

Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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Lecture 38: Grignard Reagent

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. In the last class, I started talking about the Grignard reagent. I talked about the generation of Grignard reagent, the effect of solvent and the radical mechanism for the generation of Grignard reagent. In the today's class, I am going to talk about the different type of mechanism using the Grignard reagent. So, we are going to start with the reaction with the carbonyl system.

And then of course, there will be reaction with a enone. So, there will be a chance of 1,4 versus 1,2-addition. We are going to talk about the stereochemistry and some of the cross-coupling reaction also done with the Grignard reagent. So, let us start about this.

We are going to talk about first thing is the addition of the Grignard reagent to the carbon compound. I think in the last class I talked about that you can see that there is going to form a transition state which is a six member and we also talk about that this magnesium. You know going to activate this one of this magnesium going to activate this oxygen of this carbonyl group. And if you think about this is having R also wrote about that there is a magnesium then there is another R and you can think about a transient state like this. So, there will be a there will be a six-member ring.

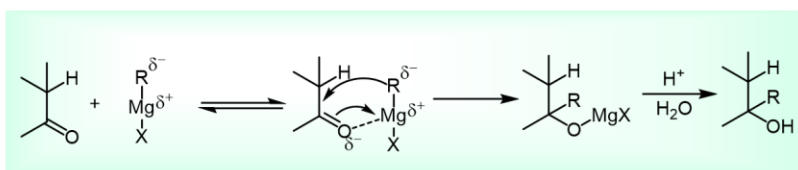
So, if you think about 1, 2, 3, 4, 5 and 6. So, these are involved and forming it that is what we informed you in the last class. So, one of the magnesium what is happening here this is acting as a Lewis acid to activate this carbon group. So, the another, magnesium can this attack to the carbon group. Again, I think you can see if you have bulkier Grignard reagent then it can happen here it can also you can write something like this here.

The single magnesium can also activate this oxygen here in the carbonyl and this R group can attack here to form this -OMgX from there it can go to the corresponding alcohol. Now you can think about there are different type of carbonyl group means, it can be a ketone it could be ester it could be amide and the reactivity rate is aldehyde will be reacting faster than ketone. then ester then amide ok. So, now, we are going to learn that

the Grignard reagent not always going to react with the carbon compound. So, there are two other possibilities can happen.

➤ **Reactions of Grignard Reagents with Carbonyl compounds:**

- ✓ Grignard reagents are capable of nucleophilic additions to carbon-heteroatom double bonds.
 - ✓ Reactivity of carbonyl group towards Grignard reagents decreases in the order: aldehyde(most reactive) > ketone > ester > amide(least reactive)
- A possible mechanistic scheme for the polar concerted reaction of a Grignard reagent with an aldehyde or a ketone is depicted below:



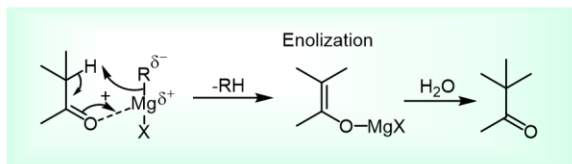
The second possibility can happen if it is really bulky that it cannot add for 1,2-addition then it can go for a formation of an enol that means, it can act as a base. So, in the previous slide I talk about that it can act as a nucleophile go for 1,2-addition. Now, it can act as a base to abstract this proton here to form an enol which can be protonated to form the corresponding carbonyl compound. It is going to go back to the corresponding carbonyl compound or if you can treat some electrophile then there will be electrophile going to come. So, what is happening here? So, here it is acting as a base.

Now, there is another important thing here there is a hydride transfer that is another important parameter. I think you must have heard about hydride transfer like if you use sodium borohydride remember to reduction of the carbonyl compound. So, here we also found that in case of some Grignard reagent where instead of going for 1,2-addition if you cannot go for 1,2-addition and if it does not have this type of proton of the alpha to the carbonyl group to abstract means if the analysis is stopped. Then the last thing it can do is, it can go for a hydride transfer, you can think about this minus (-) can come back here and then this hydride can transfer to the carbonyl group. What it will end up making from the carbonyl group to it will go for a reduction reaction happen to convert to the corresponding alcohol.

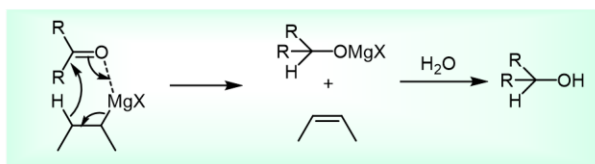
So, in what you have learned that depending on the Grignard reagent there will be three, one is a 1,2-addition that means, Grignard is acting as a nucleophile. It could go for an enolization if you have a bulky Grignard reagent. So, here it is acting as a base to abstract the proton alpha to the carbonyl group or if you have a scenario where it cannot go

for 1,2-addition and it cannot go for enolization. Then it can go for this hydride transfer to reduce the carbonyl group to the corresponding alcohol. So, here is an example I am trying to show you.

- Organomagnesium can not act as a nucleophile but also as bases , converting ketones with enolizable hydrogens to the corresponding magnesium enolates.



- If the Grignard reagent has a hydrogen in the β -position, reduction of the carbonyl group by hydride transfer may compete with addition reaction.



You will be convinced with this data that if you start with this corresponding ketone and now you treat with the Grignard reagent first with CH_3MgX you see 95% of 1,2-addition. Once you think about a CH_3MgX is reacting it is actually adding to the carbonyl group to form the corresponding product which is once you treat with the H_3O^+ is going to form the OH with the CH_3 . So, this will be your 1,2-product. Now, what is happening once you go for a tertiary. So, what is happening here you are seeing 35% enolization and 65% reduction happening.

So, what is happening here again you can see here in these cases once you have this bulky Grignard and you can see this ketone is also bulkier. So, there is this proton this can this proton can be abstract easily by this. So, it can act as a base ok to abstract this proton this will go to the forming an alcohol ok. And then also you can see it can also go for a reduction as you can see both the Grignard and this one is bulkier sometime the enolization is not that not that favorable. So, instead of that what is going to happen you can think about this methyl as having three hydrogens.

So, it can go for this type of reaction it can form isoprene and it can attack to this this hydride can attack to the corresponding carbon compound to form a corresponding alcohol. So, this is your reduction product. So, you are seeing a mixture of enolization and reduction. Now, if you use a Grignard reagent let me write down the structure of this. So, you can think about this is the structure you have a tert-butyl then CH_2 then Mg.

So, if you think about this Grignard reagent what is the important of this Grignard reagent there is no proton here, we replace there is three CH_3 group here. As you see there is you

need a β -proton for the hydride transfer to be happen, but there is no β -proton here. So, that is why one thing is happening this can only participate in enolization that is why you can see 90% enolization happening with this, but there is 0% reduction.

➤ Influence of structure on Grignard reactivity:



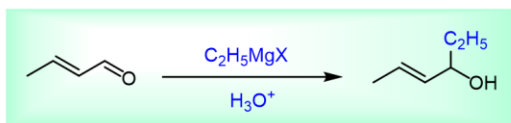
Grignard reagent	Addition	Enolization	Reduction
CH_3MgX	95%	—	—
$(\text{CH}_3)_3\text{CMgX}$	0	35%	65%
$(\text{CH}_3)_3\text{CCH}_2\text{MgX}$	0	90%	0

Magnesium is not so hard with the like lithium it is not that soft like copper, it is in between. And, again you can still think that once you have this type of α,β -unsaturated ketone or aldehyde, specially, then as the aldehyde is very reactive that the Grignard will go for the 1,2-addition only majorly.

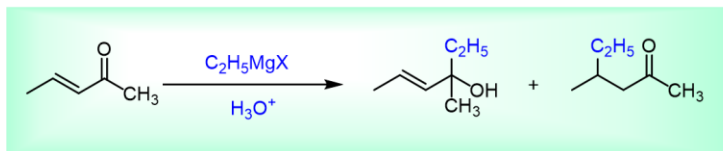
But once you have the ketone as I said the ketone reactivity is less compared to aldehyde you will see the major is this 1,2-addition and same time you will see some 1,2-addition is going to happen as well.

➤ Reactions with Grignard reagents:

- ✓ Mg is not so hard like Li and not so soft like Cu.
- ✓ With α,β -unsaturated aldehydes facile addition to carbonyl.



- ✓ But α,β -unsaturated ketone undergo both 1,2 and 1,4- addition reaction.



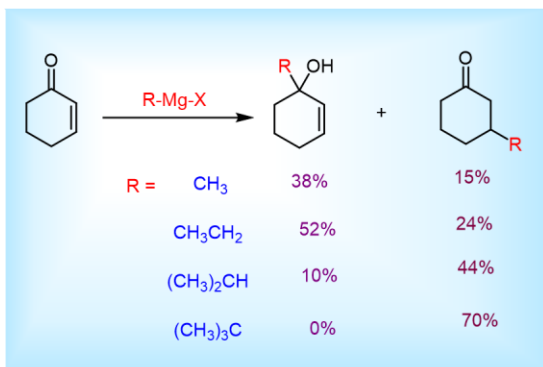
So, here is an example again given here if you start with this enone and once try to change the Grignard. For this particular one what we are seeing here, majorly the 1,2-addition happened and then you will see some amount of 1,4-addition. Again, this type of alkyl Grignard reagent we are seeing this primary alkyl Grignard. What we are seeing here? we are seeing their formation of this 1,2-addition as a major one.

You started with the secondary one what you are seeing 1,4-addition product is getting increased and then in the tertiary. Of course, in the tertiary there is other thing is going to happen of course, there is one thing going to happen it can give you some product of enolization and some product of the hydride transfer also going to come out. So, but the thing is now the question arises can you find a method where the Grignard reagent can only go for 1,4-addition, is it possible? You can do it; you must use some copper catalyst. We are going to come back to that.

So, you can convert this Organo Grignard reagent to organocopper reagent and then it can go to participate only for 1,4-addition. Because, it is a softer one it will be going to participate in a 1,4-addition instead of the 1,2-addition. So, we are going to discuss this in more detail in the organocopper chemistry.

➤ Reaction with α, β – unsaturated carbonyl-compounds:

- ✓ Grignard reagents reacts with α, β - unsaturated carbonyl compounds usually leads to a mixture of 1,2 and 1,4- addition.
- ✓ Allyl or phenyl-magnesium halide only offers 1,2- addition.



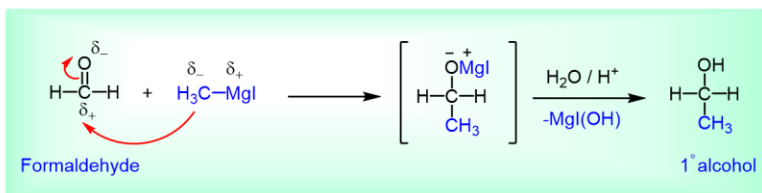
Grignard reagent in the presence of copper catalyst can take part in 1,4-addition

Now, if you treat with a formaldehyde here it is going to form the corresponding 1^o-alcohol after the Grignard addition and then quenching with the H₃O⁺.

➤ Reaction with Carbonyl compounds:

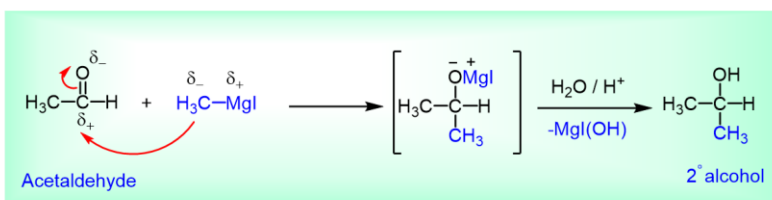
- ✓ Grignard reagents react with carbonyl group of aldehydes and ketones forming an addition product, which on acid hydrolysis give different types of alcohols.

i. Reaction with formaldehyde (primary alcohols synthesis):

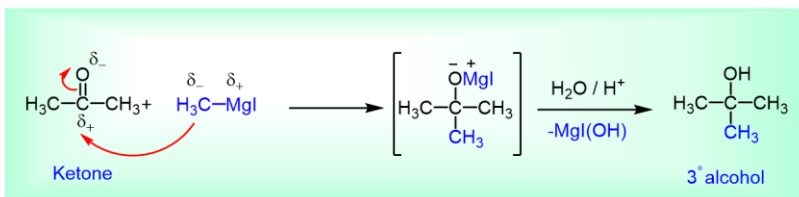


If you have an acetaldehyde, it will go to the secondary alcohol and if you have a ketone, it will form the tertiary alcohol. So, depending on if you want a primary alcohol, you have to go for formaldehyde, secondary alcohol, acetaldehyde and tertiary alcohol, then you have to go for the corresponding carbonyl compounds.

ii. Reaction with Acetaldehyde to produce secondary alcohol:



iii. Reaction with Ketones to produce tertiary alcohol:



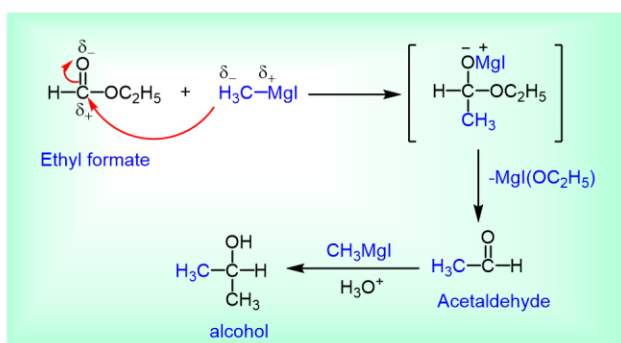
Now, if you have ethyl formate, what is going to happen? So, now, we are talking about reaction of Grignard reagent with ester. Of course, the first reaction is that it will form this intermediate this is a going to get out it is going to act as a leaving group. So, to form this corresponding acetaldehyde, now the question is the reaction will stop here? This reaction will not stop here why because you formed a more reactive compound. In the product you have generated if you think say I will use one equivalent of Grignard and I can get one equivalent of product. No, you cannot because as soon as your Grignard started reacting with ethyl formate and it is start generating the corresponding acetaldehyde.

Now, the Grignard is going to choose acetaldehyde more compared to ethyl formate, because acetaldehyde is much more reactive compared to this ethyl formate as is the aldehyde that is ester. That is why the Grignard will react again with this to take you to all the way. to forming a secondary alcohol. That means, if you want to make a secondary alcohol you do not have to start with acetaldehyde you can start with the corresponding ethyl formate as well.

iv. **Reaction with Esters:**

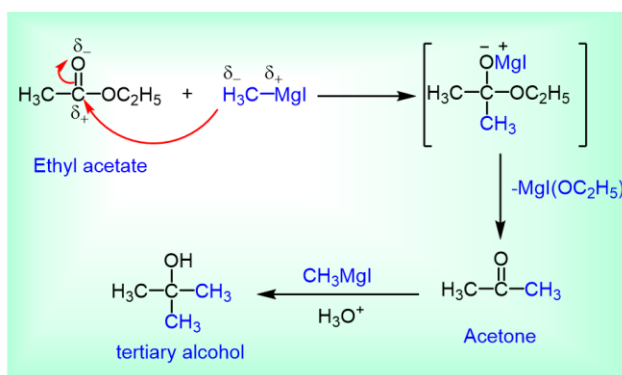
a. **Reaction with Ethyl formate** initially formed aldehyde, but reaction can not stop .

b. Further react with Grignard reagents and formed alcohol.



Again, you have to remember in this ester reaction you have to I think it is better if you want to get to the 100% of this product what you understood that a two equivalent of Grignard agent actually added correct. So, 2.0 equivalent is adding here. So, that is why in the reaction also you should add little more than 2.0 equivalent for a complete conversion.

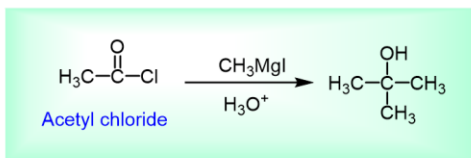
➤ **Formation of tertiary alcohol from ethyl acetate by Grignard reagents:**



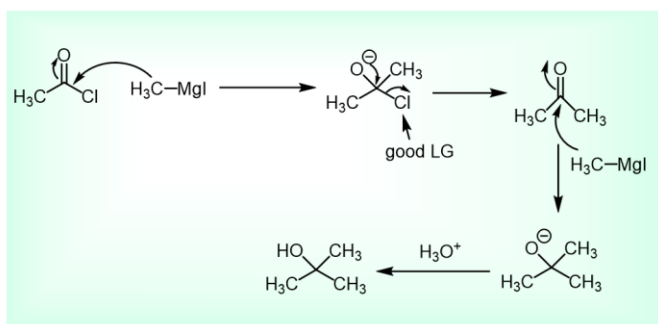
Again, if you start with the corresponding acetyl chloride the first thing is it is going to attack here. Now chlorine is a good leaving group it is going to form the corresponding acetone from this acetyl chloride.

Now, again the acetone is more reactive than corresponding acetyl chloride. So, Grignard will not be going to stop here it is going to add here to take you all the way to the corresponding tertiary alcohol.

➤ Reaction with Acid Chlorides to form tertiary alcohol:



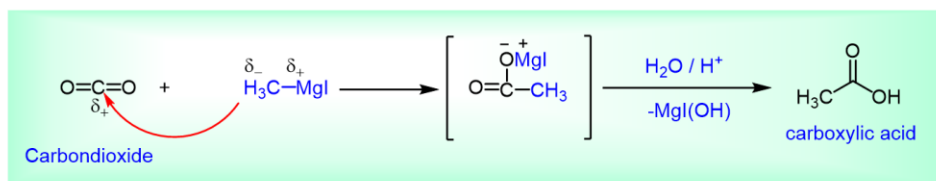
Mechanism:



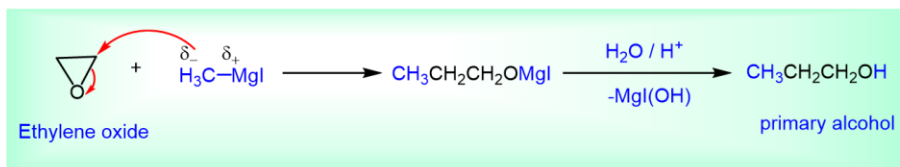
If you have a carbon dioxide, I think very similar to the organolithium, it is going to react with the carbon dioxide it is going to add to the carbon then once you treat with the H_3O^+ it is going to form the corresponding carboxylic acid. Again, you might be thinking sir is it the reaction why it is stopping in the carboxylic acid again once you have a carboxylic acid then the Grignard can abstract this acidic proton correct. Once the Grignard is abstracting the acidic proton then it cannot attack to the corresponding here it can attack to the epoxide ok.

It can attack to the epoxide and epoxide can form the OMgI , which will treat with the H_3O^+ , you know a protonated water to form the corresponding primary alcohol.

- Reaction with carbondioxide to produce carboxylic acid:



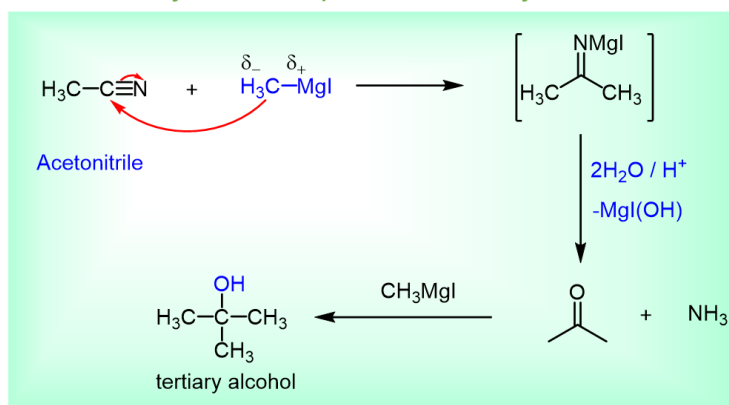
- Reaction with ethylene oxide to form primary alcohol:



You know very similar to the organolithium it can attack to the corresponding acetonitrile or corresponding than the cyanide it is going to form this corresponding imine and then the imine going to hydrolyze to form corresponding ketone ok.

Again, I think in this reaction once it is forming the corresponding imine, I think it is going to stay here in the imine because what is going to happen here after the formation of the imine the you know the Grignard has one thing Grignard can ou know act to the corresponding imine because I think you know this can happen after the workup correct. Once you have imine and if you go for workup, you will get only this. So, then you know this is not going to happen correct, but I think in these particular cases also what people found out that. In some cases, if you have some moisture, tress of moisture and if some ketone is started forming then that is going to also get reacted otherwise you can convert this to corresponding ketone at the end.

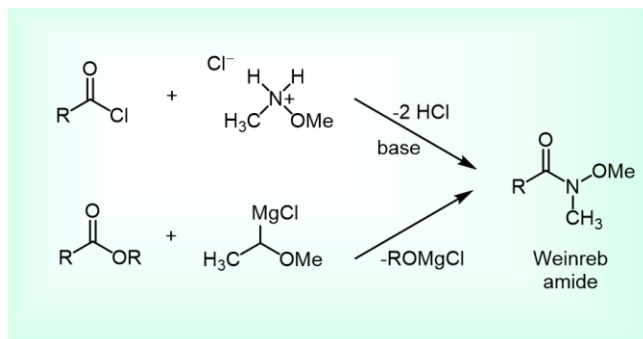
- Reaction with Cyanides to produce tertiary alcohol:



Now, the question comes then is there any other way to solve this problem. So, what we stuck with the problem that if we use this type of compound like acid chloride or if you use this ester what we are seeing there we are majorly seeing the reaction is going all the way to the corresponding tertiary alcohol. Means 2.0 equivalent of Grignard is attacking how to stop it for that it was developed the Weinreb amide you know amide was synthesized. So, this is a very clever approach you are going to learn in a minute why that is very important and why you have to synthesize this particular amide.

So, here I think the synthesis is very easy you can take this particular amine and then once you react with the corresponding acid chloride or ester, you can have this corresponding NMe_2MgCl with this type of Grignard reagent. If you treat with the ester or in these cases if you treat with the corresponding acid chloride then what is going to happen it is going to form this corresponding Weinreb amide here ok.

➤ Weinreb Ketone synthesis:



So, now once you form the Weinreb amide and now once you treat this one to the corresponding organolithium or corresponding Grignard agent, what is happening here? Once you treat them with the corresponding organolithium or corresponding Grignard agent, we found out after the reaction is happen once you do work up, every cases we end up getting this ketone as a as a product, we isolate this as a product. So, what is happening here?

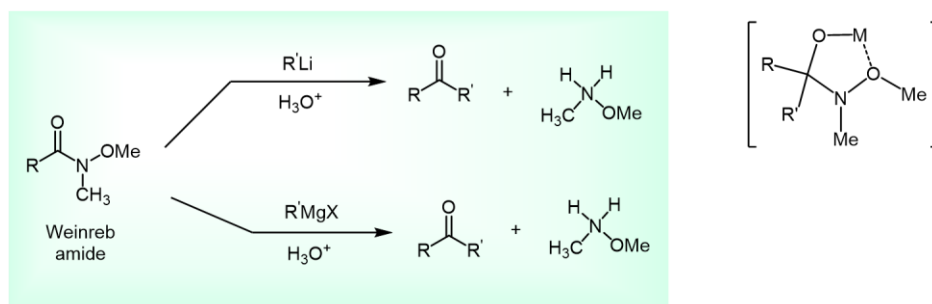
You might be asking this question, sir if this is attacking in the in the reaction. And if it is forming this ketone in the reaction, then why this Grignard is stopping there, why it is not attacking to the ketone. So, the thing is it is not that simple here, because you can think about that once this reaction is happening, I think I can try to show you that once this reaction is attacking to this R- i.e RMgX you can write or RLi . When this is attacking to the Weinreb amide forming this O- , now if you try to think about the corresponding transition state here. Because this in this reaction it is not forming a ketone, it is actually staying in this form and here. this methoxy is playing a very important role this NO everything is playing a very important role here. Because once this the attack is happening by the Grignard reagent then this metal could be a magnesium or could be a

lithium forming a chelate with the oxygen. So, in the reaction it is staying in this chelate form.

So, you have this one extra RMgX or RLi in the reaction. So, these are lying in the reaction extra. So, now, if you quench the reaction this is now, you put H₃O⁺ only then only it is going to convert to the corresponding ketone. So, till then it is in this form. So, that is why it is not getting attacked ok.

Then your extra Grignard is getting quenched also once you treat with the H₃O⁺ that can convert to RH ok. That is the important tricks here.

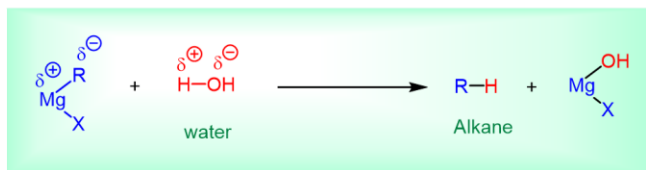
- After derivatisation to the Weinreb amide, reaction with organometallics does give the desired ketones and does not undergo further reaction.



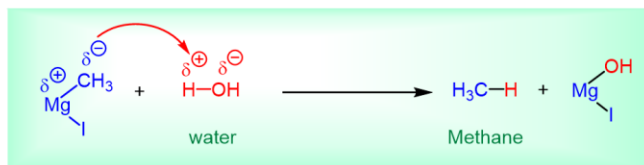
That is the important tricks here. Again, the Grignard, if you have any water or if you are synthesizing this Grignard if you are careless then the Grignard is getting quenched here. If you have the Grignard getting quenched to alkane. So, you have to be very careful when you are making Grignard you should be make sure your glassware is completely dry.

❖ Hydrolysis of Grignard reagent:

- ✓ Grignard reagent on hydrolysis gives alkane.



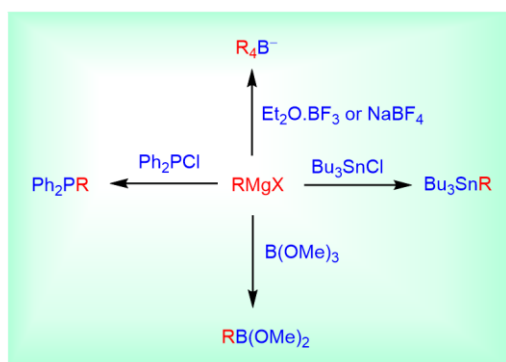
- ✓ For example:- Methyl magnesium iodine on hydrolysis gives methane.



Then Grignard reaction can be participated in alkylation. So, we have learned about the Grignard reaction is only doing some reaction with the carbon compound with epoxide with ester. It can also react with heteroatoms, it can react with phosphorous. It can react with the tributyl tin chloride with BF_3 treat it can also react. It can also react with trimethoxy boron to form the boronic ester or corresponding tin compound corresponding phosphorous compound. So, Grignard reaction have lot of importance to form the heteroatom bonds as well.

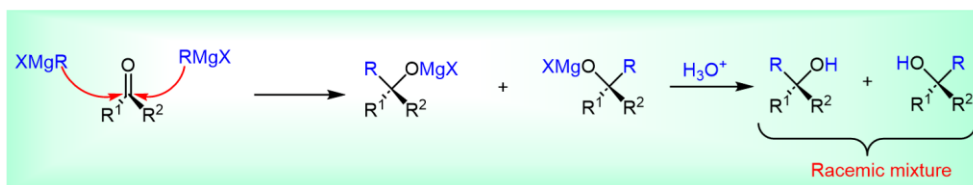
❖ Alkylation of metals and metalloids:

- ✓ Like organolithium compounds, Grignard reagents are useful for forming carbon-heteroatom bonds.



The other important question is if you think about the addition of Grignard to a carbonyl group then it can add to the above phase as you guys remember the carbonyl group has a Si and the Re face. So, it can attack to either of the face so that means, what is going to happen? If you take a Grignard reagent and if you have R_1 and R_2 is a different group you end up forming a racemic mixture.

- ✓ The carbonyl carbon of an unsymmetrical ketone is a prochiral centre.
- ✓ The addition of a Grignard reagent can take place on either face of carbonyl group with equal chance.



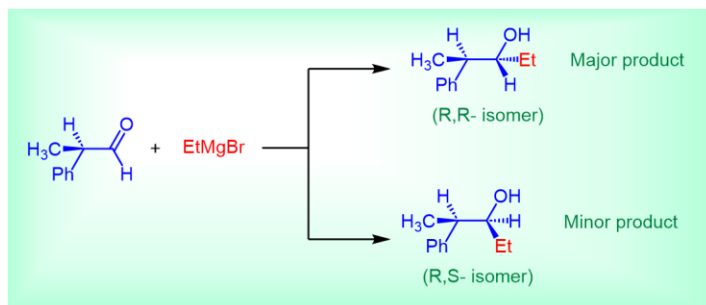
- ✓ Hence a racemic mixture is formed in absence of asymmetric induction.

So, here the question comes if you have a scenario here you have a chiral center and you have an aldehyde and now you are shooting with a Grignard reagent. So, the question comes which of them will be major is it going to be this one going to be the major R,R-

isomer or the R,S-isomer going to be major that means, now which phase of this carbonyl group the ethyl group going to be approach.

- ✓ A mixture of diastereomers is formed when the ketone or aldehyde contains one chiral center.
- ✓ Predominant stereoisomer formed in this case can be predicted by using Cram's rule.

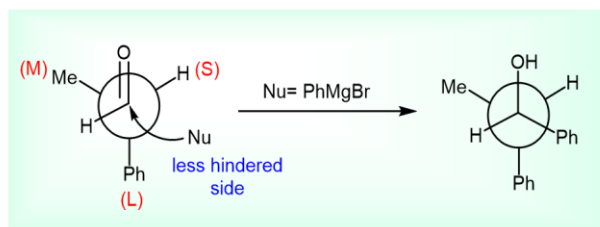
❖ E.g. The reaction of (R)-2-phenylpropanal with ethylmagnesium bromide, an achiral Grignard reagent gives (R,R)-2-phenyl-3-pentanol as major product.



So, to explain that you have to try to understand the cramps rule and the cramps model I think it was clear from this model that whatever groups will be present it is. So, the nucleophile always goes to attack from the less hindered site, which means if you can think about there will be groups that can be medium size, small size and large size ok. So, nucleophile will always try to approach from a less hindered site. So, this will be the less hindered site. between this where the nucleophile can attack once that is happening you end up getting to a stereoselective product.

- ✓ Stereochemistry of Grignard reaction predicted by the Cram's rule.
- ✓ Designing the groups adjacent to the carbonyl group as small(S), medium(M) and large(L).
- ✓ According to Cram's rule nucleophilic attack to the least hindered side.

For example: Reaction with 2-phenyl-propanaldehyde with phenylmagnesium bromide nucleophilic attack takes place from the least hindered position.

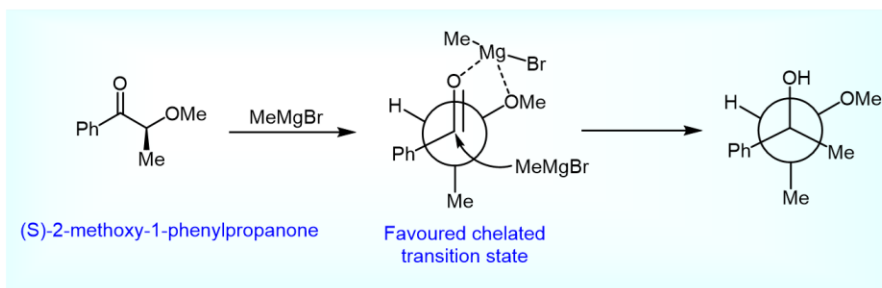


Now, the question comes if you have a compound where you have the carbonyl group going to get attacked, but you have a methoxy group what that can act that can form a chelation. Now, you know the Grignard is going to form a chelation with the oxygen we have already learned about that. and now this O-methoxycube is also from chelation. So, that can also going to favor the chelate tangent state. So, now, you can see this can it is not going to follow now the Cram's rule original hypothesis.

Now, this chelation going to be drive the reaction towards product ok. So, because of the chelation now the nucleophile going to attack from this side to form this product as a major product. So, we have learned about the carbonyl addition.

- When Grignard reagent addition to the chiral substrates that possess a heteroatom α - or β position, a modification in the in the application of the Cram's rule is required.

For example: Reaction between (S)-2-methoxy-1-phenylpropane with methyl magnesium bromide, a cyclic structure where methoxy group is syn periplanar to carbonyl group is formed.



Now, we are going to learn about some cross coupling reaction. So, it was discovered a lot early that if you take a Grignard reagent like if you take an aryl Grignard reagent, ArMgX and if you treat with the iron catalyst FeCl_2 , then what is going to happen? It was known that it was going to convert to a biaryl, and not only iron.

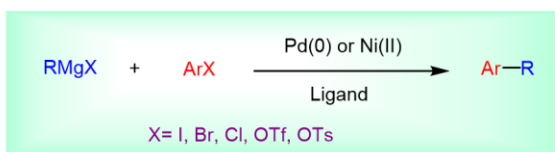
There were a lot of other catalysts that was developed, that could convert the Grignard to biaryl. But now I am going to talk about if you have an alkyl magnesium halides or you have aryl magnesium halide and aryl and you have a aryl halides ok. So, now this thing can be coupled. Depending on if you have a aryl versus alkyl then you can use some you can use palladium or the nickel catalyst once you have alkyl. And then using a ligand you can able to go to the corresponding again it can form a biaryl if you have a two aryl groups here or it can form a substituted aryl compound.

So, this is going to introduce you to Kumada coupling. It was the first with the with it was discovered with using palladium or using a nickel catalyst reaction. So, this is again going to follow the various I think you guys heard about the in the organometallic chemistry about the Suzuki coupling. If you remember, in the Suzuki coupling, we use

the organoboron as a nucleophile partner and the aryl halide as electrophile partner. but here in the Kumada coupling the Grignard reagent is used as a nucleophile partner.

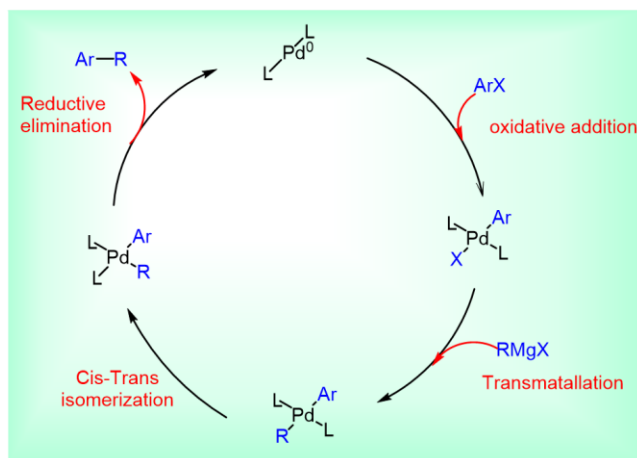
❖ Kumada Coupling:

- ✓ The Kumada Coupling was the first Pd or Ni- catalysed cross coupling reaction.
- ✓ Coupling of Grignard reagents with alkyl, vinyl or aryl halides under Ni- catalysts.
- ✓ Kumada coupling is the method of choice for the low cost synthesis of unsymmetrical biaryls .



So, mechanistically, it will be very similar once the palladium(0) catalyst will be generated in the medium it can go for oxidative addition, then there will be a transmetallation of Grignard reagent to get rid of this halide, then there will be cis-trans isomerization and finally, reductive elimination to get to the product to get by the palladium(0) in the catalytic cycle.

➤ Reaction Mechanism:



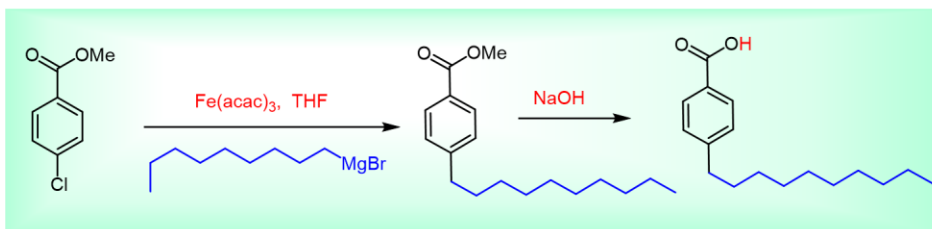
Again as I mentioned the iron(III) catalyst or iron(II) catalyst can also use for this type of reaction here. Here, is an example if you start with this corresponding chloride and if you can use this the iron catalyst then what can happen? Not only this reaction will work for the corresponding bromide, but you can use this corresponding chloride for the cross-coupling as well. So, now you can use this Grignard reagent here. That can

participate in a cross coupling to synthesize these substituted esters ok, which can be convert to the corresponding benzoic acid derivative.

❖ **Coupling with organohalides:**

- ✓ Grignard reagents do not react with organic halides.
- ✓ Due to their high reactivity with other main group halides.
- ✓ In the presence of metal catalysts, Grignard reagents participates in C-C coupling reactions.

❖ **For example**, nonylmagnesium bromide reacts with methyl p-chlorobenzoate to give p-nonylbenzoic acid.

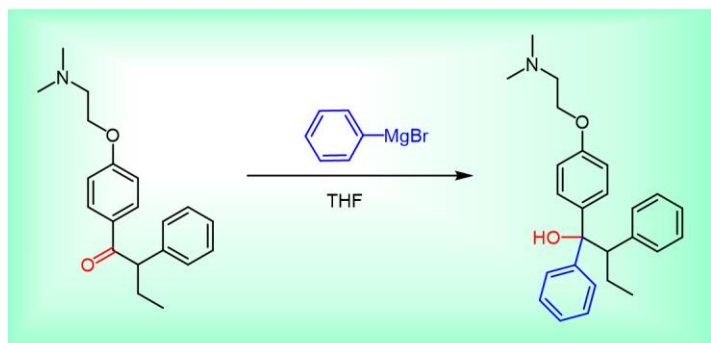


So, now, I think, I am going to show you that you know. So, again there are lot more cross coupling again this particular course, I am not again. So, we are not going into the lot of the different cross-coupling reaction using the organometallic reagent, we are just showing you some of them. And of course, if you are taking organometallic course mostly which are dealing with a cross-coupling reaction with palladium you can see more detailed study there. Here I am going to show one of the importance of this particular reaction if you have a Grignard reagent like aryl magnesium bromide.

Here what is happening you have a carbonyl compound here. So, this particular example so, here the Grignard reaction was used in a industrial production of tamoxifen. So, tamoxifen is a anti-cancer drug. So, you can see a tamoxifen actually is a tetra substrate olefin you can see this will be the structure of a tamoxifen you have a phenyl group here, you have an ethyl group here, you have a phenyl here. So, now you can see this can be synthesized through tamoxifen, but first thing is the Grignard is adding to the corresponding carbonyl compound. So, this carbonyl compound was synthesized first, now the Grignard group is adding to the carbonyl compound to form this corresponding tertiary alcohol.

From there after the dehydration, it can form this corresponding olefin ok. So, this is the industry scale synthesis of tamoxifen where the Grignard reagent is also utilized.

➤ An example of the Grignard reaction is a key step in the industrial production of Tamoxifen, currently used for the treatment of estrogen receptor positive breast cancer in women.



So, in this particular segment I talk about the reaction of Grignard reagent with a carbonyl compound I started with that aldehyde will be much more reactive than a ketone then ester also I talk about in case of ester it is going to form two equivalent of Grignard going to attack to form tertiary alcohol. you can stop this if you can make a Weinreb bromide then it can go to the corresponding ketone. And then also I talk about if you have according to the where it will be going to attack.

It is going to attack to the less hindered side to the carbonyl group and also, I show you the application as well ok. Again, you know these are the references you can follow and again thank you to the coming to the class and in I am going to see you in the next class. In the next class my plan is to talk about the organocopper chemist.

Thank you.