

Principles of Organic synthesis
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Lecture 7
Organometallic Reagents

Welcome you all to principles of organic synthesis. So far we have studied the formation of carbon-carbon bond using acid as well as base as the catalyst or reagent. Today we will start a new module where you will study the formation of carbon-carbon bond using organometallic reagents.

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Principles

- ❖ Carbon atom bonded to an electronegative element is positively polarized. The carbon is susceptible to react with nucleophile.

$$\text{CH}_3\text{I} + \text{OH}^- \rightarrow \text{HO-CH}_3 + \text{I}^-$$

$\text{C} = 2.5$, $\text{I} = 2.7$
 $\text{C} = 2.5$, $\text{O} = 3.5$
- ❖ Carbon atom bonded to an electropositive element - a metal - is negatively polarized. Because metal can donate a bonding electron-pair to form a cation. The carbon is susceptible to react with electrophile.

$$\text{R}_3\text{N} + \text{CH}_3\text{-Mg-Br} \rightarrow \text{R}_3\text{N}^+-\text{C}^-(\text{MgBr})\text{H}_3$$

$\text{C} = 2.5$, $\text{Mg} = 1.3$
 $\text{C} = 2.5$, $\text{O} = 3.5$
- ❖ Organometallic compounds are versatile reagents. Their reactivity depends on the nature of the metal atom.

$$\text{Me-Li} \quad \text{Me-Mg-Br}$$

The principles of the formation of carbon-carbon bond using organometallic reagents are shown here. As all of you know, when a bond is polarized it can readily react with electrophile and nucleophile. For example, you take methyl iodide and acetone, and look at the electronegativity of carbon (2.5), iodine (2.7) and oxygen (3.5). In methyl iodide, iodine is more electronegative compared to carbon, therefore, the bond pair is polarized towards iodine. In other words, the carbon is electrophilic. Similarly, when you look at acetone, oxygen is more electronegative compared to carbon. Therefore, the pi-bond pair is polarized towards oxygen. In other words, the carbon is electrophilic.

Thus, when you react with a nucleophile, for example, hydroxide ion, it can readily undergo substitution reaction with the carbon to produce methanol as the product. Similarly, if you react acetone with, for example, amine, it can undergo addition reaction to give salt as a product.

Now let us compare with organometallic reagents, for examples, methyl magnesium bromide and methyllithium. Electronegativity of lithium is 1 and magnesium is 1.3. Already, we know the electronegativity of carbon as 2.5. Thus, the bond pair is polarized towards carbon. So whenever the carbon is bonded with electropositive element the bond pair is polarized towards carbon. Therefore, the methyl group can act as a nucleophile. For example, it can undergo substitution reaction with methyl iodide to give ethane as the product. If you react with acetone, it can undergo addition reaction as we have seen earlier to generate tertiary butanol as the product.

If you compare the reactivity of methyllithium with methyl magnesium bromide, the former shows greater reactivity compared to the latter, because Li-C bond is polarized greater extent compared to Mg-C bond. In summary if the carbon is bonded with the electronegative element, the carbon is positively polarized and can readily undergo reaction with the nucleophiles. On the other hand, if the carbon is bonded with an electropositive element, the carbon is negatively polarized and can act as a nucleophile or base. In case of organometallic reagents, the reactivity of the reagents depends upon the nature of the metal atom present in the reagent.

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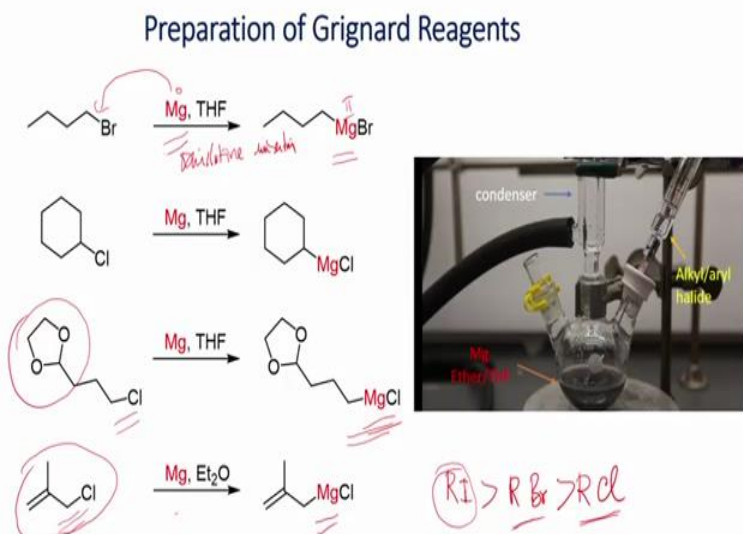
Organomagnesium Compounds (Grignard Reagents)



Victor Grignard
(1871 – 1935)

Now let us look at the reaction of Grignard reagent. An example is shown here, isopropyl chloride undergoes reaction with magnesium to give isopropyl magnesium chloride, which leads to addition reaction with aldehyde to give secondary alcohol as the product. Where you generate a new carbon-carbon bond between the carbon of the isopropyl chloride and carbonyl carbon, which is shown in red colour.

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Now let us look at the preparation of the Grignard reagents. First example involves the reaction of butyl bromide with magnesium to give butyl magnesium bromide. Next example involves the reaction of cyclohexyl chloride with magnesium to give cyclohexyl magnesium chloride.

The next example involves the reaction of alkyl chloride with the magnesium where you can see the presence of acetal functional group which is stable in basic conditions. You can readily react this alkyl chloride without affecting the acetal functional group to give the alkyl magnesium chloride. Similarly, you can react the allyl chloride with the magnesium to give the allyl magnesium chloride.

If you look at these halides, allyl chloride shows greater reactivity compared to alkyl chloride. In addition, if you see the reactivity order of the alkyl halides, alkyl iodide shows greater reactivity compared to alkyl bromide, which shows greater reactivity compared to alkyl chloride.

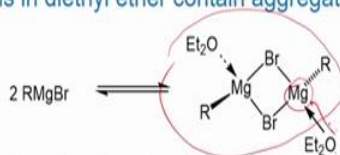
Here an experiment is shown, where you can see the preparation of the Grignard reagent. The reagent is sensitive to moisture and air. Therefore, we have to carry out the reaction under dry conditions. Since the reaction is exothermic, you have to attach condenser with water circulation, which is connected to an inert atmosphere. Through the side neck, alkyl or aryl halide, which is dissolved in solvent, is added.

You have to take a pure magnesium. One of the ways is, you can try to wash using the dilute hydrochloric acid and then with the water and dry well. You have to calculate the amount solvent is needed. Because too much concentration can lead to self-coupling. You take the magnesium turnings and add little solvent. Then, add halide in solvent drop wise and to form the Grignard reagent. This can be added to electrophile to give the substitution or addition products.

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Properties of Grignard Reagents

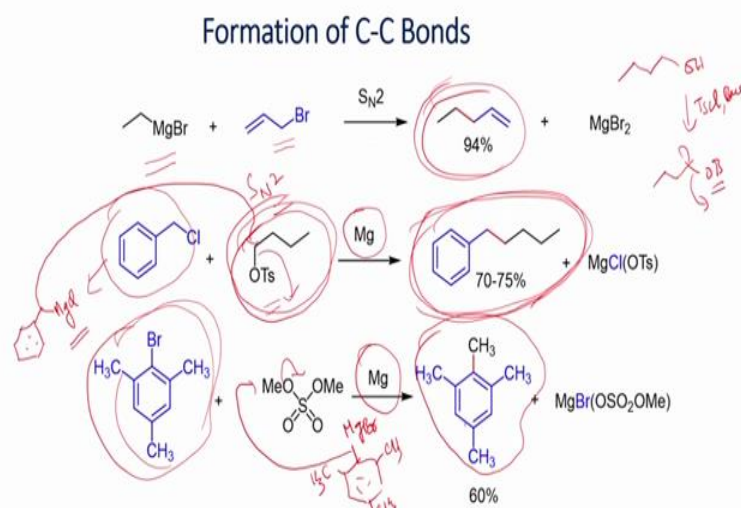
- ❖ Strong alkalis. Thus, they react with compounds which can supply H^+ ions
- ❖ Strong nucleophiles
- ❖ Should be kept in dry environment (in dry ether). If moisture or water is contact, it is destroyed
- ❖ Solutions in diethyl ether contain aggregated species



- ❖ In THF, there is a less tendency to aggregate, and several alkyl and aryl Grignard reagents are found to be monomeric

Grignard reagents are basic in nature. They are strong nucleophile and undergo substitution and addition reactions. They are sensitive to air or moisture. Thus, you have to keep them in a dry environment. They exist in an aggregated form, which are stabilized by the solvent. Usually, we use THF or ether as the solvent. The lone pair of the ether can make chelation with magnesium and stabilize the reagent.

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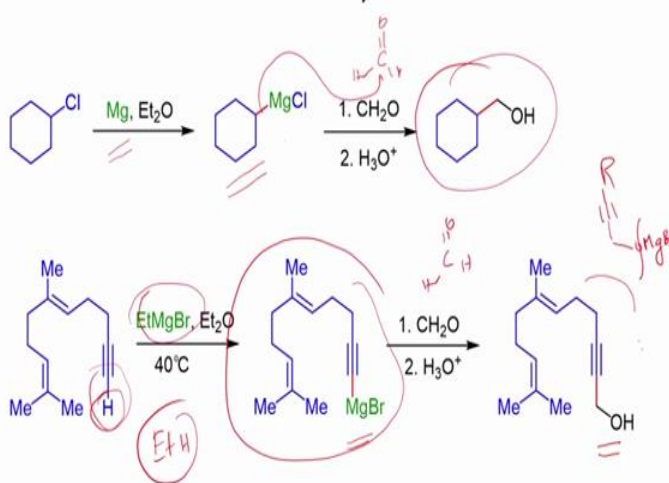


Now let us look at the reaction of Grignard reagents. The first example involves the substitution reaction. If you look at here, ethyl magnesium bromide undergoes reaction with allyl bromide by $\text{S}_{\text{N}}2$ path way to give the alkene as the product. The next example involves the coupling of benzyl chloride with the tosyl derivative to give alkyl benzene in the presence of magnesium. Benzyl chloride first reacts with magnesium to give benzyl magnesium chloride and then reacts as nucleophile vis $\text{S}_{\text{N}}2$ path way to give the alkyl benzene as the product. This is is good example, if you have alcohol, you can convert to the tosyl derivative and can be reacted with the Grignard reagent.

The next example involves the reaction of bromotrimethylbenzene with dimethyl sulfate in the presence of magnesium. The reaction of bromotrimethylbenzene with magnesium gives the trimethylphenylmagnesium bromide that undergoes substitution reaction as sulfate is very good leaving group to produce tetramethylbenzene as the product.

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Formation of Primary Alcohols



Now let us look at the application of Grignard reagents for the formation of primary alcohol. If we have alkyl chloride, for example, cyclohexyl chloride, which can react with magnesium to form cyclohexyl magnesium chloride. Which can undergo reaction with formaldehyde to generate this primary alcohol as the product.

The next example involves the reaction of alkyne with formaldehyde to give propargylic alcohol. In this reaction, ethyl magnesium bromide undergoes reaction with the terminal alkyne to give Grignard reagent via the deprotonation of the acidic hydrogen. Which can undergo addition reaction with formaldehyde to give propargylic alcohol as the product.

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Formation of Secondary Alcohols

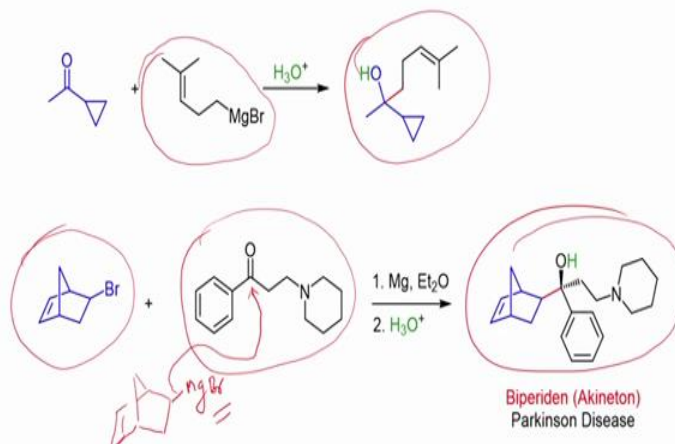


The next example involves the reaction of aldehydes with Grignard reagent to give secondary alcohol. In this reaction, the aldehyde with vinyl magnesium bromide gives the allylic alcohol.

The second example involves the reaction of methyl magnesium chloride with α,β -unsaturated aldehyde. The reaction undergoes selectively at the carbonyl carbon to give the secondary alcohol as the product. Similarly, you can react acetaldehyde with isopropyl magnesium chloride to give the corresponding alcohol as a product. So Grignard reagent can readily undergo addition reaction with aldehydes to give the corresponding alcohols as the products.

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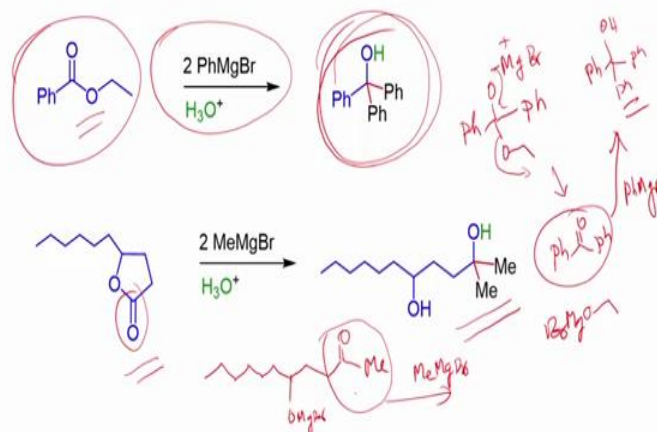
Formation of Tertiary Alcohols



Now let us look at the reaction with the ketones. The first example involves the reaction of methyl cyclopropyl ketone homoallyl magnesium bromide to give the tertiary alcohol as the product. The next example involves the reaction of the bicyclic bromo derivative with the ketone. When you react the alkyl bromide with magnesium you will be able to generate the magnesium bromide, which can undergo the addition reaction with ketone to give the tertiary alcohol as the product which is an important molecule as we use for the Parkinson disease.

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Formation of Tertiary Alcohols



The next example involves the reaction of ester with phenyl magnesium bromide. In this reaction, the ester reacts with phenyl magnesium bromide to generate the tertiary alcohol as the product. First Grignard reagent undergoes 1,2-addition reaction with the ester to provide benzophenone, which can undergo further reaction with another equiv of the Grignard reagent to the tertiary alcohol as the product. Thus, two equiv of the Grignard reagent is required in the reaction with the ester to generate selectively the tertiary alcohol as the product.

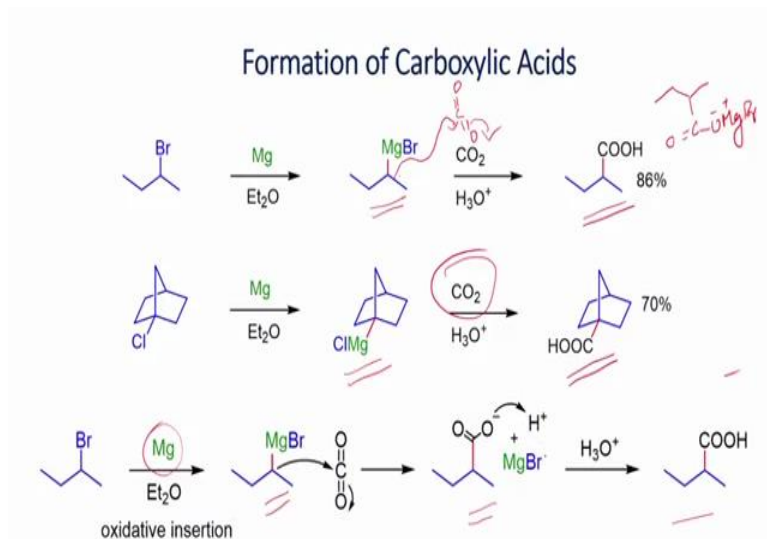
The next example involves the reaction of lactone with 2 equivalent of methyl magnesium bromide. Reaction of the methyl magnesium bromide with the carbonyl group can generate the ketone. Which can undergo further reaction with another equiv of methyl magnesium bromide to generate the tertiary alcohol as the product.

If you look at the reactivity of the ketone and ester, ketone is more reactive compared to ester. Therefore, as soon as, you form the ketone, which can readily undergo a reaction with Grignard reagent compared to ester. Thus, using an excess Grignard reagent, you can readily convert ester to tertiary alcohol as the product.

So far we have seen three types of reactions for the formation of alcohols. If you have formaldehyde you can try to react with the Grignard reagent to generate the primary alcohol as the product. If you have substituted aldehyde you can try to react to generate secondary alcohol as a product. On the other hand, ketone can undergo the reaction to form tertiary alcohol as the

product. In addition, ester or lactone can undergo the reaction with the excess Grignard reagent to produce tertiary alcohol as the product.

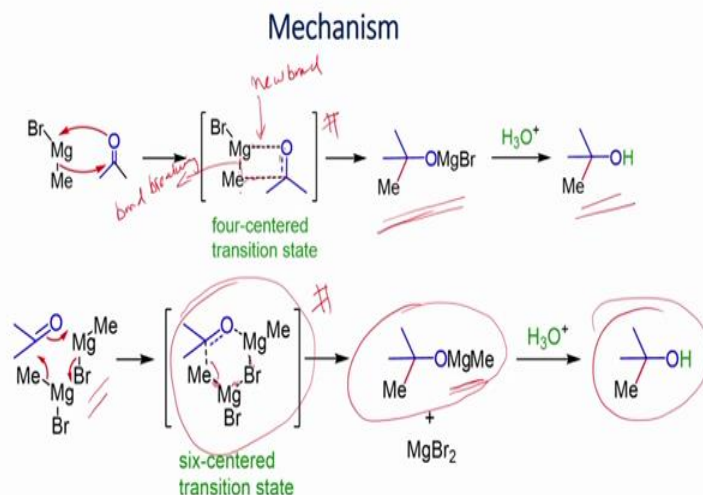
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Now let us look the reaction with carbon dioxide. The first example involves the reaction of alkyl bromide with magnesium to generate the alkyl magnesium bromide, which reacts with carbon dioxide to give the carboxylic acid as the product.

Similarly, the bicyclic chloride derivative with magnesium gives the alkyl magnesium chloride, which can readily undergo reaction with carbon dioxide to generate the bicyclic carboxylic acid. The mechanism of is here shown. Alkyl bromide undergoes oxidative insertion with magnesium to give the alkyl magnesium bromide, which undergoes addition with carbon dioxide to give the salt that can be converted into carboxylic acid using proton source.

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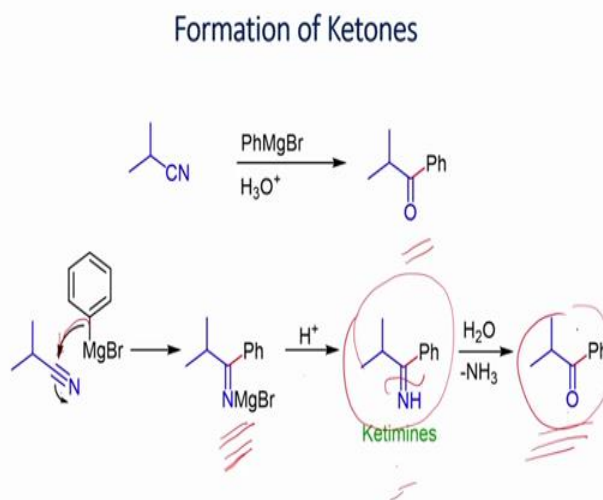


There are two possibilities when you go for the mechanism of the reaction of the Grignard reagent with the carbonyl compounds. The first one involves the bond breaking and bond formation between magnesium and methyl group as well as methyl group and the carbonyl carbon at the same time. What you do here is you make a new bond between magnesium and oxygen. The same time we also break this old bond between the magnesium and methyl group and you also form the new bond between the magnesium and carbonyl carbon. You also break the pi bond between the oxygen and carbonyl carbon. This may take place as shown in the transition state via the constructed path way. Both the simultaneous bond breaking and bond formation can generate the alkoxy magnesium bromide, which can be converted to the alcohol after the work up.

The other possibility is that two molecule of the Grignard reagent can involve as shown here through the six membered transition state. In this case, you generate that magnesium derivative and magnesium bromide, which when you do the work up you will be able to form the alcohol.

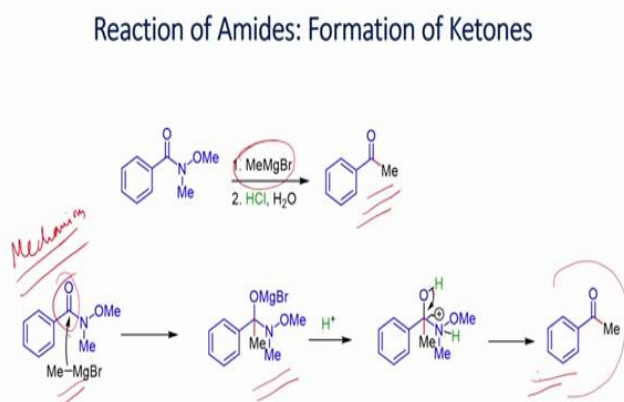
So the first one involves the four centered transition state and the second one involves the six centered transition state. However, the mechanism is complicated as there are some other possibilities for the addition of the Grignard reagent to the carbonyl compounds.

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The next one is the reaction of nitrile. If we have the nitrile that can undergo reaction with Grignard reagent to give the ketone as the product. The mechanism of is here shown. Grignard reagent can undergo addition with nitrile in triple bond can to generate the ketimine, which on hydrolysis gives the ketone as the product.

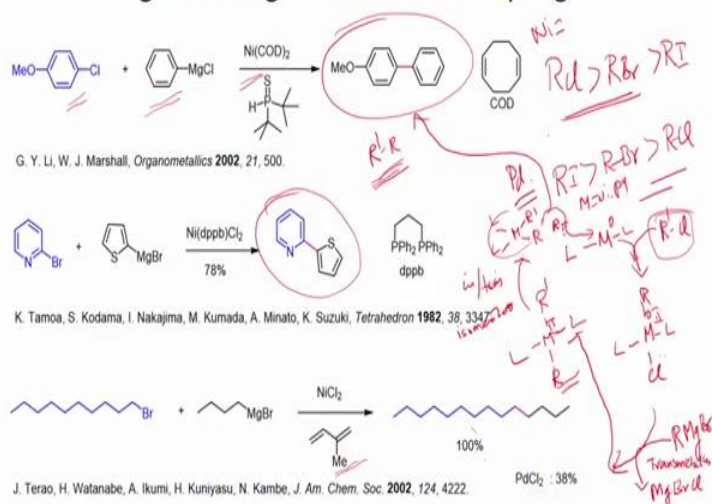
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In place of nitrile you can also use amide to produce ketone. Amide can react with magnesium bromide to give the ketone. The mechanism involves the addition the Grignard reagent to the amide carbonyl group to give the tetrahedral intermediate, which on protonation during work up produces the ketone as the product.

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Grignard Reagents: Kumada Coupling



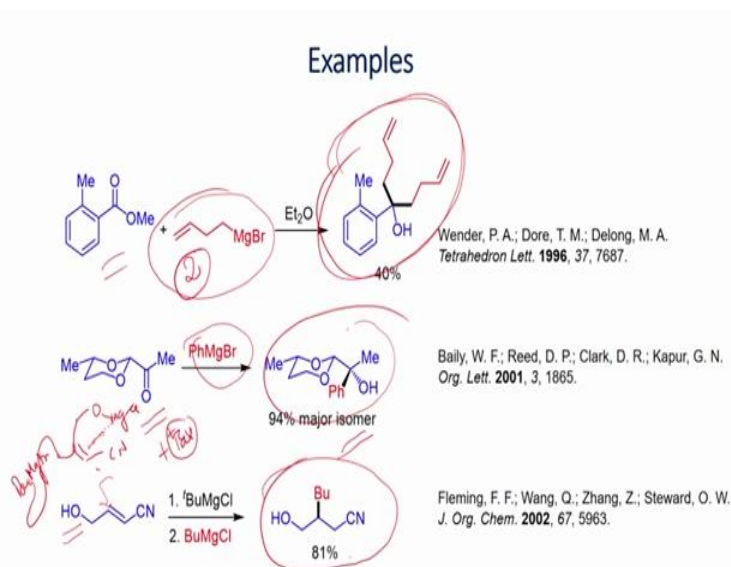
So far we seen some of the common reactions. In addition, in recent years, Grignard reagent finds the important place in cross-coupling reactions for the carbon-carbon bond formation. If we look at the first example, it involves the coupling of 4-methoxychlorobenzene with phenyl magnesium chloride in the presence of nickel cod complex to give the biphenyl derivative. The next example shows the coupling of the heterocyclic systems, where reaction of 2-bromopyridine with 2-thiophenyl magnesium bromide gives the C-C coupled product in the presence of nickel through complex.

The third example involves the coupling of alkyl magnesium bromide with alkyl bromide. This nickel-catalysed reaction is found to be effective in the presence of 1,3-butadiene. You can also carry out the C-C coupling reaction using palladium as the catalyst.

When you look at the reactivity order, when you use nickel as the catalyst, the chloro derivative shows the greater reactivity compared to bromo and iodo compounds. For example, if we have the alkyl chloride, which shows greater reactivity compared to alkyl bromide that is more reactive compared to alkyl iodide. On the other hand, when you use palladium as the catalyst, the reactivity order is reverse, which shows alkyl iodide greater reactivity compared to the alkyl bromide, which is more reactive compared to the alkyl chloride.

If you look at here, first the metal undergoes oxidative addition with the halo derivative to form the intermediate. Which undergoes reaction with the Grignard reagent through transmetalation to generate the intermediate that leads cis/trans isomerization. The latter can give the product and regenerate the catalyst by reductive elimination to complete the catalytic cycle. This reaction has been widely used in synthetic chemistry to couple alkyl or aryl halide with the Grignard reagent to make variety of compounds.

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From the recent literature some examples are here shown. The reaction of an excess of homoallyl magnesium bromide with the ester gives the tertiary alcohol as the product.

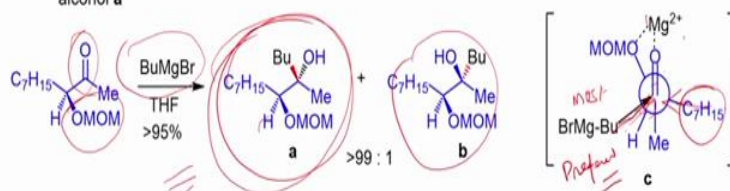
The next example involves the reaction of phenyl magnesium bromide with the ketone to generate tertiary alcohol in quantitative yield.

The third example involves the reaction of the conjugated nitrile with tert-butyl magnesium chloride to give the conjugate addition product.

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Stereochemistry

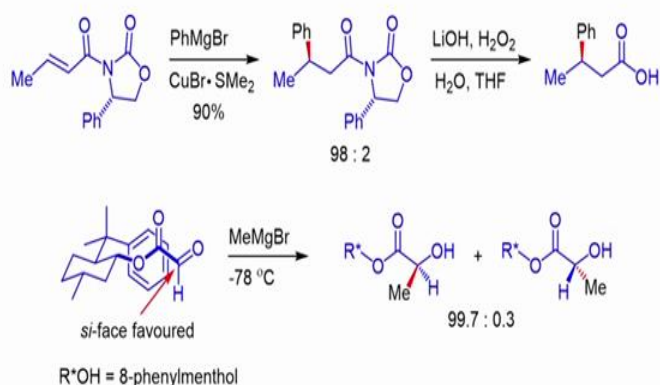
- ❖ Addition of Grignard reagent to chiral aldehyde or ketone can be stereoselective for the **Cram** or chelation-controlled product
- ❖ When a heteroatom is present at the carbon atom, then chelation often dominates
- ❖ Addition to alkoxy ketones gives the cyclic chelate, represented by the **Newman projection c** and therefore favours the formation of the chelation-controlled product alcohol **a**



If the carbonyl carbon is bonded to a chiral carbon, you can generate a new stereogenic centre diastereoselectively. In this example, the chiral carbon is bonded with heteroatom. Grignard reagent chelates with the carbonyl group as well as OMOM substituent to form the conformation **c**. Addition of the Grignard reagent through the sterically less hindered side adds to the carbonyl group can lead the formation of **a** as the major product. This is an example for the chelation controlled reaction.

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Stereoselectivity using Chiral Auxiliaries



Here the first example involves the conjugate addition. The next example involves the addition to aldehyde. You have the chiral centre and the back side is blocked by the phenyl group. Thus, the Grignard reagent approaches from the top face that leads the selectivity.

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Summary

- ❖ Principles of the reaction of organometallic reagents
- ❖ Preparation of Grignard Reagents
- ❖ Application of Grignard Reagents
- ❖ Transmetallation
- ❖ Diastereoselectivity

In summary, we have seen the principles of the reaction of organometallic reagents for carbon-carbon bond formation. If the carbon is bonded with the electronegative atom, which can act as

an electrophile. On the other hand, if the carbon is bonded with the electropositive element that can act as a base or nucleophile.

Next, we have seen the preparation of Grignard reagent that involves an oxidative addition of magnesium with alkyl or aryl halide. The reagent is basic in nature, air and moisture sensitive, and can act as a nucleophile. We have seen the application in organic synthesis. First we have seen the substitution reactions. If we have alkyl, aryl halide or a substrate having good leaving group, you can try to react with Grignard reagent via substitution to make carbon-carbon bond. Grignard reagent can be utilized for the addition reaction with aldehydes, ketones and esters to form alcohols. We have also seen reaction with nitrile and amides to form ketones as well as reaction with carbon dioxide to give carboxylic acid.

We have then seen their application C-C cross-coupling reaction. For examples, Grignard reagent can be coupled with alkyl or aryl halides via transmetalation using nickel and palladium based catalyst systems.

Finally, stereoselective addition of Grignard reagent to aldehydes bearing chiral centres has been discussed. These reactions depend on the nature of the substituents and the Grignard reagent can add one of these face selectively to generate a new stereogenic centre with diastereoselectivity. This depends on the substituent as well as chelating group present in the substrate. With these, we conclude this lecture. Thank you very much!