Metal Mediated Synthesis - I

Prof. Debabrata Maiti
Department of Chemistry
Indian Institute of Technology, Bombay

Lecture - 20
Pauson - Khand reaction

Hello, welcome back. Today we will discuss Pauson-Khand reaction; mainly the Pauson-Khand regiochemistry. In the last class we have introduced the Pauson-Khand reaction; it is a oxidative cyclisation reaction between alkene, alkyne and carbon monoxide. We get cyclopentenone as a product; that is a very interesting fact. Now how to put together all these three components to give only one product is really an interesting task; we have seen that mechanism also in the last class.

Today, we will discuss more about the regiochemistry of this reaction and also the real examples; how it was a stoichiometric reaction first and then an intramolecular version of it and subsequently it has become catalytic as well as inter-molecular reactions, are nowadays possible. This has been utilized quite a lot for natural product synthesis; even a symmetric version of the Pauson-Khand reaction is possible. So, all these will be discussed today, let us look at the key factor that determines the regiochemistry in the Pauson-Khand reaction; so, Pauson-Khand regiochemistry.

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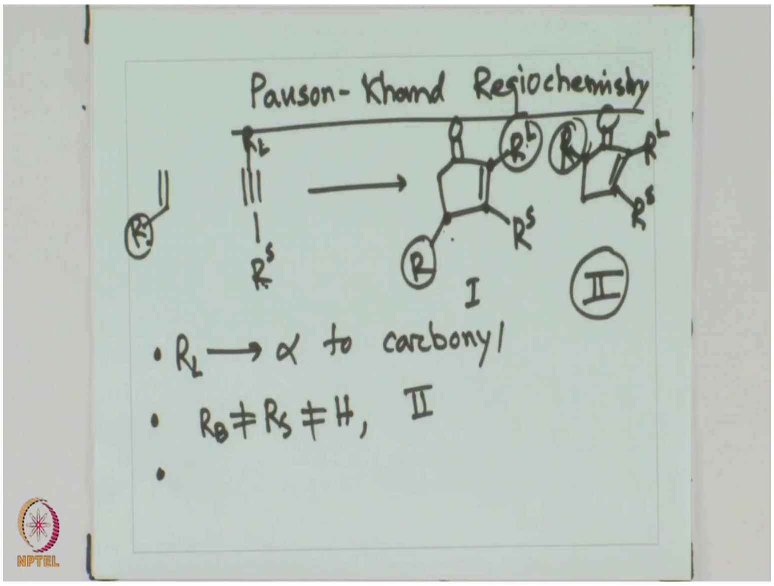

Pauson- Khand Regiochemistry

- $R_L \longrightarrow \alpha$ to carbonyl
- $R_B \neq R_S \neq H$, II
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Now, as we were mentioning; the substrate we have in hand is olefin and an alkyne; usually terminal alkyne works better. But if it is an internal or disubstituted alkyne, still it works let us say you have R S small group and R L large group, one large group on the alkyne, another small group on the alkyne and if they are same; you do not have any problem.

If you have olefin; let us a substituted as R the product or rather products in this case; one can have is two different one, where R L could be there R L usually at close to the big L or R group will be close to the carbonyl and the small R will be far from the carbonyl. Now in one orientation you can have R at this position close to S, another orientation you can have or another regiochemistry you can have where R is close to the carbonyl; always R L is close to the carbonyl.

So, as you can see R L and R S; one is large one is small, the large one is always close to the carbonyl; large substituent is close to the carbonyl, the small substituent is far from it. Now in this cyclopentenone, the R which is coming from this olefin; this R, now this R can be far from carbonyl or close to carbonyl; these gives rise to that two regioisomers.

Now as we are saying; R L or the large substituent will be always close to carbonyl. And if these R L and R S is not or are not H or if these are not hydrogen, then mostly we get this compound II. So, the first fact is you will have R L always alpha to carbon; nil, R L will be alpha to carbonyl that is the first fact. Second fact would be if R B is not equal R S is not equal H, then we get II as the product; the second product we always get. If regiochemistry at alkene actually that so the R; whether it is at the far position or close to the carbonyl; it will dependent on the alkene; as well as alkyne. So, the type of alkene and type of alkyne will determine, whether R is at this position or R is at that position.

Also this can be controlled by ligation on the different metal centre that we will be discussing in a moment. So, what we have seen so far is the rule that governs; to give the regioisomers two isomers are possible, as you can see the substituent R on the olefin can be closed to carbonyl or far from carbonyl.

Now, that will be determined by the olefin itself and in combination with alkyne substituent. Also we know that the ligand on the metal center required for this reaction can influence the regiochemistry of the product formation. Another important thing is, if your; those alkyne substituents are not H then usually we can get the product where R from the olefin is alpha to the carbonyl moiety.

So, these are the things we will see again and again; as I was alluding to there was first the stoichiometric version for long and then subsequently in the mid 90’s; we have seen the catalytic version of this reaction, not only intramolecular reaction; even intermolecular catalytic version was also put forward later on. Let us look at some of the Pauson-Khand reaction examples and we will be discussing two three examples in terms of the natural product or complicated molecule synthesis first. Then we will be moving to the catalytic version of these reactions; Pauson-Khand examples.

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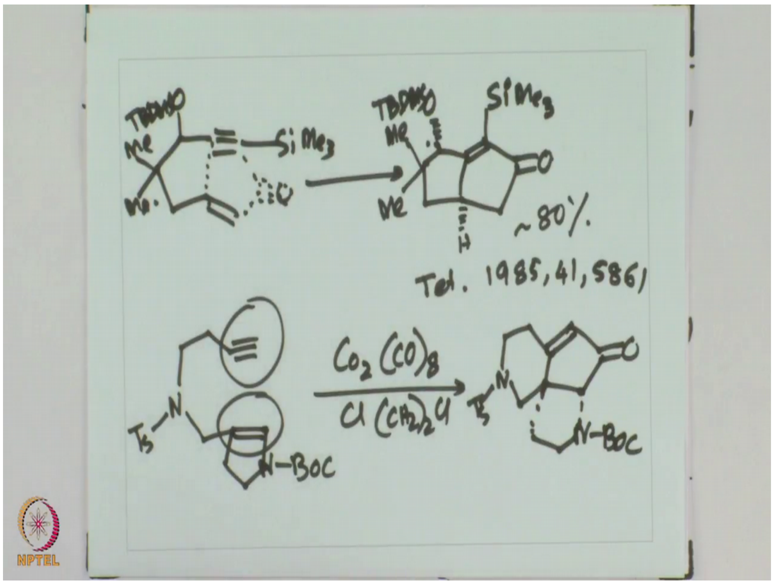

Let us look at a substrate where you have O; TBDMSO and an alkyne together with an olefin. You have this olefin and alkyne together, you would like to do the Pauson-Khand reaction in presence of C O; under the standard reaction condition of the Pauson-Khand what you will get it is at stoichiometric reaction. At the beginning as I said, this is the product you get cyclopentenone with this very good yield something like it; nearly 80 percent yield can be obtained and this is the major product 26 is to 1 regio selectivity or the or the regeochemistry can be maintained quite very effectively.

Now this is reported in tetrahedron in 1985 by Magnus, this is an intramolecular reaction as you can see the bond formation between this alkyne and olefin and then there is a carbonyl that is coming into picture. So overall, you see the Pauson-Khand reaction occurs quite efficiently nearly 80 percent yield and 26 is to 1 for the major product formation.

Let us look at another example, where similarly an alkyne and olefin will be put together along with carbon monoxide C O 2, C O 8 and stoichiometric amount of them and then this reaction will be you know giving you to the desired product. Another example N T S; of course, alkyne should be straight, but just to give you the real feeling how it might will be happening we have drawn like that.

Now this is once again you have an alkyne, you have an olefin together and you are doing this reaction in presence of dicobalto octa carbonyl and then with dichloroethane. Overall in this reaction what you get, this is again by Magnus in tetrahedron later 2002; you get the desired product and that is the cyclize it defused cyclic (Refer Time: 09:33) compound that you one get.

So, the 5 member cyclopentenone and then your desired product that is there in very good yield depending on this nearly the 60 to 70 percent yield can be obtained. Now these are the really powerful reaction for constructing the cyclopentenone known kind of a intermediate.

Now, we will see another example where once again an alkyne and olefin along with the carbon monoxide will put together in presence of dicobalto octacarbonyl spaces; for giving you the cyclopentenone intermediate. Let us look at one more example of this series to establish the fact that; these oxidative cyclisation are a reliable technique for synthesizing these cyclopentenone products.

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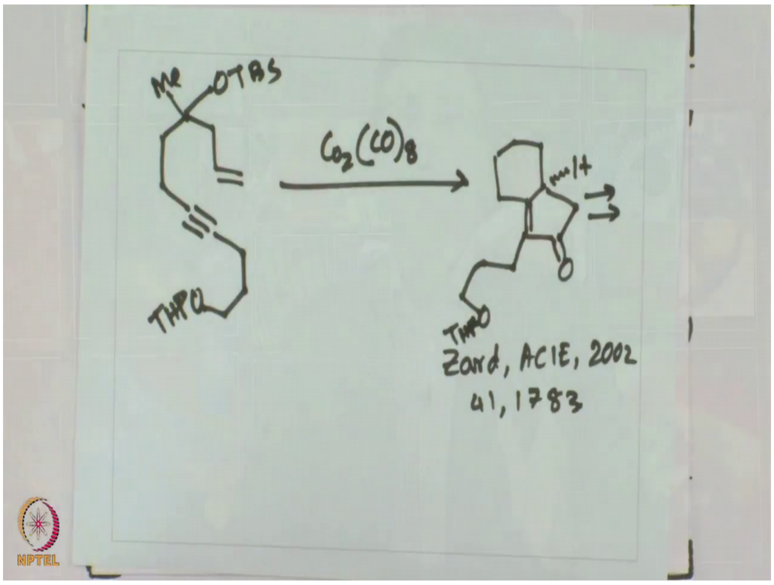

Now the example we have had in hand is the one, where it is substituted very efficiently. Once again an olefin, terminal olefin and an internal alkyne are participating; this is a report by Zard in ACIE 2002.

So, this is by Zard ACIE; 2002 41, 17, 8, 3 the product in this case; the starting material you need is again the dicobalto octacarbonyl species. And overall you get this product very efficiently and the desired cyclopentenone is formed rather easily in this cases. So, from there on plus minus 13 dioxide carotene can be synthesized. Those are the natural product synthesis can be done very effectively under this condition.

So, what once again you have seen here is an terminal olefin and an internal alkyne put together in presence of carbon monoxide to give you the desired product, which is going to be your cyclopentenone; which can then be further taken towards the natural product synthesis. These are indeed very powerful technique and whenever you see a 5 membered ring with the cyclopentenone motive or any you know further functionalized motive, this is the way perhaps to synthesize it reliably and the yields are usually quite very good.

Now let us look at the catalytic version of this reaction, where in mid 90’s; it was first reported. And we will see first reaction of course, was intramolecular catalytic version and then subsequently people put forward. Even the intermolecular catalytic version for this, but of course, there is a limitation in terms of substrate huge for this reaction and we will discuss that in a moment. Let us look at the catalytic version of these reactions; first catalytic Pauson-Khand reaction.

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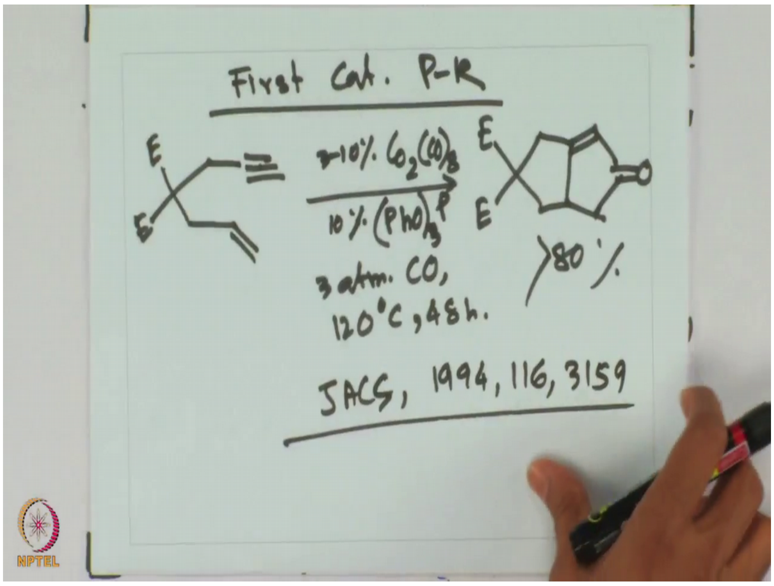

Pauson Khand reaction; now the substrate and surprisingly it is an intramolecular substrate, where you have alkyne and olefin; terminal alkyne and terminal olefin together. Now the catalyst that was taken is 3 to 10 percent; that is again the catalytic first catalytic version and dicobalto octacarbonyl species 10 mole percent of the ligand that is ether version of it. And three atmosphere pressure of C O; 120 degrees C in DME (Refer Time: 13:53) and 48 hours and so on and the product as expected is the one oxidative after oxidative cyclisation under Pauson-Khand condition.

Now, this becomes very standard and nearly 80 percent yield greater than 80 percent yield can be obtained for these products. Now that becomes the standard or the hallmark for this sort of reaction. We have seen nowadays, whatever Pauson-Khand reaction we do see; usually the reaction conditions are quite similar to these. A variety of the substituted Pauson-Khand product cyclopentenone can be synthesized by utilizing this technique, the yields are usually on a higher side 80 to 90 inch; 80's and 90's; for this different substituent can also be tolerated under this condition.

Well, let us look at more of an intermolecular version where we will see; always we were so far discussing the substrate where alkyne and olefin together within one. Now, we will get the intermolecular filling for these reactions. Well let me first give you the reference;

this is a JACS by Zhang and Zhuang 1994, 116, 3159; this is the reference for this and then we will now discuss the intermolecular version; where we will take norbornene type of substrate. So, it is highly substituted one and of course, it is also a strained one; now that alkene as a substrate and first intermolecular version once reported. Once again with catalytic amount of cobalt that is considered quite a way forward for this kind of reaction at that stage; let us look at intermolecular catalytic Pauson-Khand reaction.

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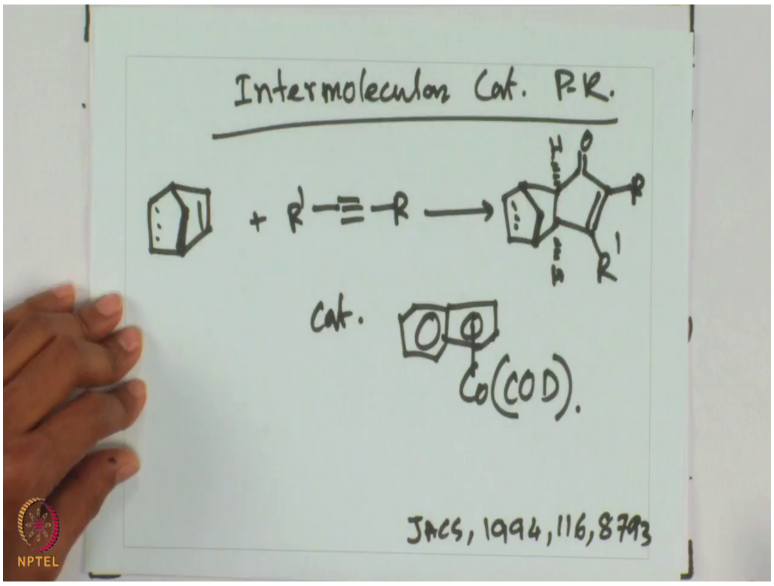

Intermolecular Cat. P.K.

JACS, 1994, 116, 8793

So, you need strained olefin for inter molecular reaction; the simple olefins simply does not work; you need strained olefin and you can react it with alkyne; terminal alkyne of course, is the best; overall you get the product that one would expect for this short of reaction. And that is the strained cyclo pentanone type of moiety can be synthesized very easily. And the catalyst that is used for these reactions are the one, where you have the cobalt in it along with cobalto sin cod moiety together.

Now this is reported by once again Zhang and Zhuang in JACS 1994 and this is a very good effective reaction; not only this, you can take terminal alkyne; different alkyne can be reacted quite efficiently utilizing this technique. Let us look at some of the specific example by utilizing this norbornene or norbornadiene as in olefin counterpart, along with the internal alkyne or terminal alkyne to give you the Pauson-Khand product which was reported in mid 90’s. Let us look at those examples.

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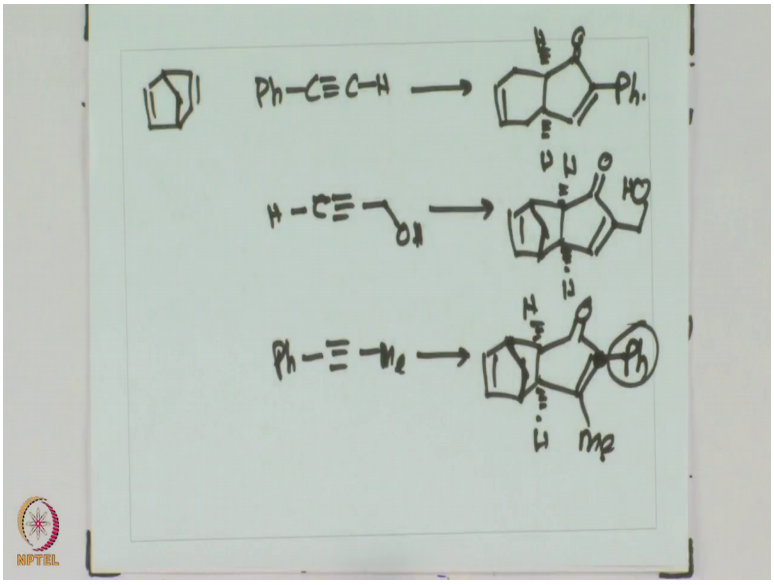

So, we will take norbornadiene as the first example where phenylacetylene is utilized as the substrate to give you the final product; where once again the desired cyclopentenone ring is formed quite efficiently. This is nearly 90 percent yield and if you are taking a propyl alcohol; once again you can get the desired product with the; once again with norbornadiene.

And this regiochemistry is quite efficient and only one product is forming; usually for these cases. And if you are taking an internal alkyne; that is also possible to react quite efficiently and that gives the product; once again quite efficiently under the condition; the desired cyclopentenone product are formed as you see phenol is right next to the carbonyl, methyl is there.

So, these are quite efficient of course these intermolecular reaction conditions; intermolecular Pauson-Khand reaction and that is under the catalytic amount of the cobalt catalyst; cobalt is used for these reaction. You can usually, the only limitation that we can see for these reactions is it has to be strained olefin; such as norbornene or norbornadiene as we have seen in these cases.

Of course, under these reaction conditions; one can do the intramolecular reaction as well; without any problem, the yields are even pretty good; 100 percent product formation can be obtained with it of course. So now, as I was telling not only it is possible to do the catalytic Pauson-Khand reaction; it is possible to do intermolecular catalytic Pauson-Khand reactions; it is also possible to do the asymmetric version of these reactions by utilizing a suitable ligand for the metal center. Now instead of cobalt; initially people who are using titanium as the; tetanus in compounds for this sort of reaction. Let us look at the asymmetric version of this Pauson-Khand reaction which could be quite interesting, because there are desired target molecules; where we need these stereocenter to be generated, so asymmetric Pauson-Khand reactions.

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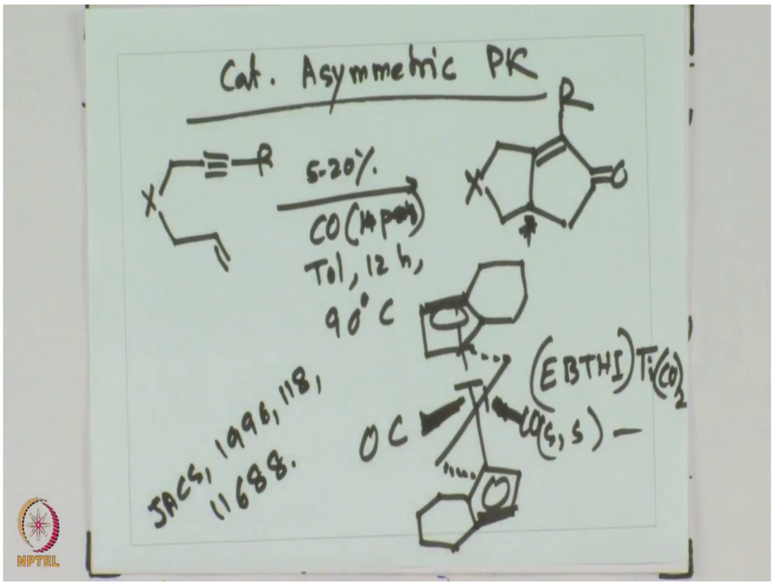

Of course, these are again catalytic asymmetric Pauson-Khand reaction. Well we will take the intermolecular version of course, at this point. So, that is rightly and nicely set; you take 5 to 20 percent of the titanus complex and C O; 14 psi; toluene and 12 hour; 90 degree C, you get the stereocenter that could be generated right over here and then cyclopentenone can be generated from these product quite efficiently.

The catalyst that is used for these cases are quite interesting one and now a days, it is a very familiar one and popular one as well. And this gives the product quite efficiently and this product formation can be done under very relatively mild coordination as you see 90 degree C is very efficient for this sort of product.

So, if this is EBTHI; that is how they abbreviate titanium dicarbonyl species; this is S S version of it. And this is giving the product quite efficiently; as we mentioned and we get the asymmetric center generated in a very high EE; something like greater than 90 percent EE, for most of these cases.

This is reported by Buchwald in JACS 1996, 118, 11688 and also there is a recent review in 2006 by Sebata in advance in kept in 2006; you may want to read. So, the yields for this sort of reactions are quite good and anuncio selectivity is usually greater than 90; that is efficient for this sort of reaction. And as you can see by using these tightness in reagent; Buchwald and co workers were able to get very efficient reaction and the stereochemistry can be set quite nicely and that could be a very useful method for natural product synthesis.

So, we have once again seen intra molecular version of the Pauson-Khand reaction where alkyne and olefin are put together along with carbon monoxide; 14 psi; carbon monoxide at 90 degree C which is a very good reaction condition to give you the good yield and good enunciation activity for these reactions. A plenty of examples you can look at in that reference or different substituents are also tolerated; different functional group were also tolerated under these reaction condition.

Let us look at another example of a asymmetric Pauson-Khand reaction before we close this. So, we will be looking at Pauson-Khand reaction in a asymmetry version once again; so catalytic asymmetric for Pauson-Khand reaction.

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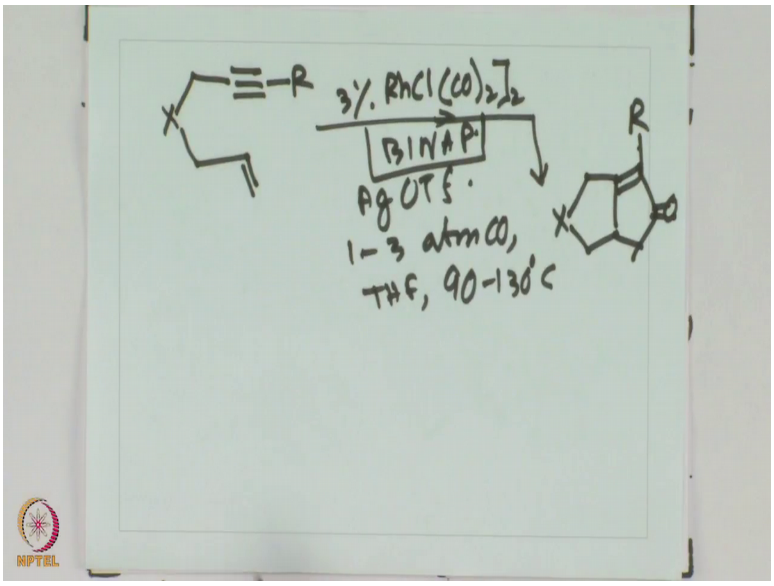

In this case, we will be looking at the example where; you have an internal alkyne yet; we will come back to the mechanism of it and 3 percent rhodium chloride; rhodium 1 C

O 2; 2 was used along with BINAP and silver; O T f; 1, 2, 3 atmosphere pressure of carbon monoxide T H f; 90 to 130 degree C is usually used.

This is; using 3 percent rhodium catalyst, now this can also give the very; so, BINAP is the one which is the chiral ligand in there. And you can get the desired product efficiently by utilizing this method and in these cases, yields are usually 80 to 90's; (Refer Time: 24:55) could be little low 70's, but those are quite efficient without any problem, this can be done. And different variations as well as the substituents are tolerated under these reaction conditions.

So, we have seen two asymmetric reactions; one was with tightnessing compound, another was with BINAP rhodium compound; which is quite interesting and you can get the reaction yield quite high. EE could be varying from 60 or 70 to 90's, but overall this is a reliable method to form the desired Pauson-Khand product with an asymmetric center in them. In a moment, we will look at the mechanism of that Buchwald example where titanium catalyst is used.

So, once again this is a very simple Pauson-Khand type of reaction mechanism that we were discussing earlier. Let us look at that example where Pauson-Khand reaction mechanism is discussed.

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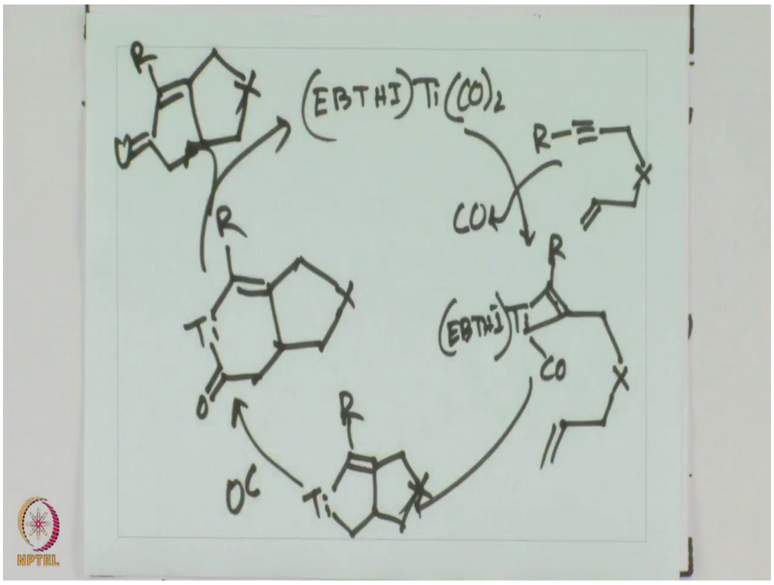

So, the ligand that we were using that EBTHI; titanium dycarbonyl species; from here on the substrate that is required is intramolecular; this alkyne and olefin one and this substrate comes in; one of the carbon monoxide goes out and overall you form a titane cyclopropene intermediate and that gives the substrate interaction first. So, that alkyne interacts fast with titanium and then the olefin is right over there.

Of course, if you have EBTHI that ligand with it and subsequently you get the product where titanium is in 5 member metal a cycle formation board. And with the substituent show the alkyne; oxidative cyclisation between the alkyne and olefin is taking place right now and that gives you the intermediate like 2 fuse 5 member intermediate. From here on carbon monoxide can be inserted into this titanium metal a cycle intermediate overall giving a 6 member intermediate right now. Subsequently, reductive elimination can give you the product formation from these cases.

So, the desired product, Pauson-Khand product can be formed with asymmetric center in it quite efficiently by utilizing this technique. So, in this mechanism what we have seen so far? The titanium reagent is interacting with the alkyne first to form the titanium cyclopropane intermediate. Of course, the chiral ligand is attached with it; with the titanium and then this intermediate cyclopropane titanum intermediate interacts with the olefin and cyclisation occurs.

So, it gives you the fused 5 member; 5 member intermediate where one of the 5 member is having the titanium in it. Then carbon monoxide gets into that 5 member metal a cycle intermediate and finally, reductive elimination gives you the product Pauson-Khand product with asymmetric center induction in it.

So, the cyclisation taking this path or cyclisation step its determining the stereochemistry of the product that we see finally; of course, during the reductive elimination once regenerate the catalyst to go on for the next cycle. Well we have seen the versatile Pauson-Khand reaction, their application for various natural product synthesis.

We have seen the stoichiometric version fast intramolecular stoichiometric version; then intermolecular reactions along with the catalytic version catalytic intra and intermolecular version. And finally, we have seen the asymmetric version of these Pauson-Khand reactions. We have seen one example from Buchwald group, another we have seen with the rhodium along; with this and the mechanism also has been discussed briefly for this sort of reaction.

Now as you see various other metal in of course, it started with cobalt; then we have seen titanium and rhodium also have been used. So, now Pauson-Khand reaction is widely applicable; both in industry and academia and it is the most reliable technique to synthesize cyclopentenone or its derived compound. And it can be reliably synthesized as you see when the initial selectivity can be very high for these reactions.

So, with this we would like to conclude today’s class and keep studying this oxidative cyclisation reaction and feel free to ask question as you may have.

Thank you.