Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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Lecture 33: Organolithium

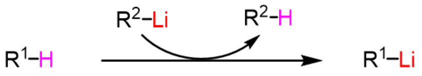
Welcome back to this NPTEL online certification course in "molecular arrangement and reactive intermediates". In the last class, we started learning about the organolithium compounds. So, I started talking about the organometallic compound. In this particular segment, first, we are going to learn organolithium, then Grignard reagent, organozinc, and organocopper. So, in today's class, I am going to discuss a very important topic about the lithium reagent called the metal-halogen exchange. So, this is a very important technique, how you can make the organolithium reagent. So, this is called metal-halogen exchange. I think in the first-class I talked about this, but now we are going to learn about what is the history, what are the different methods for the formation, and how this reaction is controlled.

In this particular segment, we are also going to learn about the synthesis of organolithium by deprotonation, then there will be transmetalation we are going to discuss, reductive lithiation, and carbolithiation.

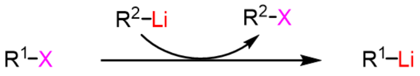
➢ General points:

❖ Organolithiums formed by the following distinct methods -

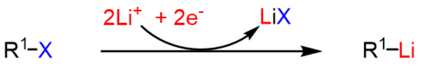
✓ By deprotonation:



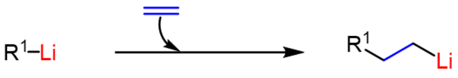
✓ Transmetallation and Halogen-metal Exchange:



✓ Reductive Lithiation:



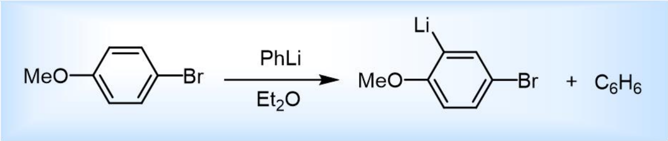
✓ Carbolithiation:



But as I mentioned in today's class my first thing is to teach you the metal-halogen exchange. So, this is a very important reaction and you can understand from this terminology that there is a metal and halogen. So, they are getting exchanged. So, now, we are going to learn first the history of this reaction and how this reaction was discovered. So, you must have heard about Prof. Wittig not only for the Wittig reaction, but he has also discovered several other things. There are several name rearrangements, you have seen Wittig rearrangement I have already covered some of the things in the classes. So, in 1938 he first discovered an important type of transformation. If you see these two equations here let us try to understand what is happening here. First, you can see this is p-bromo anisole, if you treat it with the phenyl lithium in diethyl ether, it is going for a proton abstraction. So, there is a proton getting abstracted here. So, they generate corresponding lithium. Some sort of deprotonation happens in the presence of phenyl lithium. But once the reaction was done with this particular compound where you have this 1,3-dimethoxy-4,6-dibromobenzene and treated with phenyl lithium, then what happened was that one of the carbon-bromine bonds got cleaved and that was replaced by lithium and then once it was treated with water it ended up making this product. So, it ends up forming this compound. So, this was the first observation by Prof. Wittig that in this particular reaction, there is a metal-halogen exchange going on that only can explain why this particular product is formed.

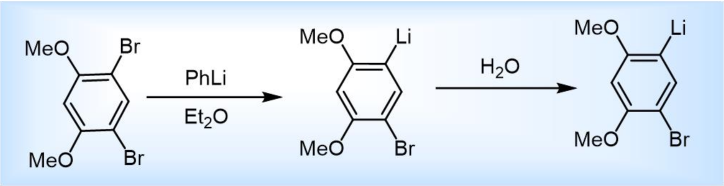
➢ History of lithium-halogen exchange reaction:

- ✓ In 1938 Wittig, first discovered lithium-halogen interconversion.
- ✓ After monitoring the lithiation process of p-Bromo anisole using phenyl lithium, Li-hydrogen exchange takes place.



Georg Wittig

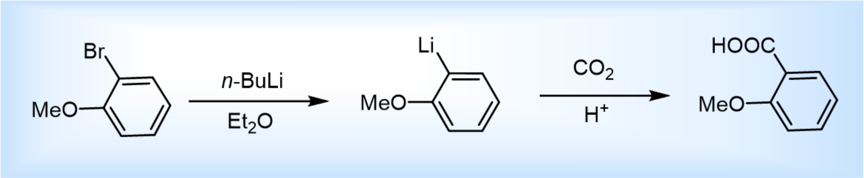
- ✓ When 1,3-dimethoxy-4,6-dibromobenzene reacted differently i.e. lithium-bromine exchange takes place not Li-hydrogen exchange.



And then later the Gilman group also contributed to this area. I think three to four months later Gilman group also proposed that if you start with o-bromo anisole and treat with the n-butyl lithium instead of the phenyl lithium in the previous case we have learned, what is going to happen here. It is forming a lithium. So, it is a formation of the lithium first by the metal-halogen exchange and now once you treat it with CO_2 it is going to react with CO_2. So, it is going to attack the CO_2, once the nucleophilic attack happens you end up making the corresponding carboxylic acid. So, now you can see these two discoveries set the stage for this metal-halogen exchange. You start with this aryl bromide, treat it with the organolithium, and you end up generating aryl lithium. So, you started from aryl bromide generated aryl lithium which was trapped with different electrophiles to get to the different types of products.

➢ The concepts of multiple discovery:

✓ Gilman first reported that carbonation of a reaction mixture, prepared by the addition of *o*-bromoanisole in ethereal solution of *n*-BuLi.



Alfred Gilman

✓ Since intermediate *o*-lithioanisole was derived from lithium-bromine exchange.

resulted in a 47% yield of *o*-methoxybenzoic acid.

So, when Gilman was trying to understand this reaction what was going on in this reaction? One thing he observed the reaction is happening nicely if you have chloride and bromide. Once you have a bromobenzene or chlorobenzene the reaction is happening and the order of the reaction is iodine first then bromine then chlorine. So, that is telling the bond energy, you have already learned in the previous segment also that this carbon-iodine bond is weaker than carbon-bromine. So, that is why the rate will be faster for the corresponding iodide then bromide then chloride. And then one of the interesting facts is that if you have fluoride and chloride they do not undergo the metal-halogen exchange. I think you have already learned when we talked about benzyne in the previous segment, I was talking about benzyne and you have seen that if you have this fluorobenzene if you use a strong base there is a deprotonation happening instead of the metal-halogen exchange and that ends up forming benzyne. So, in the presence of the RLi you have seen that it can abstract this proton then it will form corresponding benzyne. So, that is happening if you have a fluoride or chloride you end up instead of a metal-halogen exchange it will go for a deprotonation to form benzyne or aryne I think I already discussed in the previous part. This is another important fact about the metal-halogen exchange, it is a reversible process leading to an equilibrium mixture. Because you can see from this reaction what is happening here, if you write as an aryliodo or bromo whatever you can write, and RLi, you think about this reaction, you are generating ArLi and RBr. So, on both sides you can see there is a lithium and corresponding aryl halide and here you have aryl lithium means you have a lithium and electrophile, here also you have a lithium and electrophile. So, that is why this reaction is reversible. So, we are going to learn slowly what is the driving force for this reaction. Also once this type of metal-halogen exchange is happening there is a Wurtz type of reaction or Wurtz coupling we are going to learn in a minute that once you have this corresponding aryl lithium and alkyl halide formation happening they can also react among themselves. Now you can see this can do some sort of an S_N2 reaction to generate this type of product. We are going to learn that there is some sort of a side reaction also happening.

- Gilman observing a useful guide to understanding interchange reaction:
  - ✓ Aryl fluorides and chlorides do not undergo interchange
  - ✓ The rates of interchange of aryl halides decrease in the order I> Br> Cl
  - ✓ Interchange is a reversible process leading to an equilibrium mixture favouring the more stable organolithium.

- History of metal-halogen interchange and Wurtz-type coupling:
  - ✓ Wurtz reaction , involves formation of alkanes by dimerization of alkyl halides over sodium metal.
  - ✓ It is one of the oldest name reactions in organic cgemistry.

Now if you try to think about that first thing, as I mentioned once we try to talk about this metal-halogen exchange that means, we are trying to talk about reactions where if you take a lithium wire and an alkyl halide let's say RX what is going to happen here? You end up making RLi and lithium halide. So, we are talking about this sort of reaction here. So, now you are generating this RLi and LiX. Now, once you have this scenario, you have RM and R'X. If you have this corresponding R'X and RLi. they can couple between themselves to form this RR' and LiX. So, that is the reaction we are talking about, the Wurtz coupling. That means once the lithium is forming and there is an alkyl halide they can react between themselves or it can go for the metal-halogen exchange. So, that means, once this metal-halogen exchange is happening there are some sort of side reactions also happening.

Now, we are going to learn that if you perform this metal-halogen exchange, once you are doing it in the laboratory we always try to do this reaction at a very low temperature. Like in cryogenic conditions, -78 °C. One of the logic that you want to suppress this type of side reaction, is to suppress this type of S_N2 reaction. Again the metal-halogen exchange if you just give this terminology as a general name instead of lithium then you can have different types of metals here that can get exchanged. Now, in the case of organolithium as I

- In 1910, Organolithium compounds were produced as intermediates in the coupling of organohalides over lithium metal:

$$RX + 2\,M \longrightarrow RM + MX$$

$$RM + R'X \longrightarrow RR' + MX \quad \text{(Wurtz coupling)}$$

$$RM + R'X \longrightarrow R'M + RX \quad \text{(metal-halogen interchange)}$$

- ✓ Since Gilman and Jones also believed that organometallics were intermediates in Wurtz –type processes.

mentioned there are two different types, either you start with the lithium wire and then treat it with organic halides, you can generate the corresponding organolithium reagent or if you have an aryl halide, and if you have an organolithium it could be *n*-butyl lithium, or *tert*-butyl lithium that can generate corresponding organolithium here. So, starting from this RX you generate corresponding lithium which means, there is an exchange happening between this halide and lithium. So, that is why it is a metal-halogen exchange. So, if you are working in a laboratory or if you heard about this lithium reagent this is generally sold by different types of companies and they sell it in non-polar solvents. And then the other thing is most of them such as n-butyl lithium or methyl lithium are generally prepared through this method. The first one is what I am talking about here if you think about alkyl lithium, then the alkyl lithium you will find out that most of the time the alkyl lithium was prepared using the first method. So, you start with the lithium wire and RX to make this. Because if you follow the other method you will end up getting other different types of side reactions.

- Metal-Halogen exchange:
  - ✓ Reaction commonly involves use of electropositive metals (Li, Na, Mg) with halides.

❖ Two kinds of lithium-halogen exchange can be considered:

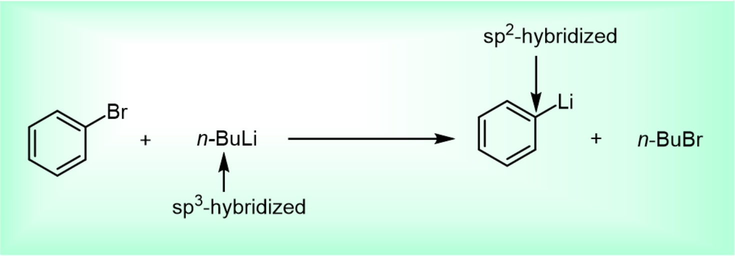
- ✓ Reactions involving organolithium compounds
- ✓ Reactions involving lithium metal

$$R{-}X + 2Li \longrightarrow R{-}Li + LiX$$

$$R{-}Li + R'{-}X \longrightarrow R{-}X + R'{-}Li$$

Now we are going to understand why this reaction which we started at the beginning if you start with this corresponding aryl bromide and *n*-butyl lithium we are saying that you got this corresponding lithium and n-butyl bromide. Why this reaction is getting favorable? If you think about this equilibrium, then why this equilibrium is getting favorable to this side? So, the question comes that this reaction which I was trying to explain to you at the beginning depends on the stabilization of this carbanion. So, what type of lithium is forming that stability is very important. That is why if you think about the generation of aryl lithium or vinyl lithium So, this type of lithium is more stable. I think I have already explained if you remember during the carbanion chemistry. I explained that if you have an aryl and vinyl group, then they have a sp^2 hybridized carbon and they have more *s*-character. If it has more *s*-character, then the nucleus can pull the electron density. That way it can stabilize the carbanion more. So, that is the driving force for this reaction. So, the s-character driving this reaction towards the formation of the corresponding aryl lithium.

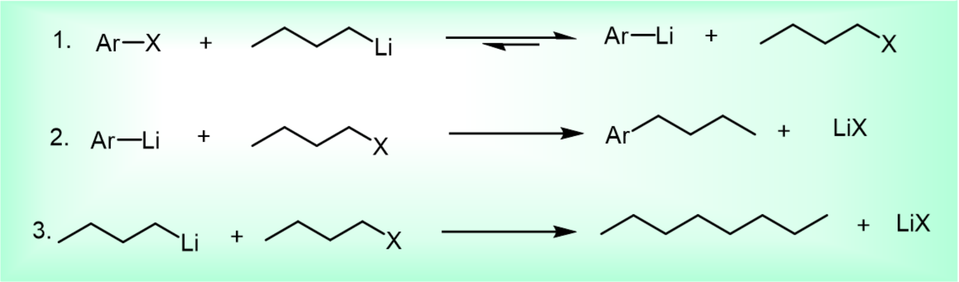
- Lithium-halogen exchange of aryl halides and vinyl halides:
  - ✓ Aryllithiums,vinyllithiums, and cyclopropyllithiums are more stable than alkyllithiums.
  - ✓ The exchange of an aryl bromide or iodide with an alkyl lithium is a high yielding process.
  - ✓ Formation of aryl lithium, the anionic carbon having a high S-character compared to aliphatic lithium compounds.



Now, again if you do this reaction as I mentioned there will be some byproduct. So, that is the important byproduct here, we have learned about this first reaction, but the byproduct is once you have aryl lithium it can react with the alkyl halide to form this product here. So, to suppress that -78°C is required as I mentioned to you. So, at low temperatures, you have to conduct the reaction, so that you can suppress this S_N2-type reaction. Then there is another type of reaction can happen, if you have extra *n*-butyl lithium remaining then it can also react with the corresponding *n*-butyl halides. So, that is why you see that low temperature is a very important key.

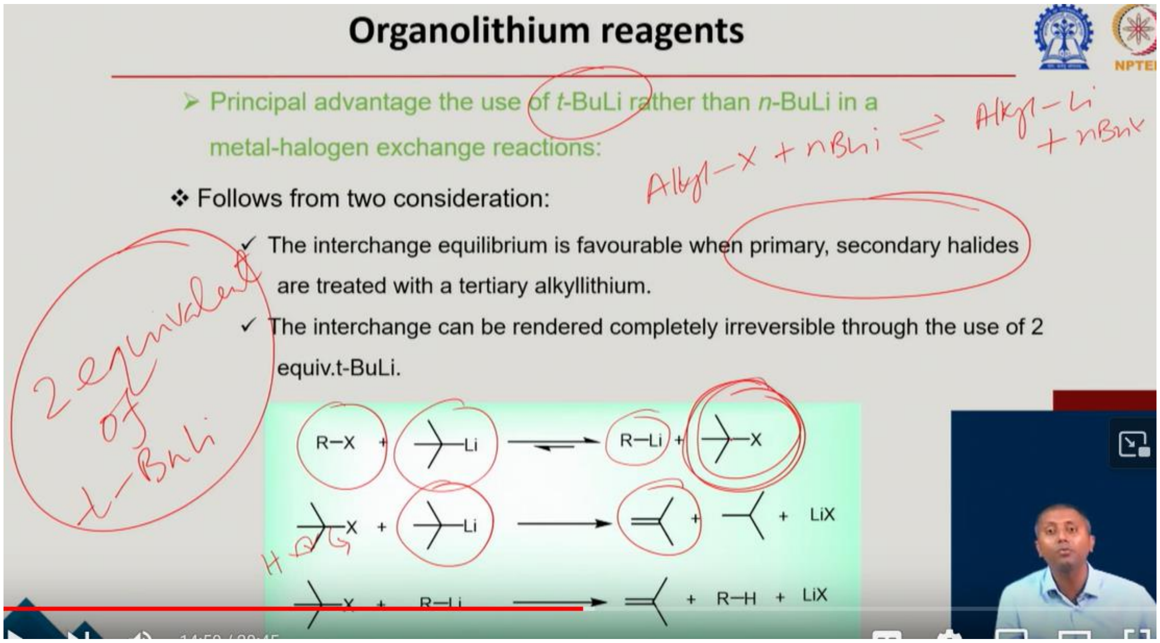
Now, we are going to learn that sometimes you might have seen that people have used *tert*-butyl lithium rather than *n*-butyl lithium for this metal-halogen exchange. So, sometimes it is advisable that in case you are dealing with primary secondary halides. If you have a

➢ Industrially prepared aryllithiums from aryl bromides:



- ✓ Aryllithiums are prepared from aryl bromides, at low temperatures slightly more than one equivalent of *n*-BuLi.
- ✓ Reactions are conducted at low temperatures to avoid side reactions, n-Butyl halide cogenerated in the exchange may consume the aryl lithium product.

primary alkyl halide, then you can understand that if you have an alkyl-halide and you are trying to go with n-butyl lithium and the problem happening now your equilibrium can't be favorable to one side, because on both sides you will generate an alkyl lithium and *n*-butyl halide. So, now, if you understand in both cases this is alkyl halide. So, this can also react at the same time the product can also react and come back to the starting material. But once you come to *tert*-butyl lithium there is some advantage here. So, let us try to understand. So, that is why once you are using *tert*-butyl lithium as organolithium, we always recommend that use two equivalents of *tert*-butyl lithium. So, the question comes why? Why do we say students to use two equivalent *tert*-butyl lithium and why this is a very good method for metal-halogen exchange with alkyl lithium? So, both the answers are you know lying here, if you use *tert*-butyl lithium, the first thing is there will be metal-halogen exchange and generation of corresponding lithium. Now, the thing is this is the culprit we have to get rid of this corresponding *tert*-butyl halide, but if you use another equivalent of *tert*-butyl lithium, then it is going for deprotonation from this because it is a hindered lithium. So, it cannot go for S_N2, it is going for a deprotonation and once it is going to deprotonate, it going to synthesize this isoprene and kill this corresponding alkyl halide which is generated in the reaction medium. That is why you generally use two equivalents of *tert*-butyl lithium to form alkyl lithium from alkyl halide. So, now I am going to show you some examples.



Organolithium reagents

- Principal advantage the use of *t*-BuLi rather than *n*-BuLi in a metal-halogen exchange reactions:

Alkyl–X + nBuLi ⇌ Alkyl–Li + nBuX

❖ Follows from two consideration:

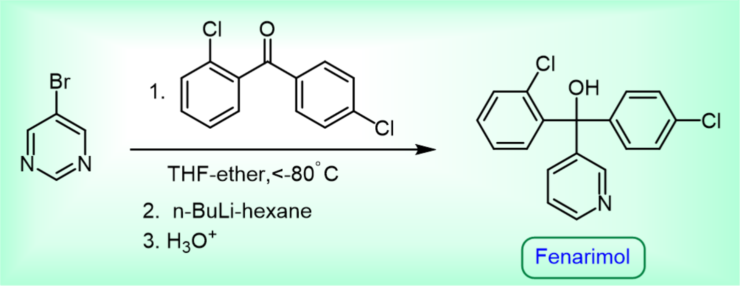
✓ The interchange equilibrium is favourable when primary, secondary halides are treated with a tertiary alkyllithium.

✓ The interchange can be rendered completely irreversible through the use of 2 equiv.t-BuLi.

2 equivalent of t-BuLi

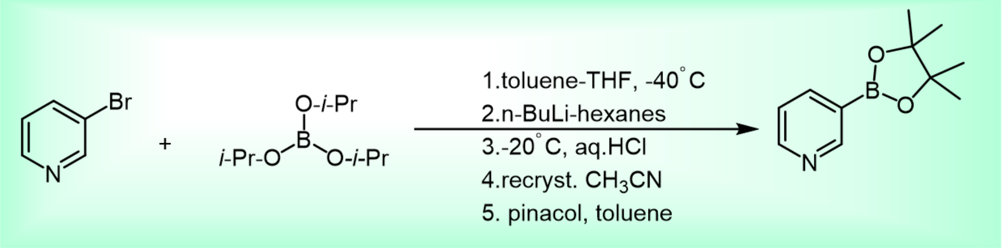
So, in 1970 Eli Lilly first synthesized Fenarimol, a fungicide. So, this compound when they synthesize they use this process. People have started using a lot of organolithium in the industry and you can see nowadays it is also used. So, the reaction they are using is this metal-halogen exchange to generate a corresponding lithium. Once you have this RLi, you are going to add it to the corresponding carbonyl group to get to the product. Now to minimize the side reaction they have done this reaction on a kilogram scale which is the first thing. So, you can see this type of reaction can be done on a large scale and the second thing is THF-ether solution which means solvent has a very important role in this reaction to control the reactivity of this reaction. So, it can decrease the side reaction.

- First large-scale organic synthesis using n-BuLi by lithium-bromine exchange:
    - ✓ In 1970, first prepared the Eli Lilly fungicide, Fenarimol by lithium-halogen exchange.
    - ✓ To minimize side reactions, required dissolution of the 5-bromopyrimidine substrate and the dichlorobenzophenone electrophile in THF- ether solution .

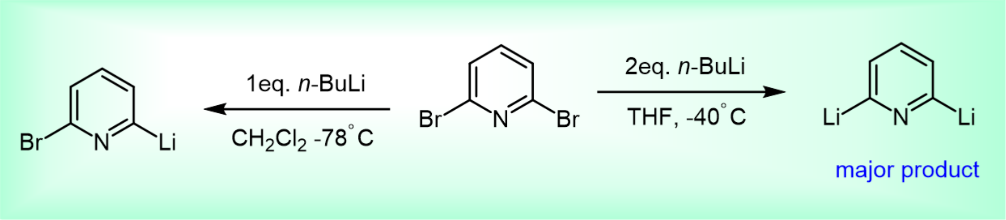


Here also you can see a similar example, starting from this corresponding pyridine the metal-halogen exchange happens, but you can see we have to use a solvent of toluene and THF. So, that means, this type of mixture solvent is very critical for metal-halogen exchange. So, there is a huge effect of the solvent. So, if you are using a random substrate you need to optimize this reaction. So, this is a simple lithiation and then borylation. Again another important reaction here, if you treat 2,6-dibromopyridine with n-butyl lithium in DCM then mono lithiation happens, if you use THF then both sides get lithiated. So, that is the important fact that the solvent has an important role here.

- ✓ After Lilly procedure, a crystalline borate ester prepared by this method.
- ✓ Solvent play an important role in toluene-THF , adding n-BuLi in hexane to give borate ester with good yield.



- ❖ Variation of solvent and temperature condition:



So, now, we try to understand the mechanism of this reaction. There are three different mechanisms proposed at the beginning. So, the first thing is there could be a radical process, people started thinking about there will be a radical process happening, a single electron transfer is happening forming a radical cation and radical anion. So, that could be one of the approaches and then the most acceptable approach is still now is the formation of ate-type intermediate. That means, once you have lithium and X, it attacks the X to form some sort of an ate-type intermediate from there it forms the product. there is a four-center state model where the head and tail come closer to form a four-center transition state and from there, it is going to form the product. But again still now the majorly accepted mechanism is the nucleophilic mechanism via formation of the ate-complex.

➢ Mechanistic studies for Li-Halogen exchange:

$$R^1\text{–}X + Li\text{—}R^2 \rightleftharpoons Li\text{—}R^1 + R^2\text{–}X$$

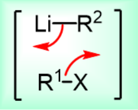
- ➢ Since metal-halogen exchange reactions takes place by the following process:
  - ✓ Electron transfer (radical) process

$$\left[R^1Li^{\bullet +} \qquad R^2Li^{\bullet -} \right]$$

  - ✓ Nucleophilic mechanism via halogen “ate”-type intermediate

$$\left[R^1\text{–}X\text{—}R^2 \right]^- M^+$$

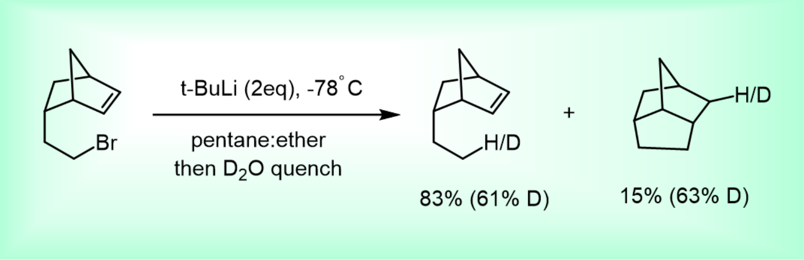
  - ✓ Four-centered transition state model



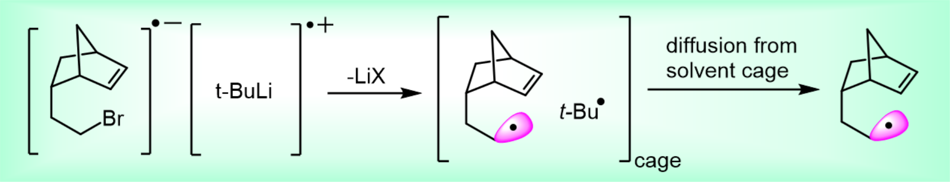
Still, I am going to show you there are some reactions if you talk about the lithium-halogen exchange using the alkyl bromide, people found out that most of the time it goes through the radical mechanism and there is evidence here. For this particular substrate, once people are trying to go for the metal-halogen exchange using *tert*-butyl lithium, they also observe 15% of this product. We can clearly understand how this product is forming. This is

➢ Radical mediated mechanism:

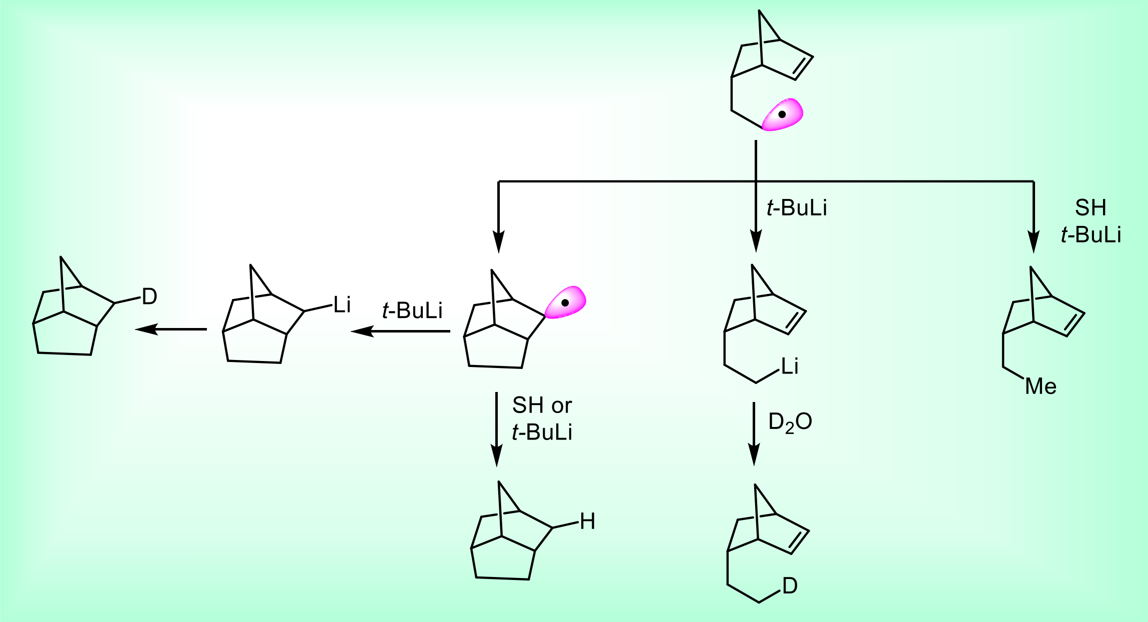
✓ For example, reaction with Norbornene and *t*-BuLi follow radical mechanism



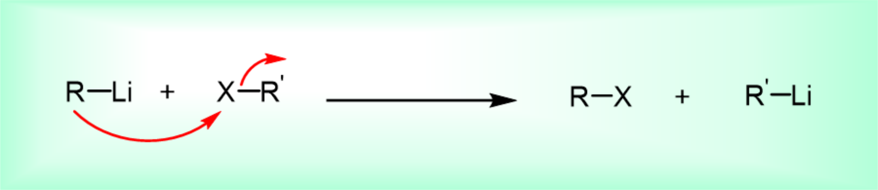
Mechanism:

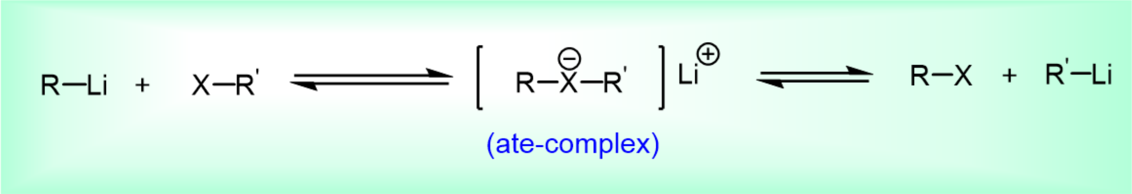


forming through a metal-halogen exchange, you are generating corresponding lithium here and then the lithium can get to the corresponding anion and get to the corresponding deuterium here. But now what they are proposing, no there is also a possibility of a radical intermediate if you have a corresponding alkyl bromide. Once you have a radical intermediate, it can diffuse in the solvent case, and now once it is diffused in the solvent case it can add to the double bond, forming a radical here. So, from there it can take another electron to make the corresponding lithium and then it will go to the corresponding product. So, this type of 15% product formation gives evidence that this reaction going through a radical intermediate.

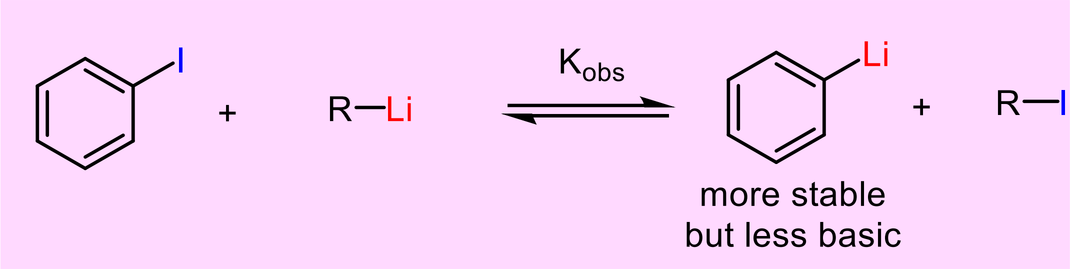


Gilman proposed the reaction is going through an ate-complex. So, this is the most acceptable one that there is an ate-complex formation happening when the organolithium is adding to the corresponding X. It is forming some sort of an ate-complex from there it is forming the corresponding organolithium and RX. Again you can see the ate-complex formation happening because you have an electropositive metal and corresponding halogen. So, both are forming a corresponding ate-complex.



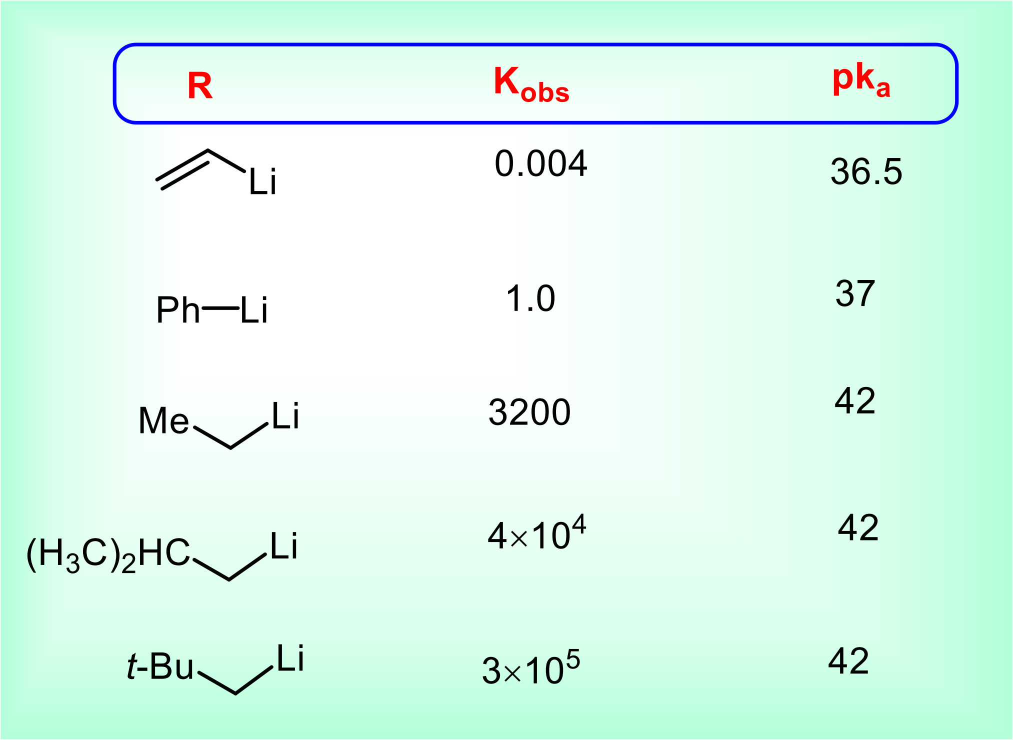


Again in this equilibrium process as I mentioned the stability of this corresponding organolithium which is forming that is the driving force for this reaction. I have already mentioned that this equilibrium is driving in this direction because of the formation of the stable organolithium.



more stable
but less basic

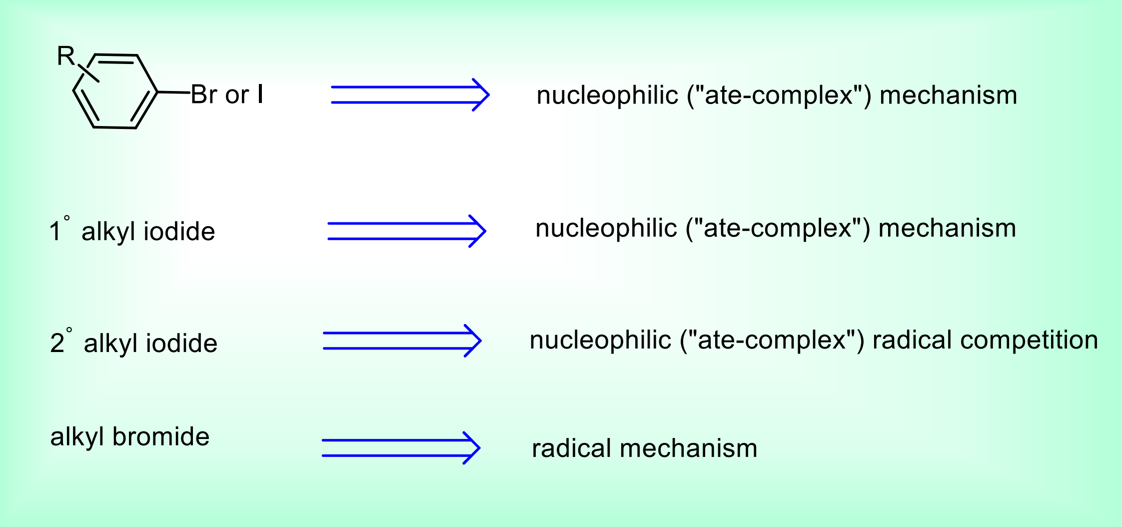
Again this is the concept that you can see in the previous slide I have mentioned there is this K_{obs}. So, that rate depends on the stability which means, as you can see equilibrium constants are determined by the carbanion stability more stable carbanion gives lower values of the K_{obs}. Now, we are talking about two things here, if you are using an organolithium, the equilibrium reflects the measure of the relative carbanion stability as I mentioned the sp is more stable than sp^2 than sp^3. Because aryl lithium and vinyl lithium are more stable than alkyl lithium, the equilibrium is favorable when treated with the aryl and vinyl bromide with an alkyl lithium reagent. So, let us try to understand there are two different facts here. So, one thing we are talking that if you have RX plus R'Li then there will be RLi and R'X. So, there are two different lithium we are talking about, one is that



R	**K_{obs}**	**pk_a**
Li	0.004	36.5
Ph—Li	1.0	37
Me Li	3200	42
$(H_3C)_2HC$ Li	4×10^4	42
t-Bu Li	3×10^5	42

lithium stability is driving the reaction and the other is this lithium the R'Li. So, we are talking about this lithium. So, now, if you think about this particular lithium here, if you think about this lithium is more stabilized, if you are starting lithium is more stabilized what is going to happen? Your reaction rate will be slower because if you have reactive lithium like this more electron-rich secondary or primary alkyl lithium, they are more reactive because there is no stabilization factor. These are sp^3, but once you come to something like phenyl lithium or vinyl lithium they are sp^2 they are stabilized. So, that is why the K_{obs} will be less here. Once you go to the corresponding sp^3, that type of lithium is very reactive. Once you increase the chain length you are also increasing the reaction rate because you can see the number of hyperconjugation increases. So, that gives more electron density to the lithium. So, as the electron density increases this lithium becomes more reactive, and this K_{obs} becomes higher here that is why you can see going down in this direction the stability decreases, the reactivity increases and the K_{obs} increases as well.

So, in this segment, we have learned that if you have corresponding aryl halide then the reaction is mostly going through nucleophilic ate-complex. So, these are the four things accepted in most of the literature, you will find out that if you have a 1° alkyl iodide or 2° alkyl iodide, in case of the 1° alkyl iodide the reaction is going via the nucleophilic ate-complex. If you have a 2° alkyl halide then in some cases it is the formation of the ate-complex, some cases it is going through a radical mechanism. Once you have an alkyl bromide in the reaction it goes through the radical mechanism.

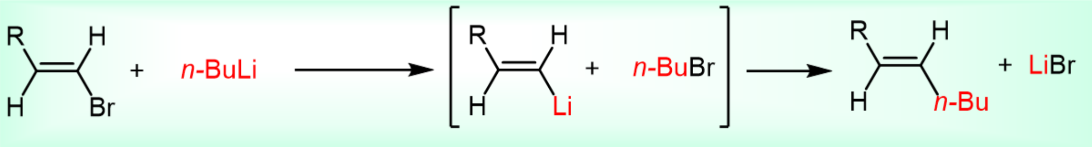


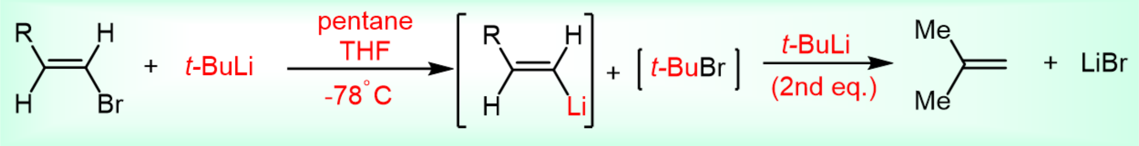
So, I am going to start with *n*-butyl lithium, you can purchase them from Sigma-Aldrich. So, this organolithium is synthesized from this corresponding alkyl halide. So, *n*-butyl halide you can use for the synthesis of corresponding n-butyl lithium. Again people use this reaction in cyclohexane, benzene, or diethyl ether. So, these are the solvents people use for this because again you want some solvents which are not going to react. Once you make n-butyl lithium you can use it for metal-halogen exchange, deprotonations, and 1,2-addition reactions, you can also use it for the polymerization of diene to make some

$$C_4H_9X \quad + \quad 2\,Li \longrightarrow C_4H_9Li \quad + \quad LiX$$

$$C_4H_9Li \quad + \quad CH_2{=}CH{-}CH{=}CH_2 \longrightarrow C_4H_9{-}CH_2{-}CH{=}CH{-}CH_2Li$$

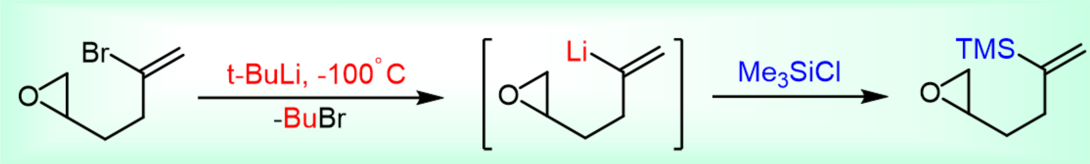
polymerization of dienes

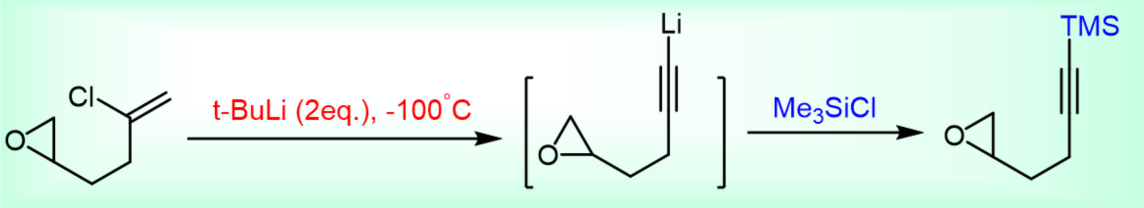




polymers from this 1,3-diene. Again the methyl lithium, ethyl lithium you will see all these different types of alkyl lithium synthesized through this method. And again I think I taught you another method, you can use *tert*-butyl lithium. So, if you want to synthesize in the lab you can also use *tert*-butyl lithium for this reaction as well. The other important thing is if you are synthesizing an alkenyl lithium like vinyl lithium then again you can use *n*-butyl lithium here, but again once you make this lithium it can react to form this corresponding alkene. So, that is why you use *tert*-butyl lithium that would be better because as you know the *tert*-butyl bromide will be killed it will convert to corresponding isoprene. So, your corresponding lithium will be stable.

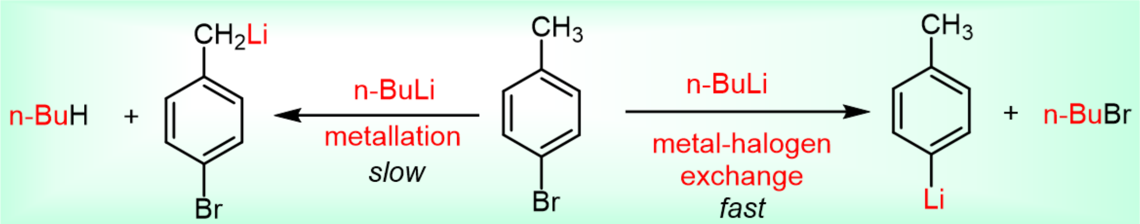
This is another interesting example here, you can see these two substrates if you try to look into this substrate, So, let us try to understand what is happening, in one case you have a bromine here in this top one, and in the bottom one you have a chlorine here. We are treating with the *tert*-butyl lithium in both cases. So, we are treating with the *tert*-butyl

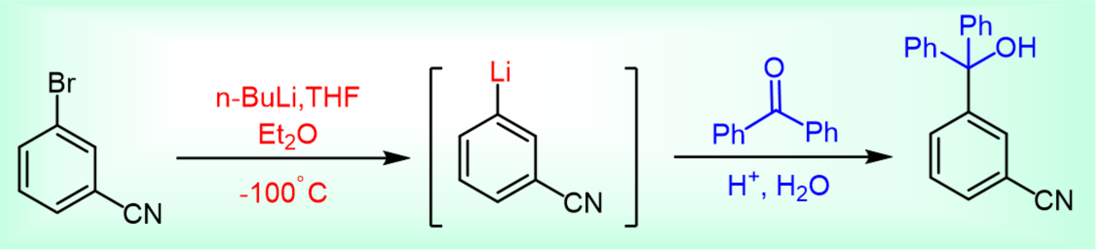




lithium because this is a vinyl bromide just now we have learned that we want to use a *tert*-butyl lithium instead of *n*-butyl lithium. So, if you have a *tert*-butyl lithium here it is going for the metal-halogen exchange to generate this corresponding lithium and if you take a trimethylsilyl chloride as an electrophile it can able to trap to form this compound. But once you start with corresponding chlorine as I mentioned if you have a corresponding chlorine what is the problem here, in the case of chlorine there will be a proton abstraction going to happen. So, this proton is going to get abstracted instead of the metal-halogen exchange. So, that will generate the corresponding alkyne. So, from here you will generate this corresponding alkyne and as you have this corresponding lithium here you will generate this alkyne, now this alkyne proton will be abstracted by *tert*-butyl lithium to form this corresponding alkynyl lithium which will be trapped with the TMS chloride to get to this product.

Again some cases you will see the lithium-halogen exchange reaction is very fast even at low temperatures, particularly in an electron-donating solvent. So, you will see we are going to talk about these two scenarios here, in this particular case you will see there is a metal-halogen exchange happening and then there is a deprotonation happening from this CH_3. We are going to talk about this type of deprotonation in the next class. So, here the metal-halogen exchange is a much faster reaction. You can see there is an example here, if you have a functional group like cyanide, if you are using *n*-butyl lithium you have to use at a very low temperature. One of the reasons you are going for -100°C because you do not want the lithium to react with the cyanide. You can generate the corresponding lithium in the metal-halogen exchange, you can add to the corresponding benzophenone to get to the corresponding alcohol.



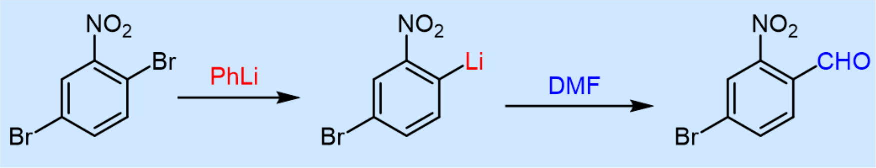


If you have a nitro group and two bromides, you want to go for metal-halogen exchange then the lithium will form next to the ortho to the nitro because if you form a carbanion next to the nitro it can get stabilize because nitro is an electron-withdrawing group. You can trap with the DMF so you will get the aldehyde here after reacting with the DMF.

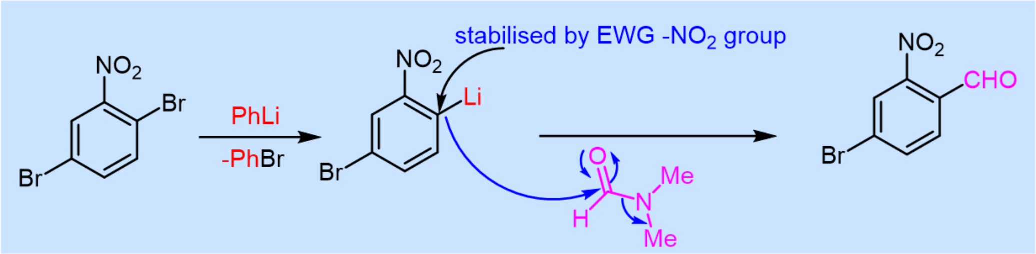
Again the same thing we are trying to explain here is that because of the stabilization, it is going to form a carbanion ortho to the nitro.

➢ Example of monolithiation of a dibromide compounds:

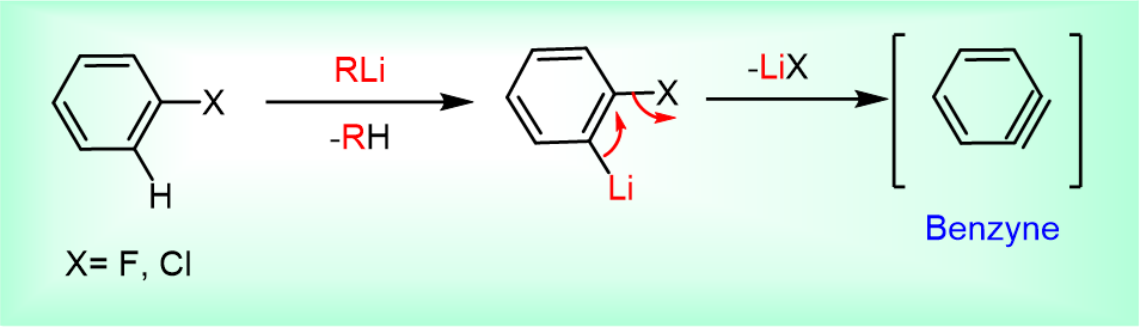
- ✓ Monolithiation of dibromide is a thermodynamic process.
- ✓ When bromo-substituents are non-identical, the result is always the more stable of the two organolithiums.

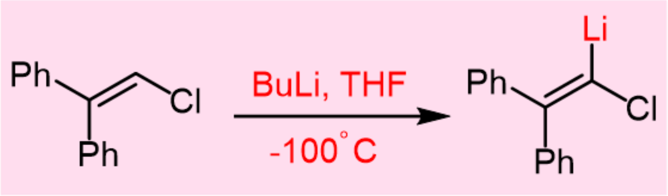


❖ Mechanism:



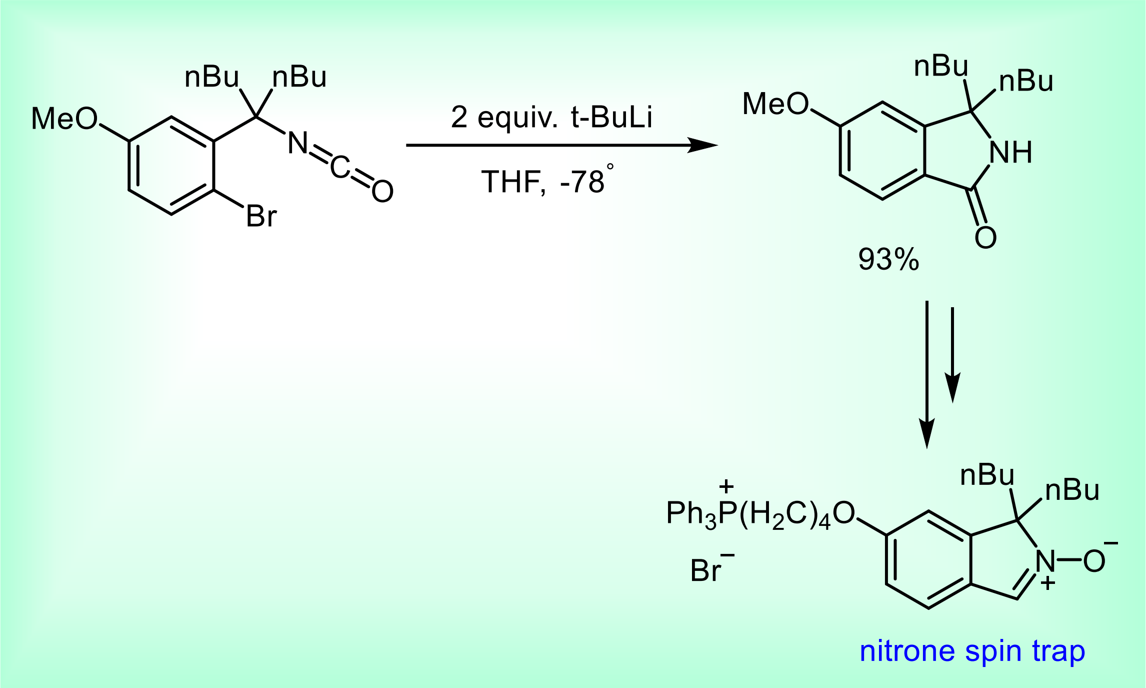
As I mentioned if you have fluoride or chloride then you will not see the metal-halogen exchange. I think I already told you at the beginning that there you will see deprotonation is going to happen. Once there is a deprotonation, then there will be elimination that will end up making a benzyne. It is not only happening in the case of the aryl halide, once you go for vinyl chloride a similar thing is happening here. You can first generate this

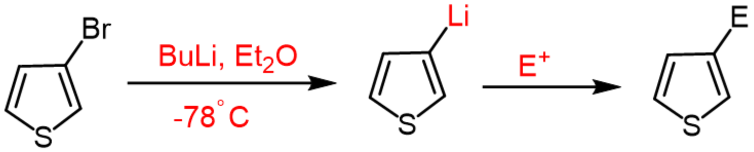


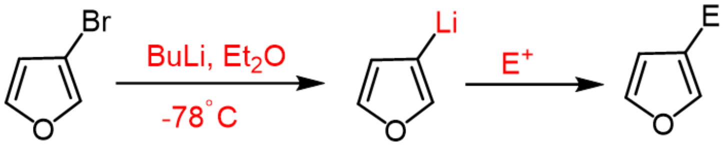


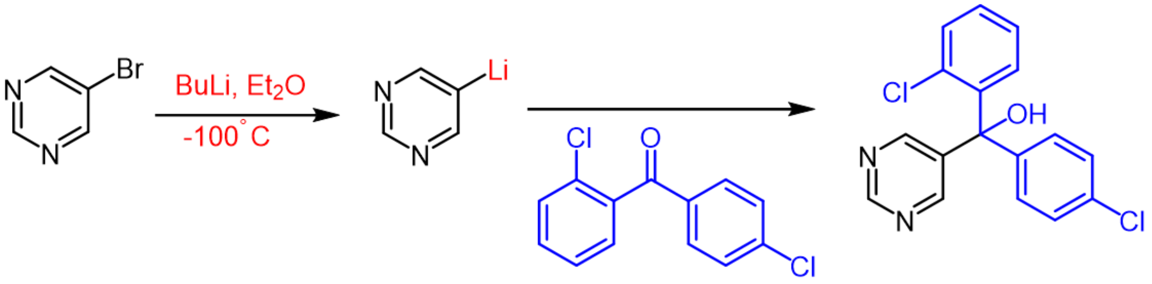
corresponding lithium here, because you do not have any other protons here. So, it is going to form the lithium here. So, it is going to stay here like a corresponding lithium, but it is not going to go for the metal-halogen exchange.

Again if you have this corresponding lithium formation happening here from this corresponding bromide, it can go for a Parham cyclization, it can attack here. So, if you have a lithium it is going to attack here and then go back and form this type of compound which can be used further spin trap in the EPR.









There are more examples you can see from thiophene we are using the butyl lithium in ether to get to the corresponding lithium and we can trap with the electrophile. In the case of Furan very similar thing happens there is a metal-halogen exchange formation of the lithium and trapping with an electrophile. Then again with an example with an electron-deficient ring like here you can see also that there will be a metal-halogen exchange, it will react with this corresponding ketone to form this corresponding alcohol.

So, in this part, I think I can convince you that what is the definition of metal-halogen exchange, what is the history, how the reaction started, what the different types of rules that why the reaction equilibrium will go towards the right-hand side and then we have shown you the various application. Again these are the reference books you can download and then again thank you so much for coming to the class and I am going to see you guys in the next class. Thank you.