Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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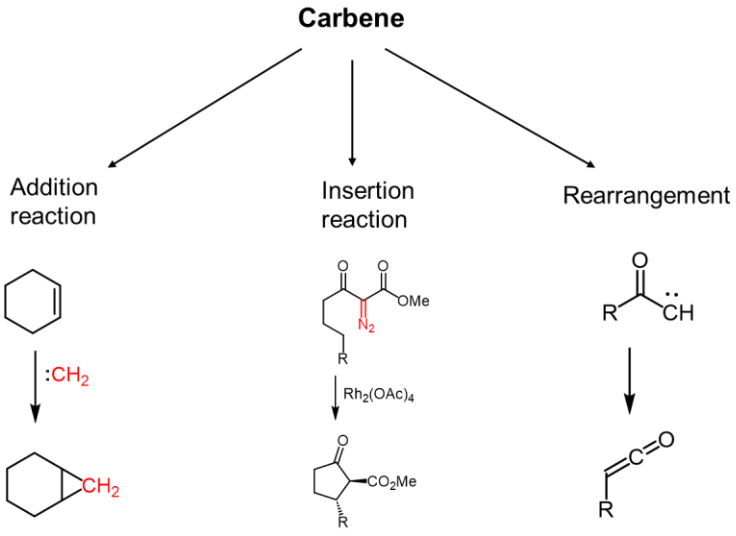
Lecture 12: Carbene

Welcome back to this NPTEL online certification course and reactive intermediates and molecular rearrangement. In the last class, I was talking about carbene, I have introduced the singlet and triplet carbene, I have introduced their bonding, their structure, some of the different reactivities. In the today's class I am going to specially focus on various different reactions using carbene. So, I am going to start with the addition reaction, I am going to show you what is the difference of singlet and triplet carbene once it adds to the olefin. Then, I am going to talk about the Simmons-Smith reaction and various different example and there are some diastereoselective reactions I am going to talk about.

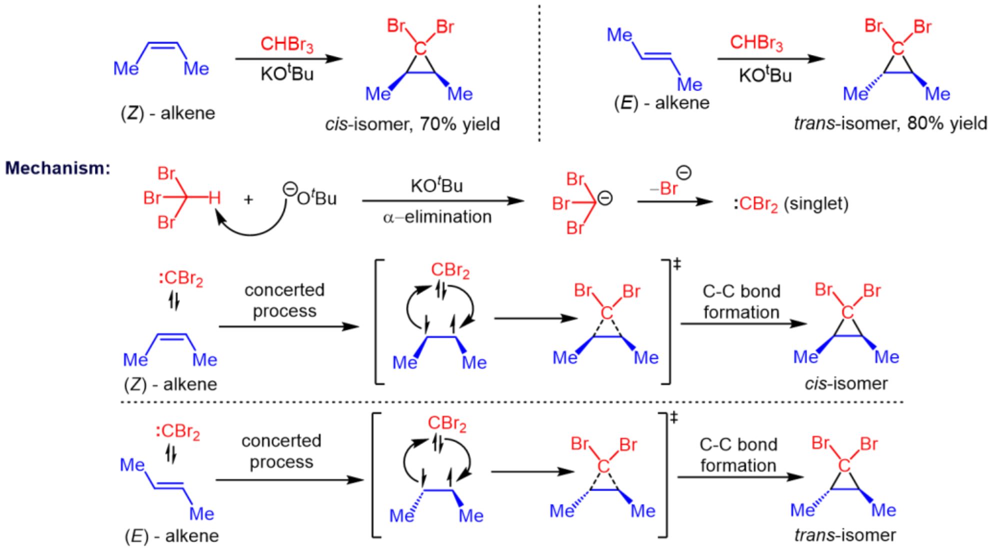
Also, I am going to talk about some enantioselective version of that. Then, I am going to talk about the insertion reaction using carbene. I am going to introduce you to the carbenoid. and carbene the metal based carbene I am going to introduce you. So, let us start with the addition reaction which you want to start.

So, in this course I am going to start with the addition first and then going to the insertion reaction and then finally, I am going to talk about the rearrangement.



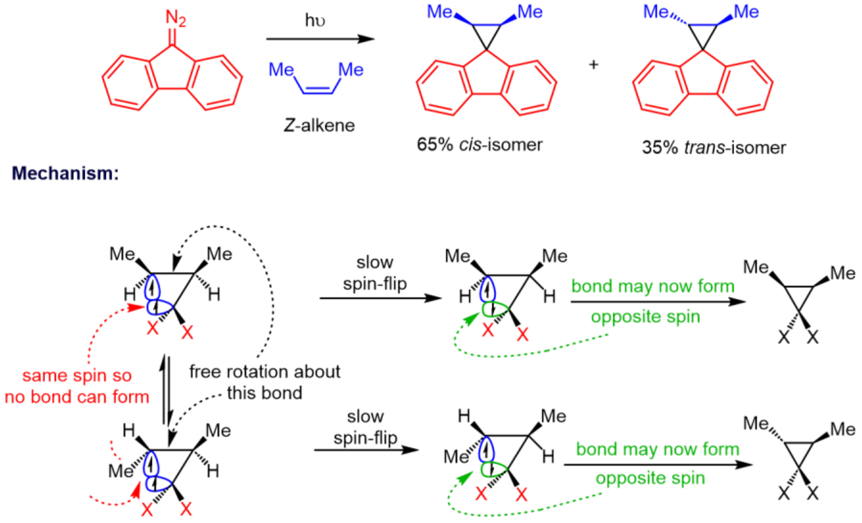
So, first thing we are going to learn that once the singlet carbene adds to the olefin, why this reaction is stereospecific?

But once this reaction happens with triplet carbene the reaction is not stereospecific. So, to explain that let us take an example here. So, here we are we are talking about generation of dibromo carbene which is generating from this from $CHBr_3$ using potassium tertbutoxide. So, using the *Z*-alkene it is giving the cis-isomer as a major product and then using the *E*-alkene it is giving the corresponding trans-isomer as a major product. So, why that is happening? So, let us try to understand the reaction first. I think the formation of this singlet carbene is well understood. I have already explained about the α-elimination in the previous class. So, after formation of this singlet carbene it is actually react with olefin through a concerted process. You can see this: CBr_2 carbene has these 2 electrons in the opposite spin and the double bond also has the 2 electrons in the opposite spin. So, they react in a concerted manner to form the corresponding product. that is why as the reaction happening in a concerted manner. So, that is why the reaction is very stereospecific giving the *cis*-isomer from the *Z*-alkene and very similarly if you start with *E*-alkene it is forming the corresponding *trans*-isomer.



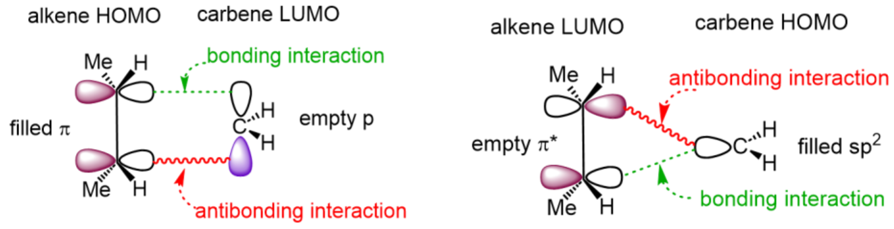
So, now we will try to understand what is happening in case of triplet carbene. So here is an example of triplet carbene, which is forming from this fluorene diazo compounds. So now what is happening? Now, once it is reacting with the *Z*-alkene, instead of forming this corresponding *cis*-isomer as an exclusive product, what is happening? It is giving 65% of *cis*-isomer and 35% of *trans*-isomer. So, now, we will try to understand what is happening in the reaction mechanism.

So, first thing is once this carbon is forming this is a triplet carbon. So, first the carbon-carbon bond formation is happening here. So, we can understand this clearly. Now, there is a problem. Now, these two electrons which supposed to form bonds are actually have a same spin. So, there is a spin flipping is required for formation of this bond. So, when the spin flipping is happening as this process is slow in the meantime there is a free rotation happening between this carbon-carbon bond. As there is a free rotation happening now this two methyl which was initially in the *cis* now they become trans after the free rotation. So, now starting from this intermediate, it can go for the spin flipping and then after that it can forms the bond to make this corresponding *cis*-isomer. At the same time, it has already this particular intermediate. From there, it can form a bond here and form the corresponding *trans*. So, because there is a spin flipping happening, at the same time, there is a bond rotation happening. So, that is giving the mixture of *cis* and *trans*.

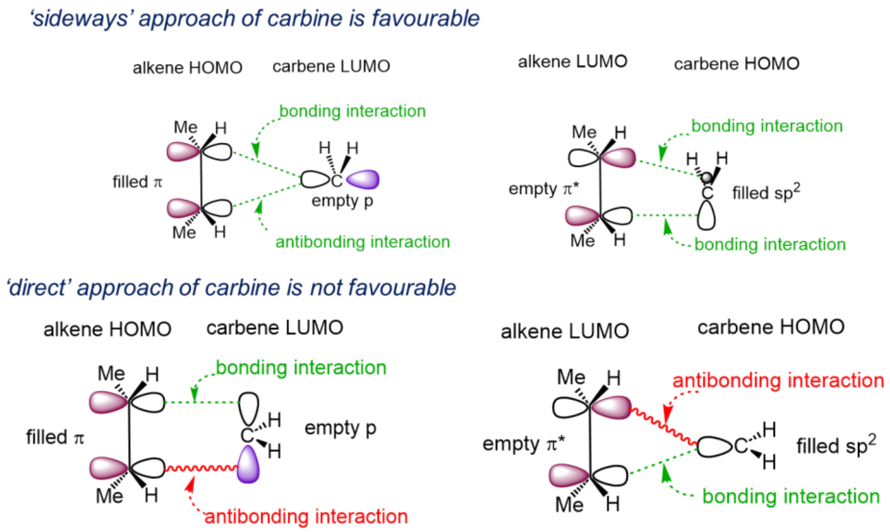


So, here we can explain them through the molecular orbital diagram. There is two different approach you can explain one is the direct approach and one is the side-on approach which you have explained here.

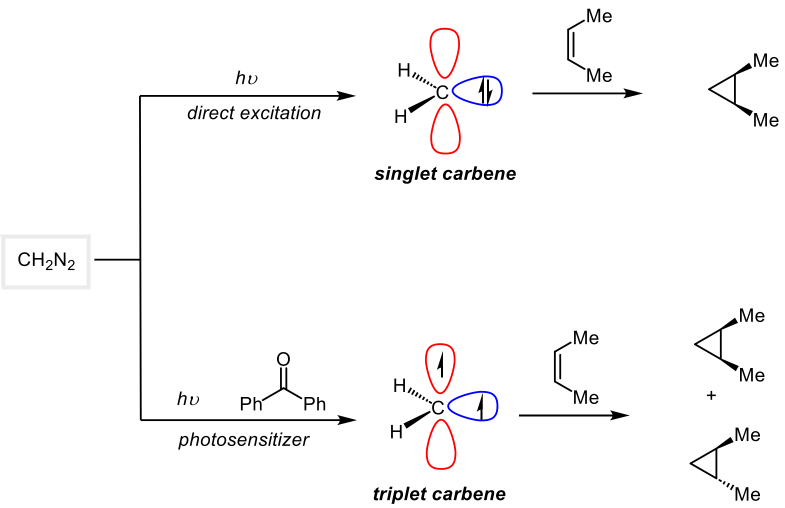
'direct' approach of carbene



So, we can explain the both of this thing in this slide. If you try to think about the direct approach which I was trying to show you in the previous slide which is not favorable because if you see an alkene HOMO and a carbene LUMO then in one case there is a bonding interaction between this, but in other side of this lobe, there is a antibonding interaction. And if you consider the alkyl LUMO with a carbene HOMO in that case also we are seeing one side there is a bonding interactions and other side there is a antibonding interaction. So, that is why the direct approach of carbene to the olefin is not favorable, but if it is go for a sideways approach that is favorable. So, what is do you mean by the sideways approach? Now, if you try to draw this carbene in a sideways approach to it is coming to the olefin. Now, in both the side it is forming a bonding. If you take alkyl LUMO and the carbene HOMO also we are seeing the very similar thing there is a bonding interaction happening.



So now I'm going to talk about the generation of carbene from diazomethane. I think I already talked about that. What is happening? Under light what is happening? It is forming a singlet carbene at the first and it is forming this corresponding product in a stereospecific manner. Once it is reacting with the olefin, but here what is happening once you use a photosensitizer like benzophenone then it is forming a triplet carbene. So, now you can see it is giving a mixture of *cis* and *trans* product. So, in the previous class, I have already talked about the generation of singlet and triplet carbene, but you can verify that by reacting with the corresponding olefin.



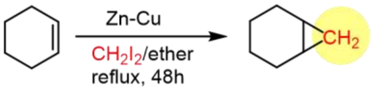
So, now I am going to move to the Simmons-Smith reaction. One of the very important reaction for the synthesis of cyclopropane and this reaction was applied for several natural product syntheses. So, using this Zn-Cu couple and then using the diiodomethane in ether it can convert this corresponding double bond to the cyclopropane.

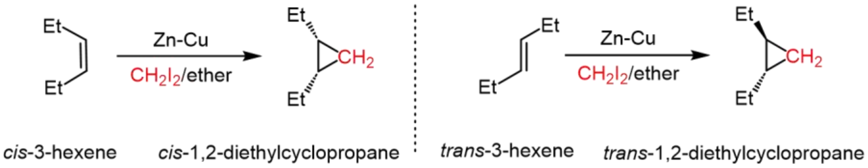
So, again what we are seeing here from corresponding *cis*-olefin. We are getting the corresponding *cis*-product and from trans we are getting to the corresponding trans product which kind of suggesting that the carbene which is forming is actually in singlet in nature.

- first reported by Howard Ensign Simmons Jr. and Ronald D. Smith in **1958**

Howard Ensign **Simmons** Jr.

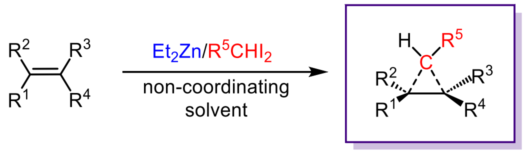
Original work:



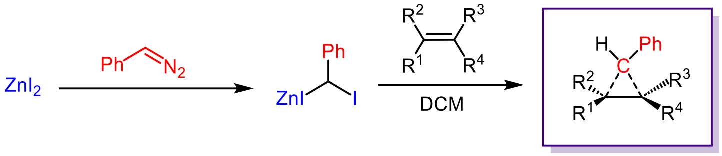


So, there is a modification by Furukawa group. So, what they found that they replace this Zn-Cu couple with dialkyl zinc. Using the diethyl zinc also this reaction is possible to convert the olefin to the cyclopropyl. There is another modification by Charette group. So, they found that instead of CH_2I_2, they can replace by aryl diazo compound. So, this aryl diazo compound can also go for the diazo decomposition and then after reacting with the ZnI_2 they can form this corresponding starting material which is a carbenoid. As you know I think I am going to discuss about carbenoid in the later slides that it is actually a carbon which has four different groups and one of them is a metal and one of them is a leaving group. So, this carbenoid now can be reacting with this olefin to form this corresponding cyclopropane.

Furukawa modification: replacement of the zinc-copper couple with dialkyl zinc

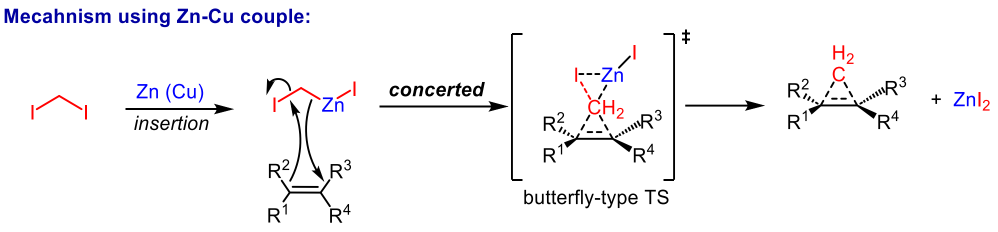


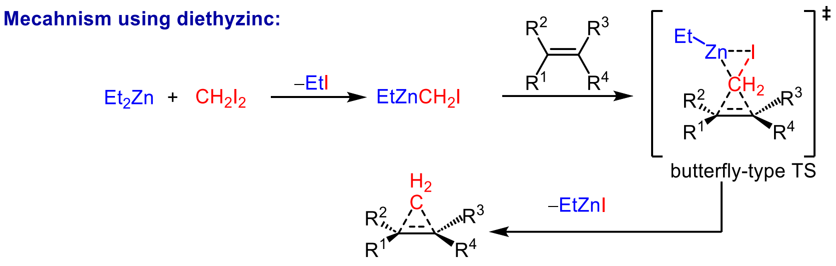
Charette modification: replacement of CH_2I_2 with aryldiazo compound



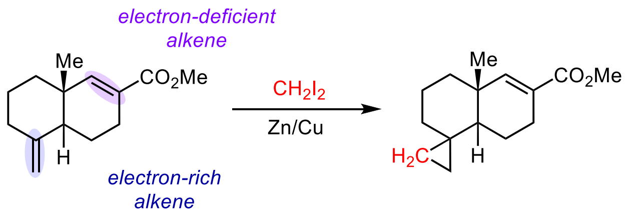
So, now I am trying to show you the mechanism of this reaction. As I said, at first this corresponding carbenoid which is going to form after the zinc got inserted between this C-I bond, then this carbenoid is reacting with the olefin.

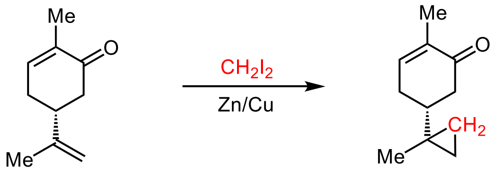
So, what is happening here literally you can see this once the Zn. So, this zinc carbon bond, this carbon has some sort of a carbanion property and it is giving the electron density to this π* orbital of this bond and at the same time there is also this carbon iodine bond is getting eliminated to form a cyclopropane. It goes by a butterfly type transition state to form this corresponding cyclopropane. Again using the dialkyl zinc what is happening dialkyl zinc react with this diiodomethane to form these compounds. So, again it is forming this corresponding carbenoid which is reacting with this olefin through this butterfly like transition state it can form the corresponding cyclopropane.



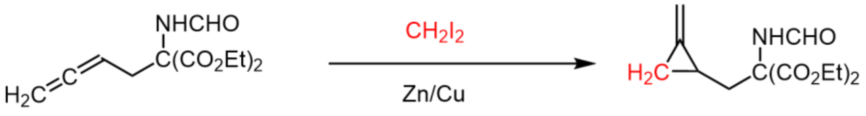


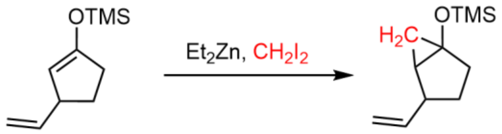
So, here is an example now we are talking about the electronics that means you have two different olefins. One is electronically deficient another is not electronic deficient. So, that is you can say electron rich. So, that means, now the reaction is happening to the electron rich one not the electron deficient one. Here is another example also very similar thing electron deficient and this electron rich. So, the reaction is only happening to the electron rich olefin.





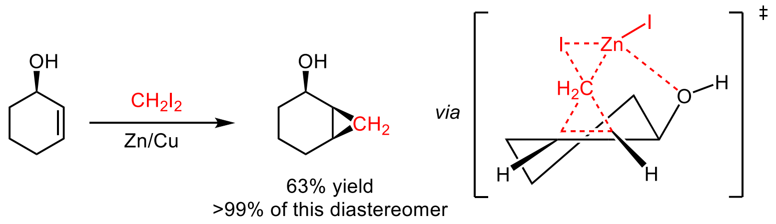
So, here is an example here we can talk about that you have olefin one is a terminal olefin, one is internal. So, this is an allene. So, now the reaction is happening to the internal one because you can see the internal one is actually has is electronically rich compared to the terminal one. There is another example here you have a -OTMS ether versus a terminal olefin. So, this is an interesting example because you can see the -OTMS group is donating electron density to this double bond. So, this is electronically rich that is why cyclopropanation is happening in this position. Of course, in this reaction there is also mixture of product forms. So, this is the major one and then there is other product where you get the cyclopropane formation happening both here and in this position as well.

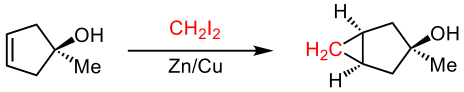


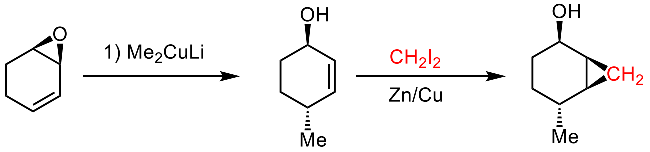


So, now, I am going to talk about very interesting things the diastereoselectivity in Simmons-Smith reaction. What is happening if you start with this corresponding allylic alcohol? This allylic alcohol, you can see this alcohol, this oxygen is actually up. So, now, this cyclopropane is forming at the same side of this -OH group. That means, the -OH group acting as a directing group for this reaction. So, it is actually coordinating with the Zn that is allowing the cyclopropanation happening to the same phase of this -OH group. So, that is why we are ending up with this product with 99% of this diastereomer is forming.

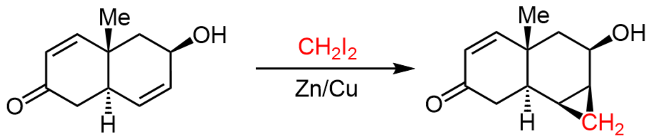
A very similar thing happening here you can see this -OH group also acting as a directing group for the cyclopropanation to happening in the same side of the -OH group. Another example here I think after opening up this epoxide, it is forming this compound, this is allyl alcohol. Again, this -OH is acting as a directing group.

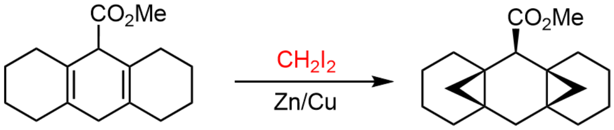


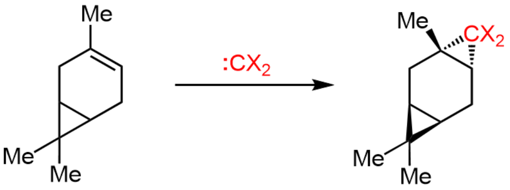




There are some more examples. Again, in this one you can see there are two different scenarios. One is α,β-unsaturated ketones that means this double bond is electronically deficient, you have another side allylic alcohol which is going to take part in the cyclopropanation and -OH is acting as a directing group for this diastereoselective reaction. There is another case here you can see this ester group can also act as a directing group to form in some sort of a bonding with zinc. So, the ester oxygen is going to form a bonding with the Zn for the cyclopropanation in the same side of the ester. There is another example here because if you have a cyclopropane here what is happening? Now the cyclopropanation is happening to the other side to avoid a steric interaction.

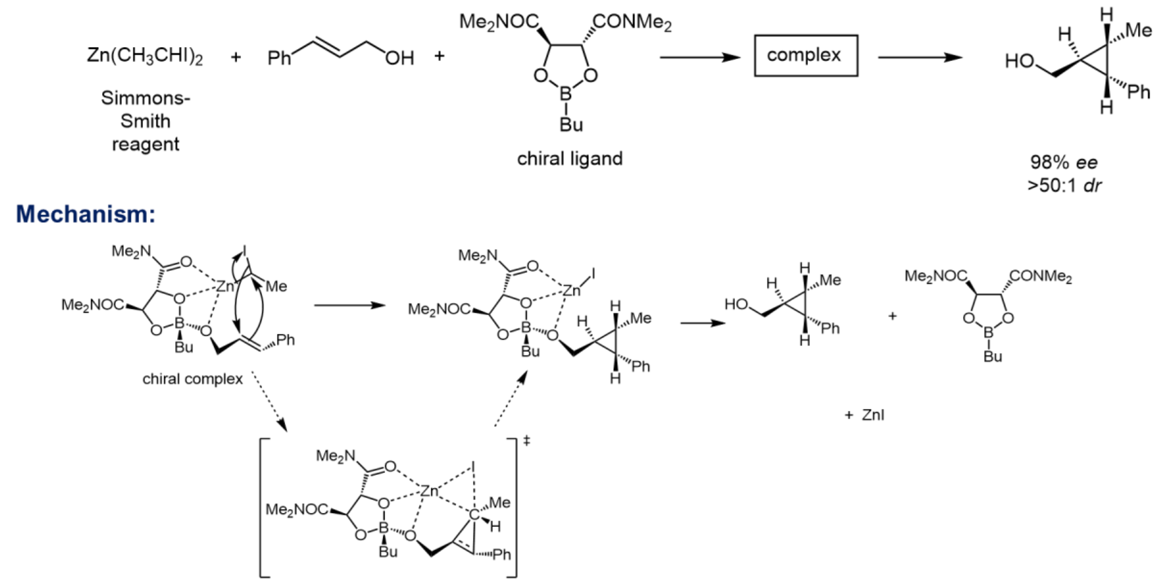






So, here is an example of asymmetric. So, I talk about the diastereoselective. Now, I am going to talk about asymmetric example here. So, starting from this corresponding allylic alcohol, they can able to get to this corresponding cyclopropane with 98% *ee* and 50:1 *d.r.* So, what is happening here?

Let us try to understand. So, you can see in this reaction the important thing is you need to use the Simmons-Smith condition with you have to use this chiral ligand. In this chiral ligand you have this boron here which is actually attached with the chiral diol. So, now, in the transition state the important thing is happening the zinc actually getting coordinated with this oxygen of this carbonyl group. It is also coordinating with this oxygen next to the boron and this allylic alcohol actually first reacting with the boron and forming this complex, then zinc is also coordinating with the oxygen forming some sort of a chiral complex because now what is happening because of this coordination this cyclopropanation is happening only one particular phase of this olefin as olefin has two different phase, but because this zinc is getting coordinated with this chiral boron. So, this cyclopropanation happening with a particular phase which is shown here to get to this corresponding product.

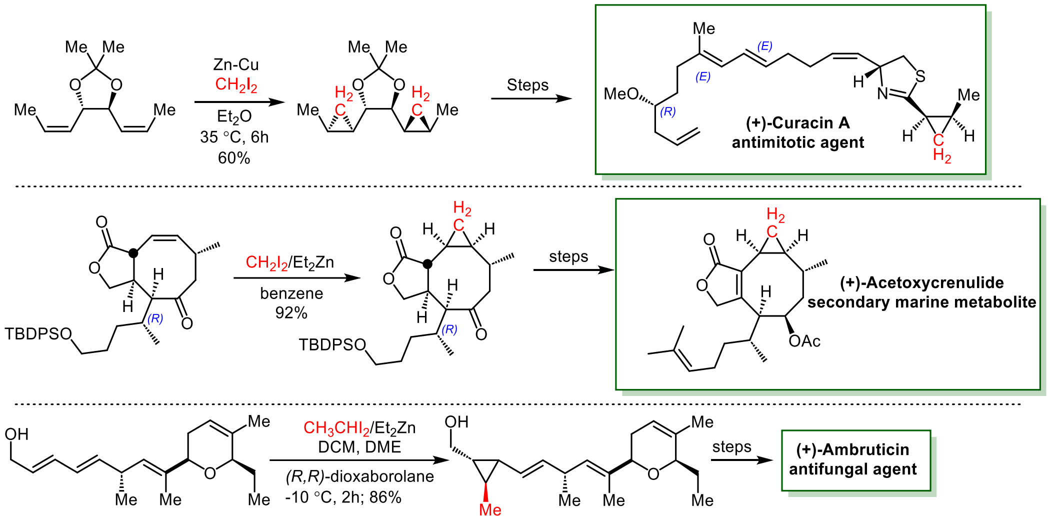


T. Wang, Y. Liang, Z. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 9343-9353

So, now some application of this cyclopropanation reaction in the natural product synthesis as I told you at the beginning you can see there are two olefins here C_2 symmetric.

So, it can form a cyclopropane first and then after some steps it can form this corresponding natural products. There is another example here you can see there is this olefin here which can form cyclopropane under the Simmons-Smith condition and then further after few steps it can form the corresponding natural products. There is another interesting example here you can see this one has several different olefins 1, 2 and 3, but now once you are using this condition where there is some sort of a coordination with oxygen going to happen with the boron. So, the boron is going to coordinate with the oxygen of this boronic ester. So, then what is going to happen then the cyclopropanation is happening selectively on that particular position because of this -OH group.

So, this is acting as directing group to activate to get the cyclopropanation selectively into this position once you conduct the reaction at low temperature. So, once you are conducting this reaction at low temperature, this type of effect is getting prominent.

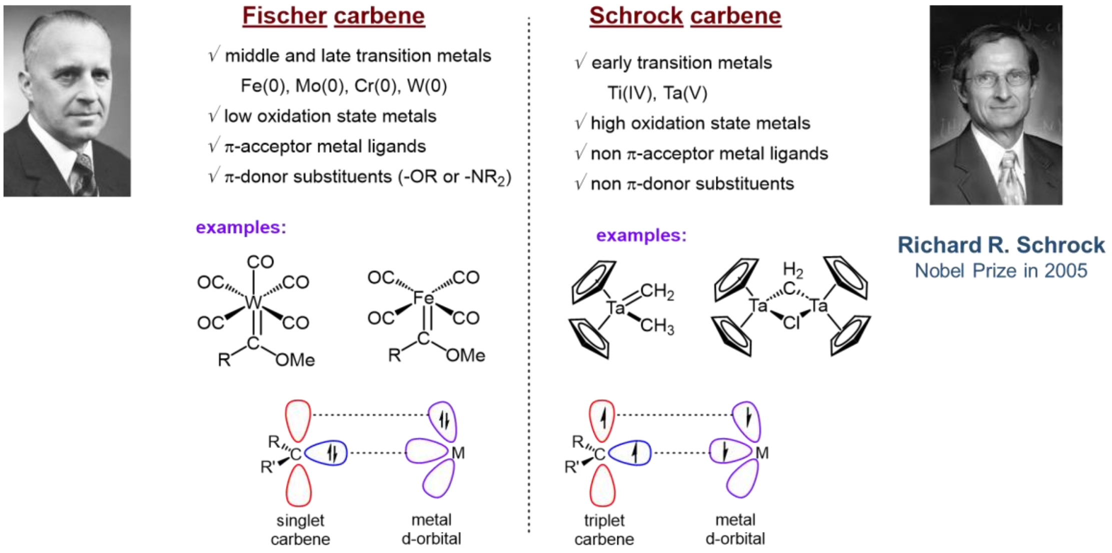


So, now I am going to briefly talk about the metallocarbene I think the metallocarbene is not part of this course there are other NPTEL lecture which is covering the metallocarbene. I am going to just briefly talk about there are two different metallocarbene one is the Fischer carbene another is the Schrock carbene. One of the important thing is that the Fischer carbenes actually are singlet carbene and the Schrock carbenes are triplet carbene.

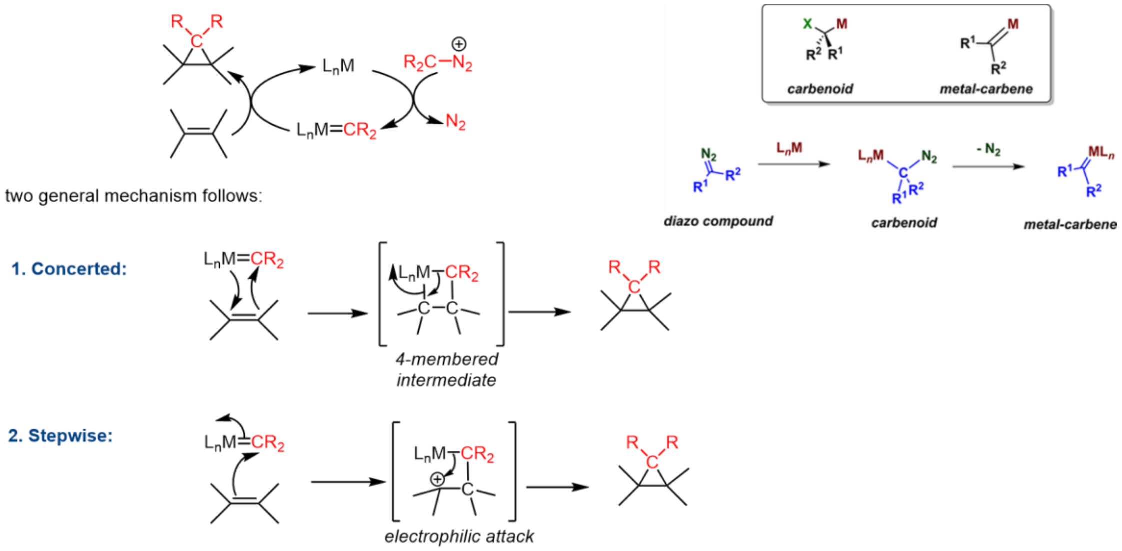
Now what type of transition metal is participating in the Fischer carbene you can see middle and late transition metals with a low oxidation state that is the other important thing. Like we have given some example here and the ligand has to be a π-acceptor that is another important thing for a Fischer carbene. I have already shown here in this diagram and then there will be a π-donor substitution.

So, this type of metal carbene complexes called Fischer carbene.

Then other side on the Schrock carbene there will has to be early transition metal with a high oxidation state and then there should be a non-π-acceptor and non-π-donor, non-π-acceptor metal ligands and non-π-donor substitution. So, they are going to form a Schrock carbene, which is also shown in this diagram. So, now I think why I have introduced you to the metallocarbene because there are lot of cyclopropanation which is done using the metal carbene.

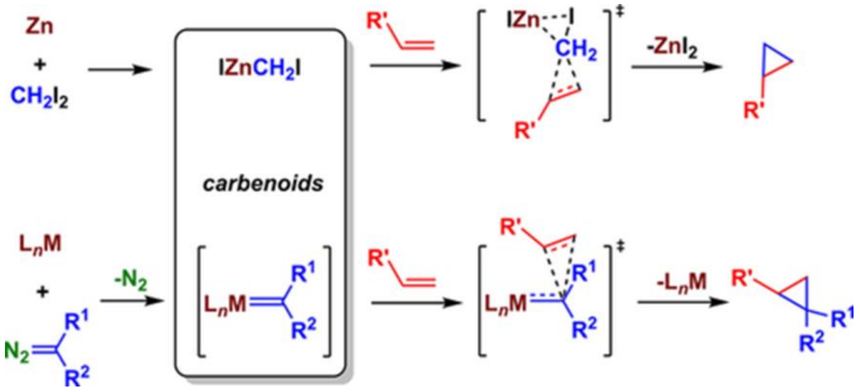


In this type of transition metal catalyzed cyclopropanation what is happen generally this diazo compounds are used. So, what is going to happen those diazo compounds are actually going to form the metal carbene which actually react with the olefin to form cyclopropane. There are two different pathway it can either go by this concerted pathway, where it can form some sort of a four member intermediate, the four member transition state. Then, it goes to the product or it can go via some sort of a stepwise mechanism to a electrophilic attack and then finally, this bond can come here and there getting out the metal to form this corresponding cyclopropane.



So, I have tried to give you an example here from the diazo compound, if you want to use this transition metals, they form the first thing called carbenoid. So, we should be careful when we say metal carbene versus carbenoid. So, these are the things called carbenoid as I said the definition of carbenoid the carbon is in tetravalent one of them is in the metal and there is a leaving group. Finally, after the N_2 extraction, it can form the corresponding metal carbene which can take part very similar to this Simmons-Smith reaction you can see this can also take part in the cyclopropanation reactions.

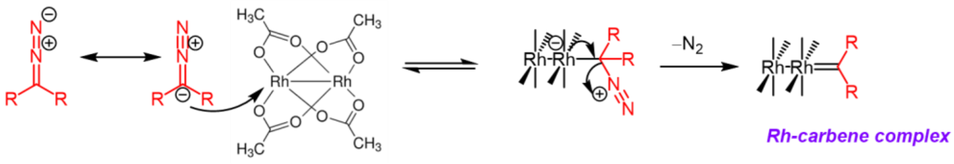
As I mentioned there are either it can go by a concerted mechanism or a stepwise mechanism to form this corresponding cyclopropane.



So, here is an example about the $Rh_2(OAc)_4$. So, $Rh_2(OAc)_4$ you have this axial position where this diazo compound can get attacked here. Then, after elimination of nitrogen, it can form this corresponding Rh carbene complex and this in Rh carbene complex can react with a olefin to form the cyclopropane.

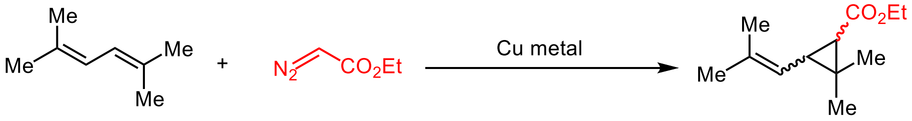
Then this can happen using the Cu very similarly it can form some sort of a carbenoid species then goes to the Cu carbene from there it can goes for the corresponding cyclopropane.

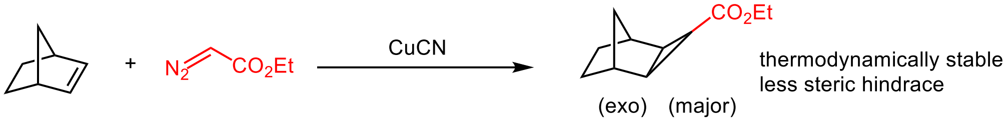
Reactions with rhodium:



Reactions with copper:

So, here is some example using Cu, you can see using copper metal it can form the corresponding cyclopropane. But the problem is in this type of reaction using Cu for the cyclopropanation using the diazo compounds, the diastereoselectivity is not very good. But here what is happening, it is forming this corresponding exo product as a major product because this is a thermodynamic stable product.

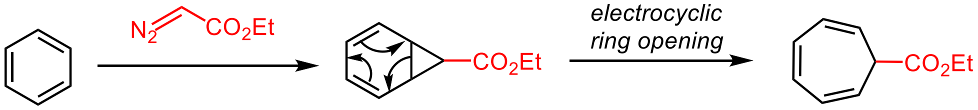


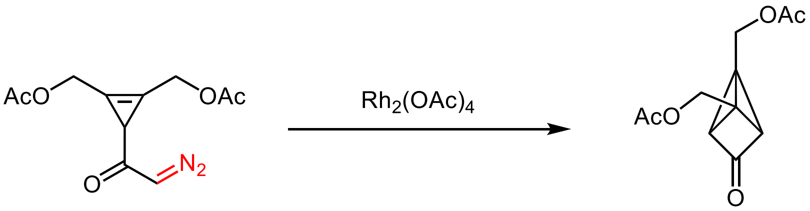


Then there are some example using the Rh.

Now you can see from this phenyl ring, it can react with one of the olefin then after that it can go for electrocyclic ring opening to form this compound which is shown here.

So, then there is other example here I think again the Rh carbene can be formed corresponding to diazo decomposition. Then there is an olefin here which can form a cyclopropane to make some sort of a strain molecule.



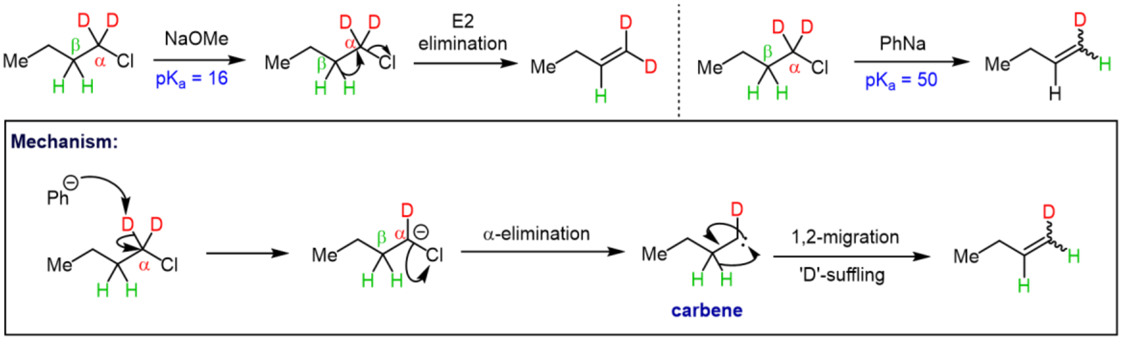


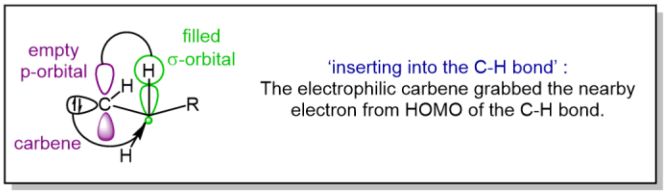
Then I am going to introduce you another important reaction of this type of metal carbene species called the insertion reaction. So, first thing I am going to explain you very basic reaction here if you see in this compound once you use the NaOMe.

Now, this proton can be abstracted for the E2 elimination it can form this particular compound. Now, instead of NaOMe if you use PhNa which have a pKa 50 then it is ending up forming this where you can see one of the D is missing in the product. Let us try to understand what is happening here.

So, once you using the strong base it is going for the α-elimination. It is getting, it is leaving this C-D bond, generating a carbanion, going for α-elimination to generate a carbene. After formation of carbene there is this C-H insertion is happening. So, we call this 1,2-migration or there is a D-suffling is happening to end up this product. We can understand this from this orbital diagram what is happening here you can see this σ-bond, this σ C-H bond is drawn here, is giving electron density to the empty orbital of the carbene. So, there is a empty orbital in the empty p-orbital in the carbene where this σ C-H bond electron density is transferred.

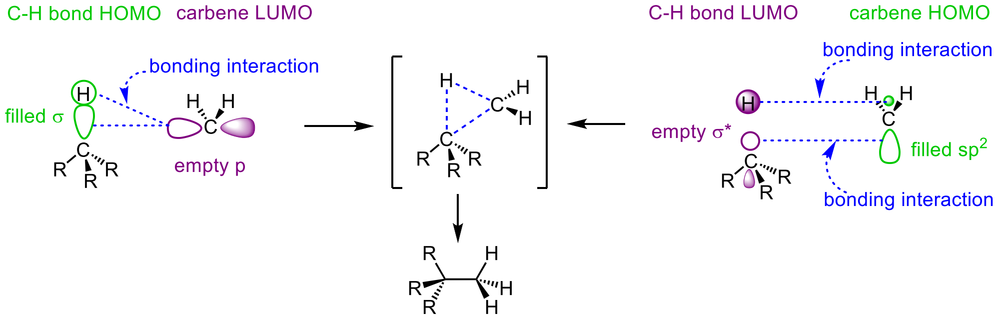
And then what is happening, at the same time there is you can see there is a filled orbital filled electron which can fil in a pair of electron getting transfer at the same time. So, once you are drawing this, you can write that way that first this bond is getting here this electron density. At the same time, this is coming back here to formation of this type of olefin.



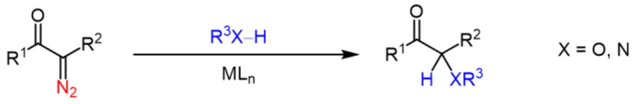


'inserting into the C-H bond' :
The electrophilic carbene grabbed the nearby electron from HOMO of the C-H bond.

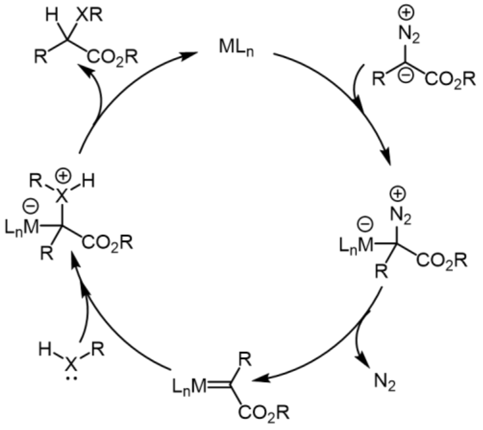
So, again we are explaining that there this type of reaction what is happening this is a C-H HOMO and then the carbene LUMO and you can see in the both cases there is a bonding interaction happening here. Also if you start from the C-H LUMO and the carbene HOMO also we observe there is a bonding interaction. Once they are interacting in a sideways overlap to form this. So, after the C-H insertion it can form this type of corresponding product.



So, here is an basic example that if the transition metal based carbenes was used then you can see here first thing is the diazo decomposition happening and the generation of the transition metal based carbene. So, after it forms, this is a carbenoid then N₂ release formation of the transition metal carbene. Now, this X-R, it could be any type of heteroatom which can interact with this the metal form from this type of transition state from there it can goes to the product and the metal goes back to the system again.

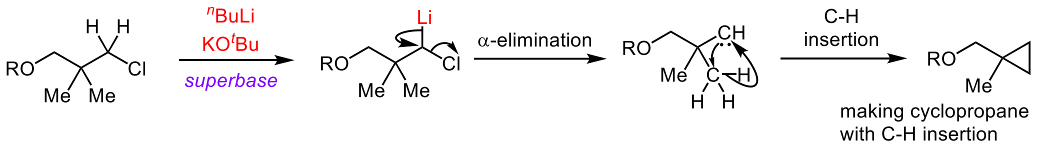


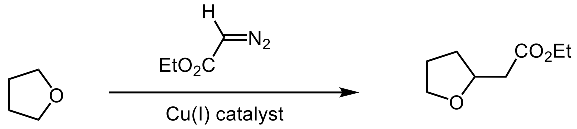
General mechanism for X-H insertion:



There is an example here first thing we can see there is a C-H insertion happening. So, first thing again generation of corresponding carbene here, after the α-elimination, it can take this proton from this methyl group to form this corresponding cyclopropane.

We can see another example here using this type of THF, then using this diazo compound and the Cu catalyst. So, again there is a insertion happening of this C-H bond is getting inserted to form this corresponding product, which is actually next to oxygen.



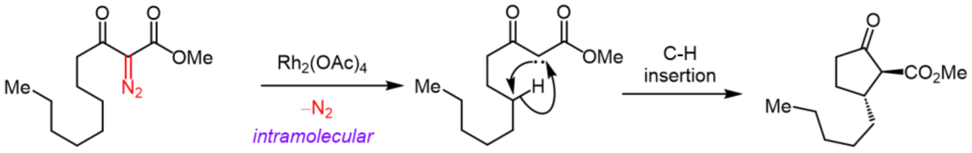


So, now, we are going to talk about a intramolecular version here. So, now, once this intramolecular C-H insertion happening, one of the important fact here, they are end up with this particular product where this ester and these groups are actually trans. So, now we try to understand why this insertion getting favorable and forming this trans product.

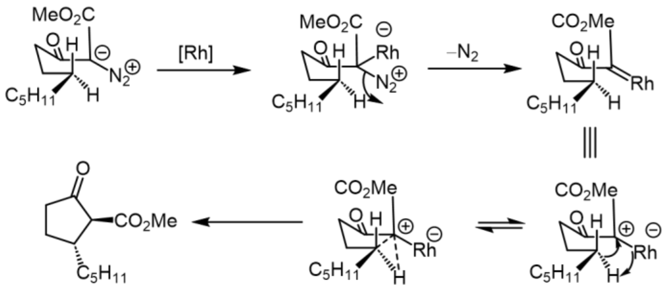
To understand that we have to go to the corresponding transition state where this reaction is happening. So, after the formation of this corresponding carbenoid which is here after the N_2 expulsion happening, is forming the corresponding Rh carbene.

Now you can see in this transition state where this C-H insertion is taking place, this ester group and this group, this two bulky group not going to be in the 1, 3-diaxial position. They will try to be in the *anti*-position so that they do not have to face some sort of 1,3-diaxial interactions.

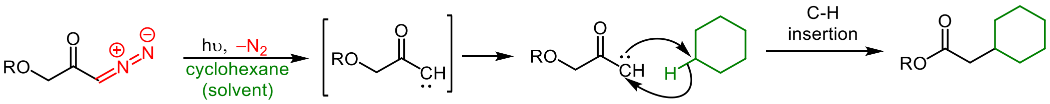
To avoid that you can see these groups and these groups are in the opposite side which end up giving the product as a trans.



D. F. Taber, K. K. You, A. L. Rheingold, *J. Am. Chem. Soc.* **1996**, *118*, 547-556



So, now the question comes in this reactions if you do not have a anything else, suppose you have a solvent in the medium. Now, once this type of carbene is formed, these are very reactive, it can take the solvent molecule. So, C-H insertion is happening in the cyclohexane to get to this type of product.

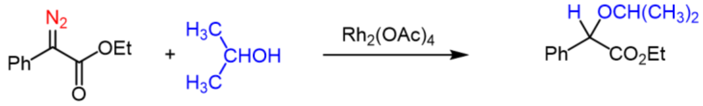


so reactive that it react with solvent molecule
if no other reagent is present

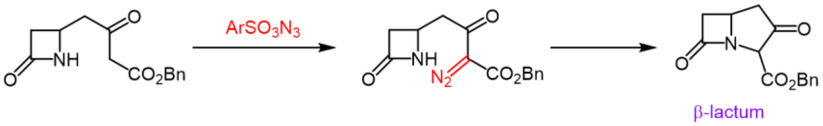
Now, we can see this type of reaction can also happen with the alcohol. Once you take the alcohol and then once you take this corresponding diazo compound.

In case of Rh catalyst again it forms the corresponding Rh carbene. So, I have talked about this oxygen lone pair can give electron density there and then finally, it can form this corresponding product. There is a N-H insertion happening here after forming of this corresponding diazo compound once you treat with the Rh catalyst. What is happening? Again you can see this nitrogen has a lone pair which can give electron density to this corresponding the Rh carbene and then this minus can catch this H to form this corresponding β-lactum.

- **O-H insertion reaction:**



- **N-H insertion reaction:**



So, in this particular part I think I started with talking about different type of reaction.

So, initially I start talking about the formation of the cyclopropane and then I was talking about the Simmons-Smith reaction. I talk about the diastereoselective version; I talk about if you use a chiral ligand then you can also make this reaction enantioselective. Then after covering that part I also moved and talk about what is called the metal based carbene and the carbenoid. I introduce the terminology and then I explain some cyclopropanation using transition metal and then also talk about some more example of the cyclopropanation and then some C-H insertion reaction. In the next part I am going to talk about some of the rearrangement reaction done with carbene. So, thank you all and you know thank you for coming to the class.

Thank you.