Introduction to Organometallic Chemistry

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Lecture - 35
Organometallics promoted C-X coupling

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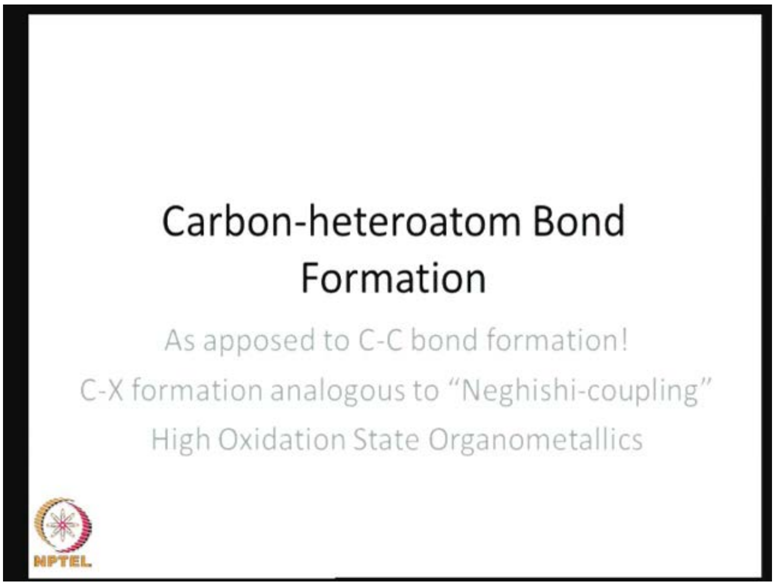

Carbon-heteroatom Bond Formation

As apposed to C-C bond formation!

C-X formation analogous to "Neghishi-coupling"

High Oxidation State Organometallics

This lecture is about carbon heteroatom bond formation, and this is a reaction, which is similar to what we have looked at when we studied the Neghishi-coupling, where the carbon-carbon bonds were formed. So, in this lecture we will look at carbon heteroatom bond formation. And we will also talk a little bit about high oxidation state of organometallics, because recently, it has been found that some of these coupling reactions could actually proceed through higher oxidation states.

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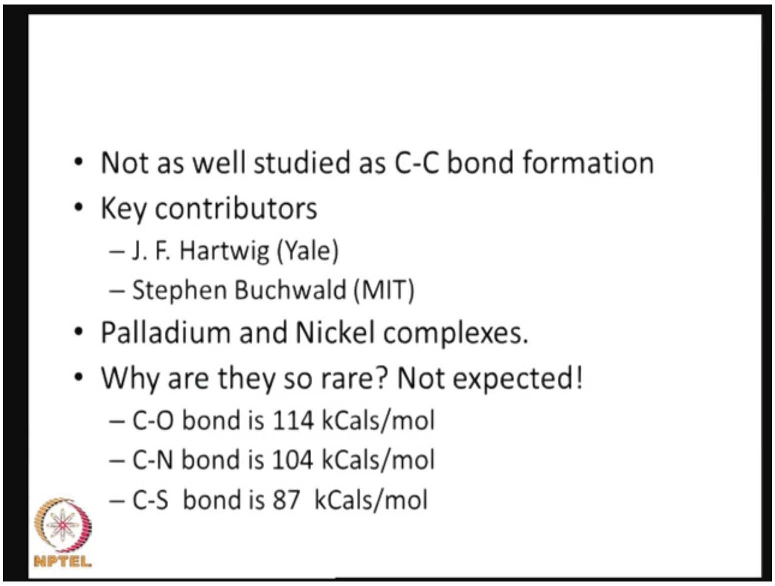

- Not as well studied as C-C bond formation
- Key contributors
  - J. F. Hartwig (Yale)
  - Stephen Buchwald (MIT)
- Palladium and Nickel complexes.
- Why are they so rare? Not expected!
  - C-O bond is 114 kCals/mol
  - C-N bond is 104 kCals/mol
  - C-S bond is 87 kCals/mol

So, first let us take a look at what we had studied in the carbon-carbon bond formation. The carbon-carbon bond formation was mostly catalyzed by palladium. And the carbon heteroatom bond formation was not as well studied as the carbon-carbon bond formation. The key contributors in recent times have been two people, Hartwig and Buchwald from two universities in the US. And they have shown very clearly that there are features which can be controlled by the ligand, and it can be useful to have specific catalysts generated for the reactions that we want to look at.

Most of these reactions have been carried out with palladium and nickel complexes. And first we look at the point. Why is it so rare? Why is carbon oxygen bond formation so rare? If you look at the carbon oxygen bond strengths, the carbon nitrogen bond strengths and so on. It is quite surprising that this reaction has not been studied to a significant extent. These bonds are quite strong. They are 114 kilo calories per mole for the carbon oxygen bond. And if you look at the palladium oxygen bond, it is indeed much weaker. Although, the single bond energy is not available. The palladium oxygen bond would be roughly 90 kilo calories per mole based on the bond strength of the palladium oxide. So, one now has to answer this question. Why is it so difficult?

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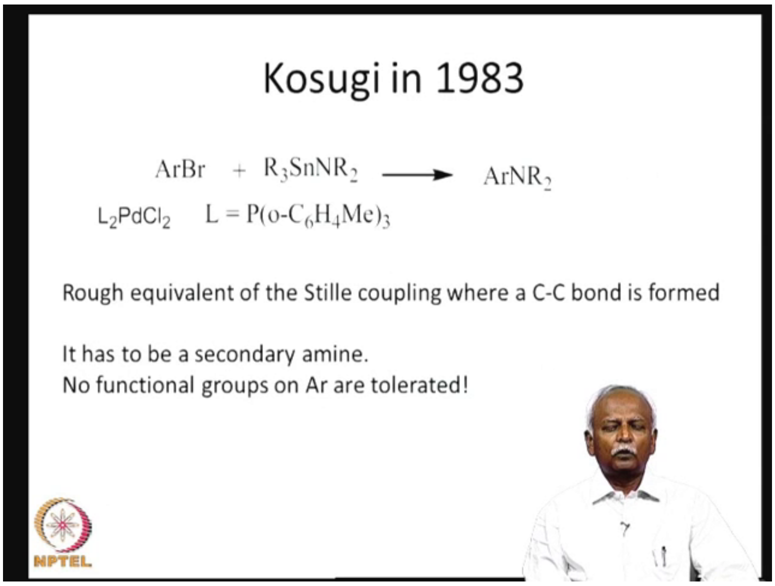

Kosugi in 1983

$ArBr + R_3SnNR_2 \longrightarrow ArNR_2$

L_2PdCl_2 $L = P(o\text{-}C_6H_4Me)_3$

Rough equivalent of the Stille coupling where a C-C bond is formed

It has to be a secondary amine.
No functional groups on Ar are tolerated!

Now in 1983, Kosugi reported that there was a variant of the Stille reaction, where the aryl bromide could be coupled with the tin amide. Now this reaction, which you have in front of you on the screen, was catalyzed by palladium chloride. And palladium chloride with a phospherous ligand and the oxidation state of palladium was plus 2. But in the presence of phosphenes and in a reaction very often, you could have a reduction of the palladium 2 to palladium 0.

So, it would be possible to have a reaction similar to the Neghishi reaction or the Stille reaction mechanism in this particular case. There were two serious limitations for this reaction. One of them was the fact that no functional group on the aryl group was tolerated, which means if I have an aryl group with some other functionality, other than the bromine, the reaction would not proceed. Similarly, if you have a primary amine, the reaction would not work. So, these are two serious limitations. These two limitations were quite serious and the Kosugi reaction, the Kosugi reaction was not popularized significantly.

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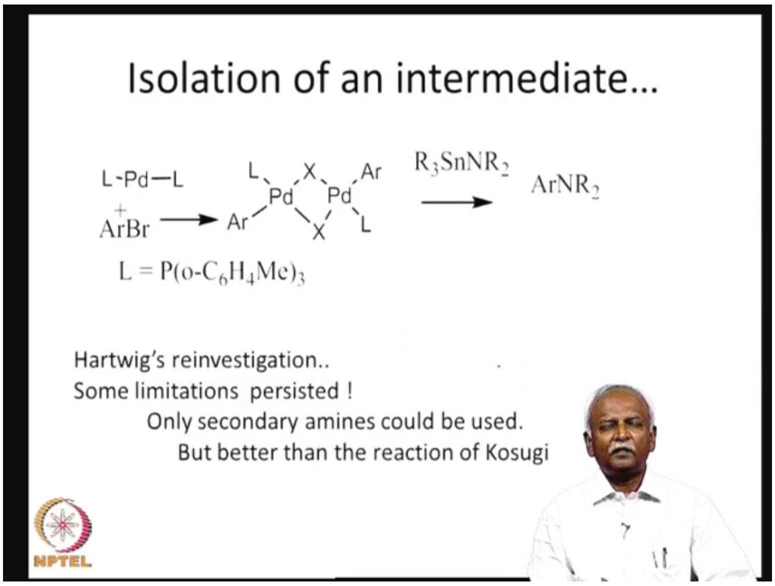

Isolation of an intermediate…

L = P(o-C_6H_4Me)$_3$

Hartwig's reinvestigation..

Some limitations persisted !

Only secondary amines could be used.

But better than the reaction of Kosugi

Sometime in 1990s Hartwig and Buchwald started reinvestigating this reaction. And almost simultaneously in 1995, they published this procedure for making aryl amines. And Hartwig’s reinvestigation showed that there could be significant improvements in the reaction, if one could isolate palladium complex that was formed on reaction of the palladium 0 intermediate. This is a palladium 0 intermediate that we are talking about. And that is generated insito. If that reacts with aryl Bromide, then an oxidative addition leads to a dimeric complex. In fact Hartwig was able to characterize this complex thoroughly. And then a reaction with the tin amide gave the aryl amine.

Now, this tells you that if you have a palladium 0 intermediate, palladium 0 catalytically active species. It would oxidatively add the aryl bromide, and generate a stable intermediate, which can then react with the tin complex. The isolation of this intermediate also helped Hartwig to tune the reaction, so that some improvement could be made, specifically he found that if you have sterically bulky phosphene’s then the reaction was more successful, better yields were obtained. But inspite of these limitations, inspite of these improvement he found that only secondary amines could be used. This was a limitation which was there in the Kosugi reaction also. But what is interesting was that it was now possible to have substituents on the aryl group.

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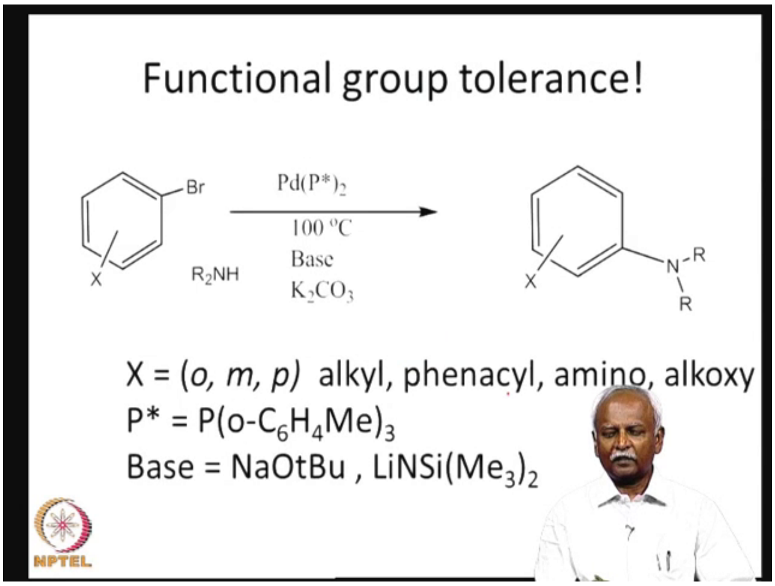

Functional group tolerance!

X = (*o, m, p*) alkyl, phenacyl, amino, alkoxy

$P^* = P(o\text{-}C_6H_4Me)_3$

Base = NaOtBu , $LiNSi(Me_3)_2$

So, typical reaction in this particular case is shown here, where you have a phosphorous stabilized palladium 0 as a resting state of the catalyst. And in the presence of a base, and the base is usually it could be K 2 C O 3 as it is indicated here. It could also be other organic bases like sodium tertiary butoxide and the amide that I have mentioned here. So, these bases could also function equally well. In general, the reaction proceeded well if you carry out the reaction at about 100 degrees or so at a slightly elevated temperature, and in the presence of a solvent an ether solvent like dioxine. You need an either solvent like dioxine in order to heat the compound to about 100 degrees without any difficulty. Now, if you have bulky phosphene, then the reaction would work even in the presence of substituents on the aryl group.

So, you can have a variety of substituents and all these substituents were quite. Substituents were quite bulky and close to the bromine and inspite of that the reaction worked. Some of them were highly coordinating like the amino group or the phenacyl group and inspite of that the reaction proceeded effectively. So, this is a significant improvement on the Kosugi reaction. And this was brought about by the fact that the Palladium 0 intermediate that Hartwig was able to characterize and show what, where the factors that were stabilizing the intermediate.

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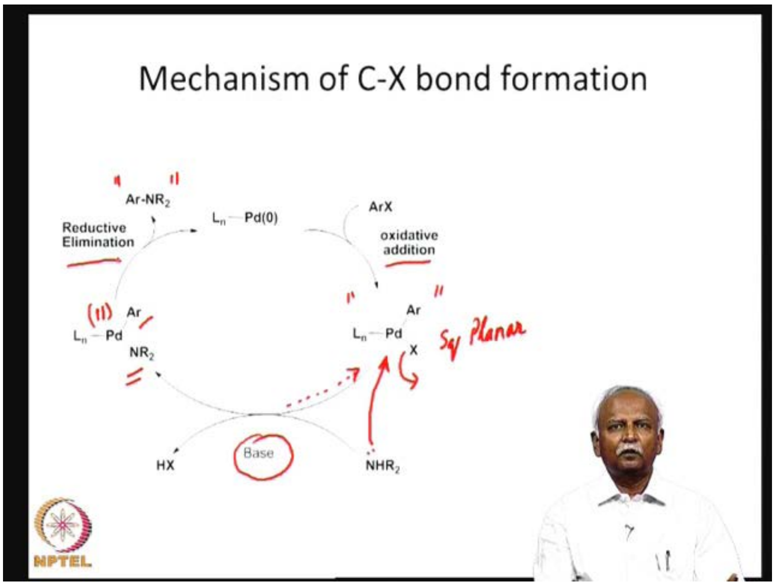

Mechanism of C-X bond formation

Now, we can ask ourselves a question. What is the mechanism of this particular process? The mechanism of this process could be a very simply modeled after the reactions that we have studied with the Neghishi coupling. So, if we take a palladium 0 intermediate and do an oxidative addition you would end up with a species, which could be three coordinate or four coordinate, depending on the number of phosphorous atoms that are attached to palladium. In most cases you would expect the palladium to have a square planar intermediate, a square planar intermediate which would be true phosphorous ligands. And he also showed that if you have cis related phosphorous ligands, stabilizing the palladium. Then that reaction worked much better in some cases.

So, after you make this oxidatively added product where you have aryl and X groups. The X group can be replaced with amine. And when you do that, when you have an Amine coordinating to the palladium and displacing the X as X minus, X minus comes out, this group comes out. And the amine is the one which is going on to the palladium. And during this process the base would mop up the HX that is generated in the reaction medium. This is very important, because if you have these HX. The reaction can go back in the reverse direction.

That means, you could have the reverse direction, reverse reaction actions happening. You could also have other unnecessary side reactions as we shall see in a moment. Once you form the palladium compound which has got the Aryl groups and the N R 2 group simultaneously coordinated to the palladium. And now this is a palladium two species.

It can reductively eliminate palladium 0 and the product can be formed. So, this is the product which is formed as a result of reductive elimination. So, as we have found in the previous reactions with Neghishi coupling and Suzuki coupling. You have an oxidative addition of the sigma bonded intermediate and a reductive elimination in the final step which gives you a product and regenerates the catalyst. In between you could have insertions, you could have transmetallation, you could also have an exchange reaction, a sigma bond metathesis kind of reaction as it is shown here.

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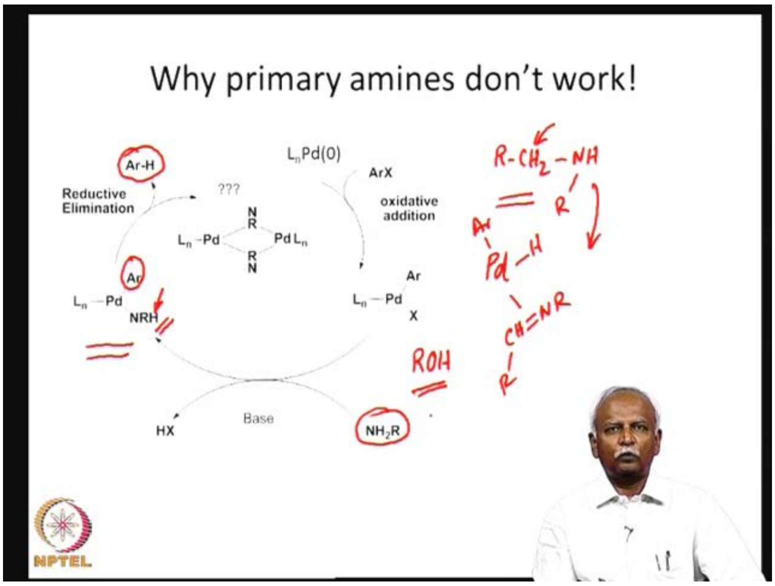

Why primary amines don't work!

So, if you look at the reaction, it is also easy to understand why primary amines cannot be used or amines where there is a beta hydrogen present in the amine. So, you cannot use in these reactions R C H 2 and R. So, if you have an R group in which there is a beta hydrogen there also the reaction does not work. And this helps you to understand why this restriction is present, after the oxidative addition and the sigma bond metathesis or the substitution by the Amine. You would end up with a species where if I have an NH group, that is if it is a primary amine. I would end up with an R NH group. And this hydrogen would be capable of doing a reductive elimination with a A r group.

So, the A r group and the hydrogen, this hydrogen can be eliminated together as Ar H. And that is a serious side reaction that is present in the reaction, which converts the important aryl halide to a simple arene. And so, you cannot carry out the reaction when you have the possibility of a beta hydrogen elimination. As I have shown here you can have a beta hydrogen elimination which can give you a palladium hydride and that palladium hydride will eliminate. We can write that out. We can heave a species like this. You can have a species like this which would eliminate the Ar H. That is also feasible if I have an amine which has got a beta hydrogen or as I have shown here.

If I have an R NH primary amine and I carry out the reaction. Then the primary alpha nitrogen has got a hydrogen which can be reductively eliminated. So, these two are complications which plagued this kosugi reaction variant which was promoted by Hartwig and Buchwald. But the way in which they were able to isolate the intermediate and also improve the reaction is remarkable. And that lead to the recent resurgence of CX bond formation. If this is the way in which the amine reacts, one can also have an alcohol reacting in the same fashion. So, if an amine can be a Nucleophile and ROH or an alcohol can also be a nucleophile and it can also carry out a similar reaction.

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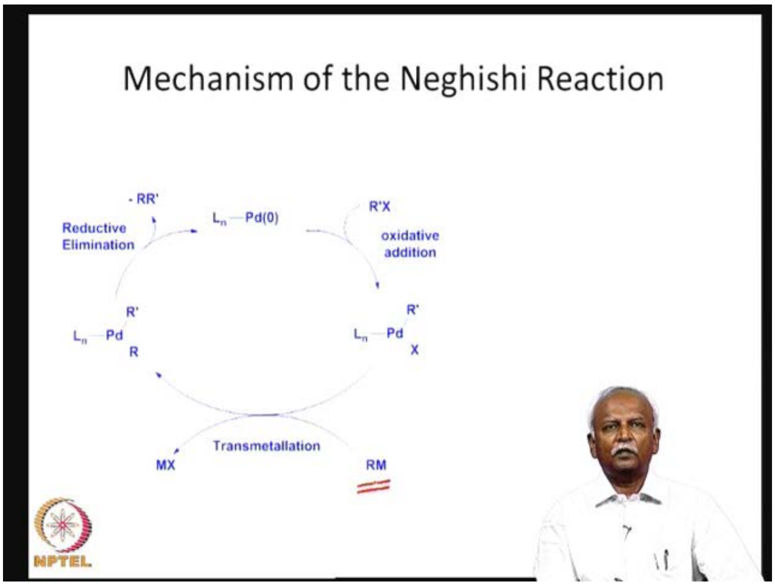

Mechanism of the Neghishi Reaction

So, just to remind you that this is identical to the or very similar to the Negishi reaction. I have shown for you here the Neghishi reaction in this slide where the only difference is this transmetallation. Instead of an amine you have a metal which is doing, carrying out a transmetallation and everything else in this catalytic cycle is exactly the same.

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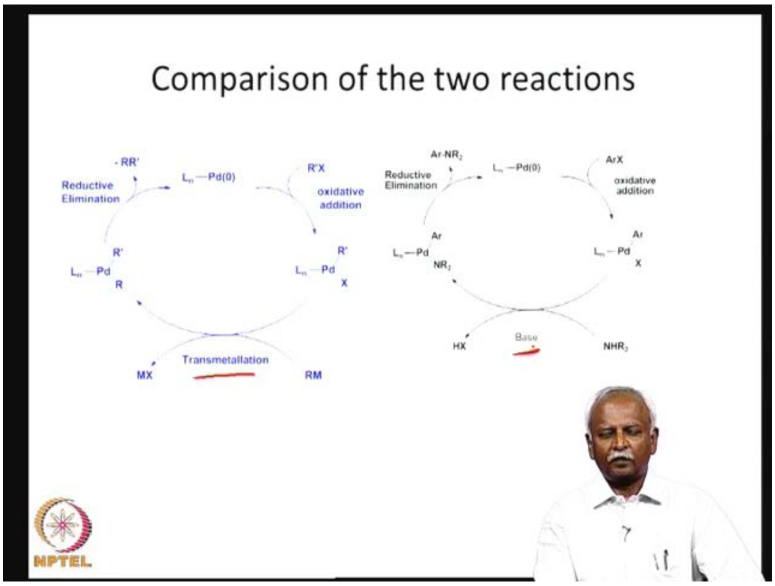

Comparison of the two reactions

So, here are the two catalytic cycles together and you can see that the parallel is remarkable. It is only in this one transmetallation step or the reaction with the amine that the two reactions differ.

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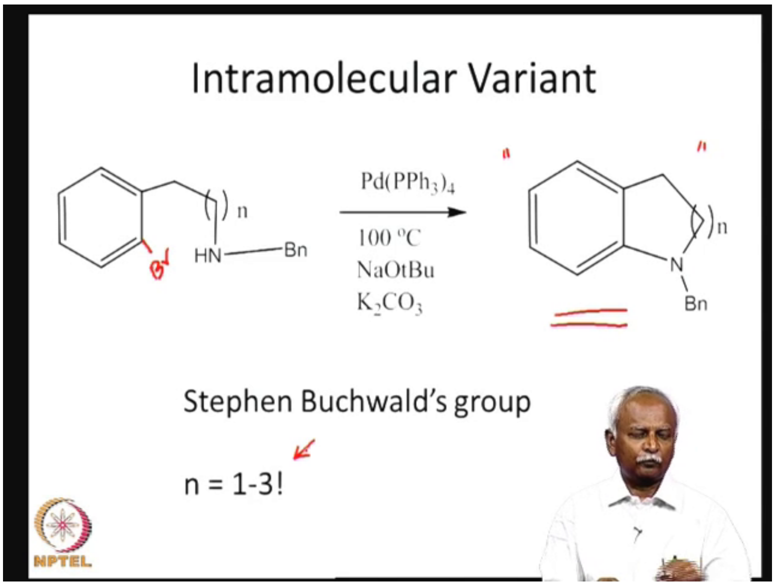

Intramolecular Variant

Stephen Buchwald's group

n = 1-3!

Now, during this time it was both organic chemists and organometallic chemists developed this reaction significantly. And interestingly if you have an intramolecular attack of an amine, as it is shown here. The reaction is much more tolerant to the groups which are present and the reaction can be carried out at a much milder condition. And so here you have the Buchwald's group as shown for example. During this time that you can have an intramolecular variant where you have a orthobromo group here, which is missing in this slide and we will put that in.

So, this orthobromo group can be eliminated in order to generate the cyclic generate the cyclic compound which is pictured here. Which is a very familiar a group or which is a recurrent moiety in many drug molecules. So, it is very important to have this type of a intramolecular attack of the amine, in order to form an indole complex, indole compound. So, this was developed by Stephen Buchwald's group and surprisingly you can have, the ring size can be in fact varied and you have variety of a rings that can be generated. Not just a indole that I have shown for you as an example where n equals 1.

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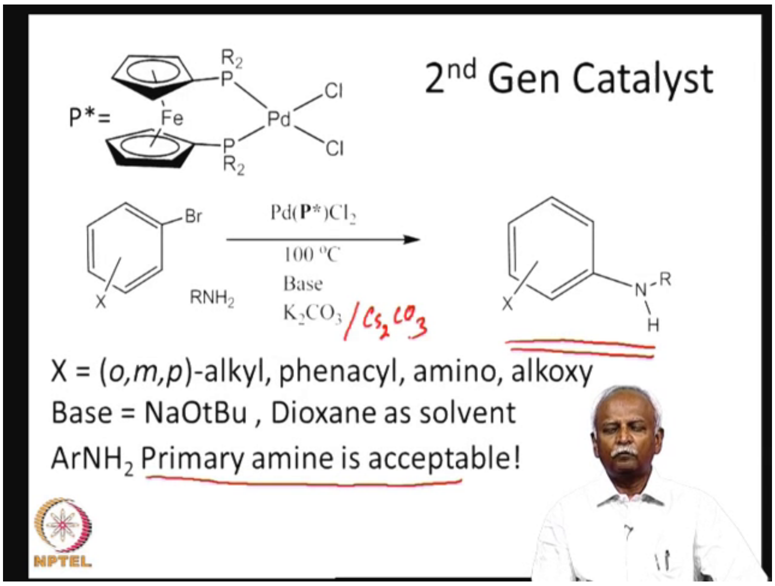

2nd Gen Catalyst

X = (*o*,*m*,*p*)-alkyl, phenacyl, amino, alkoxy

Base = NaOtBu , Dioxane as solvent

$ArNH_2$ Primary amine is acceptable!

So, after the generation the isolation of the catalyst and the first generation catalyst as it was called, where you had only bulky substituent's on the phosphorous atom. It was shown by Hartwig that it would be better to have if you have a chelating phosphene. Then it is possible to even to carry out a reaction with primary Amine. So, in some ways the primary amine reaction, side reaction that was described for you a few minutes ago is not possible when you have a chelating amine, chelating phosphorus on the palladium.

So, apparently the palladium goes to palladium 0 and is stabilized by this phosphorous ligand. And the same catalytic cycle can be present. Except that, now you do not have the possibility for the A RH elimination and so you get very good yields of the desired product. And the same type of conditions have to be followed. It is approximately 100 degrees and a base. And potassium carbonate or cesium carbonate are good bases that are inorganic bases that can used. These are called solid bases and they are very useful because they are very efficient in mopping up the acid that is generated in the reaction medium, without causing any side reactions.

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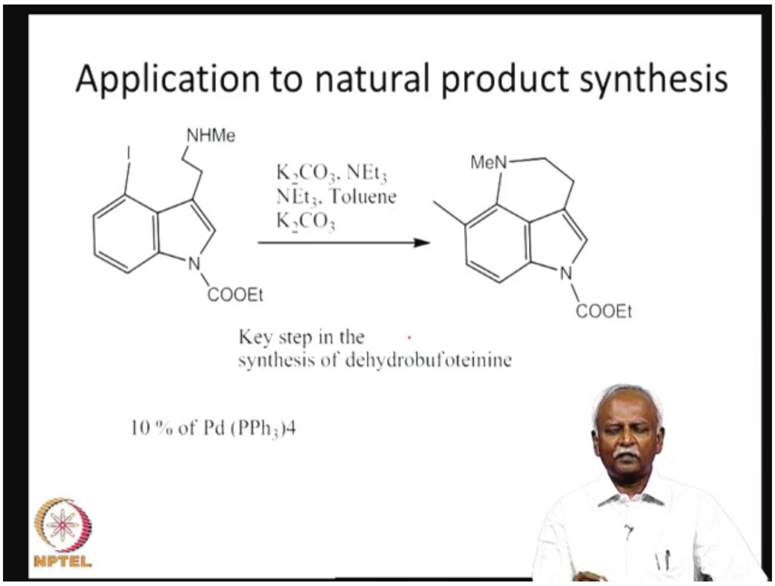

Application to natural product synthesis

K_2CO_3, NEt_3
NEt_3, Toluene
K_2CO_3

Key step in the
synthesis of dehydrobufoteinine

10 % of Pd $(PPh_3)4$

So, here is an example of a natural product that was synthesized using this reaction in a very efficient way. One of the key steps involved in this reaction was this cyclization reaction. So, in this particular compound it was possible to use a simple Palladium Phosphorous tetra triphenyl phosphene ligand complex of palladium. So, this is an extremely simple step that has to be carried out. It does not even require the first generation catalyst, the bulky phosphorous ligand on the palladium in order to carry out this reaction very efficiently. So, you can see that this can be an extremely useful reaction extremely useful and valuable reaction for fine chemical synthesis.

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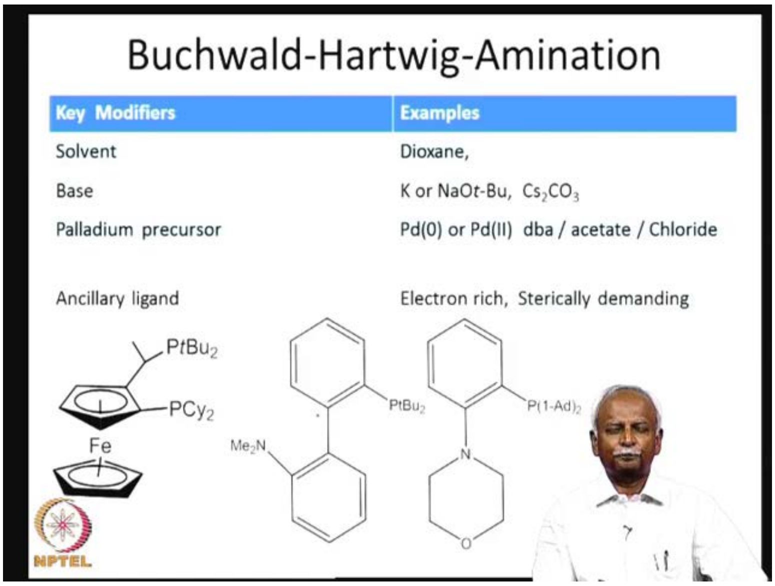

Buchwald-Hartwig-Amination

Key Modifiers	Examples
Solvent	Dioxane,
Base	K or NaO*t*-Bu, Cs_2CO_3
Palladium precursor	Pd(0) or Pd(II) dba / acetate / Chloride
Ancillary ligand	Electron rich, Sterically demanding

Now, we can give several examples but what we will do is to summarize the key findings that are available for us due to the extensive work done by Buchwald and Hartwig. The key variants or the modifiers that they have used are mentioned here. Primarily it is the ancillary ligand that was changed significantly. And some of the ancillary ligands are shown for you here on the slide. They are extremely electron rich. If they are more electron rich, the reaction proceeds to a better degree and that in an easier fashion and it has been possible to activate even chlorides.

And that is understandable because you can have easy oxidative addition when you have an electron rich phosphorous atoms which have ligands on the palladium. And secondly if you have a bulky substituent on the phosphorous, then there is a weak interaction. There is a stabilizing interaction where the bulky group prevents other moieties from attacking the palladium, two coordinated palladium complex.

And which is susceptible to oxidative additions. So, it is important to have bulky substituent’s and that is also mentioned here as sterically demanding. And in some cases in the second generation catalyst it is impossible to have. It is advantageous to have a secondary amine in the ligand so that it would stabilize the palladium intermediate that is formed.

So, there is a weak interaction between the palladium and this nitrogen which is indicated here. So, that weak interaction stabilizes the intermediate step or the intermediate that is formed after the reductive elimination. And it only carries out oxidative addition and this reductive elimination without carrying out beta hydride elimination. That is even allowed ammonia to be used as an incoming species so that you can make primary amines as a result of this reaction. Of course, palladium precursor it can be either palladium 0 or palladium 2. And I have mentioned here dba, which dibenzylene acetone, which is capable of stabilizing palladium in palladium 0 state.

So, this is used to be palladium 0 and the acetate and the chloride are used with palladium 2. So, these two are used with palladium 2. Now the base as I have shown you. It is either potassium or sodium tertiary butoxide, butoxide again a bulky ligand, which even if it is substitutes on the palladium is readily replaced by the less hindered amine. But cesium carbonate is an extremely useful effective and good base that can be used for generating this reaction in very high yields. As I had mentioned earlier dioxine as a solvent is the most convenient solvent, for the simple reason that one can heat it to higher temperatures without loss of the solvent or having recourse to a high pressure reactor.

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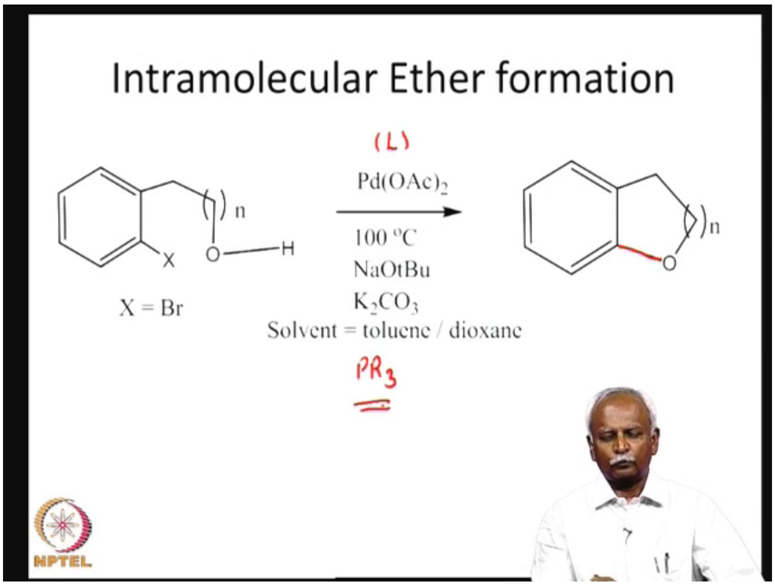

Intramolecular Ether formation

(L)

$Pd(OAc)_2$

100 °C

NaOtBu

K_2CO_3

Solvent = toluene / dioxane

PR_3

X = Br

So, having discussed the Amine it is not very difficult to push this one step further and have a CO bond formation. So, this is the bond that is formed as a result of this reaction. And we can see that this intra molecular ether formation is in fact a exact analog of the C n bond formation. And everything else would be identical in terms of the mechanism or in terms of the ligands that have to be used. So, you need a phosphorous stabilizing ligand which is usually a PR3 as a ligand is used in this reaction also.

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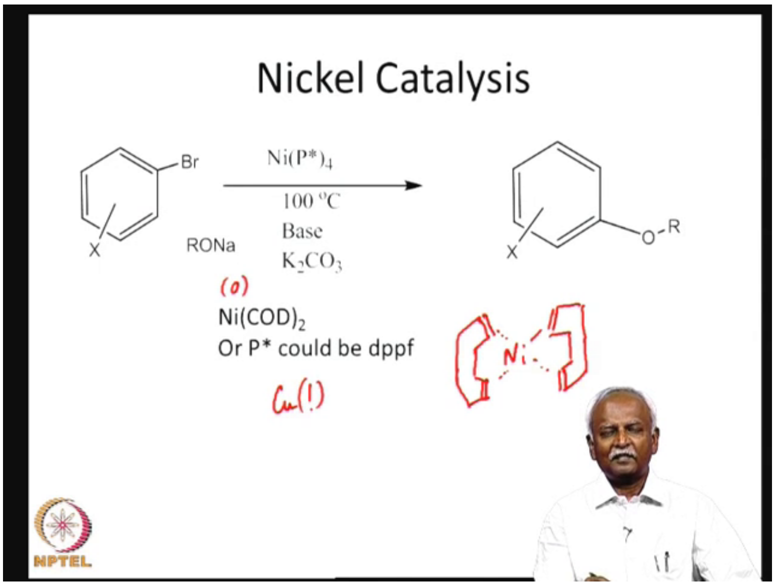

Nickel Catalysis

(0)

$Ni(COD)_2$

Or P* could be dppf

Cu(I)

Now, it is possible to replace palladium with nickel. In the case of the Ether formation it is been shown that nickel 0 as nickel COD twice. So, this is nickel 0 where COD is cyclooctadiene and you can have cyclooctadiene coordinating to the palladium. And that is a very readily displaced ligand. So, this falls away from the nickel generating nickel 0 species which is extremely reactive.

And so this is the, this COD nickel species that is used very often as a good starting material. And what was called by Wilkay as naked nickel and it is as convenient to use this in these reactions. So, everything else appears to be the same and so nickel zero just be also going through the nickel 2 intermediate. However these two species nickel 0 and even copper, copper 1 which has been shown to be a useful alternative they are not as effective as a palladium.

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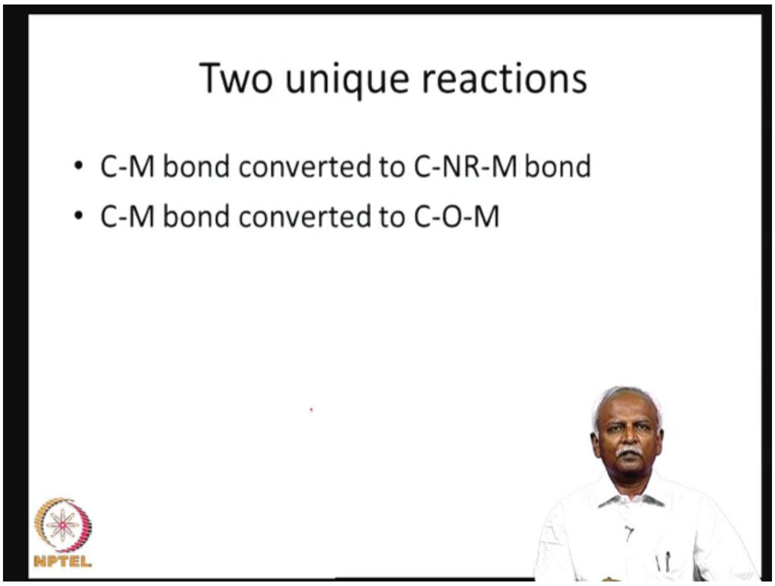

Two unique reactions

- C-M bond converted to C-NR-M bond
- C-M bond converted to C-O-M

Now, before we proceed further I would like to point out that there are two small variations of this ether and amine formation reactions. And these are interesting variants which allow us to start our discussion on high oxidation state chemistry.

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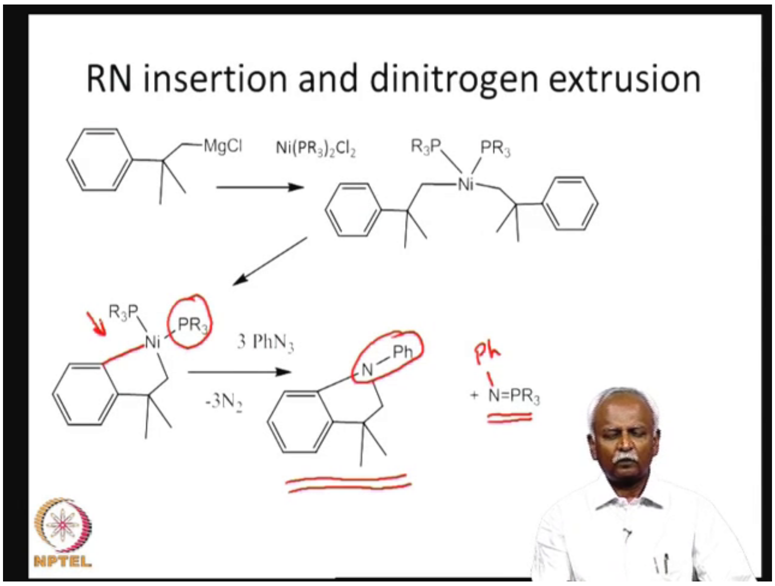

RN insertion and dinitrogen extrusion

So, here is a reaction that has been studied. Now you first make a nickel complex which has got two phosphorous atoms coordinated to it. And if you treat it with phenyl azide which is P h N double bond N double bond N, then it is possible to insert a nitrogen, a phenyl nitrogen which is this group here, directly into the carbon nitrogen bond. So, this is the carbon nickel bond.

This is a carbon nickel bond and if you introduce the P h N 3 here, you tend to form this five numbered indole moiety or indole derivative which I have drawn for you here. And during the course of this reaction, this turns out to be a stochiometric reaction because the phosphorous atom gets oxidized to the species which is given here. So, this is the variant of the Schrodinger reaction which is during which also you have the oxidation of the phosphorus. But in this reaction you also have a insertion of a P h N group between a nickel carbon bond which is indicated here.

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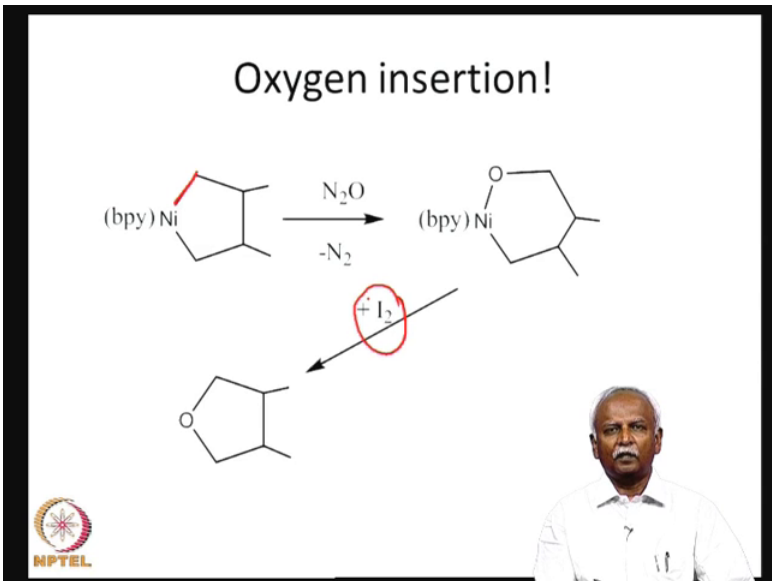

Oxygen insertion!

So, we can have a oxygen insertion in a similar fashion and this turns out to be conveniently carried out with into nitrous oxide. And here is an example where oxygen is inserted between the nickel carbon bond. So, the nickel carbon bond is the one which I have converted to red bond and I have inserted N 2 O. And it is not very clear what the intermediates are it is possible that a you have a coordinated N 2 O to a nickel, which then inserts the oxygen to the carbon nitrogen bond. And then you have of course, the ether formation after oxidation with iodine.

So, these are stochiometric variants there are no catalytic variants for these. Because invariably the N 2 O and the phenyl azide which we discussed in the previous slide, they destroy the complex completely. And so these are stochiometric reactions, but that seems to suggest that if you have a source of oxygen, you can add it between the metal carbon bonds and there are instances where you want to do that. Suppose, you want to from an epoxide or you want to insert an oxygen into a ketone, a cyclic ketone inorder to generate an ester, a cyclic ester. These are examples where it would be nice if you can insert an oxygen or for that matter an amine group.

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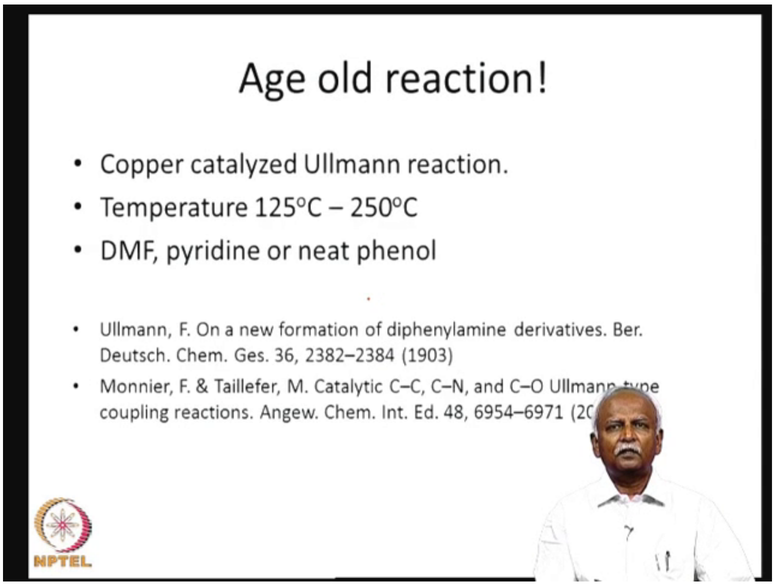

Age old reaction!

- Copper catalyzed Ullmann reaction.
- Temperature 125°C – 250°C
- DMF, pyridine or neat phenol

- Ullmann, F. On a new formation of diphenylamine derivatives. Ber. Deutsch. Chem. Ges. 36, 2382–2384 (1903)
- Monnier, F. & Taillefer, M. Catalytic C–C, C–N, and C–O Ullmann-type coupling reactions. Angew. Chem. Int. Ed. 48, 6954–6971 (20

So, we will discuss those later. Now I want to talk about the ether formation which was known for a long time. Slightly more drastic condition was used in the Ullmann reaction and copper was the catalyst that was used. And in this reaction you normally used dimetal formamide as the solvent and it also needed a base. And this is discovered as early as 1903 but no mechanism for this reaction was available. The mechanism was not known, but Ullmann showed that you can very efficiently make a variety of ethers using this particular procedure. This is being recently reviewed and you can have Ullmann type coupling reactions of copper at fairly facile fashion.

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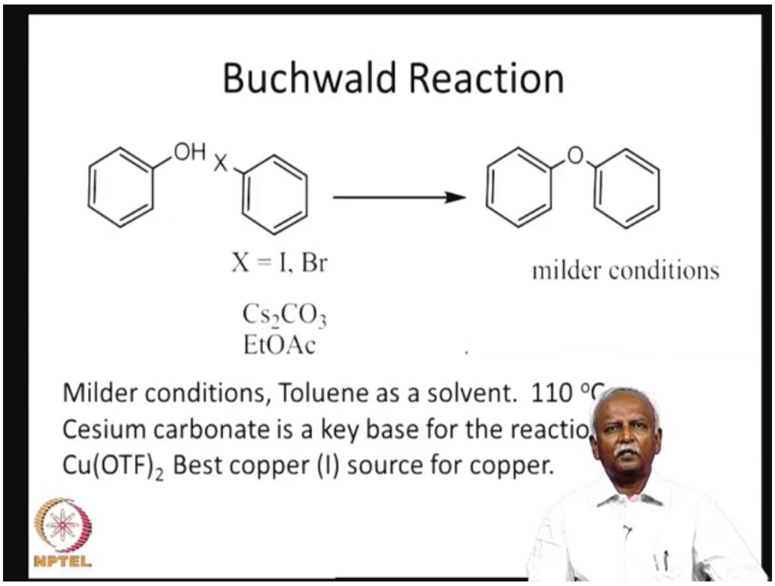

Buchwald Reaction

X = I, Br

Cs_2CO_3
EtOAc

milder conditions

Milder conditions, Toluene as a solvent. 110 °C
Cesium carbonate is a key base for the reactio
$Cu(OTF)_2$ Best copper (I) source for copper.

Now, Buchwald showed that much milder conditions could be used and cesium carbonate can be used as a base. And the reaction can be carried out in the presence of palladium and in presence of copper. If you use copper if it was shown that if you have non-coordinating bases as anions. Then they are the best for this whole reaction. So, usually cesium carbonate is the best base. And if you have a copper triplet as it is shown here or for example, perchlorate it is also possible to carry out this reaction in reasonably mild conditions.

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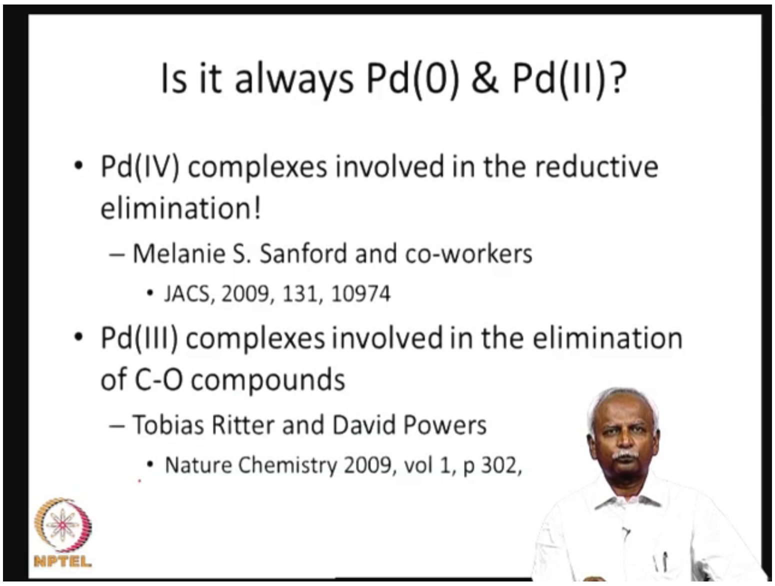

Is it always Pd(0) & Pd(II)?

- Pd(IV) complexes involved in the reductive elimination!
  - Melanie S. Sanford and co-workers
    - JACS, 2009, 131, 10974
- Pd(III) complexes involved in the elimination of C-O compounds
  - Tobias Ritter and David Powers
    - Nature Chemistry 2009, vol 1, p 302,

So, now we can ask this question. I want to move over to this question of oxidation state. In all the reactions that we have shown here we have carried out the reaction with palladium 0. We have carried out a reaction with palladium 0 or with palladium 2, but with a possibility of converting palladium 2 to palladium 0. So, the catalytic cycle basically involved oxidative addition on palladium 0 to convert it to palladium 2. And then a reductive elimination step regenerated the catalyst. But is it possible that palladium 2 gets converted to palladium 4 through oxidative addition? And then a subsequent reductive elimination regenerates to palladium 2.

Now palladium 4, copper 3 and other such high oxidative state species have always been proposed in some instances. But it has been difficult to isolate and characterize the intermediates. Recently Melanie Sanford from the university of Michigan showed that it is possible. And they carried out some excellent studies with palladium four complexes isolated them and characterized them. And then shown that reductive elimination can happen from these palladium 4 intermediates. So, in fact it is possible to cycle between palladium 4 and palladium 2. And if you did that you can generate both C O and C C bond forming reactions.

Both of them were possible in those cases. Now interestingly, a very close to the discovery of this palladium four; it was Tobias Ritter from MIT who showed that it is possible to have even palladium 3. And this he showed starting with palladium 2, a dimer so that two palladium units are involved. And both palladium were oxidized to palladium 3.

So, reductive elimination can then happen from this palladium 3 intermediate and generate palladium 2. In other words you can have all the oxidation states that are listed here. palladium 0, palladium 1, palladium 2, palladium 3 and palladium 4 all of them participate in the reaction, it is not an impossibility. So, it should be possible to see much more chemistry coming out from these interesting species that have been discovered by Ritter and Sanford.

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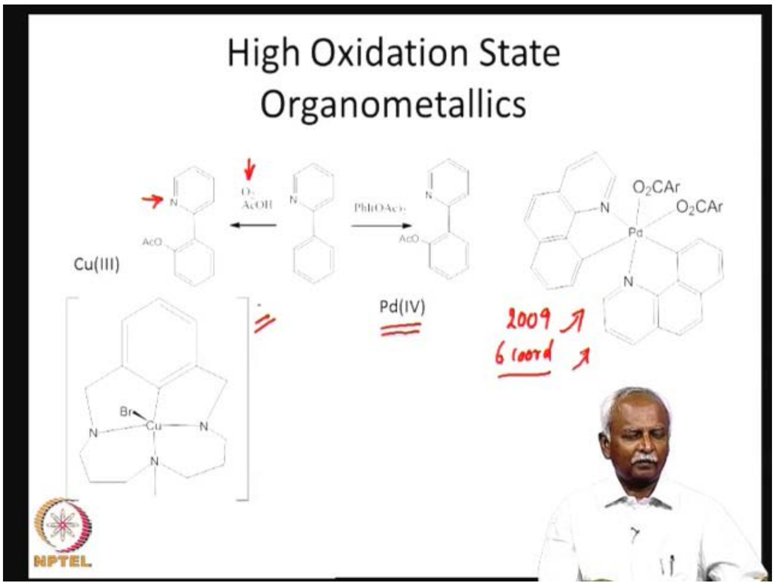

High Oxidation State Organometallics

So, let me just show you what has been discovered. This is from a paper by Melanie Sanford and recent times and 2009 paper which is the 2009 that has been shown here. So, here what she has shown is that copper three has an intermediate there is a plus charge here. So, you can have copper three which is capable of carrying out in the presence of oxygen, the oxidative acetoxylation of an amine group. But this happens in the ortho position or in the adjacent position in the ortho position of the adjacent ring to a palladium moiety.

So, at the same thing is capable or possible with palladium 4. And that of course, happens to the intermediacy of the complex of this six coordinated six coordinated palladium 4 intermediate that I have picture for you here. So, this is high oxidation state organometallics, where there are very clear indications for a palladium carbon bond being involved in the reaction medium.

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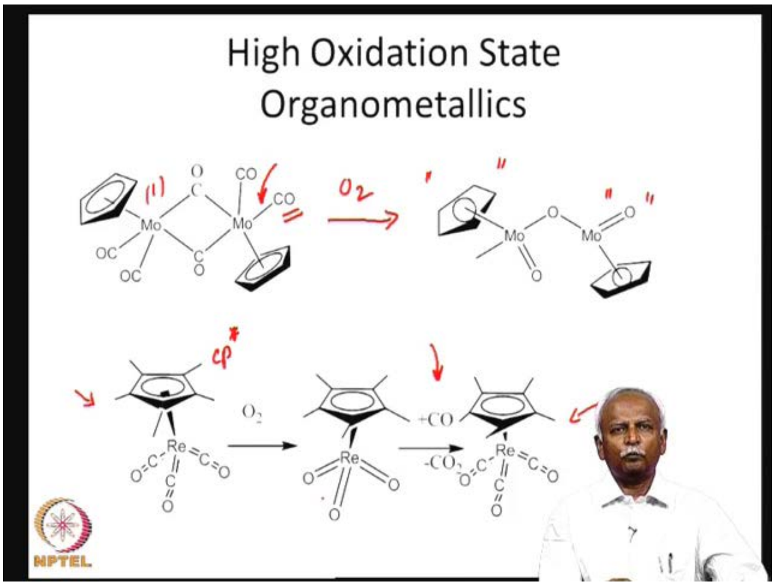
High Oxidation State Organometallics

Now, high oxidation state organometallics although we have not discussed it in great detail, we do find it occasionally in the literature. The reason for it is absence from the literature to a great degree stems from the fact that we have concentrated on carbon monoxide based chemistry. Carbon monoxide requires that we have low oxidation states, if you want to stabilize the metal carbon monoxide bond.

So, the metal carbon monoxide bond is significantly weakened if you oxidize the metal center. So, here is a reaction, where if you take a molybdenum species, which is molybdenum 1 singly oxidize it to presence of cyclopentadivinyl group. If you have a molybdenum 1 species and if you pass oxygen into the reaction mixture you end up with a dimeric species which is got a oxoligand.

This oxoligand is in fact a strange species because it is not expected to be formed in combination with a cyclopentadivinyl group. One would expect this group to be oxidized further. In fact in the case of rhenium, here you have a rhenium carbonyl compound which is rhenium one and it is having three carbon monoxides. So, this is C P star it is got these or these metal groups attached to the cyclopentadivinyl unit and you have five of them.

So, this is C P star. We write this as C P star ligand. And this c p star ligand stabilizes the rhenium. And it possible to oxidize it with oxygen and generate a rhenium trioxo ligand. So, this is all oxygen that I attach to the rhenium and we normally write it as oxo groups, because of the bond distance is indicative of multiple bonding between oxygen and rhenium. Now, interestingly if we use a high pressure of carbon monoxide you can convert it back to the rhenium carbonyl complex.

So, you go from the carbonyl complex, you can oxidize it with oxygen and then carbon dioxide is liberated on the reaction with a high pressure of carbon monoxide. And you regenerate the carbon monoxide complex. So, it is possible to have high oxidation states. And it is possible to carry out these reactions very easily by adding oxygen, but very often you would end up horrible mixtures at the compounds are completely oxidized. The carbon content in ligands are also oxidized, but if you have a C P star ligand it seems to stabilize it and you can have some chemistry which is being actively pursued. So, we will discuss a few cases where oxygen can be introduced into organic molecules with the help of these oxo complexes.

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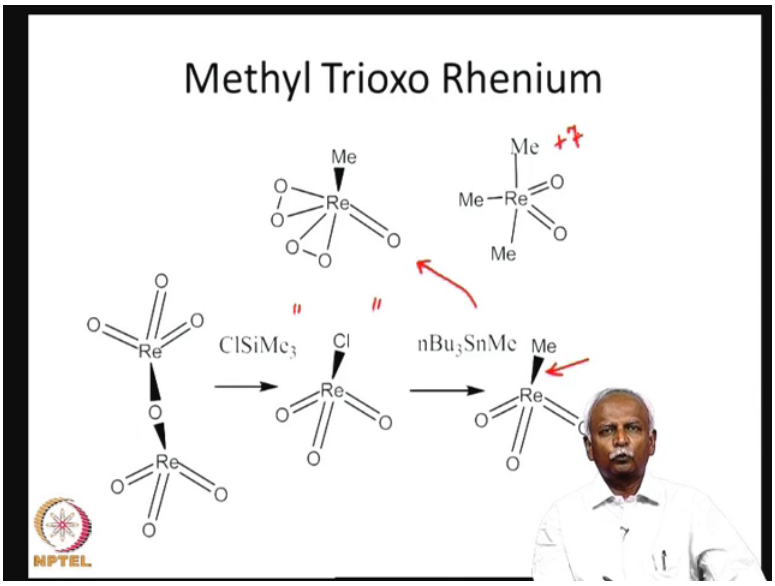

Methyl Trioxo Rhenium

Now, in the rhenium complex that I just introduced to you in the previous slide turns out to be a very interesting molecule, because you have rhenium in the plus seven oxidation state, the highest oxidation state that you can think of. And in this highest oxidation state in which the rhenium is present can be converted into an organometallic species. And this is of course, a alkyl organometallic species. You have a very clear metal rhenium, metal which is rhenium and methyl group.

So, you have a carbon rhenium bond. And this is a extremely stable molecule. And this stable molecule, this R group that is introduces by this trynl butane Tin here. Or it could be any other R group. It can be transferred on to the rhenium, turns out to be the stable species. And there are some variations which are shown here. Here I have oxidized it further.

Suppose, you have hydrogen peroxide, this tri oxo Rhenium can be converted to this peroxo complex and that is also been characterized. Here is another species where you have rhenium in the plus seven oxidation state. And we have three methyl groups and so of the single methyl group which as shown earlier. So, these are species where rhenium is supporting an alkyl group and forming a metal carbon bond and at the same time having oxo groups. And these two seem to be compatible.

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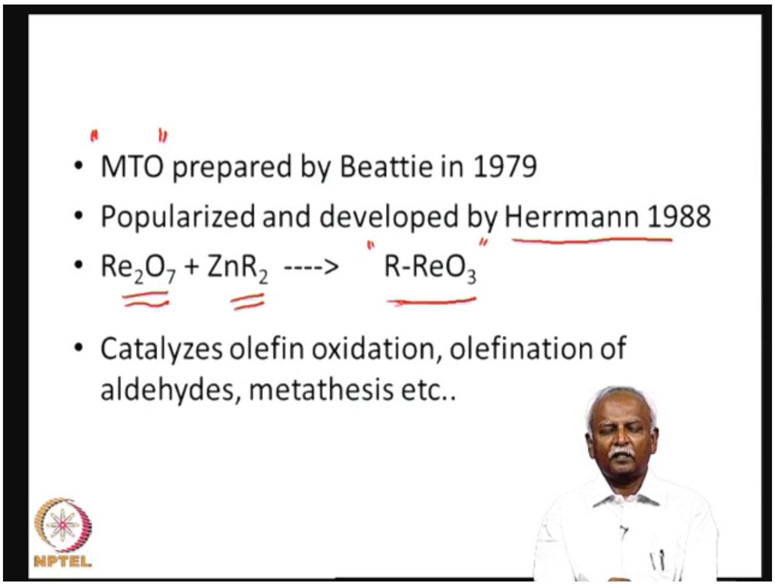

- MTO prepared by Beattie in 1979
- Popularized and developed by Herrmann 1988
- $Re_2O_7 + ZnR_2$ ----> "R-ReO$_3$"
- Catalyzes olefin oxidation, olefination of aldehydes, metathesis etc..

So, it must be possible to have significant chemistry with these species. In fact M T O or methyl tri oxo rhenium, MTO is a little deceptive because it does not talk about the rhenium or the R is missing, but MTO is the abbreviation that is used in the literature methyl tri oxo rhenium. This species right here where R is methyl was prepared as early as 1979. But its value was not realized until Hermann Wilston Hermann who took over as a professor in Munich after Fischer who discovered the arene complexes started popularizing it.

He showed that it is very easy to make these alkyl rhenium oxo complexes. And these alkyl groups can be anything. It can be transferred from a zinc alkyl and an inorganic oxide, R E 2 O 7 is an organic oxide. And that can be these two can be reacted in order to generate a inorganic alkane. So, here was R E O 3 which is an inorganic alkane. And that was soluble in water. So, it had some very interesting properties and he looked at the catalysis of that is capable with these metal centers. And he showed that olefin oxidation olefination of aldehydes. And even metathesis could be carried out by these interesting inorganic alkenes.

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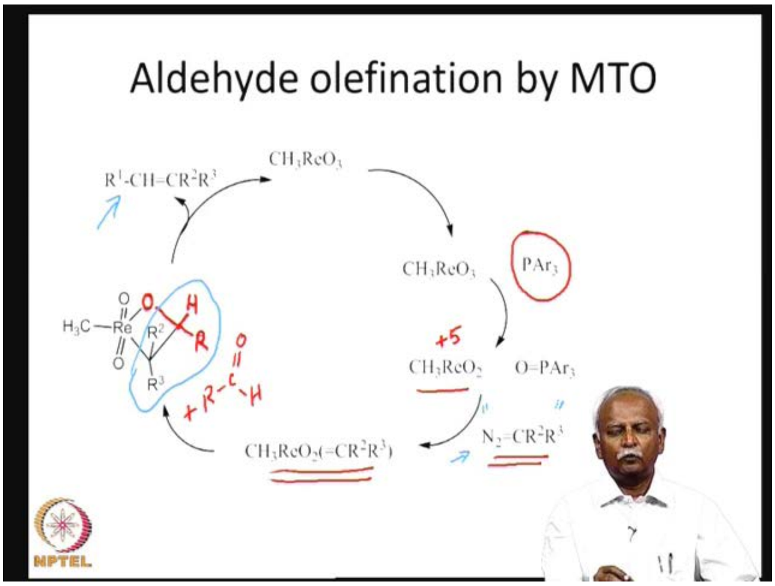

Aldehyde olefination by MTO

So, here is the catalytic cycle which is in the presence of a which is olefination of an aldehye. And this is a reaction which requires a conversion of, removal of an oxo group using triphenyl phosphene. So, triphenyl phosphene because of its oxophilic nature removes one of the oxo groups from the rhenium.

And so, you now have a rhenium five. This is an plus five oxidation state and this coordinates too are carbene source, which is a diazoalkane. The diazoalkanes generates a carbene complex and this carbene complex now can react with a aldehyde. So, you need a R C O H here. And you can see that this is your R C H O. So, this is the R C H O which is added on to the rhenium center and now you can see that olefination can take place very easily because this rhenium center can now become R E O 3. And you can have for the sake of clarity we will just use a different color.

So, this group can be eliminated as the product which is going here. So, it is possible to have olefination of an aldehyde very catalytically you can carry out this olefination, that is another advantage. Only thing you are doing is that you have indirectly carried out a witty type of a reaction. So, where you have used a phosphorous, a phosphene to remove an oxygen exactly the way virthgi, but you have used an azide in order to generate a methylene fragment. So, these two fragments have been reacted on a metal center and you can do this catalysis.

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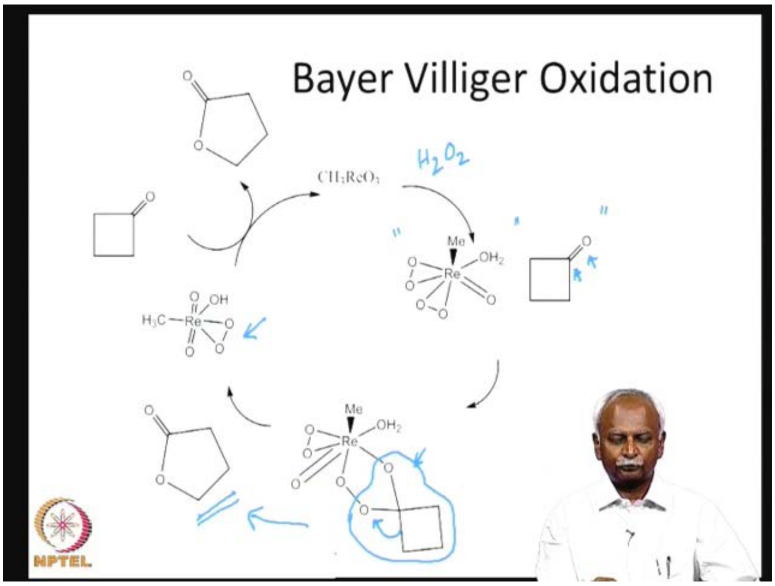

Bayer Villiger Oxidation

So, here is another example where you have a Bayer Villiger oxidation being carried out, but this example is being restricted because it has been done with cyclobutane Butanone. And the cyclobutanne moiety reacts with the peroxo complex of rhenium that we just saw a little earlier. And this peroxo compound can be generated by reacting it with H 2 O 2, hydrogen poeroxide and two molecules of hydrogen peroxide are required to carry out this reaction where we have rhenium peroxo bond. This rhenium peroxo bond can react with the cyclobutanone in such a way that it adds on to this double bond here.

So, it adds on to this double bond, the R E double bond O. And you end up with the trioxo system. Bicyclic trioxo system and that can do a rearrangement. And that rearrangement is easy to envisage. You just have to move this carbon-carbon bond to a carbon oxygen bond and you would end up with a reaction in which you have a cyclic ester being eliminated. And which comes from these groups.

These groups if they are eliminated you would end up with this organic molecule. And you have one more oxo peroxo group on the rhenium which can carry out the same reaction once more and regenerate the C H 3 the R E O 3 molecule. So, this reaction can, this hydrogen peroxide generated intermediate, which is a diperoxo molecule can do can carry out two oxidations of two molecules of cyclobutanone.

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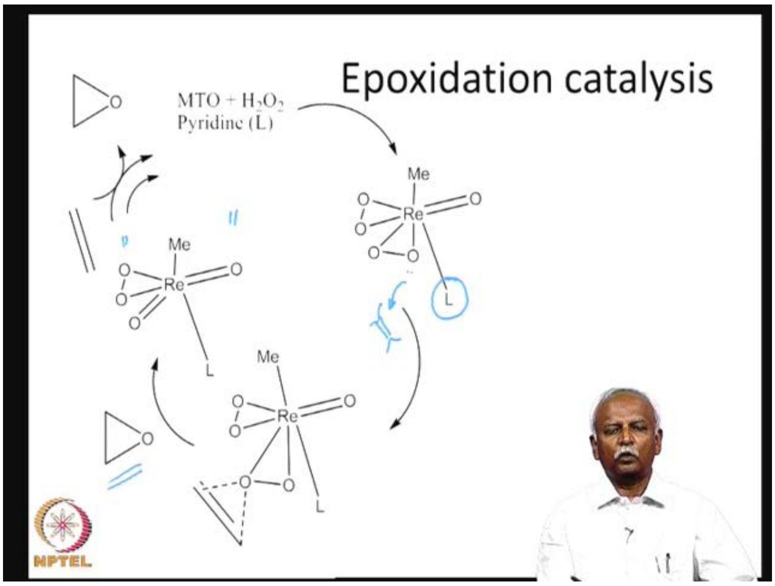

Epoxidation catalysis

MTO + H_2O_2
Pyridine (L)

And so you have one more possibility, you can just transfer the oxygen to an olefin that is an epoxidation reaction. If you do that you will get an epoxide which is pictured here. So, here so here again you end up with a rhenium peroxo complex, rhenium peroxo complex has got a ligand. Usually a pyradine which stabilizes the system and once you have this pyradine stabilizing the rhenium. It turns out that it adds on to olefins or this oxygen tends to attack olefins directly.

And this is the intermediate that is that is formed where you have again a spirocyclic type of compound, where oxygen is at the bridge head and this can eliminate epoxide and generate one more oxidate, oxygen rich intermediate which carry out one more oxidation. So, you can see that the methyl trioxo rhenium is a regenerated at the end of this reaction and pyradine is also present as a catalyst. So, all you are carrying out is hydrogen peroxide and ethylene is very green chemistry. And the catalyst is itself soluble in water. And so you get methyl trioxo rhenium is soluble in water and so you can carry out this reaction extremely efficiently.

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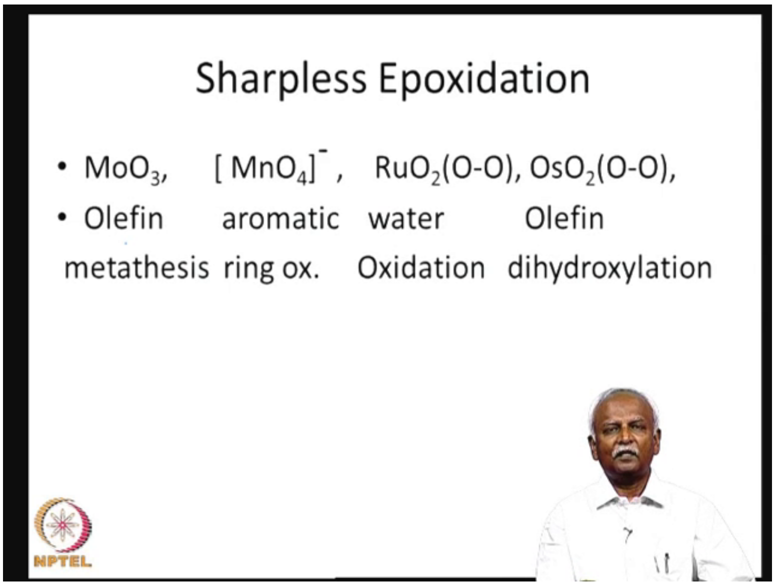

Sharpless Epoxidation

- MoO_3, $[MnO_4]^-$, $RuO_2(O\text{-}O)$, $OsO_2(O\text{-}O)$,
- Olefin metathesis, aromatic ring ox., water Oxidation, Olefin dihydroxylation

Before we proceed or close this discussion on high oxidation chemistry, we should mention sharpless oxidation, where you can have epoxidation using oxo groups. And this is a reaction which is been extremely useful and we will discuss the Kyrall variant of this reaction little more detail. But sufficed is same that the oxo groups that are generated by various metals molybdenum, manganese, ruthenium and osmium are capable of carrying out oxidation of different substrates.

So, it is not always epoxidation or the Bayer Williger oxidation that we have seen here. A variety of substrates can be used. And here are some reactions of the oxo containing metals, complexes. And these complexes are sometimes, the intermediates have been characterized. But sometimes the intermediates have not been characterized and so it has led to some debate about whether these reactions are really organometallic species.

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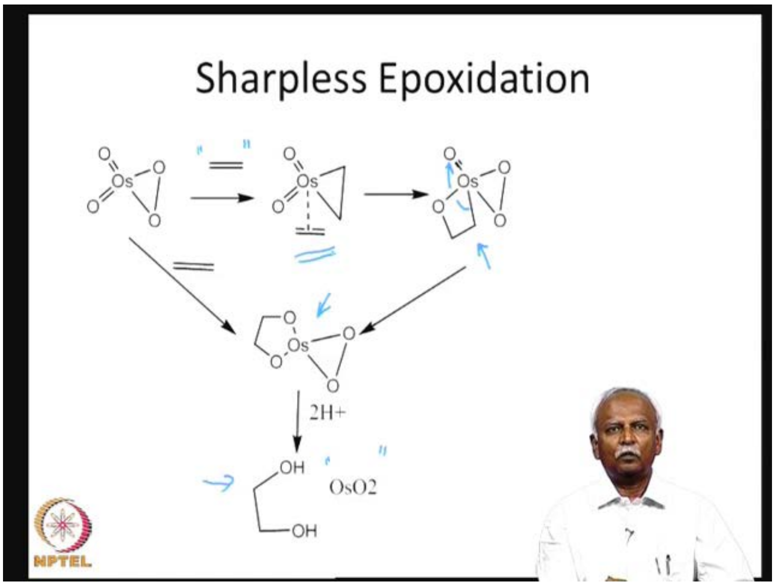

Sharpless Epoxidation

Let me give you the sharpless epoxidation catalytic cycle and tell you why this is the case. So, the sharpless epoxidation, the osmium tetroxide can in fact react with olefin. So, here is the olefin coming in and it can in fact react with the olefin to form an osmium olefin bond, which can react in add on to the oxo group and form a metalless oxo osmium matallo cycle. And that is picture here and if you now expand this ring.

If you expand this ring, if this carbon moves over to this oxygen, if it moves over to this oxygen you would end up with another spriocyclic compound with osmium at the bridge head, which can easily regenerate another catalyst in the presence of water to give you a diol. And osmium dioxide which can in fact can be oxidised further with hydrogen peroxide to osmium tetorxide. So, this sharpless epoxidation was postulated to go through this osmium olefin complex. But many people believed that it is not necessary to form this complex.

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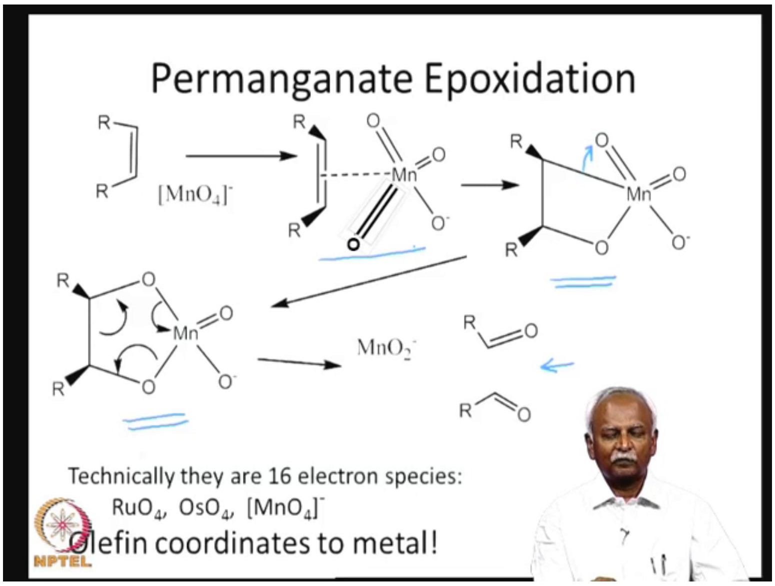

Permanganate Epoxidation

Technically they are 16 electron species:

RuO_4, OsO_4, $[MnO_4]^-$

Olefin coordinates to metal!

And here I have for you the reasons why we need not do this. It is permangante which is again a high oxidation state species. We know that it carried out a dihydroxilation reaction. The dihydorxilation reaction, it first forms a complex manganese olefin complex or atleast it is possible to form the manganese olefin complex. And which can now add on to the oxo group, which can add on to this oxo group. In this particular slide you should have three oxo bonds.

So, this hydrogen is not there and so you have a formation of a oxametallo cycle, which can again ring expand as in showed you in the previous transparent sheet to give you this 5 numbered manganese cycle, which can eliminate M N O 2 minus and generate two aldehydes. So, technically this is the key species is the 16 electron species. And it can coordinate an olefin.

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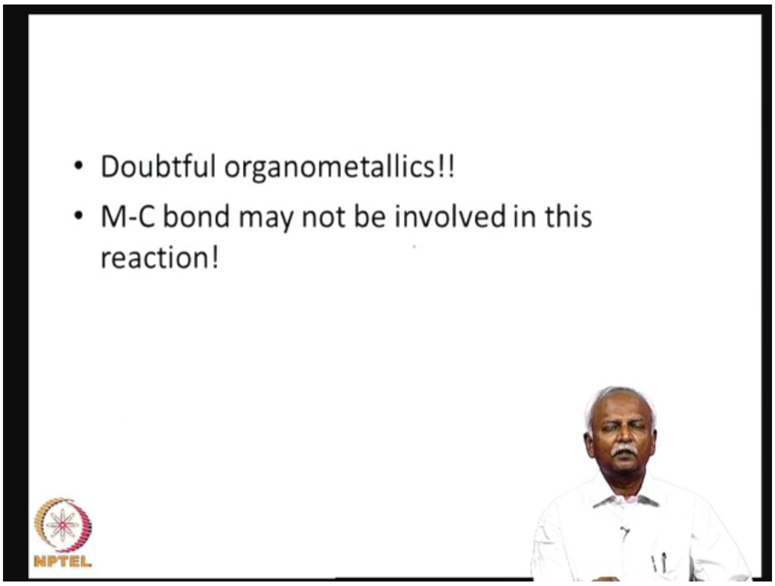

- Doubtful organometallics!!
- M-C bond may not be involved in this reaction!

But in the reaction the people doubted the value of this organometallic complex being formed,

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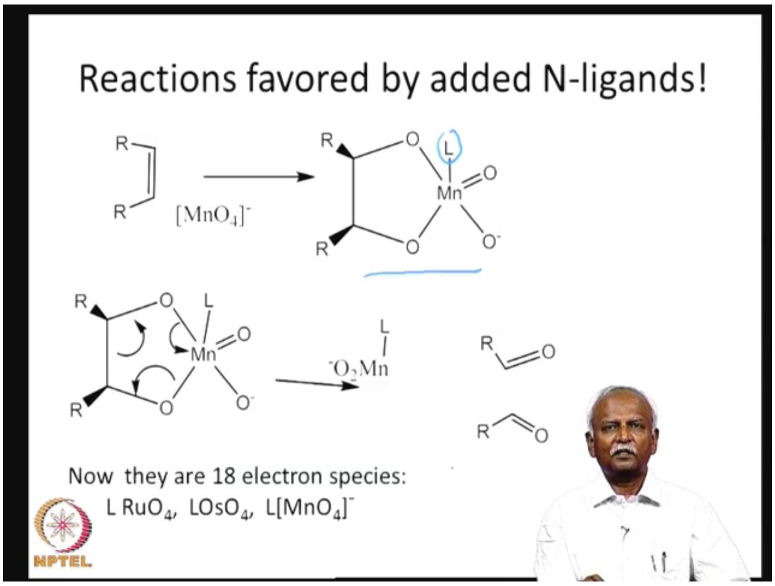

Reactions favored by added N-ligands!

Now they are 18 electron species:
L RuO_4, LOsO_4, L$[MnO_4]^-$

purely because the reaction is much better carried out in the presence of a ligand. Such as L, a pyradine or an organic base which coordinates to the manganese. And if that is indeed the case then there would be no 16 electron intermediate and the olefin complex need not be formed in the first place before generation of this key intermediate. So, the same reaction could be carried out without coordination of the olefin to the metal.

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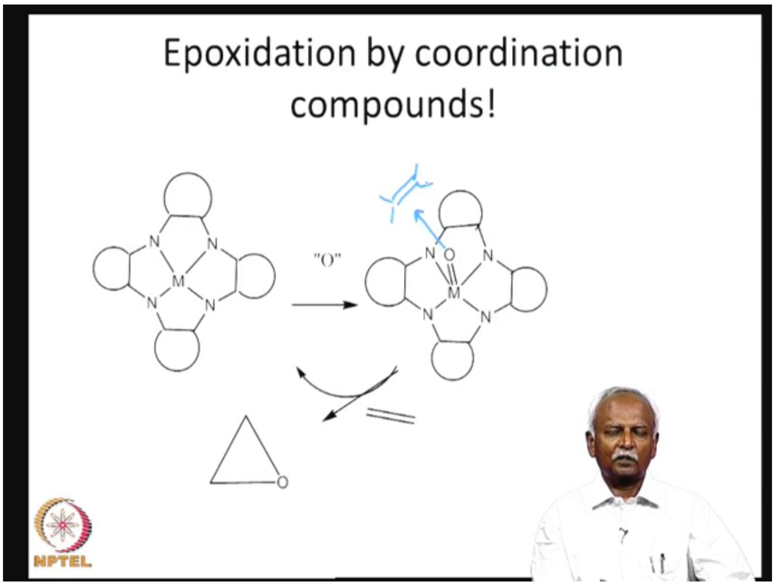

Epoxidation by coordination compounds!

Now, epoxidation by coordination compounds is quite well known, a variety of biologically relevant systems paraffin systems are capable of carrying out this epoxidation reaction. And so epoxidation chemistry is known. And in many of these cases, there is no possibility for the metal to interact with the olefin, because the oxygen if it is present on one side and the olefin would be present on the other side. So, a direct attack of the oxygen on the double bond is what is envisaged. So, here are cases where you have epoxidation of an olefin, but then there is no organometallic chemistry that is really involved. So, let me close by summarizing what we have just seen in today’s lecture.

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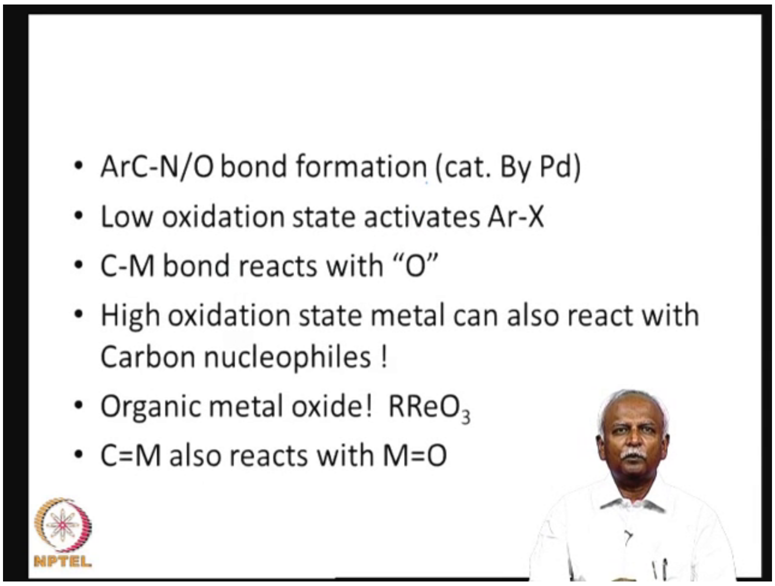

- ArC-N/O bond formation (cat. By Pd)
- Low oxidation state activates Ar-X
- C-M bond reacts with "O"
- High oxidation state metal can also react with Carbon nucleophiles !
- Organic metal oxide! $RReO_3$
- C=M also reacts with M=O

We have the possibility for forming aryl carbon to nitrogen or aryl carbon to oxygen bonds. And these reactions are mostly catalyzed by palladium. Palladium seems to be the metal of choice. Although nickel and to lower extent copper is possible to have catalyst from those groups also. And it is possible that low oxidation states are involved in the oxidation, oxidative addition of A r X, because you need a phosphorous atom to stabilize the palladium in the Buchwald reaction. And it is most probable that palladium 0 is indeed involved in those reactions, but it is possible to have high oxidation states also. And these high oxidation states are stabilized with more nitrogen and oxygen coordinating ligands as shown in Melanie Stanford.

So, these high oxidation state metals can in fact have very interesting chemistry. And although these are being not been extensively explored, it is possible to see some interesting chemistry coming out of these rhenium trioxo complexes or manganese oxo complexes. So, you can have these reactions between C double bond M and M double bond O. So, here you have the possibility for a carbon attached to metal, which is palladium and an oxygen during a reductive coupling to give you M plus C O.

And you have also the possibility for C M interacting with M O to generate the metathesis type of intermediates from here. So, it is possible to have a variety of interesting chemistry with these oxo compounds that we have looked at. And these are these intermediates are possibly going to be very valuable in the future for some carrying out some chemistry with them.