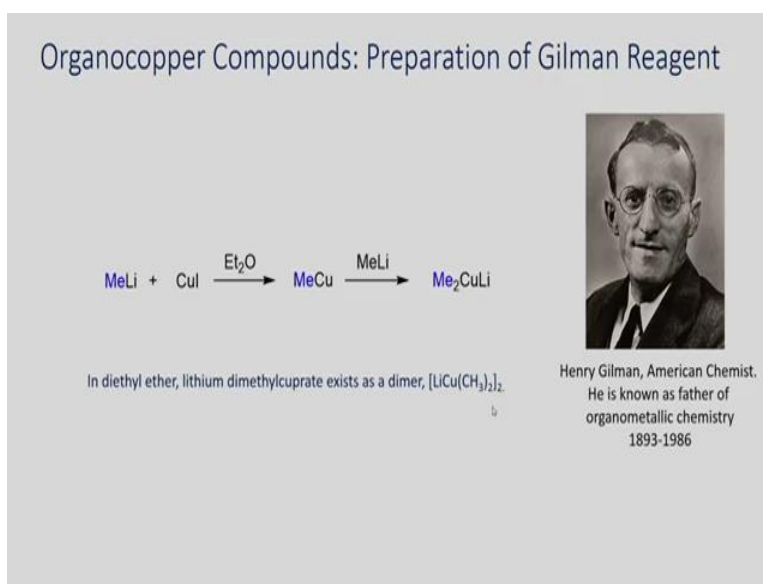


**Principles of Organic synthesis**  
**Professor T Punniyamurthy**  
**Department of Chemistry**  
**Indian Institute of Technology Guwahati**  
**Lecture 9**  
**Organometallic Reagents**

Welcome you all to organometallic reagents. In this module, we had two lectures. In the first lecture, we studied Grignard reagents, and the second lecture focused on organolithium reagents. In this lecture, we will cover organocopper, organozinc and oxymercuration-demercuration reactions.

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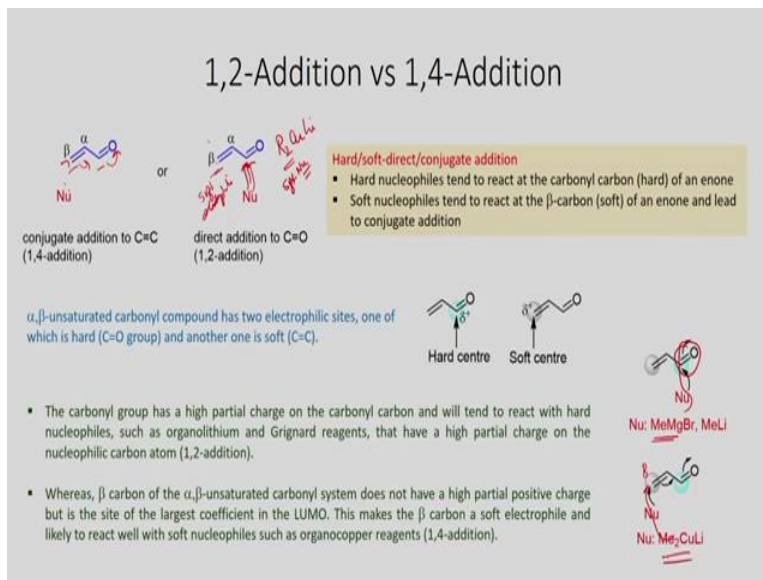


Here the preparation of organocopper reagent is shown. When you react alkyl or aryllithium with copper(I) iodide, you can generate organocopper, which can further undergo reaction with organolithium to give the Gilman reagent. Professor Gilman is known as father of organometallic chemistry.

In this example, methyllithium undergoes reaction with copper(I) iodide in diethyl ether to give methyl copper complex, which undergoes further reaction with methyllithium to give the dimethyl organocuprate. The reagent exists as a dimer in diethyl ether. In place of methyl group, you can also have other alkyl (primary, secondary, tertiary), alkenyl and aryl groups. They can undergo reaction with copper(I) iodide to give the corresponding organocopper complex, which

can be further reacted with another equiv of organolithium reagent to give the respective Gilman reagent. This is also known as lower-order cuprate.

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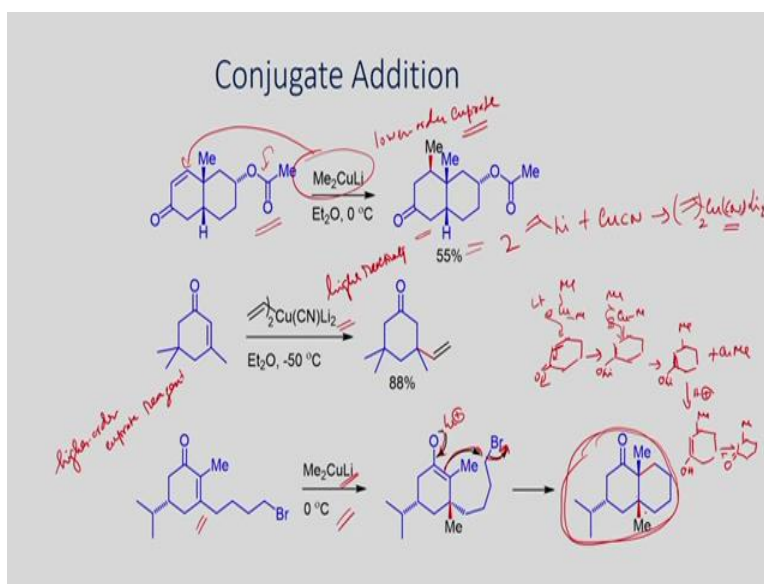


Now, let us look at the reactivity of the Gilman reagent. If you look at  $\alpha,\beta$ -unsaturated carbonyl compound, you can see there are two electrophilic centers, this is a hard (carbonyl carbon) electrophile and this is a soft ( $\beta$ -carbon) electrophile. If you remember organomagnesium or organolithium compounds (strong nucleophile), they undergo 1,2-addition with carbonyl group (hard electrophile) to give the addition product.

However, when you use the Gilman reagent, the reaction takes place at the  $\beta$ -carbon (soft electrophile). Because the Gilman reagent is a soft nucleophile, and undergoes reaction with the soft electrophile. Therefore 1, 4-addition is favored in the case of Gilman reagent.

Thus, methylmagnesium bromide or methyllithium readily undergoes reaction with carbonyl group. On the other hand, Gilman reagent reacts at the  $\beta$ -carbon to give the 1,4-addition product. Further, cuprate reagent does not react with ester or amide, whereas Grignard/organolithium reagent reacts, which are the differences between the Gilman and organomagnesium or organolithium reagents.

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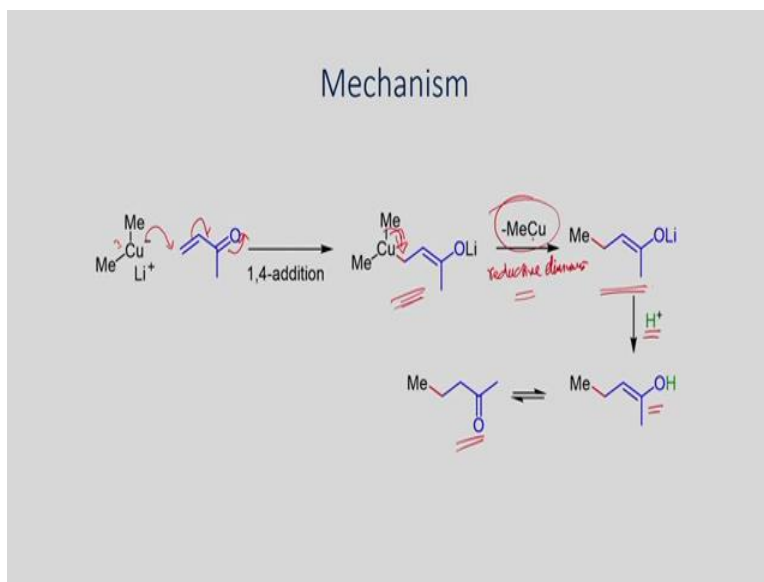
Let us look at the application part. If you look at the first example, dimethylcuprate undergoes 1,4-addition reaction in 55% yield. The reaction involves copper(III) intermediate, which undergoes reductive elimination to give the product.

The next example involves the reaction using the higher order cuprate, which shows slightly greater reactivity compared to the lower order cuprate. Higher order cuprate can be prepared from two equiv of organolithium and copper(I) cyanide. In which, cyanide is not bonded with the copper.

The another example involves the reaction of dimethyl cuprate with  $\alpha,\beta$ -unsaturated ketone. The addition reaction gives the enolate, which leads to  $\text{S}_{\text{N}}2$  substitution to give the bicyclic ketone as the product. The asymmetric version of the reactions has also been considerably done.

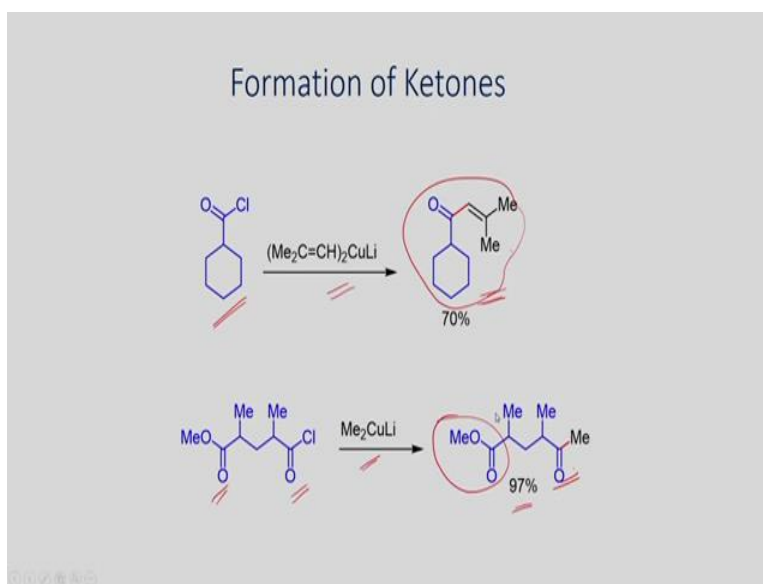
For your understanding I have taken three simple examples. In the first example, the ester group is intact, so you can try to selectively react with the  $\alpha,\beta$ -unsaturated double bond and through 1,4-addition you can get the addition compound. So this is different from the Grignard reaction, where the ester also undergoes reaction but under this condition since methyl of dimethylcuprate is less nucleophilic in nature, selectively it undergoes the 1,4-addition to get the addition product.

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Mechanism of the conjugate addition is shown here. Addition of dimethylcuprate can give the copper(III) intermediate. This can lose MeCu to produce the lithium enolate via the reductive elimination. When you do the workup you will be able to protonate the enolate, which can isomerize to the ketone. This is how the reaction takes place. So in this reaction, if you look at, we generate one equiv of MeCu as a by-product.

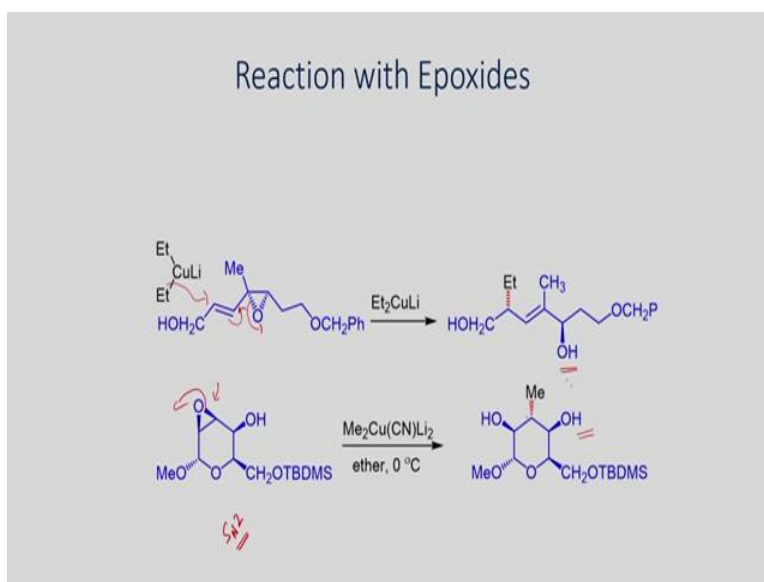
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Here the reaction of acid chloride into ketones is shown. You can also try to react Gilman reagent with acid chloride to give the ketone. Vinyl cuprate with cyclohexyl chloride gives the cyclohexyl vinyl ketone as the product.

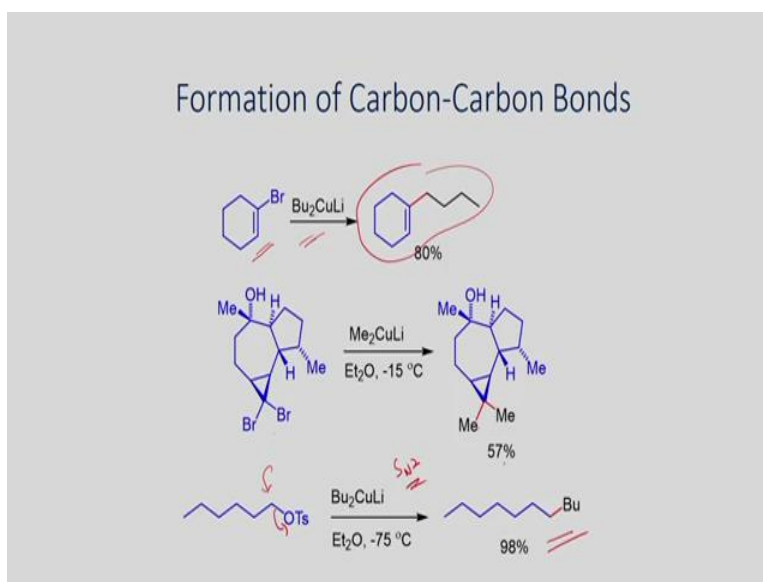
Similarly, the acid chloride which also has ester functional group can be reacted with dimethyl cuprate to give the ketone as the product. These are important transformations because you cannot make these compounds using organomagnesium, or organolithium reagents.

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The next example is the reaction with epoxides. You can also carry out the opening of the epoxide. In this case, the reaction takes place at less hindered side and stereospecifically you can open to get the alcohol as a product. Similarly, you can open up the epoxide via S<sub>N</sub>2 pathway, the product stereospecifically. The Gilman reagent approaches from the less sterically hindered side. And you will be able to form the corresponding alcohol as the product.

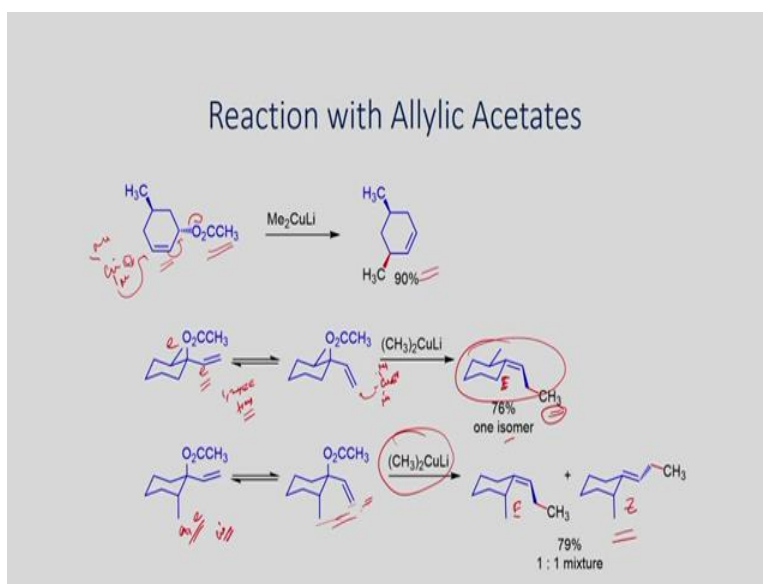
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Here the substitution reactions are shown. The reaction of vinyl bromide with dibutylcuprate gives the C-C coupled product. Similarly, the gem-dibromo derivative with dimethylcuprate gives the gem-dimethyl derivative. Further, organocuprate can be reacted with tosyl derivative via  $\text{S}_{\text{N}}2$  pathway. You will be able to form the long-chain alkyl molecule in good yield.

So far we have seen three types of reactions. First we have seen the conjugate addition reaction, then we have seen the opening of epoxides and acid chloride. You can also carry out the coupling of vinyl or alkyl halides or alkyl tosylate with organocuprates in good yields.

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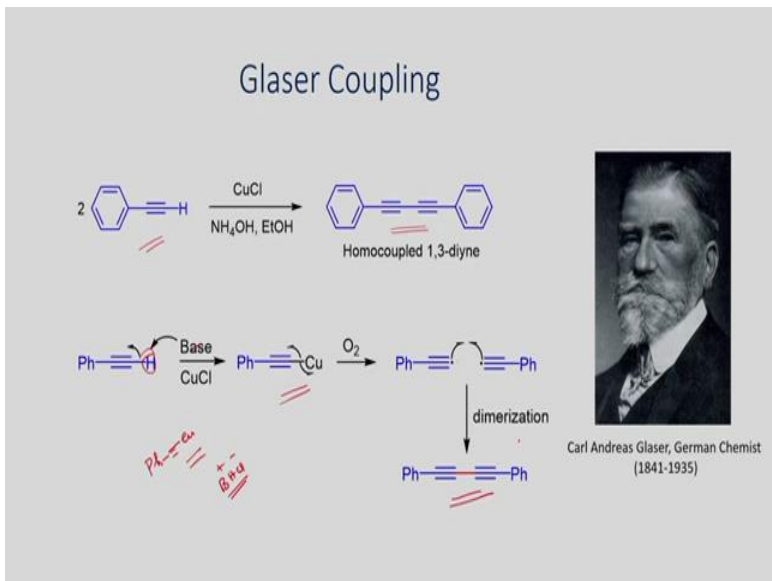
You can also carry out reaction with allylic acetates. Some examples are here shown. If you look at the first example, dimethylcuprate approaches the opposite side of the acetate group to give the product with the excellent stereochemistry.

The next example involves the reaction of dimethylcuprate with 2-methyl-1-vinylcyclohexyl acetate. If you look at the substituents at the equatorial position, the reaction of dimethyl cuprate will produce a single isomer in good yield.

On the other hand, if you take methyl at axial and vinyl at equatorial, and it exists in an equilibrium as shown here, they can undergo reaction with dimethylcuprate to give a mixture of alkenes. If you look at you get a 1:1 mixture of *E* and *Z* geometrical isomers.



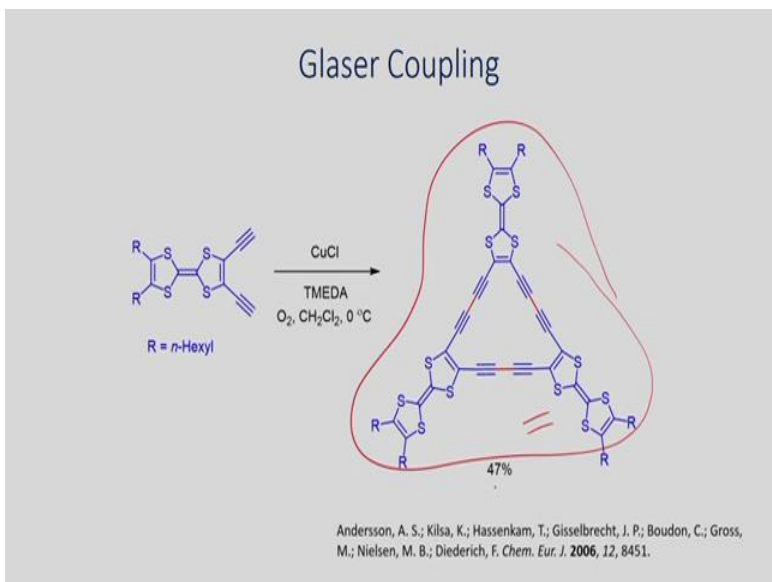
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Next, let us go for the Glaser coupling. If you have a terminal alkyne, you can dimerize using copper(I) chloride in the presence of base under oxygen atmosphere. For example, if you take phenylacetylene, it can dimerize to give homocoupled 1,3-diyne as a product.

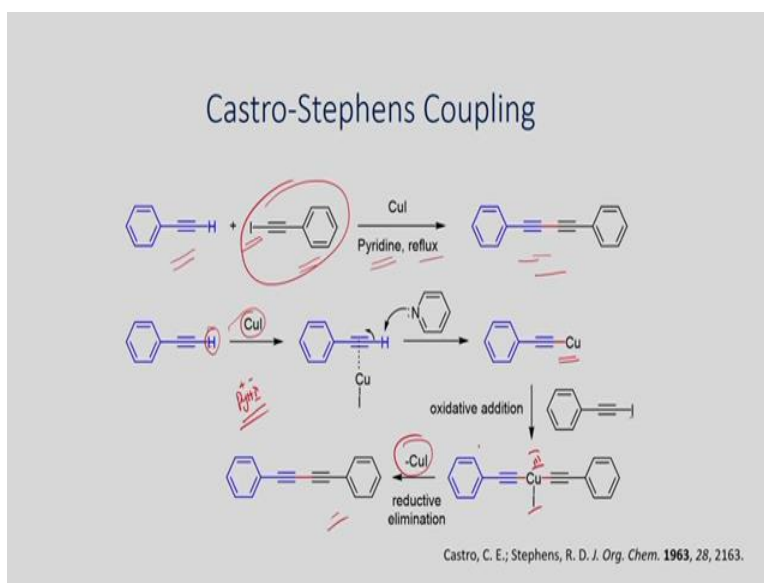
Deprotonation of this acidic hydrogen of alkyne and followed substitution with copper(I) chloride can generate the copper(I) acetylene, which can undergo homolytic cleavage to produce the alkynyl radical that can dimerize to the homocoupled product.

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Here an application of the homocoupling of alkyne is shown. For example, you can make the cyclic polyalkyne from dialkyne derivative using copper(I) chloride in the presence of DMEDA in dichloromethane at 0° C under oxygen atmosphere. You can try to trimerize to produce the macrocyclic molecule in 47 percent yield.

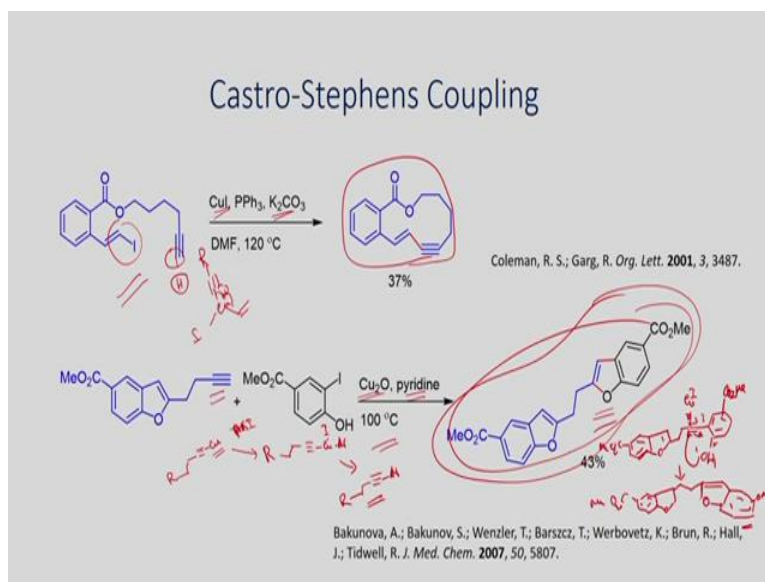
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Just we have seen the homocoupling of phenylacetylene. On the other hand, you can also carry the heterocoupling. For example, phenylacetylene can be coupled with (iodoethynyl)benzene using copper(I) iodide in the presence of base.

First, the base can deprotonate the acidic hydrogen, which can undergo substitution reaction with copper(I) iodide. Oxidative addition with (iodoethynyl)benzene can give the copper(III) intermediate, which can give the heterocoupled product by reductive elimination. So catalytic amount of copper(I) is sufficient to carry out the reaction. You can do heterocoupling of two different alkynyl derivatives under these conditions.

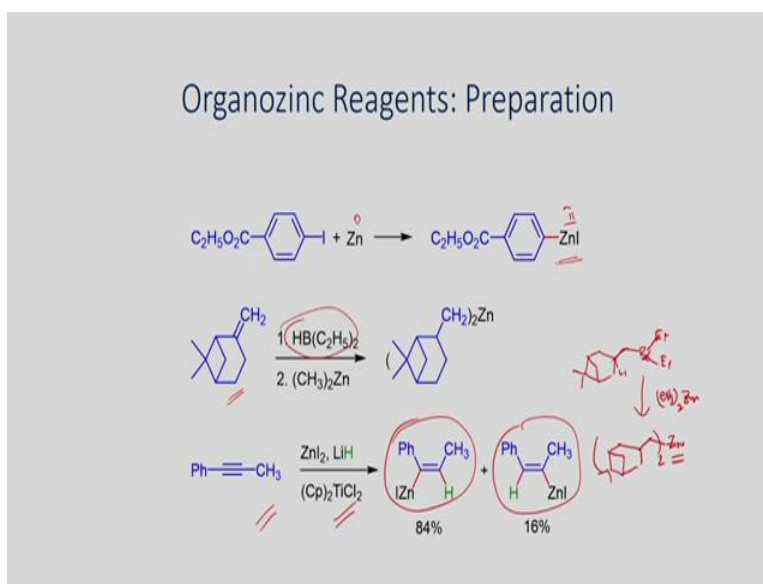
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Now let us look at an application of the Castro-Stephens coupling. For example, intramolecular coupling of alkyne with vinyl iodide is shown using copper(I) iodide in the presence of  $K_2CO_3$ . As we have seen just now, deprotonation of this acidic hydrogen by base and substitution with copper(I) iodide can generate copper(I) alkyne derivative, which can undergo oxidative addition with vinyl iodide to produce the copper(III) intermediate that can give the C-C coupled product by the reductive elimination.

In the second example, the intramolecular coupling of the terminal alkyne with aryl iodide is shown using copper(I) oxide in the presence of pyridine under heating. In this case, deprotonation of alkyne followed by reaction with Cu(I) can generate the alkynecopper(I) derivative, which can undergo oxidative addition with aryl iodide to give copper(III) intermediate. Reductive elimination can produce the C-C coupled product. Chelation of copper(I) with triple bond followed by intramolecular cyclization of the aryl OH group can lead to the formation of a benzofuran derivative. So far we have seen the reaction of organocopper reagents. Now let us move to the reactions of organozinc reagents.

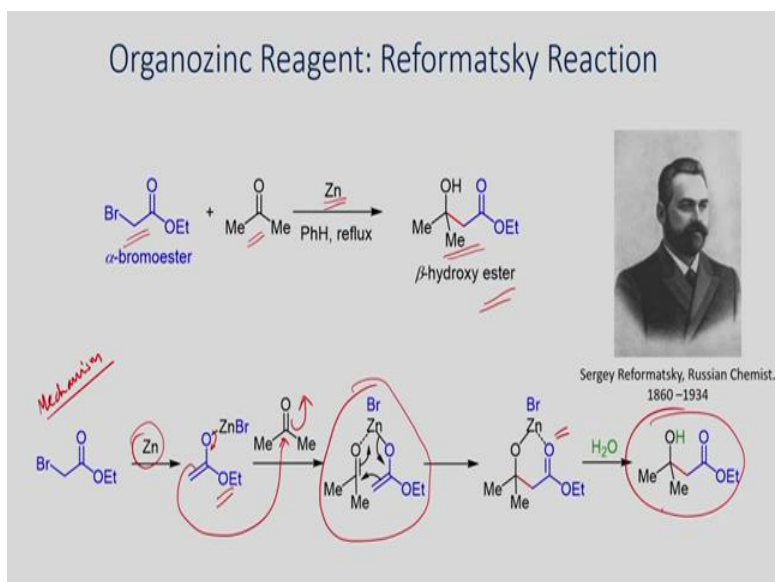
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There are several methods to prepare organozinc reagents. Here some of the examples are shown. If you have the aryl halide, for example, iodobenzene derivative, which can be reacted with zinc by insertion to get the organozinc reagent. Similarly, if you have alkene, you can react with dialkylborane to give trialkylborane that can be reacted with dialkylzinc via transmetalation to generate organozinc reagent.

Similarly, using titanium catalyst, you can try to react alkyne with zinc iodide and lithium hydride to produce vinylzinc iodide as a mixture geometric isomers. The regiochemistry depends on the alkynes. So there are several methods are available to make the organizing reagents.

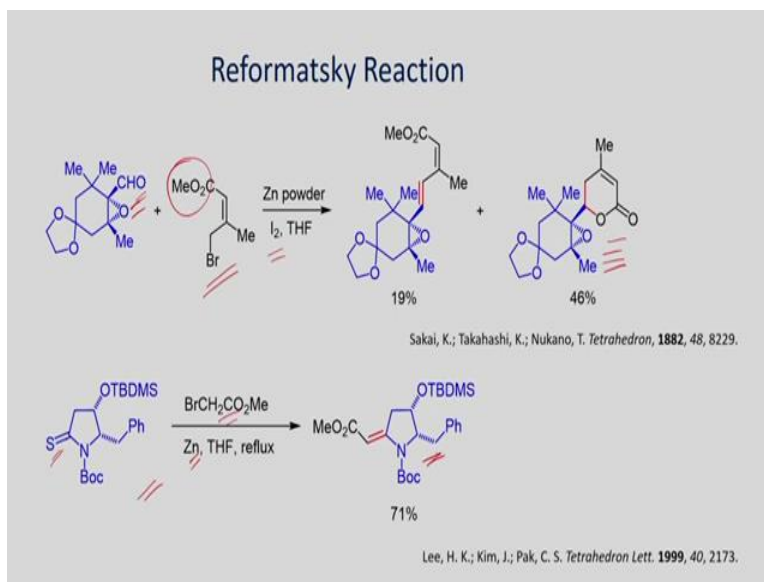
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Now let us see some of the important and common applications of the organozinc reagents. One of the popular reactions is the Reformatsky reaction. All of you know very well, when you have the  $\alpha$ -bromo ester, you can react with zinc to give the alkylzinc that can lead to 1,2-addition to ketone to give  $\beta$ -hydroxy ester as a product.

Mechanism involves the oxidative addition of  $\alpha$ -bromo ester with zinc to give alkylzinc that can undergo 1,2-addition to ketone through cyclic transition state to give the enolate, which on work up generates the  $\beta$ -hydroxy acetate as a product.

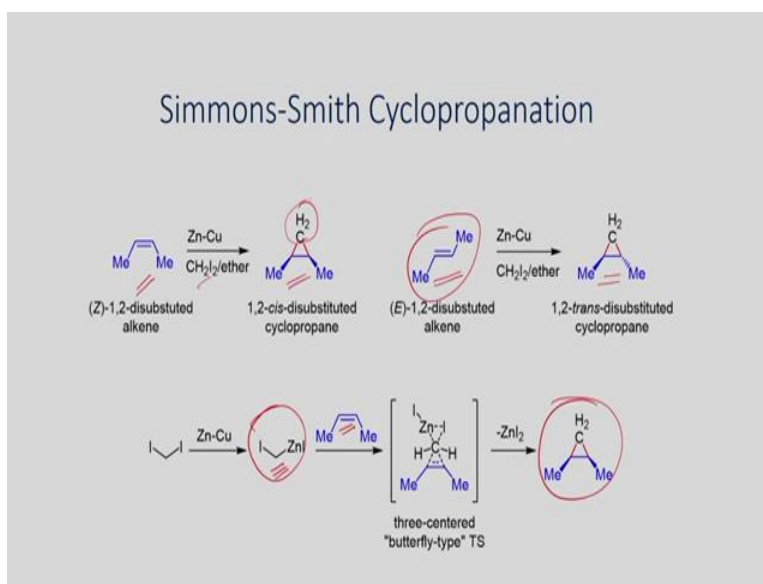
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Here some of the examples are shown where you can find the use of Reformaratsky reaction. The reaction of allyl bromide with aldehyde using zinc powder and iodine produces a mixture alkene and lactone as the products. The lactone can be formed by intramolecular reaction of hydroxyl group with ester. Similarly, the dehydration can lead the alkene as the product. Under these conditions, the epoxide and ketal are stable.

The next example shows the reaction of  $\alpha$ -bromo ester with thiolactam in the presence of zinc under reflux. The reaction involves 1,2-addition followed by desulphurization to give pyrrolidine derivative as a product.

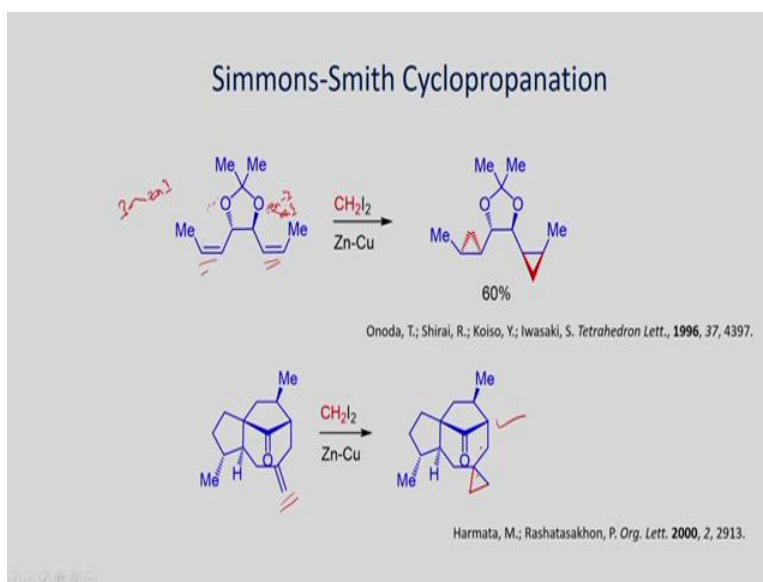
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The other interesting reaction is the Simmons-Smith cyclopropanation, which involves a zinc carbenoid. When you react Zn-Cu with diiodomethane, you will be able to form organozinc intermediate, which undergoes reaction with alkene stereospecifically to give the cyclopropane derivative.

For example, you can react cis-alkene with diiodomethane using Zn-Cu to produce cis-cyclopropane. Similarly, trans-alkene can react with diiodomethane using Zn-Cu to give trans-cyclopropane. This reaction has been well explored.

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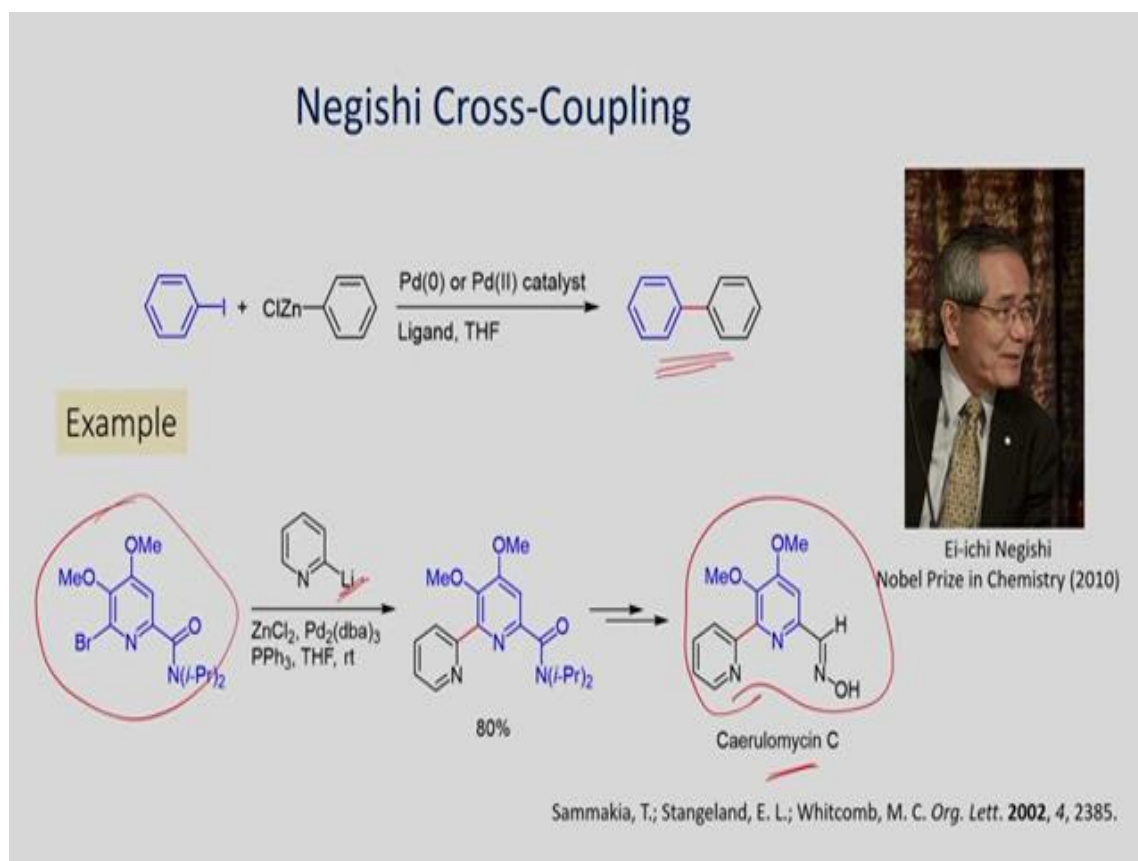


Let us see the application of Simmons-Smith cyclopropanation. The first example has two double bonds. The top as well as bottom face of the alkenes can selectively react due to chelation of the ketal oxygen with the zinc carbenoid intermediate. So when you have the chelating group, and the reagent can make chelation and try to transfer the methylene on the top or bottom side depends upon the stereochemistry of the chelating group.

In the second example, the carbonyl group makes chelation with zinc carbenoid and facilitates the cyclopropanation at the top face of the alkene.

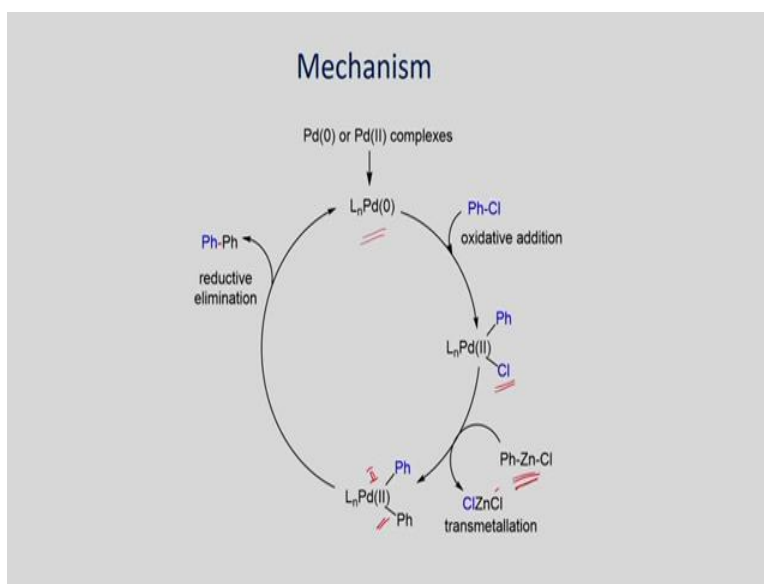


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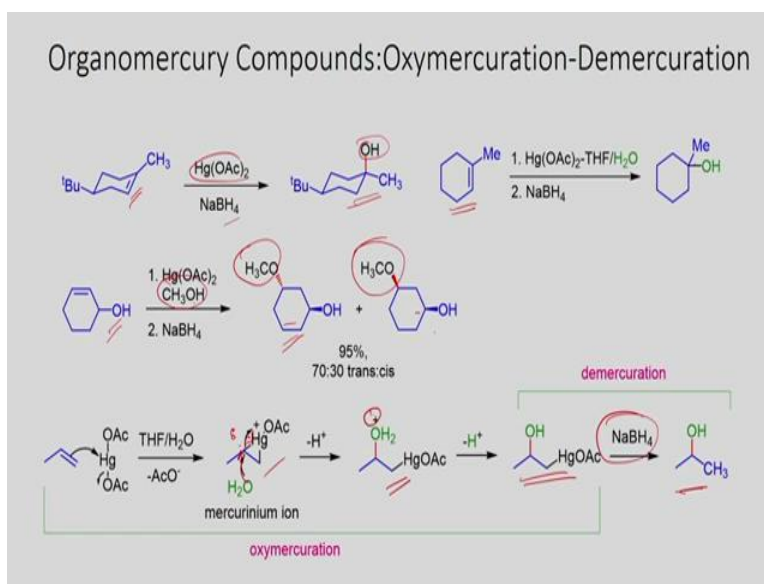
The other interesting reaction is the C-C cross-coupling. Whenever you have the aryl halide, you can couple with organozinc reagent using palladium-catalysis. For example, 2-bromopyridine derivative can be coupled with 2-pyridyllithium in the presence of  $\text{ZnCl}_2$  and Pd-phosphine complex to the C-C coupled product, which has been converted to caerulomycin C. This is known as Negishi coupling, who shared Nobel Prize in 2010 for the cross-coupling reaction. This reaction has wide applications in carbon-carbon bond formation.

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The mechanism involves an oxidative addition of aryl halide with Pd(0) complex to give the Pd(II) intermediate. Which undergoes reaction with organozinc via transmetalation to give the diarylpalladium(II) intermediate. Cis-trans isomerization followed by reductive elimination gives the product and the active palladium(0) species to complete the catalytic cycle.

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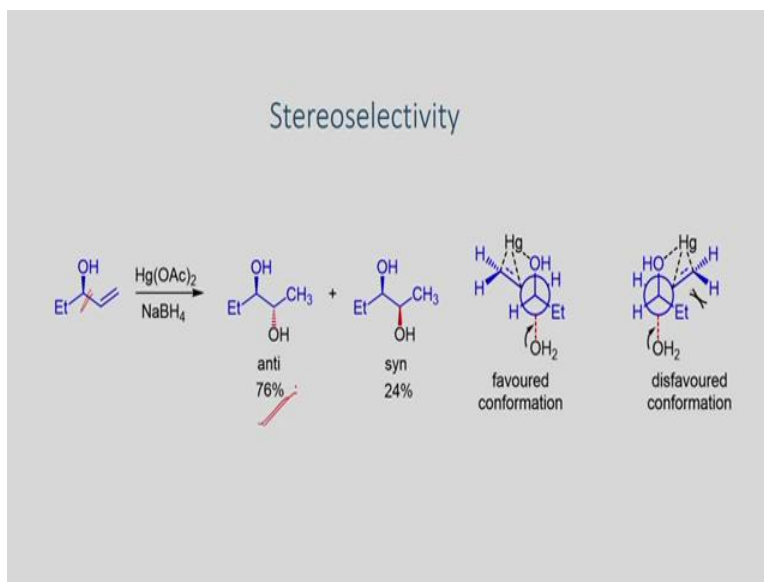


Now let us see the reaction of organomercury compounds. Oxymercuration-Demercuration is an important reaction. If you want to transform an alkene to alcohol with regioselectivity, it has wide applications. For example, when you react the alkene with mercury acetate and followed by reduction, you will be able to introduce the OH group at the more substituted carbon.

Similarly, allylic alcohol reacts with mercury-acetate in the presence of methanol to give a mixture methyl ether. The mechanism of the reaction is shown here.

Alkene can react with mercury acetate to give the mercurinium ion intermediate. Now this carbon is more electrophilic (like carbocation) and undergoes reaction with nucleophile to generate this intermediate. This can lose the proton to have the hydroxyl derivative, which can be converted to alcohol by using the sodium borohydride reduction through demercuration.

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The stereoselectivity of the reaction is here shown. If you have chiral center next to the double bond, you can try to generate diastereoselectivity. In this case, the *anti* diastereomer is the major compound, which can be understood from the Neumann projection shown here. The extreme right is disfavoured one due to steric reason. The left conformation is favored therefore you get the *anti* diastereomer as the major product

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In summary, we have seen the preparation and reaction of organocuprates. Organocuprates are used for the conjugate addition. In addition, you can also try to use for reaction of allylic acetates, substitution reactions, opening of epoxides and reaction with acid chloride to generate ketone as the product. Then we have seen the Glaser coupling, which involves the dimerization of alkynes in the presence of copper(I) halide and base and oxygen.

You can also try to couple two different alkynes through Castro-Stephens coupling. One of the alkynes should have the terminal CH bond which can be deprotonated using base can be reacted with the copper(I) halide to give copperalkyne intermediate, which can be reacted with another alkyne having the halogen. It involves an oxidative addition to produce copper(III) intermediate, which can give the product by reductive elimination.

Next, we have seen the reaction of organozinc reagent. There are several methods are available to prepare organozinc, If you have aryl or alkyl halide, you can try to react directly with zinc to make the organozinc reagent. Alternatively, you can make through transmetallation. We have seen one example where dialkylborane reacts with alkene to give trialkylborane, which can be reacted with dimethylzinc to give the organozinc reagent.

Then, we have seen some applications. We have seen the application of Reformatsky reaction to make macrocyclic system as well as inter and intramolecular reactions. Next, we have seen the Negishi coupling reaction. Organozinc can be coupled with alkyl or aryl halide in the presence of palladium-catalysis. This reaction affords powerful synthetic tool for the carbon-carbon bond formation.

At the end, we have seen the reactions of organomercury compounds. We have seen some examples of the reaction of alkenes to alcohols and ethers by the oxymercuration demercuration, with this we conclude this lecture, thank you very much.