Rearrangements and Reactive Intermediates in Organic Synthesis

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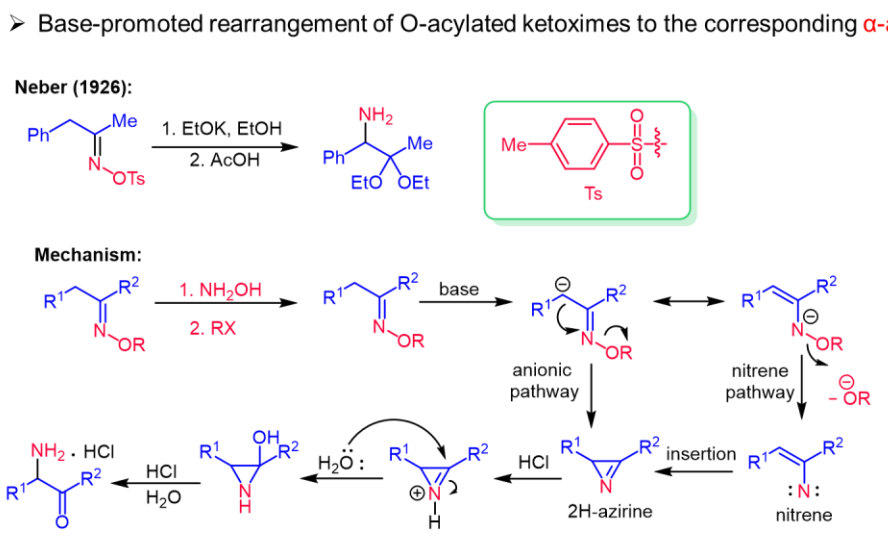
Lecture 08: Carbocation

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. So, in the last class, I started talking about the generation of carbanion and their stability. I talked about the pK_a scale and about their reactivity. In today's class, my focus will be on several rearrangement reactions that were done using carbanion. So, I am going to talk about various different rearrangement reactions. So, starting with the Neber rearrangement, Smiles rearrangement.

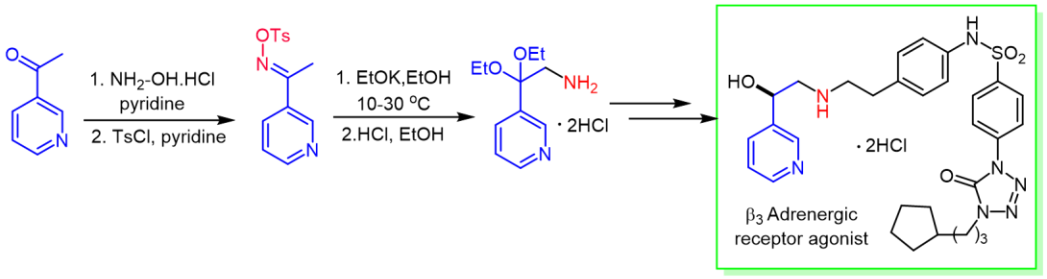
- Neber rearrangement
- Smiles Rearrangement
- Truce-Smiles Rearrangement
- Claisen- Rearrangement:
  - Introduction
  - Thermodynamic stability
  - Mechanism
  - Enantioselectivity
- Variation of Claisen Rearrangement:
  - Aromatic-Claisen rearrangements
  - Ireland-Claisen rearrangements

I am going to talk about the truce-smiles rearrangement and introduce you to the Claisen rearrangement and different variations. So, my first rearrangement for today's class is going to be the Neber rearrangement, which is going to be a rearrangement of O-acylated ketoximes, which is going to convert to the corresponding alpha-amino ketones. So, you guys are familiar with this type of ketoxime if you remember in the previous class in the carbocation when I was talking about the Beckmann rearrangement, I was talking about this formation of the -OTS and if you remember, I was talking about some sort of fragmentation because if you have a stable carbocation generation tendency Then, instead of the Beckmann rearrangement, fragmentation happens. I also talked about those things. So, here I am talking about something else. If you start with this type of O-acylated ketoxime starting material here and treat with, you have a potassium ethoxide in ethanol, and acetic acid is going to convert to an alpha-amino ketone, which can be converted to the corresponding -OEt. It will be a ketal formation going to happen in the presence of

you having acetic acid already there and ethanol. So, it is going to form this ketal. So, what is happening in the mechanism? Let us try to understand that you have this starting material. It was treated. So, it is a form after you treat with the NH_2OH. So, you start with the corresponding carbonyl treated with hydroxylamine, then you try to make it as a leaving group. So, you try to make this OR as a leaving group. Once you treat with base, it is going to abstract this proton here and generate a carbanion. So now this carbanion can attack the nitrogen and eliminate this OR going to form this 2H-azirine. Once it forms this 2H-azirine, in the presence of a proton, this nitrogen gets protonated. So this nitrogen is getting protonated. Now, the water can attack here in this position and then the formation of this particular intermediate. Now, in the presence of acid, what is going to happen? It can even protonate again and this will allow to open up. The aziridine is going to form this alpha-amino ketone. It can also be proposed that this reaction can also go through a nitrene intermediate, and after the formation of the nitrene, it can just go for insertion to get to this particular 2H-aziridine compound, which can further go for this reaction, and goes to the corresponding alpha-amino ketone compound.

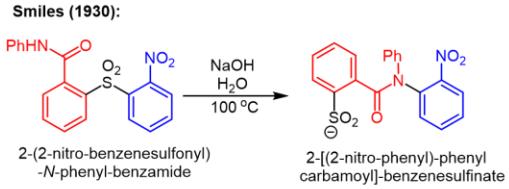


I hope you guys understand this rearrangement. And I'm going to give you some examples here. You can see that the first thing is the presence of hydroxylamine. And then in place of tosyl chloride and pyridine. I have already told you about the structure of tosyl chloride. So it's a p-toluenesulfonyl chloride. It's going to make this N-OTS. Now, in the presence of potassium ethoxide and ethanol. And then with the HCl, it's going to form this alpha-amino ketone, which is going to form the corresponding ketal. And this actually further converted to a very important bioactive compound. So, as I told you about this rearrangement, these reactions are not stereospecific. The reaction is generally carried out in an alcohol solution containing an alkoxide base which we have seen before like potassium alkoxide in ethanol.

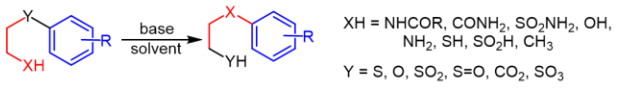


- The reactions are not stereospecific.
- The reaction is generally carried out in an alcohol solution containing an alkali alkoxide as a base.

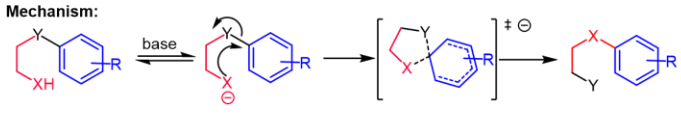
So, now I am going to move to another rearrangement is called Smiles rearrangement. So, Smiles rearrangement is a very important reaction here. What is going to happen here? It is an intramolecular aromatic nucleophilic substitution. I am sure all of you are very familiar with aromatic nucleophilic substitution. Here what is going to happen? We are going to add one more term here: intramolecular. So, if you see the first example which was discovered in 1930. Going from this starting material to the product, what changes happened? I can clearly see that this bond between this nitrobenzene and this SO_2 is actually broken, and then this nitrogen of this Pthalimide actually now came and formed a bond here. So, we can clearly see that this nitrogen is attacking here and forming a bond with this nitrobenzene, and then this SO_2 is getting out. So, what is happening here in this reaction? So, you have this type of XH in your reaction, which could be amine, alcohol, or NaCOR, like a protected one. So, a different type of heteroatom, where you have a proton that can be easily abstracted to make a carbanion, some sort of anion, not a carbanion; sorry for that; it will be an anion that is going to attack here. So, it will go for some sort of an ipso substitution, you can see clearly. It is going to attack there, and then it can cleave that bond through this type of transition state, and then after that, it can form this product.



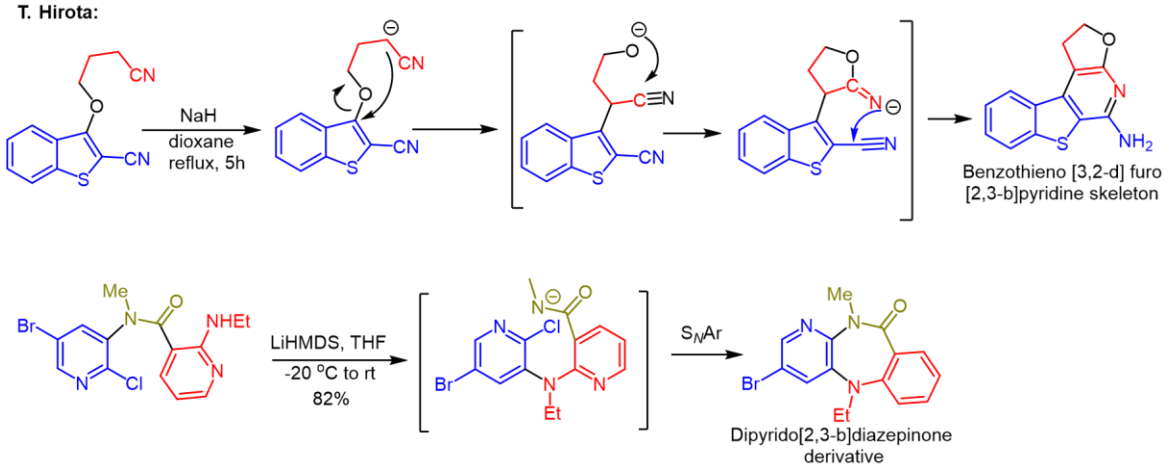
- Smiles Rearrangement is an intramolecular aromatic nucleophilic substitution.



Mechanism:

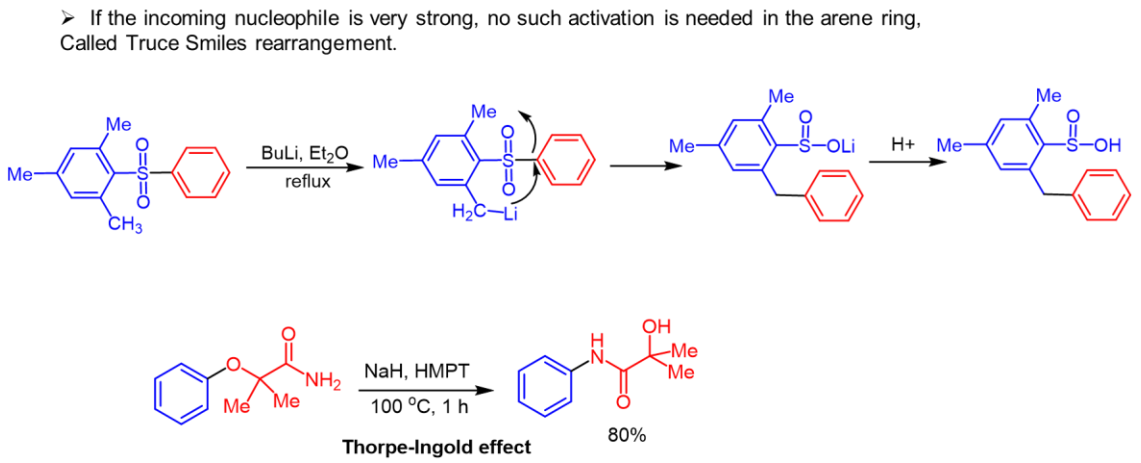


So, I am going to give you more examples of this reaction here. So, starting from this particular compound, which has a benzothiophene. So, first, in the presence of sodium hydride, the more acidic proton is going to be abstracted here. This is getting abstracted to generate a carbanion. Now, this carbanion is going to take part in some sort of a Michael-type addition here because you have this α, β-unsaturated cyano group. Now, it is going to generate a negative charge here. So, if you try to draw this, then what is going to happen here is that there will be cyano, there will be a negative charge, and then there will be oxygen, which is attached here, and there will be -CH_2, and then there is another carbon, and then there will be a cyano group. So, now what is going to happen? Now, actually, this negative charge is going to come back and break this carbon-oxygen bond. That is going to form this type of O- species, which is now going to attack cyanide to form this species. Now, this N- can attack another -CN here and finally, through this condensation, it is going to form this benzothionofuro pyridine skeleton. So, what is happening? One after another first forming a carbanion-stable carbanion; then, it attacks one after another centre, one after another cyano group, and then forms this product. There is another example here. If you look into this molecule, once you treat it with a base like LiHMDS, I have already introduced you to LiHMDS in the last lecture, and I talked about their pKa. So, it is a strong base, so it is going to abstract an acidic proton here. So now it is going to abstract this proton from this NH-Et, forming this type of N- species. Now, that can go for an S_NAr to take part in nucleophilic aromatic substitution to get rid of this corresponding chlorine to form this product.



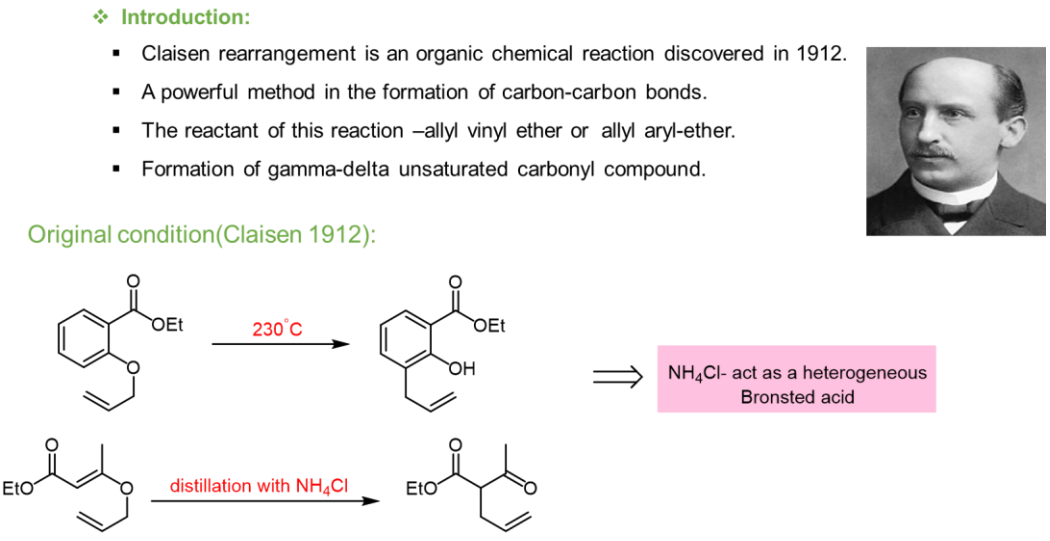
Now, moving further we are going to Truce-smiles rearrangement. So, it is one type of Smile rearrangement, but the incoming nucleophile is very strong. So, no such activation is needed in the Arine ring. What does that mean if you saw in the previous example, we are talking about that, the ring that is getting attacked will always have some sort of

electron withdrawn group like a nitro group. So, you need some sort of arene activation, but here, you do not need it. So, starting from this compound, once you treat it with butyllithium, what is going to happen is that these toluene protons are abstracted here to generate a carbanion. Now, this carbanion ion is attacking to this carbon here. A nucleophilic attack is going to stabilize the carbanion, followed by the cleaving of this carbon-sulfur bond to generate this compound, which will take a proton to form this desired product. We can also do this reaction using using sodium hydride and HMPT. So, sodium hydride is going to abstract this NH_2 proton of this amide, and then this NH- species go for. So, once it forms this, NH- it is going to go for another sort of an attacking in this carbon and then after that, the cleavage of this carbon-oxygen bond is going to generate this corresponding product.

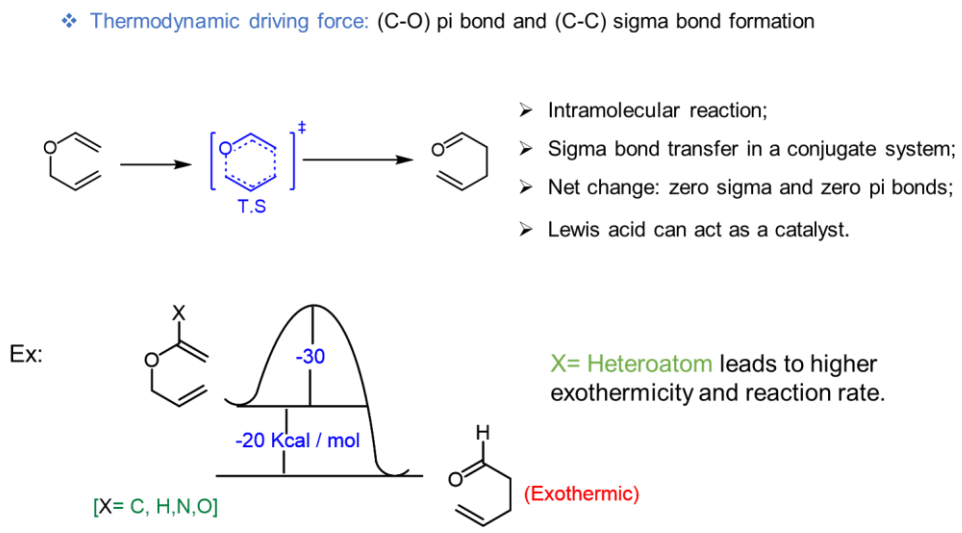


So, moving further, we are going to introduce you to the Claisen rearrangement. So, Claisen rearrangement was actually discovered in 1912. It was discovered by Rainer Ludwig Claisen. So, this is a very powerful reaction for the formation of carbon-carbon bonds, and there are different variations of this rearrangement that developed over the years. It is still a very important reaction you will see for a natural product synthesis. A lot of times, this reaction was used. Now, we are going to talk about the reactant. So, what is the reactant, and what is the product? So, the reactants are allyl vinyl ether or allyl aryl ether. So, what is happening here? So, this compound has an aryl group here, and then there is an allyl group here, which is connected through oxygen. So this is called an aryl allyl ether, or you can have a class here where you have a vinyl group next to the oxygen and then an allyl group. Here, we call it allyl vinyl ether. So, once you treat this compound under heat, it is going to rearrange because there is nothing that there is there is no change in the molecular weight. The only thing there is a rearrangement where this allyl groups, which was with the oxygen at the beginning now move to the carbon. So, it moves from this oxygen to carbon. So, now, because this carbon-oxygen bond is getting cleaved, it is forming a phenol. In the case of vinyl and allyl ether, what is happening here? In this reaction, a carbon-oxygen bond formation occurs. So, it is a carbon-oxygen

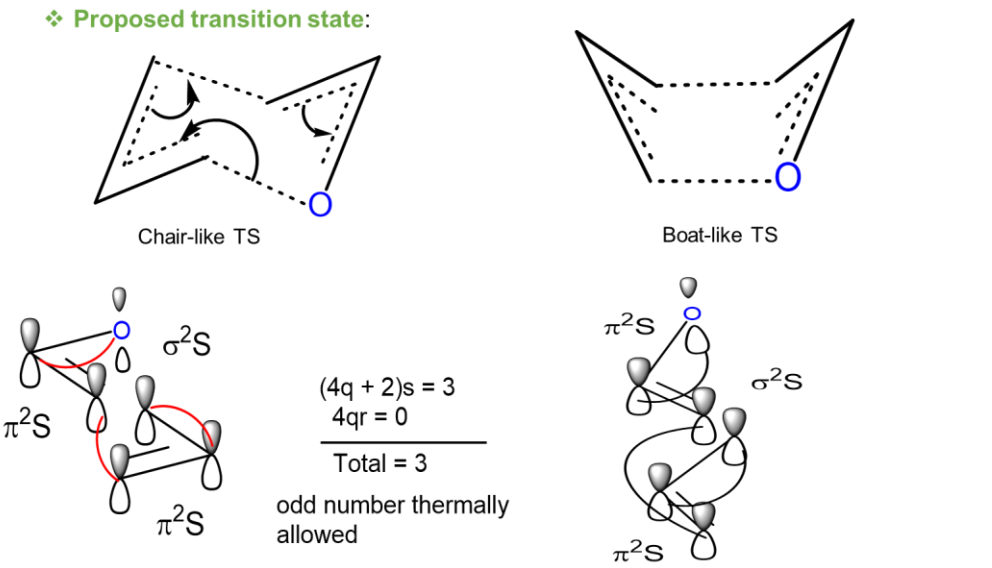
double bond formation happening, and there is a double bond formation. So, what is happening in this reaction is that there is a cleavage of this carbon-oxygen single bond. And the same time, there will be a formation of a carbon-carbon bond and carbon-oxygen double bond. and so, this type of compound is actually so if you talk about α, β then this is a ɣ and then δ, so it is a ɣ, δ-unsaturated carbonyl compound which can be formed by Claisen rearrangement.



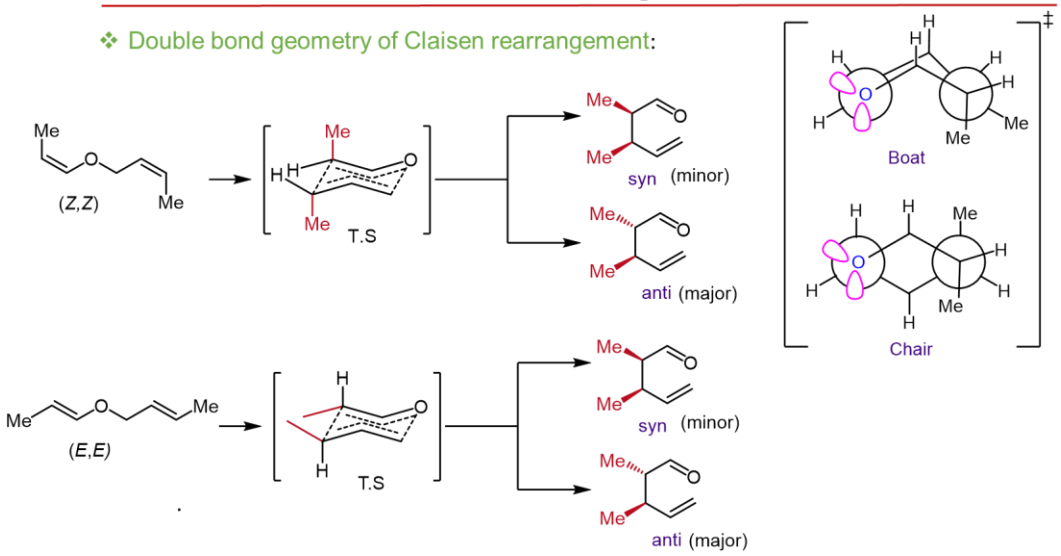
We are going to try to understand the thermodynamic driving force of this reaction. As I mentioned, you are forming a carbon-oxygen π-bond, and at the same time, you are forming a carbon-carbon σ-bond. So, there is the driving force here, of course. This reaction is exothermic, and this reaction actually goes in an intramolecular fashion and actually, it goes by some sort of a cyclic transition state, which I am going to come about in a minute. So here, actually, as I said, there is no change will be zero σ and zero π bonds, so that means you are seeing here that there is a pi-bond which is also getting broken, and there is a new bond is formed. At the same time, there is a carbon-carbon bond, and a carbon-oxygen double bond are forming. I told you that this reaction is exothermic, and the reaction rate or exothermicity will be increased if you are able to bring a substitution in this position, which can push electron density. So, if the X will be a group of nitrogen-oxygen or some sort of a group that can push electron density, that is going to make this reaction even faster. So, we are going to talk about several variations of this type of reaction where we change this X to oxygen and nitrogen.



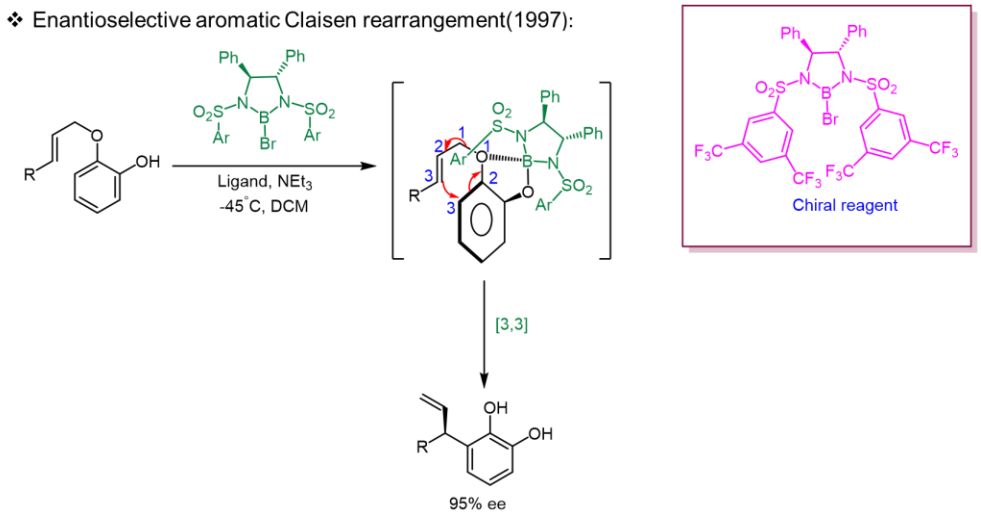
As I told you in the last slide, I will talk about the transition state. The reaction goes via chair-like transition state. Also, we can explain this reaction through a boat-like transition state. Here, you can see there will be a formation of this carbon-oxygen double bond. There will be a breakage of this σ-bond here, and then there will be the formation of a σ-bond here. So, now we are trying to explain this reaction through the Woodward-Hoffman rule. So, if you try to look into this orbital here which is forming the bonds here, we can see these bonds are forming through a suprafacial manner. So, there are three different suprafacial bond formations happening here. And they are all 2π systems. So, we can see the (4q+2)s will be 3. There is no 4qr system as there is no 4π system here. So, the total will be 3, which is an odd number that is that means this reaction is thermally allowed. This can also be explained through the boat-like transition state as well.



So, now, we are going to talk about different types of variations of this, Claisen rearrangement. So, the first question arises in the Claisen rearrangement: what happens if we start with these two terminals? So, if you have these two methyl groups in the two terminal positions, now the question comes: what type of substitution do they have? Suppose we are talking about a Claisen rearrangement here. Now, we are talking about if both are trans, which means this is a trans, this is a trans, or they are both Z or E. So, if it is (E, E) like this or if it is (Z, Z), what will happen, and do you know what will be the major product in this Claisen rearrangement? So, what happens when you find out if it is a (Z, Z) or (E, E), In both cases, the anti product means both the methyl will be anti position will be the major product, and the C will be the minor product. So, then, we are trying to understand this type of transient state happening here. In the transition state, if you see that in particular, this transition state where both are actually Z, you can see that this is a methyl, which is a Z, and this is an E configuration. Now, you can see once they are forming bonds, this methyl is up, and this is down. So, this is forming the anti-product as a major product. In the case of once both are E, what is happening at the junction? So now I have drawn them, both the methyl group here, so this is a methyl, this is a methyl, so they have only a gauche-butane interaction. Once they are forming the bonds, again, one of the methyls is up, and one is down, which is given to the corresponding anti as a major product. In both cases, you can see in the first case, they have both the methyl in the anti position here, they have gauche-butane interactions.

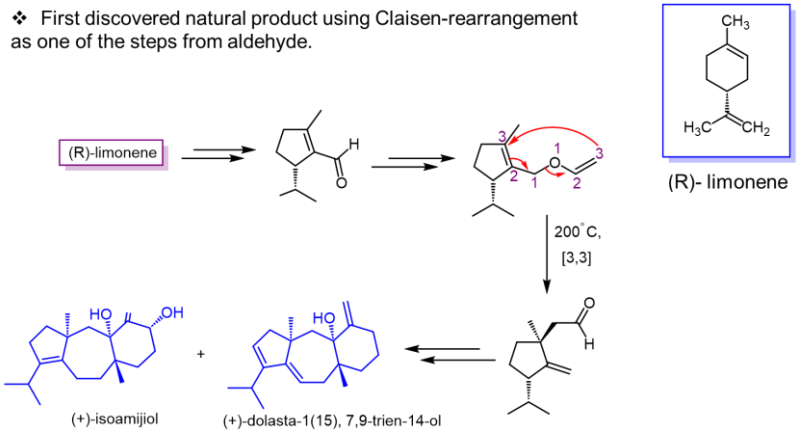


So, I can introduce you to the enantioselective Claisen rearrangement. So, if this reaction needed to be asymmetric, it was done in the presence of some sort of a boron-based Lewis acid using a chiral backbone. So, for this particular compound, once it is reacting with this particular boron compound, it is actually forming some sort of a chelation complex. So, both of these oxygen actually attack the boron, forming this type of some sort of boronate complex. Now, what is happening? As this boron is bound to this phenyl ring, it is actually blocking one of the phases of the phenyl ring. So, now, what is happening? This Claisen rearrangement is only one of the particular phases of this phenyl ring. So, it is happening through the top phase, given to this particular product with 95% *ee*.

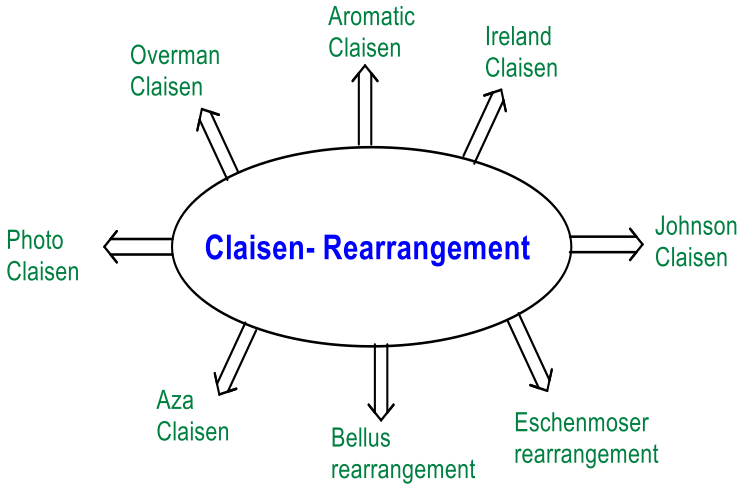


Some more examples of the Claisen rearrangement start from the limonene this compound can be synthesized easily after, the reduction of this aldehyde group and then

followed by the synthesis of this type of vinyl and then allyl ether Then, once this compound is heated at 200°C, it can go for a 3,3-Claisen rearrangement to get to this particular compound. You can clearly see this Claisen rearrangement happening, and it is actually coming up instead of down because to avoid some sort of a steric interaction with this stable isopropyl group. So, this compound can further able to convert to the corresponding natural product after some successive transformations.

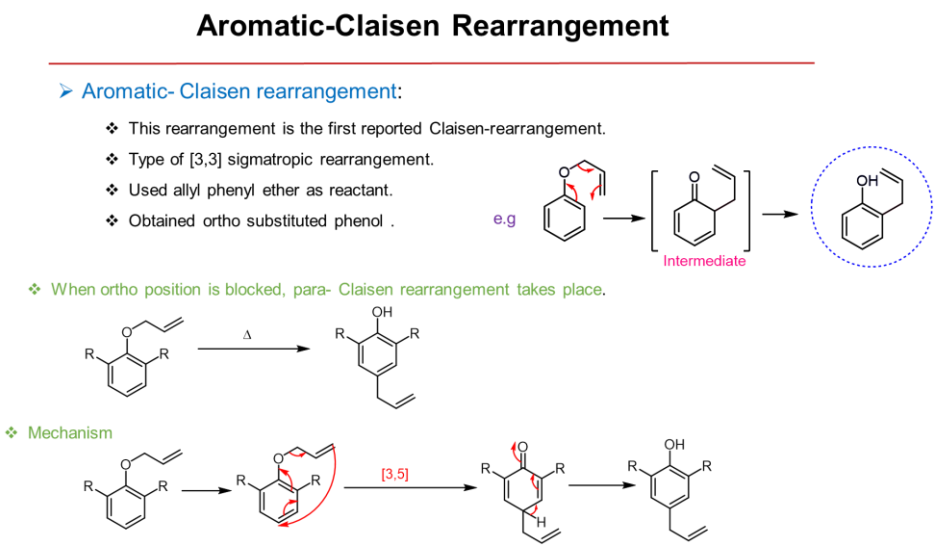


So, there are different variations of Claisen reagents, I am going to explain each of these variations to you. I am going to talk about the aromatic Claisen; I am going to talk about the Ireland-Claisen, Johnson-Claisen and Eschenmoser-Claisen.

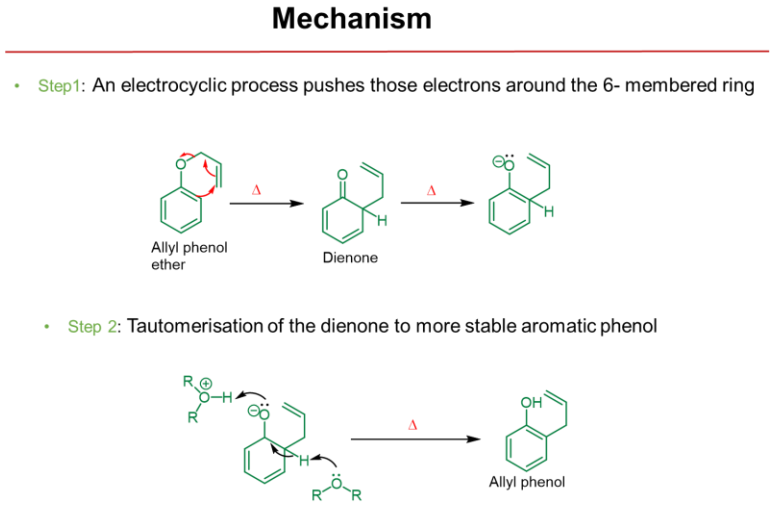


Let's start with the aromatic Claisen rearrangement, as I mentioned in the introduction to the Claisen rearrangement. This type of aromatic Claisen rearrangement was the one that was done at the beginning. So, it was the one that was discovered at the beginning. So, it actually goes through this type of 3,3-sigmatomic shift. You can assign this 1,2,3 and at the same time 1,2,3. It goes through this type of intermediate where you can see there will be a proton abstraction going to be, which is finally going to get to the corresponding phenols. So, I think the mechanism is given here clearly. Now, the question comes that if

your ortho position is blocked with two groups, what is going to happen? Now, instead of happening a 3,3-sigmatropic shift, it will go for a 3,5-sigmatropic shift. Proton abstraction from here is going to get to the corresponding phenol.



Again, this thing was given here starting from this allyl phenol ether; you can see this because this is attached to the phenol ring. We can see this allyl phenol ether goes to this dienone first, and then it goes to the corresponding product.

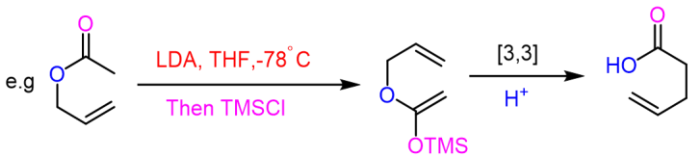


I think the first variation of this Claisen rearrangement is the Ireland Claisen rearrangement. So, this is another important Claisen Rearrangement reaction. So, this actually goes via the formation of the silyl stabilized enolate derivative. So, this is the one going to form and then what is going to. So, this is the important thing that goes via the formation of this silyl stabilized enolate derivative. So, starting from this ester what is happening first So, this proton is getting abstracted. By using the stronger base LDA to form this type of silyl stabilized enolates. After it reacts with the TMS-chloride. Then, it

participates in the 3,3-sigmatomic shift. It is going for a 3,3-sigmatropic shift. Now it is forming alpha, beta, gamma and delta. So, it is forming the γ, δ unsaturated carboxylic acid. Instead of the ketone that forms in the Claisen.

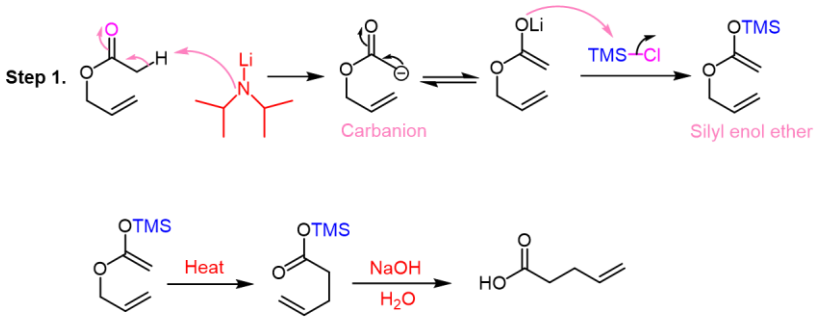
Ireland-Claisen Rearrangement

- This is a type of [3,3]- sigmatropic rearrangement.
- It is silyl-stabilized enolate derivatized from an allylic ester.
- Used non-nucleophilic strong base e.g LDA.
- Obtained gamma-delta unsaturated carboxylic acid.
- This rearrangement offers ready to chain-extended carboxylic acid.



So, this is the mechanism that I was showing in the previous slide that it is going to abstract this proton to form this carbanion, which is going to form this corresponding lithium, which is going to be trapped with TMS to form this corresponding silyl enol ether which is going to participate in the Claisen rearrangement in terms of heat to get to this corresponding carboxylic acid. which has a γ, δ-unsaturation.

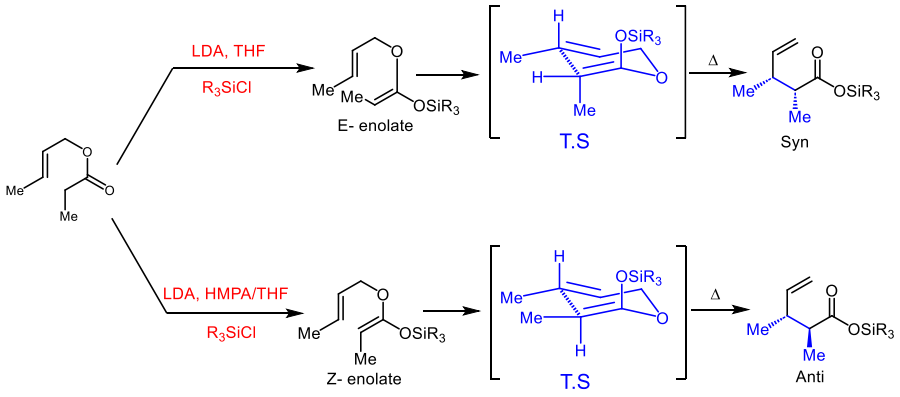
- Mechanism of Ireland- Claisen rearrangement:



- Formation of the corresponding enolate upon deprotonation with LDA.
- The enolate is trapped with a trialkylsilyl halide.
- [3,3]- sigmatropic rearrangement.
- Hydrolysis

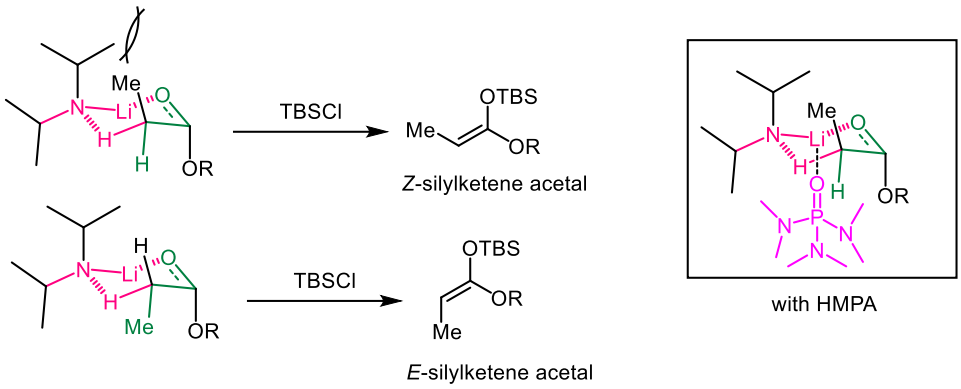
Here is one important example here, so what is happening in this particular compound? I think I have explained to you during the Claisen rearrangement that if you have two methyls here, now you have a very similar scenario. In place of LDA, in place of THF, using the corresponding silyl chloride, it is forming the *E*-enolate, and that *E*-enolate is

participating in Claisen rearrangement to form the *syn* product. But once you treat with LDA with HMPA. So once the HMPA was added, *Z*-enolate was formed instead of *E*. And now it is actually forming an antiproduct instead of the *syn*. So now we try to understand the transition state of the syn product first. Let us try to understand this one. So, from *E*-enolate, if you try to draw the corresponding transition state, you can clearly see. So, this methyl and this methyl actually both are down, which is going to end up making the *syn* product, and they have only a gauche-butane interaction present there. Very similarly, if they are *Z*-enolate, then you can see that this methyl is actually down, but this methyl is up, and they have Gauche-butane interaction, and from this transition state, they can form the anti-product. Now, we will try to understand why it forms an E-annulate in the presence of LDA/THF and why it forms a *Z*-enolate once you put HMPA.



So, in general, once this enolate formation is happening, if you try to draw a transition for that using this LDA, which has these two isopropyl groups here attached to the nitrogen. Now, you can see in this particular transition when this methyl is in the axial position, and this may be in a better shape to keep this methyl in the axial, then there will be a 1,3 di-axial interaction between this isopropyl and methyl. So, it will always prefer putting this methyl here keeping this hydrogen up. So, what is happening, in that case, is that from this particular transition state, it is going to generate the corresponding *E*-silyl ketene acetal. So, it is going to generate the corresponding E enolate and then it is going to generate the *E*-silylketene acetal. But the question comes once you add HMPA, what is happening? Once you add HMPA, now the HMPA actually binds with the lithium, which I have shown here. Now, once the HMPA is binding with the lithium, this is actually a bulky group. Now, what is happening? It is not going to be preferred for this particular conformation where you have a methyl because now if you have, if you can imagine that you have an HMPA here, which is a bigger group, and you have a methyl here, then they can be going to interact. So, stop there. It is preferred for this particular transition state at least to avoid this type of interaction. It still prefers to put methyl in this axial position,

not in the other position, to avoid this type of interaction. That is why, in the case of HMPA, the *Z*-silylketene acetyl will be measured.



Now, there is another example people used zinc chloride for this reaction to make some sort of a chelated complex. So, starting from here, first thing in place of base, it is going to abstract this proton, then it is going to make corresponding. So, it is going to make the corresponding enol. Now, this enol is getting stabilized with nitrogen and oxygen. The zinc going to form a complex to stabilize this corresponding transition state, which is going to take part in the Ireland-Claisen rearrangement to get to the corresponding γ, δ-unsaturated carboxylic acid.

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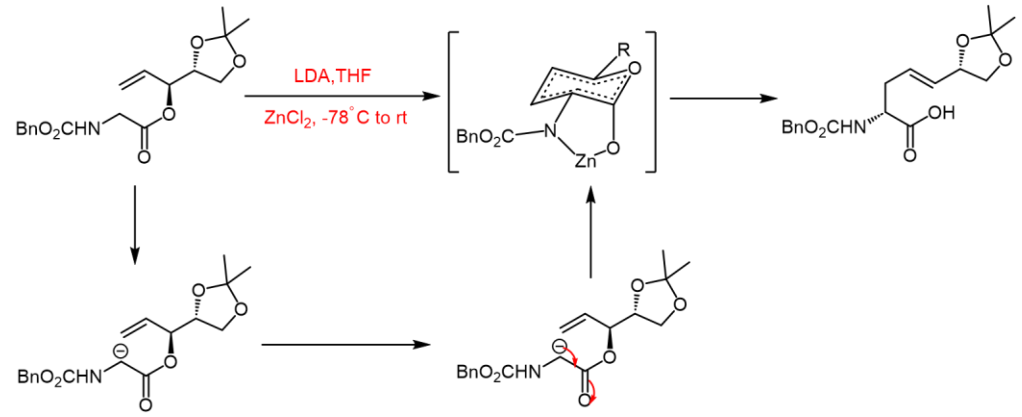
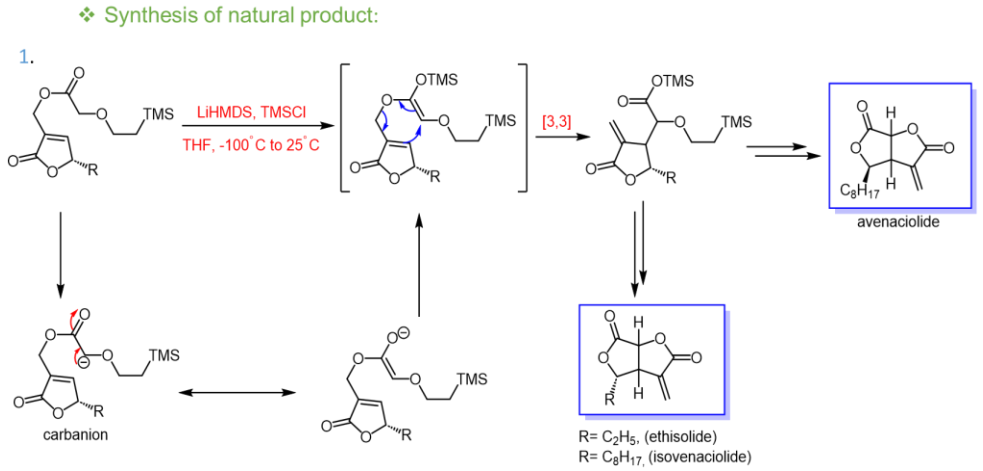
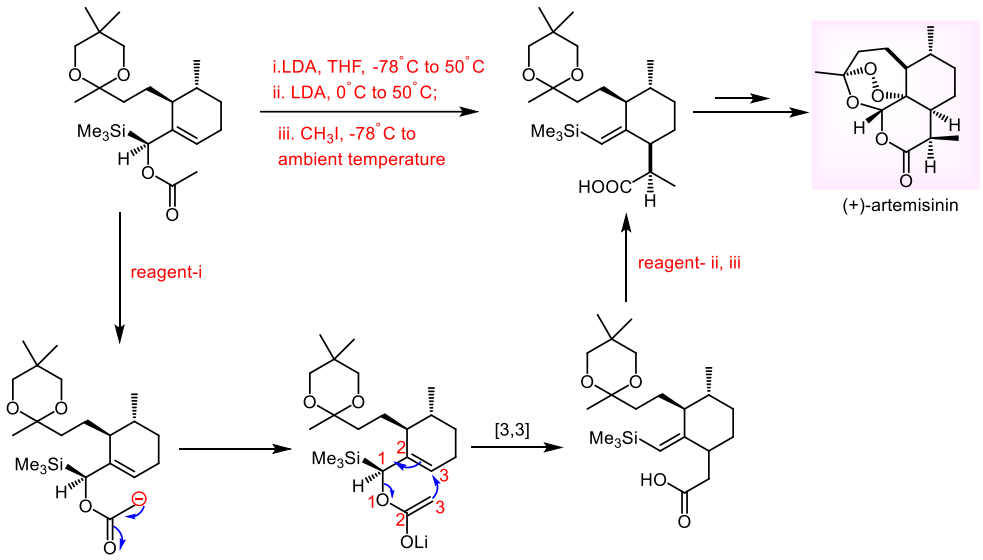


There is another reaction for this Ireland-Claisen rearrangement in this particular reaction, which is happening in the presence of a LiHMDS, which is a base that is abstracting this proton to form this carbanion. Now that carbanion can go for enolization, and then it is going to trap with the TMS-chloride to form this corresponding -OTMS, and then once you have this one ready, it is actually ready for this 3,3-sigmatropic shift. you can now clearly see that 1, 2, 3 and then 1, 2, 3 is going to form after the 3.3-sigmatomic shift. It is going to form this corresponding product, which is going to convert to the natural product.

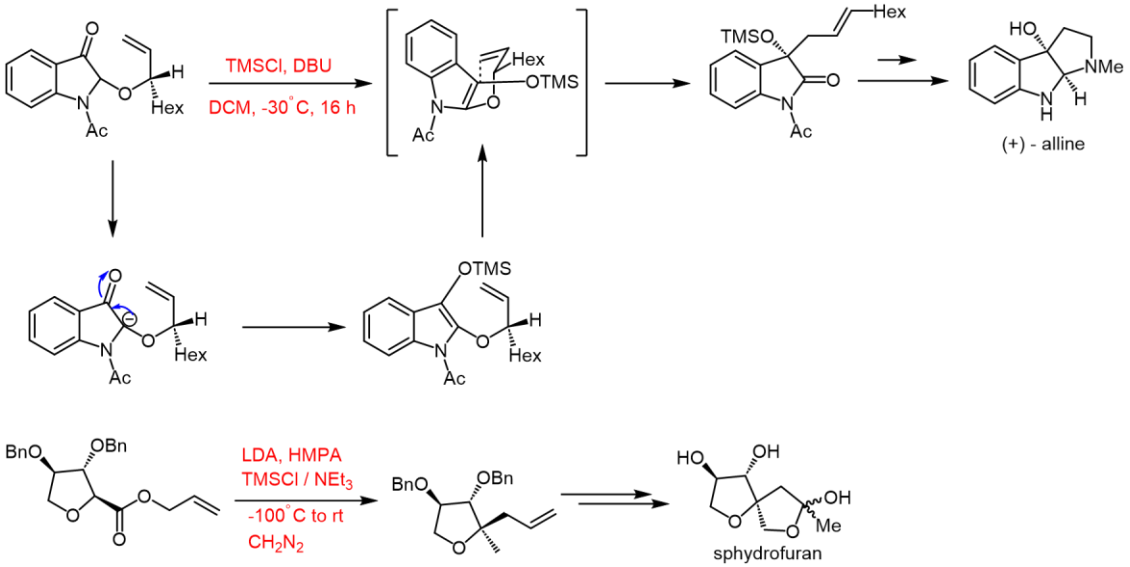


There are more examples here we can bring. So, in the case of LDA, what is happening is abstracting this photon. Forming a carbanion then it is forming the corresponding enol. Now, once it forms the corresponding enol, it is going to trap with the corresponding. It can react in this way also that once it forms the enol, it can also go for this 3,3-sigmatropic shift to get to this corresponding you can see now also it is this α β γ and δ. So, it is the γ, δ-unsaturated carboxylic acid that is going to form after using several different reagents. It is going to convert to the corresponding natural product starting from this, it is going to after several transformations, it can convert to the corresponding natural products.

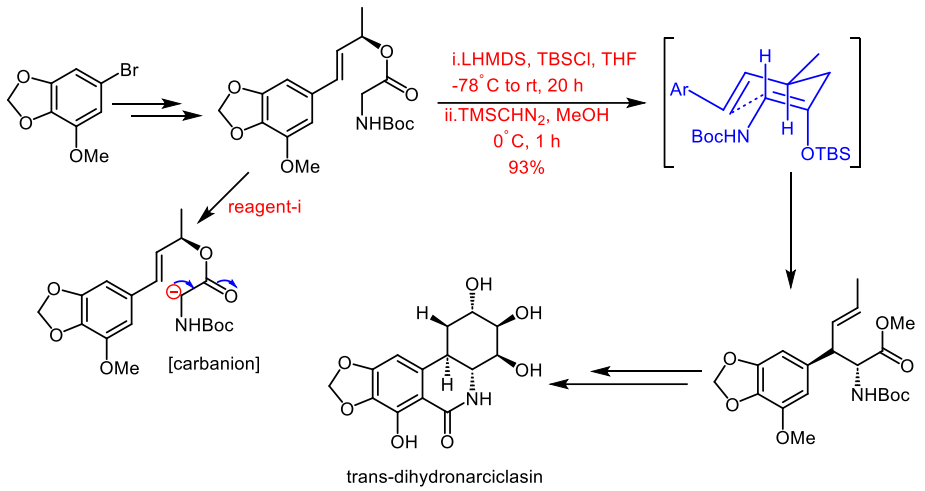


There is another example here. I think this is a very interesting example. First, using this base, DBU can abstract this proton here to form this corresponding carbanion. Now, this carbanion can form the corresponding enol, which can be trapped with the corresponding

TMS-chloride to form this corresponding -OTMS. And now, if you see, it is already ready for your 3, 3-sigmatropic shift because it is 1 2 3 and 1 2 3 going through this type of transition state to get to this corresponding product. It can be converted to natural products. Once you use LDA with HMPA again, we have learned that with LDA/HMPA is going to abstract a proton from here, so now you can see there will be a proton abstraction from here that is going to form this O- is going to trap with your TMS-chloride, then it is going to go for a 3,3-sigmatropic shift to make this corresponding compound. So now, once you have this, you know -OTMS here, so it will form a double bond and a -OTMS. Then, it is going to perform this 3,3-sigmatomic shift to form this compound, which will be further converted to corresponding natural products.



So, there is another example of the Ireland-Claisen reaction. So, here is what we are seeing: if you have a particular stereochemistry, what is going to happen in the product? So, suppose starting from this particular compound, what is happening first thing is the deprotonation of either of this proton from here, one of this proton. formation of carbanion, and then what happens after the formation of carbanion? You are using the TBS-chloride. So, once you form this double bond here and here, you will be -OTBS. Now, it is going to be ready for the corresponding 3,3-sigmatropic shift. Once you are going to take part in the 3,3-sigmatropic shift, we have shown the corresponding tangent state here. And then from this transition state through this sigmatropic shift, it is going to form this corresponding product here because you have, and it is going to convert to corresponding ester here because we have used this TMS diazomethane here who is going to convert this corresponding acid to corresponding ester in the product. From there, it can able to convert to this particular natural product. So, here is what you have seen here. We started with this particular stereochemistry of this allylic alcohol, and you can see in the product that after this 3,3-sigmatropic shift, the stereochemistry actually remains intact here.



In this part of this course, what you have learned is that you know different types of rearrangement using carbanion. We have learned about the Neber rearrangement. If you remember, we talked about the Smiles rearrangement as well, and then truce smiles rearrangement, where you have a stronger base and you have an unstabilized carbanion, which can go for the truce-smiles rearrangement. Then I talked about Claisen rearrangement; I talked about the transition state of the Claisen rearrangement and the different variations of the Claisen rearrangement. I introduced you to the Ireland-Claisen rearrangement, and we talked about different examples. In the next segment, I am going to introduce you to the other Claisen rearrangements, which are the Johnson-Claisen rearrangement and the Eschenmoser-Claisen rearrangement. You should go through this textbook, which is the S. Warren, which is a very good textbook for this with Clayden and S. Warren, and then you can go through this another textbook for Carey Sundberg, and of course, I think these books should be perfect for going through all the different topics I cover in class.

Thank you all for listening, and I am going to see you in the next class. Thank you.