Metal Mediated Synthesis - I
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Lecture - 19
Kulinkovich Reaction and its mechanism

Welcome back. Today, we will discuss catalytic cyclobutene information reaction. We started the reaction in the last class. After catalytic cyclobutene formation, we will then move on to cyclopropane alcohol synthesis cyclopropanol synthesis Kulinkovich reaction that is another very beautiful reaction to form the cyclo butane along with it an alcohol or an amine. Subsequently, we will discuss the Pauson-Khand reaction and briefly we will discuss the mechanism in this class: First, then cyclobutene formation and then cyclohexane hydroxide synthesis or cyclohexane amines synthesis. Subsequently, we will move on to the cyclopentenone synthesis by Pauson-Khand reaction. Let us look at the catalytic cyclobutene formation.

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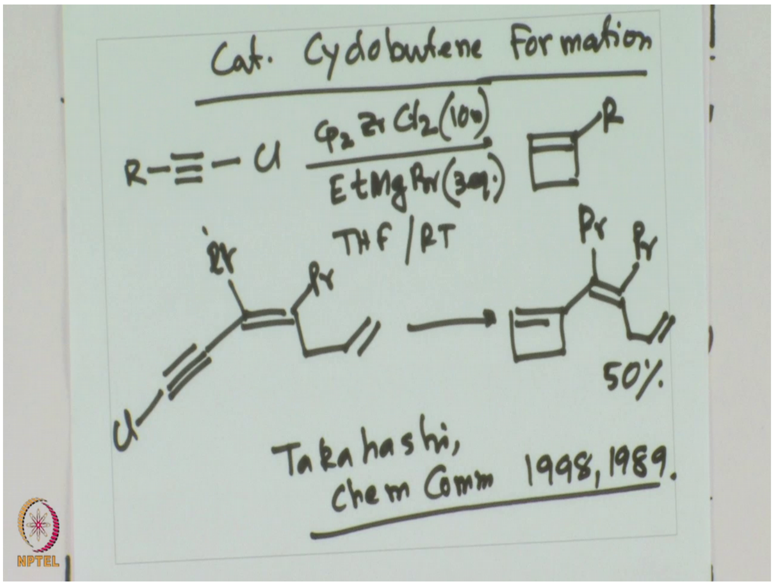
Cat. Cyclobutene Formation

Takahashi, Chem Comm 1998, 1989.

The reagent as you were mentioning in the last class that is required for this reaction is alkenyl halide. Alkenyl halide will react with dicyclopentadienyl zirconium. For example, dichloride you need a Grignard reagent to get the dicyclopentadienyl zirconium reagent from it that is why the ethyl magnesium bromide.

You need ideally that you know what is used over here is 3 equivalent THF room temperature and 10 mole percent of this gives rise to the cyclobutene species from this reaction and you can have the variation of it. For example, if you have cyclobutene chloride along with an olefin still selectively olefins will react with it to give rise to the desired cyclobutene product without touching the olefin that is associated with this starting material. This this species will remain unreacted from this synthesis and this is reported by takahashi chem comm 1998-1989. That is the phase number. It is a catalytic cyclobutene formation reaction which is beautifully done by starting from alkyl halide by reacting with dicyclopentadienyl zirconium unsaturated compound.

How did you synthesize di cyclo pentadienyl zirconium unsaturated compound? That is by starting with the zirconium dichloride species and reacting with the Grignard reagent such as over here. We have taken ethyl magnesium bromide for this purpose. Let us look at the mechanism of this which involves the oxidative cyclisation reaction as one would imagine let us look at the mechanism of it.

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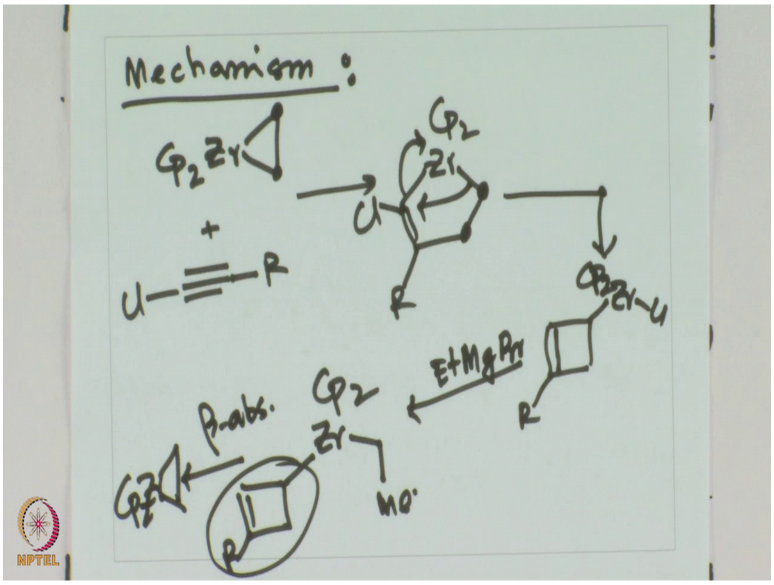

Overall, we will have the mechanism of this cyclo butrne formation. We in the process of course, di cyclopentadiene zirconium the cyclopropane ring will be formed. This is the ethyl magnesium bromide partner that is generating this intermediate. We have let us say R alkyl chloride and we will get a 5-member intermediate where di cyclopentadiene zirconium is part of that ring. Overall, we then have R and chloride over there and this is the 1 this ethyl. It is an oxidative cyclisation between this olefin and the alkyne overall, we will we will then get a 5-member intermediate from there on. This 4-membered ring formation happens and zirconium goes out with the help of ethyl magnesium bromide. We do need a cyclopropane ring formation that is the ring formation between this carbon.

And that carbon and then overall from there on the zirconium chloride and CP2 reacts and stage with it. And finally, we do have ethyl magnesium bromide that is used for the reaction participating in this again mgbrcl will go out zirconium alkyl intermediate coming into the picture and from there on we will see that beta abstraction will take place overall to give rise to the final product by beta abstraction to give the cyclo pentadienyl zirconium. You know 3 membered ring along with the B cyclobutene formation.

This part will give you the cyclobutene formation. This mechanism is as expected on a simpler note where cyclopentadienyl zirconium reagent is giving you the 3 membered metellacycle species of that is originated from ethyl magnesium bromide which then react with alkenyl halide to give rise to the 5-membered intermediate rearrangement from there on gives to the intermediate where zirconium chloride and cyclopentadinyl is a substituent on the cyclobutene ring that is just form and from there on another equivalent of ethyl magnesium bromide will give to the alkyl substituent on the zirconium. Where chloride is going out from there on beta abstraction will give rise to the cyclobutene formation and overall you will get back the zirconium this 3-membered intermediate zirconium metallacycle intermediate which then can be recycled for the catalytic cycle.

This is a very simplified mechanism for a cyclobutene formation which is a otherwise very difficult to synthesize by other technique from a readily available starting material. This simple cyclobutene formation then leads to the variety of product formation where even if you have other olefin associated with the cyclobutene ring still those can be tolerated under the reaction condition which is quite remarkable for oxidative cyclisation reaction. Then we will discuss Kulinkovich reaction which is the cyclopropane alcohol synthesis or cyclopropane amine synthesis from a suitable starting material. Let us look at how the cyclopropane alcohol or cyclopropane amine can be synthesized even from the simplest starting materials for example, ethyl acetate or any ketone and combination.

Any ester or amide in combination with the suitable olefin can give rise to the cyclo propane ring along with that hydroxo or amine substituent on it is. Let us look at Kulinkovich reaction and after this we will be looking at the Pauson-Khand reaction, Kulinkovich reaction.

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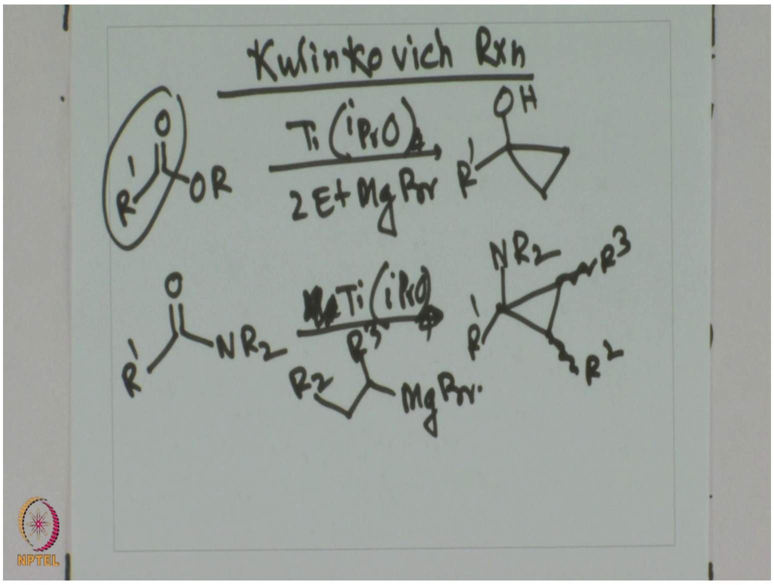

it is a as I mentioned it is a reaction of an ester and titanium tetra isopropoxide right with 2 equivalent of ethyl magnesium bromide, that will give rise to the cyclopropane ring with titanium titanus in intermediate will be formed and overall you will get the cyclopropenyl where this part is reacting with the titanus in reagent to give the cyclopropanol. A variety of different versions are known both stoichiometric and catalytic versions are known if you are taking an NR2 over here amide. You can have an amine substituted cyclopropane in this case methyl titanium isopropoxide was taken as the reagent and for example, you know isopropoxide again was taken and if you are taking R2 and R3 as the reagent from this we will have cyclopropane ring formation with amine substituent with it. For example, over here we can have substituent coming from different substituent coming from the alkyl Grignard reagent.

This reaction Kulinkovich reaction is a powerful technique for synthesizing rhe cyclopropane ring with alcohol or amine substituent on it. The first formation will be the titanus an intermediate where 3 membered titanium intermediate will be formed. Starting with a Grignard reagent if you for example, it is a it is a cyclopropane ring formation with titanium in it. For the ethyl magnesium bromide or any other Grignard reagent with substituent at the alpha carbon or beta carbon without any problem can be tolerated.

And these 3 members titanus in intermediate then can react with ester or amide to give the alcohol or amine substitution. On the cyclopropane ring let us look at the mechanism of it which is as you can expect. It is quite simple by involving the titanium cyclopropane ring formation reactions.

Let us look at the mechanism of it.

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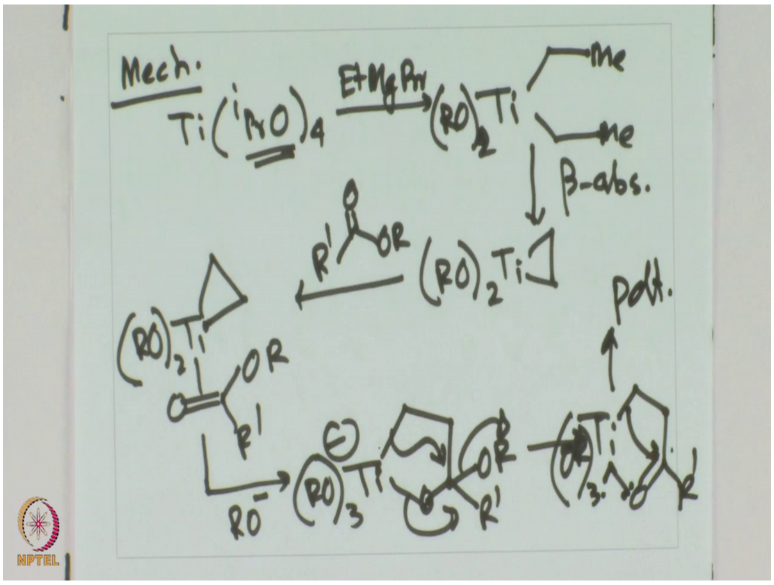

The mechanism adds as you would expect the first step as before it is isopropoxide for reacting with ethyl magnesium bromide to give titanium di alkyl intermediate if you want to go through it. RO2 from there on a beta abstraction will set to the ethane and that titanus a intermediate where different RO groups can be reacted from there on for example, the ester if we are talking esters can be reacted to give rise to the coordination first of the ester with the titanium intermediate with cyclopropane ring on it and overall.

Then this intermediate can gives react with the RO minus that alkoxide that we were using for the titanium this alkoxide can react or attack the titanium to make it RO3 minus and a 5 member. Now, oxidative cyclisation between these 3-member metallacycle and the ketone will take place to give the overall 5 membered intermediate giving rise to a species, where this ester is attacked by this cyclopropane ring. And finally, this will then move on to give you give you overall this intermediate from where formation of the cyclopropane ring can be envisioned very easily. This is the intermediate where the cyclopropane ring will be forming of course; this lone pair can be coordinated with it.

We have over 3 along with it and r prime from here the product formation can be envisioned. Overall as you can see it is a titaniusm intermediate formation with a 3 member cyclopropane like intermediate that is reacting with the ester where ester is first coordinated with this titanus in intermediate and then oxidative cyclisation gives rise to the 5 membered intermediate which upon rearrangement of course, the ester living group OR will go out upon rearrangement and it can ring closed to give the cyclopropane with substituted with the alcohol substituent as one would see quite easily. Now this Kulinkovich reaction not only can be reactive with various with various this Grignard reagent partner that can that can be envisioned.

Of course, if the cycle metallo titanus in reagent can be exchanged with another olefin that for example, styrene if you are interested in bringing in the styrene. Styrene can be reacted with for example, ethyl acetate or any suitable ester to give rise to the cyclopropane ring. That 2 carbons will be coming from styrene double bond and carbonyl center carbon will be forming the 3-membered cyclopropane ring from there and we can also get the corresponding alcohol. So, cyclopropanol synthesis can be can be simplified by this Kulinkovich reaction which is a very powerful technique for synthesizing such compound. Let us look at the look at the styrene example where we will see that styrene is participating in these reactions.

We will be discussing the example with styrene and ethyl acetate Kulinkovich reaction continuing.

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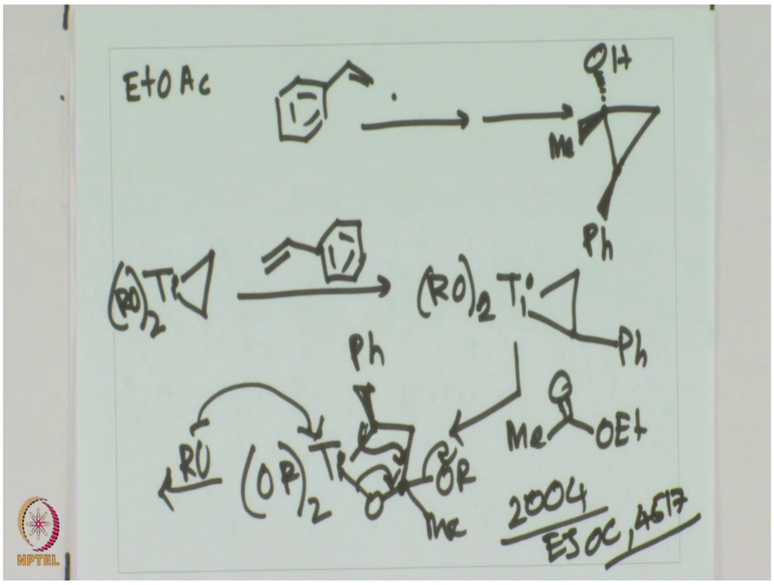

Ethyl acetate is reacting with styrene to give rise to the of course, the reaction condition is similar as we have discussed ethyl magnesium bromide titanium isopropoxide 10 mole percent. Overall, for from this Kulinkovich reaction we get an intermediate where we have cyclobutene formation from this and you know eth methyl is coming from the ethyl acetate that methyl and this hydroxy in forty 2 percent yield.

Now, this is again starting from a titanium cyclopropenyl like intermediate. We can then swap with the styrene this olefin can be swapped with the styrene. Overall then we will have di alkoxide titanium this cyclopropane intermediate where this phenyl is associated with it. Subsequently, we can have ethyl acetate for example, over here will interact with titanium will interact with this first and during the process it will it will generate the chiral center as 1 or 1 of the diastereomer that would be generated over here.

And this will be up and we can have the OR di isopropoxide intermediate from there on another alkoxide will be attacking the titanium, overall to give the RO3 minus just like before and during the during the cyclisation this step that step will proceed with the retention of configuration at the migrating carbon.

This carbon center during cyclisation when it is migrates over there. This will go out and this, remember will coming in during this during this migration. It occurs with retention of configuration that is quite interesting. Overall you will see that these diastereomer formations are quite interestingly set up by this Kulinkovich reaction published in ejoc 2004.

2004 ejoc 4517 is the page number this is again a beautiful reaction, Kulinkovich reaction. Where we have seen styrene can be participated for example, also with ethyl acetate CH3CO acyl part is participating in to the cyclopropane ring formation with this styrene intermediate. Where styrene reacting with the acetyl part to give the cyclopropane ring and cyclopropanol formation is happening with retention of configuration at the key bond making step that we were discussing.

The mechanism for these reactions are very simple oxidative cyclisation is at the core of these processes where, we have seen that metal oxidation step goes up by plus 2 during the oxidative process and then cyclisation kicks in wherein we do see that the prod interesting product can be generated by this technique. Well now we will move to the next example of this oxidative cyclisation process. Where olefin and alkyne along with carbon monoxide can be participating and giving rise to the beautiful cyclopentenone product formation. These are the name reaction and very famous reaction known as Pauson-Khand reaction, where olefin and alkyne is participating with carbon monoxide overall to give the 5 membered cyclop cyclopentenone formation quite efficiently.

The mechanism of these reactions are quite if is quite simple, but it is quite attractive as well and the application of these reactions are far reaching and many natural product synthesis has been utilizing this technique or this strategy beautifully over the years or decades. I would say now, let us look at the Pauson-Khand reaction where 3 membered intermediate or 3 membered reagents or 3 reagents are participating in in in the cobalt side to form the final product Pauson-Khand reaction.

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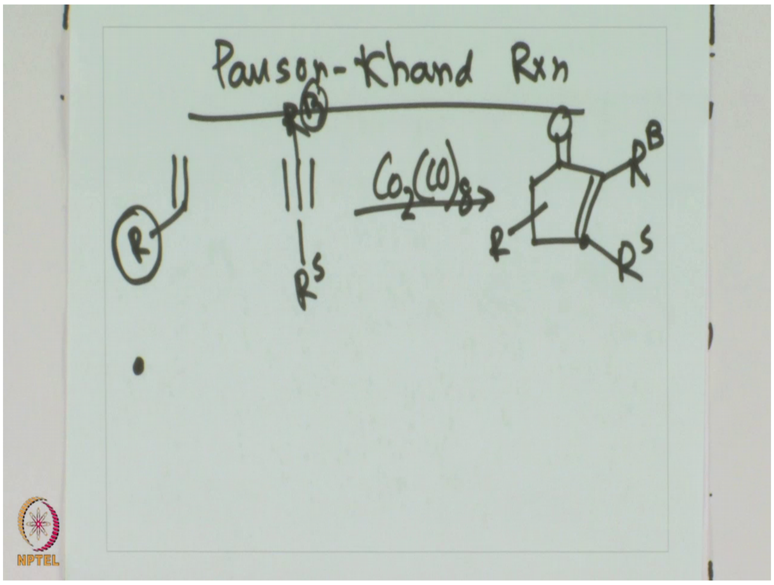

Pauson-Khand reaction is one of the very widely studied reactions. Pauson-Khand reaction usually, it is an olefin substituted of course, and then alkyne again it can have small group and a big group this is big and this is small. Overall you will see that reacting with di cobalto di cobalt centre CO2 CO8 and giving rise to the cyclobutinone product where big substituent is near the ketone side and the small substituent on the far from the ketone and the R can be at alpha or the beta position. Usually, acetylene and terminal alkyne works based that is that is from the alkyne part acetone and terminal alkyne works based. It is very sensitive to alkene substituent the type of substituent will control the reaction quite a lot.

In general, tri and tetra substituted alkenes really do not work that very well. Excellent functional group compatibility is same for this reaction and most commonly it is performed with stoichiometric amount of this cobalt to di cobalto CO2 CO8. In there are; however, many instances where we have seen that huge of alkyne complex that is CO2 CO6 alkyne complex. This this as you see is a very powerful technique for formation of cyclobutinone cyclopentenone cyclopentenone synthesis can be always very simplified and whenever a cyclobuti cyclopentenone ring is there or any advance analog is there. That is usually trusted with this natural product synthesis for utilizing the Pauson-Khand reaction. It is between an olefin and an alkyne along with a carbon monoxide to give the 5 membered cyclopentenone reaction intermediate.

Now, as you have seen olefin can be of different substituting substitution pattern; however, tetra substituented tetra substituted olefin or tri substituted olefins are usually problematic for these cases. It works beautifully for alkynes which are terminal in nature or acetylenic in nature otherwise functional group tolerance is quite high for these reactions and that is a very good news usually stoichiometric amount of CO 2 CO 8 is used for this reaction di cobalto octa carbonyl species are used, but sometime it is also CO 2 CO 6 alkyne species are used for these processes. Let us look at the mechanism of these processes how olefin and alkyne is put together along with carbon monoxide to give the 5 membered this organic intermediate, which are cyclopentenone of in nature and we will see the subsequent application of this method in the next classes.

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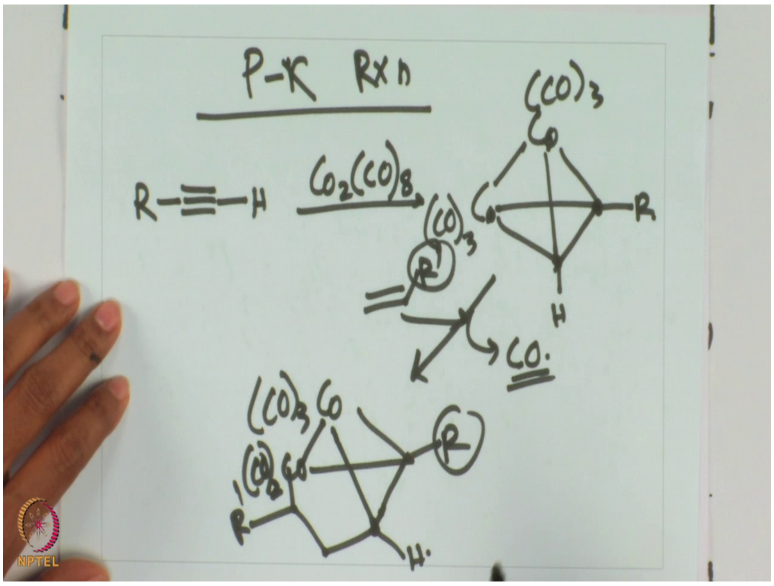

Pauson khand reaction and mechanism we are going to discuss PK reaction Pauson-Khand reaction. Now usually as you was telling it is although it has excellent functional group compatibility. It is very sensitive to alkene substitution; in general try and tetra substituted alkenes do not work that very well. Acetylene and terminal alkynes are the best one. Let us therefore, take the terminal alkyne; one of the terminal alkyne is reacted with the starting material which is used usually in stoichiometric fashion. We can have COCO3 and another cobalt CO 3 reagent in another center.

Overall, we can have this alkyne incorporated interacting with the di cobalt centers as is shown and this is both the cobalt centres are interacting with both the carbon centers.

This cobalt center interacting with this carbon center this cobalt center is also interacting with this carbon center. There is a bond between them and this cobalt also interacting with that one this cobalt also interacting with that 1 this is the insertion that controls the regiochemistry the insertion that we will see right now; where 1 of the carbon monoxide will go out from let us say, one of these processes usually the 1 where the substituent is you know far from it. This carbon center is attached with attach to it both the center, but the substituent which are which are having both the carbonyl.

In tris carbonyl spaces one of the unsaturation is created by leaving the CO and the insertion is controlling that chemistry over here. We will see the insertion of olefin let us take taking olefin here insertion of olefin will take place in a moment where COCO3 and R that this R is coming from the alkyne and this carbon center is associated with it this insertion is occurring over here. This is the R prime this is R prime olefin that is that is interacting over there we have taken this di cobalto species for this reaction and overall this is the intermediate where insertion is happening and insertion of the olefin over here gives rise to this intermediate from which alkyl migration and reductive elimination will give rise to the product formation will draw in the next space.

What we have seen in this reaction mechanism is alkyne reacting with the di cobalto reagent to give rise to the intermediate which is very efficiently giving rise to the alkyl migration, which is controlled by the which is the center where the geochemistry is control. From where on we will see how the subsequent reactions are going by migration and reductive elimination processes. From that intermediate let us try to draw the alkyl migration.

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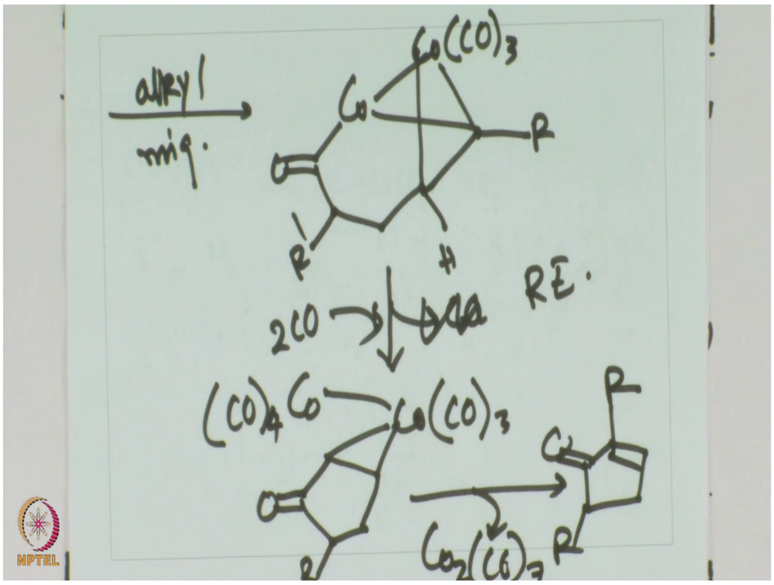

From that previous intermediate alkyl migration happens and it gives rise to the very beautiful intermediate that is leading to the product formation. It is already looking like product now that is great news and from there on we will see that subsequent reductive elimination will lead to the product formation.

Here reductive elimination and will lead to that we need 2 equivalent of CO. Of course, reductive elimination in this step will lead to an intermediate where mono cobalt intermediate is inserted into the ring and overall this species then forms subsequently to give the product final product. This is then can taken to the cyclobutene product formation that is involved into the process. From here CO 2 CO 7 will go out. In this case what we have in particular seen that an alkyne terminal alkynes in particular we have taken. Terminal alkyne first reacted with this di cobalt center, to form the intermediate which then can incorporate the olefin which insert selectively and that the olefin insertion is the selectives step.

From there on alkyl migration onto one of the CO with cobalt species happens and then subsequent reductive elimination closes learning to give you the cyclo pentinone intermediate. During this process of course, cobalt CO 2 CO 7 goes out from the species. Overall then this process is quite powerful in putting olefin and alkyne together. Although, all the substituent on the olefin an alkyne cannot be tolerated, but quite a wide variety of dye substituted olefin mono substituted olefin can be taken along with the alkyne which are limited by the you know acetylene or a you know terminal alkyne. Mainly these are the ones which is incorporated along with the carbon monoxide to give rise to the cyclo pentinone intermediate.

The steps involved is the incorporation of alkyne then the migratory insertion of the olefin into the resulting intermediate. From there on the alcohol migration into the carbon monoxide of the one which is associated with the cobalt and from there on reductive elimination closes the ring to give the final product.

With this we will conclude today’s class. In the next class, we will continue discussing the Pauson-Khand reaction and some application of this. Please do keep studying these new reactions that Kulinkovich reaction Pauson-Khand reaction on also cyclobutene ring formation that we have discussed today, till then bye-bye.