# Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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## Lecture 14: Carbene

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. In the previous class, I talked about carbene, I talked about various reactions in carbene, I talked about the addition reaction and the insertion reaction. And in today's class, I plan to talk about several other reactions using carbene. So, I am going to start with the generation of carbonyl ylide, and then I am going to talk about the generation of sulfonium ylide. then I am going to talk about N-heterocyclic carbene and briefly talk about Grubb's catalyst because, as you can see, metal carbene is not part of this course, and then also briefly talk about the metathesis reaction as well. And then, at the end, I am going to talk about some of the questions from the previous exams, ok? So, the first thing I am going to talk about is the generation of this ylide species.

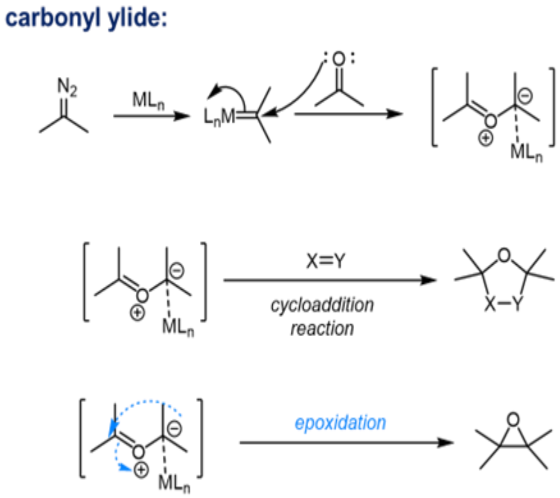
So, what is happening, I think, is the generation of carbonyl ylides. So, we have learned in the previous class that from the diazo compound, once you take the transition metal, like rhodium tetra acetate or copper, you had seen that it generates carbene species. So, how it is forming? I think I have already told you about this, that it is going to form a species like this. So, it has a metal, then there will be $N_2$ going to get out from here.

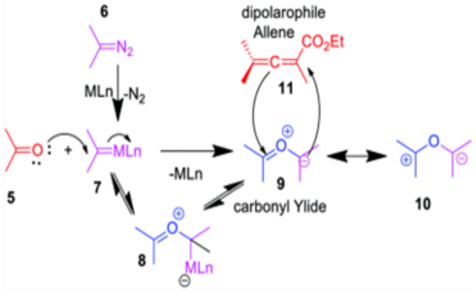
which will end up generating this type of species. So, we call this species as a carbenoid. So, this species is carbenoid I think I explained this in the last class, and these are called transition metal-based carbene. So, what is going to happen? Now, the oxygen lone pair is going to attack here, and then it generates an ylide species, called carbonyl ylide. In the carbonyl ylide, if you see a lot of places people do not write this $ML_n^-$ here, people just write like just a plus and a minus.

But if you see in the literature, this metal is, attached in this stage. After the reaction was done, the metal gets out of here and gets back to the catalytic cycle. Once, it forms this ylide, you can now see this act as a 1,3-dipole type of system. So, it can participate in a cycloaddition reaction with olefin ok. So, it will be a [3+2]-dipolar cycloaddition going to form this above 5-member ring.

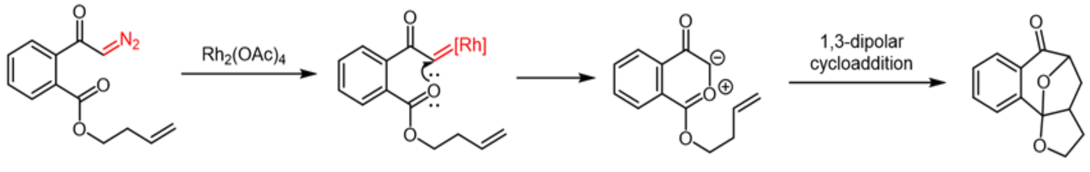
It can also participate in the epoxidation reaction if you do not have olefin here; it can attack here and then form a corresponding epoxide. So, everything you know, a very similar thing is that from this diazo compound, it is forming this tungsten metal-based carbene and then it attacks the carbonyl group. So, here we are showing some sort of cycloaddition using the allene ok. So, now I am going to show you some examples of it. You can see this is an α-keto diazo compound, in the presence of rhodium tetra acetate, it forms this corresponding metal-based carbene.

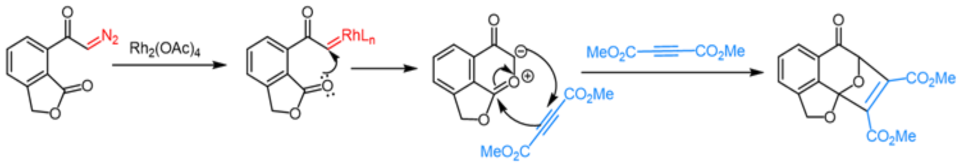
which can get attacked by this carbonyl oxygen lone pair, which ends up generating this 1,3-dipole, which can participate in a 1,3-dipolar cycloaddition in an intramolecular fashion. So, as you can see, these two fragments can come together to form this corresponding product.





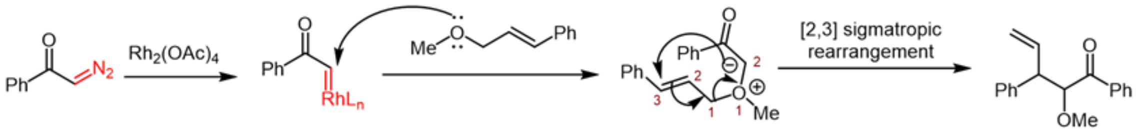
There is another example here, and here also you can see it is in this α-keto diazo compound form, the corresponding carbene, and then this carbene is getting attacked with the oxygen lone pair formation of this 1,3-dipole. Then the reaction with this alkyne with two electron-withdrawing groups forms the corresponding product here. So, then there is another example here.

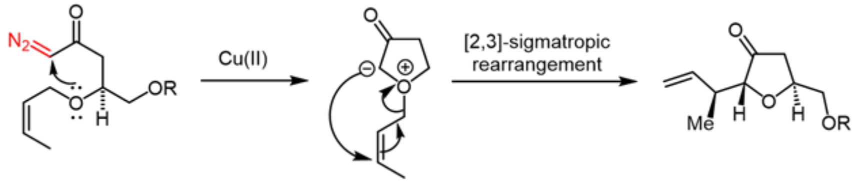




I think this example is interesting because here the first thing is that starting from this corresponding α-keto diazo compound, the formation of this rhodium-based happened. Now, getting attacked by this oxygen lone pair of this -OMe group. Then, in this particular transition state, what is happening? You can see the generation of this in a negative charge here, which is allowing a 2,3-sigmatropic rearrangement. So, instead of a cycloaddition, once it is attacking, it is going to generate a negative charge. So, now this negative charge can attack here, and then the double bond can move here and cleave this C-O bond.

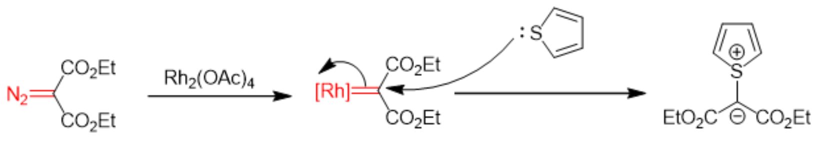
So, via 2,3-sigmatropic rearrangement, it is going to form this product. There is another example here using copper instead of the rhodium. I think I have already discussed that also the generation of the corresponding carbene transition metal based carbene species in the previous class. Here also what is happening? At the beginning, there will be a generation of metal-based carbene. which is getting attacked by the oxygen lone pair here to generate this ylide species, that will participate in this 2,3-sigmatropic rearrangement. And then the cleavage of this C-O bond will generate this compound.

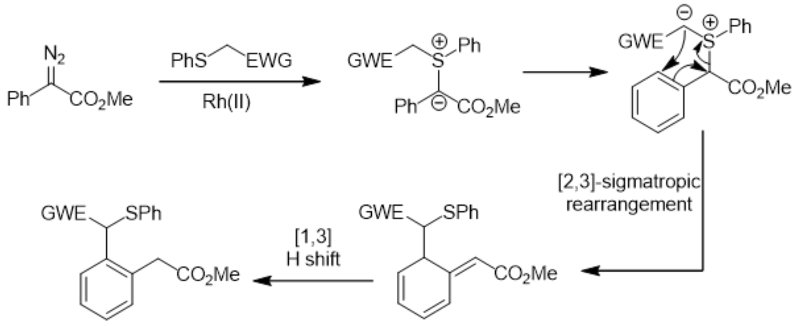




Now, I am going to talk about sulfonium ylide. So, what is going to happen here? Again, you can see using this type of diazo compound here, using the $Rh_2(OAc)_4$, it can form the corresponding carbene species, which is going to attack with this thiophene. The sulfur has a lone pair here, which is going to get attacked here.

.And then it will form ylide species here. Once it forms the ylide species, it can undergo several different transformations. Some of the examples are given here; starting from this particular diazo compound, it is forming this this compound. Now, once you have electron-withdrawing group here, the negative charge moved in this position, which will allow this 2,3-sigmatropic rearrangement. The negative charge is attacking here this C-S bond is getting cleaved once the C-S bond is getting cleaved now you can now get to this type of intermediate, which happening here, is a 1,3-hydride shift so this is shifting here. And form this corresponding product.



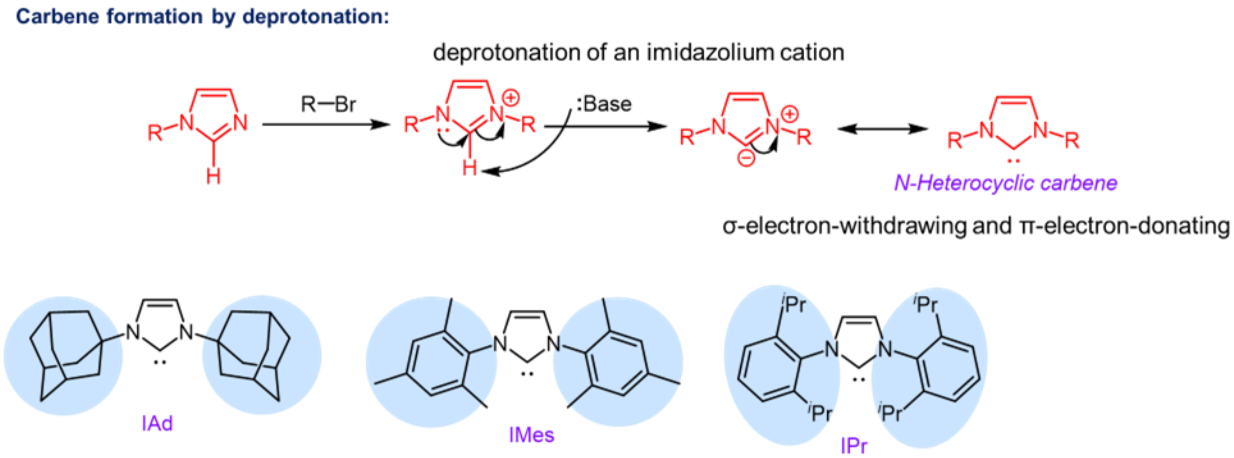


So, these are very interesting reaction you can see starting from this diazo and then in the tungsten metal and then using a carbonyl compound or a corresponding sulfur analog you can able to do this type of cool rearrangement I think professor Padova group actually developed this type of chemistry. And, there are lot of development in this area. So, there are a lot of different cycloaddition reactions done with this type of ylide. So, now I am going to move to this N-heterocyclic carbene.

You have seen at the beginning when I was talking about the isolation of a stable carbene. I think I talked about the Arduino carbene, which was isolated, and can be stored. So, those were the things I was talking about at the beginning, and if you remember, I was talking about how the NHC has two adamantyl groups. So, that the NHC cannot able to dimerize. So, now I am going to talk about about this N-heterocyclic carbene.

Of course, I cannot spend too much time, but I just briefly talk about how they form, what are the different types and how this N-heterocyclic carbene is stable. So, you can see in the first example it is the deprotonation of imidazolium cation. So, you are generating this imidazolium cation by the alkylation, and then what is happening now? It is the abstraction of this C-H. So, once this deprotontation is happening, that is generating this N-heterocyclic carbene. So, one of the important facts about the N-heterocyclic carbene that it is σ-electron withdrawing and π-electron donating.

So, you can see I think I have already gone to explain the same thing in the in the next slide through the you know molecular orbital ok. So, there are various type of bulky group you can see. So, those bulky groups kind of stop it is going for making as a dimer. So, there are you can use this 2, 4, 6 trimethyl. It could be a 2 and 6 position the isopropyl group here, ok. So, there are lot of variation in this type of NHC carbene.



I have tried to put some of the variation here. You can see I already talked about this one at the beginning. Now, you can see it could be imidazolylidene, that means you do not have this double bond here. And, then there are several variation issues of the nitrogen, it could be nitrogen in one side, then the other side will have oxygen or sulfur, so that could be thiazolylidene or oxazolylidene. And, then there is other variation of carbon variation here also.

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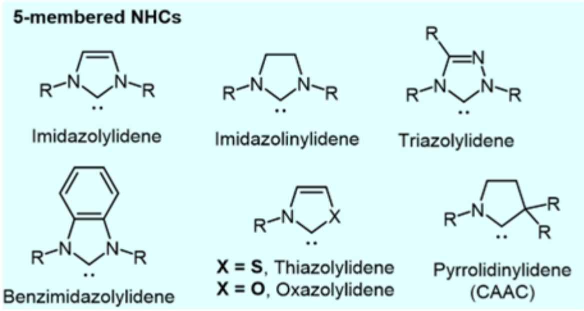
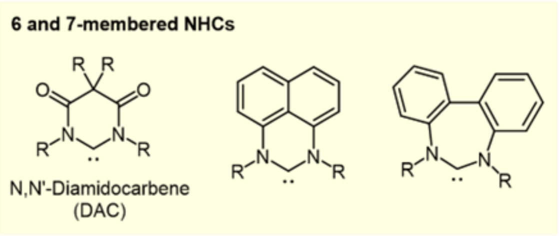
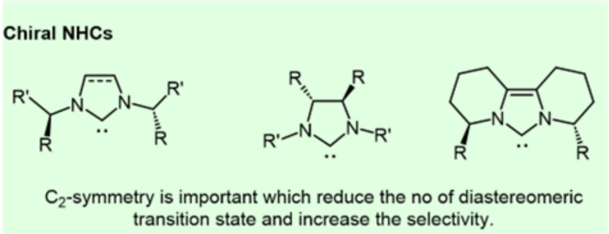






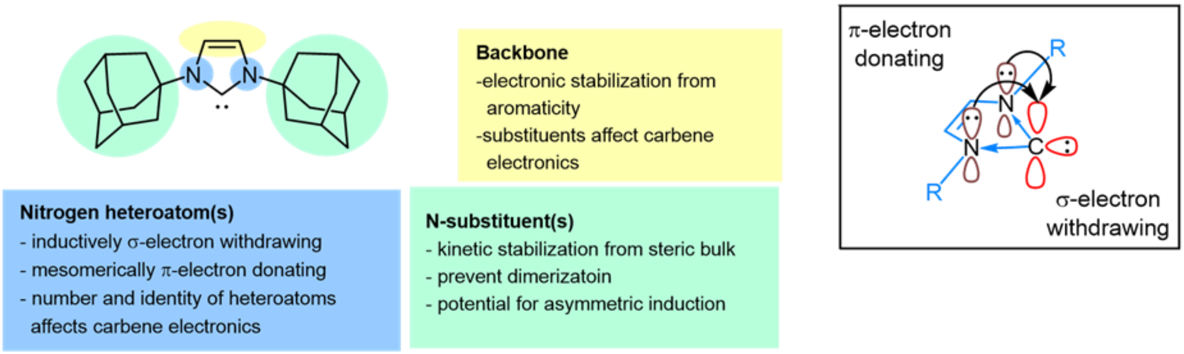
$C_2$-symmetry is important which reduce the no of diastereomeric transition state and increase the selectivity.

So, here I am going to make a summary of N-heterocyclic carbene that. So, they have these important things here, which I was trying to tell you from the first slide that there is a π-electron donating and σ-electron withdrawing. So, these are the two important effect which makes this N-heterocyclic carbene stable. So, one of the things is what is the σ-electron happening because the σ-electron withdrawing.

You can see here this arrow is given here. So, it is getting the σ-electron is getting pulled, and at the same time there is this the non-bonding electron from the nitrogen is getting transfer to the empty P-orbital of the carbene. So, that is an π-electron donation. So, this is the two effect. So, I think I have explained here.

So, the inductively σ- electron-withdrawing and then the π-electron donating ok. Again. So, the kinetic stabilization from the steric bulk as I mentioned. So, that is one important factor the kinetic stabilization comes from the steric bulk it prevents the dimerization which I was trying to tell you from the first slide onwards. There it prevents the dimerization that is why this bulky groups are important ok.

And then of course, these are potential for asymmetric induction. I am going to show you in the last slide there are lot of chiral NHC which was regularly used for lot of different asymmetric transformations.



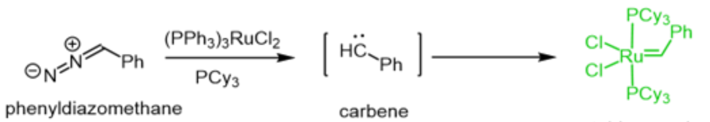
**Backbone**
-electronic stabilization from aromaticity
-substituents affect carbene electronics

**Nitrogen heteroatom(s)**
- inductively σ-electron withdrawing
- mesomerically π-electron donating
- number and identity of heteroatoms affects carbene electronics

**N-substituent(s)**
- kinetic stabilization from steric bulk
- prevent dimerizatoin
- potential for asymmetric induction

So, now I just going to show you just some examples of the graphs metathesis in reaction and you know generation of the ruthenium the carbene complex again some text book call this as a carbenoid, but I say thing it is better to call this type of complex as a ruthenium carbene complex. So, what is happening first thing this generation of this stable complex how this is happening again from this corresponding diazo compound using this the ruthenium catalyst and tricyclohexyl phosphine and once this stable complex is formed this complex can be used for various type of metathesis reaction. So, there are several developments in this catalyst.

- decomposition of phenyldiazomethane in the presence of a ruthenium(II) complex gives a stable carbene complex



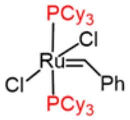
phenyldiazomethane

carbene

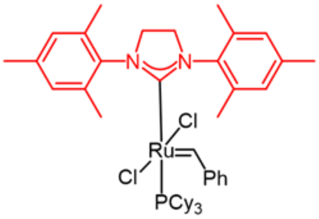
stable complex
stored for months

Robert Howard Grubbs
Nobel Prize in Chemistry (2005)

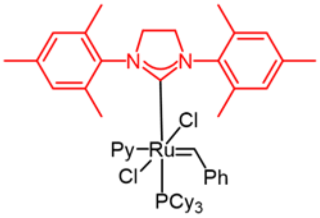
So, I think just now I talk about the first in the Grubbs catalyst in 1995. After that the Hoveyda group and the first the Hoveyda Grubbs catalyst was developed. You can see the skeleton is getting changed instead of this you can see now there are you know different variation in this in the skeleton in the second generation of the second Grubbs catalyst the NHC came into the play. So, that is as you have seen the you know NHCs are you know very good ligand for this type of reaction and it is actually a very stable carbene as I mentioned and then it you know there are some third-generation graft catalysts and more. We are going to briefly learn about that what this type of catalyst are used for.



**1st Grubbs catalyst**
**Grubbs, 1995**

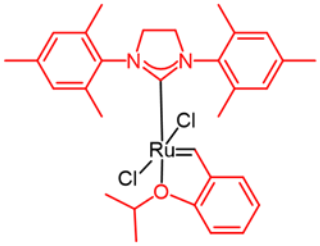


**2nd Grubbs catalyst**
**Grubbs, 1999**



**3rd Grubbs catalyst**
**Grubbs, 2001**

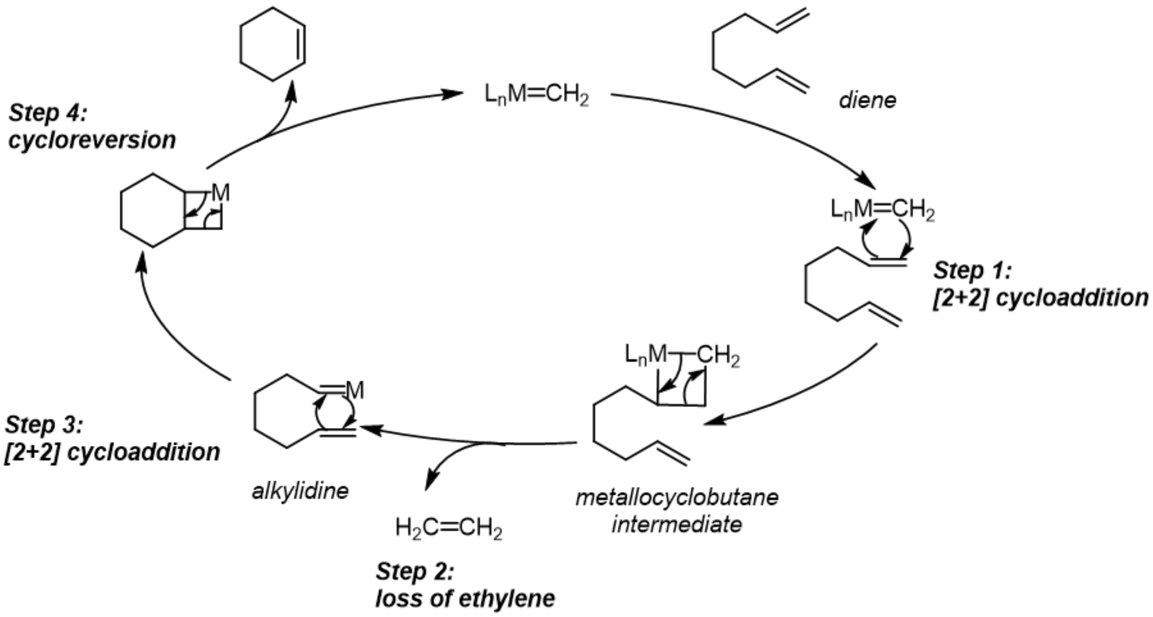
**1st Hoveyda-Grubbs catalyst**
**Hoveyda, 1999**



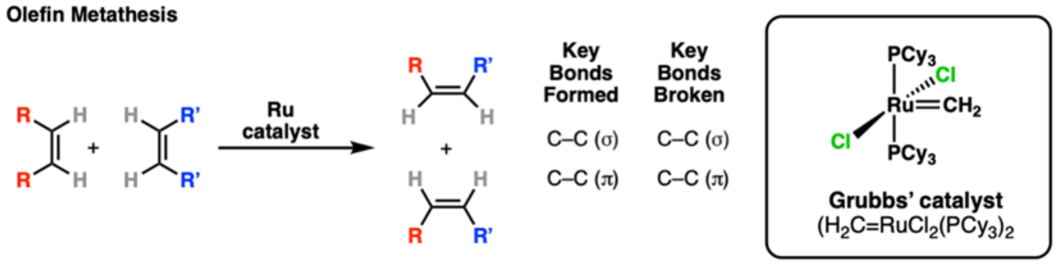
**2nd Hoveyda-Grubbs catalyst**
**Hoveyda, 2000**

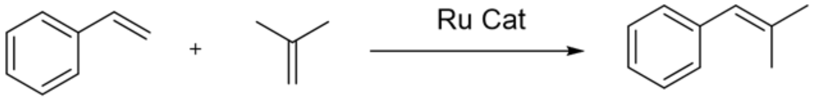
So, one of the important reactions is re-enclosing metathesis ok. And you know for this important discovery and Grubbs received a Nobel Prize in 2005 for this metathesis reaction ok. So, here I can show you the general mechanism of the ring closing metathesis, you can see from this type of corresponding transition metal based carbene the ruthenium carbene species. First thing what is happening a [2+2] cycloaddition, once it is react with a olefin. So, it taking this olefin forming going for the [2+2] cycloaddition forming this metallocyclobutane intermediate.

That is a very important thing that it forms this metallocyclobutane and then after that what is happening it lost the ethylene. So, you can see it lost the ethylene and then it is forming the alkylidene. It is forming this corresponding alkylidene means again that the transition metal based carbene species is getting formed which is participating for another [2+2] cycloaddition. to form again this type of the metallocyclobutan intermediate from there again you can see it is the catalyst is getting back after eliminating this type of cyclohexene as a product. So, this is happening what is happening it is forming a ring from the two terminal olefin it is forming a ring.



There is cross metathesis reaction instead of using a intramolecular version if you have two different olefin and using this type of ruthenium catalyst you can able to get a cross metathesis product So what is happening you can see from this part if you just cleave here then there is a $CH_2$ and there is a this $CH_2$ that means an ethylene which is actually get out from here to get to this corresponding product again mechanistically is going to be very similar it takes this olefin and then first from the cyclobutene, then the decomposition of the cyclobutene, the metal cyclobutene, then it is going to add with a another olefin and then further going to form the corresponding product then there are other class of reaction like ion metathesis.



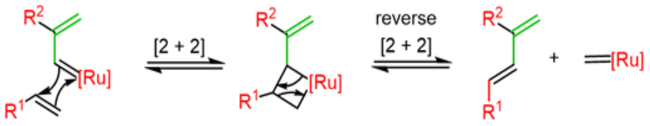


So, here what is happening the reaction is happening with an alkyne ok. So, you know that is the first thing again I think the [2+2] forming this type of now it is a metallocyclobutene intermediate then there is a reverse [2+2]. So, that means this cyclobutene is getting decomposed to form this type of once it is forming this it is participating another [2+2] here. So, now, you have a double bond.

So, it is, you know, with this type of, you know, metallocarbene, there is a double bond attached. So, now, it is a kind of diene type structures which going to now participate in another [2+2]. with another olefin now, it is going to form this metallocyclobutane and then again, the reverse [2+2] going to give this the 1,3-diene compound and this ruthenium catalysis coming back to the catalytic cycle ok.

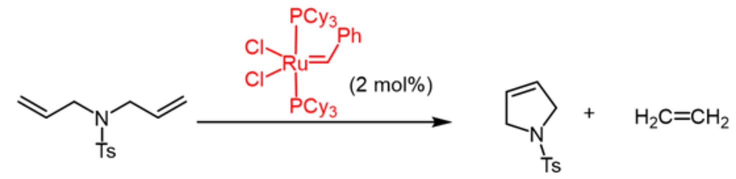
step 1: First the ruthenium carbene catalyst undergoes [2 + 2] cycloaddition with the alkyne, then reverse [2 + 2] takes place and forms the new carbene complex.

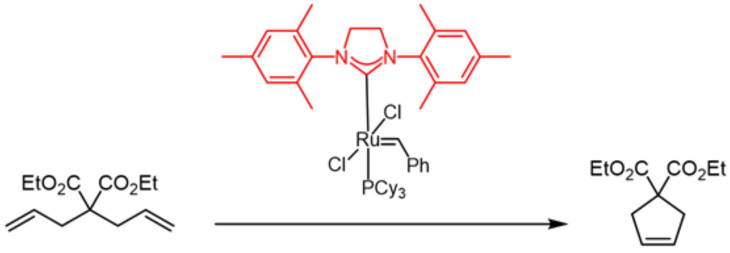
step 2: Now the new carbene can undergo [2 + 2] cycloaddition and reverse [2 + 2] cycloaddition again, this time with the alkene component, and out comes the diene, plus a Ru carbene ready to start the cycle again.

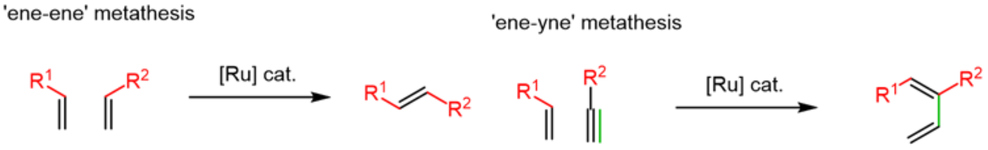


So, now I am going to talk about the ring closing metathesis here you have seen that there are two terminal olefins here which is participating in the ring closing metathesis to form this compound ok. There is another example here you can see again these two terminal olefins is participating in the ring closing metathesis to form a cyclopentene.

There are some other classes as I said I am not going to explain in a lot of the things just for a part of a carbene things I just try to explain some of the basics about it, but there are other lectures where you can able to see which is going to cover more depth about this type of metathesis reaction. There is ene-ene metathesis where two different olefin that can also form one olefin where you can see both the olefin where you will see the $CH_2$ part will get out to make this corresponding olefin. Then there will be metathesis it could be one in and another is alkyne again going to form this which I have already explained in the previous slide.



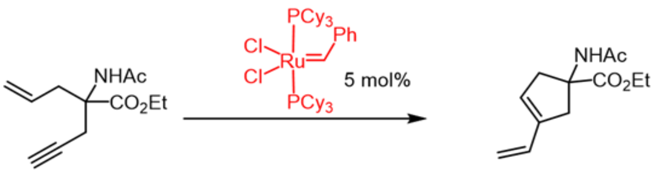


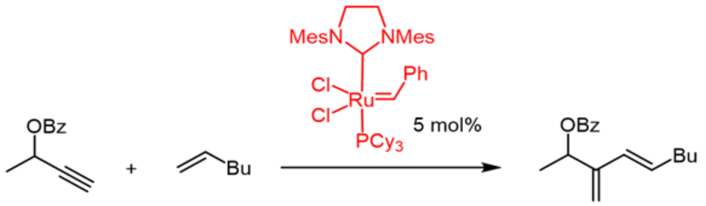

'ene-ene' metathesis

'ene-yne' metathesis

Some more example about the metathesis reaction where you can see there is an yne system and then there is an ene which using the corresponding ruthenium catalysts is going to form. So, you can see it is forming a cyclopentene with a with a olefin attached with it ok.

Some more example about the metathesis reaction where you can see there is an yne system and then there is an ene which using the corresponding ruthenium catalysts is going to form. So, you can see it is forming a cyclopentene with a with an olefin attached with it ok.





So, let us talk about some of the question. So, the first question is starting from this cis or molybdenum once you use a singlet carbene. So, what will be your product? I think I already talked about the singlet carbon, reaction will be stereospecific.

So, it should be forming a stereospecific product that means, you should end up getting to the this particular answer will be your choice not the other things because you can see the other option if you see this is the trans one which is not going to form and it is not going to give you 50:50 mixtures and neither this one ok. So, here you can see that as I told I think in the singlet carbene the reactions are very much stereospecific that is why we end up getting to this product. This reaction goes by concerted reaction. So, if you go to my I think the second lecture about carbene you will find that.

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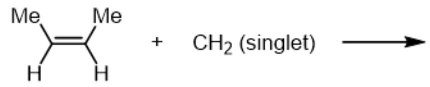
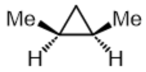
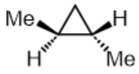
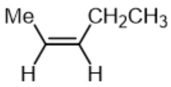


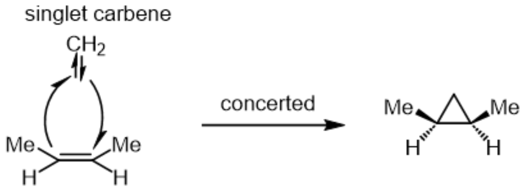
(a)


(b)


(c) 50:50 mixture of above two compounds

(d)


**solution:**



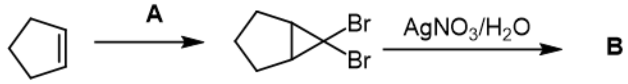
Then there are some other questions here once you take this olefin go for this type. So, you take the $CH_2Br_2$ in place of base to make to this corresponding the cyclopropane. So, this will be addition of corresponding carbene and then once you treat with the silver nitrate what will be your product ok. So, here what is happening? So, in this question there are 4 answer is given. So, let us think about the what will be A, the A will be of course, the corresponding chloroform which is going for alpha elimination. So, it will be $CHBr_3$ not chloroform sorry it will be a bromoform which will in place of $K^tBu$.

It will form the corresponding $CBr_2$. Now, it will form this corresponding cyclopropane and that then once you treat with silver nitrate. We have already learned once you treat with silver nitrate it will cleave this one of the C-Br bonds to generate a carbocation here. Once you have a carbocation what is going to happen now it is going to. So, this bond is going to get break to form another carbocation here. So, you can see there will be another carbocation here which going to get a protonated.

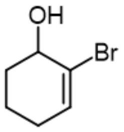
In place of water, it will end up making this corresponding allylic alcohol. So, now we must look for the answer. So, I think some of the cases they have given the $CH_2Br_2$ it is not going to be the choice. So, you must look for somewhere where you have $CHBr_3$ and then you must look for the structure of B.

So, the structure of B will be this one correct. So, you can see that will be your. So, the answer D will be your right answer.

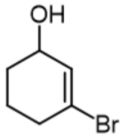
2)



(a) **A** = $CH_2Br_2$ and KO$^t$Bu, **B** =

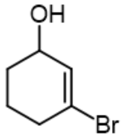


(b) **A** = $CH_2Br_2$ and KO$^t$Bu, **B** =



(c) **A** = $CHBr_3$ and KO$^t$Bu, **B** =

(d) **A** = $CHBr_3$ and KO$^t$Bu, **B** =



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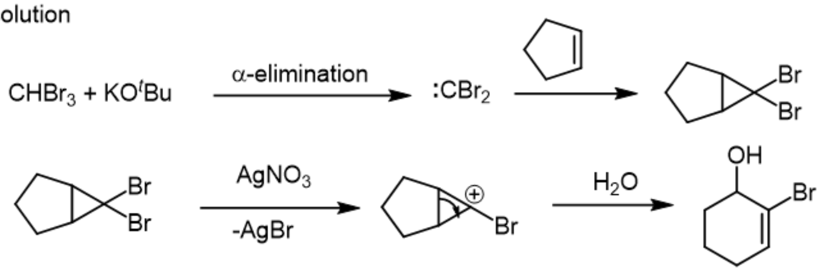
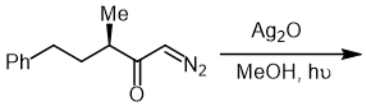


So, in the next question I am going to talk about a reaction here you can see using the silver oxide and methanol what is going to be your product. So, let us try to understand once you have a silver oxide. I think we already talked about this that it is going to form a ketene intermediate.

So, when I was talking about the wolf treatment and the Arnold Escher synthesis, if you remember that time, I was talking about this, you are going to generate a ketene intermediate in the presence of silver oxide. Now, once you have a ketene intermediate, if you treat it with methanol, it is going to attack this carbon to form the corresponding ester. So, we will we look for an answer because now the one important thing is this methyl stereochemistry will remain intact because this, we are not doing anything on this stereocenter. So, that is why you have to look for a answer where the methyl stereochemistry going to remain answer.

3)



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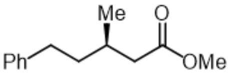

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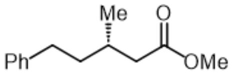

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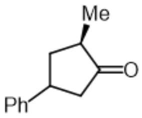

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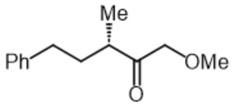

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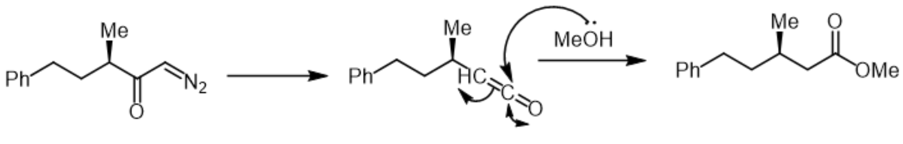
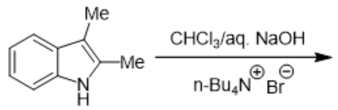
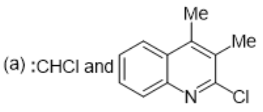
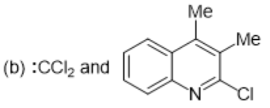


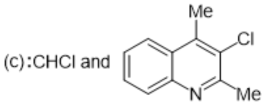
So, that means this this will be your right answer. Then there is a example I think, I already talk about a very similar example in the class where I talk about using indole here they have used the C-2, C-3 dimethyl indole. So, now, if you take the condition of this $CHCl_3$ aqueous NaOH we know this is going to generate the $CCl_2$ carbene and we once are going to generate the CCl2 carbene. The next thing that is going to happen it is going for addition with this double bond to make the corresponding cyclopropane. And now once you treat with the base, we have learned about that in this condition it there will be a ring expansion going to happen it is going to take this N-H proton. it is going to come back and open the cyclopropane ring and then eliminate one of the -Cl that will generate now you end up making a quinoline which is substituted at the C-3 position you have a -Cl here.

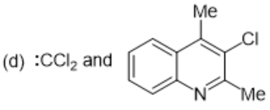
So, now you can look for answer that matches this. So, that means you have to find out. So, of course, in the question, they might ask for both the which means what carbene is going to generate and what will be your product. So, in that case you can see this is going to be right answer because it is going to generate the $CCl_2$ and it is going to form 3-chloro, and then this corresponds to the 2 and the 4-methyl quinoline.











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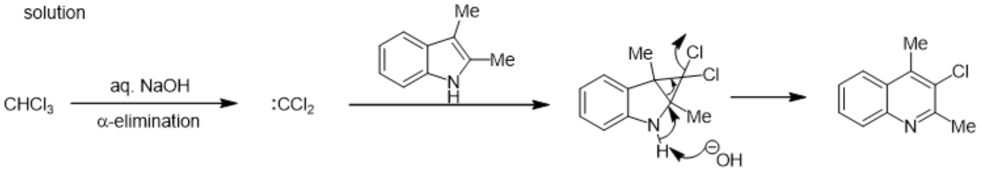
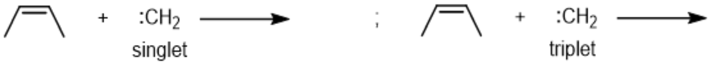


This is a very simple questions I think it is we have already discussed about the addition reaction of singlet and triplet. So, in this question asking that if you start with this type of cis olefine, then if you take a singlet, what will be your product? If you take a triplet, what will be your product? Of course, we have learned that once you have a triplet you end up getting a mixture and once you have a singlet the reaction will be stereospecific.

So, we must see that in case of singlet. So, this two methyl will be in the same site, but once you are triplet that means I think we must look for an answer where the where in case of singlet there will be single product in case of triplet you have a C-center. So, the I think the option one will be correct ok. So, you can see the singlet is this and then because of triplet you are getting a mixture.



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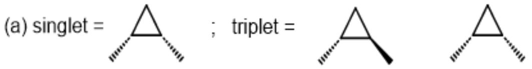
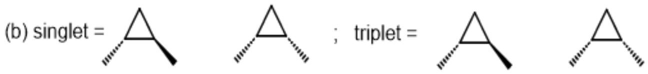
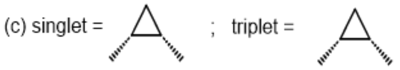




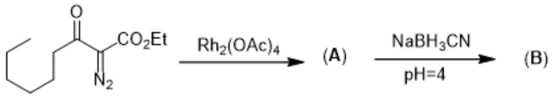


Then there is a question I think I have already covered a very similar question in the class. So, what is going to happen if you take this the rhodium tetra acid with this compound because this is a diazo compound.

So, it will first form a corresponding carbenoid then it will be going to create the rhodium carbene. And now what is going to happen you can see in this particular scenario once the rhodium carbene is going to form it is actually going to participate in some sort of a insertion reaction, and the important part is in this insertion reaction which I am trying to explain here it is going to form the corresponding trans product. I think I have already tried to explain you during the discussion the important part is that once you try to draw this because it is going to make a 5 member. So, you must understand that that there will be two things happening here.

So, one is you whatever groups are attached here. So, that means, if you have two different positions, you will try to avoid suppose this is my C-H which is going to get inserted, and you know this will be my $CH_3$. So, this will be my n-propyl group because, at the end of the day you will see the insertion happening from this hydrogen is getting inserted. So, now, the important part is that these two groups here that you have this $CO_2Et$ and this n-propyl ok. So, there will be a rhodium here, then there will be a CO. So, now if you see that in this transition when the when it is going to abstract this C-H, these two groups can stay in the trans position.

To avoid the steady that is why it will end up making to this particular product not the other one. And then what is going to happen if you treat with the $NaBH_3CN$ sodium cyanoborohydride it is going to reduce the corresponding ketone not the ester I am sure you have learn this during the oxidation reduction and now. So, so this will be your product ok you can end up seeing this product. So, now you can look for this product here. So, this is going to be option number b will be the right option ok.



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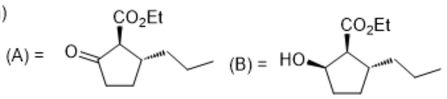

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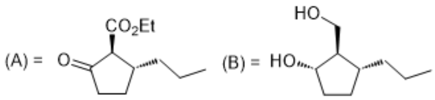

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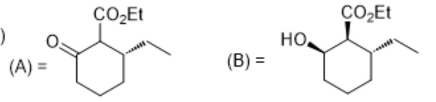

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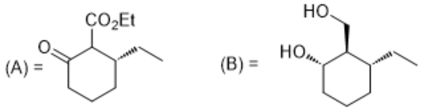
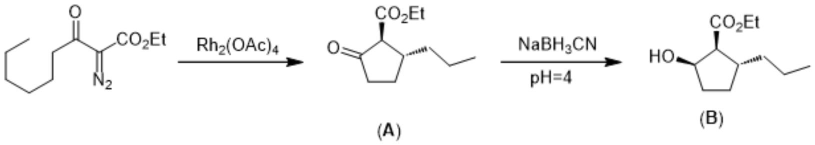
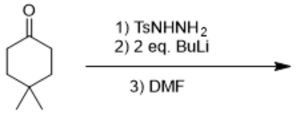


solution



Then there is another example here I think once you look into this the tosyl hydrogen and n-butyllithium you can immediately think about a reaction I already cover which is a Sapiro reaction ok. So, we have already learned in the class that from the Sapiro reaction what is going to happen it is going to form the corresponding hydrazone n-butyllithium going to abstract this N-H proton then later it is going to abstract the α-proton. And then there will be elimination of this tosyl and the $N_2$ generate this type of carbon ion which will be trapped with the DMF to make this corresponding aldehyde. So, the aldehyde will be the right answer.



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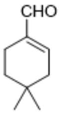

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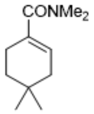

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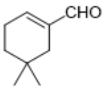

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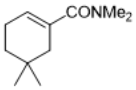
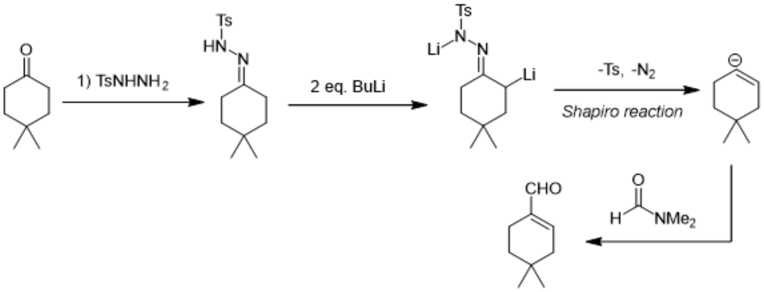


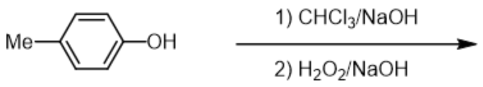


So, this is another question here I think I already talked about the Reimer-Tiemann reaction in the previous class.

So, you can see. So, this is very important problem about the Reimer-Tiemann reaction. Now, you can see in this substrate para poison have a methyl group. So, the ortho, there is no other group here. So, what is going to end up and then what they are you know using after them they are you know treating with $H_2O$ to NaOH. So, that is important thing that if you give $H_2O$ to NaOH what is going to happen.

So, let us try to understand the Riemer-Tiemann reaction. So, Reimer-Tiemann reaction going to give you this product which I already explained. So, this is a formulation of the phenol using this corresponding $CCl_2$ . So, now after that once you treat $H_2O$ to NaOH what is going to happen it will participate in a bare vinegar oxidation. So, once the oxidation going to happen so, there are two groups there is a phenyl and H.

So, phenyl going to migrate then after the hydrolysis of this corresponding. So, now the now the O is going to attack here then then after the hydrolysis is going to generate this corresponding phenol ok. So, so this will be the right answer which will be the answer B here. So, there is two different thing we merge. First thing, is going to happen is the Reimer-Tiemann and then the Baeyer-villiger.



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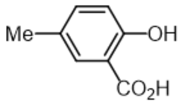

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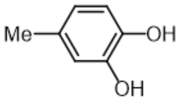

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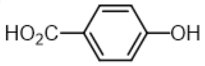

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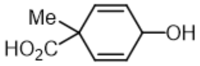

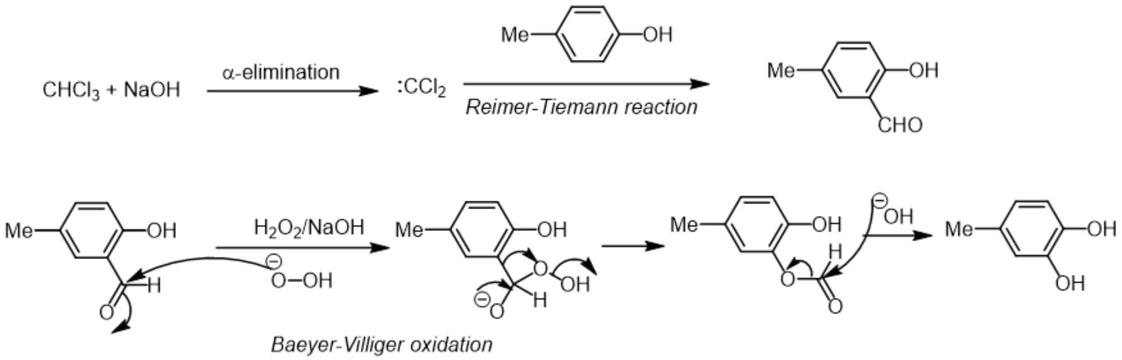

I think I already talked about both the things in the class. Again, I think you know these are the some of the problems from the previous exam and I also suggest you to you know go through the different chapters of these books and at the end of the chapter there are also lot of problems. So, you can also practice them ok. So, thank you and you know thank you for coming to the class and I am going to see you guys in the next class. Thank you.