Advanced Transition Metal Organometallic Chemistry
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Module - 9
Lecture - 44
C-heteroatom Coupling

Welcome to this course on Advanced Transition Metal Organometallic Chemistry. Today we are going to be talking about C, carbon-heteroatom coupling with regard to our overall discussion on C-C bond forming reactions that we had done in the last few lectures. Now, one of the main advantages of these organometallic catalyst mediated carbon-carbon or carbon-heteroatom bond forming reaction is the fact that these catalyst have achieved this reaction proceed under very mild conditions.

So, these in a nutshell is the main achievement of organometallic catalyst. So, what this catalyst has achieved is in reduction of stringent conditions in which they, this reaction occur in absence of this catalyst. So, this can be seen as a main advantage of using organometallic catalyst is that they are able to carry out all these reactions, the reactions that would form various types of carbon-carbon bond or carbon hetero atom bond.

And this bond would be formed under mild conditions which are easily accessible. So, this in my opinion is the main reason why all of these palladium based organometallic catalyst or nickel based organometallic catalyst that we have been talking about, for C-C cross coupling reaction or that we would be talking about now about C-heteroatom coupling reactions they have become very popular for.

Now, to go in bit more details, these reactions particularly with respect to C, carbon-heteroatom coupling reactions, they can be formed by 2 different ways. 1 is nucleophilic aromatic substitution reactions which require drastic conditions. Or otherwise, they can also be formed by addition of alkene or alkyne which also is a very challenging reaction to perform in absence of this organometallic catalysis.

So, with that being said, what we see or what we would see is that all of these types of reaction would become very favourable when influenced by this organometallic catalysis. So, with this let me start my topic today, which is about carbon-heteroatom coupling reaction.

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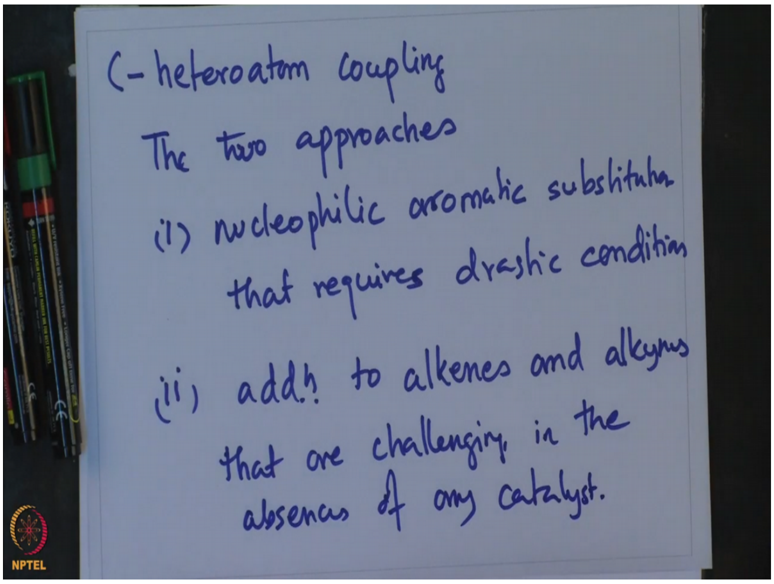

C- heteroatom coupling

The two approaches

(i) nucleophilic aromatic substitution that requires drastic condition

(ii) addn to alkenes and alkynes that are challenging in the absence of any catalyst.

The 2 classical ways or 2 approaches that it, for making carbon atom bonds are: 1, through nucleophilic substitution reaction aromatic substitution which requires drastic conditions. And the other approach obviously involves addition to unsaturated compounds like alkenes and alkynes which also is challenging in absence of catalyst. Now, the reason for addition reaction being challenging in absence of catalyst, because both the nucleophile that is being added, as well as the alkene or alkyne, both are considered to be electron rich entities.

And so, they are mutually averse to the reacting with each other. And hence, this addition reactions to alkynes and alkenes are in fact very challenging in absence of this catalyst. So, what we see over here, the ground already made for the acceptance of these transition metal catalysed carbon-heteroatom coupling as such coupling would find a way around this type of existing methods which are nucleophilic aromatic substitution reaction that require drastic condition or this addition reactions to alkenes and alkynes, which in absence of catalyst are very challenging.

So, this new-found transition metal mediated reactions coupling reactions, would find way around to perform the same reactions under very mild conditions in a effective manner. And in this context, what we going to be; we are going to be discussing a number of reactions which have, which would be catalysed by organometallic catalyst.

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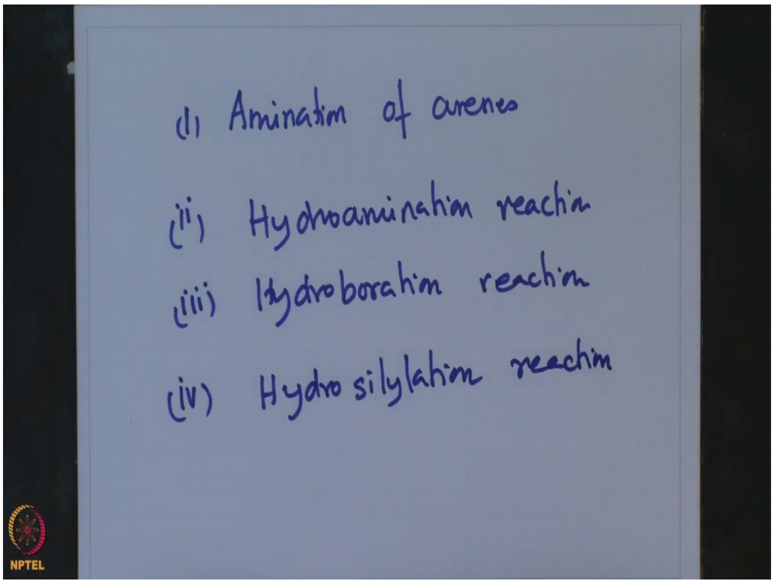

(i) Amination of arenes

(ii) Hydroamination reaction

(iii) Hydroboration reaction

(iv) Hydrosilylation reaction

And among these, them, among these are amination of arenes, hydroamination reaction, hydroboration and hydrosilylation reaction. And in these, the first one would be C-N bond formation; hydroamination would also give C-N bond formation, hydroboration would give C-B bond formation. And hydrosilylation as the name suggests would give C-Si bond formation.

So, these are some of the reactions which would, we are going to be taking up that would show that how this transition metal based organometallic catalyst help perform this reactions, which otherwise in absence of catalyst would be extremely difficult to do so. So, having said that we are going to focus on carbon-heteroatom coupling, particularly on amination of arenes.

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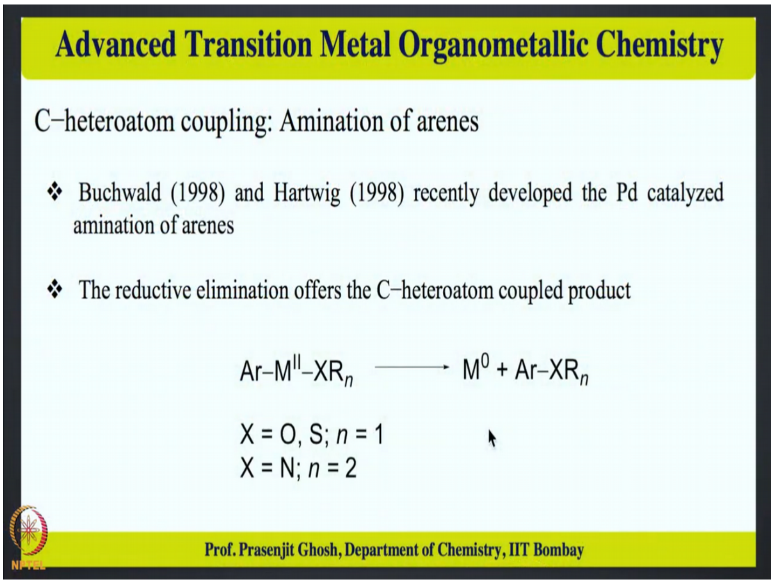

Advanced Transition Metal Organometallic Chemistry

C–heteroatom coupling: Amination of arenes

- Buchwald (1998) and Hartwig (1998) recently developed the Pd catalyzed amination of arenes
- The reductive elimination offers the C–heteroatom coupled product

$$Ar–M^{II}–XR_n \longrightarrow M^0 + Ar–XR_n$$

$X = O, S; n = 1$
$X = N; n = 2$

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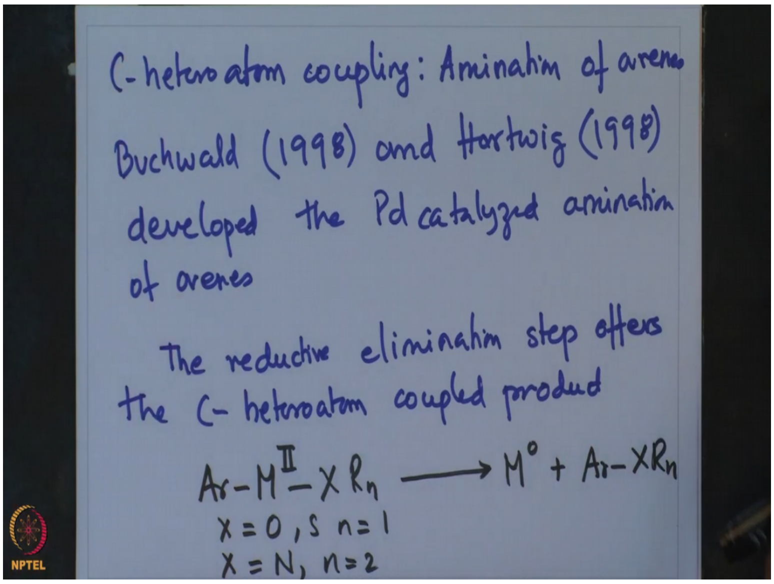

C-heteroatom coupling: Amination of arenes

Buchwald (1998) and Hartwig (1998) developed the Pd catalyzed amination of arenes

The reductive elimination step offers the C- heteroatom coupled product

$$Ar-M^{II}-XR_n \longrightarrow M^{\circ} + Ar-XR_n$$

$X = O, S \; n = 1$
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This reaction was recently developed, by recent I mean, about 2 decades back, by professor Buchwald at MIT and professor Hartwig at Yale University, who developed this reaction as recent as 1998 for this amination of arene. So, Buchwald 1998 and Hartwig 1998 recently developed the palladium catalysed amination of arenes. And we are going to be discussing the catalytic cycle in bit more details.

But what is important to know is the reductive elimination step, leads to the formation of these carbon-heteroatom couple product. The reductive elimination step offers the carbon-heteroatom coupled product. And this is a sort of explained by this equation over here where it is Ar M II X Rn. X can be a heteroatom oxygen, sulphur; then n = 1. X can also be nitrogen when n = 2. So, that will reductively eliminate to give M 0 and this carbon-heteroatom cross coupled product Ar XRn.

So, what we see is that this reductive elimination which leading to the formation of carbon-heteroatom coupled product or formation of the coupled carbon-heteroatom bond, similar to what we had observed for various cross coupling reaction, where too we saw carbon-carbon bond was indeed formed in the reductive elimination step. So, this is sort of a similar translation of the chemistry that we see in carbon-heteroatom bond formation to what we had observed for carbon-carbon bond formation.

That is the reductive elimination step indeed leads to the formation of carbon-heteroatom bond similar to what was observed in the cross coupling chemistry that we had discussed in our earlier classes. So, with that said, let me just briefly elaborate the catalytic cycle for this amination of arene reaction, so that we can compare the catalytic cycle with that we had discussed for carbon-carbon bond forming catalytic cycles earlier on in our lectures.

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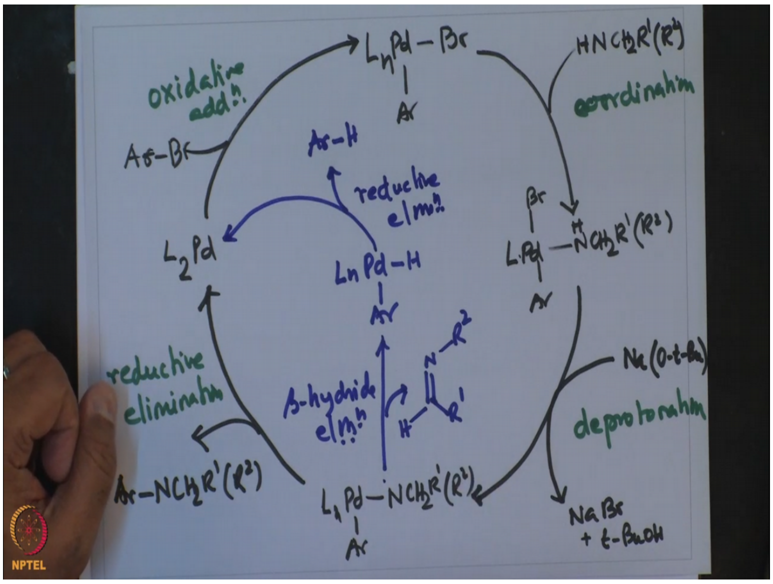

So, the reaction starts with the palladium 0 species L 2 Pd. So, that adds aryl, bromide. Now, this step is similar to the oxidative addition step to give the product L n Pd, Br, Ar. Now, in this case, after immediately, after oxidative addition coordination of amine to palladium occur. Now, this is a sort of different. Then, what we had observed in C-C cross coupling reaction where it was transmetallation reaction.

But, in this case, what we see coordination of amine occurring onto the palladium. And this is illustrated by in the scheme as shown over here, H N CH 2 R 1 R 2. So, this amine comes and coordinates to palladium during L Pd, Br, Ar, N H CH 2 R 1 R 2. So, after the amine is coordinated; so, this is the coordination of the amine. The next comes a base initiated deprotonation which occurs using the base sodium t-butoxide giving sodium bromide + t-butanol.

So, sodium bromide comes off and this proton protonates the butoxide giving t-butanol, resulting in the formation of this Ln Pd, Ar, N CH 2 R 1 R 2. So, this step is now the deprotonation step, amine deprotonation step. And the deprotonation of amine, results in formation of a amido functionality. So, this is a neutral amine, which is cationic after its lone pair gets coordinated to the palladium, becomes an amido functionality after deprotonation with sodium t-butoxide giving sodium bromide and butanol, which will undergo reductive elimination to give the desired product Ar N CH 2 R 1 R 2.

And this step is called reductive elimination. This step is called the reductive elimination. And this is how the catalytic cycle proceeds. So, if one were to compare these catalytic amination of arene catalytic cycle with that of Suzuki catalytic cycle, one would also see that here too there are 4 elementary steps. And 2 of which are common similar to what was observed for Suzuki. That means the oxidative addition and the reductive elimination.

However, the other 2 elementary steps the amine coordination and amine deprotonation are different from what was observed for the palladium mediated cross coupling reaction in which it was transmetallation and trans-cis isomerization reaction. So, what we see is the fact that we had stated earlier as well, that carbon-heteroatom bond is indeed formed during the reductive elimination step.

There is a competing decomposition pathway that may also occur. And that is this, if there is a beta hydrogen on the nitrogen, there is this beta hydride elimination pathway, marked in the blue giving imine. And corresponding palladium hydride complex which; so, this is a beta hydride elimination pathway which gives the imine along with the palladium hydride aryl hydride complex, which eventually undergoes reductive elimination to give aryl, arene, aryl hydride and with the generation of the palladium 0 L 2 Pd species.

So, this is reductive elimination. So, what we see is that, in addition to the catalytic cycle involving amination of arene. If the amine has a beta hydrogen, a secondary pathway may be possible, in which generation of imine would be accompanied through a beta hydride elimination pathway alongside the formation of Ln Pd aryl hydride complex that eventually again would reductively eliminate to give arene and the palladium 0 species which can then again participate.

So, what we see is that the decomposition pathway would turn out 2 different products; 1 is imine and arene. And that, the presence of these 2 compounds the imine and the arene, would definitely indicate the existence of the decomposition pathway as shown in blue. Otherwise, the main pathway which would lead to the imination of arene is shown in black as usual. Now, as has been discussed in details that this reaction is a has a large scope of broad scope of utility.

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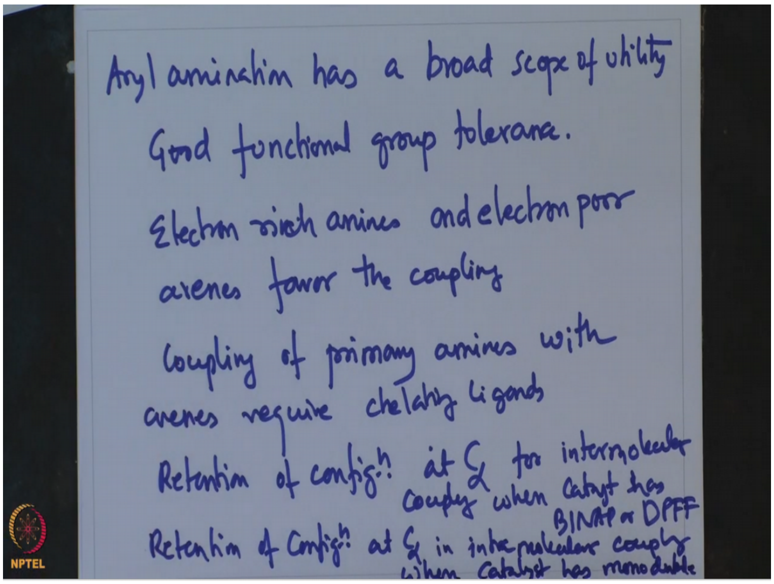

Aryl amination has a broad scope of utility

Good functional group tolerance.

Electron rich amines and electron poor arenes favor the coupling

Coupling of primary amines with arenes require chelating ligands

Retention of config^{n} at C_α for intermolecular coupling when catalyst has BINAP or DPPF

Retention of Config^{n} at C_α in intramolecular coupling when catalyst has monodentate

Arylamination has a broad scope of utility. 1, it is good functional group tolerance and preferably electron rich amines and electron poor arenes favour the coupling. So, electron rich amines means the nucleophile is extremely nucleophilic and electron poor arenes means the electrophile is extremely electrophilic. So, significantly nucleophilic reagent would definitely react faster with a significantly electrophilic substrates.

And that is quite intuitive. And that is spelled out in the lines over here, that says electron rich amines and electron poor arenes favour the coupling. The coupling of primary amines with arenes require chelating ligands. And retention of configuration is observed in the alpha position for intermolecular coupling in terms of asymmetric reaction at C alpha for intermolecular coupling when catalyst has BINAP or DPFF.

Whereas, also retention of configuration at C alpha in intramolecular coupling when catalyst has monodentate ligand. So, with this, I would like to conclude today's discussion on amination of arenes. And today, in, as a part of the carbon-heteroatom coupling, what we talked about is this amination of arenes which was developed by Buchwald Hartwig as late as 1998. And which uses palladium in carrying out this amination of arenes under mild condition.

When looked, and what we discussed is the fact that this carbon nitrogen bond formation in arylation of amine took place during the reductive elimination step. And we have also looked at the catalytic cycle for this amination of arene. And what we had observed that, this catalytic cycle contains 4 elementary step that involves oxidative addition, amine coordination, amine deprotonation, followed by reductive elimination.

And when we compare this catalytic cycle with that of the palladium mediated cross coupling reaction, what we had seen is that 2 of the 4 elementary steps are common with that of the palladium mediated cross coupling reaction. And these 2 steps were oxidative addition and reductive elimination. However, in aryl, amination of aryls, there are 2 steps which are different than what was observed for palladium mediated cross coupling reaction.

And these 2 steps were amine coordination and amine deprotonation, leading to the formation of a palladium imido species. Now, we have also looked at the decomposition pathway that maybe existent if there is a alpha hydrogen and the amine. And what we had seen that, there is a beta hydride elimination pathway is possible if there is a presence of alpha hydrogen in the amine.

And that pathway leads to the formation of imine along with the palladium aryl hydride species which undergoes reductive elimination to give arenes along with the formation of palladium 0 species. Now, 1 thing which has made this arylamination is its broad scope of utility, its good functional group tolerance and what has been observed that electron rich amines which are extremely nucleophilic favours coupling with electron poor arenes which are more electrophilic.

And the coupling of primary amines with arene require chelating ligands. Also it has been observed the in the symmetric form, the retention of configuration at alpha in intermolecular coupling requires chelating ligands, whereas retention of configuration at alpha intramolecular coupling require monodentate phosphine ligands. So, with this, I am going to conclude today's discussion on amination of arenes.

And we are going to be discussing a bit more on the various applicability that have been reported for amination of arene in the next class. And then take up another important example of CN bond formation particularly from the perspectives of hydroamination reaction. I once again thank you for patiently being with me in this lecture and I look forward to covering this topic of amination of aryl in bit more detail in the next lecture. And then, take up this new topic of hydroamination in the next lecture. Till then, goodbye and thank you.