Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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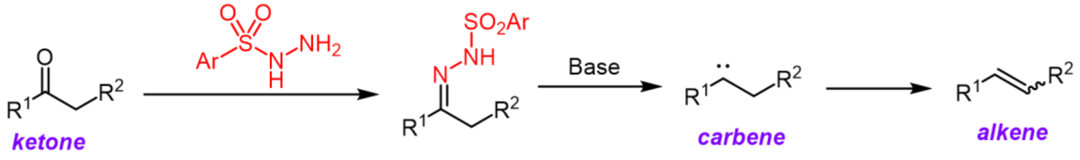
Lecture 13: Carbene (Continued)

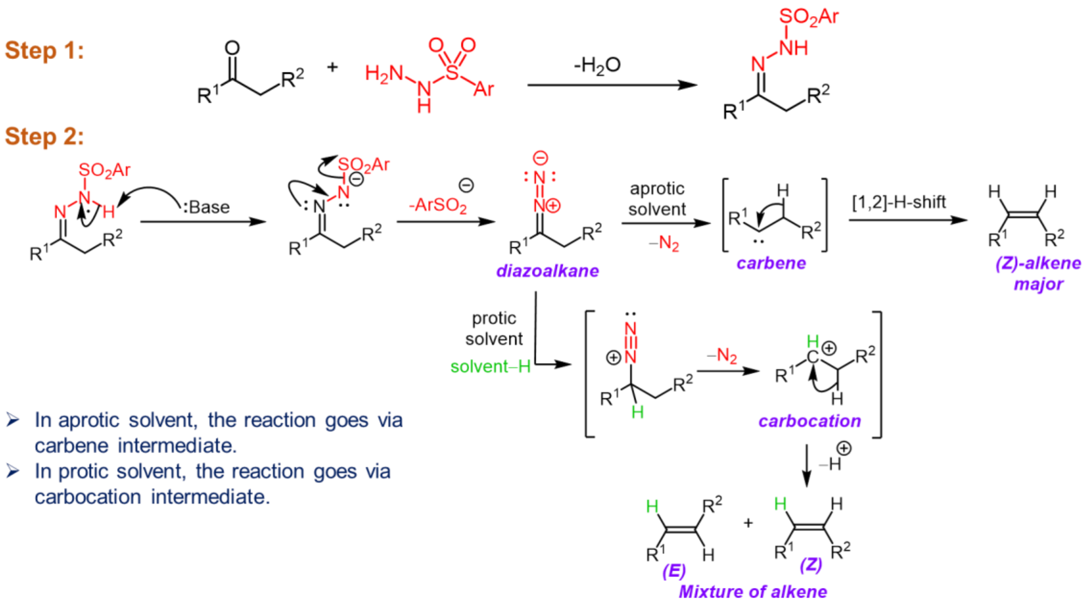
Welcome back to this NPTEL online certification course in the molecular rearrangement and reactive intermediates. I am teaching carbene in the last two classes. So, in this class I am going to talk about some of the molecular rearrangement using carbene. So, and then also some other reaction using carbene. So, first I am going to start with the Bamford-Stevens reaction and then I am going to talk about Shapiro reaction, Reimer-Tiemann reaction, then some of the rearrangement reaction of carbene like Wolff then I am going to talk about the Doering-LaFlamme allene synthesis and then the Skattebol rearrangement. So, I am going to cover all of this different topic in the today's class.

So, let us start with the Bamford-Stevens reaction which was discovered by Bamford and Stevens in 1952. So, starting from ketones and using tosylhydrazide it can convert to the corresponding alkene. have to use a base. So, first is the formation of the corresponding hydrazone, then in the presence of base it is going to form this carbene which is going to convert to the alkene.

- *First reported by W. R. Bamford and T. Stevens in 1952*
- *Conversion of ketone to alkene*



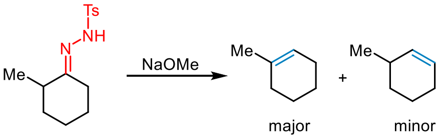
So, let us start about the mechanism for this reaction. So, first step is the formation of this hydrazone you can see after the reaction of this carbon compound and this corresponding tosylhydrazide can form the hydrazone. And once the hydrazone was treated with the base; first abstraction of this proton and then it is actually generating the corresponding diazoalkane after the elimination of this compound. And now the thing is starting from this diazoalkane there could be two things happen; in place of aprotic solvent, it can form this corresponding carbene here and then there will be a [1,2]-shift to form the corresponding Z-alkene. but if it is in the proteic solvent then it after the elimination of

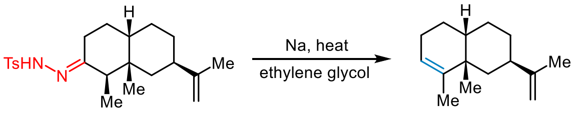


- In aprotic solvent, the reaction goes via carbene intermediate.
- In protic solvent, the reaction goes via carbocation intermediate.

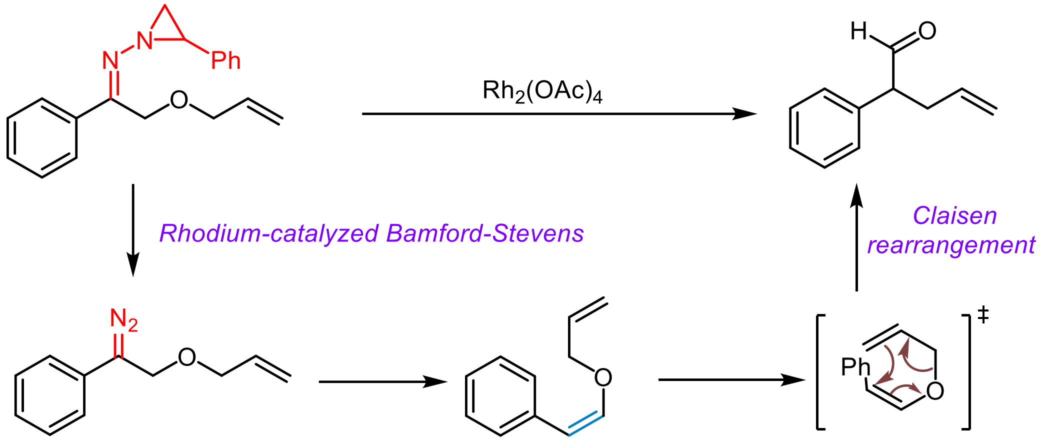
the N_2 it can form this corresponding carbocation then there will be a proton abstraction which can give a mixture and mixture of *E* and *Z* alkene.

So, here are some examples here using the sodium methoxide here as a base. Here they isolated both major and minor product. you can see the reaction actually the abstraction of the C-H is happening from the more substituted position. There is another example here the sodium heat in presence of ethylene glycol here what is happening again there will be so there is a product solvent here so generation of a carbocation going to be happening in this position After formation of the carbocation there could be a hydride shift to form the more stable carbocation and then finally, it can abstract a proton to get to this corresponding product.





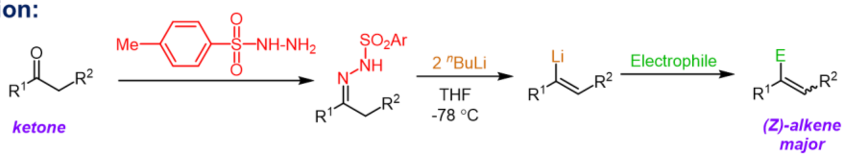
The reaction can happen in presence of the $Rh_2(OAC)_4$ which can decompose the diazo compound see this C-H bond can go for a shift to go to this corresponding olefin. So, starting from this compound at first the Rh can able to decompose the diazo can generate the carbene, then there will be a [1,2]-shift of this C-H bond to generate this product which can go for a [3,3]-sigmatropic rearrangement or we call Claisen rearrangement to form this corresponding product.



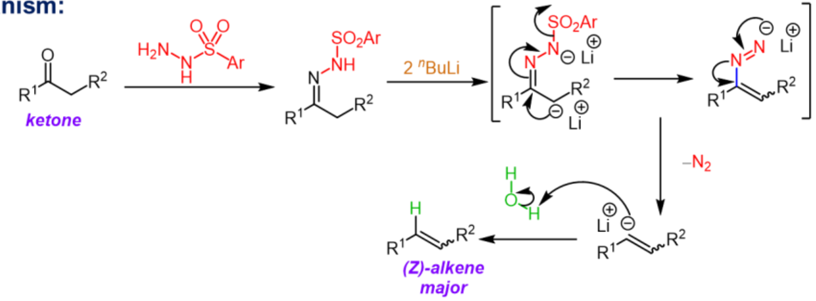
Then I am going to talk about the Shapiro reaction which is again very similar to the Bamford-Stevens reaction, but there is a difference, here I am going to explain in a minute. So, starting from ketone using this type of hydrazine. So, in presence of butyllithium it can form this corresponding lithium which can trap with the corresponding electrophile. Again, what is happening at the beginning formation of hydrazone then in place of butyllithium again there.

- **Discovered by Robert H. Shapiro in 1967**

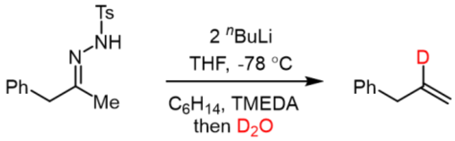
General reaction:

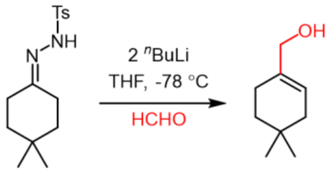


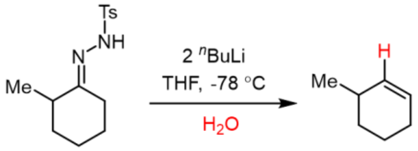
Mechanism:

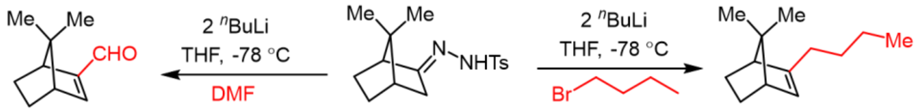


So, this is abstracting the proton from here in presence of butyllithium it is forming a carbanion, then it is going to this sort of an intermediate after that there is an expulsion of N_2 to form this carbanion. You can see here in this example starting from here it is abstracting the proton from this side to get to this corresponding product which can trap with the D_2O. In this particular example, we are seeing at low temperature the kinetic control product is forming. So, here also the proton is abstracting from the less substituted position to get to this type of product. So, this is the kinetic control product. Again, we are seeing here using this very similar condition we are also able to trap with the formaldehyde to get to this corresponding allylic alcohol. Again, there is an example here after the formation of the carbanion which can attack to DMF to form the aldehyde or it can attack to the alkyl halide to get to the corresponding vinyl product.

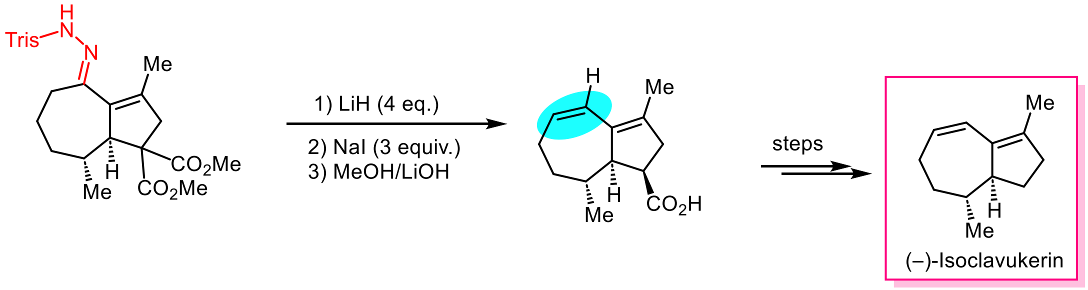


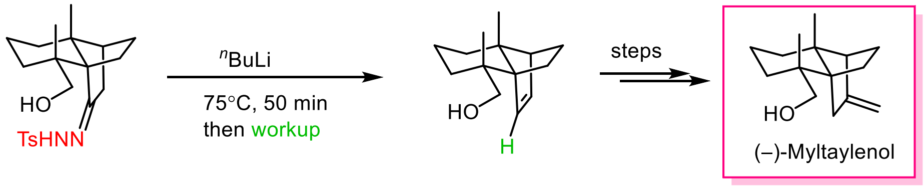


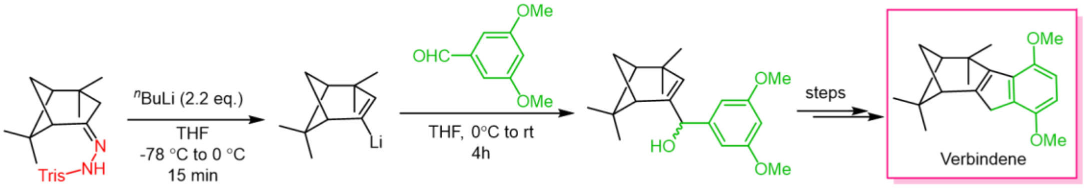


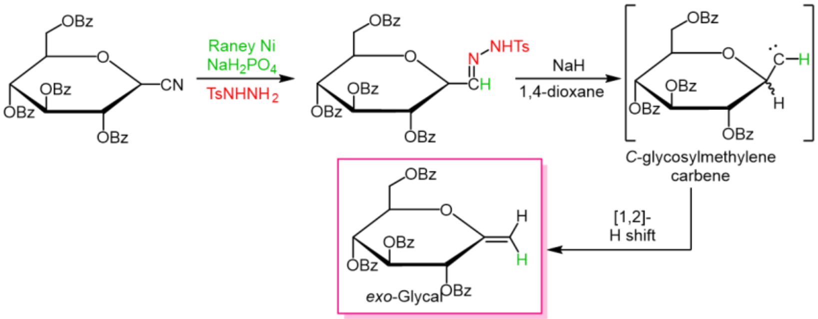


Another example here I think after formation of the carbanion here it is abstracting the proton from here to get to this corresponding product. which can convert to the natural product after few steps. Again, in this example you can see here first thing is that once using the butyllithium you are again generating a vinyl carbanion which can trap with the water to get to this compound which can after some step able to convert to this natural product. Another example here first thing is formation of this corresponding the vinyl lithium species which add to the aldehyde. and goes to this compound which after some step able to convert to this natural product. Another example here generation of this type of the hydrazone then after in place of base it is generating this. So, here what is happening in presence of the NaH and the dioxane it is generating this type of carbene which is go for [1,2]-shift to form this compound.





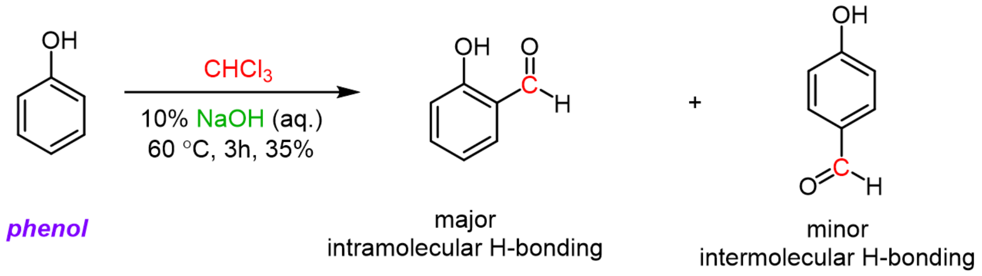




So, now I am going to move to the Reimer-Tiemann reaction. So, I talked about the Bamford-Stevens reaction and the Shapiro reaction. Another important reaction using this carbene chemistry is the Reimer-Tiemann reaction. It was first discovered by Karl Reimer and Ferdinand Tiemann in 1876. So, it is a formylation of phenol. So, starting from the phenol you are actually putting the formyl group at the ortho or at the para position. So, it is an electrophilic aromatic substitution reaction. So, this is a major product because of the intramolecular hydrogen bonding and there is also an abnormal Riemer-Tiemann product which we are going to explain in the future slides.

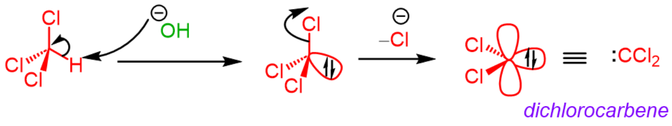
- ✓ *first reported by Karl Reimer and Ferdinand Tiemann in 1876.*
- ✓ *Formylation of phenols using chloroform under aqueous alkaline medium.*
- ✓ *It is an electrophilic aromatic substitution reaction.*

Original work:

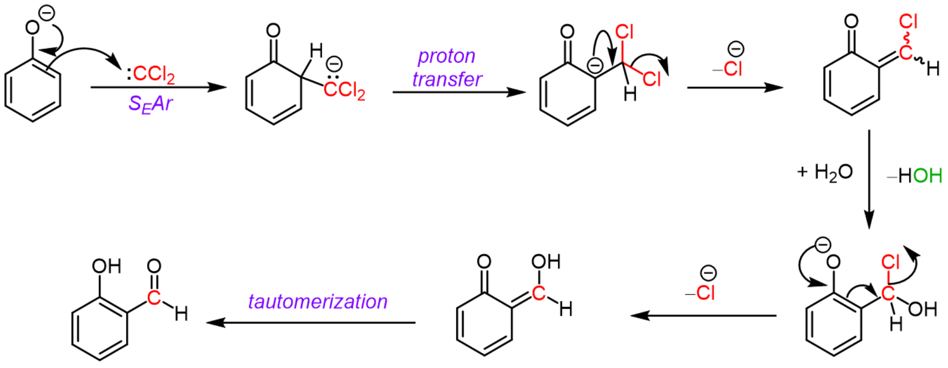


So, here at first, the formation of the α-elimination to generate this type of dichloro carbene species which actually taking part in this electrophilic aromatic substitution. So, what is happening here in this electrophilic aromatic substitution? It is actually reacting with this corresponding carbene to get this type of intermediate then there is a proton transfer happening to form from this intermediate after that, the elimination of the first Cl and then you can see the H_2O can attack here to get back to this type of intermediate and then finally, this O^- is coming back to get rid of the Cl to get here and then after tautomerization it is going to convert to the corresponding the formylated compound.

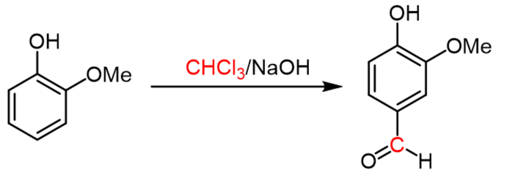
Step 1: dichlorocarbene formation:

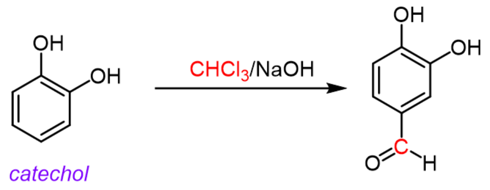


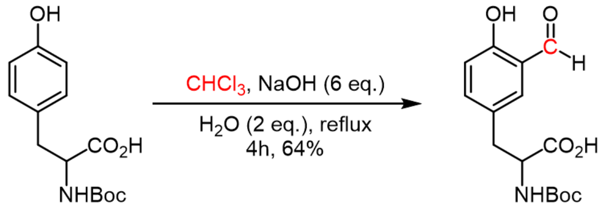
Step 2: reaction with phenol:



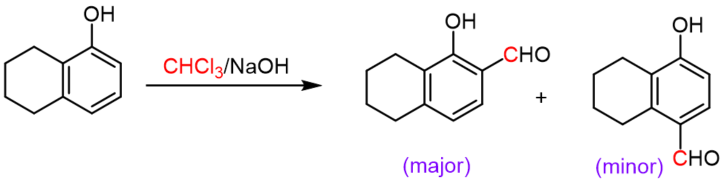
Again, if you start with ortho position is blocked what is going to happen? the para compound will be the major one, but you can also get some product where you have also gotten formylating in this position also, but this will be the major product to avoid the steric. you start with the catechol then again very similar thing happening this para compound is getting the major product. In this particular example also the para position is blocked. So, the reaction is happening in the ortho position to get to this product with a 64% yield.

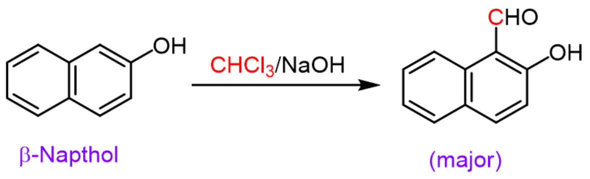


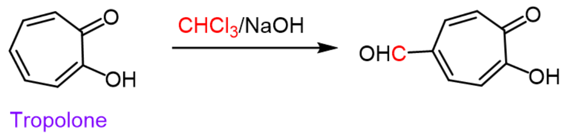




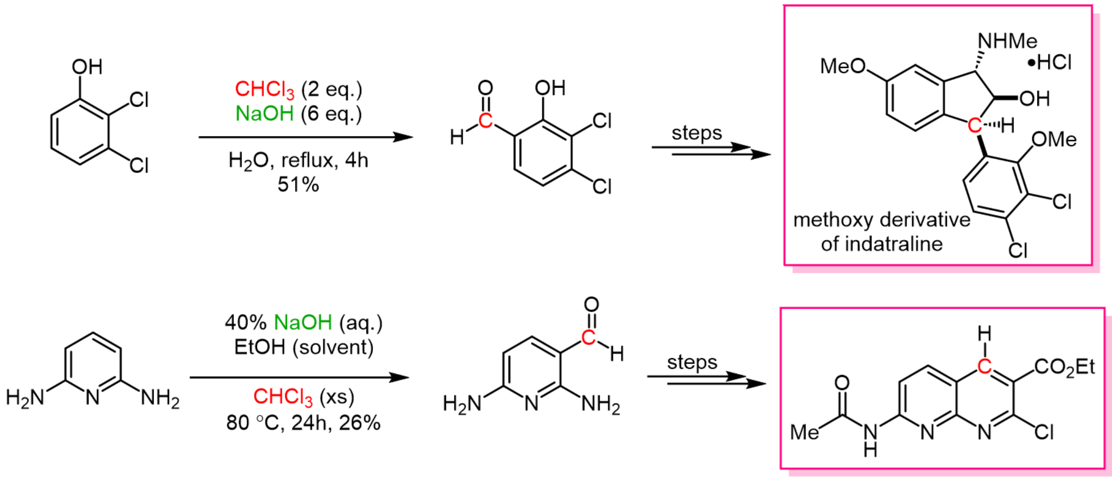
There are some other examples of Riemer-Tiemann reaction. In this case where you have a phenol with this cyclohexane which attached here in this scenario you can see the ortho product is getting as a major product. And then in case of β-naphthol also in a very similar thing happening because of β-naphthol also this is the position where the formylation is happening. Because you can see the para position actually is already have this methyl group. there is another example Riemer-Tiemann reaction of tropolone actually end up giving this this particular compound.



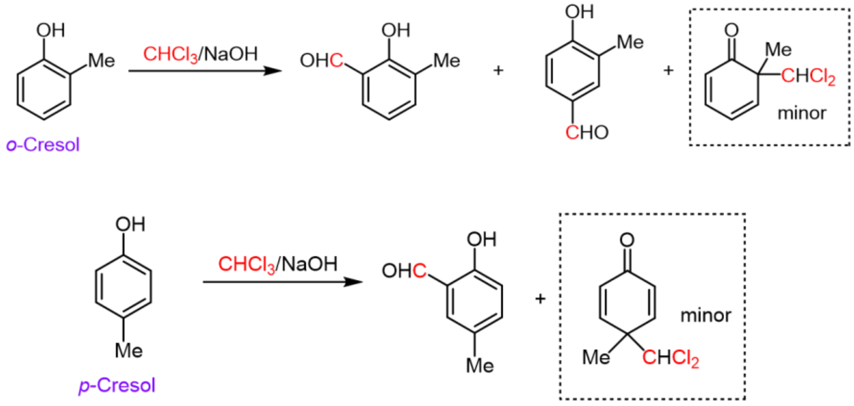




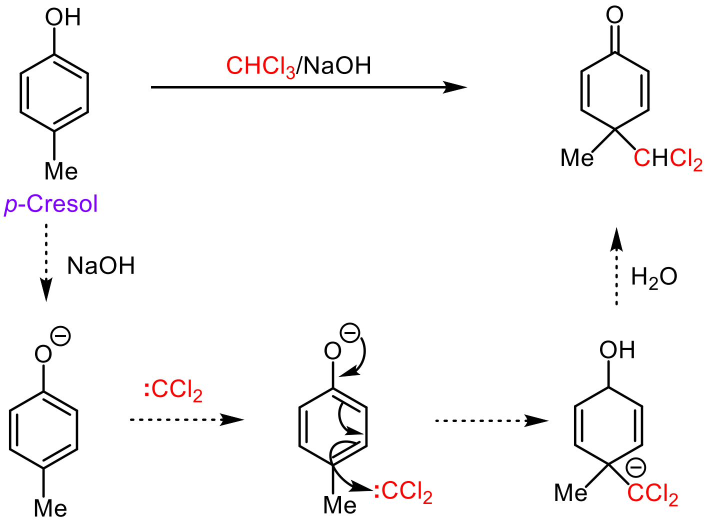
So, now we are going to learn about some of the Riemer-Tiemann reaction and its application to the natural product synthesis. So, in this reaction what is going to happen at the first you can see in this example. So, there is this ortho product which is forming as a major product in this Riemer-Tiemann condition and after the few steps it is able to convert to this corresponding natural product. There is another important example here from this starting material. once you have a pyridine where you have a amine group into that into the 2 and 6 position once you treat with this the Riemer-Tiemann condition this is getting formylation and then very important the C3 position which can further functionalize to this compound.



So, now we are going to talk about the abnormal Riemer-Tiemann reaction product. What is the abnormal Riemer-Tiemann reaction product? Because always not only it is forming this if you start with this ortho-cresol, it is not only giving you these two compound, it is also giving you this compound as a minor compound. So, what is happening? How you are getting into this compound? Also, very similar thing happening if you start with from para-cresol. If you start from para-cresol not only it is giving this product as a major product, it is giving this one as a minor product.

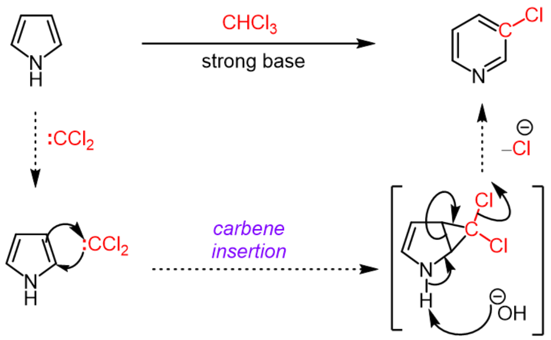


So, we going to learn about this product how it is forming? So, it can also be what you have learned at the beginning that it is taking from this ortho, but now it is coming and taking this carbene from the para position and then it is forming this type of species which after taking protonation is forming this compound. So, we are making some sort of a compound here we can see this is a quinone type compound is forming as an abnormal Riemer-Tiemann product.

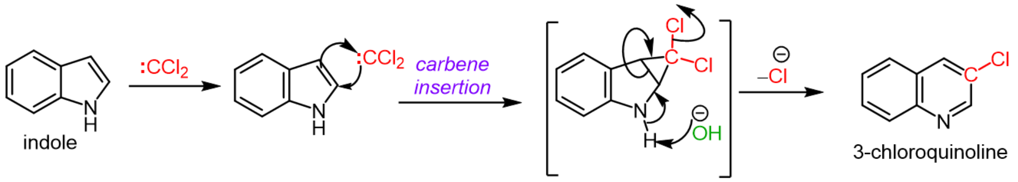


Here is another very important rearrangement reaction. So, if you see about this rearrangement very important thing happening here. starting from this type of dichloro carbene, once you react with the pyrrole. So, once you react with the pyrrole first thing is carbene insertion happening. into the olefin and then the most important thing the base can come and abstract this NH proton and then it can able to cleave this C-C bond and there will be elimination of this Cl. So, there is a ring expansion happening to form this type of 3-chloropyridine. This is a very important reaction because this is a method where you can able to introduce a substitution at the C3 position of pyridine. So, this reaction not only happen with the pyrrole you can also expand with the indole. if you start with indole first thing is the formation of this cyclopropane here with this double bond and then in presence of base it is abstracting this NH proton forming this N- which is forming this bond and then leaving of this the cyclopropane and there will be ring expansion happening to form this corresponding 3-chloroquinoline. So, again you can able to isolate a very important compound starting from a simple indole.

Reaction with pyrrole:

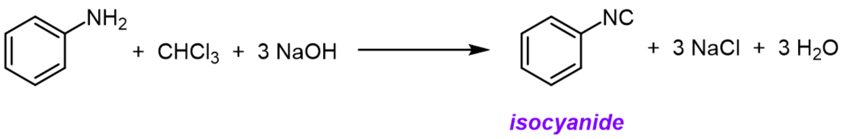


Reaction with indole:



And this reaction is really going to be very useful and nowadays also you can find in several literature of this reaction. So, now, we will talk about the carbylamine reaction another important reaction using this carbene species. So, this reaction can be also called the Hoffmann isocyanide synthesis. What is happening? from starting from aniline it is forming the corresponding isocyanide under the very similar the Riemer-Tiemann condition. So, we have learned that if you are starting from the phenol then what is happening you are getting to the formylation happening. You can get a formylation at the ortho position or you can see the formylation happening if the ortho position is blocked then the formylation happening in the para position. But here if you start with aniline then what we are end up getting isocyanide. So, you can see a completely different type of product formation happening.

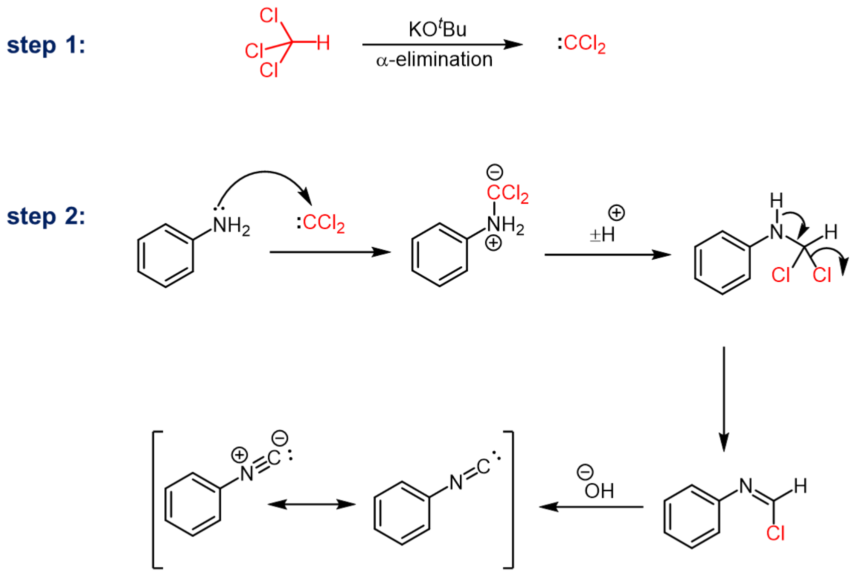
- *also known as the Hoffmann isocyanide synthesis.*
- *synthesis of an isocyanide by the reaction of a primary amine, chloroform, and base*
- *involves the intermediacy of dichlorocarbene*



So, let us try to understand the mechanism. So, first form starting from this chloroform through alpha elimination it can generate this corresponding the dichloro carbene.

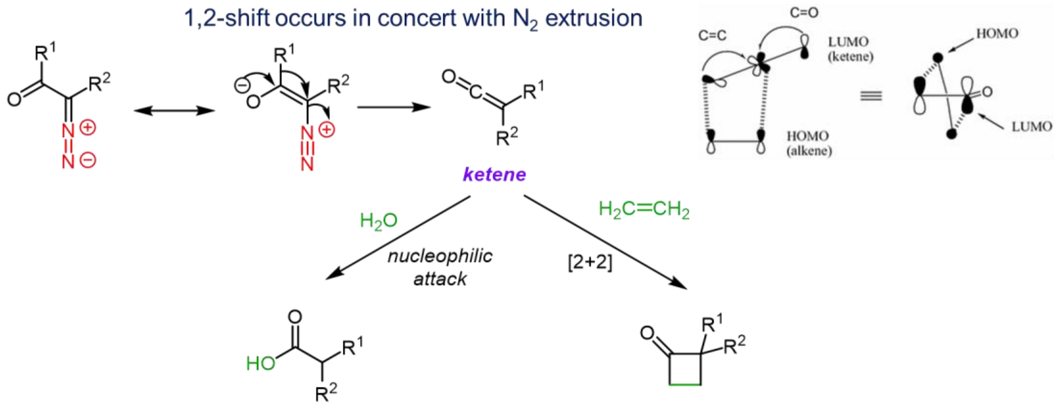
So, this dichloro carbene is now reacting with the aniline. So, what is happening? The aniline is giving nitrogen to this empty orbital and then it is forming this type of species. It can take a H^+ to get to this type of intermediate. Now, you can see you have an amine and you have a 2Cl. Now, the lone pair of N-H can give the electron density to get rid of this Cl as a Cl^-, to get to this intermediate. Now you have this nitrogen lone pair which can now give another electron density here to get you to another chlorine as a Cl^- to finally form this corresponding isocyanide So, we have learned about the formation of the isocyanide and now we are going to move to some of the important rearrangement reaction the carbene chemistry.

Mechanism:



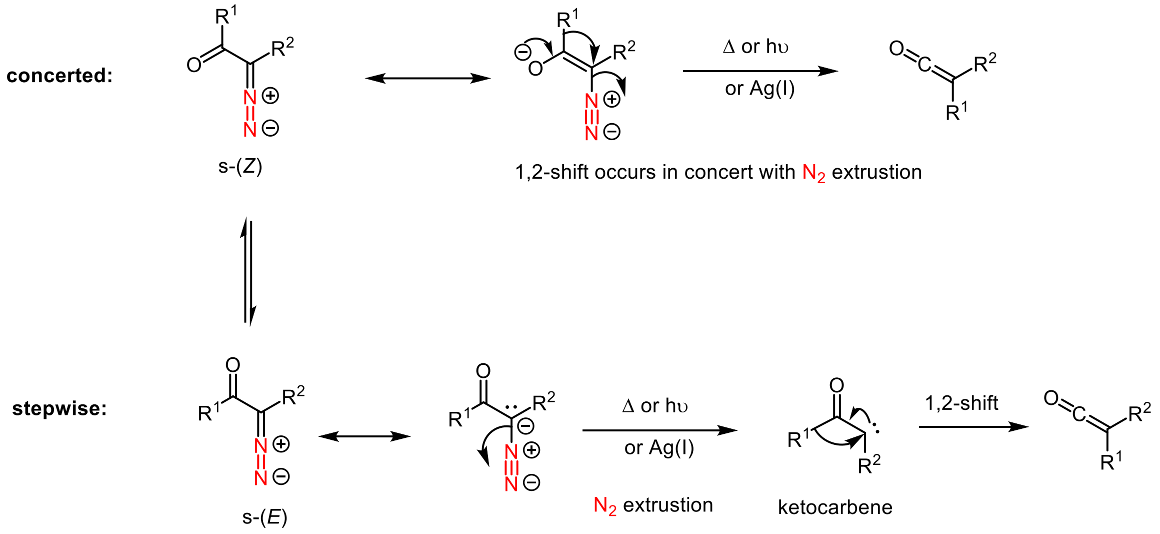
The first important rearrangement is the in the Wolff rearrangement we are going to discuss today. So, it was discovered by the Ludwig Wolff and in 1902. So, it is a thermal or photochemical rearrangement of α-diazoketone to form the ketene. So, starting from this α-diazoketone compounds it is actually forming a ketene if you see the reaction there is a [1,2]-shift of this R^1 group happening from this carbon to this carbon there is a [1,2]-shift happening to form this ketene and now once you form ketene if you treat with the water it can form the corresponding carboxylic acid if you give a olefin then it can form this corresponding [2+2] product.

- Discovered by **Ludwig Wolff** in **1902**.
- Thermal or photochemical rearrangement of α-diazo ketones to form ketenes.

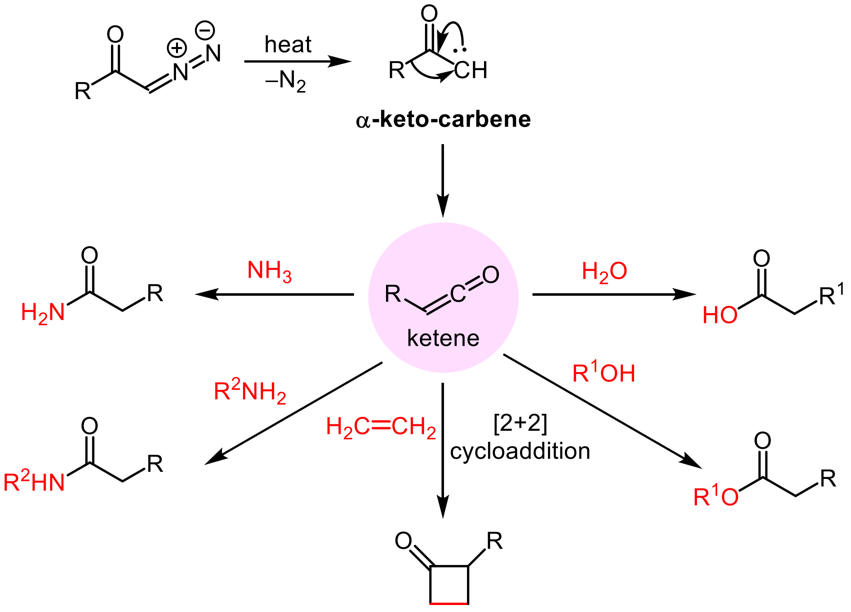


Now, there is a very important fact that we have learned that if you talk about [2+2] cycloaddition does not happen in thermal. I think you have learned in the photochemistry because if you try to bring their HOMO and LUMO next to each other then one side they will be bonding another side they will be antibonding. But if there is a ketene then this reaction is possible the [2+2] cycloaddition can happen in the thermal condition. Now, we can try to learn from here. So, if you see this molecular orbital diagram what we can see clearly here. So, this is the LUMO of this C-C bond of the ketene which is participating in the reaction can interact of the HOMO of the alkene. So, the HOMO of this alkene can participate with the LUMO of this carbon carbon bond we can see the both side there will be a bonding interaction we can see clearly here. So, these are so, this type of interactions are bonding interactions. And then also there will be interaction with the LUMO of the C=C, and then also there will be a HOMO C-O bond that can also interact with that. So, now we are going to learn about the mechanism of this reaction.

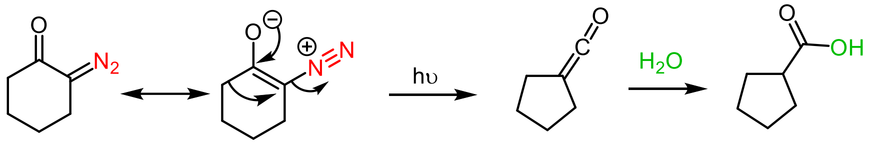
So, in general once the α-diazoketone compounds are forming it can either form as a s-(*Z*) or it can form a s-(*E*). you can see in the s-(*Z*) this R^1 and the R^2 are in the same side, in the s-(*E*) the R^1 and R^2 in the opposite side. now they are in the equilibrium. So, once you treat this in the under heat or hν or in the or in place of silver what is happening that once they are in the (*Z*) means in this particular confirmation what is going to happen now this R^1 group is in the anti-periplanar with this N_2. So, because it is in the anti-periplanar now this σ of this bond can give electron density to the σ* orbital, because the anti-periplanar this reaction goes by a concerted pathway. So, it actually goes by concerted pathway to form this ketene, but if you start this reaction from this s-(*E*). So, here that is not possible because you can see now, they are not anti-periplanar. So, what is happening first there will be release of this N_2 to get to form this α and once this α-ketocarbon is going to form now it can go for this. So, this carbon can form bond here and can go for the 1, 2 shift to get to this corresponding ketene.

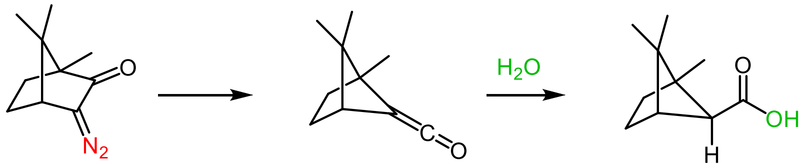


And then from the ketene once you treat the nucleophile it can go to the corresponding acid, amide based on the nucleophile you choose. So, all the example are given here. So, from ammonia it can form the amide. from the water it will form the acid, from alcohol it will form the ester and if you take the olefin it will go for the [2+2] cycloaddition starting from the α-ketocarbene.



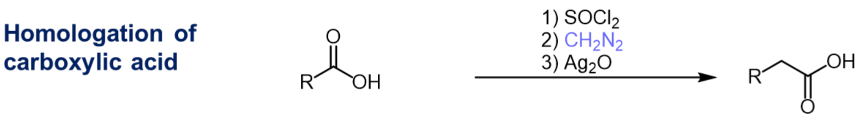
So, here are some examples here. So, starting from these have corresponding α-ketocarbene which is from the cyclic ketone. So, cyclohexanone after this Wolff rearrangement it is forming this corresponding ketene once it is treated with the water it is forming the cyclopentyl carboxylic acid. So, starting from a cyclohexanone. So, that is there is a ring contraction is happening and this can actually remember about the Favorskii rearrangement. In Favorskii rearrangement you have learned if you start with this compound α-bromocyclohexanone and using this under the Favorskii condition what is going to happen in case of base or sodium methoxide. If you remember I taught in the class you can end up making this compound. So, what is happening in this reaction? So, here also you are making ester here you are making acid, but both cases you are seeing there is a ring contraction happening starting from the cyclohexanone. There is another example here you can see after the release of the N_2 there will be a ring contraction and then once you treat with the water it will go to the corresponding carboxylic acid.

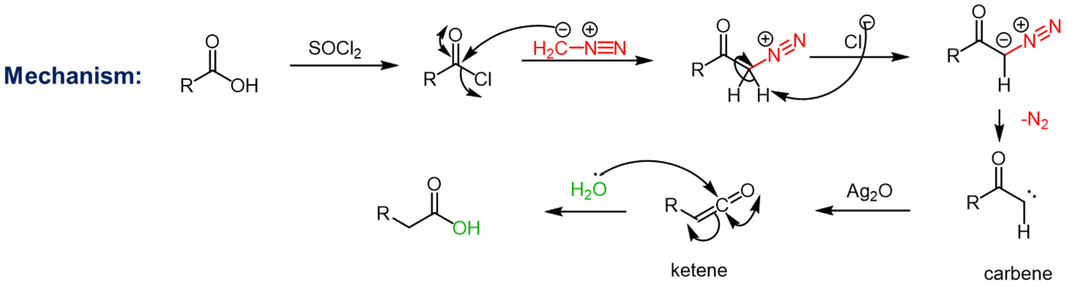


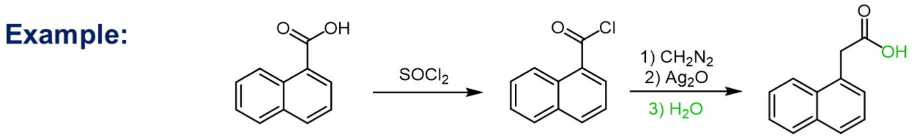


So, now I am going to talk about another very important reaction called Arndt-Eistert reaction. So, these are the very important reaction using the diazomethane. So, here what is happening using diazomethane the homologation of carboxylic acid is happening. Starting from the carboxylic acid you can see there is a new CH_2 which getting inserted. So, this is called a homologation. So, first thing you have to convert the acid-to-acid chloride using thionyl chloride. Once you treat with the diazomethane it can form this species.

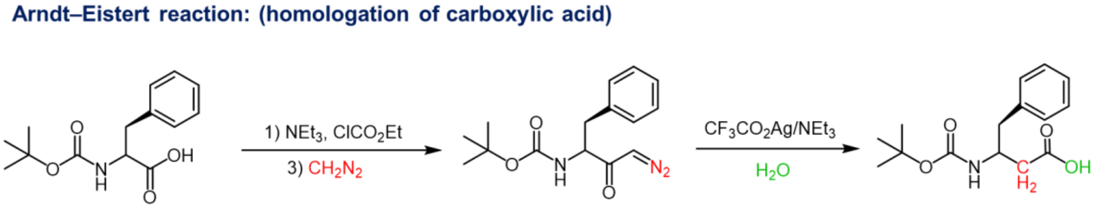
So, it can form this type of after forming this type of species. So, you can see there will be a β-ketodiazo species here which can go to from this corresponding compound once you treat with the silver oxide. Once you treat with the silver oxide there will be a N_2 release and formation of this corresponding carbene. And this can allow you to this as I mentioned previously this can allow this one to shift to get to this ketene and once you treat with the water it will form this corresponding carboxylic acid. So, from this diazomethane the CH₂ group is transferred. There is an example from starting from this acid using thionyl chloride, diazomethane and silver oxide and water it can convert to the corresponding carboxylic acid, but there is a homologation happen. So, that means there is a CH₂ group getting inserted here. So, there is an Arndt-Eistert reaction here you can see this is a carboxylic acid here.





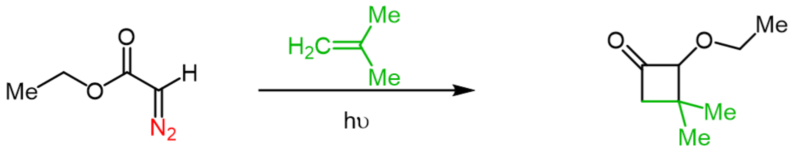


So, once you treat with this reagent it goes for the formation of this α-diazoketo compounds. So, it forms the α-diazoketo compound once you treat with the silver reagent, it is goes for the the formation of the corresponding ketene and now if you treat with the water, it will form this corresponding carboxylic acid, but this CH₂ group get inserted.

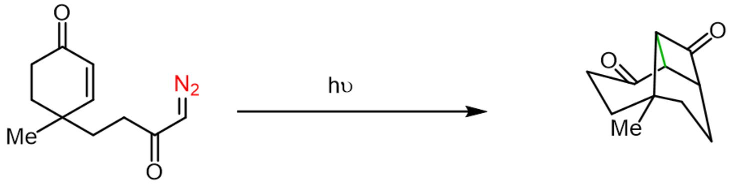


So, there is a homologation happen. Also, there are example of in the cycloaddition reaction as I mentioned that once you form the corresponding ketene from this species, it can go for the intermolecular cycloaddition reaction to form this corresponding cyclobutanone. In this species it can also form this corresponding ketene. and it can also go for a cycloaddition to form this important compound here. After formation of the ketene, it undergoes [2+2] cycloaddition to form this type of cyclobutanone here.

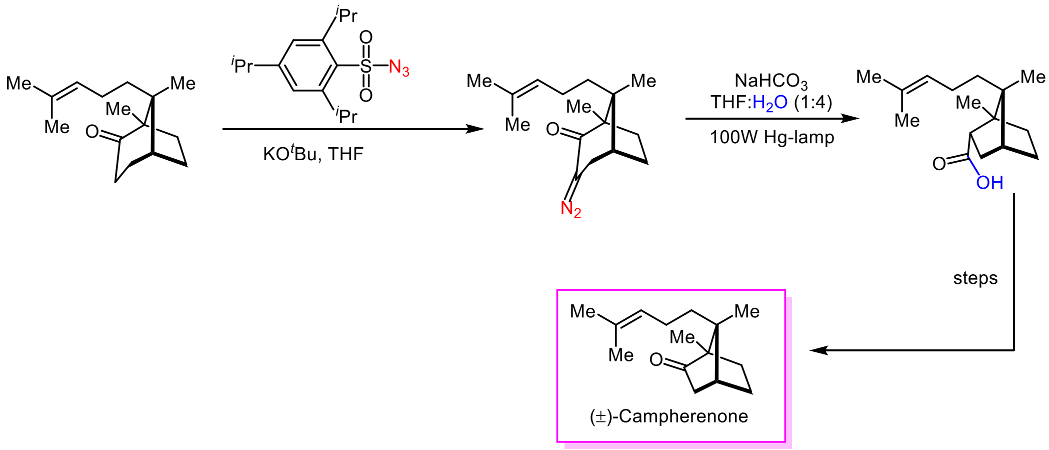
intermolecular:



intramolecular:

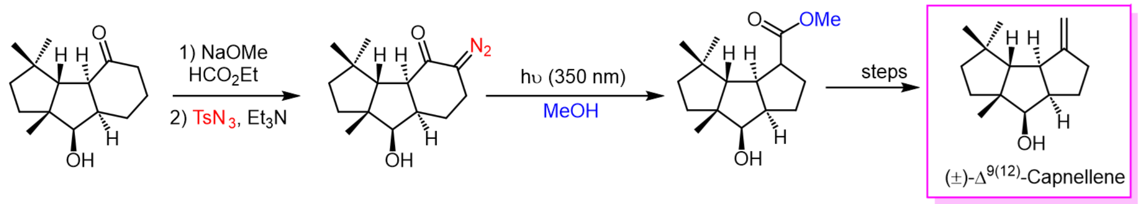


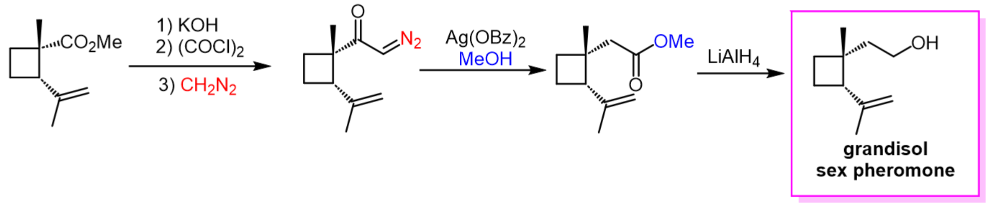
So, some of the examples of this reaction in the natural product synthesis. Starting from this compound. So, this reagent can introduce you diazo next to this carbonyl species here it can introduce a diazo. So, you have made this α-diazo compounds. Now, once you treat with the mercury lamp in presence of the water it will form this corresponding carboxylic acid which can finally convert to this compound.



(±)-Campherenone

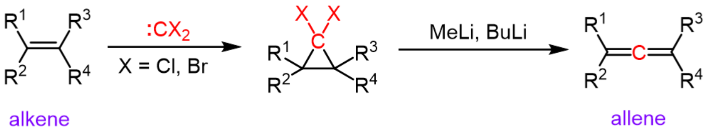
There is another important application here in in this natural product what is happening starting from this compound if you see initially, it is 5 5 6 but, in the product, if you see 5 5 5. so, there is a ring contraction is happening so now starting from this ketone once there is a formation of this corresponding the α-diazoketo compound using tosyl azide in presence of base it is going to abstract a proton from here and then form this corresponding α-diazoketo compounds once you treat with the under light and methanol it can form this corresponding ester which can further convert to this natural product. So, what is happening at the end you can see is becoming 5,5,5 because there is a ring contraction happening. In this example also similar thing is happening you can see there is formation of this α-diazoketo compounds and in presence of silver there is a homologation happening and introduction of this CH_2 group here, which can convert to this natural product after using the lithium aluminum hydride.





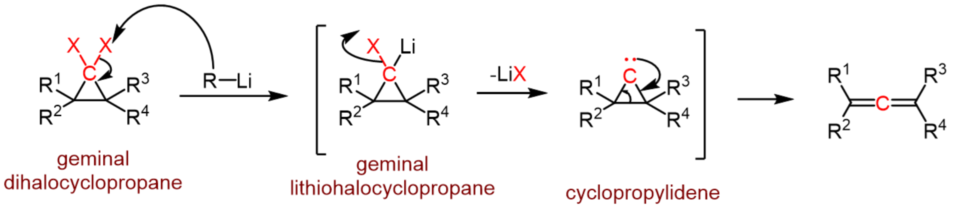
So, now I am going to talk about the the Doering-LaFlamme allene synthesis. So, we have learned about the cyclopropanation at the beginning that if you take alkene and if you take carbene it will form a cyclopropane. You have learned if you have this dichloro carbene we have learned these are singlet carbene is going to form the cyclopropane in a stereospecific manner. Now if you treat them with methyl lithium and butyl lithium then it going to form this allene. What is the mechanism here? First thing it is going to cleave this carbon halogen bond. So, there will be a metal halogen exchange to form this corresponding lithiohalocyclopropane which is forming here. Now, there is an elimination of this LiX to generate. So, there will be α-elimination to generate this corresponding carbene which going to rearrange to form this corresponding allene.

✓ *two-step one-carbon homologation procedure to prepare allenes from alkenes*

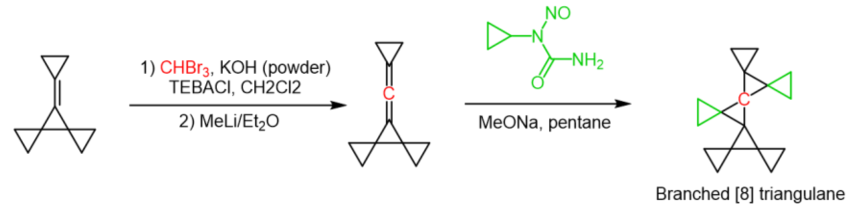


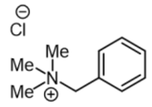
**W. Doering and
P.M. LaFlamme
in 1958**

Mechanism:

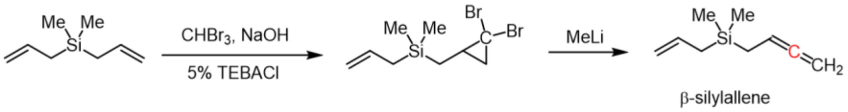


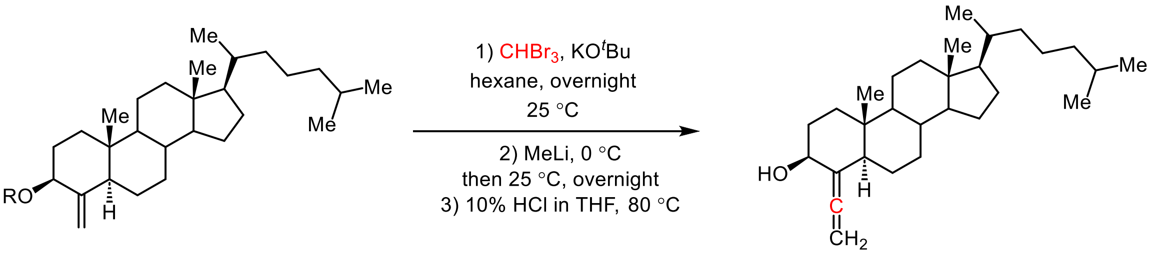
So, we are going to see some of the examples of formation of this type of cyclopropylidene. So, starting from this you can see in this type of strain compound you have this olefin here tetra substituted olefin which actually once you treat with this condition it is going to participate in the Doering-LaFlamme allene synthesis to form this allene. Now, from this allene once you try to use a reagent which can generate a cyclopropylidene means cyclopropyl based carbene now you can able to make this very strain molecule. There is another example here you can see there is an olefin here. So, that means it can participate and form this type of cyclopropane with the dibromo and then once you treat with the methyl lithium it will participate in the Doering-LaFlamme allene synthesis to form this allene. There is another example here you can see you can you have the olefin here first thing formation of the cyclopropane then once you treat with the methyl lithium it will participate in the rearrangement to get to the corresponding allene.





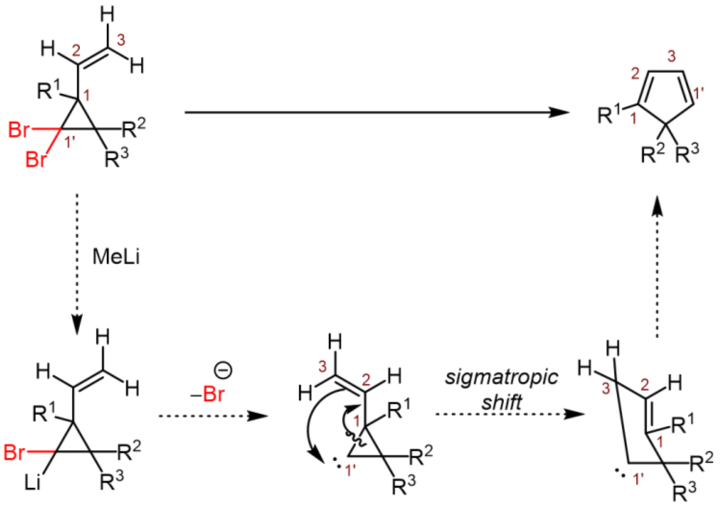
TEBACl
benzyl trimethylammonium chloride



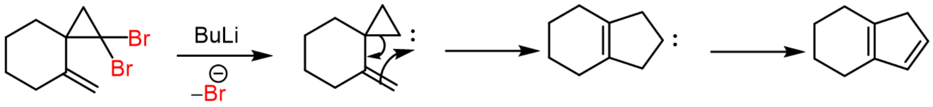


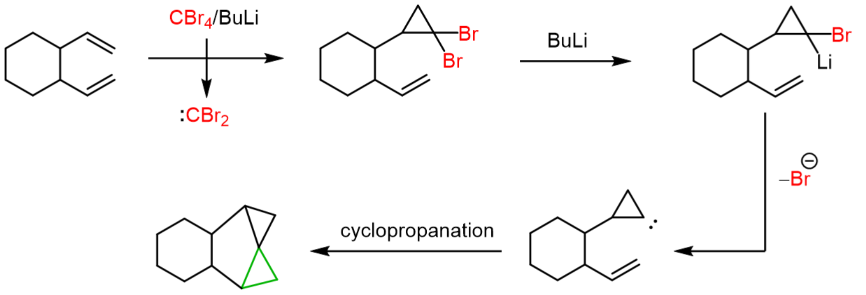
There is another rearrangement the Skattebol rearrangement. So, what is happening? This is a rearrangement of geminal dihalo cyclopropane. So, you have a cyclopropane with this dihalo, but it you have the olefin which is attached to the cyclopropane. If that is the scenario and you treat with methyl lithium. So, it is the very similar thing you have learned in the previous reaction, but here you have a extra thing is you have a olefin. Now, you have a olefin attached then what is going to happen? it is going to form this corresponding carbene up to this it is fine, but now there will be some sort of a σ-shift

- ✓ Rearrangement of geminal dihalo cyclopropane.
- ✓ Carbene to carbene rearrangement.



going to happen that means this double bond electron density going to move here to give to the electron density to the empty orbital at the same time this bond with the carbon going to get cleaved to neutralize the positive charge which is going to form on the C2 carbon which is going to form at the end it can form this type of cyclopentadiene. So, after forming this it can abstract on this CH to form the cyclopentadiene. You know there are some examples here you can see. So, you can see there is this type of cyclopropane going to form once you react with this dibromo the carbene with this type of the double bond which is here.





Now, you can see there is this allyl. So, this is some sort of allyl cyclopropane you can see. So, now this allyl cyclopropane is participating in the Skattebol rearrangement to get to this corresponding carbene which can able to go for a CH insertion. So, there will be a [1,2]- H shift you can say and at the same time it is giving electron density here to form this corresponding olefin. is another example here now you can see.

So, these are they are not allylic it is actually homoallylic. So, after formation this corresponding dibromo species treated with butyllithium it is forming. So, going for the metal halogen exchange then there will be α-elimination to form this corresponding carbene. and now this carbene is forming just cyclopropane here. So, in this part I think I talk about various different rearrangement reaction using carbene and I hope you guys liked it and there is different reference here which you guys can go through them and thank you all for coming to the class and I am going to see you guys in the next class. Thank you.