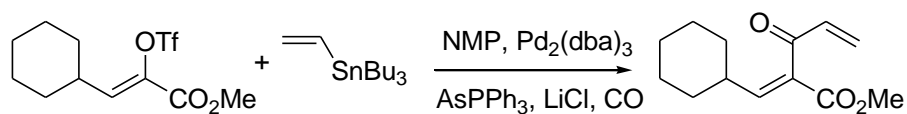
### 11.8.4 Stille Coupling

The coupling of vinyl stannanes with vinyl halides or triflates using palladium catalysis is one of the powerful methods for the carbon-carbon bond formation (Scheme 10). It is effective under relatively neutral conditions and compatible with many functional groups. Please see section 10.5.1 for mechanism



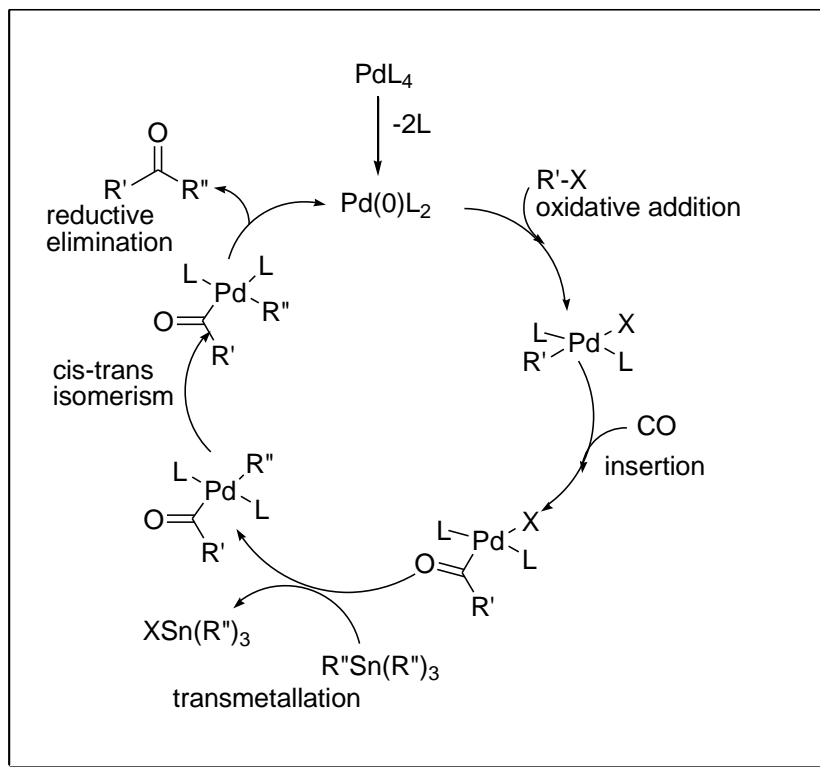
### 11.8.5 Stille Carbonylative Coupling

The coupling reaction of aryl or vinyl triflate with organostannane using palladium-catalysis in the presence of carbon monoxide and lithium chloride takes place under relatively mild conditions to give good yields of ketones (Scheme 11).



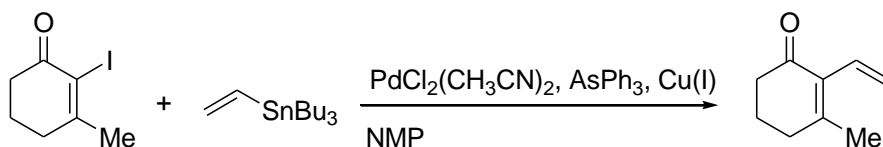
## Mechanism

The reaction occurs via oxidative addition, carbonyl insertion, transmetallation and reductive elimination processes (Scheme 12).

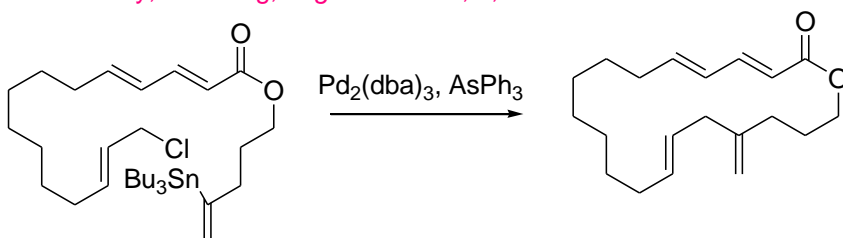


Scheme 12

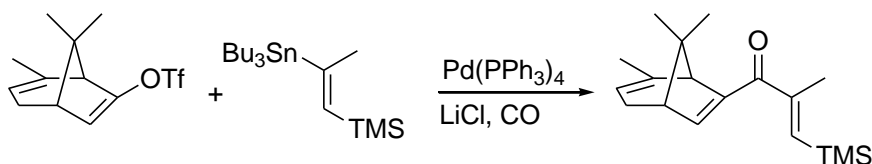
**Examples:**



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



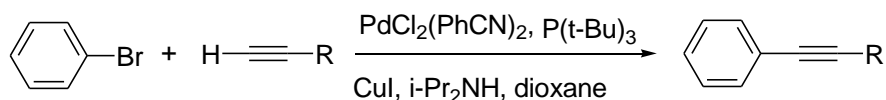
C. Boden, G. Pattenden, *Synlett* **1994**, 181.



R. D. Mazzola, Jr., et al., *J. Org. Chem.* **2004**, *69*, 220.

### 11.8.5 Sonogashira Coupling

The reaction involves the coupling aryl halides with alkynes using the combination of palladium and copper catalysts in the presence of base at moderate temperature (Scheme 13). It is compatible with functional groups such as hydroxo, carbonyl, amino, acyloxy, acetal, esters and amides, and finds extensive applications in organic synthesis.

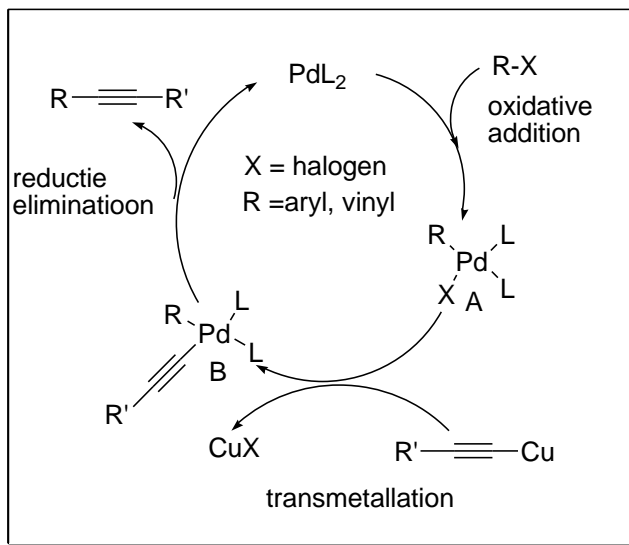


Scheme 13



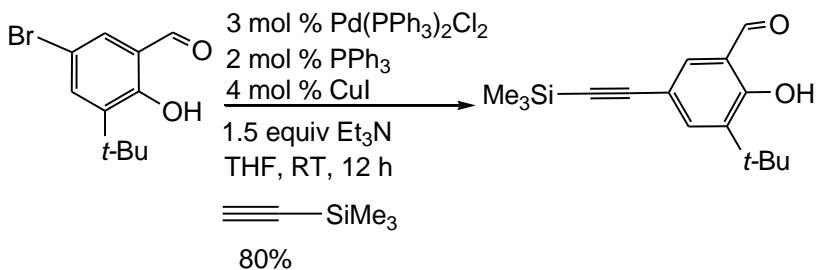
**Mechanism**

Oxidative addition of Pd(0) with aryl halide gives Pd(II) intermediate A that undergoes reaction with *in situ* generated alkynyl copper to give intermediate B. The latter completes the catalytic cycle by the reductive elimination of the substituted alkyne (Scheme 14).

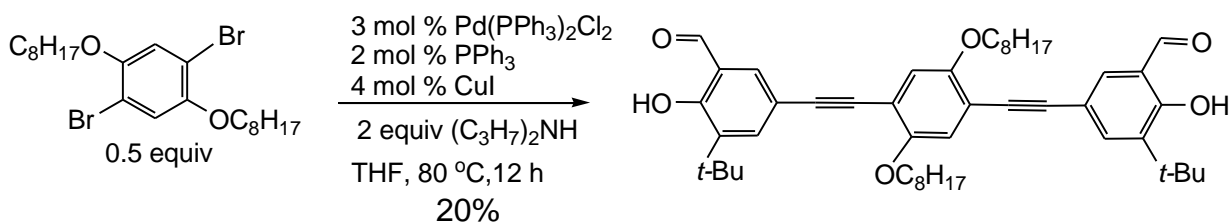


Scheme 14

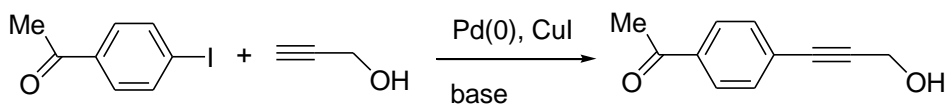
**Examples:**



S. Jammi, L. Rlout, T. Punniyamurthy, *Tetrahedron: Asymmetry* **2007**, 17, 2016.



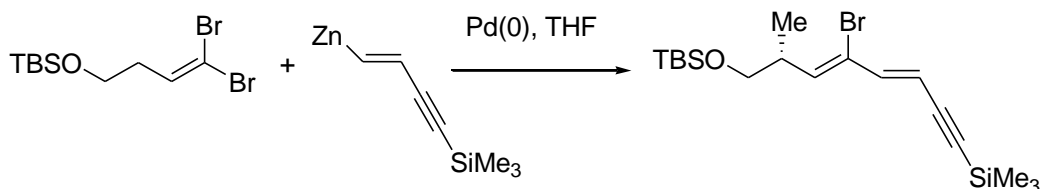
S. Jammi, L. Rlout, T. Punniyamurthy, *Tetrahedron: Asymmetry* **2007**, 17, 2016.



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

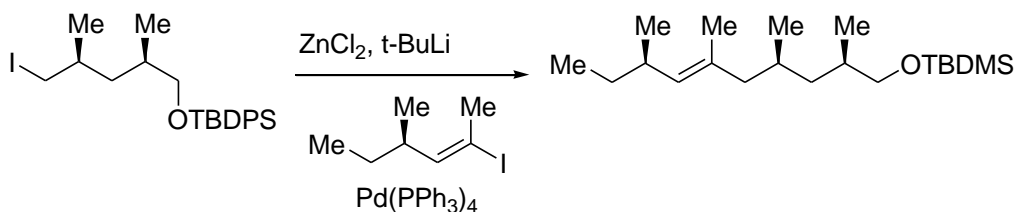
### 11.8.6 Negishi Coupling

The coupling of organozinc compounds with alkenyl, alkynyl, aryl, allylic and benzyl halides using Pd(0) provides another powerful method for carbon-carbon bond formation (Scheme 15). Section 3.3.3 presents the mechanism.

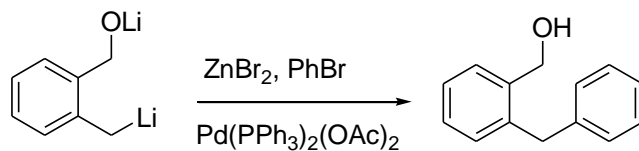


Scheme 15

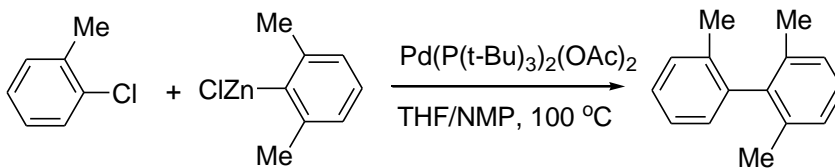
#### Examples:



G. D. McAllister, R. J. K. Taylor, *Tetrahedron Lett.* **2004**, *45*, 2551.



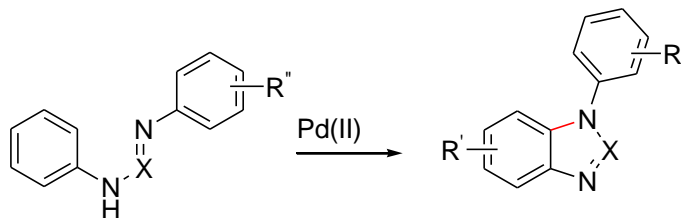
M. Yus, J. Comis, *Tetrahedron Lett.* **2001**, *42*, 5721.



C. Dai, C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719.

### 11.8.7 C-H Activation

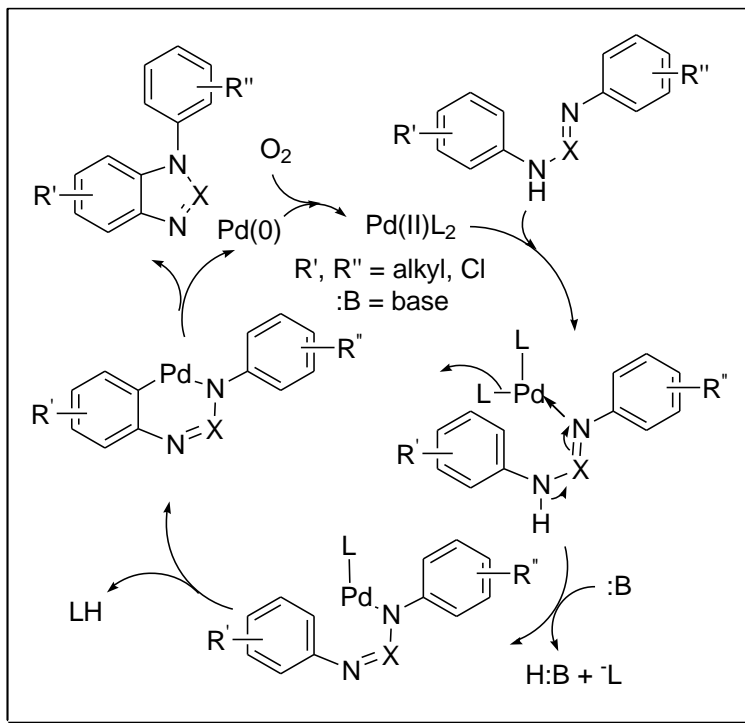
Palladium-based catalysts have been explored for carbon-heteroatom bond formation via cross-coupling as well as C-H activation. For example, the synthesis of 1-aryl-1H-benzotriazole can be accomplished from triazene via C-H activation using  $\text{Pd}(\text{OAc})_2$  under aerobic conditions (Scheme 16).



Scheme 16

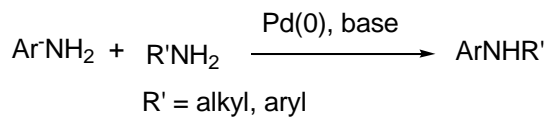
### Mechanism

Molecular oxygen reoxidizes the reduced palladium (0) to palladium (II) to complete the catalytic cycle (Scheme 15).

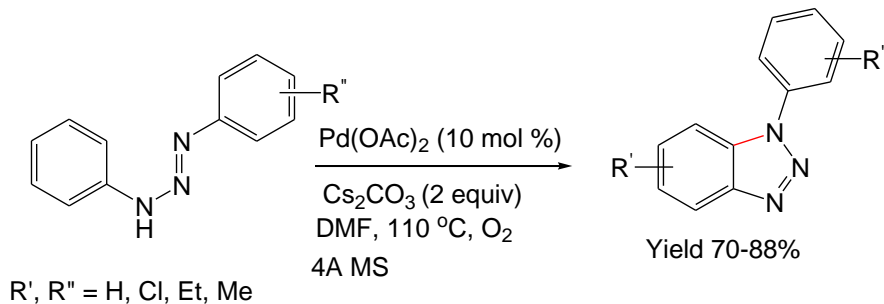


Scheme 15

**Examples:**



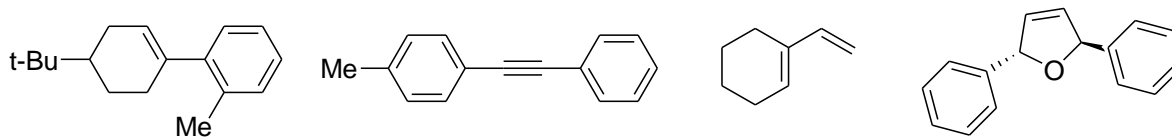
J. P. Wolfe, S. Wagaw, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805.



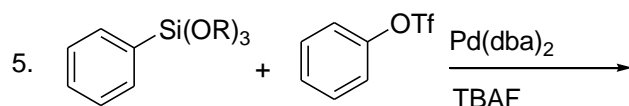
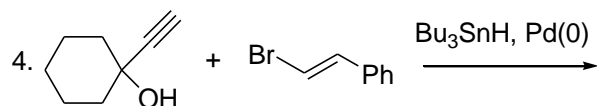
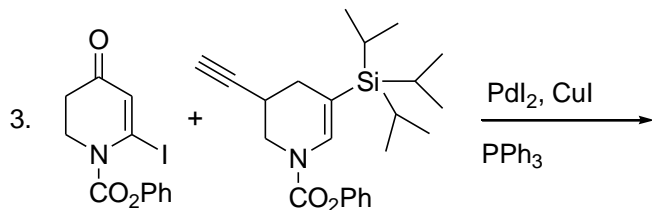
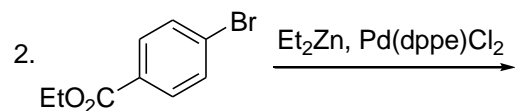
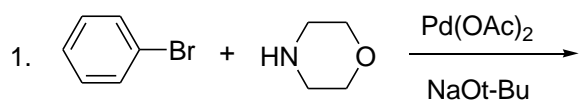
R. K. Kumar, M. A. Ali, T. Punniyamurthy, *Org. Lett.* **2011**, *13*, 2102; *Synfacts* **2011**, 596.

**Problems**

A. How will you synthesize the following compounds using the Heck and Suzuki couplings?



B. Complete the following.



**Text Book**

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

## Lecture 35

### 11.9 Nickel Catalysts

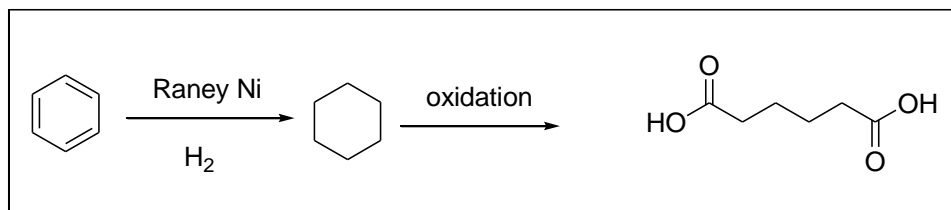
Nickel-based catalytic systems are used in the production of many industrial and consumer products, and play a key role in organic synthesis.

#### 11.9.1 Hydrogenation

Raney Ni (Ni-Al) is produced when a block of Ni-Al alloy is treated with concentrated NaOH. This treatment, called "activation", dissolves most of the Al out of the alloy. The porous structure left behind has a large surface area, which gives high catalytic activity. The ratio of Ni to Al is around 1 for the original material used by Raney, and may vary from about 1 to 4.

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.

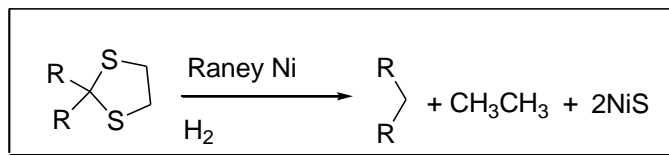
It is one of the common catalysts used for the hydrogenation of aromatic compounds. A practical example is shown in Scheme 1, where benzene is reduced to cyclohexane.



Scheme 1

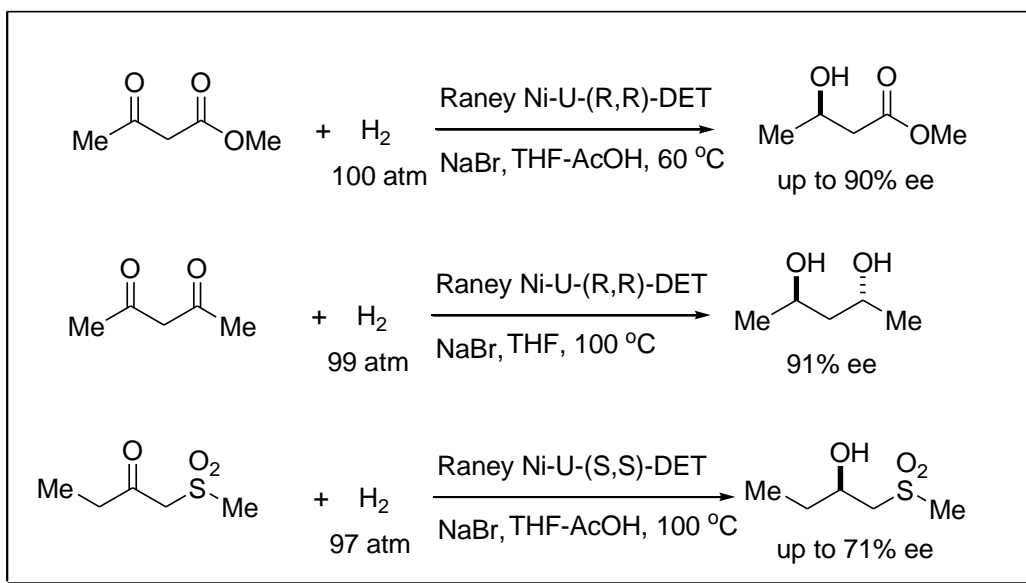


Raney Ni is also used for the reduction of a series of functional groups. For example, Raney Ni is particularly useful for the cleavage of C-S bond (Scheme 2).



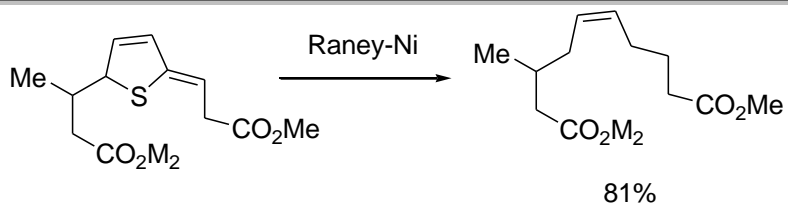
Scheme 2

The Raney Ni modified by tartaric acid and NaBr is an excellent catalyst for asymmetric hydrogenation of  $\beta$ -keto esters,  $\beta$ -ketones and  $\beta$ -keto sulfones (Scheme 3). Appropriate pH, temperature and concentration of NaBr should be carefully chosen.

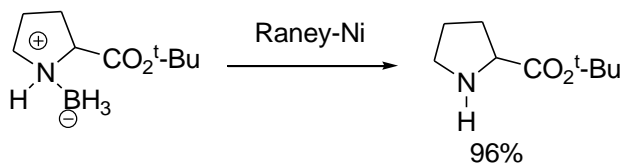


Scheme 3

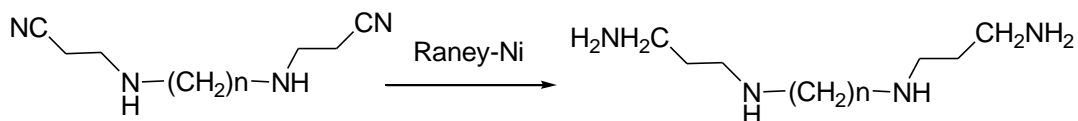
**Examples:**



S.-M. Yang, S. K. Nandy, A. R. Selvakumar, J.-M. Fang, *Org. Lett.* **2000**, 2, 3719.



M. Couturier, J. L. Tucker, B. M. Andresen, P. Dube, J. T. Negri, *Org. Lett.* **2001**, 3, 465.

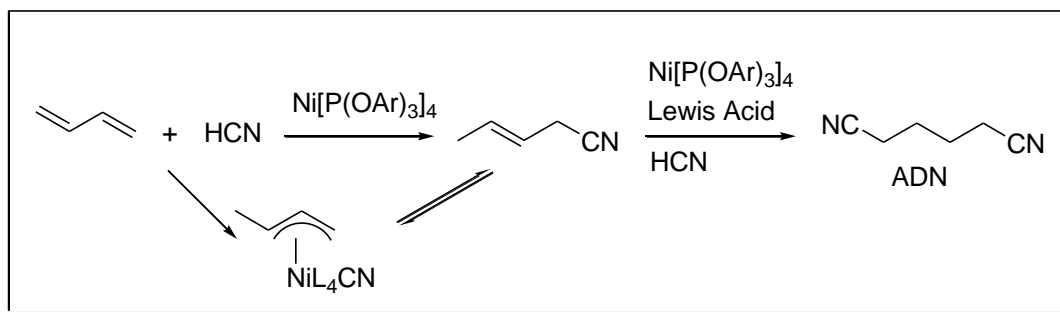


B. Klenke, I. H. Gilbert, *J. Org. Chem.* **2001**, 66, 2480.

### 11.9.2 Hydrocyanation

Organonitriles are key intermediates for the synthesis numerous compounds including polymers, fibers, agrochemicals, cosmetics and pharmaceuticals. Nickel complexes find wide applications for the hydrocyanation of alkenes and alkynes. For example, triarylphosphite nickel complex catalyzes the reaction of 1,3-butadiene with HCN to afford nylon 6,6-precursor AND (adiponitrile) by anti-Markovnikov fashion (Scheme 4).

Using this process annually 1 billion pounds of AND is produced.

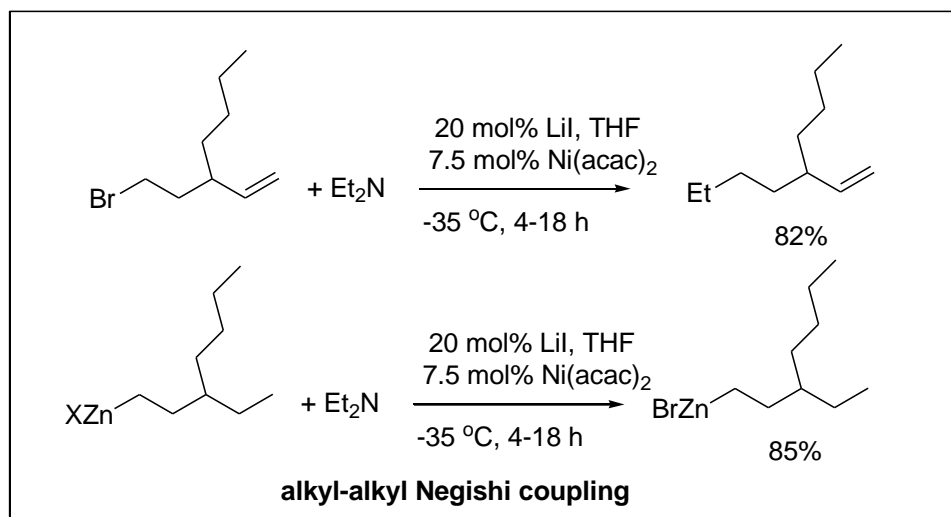


Scheme 4

## 11.9.3 Cross-Coupling Reactions

### 11.9.3.1 Negishi Coupling

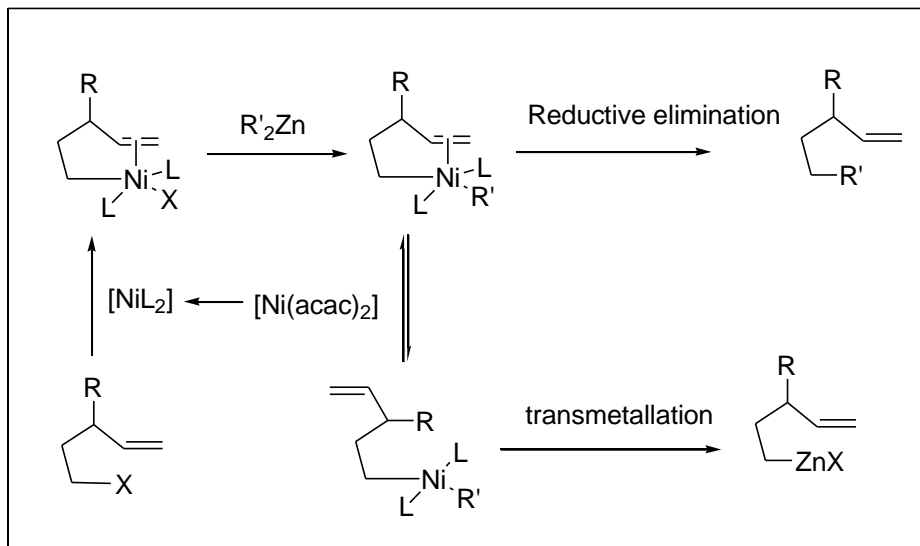
Unsaturated alkyl bromide proceeds C-C cross-coupling with  $\text{Et}_2\text{Zn}$  in the presence of  $\text{Ni}(\text{acac})_2$  (Scheme 5). Under this condition, saturated alkyl bromide produces the bromide-zinc exchange product.



Scheme 5

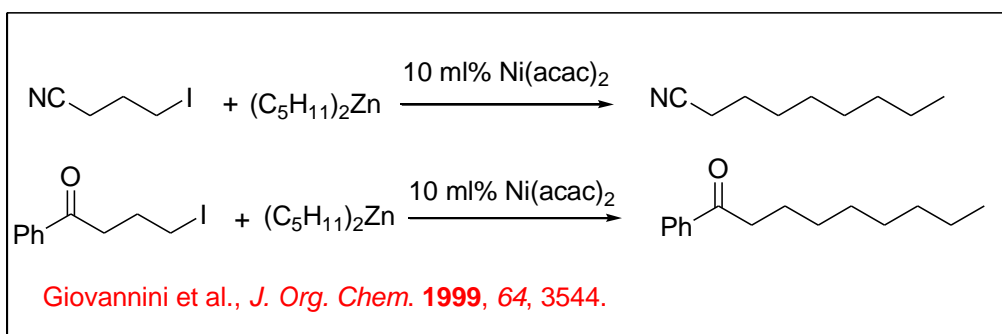
### Mechanism

The coordination of the remote double bond to the nickel center is crucial for the cross-coupling reaction (Scheme 6).



Scheme 6

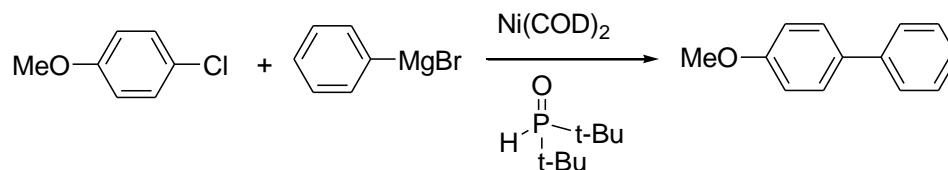
The presence of a remote carbonyl and cyano groups in the alkyl halides also facilitates their cross-coupling with diorganozincs. For example, functionalized diorganozincs and alkyl iodides can be cross-coupled using *m*- or *p*-trifluoromethyl styrene as a promotor and  $Ni(acac)_2$  as a catalyst (Scheme 7).



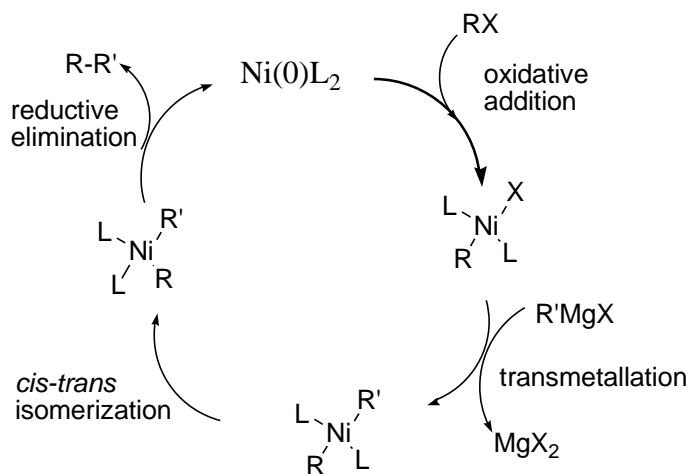
Scheme 7

### 11.9.3.2 Kumada Coupling

The coupling of Grignard reagents with alkyl, vinyl or aryl halides under Ni-catalysis provides an effective route for carbon-carbon bond formation. For example, the synthesis of unsymmetrical biaryls can be accomplished from phenylmagnesium bromide and 1-chloro-4-methoxybenzene using  $\text{Ni}(\text{COD})_2$  which is an example for low cost production of biaryl compounds (Scheme 8).



Scheme 8

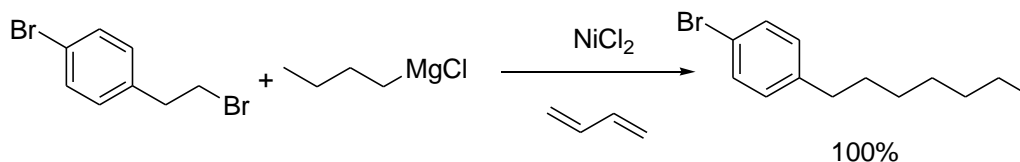


Scheme 9

### Mechanism

The reactions involve the oxidative addition followed by reductive elimination *via* transmetalation and *cis-trans* isomerization (Scheme 9).

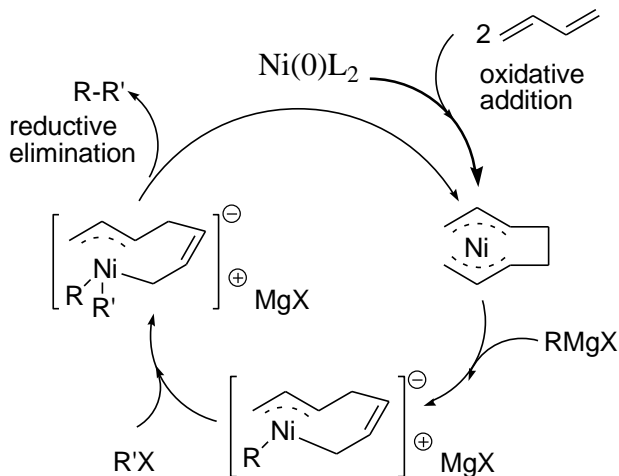
In case of alkyl halide, an influence of 1,3-butadiene on the reaction has been noted (Scheme 10).



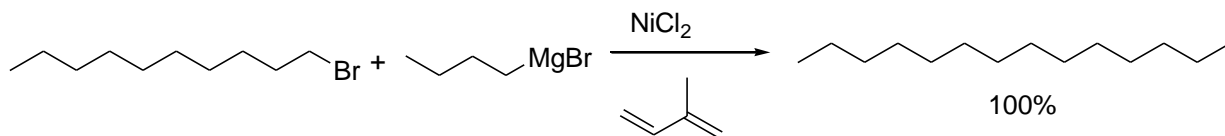
Scheme 10

## Mechanism

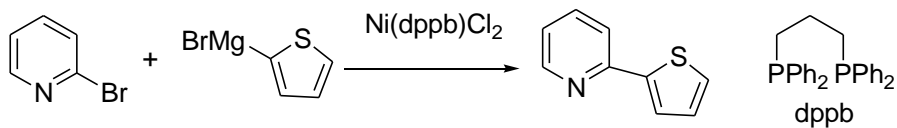
The acceleration of the reaction with butadiene is described in Scheme 11.



## Examples:



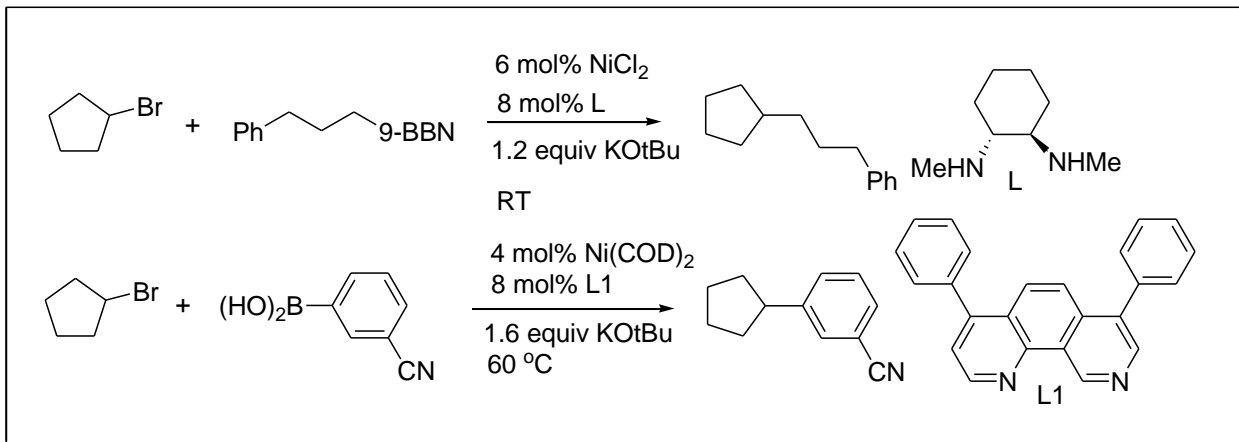
J. Terao, H. Watanabe, A. Ikumi, H. Kuniysu, N. Kambe, *J. Am. Chem. Soc.* **2002**, *124*, 4222.



G. Y. Li, W. J. Marshall, *Organometallics* **2002**, *21*, 590.

### 11.9.3.3 Suzuki Coupling

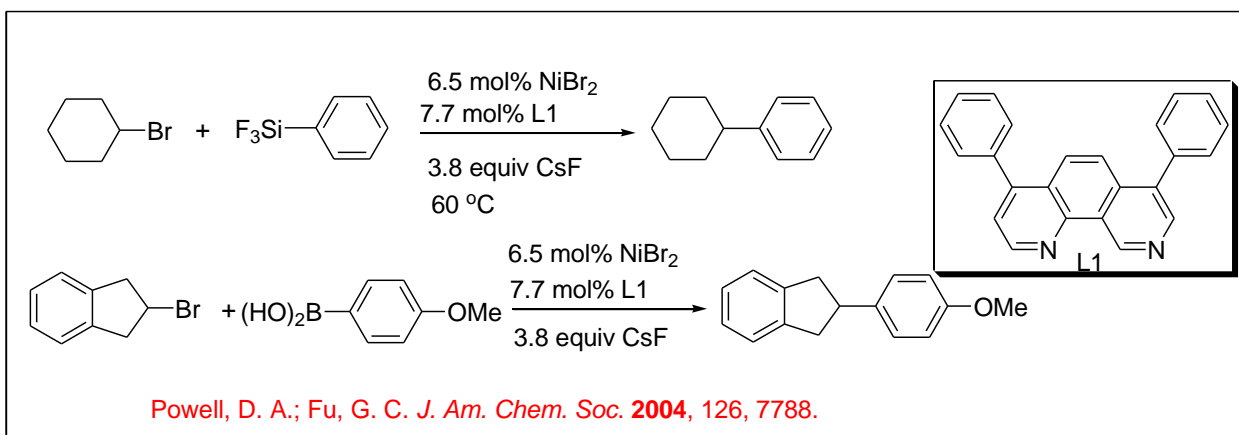
Nickel complexes having nitrogen based ligands catalyze the Suzuki coupling with secondary halides (Scheme 12).



Scheme 12

### 11.9.3.4 Hiyama Coupling

Hiyama coupling can be successfully carried out using nickel catalysts at moderate temperature (Scheme 13).



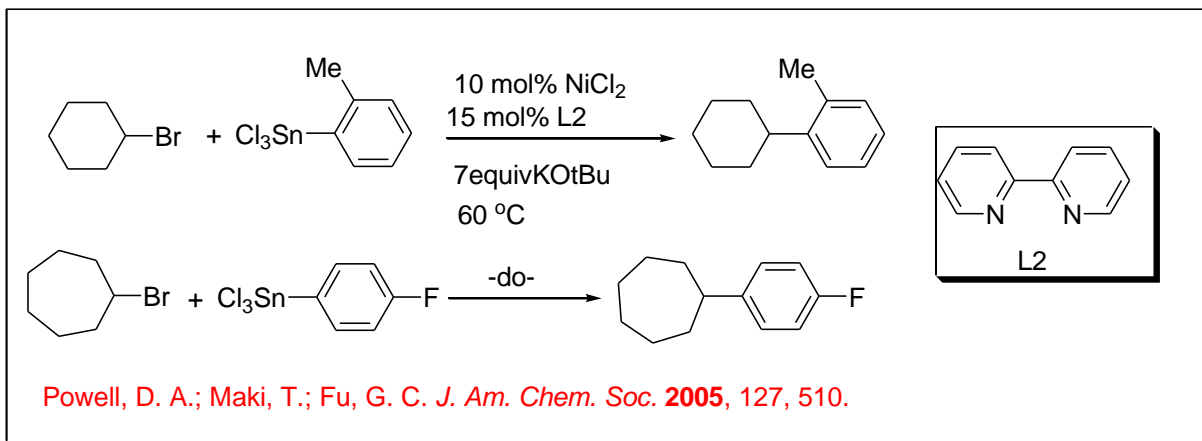
Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788.

Scheme 13

### 11.9.3.5 Stille Coupling



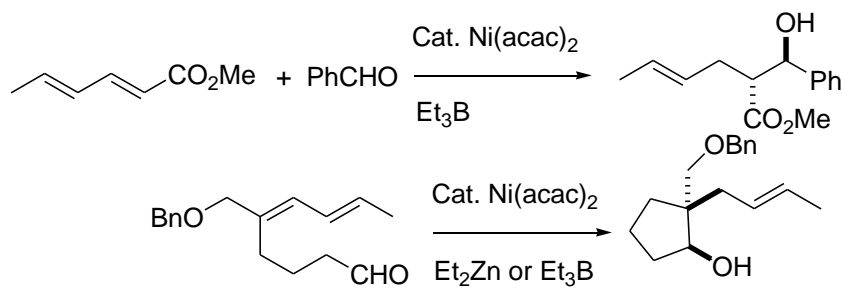
Stille coupling is also effective with nickel complexes at moderate temperature (Scheme 14).



Scheme 14

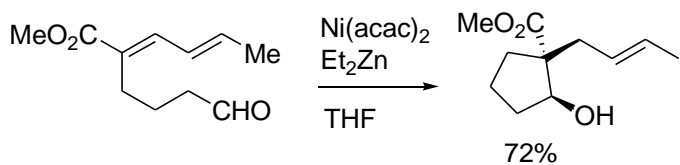
### 11.9.3.6 Reductive Aldehyde and Diene Coupling

Addition of dienes to aldehydes has emerged as a useful reaction to yield  $\rho,\delta$ -unsaturated or  $\delta,\varepsilon$ -unsaturated alcohols (Scheme 15). The reaction is initiated either by formation of an oxametallacycle or by hydrometallation of the diene.

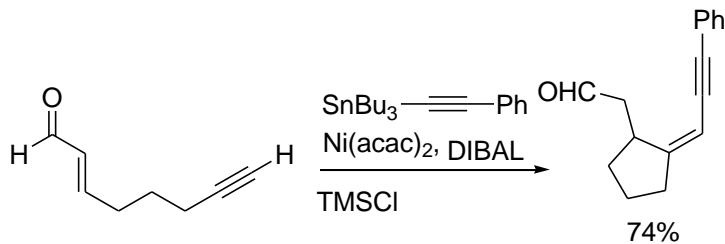


Scheme 15

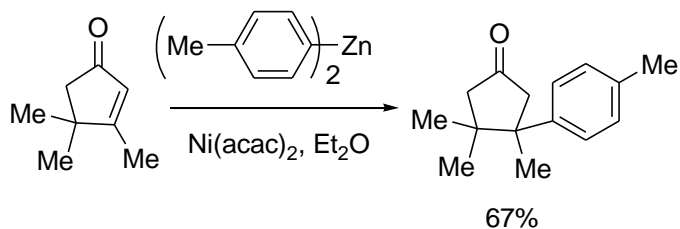
**Examples:**



K. Shibata, M. Kimura, M. Shimizu, Y. Tamaru, *Org. Lett.* **2001**, 3, 2181.



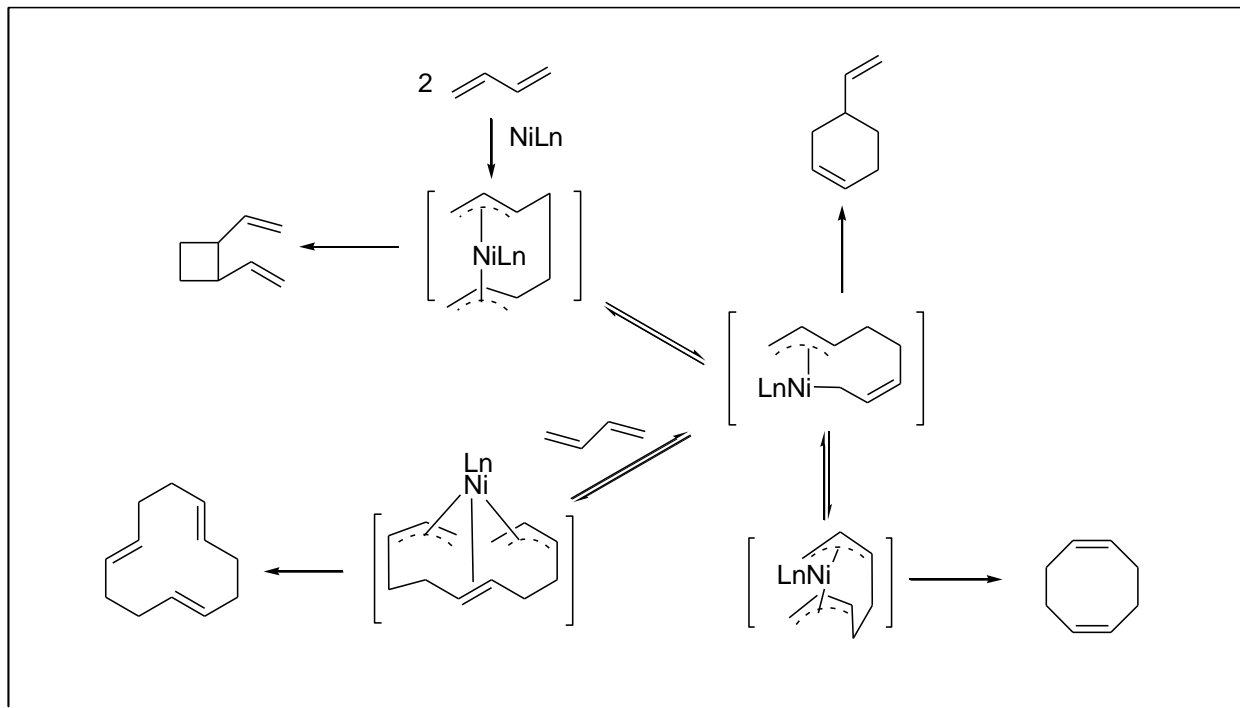
M. Lozanov, J. Montgomery, *J. Am. Chem. Soc.* **2002**, 124, 2106.



A. E. Greene, J. P. Lansard, J. L. Luche, C. Petrier, *J. Org. Chem.* **1984**, 49, 931.

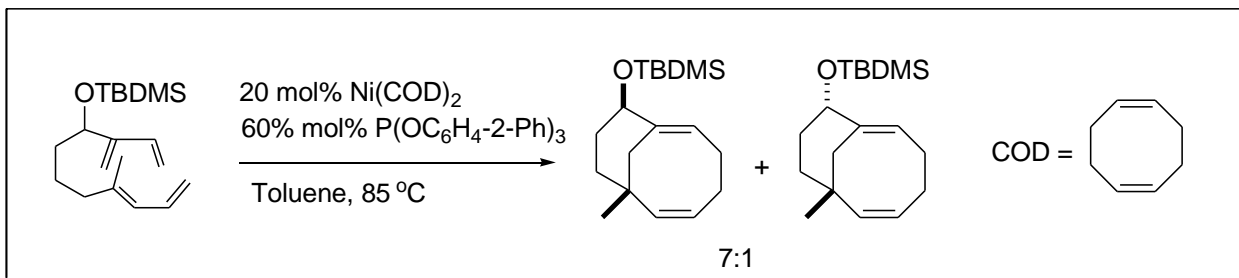
### 11.9.3.7 Cycloaddition

The most widely used application of the nickel-diene complex is the different mode of coupling of 1,3-dienes, including dimerization, trimerization and oligomerization (Scheme 16).



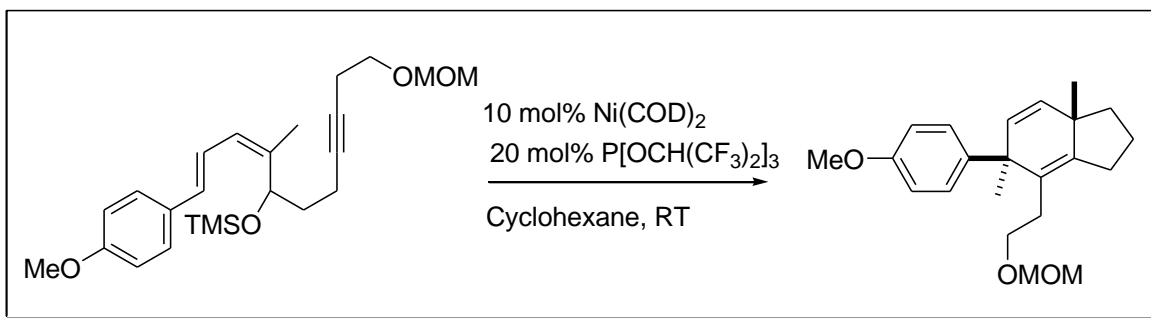
Scheme 16

For example, the structurally complex eight membered rings can be constructed via [4+4]-cycloaddition (Scheme 17).



Scheme 17

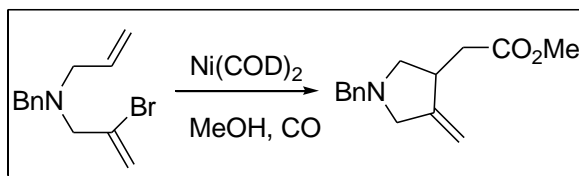
Compared to the [4+4]-cycloaddition, the [4+2] is stereospecific and effective at low temperature (Scheme 18).



Scheme 18

### 11.9.4 Carbonylation

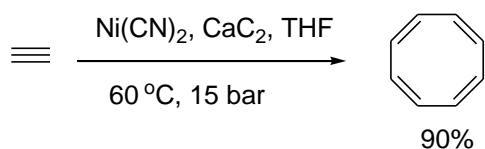
Ni catalyzes the addition of carbon monoxide to alkenes and alkynes in presence of water or MeOH to give carboxylic acid or ester, respectively, which are very useful processes in organic synthesis (Scheme 19).



Scheme 19

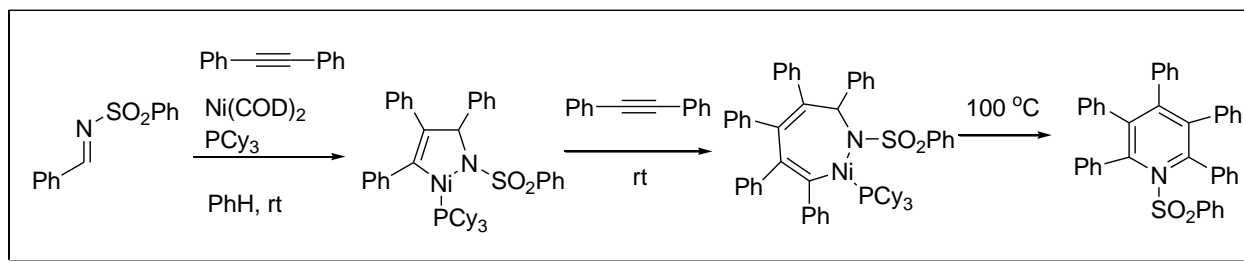
### 11.9.5 Alkene/Alkyne Oligomerization Reactions

In the presence of catalysts, alkynes and alkenes can react itself or with many other organic and inorganic compounds. Nickel catalysts are found wide applications for this purpose. For example, Reppe synthesis of cyclic polymerization of acetylene gives cyclooctatetraene, which represents a true milestone in transition-metal-catalysis (Scheme 20).



Scheme 20

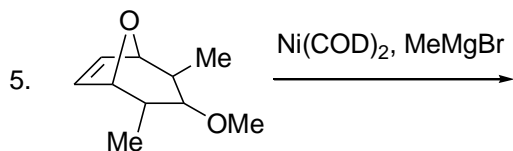
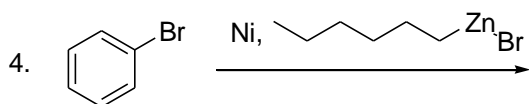
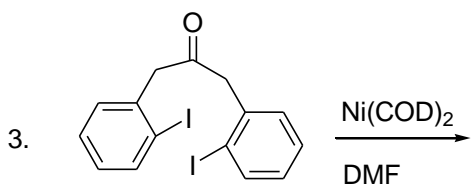
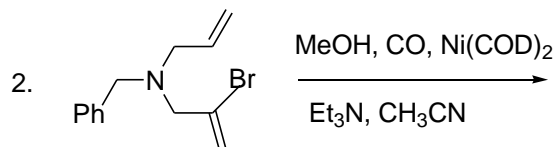
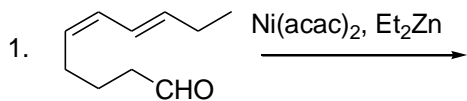
The formation of organonickel compounds have been revealed by a carefully designed experiment (Scheme 21).



Scheme 21

**Problems**

Complete the following with major products.



**Text Book:**

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