Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

Prof. Santanu Panda

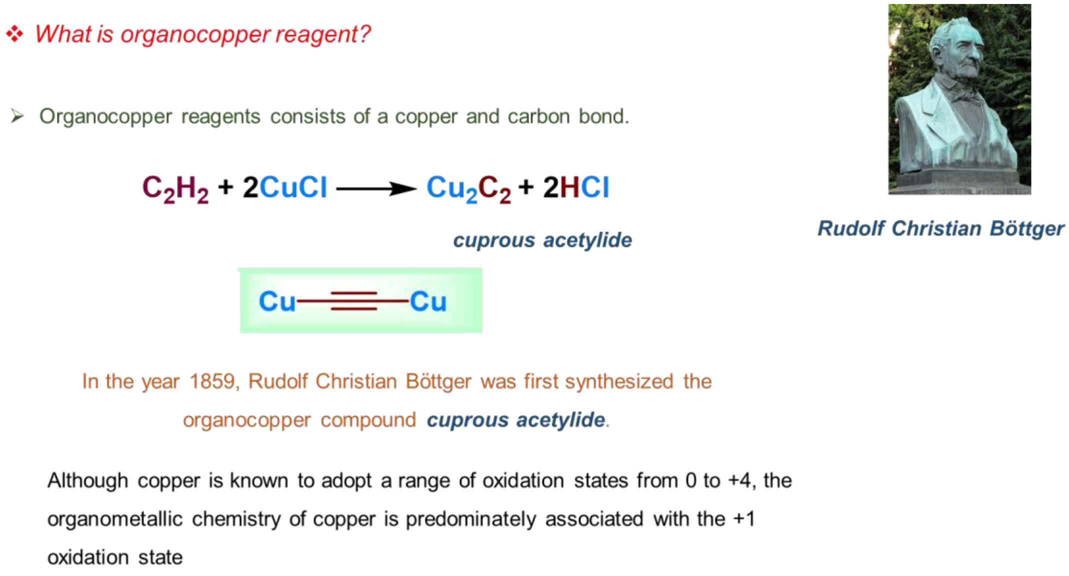
Department of Chemistry

Indian Institute of Technology, Kharagpur

Lecture 39: Organocopper

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. In the last couple of classes, I was talking about organolithium, and then I talked about organomagnesium or the Grignard reagent. In today's class, I am going to start with the organocopper reagent. Then in the next class, I am going to talk about organozinc. So, in today's class, I plan to talk about the definition of an organocopper reagent. And what is the structure going to look like? Then, I am going to talk about the different types of reactions using an organocopper reagent.

So, the organocopper reagent was discovered in 1859 when Rudolf Christian Böttger discovered the cuprous acetylide. So, that is the first organocopper compound. Again, in the definition of an organometallic compound, there will be an organic part and metal. So, similarly, copper will be attached to an R group, which could be an alkyl or aryl. So, it consists of a copper and a carbon bond. Again, I think that is not all. I think there are more variations, of course, you will see. So, this is the compound that was the early discovery of the cuprous acetylide, and although copper has adopted a different range of oxidation states from 0 to +4, you are going to see the organometallic chemistry of copper is mostly associated with the +1 oxidation state.



❖ *What is organocopper reagent?*

- Organocopper reagents consists of a copper and carbon bond.

$$C_2H_2 + 2CuCl \longrightarrow Cu_2C_2 + 2HCl$$

cuprous acetylide

$$Cu-\equiv-Cu$$

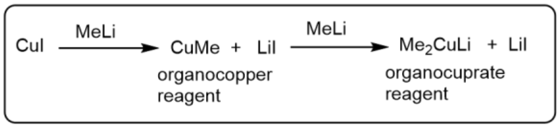
Rudolf Christian Böttger

In the year 1859, Rudolf Christian Böttger was first synthesized the organocopper compound ***cuprous acetylide***.

Although copper is known to adopt a range of oxidation states from 0 to +4, the organometallic chemistry of copper is predominately associated with the +1 oxidation state

So, let us start with another earlier discovery. So, you have seen that the earlier organocopper compound discovered is the cuprous acetylide. Now, I am going to talk about another discovery by Henry Gilman. So, I think you guys are familiar with the Gilman reagent. I think you must have heard about this reagent if you have learned reagent chemistry. So, now I am going to talk about the discovery in 1936 when Henry Gilman actually synthesized lithium dialkyl cuprate. So, I am talking about organocopper first, and now I am talking about cuprate. So, let us try to understand what the difference is here. So, when you take methyl lithium and add it to copper iodide, it will generate copper methyl. So, this is an organocopper reagent, as I mentioned in the previous slide, copper with R, but now, once you use another equivalent of methyl lithium, then what is going to happen is forming a Me_2CuLi. So this is called a cuprate reagent. So, this is a dialkyl cuprate reagent. So, that is the discovery that was done by Henry Gilman. So, once at the beginning, when the organocopper reagent started synthesizing, there were a lot of limitations because organocopper reagent has a lot of issues like poor solubility, poor reactivity, and also thermal instability. But once you think about this cuprate reagent, the Gilman reagent or the cuprate reagent is relatively more soluble than the cuprous reagent. Then, they are thermally stable, and the most important thing is they are even more reactive compared to the organic copper reagent. So, here are the structures. So, this is a dimeric form of lithium dimethyl cuprate in a solution. This is also a dimeric form of lithium diphenyl cuprate in a solid state. Again, these are going to be confirmed from an X-ray crystallography of these compounds in the solid state.

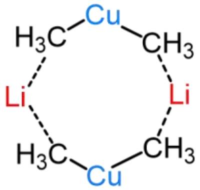
- In the year 1936, Henry Gilman synthesized the lithium dialkyl cuprate, is known as Gilman reagent.



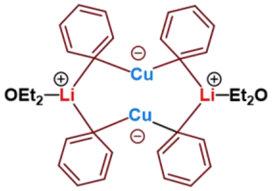
$$CuI \xrightarrow{MeLi} \underset{\text{organocopper reagent}}{CuMe} + LiI \xrightarrow{MeLi} \underset{\text{organocuprate reagent}}{Me_2CuLi} + LiI$$

Henry Gilman

Organocopper species have low solubility, poor reactivity, and thermal instability
Organocuprates are more reactive, soluble, and thermally stable



Dimeric form of lithium dimethyl cuprate in solution



dimeric form of lithium diphenyl cuprate in solid state

So, now, we are going to learn about some of the different types of organocopper reagents. So, we have learned about the organocopper and the cuprate. Now, you can think in the cuprate, we need to consider these three important classes. One is the neutral homoleptic organocuprate, which Gilman initially discovered. You can see these are homoleptic because one donating ligand is attached. If there are two different, then we are called heteroleptic. I am going to come back to that. So, the first thing is this is the neutral homoleptic organocuprate. And then there are ionic species. We are going to talk about some of these that are often obtained by strongly coordinating molecular species like crown ether. Then there are heteroleptic cuprates I am going to talk about. There will be different ligands bound with the copper. So, I am going to talk about some of the heteroleptic cuprates, and you will see that sometimes there will be one particular group, there will be two different groups, and one particular group going to participate in a reaction.

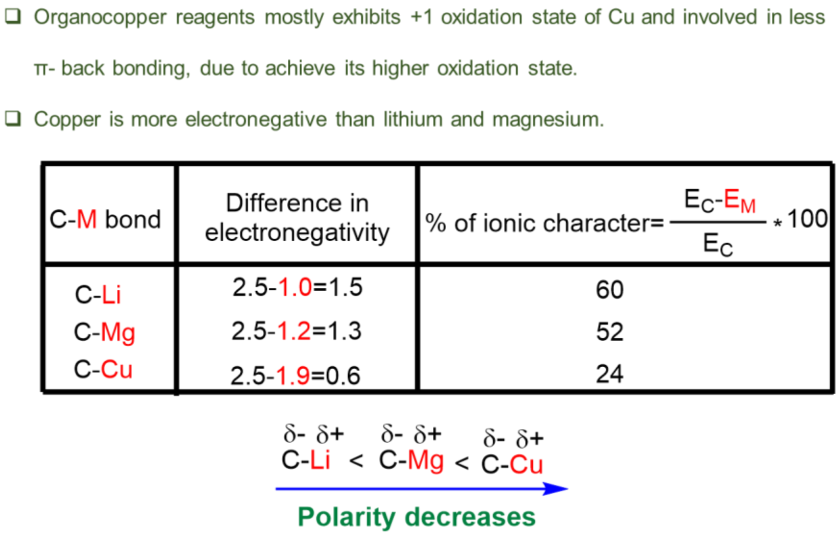
In principle, three different types of organocuprates need to be taken into account of.

(1) The neutral homoleptic organocuprates, as initially discovered by Gilman

(2) Ionic species, often obtained by adding strongly coordinating molecules such as crown ethers to neutral organocuprates.

(3) Heteroleptic cuprates, of which the cyanocuprates are the most important and most extensively studied representatives.

I am going to talk about all these different things. So, before I go again, and I think before I discuss any of these organometallic reagents, I always talk about the reactivity of that reagent compared to the organolithium or Grignard. So, one of the important things is the difference in electronegativity. You must have heard in the previous time when I was discussing organic lithium or Grignard. That is one of the important factors that decide the polarity of the bonds. So, you can see here the difference here is very high. In the case of lithium, it is going down in this direction. As you can see here, once you go in this direction, the polarity decreases as the electronegativity difference is getting decreased the polarity getting decreases. At the same time, another thing is decreasing: the percentage of ionic character decreases once you go from lithium to magnesium to copper. As the percentage of ionic character decreases, these compounds become more covalent. Again, you can see another important thing you will know; I think I have mostly talked about that you will see the organocopper reagent; you will find mostly a +1 oxidation state of copper. Then, you will see less π back bonding due to achieving its higher oxidation state. So, you can see that the organocopper is much less reactive compared to the organolithium. So, these are kind of a softer region, you can say.



- Organocopper reagents mostly exhibits +1 oxidation state of Cu and involved in less π- back bonding, due to achieve its higher oxidation state.
- Copper is more electronegative than lithium and magnesium.

C-M bond	Difference in electronegativity	% of ionic character= $\frac{E_C-E_M}{E_C} * 100$
C-Li	2.5-1.0=1.5	60
C-Mg	2.5-1.2=1.3	52
C-Cu	2.5-1.9=0.6	24

$$\overset{\delta-\ \delta+}{\text{C-Li}} < \overset{\delta-\ \delta+}{\text{C-Mg}} < \overset{\delta-\ \delta+}{\text{C-Cu}}$$

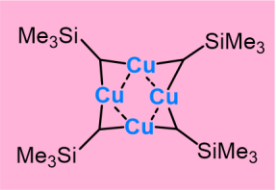
Polarity decreases

So, these are some of the properties of the organocopper reagent, one of the properties of which the alkyl complexes are thermally unstable. I mentioned at the beginning that the organocopper complex is unstable, decomposes below 0 °C, and sometimes it can even explode. Again, these are the order of thermal stability of organocopper compounds. Again, you can see that alkenyl is more stable than alkenyl, then aryl, then alkyl, and you can see these are very similar trends you have seen when I talk about carbanion stability, correct? So, that is the order it follows because the s character is very high in the case of alkenyl, but it decreases to alkenyl and even decreases in alkyl. So, this is an example of an alkyl copper complex that is stable because here, when the alkyl copper complex is getting decomposed, one of the mechanisms is going through the β-hydride elimination process. So, now, in this type of compound, β-hydride elimination is stopped because it does not contain β-hydrogen. That is why this compound was well characterized. It is a well-characterized alkyl copper complex.

- Alkyl copper complexes are thermally unstable. Alkyl copper complexes decomposes below 0 ^{0}C. Methyl copper explodes at above -15 ^{0}C.
- Thermal stability of organocopper compound increases in the order-

alkyl < aryl ≈ alkenyl < alkynyl

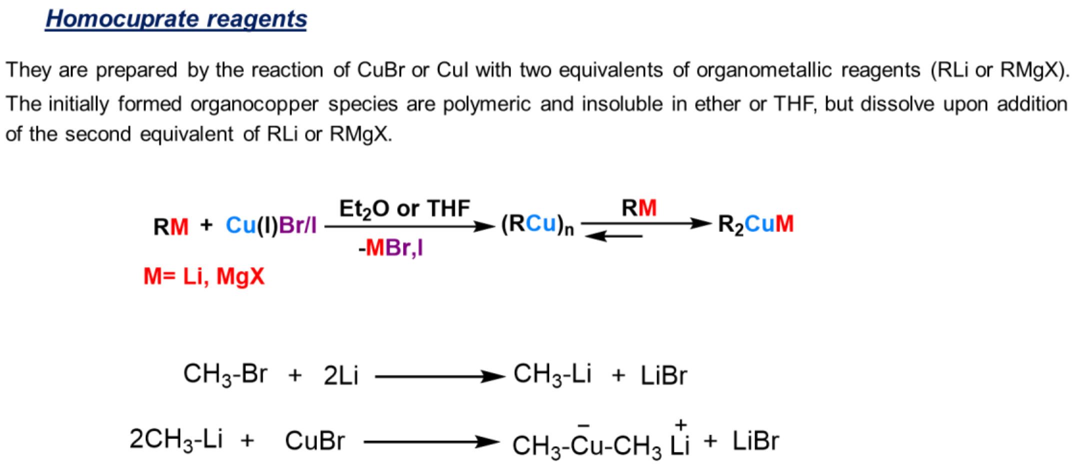
- Decomposition of alkyl copper compounds proceeds through β-hydrogen elimination process



First well characterized alkylcopper(I) compound

Which does not contain any β-hydrogen

So, as I mentioned, I am going to talk about the different types of organocopper reagents. First, I am going to talk about the homocuprate reagents. So, again I mention about this in the definition of the homo and the hetero correct. They are prepared by the reaction of copper(I) bromide and copper(I) iodide with two equivalent organometallic reagents, which you have seen at the beginning when I started talking about the cuprates. So, that means it is the first equivalent from the organocopper, which you can see here, and then the second equivalent reacts with that to form the corresponding cuprates. Again, as I mentioned, the organocoppers are not always soluble. They are insoluble in some cases, but once you make them to the corresponding cuprates, they are soluble. Here, you can see that you can have transmethylation, which means corresponding organolithium and corresponding copper(I) bromide can form these corresponding dialkyl copper compounds. I mentioned you can do it first in one equivalent and then another equivalent to form this type of dialkyl cuprate.



Homocuprate reagents

They are prepared by the reaction of CuBr or CuI with two equivalents of organometallic reagents (RLi or RMgX). The initially formed organocopper species are polymeric and insoluble in ether or THF, but dissolve upon addition of the second equivalent of RLi or RMgX.

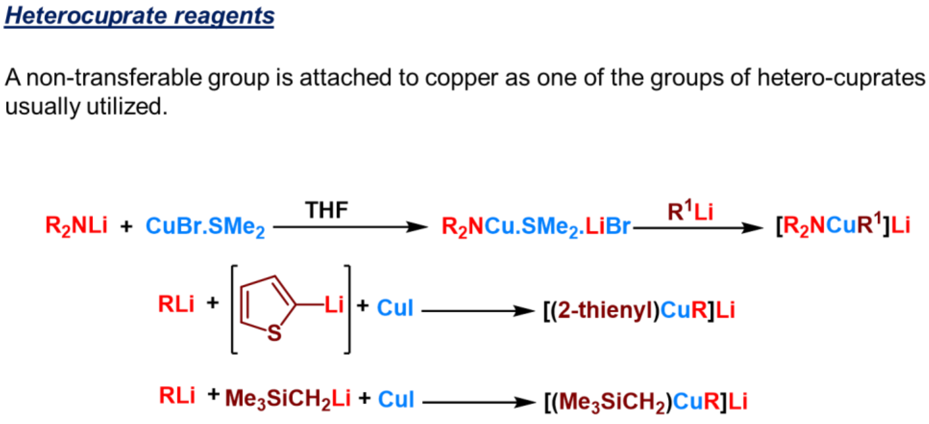
$$RM + Cu(I)Br/I \xrightarrow[-MBr,I]{Et_2O \text{ or } THF} (RCu)_n \overset{RM}{\rightleftharpoons} R_2CuM$$

M= Li, MgX

$$CH_3\text{-}Br + 2Li \longrightarrow CH_3\text{-}Li + LiBr$$

$$2CH_3\text{-}Li + CuBr \longrightarrow CH_3\text{-}\overset{-}{Cu}\text{-}CH_3\ \overset{+}{Li} + LiBr$$

Then, there are heterocuprate reagents. So, you can see, now you have two different groups here. You can see the copper(I) bromide having the SMe_2, and then you also have R_2N. So, that means you have an R_2N, which you can know. So, this copper complex now reacts with R^1 lithium to form this type of hetero-cuprate reagent where you have the nitrogen and R^1. So, two different types of ligands are attached to them. So, you can see some variations here in the synthesis of the hetero-cuprate, which is, I think, one of the popular ones with this thionyl one. So, it is a two-thiophene lithium with the RLi, and in place of copper(I) iodide, it is going to form this hetero-cuprate reagent. Again, there is another example here as well, and I am going to talk about some of the reactivity of this reagent.



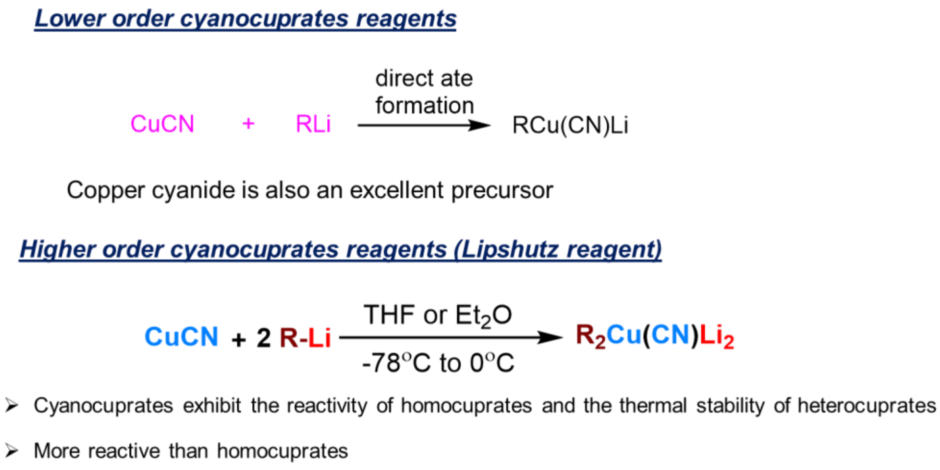
Heterocuprate reagents

A non-transferable group is attached to copper as one of the groups of hetero-cuprates is usually utilized.

$$R_2NLi + CuBr.SMe_2 \xrightarrow{THF} R_2NCu.SMe_2.LiBr \xrightarrow{R^1Li} [R_2NCuR^1]Li$$

$$RLi + Me_3SiCH_2Li + CuI \longrightarrow [(Me_3SiCH_2)CuR]Li$$

Then, we are going to talk about some of the lower-order cyanocuprate reagents. So, that is another important thing that depends on what type of copper(I) iodide and copper(I) bromide you have. I talked about it before; now, I am going to talk about copper cyanide. Once again, copper cyanide can react with RLi to form RCu(CN)Li and lithium. These are the lower-order cyanocuprate reagents. But, once you add two equivalents of it with the copper cyanide, then you end up making the corresponding cuprate, as I said. So, this is a very important reagent. It is a higher-order cyanocuprate reagent. So this is called lipshutz reagent, and after this discovery, this type of organocopper compound was used for several transformations. You know, not only the lipshutz group, there are several other groups. We have also developed organic transformation using this lipshutz reagent. So, one of the important facts is that this is much more reactive than the other copper reagents and has better thermal stability. So, we are going to see some reactions where you see the other organocopper did not work, but you can see using the lipshutz reagent, we can see the transformation is happening.



Lower order cyanocuprates reagents

$$CuCN \quad + \quad RLi \xrightarrow{\text{direct ate formation}} RCu(CN)Li$$

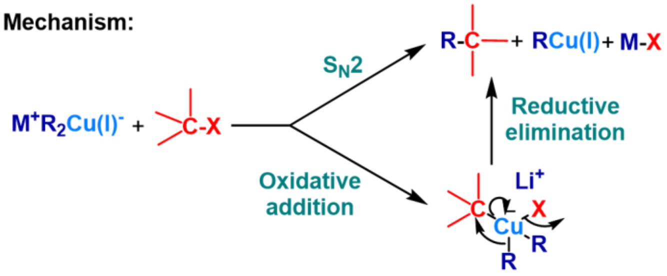
Copper cyanide is also an excellent precursor

Higher order cyanocuprates reagents (Lipshutz reagent)

$$CuCN + 2\ R\text{-}Li \xrightarrow[-78^{o}C \text{ to } 0^{o}C]{THF \text{ or } Et_2O} R_2Cu(CN)Li_2$$

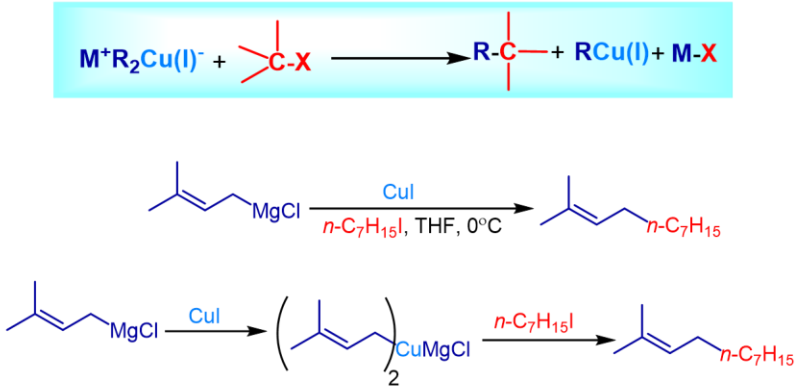
- Cyanocuprates exhibit the reactivity of homocuprates and the thermal stability of heterocuprates
- More reactive than homocuprates

So, now we are going to move to the different chemistry, which was done with organocopper reagent. I think this is the most important part for you because you are going to see a lot of types of questions in the exam, mostly from the reactions of the organocopper. First, we are going to start with the substitution reaction, which means the question now arises: if you make an organocopper, can it participate in some sort of S_N2 reaction? So, now, what is happening? You can see here it can participate in S_N2 reactions. If you talk about this cuprate and take this corresponding alkyl halide, it is going to participate in an S_N2 reaction. So, there could be two different types of mechanisms: one could be like the S_N2 mechanism, or one could be some sort of oxidative addition that is going to happen. So, this C-X and this organocopper, the copper, is going to go for oxidative addition to go from copper(I) to copper(III) here. Then, the reductive elimination will be used to get back the copper(I) and the product.



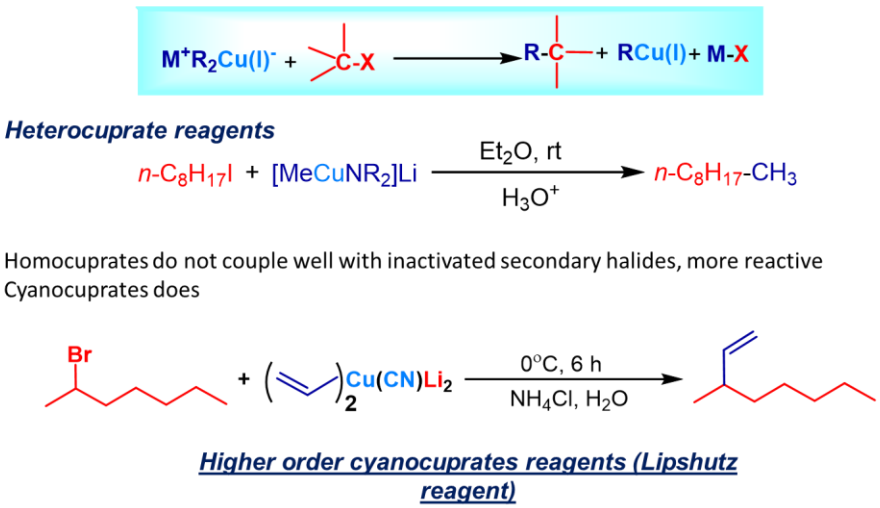
So, here we are talking about the substitution reaction using the homocuprate reagents. So, you can see a very similar thing happening: you have this corresponding Grignard reagent, and you use copper iodide and alkali iodide. Now, what is going to happen? The Grignard reagent is going to go for a transmetallation with the copper(I) iodide to form the corresponding cuprate, and now it is going to react with the corresponding alkyl iodide to get to the corresponding product. So, this is the homocuprate reaction. And then you have seen the mechanism here. It reacts with the copper(I) iodide to form this corresponding homocuprate. Now, it is going for S_N2 reactions, or it can go for the oxidative addition and the reductive elimination to get to the corresponding product. One of the important things is that this homocuprate always participates in an S_N2 or substitution reaction with a primary iodide.

Substitution reaction: **Homocuprate reagents**



Homocuprate reagents readily undergo substitution reactions with primary iodides

So now, if you bring a secondary iodide, what is going to happen? The homocuprate actually is not very good with the secondary. So, at least if you go for secondary bromide, you will not see much reactivity there or in the case of secondary iodide. So that's why the heterocuprates are very good in that regard. If you have heterocuprates, Then what is going to happen? In the heterocuprates, one of the groups, the methyl one, is going to participate in the reactions for the S_N2 reactions. So, in the heterocuprates, there will be two different groups; one will be more coordinated with the copper, and then the other one is going to participate in the reaction. Here, this R group is going to take part in the reaction to, after the S_N2 reaction, it will form this product. Again, the question comes once you have this corresponding bromide. Now, this homocuprate or this heterocuprate, does not work for this reaction. Now, you have to use this lipshutz reagent. As I was telling you, the lipshutz reagent is much more reactive compared to this homo or this heterocuprate. So, now, lipshutz reagent can participate in this reaction here, this substitution reaction to form the product.



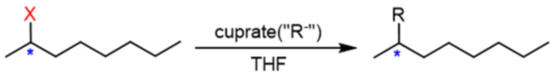
Heterocuprate reagents

$$n\text{-}C_8H_{17}I + [MeCuNR_2]Li \xrightarrow[H_3O^+]{Et_2O,\ rt} n\text{-}C_8H_{17}\text{-}CH_3$$

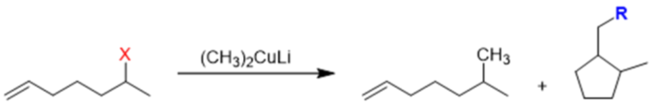
Homocuprates do not couple well with inactivated secondary halides, more reactive Cyanocuprates does

Higher order cyanocuprates reagents (Lipshutz reagent)

So, now, if you can understand the importance of lipshutz reagent, One of the important facts about the substitution reaction that I found out is that once you have an AX equal to iodo, if it is a secondary iodide in place of a cuprate, it is the racemization that is happening here. So, this stereocenter, which, if you start with the chiral compounds here, the chiral halide, you end up getting a racemized product. So you will end up getting a racemized product here. But once you have a bromo here, once you have a bromo or the OTS, in that case, there is an inversion happening, very similar to a S_N2 reaction. You are seeing an inversion happening and you see the stereochemistry. If you start with S, you end up getting to the R. Again, now we are trying to understand some of the evidence that if you have a secondary, suppose you have an iodo here X equal to iodo in this particular substrate. Instead of forming the desired product, another important compound is formed: this one. So, you can see here that you can kind of get up to 65% when the I is equal to iodo. So, what is happening here? Now you can understand that if I am equal to iodo, then there is a formation of a radical. So, once you have this radical, you can see if you give them a 1, 2, 3, 4, 5, or 6. Again, we have learned that if a radical formation is happening, the radical can participate in a 5-exo-trig. Okay, that can end up giving to this product. So that kind of justifies that it's going through radical intermediate.



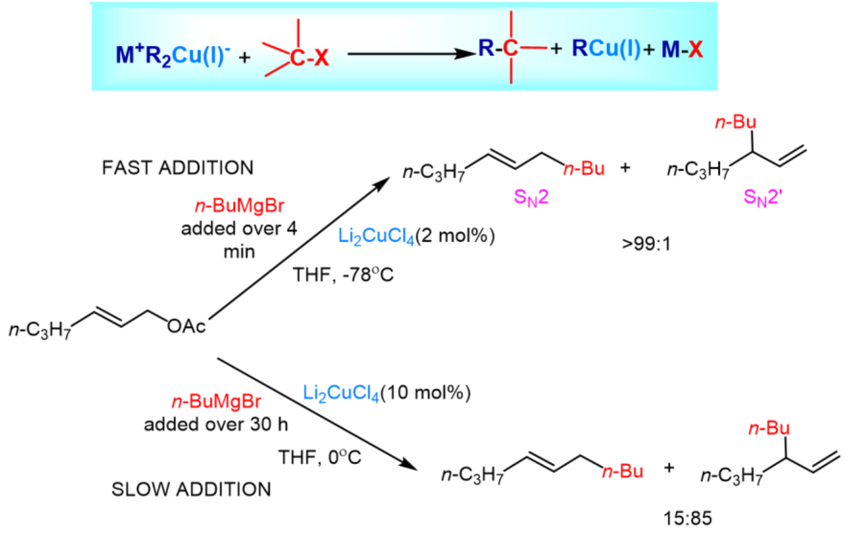
X	outcome at C*
I	racemization
Br	inversion
Cl	unknown
OTs	inversion



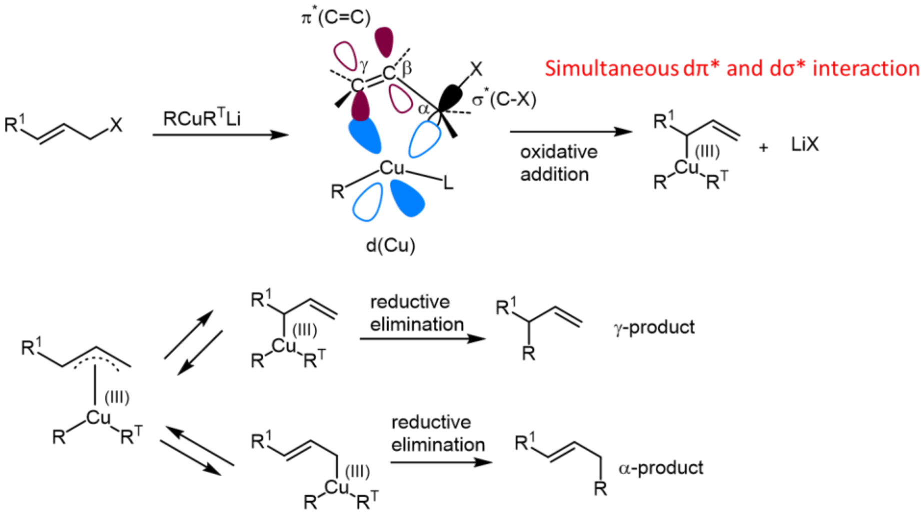
X	%	%
I	18	(R=H) 6% and (R=CH$_3$) 65%
Br	68	(R=H) 5% and (R=CH$_3$) 0%

Now, the substitution of allylic substrate. I think this is a very important topic. So what is happening if you have allylic acetate here? And if you treat it with the Grignard reagent, you will have a Grignard reagent with a 2 mole% of this corresponding copper salt; what is going to happen? It is going to form now if you have two different additions here. One is fast addition, which means you add them first. You know, over 4 minutes, you take your substrate, this organocopper, and add Grignard into the reaction. Now, if you add the Grignard in over 4 minutes, you end up getting to the majority of the S_N2 product in a very fast addition. So, there are two possibilities: it can either go for an S_N2 like directly attacking here, or it can go for an S_N2'. So, now this is happening, and once the reaction, the addition is slow, which means you are adding this butylmagnesium bromide over 30 hours. Once you add for a longer time, you get majorly to the S_N2', and then the minor is the S_N2. So, this is just a single scenario, but you see, these types of allylic substrate S_N2 versus S_N2' depend not only on the addition but also the temperature; it is also dependent on the substrates and the Grignard reagent. So, studies have been done, and everything has been published about it. So, now what is happening is the author of this publication has reported that when you are doing a fast addition and a slow addition, they are things that, in the case of fast addition, form some sort of an organocopper species, which going for S_N2 and here the when you go for slow addition it is forming a cuprate. It forms a cuprate with a 100% formation of cuprate, allowing for the S_N2' reactions. That means they are saying if you have a cuprate, then that is going for S_N2' majorly. That is why you are forming what you are getting as a major product here.

Substitution of allylic substrates:

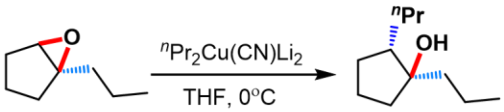


We are trying to understand what is happening here. So, you can see here if you think about this particular compound, this allylic halide or allylic acetate you can think about. So, we are talking about the π* interacting with the d orbital of the copper. So, the d orbital is copper interacting with the π* of this double bond and the σ* of this carbon halogen or the C-X, whatever the bond is. So, a simultaneous dπ* and dσ* interaction happens in the transient state. From there, it is oxidative addition happening. Copper is going to the copper(III), and from there, it forms this allylic complex, and then it can go for S_N2, or it can go for an S_N2'. So, it can form this. It can keep two different copper(III) species. After that, reductive elimination is used to form the two different products. It can go for either the S_N2 product or the S_N2'. Again, in this reaction, I did not put the example here, but you can clearly understand if it is going through this type of copper π allylic species. Now, if you have a chiral ligand attached here and an L here, which is chirally attached to the copper, that can also control the enantioselectivity in this reaction. You can end up getting to the chiral product using a chiral ligand.

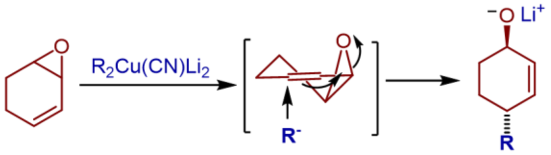


The use of chiral ligands can control the enantioselectivity

The other important reaction is the epoxide cleavage reaction. You can see that if you use a cuprate, it is going to attack the less hindered position of the epoxide to form this corresponding tertiary alcohol. You can see substitution take place with a complete inversion of the configuration. Here, you can see in this particular case, this is an allylic epoxide; in the case of allylic epoxide, once you are using a cuprate, as I said, in the case of cuprate, you will observe that it is going majorly to the S_N2'. So, you will see the major product will go from attacking here, it is shown in this corresponding in a transition state, and you can see there here it is if you try to draw them you can see this is the position where the nucleophile can approach to form this corresponding product.

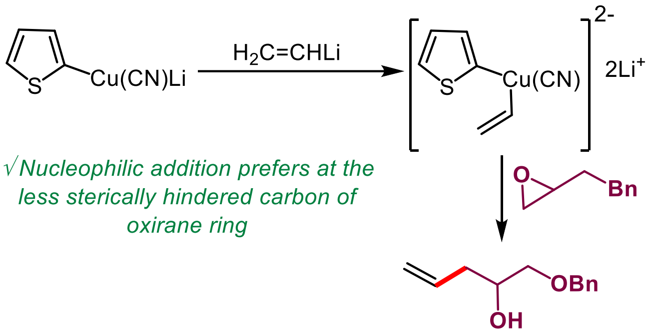


√Substitution takes place with complete inversion of configuration at the electrophilic carbon



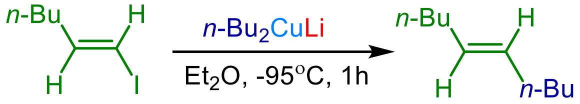
Via anti S_N2'-type mechanism

Another example of the epoxide cleavage again, as I said, if you use this copper with thiophene, then that is not going to get migrated to the other nucleophile or the R group, which you are going to add to the copper that is going to form this di anionic complex. Once you form this di-anionic complex, this corresponding cuprate that can take part in a reaction with the epoxide again is going to attack from the less hindered phase of the epoxide to form the product.



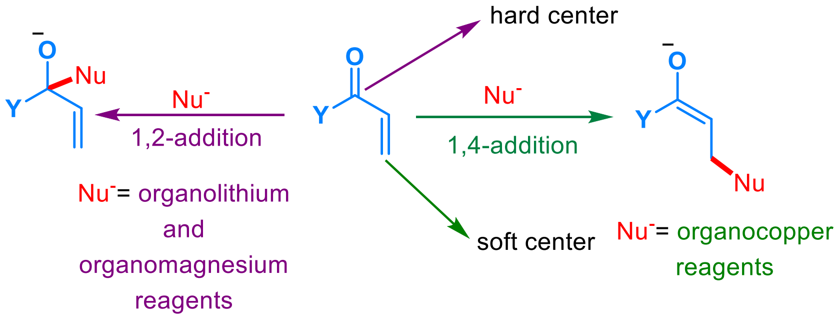
√Nucleophilic addition prefers at the less sterically hindered carbon of oxirane ring

Then, reaction with the vinyl halide, vinyl halide can also react with this corresponding cuprate. So, there is an sp² hybridization, but still, the reaction is happening with the copper. Again, you can see that it can go through this type of oxidative addition and reactive elimination to introduce this n-butyl group with high stereoselectivity.

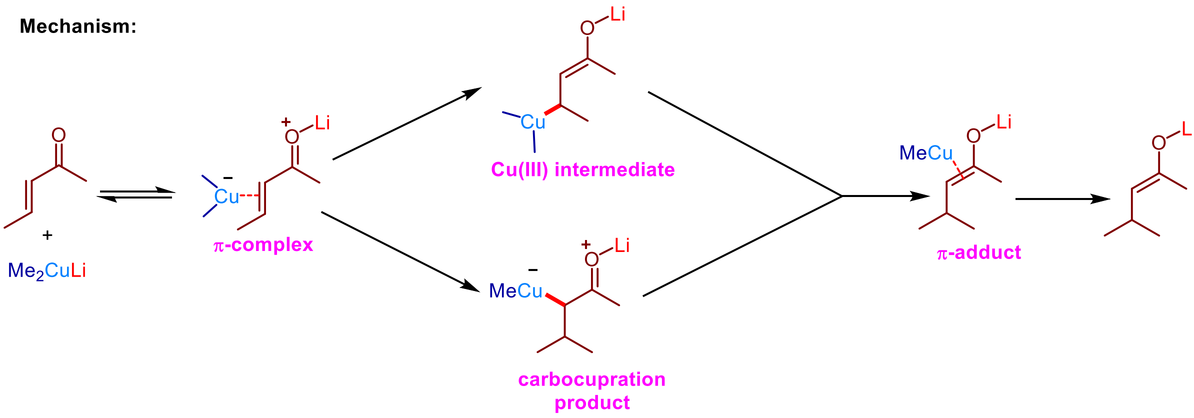


highly stereoselective

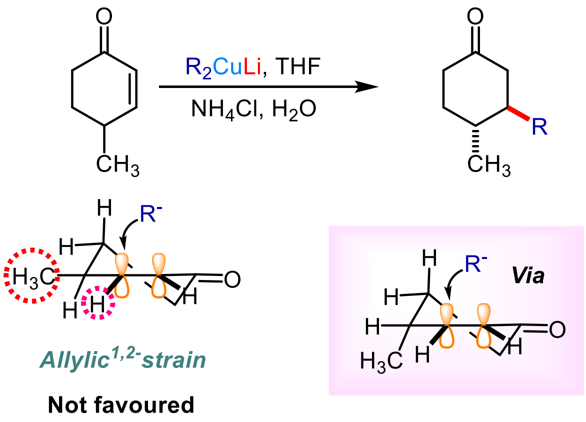
Another very important thing I think about if we talk about organocopper is that this is the important reaction. We always talk about the use of Gilman reagent for this 1,4-addition reaction. So, you have learned that if you have this enone type of compound, you have a carbonyl group and a double bond. Now, if you have a nucleophile, there are two possibilities: one is the 1,2 addition, and the other is the 1,4 addition. So, if it can attack here, then it is a 1,4 addition, and if it is attacked here, this is a 1,2 addition. Now, you have to see if you have a very hard organometallic compound like organolithium. So, for the beginner, you have seen that the 1,2 addition is preferable. This is a hard center, which is why these reagents are going to attack here. But if you see about organocopper reagents, these are soft reagents. So, you can see this is the soft center. So, now, the nucleophile is, if you have an organocopper species, it will going to attack here to go for a 1,4 addition.



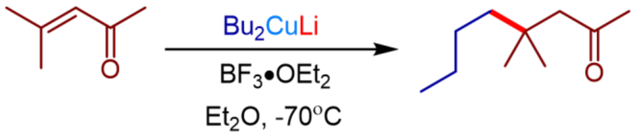
So, let us try to understand the mechanism of this reaction. Once you have this cuprate, there is a first formation; this copper olefin π complex formation is happening here, which again involves the d,π* back-donation. And once the π complex formation is happening from there, that could be one possibility of a carbocupration happening here. It introduced the methyl already here, the methyl transfer from this place to this carbon, to form this carbocupration intermediate, or it can go for this copper(III) intermediate species here. Here it can go, as you can see; it is first going for a copper(III) species. After that, some sort of oxidative addition happens to go to the copper(III), and then a reductive elimination happens to give the methyl back here to form this type of π-adduct. So, it is going to form an enol, and from there, it is going to form the π-adduct of the copper and the double bond of this enol, and then finally, it is going to form the product. You can have this type of enol, and then once you have a H_3O^+, it is going to form the corresponding product here.



So, now the question comes: Stereochemistry will be important. Now, if you have a compound here or you have a CH_3 group in this type of cyclohexenone, you have a CH_3 group in the 4 position. So now the question comes, once this nucleophile is going to attack, what will be the attack? It is going to be an attack from the up or the down because there will be two possibilities. Either the product could be anti, which is here, or it could be a syn. Now, that can be explained by the corresponding transition state. If you look into the corresponding transition, the allylic 1,2-strain is going to be one dictating factor, which is going to happen if the R is approaching from this side, from the same phase of the methyl group. However, in the other cases, if the methyl is not here, the methyl is in the other phase, and then the R can approach from here to form the corresponding product. That is why we end up getting to the anti-product as a major product.

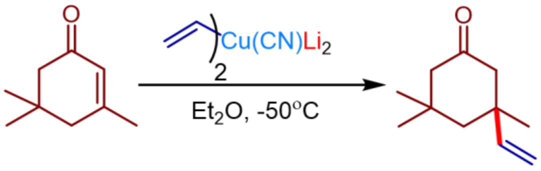


β,β-disubstituted enones are less favorable with organocuprate due to the steric crowding. So, again, if you have a disubstituted group here in the position where the nucleophile is going to be attacked and the organocuprate is going to be attacked, then they are less favorable. In that case, you have to use a Lewis acid. So, $BF_3 \cdot Et_2O$ is a very common Lewis acid that activates this oxygen. So, you have this BF_3. The boron is a Lewis acid, which can take the electron density from the oxygen and make it more activated, decreasing the HOMO-LUMO gap. So, that nucleophile can now attack here to form the corresponding product. Again, there is another example here using this vinyl cuprate that can be added here to get to the corresponding product with a quaternary stereocenter.

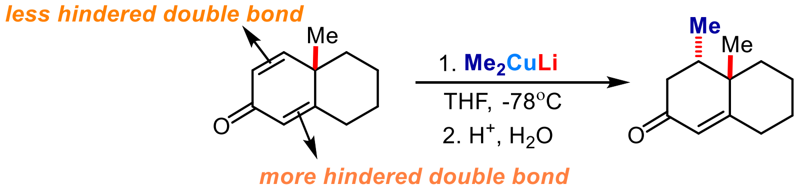


β,β-disubstituted enones less favourable with organocuprates due to steric crowding

use of Lewis acid activate the ketone by coordination

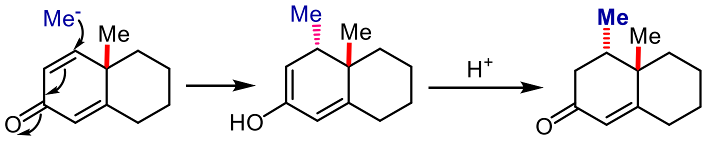


Again, there are substrates where two different positions can be attacked. One, it can attack from this side, which will be less hindered compared to this side, which will be more hindered. So, you can see the nucleophile is attacking from the less hindered side, which is this side, and it is also attacking the opposite side of this methyl. The methyl up this methyl approaches from the other phase. It is shown here in the mechanism. And after that, once you take H_3O^+, it is going to get to the corresponding product.

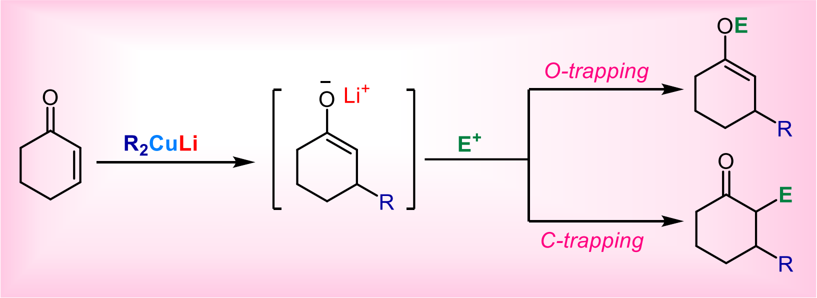


chemoselective addition reaction- prefers less hindered double bond

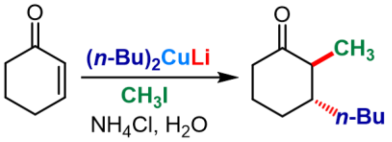
stereoselective addition reaction- prefers less hindered side of the molecule

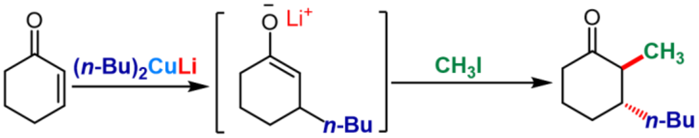


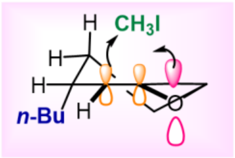
So, now we are going to talk about what we have learned about 1,4 addition, but what about we have learned that in the 1,4 addition, we are always making this type of enolate because you can see we have this R_2CuLi and you can see the lithium always bound here in this with the oxygen. So, to form this type of enolate species. Now, if you have this enolate species and give it an electrophile, then you can trap this enolate with an electrophile that can give you the simultaneous formation of two different bonds. One, it could be. So, the first thing is that this is a 1,4 addition, and now this is an enolate trapping. So, that means you can able to form these two bonds here. This trapping could be with carbon, which means once you have this enolate, it can be trapped in the carbon or trapped with oxygen. This means if you use something like silicon and all these like tin, then that can go to the oxygen, and if you have some alkyl halide, then of course they are. You can see again that this hard-soft concept comes into the picture. So, this carbon is in a softer place. So, it can take with the carbon-based electrophile, and then you will see the substitution here. So, that's why we are going to show you some examples of carbon trapping here.



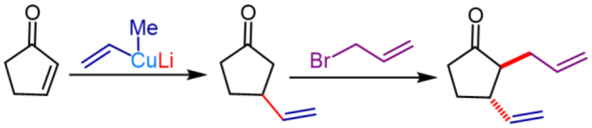
As I mentioned here, if you treat with this in (n-Bu)₂CuLi, this cuprate is going to go for 1,4 addition. And then what is going to happen once the 1,4 addition is happening? From this transition state, you can understand that after the 1,4 addition, it is happening. Now, this enolate is going to take the electrophile on the opposite side, the opposite face of the butyl group, because, again, to avoid this steric interaction, we have seen it there. So, that is why it is going to take methyl iodide in this phase to form this product as an anti as a major product.

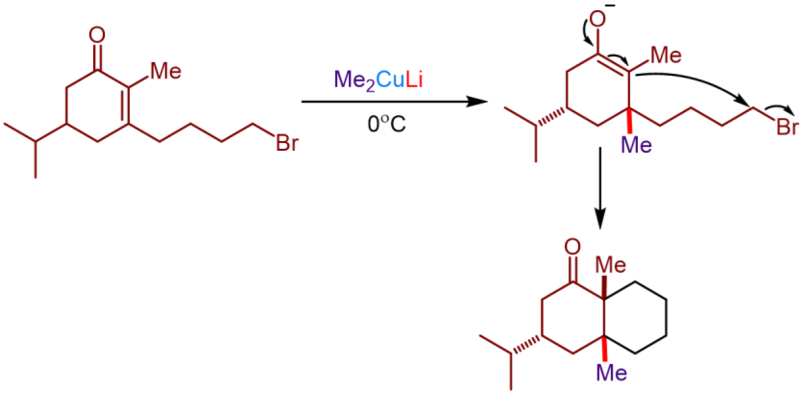




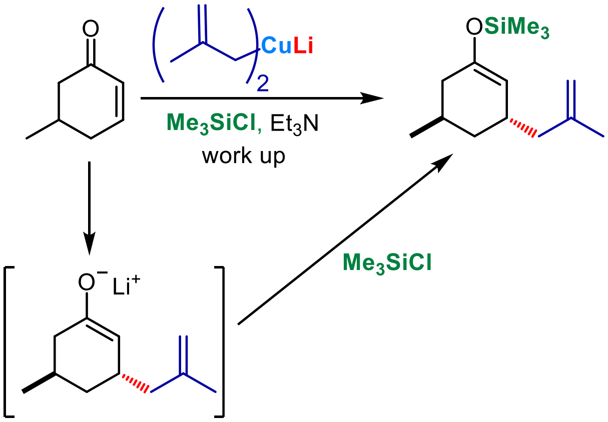


Again, there is an example here. First, there is a 1,4 addition, then it takes this allyl bromide, which can go for which can attack this form, with the anti-product as a major product here. So, you can introduce a vinyl in this position and the allyl in the next position. So, in one particular sort, you can first add the copper reagent, and then at the end of the reaction, you can add the electrophile and continue the reaction that can completely consume the electrophile to give it to this product. There is another example here. I think the reaction is happening in an intramolecular way. The first thing is, of course, you add the methyl. This methyl is going to attack here. So, this is the 1,4 addition first going to happen, and then after that, If this enolate is going to form, it is going to attack the corresponding alkyl halide to form this corresponding bicyclic compound.

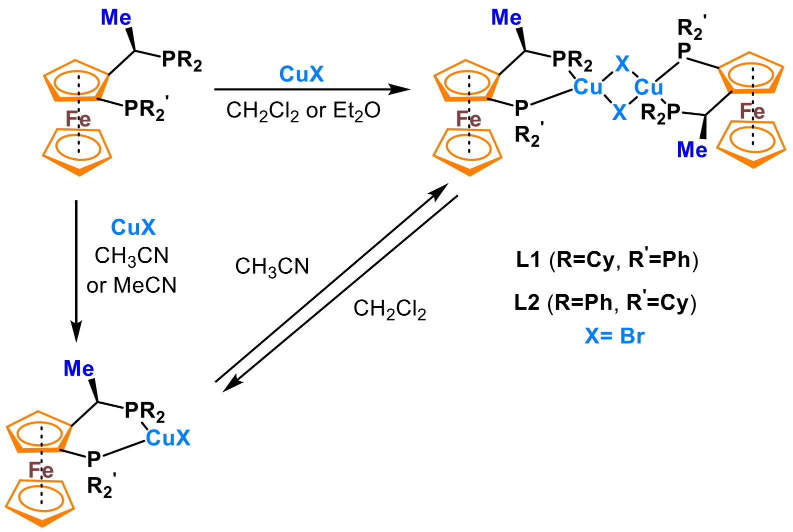




Now, as I said, if you have this trimethylsilyl chloride, then again, these are going to favor with oxygen. We know about that. Again, this hard-soft concept comes into the picture. So, this is going to bind with the oxygen to form this OTMS. So, after this step, instead of attacking the carbon, it is going to take and form the corresponding OTMS. Of course, if you get this corresponding OTMS, this compound can again be treated with an electrophile.

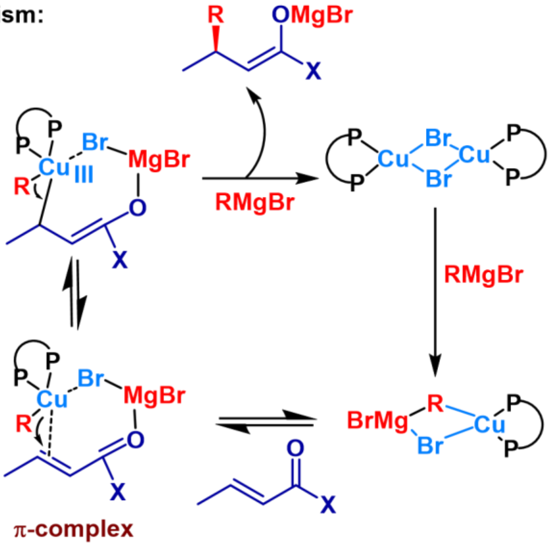


So, now I am going to talk about the asymmetric conjugated addition reaction. So, we have learned about the conjugated addition reaction. The question that comes up in this conjugated addition reaction in the copper is: Can you bring a chiral ligand? Then you can control the chirality, and you can now make a product where you have particular enantioselectivity, which means it could be R or S, and you can control them using a Josiphos ligand. So, that was the early ligand Feringa group developed, and they tried to study the mechanism. So, again, I think the understanding from this particular thing they try to do is the mechanistic understanding for this type of asymmetric conjugation reaction. They found that once treated with these corresponding copper halides, some dimeric species formed here with a halide bridge with the copper. So, and then it is going to take part. So, they mention that it first forms this, and then it forms this one. So, it is kind of in an equilibrium.



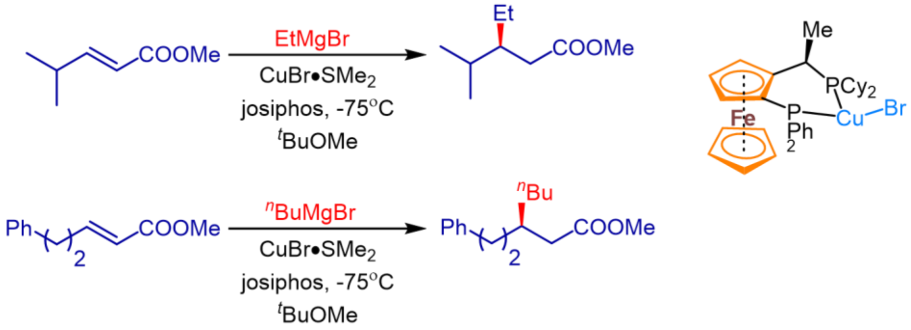
And then what is happening again? The reaction mechanism is very similar. Once you have this RMgBr, it will be able to generate the corresponding copper species, which will take part in the 1,4 addition reaction. Again, the MgBr is going to activate to form this π complex. As mentioned in the 1,4 addition mechanism, forming the π complex is the first step. This MgBr acts as a Lewis acid to activate this oxygen; now, it can go for this oxidative addition to this copper(III) species and reductive elimination to the corresponding product.

Mechanism:

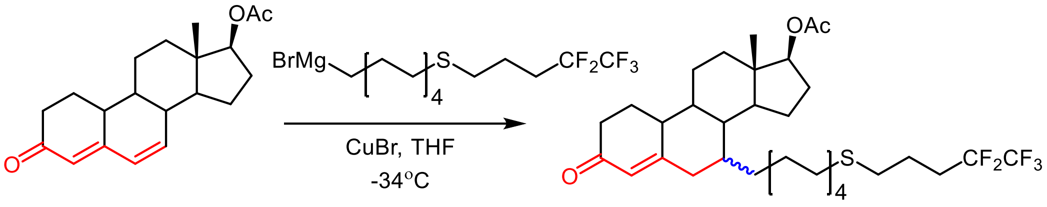


The results indicate that Mg^{2+} not only activates the enone (enoate) via coordination with oxygen (Lewis acid effect), but also associates to the Cu-complex through the bridging halogen

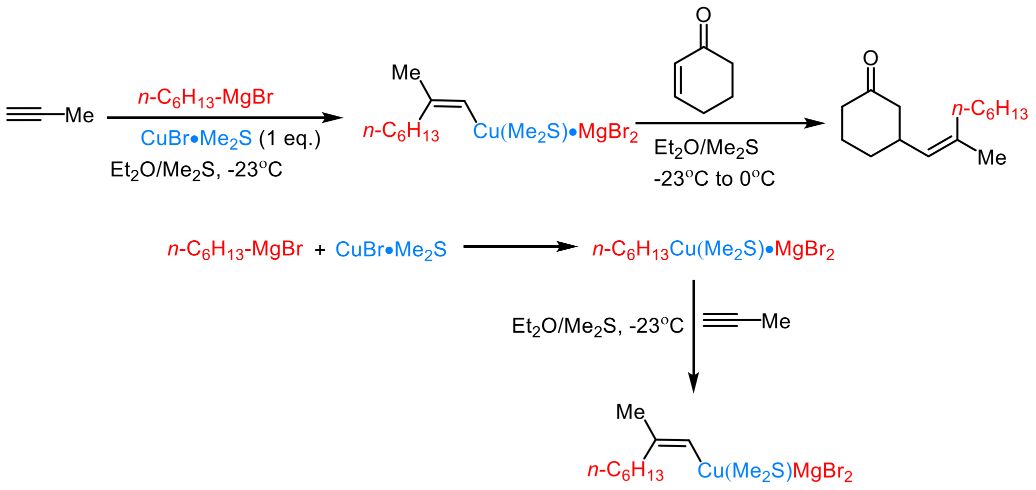
Again, there are some examples here using this type of Josiphos ligands; you can get to this product with high enantioselectivity.



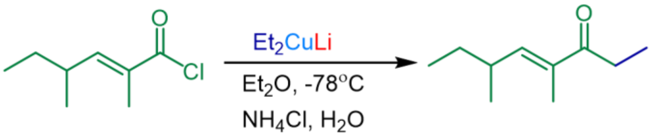
So, in the previous slide, we learned about this 1,4 addition. Now, you can see in this particular case that if you have an enone and then if it is conjugated, there is another double bond here. You see, this 1,6 addition is becoming predominant. So, you will see this 1,6 addition is happening, and then you get some of the little amounts of 1,4 addition, but the major will be 1, 6 addition product. To that, you have to understand that if you find an enone and again, you can see this position is also hindered. So, this is also a tri-substitute; you have both substitutions here. So, in this double bond, it is disubstituted. So, this is going to form a quaternary carbon. So, sometimes, one cis addition is preferred if you have a conjugation.



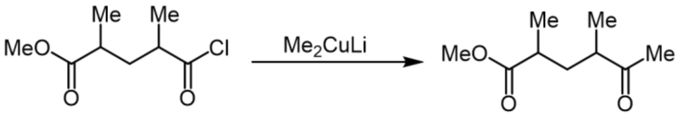
The other important reaction is the carbocupration reaction. So, if you treat a Grignard reagent with a copper bromide, then you end up with a carbocupration reaction by forming this species here. So, you have this C_6H_3MgBr with CuBr, forming the $RCu(Me_2S)\cdot MgBr_2$. So, I think I talk a lot about this RLi, correct? I talk about the organolithium and the copper. Now, here I am talking about organomagnesium. So, once you take organomagnesium and then if you have alkyne, it can go for carbocupration. I think I mentioned the carbocupration. Once, I talked about the mechanism previously there. So, after the carbocupration, what is happening? Both the copper and the alkyl groups are added to the alkyne in a syn addition to form this. And once you have the vinyl copper species, now you can, if you have this enone, cyclohexenone, it can go for 1,4 addition here comfortably to get to this product.



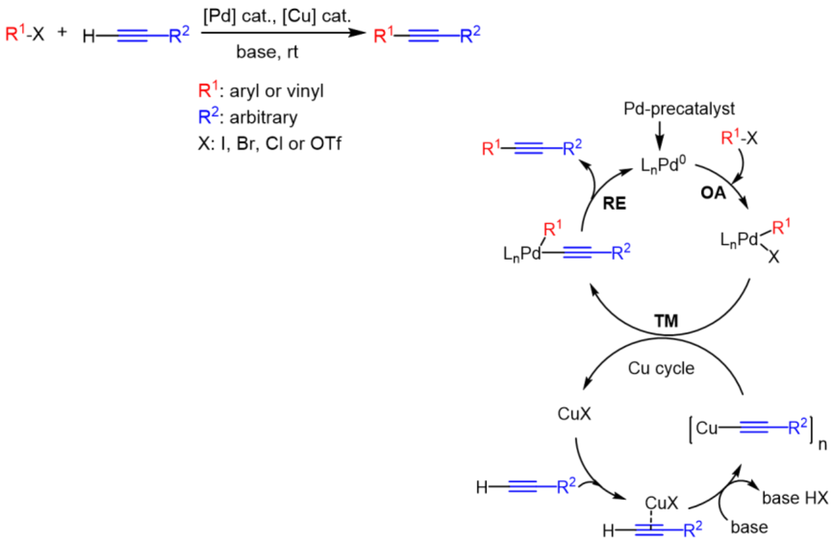
Another type of reaction I should also mention is called acylation reaction. If you have acyl chloride, now you have learned that if you treat it with organolithium or Grignard, what happens, correct? It is going to attack the corresponding ketone, and it is not going to stop there. This ketone is going to get attacked again. But if you have this organocopper reagent, then there is an advantage here. Using an organocopper, you can introduce the alkyl group comfortably to form the ketone. And this is not going to attack again with the organocopper. So that is a very important thing. So, there is a chemoselectivity here. You can see an example here. This corresponding acid chloride in the presence of Me_2CuLi is introducing the methyl group here. You can think that if you take methyl lithium or methyl magnesium bromide, you will not be able to get to this product. The other important thing in this slide is to mention ester versus acid chloride. I think this is very important, so there is important chemoselectivity here. You see, the reaction only happens to the corresponding acid chloride, and to get to this ketone kind of ester, it remains untouched, which will be difficult using a Grignard or corresponding lithium.



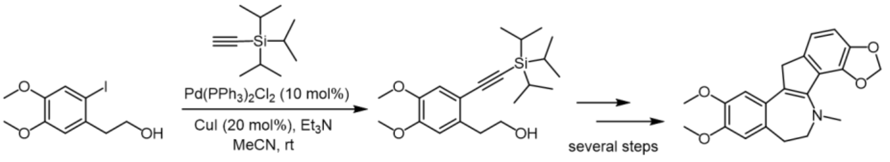
Chemoselective reaction for acid chloride

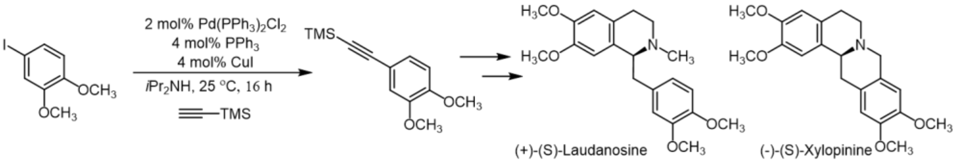


In the final slide, I am going to talk about Sonogashira coupling; this is, again, a very important cross-coupling reaction. What is happening in this cross-coupling? You have this aryl halide. It could be a bromide, chloride, or iodide, and then you have alkyne. So, what happens once if you use a palladium catalyst? We have previously learned that if you have an aryl halide with aryl bromide or iodide mostly, you will find that that is going to participate in oxidative addition to form palladium. So, palladium is oxidized to palladium(II) from palladium(0). So, we have learned about that. And we have learned in the Kumada coupling that if you have a Grignard reagent, it is going to transmetallate. Then, it goes for reductive elimination to form bonds. And then you have seen that. Here, you have an alkyne and, in the presence of base and copper iodide, the catalytic amount of copper iodide. What is happening here? The copper is forming a corresponding copper acetylide. Now, this copper acetylide is going to participate in transmetallation. So, in this transmetallation event, you see again that palladium will be palladium(II), but you now have an alkyne group here. Now, it is going to go for a reductive elimination to form this alkyne. So, now you convert this RCHCHAr. So, this is the product you have this Ar. So, that will be the final product here.



There are some examples here; if you have a compound with this aryl iodide and if you take this corresponding acetylene, TMS, not only TMS, it is a tri, isopropyl, silyl group here, and there is an alkyne here. If you take the palladium catalyst, copper iodide, and triethylamine, this is a very common condition for Sonogashira coupling. What is going to happen is that you introduce this alkyne here, replace this iodine, and introduce the alkyne, which can further transform into bioactive compounds. Here, if you can see another example, you have aryl iodide, palladium catalyst, ligand, and copper, and in the presence of this base, it is going to introduce again replace the copper, replace the corresponding iodo, and replace the alkyne, which is going to form this corresponding natural product.





Again, I hope you are convinced that organocopper chemistry is very powerful. There are a lot of different types of carbon-carbon bond formation that can happen using organocopper chemistry. You know, here are some of the reference books you can study. Again, thank you so much for coming to the class. I am going to see you guys in the next class. Thank you.