Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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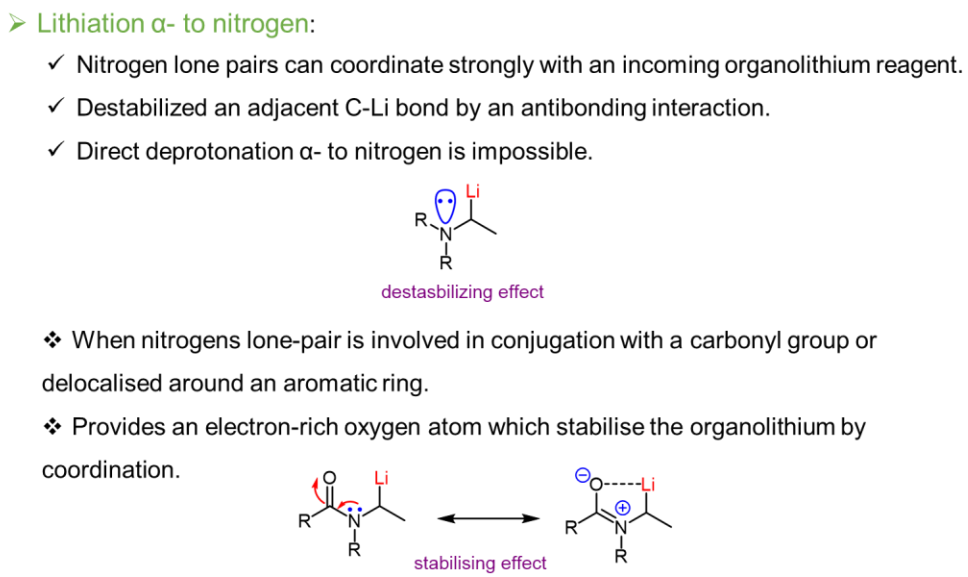
Lecture 34: Organolithium

Welcome back to this NPTEL online certification course in molecular arrangement and reactive in intermediates. In the last two classes, we have been learning about organolithium. So, I taught you about the metal halogen exchange in the last class. So, Today, I am going to talk about another important method: How you can generate organolithium species through deprotonation. And there will be something called a directed metalation So, you see different strategies we have used to deprotonate it from the Sp^3 C-H or the Sp^2 C-H. So, we are going to learn about lithiation alpha to the heteroatoms. So, you see how the heteroatom affects this type of lithiation. We are going to learn about directed metalation and Ortho metalation. Some stabilization factors for this type of reaction, and then the anionic Fries arrangement, and also, we are going to learn about something called lateral lithiation. So, you will see that kinetics and thermodynamics are going to play a very important role in this type of lithiation reaction. Again, these are the topics I am going to cover here.

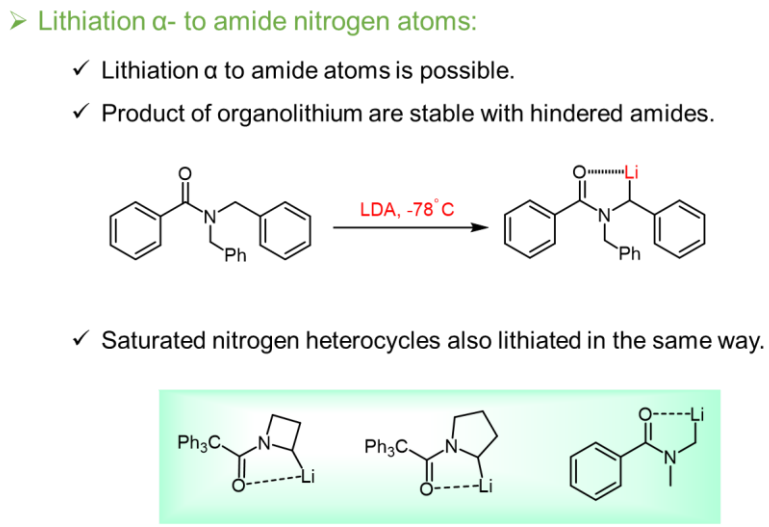
So, the first thing we will learn is what happens if you have a nitrogen or oxygen atom. The alpha to that C-H is going to get abstracted. Now, the problem is if you are talking about something like that, like if you have a scenario like this. So, these R groups are playing a playing a very important role here because if you think about the nitrogen having a lone pair here. Now, we are talking about if you use a corresponding alkyl lithium, it is going to abstract this proton. Now, it will only abstract this proton once you have R-groups. We will have some electron withdrawing groups because otherwise, once you go for this, treat R-Li, and generate the product, let us try to understand what will happen. You have this lone pair, and you have this carbanion, correct? So, now, this going to repel because you have now a lone pair and a carbanion they are going to repel. To stop this repulsion, what you have to do you have to attach with some group on the nitrogen or oxygen, which can pull the electron density of the nitrogen. That is why what we are saying is that if you have nitrogen. The lone pair that can coordinate strongly with an incoming organo-lithium is good because nitrogen will be going to because nitrogen will be some Lewis basic. You have a Lewis acidic in lithium. So, that is going to coordinate with the nitrogen. So, that is fine, but the next thing is you have to understand that direct deprotonation will be impossible as long as you are not putting an electron-

withdrawing group. So, of course, there will be an antibonding interaction of the carbon-lithium bond to generate this corresponding lithium. So, that is why you will see here that we are talking about some sort of a stabilizing effect if you have an electron-withdrawing group attached here. Now, you can see that the nitrogen lone pair will be pooled towards the carbonyl group here. So, Now, what is going to happen? Now, it is going to form this corresponding lithium. There are a couple of important things here. One is you can think about that this is pulling the electron density at the same time. Once you have this -N-C=O, it can stabilize the lithium interaction. So, there first, the lithium is approaching. It is going for this deprotonation to deprotonate this acidic proton, and then it is getting some sort of stabilization with chelation. So, the chelation is an essential factor, and for that, you also have to introduce an acetyl group to get the electron density from the nitrogen. It can make some sort of a chelate with electrophoretic lithium.



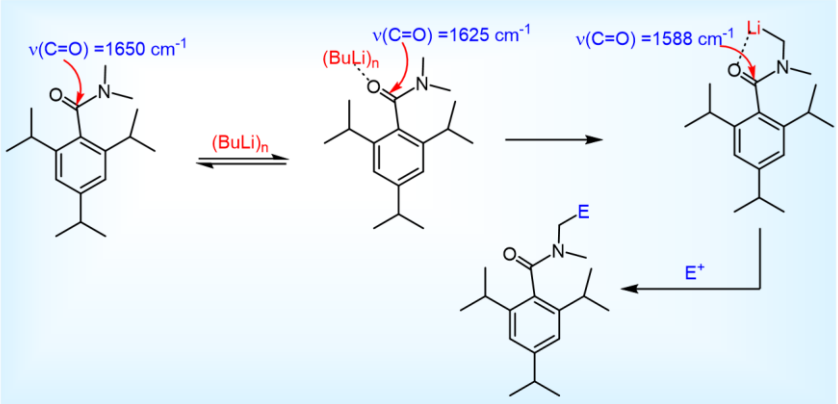
So, here again are some examples. Here you can see this particular amide. Here you can see this is a carbon. This is a ketone group that is pulling the electron density from this nitrogen. Once you are able to deprotonate here, once you deprotonate this C-H and generate this corresponding lithium in the presence of LDA, then this lithium is also getting stabilized. So, that stabilization is very important, you know, as I mentioned at the beginning, in the case of the metal halogen exchange. Also, I have explained to you that stabilizing the carbon and the corresponding lithium, which is forming, is very important for driving the reaction towards the right-hand side. You can also see that stabilization is a very important factor here. So, you can see here there are different types of variation. I think I am going to cover only a few slides here, but you will be able to get a lot of questions in practice. So, where I can supply some of the questions on this particular topic. You can see here it could be a four-membered ring, or it could be a five-membered

ring. So, you have seen that there could be different types of protecting groups here; it could be blocking protection that can also act as a directing group. The lithium can be directed through this to abstract this C-H. Lithium can be directed through this oxygen to after this C-H to form this corresponding lithium here. So, this C-H will be replaced to get the corresponding Lithium. You can see there are several different things, several different variations. Still, in every case, one of the things is very common: you put an electron-withdrawing group with nitrogen, and oxygen also acts as a chelating agent here.



Then there is an example in this particular case of what we are seeing in this molecule: a 2,4,6-triisopropyl group. So, once you have an isopropyl group and you have this amide here now, once you have this lithium, the lithium will coordinate with this oxygen, as you can see here. So, you can see that once the lithium is coordinated, there will be a change in what happens. So, there will be this bond going to get weaker. That is why the frequency is going to decrease from 1650 to 1625. What will happen here, as these ortho protons are already not there if we place them in an isopropyl group? That is why it is going to abstract proton from this N-methyl. Through coordination, once you are forming the corresponding lithium, the lithium also gets stabilized through coordination with oxygen. As I said, Lithium is electropositive. It can make a coordination. So, that will make a stable organolithium.

- Following lithiation model are used for directed lithiations to the α- heteroatoms.
- Complex between the amide and organolithium forms much faster than amides lithiated by studies IR-spectroscopy.



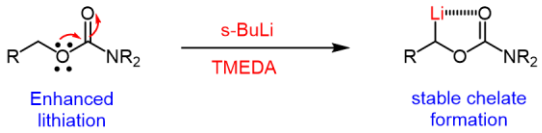
Now, we are going to learn about the oxygen. So, what will happen if you have an oxygen atom and there is a C-H here in this particular compound? So, we have learned about nitrogen very similarly. The oxygen will have an -OCONR$_2$, which means you made some sort of a carbamate here. The first thing is from alcohol you made that from alcohol, you can make this corresponding carbamate, and once you make the carbamate and once you treat it with the fake butyl lithium and TMEDA, that can able to abstract this particular proton.

➢ Lithiation α- to Oxygen:

- ✓ Deprotonation α to oxygen atom is unfavourable, due to the antibonding interaction of the oxygen lone pairs with the C-Li bond.
- ✓ This repulsion are minimized if the lone pairs lowered in energy by delocalization.

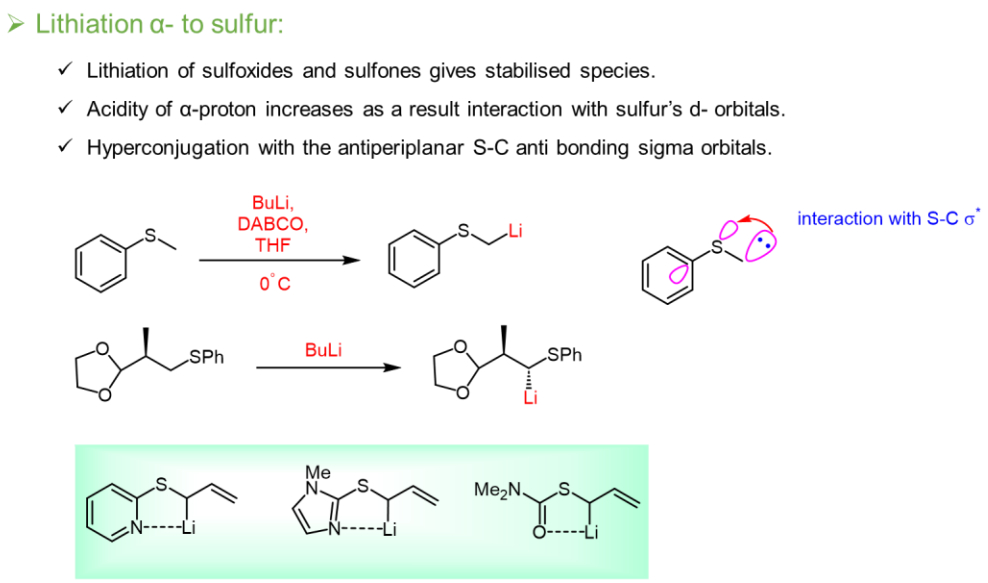
Example:

- ✓ Lithiation α to oxygen are deprotonation of hindered carbamates by s-BuLi under the influence of TMEDA.

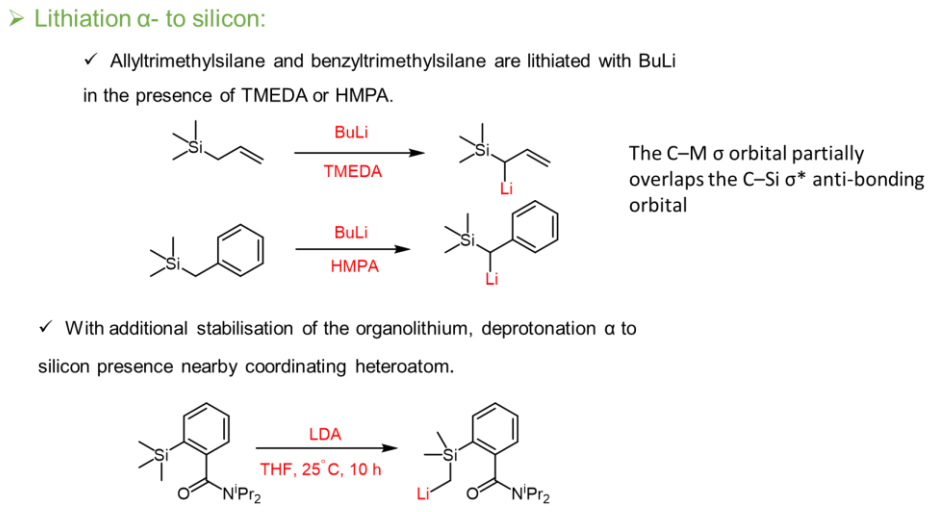


Now, we are talking about the next to sulfur. In this compound, one side of sulfur is phenyl, and one side is methyl. Then, in the case of the BuLi, DABCO and THF, we will abstract this proton here to form this corresponding lithium. So, that is happening through this interaction with the sulfur-carbon antibonding. So, that is how they are they are

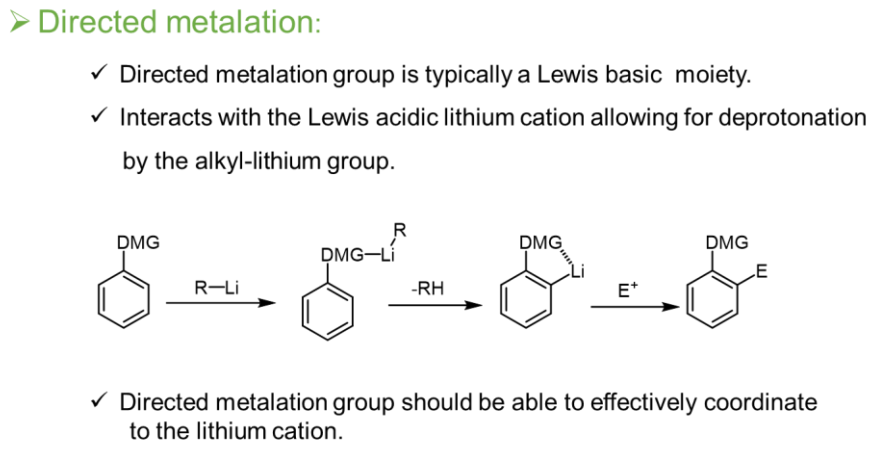
generating this. Again, you can see several examples here for the generation of this type of organolithium species. Once you have this type of allyl species here. So, this proton will be the acidic proton. So, here it is forming the corresponding lithium, and here you have pyridine nitrogen that is electron deficient and can make some sort of a chelate complex here. And suppose you have oxygen like something like this, some sort of a thiocarbamate here. In that case, you can see again here also the formation of the lithium, and that is getting coordinated with the corresponding oxygen.



So, now we are talking about silicon. So, suppose you have allyl silicon and allyl silane. In that case, if you treat it with butyllithium and TMEDA, it will abstract this proton here from this position to generate this corresponding lithium here. It is very similar if you have a benzylic group here then again, this proton, this carbonyl, will be even more stable. So, it can be stabilized in two effects here. The first thing is that it is benzylic or allylic, and the next thing is the silicon has an alpha effect. We have already learned about this silicon alpha effect, and we will also discuss that once I teach you silicon chemistry. If you have this the sigma orbital of this corresponding lithium is interacting with the carbon and silicon antibonding orbital. So, this sigma orbital interacts with this sigma-star orbital, which is the carbon-silicon sigma-star orbital. So, that overlap actually stabilizes the anion alpha to the silicon. So, there is another example here. In this case, what is happening again, you can see here in the case of LDA. So, this is acting as a directing group to abstract the proton from this. Through chelation because, again, you can understand now how this directing effect is important once the lithium is coordinated with the electropositive oxygen. So, it is finding the nearby protons, and now you have found the CH_3 proton, which is getting abstracted to generate corresponding lithium here. Again, the alpha effect is another important factor.

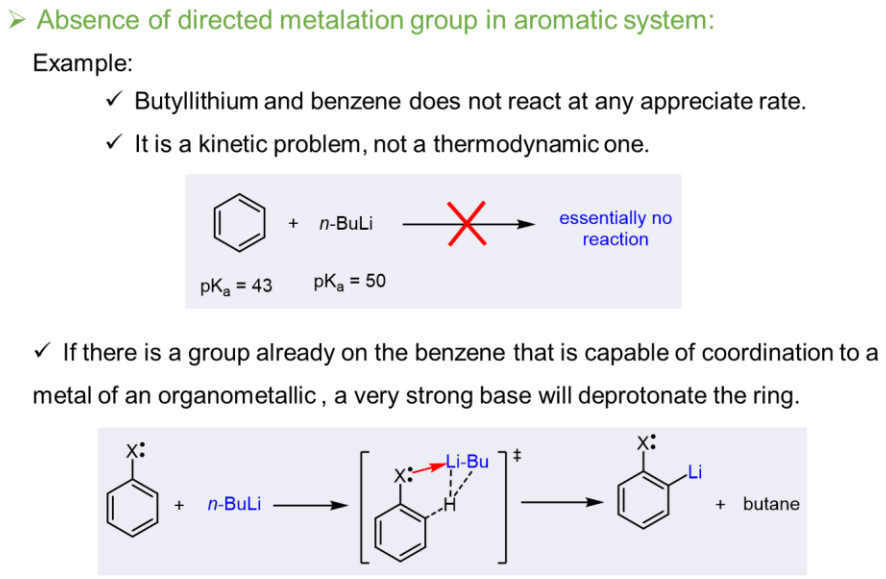


So, now I am going to talk about the different types of directing groups. So, in all these types of directed metalation, what do you find out that directed metalation, this type of the directed group has a common nature that has some element that is electropositive or Lewis basic. So, that means, if you have a Lewis base, then you have a Lewis acidic lithium going to coordinate with that. So, some sort of coordination is going to happen between them. That is going to coordinate now if you have a R-Li suppose then you can think about. So, this is the photon, and you have a Li, and if you can write this way, then you can think about that because it is getting coordinated. This can now, this R can come and take this H and generate some sort of anion here. And then also another important thing is that you have this type of electropositive element here that is going to also form some sort of a chelate to stabilize this carbanion. As I mentioned, stabilization is very important; now, you can trap with an electrophile to get to the corresponding product.



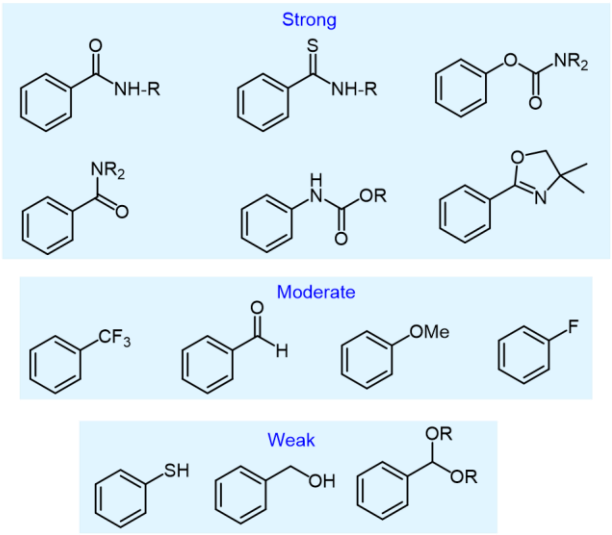
Again, you can see here that the difference is that if you have normal, just like benzene. If you treat the butyl lithium, you will not find that corresponding phenyl lithium formation

happening. But as soon as you put a directing group here, things become very important because the stabilization of the lithium and it's very important, and most of the time, you will find out that all this type of directing groups has a very common thing that they have a stabilization effect of the corresponding lithium. That is the important thing which is missing here in case of benzene that is why because of the stabilization effect you can write this like that. Because of the stabilization effect. So, this type of reaction happens very fast, but you will not find it happening once you have it.



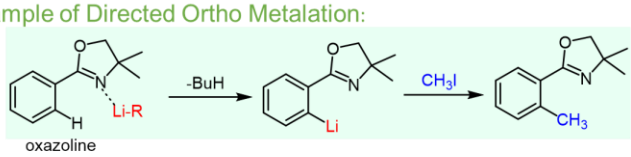
So, here is the list. I think the least could be even more. You can see the different types of groups we are talking about here. Most of the time, you will see a carbonyl group, and this oxygen is the one that is always going to form a chelate with this lithium. Or there will be a carbon-sulfur again carbon-oxygen bond. These are the very strong things going to bind here. So, if you have this type of directing group, the reaction is going to happen first to form this corresponding phenyl-lithium, but if you have CF_3 or the corresponding aldehyde or the -OMe. So, these are also very important. So, here also the lithium going to bind to go for some sort of you can see because you have oxygen electron rich lithium is electron positive. So, that can bind here and if you have R group that can abstract the ortho proton here. And then, in the case of these groups, they are weak, of course, compared to this because these are not even connected here. Still, you are going to see in one particular class here ah, which is this one once you have an N, N dimethyl or if you have an NR_2 in this particular class lithium because of the nitrogen electron very rich. it can coordinate here and it will go for a metal halogen we are going to talk about that also.

➢ Directed metalation group(DMG):



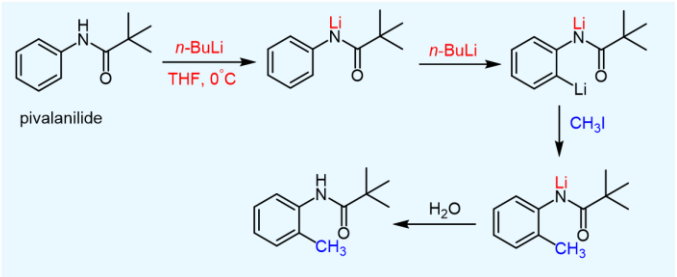
So, the first thing you see in the case of this particular oxazoline you can clearly see this -C=N- this imine nitrogen. is now coordinating with the lithium which is electropositive and now this C-H bond. So, this C-H bond in getting broken then it is going to generate this corresponding organ-lithium which can trap with CH_3-I to introduce CH_3 is there. So, this directing effect is allowing to abstract this ortho proton not the corresponding para proton. So, in the case of the pivanilide. So, if you start with the corresponding amine and then if you make a block protection of it, then what is going to happen now? This can act as a directing group here, but you have this N-H who is going to abstract first, and then once you have another equivalent of butyllithium. So, you need two equivalents of butyllithium here because you have acidic proton in the directing group. So, now what is going to happen is the n-butyllithium is going to coordinate with this lithium to coordinate with the oxygen. It is going to get rid of this ortho proton to form the corresponding lithium, which is going to trap with a CH_3-I.

➢ Example of Directed Ortho Metalation:



oxazoline

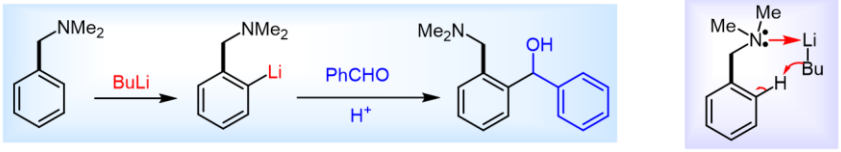
✓ Ortho-metalated intermediate can be reacted with a variety of electrophile.



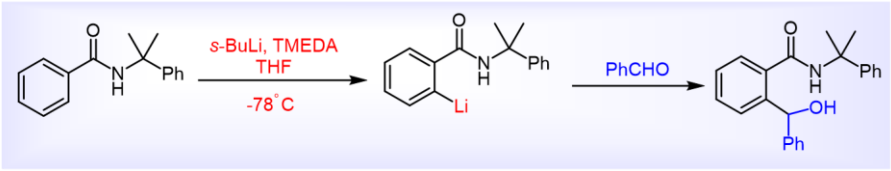
pivalanilide

As I mentioned, if you have a dimethylamine here. So, benzyl dimethylamine, I think I was telling you in the previous slide, acts as a directing group here nicely because you can see because the nitrogen is electron rich it is as it can coordinate with the lithium very nicely, and that can allow you for the directing to after this C-H bond here. To generate this corresponding lithium, cleave this corresponding C-H bond to create lithium after the proton abstraction, which can form the lithium that can act on the corresponding aldehyde. Again, if you have an N-cumyl benzamide here in this particular compound using the sec-butyl lithium, I think it is also going to go for a proton abstraction, and then it is going to abstract this through a directing effect of this carbonyl group here. It is going to generate this corresponding lithium, which is going to act with the corresponding aldehyde. Again, I think her you can see this N-H, which is also going to convert to the corresponding lithium as well. Once you treat it with the aldehyde and H_3O+, it will get to the corresponding product here.

- In the case of benzyl-dimethyl-amine, the nitrogen atom directs butyl-lithium.



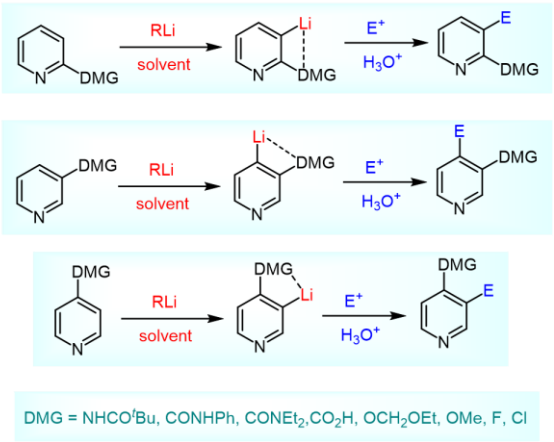
- *N-cumylbenzamide* with excess *sec*-butyllithium in the presence of *TMEDA* gives Ortho lithiated intermediate that readily reacted with benzaldehyde to give product.



So, now, we are going to talk about the directed lithiation of pyridine because pyridine itself is electron deficient So, the problem is if you take an organolithium and treat it with pyridine, what is going to happen? It is going to go for a 1,2-addition. It can be added to the C-2 or in the C-4 position. So, that is why if you want to go for a proton abstraction to generate a lithiated pyridine species, then the directing group is very important. So, you are allowing the lithium to coordinate with the directing group first, and then it can go for a proton abstraction to generate this lithium, which can trap with the corresponding electrophile. So, there is an example here given that if you have a directing group here, it can able to abstract this corresponding lithium, then it can trap with the electrophile or in para position if you have a directing group, then it can form the lithium in the meta position to get to the corresponding product, and again there are several different types of directing group is used here. So, one question you might be thinking is, why, in this

particular reaction, when you have a directing group in the meta position, are you abstracting the proton from the C-4 position? Why not from the C-2 position? So, one of the major important things here is that once you abstract this now, once you generate a carbon ion here and once you have a nitrogen have a lone pair, there is a repulsion between them. So, this carbanion and this lone pair of nitrogen have a repulsion, which is why if you see the rate of abstraction of this pyridine proton and if you think about the C-4 come first, then the C-3 and then the C-2. So, this has much higher rate compared to C-2 because of this.

➢ Directed lithiation of pyridine:



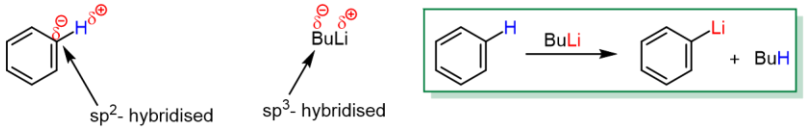
DMG = $NHCO^tBu$, $CONHPh$, $CONEt_2$,CO_2H, OCH_2OEt, OMe, F, Cl

And now we are talking about that ortho lithiation directed metalation happening because you are forming a more stable lithium. So, that is again we are trying to tell you here that if you have a Sp^2 hybridized versus a Sp^3 hybridized. So, this is having more S characters more stabilized. That is why this reaction is driving towards this side. It cannot come back in this direction that the phenyl lithium will take hydrogen from the butane because of the stability.

➢ Ortholithiation:

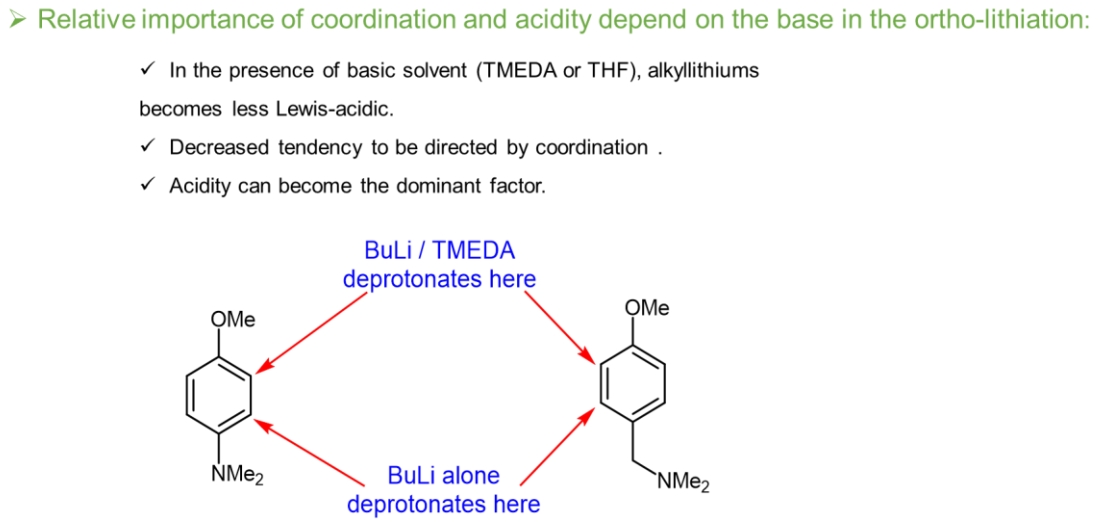
- ✓ Ortholithiation-directed metalation of an aromatic ring adjacent to a heteroatom containing functional group.
- ✓ Involved deprotonation of a substituted aromatic ring by an organolithium usually n-, s-, or t- butyllithium or LDA.
- ✓ Aromatic proton more acidic than butane.

❖ Driving force:



The higher the s-character, the higher the stability of the carbanion.

So, here we are talking about that if you have a butyllithium and a TMEDA versus if you have butyllithium alone. And in these two substrates what is happening, the deprotonation is happening from this position if you have alone butyllithium. So, what is happening? You can understand clearly this particular compound; if you have a butyllithium, lithium is going to coordinate here. Now, the carbanion is going to abstract this particular proton to generate this corresponding abstract. So, it is going to cleave this carbon-hydrogen bond to generate this corresponding carbon in this position, but once you have the butyllithium and a TMEDA. Now, your butyllithium already has this type of structure. I think I already explained to you in the previous classes that once you have a TMEDA and butyllithium, it forms some sort of a dimeric structure. And what is happening now is once it is trying to abstract a proton, it is finding out that you know where it is going to abstract. So, based on these two protons if see if you are thinking about this particular proton, we have already learned that once you have a -OME group here, the carbanion will be more stabilized. So, now, the directing effect is not playing an important role. Now, the inductive effect the -I effect of the -OME group actually playing the role here once you have a TMEDA And once you have a the butyllithium alone then it can coordinate. So, the directing. So, two things are happening: On one side, a directing effect is playing a role. On one side, the stability of the negative charge plays a role once you have a TMEDA bound with it.

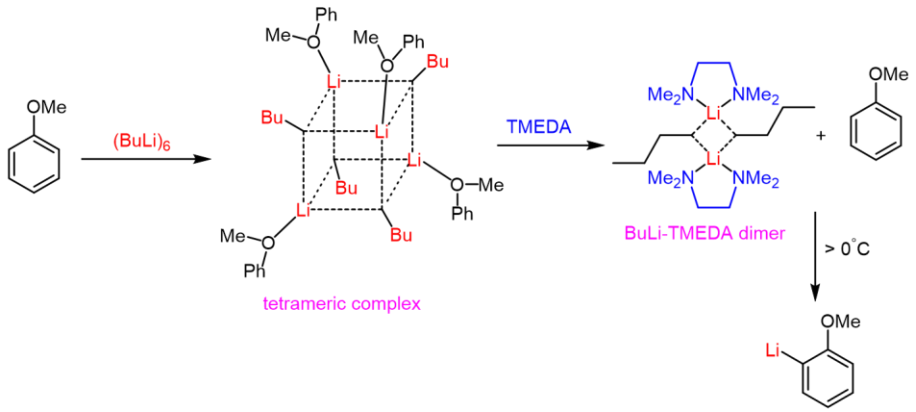


So, here again, it is shown that we know once you have anisole, it can also it can actually convert the hexametric structure of butyllithium to a tetrameric butyllithium anisole complex from there, the TMEDA comes into play, and then it can. So, if you are using this particular anisole, you are trying to deprotonate, and then people use the TMEDA within butyllithium. What is going to happen that can break down to a butyllithium

dimer? Now, which can able to abstract. So, this proton forms this corresponding lithium, which can stabilize through the -OME group.

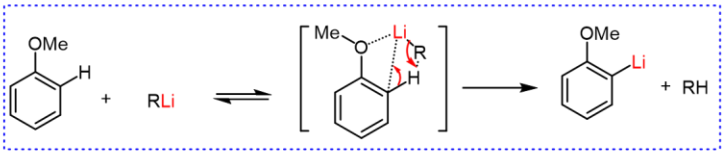
➢ For example:

✓ Anisole deaggregates the BuLi hexamer to form tetrameric BuLi-anisole complex.

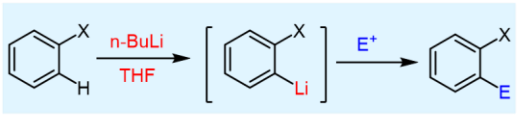


Again, you can see here that we are showing here that is corresponding. So, it can also form it. As I mentioned at the beginning, once you have oxygen-nitrogen, it can form some sort of a chelate because this is the electropositive. It is electro-negative, and then it can take this hydrogen and then form this corresponding organolithium here. So, you can write in general here that if you have a depending on the x-group, if you have oxygen-nitrogen, all these types of groups or if you have all these cases, it is going to form this corresponding lithium here.

➢ Mechanism:



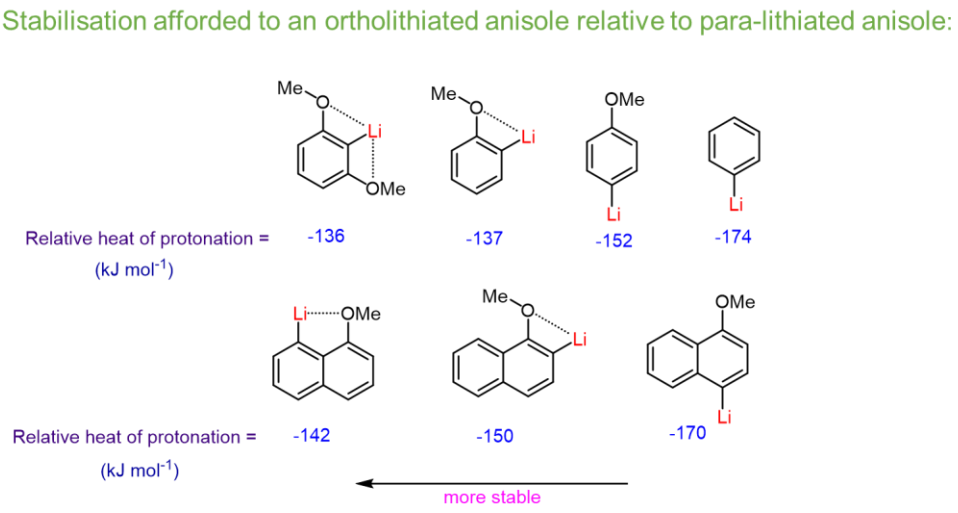
➢ In general we can write:



X = -OR, -NR_2, -CH_2OR, -$CONR_2$

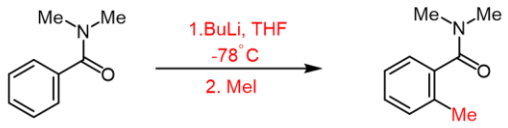
E^+= CO_2, DMF, RCHO, R_2CO, primary alkyl halides

So, now, you can see we are talking about here the relative heat of protonation. So, the stabilization afforded to an ortho-lithiated anisole relative to a para-lithiated anisole. So, here you can find out the rate is decreasing in this direction because you can see the heat of the protonation. The value is decreasing because of the stabilization. So, the formation of the corresponding lithium stabilization is the driving force as I mentioned. So, if you have two methoxy groups here, then it is going to abstract, not this proton; the proton is the middle of these two methoxy, because now it can form more stabilization through both the methoxy group. Now, if you have an ortho, which will be the next? If you have a para, then of course, it will be the lowest than that, and then if you have only phenyl lithium, it will be the lowest there. A very similar thing is happening in the case of the naphthalene here. We are going to come back to that also here if you are going in this direction. So, in this direction, they are more stable. They are less stable because you can see your lithium is in the para position here. So, there is no coordination between the lithium and the methoxy.

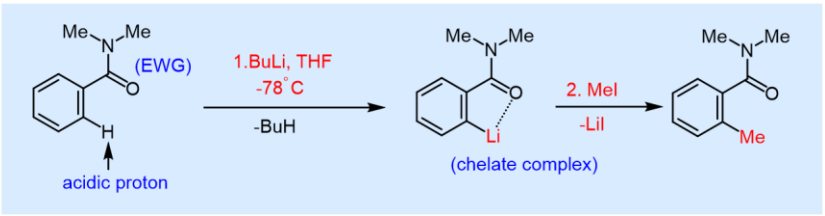


So, here you can see if you have this type of directing group as I mentioned it before, your lithium can able to co-ordinate with this oxygen now you have -R, this can take this -H to generate this corresponding lithium, and now this will form a chelate complex. The lithium with oxygen will be able to travel with the electrophile.

➢ Example:



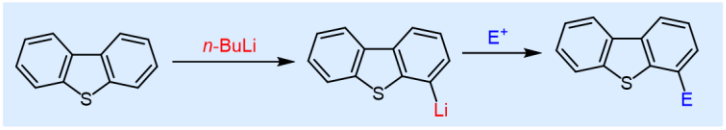
➢ Mechanism:

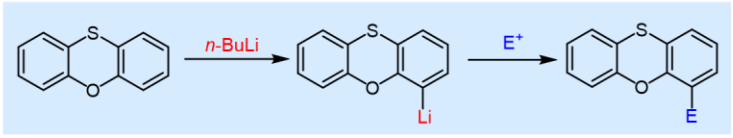


So, here is an example: if you have sulfur versus you have oxygen. So, the diaryl sulfide is lithiated ortho to sulfur but less efficiently than the diaryl ether. So, once you have the oxygen here, as you see, compared to oxygen and sulfur now, the oxygen will be able to coordinate with the lithium more. So, that will allow the formation of this lithium corresponding lithium and then in the corresponding product much faster compared to the sulfur.

- Diarylsulfides are lithiated ortho to sulfur, but less efficiently than diaryl ethers.
- Highlighting preferential lithiation at the more acidic positions ortho to oxygen rather than sulfur .

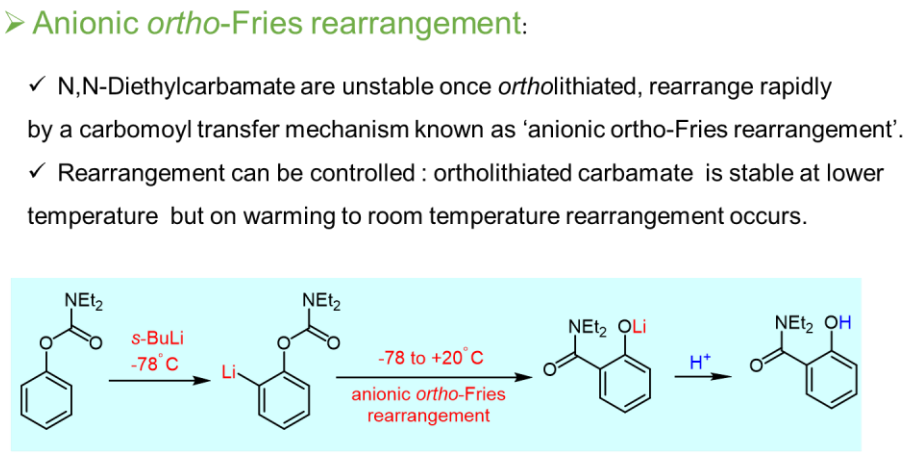
Example:





So, now, I am going to talk about ortho-fries reagent and what is going to happen for this particular reacting group if you have some sort of diethyl carbamate N, N-diethyl carbamate. If you use carbamate as a reacting group, then this corresponding lithium is unstable. Once the corresponding lithium forms, this lithium goes for an intermolecular reaction. It is going to attack here, and then it is going to come back, and it is going to cleave this oxygen-carbon bond. to generate this corresponding -OLi, which will go with

the proton to get to the corresponding OH. So, what is happening here if, from starting this compound, you synthesize this corresponding phenol ok that is going through this type of Anionic ortho-Fries rearrangement. So, here it is acting as a directing group, and at the same time, it is getting attacked and cleaved to get to the corresponding product.

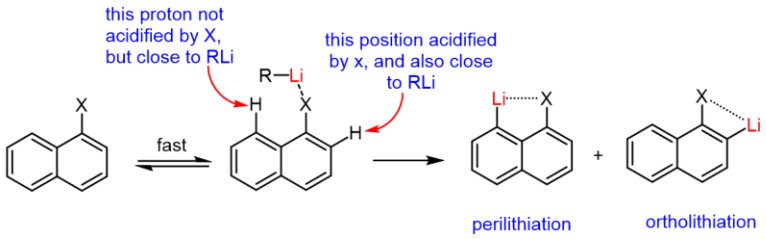


Once you have naphthalene, there are two different scenarios. Suppose you started with this. So, in the case of naphthalene, things are a little tricky and selective lithiation is still challenging. So, suppose you have a -OMe group here or here in this or in the α or β position; what is going to happen there? There are two different protons. So, we can tell them that this proton does not acidify by X but is close to R-Li. So, this is one of the things this proton is. Still, they are also close to RLi, and we have given them as a peri-lithiation or ortho-lithiation, which means if you think about this proton abstraction, then if you generate negative this -OMe you can stabilize. So, that is how it is forming the ortho lithiation. You will see that the ortho lithiation is happening in a major, but at the same time, the peri lithiation is also happening. This is happening because once the lithium is coordinating here now, it can abstract this photon and then form the lithium here. So, that is why if you see in the literature if you are going for this type of the lithiation of the naphthalene with some sort of an X, It means some sort of a directing group like you see a methoxy or things people have ended up getting a mixture of product.

➢ Peri- and ortholithiations of 1-substituted naphthalenes:

✓ Electron-withdrawing substituents which acidify nearby protons via inductive effect.

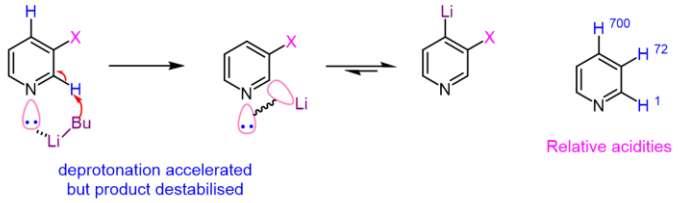
✓ Thus X (EWG)-directing lithiation by coordination can promote lithiation at either ortho or peri- position .



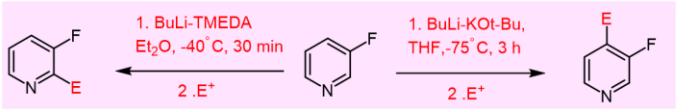
I think the same thing I was trying to explain to you in the previous slide if you have a directing group here in the 3-positions in the case of pyridine. Why is it abstracting the C-H from the C-4 position, not the C-2? The problem is the deprotonation is accelerated, but the product is destabilized once you have this product's corresponding lithium. As you can see it is 700 times faster than this one.

➢ Most stable pyridinyllithiums are those bearing Li- at the 3 or 4- position .

➢ 2- pyridinyllithium formed faster but readily isomerise to 4-pyridinyllithiums.

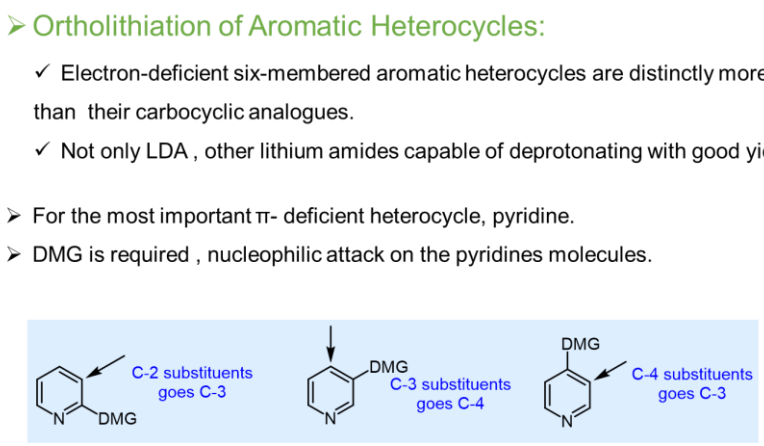


Example:

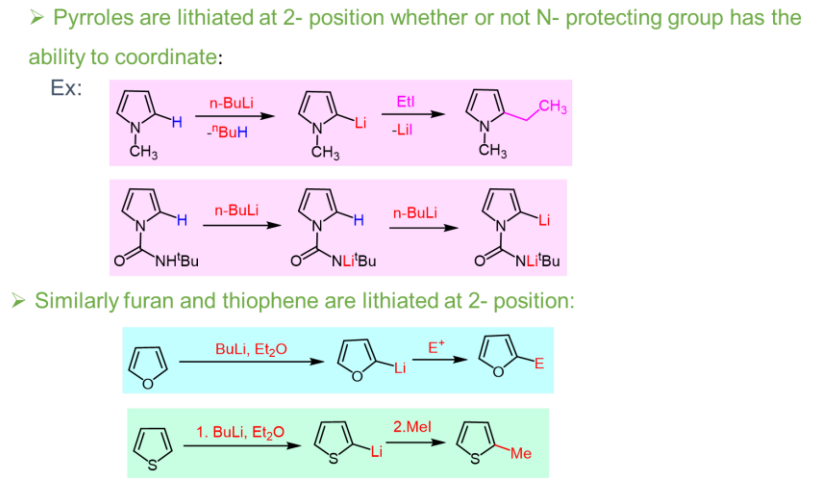


So, here again, if you have an electron-deficient six-membered heterocycle, then not only the LDA or other lithium amides are capable of deprotonating because you can see what is happening here because you have a directing group. So, that is why it is electron deficient, that is why the other lithium amides are also capable of abstracting this proton form here to generate this corresponding lithium. As I mentioned, if you are not using the directing group, then the organolithium can attack the pyridine because pyridine is electron deficient. So, here you have some sort of a five-membered aromatic heterocyclic with electron-rich atoms like oxygen and sulfur. So, what is happening in these cases is that this can also chelate with lithium because it is electron-rich. And now you can see

this is the proton next to that it is going to get if you have butyllithium this can form the corresponding lithium, which is the furan C-2 or in the thiophene here if you have a pyrrole you have to just protect the pyrrole in a n-methyl now it can also form the corresponding lithium using the butyllithium.

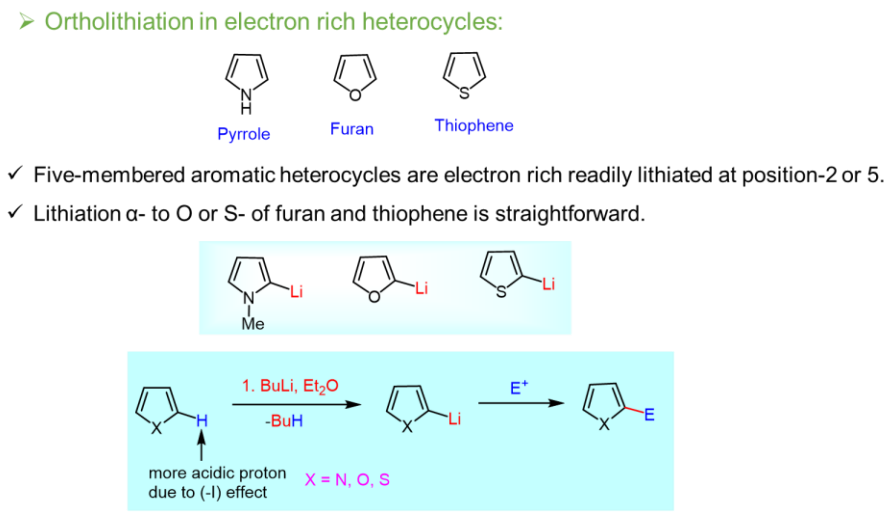


Again, here you can see if you put instead of the n-methyl if you have the -N-Boc or some sort of other protecting group here that can be deprotonated first if you have this NH-^{t}butyl that can be deprotonated, then another equivalent of butyllithium can able to deprotonate that. Similarly, furan and thiophene, as I mentioned, can able to form this corresponding lithium.

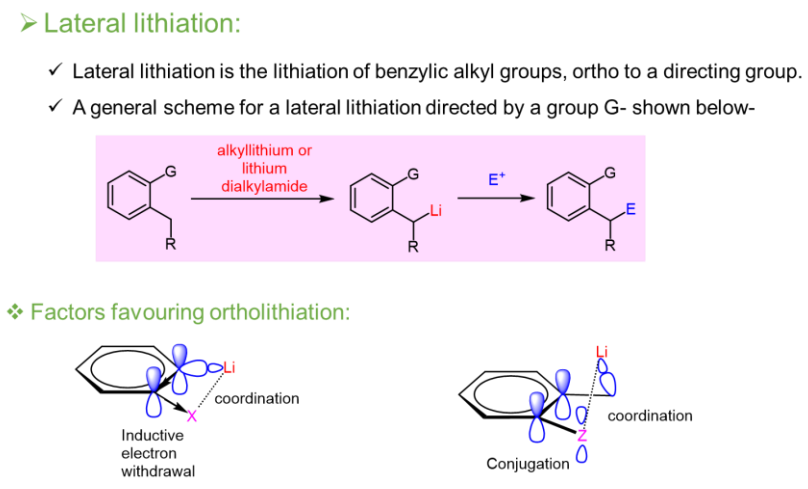


If you have indole, then things are interesting because indole has an -NH. So, first thing, if you give n-butyllithium, then the idea is you have too first. So, this proton will be abstracted to generate this corresponding lithium, which will trap the CO_2 to form this Lithiocarbamate. So, now, if you treat it with the corresponding ^{t}BuLi, it can go for a C-2 lithiation. So, in indole, if you want to generate a C-2 lithiation, then you have to treat with an n-BuLi first to get rid of this -NH. So, it will form the corresponding carbamate in place of CO_2. Then, once you use the ^{t}BuLi now, it is going to form the corresponding

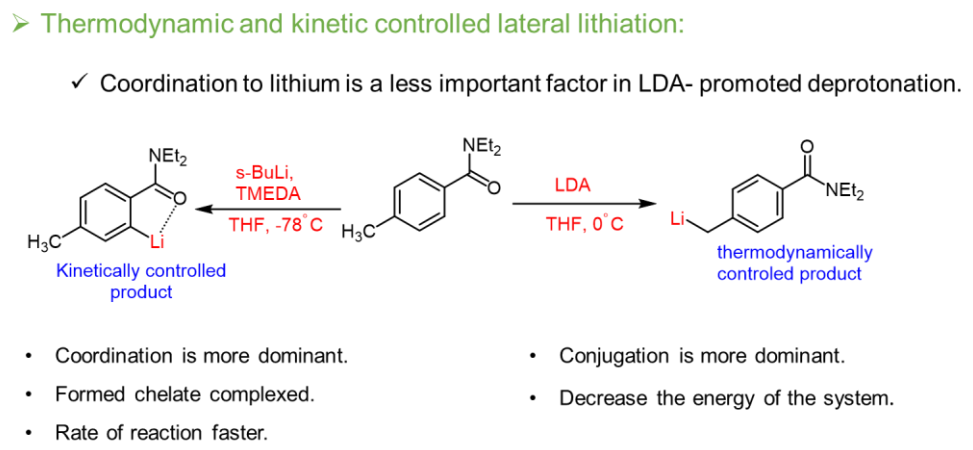
C-2 lithiation. Then there is another crucial fact about indole if you put a bulky group with the nitrogen. That means what is happening is that you are stopping this coordination of the lithium here because once you have a bulkier group, the coordination will not be good enough, and you are using ^{t}BuLi, you are using bulky lithium as well. So, bulky lithium and the bulky protecting group with nitrogen will end up forming lithium in this position because you can see this is the next proton, which is acidic and can be brominated further.



Then we are going to talk about the lateral-lithiation. So, if you have some sort of a benzylic group here and a directing group in the benzene ring, then what is going to happen is that it can abstract this proton from here to generate this corresponding Lithium, which is going to form some sort of a chelate to stabilize it. It is going to create it going to react with the corresponding electrophile. Again, this type of inductive electron withdrawal is a very important thing here that is another important factor for this reaction going towards the product, or there is another thing called conjugation. So, we are going to come to this factor. So, there is an inductive effect versus a conjugation.



So, this is an interesting example here in these cases. So, if you see $CONEt_2$ and then you have a CH_3 group in the para position. If you treat the Sec-BuLi with TMEDA, then there is an ortho lithiation happening here or like ortho metalation to form this corresponding lithium. It is a kinetically controlled product happening at -78 °C. And if you go to 0°C, then what with the LDA, then it is forming the thermodynamic control product through conjugation. So, this stabilizes through conjugation because the negative charge is stabilized through conjugation. Here the negative charge is getting stabilized through the formation of a chelation. So, what is happening here is once you use the s-BuLi in TMEDA the low temperature, the oxygen is the one that is going to chelate with the lithium, and that is going to direct this abstraction of the C-H to form this corresponding lithium here. So, coordination is the most important thing here, but once you use LDA, you can see that there is a difference between the structure and the LDA and the sec-BuLi In the case of LDA, what is happening now is that LDA is also bulkier in the structure. So, it is going to find the protons, which are acidic here and will stabilize and get stabilized. So, if you form this carbon ion, this is getting stabilized here, that is why you know, and so, here what is happening is the $-CONH_2$ is kind of acting as an electron-withdrawing group through -I affect to stabilize this carbanion. So, on one side, there is -I effect of stabilization one side they are just chelation control.



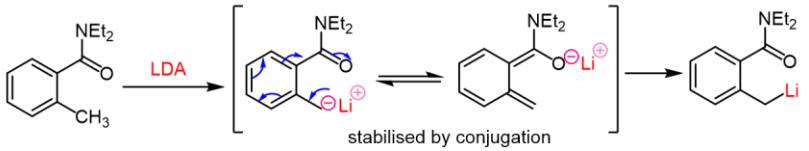
Again, in this particular example, if you have a group in the ortho position, not in the para position, then you are getting both the affects you are getting both the chelation effect as well as the conjugation effect here. That means, what is what I am trying to say here is that once you are lithium is here, it has some chelation effect, which can abstract this CH proton to form the corresponding lithium. This lithium is also stabilized through conjugation. So, both effects are operating. So, this is happening very fast.

➢ Example of lateral lithiation:

✓ Lateral lithiation of amide , assisted both by coordination of the amide to the lithium and by conjugation with aromatic ring.

✓ Conjugation is more important than coordination stabilising benzylic Organolithiums.

Mechanism:



In this particular topic, what I have tried to cover is the deprotonation reaction. So, how do we generate a corresponding lithium through deprotonation? And I started with the deprotonation once you have a, you know, different type of heteroatom like oxygen, nitrogen, sulfur. Then, I talk about different types of directing groups for ortho-metalation. I have shown you a different type of example here on this particular topic; please go through this type of reference book here for more knowledge, and many more examples will be given. Again, thank you so much for coming to the class, and I will see you guys in the next class. Thank you.