Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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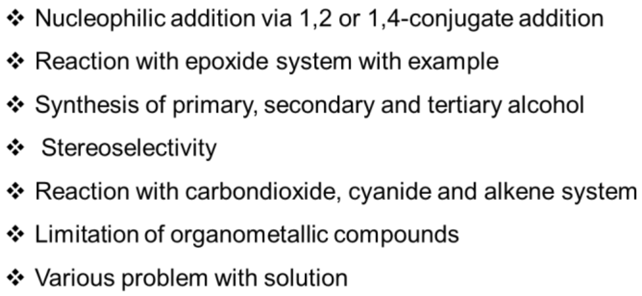
Lecture 36: Organolithium

Welcome back to this NPTEL online certification course in molecular arrangement and in reactive intermediates. So, last couple of classes we have learned about carboanion, mostly we talked about the organolithium reagent. We talk about the generation of organolithium using the metal halogen exchange, the transmetallation reaction in the last class and in the today's class I am going to show you some of the reactions of the organolithium reagents. So, I am going to talk about the nucleophilic addition. So, there could be a 1,2 versus 1,4-addition.



- ❖ Nucleophilic addition via 1,2 or 1,4-conjugate addition
- ❖ Reaction with epoxide system with example
- ❖ Synthesis of primary, secondary and tertiary alcohol
- ❖ Stereoselectivity
- ❖ Reaction with carbondioxide, cyanide and alkene system
- ❖ Limitation of organometallic compounds
- ❖ Various problem with solution

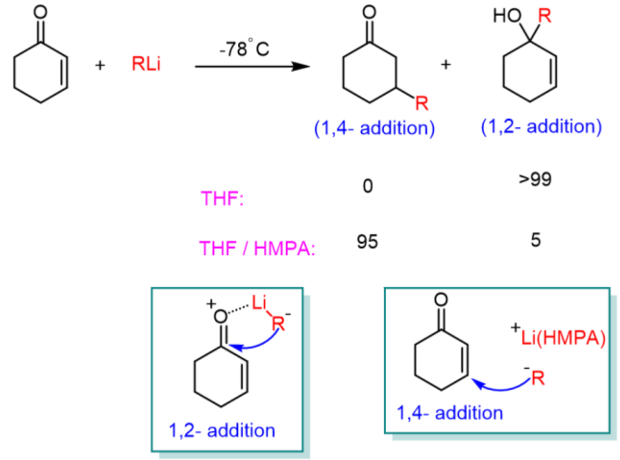
Then the reaction with the epoxide aldehydes and then you can see about the stereoselectivity of the reactions and of course, I am going to talk about the reaction with cyanide and and others. And then at the end I am going to talk about couple of problems. So, first thing is we are going to talk about the if you have organolithium and if you have a enone system here. Then the question comes whether it is going to go for a 1,2-addition or 1,4-addition.

So, now, we are talking about it will be a 1,2 means, you are adding here the nucleophile to give this product or it can go for a 1,4 that means, the nucleophile is attacking or the RLi going to attack from this side to form this product. what is happening most highly reactive organolithium favors the 1,2-addition. That means, if you see the once the organolithium is very reactive like the methyl lithium, butyl lithium all if you add here it is going to go for this 1,2-addition as a major. But once you have some stabilization if you use some sort of a stabilizing group with the organolithiums which are where you can you have to use a HMPA. As I mentioned about HMPA in the previous classes what you have learned that HMPA can also able to coordinate with the lithium.

So, now what is going to happen is the HMPA can coordinate with the lithium that can make the lithium go for 1,4-additon. So, you can see here if you have a THF that is the 1,2-addition is the major once you add HMPA then we will see that the 1,4-addition happening 95%. Again, this depends on whatever lithium is used. You have to also think about the lithium you are choosing for this type of reaction. The lithium which was used in this particular addition is kind of a stabilized lithium.

So, if you have a non-stabilized lithium, it is mostly go despite the condition go for 1,2-addition. Once you have a stabilized lithium and once you use a HMPA which can stabilize the lithium even more then found out that you can go for a 1,4-addition.

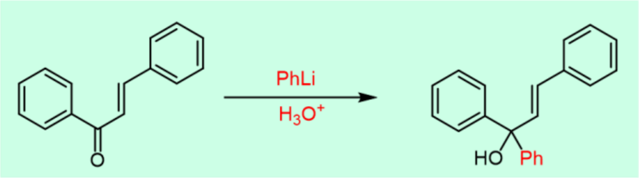
- Nucleophilic addition via 1,2 or 1,4- conjugate addition:
  - Two sites of nucleophilic addition are possible.
  - Most highly reactive organolithium favours 1,2- addition.
  - 1,4- adduct is more thermodynamically favourable species follows conjugate addition.



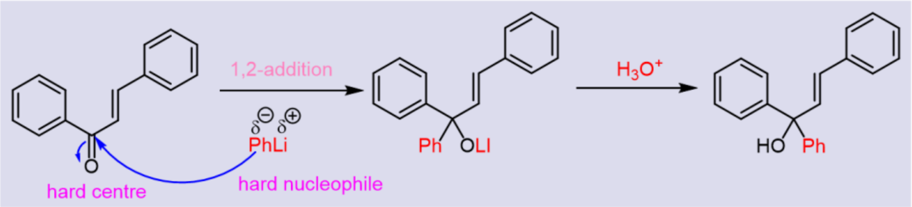
I am going to come back with some examples in a minute. So, you can see here in the particular cases, if I using a phenyl lithium without any type of additives here again as I said the phenyl lithium is a reactive one, it is going to attack to the hard center here. So, the organolithiums are hard nucleophile. So, mostly you will end up seeing a 1,2-addition product to get to the corresponding alcohol after treating with a water.

➢ Reaction with α,β- unsaturated carbonyl compounds:

✓ Organolithium reagents undergo reaction exclusively to give 1,2-addition products.



Mechanism:



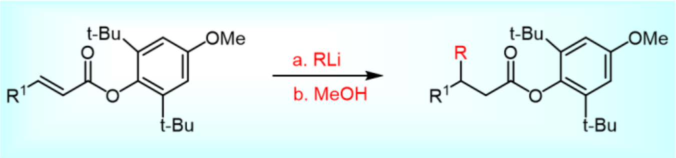
Again, if you have a hindrance. So, there is another important thing here that if you have a carbonyl group here. So, which is not getting a place to attack because the nucleophile cannot approach here because of the steric factor. In that case what is going to happen then in that case you will see the using organolithium also you will only see the 1,4-addition going to take place.

So, the lithium can coordinate with the oxygen to make it more electrophilic and now there will be one for addition going to take place here to get to this type of after you treat with the methanol it is going to get to this corresponding product here.

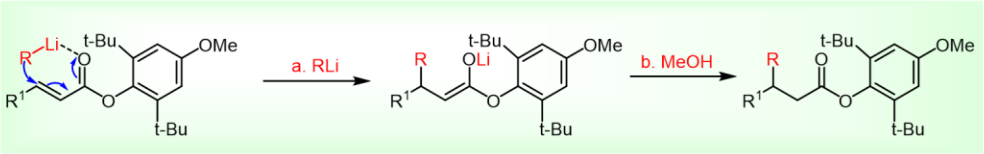
➢ Conjugate addition reactions of lithium reagents:

✓ Alkyl and aryllithium reagents usually attack the carbonyl group of α,β- unsaturated carbonyl compounds (1,2-addition), conjugate addition (1,4-addition) takes place very hindered substrates .

Ex:



➢ Mechanism:

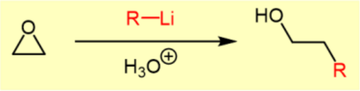


And, if you have an epoxide, you know nucleophiles can attack the epoxide to open the epoxide here. So, as you see these are very strong nucleophiles the RLi that can attack to the epoxide to open and form the corresponding alcohol.

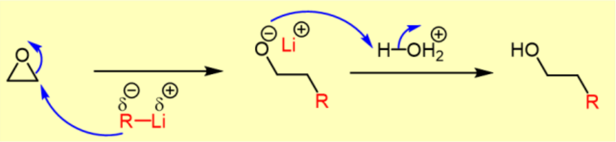
➢ Reaction of organometallic reagents with epoxides:

- ✓ Reaction with an epoxide , organometallic reagents opens epoxide ring, forms alcohol.
- ✓ Backside attack on epoxide ring followed by protonation gives alcohol product.

➢ Example:



➢ Mechanism:

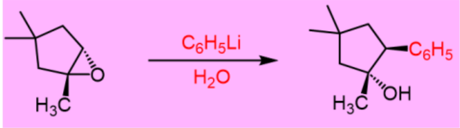


Again, there is an example here you can see here there is two different side the nucleophile can attack but you know this side is more hinder. So, you know, it will allow to attack from this side.

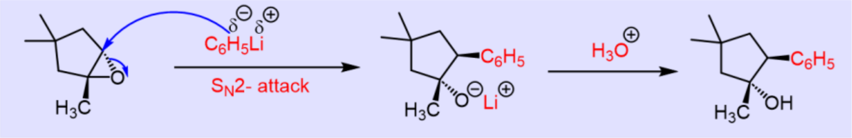
So, this is an S_N^2 reaction happening. So, then it is going to happen only from the back side correct. So, if you treat with a phenyl lithium here, it is going to go for a S_N^2 reaction and mostly as I mentioned the, some sort of a phenyl lithium or the other stabilized lithium where you have two stabilizing groups. In that case, only you will find out that your reaction is going through S_N^2 reaction. But once you have an unstable lithium like RLi with alkyl lithiums then you will see it is not a stabilized lithium and mostly you do not find a S_N^2 reaction with them, and you know, try to go for an in S_N^2 reactions, then you always have to choose a stabilized lithium. But of course, for epoxide the nucleophile going to attack here because that is the only place to attack and after the S_N^2 it can form the corresponding product.

Example:

1.



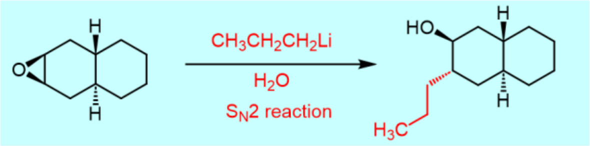
Mechanism:



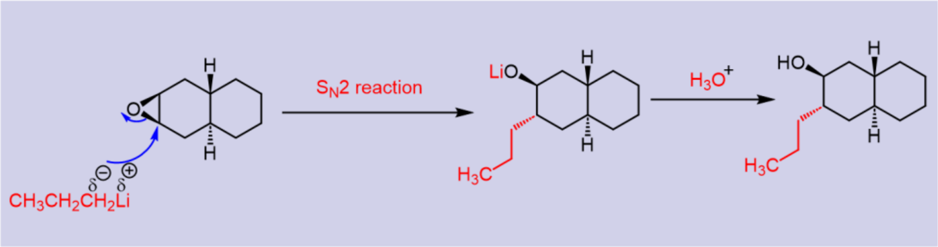
- ✓ Nucleophiles attack epoxide from the back side of the ring.
- ✓ Followed protonation giving the product.

Again, here the nucleophile is attacking. So, you can see the both side is kind of symmetric it will attack from this side or that side only thing it has to attack from the back side. So, this is an S_N^2 reaction using this corresponding alkyl lithium here to form this corresponding product. As I said, these are very reactive lithium, and there is no other group to be attacked. So, epoxide is getting attacked to form the corresponding alcohol.

2.



Mechanism:



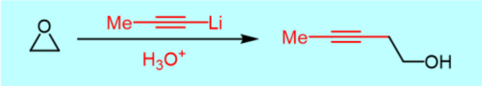
✓ Nucleophile attacks the epoxide , then protonation gives the desired product.

Again here, two things are happening here you can see that the alkynel lithium can also attack to the epoxide, as I said these are very in the reactive nucleophile here you have the same scenario. It can attack from this side or it can attack from this side, but you can see as it is allylic position this side is getting attacked to form this corresponding product here. In these cases, you are using a BF_3 as a Lewis acid, which can activate the oxygen now the nucleophile can attack from either side it can attack to get to the corresponding alcohol.

In this case also, you can see here that generally, if on one side, there will be substitution, then the nucleophile prefers to attack from the less hindered side. So, that is how it is going to end up this product.

Similar examples:

3.



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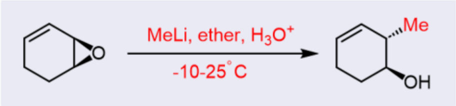

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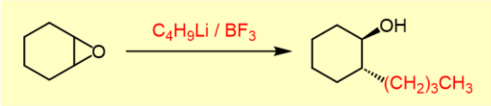

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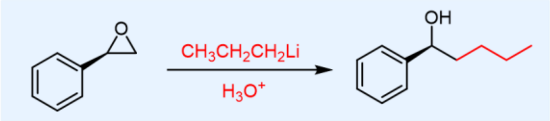
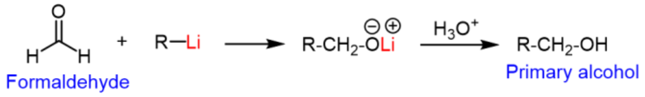


If you have a formaldehyde or different aldehyde groups, then there1,2-addition is going to take place. Here, in every case what is going to happen? You know depending on the substitution in formaldehyde there will be primary alcohol. If you have acetaldehyde, you end up making a secondary alcohol, and if you have ketones, you end up forming a tertiary alcohol after the protonation.

➢ Reaction with carbonyl compounds:

- ✓ Organolithium reagents react with aldehyde to form secondary alcohols and with ketones to form tertiary alcohols.
- ✓ Primary alcohols are obtained by treatment with formaldehyde.
- ✓ Compared to Grignard reagent, organolithium reagents gives better yield of alcohols.

1.



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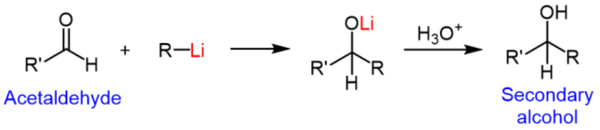

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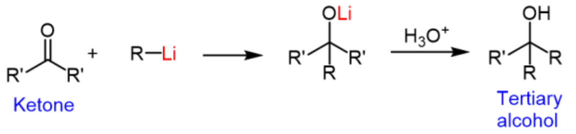
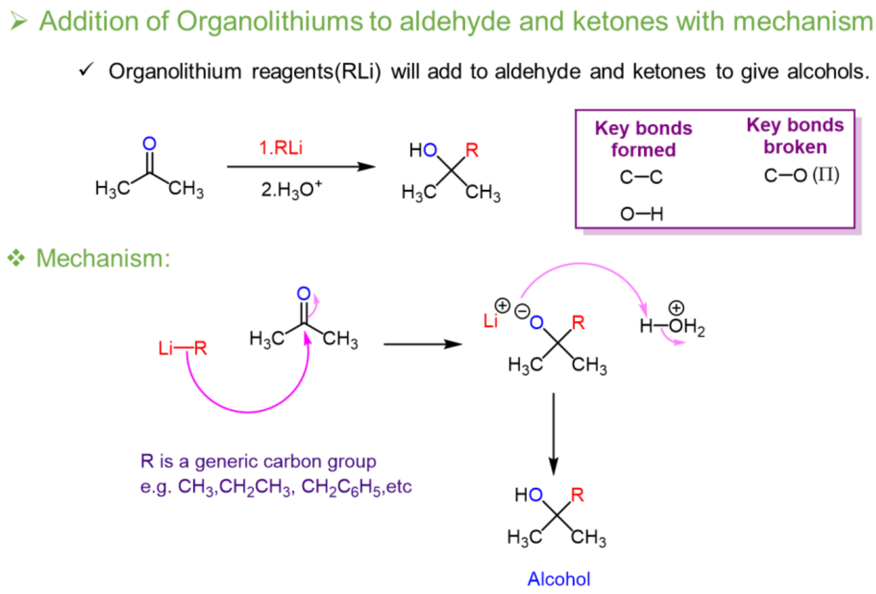


Again, I think it is shown here the mechanism that you know of course, that the lithium are very hard nucleophiles. So, that is why it is going to attack it. In this 1,2-addition to attack the carbon here and then it is taking proton to get to the corresponding alcohol.



- Addition of Organolithiums to aldehyde and ketones with mechanism:
  - ✓ Organolithium reagents(RLi) will add to aldehyde and ketones to give alcohols.

Key bonds formed	Key bonds broken
C–C	C–O (II)
O–H	

- Mechanism:

R is a generic carbon group
e.g. CH_3, CH_2CH_3, $CH_2C_6H_5$, etc

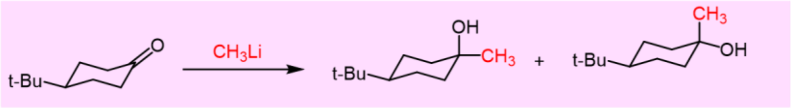
Alcohol

So, with hindered ketone, the stereoselectivity is not high, but preferentially equatorial attack to give the corresponding axial alcohol. That means, once you have got the in the equatorial position now what is going to happen if you use no lithium perchlorate you still see 65% of this product.

That means, what is happening the nucleophile is preferring to attack from this side, but once you use this the lithium perchlorate what is happening the lithium perchlorate is also coordinating with the oxygen. Once it is coordinating with the oxygen here, what is happening? The first side attack the attacking from this side is also getting you know hinder because of this the lithium percolate which is coordinating in this position here. So, once the Lewis acid is coordinating here, now your nucleophile attack will be majorly happening from the equatorial side, from the bottom side, to form this product.

➢ Stereoselectivity of addition to ketones:

- ✓ With unhindered ketones, stereoselectivity is not high but preferentially equatorial attack to give the axial alcohol.
- ✓ Equatorial approach increases with increased the alkyllithium reagents.



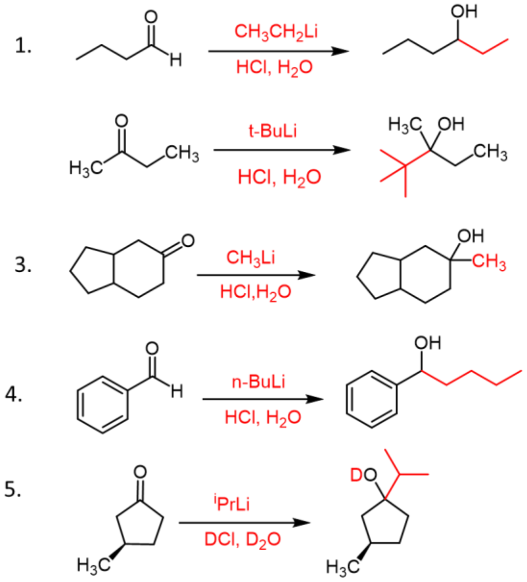
No $LiClO_4$	65%	35%
1 equiv $LiClO_4$	92%	8%

- ✓ In presence of lithium perchlorate, enhance the rate of axial alcohol in the addition of methyllithium to 4-t-butylcyclohexanone.

There are some examples and you might see some of the question in the exam that if you have a aldehyde you can treat with the organolithium you can get with the alcohol here. The ketone will give you the corresponding tertiary alcohol as I said.

If you have a benzaldehyde again it is going to attack. if you have a ketone it is going to form the corresponding alcohol. Now if you treat with the corresponding deuterium chloride at the end, you have to be careful D_2O you end up getting the -OD there because the lithium will be taking the deuterium from the D_2O.

Example:



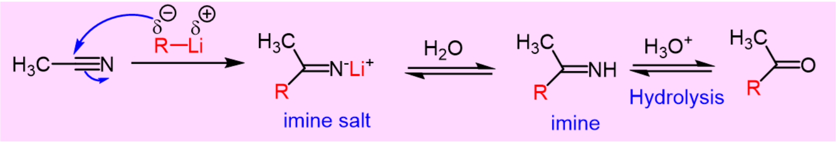
If you have a cyanide here the organolithium attacks here from the imine salt first it will form the imine and then finally hydrolyzed to corresponding carbonyl compound.

And if you trap with the CO_2, as I was showing in one of the examples in the last class, you end up with what is happening: the RLi attacks here to the carbon from the carboxylate, then it is going to attack one more time. And, finally, it is going to take the proton and at the end it is going to convert to the corresponding ketone here. So, that is going to happen if you again treat with the ester as well. You end up with tertiary alcohol. So, here what is happening you are forming ketone, but if you attack with the ester with this compound what is going to happen? Let us try to write down what is going to happen here.

Then the R- going to attack here So, now you will think that it will end up at the ketone, but that is not the case here. You have extra RLi in the medium. So, that will keep on attacking because now this is the carbonyl will be more prone to attack with the lithium here. So, this can attack again here and once you get protonated you end up generating a corresponding tertiary alcohol.

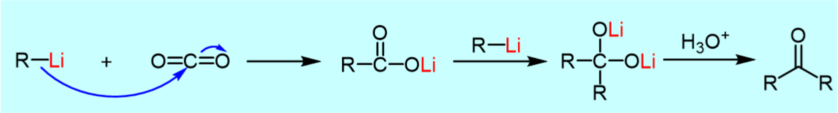
➢ Reactions with alkyl cyanide:

- ✓ Organolithium reagents also react with Alkyl cyanides to give imine salts.
- ✓ After protonation gives the imine, then hydrolysis to generates ketone.



➢ Reaction with carbondioxide:

- ✓ Organolithium reagents, carboxylate ion formed reacts with another Equivalent of organolithium to generate a ketone.



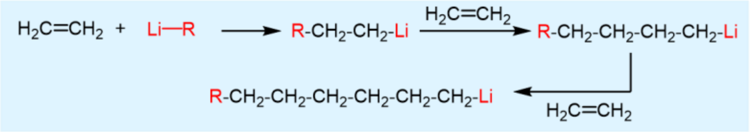
Again, I think, I mentioned it can go for this type of carbolithiation. I talked in the in the last class that if you have organolithium reagent it can attack to the corresponding olefin go for carbolithiation and then finally, attack to another olefin. So, you can see we have already talked about this. I think the first lecture that if you have this type of organolithium, it can also be used as an initiator for forming a polymer. So, this can constantly add and form a polymer because of this carbolithiation. And of course, if you have water in the medium or alcohol or amine.

That is if you have some proton in the medium which can be abstracted, then the lithium is going to abstract that first to generate the corresponding alkane.

➤ Reaction with alkenes:

✓ Compared to Grignard reagents Organolithium reagents is more reactive .

✓ React with alkenes to give alkyl-lithium , then reacts with a another alkenes to give alkyllithium.



$$H_2C{=}CH_2 + Li{-}R \longrightarrow R{-}CH_2{-}CH_2{-}Li \xrightarrow{H_2C=CH_2} R{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}Li \xrightarrow{H_2C=CH_2} R{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}Li$$

➤ Reaction with active hydrogen:

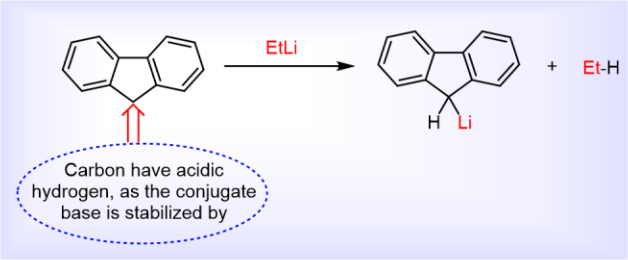
✓ Organolithium reagent react with substrate having active hydrogen such as water,alcohol and amine to give corresponding hydrocarbons.

$$R{-}Li \ + \ H{-}OH \longrightarrow R{-}H \ + \ LiOH$$

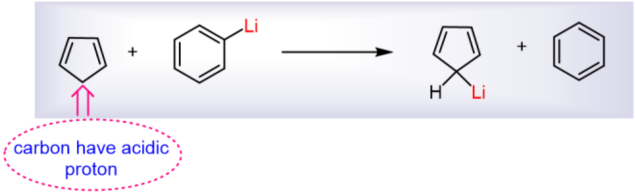
Again, if you have a compound that has active hydrogens, which are acidic. So, now, if you can see these are the very strong bases. So, they can able to attack here as there is no group to attack. Now, if you use organolithium, they can act as a base here to abstract this proton, to generate this corresponding organolithium.

You know here also if you think about the cyclopentadiene, it is going to abstract this proton and convert to an aromatic compound, with the corresponding lithium. So, these are the acidic protons that are abstracted with the lithium reagent.

➤ Compounds containing acidic hydrogen easily converted into organolithium compounds by treatment with organo-lithium compound.



Carbon have acidic hydrogen, as the conjugate base is stabilized by



carbon have acidic proton

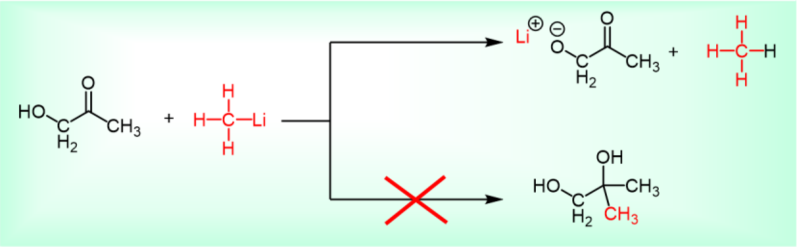
Again, I think in the previous slide I mentioned that if you have some acidic proton in the reaction, you are not supposed to use organolithium. Because, instead of attacking the first thing if you are thinking that the organolithium might going to attack here, but that is not going to happen first. First thing it is going to abstract this proton.

Now if you use excess lithium of course, that is that can attack here. But first thing it is going to go for this abstraction of the acidic proton. if you have alcohol, amides or carboxylic acid, then this proton will be abstracted first.

- Limitation of Organometallic reagents:

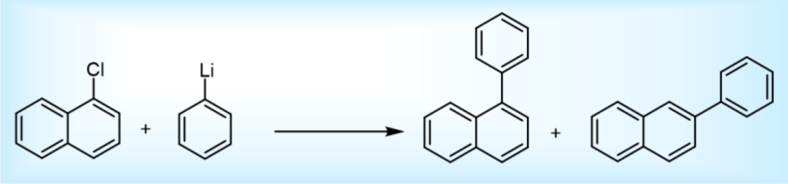
- ✓ Organolithium reagents are powerful bases.
- ✓ Because of this they cannot be used as nucleophile on compounds , containing acidic proton.
- ✓ The functional groups which cannot be used are: alcohols, amides, carboxylic acids and terminal alkynes.

Example:



There is an interesting example here, if you have this chloronaphthalene, what is going to happen? if you treat with phenyl lithium. What you end up seeing? you end up seeing some sort of an arylation happening here. Now, if you think about it, we have learned about this S_N^2 reaction of alkyl lithium with sorry, the aryl lithium or some sort of a stabilized lithium we have learned, but you cannot think about that this is going to participate in a S_N^2 reaction with a vinyl halide. So, if I ask you whatever intermediate this reaction is going to get to the product, you cannot say it is just going through an S_N^2 mechanism. You know what is happening here? Here something else is happening. I think I already covered in the class this is going through a benzyne or aryne intermediate. So, that is how this product is forming here.

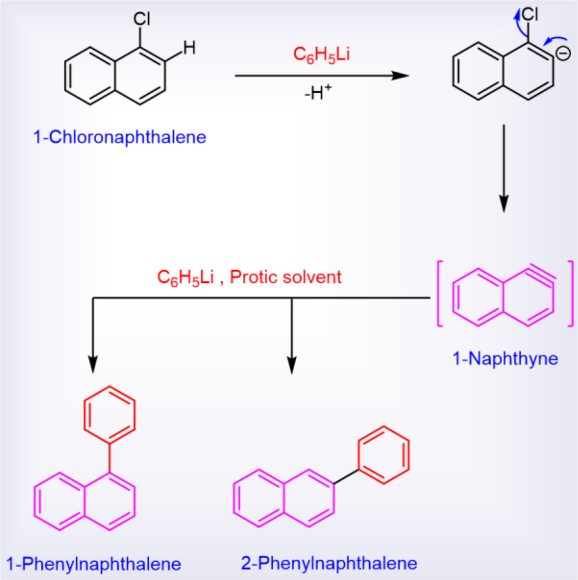
- Aryl halides can be reacted with alkyl and aryl lithium reagents to give hydrocarbons.
- Reaction with alkyl halides with alkyl lithium takes place by SN2 mechanism.
- Aryl halides with phenyl lithium take place via elimination-addition pathway.



- Phenyl lithium act as strong base to abstract *O*- hydrogen creating a carbanion and act as nucleophile in addition to naphthyene.

because I think if you remember I had already mentioned that once you have this type of chloride or fluoride in the aromatic ring then the metal halogen exchange does not happen instead of that it is try to abstract the ortho proton. So, then what is going to happen to form this corresponding the negative charge here. is going to form this corresponding anion and then go for elimination to generate this corresponding benzyne. So, now the phenyllithium is going to attack to the benzyne. You can see it can attack through this position or it can attack through the other side that is how it is going to end up making both the product.

- Mechanism:

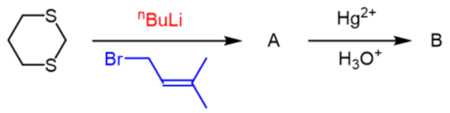


So, now, I am going to talk about some of the examples I think we have learned about the generation of organolithium and the some of the reaction. Now, we are going to go through some of the examples here in this particular part. So, first thing is we are going to talk about this particular compound. You can see these are the acidic protons here. So, you can see this is a dithiol protection we always use for the protecting of aldehyde group and if you remember, we use Hg^{2+} for the deprotection, but in between that there will be something going to happen.

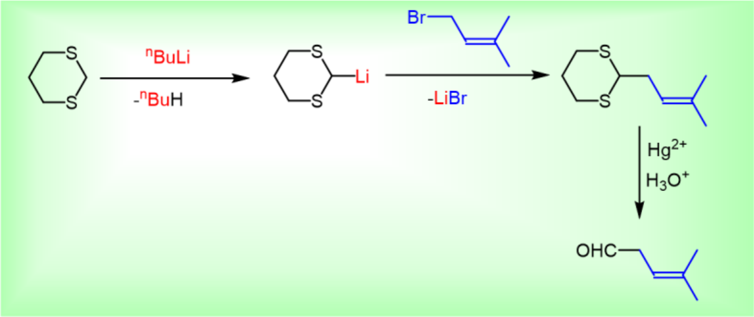
So, first thing is once you take n-butyl lithium then it is going to abstract this acidic proton to generate the corresponding lithium and these are the lithiums is as I said these are the stabilized lithium because it has two heteroatom next to it. So, once you have this stabilized lithium now it is going to take part as I said the stabilized lithium is going to take part in this S_N2 type reaction. So, it is going to take part S_N2 reaction to get to this compound. Now there will be a deprotection as I said, going to happen to get to the corresponding aldehyde.

➢ Problem :

1.



Solution:

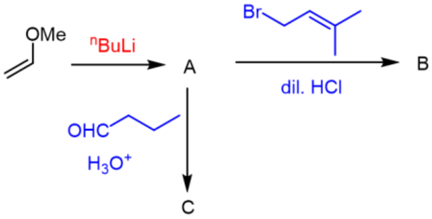


Again, here what is happening? You can see first thing is this as I said you have this OMe group and this is a vinyl proton here.

So, that is going to generate this more stable lithium as I said that reacting force of this generation of lithium that you are generating a more stable lithium. So, you are starting with N-butyl lithium and you are generating a vinyl lithium here. And now as I said it is a vinyl lithium that means it is a more stable lithium. So, what is going to happen it is going to take part in S_N2 reaction here. and you know once it is going to take for S_N2 reaction it is going to form this compound.

Now, once you treat with the dilute HCl what is going to happen? It is going to protonate here and after the hydrolysis it is going to form this carbonyl compound. As you say this is a stabilized lithium it can also react with the corresponding aldehyde. It can attack to the aldehyde to form this alcohol and now once you use a H_3O^+, what is going to happen? It is going to convert to the corresponding carbonyl group to this corresponding hydroxy group. You know, this is the alpha hydroxy carbonyl compound.

2.



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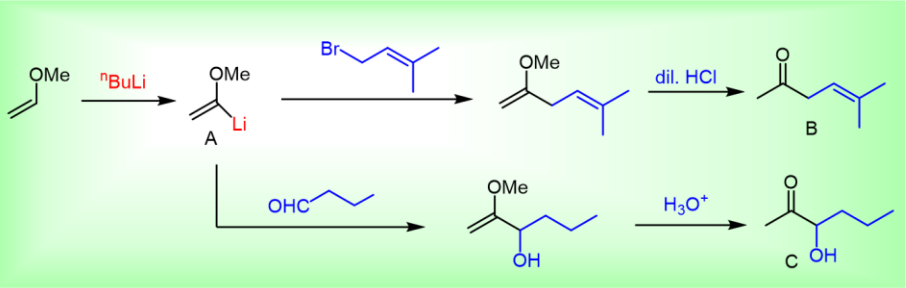
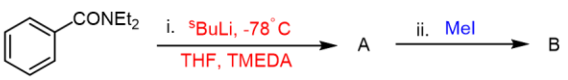


So, in the next problem, we are going to see that we started with this compound here. And now once, you treat with the sec-butyl lithium at -78 ºC, what is going to happen here? First that will be A and now if you treat with the methyl iodide that will be product B. So, we have learned in the directed lithiation that if you have this directing group with oxygen what you have learned then that can direct the lithium to come here. And now that is going to abstract this proton to generate this corresponding lithium and that can also form some sort of a stabilization with this Lewis acetic oxygen atom. With this electron-deficient oxygen atom sorry and then it is going to now you have this aryl lithium which is going to trap with methyl iodide to form this corresponding product.

Again, there is another example. So, this could be also used as a protecting group. So, this carbamate can act as a protecting group here first will be again very similar condition. There will be the formation of this corresponding aryl lithium here, which can react with the DMF to form this to introduce the corresponding aldehyde.

3.



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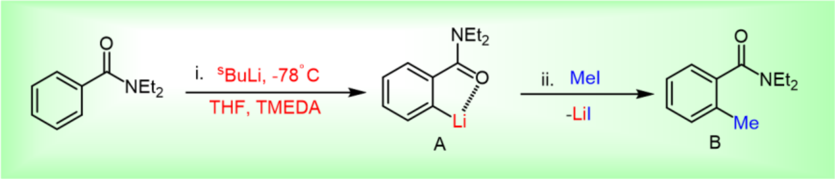

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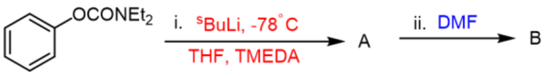

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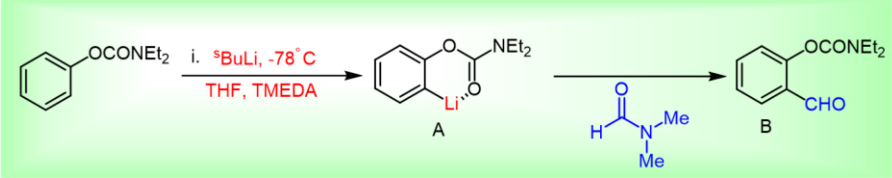
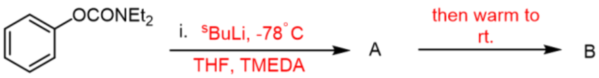


Again, there is another example here what we have done here this is very similar to the previous example. First thing is of course, the diverted lithiation to generate the lithium here, but now if you suppose you just warm the reaction to room temperature.

If you have not added any electrophile and you have added you have just warmed the reaction to room temperature, then what is going to happen this lithium is now internally going to get attack. So, this can attack to this carbonyl. So, this is going to attack here, form some sort of a four member. Now it is going to come back and clip this bond.

So, once it is happening you end up. So, you at the initially this is a O^- Li^+, now this will be at the end to generate this and once you take H_3O^+ this O-Li+ is going to take proton become OH and it will be $CONEt_2$. So, I think I talk about this anionic Fries arrangement. So, this is the anionic Fries rearrangement here again.

5.



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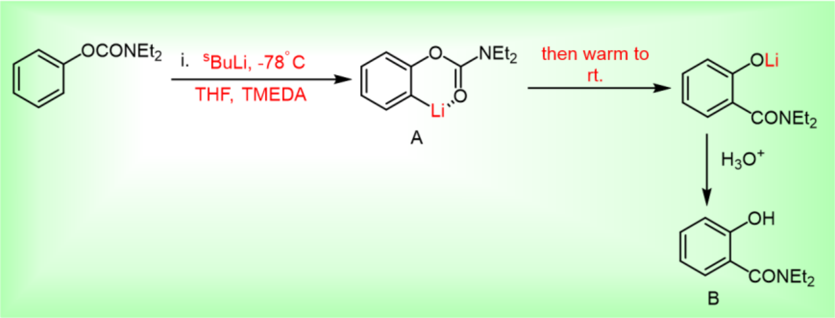
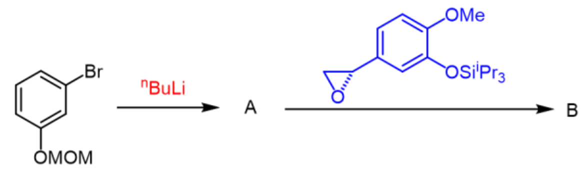


So, here the question starts that if you have this compound and you treat with n-butyl lithium what will be compound A first and then the next thing is if you treat with this epoxide what will be the compound B? So, first thing if you see a bromo here and you have n-butyl lithium you should remember about the metal halogen exchange, because starting from n-butyl lithium if you remember the logic of the metal halogen exchange that will generate a more stabilized lithium. So, using n-butyl lithium you are generating aryl lithium here.

After the metal-halogen exchange it can add to the epoxide and it will be going to attack to the less hindered side of the epoxide. As I mentioned before, how the reaction is going to happen and then after it will take the H_3O^+ to form this corresponding alcohol. So, this will be a product B and this will be a product A.

6.



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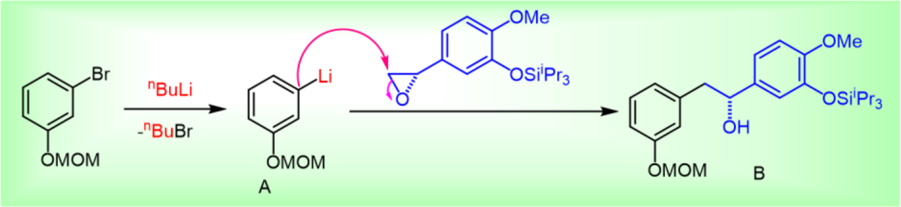
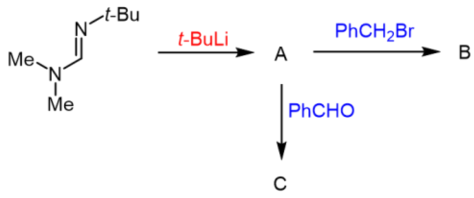


Now, the next example you can see here we did not talk about in the class, but if you have the instead of carbonyl you have some sort of imine here. Again, I think the imine can also be acting as a directing group correct.

So, using the tert-butyl lithium what is happening? you can see this can act as a directing group. Now, these are the protons of the methyl group which can be abstracted to form this corresponding lithium and you know this lithium can coordinate because the again the imines are imine nitrogen will be electron rich which can coordinate this electron deficient you know lithium. And now it is once it is treating with the different type of electrophile. it can it can go for S_N^2 attack here to form this product or it can attack to the aldehyde to get and then after the treated with the H_3O+ it can go to this product. So, that is how we can see you can now see this will be your A, this will be your B and finally, this will be your C.

7.



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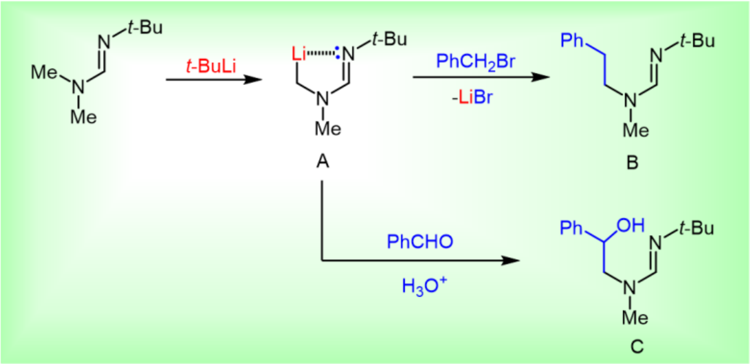
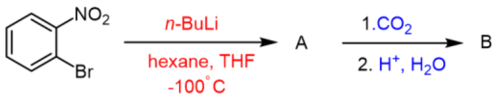


Again, you know these are the questions which are came in the GATE and JAM and in the previous. Another important question here I think we already talked about that once you have this aryl bromide and you treat with n-butyllithium. Again, you can see we are using at -100 ^{o}C that means, why I think I already told you that if you have a functional group like nitro, you then you want to keep them inert then you have to do the reaction at very low temperature. So, that case you only go for the metal halogen exchange, this lithium next to the nitro ortho position of nitro will be stabilized. So, that can react with the CO_2 to form this corresponding after it treat with the H_3O+ it is going to form the the ortho-nitro benzoic acid.

8.



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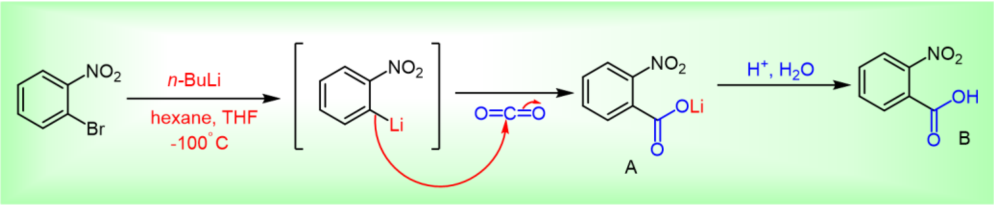
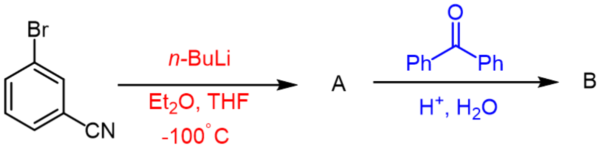


Another example here in this example you have a cyano group here you have a you know bromide here this allyl bromide you treating with n-butyllithium, ether THF, -100 ^{0}C. Again, this is the condition you are using for metal halogen exchange to generate this corresponding lithium. Once you generate a lithium it is going to react with the benzophenone here. after you treat with the H_3O+ it is going to form this corresponding tertiary alcohol. So, the A will be your corresponding lithium pieces and the B will be this corresponding alcohol.

9.



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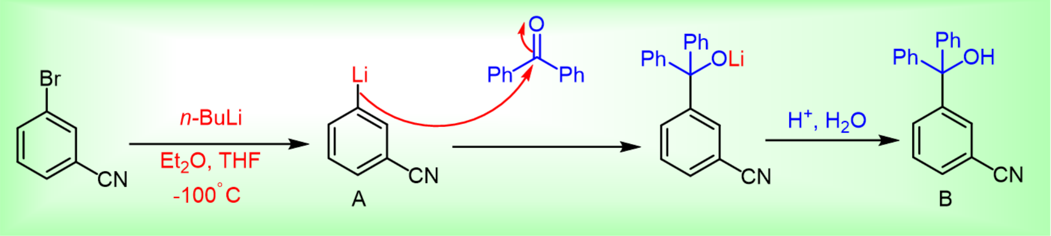
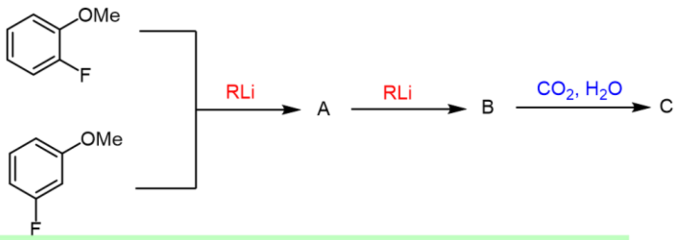


This question is interesting that you start with this compound where you have a fluorine and the methoxy the 1,2-position versus, meta position or with the 1,3-position. If you treat the RLi you get a intermediate A or a compound A which will treat with the RLi is going to give you B and you treat with CO_2 to get to the compound C. So, if you see this type of example here that again I think if you see there is a example where first thing you should remember that benzene ring having a fluoro or a chloro and you are treating with a RLi, you should always remember about formation of the benzyne because they cannot go for a metal halogen exchange. So, they will go for a deprotonation and once it is going to a deprotonation, it is going to end up forming a benzyne. And now the benzene I think you have learnt in the benzene classes that the nucleophile can attack from the meta position or from the ortho position and we saw that we already told that meta position will be the most favorable attack.

It will generate the corresponding lithium which will be stabilized by the inductive effort of the O-methoxy group which will react with the CO_2 to form the corresponding carboxylic acid as a major product. So, that means, I think in this type of questions you can write the if you have a option of B is given, if your option is B given then you should choose this option. If it is not given, you can write both the things you can write this one as well as that one. And once you treat with CO_2 you can write this as a major and that will be your minor product.

10.



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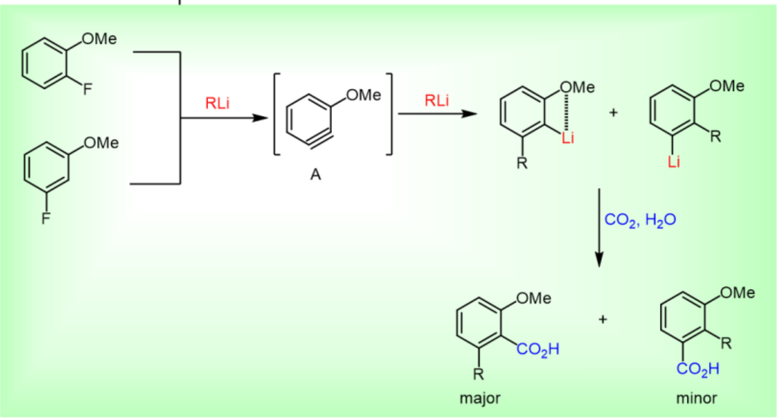

So, in this particular segment, I talk about the different type of question from all different topic and then also at the beginning I started talking about the if you generate an organolithium and you treat with the aldehyde what will be a product if you treat with the epoxide what will be a product. So, we talk about all the different type of reactions and I think that is all about the organolithium chemistry and here are the references in the next classes we going to talk about the organocopper and the Grignard chemistry and again thank you so much for coming to the class and I am going to see you guys in the next class.

Thank you.