Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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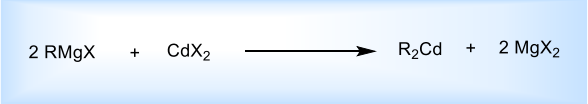
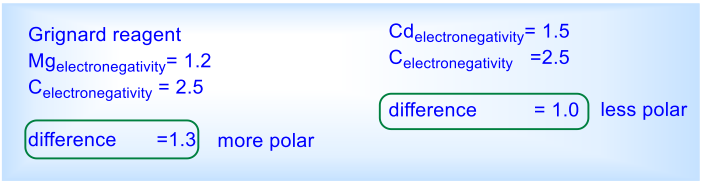
Lecture 35: Organolithium

Welcome back to this NPTEL online certification course in molecular arrangement and reactive intermediates. In the last couple of classes, I started talking about organolithium. I talked about the generation of organolithium and several different types of reactions. Then, I started talking in the last class about the metal halogen exchange and how that equilibrium depends on the stability of the organolithium. In today's class, I am going to talk about another essential talk topic transmetallation. So, that is another way of generating organolithium reagent, and then towards the end, I am going to talk about how you can make you can create the lithium as a chiral, which means you can make use of a chiral ligand to generate a chiral lithium reagent which then their applications.

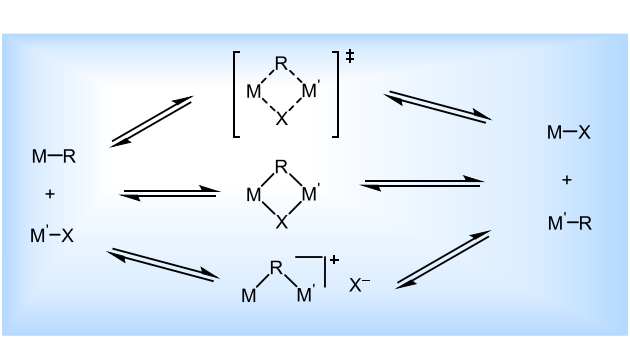
So, let us start with the first thing, the transmetallation reaction. I think you must have heard that term in organometallic chemistry again from the definition, you can understand there is one metal going to be replaced with another one. So, that is why transmetallation is going to happen if an organometallic in a region is added to a metal halide whose metal has electronegativity closer to that of a carbon atom. So, that is an important thing about the transmetallation that here we have given an example. That you have RMgX, a Grignard region, reacted with the cadmium halides to form this MgX_2 and the organic-cadmium compound. So, if you see in this reaction what we are talking from the beginning, that this reaction is going through a transmetallation and if you try to compare the electronegativity of the Grignard region, that between the magnesium and the carbon, it is 1.3. So, it is more polar, but once you go for transmetallation, you generate a less polar compound. That means now you can see you have the cadmium and the carbon. You can see the electronegativity difference one. So, what is happening through a transmetallation process is you are going through a reaction where there is an exchange happening, and it is generating a compound that has a metal-carbon electronegativity difference less, which means it will be a less polar compound.



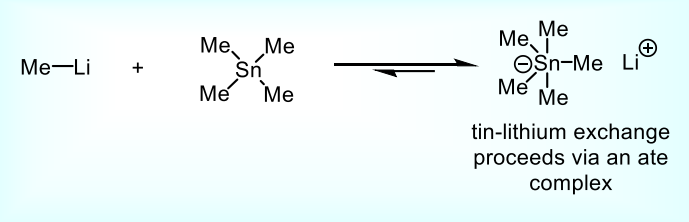


And then we are going to also about going to learn about transmetallation using organolithium region. So, if you want to generate an organolithium reagent through a transmetallation. So, that could be this R-M could be R-Sn, which means organotin organomercury and then organosulfur. Or Organoselenium, if you treat it with an organolithium reagent, an alkyl lithium region, it ends up generating the R-Li, which could be vinyl or aryl, and then it could be the R-M, which is the corresponding Organotin compound. So, here is the driving force for this type of reaction you are going to see mostly in this type of transmetallation reaction using organotin you will see mostly vinyl-tin or the vinyl or aryl-tin are going to be used here because these are the important things for this metal hydrogen exchange because at the end, they are going to generate the corresponding vinyl lithium or the aryl lithium. So, if you are generating corresponding lithium, which is stable, as I mentioned in the previous class about the metal halogen exchange the stability of the organolithium, which is forming, is a driving force for this reaction to go in this direction. So, here is what will happen because it generates the vinyl or aryl. That is why you will see this type of reaction mostly happening when using the vinyl or, in the case of the corresponding aryl tin reagent. Of course, some other reagents are also used, but you will see most of them.

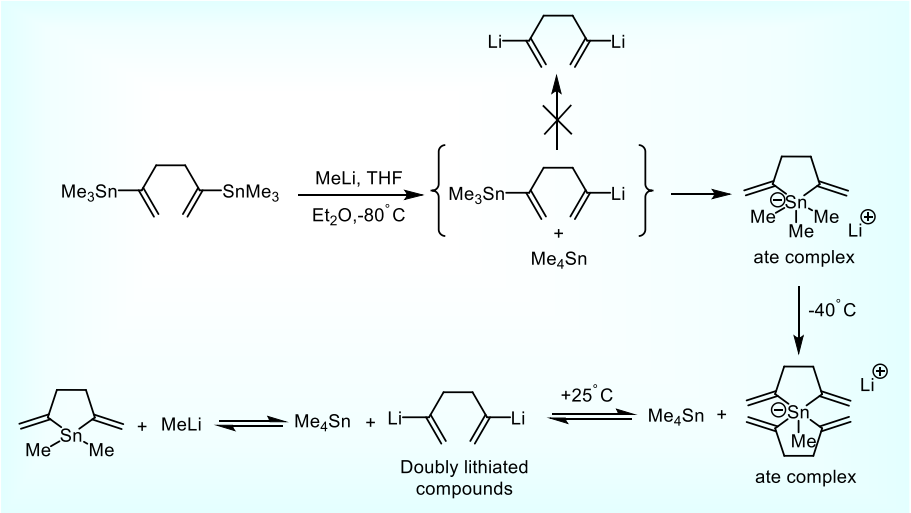
Again the reaction mechanism if you come back to the reaction mechanism the very similar way they are explaining that it is going through either through eight complexes, Which you explained in the last class, or it can go through some sort of a type transition state where there is one side, there is a head, another side, there is a tail that can so replace each other and then going to form the product. Again, you will not see that there is no oxidation change happening. So, going from the starting material to the product, you will not see any change in the oxidation state.



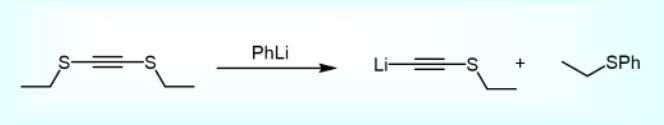
So, here we are talking about the tin and the lithium exchange. So, if you take the methyl lithium and take this tetramethyl tin, what is happening here? The first thing is this lithium attacking tin. As I was telling there is a tin-lithium exchange going to happen. So, that is an important thing here. So, lithium exchange will happen, and that is the important step for this transmetalation reaction So, the exchange is going to happen generally in the low temperatures, and once the temperature is going, the corresponding organolithium reagent. Again, as I mentioned, it is going to form the thermodynamic control, and so it is going to produce the more stable organolithium reagent. So, that will be the driving force for this reaction going forward.

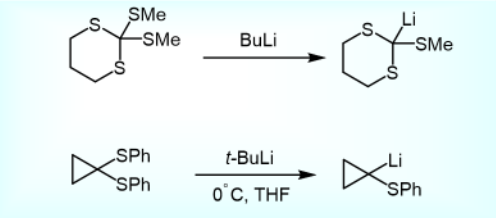


So, in some of the examples given here, you can see, as I mentioned, that you will mostly see the vinyl-tin or aryl-tin because one of the important reasons is that you know you are making corresponding lithium, which is the more stable lithium. So, using methyllithium, you generate vinyl-lithium. So, that is the driving force here, and then you are generating the tetramethyl tin here, which can go for another. So, this lithium can attach to the tin. Form this ate complex. So, in this particular reaction you are seeing, it can establish the mechanism and show how this transmetallation is going on. And then in the -40 °C. So, you can see it is getting warm up from -80 to now -40 °C. So, at the time, what is going to happen now is it can form another ate complex. Here, you can clearly see that it is a dimeric form. From there, it is going to come out that the tetramethyl tin is going to come out, and it is going to form the vinyl lithium compounds.

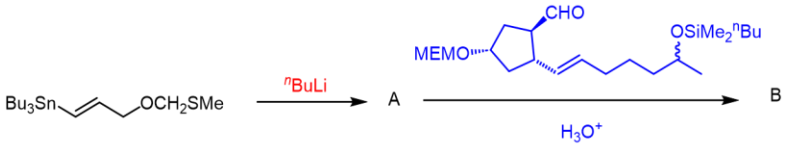


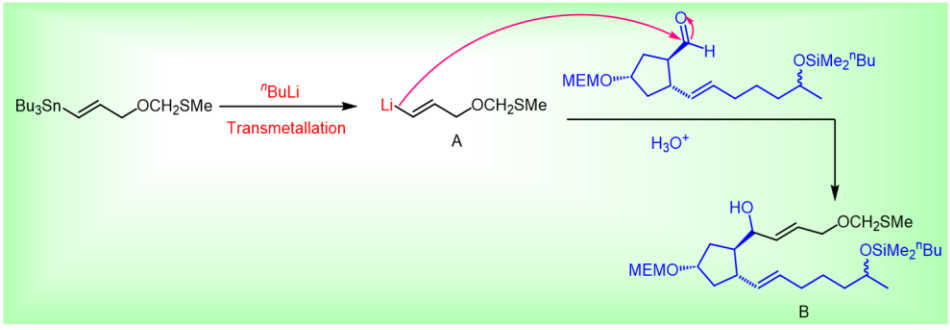
It can also go for sulfur-lithium exchange. So, it can happen that from this compound, once you treat it with the phenyl lithium, it can attach the sulfur from the corresponding ate complexes; then it will get rid of this one and form the corresponding lithium. In this particular compound, the -SMe bond can be cleaved. So, now I am going to talk about some examples for this particular chemistry here. You can see this particular example here starting from this corresponding tin compound corresponding vinyl tin using the n-butyllithium. It is going to generate the corresponding vinyl lithium here.



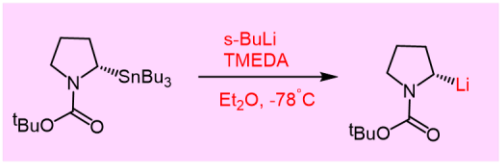


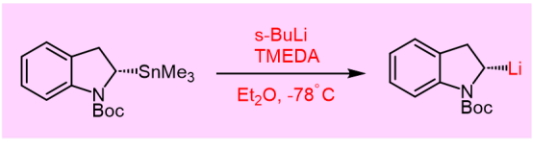
So, you can see there is a transmetallation is happening. So, the n-butyllithium will attack the tin, cleaving the carbon-tin bond and generating the corresponding lithium through the transmetallation.

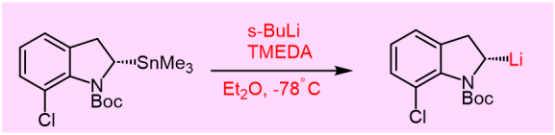




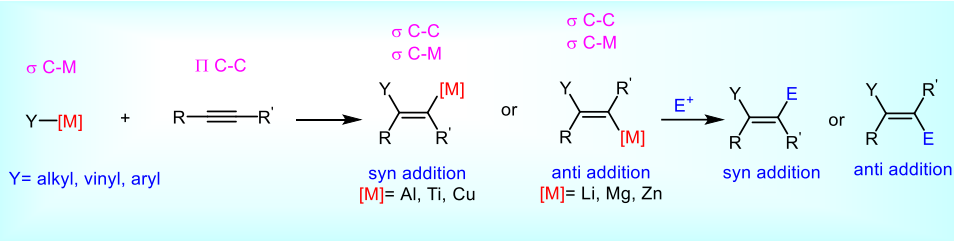
Now, it is going to attack the corresponding aldehyde in this molecule. So, it will attack the aldehyde and form the corresponding alcohol after treatment with the water. You can see here in this particular reaction that one of the important facts is that you are generating a more stable organolithium. So, you are reacting with an N-butyllithium and generating a vinyl lithium.



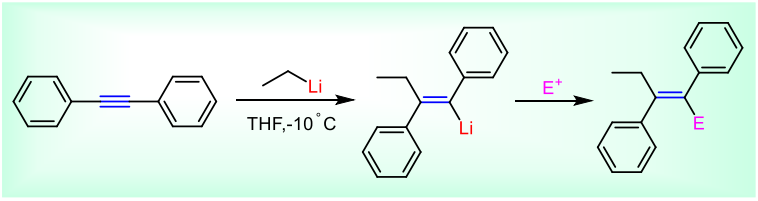




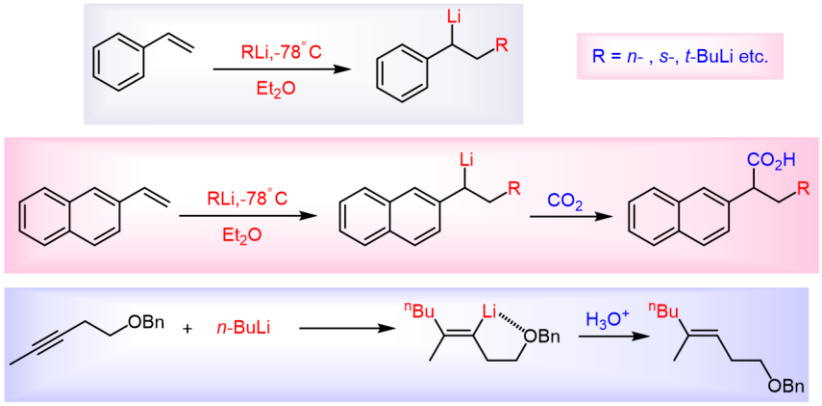
So, there are some examples here: this carbon and the tin bond is getting cleaved again using the Sec-butyllithium. It can generate the corresponding lithium here. Again, if you are generating lithium, this lithium can also get stabilized by coordinating with the oxygen. I think I have explained several of this type of chemistry in the last class, where I talked about deprotonation. Here, you can see very similarly that this bond is also getting cleaved. In the presence of this, you have a very similar condition to generate the corresponding lithium region. The other important fact here you can see the stereochemistry getting retained here. So, once there is a transmetalation happening, if you start with a particular stereochemistry of the tin reagent when it is going to get converted to corresponding lithium, it is getting a retention here. Again, very similar things are happening in this case. Also, we are seeing retention and formation of this corresponding lithium. So, now we are going to learn about another important reaction that we have learned about. If you have halide like aryl halide or alkyl halide, it can go for a metal halogen exchange. We have also learned about transmetallation. If you have some sort of a like tin or sulfur or selenium, that bond can be cleaved to generate corresponding lithium. So, here we are going to learn that if you have a corresponding alkyl lithium and if you have an alkyne or an alkene, then sometimes also it was observed that it can act to the corresponding π-system that lithium can interact with this. The π-system generates the corresponding lithium again. So, it can be added here. So, here is what is happening. So, this organolithium is added to the corresponding alkyne. So, generate a carbanion or the corresponding lithium region, which can be, you know, trapped with other metals and can now be trapped with an electrophile. So, what is happening? The first thing is lithium, which is added here, generating an anion here, which is trapped with the other transition metals, like titanium and aluminium, and then it can be trapped with the electrophile to get to the corresponding product.



Here is an example: you have an alkyne here with two phenyl groups if you have a phenyl group again, you are going to if use this ethyl lithium at -10 degree celcius and can add to the corresponding alkyne to generate the corresponding lithium here So, now, you can see you are generating vinyl lithium, which is the most stable lithium compared to the lithium you started with. So, now, it can be trapped with a different electrophile type to make this product more stereoselective. Again, you can see once it is formed, the stability is also important, and once the two phenyl groups are in the trans position, they will be the most stable conformation compared to the other one, which is the cis. And here what is happening is the lithium is attacking here. So, it is forming this corresponding lithium is attacking in this position. So, it is forming the lithium in the transposition as well.

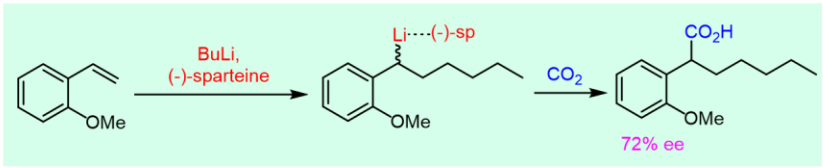


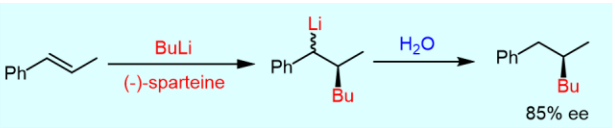
As I mentioned, there is an example with an olefin that can add to the corresponding styrene. Again, these reactions are depending on the solvents and the known additives that are used in this reaction. So, here it can be added here the R-group can be added here. To generate a more stable organolithium. So, it is a benzylic lithium. So, it can be further functionalized with the electrophile to make this type of product. Then there is an example with the naphthyl here. So, here, the RLi is also going to be added to the terminal position to generate more stable benzylic lithium, which can be trapped with CO_2 to get to the corresponding carboxylic acid. Again, there is another example here in this particular case. Also, you see the n-butyllithium is added to the corresponding alkyne to generate this lithium because it can attack from this side or it can attack from the other side. Now, the question comes: the stability of lithium is essential. So, in this particular attack, if it is attacking from the terminal side here, then what is happening is it is generating the lithium, which is getting stabilized through the oxygen. So, Oxygen has a Lewis basic property. Lithium is acidic; it can coordinate and stabilise, which can finally trap with H_3O+ to get to the corresponding product.



And now there is an example here we are going to come back to this type of example that if you want to make this centre chiral, that means this lithium which was generated. Of course, people have used it. I will return to the spartein structure and how it generates the chirality in the product. So, then, you can control the stereochemistry of this. So, you can able to generate a particular enantiomer of this compound. So, now the lithium will be chelating with the spartein to make a particular enantiomeric lithium, which can be trapped with the electrophile to get to the product with a good enantiomeric excess. There is an example here also. So, there is first there is a Carbolithiation happening, and then the butyllithium is added here, and then the spartein to going to bind with it. And then that can control the formation of the corresponding product. So, I think this stereochemistry is gone once you are treated with water. You have replaced it with hydrogen here, and then you see the other stereochemistry will be maintained there. So, you make a stereoselective product here.

- Enantioselective carbolithiation:
  - ✓ (-)-sparteine is a powerful promoter of carbolithiation .
  - ✓ Leading to a good levels of asymmetric induction in the addition step.
  - ✓ Successful enantioselective carbolithiations involved funtionalised styrenic double bond.
  - ✓ Potentially, two new stereogenic centre are formed in most reactions of this type.
- Example:

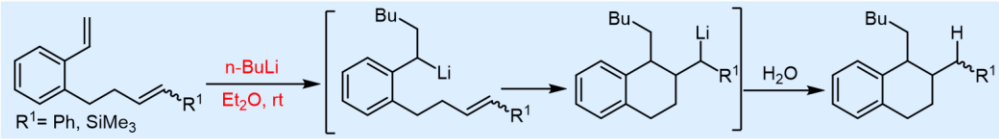




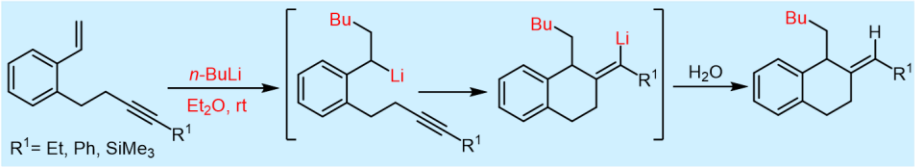
Another example here is what is happening. The first thing is there is a carbo-lithiation happening in this particular; you can see, as I mentioned, in these two double bonds, if

you think about attacking n-butyl lithium, then in this styrene only, it can only generate this benzylic lithium. So, if you think about the generation of stable lithium, then the benzylic will be much more stable. That is why it is going to attack the corresponding styrene, and now it is going to participate in some sort of intramolecular cyclization to generate another lithium, which will be protonated after treatment with the water. And then there is another reaction here. The first thing again is that it attacks the styrene, which generates this lithium and adds to the corresponding alkyne. Another carbolithiation is happening, so there are two carbolithiations. The first is attacking the first carbolithiation, and the second is this corresponding benzyl lithium, which is added here to generate this lithium, which will take a proton to form this corresponding product.

- Regioselective carbolithiation styrene bearing unsaturated alkene side chains at *o*-position:



- Regioselective carbolithiation styrene bearing unsaturated alkyne side chains at *o*-position:

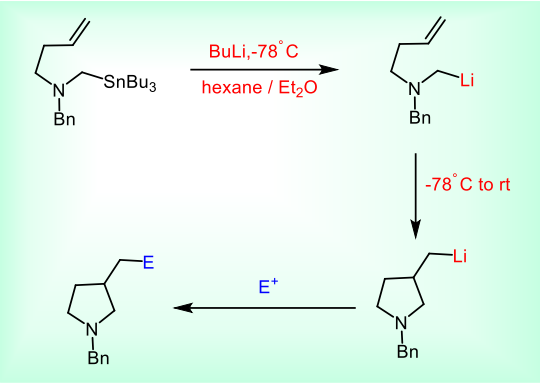


Again, there is another example of an intramolecular one. So, this is where you can see the first thing. So, here, I think two things are happening. The first thing is the transmetalation happening in the case of butyllithium at -70°C. It is forming the corresponding lithium; as you can see, it is next to nitrogen. So, it is immediately going to react. So, it is going to take part in a carbolithiation reaction to form the corresponding lithium. It is going to be added here to generate this lithium species, which can able to trap different types of electrophiles to get to the corresponding product. So, you can make a lot of this type of pyrrolidine unit from this type of intermolecular cyclization reaction.

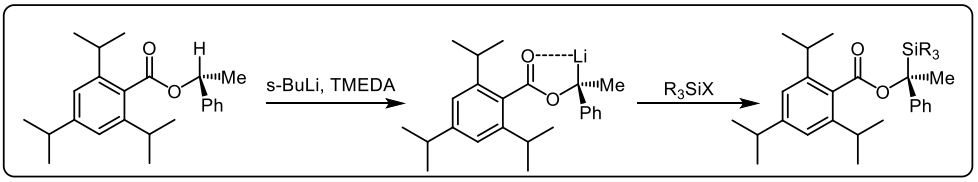
- Example of Intramolecular carbolithiation:

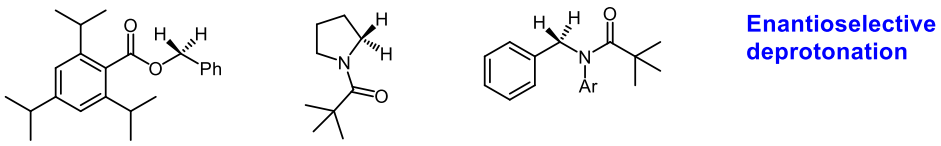
  - ✓ Intramolecular carbolithiations is the requirement to generate the organolithium

  In the presence of the electrophilic alkene or alkyne.

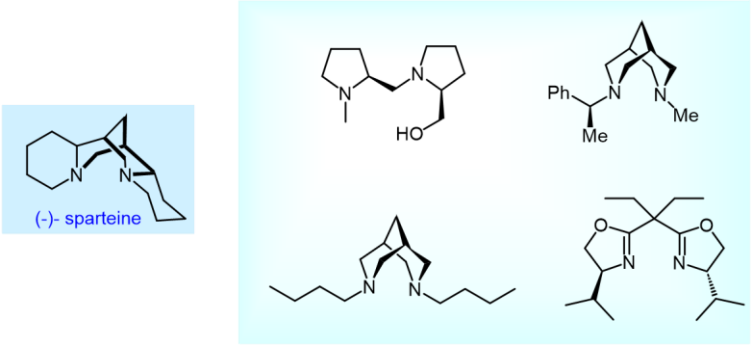


So, now, we will talk about the stereospecific deprotonation. I think I talked about that in the last class. If you have seen this type of stabilising group here, you can see it here. So, this is ester; now, if you see in place of the sec-BuLi and TMEDA, what is going to happen? It is going to generate this corresponding lithium. Now, this is a benzylic lithium. At the same time, this is getting a stabilization with the coordination with the oxygen. And now, once you treat with the R_3SiX So, now this stereochemistry will depend on the electrophile; sometimes, you will see there will be retention or there will be inversion. So, we are going to come back to that discussion. And the other thing I am going to talk about is that now if you see here, you have a this if you see in this ester, this particular group has a particular stereochemistry. So, the only thing that is happening is a stereospecific deprotonation, and you can see this C-H bond is replaced by C-Li. But now the question comes: if you have two hydrogens here, if you do not have a chiral centre here, then one could be a pro-R and one could be a pro-S. So, this can be able to to selectively form a chiral lithium. Now, you have to use a chiral chelating ligand. Now instead of using the TMEDA So, now what is happening? Now, the TMEDA is used for the sec-BuLi We know what TMEDA does. You might have seen this in the previous lecture. I already talked about how the TMEDA forms a chelate with the lithium where the lithium forms. So, now the question comes that if you replace this type of diamine with some sort of chiral diamine, then we can achieve this goal, and then we can selectively take the pro-R or pro-S to generate a chiral centre there.





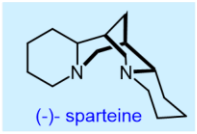
So, you can see several different types of chiral diamines; there is one, of course, the most successful one is the sparteine, and then there are also several different varieties you can see there are all chiral diamines. So, they are going to form the chelate with the lithium. Now, as you see there is chirality. So, that is going to make the diastereotopic transition state. So, based on that, you will see there will be two different diastereomeric transition states going to form once the lithium is going to coordinate with this type of chiral ligand, and based on their equilibrium, you will see a formation of a significant product versus a minor product.



Again, sparteine is an extremely useful chiral ligand, and it has a wide range of asymmetric reactions. People have screened this type of reaction with different types of ligands, and they found that using spartein, the enantioselectivity is much higher compared to others. Of course, these are naturally occurring lupin alkaloids. It was isolated from the plants. We would learn about some of the reactions.

❖(-) sparteine:

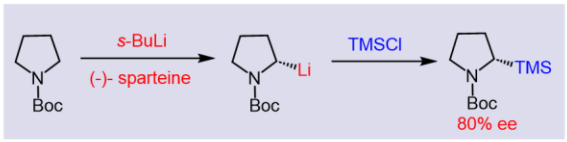
- ✓ (-)-sparteine is an extremely useful chiral ligand for a wide range of asymmetric reactions.
- ✓ It is naturally occurring lupin alkaloids, isolated from leguminous plants.
- ✓ This is a cage like ligand and its isomers having 2 and 3
- ✓ This natural product is a cardiovascular agent.



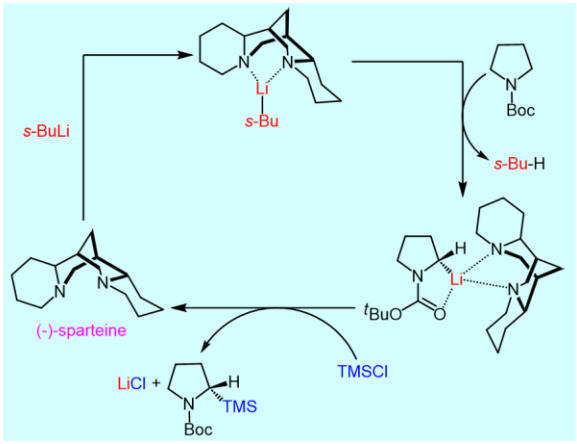
First thing, I am going to talk about the asymmetric synthesis here. So, again you can see here as was telling you Iin the previous slide, that there is two protons here you can call them pro-R and Pro-S Now, the sparteine using spartan you can able to generate this corresponding chiral lithium here which can give you if you try to travel with the TMS chloride you can get to this corresponding TMS with the retention of the configuration with 80% .Now we will try to learn that you know how portion is involved in this

reaction. You can see first the sec butyllithium will be forming a chelate with this portion. So, the lithium is forming a chelate here. So, this is a creating a chiral environment. So, what is going to happen once it comes to this particular substrate. There is another chelation happening with this oxygen. So, there is a chelation with the oxygen and the two nitrogens here. So, now it is going to take only one particular proton going to be abstracted from here. This is forming. So, you can see there will be a diastereotopic transition state here. So, from there, it is going to end up going to the corresponding product with a very good enantioselectivity. Now, the question comes why the enantioselectivity is 80% and not 100 %. So, that depends on the following: As I mentioned, there will be two different diastereomeric transition states. One could be with this. So, one could be with the other hydrogen. So, that is how we can end up getting the two different enantiomers. So, if you think about this reaction, if you start with these two different transition states, then what is happening is there will be different activation barriers for this corresponding tangent to the corresponding product. So, first of all, there will be equilibration happening between these two diastereotopic transition states and the next thing is the rate of reaction. So, it also depends on the electrophile. So, what electrophile will be chosen that can also control this ee? So, by changing the different electrophiles, sometimes you see the ee will vary because of the rate of the equilibration and the rate of the reaction. So, the rate of the substitution reaction has to be matched to get to a very high enantioselectivity. So, most of the time, what is the rate of the SN_2? If it is a faster reaction happening, then you will see ee is higher compared to if it is a substitution reaction, which is slower, and by the time there is an equilibration happening.

➢ Example:

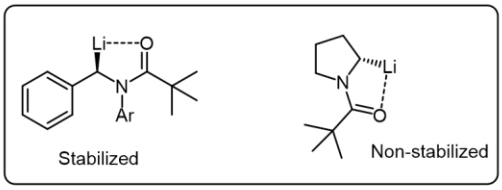


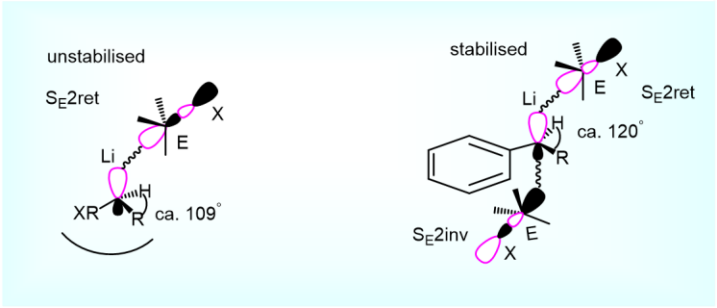
Mechanism:



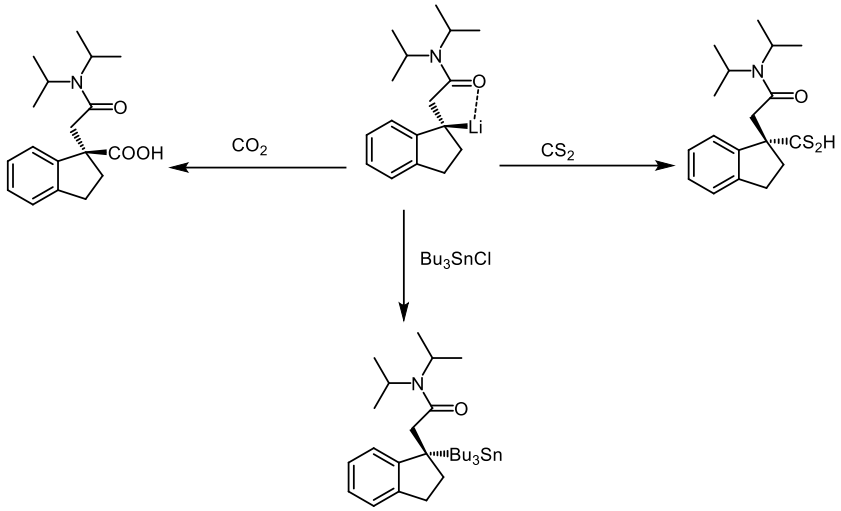
So then you must also there is another important point that I should tell you guys that you will see that a lot of times in the case of the benzylic system, especially in the case of

benzylic lithium which, of course, getting stabilized, but the type of this type of organo-lithiums this is called the stabilized. We have learned before that once you have non-benzylic, there is also a stabilization of the lithium with the oxygen. These are called the non-stabilized. So, what is happening in the case of the non-stabilized or the unstabilized cases observed is that if you treat it with an electrophile, it will be majorly as a retention. So, if you treat it with the different types of electrophile, you will see it is going via retention. Still, once you have a stabilized one, what is happening here is that there is a possibility of an inversion, or there will be the possibility of retention based on the different electrophiles. As I said, there is stabilization, which means once stabilization comes, you can understand this in equilibrium. So, now, the equilibrium and the SN_2 rate the substitution rate will be different. So, now, this effect of varying the different types of electrophiles will be more prominent once you have some sort of stabilized one. So, you will see that there will be a certain case where you will see an extreme selectivity of one particular electrophile giving complete retention while one particular electrophile is giving you complete inversion.

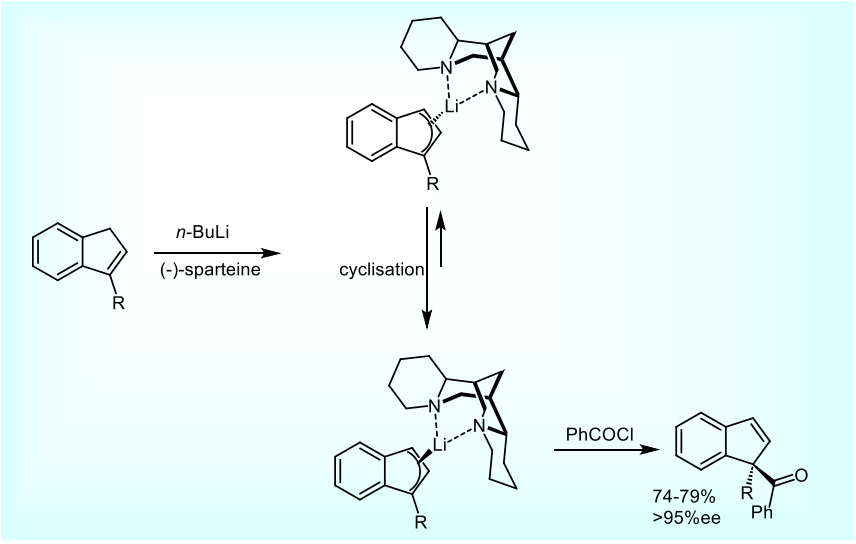




So, here is an example. You can see. This is the known corresponding lithium I am going to talk about. This is a benzylic. So, now, if you use a CO_2 you have seen that CO_2 is a complete retention happening here in this product. As soon as you use a CH_2, you will see an inversion. In every case, it was over 90% observed, and once you tributyltin chloride again, you are observing it is a having with an inversion. So, why is this happening? As I mentioned, once it is a benzylic, there are a couple of things you have to consider, as I said, the rate of reaction of this lithium with an electrophile and the rate of equilibration between these two different diastereomeric transition states.



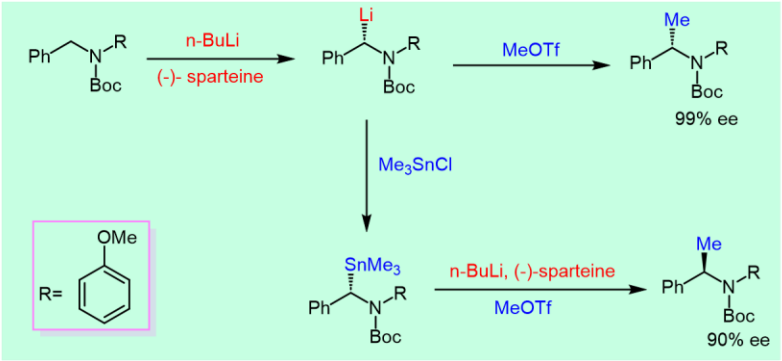
Another example here is using sparteine, as I was saying here, so this is a reaction here to what is happening. You can clearly see there is a proton going to get abstracted here, so this is going to be allylic carbanion and once you have this, allylic carbanion in place of sparteine what is going to happen that can make this allylic So, this allylic lithium is going to coordinate with the sparteine to make a transition state; as I was telling you here, you will end up seeing two different diastereomeric states, and they will be in equilibrium, which I was telling you. And once there is an equilibrium, what is happening if you use this particular electrophile? What we end up seeing is that we end up seeing this product with almost over 95% ee. So, an equilibrium is happening, which is why you can see based on the equilibrium and the reactivity. So, you can end up seeing, and also you have to understand between these two different diastereomeric transitions which one going to react faster and which one going to react slower. So, this type of dynamic kinetic resolution things comes into the picture. So, that is how it is going to give you this product here as a major product.



Another example here, as I was saying at the beginning, is that once you treat n-BOC with a benzylic one, it will abstract this proton and generate lithium. We know about this now: if you use a sparteine that will generate a chiral lithium through the coordination, you can write a lithium with sp that kind of indicates that you have the sparteine actually coordinated with the lithium, and once you treat with the methyl triflate it is going to give you the methyl with retention, but once you go for the the metal halogen exchange. If you use a trimethyl tin chloride, then it will go for the corresponding tin reagent. Now, if you go for this transmetallation using the n-butyllithium sparteine methyl triflate, you will have an inversion happening from here to here. So, you can see if you want to get both different types of enantiomers of this particular compound, then this is called the sterile trick you have to use. So, what you have to do first you have to convert it to a corresponding stanile reagent and now, if you treat it with the very similar thing you have learned in the transmetalation condition. Then what is going to happen here? There will be an inversion happening here. Again, this inversion depends on several things, and as I mentioned, there is once the inversion happening again; the other thing is that I told you before that there is an equilibration versus there is a reaction. So, once this transmetalation is happening at the same time, there will be a change you can see there will be an inversion happening. So, that inverted lithium will trap with the corresponding methyl triplet to get to this corresponding product.

➢ Enantioselective synthesis with n-BuLi in the presence of (-)-sparteine:

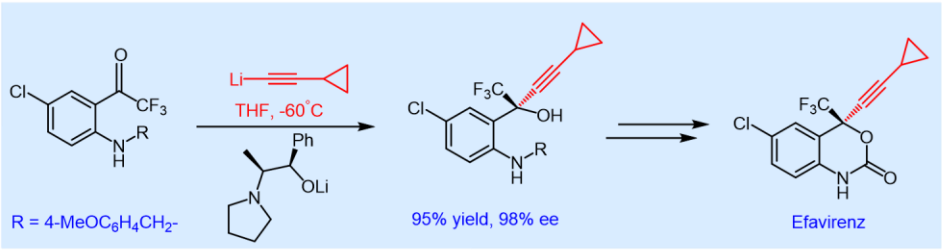
Example:



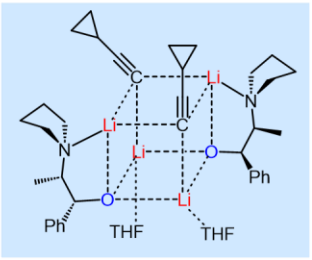
Another example here you can see this alkynyl-lithium going to add to this corresponding carbonyl group here. If you use some sort of a chelating ligand here, you can see that it can form a tetramer with a nice tetramer with the corresponding organ lithium reagent. So, lithium is coordinating with oxygen and nitrogen and as it is getting coordinated in the corresponding. So, now, what is going to happen is you end up with the corresponding 1,2- addition product with a very high ee, and then it can be converted to a bioactive product.

✓ Organolithium reagents can also perform enantioselective nucleophilic addition to carbonyl.

✓ Lithium acetylide is added to a prochiral ketone to yield a chiral alcohol product.



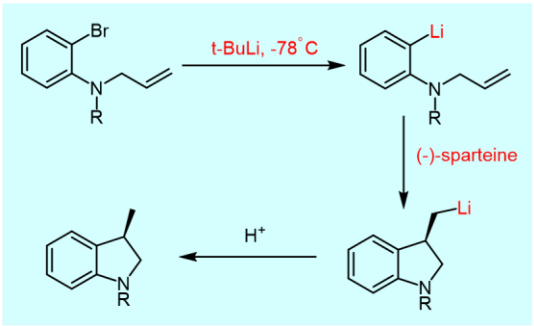
Tetramer =



First thing is a metal halogen exchange to generate a corresponding lithium from carbon bromine bond. Now, it can add to the corresponding double bond through a carbolithiation to generate the corresponding lithium. Using spartein you can able to generate the lithium chiral and now if you treat with the proton it can introduce the methyl group in this position. And you can see in every case they are getting again as you can see this type of the ee also depend on what is the -NR group here. That means, again the important thing is when this lithium is attacking here and generating the corresponding lithium that time that there will be again there will be a two diastereomeric transition state. And that formation of that also depend on what type of inner groups are present.

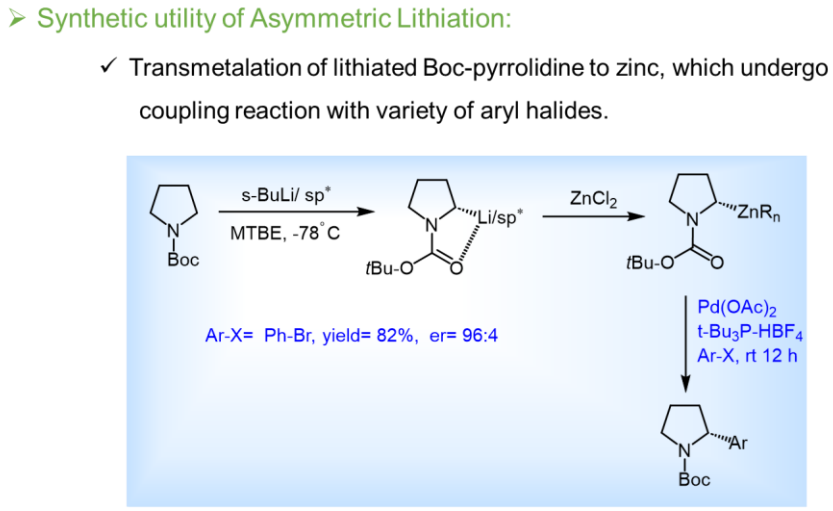
➢ Cyclisation of achiral organolithiums in which (-)-sparteine governs facial selectivity of the attack on the alkene can also give good enantioselectivity.

➢ Transmetalation generates an organolithium which cyclises to give desired product.



So, again the synthetic utility of this transformation. So, starting from the secbutyl lithium and the sparteine, it can generate the corresponding chiral lithium. which can go

for a transmetalation with a zinc to generate the corresponding zinc reagent which can participate in a cross-coupling reaction I am going to discuss this a a palladium catalyst a negishi coupling reaction to form this corresponding product to introduce a aryl group here. So, starting from here to hear what you have observed that it is replacing this H and also introducing an Ar group with a very high enantioselectivity.



So, in this particular part, I have talked about the transmetallation reaction. I have shown you, the generation of the organolithium from the organotin reagent. I also talk about the generation of chiral organolithium using the sparteine and some cases there are retention or inversion that is also depend on if you have a stabilized versus a non-stabilized carbonyl. Again, these are the references. thank you for coming to the class, and I am going to see you guys in the next one. Thank you.