Lecture 5

3.0 Organometallic Reagents

Organometallic compounds are those compounds which have metal-carbon bond. Due to the significant difference in electronegativity between metals and carbon, they are highly polar in nature. However, this definition is not quite explicit as many reagents deemed to be organometallic in nature do not possess a metal carbon bond. Wilkinson catalyst, ($RhCl_2(PPh_3)_2$), a popular organometallic catalyst for hydrogenation reaction does not possess a metal–carbon bond. Thus, the above definition may be modified to include compounds containing metal- electronegative atom bonds in the gambit of organometallic compounds.

Li 0.98											C 2.55	N 3.04	O 3.44		
Na 0.93	Mg 1.31										Al 1.61	Si 1.9	P 2.19		
K 0.82					Fe 1.83	Co 1.88	Ni 1.91	Cu 1.9	Zn 1.65						
					Ru 2.2	Rh 2.28	Pd 2.2		Cd 1.69						
					Os 2.2	Ir 2.2	Pt 2.28		Hg 2.0						

Fig 1: Elements commonly involved in formation of organometallic compounds. (Elements highlighted in blue are the source of most common organometallic reagents used for organic synthesis)

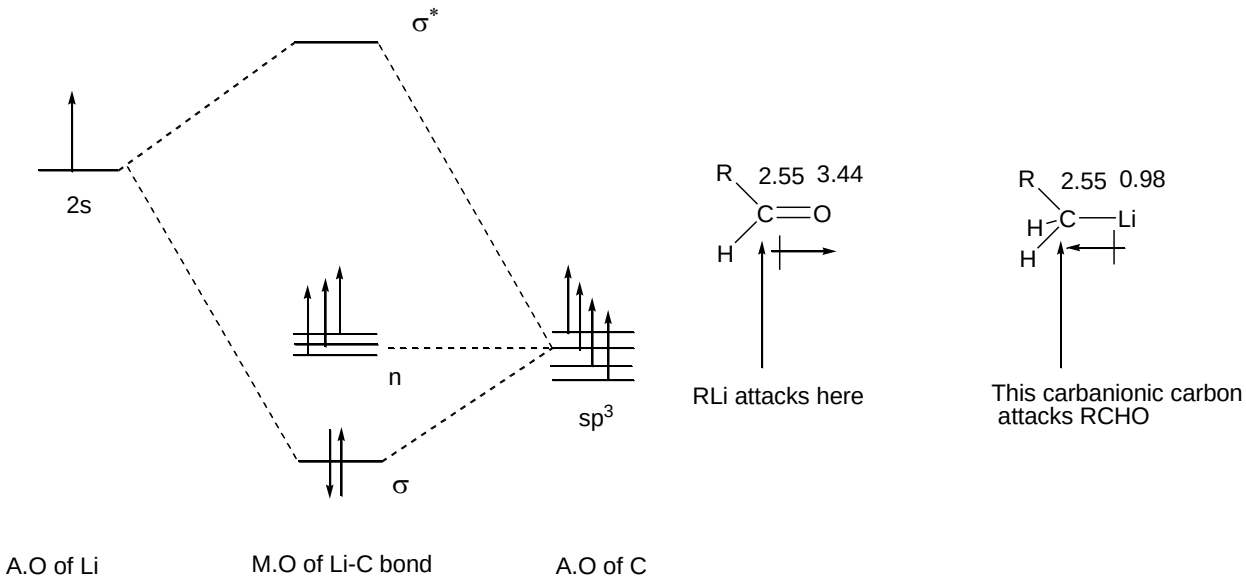


Fig 2 : M.O diagram of C-Li bond showing the high degree of polarization.

The high polarity of the metal-carbon bond is responsible for the high ionic nature of the organometallic compounds (Fig 2). As such these reactions mostly involve nucleophilic attack of the carbanion on the electrophillic center of an organic molecule.

TRIVIA

The first organometallic compound was synthesized by French Chemist Louis Claude Cadet de Gassicourt in 1760 by the reaction of potassium acetate with arsenic trioxide. This red coloured liquid is called Cadet's Fuming Liquid in his honour.

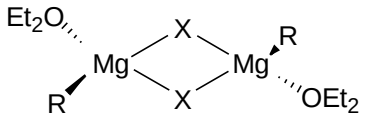
$4\ CH_3COOK + As_2O_3 \rightarrow As_2(CH_3)_4O + 4\ K_2CO_3 + CO_2$

3.1 Classification of Organometallic Compounds

Organometallic compounds may be classified in different ways. They may be classified according to the type of metal-carbon bond or according to the metal center involved in these compounds. For our convenience we will follow the latter classification throughout this text.

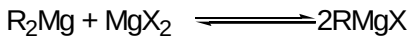
3.1.1 Grignard Reagents

Grignard reagents are organometallic compounds having Mg-C bond. Magnesium can form two covalent bonds with carbon. Of the various organomagnesium compounds possible, organomagnesium halides and to a lesser extent dialkyl magnesium compounds are widely used for synthesis. Although the Grignard reagents are usually formulated as RMgX, but in reality they are a mixture of a variety of species. The ratio of the species in solution varies with the organic group, the halogen, the solvent, the concentration and the temperature. It is believed that in case of organomagnesium chlorides (RMgCl) in diethyl ether, the predominant species over a wide range of concentrations is a solvated, halogen-bridged dimer **1**. The degree of association varies as the halide is changed to Br or I.



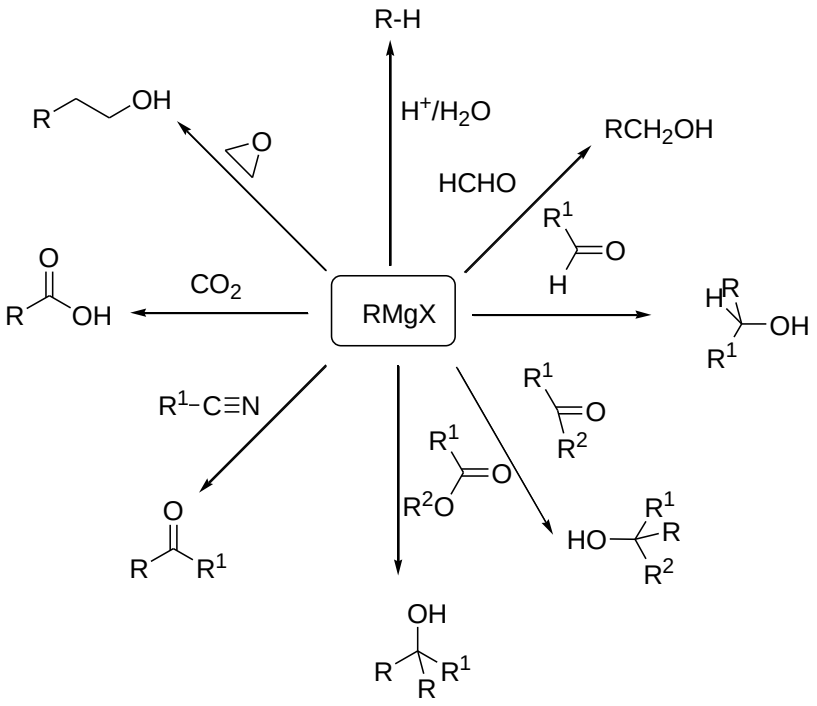
1

However, in case of THF, due to the highly coordinating nature of the solvent, there is a lesser degree of association. Therefore, monomeric species dominate in THF, however, there are significant concentrations of R_2Mg, MgX_2 and RMgX in equilibirium.



3.1.1.1 Addition of Grignard Reagents to Carbonyl Groups

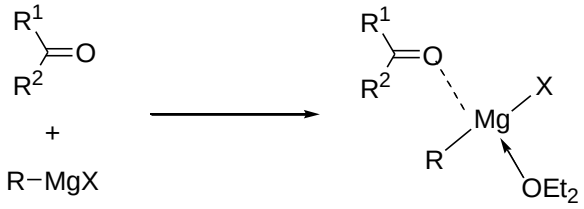
The addition of Grignard reagents to carbonyl group is one of the most important methods for carbon-carbon bond formation. Though the overall reaction is quite simple but it is highly susceptible to a number of side reactions. The reactivity of Grignard reagents towards different carbonyl group containing compounds also varies thus giving rise to different end products depending on reactants (Scheme 1).



Scheme 1

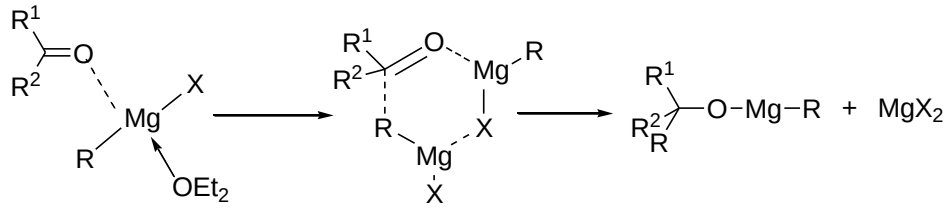
The mechanism of this reaction is usually depicted to consist of the following steps-

- Complexation of the organomagnesium species with the substrate (Scheme 2).



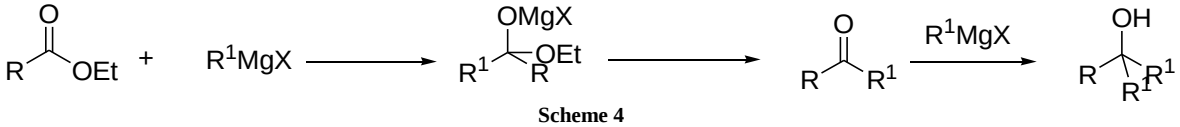
Scheme 2

- The next step involves nucleophilic attack of organic moiety of Grignard reagent on the electron deficient carbon of carbonyl group *via* a molecular complex (Scheme 3).



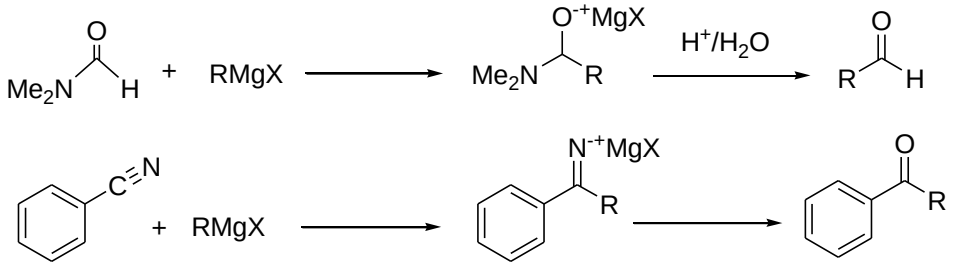
Scheme 3

- The intermediate formed in the above step is hydrolyzed to give a tertiary alcohol. However, if the carbonyl group is attached with a leaving group (i.e., if R^1= OR) then the tetrahedral adduct can break down to regenerate a C=O group that undergoes a fast second addition step (Scheme 4).



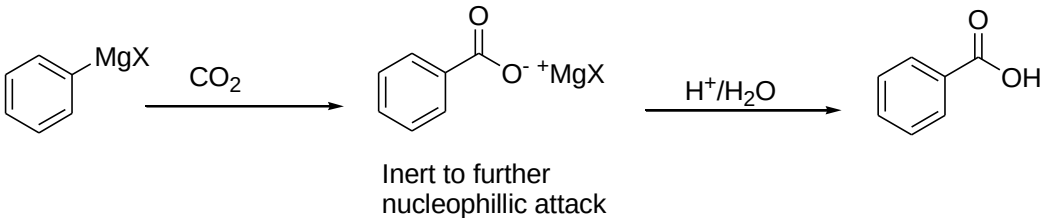
Scheme 4

However, a number of methods have been devised to stop the reaction at the aldehyde or ketone stage. Such protocols involve the formation of a masked carbonyl compound, which releases the desired compound on hydrolysis (Scheme 5).



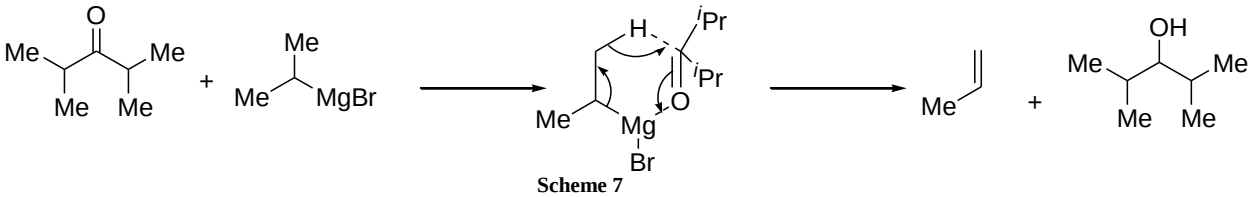
Scheme 5

In case of reaction of Grignard reaction with carbon dioxide, the reaction stops at the carboxylate (RCO^{2-}) stage as it is resistant to further nucleophilic attack (Scheme 6)



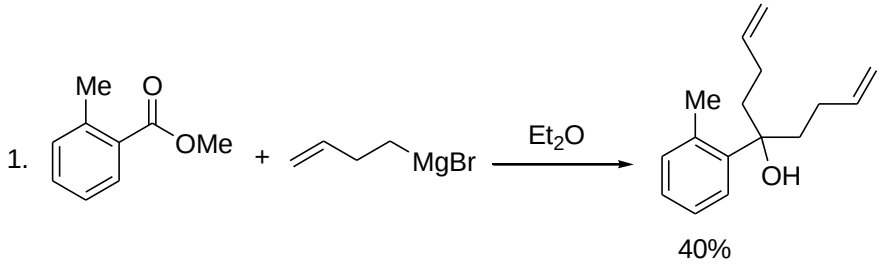
Scheme 6

Grignard reactions are prone to undergo side reactions. The reaction of a sterically hindered ketone with a Grignard reagent having a β-H shows a tendency towards reduction of the carbonyl group (Scheme 7).



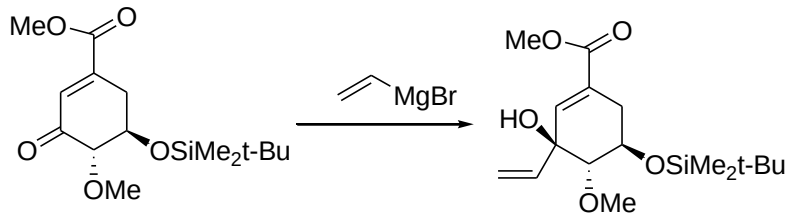
Scheme 7

Examples:



P. A. Wender, T. M. Dore, M. A. Delong, *Tetrahedron Lett.* **1996**, *37*, 7687.

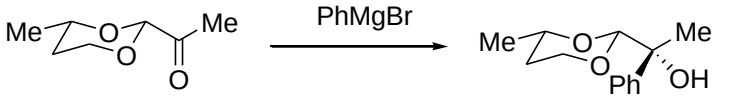
2.



90%

S. Hanessian, J. Pan, A. Carnell, H. Bouchard, L. Lesage, *J. Org. Chem.* **1997**, *62*, 465.

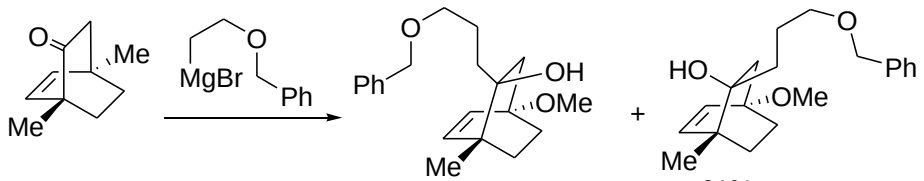
3.



94% major isomer

W. F. Bailey, D. P. Reed, D. R. Clark, G. N. Kapur, *Org. Lett.* **2001**, *3*, 1865.

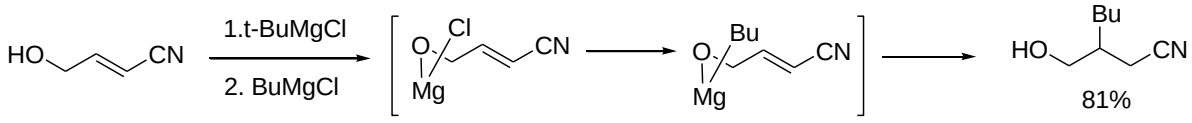
4.



37% 61%

T. Uyehara, T. Marayama, K. Sakai, M. Ueno, T. Sato, *Tetrahedron Lett.* **1996**, *37*, 7295.

5.



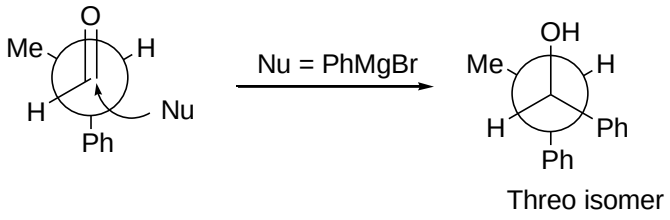
81%

F. F. Fleming, Q. Wang, Z. Zhang, O. W. Steward, *J. Org. Chem.* **2002**, *67*, 5963.

3.1.2 The Stereochemistry of Grignard Reaction

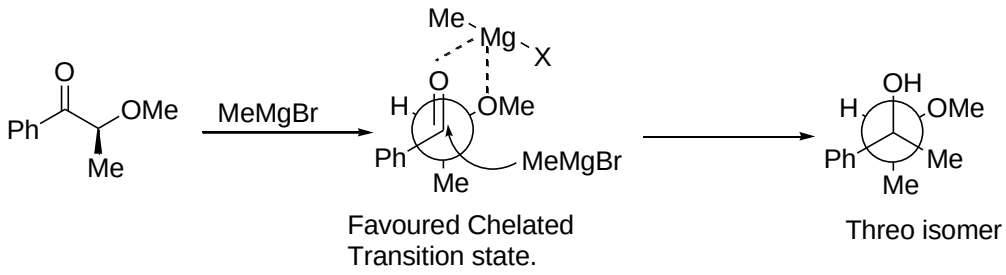
The stereochemical outcome of Grignard reaction can be predicted on the basis of Cram's rule. To apply Cram's rule we designate the groups on the carbon adjacent to the carbonyl group as small (S), medium (M) and large (L). The preferred conformation of 2-phenyl-propanaldehyde has carbonyl group staggered between methyl group (M) and

hydrogen atom (S). Now according to Cram's rule, the nucleophilic attack by phenylmagnesium bromide will take place from the least hindered position between methyl group and hydrogen atom (Scheme 8).



Scheme 8

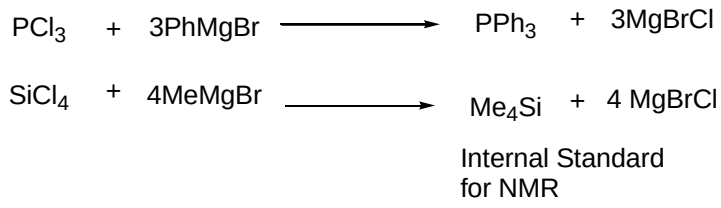
In the case of the Grignard addition to chiral substrates that possess a heteroatom in the α- or β- position, a modification in the application of the Cram's rule is required. In the reaction of (*S*)- 2-methoxy-1-phenylpropanone with methyl magnesium bromide, a cyclic structure where the methoxy group is synperiplanar to carbonyl group is formed. This results in the restriction in the freedom of the diasteroselective transition state and thus the attack takes place from the least hindered side having the methyl and the methoxy groups (Scheme 9).



Scheme 9

3.1.3 Other Uses of Grignard Reagents

Grignard reagents are not only useful reagents for organic transformation but they are also useful in the synthesis of other useful organometallic reagents such as organosilicon and organophosphorus reagents. For example, the reaction of Grignard reagents with $SiCl_4$ and PCl_3 gives triphenylphosphine and tetramethylsilane, respectively (Scheme 10).



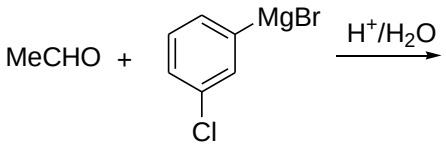
Scheme 10

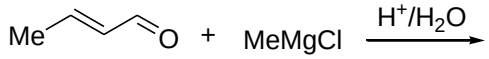
TRIVIA

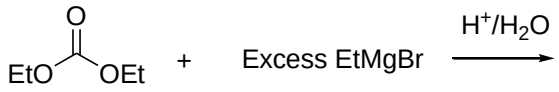
Victor Grignard was awarded the Nobel Prize in Chemistry in 1912 for the discovery and application of organomagnesium reagents.

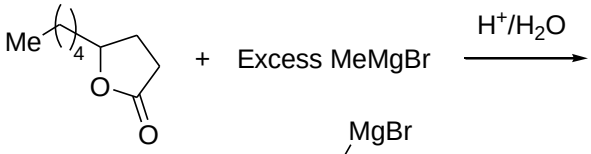
Problems

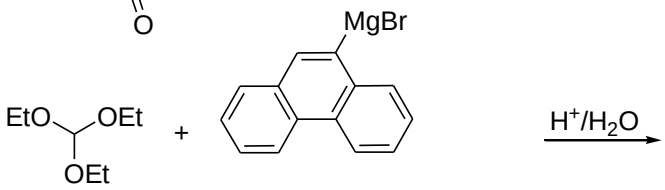
Predict the major products of the following reactions.

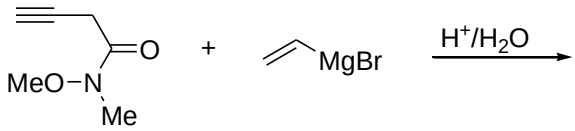
1. 

2. 

3. 

4. 

5. 

6. 

Text Book

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

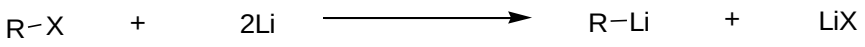
Lecture 6

3.3 Organolithium Reagents

Organolithium reagents are one of the most useful nucleophillic reagents in organic synthesis. They are also highly basic in nature. However, due to their thermal instability and extremely high reactivity they require elaborate precautions during use. Many organolithiums are commercially available as dilute solution in hydrocarbon solvents. In such solvents they are polymeric species with n = 4 to 6. In ethers, however, they are mostly tetrameric in nature. In the presence of strong donating molecules such as HMPA and DMPU, the degree of association decreases and they exist as monomeric species. This leads to an enhancement in their reactivity. Tetrameric structures are based on distorted cubic structures where the lithium atoms occupy alternate corners of the cube and the alkyl groups occupy a face of the cube.

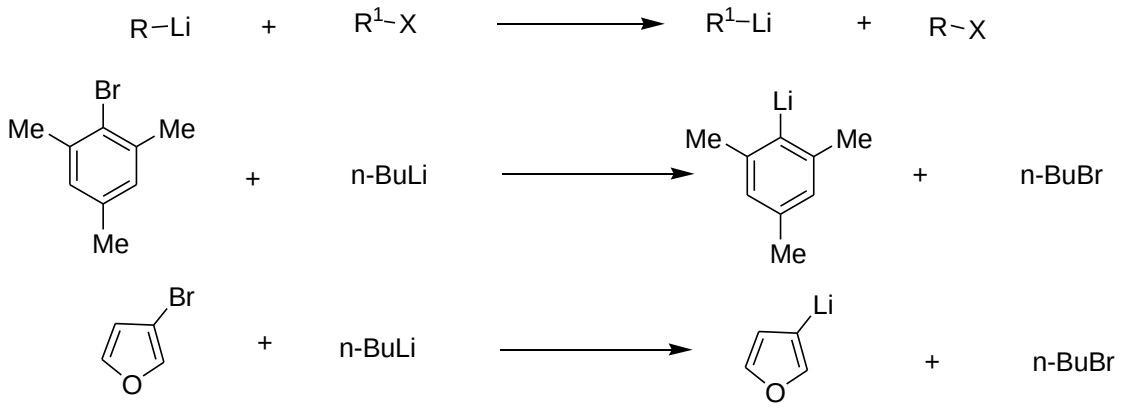
3.3.1 Preparation

Organolithium reagents are usually prepared by the reaction of organic halides with lithium (Scheme 1). The order of reactivity of the organic halides decreases in the following order RI > RBr > RCl.



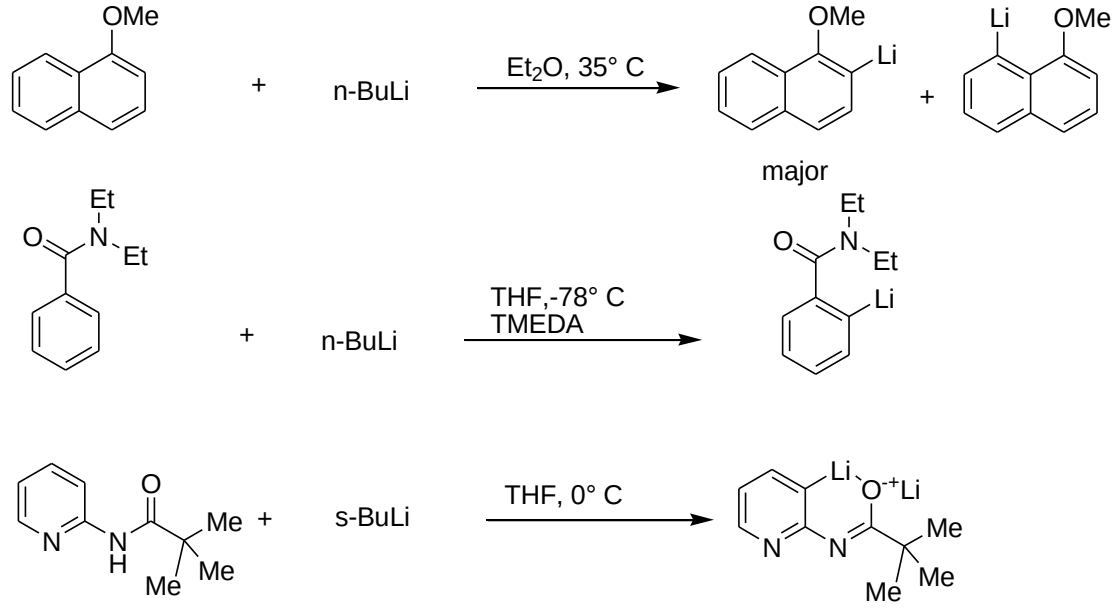
Scheme 1

Another route to organolithium compounds is the use of metal halogen exchange reactions. In these reactions the equilibirium lies to the right if the organic group is able to accommodate the electron density than the organic species on the left (Scheme 2).



Scheme 2

The replacement of a hydrogen by a lithium (known as lithiation) can also be used to generate organolithium species. This reaction is essentially an acid base reaction. However in case, where there is activation by a coordinating group, the reaction occurs with considerable ease. This type of activation is particularly helpful in introducing an *ortho* substituent to a preexisting coordinating group (Scheme 3).

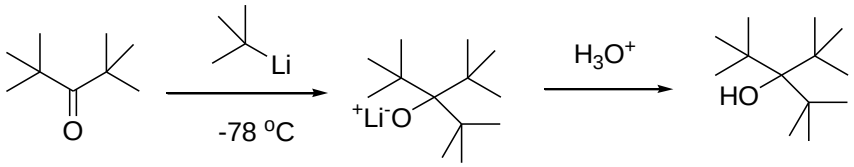


Scheme 3

The *ortho*-directing groups are usually arranged in the following order in order of their reactivity: SO_2NR_2 > SO_2Ar > $CONR_2$ > oxazolinyl > CONHR > CSNHR, CH_2NR_2 > OR > NHAr > SR > CR_2O^-. .

3.3.1 Reaction with Carbonyl Compounds

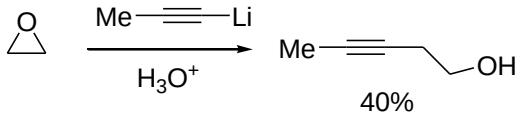
Organolithium reacts with carbonyl compounds as that of the Grignard reagents. In comparison to Grignard reagents, organolithium reagents are less susceptible to steric factors and react with hindered ketones to give the corresponding tertiary alcohols (Scheme 4).



Scheme 4

3.3.2 Reactions with Epoxides

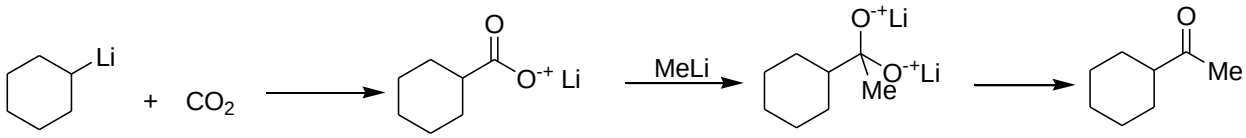
Epoxides react with organolithium reagents to give primary alcohols (as in the case of Grignard reagents). Use of unsaturated organolithium reagent gives unsaturated alcohols (Scheme 5).



Scheme 5

3.3.3 Reactions with Carbon Dioxide

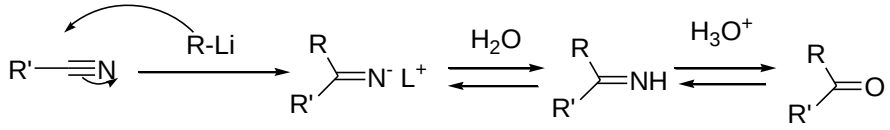
A major difference between the reactivity of Grignard reagents and organolithium reagent is observed in their reactivity towards CO_2. The reaction of Grignard reagents with CO_2 stops at the carboxylate stage, while in case of organolithium reagents, the carboxylate ion formed reacts with another equiv of organolithium to generate a ketone (Scheme 6).



Scheme 6

3.3.4 Reactions with Alkyl Cyanide

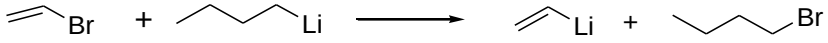
As in the case of Grignard reagents, the reactions of organolithium reagents with alkyl cyanides give imine salts, which undergo hydrolysis in the presence of water to give ketones (Scheme 7).



Scheme 7

3.3.5 Electrophilic Displacement

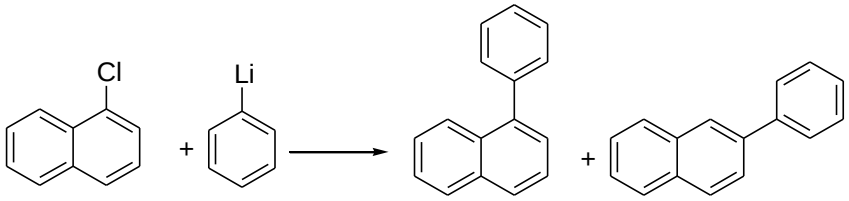
Reaction of an organic halide with an organometallic compound is known as metal-halogen exchange reaction is example for electrophilic displacement. This reaction is useful for the synthesis of vinyl- and phenyl lithium (Scheme 8).



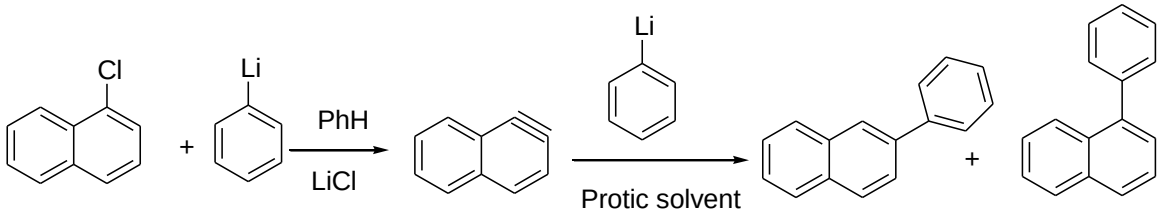
Scheme 8

3.3.6 Nucleophilic Displacement

Reactions of alkyl and aryl halides can be reacted with alkyl and aryl lithium reagents to give hydrocarbons. The reaction of alkyl halides with alkyl lithium takes place by S_N2 mechanism. While aryl halides react with aryl lithum via addition-elimination process (Scheme 9).



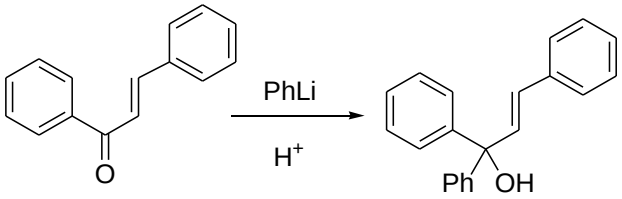
Mechanism



Scheme 9

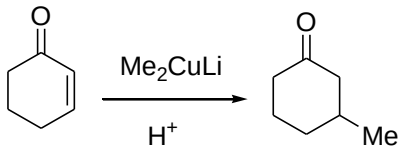
3.3.7 Reaction with α,β-Unsaturated Carbonyl Compounds

In the case of Grignard reagents, α,β-unsaturated carbonyl compounds undergo reaction either at 1,2- or 1,4-addition depending on the structure of the carbonyl compound. The main reason is steric hinderance. While the organolithium reagents undergo reaction exclusively to give 1,2-addition products (Scheme 10).



Scheme 10

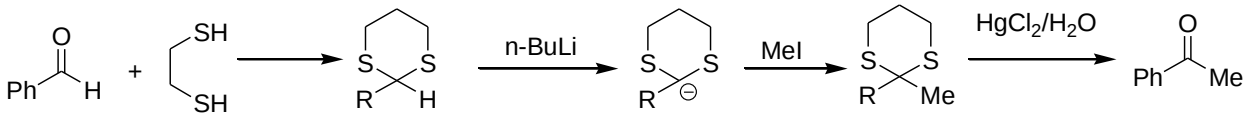
Exclusive formation of 1,4-addition product, however, can be achieved using lithium dialkylcuprates (Scheme 11).



Scheme 11

3.3.7 Deprotonation

The basic nature of organolithiums can also be put to good use in achieving umpolang at the carbonyl centre of an aldehyde. In this protocol a C=O function is first protected by 1, 3-dithiane and then the proton is removed by an organolithium (Scheme 12).

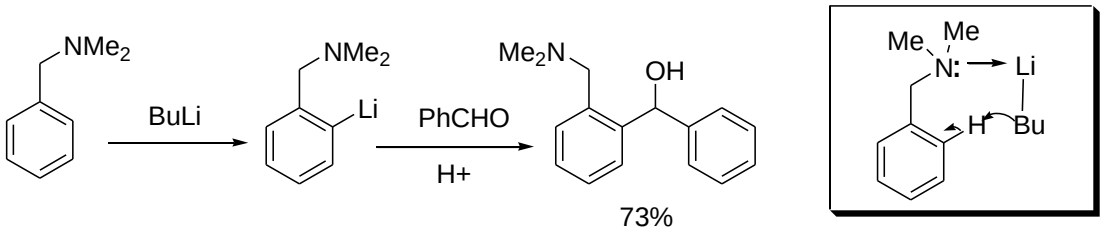


Scheme 12

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

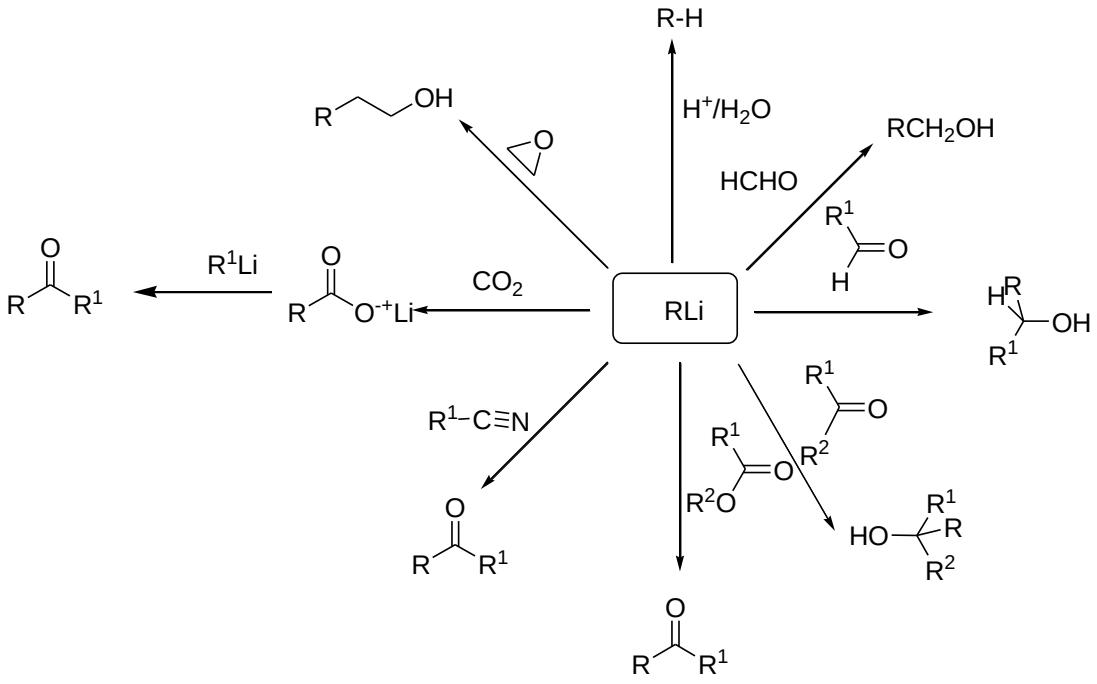
3.3.8 Ortholithiation

It is useful because the starting material does not need to have a halogen atom. For example, in the case of benzyldimethylamine, the nitrogen atom directs attack of the butyllithium (Scheme 13).



Scheme 13

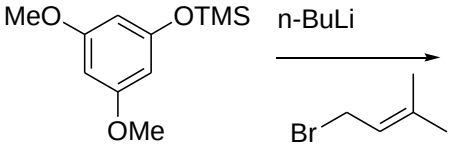
Summary of the Reactions of Organolithium Reagents

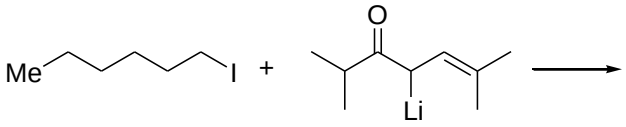


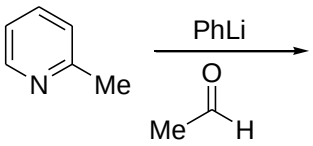
Scheme 14

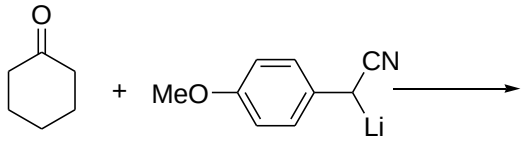
Problems

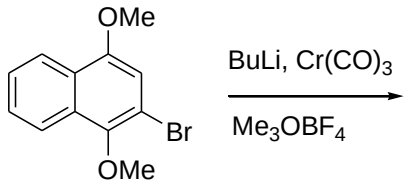
Predict the major products of the following reactions

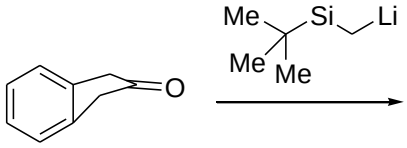
1. 

2. 

3. 

4. 

5. 

6. 

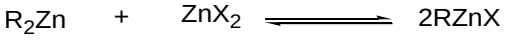
Text Book

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

Lecture 7

3.2 Organozinc Reagents

Organozinc reagents are one of the most important of organometallic compounds. The first instance of an organozinc compound goes back to 1849 when Edward Frankland discovered that heating a mixture of zinc and ethyl iodide gives highly pyroporric diethyl zinc. Organozinc compounds in general are sensitive to oxidation, dissolve in a wide variety of solvents whereas protic solvents cause decomposition. Organozinc compounds also exhibit the Schlenck equilibrium like Grignard reagents (Scheme 1).



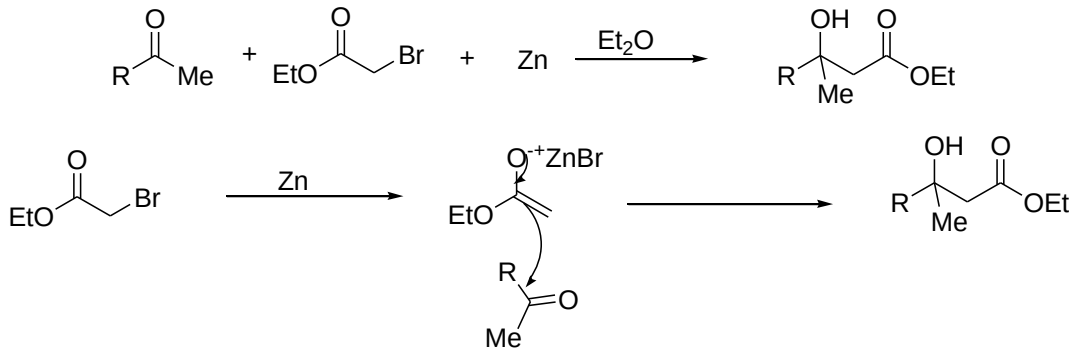
Scheme 1

In terms of reactivity, organozinc compounds are less reactive than Grignard reagents. This can be explained on the basis of relative position of Mg and Zn in the periodic table. Since zinc is more electropositive than Mg thus the Zn-C bonds have a higher degree of covalency compared to the Mg-C bond. In a typical case, the electrons forming the C-Zn bond reside in two *sp* hybridized molecular orbitals resulting in linear geometry about the zinc centre.

3.2.1 Nucleophilic Addition by Organozinc Reagents

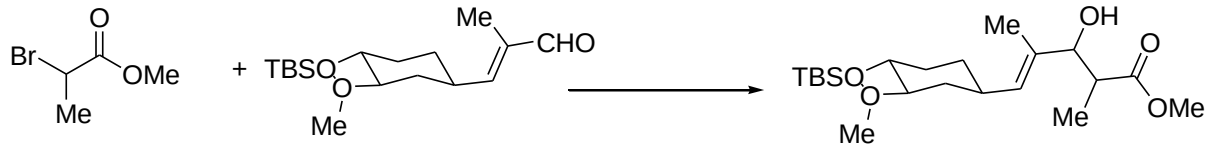
Organozinc reagents are less reactive than organomagnesium and organolithium reagents thereby allowing a higher functional group tolerance. However, this low reactivity means that they need to be often aided by additives or catalysts.

Reformatsky reaction is one of the most important applications of organozinc reagent formed *in situ.* In this reaction zinc, α-haloester and a carbonyl compound react to give β-hydroxyester. The reaction involves the formation of a zinc enolate which attacks the carbonyl group (Scheme 2). As the zinc enolate is only weakly basic so the reaction works even in the presence of highly enolisable carbonyl partner. Sterically hindered ketones do not pose a problem for this reaction.



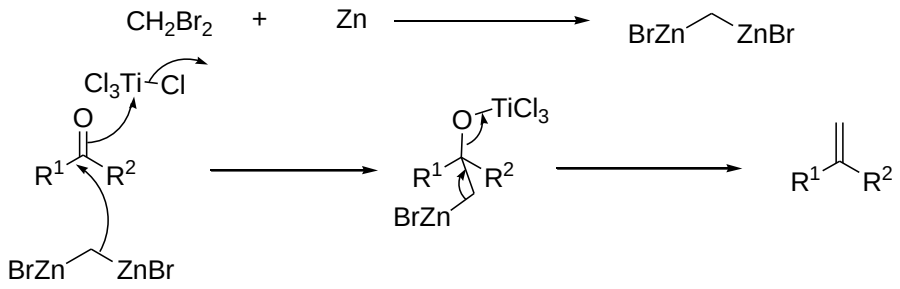
Scheme 2

In case of α,β-unsaturated carbonyl compound the addition takes place regioselectively in a 1,2 fashion (Scheme 3).



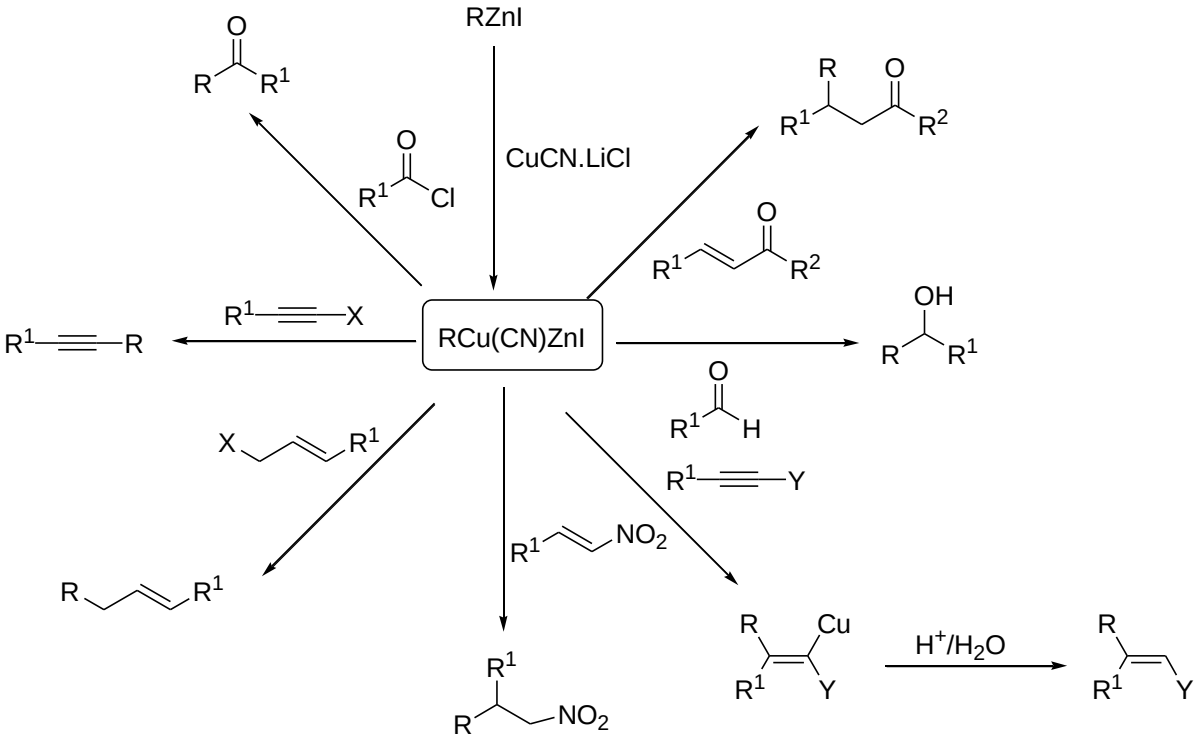
Scheme 3

The combination of $Zn/CH_2Br_2/TiCl_4$ is known as Lombordo's reagent which can convert ketones to methylene group. The reaction is believed to proceed through a dimetalated intermediate which adds to the ketone (Scheme 4).



Scheme 4

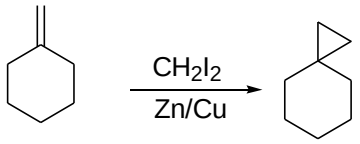
Organozinc reagents readily undergo transmetallation thereby making them suitable candidates to be used in conjunction with transition metal salts. Thus, RZnI reacts with THF soluble salt CuCN·LiCl to form new copper-zinc reagents which are usually formulated as RCu(CN)ZnI. The reactivity of this reagent is shown in Scheme 5.



Scheme 5

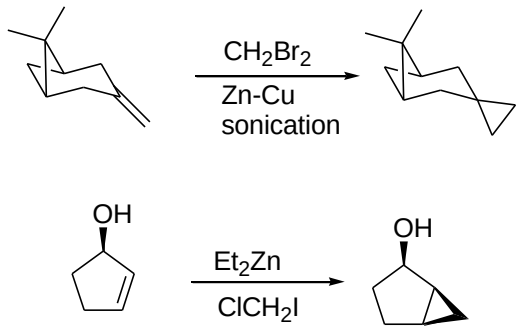
3.2.2 Cyclopropanation by Organozinc Reagents

Alkenes may be conveniently converted into cyclopropanes by treatment with methylene iodide and Zn/Cu couple. This reaction is known as Simmons Smith reaction. The reactive species is iodomethylzinc iodide (Scheme 6).



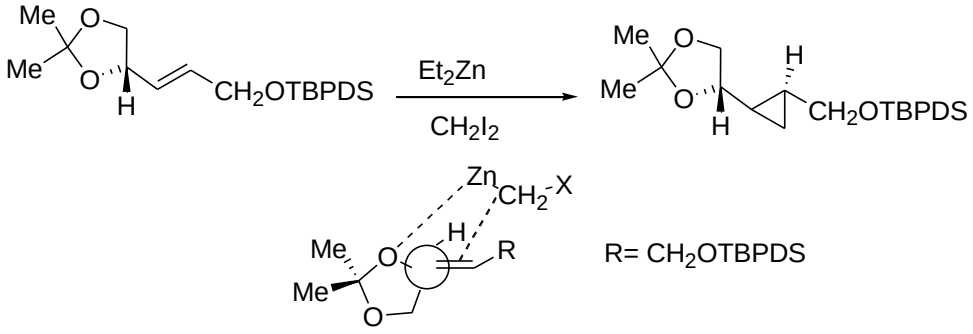
Scheme 6

Several modifications are available to allow the use of less reactive methylene group donors like chloroiodomethane. Such methods employ the use of Lewis acids like $TiCl_4$ or organic reagents like acetyl chloride or trimethylsilyl chloride (Scheme 7). This reaction is also sensitive to the purity of zinc. Thus electrochemically prepared zinc is more effective than metallurigically prepared zinc.



Scheme 7

Simmons Smith reaction is highly stereospecific reaction as it does not involve a carbene intermediate ($:CH_2$). In case of additional directing groups, the reaction exhibits considerable stereoselectivity. In Scheme 8, the stereoselectivity of the reaction is explained by the coordination of zinc to allylic oxygen in the transition state.



Scheme 8

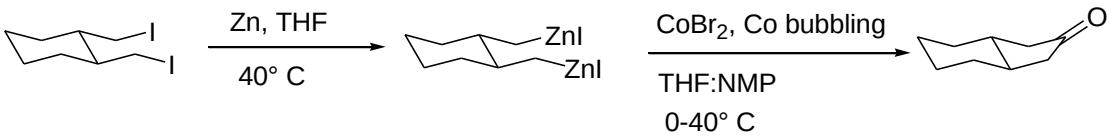
Other reagents have been developed having aryloxy or acetoxy anions. These reagents are effective for cyclopropanation of unactivated alkenes. They are prepared by the reaction of diethyl zinc with a suitable oxyanion precursor such as trifluoroacetic acid followed by reaction with methylene iodide to generate reagents having formula $ROZnCH_2I$. The reactivity of the oxyanions are in the order $CF_3COO^- > ArO^- > RO^-$.

3.3.3 Transition Metal Mediated Addition of Organozinc Reagents

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

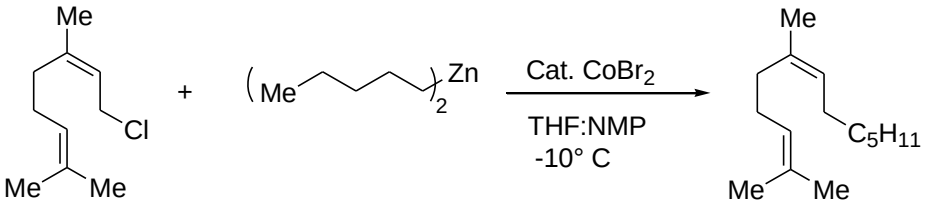
One of the most useful reactions using Co is the carbonylation reaction. Organozinc reagents when treated $CoBr_2$ generate organocobalt reagents which are stable for several

hours at low temperature. Carbonylation is now possible by simply bubbling CO through such a solution (Scheme 9).



Scheme 9

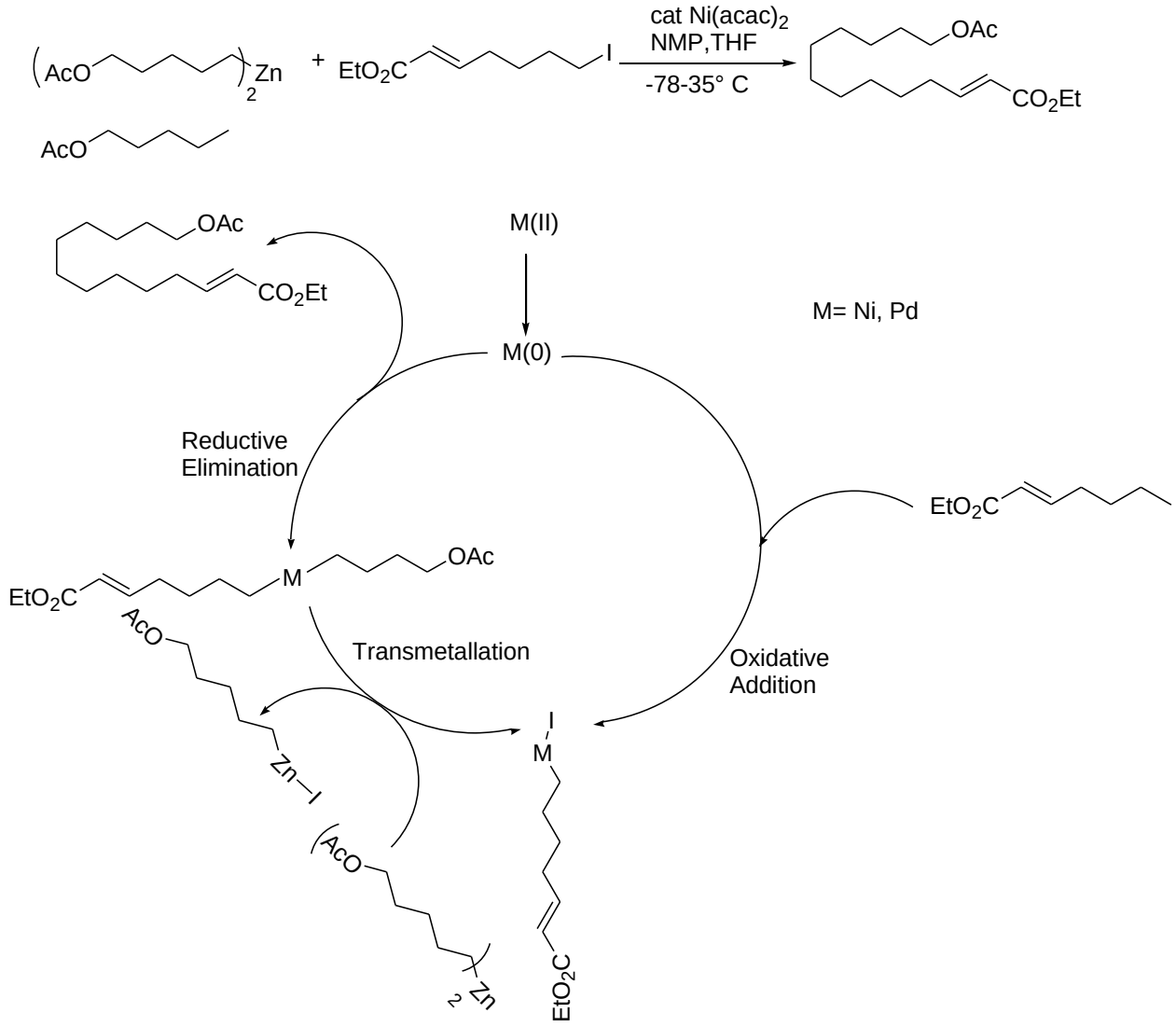
Addition of cobalt salts in catalytic amount is known for acylation and allylation reaction of diorganozincs. The reaction occurs in a S_N2 fashion but, not by S_N2' fashion, thereby leading to a complete retention of double bond geometry (Scheme 10).



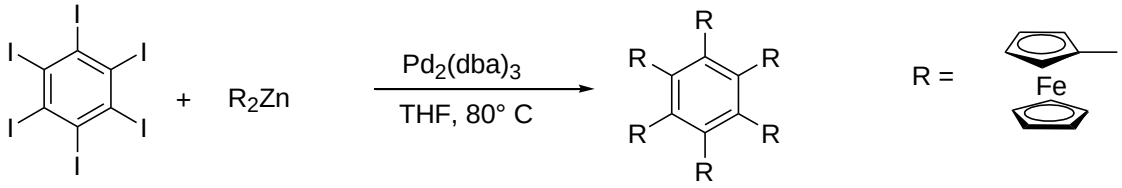
Scheme 10

The reaction between organozinc compound and an organic halide in the presence of Pd(0) or Ni(0) species is known as Negishi cross-coupling reaction which is one of the most widely used cross-coupling reactions. The mechanism of this reaction involves oxidative addition followed by transmetallation with the zinc compound and subsequent reductive elimination (Scheme 11). This reaction can be applied to highly substituted substrates. An interesting example of application of Negishi coupling is the synthesis of hexaferrocenyl benzene (Scheme 12).

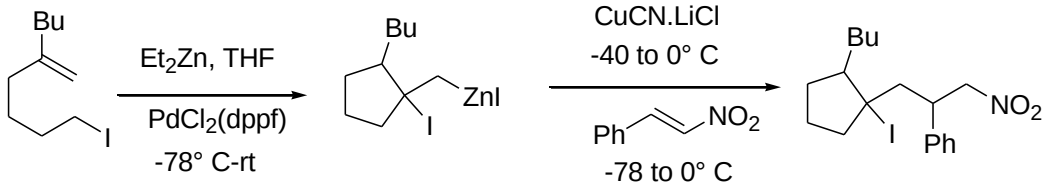
Besides Negishi cross-coupling, Ni and Pd salts are also known to catalyze the cyclization reactions of organozincs *via* a radical pathway. In these cases, an intermediate Ni(0) or Pd(0) is formed which initiates a radical chain providing a new zinc derivative which can further undergo reaction with other electrophiles (Scheme 13).



Scheme 11



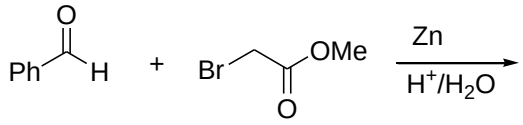
Scheme 12

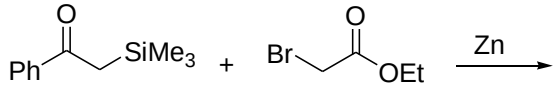


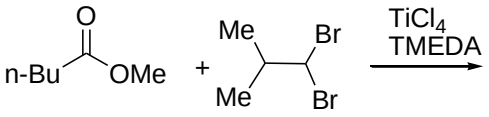
Scheme 13

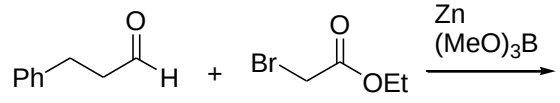
Problems

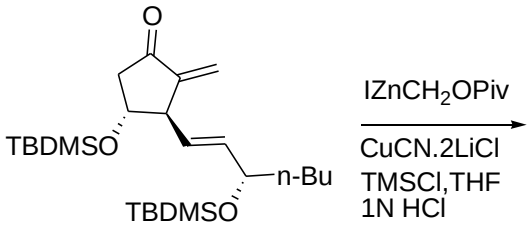
Predict the major product for the following reactions.

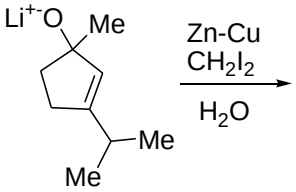
1. 

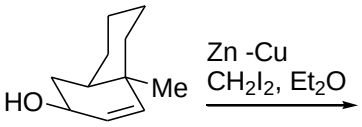
2. 

3. 

4. 

5. 

6. 

7. 

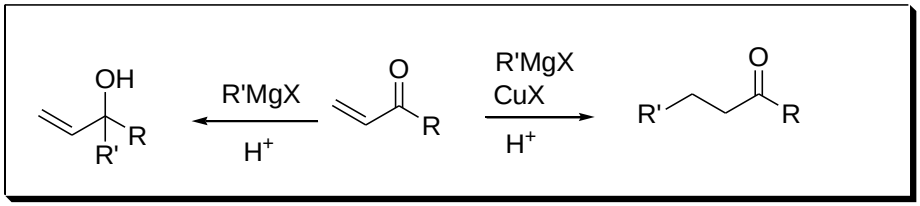
Text Book

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

Lecture 8

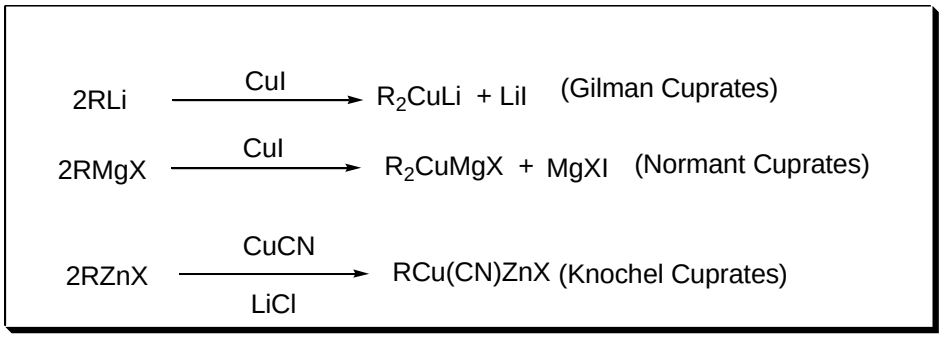
3.5 Organocopper Reagents

The pioneering work from the Gilman group in 1936 marked the beginning of the era of organocopper reagents, describing the preparation of mono-organocopper reagents and their considerable synthetic potential in organic chemistry. The use of copper salts as catalysts in organometallic reactions has then been become popular. The observation that catalytic amounts of copper halides favored 1,4-addition over the usually observed 1,2-addition in the reaction between Grignard reagents and α,β-unsaturated ketones was of crucial importance for the further development of organocopper reagents as synthetic tools in organic chemistry (Scheme 1).



Scheme 1

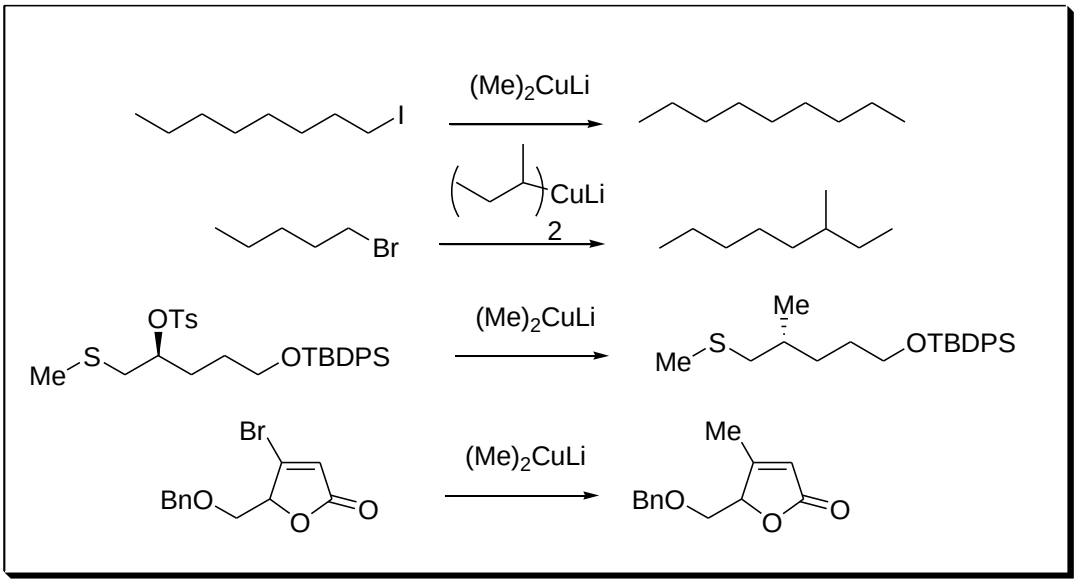
Organocopper reagents can be prepared by transmetallating the Grignard or organolithium reagent (Scheme 2).



Scheme 2

3.5.1 Reactions with Alkyl or Aryl or vinyl Halides and Tosylates

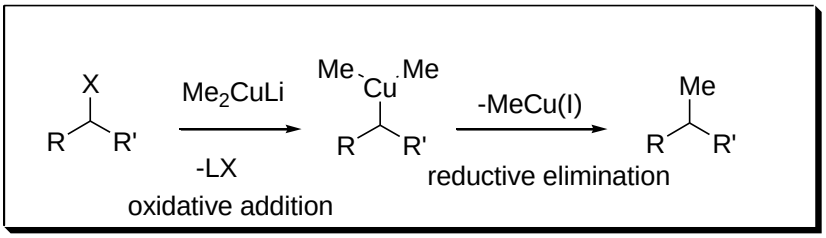
Alkyl, aryl or vinyl halides and tosylates react with organocuprates to give cross-coupled products (Scheme 3). The method affords an effective route for the synthesis of hydrocarbon from two different alkyl, aryl or vinyl halides.



Scheme 3

Mechanism

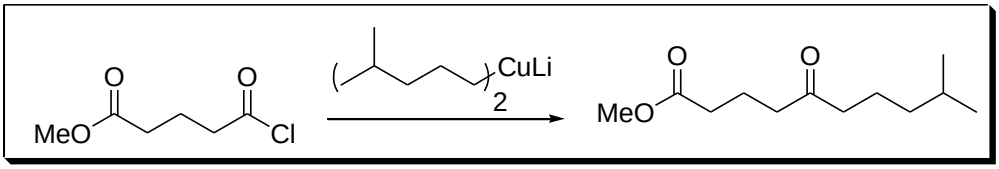
The reaction takes place via oxidative addition followed by reductive elimination (Scheme 4).



Scheme 4

3.5.2 Reactions with Acid Chlorides

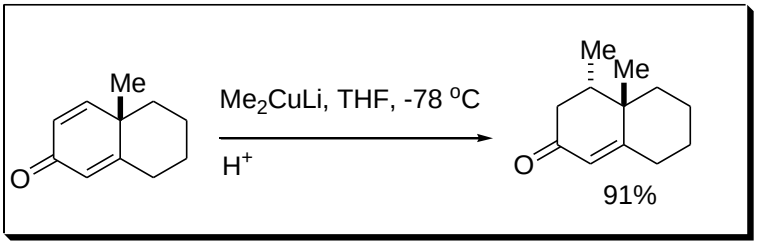
Acid chlorides react with organocopper reagents to give ketones (Scheme 5).



Scheme 5

3.5.3 Conjugate Addition

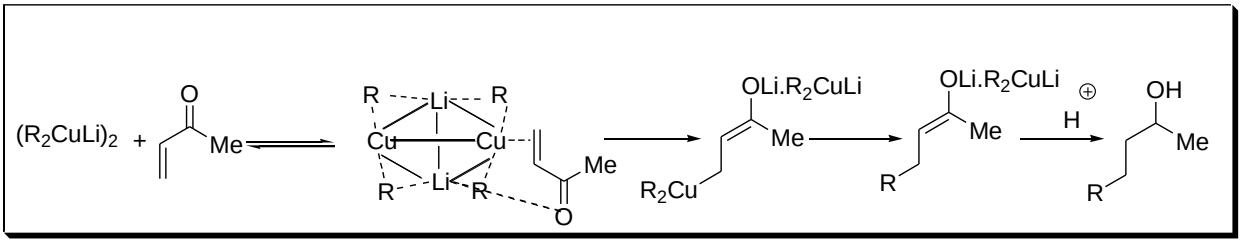
Organocopper reagents undergo 1,4-addition to α,β-unsaturated carbonyl compounds. The reaction can be stereoselective. For example, the less substituted double bond undergoes reaction from the less hindered side to give stereoselective product (Scheme 6).



Scheme 6

Mechanism

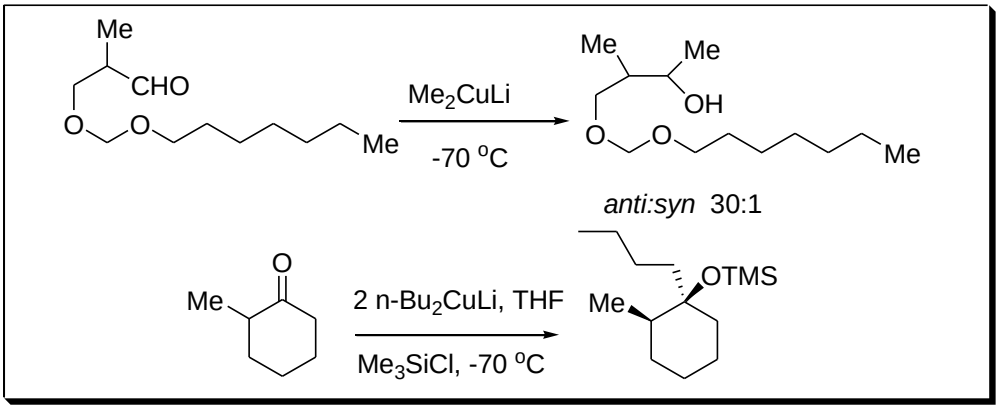
The reaction takes place via copper(III) intermediate (Scheme 7).



Scheme 7

3.5.4 Reactions with Aldehydes and Ketones

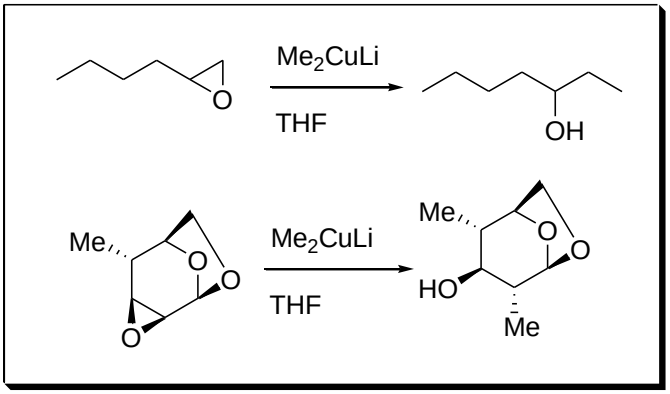
Aldehydes readily react with organocuprates to give alcohols (Scheme 8). However, ketones are less reactive, but their reactivity can be accelerated using chlorotrimethylsilane.



Scheme 8

3.5.5 Reactions with Epoxides

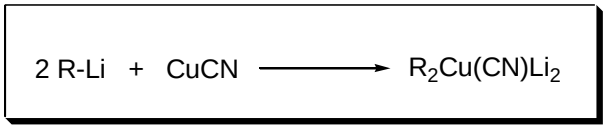
Epoxide reacts with organocopper reagents at the least substituted carbon atom to provide the corresponding alcohol (Scheme 9).



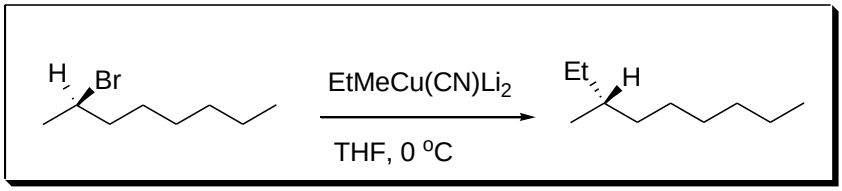
Scheme 9

Higher Order Cuprates

The reaction of organolithium reagent with cuprous cyanide yields higher order cuprate (Scheme 10). Higher order cuprate is more reactive compared to Gilman reagent towards alkyl halides. For example, (*S*)-2-bromooctane reacts with EtMeCu(CN)Li at 0 ^{o}C to give *(R)*-3-methylnonane in 72% yield (Scheme 11).

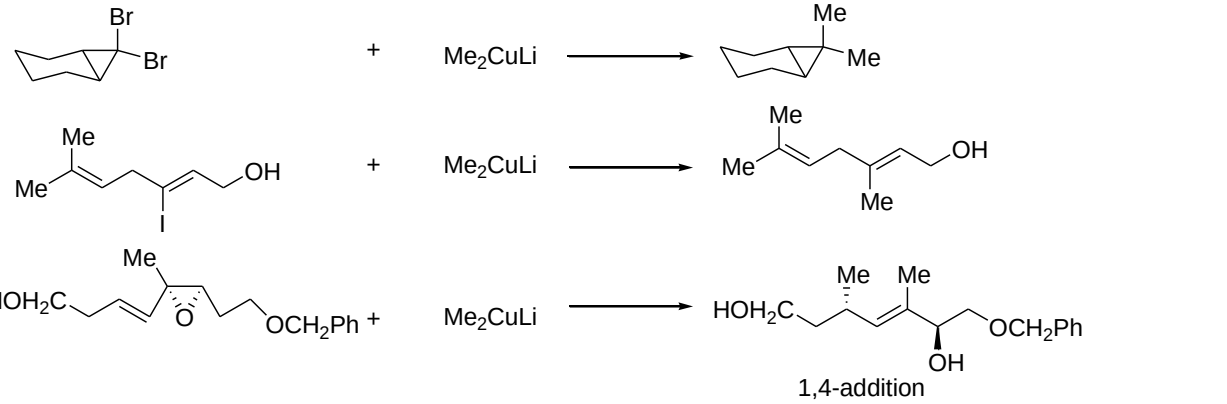


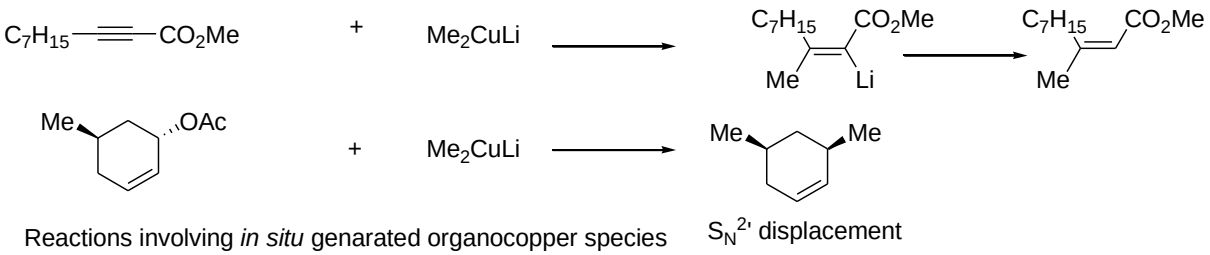
Scheme 10

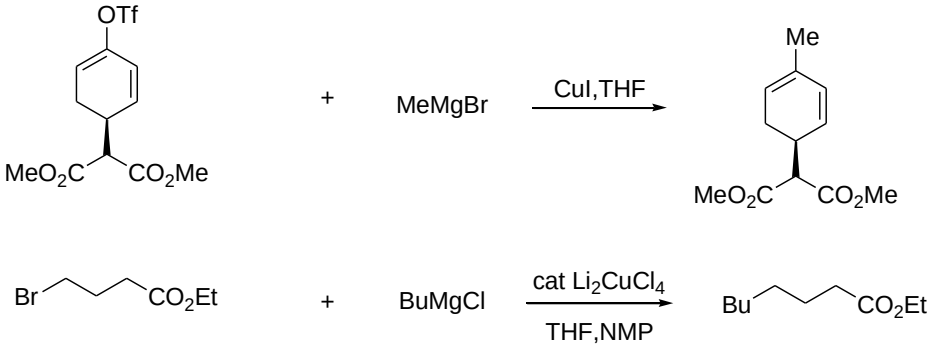


Scheme 11

Examples:

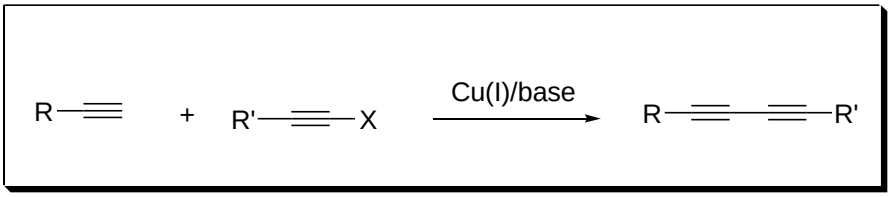

Br
Br
+
Me2CuLi
Me
Me
Me
Me
OH
I
+
Me2CuLi
Me
Me
OH
Me
Me
HOH2C
O
OCH2Ph
+
Me2CuLi
Me
Me
HOH2C
OCH2Ph
OH
1,4-addition


C7H15
CO2Me
+
Me2CuLi
C7H15
CO2Me
Me
Li
C7H15
CO2Me
Me
Me
OAc
+
Me2CuLi
Me
Me
Reactions involving *in situ* genarated organocopper species
SN2' displacement


OTf
MeO2C
CO2Me
+
MeMgBr
CuI,THF
Me
MeO2C
CO2Me
Br
CO2Et
+
BuMgCl
cat Li2CuCl4
THF,NMP
Bu
CO2Et

3.5.7 Cadiot-Chodkiewicz Coupling

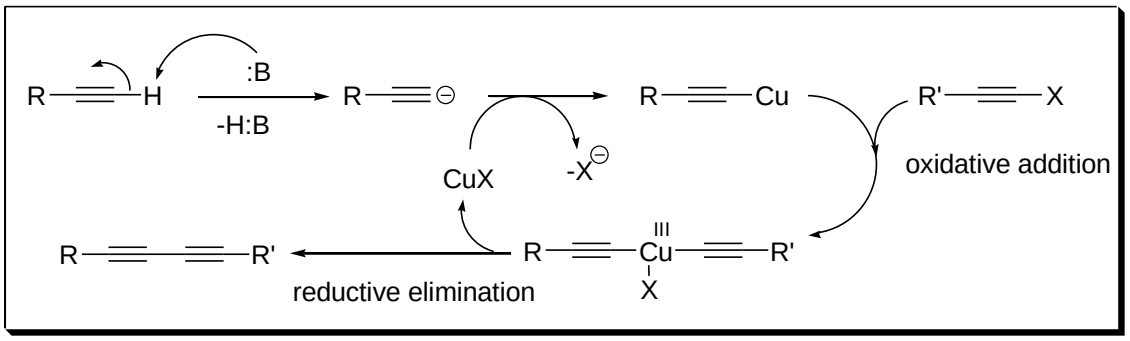
Monosubstituted alkynes reacts with alkynyl halides in the presence of copper(I) salts to offer unsymmetrical bisacetylenes (Scheme 12).



Scheme 12

Mechanism

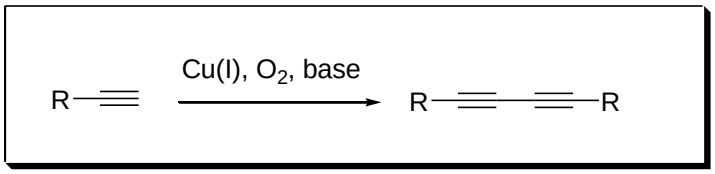
Proceeds via oxidative addition followed by reductive elimination (Scheme 13).



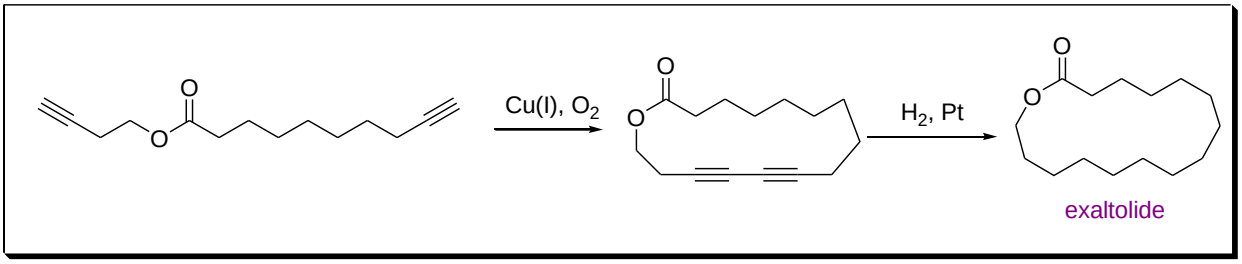
Scheme 13

3.5.6 Glaser (Oxidative Coupling)

Terminal alkynes can also be coupled by oxidative coupling using copper salts in the presence of molecular oxygen (Scheme 14).



Scheme 14

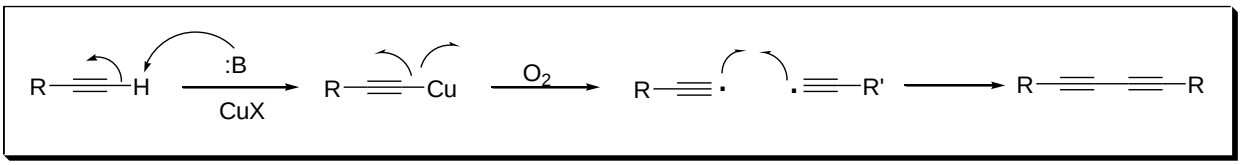


Scheme 15

Using this method the synthesis of macrocyclic lactone, exaltolide, that is partly responsible for the sweet odour of the angelica root, can be accomplished in high yield (Scheme 15).

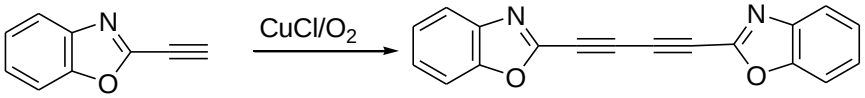
Mechanism

Proceeds via radical intermediate (Scheme 16).

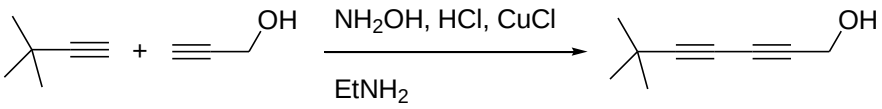


Scheme 16

Examples:



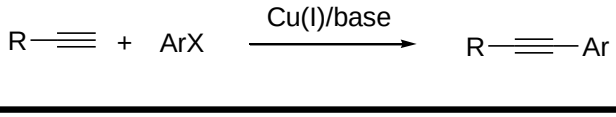
U. Fritzsche, S. Hunig, *Tetrahedron Lett*. **1972**, *13*, 4831.



J.-P. Gotteland, et al., *J. Med. Chem.* **1995**, *38*, 3207.

3.5.6 Castro-Stephens Coupling

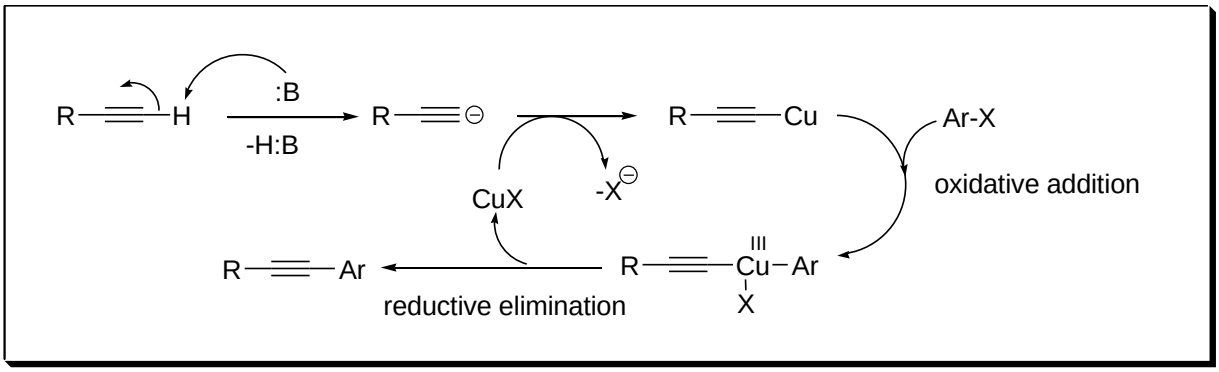
The coupling of alkynes with aryl halides employing copper salt in the presence of base affords aryl acetylenes (Scheme 17).



Scheme 17

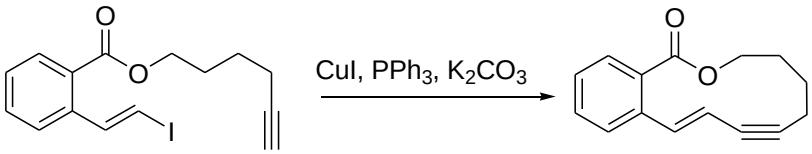
Mechanism

The reaction takes place via oxidative addition followed by reductive elimination (Scheme 18).

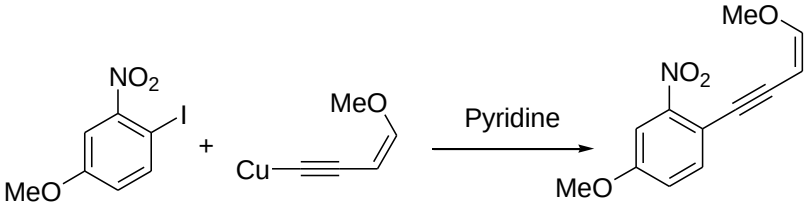


Scheme 18

Examples:



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

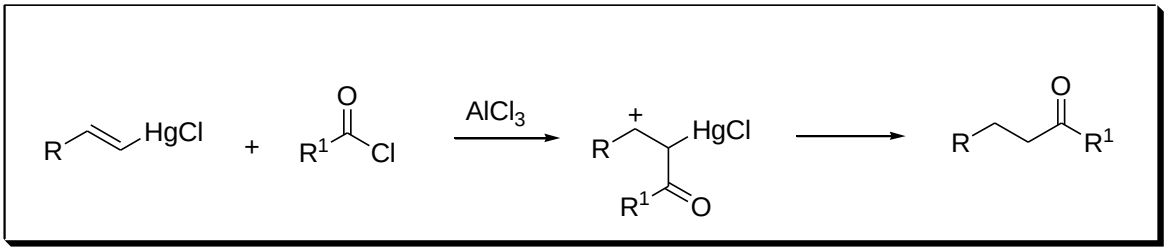


G. A. Krause, K. Frazier, T*etrahedron Lett.* **1978**, *19*, 3195.

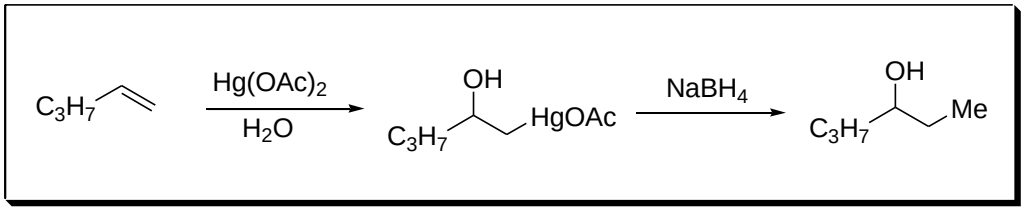
3.6 Organomercury Reagents

Organomercury reagents are usually prepared by the metal exchange reaction between mercury(II) salt and Grignard reagent or organolithium. Organomercury compounds have a significant degree of covalency in Hg-C bond. Hence, they are less effective as nucleophiles compared to Grignard reagent or organolithium. Thus, they do not react with aldehydes or ketones but they react with acid chlorides in the presence of a Lewis

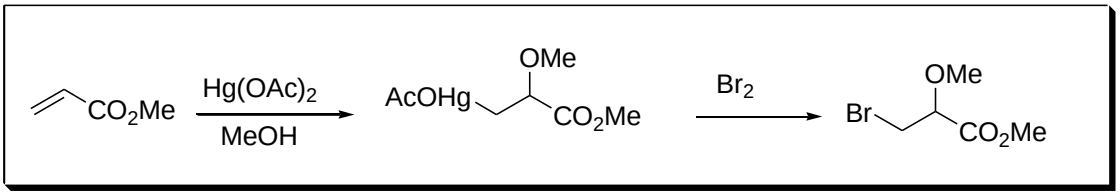
acid (Scheme 19). The most significant reaction involving an organomercury reagent is oxymercuration-demercuration protocol for hydroxylation of alkenes (Scheme 20). Unlike hydroboration, this reaction follows Markovnikov's principle. Another application of these reagents includes Hoffman-Sands reaction where an alkene can be converted to monobrominated alkanes (Scheme 21).



Scheme 19



Scheme 20



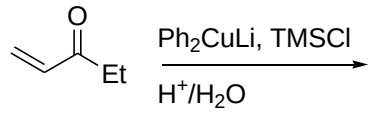
Scheme 21

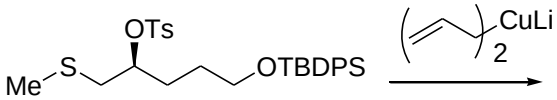
TRIVIA

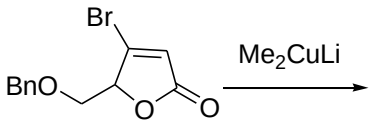
Organomercury compounds are extremely poisonous. They are readily absorbed through skin and attack the central nervous system causing severe neurological problems. The Minamata disease in Japan was caused by the release of methyl mercury wastes into the Minamata Bay which accumulated in fish which were then consumed by humans in the region.

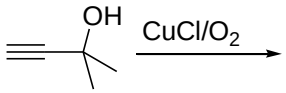
Problems

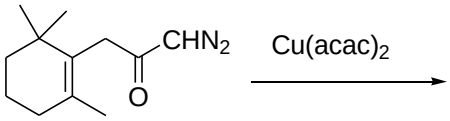
Predict the products of the following reactions

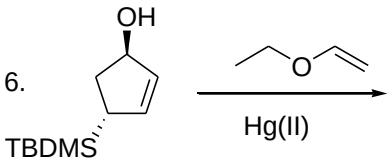
1. 

2. 

3. 

4. 

5. 

6. 

Text Book:

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

Lecture 9

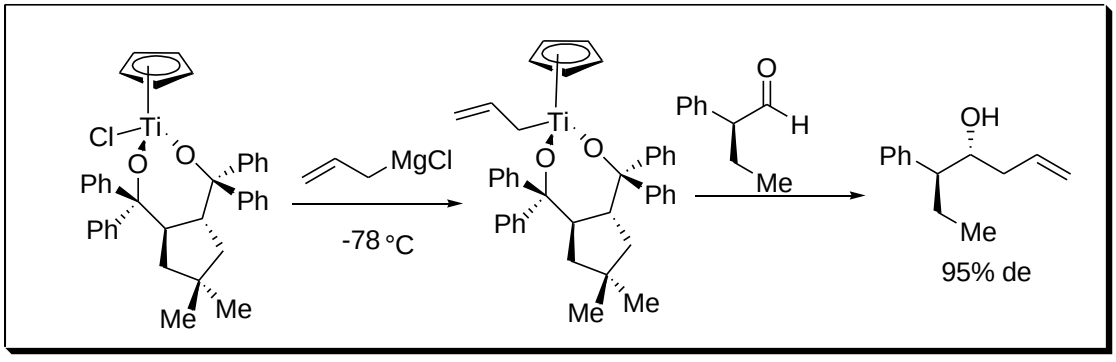
3.7 Application in Asymmetric Synthesis

The process of introducing a new chiral centre enantioselectively is referred to as asymmetric synthesis. It is important because both the enantiomers are not equally effective for a specific task. In case of dopamine precursor L-DOPA, only the L–isomer is biologically active. As we have seen, organometallic reagents are nucleophillic in nature, so if they can be made to add to a prochiral substrate in such a manner that the addition takes place in only direction or face then, it is possible to synthesize a compound enantioselectively. This forms the basic principle for asymmetric catalysis using organometallic reagents. One of the most common ways to achieve this is to use enantioselective induction using chiral ligands or metal-ligand complexes. In these reactions, an additional metal species (usually Lewis acid) in catalytic amount may or may not be needed to obtain this objective.

Some examples of the use of magnesium, lithium and zinc based reagents/catalysts in asymmetric synthesis follow.

3.7.1 Reactions with Magnesium Reagents

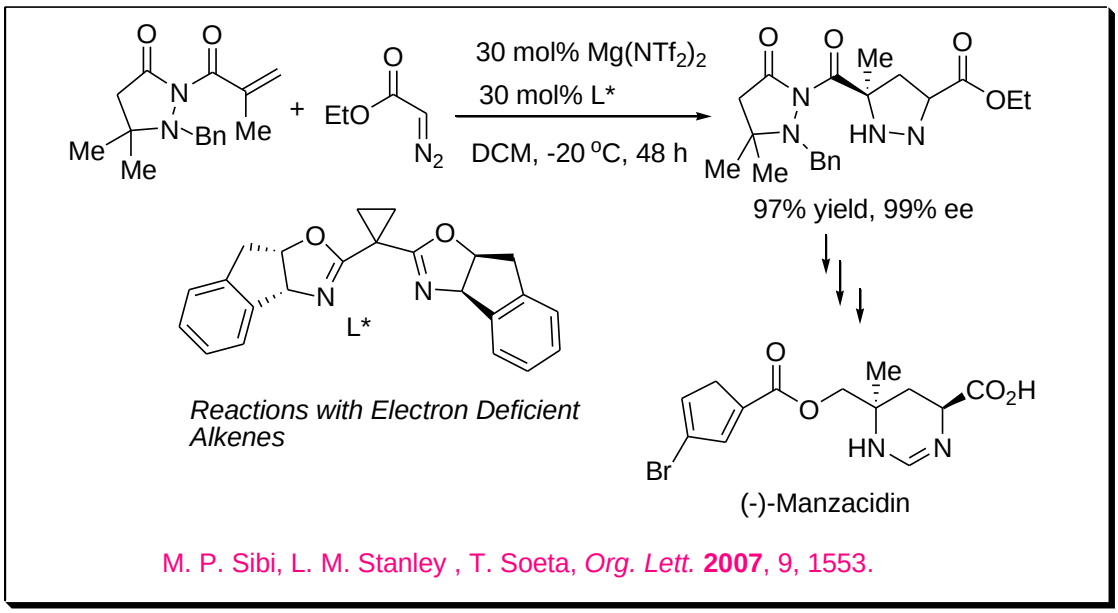
Aldehydes react with allylic Grignard reagents in an enantioselective manner in the presence of chiral Ti-catalyst to give the corresponding alcohol in < 95% de. This two step one pot process



Scheme 1

involves generation of allyltitanium species by transmetallation of allyl Grignard reagents and then addition to the aldehyde (Scheme 1).

Magnesium complex derived from $Mg(NTf_2)_2$ and chiral bisoxazoline has been used as chiral Lewis acid for the cycloaddition of diazoester with electron deficient alkenes (Scheme 2). The resultant product is used as an intermediate for the synthesis of (-)-manzacidin.

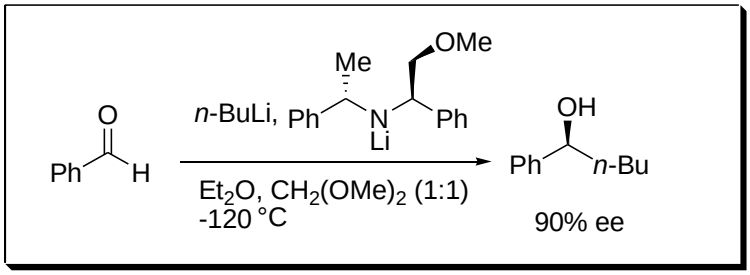


M. P. Sibi, L. M. Stanley , T. Soeta, *Org. Lett.* **2007**, 9, 1553.

Scheme 2

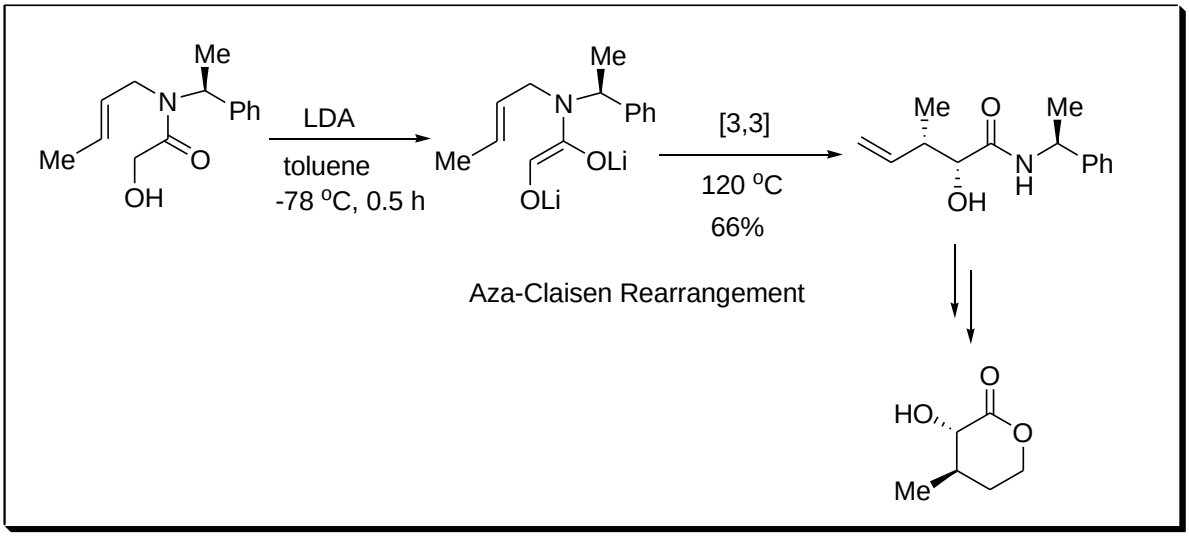
3.7.2 Reactions with Lithium Reagents

Organolithium reagents have been extensively used in enantioselective synthesis. In the example shown below, the organolithium having the amine functionality binds with the aldehyde which then undergoes attack by *n*-BuLi enantioselectively (Scheme 3).



Scheme 3

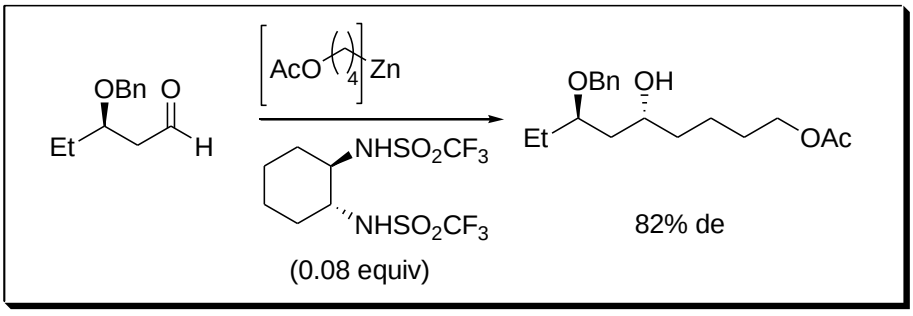
Chiral lithium enolate derived from LDA and optically active amide undergoes (3,3)-aza-Claisen rearrangement to afford an intermediate for the synthesis of (-)-verrucarinolactone (Scheme 4).



Scheme 4

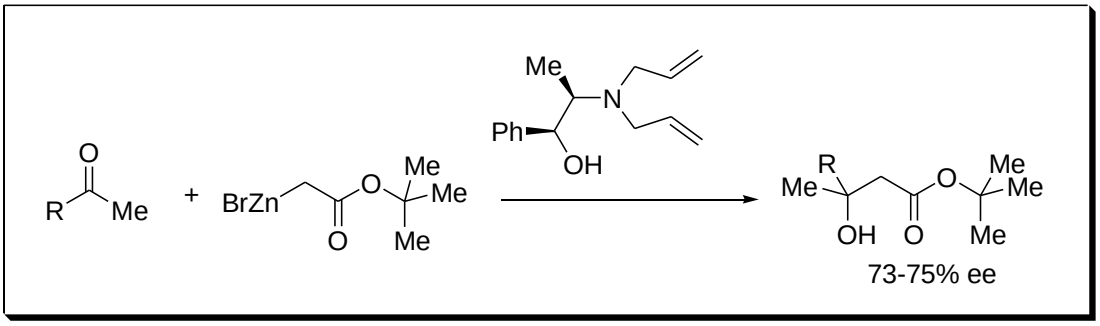
3.7.3 Reactions with Zinc Reagents

Organozinc reagents react with the aldehydes in the presence of a chiral ligand to form the corresponding alcohol enantioselectively. In this case, first the organozinc reagent reacts with the chiral ligand to form a chiral alkylating species that reacts with aldehydes (Scheme 5).



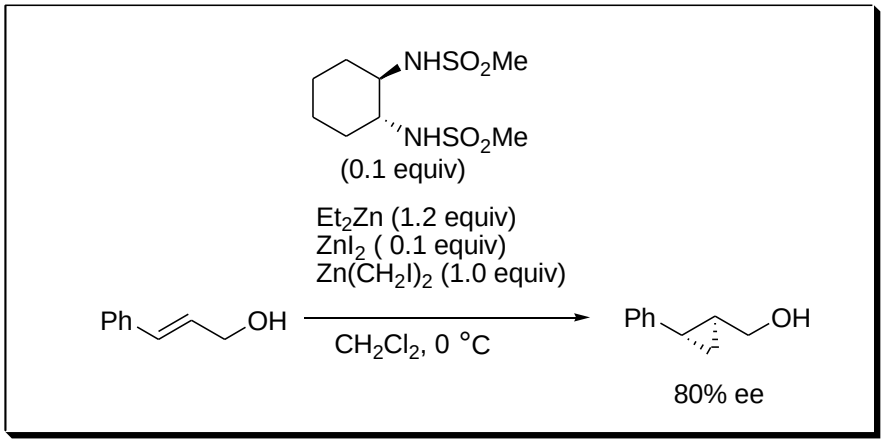
Scheme 5

On similar lines the enantioselective addition of a Reformatsky reagent to an aldehyde or ketone in the presence of *N*,*N*-diallylnorephedrine or (1*S*,2*R*)-*N*,*N*-di-*n*-butylnorephedrine has also been achieved to afford corresponding β-hydroxyesters with up to 70% ee (Scheme 6).



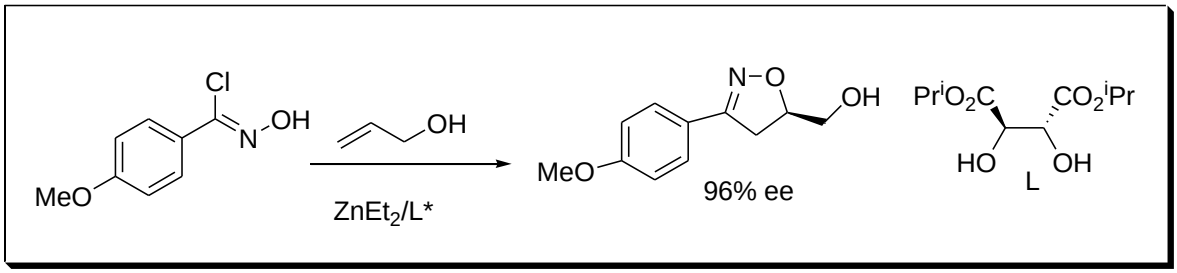
Scheme 6

Enantioselective cyclopropanation of *cis* and *trans*-allylic alcohols can be achieved by using a chiral ligand under Simmons-Smith reaction conditions (Scheme 7). In this case, the hydroxyl group on the substrate is necessary to coordinate with Zn.



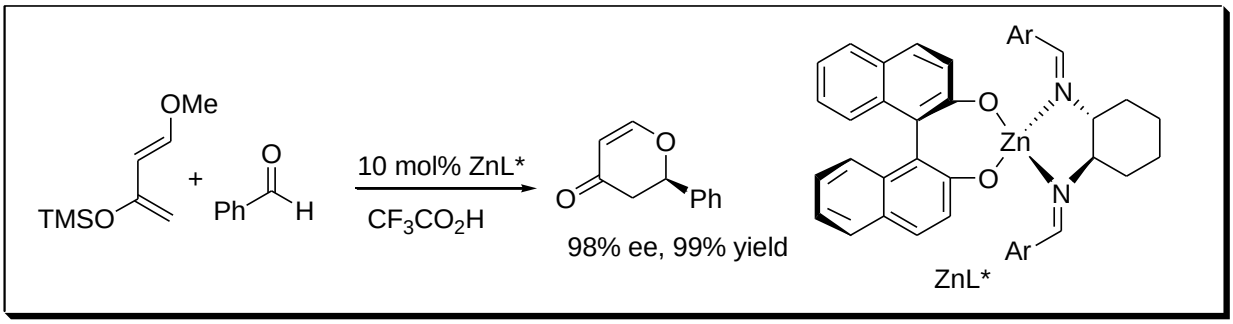
Scheme 7

Several studies have focused on the use of chiral Zn(II)-complexes for cycloaddition reactions. The complex derived from Et_2Zn and (*R*,*R*)-diisopropyltartrate can be used for the cycloaddition of hydroxylimine with allylic alcohols to afford dihydroisoxazole in 96% ee (Scheme 8).



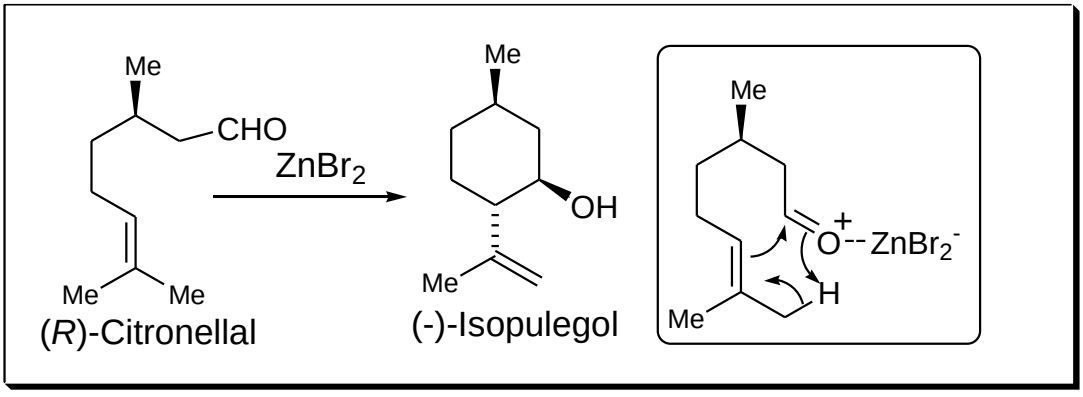
Scheme 8

Chiral Zn(II)-complex derived from (*R*,*R*)-BINOL and Schiff base derived from (*R*,*R*)-cyclohexane-1,2-diamine can be used for hetero Diels-Alder reaction of aryl aldehydes with 1,3-diene to give 2,3-dihydropyra-4-one derivative with excellent enantioselectivity (Scheme 9).

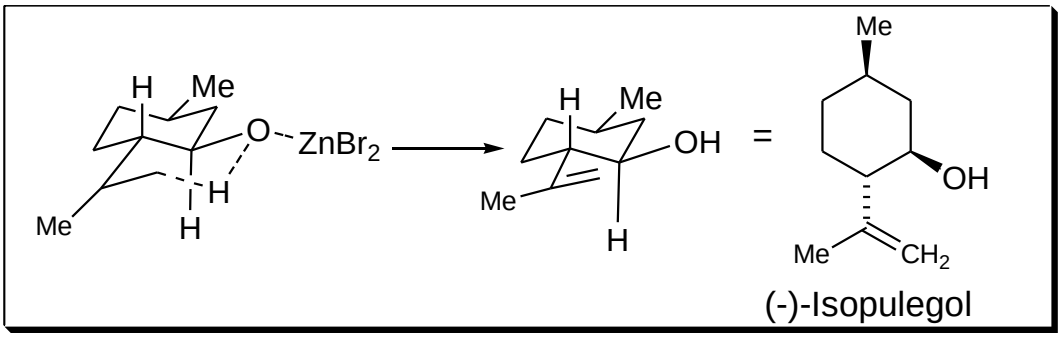


Scheme 9

The industrial process for the transformation of (*R*)-citronellal to (-)-isopulegol uses $ZnBr_2$, which takes place *via* ene reaction (Scheme 10-11).

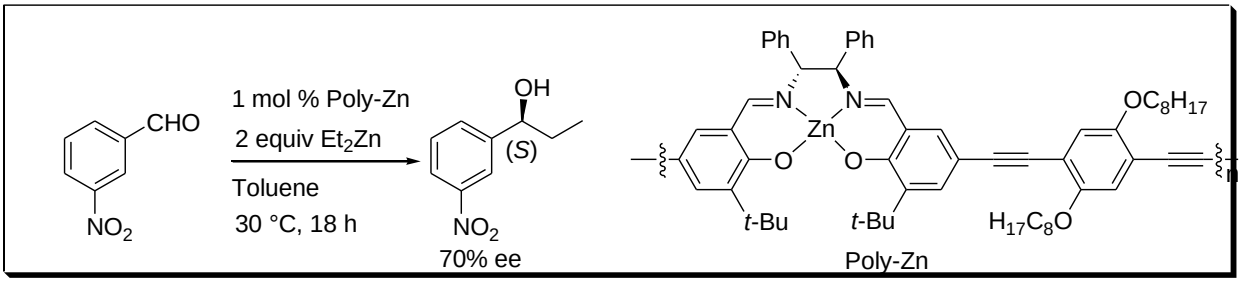


Scheme 10



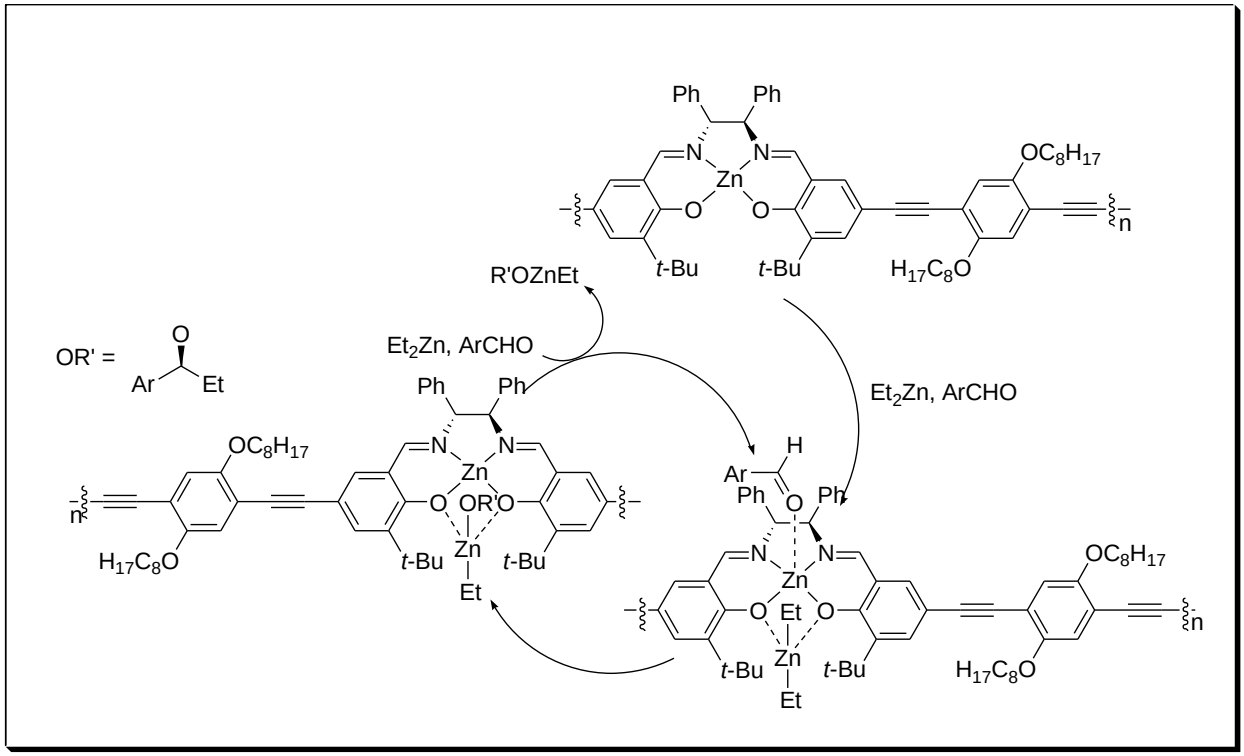
Scheme 11

Polymer based catalysts have also been developed for the addition of Et_2Zn to aldehydes with good to excellent enantioselectivity. For example, chiral 1,2-diamine based polymer has been used with Et_2Zn as recyclable catalyst for the Et_2Zn addition to aldehydes (Scheme 12-13).



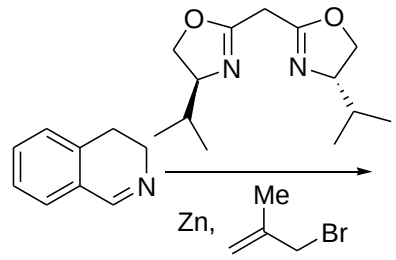
Scheme 12

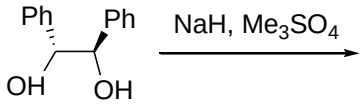
Mechanism

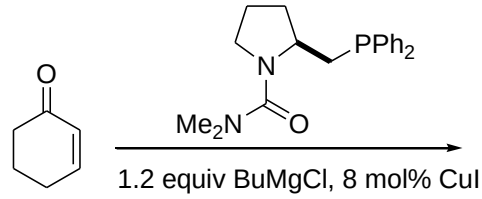


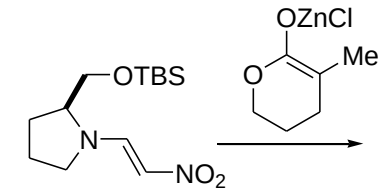
Scheme 13

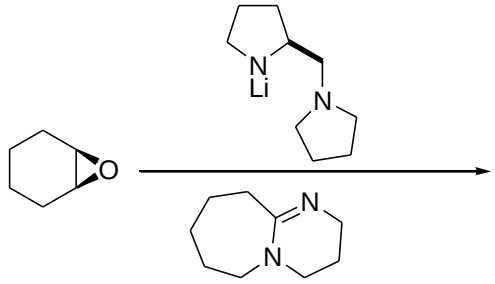
Problems

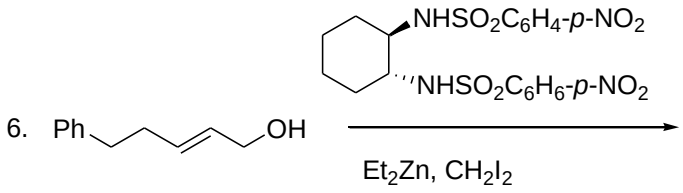
1. 

2. 

3. 

4. 

5. 

6. 

Text Book

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