# Metal Mediated Synthesis - I

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## Lecture – 18

## Synthesis of reactive metallacycle Intermediate via – β - abstraction and their applications

Hello, welcome back to today's discussions, we will continue on discussing on the dicyclopentadiene zirconium species formation and how they are utilized for the strategically for different synthesis. In the last class we have seen the reactive metal fragment that is used for the di cyclopentadienyl zirconium species formation.

Today's oxidative cyclisation discussants mainly will focus on at first discussing how to generate di cyclo pentadienyl zirconium species from an alternate method namely, the beta abstraction method once briefly discussing that then we will move to titanium isopropoxide tetra isopropoxide method to give the titanium di isoproxide reactive intermediate and to utilize it for oxidative cyclisation reaction.

Subsequently we will see the cyclo butane ring formation and then we will try to move in the end of it, we will try to move to the other metal mediated transformation that we will see for this course. So, in the first plot let us see how one can generate cyclopentadienyl zirconium species directly without undergoing the reactive metal fragment that we were discussing in the last class. So the beta abstraction method for cyclopentadienyl zirconium species formation of course this is unsaturated version.

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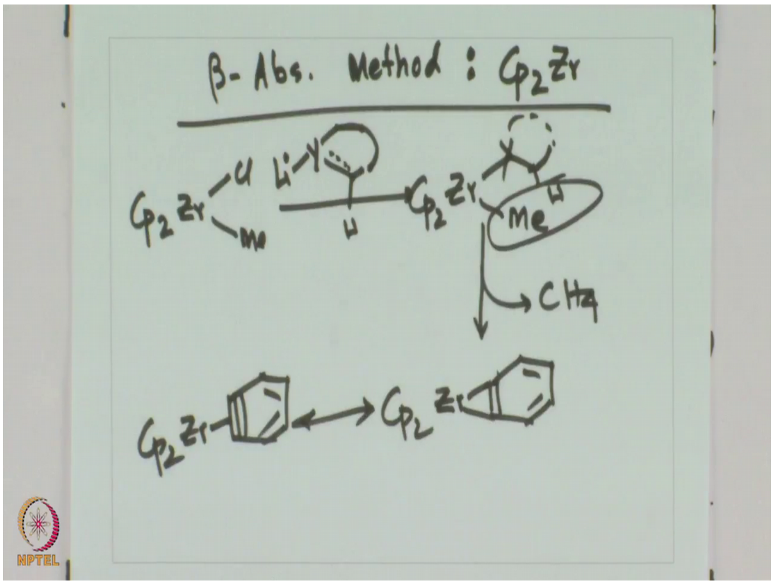

So, what we can do is, we can take cyclopentadienyl zirconium chloromethyl and take the lethiated intermediate, let us say you know we can have any cyclic intermediate or a cyclic intermediate does not really matter, overall the main thing is it has to be lithiated and we can then synthesize the letheated this intermediate, where this cyclic intermediate is part of the zirconium species along with this.

Then we will get the methane formation from their overall this is a beta position beta hydride a beta it is not a beta hydride elimination, but the beta abstraction because zirconium is in plus 4 oxidation state, for beta hydride elimination it will not be possible and then therefore it undergoes the beta abstraction to give out the methane this 2 part and directly it forms the complexes of high energy species that is for example, with benzyne or so we can get the get the zirconium intermediate right.

So, for example, if it is benzene you can put over all benzene information from here on. So, from this intermediate we know that this is cyclopentadienyl zirconium benzyne intermediate formation right. So, this is a method which avoids the intermediacy of reactive metal fragment as we have seen in the last class, also it allows the preparation of complexes of high energy species such as benzyne; this benzyne species formation 1 can see by this method also it solves the problems of chemo and regioselectivity that were appearing in the last discussions as we have briefly looked upon. So, once again this is a beta abstraction method to prepare the cyclopentadienyl zirconium species.

Previously we have seen that dicyclopentadienyl zirconium dichloride for example, was reacted with organolithium in butyl lithium, for example 2 equivalent of it and from there on dicyclopentadienyl zirconium species unsaturated 1 synthesized; but today what we have seen is it is an alternate method of preparation of this cyclopentadienyl zirconium species, which is much cleaner and it can gives rise to the cyclopentadienyl zirconium unsaturated intermediate quite efficiently and therefore, those similar application as we have seen in the last class even for natural product synthesis, this dicyclopentadienyl zirconium species can be used. On moving on these all oxidative cyclisation reaction, now we would like to discuss the titanium reagent. So, titanium tetra isopropoxide reagents are the starting material from there on.

So, di isoprop propoxy titanium reagent can be generated, but how they can be generated and how they can be applied strategically for organic synthesis is the next point of attraction for this course; let us discuss the titanium reagent. So we will be discussing the hybrid mode, hybrid titanium isopropoxide and the Grignard reagent combination to give the di isopropoxide titanium reagent.

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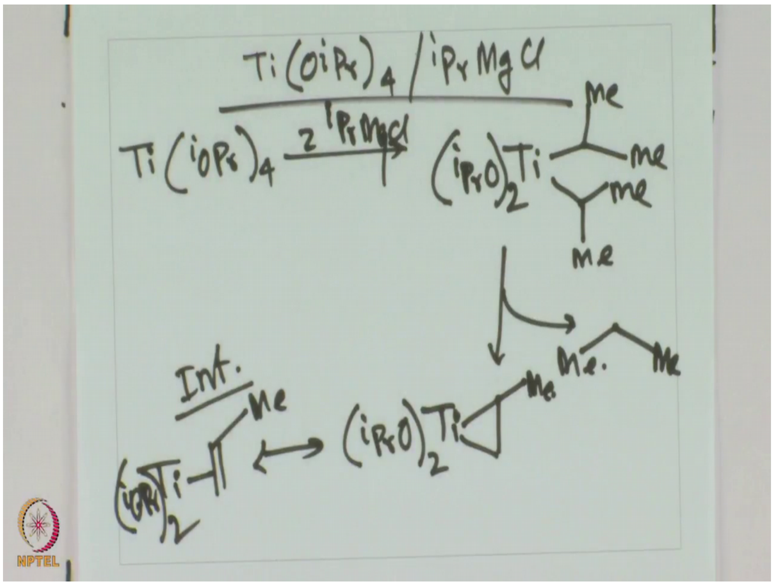

So, we will be discussing titanium O isopropoxide and then isopropyl magnesium halide for examples, reagent for generating different titanium reagent which can be utilized for further organic transformation.

Let is say for example, we have we have titanium isopropoxide 4 and we are reacting with 2 equivalent of isopropyl magnesium chloride, overall what we will get is that titanium di isopropoxide intermediate, along with this di isopropyl unit that is coming from here right. So, overall we will get this intermediate first from there this isopropane will go out and then a cyclo cyclobutane, titanium containing cyclobutane ring will be generated. So, 1 of the h so the namely beta abstraction from this CH 3 will give rise to the isopropane or in this case simply propane and then we will get this 3 member intermediate with the metal in it. So, metallacycle will form and a 2 of the isopropoxide will be attached to it this is nothing, but if you look at very carefully this is nothing but the olefin coordinated titanium di isopropoxide right, di isopropoxide intermediate.

Now this is this is the intermediate from where we can get rid of olefin if we want for example, if we wanted to react this intermediate let us say this is an intermediate. Now this intermediate if we want to react with an alkyne and we can we can then react and then get the cyclopropene type of intermediate titano cyclopropane intermediate, we can get let us see how this intermediate that we generate right.

Now with this isopropyl magnesium chloride reagent, how this can be utilized further to incorporate a new reagent or make them reactive under the reaction condition let us look at that. So, we are taking that intermediate if you remember that was having the propane associated with titanium with 2 di isopropyl oxide let us say take that intermediate and then react with another alkyne.

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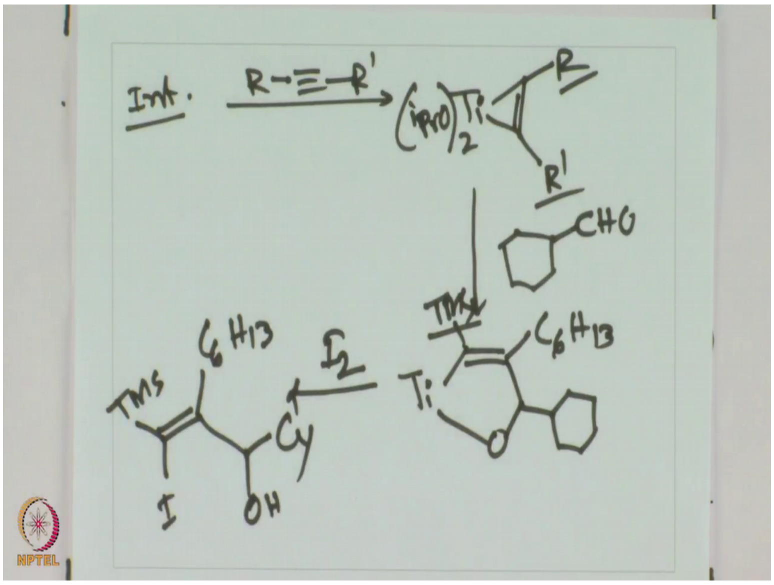

For example, R prime this alkyne overall then we will what will get that is that olefin will go out and this 3 member type titanium intermediate will be formed and this will be then reactive towards a number of species that will be seeing. So, similarly this is species as you know it is similar to this di cyclopentadine titanium reagent or the zinc or the zirconium reagent that we were discussing.

Now this intermediate from here on for example, if we are interested in reacting with another aldehyde, this aldehyde will be able to interact with this 3 member matallacycle and overall then into this aldehyde double bond this cyclopropene will be able to insert and then the final species, that we will be getting in this case is a 5 member intermediate where we have.

For example, C 6 H 13 and TMS if these are the R and R prime we are taking and from there on we can get the cyclohexyl, of course cyclohexyl we can get and cyclohexyl overall it is giving a 5 member intermediate from which iodine can react to give the open chain. So, this is more of an electrophilic attack on this 5 member metallocycle and from there on we have the reaction with iodine to give rise to the olefin in product that 1 might will be interested in synthesizing, overall cyclohexanone cyclohexane aldehyde is incorporated in the form of cyclohexanol and then we do have the olefin incorporated into the ketone.

So, this is a nice oxidative cyclisation reaction as you can see we started with an aldehyde, we started with an alkyne, it is the combination of alkyne and aldehyde that gives rise to the final product alkyne, but you have seen it form the olefin with the iodine in it and the other center of the alkyne is now associated with an aldehyde to give you the secondary alcohol.

Now this these are the powerful technique to synthesize a number of interesting molecules, specifically if you are looking for a retro analysis you can rely on this method quite confidently and can deliver the desired product quite efficiently. let us look at some of the similar type of reaction as you have seen in the last class; in enyne type of chemistry in this case we will be taking an amine along with an alkyne to form the cyclic product that that is similar to what we have seen in the last class. So, we will be we will be seeing these are you know the reactivity of these titanium reagent.

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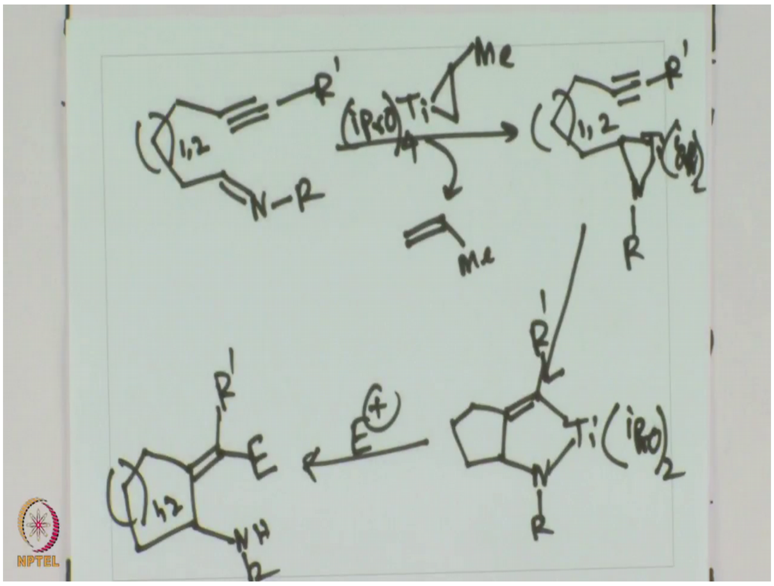

Let us for example. one we will be having so various amines containing 1 along with an alkyne appended to it, if we are reacting with that titanium intermediate. So, that we have drawn previously how to generate it we have seen it from titanium tetra isopropoxide, overall this process will give rise to the this propane intermediate will go out and this will react titanium reagent will react with the amine to give you the 3 member intermediate with the titanium and nitrogen in it that is a very interesting intermediate isopropoxide 2.

Along with it there will be this alkyne that is associated with it, overall from this intermediate we then will be able to get the oxidative cyclisation will give rise to the another 5 member intermediate, in addition to what we have seen in the organic fraction and this cyclo you know 5 member intermediate will then can be reacted with another; you know electrophile very confidently and it should be giving the final product beautifully. Now this is the reaction reported by sato in 1995 and a lot of application has been has been planned, based on the synthesis of this 5 member organic molecule with various electrophile in it.

So in this example what we have seen right now is the titanium reagent, that you know cyclopropane type of reagent. So, it is a 3 member titanium reagent that metallacycle, now have reacted with an amine where olefin goes out and amine is now coordinated oxidatively with the titanium space with the titanium center; now that titanium nitrogen containing intermediate will be reacting with the alkyne in C2 which is sitting within the substrate to give rise to the cyclic 5 member organic intermediate and then from there on we can add an electrophile, to finally get rid of the titanium reagent from the product; overall then this can be seen as the true manifestation of the oxidative cyclisation processes, where versatile organic compound can be synthesized rather easily and then we will be also discussing further on this processes.

Not only these you know this simple organic molecule with the 5 to 6 7 member ring, even can be synthesized we can see that various heterocyclic synthesis can be also planned by utilizing this technique, this is a clever application of the pyrole synthesis which is utilizing this titanium reagent for this oxidative cyclisation processes. Overall will see quite a few rearrangement to come up with the pyrrole synthesis in presence of carbon monoxide and the reagent let us look at that pyrrole synthesis.

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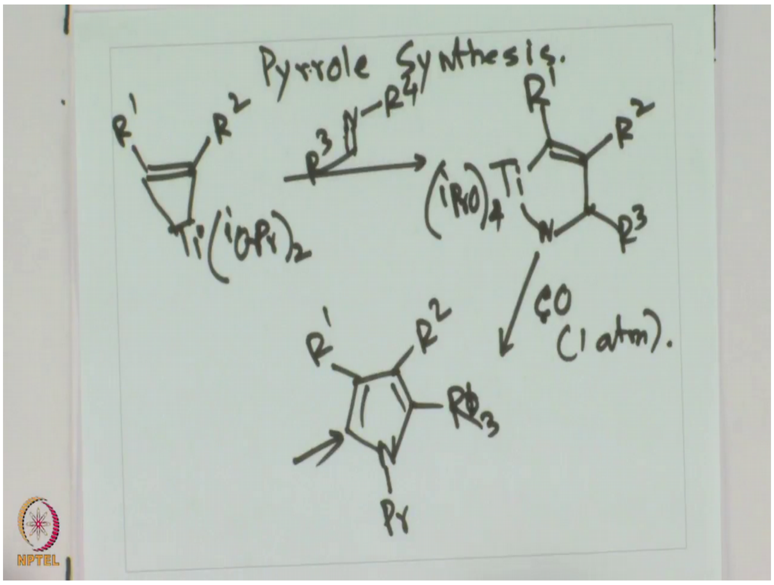

So, pyrrole synthesis by using these titanium reagent well we can have from an alkyne, we can have these over all these 3 member Titanium intermediate with isopropoxide species in it; now as you have seen previously it can react with an amine. So, for example, R 4 and R 3 these are the 2 reactive species if we are taking as you can see from the oxidative cyclisation technique, we will get the 5 member titanium reagent along with the ring over there.

So, overall if you look at it is a fully substituted version of this titanium isopropoxide reagent, subsequently if we are reacting with carbon monoxide 1 atmosphere of it under 1 atmosphere carbon monoxide this carbon unit will be incorporated over here. So, overall we have 1 2 3 carbon another carbon from this carbon monoxide and for the rearrangement we will see the pyrrole ring formation is going on quite well for these reactions.

So, for example, if we have R 3 here and R 2 here and R 1 here this carbon is coming from the carbon monoxide, well it is overall what we you will see that carbon monoxide is inserted into this tightness in reagent to give rise to the 6 member intermediate, from their own extrusion of this carbon monoxide oxygen to the titanium centered over all will give the product. So, what now we have seen them from an alkyne and an amine we can put together, an alkyne an amine along with carbon monoxide to give the pyrrole the fourth carbon in the pyrrole is coming from the carbon monoxide; a interesting quite an interesting rearrangement reaction that is involved after these 5 member tight titanium metellacycle intermediate. We will see the carbon monoxide insertion and then extrusion of the oxo or the oxygen atom from the carbon monoxide on the titanium center to give you the titanium oxo species; finally gives rise to the rearranged product that leads to the pyrrole synthesis, let us look at the pyrrole synthesis mechanism by utilizing this technique.

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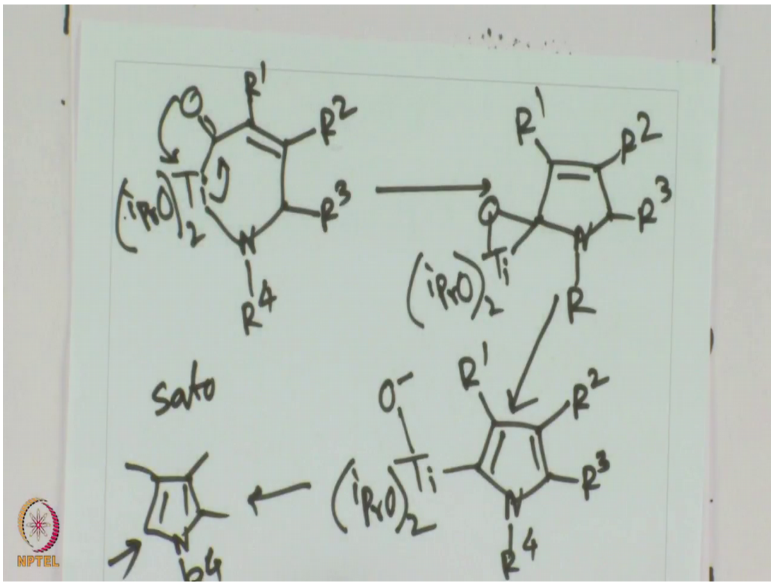

So, overall it will from this 5 member intermediate we will have a 6 member carbon monoxide containing species, where we will see that substituent are quite efficiently placed beautifully R 1 R 2 R 3 and R 4; over all these titanium isopropoxide then can be involved and as you can see this is overall will be a rearrangement reagent reaction, where the 5 member intermediate now will be forming to give rise to the you know pyrrole back bond and this substituent are in the correct place as we want them and from there on the titanium 3 member intermediate with the oxo in it can be synthesized quite easily by utilizing this technique.

Subsequently we can have titanium oxide relieved from this intermediate to give rise to the desired product, now these intermediates are quite efficient in synthesis of this pyrrole and high yield of pyrrole can be generated from this species. So, this is the final species and from there you get the substituted pyrrole and quite efficiently even in the yields are usually very high 60 to 90 percent yield can be can be obtained, this is reported by sato of course, R 1 R 2 R 3 and R 4.

This carbonate form carbon monoxide now this is once again a very beautiful and clean synthesis of pyrrole starting from an alkyne and an amine. So, alkyne 2 substituent and amine 1 substitute and will be there and pyrrole nitrogen is coming from the pyridine from the amine and the extra carbon that is required for pyrrole synthesis that it is indeed coming from the carbon monoxide, where titanium reagent will be capturing the oxo to give the titanium oxo; where carbon from carbon monoxide gets in into the pyrrole cycle to give the final product.

Now this is utilized quite well for pyrrole synthesis now we will see this titanium reagent for natural product synthesis or the fragment of the natural product synthesis; let us look at briefly 2 such example where this titanium reagent are used for natural product synthesis. We will be first synthesizing the model complexes of Mitocin. So, synthesis of mitocin models.

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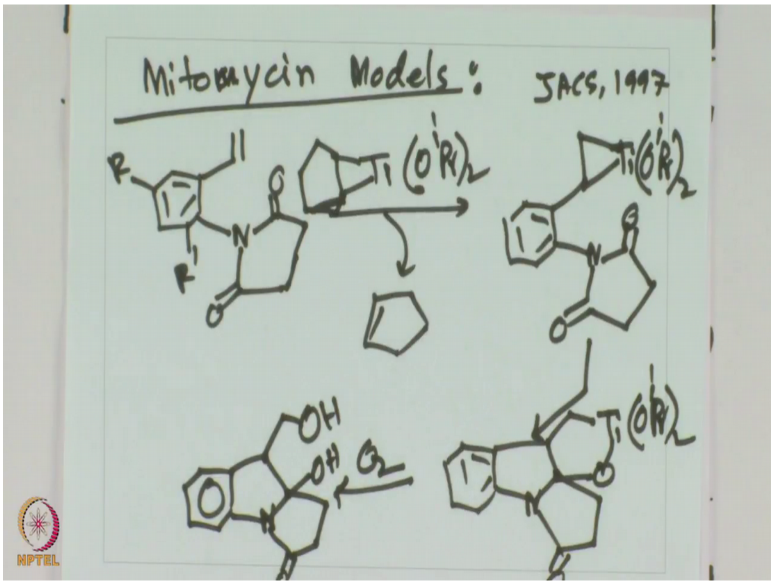

Mitomycin models well the reagent that we need can be prepared quite rather easily and this is reported in JACS 1997, where we have this advanced intermediate we see that olefin and the keto is rightly placed and if we are able to bring a suitable reagent; for example, titanium reagent we can start with this titanium cyclo propane type intermediate which was generated from the cyclo pentene intermediate. So, let us say over here overall we can get rid of this cyclo pentene.

Intermediate and from here on titanium can move on of course, titanium o isopropoxide is over there titanium can move on this olefin and it can form a 3 member ring, as one would expect and this is this oxidative cyclisation is once again very efficiently done and as you can see there is another keto that is right now sitting very close to this titanium reagent, from here on this keto reagent can be reacted with the cyclo metallocyclopropane ring, overall giving rise to an intermediate that you will have the 3 4 rings together form along with the metellacycle intermediate.

Then subsequently what we will see that this the oxidative cyclisation between this 3 member ring and the ketone will give rise to the cyclic titanium intermediate which will be very efficient in opening up with oxygen finally, giving rise to the product where of course, the substituent benzene substituent are there in the right place and overall we can get the di hydroxy intermediate which is a mitomycin model quite efficiently and we the yield was up to 60 percent.

So, what we have seen right now is in presence of an olefin and a keto which is just a posed placed beautifully within 1 molecule it is an intermolecular reaction we are trying to promote, starting with the titanium reagent titanium di isopropo propoxide unsaturated version of it if we are reacting with it initially of course, the olefin reacted to give the new titan syn intermediate with this 3 member intermediate with titanium in it.

That can then cyclize with the ketone overall to give rise to the 5 member ring which can then ring open to give to react with oxygen. So, therefore, the di hydroxyl intermediate can be generated quite efficiently by utilizing this technique. Will then move on to synthesize some various version of the short of oxidative cyclisation reaction; for example, next we will be discussing the application of this method for some few more organic molecule synthesis.

So, we will we will be synthesizing then cyclo butane. So, catalytic cyclo butane formation will be then focusing on which will be again very interesting for the organic chemistry perspective. So, strategically the cyclo butane reagent can be generated which are otherwise very difficult to synthesize. So, we will look at the catalytic cyclo butane formation by utilizing this Oxidative cyclisation technique in a moment.

We will not discuss many examples of it but main mechanism of the cyclo butane formation will be discussed in conjunction with the oxidative cyclisation processes let us go on Catalytic cyclo butane formation.

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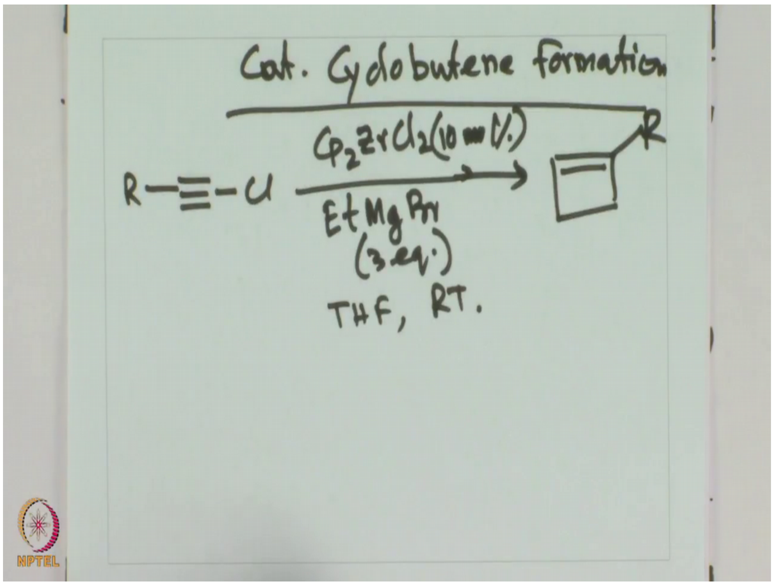

Well the reagent that is required for it can be an alkyne halide with it we can have for example, now dicyclopentadiene zirconium chloride which is used quite efficiently and a Grignard reagent 3 equivalent of it in presence of let us say 10 mole percent of the cyclopentadienyl zirconium reagent, overall it is a very beautiful reaction that gives rise to the cyclo butane by utilizing the simple reaction condition THF at room temperature.

So, overall this is a powerful technique where you will see in a moment, that the di cyclopentadienyl zirconium reagent is forming a 3 member ring which can then react with this reagent to form the 5 member zirconium intermediate, from there on further rearrangement will give rise to the cyclo butane formation. So, this is this is a once again a very powerful technique from synthesized from, since for synthesizing this cyclo butane ring where it is an alkyne halide alkyne halide is reacted with dicyclopentadienyl zirconium reagent.

We can have the zirconsin these 3 members zirconsin intermediate for example, by reacting it with Grignard for example Ethyl magnesium halide, which can give rise to the cyclopropane type of intermediate where zirconium is in there in the 3 member ring and from there on reacting that with the alkyne halide we can get the product.

So, we will come back with the mechanism of such reaction, for the cyclo butane reacts cyclo butane synthesis in the next class, till then please keep studying the oxidative cyclisation reaction and the application of this oxidative cyclisation reaction in organic synthesis. We will continue in the next class discussing on the cyclo butane and we will also start discussing mainly the reaction by utilizing a similar technique of oxidative cyclisation process, till then bye see you in next class.