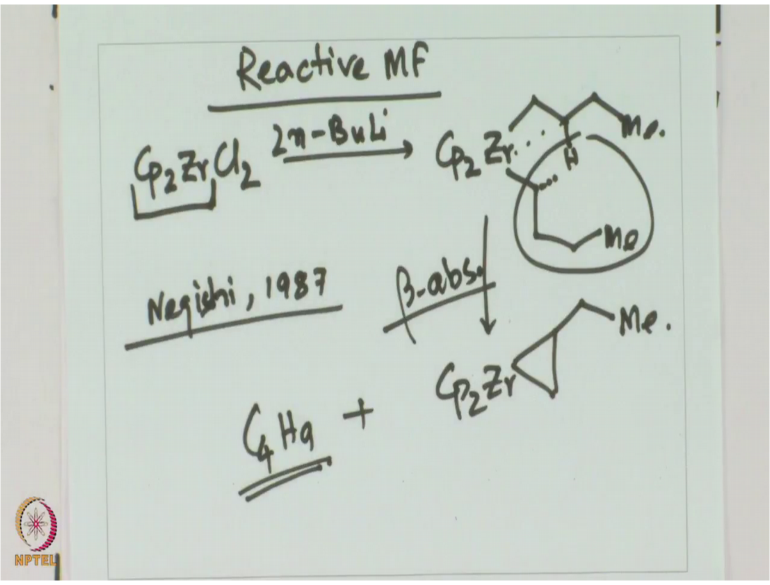
Metal Mediated Synthesis - I
Prof. Debabrata Maiti
Department of Chemistry
Indian Institute of Technology, Bombay

Lecture – 17
Application of oxidative cyclization in natural product synthesis

Hello, welcome back in the discussion of the oxidative cyclization reactions, we have seen oxidative cyclization processes in 3 different categories mainly, but today will mainly focus on the application of this oxidative cyclization technique mainly for the natural product synthesis; all let is before that let is look at these oxidative cyclization method and what are the transformation we can utilize or we can incorporate into this oxidative cyclization method, after discussing that we will get into the discussion of few natural product fragment synthesis by utilizing these very useful techniques.

(Refer Slide Time: 01:05)



So oxidative cyclization reactive intermediate we can first discuss reactive metal fragment, well first most important thing is to deliver the cyclopentadienyl zinc or zirconium intermediate by utilizing this technique. So, cyclo pentadienyl zirconium species are available with let is say for example, you can prepare very easily zirconium chloride; but from there on what we are essentially looking at the cyclo pentadienyl zirconium species.

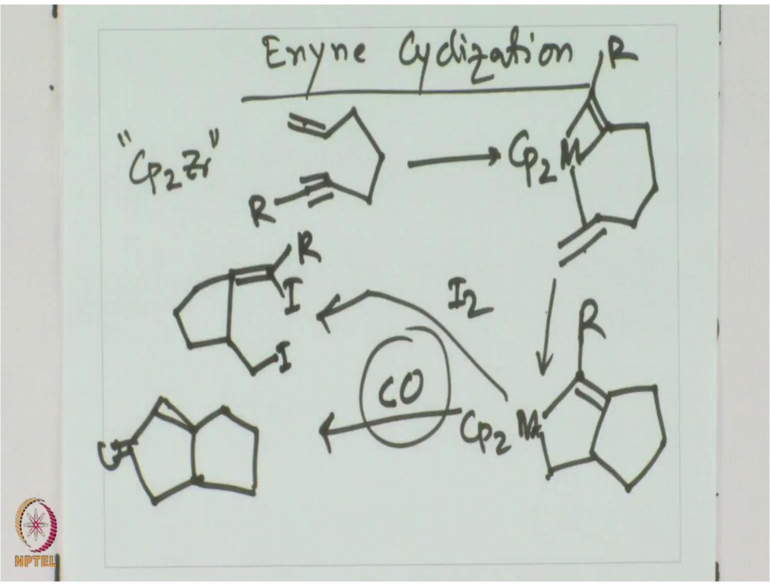
For this purpose as you can see that 2 chlorides are there we can take 2 equivalent of n butyl lithium this is reported by Negishi in 1987, 2 equivalent of n butyl lithium can be reacted to give you the Cp 2 zirconium and di alkyl intermediate right, from there on you can have these you know these processes where this hydride is basically undergoing beta abstraction, this is alpha beta zirconium in zirconium fourth class. So, therefore, there is no possibility of undergoing a beta hydride elimination from this process, from here on a beta abstraction at this position will gives rise to the intermediate formation that will see Cp 2 zirconium and then cyclopropane intermediate utilizing zirconium and your ethyl part over their overall from this part you will get the C 4 H 9 formation, which is the alkene information from there.

So, this is the beta abstraction intermediate that gives rise to the zirconium Cp 2 and then cyclopropane intermediate. What we have just now then seen how to prepare free or you know so called free cyclo pentadienyl; zirconium intermediate because thus that zirconium cyclopropane intermediate we can get rid of this cyclopropane intermediate in the form of a olefin right. Before that what we started with is cyclo penta dicyclopentadinal zirconium chloride which then can be reacted with n buli to give you of course, all the 2 equivalents of lithium chloride and 2 alkyl unit on the zirconium, from there on there since zirconium is in plus 4 oxidation state through at the first 2 steps, then what we have seen is it cannot undergo the beta hydride elimination because, for beta hydride elimination you need to have the electron available to participate into the process.

Therefore 1 alkyl group will take up the beta position hydride, directly to give the alkane and in during the process we will get a metallo cyclopropane ring formation by doing. So, we will have an intermediate which is ready to leave the metallo cyclo propene to an olefin intermediate to give you the Cp 2 zirconium, which is the active species which is what we need for our substrate such as alkyne and olefin to put together. So, the reaction whatever we have seen just right now are of not much importance except the fact that it can cleanly provide the formation of dicyclopentadiene nile zirconium species which is the real active species, that will be required for the next step of the process that is our the main goal or that is the main thing we were looking for.

So, all this reaction what we have discussed is nothing but for the formation of Cp 2 zirconium where this olefin can go out, let us look at this enyne cyclization where we will be discussing 1 in substrate another. I mean; that means, alkyne substrate 1 olefin 1 alkyne put together we will try to build a complicated molecule by or the value added molecule by utilizing the Cp 2 zirconium species, we have just right now seen how to generate the cyclo pentadienyl zirconium species; now utilizing those cyclo pentadienyl zirconium species we would like to get that enyne chemistry, let us get into the in enyne chemistry.

(Refer Slide Time: 05:47)



Enyne cyclization what we have essentially is quote unquote you can put it in quote. This is not really the you know directly form intermediate you have to synthesize in C 2 and along with it if you have olefin with it, we do have in enyne as an intermediate from here on; what we do see that cyclopentadienyl metal and this olefin and alkyne is reacting with it, first the alkyne will be reactive and therefore, we get the intermediate where olefin is appended from the metal center. So, olefin is kind of coordinated with the metal center you can draw that bond, so interaction between the metal and olefin. So, first alkyne interacting with the dicyclopentadienyle zirconium species to form this cyclopropane intermediate, from there on the olefin can coordinate with the metal center to gives rise to an intermediate or a process where the insertion of the olefin can then take place to the cyclopropene intermediate, overall then we will have cyclo dicyclopentadienyle metal and these organo metallic intermediate where it is nothing, but a metallo cyclo pentene intermediate with a another 5 membered ring associated with it right.

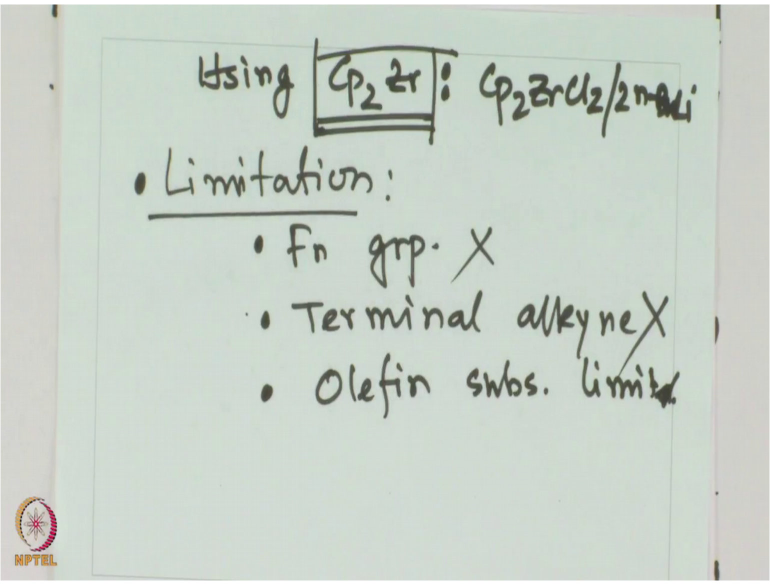
From there on if 1 wants one can look for so let us say for example, we are putting r. So, we should follow the r and then we can put for example, carbon monoxide to it to give rise to the overall the process where we have the cyclopentane ring, along with this we have a keto and the intermediate that can be cyclized further. So, that carbon monoxide can be inserted at this position to give rise to this.

You know the beautiful molecule if you are reacting with iodine for example, this metal carbon bond can be iodinated very beautifully to overall gives rise to the species, where extra cyclic double bond and r and di iodo can be synthesized from these processes. So, what we have seen right now is a very powerful technique, where both alkyne and olefin are together in 1 substrate dicyclopentadienyle zirconium participate in to the reaction by interacting with alkyne first in the way it forms the cyclo propene intermediate; that cyclopropene intermediate then interacts with the olefin the remaining olefin which was in less reactive compared to the alkyne.

Now that is that interaction leads to the Incorporation of the olefin into the cyclopropane ring to form the 5 member metallacycle Intermediate; that 5 member metallacycle intermediate then can be reacted with other for example, other electrophone such as iodine can be reacted because, this is a organ metallic intermediate already there. In fact, 2 of them both of those metal carbon bond can be for example, iodinated or we have seen carbon monoxide can be incorporated into this metal carbon bond.

Overall we can then have a 2 cyclopentane ring cyclo in a 5 membered ring or a 5 member and a 6 membered ring together for this oxidative cyclization processes; let is look at it the few more characteristic of these of the these oxidative cyclization process.

(Refer Slide Time: 10:00)



Using $\boxed{Cp_2Zr}$: $Cp_2ZrCl_2/2\,n\text{-BuLi}$

- **Limitation:**
  - Fn grp. X
  - Terminal alkyne X
  - Olefin subs. limited

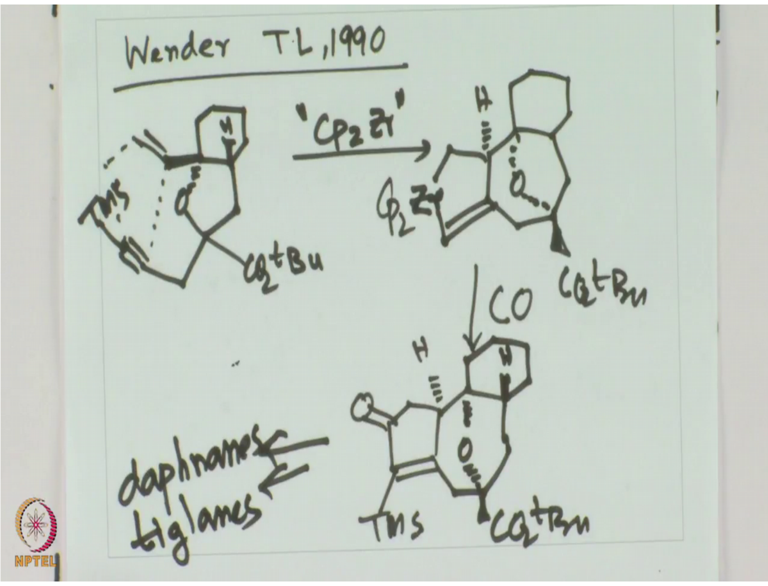
So, using this cyclopentyle zirconium species which is nothing, but your Cp 2 zirconium chloride and 2 equivalent of n buli that is what you need, di cyclo cyclopentadienyl zirconium species is in C 2 generated by to pentadienyl zirconium chloride and 2 equivalent of n butyl lithium, overall this is the reactive species this is a experimental very simple procedure and works to provide 5 or 6 in own system also terminal alkynes not tolerated under this reaction condition and substitution on olefin; however, is also limited functional group compatibility also is shown and terminal alkynes are not tolerated during these processes. So, overall we now know that there exists some limitation of the processes, if we have the substitution at these different olefin and alkyne some of the substitution will not be tolerated.

However, still this is a very important method despite some limitation as we said they still these are important method for synthesizing natural products, we will come in a moment let us first point out the limitation of these methods. So, limitation of these methods are very simply you know functional group compatibility is not that very high, we have terminal alkyne does not work for this process. We have to always then deal with the internal alkyne and in a substitution on olefin substitution is limited that is also another problem.

But the good things are it is experimentally simple procedure and watch to provide 5 or 6 different these in own systems.

So, there are good things but there are limitation of the method as well for these processes; let is look at them few of the natural product synthesis where these enyne method or enyne the technology can be utilized for a value added compound synthesis. So, for the rest of the class we will discuss how different natural product can be synthesized or is reported by utilizing this technique.

(Refer Slide Time: 12:50).



So, first we will discuss the natural product synthesis by wander back in 1990, they have reported it what they have reported simply is an advanced intermediate where or all these in an eyne are beautifully placed to give rise to an intermediate where CO2 t butyl and this alkyne is appended with it. Of course, as we said we cannot have a terminal alkyne. So, internal alkyne is fine tms protected which is nothing, but you know a bare alkyne if you would like to have it if your process is not tolerant of terminal alkyne, that is what you put a tms which can be deprotected later on and so what we have here is in an eyne.

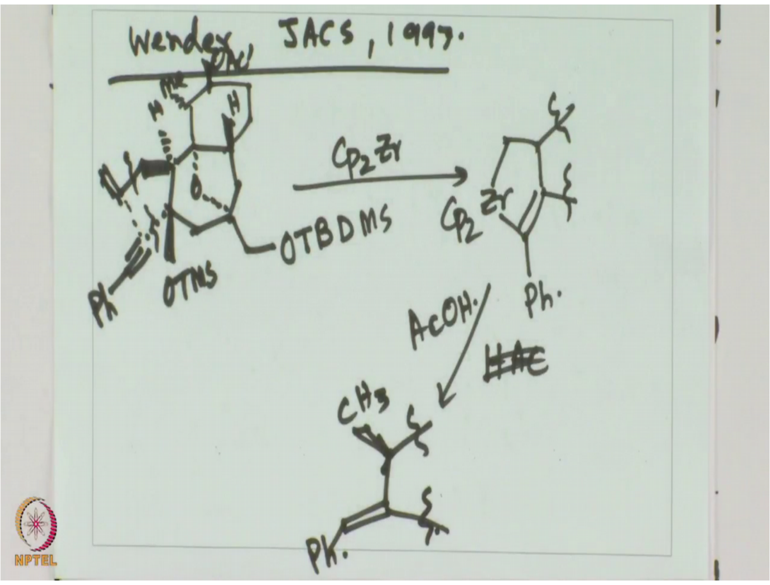
So, in eyne chemistry we are looking at the cyclopentadienyl zirconium species, as you know cyclo pentadiene zirconium dichloride and in butyl lithiums can be used to form this overall, then we will have an intermediate where this whole compound can be drawn correctly, can be formed correctly as well to gives rise to this intermediate; where you have these cyclo pentadiene as or zirconium 5 member intermediate right.

So, overall we are seeing the bond formation between this and zirconium is getting incorporated in here right. So, therefore, what we have seen that zirconium Cp 2 intermediate is formed from there on, if you are reacted with CO you should be able to incorporate the CO over there to form you the advanced intermediate that is required for the daph name synthesis.

So, let me draw this intermediate where you will have both a 6 member and a 5 member as well as this larger hetero cycle, where we have different substituent at this position that is tolerated for this value added product synthesis, which is then converted to corresponding daphname synthesis. So, the natural product daphnames can be synthesized, daphnames tiglanes can be synthesized by utilizing this technique. So, this is a very powerful technique, what you have also seen here is the functional group although these process is not that great for tolerating different functional group; we have seen ester is tolerated in the process we have olefin and alkyne put together in these processes to form a 5 membered ring which is coupled with a another large member heterocycle 1 2 3 4 5 6 7 membered heterocycle over all.

So, 5 membered 7 member and 6 member heterocycles are over all put together by utilizing this technique, this is going to be a useful technique for synthesizing a number of natural product we will see few of them right away. Some more natural product synthesis by utilizing this enyne chemistry which has already been reported and these are turned out to be quite an efficient method for preparing these fused, you know multi cyclic intermediate which is required for a number of natural product synthesis, let is look at the another wander synthesis wander this is jacks 1997.

(Refer Slide Time: 17:01)

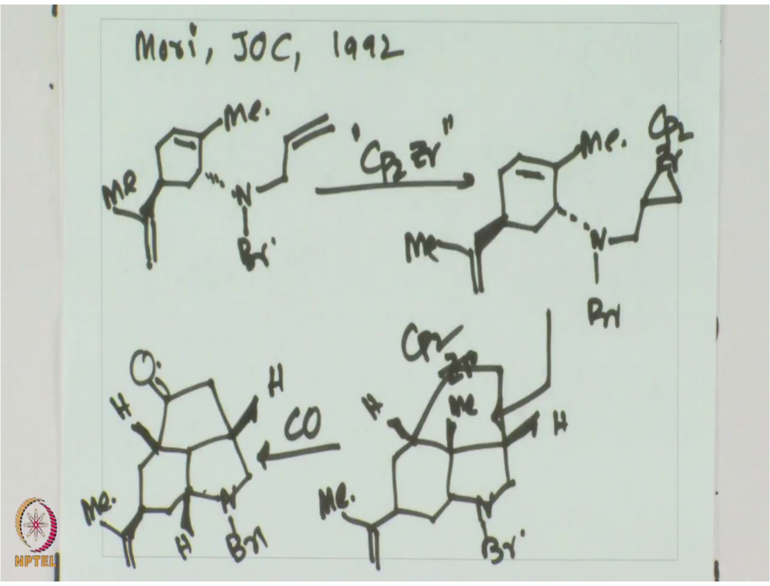


This is once again very advanced intermediate we will draw from here on, this is a 7 membered intermediate 1 2 3 4 5 6 7. So, 7 member intermediate would like to draw here and in the process we what is essential is to have an in enyne into the business right, into the substrate we have in and we have the enyne once again this is an internal alkyne and we have the alcohol a tertiary alcohol protected by TMS and we also have OTBDMS protection over therefore, for this another alcohol that is out there for the natural product synthesis; now we have a 6 member intermediate at as well were o acetate and methyl is there and then we have a hydrogen up there.

From this intermediate if you have the cyclopentadienyl zirconium what once again you can put together is this a olefin and the alkyne can be incorporated can be stitched together. So, let us not draw the remaining part. So, simply we can have zirconium Cp 2 intermediate that is incorporated into the substrate to gives rise to we are not drawing the rest of the intermediate. So, rest of the intermediate can be so this from this part and that part that can go on and finally if we are taking acetic acid ACOH acetic acid into the picture, what we overall get is the formation of a methyl and a terminal or internal olefin in this case to gives the advanced intermediate for a natural product synthesis as well.

Well this is very powerful technique as you can see that chemistry is very simple, you have been an enyned that is 1 in and 1 enyne 1 olefin and 1 alkyne you can put them together with cyclo pentadiene zirconium intermediate and finally depending on the target molecule you can incorporate either proton or iodo or even carbon monoxide or even other electrophile during the processes for synthesizing the natural product or any complex molecule of interest. we will see few more example of the similar type where again once again in and enyne are put together to give rise to the desired product formation; let us look at one more compound where indeed now we will see that olefin and olefin coupling is happening rather than in and enyne, that is also possible.

(Refer Slide Time: 20:06)


Mori, JOC, 1992

Let us look at one such example this is by Mori in JOC 1992, the substrate that we have in hand is the one where we have a terminal alkyne and well 2 terminal alkyne once is less substituted, another is more substituted and another internal alkyne as you see in here. We have this substrate we have terminal olefin an internal olefin, but this is di substituted this is mono substituted; obviously, this is the one which is more reactive and it would be reacting with dicyclopentadiene zirconium intermediate as one would expect subsequently, we will get the cyclize intermediate from there on we can have this zirconium Cp 2.

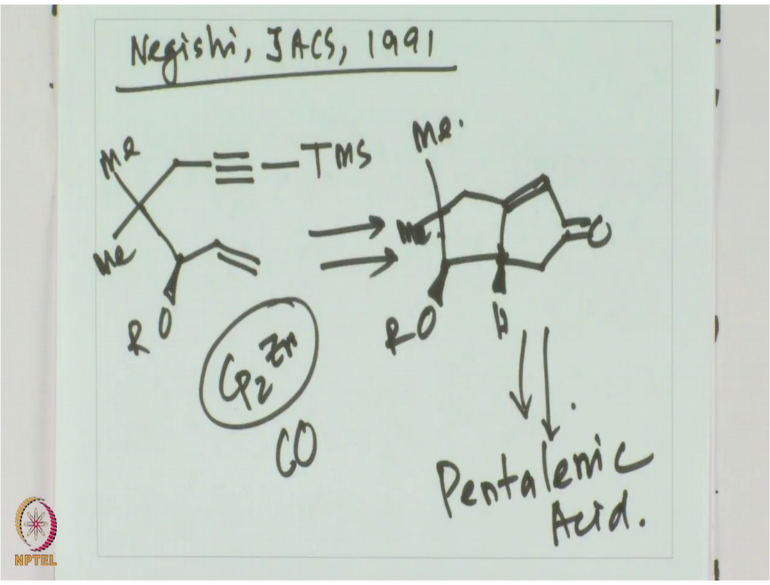
Cycloid cyclopropane type of intermediate other things are remaining intact without any problem and from there on what we do get is the attack of or in a participation of this olefin with this cyclopropane ring overall to give a very interesting intermediate that would lead to the dendrobium synthesis. Let is look at this natural product synthesis where a fused 6 membered ring with the 5 membered ring, now with n b n and of course, then we can have a methyl group on top overall we do have the hydrogen on top in this case and in the process we have zirconium incorporated and Cp 2 ring on also in there.

So 2 zirconium sorry to cyclopentadiene ring with zirconium this is a 5 membered ring and another 5 membered ring and a 6 membered ring appended with a di substituted olefin is produced over all over here in place of zirconium, we can introduce thus carbon monoxide in there to synthesize the dendrobium which is a very interesting natural product, but can be put together very easily by utilizing this you know cyclization technique by which is reported by Mori in 1992. Overall the final compound will look like from this oxidative cyclization reaction, we can get then in benzyl intermediate along with all the decoration that is required for this product formation, we have keto that is coming from here we have Cp 2 zirconium intermediate that will give rise to this product formation very efficiently.

By utilizing this oxidative cyclization technique well that is once again is a very powerful technique as you have seen here we have instead of an in an enyne, we have 2 in one is terminal olefin mono substituted another is internal one of course, that is the one which is very close to the terminal one that can participate into the cyclization reaction. The other one olefin that we are having the di substituted although this is terminal, but it is not placed in a faraway place which cannot be really participating that easily for the cyclization reaction; overall then we have an intermediate where quickly dif you know fused 6 5 ring formation is possible to give rise to the one of the very beautiful natural product simple and very beautiful natural product.

Well let us look at some more example of this type of oxidative cyclization reaction that is required for these various product formations processes well. Now look at the pentalenick acid synthesis by utilizing this in enyne chemistry, this is a very powerful technique again it is reported by Negishi JACS 1991.

(Refer Slide Time: 24:24)



What we see here is now once again back to the in enyne chemistry, we have a protected alkyne and a protected alcohol because, otherwise it will not be tolerated; overall what we see an enyne chemistry which will give rise to the simple intermediate with RO alkyl alcohol protected and methyl dimethyl one and the hydrogen should be over here; overall we have a double bond and CO generated from this process. So, of course, we are using the cp two. So, we are using Cp 2 zirconium intermediate from Cp 2 zirconium dichloride and along with n butyl lithium, along with this we are utilizing carbon monoxide to gives rise to this intermediate which can then further converted to pentalenick acid by using the further transformations.

So, once again we have seen various natural product synthesis by utilizing this technique, which is very interesting and what in the next class we might will be then discussing is the beta abstraction and how the beta abstraction will gives rise to this alkyne intermediate, from which we can do once again this beautiful chemistry that in enyne type of chemistry that 1 might will be interested in doing.

There remains a number of limitation of these in enyne chemistry as we were discussing for this type of you know reactive intermediate formation, this is where beta abstraction by this other method to prepare cyclo pentadiene zirconium can be very useful that we will be seeing in the next class. In today’s class we have seen then in enyne chemistry where both the double bond and alkyne is participating into the reaction beautifully. In fact, in 1 case we have seen 2 olefin are even participating together, but in all these cases we can synthesize a number of natural products, which are very complicated looking fused drinks it could be 6 7 6 or 6 5 5 or different variety of other variation of these fused rings that can be synthesized by utilizing this cyclo pentadienyl zirconium chemistry.

For cyclo pentadienyl zirconium synthesis we have started with dicyclopentadienyl zirconium dichloride intermediate and reacted it with the organolithium reagent in buli, which then gives rise to the di alkyle zirconium dicyclopentadyne species, from where a beta hydride elimination is unlikely and therefore beta abstraction goes on to give you the alkane that is cyclo that is butane and the remaining part can give you the cyclopropane metalla intermediate which can then gives rise to the or you know get rid of the olefin to give the cyclo pentadiene zirconium product.

Now this cyclo pentadiene zirconium is almost can be thought as a free cyclo pentadienyl zirconium species, which is free to react with an in enyne formation or to give specifically reacting fast with alkyne which is more reactive towards this zirconium and then those in cyclopropane intermediate can usually react with olefin to give the desired product in the next class.

We will discuss more of these oxidative cyclization technique and also we will be discussing 2 plus 2 cyclo trimerization reaction, along with the pauson khand reaction and till then please keep studying these methods, which are very powerful for synthesizing very complicated molecules which is otherwise might will not be possible by any other technique that very easily alright till then bye.