Reagents in Organic Synthesis
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Lecture No. 23

Copper based Reagents in Organic Synthesis

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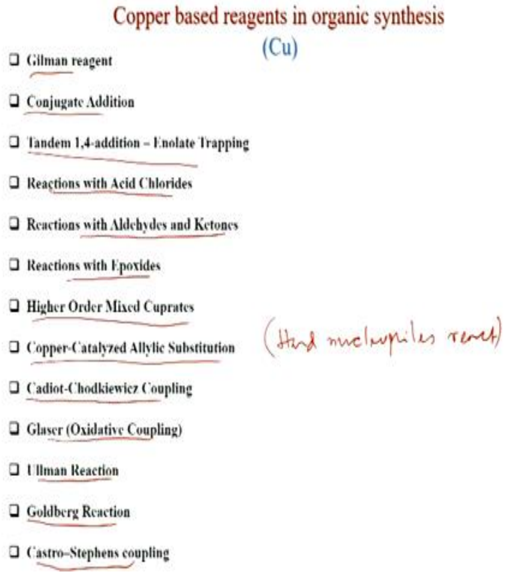

Copper based reagents in organic synthesis

(Cu)

- Gilman reagent
- Conjugate Addition
- Tandem 1,4-addition – Enolate Trapping
- Reactions with Acid Chlorides
- Reactions with Aldehydes and Ketones
- Reactions with Epoxides
- Higher Order Mixed Cuprates
- Copper-Catalyzed Allylic Substitution (Hard nucleophiles react)
- Cadiot-Chodkiewicz Coupling
- Glaser (Oxidative Coupling)
- Ullman Reaction
- Goldberg Reaction
- Castro–Stephens coupling

Welcome again, today we will discuss copper based reagents in organic synthesis, as you know copper is very cheap metals. So it has been used in many organic transformations. So first one will discuss Gilman reagent and then will discuss reactions of Gilman reagents, conjugate addition, tandem 1,4-addition- Enolate trapping, reactions with acid chlorides that is also very important reaction.

Reactions with aldehydes and ketones 1,2- fashion, reaction with Epoxide, higher-order mixed cuprates. They are much useful, we will see and copper catalysed allylic substitution and here, generally hard nucleophiles react with copper catalysis allylic reaction. And Cadiot-Chodkiewicz coupling will see, Glaser oxidative coupling, Ullman reaction for biaryl synthesis, Goldberg reaction imine synthesis. And Castro-Stephens coupling for alkyne synthesis will see.

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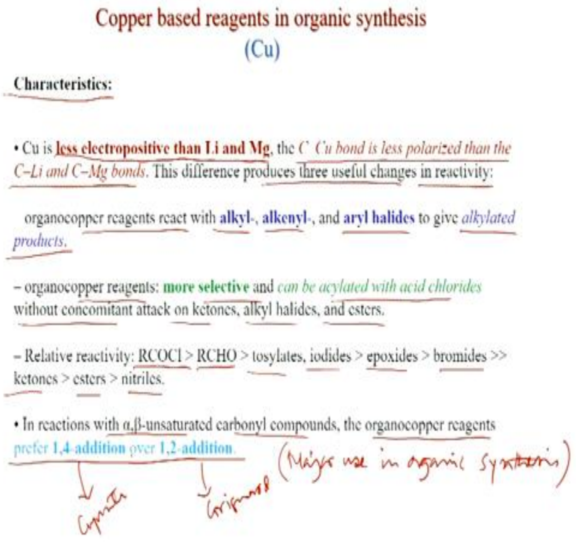

Copper based reagents in organic synthesis
(Cu)

Characteristics:

- Cu is **less electropositive than Li and Mg**, the *C–Cu bond is less polarized than the C–Li and C–Mg bonds*. This difference produces three useful changes in reactivity:

organocopper reagents react with **alkyl-**, **alkenyl-**, and **aryl halides** to give *alkylated products.*

– organocopper reagents: **more selective** and *can be acylated with acid chlorides* without concomitant attack on ketones, alkyl halides, and esters.

– Relative reactivity: RCOCl > RCHO > tosylates, iodides > epoxides > bromides >> ketones > esters > nitriles.

- In reactions with α,β-unsaturated carbonyl compounds, the organocopper reagents prefer **1,4-addition** over **1,2-addition**.

(Major use in organic synthesis)

Cuprates

Grignard

So first will discuss some characteristics of organic copper compounds. So copper is less electropositive, than lithium and magnesium. So C-Cu bond is less polarized than the C lithium and C magnesium bond. This difference produces three useful changes in reactivity. Like organocopper reagent reacts with alkyl, alkenyl and aryl halides to give alkylated products. So this is very important, unlike lithium and magnesium they give the coupling reaction with alkyl, alkenyl and aryl halides.

Organocopper reagents more selective and can be acylated with acid chlorides without concomitant attack on ketones, alkyl halides and esters. So the relative activity is RCOCl is higher than aldehydes, so it is possible to react with acid chloride in presence of aldehyde. Then tosylates, iodides, epoxides, bromides, ketones, esters, nitriles.

Also in reactions with alpha, beta unsaturated carbonyl compounds, the organocopper reagents prefer 1,4-addition over 1,2-addition and that it is major use, major use in organic synthesis, the 1,4-addition compare to 1,2-addition. Because we know the Grignard give 1,2-addition and for 1,4-addition you have to use the Cuprates.

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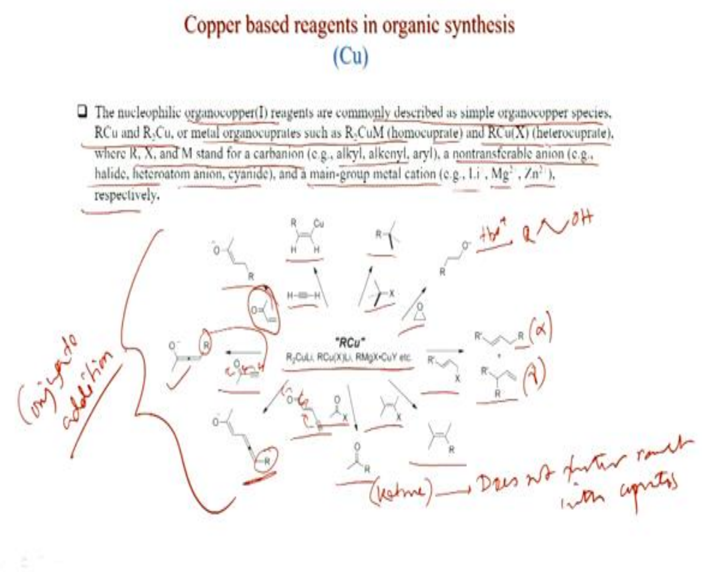

Copper based reagents in organic synthesis

(Cu)

❑ The nucleophilic organocopper(I) reagents are commonly described as simple organocopper species, RCu and R_2Cu, or metal organocuprates such as R_2CuM (homocuprate) and RCu(X) (heterocuprate), where R, X, and M stand for a carbanion (e.g., alkyl, alkenyl, aryl), a nontransferable anion (e.g., halide, heteroatom anion, cyanide), and a main-group metal cation (e.g., Li^+, Mg^{2+}, Zn^{2+}), respectively.

So now we will see just an overview of different reaction. The nucleophilic organocopper(I) reagents are commonly described as simple organocopper species RCu or R_2Cu or metal organocuprates such as R_2CuM. Homocuprates and RCuX where X is cyano or halide heterocuprate. Where R, X and M stand for a carbanion as for example alkyl, alkenyl, aryl a non-transferable anion as for example halide, heteroatom anions, cyanide, and a main group metal cation as for example Li^+, Mg^{+2}, Zn^{+2} respectively.

So this is the Reagent RCu, this is R_2CuLi and RCuXLi, this is heterocuprate and this is RMgX.CuY. So this we can derive from the Grignard reagent. So this reagent can react with alkyne to generate this vinylcuprate. Also it can do substitution reaction with alkene halide to give this product. Also it can react with epoxide to generate an alkoxide which after aqueous workup will give you the alcohol and with allylic acetate or halide this kind of allylic substitution is possible.

So here, this is alpha substitution, this is gamma substitution will see the selectivity. Also vinyl halide in can give this coupling product and here the olefin geometry does not change, so will see also this is the useful reaction with acid chloride you can get the ketone, ketone. And this ketone does not further react, does not further react with cuprate. So this is very important.

Then the conjugate addition to ene-yne system with the carbonyl compound you get this kind of allene system after the addition of R, this triple bond becomes like this. And with an alkynyl ketone also you can get this addition like this to get this product. And here also you can get this, this is the alpha,beta unsaturated ketone that is the conjugated addition. So all these three cases conjugated, conjugate addition is happening. So this is the major use.

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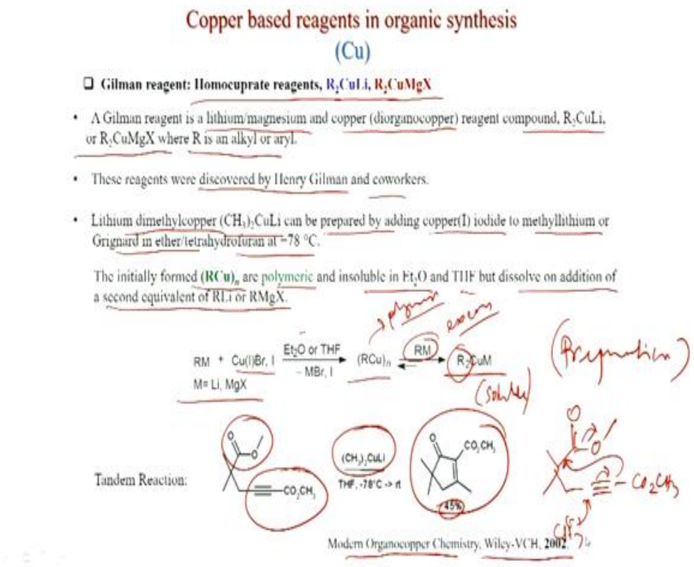

Copper based reagents in organic synthesis

(Cu)

☐ **Gilman reagent: Homocuprate reagents, R_2CuLi, R_2CuMgX**

- A Gilman reagent is a lithium/magnesium and copper (diorganocopper) reagent compound, R_2CuLi, or R_2CuMgX where R is an alkyl or aryl.
- These reagents were discovered by Henry Gilman and coworkers.
- Lithium dimethylcopper $(CH_3)_2CuLi$ can be prepared by adding copper(I) iodide to methyllithium or Grignard in ether/tetrahydrofuran at −78 °C.

The initially formed $(RCu)_n$ are polymeric and insoluble in Et_2O and THF but dissolve on addition of a second equivalent of RLi or RMgX.

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

M= Li, MgX

Tandem Reaction:

Modern Organocopper Chemistry, Wiley-VCH, 2002.

Now, will discuss Gilman reagent. So Gilman reagent is a homocuprate reagent that is R_2CuLi or R_2CuMgX. And a Gilman reagent is a lithium, magnesium and copper diaorganocopper reagent compound. R_2CuLi or R_2CuMgX where R is an alkyl or aryl. These reagents were discovered by Henry Gilman and co-workers. That is why it is called Gilman reagent.

Lithium dimethylcopper $(CH_3)_2CuLi$ can be prepared by adding copper(I)iodide to methyllithium or Grignard in ether tetrahydrofuran at -78 degree centigrade. And the initially formed $(RCu)_n$ are polymeric and insoluble in ether and THF, but dissolve on addition of a second equivalent of RLi or RMgX. So this is the reaction for the preparation, so preparation.

RM that can be RLi or MgX, then copper(I)bromide or iodide in ether THF you get this polymer and further addition of RM. So RM should be excess, this should be excess RM will add to generate this R_2CuM. So this is polymeric and insoluble. That is why you have to make this R_2 species, so that it is in soluble.

And here is an example of Tandem reaction, like here you can see the alkynyl ester is there and here simple ester. So first it does a conjugate addition, if you add dimethylcuprate then it adds to conjugate fashion here. So this can be mechanism that CH_3^- is reacting here, going to here, and then a substitution kind of reaction is happening. And you get this cyclopentenone

45 percent yield. So this is an useful reaction that with cuprate, you can generate this cyclopentenone in one pot. And there is book modern organocopper chemistry, Wiley VCH, 2002.

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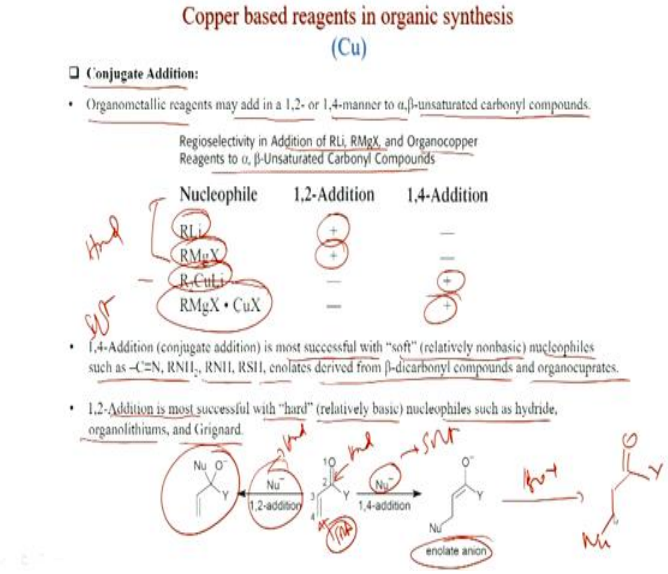

Copper based reagents in organic synthesis

(Cu)

❑ **Conjugate Addition:**

- Organometallic reagents may add in a 1,2- or 1,4-manner to α,β-unsaturated carbonyl compounds.

Regioselectivity in Addition of RLi, RMgX, and Organocopper Reagents to α, β-Unsaturated Carbonyl Compounds

Nucleophile	1,2-Addition	1,4-Addition
RLi	+	—
RMgX	+	—
R_2CuLi	—	+
RMgX • CuX	—	+

Hard

Soft

- 1,4-Addition (conjugate addition) is most successful with "soft" (relatively nonbasic) nucleophiles such as –C≡N, RNH_2, RNH, RSH, enolates derived from β-dicarbonyl compounds and organocuprates.
- 1,2-Addition is most successful with "hard" (relatively basic) nucleophiles such as hydride, organolithiums, and Grignard.

Now, will see some reactions of this Gilman reagent. So first is a conjugate addition, organometallic reagents may add in 1,2 or 1,4 manner to alpha, beta unsaturated carbonyl compounds. And here you can see the regioselectivity in addition of RLi, RMgX and organocopper reagents to alpha, beta unsaturated carbonyl compounds. So when RLi is reacted with alpha, beta unsaturated then you get selectively 1,2 addition. With RMgX also you get 1, 2 addition. On the other hand R_2CuLi you get the 1,4. RMgX CuX you get the 1, 4.

So this is very important because these two are hard and these two are soft, they are hard nucleophile and this is soft nucleophile. So 1,4 addition, conjugate addition is most successful with soft relatively nonbasic nucleophiles such as cyano, RNH_2, RNH, RSH, enolates derived from beta dicarbonyl compounds and organocuprates. So this is very important, soft nucleophiles react in the 1,4 fashion that is the conjugate addition.

And 1,2 addition is more successful with hard relatively basic nucleophiles such as hydride, organolithium and Grignard. So this is the 1,2 addition that nucleophile it is hard and we know this carbonyl centre also is hard. Then the hard nucleophile reaction is a hard nucleophile so you get the 1,2 addition. On the other hand this is the soft, so this soft nucleophile then adds in the 1,4 fashion and you get the enolate anion and which after aqueous acidic workup, you can get the ketone that is conjugated addition product.

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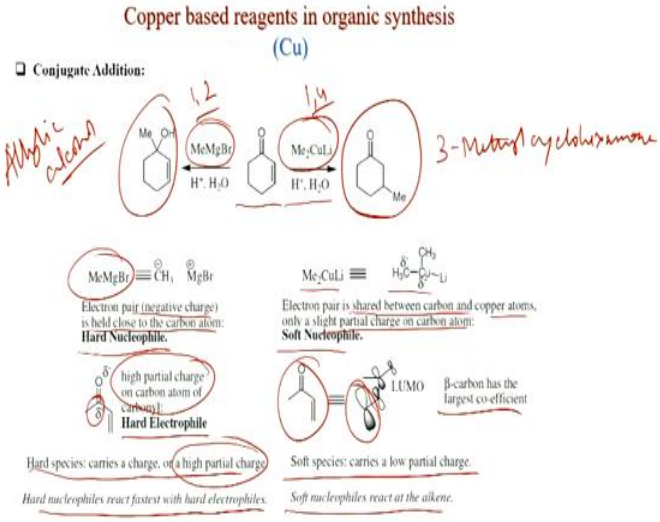

Copper based reagents in organic synthesis

(Cu)

- Conjugate Addition:

Electron pair (negative charge) is held close to the carbon atom: **Hard Nucleophile.**

Electron pair is shared between carbon and copper atoms, only a slight partial charge on carbon atom: **Soft Nucleophile.**

high partial charge on carbon atom of carbonyl: **Hard Electrophile**

β-carbon has the largest co-efficient

Hard species: carries a charge, or a high partial charge

Hard nucleophiles react fastest with hard electrophiles.

Soft species: carries a low partial charge.

Soft nucleophiles react at the alkene.

Now, will see examples like if you add cyclohexenone with dimethyl cuprate and after that acidic workup you get this 3-methyl cyclohexanone, hexanone. On the other hand if you react with methyl magnesium bromide, then you get this allylic alcohols, allylic alcohol. So that means 1,2 fashion here the reaction happens and here the 1, 4 fashion the reaction happen.

This is because Me_2CuLi this is delta plus and delta minus and CH_3^-. Electron pair is shared between carbon and copper atoms over a slide partial charge on carbon atom, so this is soft nucleophile. On the other hand, electron pair negative charge is held close to the carbon atom in case of methyl magnesium bromide and that is why it is hard nucleophile.

So here the alpha,beta unsaturated ketone the LUMO, the beta carbon has the largest coefficient. So the reaction will happen here. Soft species carries a low partial charge. Soft nucleophiles react at the alkene. On the other hand, high partial charge on carbon atoms of carbonyl, here high plus charge, this is hard electrophile. And that is why hard nucleophiles reacts fastest with hard electrophiles. And hard species carries a charge, or a high partial charge. So they will react fast the hard nucleophile and soft nucleophile will react slowly.

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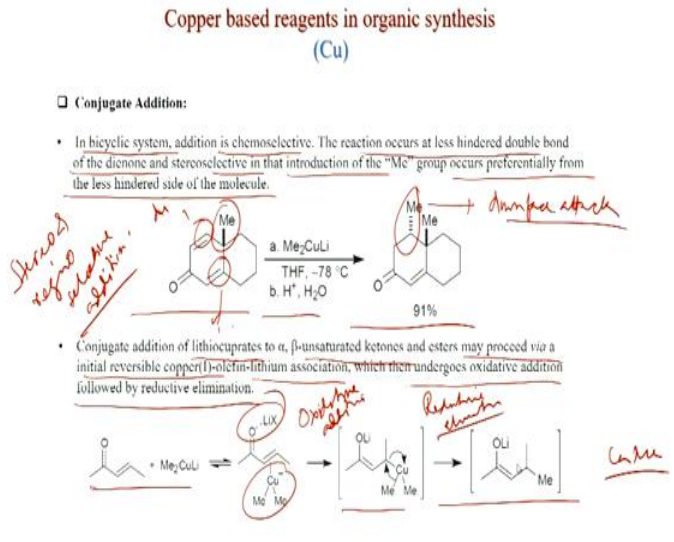

Copper based reagents in organic synthesis
(Cu)

☐ **Conjugate Addition:**

- In bicyclic system, addition is chemoselective. The reaction occurs at less hindered double bond of the dienone and stereoselective in that introduction of the "Me" group occurs preferentially from the less hindered side of the molecule.
- Conjugate addition of lithiocuprates to α, β-unsaturated ketones and esters may proceed *via* a initial reversible copper(I)-olefin-lithium association, which then undergoes oxidative addition followed by reductive elimination.

Conjugate addition, we will see some example now. In bicyclic system, addition is chemoselective. The reaction occurs at less hindered double bond of the dienone and stereoselective in that introduction of the methyl group occurs preferentially from less hindered side of the molecule. So this is very important the reaction will take place from the less hindered side of the substrate.

Like here, if you see this substrate here there is a methyl group which is in the top side. So the attack will take place on the downside, so this is down face attack. And you can see this olefin, this olefin is trisubstituted, on the other hand this is disubstituted. So this is trisubstituted, this is disubstituted. So this is stereo- and regio-selective, regioselective addition. So methyl selectively adds to this double bond and also from the down face. And after aqueous workup we get this enone in 91 percent yield.

Conjugate addition of lithiocuprates to alpha, beta unsaturated ketones and ester may proceed via a initial reversible copper(I) olefin, lithium association, which then undergoes oxidative addition followed by reductive elimination. So the mechanism will be like this, first the coordination happens like this and copper carries a negative charge here. So, lithium coordinates with the carbonyl group.

And now the oxidative addition will happen, so oxidative addition here, copper is adding to this carbon and you get this. And now reductive elimination, reductive elimination will happen that is the methyl will add and copper will eliminate. So you get this copper methyl here and you get this enolate, of course after aqueous workup you will get the carbonyl compound.

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Copper based reagents in organic synthesis

(Cu)

❑ Conjugate Addition:

Addition of Me_3SiCl accelerates the conjugate additions of copper reagents to sterically hindered enones, probably by activating the carbonyl group. So in the case of sterically hindered enones, the conjugate addition will be slow. In the case of trimethylsilyl chloride will help. In the presence of trimethylsilyl chloride the enolate initially formed is trapped to give the beta, beta disubstituted silyl enol ether in 99 percent yield. Then hydrolysis of the silyl enol ether regenerates the carbonyl group.

So will see example, like here, this is substituted cyclohexenone. So this is trisubstituted earlier, we have seen that in trisubstituted cases the dimethylcuprate did not add. But here, if you add this trimethylsilyl chloride and this is the cuprate. Then the addition will take place at -70 degree centigrade, you see this is the quaternary central formed. And you get this product in 99 percent yield, this enol silane. And this enol silane and acidic workup it give this beta,beta disubstituted ketone. So this ketone is form in 99 percent yield.

Reaction of beta, beta disubstituted enones with organocuprates are often not very successful because of steric of the carbon, carbon double bond. In this case, use of R_2CuLi BF_3. So BF_3 ether is another alternative often obviates the problem. Possibly, Lewis acid BF_3, further polarizes and activates the ketone by coordination. So in this case also, this is beta, beta disubstituted enone, beta,beta disubstituted enone.

And so that is the trisubstituted. So here also if you add BF_3 etherate then the reaction will happen with this butyl cuprate, the butyl group will add and after aqueous workup you get this ketone. So this product also is high yield.

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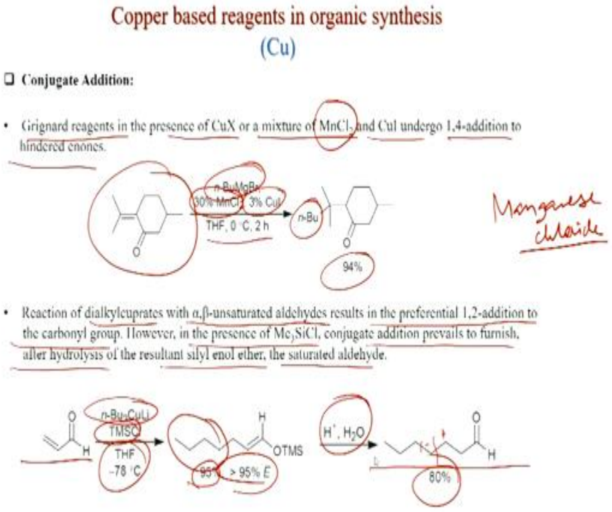

Copper based reagents in organic synthesis

(Cu)

❑ **Conjugate Addition:**

- Grignard reagents in the presence of CuX or a mixture of $MnCl_2$ and CuI undergo 1,4-addition to hindered enones.

- Reaction of dialkylcuprates with α,β-unsaturated aldehydes results in the preferential 1,2-addition to the carbonyl group. However, in the presence of Me_3SiCl, conjugate addition prevails to furnish, after hydrolysis of the resultant silyl enol ether, the saturated aldehyde.

Some more examples. Grignard reagents in the presence of CuX or a mixture of $MnCl_2$ and CuI undergo 1,4 addition to hindered enone. So we have seen that TMS chloride, then we have seen BF_3 etherate, manganese chloride. Manganese chloride also can help in this conjugated addition.

So here, this is the sterically hindered enones, here also, beta, beta disubstituted and with 30% manganese chloride, manganese chloride. And this magnesium bromide with 3% copper iodides, so this, this will be the Grignard reagent formation in situ and then THF 0 degree centigrade, you get the conjugate addition that is the n butyl group is adding. And you get 94 percent yield of this product.

Reaction of dialkylcuprates with alpha,beta unsaturated aldehydes, results in the preferential 1,2 addition to the carbonyl group. However, in the presence of Me_3SiCl, conjugate addition prevails to furnish, after hydrolysis of the resultant silyl enol ether, the saturated aldehyde. So in the case of alpha, beta unsaturated aldehydes what happens. If you add the cuprate then the 1,2 addition takes place. But if you add in the presence of TMS chloride then the 1, 4 addition will take place.

We will see an example, like here, if you react this alpha, beta unsaturated aldehyde with this cuprate, in presence of TMS chloride, THF -78 degree centigrade. So the conjugate addition will takes place, you see the butyl group added and this enol silane form 95 percent yield with greater than 95 percent E selectivity. And after acidic workup you get the aldehyde. So, if you do an electro synthesis that means here you have generate a plus, here minus. So plus means the olefin and you get this product at in 80 percent yield.

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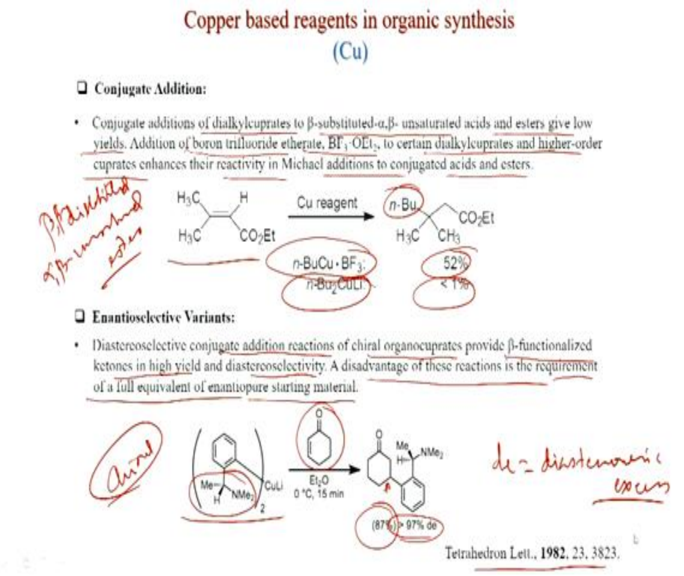

Copper based reagents in organic synthesis
(Cu)

❑ **Conjugate Addition:**

- Conjugate additions of dialkylcuprates to β-substituted-α,β- unsaturated acids and esters give low yields. Addition of boron trifluoride etherate, $BF_3 \cdot OEt_2$, to certain dialkylcuprates and higher-order cuprates enhances their reactivity in Michael additions to conjugated acids and esters.

❑ **Enantioselective Variants:**

- Diastereoselective conjugate addition reactions of chiral organocuprates provide β-functionalized ketones in high yield and diastereoselectivity. A disadvantage of these reactions is the requirement of a full equivalent of enantiopure starting material.

Tetrahedron Lett., **1982**, 23, 3823.

Some more examples, conjugate additions of dialkylcuprates to beta substituted, alpha, beta unsaturated acids and esters give low yields. Addition of boron trifluoride etherate, we have already seen to certain dialkylcuprates and higher-order cuprates enhance their reactivity in Michael addition to conjugated acids and esters.

So this is an example of beta,beta disubstituted, beta,beta disubstituted, alpha,beta unsaturated ester. So this means this centre is trisubstituted. So with n butyl cuprate you get less than 1% yield. On the other hand, if you add BF_3 that is the n butyl cuprate BF3. Then you get the conjugate addition 52% yield of this product.

Now enantioselective variants also is possible. Diastereoselective conjugate addition reactions of chiral organocuprates provide beta functionalized ketones in high yield and diastereoselectivity. A disadvantage of course of these reactions is the requirement of a full equivalent of enantiopure starting material.

So in this case we have to use enantiopure starting material one equivalent. So the cuprate itself is chiral, so the cuprate is chiral here and this cuprate you can see there is a chiral centre here. And if you add to cyclohexenone, then the conjugate addition will take place selectively. So here a chiral centre is forming, newly generated. And this product will be formed in 87% yield and greater than 97% diastereomeric excess. So this is very important, so selectivity is very good, diastereomeric excess, de means.

However, one drawback of this method that stoichiometric amount of the chiral starting material, you have to use. And this was published in tetrahedron letters 1982.

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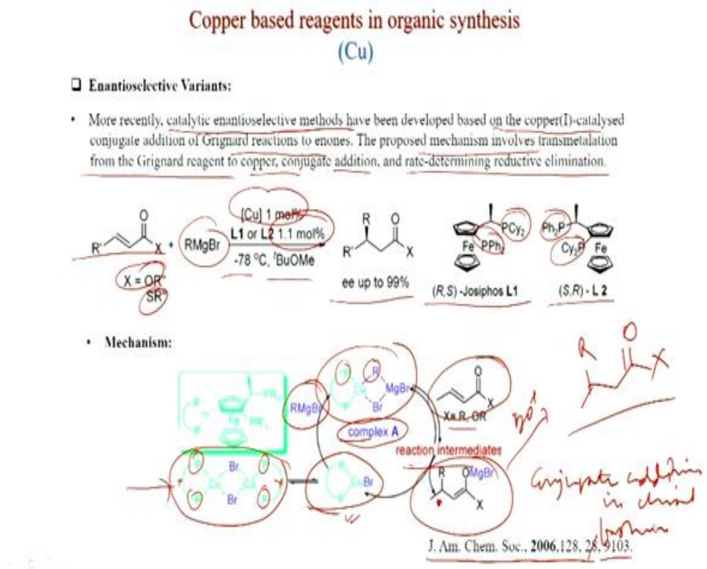

Copper based reagents in organic synthesis

(Cu)

❑ **Enantioselective Variants:**

- More recently, catalytic enantioselective methods have been developed based on the copper(I)-catalysed conjugate addition of Grignard reactions to enones. The proposed mechanism involves transmetalation from the Grignard reagent to copper, conjugate addition, and rate-determining reductive elimination.

- **Mechanism:**

J. Am. Chem. Soc., **2006**,128, 28, 9103.

So that is why the catalytic version, catalytic enantioselectivity methods have been developed based on the copper(I) catalysed conjugate addition of Grignard reaction to enones. The proposed mechanism involved transmetalation from the Grignard reagent to copper, conjugate addition, and rate determining reductive elimination. So this kind of mechanism we have seen earlier that the copper will first the oxidative addition will happen, and then the reductive elimination.

Like here, this is the alpha,beta unsaturated ester or thioester. And the Grignard is present now copper 1 mol% **L1** or **L2**. So these are the structure of the **L1**, **L1** is (R,S)-Josiphos here, triphenylphosphine is there, and here cyclohexylphosphine and here just change happen.

This become now PPh_2 and this is the PCy_2. So here, this was PPh_2, PCy_2. Now with this ligand 1.1 mol% only -78 degree centigrade tert butyl methyl ether, you get this conjugate addition product up to 99 percent. So this is very important with catalytic amount, catalytic phosphine catalyst, you can get high enantioselectivity. So, will discuss the mechanism what is happening here?

Now, first the ligand that is the phosphine ligand binds with the copper. So this is very important, you see these are the phosphine PP and it is binding with the copper. So this is chiral and dimeric species is forming that is going to monomer like this. And in the monomer it can react with Grignard and after Grignard it is forming the complex A. This kind of complex where R is binding with copper.

So this is very important, R is binding with copper and copper is binding with chiral ligands. So, what will happen? R is in the chiral environment. And now if it is adding to the alpha, beta unsaturated ester or ketone reaction intermediate. So this will have, give the intermediate that the conjugate addition is happening here, conjugate addition. And the conjugate addition in chiral fashion. So this chiral centre will be determined.

And after that this will be reductively eliminate this copper species monomeric and after aqueous workup you get the ester or ketone. So this is very important the catalytic amount of phosphine and copper can give you the product in high enantiomeric ratio. This was published in JACS 2006. 128. This is the issue and this is the page number 9103.

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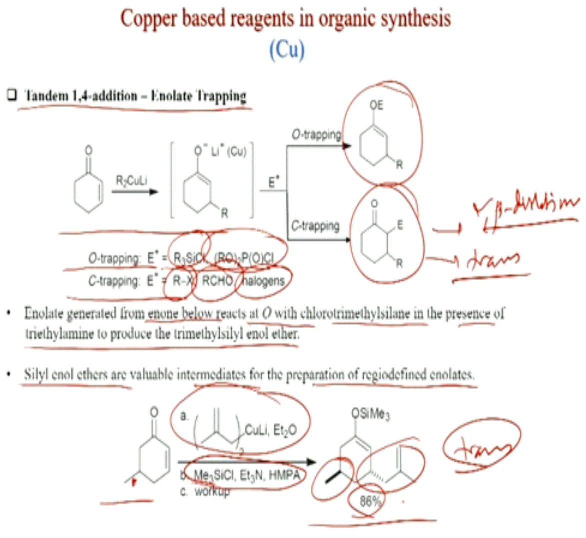

Copper based reagents in organic synthesis
(Cu)

❑ Tandem 1,4-addition – Enolate Trapping

O-trapping: E$^+$ = R$_3$SiCl, (RO)$_2$P(O)Cl

C-trapping: E$^+$ = R-X, RCHO, halogens

- Enolate generated from enone below reacts at *O* with chlorotrimethylsilane in the presence of triethylamine to produce the trimethylsilyl enol ether.
- Silyl enol ethers are valuable intermediates for the preparation of regiodefined enolates.

Now, we will discuss Tandem 1,4 addition. So, so far we have seen the only one bond formation, now we can see two bond formation. So here, after the addition you can see the enolate is forming. So this is an enolate actually and that enolate you can trapped, that enolate you can trap either that the oxygen centre O trapping that is called, an electrophile can be R_3SiCl that we have already seen and phosphorus chloride also you can use.

On the other hand, C trapping can be done by, if you treat alkene halide, aldehyde, even halogens that will give the C trapping. So, O trapping will give you this product, enol product. On the other hand, C trapping will give you this alpha beta, this is very important, alpha, beta disubstitution, disubstitution generally this product is Trans when the C trapping is happen.

Enolate generator from enone below reacts at oxygen with chlorotrimethylsilane in the presence of triethylamine to produce the trimethylsilyl enol ether. Silyl enol ether are valuable intermediates to the preparation of regiodefined enolates. Like here you see this was a, this is a chiral centre actually and when it adding with this cuprate and if you quench trimethylsilyl chloride, triethylamine in HMPA. Then this enolate is forming, this is the silyl enolate. And you can see this chiral centre, this is opposite to this methyl. So these are Trans and this product is forming in 86 percent yield.

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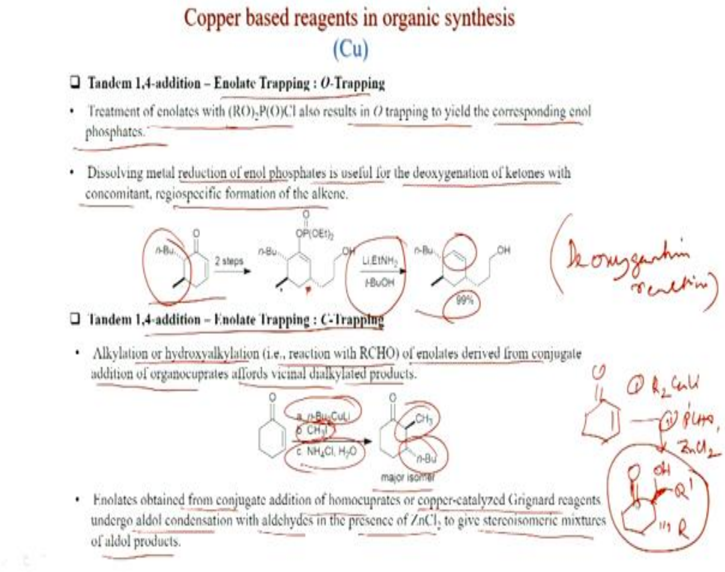

Copper based reagents in organic synthesis

(Cu)

❑ **Tandem 1,4-addition – Enolate Trapping : *O*-Trapping**

- Treatment of enolates with $(RO)_2P(O)Cl$ also results in *O* trapping to yield the corresponding enol phosphates.
- Dissolving metal reduction of enol phosphates is useful for the deoxygenation of ketones with concomitant, regiospecific formation of the alkene.

❑ **Tandem 1,4-addition – Enolate Trapping : C-Trapping**

- Alkylation or hydroxyalkylation (i.e., reaction with RCHO) of enolates derived from conjugate addition of organocuprates affords vicinal dialkylated products.

- Enolates obtained from conjugate addition of homocuprates or copper-catalyzed Grignard reagents undergo aldol condensation with aldehydes in the presence of $ZnCl_2$ to give stereoisomeric mixtures of aldol products.

Some more examples of O trapping, now treatment of enolates with this $(RO)_2P(O)Cl$ also results in O trapping to yield the corresponding enol phosphates. So earlier we have seen enol silane, now will see enol phosphates. Dissolving metal reduction of enol phosphates is useful for the deoxygenation of ketones with concomitant, regiospecific formation of the alkene.

So here, this is two chiral centres are present, now the control will be done by this chiral. So this will be down and this is up. So after two steps, you get this enol phosphate. And these enol phosphate, one usefulness of enol phosphate that earlier we have seen the enol silane the aqueous workup generate the ketones.

But enol phosphate you can generate the olefin. So this is very important, just you have to treat with lithium, ethyl amine and tert butanol solvent you get this olefin in 99 percent yield. So this is very important, this is like deoxygenation reaction, deoxygenation reaction most likely going by radical mechanism.

So far we have seen the O trapping, now we will see C trapping. So alkylation or hydroxyalkylation that is the hydroxyalkylation if you react with aldehyde of enolates derived from conjugate addition of organocuprates affords vicinal dialkylated products. So this is very important alpha beta disubstitution. Like here n butyl cuprate first the conjugate addition and then the C trapping with add a methane, you get this methyl group and there in the Trans. So this is the major isomer, this is the workup.

Enolates obtained from conjugate addition of homocuprates or copper catalyzed Grignard reagents undergo aldol condensation with aldehydes in the presence of zinc chloride to give stereoisomeric mixture of aldol products. So, if you put zinc chloride, then this. So first this R_2CuLi and then add the CHO and here if you add the zinc, then what will happen? Suppose this will be from down and this will be up so you get the OH R1. So this is the hydroxy methylation, this product, you can get.

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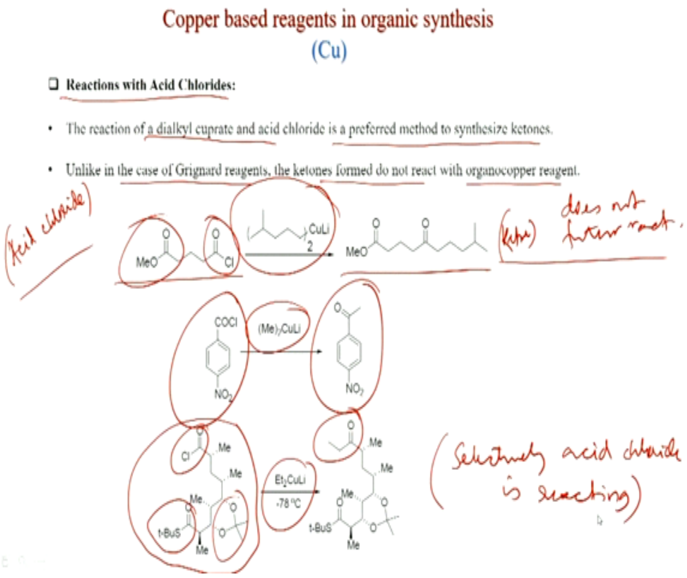

Copper based reagents in organic synthesis

(Cu)

❑ **Reactions with Acid Chlorides:**

- The reaction of a dialkyl cuprate and acid chloride is a preferred method to synthesize ketones.
- Unlike in the case of Grignard reagents, the ketones formed do not react with organocopper reagent.

Acid chloride

ketone does not further react.

(Selectively acid chloride is reacting)

Now, we will discuss reactions with acid chlorides, so far we have discuss the conjugate addition. Now, we will see the reaction with carbonyl group, first we will discuss reaction with acid chloride. The reaction of dialkyl cuprate and acid chloride is the preferred method to synthesize ketones. Unlike in the case of Grignard reagents, the ketones formed do not react with organocopper reagent. Like here it is an acid chloride and you can see there is ester motif also. Now, if you react with this cuprate what happens? The acid chloride is only react and you get this ketone. So this is very important the ester is not reacting.

This ketone is forming also this ketone is stable. So ketone does not further react that earlier I have told that ketone does not further reacts, so it is very important method then for the preparation of ketones. Like here 4-nitrobenzoyl chloride, if you treat with dimethyl cuprate, then you can get this 4-nitroacetophenone. Also, if you see this complex structure here a acid chloride motif is there, here are ketal motif is present and here a thioester motif present. And with diethyl cuprate -78 degrees centigrade, only this acid chloride reacted and you get this ketone. So selectively acid chloride is reacted.

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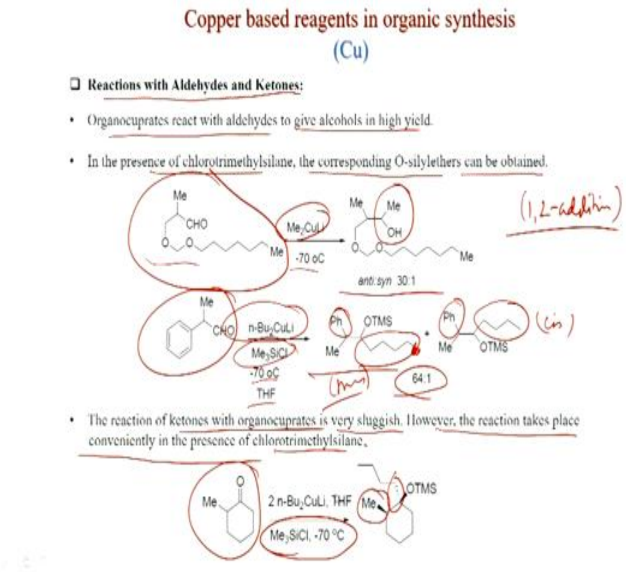

Copper based reagents in organic synthesis

(Cu)

❑ **Reactions with Aldehydes and Ketones:**

- Organocuprates react with aldehydes to give alcohols in high yield.
- In the presence of chlorotrimethylsilane, the corresponding O-silylethers can be obtained.

- The reaction of ketones with organocuprates is very sluggish. However, the reaction takes place conveniently in the presence of chlorotrimethylsilane.

Now, we will discuss reactions with aldehydes and ketones. We have told the reaction of acid chloride will be faster than aldehyde and ketone but the reaction is possible. Organocuprates react with aldehydes to give alcohols in high yield. In the presence of chlorotrimethylsilane, the corresponding O silylethers can be obtained. Like here if you react dimethyl cuprates with this aldehyde as you can see there is ether is there and -78 degrees centigrade. Then this 1,2 addition product you can get, 1,2 addition product with aldehydes selectively and you can get anti syn ratio 30:1.

Also if you have this alpha branched aldehyde and n butyl cuprate then coinciding with trimethylsilane chloride, where the reaction will be faster and -78 degrees centigrade THF you get this two products, 64:1 ratio. And you can see this phenyl, usually here, one carbon is less, so this will not be there. And this butyl group there will be Trans to each other and here they are cis to each other. So this is cis this is Trans. So Trans will be major 64:1 ratio.

The reaction of ketones with organocuprates is very sluggish. So enones will reacting 1,4 fashion. But simple ketones the reaction is very sluggish. However, the reaction takes place conveniently in the presence of chlorotrimethylsilane. So this is very important, simple ketones does not react, but if you put trimethylsilyl chloride then the reaction will happen, possibly by the activation of the carbonyl group. And here you can get this Trans you see, this Trans product form as the major product.

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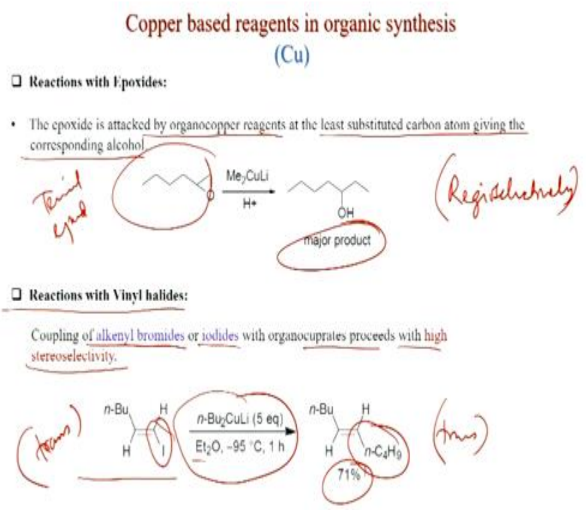

Copper based reagents in organic synthesis

(Cu)

❑ **Reactions with Epoxides:**

- The epoxide is attacked by organocopper reagents at the least substituted carbon atom giving the corresponding alcohol

❑ **Reactions with Vinyl halides:**

Coupling of alkenyl bromides or iodides with organocuprates proceeds with high stereoselectivity.

Reactions with epoxides also is possible. The epoxides is attacked by organocopper reagents at the least substituted carbon atom giving the corresponding alcohol. Like here this is the terminal epoxide, terminal epoxide and the reaction will take place regioselectively. So regioselectively, this is the major product will form. So Me_2CuLi attack from the less hindered carbon. Now reactions with vinyl halides, this is very important reaction. The coupling of alkenyl bromides or iodides with organocuprates proceeds with high stereoselectivity.

Like here, this vinyl iodide, so you can see this is trans, trans and the product also is Trans. So what happens? The double bond geometry is not changing in this process. And selectively the CI bond is replaced with this bond. So n butyl group is coming just n butyl cuprate ether -95 degrees centigrade 1 hour you get this product 71 percent. And here also the similar mechanism, the oxidative addition and reductive elimination is occurring to get this substituted olefin.

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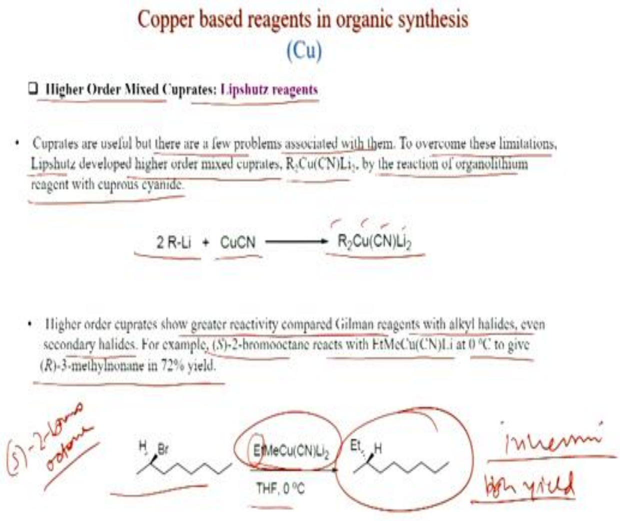

Copper based reagents in organic synthesis

(Cu)

❑ **Higher Order Mixed Cuprates: Lipshutz reagents**

- Cuprates are useful but there are a few problems associated with them. To overcome these limitations, Lipshutz developed higher order mixed cuprates, $R_2Cu(CN)Li_2$, by the reaction of organolithium reagent with cuprous cyanide.

$$2\ R\text{-}Li + CuCN \longrightarrow R_2Cu(CN)Li_2$$

- Higher order cuprates show greater reactivity compared Gilman reagents with alkyl halides, even secondary halides. For example, (*S*)-2-bromooctane reacts with $EtMeCu(CN)Li$ at 0 °C to give (*R*)-3-methylnonane in 72% yield.

Now, we will discuss higher-order mixed cuprates lipshutz reagents. So, so far, the reaction we have discussed with Gilman reagent, now lipshutz reagent. Cuprates are useful, but there are a few problems associated with them. To overcome these limitations, lipshutz develop higher-order mixed cuprates. $R_2Cu(CN)Li_2$, by the reaction of organolithium reagent with cuprous cyanide. So this is the reaction 2RLi plus CuCN, so here this cyanide group will be in the reagent $R_2Cu(CN)Li_2$.

Higher-order cuprates show greater reactivity compared to Gilman reagents with alkyl halides, even secondary halides. For example, (S)-2-bromooctane reacts with EtMeCu(CN)Li at 0 degree centigrade to give (R)-3-methylnonane in 72 percent yield. So this is very important, simple Gilman reagents gives sluggish reaction with alkyl halides. But the reactivity is increased with this lipshutz reagent.

One example, so this is the 2 bromo, (S)-2-bromooctane and when it is reacted with this $EtMeCu(CN)Li_2$, you get an inversion of course. So this is inversion, because this is say substitution reaction. But selectively the ethyl group is incorporated into the product and you get high yield also. So that is the usefulness of lipshutz reagent.

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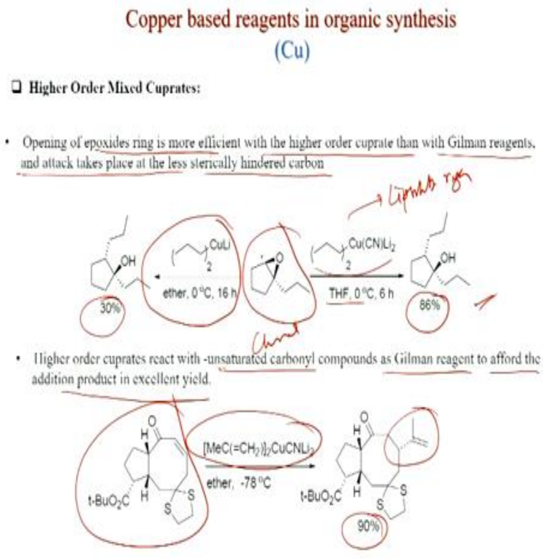

Copper based reagents in organic synthesis

(Cu)

❑ **Higher Order Mixed Cuprates:**

- Opening of epoxides ring is more efficient with the higher order cuprate than with Gilman reagents, and attack takes place at the less sterically hindered carbon
- Higher order cuprates react with -unsaturated carbonyl compounds as Gilman reagent to afford the addition product in excellent yield.

Some more example, opening of epoxides ring is more efficient with the higher-order cuprates than with Gilman reagents, and attack takes place at the less sterically hindered carbon. So this is also important that it is much reactive than the Gilman reagent. Suppose, if you have this epoxides, so this is chiral. However, the one side, this side it is tetra substituted, this side it is trisubstituted. So what will happen? The reaction will selectively happen this side only.

Now, if you add only this cuprate in ether 0 degree centigrade, you get the product that the epoxides opening product is happening, like earlier you have seen, but the yield is 30 percent. On the other hand, if you use the lipshutz reagent, then the yield is much higher, here you have to use THF solvent 0 degree centigrade, 6 hours you get 86 percent yield. The same product is forming but the yield is much higher.

Also higher-order cuprates react with unsaturated carbonyl compounds as Gilman reagents to afford the addition product in excellent yield. Like here, if you add this reagent with this substrate, this is complex structure, you can see. Now this is bicyclic system, now the addition will take place, selectively from the down face and you get 90 percent yield. So, very high yield, so conjugate addition case also very high yield for the product you can get.

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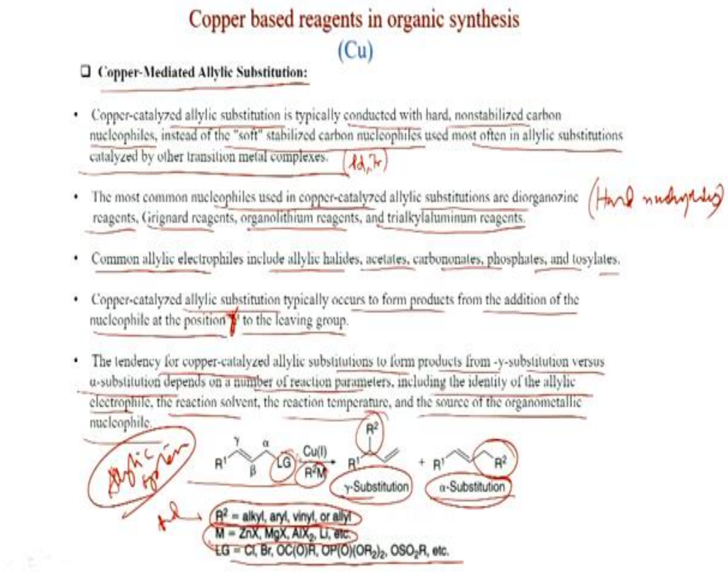

Copper based reagents in organic synthesis

(Cu)

❑ **Copper-Mediated Allylic Substitution:**

- Copper-catalyzed allylic substitution is typically conducted with hard, nonstabilized carbon nucleophiles, instead of the "soft" stabilized carbon nucleophiles used most often in allylic substitutions catalyzed by other transition metal complexes. (Pd, Ir)
- The most common nucleophiles used in copper-catalyzed allylic substitutions are diorganozinc reagents, Grignard reagents, organolithium reagents, and trialkylaluminum reagents. (Hard nucleophiles)
- Common allylic electrophiles include allylic halides, acetates, carbononates, phosphates, and tosylates.
- Copper-catalyzed allylic substitution typically occurs to form products from the addition of the nucleophile at the position γ to the leaving group.
- The tendency for copper-catalyzed allylic substitutions to form products from -γ-substitution versus α-substitution depends on a number of reaction parameters, including the identity of the allylic electrophile, the reaction solvent, the reaction temperature, and the source of the organometallic nucleophile.

R^2 = alkyl, aryl, vinyl, or allyl

M = ZnX, MgX, AlX_2, Li, etc.

LG = Cl, Br, OC(O)R, $OP(O)(OR_2)_2$, OSO_2R, etc.

Now, we will see different reaction that is the copper mediated allylic substitution. Earlier we have seen the palladium catalyzed allylic substitution. Now, we will see copper catalyzed allylic substitution and one difference is the palladium catalyses, the soft nucleophiles can be employed, but here hard nucleophiles.

So copper catalyzed allylic substitution is typically conducted with hard, non-stabilized carbon nucleophiles, instead of the soft stabilised carbon nucleophiles used most often in allylic substitutions catalyzed by other transition metals, like palladium, iridium system. The most common nucleophiles used in copper catalyzed allylic substitutions are diorganozinc reagents, Grignard reagents, organolithium reagents and trialkylaluminium reagents. So these are hard, hard nucleophile that has been used in the copper catalyzed allylic substitution reaction.

And common allylic electrophiles include allylic halides, acetates, carbonates, phosphates and tosylates. Copper catalyzed allylic substitution typically occurs to form products from the addition of the nucleophile at the position gamma to the living group. So this is actually Y means here, this is gamma to the living group.

The tendency for the copper catalyzed allylic substitution to form products from gamma substitution versus alpha substitution depends on a number of reaction parameters, including the identity of the allylic electrophile, the reaction solvent, the reaction temperature, and the source for the organometallic nucleophile. So this is very important the gamma and alpha substitution is possible.

Like here, this is the allylic system, allylic system and LG is the living group here, LG is Cl, Br, OC(O)R, OP(O)(OR$_2$)$_2$, OSO$_2$R. And R^{2}M, R^{2}M this is hard, so this is hard nucleophile R^2 is alkyl, aryl, vinyl, or allyl. And M is equal to zinc, so these are all metals. M is zinc, magnesium, aluminium, lithium etc. And this is the gamma substitution, so alpha, beta gamma substitution here and this is the alpha substitution. Alpha substitution means the same carbon where the living group was attached, so that is called alpha substitution.

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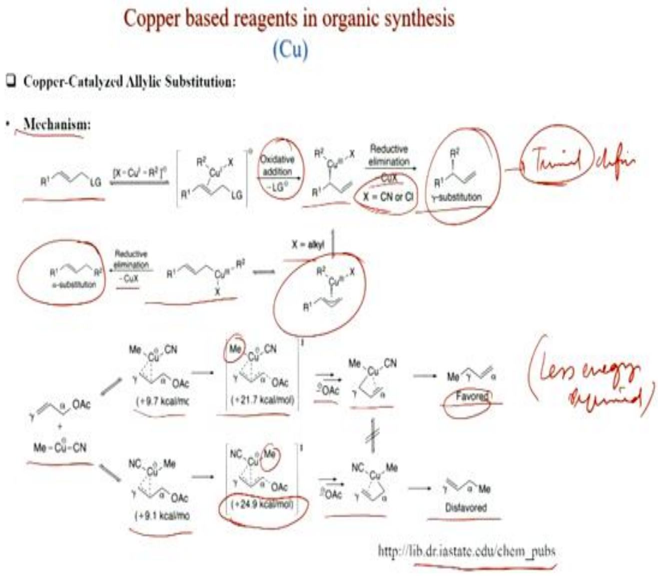

Copper based reagents in organic synthesis

(Cu)

❑ Copper-Catalyzed Allylic Substitution:

- Mechanism:

http://lib.dr.iastate.edu/chem_pubs

And the mechanism. So first we will discuss the mechanism, what happen? Here, if you have a leaving group, then the cuprate first the coordination happens earlier we have seen. Now, the oxidative addition will take place at the gamma position and the double bond doing migrate. After reductive elimination and -CuX, you get this gamma substitution product with a terminal olefin. So here the olefin is terminal.

On the other hand, X is equal to alkyl, then this kind of allylic system will form. So here X is equal to CN or Cl, then the gamma substitution and here the S is equal to alkyl. Then this will form that is the alpha substitution. So here this addition is taking place at the alpha place and reductive elimination is -CuX, you get this alpha substituted product.

So why with, when X is equal to CN or Cl, you get the gamma substitution that will see the energy barrier. So first this coordination plus 9.7 kilo calorie per mole and here you see plus

21.7 kilo calorie per mole to get the allylic system and then this is the gamma reaction, it is favoured. And on the other hand with this same system for the alpha cases this energy is little lower, but the second one is higher, 24.9 kilo calorie.

So here, methyl is this side and here methyl was other side. And after that you get alpha substituted product and this is disfavoured. So this is favoured, less energy required. So energetically favourable this gamma substitution when X is equal to CN, here you can see the details.

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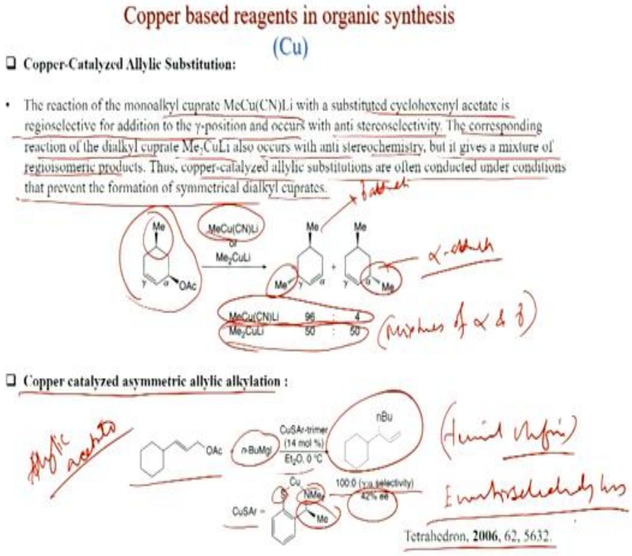

Copper based reagents in organic synthesis

(Cu)

❑ **Copper-Catalyzed Allylic Substitution:**

- The reaction of the monoalkyl cuprate MeCu(CN)Li with a substituted cyclohexenyl acetate is regioselective for addition to the γ-position and occurs with anti stereoselectivity. The corresponding reaction of the dialkyl cuprate Me_2CuLi also occurs with anti stereochemistry, but it gives a mixture of regioisomeric products. Thus, copper-catalyzed allylic substitutions are often conducted under conditions that prevent the formation of symmetrical dialkyl cuprates.

MeCu(CN)Li	96	4
Me_2CuLi	50	50

❑ **Copper catalyzed asymmetric allylic alkylation :**

Tetrahedron, **2006**, 62, 5632.

Now will see example, so the reaction of the monoalkyl cuprate MeCu(CN)Li with the substituted cyclohexenyl acetate is regioselective for the addition to the gamma position. So that you have seen when X is equal to CN, then you get the gamma attack and occurs with anti stereoselectivity. The corresponding reaction of the dialkyl cuprate Me_2CuLi also occurs with anti-stereochemistry, but it gives a mixture of regioisomeric products. Thus, copper catalyzed allylic substitutions are often conducted under conditions that prevent the formation of symmetrical dialkyl cuprates.

So here, if you see this is a chiral allylic acetate also there is a methyl group there that is also chiral. And when you add MeCu(CN)Li, what happens? You get the gamma attack. So this is the gamma attack, this is gamma attack product and this is alpha attack. And both cases the stereochemistry is opposite of the methyl group, existing methyl group. However, in the case of Me_2CuLi, you do not get the selectivity. So mixtures, mixtures of alpha and gamma. So that is the importance of cyano. In the cyano case, you selectively get the gamma product. But in the case of Me_2CuLi, you get the mixture.

Now, we will see asymmetric version, copper catalyzed asymmetric allylic alkylation that is also possible with suitable ligand. So this is the allylic acetate, allylic acetate and this is Grignard and here, this is the copper sulphide here. So sulphur is there, also amine is there that is binding with copper and with Et_2O ether 0 degrees centigrade, you get 100:0 gamma: alpha selectivity.

So here also terminal olefin is forming, terminal olefin is forming and you get this selectivity is very high 100 percent. However, the enantioselectivity 42 percent. So enantioselectivity is less because if you see the ligand there is only a methyl group. So, if you have bulky ligand then the enantioselectivity can be much higher. This was published in tetrahedron 2006.

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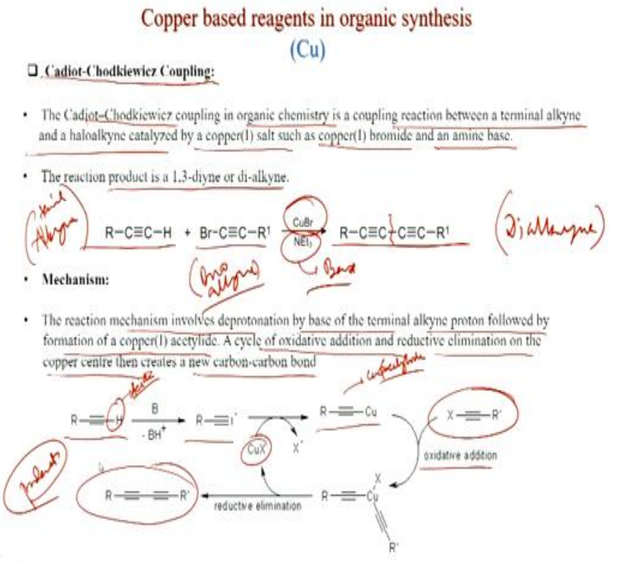

Copper based reagents in organic synthesis

(Cu)

❑ **Cadiot-Chodkiewicz Coupling:**

- The Cadiot-Chodkiewicz coupling in organic chemistry is a coupling reaction between a terminal alkyne and a haloalkyne catalyzed by a copper(I) salt such as copper(I) bromide and an amine base.
- The reaction product is a 1,3-diyne or di-alkyne.

$$R{-}C{\equiv}C{-}H \;+\; Br{-}C{\equiv}C{-}R^1 \xrightarrow[NEt_3]{CuBr} R{-}C{\equiv}C{-}C{\equiv}C{-}R^1$$

- **Mechanism:**
- The reaction mechanism involves deprotonation by base of the terminal alkyne proton followed by formation of a copper(I) acetylide. A cycle of oxidative addition and reductive elimination on the copper centre then creates a new carbon-carbon bond

Now, we will set different coupling reaction. So first will discuss Cadiot-chodkiewicz coupling, because we have discussed the copper, it can add to aryl even the triple bond halide and it can give the product, alkylated or arylated product. So the Cadiot-chodkiewicz coupling in inorganic chemistry is a coupling reaction between a terminal alkyne and halaoalkyne catalyzed by a copper(I) salt such as copper(I) bromide and an amine base.

The reaction product is 1,3 diyne or di-alkyne, so this is the reaction. So you have to use an alkyne and this is actually terminal alkyne, so the reaction will happens and this is the bromo alkyne. And copper(I) and a base, so this is base and then you get a product. So this coupling happen here C-C coupling and this is di-alkyne. So this is very important just simple copper and base it can give the coupling product.

So what could be the mechanism? The reaction mechanism involves deprotonation by a base of the terminal alkyne proton followed by formation of a copper(I)acetylide. A cycle of oxidative addition and reductive elimination and the copper centre then creates a new carbon-carbon bond. So this is the reaction, first terminal alkyne that is acidic, this is acidic. So this can be deprotonated by base to generate the anion and that can react with copper to generate the copper acetylide. So this, we have seen in the Sonogashira reaction also copper acetylide.

And now this copper acetylide will add to the bromo alkyne and this will be the oxidative addition. So this you see oxidative addition happens here and after reductive elimination, so CuX will be eliminated and reductive elimination you get this product. So this is the product. So the importance is the copper acetylide it formed then the oxidative addition happens and after the reductive elimination gives you the coupling product.

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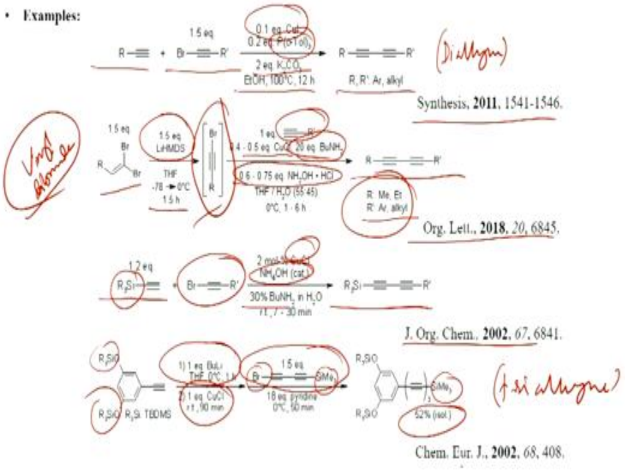
Copper based reagents in organic synthesis

(Cu)

❑ **Cadiot-Chodkiewicz Coupling:**

- **Examples:**



Synthesis, **2011**, 1541-1546.

Org. Lett., **2018**, *20*, 6845.

J. Org. Chem., **2002**, *67*, 6841.

Chem. Eur. J., **2002**, *68*, 408.

We will see some examples now. So this is the R, R can be aryl or alkyl and this is the bromo alkyne with 0.1 equivalent copper(I) that is copper iodide and you need another phosphine, ortho tolyl phosphine. This is the base 2 equivalent potassium carbonate, ethanol, 100 degrees centigrade, you get this dialkyl product in good yields. This was published in synthesis, 2011.

Also, if you see this is the vinyl dibromide, so vinyl dibromide and in situ you can generate the bromo alkyne just treatment with LHMDS. So lithium hexamethyldisilazane, this is called lithium HMDS and which THF solvent and -78 to 0 degrees centigrade 1.5 hours you get this bromo alkyne, which in situ reacted with terminal alkyne with 0.4 to 0.5 equivalent copper(I) and this is the additive 20 equivalent butyl amine and this is the base 0.6 to 0.75 equivalent ammonium hydroxide. And you get this product and the scope is broad. R can be methyl, ethyl and thus can be aryl, alkyl. And this was published in recently organic letters, 2018.

Also silyl alkyne can be also used because the silyl group later, you can use for further reaction. And with bromo alkyne, with copper(I), ammonium hydroxide, this is catalytic amount the base and this 30 percent butyl amine in water, you get this coupling product in room temperature only. This was published in JOC, 2002.

This is another reaction, this is you can see aromatic system is there and the silyl group is present here with 1 equivalent butyl lithium that is the base here. And then 1 equivalent copper(I), copper chloride here and this is a dialkyne. So $SiMe_3$ is one side and Br one side, so Br side will react. And the $SiMe_3$ will stay intact and you see this is actually trialkyne. And this is 52 percent isolated yield. This was published in chemistry European Journal, 2002.

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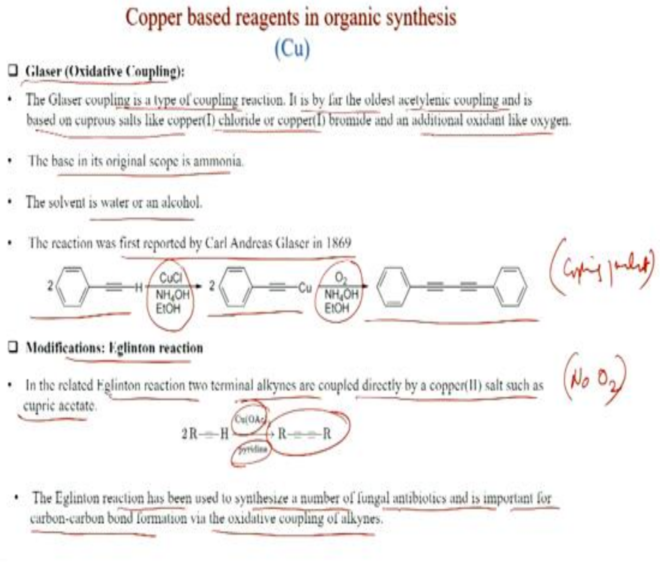

Copper based reagents in organic synthesis

(Cu)

❑ **Glaser (Oxidative Coupling):**

- The Glaser coupling is a type of coupling reaction. It is by far the oldest acetylenic coupling and is based on cuprous salts like copper(I) chloride or copper(I) bromide and an additional oxidant like oxygen.
- The base in its original scope is ammonia.
- The solvent is water or an alcohol.
- The reaction was first reported by Carl Andreas Glaser in 1869

❑ **Modifications: Eglinton reaction**

- In the related Eglinton reaction two terminal alkynes are coupled directly by a copper(II) salt such as cupric acetate.

- The Eglinton reaction has been used to synthesize a number of fungal antibiotics and is important for carbon-carbon bond formation via the oxidative coupling of alkynes.

Now, we will see Glaser that is another oxidative coupling. The Glaser coupling is a type of coupling reaction. It is by far the oldest acetylenic coupling and is based on cuprous salts like copper(I)chloride or copper(I)bromide and an additional oxidant like oxygen.

The base in its original scope is ammonia. The solvent is water or an alcohol. The reaction was first reported by Carl Andreas Glaser in 1869, so that is why it is called Glaser coupling.

Here the oxygen is actually the oxidant. So, what you have to do? This 2 equivalent of terminal alkyne with copper chloride and base you get the copper acetylide and with oxygen ammonium hydroxide ethanol you get the coupling. So this is the coupling product.

And now there are some modification Eglington reaction. In the related Eglington reaction two terminal alkynes are coupled directly by copper(II)salt such as cupric acetate. So here no oxygen because copper(II) is used, like here you need a base of course pyridine and copper(II), you can get this coupling product.

The Eglington reaction has been used to synthesize a number of fungal antibiotics and is important for carbon-carbon bond formation via the oxidative coupling of alkynes.

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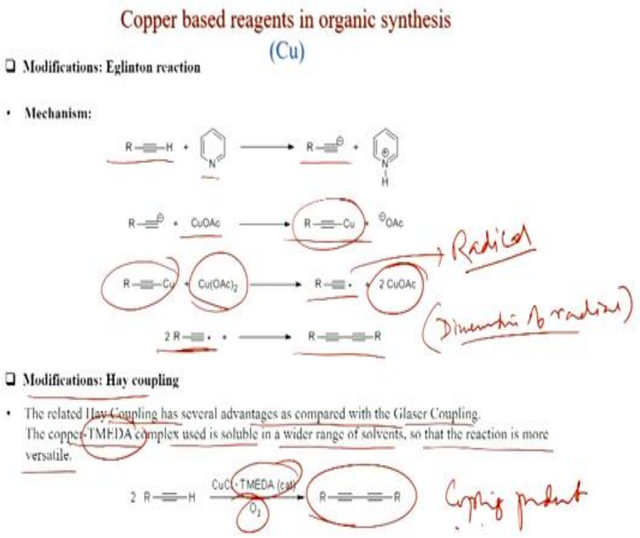

Copper based reagents in organic synthesis

(Cu)

❑ **Modifications: Eglinton reaction**

- **Mechanism:**

❑ **Modifications: Hay coupling**

- The related Hay Coupling has several advantages as compared with the Glaser Coupling. The copper-TMEDA complex used is soluble in a wider range of solvents, so that the reaction is more versatile.

So here the mechanism, the alkyne first react with pyridine give the acetylide, acetylide generate react with copper(I). So this copper(I) is generated from copper(II) actually, so that will see. And then the copper acetylide is form and this copper acetylide when react with copper(II) it generates a radical. So this is very important radical is formed. And 2 equivalent of copper acetate. So this copper acetate is reacting here actually. And then this 2 radical, the dimerization happens. So dimerization of radical, 2 radical makes a carbon-carbon bond and you get this dialkyne.

Hay coupling also there is an modification Hay coupling. The related Hay coupling has several advantages as compared with the Glaser coupling. The copper TMEDA complex used is soluble in wide range of solvents, so that the reaction is more versatile. So here TMEDA is used in the Hay coupling. So this is the reaction copper(I) TMEDA, catalytic amount and oxygen you get the coupling product. So this is the coupling product.

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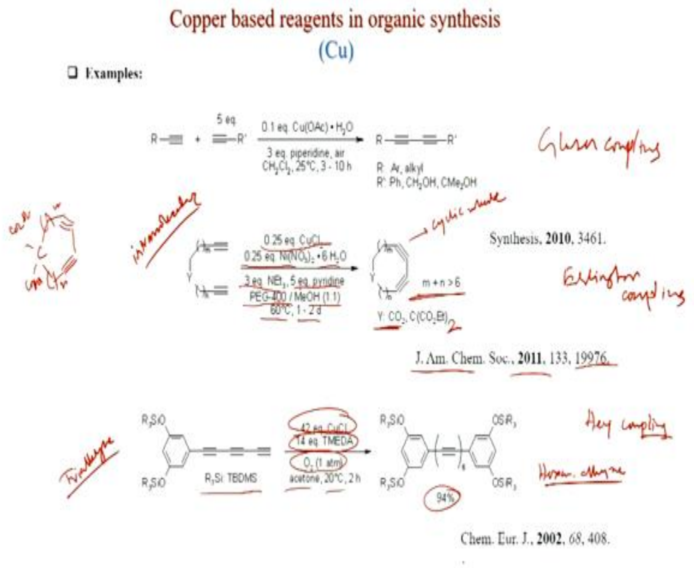

Copper based reagents in organic synthesis

(Cu)

❑ Examples:

Synthesis, **2010**, 3461.

J. Am. Chem. Soc., **2011**, 133, 19976.

Chem. Eur. J., **2002**, *68*, 408.

Examples, so this is terminal alkyne, this is another alkyne, 5 equivalent, 0.1 equivalent of copper acetate, this is copper(I) piperidine air. So this is Glaser coupling, Glaser coupling with base and 0 degrees centigrade 3 to 10 hours you get this dialkyne and R can be aryl, alkyl and R' can be Ph, CH_2OH, CMe_2OH. This was published in synthesis.

So you can see this is a dialkyne and this reaction is intra molecular. And, if this substance treated with 0.25 equivalent copper chloride, 0.25 equivalent nickel nitrate, 6 H_2O this is an additional catalyst. 3 equivalents of triethylamine. 5 equivalent of pyridine, PEG-400, methanol 1:1. 60 degrees centigrade and 1 to 2 days, you get this cycling molecule. And this is actually Eglington coupling. And Y can be CO_2 or $C(CO_2Et)_2$ and generally m+n should be greater than 6. So the cyclisation will happen efficiently. So this is macro cyclisation.

And for CO_2 the product will be like this. So one oxygen like this and then if the carbon chain and this side also the carbon chain will be there like this. And for $C(CO)_2$ also, it can be like this CCO_2Et, CO_2Et and you have the alkyne. So here more carbon atoms are there like this. And this was published in JACS, 2011, page number is 19976.

Also you can see this is trialkyne, trialkyne and this is called Hay coupling. This trialkyne, where R_3Si can be TBDMS when treated with 42 equivalent of copper chloride, 14 equivalent of TMEDA, oxygen 1 atmosphere, acetone solvent 20 degrees centigrade, then you get this dimerised product obtained in 94 percent yield. So this is actually hexaalkyne. So this is very important that a moreover converted to diyne treating with copper chloride, TMEDA and oxygen atmosphere.

And this work was published in chemistry European Journal, 2002. So these are very useful methods, this Glaser coupling, Eglington modification and the Hay modification there, if the dialkyne or trialkyne. And this was published in Chemistry European Journal, 2002.

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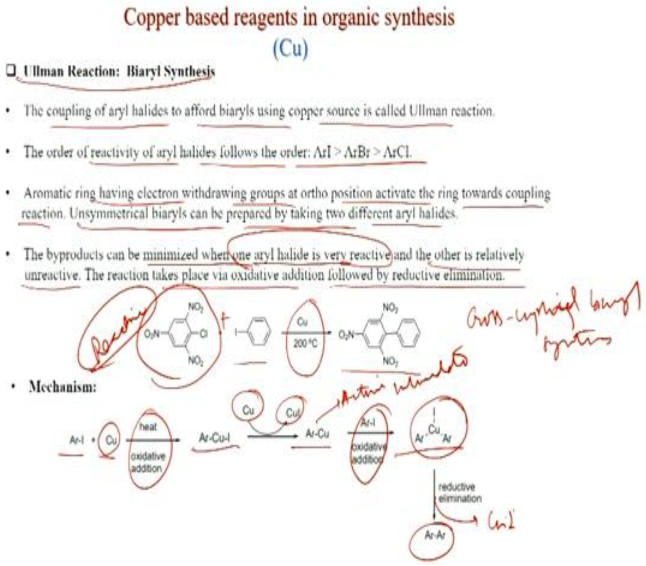

Copper based reagents in organic synthesis

(Cu)

❑ Ullman Reaction: Biaryl Synthesis

- The coupling of aryl halides to afford biaryls using copper source is called Ullman reaction.
- The order of reactivity of aryl halides follows the order: ArI > ArBr > ArCl.
- Aromatic ring having electron withdrawing groups at ortho position activate the ring towards coupling reaction. Unsymmetrical biaryls can be prepared by taking two different aryl halides.
- The byproducts can be minimized when one aryl halide is very reactive and the other is relatively unreactive. The reaction takes place via oxidative addition followed by reductive elimination.
- Mechanism:

Now, we will discuss Ullman reaction, in the Ullman reaction biaryl synthesis. The coupling of aryl halides to afford biaryls using copper source is called Ullman reaction. The order of reactivity of aryl halides follows the order aryl iodide, aryl bromide, then aryl chloride. An aromatic ring having electron withdrawing groups at ortho position activate the ring towards coupling reaction. Unsymmetrical biaryls can be prepared by taking two different aryl halides.

The byproducts can be minimized when one aryl halides is very reactive and the other is relatively unreactive. The reaction takes place via oxidative addition, followed by reductive elimination. So this is an important, this is actually, you can see this is very reactive, so this is very reactive, this one 4 nitro groups, 3 nitro groups are present here and this is the iodobenzene. Now with copper 200 degrees centigrade you can reach this cross couplings, so this is cross coupled biaryl synthesis.

Now, what could be the mechanism? So mechanism that aryl iodide just copper, with just copper heat, oxidative addition will take place and you get this species Ar-Cu-I. And now copper again will react with this system to generate copper iodide and Ar-Cu that is the active intermediate will form. So this is active intermediate. Now the oxidative addition will take place to get this species that you have seen earlier also. Like two aryl groups are connected to copper, now reductive elimination will happen and elimination of copper(I)iodide, you get this biaryl product.

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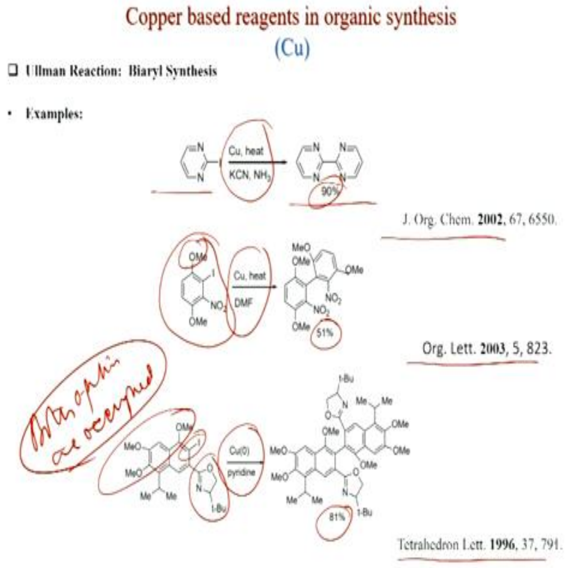

Copper based reagents in organic synthesis

(Cu)

❑ **Ullman Reaction: Biaryl Synthesis**

- **Examples:**

J. Org. Chem. **2002**, 67, 6550.

Org. Lett. **2003**, 5, 823.

Tetrahedron Lett. **1996**, 37, 791.

So, we will see some examples now. Like here these heterocyclic iodo compound, when treated with copper, potassium cyanide, ammonia, heating condition you get this dimerised product in 90 percent yield, this was published in JOC, 2002.

Also if you see this nitro to methoxy group at present in the aryl group and with copper itself DMF solvent. So this is very simple condition, you get 51 percent yield of this product, biaryl product. This was published in Organic Letters, 2003.

And this is a little bit complex structure, you can see here is motif is present, here many methoxy group is present. But, so this is quite bulky here. But with copper(0) pyridine, you can get this coupling product. So this is very interesting, this product is forming 81 percent yield. Because the both ortho is occupied, so both ortho positions are occupied. That means this iodide is in the sterically hindered position, but still the reaction happens with copper. So this is very interesting, this was published in Tetrahedron Letter, 1996.

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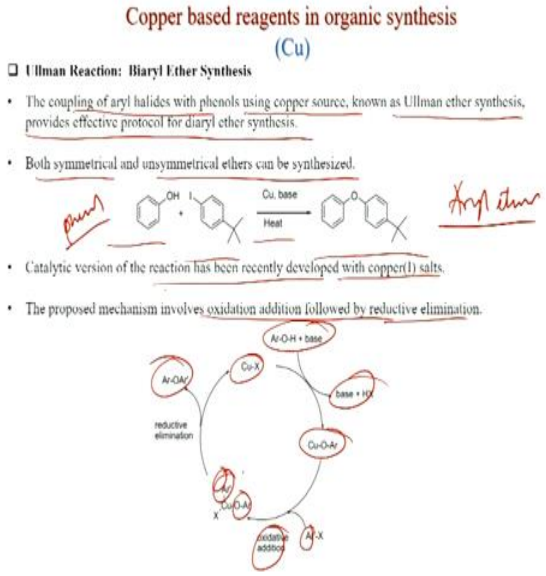

Copper based reagents in organic synthesis

(Cu)

☐ **Ullman Reaction: Biaryl Ether Synthesis**

- The coupling of aryl halides with phenols using copper source, known as Ullman ether synthesis, provides effective protocol for diaryl ether synthesis.
- Both symmetrical and unsymmetrical ethers can be synthesized.
- Catalytic version of the reaction has been recently developed with copper(I) salts.
- The proposed mechanism involves oxidation addition followed by reductive elimination.

Some more examples. The coupling of aryl halides with phenols using Cu source, known as Ullman ether synthesis, provides effective protocol for diaryl ether synthesis. Both symmetrical and unsymmetrical ethers can be synthesized. Like here phenol, so this is phenol and aryl iodide with copper, base, heat you get the aryl ethers. So this is aryl ethers formation.

Catalytic version of the reaction has been recently developed with copper(I) salts. The proposed mechanisms involves oxidation addition, followed by reductive elimination. Like this Ar-O-H base and with copper, so this copper alkoxide is formed and now oxidative addition will take place, the copper with this aryl group is coming to copper. And now the reductive elimination. So this group and this group eliminates, you get this product and the copper X is formed again.

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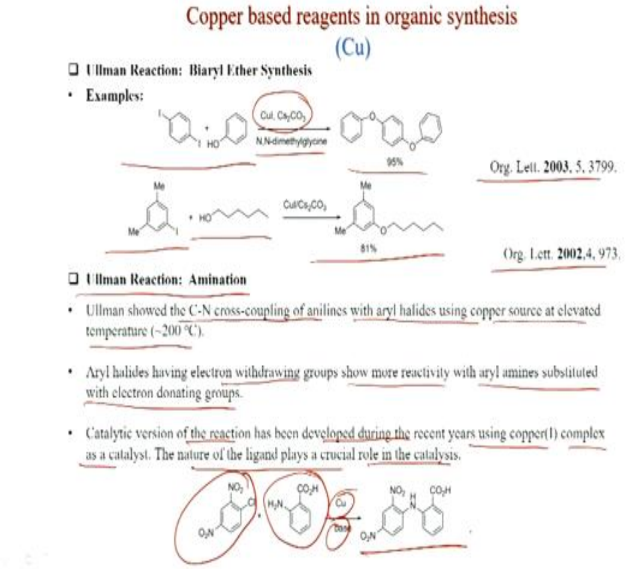

Copper based reagents in organic synthesis

(Cu)

❑ **Ullman Reaction: Biaryl Ether Synthesis**

- **Examples:**

Org. Lett. **2003**, 5, 3799.

Org. Lett. **2002**,4, 973.

❑ **Ullman Reaction: Amination**

- Ullman showed the C-N cross-coupling of anilines with aryl halides using copper source at elevated temperature (~200 °C).
- Aryl halides having electron withdrawing groups show more reactivity with aryl amines substituted with electron donating groups.
- Catalytic version of the reaction has been developed during the recent years using copper(I) complex as a catalyst. The nature of the ligand plays a crucial role in the catalysis.

So some examples we will see, suppose if you treat this phenol with diiodobenzene, 1,4 diiodobenzene with copper iodides, cesium carbonate, N, N dimethylglycine. Then you can get this product diaryl ether, two ethers are there in 95 percent yield, this was published in Organic Letters.

Also, this iodo substituted benzene with this alcohol, long chain alcohol this ether can be formed in 81 percent yield, this was published in Organic Letters also.

Even amination is possible, so we have seen the ether formation, now amination is also possible. Ullman showed the C-N cross coupling of anilines with aryl halides using copper source elevated temperature. Aryl halides having electron withdrawing groups so more reactivity with aryl amines substituted with electron donating groups.

Catalytic version of the reaction has been developed during the recent years using copper(I) complex as a catalyst. The nature of the ligand plays a crucial role in the catalysis. So here you can see the amine acid actually, so beta amine acid and this is the chloro nitrobenzene with copper base you get this C-N coupling product.

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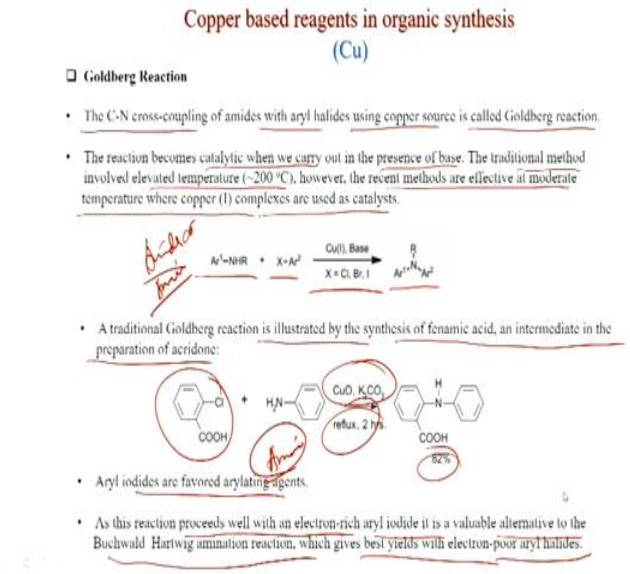

Copper based reagents in organic synthesis
(Cu)

❑ **Goldberg Reaction**

- The C-N cross-coupling of amides with aryl halides using copper source is called Goldberg reaction.
- The reaction becomes catalytic when we carry out in the presence of base. The traditional method involved elevated temperature (~200 °C), however, the recent methods are effective at moderate temperature where copper (I) complexes are used as catalysts.

- A traditional Goldberg reaction is illustrated by the synthesis of fenamic acid, an intermediate in the preparation of acridone:

- Aryl iodides are favored arylating agents.
- As this reaction proceeds well with an electron-rich aryl iodide it is a valuable alternative to the Buchwald Hartwig amination reaction, which gives best yields with electron-poor aryl halides.

Now, we will discuss Goldberg reaction. So the C-N cross coupling of amides with aryl halides using copper source is called Goldberg reaction. So coupling of amides with aryl halides. The reaction becomes catalytic when we carry out in the presence of base. The traditional method involved elevated temperature. However, the recent methods are effective at moderate temperature where copper(I) complexes are used as catalysts. So this is the amide generally, amide and this is the aryl halide, the copper(I) base you get this coupling product.

A traditional Goldberg reaction is illustrated by the synthesis of fenamic acid, an intermediate in the preparation of acridone. So this is an example, this simple amine here also. So both amine and amide can be use and this is the chloro benzoic acid with copper oxide, potassium carbonate, reflux 2 hours, you get this product in 82 percent yield. So, amide or amine.

Aryl iodides are favoured arylating agents. As this reaction proceeds well with an electron rich aryl iodide it is a valuable alternative to the Buchwald Hartwig amination reaction, which gives best yield with electron poor aryl halides. So this is an alternative of Buchwald Hartwig amination reaction.

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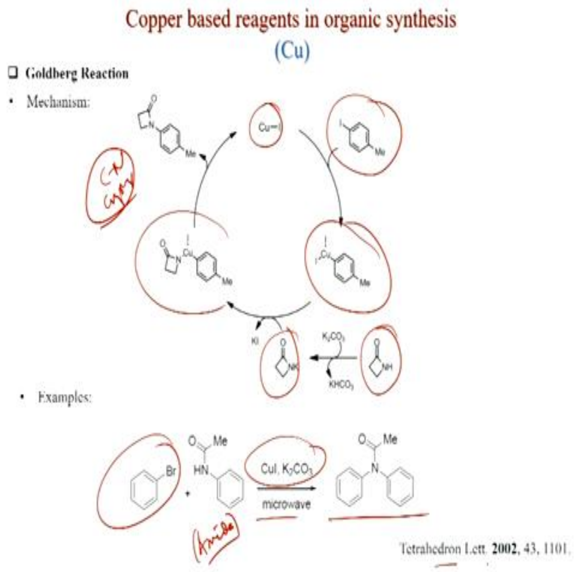

Copper based reagents in organic synthesis

(Cu)

❑ **Goldberg Reaction**

- Mechanism:

- Examples:

Tetrahedron Lett. **2002**, 43, 1101.

So the iodobenzene reacts with copper iodide to get this one, the oxidative addition and now this amide here, it is the deprotonated by base to generate the anion and that has to copper. Now the reductive elimination happens and you get the C-N, so C-N coupling happened here and you get copper iodide back. So example with amide, so this is an example with amide, earlier we have seen example with amine. So here the, amide is present and the bromo benzene with copper iodide potassium carbonate microwave condition, you get this C-N coupling product, this was published in Tetrahedron Letters.

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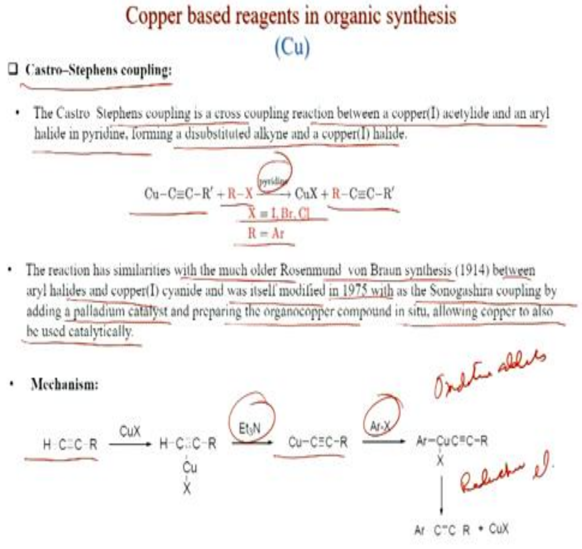

Copper based reagents in organic synthesis

(Cu)

❑ **Castro–Stephens coupling:**

- The Castro Stephens coupling is a cross coupling reaction between a copper(I) acetylide and an aryl halide in pyridine, forming a disubstituted alkyne and a copper(I) halide.

$$\text{Cu–C≡C–R}' + \text{R–X} \xrightarrow{\text{pyridine}} \text{CuX} + \text{R–C≡C–R}'$$

X = I, Br, Cl

R = Ar

- The reaction has similarities with the much older Rosenmund von Braun synthesis (1914) between aryl halides and copper(I) cyanide and was itself modified in 1975 with as the Sonogashira coupling by adding a palladium catalyst and preparing the organocopper compound in situ, allowing copper to also be used catalytically.

- **Mechanism:**

And last reaction we will discuss this Castro Stephens coupling. The Castro Stephens coupling is a cross coupling reaction between a copper(I)acetylide and an aryl halide in pyridine forming a disubstituted alkyne and a copper halide. So this is the copper acetylide and R-X, X can be I, Br, Cl. R should be aryl. And with base you get this cross coupling product.

The reaction has similarities with the much older Rosenmund von Braun synthesis between aryl halides and copper(I) cyanide and was itself modified in 1975 with as the Sonogashira coupling by adding a palladium catalyst and preparing the organocopper compound in situ, allowing copper to also be use in catalytically.

So this was an old reaction, the modified is the Sonogashira coupling. So when alkyne is treated with copper, then the coordination happens and the base, of course, then the copper acetylide formed and then the Ar-X, the oxidative addition. So this is oxidative addition and this is reductive elimination happens and you get the cross coupling product.

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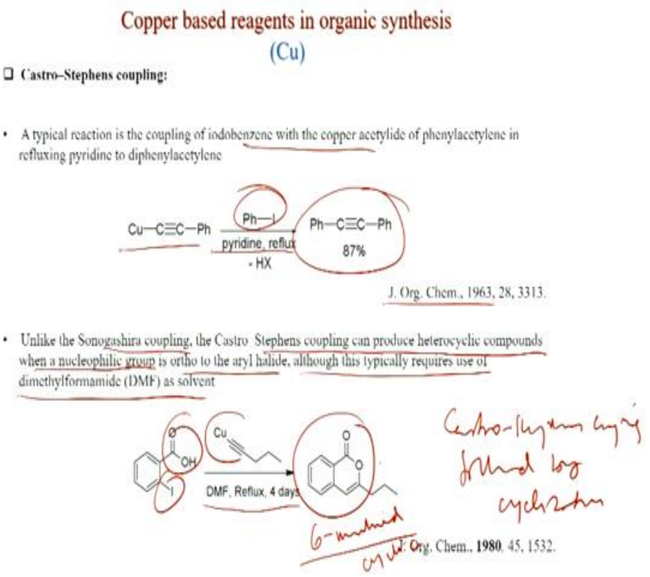

Copper based reagents in organic synthesis
(Cu)

❑ Castro–Stephens coupling:

- A typical reaction is the coupling of iodobenzene with the copper acetylide of phenylacetylene in refluxing pyridine to diphenylacetylene

J. Org. Chem., 1963, 28, 3313.

- Unlike the Sonogashira coupling, the Castro Stephens coupling can produce heterocyclic compounds when a nucleophilic group is ortho to the aryl halide, although this typically requires use of dimethylformamide (DMF) as solvent

Castro-Stephens coupling followed by cyclization

6-membered cycle

J. Org. Chem., 1980, 45, 1532.

So some examples now like here, a simple copper acetylide we can prepare and then you can react with iodobenzene, with pyridine reflux you get this product in 87 percent. This was published in JOC, 1963.

Unlike the Sonogashira coupling, the Castro Stephens coupling can produce heterocyclic compounds when a nucleophilic group is ortho to the aryl halide, although this typically requires use of DMF as solvent. So cyclisation reaction also is possible. So here the Castro

Stephens coupling followed by cyclisation. So here this coupling first happens here and then the acid group is making a cycle, so this is 6 membered cycle is form that is very favourable. 6 membered cyclic system is forming with DMF, reflux 4 days. This was published in JOC, 1980.

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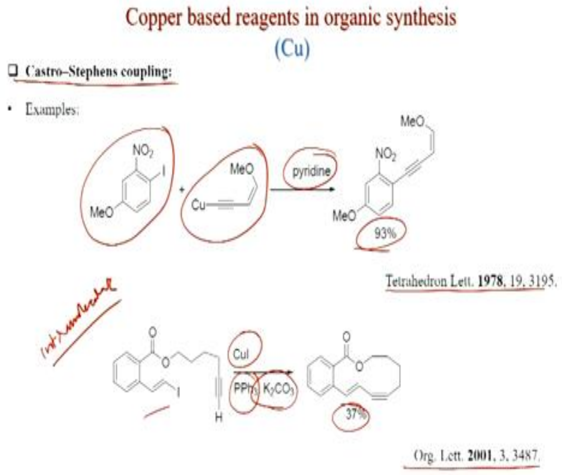

Copper based reagents in organic synthesis

(Cu)

❑ **Castro–Stephens coupling:**

- Examples:

Tetrahedron Lett. **1978**, 19, 3195.

Org. Lett. **2001**, 3, 3487.

Now, we will discuss a more examples of Castro Stephens coupling. So like this iodide having a nitro and methoxy group, when treated with copper acetylide in presence of pyridine, you get this cross coupled product. And it was obtained in 93 percent yield. This work was published in Tetrahedron Letters, 1978.

Also if you see this one, this is intramolecular, intramolecular because both vinyl iodide and alkyne having the same molecule. And when this treated with copper iodide, diphenyl phosphine which is ligand that potassium carbonate base. Then you get this coupling product and here the olefin geometries is written, here was trans, here also is trans. And this macrocyclic product is obtained in 37 percent yield. So this is very important reaction and this was published in Organic Letters, 2001, page number 3487.

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SUMMARY

❑ Gilman reagent

So today we have discussed the copper(I) reagent. So first we have discussed the Gilman reagent, Gilman reagent is R_2CuLi or (RCu) R_2CuMgX that has been use in many reactions like conjugate addition. Also Tandem 1,4 addition enolate trapping reaction we have seen. That the C trapping and O trapping you can do, and the C trapping case you get the Trans product mainly.

The reaction with acid chloride we have seen that the acid chloride actually this is very important reaction, you can get the ketones and ketone does not further react. So this kind of reaction is not possible with Grignard. Because in the case Grignard the ketone will further react. Reactions with aldehydes and ketones also you have seen and in this case aldehyde ketones you have seen the trimethylsilane or silyl chloride or BF_3 etherate and manganese chloride they can be used for the higher yield.

Then the reaction with epoxide we have seen and epoxides case we have seen the lipshutz reagent is very useful reagent you can get higher yield. And higher-order mix cuprates, we have seen that the substitution reaction also is better with the lipshutz reagent. Then we have seen copper catalyzed allylic substitution, in this case we have seen that if CuCN is there, then you can get the gamma substitution, on the other hand, it is that CuMe, then you can get the alpha substitution.

Then we have seen the Cadiot-chodkiewicz coupling, this is the copper(I) base and with bromo alkyne you can get the dialkyne. Then we have seen the Glaser oxidative coupling, here the dialkyne also is form, but with oxygen, here simply dialkyne can be used and simple copper(I) and oxygen. Then also we have seen some variation, we have seen, Eglington and Hay. Then we have seen the Ullman reaction, this is very important for biaryl synthesis. And in Goldberg reaction we have seen amine and amide coupling with copper 1. And lastly we have seen the Castro Stephens coupling that is alternative Sonogashira coupling, here also an aryl halide and alkyne can be coupled with copper(I) and with base. Thank you.