Metal Mediated Synthesis - I
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Lecture – 3
Olefin metathesis

Hello welcome back. Today we will discuss the reactivity of these carbene complexes that we were discussing in the last class. We have synthesized the carbene complex in the last class. We have seen examples of each of Fischer carbon and Schrock carbene. In today's class we will discuss the effect of these carbene complexes in organic synthesis.

Simply discarding complexes had revolutionized the organic synthesis in a way. So, that now carbon carbon bond formation is possible in a very controlled fashion, any new carbon carbon bond if one would like to synthesize he or she can take the advantage of the metal carbene species. We will today see first the olefins 2 of them are reacting to give a newer olefin.

The next will discuss olefin and carbonyl complexes reacting to give a newer olefin. So, both these processes we are getting a new olefinic compound. So, if one is interested in synthesizing any new carbon carbon bond containing compound he or she can think about having a double bond at the beginning and then if they want to reduce it or further oxidize it depending on the demand one can plan accordingly.

But by these carbene complexes one can think of generating a olefin or so to speak carbon carbon double bond containing compound and from there on pa further characterization or further transformation can take place. First let us look at the one example that we were discussing in the last class, where one of the olefin is reacting with another olefin with the help of metal carbene complex to give even newer olefin let us look at that example.

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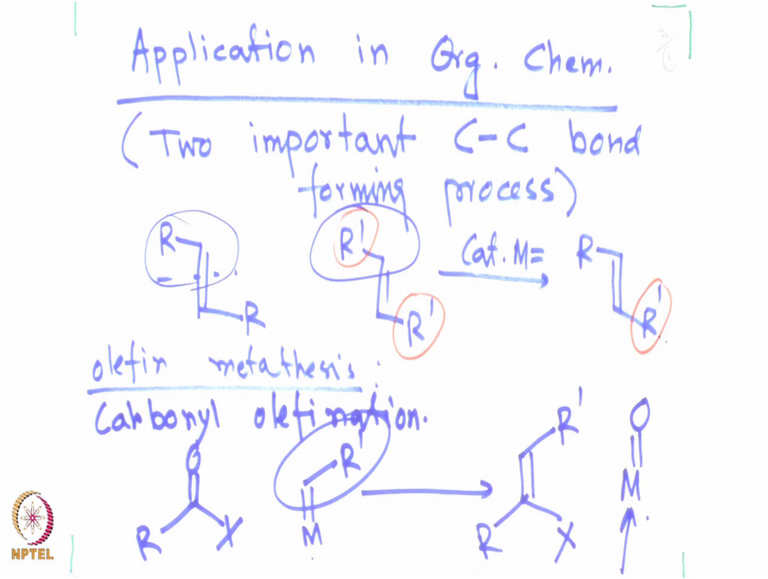

Application in Org. Chem.

(Two important C-C bond forming process)

olefin metathesis :

Carbonyl olefination.

In this particular case the starting material are having a double bond or the olefinic in nature which are one fifty kcal per mole. Now this reaction can be done at room temperature. So, this metathesis reaction it is done at room temperature one of the partner is exchanging with, another partner to give you a new or compound with olefin metal is metal is used as a catalyst and often it is used as under thermal reaction condition.

Also these reactions are reversible in nature and therefore, we can have a quite good number of synthesis of this compound without much problem. This is once again catalytic is in nature and metal is metal carene is used as catalyst these are done under the thermal condition concentration of the reaction can be varied during these processes. Now we will look at carbonyl olefination where one of them carbonyl complex will be involved during the synthesis of this final compound.

So, let say for example, we are starting with a metal carbonyl complex metal carbonyl RCO X and a metal carbene such as this one if you exchange the partner at this point what you can get is a new olefin complex, with the R prime which was associated with the metal center now exchange to give youth metal (Refer Time: 04:47), which is a very stable complex this is usually very stop stable complex and a new carbene are (Refer Time: 04:57) a new olefin is generated. These reactions are usually irreversible in nature and therefore, one would think that these metal olefination where it is going with the help of mid carbonyl species are going to be not only irreversible metal carbene need to be used in stoichiometric version.

The first example which we were discussing who had 2 different carbene so 2 different olefin was reacting to give you a newer olefin those reactions are usually reversible and metal is used in catalytic comp quantity, the latest example where carbonyl is used with another metal carbene to give you a newer olefin. In this case metal catalyst is usually used in stoichiometric amount, because the reactions are irreversible in nature the previous reaction was reversible in nature since this is irreversible the latest one is irreversible we need to use stoichiometric various and stoichiometric quantity of the metal carbon.

None the less this gives the access to the olefin from carbonyls compounds, which is quite amazing if you are thinking about the potential of these reactions for organic synthesis purpose. Now we will look at some more example of this olefin complexes yeah where you have you know one olefin is reacting with, another one it could be intramolecular it could be intermolecular depending on the demand of the ring size.

We can have a dilute compound or dilute reaction condition or a concentrated reaction condition in any way. We will first discuss the 2 plus 2 and retro 2 plus 2 with one of the examples so that the mechanism of these reactions become familiar with you guys let us look at one of the example of olefin metathesis.

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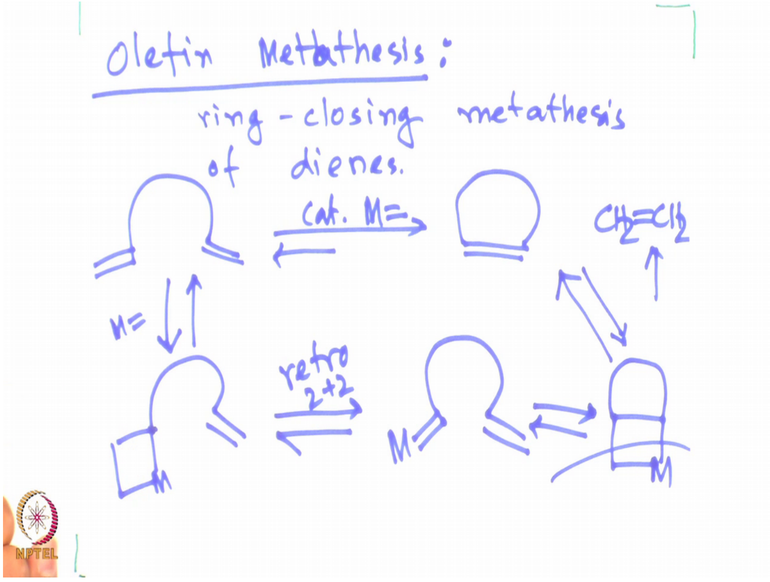

Olefin Metathesis:

ring-closing metathesis of dienes.

So, we will discuss olefin metathesis most important application of this type is ring closing metathesis of dyeing. So, ring closing metathesis of dyeing die in which is more most popular and you have let us say for example, one starting material, which looks like that you can have any variation over there and you can take catalytic amount of metal which will go the reaction will go in the forward sense and give you this compound and you will have ethaline coming out from this reaction. Overall if you look at the reaction will start in an reversible fashion where one of these terminal olefin will react with the metal carbene to give you it is a 2 plus 2 between this olefin and this metal carbene to give you the metals is in metalacycle form and 4 members metal a cyclic form.

2 with the olefin hanging right close to it or this ring size can be very big that is of no problem, usually then by retro 2 plus 2 retro 2 plus 2 you will have the metal inserted with the organic complex. So, a newer organometallic intermediate so to speak in this case may newer metal carbene is generated, once metal is incorporated within the organic molecule then you can have a 2 plus 2 once again to give rise to the metal containing new compound, which is now ready to give you or leave the metal in a metal carbene form if this metal carbene comes out and then you can get a the desired product.

So, as you can see in this example; starting with ta 2 terminal olefin we have a metal carbene intermediate reacting with one of the terminal carbene to give you the 4 membered ring from there on we can have then a 2 plus 2 to start with and then a retro 2 plus 2 leaves the metal into the organic substrate.

Which then can further undergo reaction with another olefin in a 2 plus 2 fashion to give you the cyclic complex from which you can have a retro 2 plus 2 to leave out the metal carbene. So, therefore, you can see this reaction can be catalytic in nature overall it stitches the 2 terminal carbene to give you an internal olefin. So, 2 terminal olefin can give you finally, a (Refer Time: 10:19) person or a cyclic version of the organic compound where the double bond is placed in between of those 2 terminal olefinic center. This is a extremely powerful technique to generate small size or even huge size or large you know cyclic compound by utilizing the beneficial features of the metal carbonyl. So, metal carbonyl species.

Now this metal carbene species is used usually in these cases in catalytic amount you can recover this metal carbonyl carbene complex from this reaction, but most importantly the desired carbon carbon bond can be generated. So, if you have a large molecule let say you are planning for a natural product synthesis, you can split your large molecule into half it could be exactly at the middle or even a little bit on the side.

Now as long as you split it there you individually synthesize this to fragment and if the final stage during your endgame you want to utilize those 2 fragment with terminal olefin with the help of yet another metal carbene to put them together and then subsequently you can do oxidation or reduction of that new or newly formed double bond to give you the to get the desired compound.

So, this olefin metathesis reaction has (Refer Time: 12:00) utilized both in industry and in academia most importantly in bigger molecule synthesis much more complicated molecule synthesis, which were previously unthinkable now that is delivered in a really scientific manner and in real controlled fashion. Now we will try to take a look at the little bit other examples that we might will be able to generate from these reactions.

So, what happened you can have a bigger ring sized reaction when you have a bigger ring size then the reaction is controlled under the dilute condition, if you want to really go for a bigger ring you have to make it dilute. So, that your you know completion experiment you know intermolecular competition can be ruled out and if you are having a smaller ring of course, it is both tropically favored as well as kinetically favored. And therefore, therefore, you do not need to do the reaction under the dilute condition if it is a bigger ring one usually need to synthesize these complex under the dilute condition.

If it is a smaller ring you can do it under any condition you would like to do.

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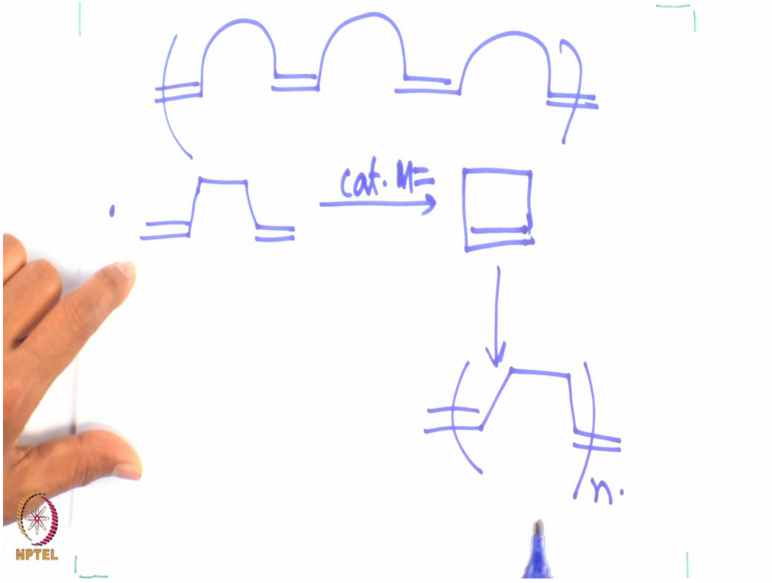

So, finally, therefore, by utilizing these techniques you can have compounds such as where the olefin where you have a alternate centers and these could be polymerized or you can start with an olefin, where you have these 2 terminal olefin attached with it you add the catalytic version of M double bond to give you the metal olefin compound from where on you have it did cyclopropene cyclope cycle butene intermediate.

And finally, this can lead to the polymerization of the intermediate which can go for ring opening metathesis polymerization reaction. So, these are called romp or ring opening metathesis polymerization.

Now these are also very powerful technique one can think of and can utilize this technique ba to generate very complex molecule. Now we will discuss one of the example which grab cells first d done it and E utilize actually Schrock carbene as I was discussing the Schrock carbene was discovered in 1974 and Grubbs really came up with the Grubbs catalyst in 1993.

In between of course, Grubbs was also working on this area organometallic area, but that time he was using you know Schrock carbene to do these transformations. Let us look at one such example where Schrock carbene was used by Grubbs to do these metathesis reactions.

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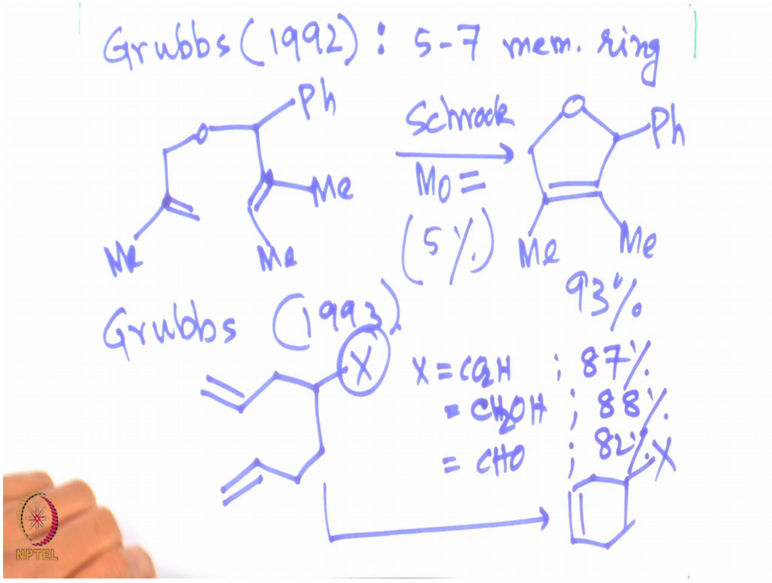

So, Grubbs again this before 1993 Grubbs was using a Schrock carbene this is in 1992 we are going to see 1 5 to 7 membered ring formation 5 to 7 membered ring formation examples, where the starting material is the 1 with 2 terminal olefin and you have very beautifully substituted compound.

Now one would be able to see that we should we should be able to generate these 2 compound outside and you know to give you the (Refer Time: 15:53) compound or the ring compound if Grubbs when Grubbs was using Schrock molybdenum complex of course, you can have ta ta you know tungs10 complex nowadays that is also a used a 5 percent of this Schrock molybdenum complex is giving you the ring closure between this carbon center and that carbon center to give you a 5 member intermediate, where olefin is in the middle and the substituted this compound can be synthesized in 93 percent yield, in by using this technique of course, one of the problem which is encounters by this Schrock carbenes is the they are not that you know not that tolerant towards various functional group such as acid, alcohol, aldehyde cannot be tolerated by Schrock carbon method or while utilizing Schrock carbon we see acid alcohol like Ch 2 oh or aldehyde can usually not be tolerated under the reaction condition.

This is where actually Grubbs catalyst become very popular and of course, perhaps widely used, because the functional group tolerance is much more in Grubbs catalyst compared to the Schrock catalyst; that is the reason why perhaps Grubbs catalyst is used and sold what worldwide in a large quantity and also in industry it is used quite hugely will.

Now, see one example where different functional group can be tolerated by using Grubbs catalyst. So, Grubbs did this reaction in 1993 to start with where this terminal olefin 2 of them are stitched together in presence of various X this could be your CO 2 H, X could be your alcohol, X could be your aldehyde and so on. Overall it gives you the complex what we want cyclohexane complex with X substituent all these functional group substituent the yield was quite good and it was tolerated most importantly towards tolerated yield was also quite good 82 percent for the aldehyde complex.

So, overall what you have seen then Grubbs ruthenium catalysts or discarding complexes are more versatile can tolerate a wide variety of functional group compared to the Schrock carbene complexes. And this is where Grubbs catalyst had some sort of advantage mean and we see both in the literature and industry it used quite extensively, but the ground work the most important discoveries are were actually done at the beginning by the by Schrock group.

So, it is it is a very utilit a useful method it is both nowadays both you know Schrock carbene as well as the Grubbs catalyst are used for this purpose, but cases where we have sensitive functional group usually Grubbs catalyst is preferred it is usually seen as more you know versatile and quite widely used. Now let us look at some more of the example while we discuss the beneficial features of this beautiful technique.

Now first we will we will discuss an asymmetric version of this reaction; asymmetric version is mainly discovered or explored by Grubbs sorry mainly by Schrock and later on joined by hoveyda Schrock hoveyda catalyst or Schrock hoveyda do research group, both of these research group put together a beautiful version of the asymmetric catalysis and these are the one which are most interesting in the current literature context and it is quite widely studied at this point. Let us look at one of the asymmetry version of the of these carbene reactions where the metathesis reactions are going on.

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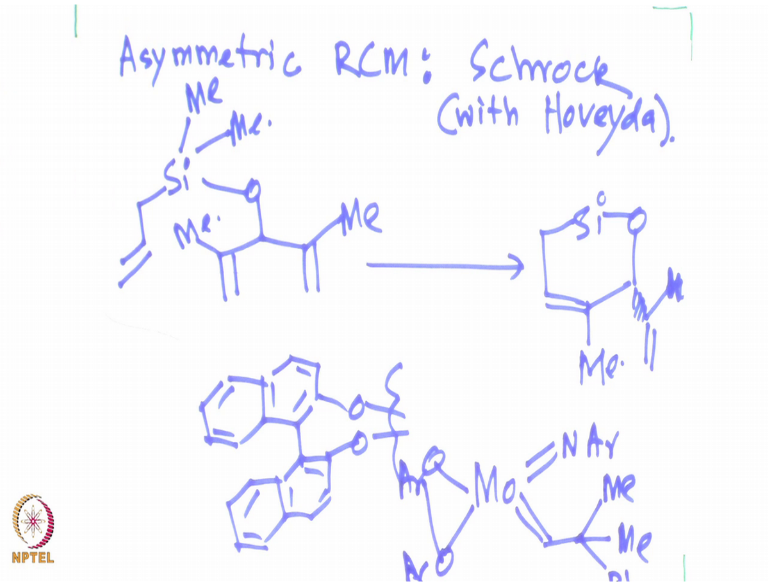

Let us look at that asymmetric ring closing meta thesis this is done by Schrock with hoveyda. Now the starting complex of course, you have to have a mono substituted olefin or they have had a monosubstituted olefin which is the most reactive one compared to the dye substituted or internal 1 and you have this species where you have 2 enantiotopic faces of these olefin. The 2 phases are (Refer Time: 21:13) in nature as you can imagine now these one of these centers can react with the other one to give you the cyclic live complex and the final complex as you might will be able to predict at this point would be the one where, you have this complex formation and you can get this in an asymmetric ring closing metathesis version.

The thing that is used for these cases are the one where you have the enantiomer of one of these substituent is used and overall you can get a very good ee for this product. The molybdenum catalyst is used as you are drawing previous in the previous class you will have these complete touch dissenters and this is your binol catalyst with aryle aryle group in there this is the one which is synthesized and utilized quite beautifully and we have very high ee for this reaction this is done by straw in with the with collaboration with the hovaydas group.

Now, that is quite interesting as you see we have the beautiful reactions going on and you can get the asymmetric version of it starting from a material, where you have a terminal olefin with the (Refer Time: 22:53) and the one where you have 2 enentiotropic faces or enantiotropic faces. Now we can get these complexes quite in in an enentio enantiomeric form that is very interesting and it can be done in a very asymmetric you know very high ee.

Now will re react or give one example where Grubbs catalyst is utilized and we can synthesize the beautiful compound starting from 2 olefin and one alkyne in the middle. Let us look at one example where olefin and alkynes are together what would be the reactivity pattern and what could be the end product that could be determining lot of reaction that one would like to plan in edit row synthetic manner let us ren closing metathesis RCM of Die na dienynes this is done by Grubbs.

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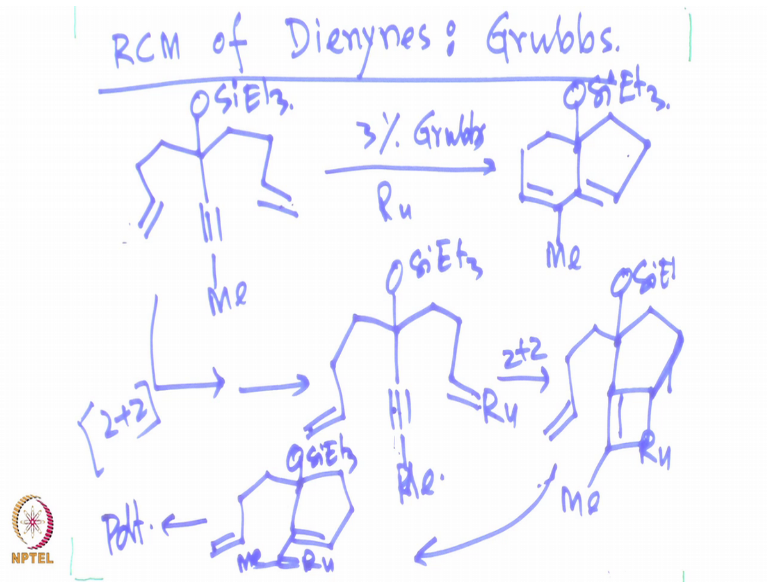

Again here what we will take is a compound a little bit interesting one and exhaustive it is synthesized in 28 steps from Aldrich available material one quite elaborate synthesis, but finally, if you have this compound what you can expect from this one if you use 3 person for example, Grubbs ruthenium catalyst the end product that you are going to get is quite interesting you may want to try to draw it by yourself what can you predict, what could be the end product as you can see it is a 6 member and 5 membered fused compound that we get.

Now look at the beauty of the synthesis you are starting with you are starting with 2 terminal olefins in between there is an alkyne. Now you are able to stitch the olefin with alkyne and then resultant olefin you can further stitch with the remaining olefin. So, overall you have a olefin which is of course, the one which is more reactive it reacts first to give the metal carbene at the olefinic carbon side and from there on it reacts with the nearby alkyne because the olefin is really further away or the ring size will be bigger.

So, therefore, it is not reacting with another olefin the metal carbene is reacting with the alkyne to give the ring closure from their own the resultant compound down ready to stitch with the remaining terminal olefin to give you the beautiful fused complex with a 6 member and a 5 membered ring. That is the beauty that is the strength of such technique where you can get this compound get the beautiful compounds from a readily available or you know pre prepared complexes.

Let us look at the mechanism of these reactions. So, you have 2 plus 2 reaction first I will just put it very briefly the left hand side im keeping intact only the right hand side im trying to react of course, the olefin will react fast here you are having or you are having 2 olefinic terminal olefin one of them im taking the right one, you can take also left one right one we have we have reacted by 2 plus 2 and retro t plus 2 we were now able to put the ruthenium within the organic molecule of course, OSi 83 is there. Now once that is incorporated this one can react now with the carbene sorry this alkyne, but this one will not go and react with this one.

Because this will gives rise to a huge member I mean it is a larger ring size right. So, this one will react with this alkyne to give first the 5 membered ring and subsequently you can get the 6 membered ring let me draw the other intermediate. So, you will get that one first and overall then these 2 plus 2 would lead to the intermediate of 5 membered ring, from there on you can go ahead and let me draw the compound further, we can have overall a compound which looks like a 5 membered ring formation fast and ruthenium over there and methyle over there from here on you have OSi 83 this ruthenium alkylating complex. Now will react with this olefin to give you the final product this is the product formation step.

So, overall what you have seen here you have 3 reactivecentres 2 terminal olefin and one internal alkyne. Of course, as we said the terminal olefin any one of them will react fast this terminal olefin will undergo 2 plus 2 and retroptive plus 2 to give the metal carbene into the organic molecule. So, you started with metal carbene or let us say you know Schrock carbene type of molecule in this case we are using Grubbs catalyst, now Grubbs catalyst you use catalytic amount where you have a metal carbene spaces.

Now that metal carbene will react with one of the terminal olefin to undergo 2 plus 2 and retro to 2 plus 2 and end up giving the metal inserted into the organic compound. From there on it has 2 choices it can react with alkyne and it can react with yet another olefin of course, reacting with the other olefin is more beneficial; however, that will gives rise to a larger ring formation and therefore, the 5 membered ring formation preferred to react or to incorporate and engage the alkyne with the metal carbene.

So, the 5 membered ring is from first subsequently the metal or ruthen ruthenium ca carbon species that we get that incorporate into the organic molecule and then further it flips to the other side to give again the 2 plus 2 and retro 2 plus 2 to give you the final 6 membered ring.

So, 5 membered rings forms first and then 6 membered ring comes to give you this fused compound from a 2 terminal olefin and an internal alkyne that is actually extremely exciting you know product formation. So, therefore, depending on your final product you can plan your endgame and can do the remaining synthesis keeping in mind that metathesis reaction is a useful technique and a very versatile and very reliable technique and therefore, the planning of a synthesis can be can be relied on breaking or making of this carbon carbon bond.

So, in the next class we will be continuing from here on we will see some more example of these complexes and reactivity pattern, we will discuss and till then you might want to practice these 2 plus 2 and retro 2 plus 2 to get the great feeling of these complexes keep practicing we will come back soon with more examples and more discussions.

Thank you very much.