Advanced Transition Metal Organometallic Chemistry
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Module - 9
Lecture - 45
C-Heteroatom Coupling: Arylamination

Welcome to this course on Advanced Transition Metal Organometallic Chemistry. We have been discussing C-heteroatom bond forming reactions using transition metal catalyst. And this discussion has been going on with respect to our earlier discussion on C-C bond forming reaction. The main advantages of the processes that we are looking at, involves the catalytic formation of C-C and C-heteroatom bond using lead transition metal catalyst, more often palladium or nickel that we have discussed so far.

And what we have also observed that this C-C or C-heteroatom bond formation have being carried out in a catalytic fashion under mild conditions with large substrate scope. And that is what makes this reaction so effective, popular and make them useful in various domains of organic synthesis. In our discussion on C-heteroatom bond forming reaction, we had discussed about carbon nitrogen bond forming reaction in this arylation of amine that we had discussed in our previous class.

Now, what we had noted over there that this carbon-heteroatom bond forming reaction can be often achieved by 2 different methods. The first one obviously is the nucleophilic aromatic substitution reaction that require drastic conditions or that of using addition reactions of unsaturated compounds like alkene and alkyne which is very challenging in absence of any catalyst as both the nucleophile and the alkene with alkynes are all electron rich entities.

So, in this perspective, this palladium mediated aromatic arene amination reaction discovered by Hartwig and Buchwald about 2 decades back assumed a significance. What was observed that in this amination of arene reaction that this carbon-nitrogen bond formation is happening in the reductive elimination step. A careful look at the catalytic cycle also reveal that this C amine carbon-nitrogen bond forming step is the reductive elimination step.

And that this amination of arene catalytic cycle proceeds in 4 elementary steps, the 2 of which are similar to that of C-C bond forming reaction that involves oxidative addition and reductive elimination. However, the other 2 steps are markedly different. Then C-C bond forming reactions and these 2 step in a amination of arene is amine coordination followed by amine deprotonation in using a base to give a palladium biimido species.

We have also noted that if the amine has a alpha hydrogen, then a beta hydride elimination pathway kicks in resulting in the formation of imine along with the production of a palladium aryl hydride species which subsequently undergoes reductive elimination to give arene and in turn regenerates the palladium 0 species which also enters the catalytic cycle. So, having discussed that, we are going to look up at the scope and utility, applicability of arynation of arene amination reaction in, with more detail in today's lecture.

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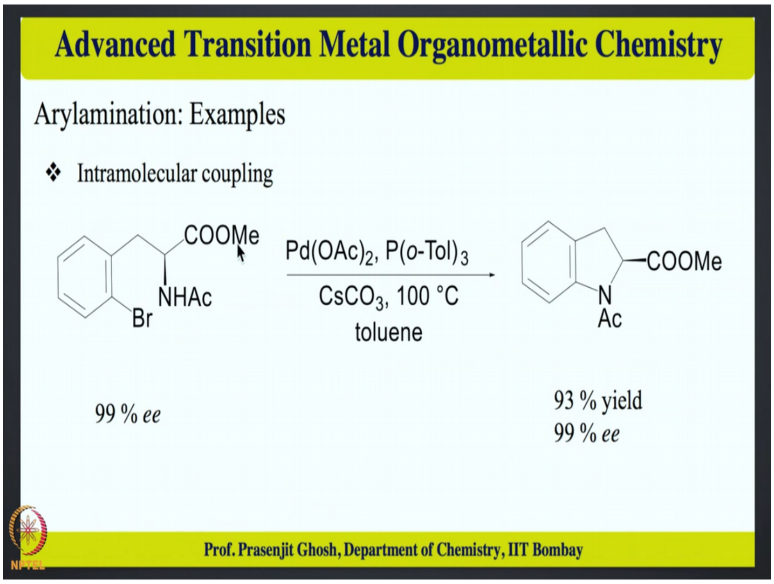

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Arylamination: Examples

- Intramolecular coupling

$Pd(OAc)_2$, $P(o\text{-}Tol)_3$

$CsCO_3$, 100 °C

toluene

99 % *ee*

93 % yield

99 % *ee*

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So, 1 important example is in asymmetric arylamination reaction.

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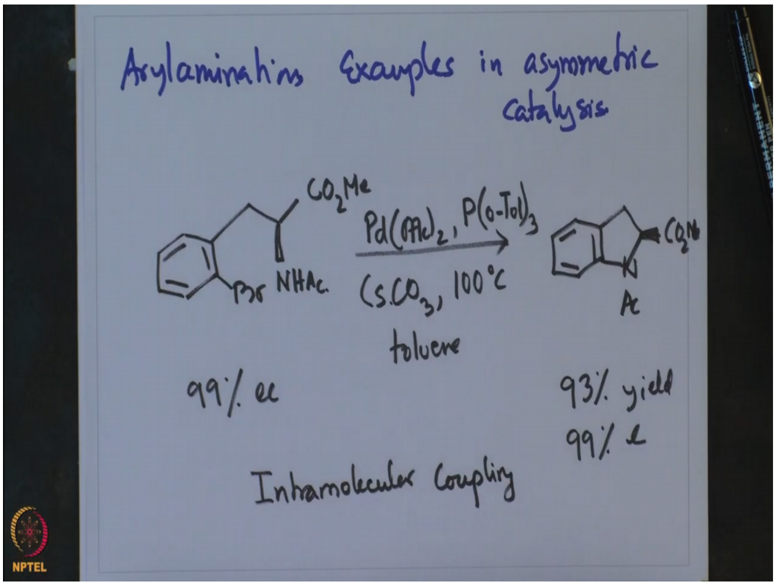

Arylaminations Examples in asymmetric catalysis

$Pd(OAc)_2$, $P(o\text{-}Tol)_3$

Cs_2CO_3, 100 °C

toluene

99% ee

93% yield

99% ee

Intramolecular Coupling

Examples in asymmetric catalysis. And this is illustrated in this example containing phenyl, bromide, N H Ac, CO 2 Me with palladium acetate as catalyst and (()) (05:25) O tolyl phosphine ligand in presence of caesium carbonate, 100 degree centigrade in toluene gives the desired complex, bicyclic complex containing of few 6 membered, 5 membered rings, N A C, CO 2 Me in 93% yield and 99% ee.

And this one also is optically pure, 99% ee. So, what we, it says that this is an extremely effective method that carries out intramolecular coupling in an enantioselective fashion. So, another example in this front is involves intermolecular coupling which we are going to be seeing right now.

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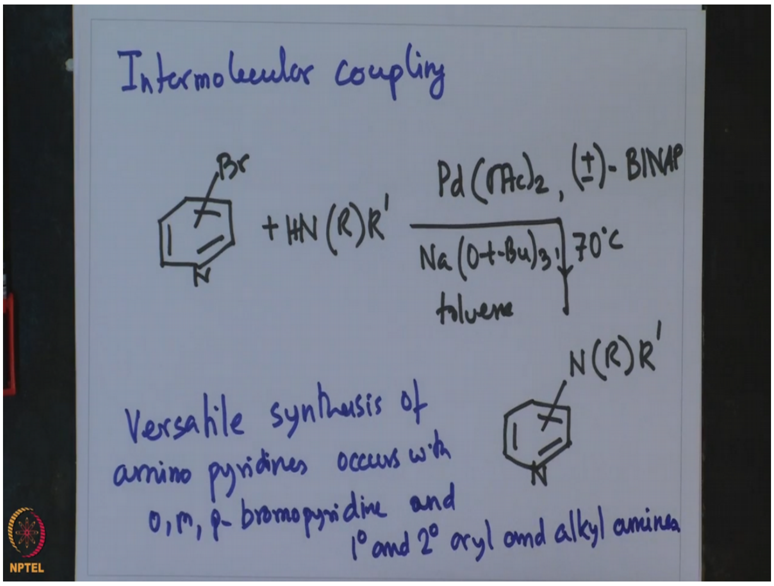

Intermolecular coupling

+ HN(R)R'

$Pd(OAc)_2$, (±)-BINAP

$Na(O\text{-}t\text{-}Bu)_3$, 70 °C

toluene

Versatile synthesis of amino pyridines occurs with o, m, p- bromopyridine and 1° and 2° aryl and alkyl amines

The previous one was an example of asymmetric intramolecular coupling.

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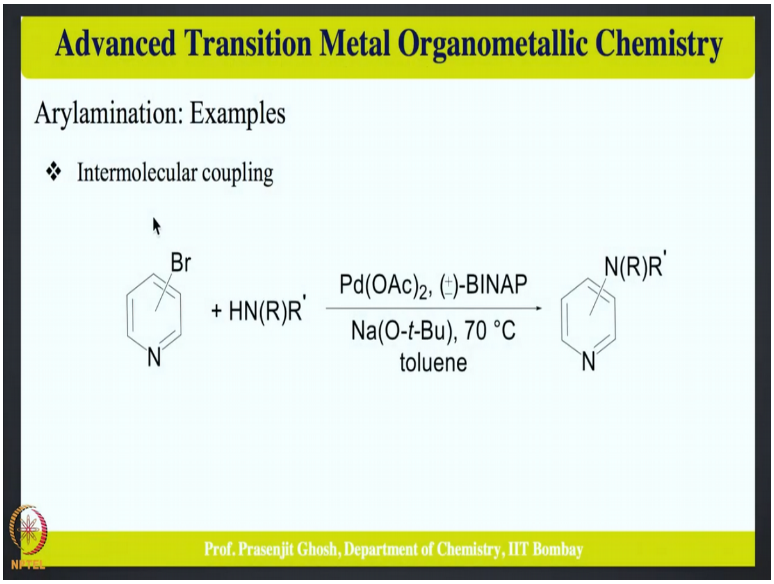

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Arylamination: Examples

- Intermolecular coupling

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And this one is going to be an example of intermolecular coupling. And this is illustrated by bromo substituted pyridine. The bromo substitution can occur any part of the ring. It is so versatile; + N H R R dashed, in presence of palladium O Ac + – BINAP sodium t-butoxide 70 degree centigrade toluene does this amination very effectively. This intermolecular amination N R R dashed.

So, this is a nice demonstration of a versatile synthesis of amino pyridines, these are amino pyridines; occurs with ortho, meta, para, bromo pyridine. So, it can be anywhere, ortho, meta, para, this amination would occur to give aminopyridine. And it occurs for primary as well as secondary, primary and secondary aryl and alkyl amines. So, this is indeed a very versatile reaction which can couple bromo pyridine with the bromine substitution being anywhere in the ring, with that of amines to give aminopyridine.

And this amines can be primary, secondary, aryl, alkyl, any type. So, one can just gauge at the depth and the breadth and the scope of this beautiful chemistry that involves intermolecular coupling of amino pyridine bromide with amines to give aminopyridines. Now, this reaction can be successfully extended for preparation of special pyridyl ligands.

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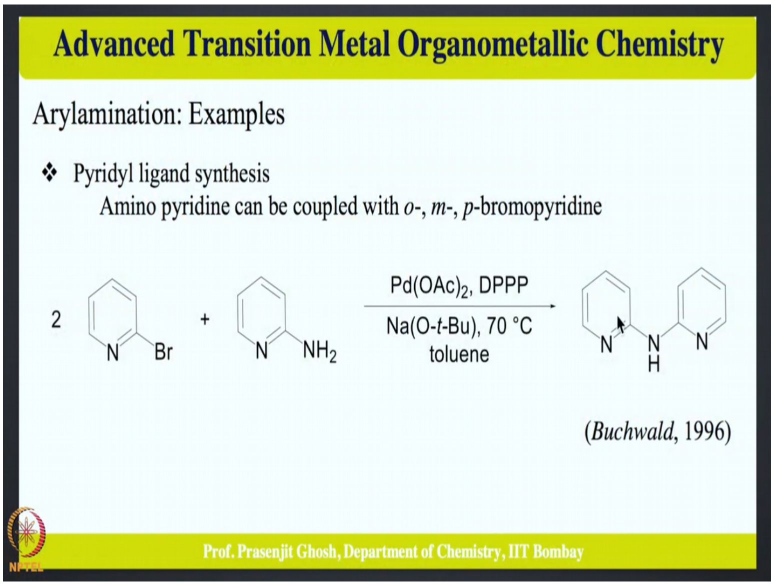

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Arylamination: Examples

- Pyridyl ligand synthesis
  Amino pyridine can be coupled with *o*-, *m*-, *p*-bromopyridine

(*Buchwald*, 1996)

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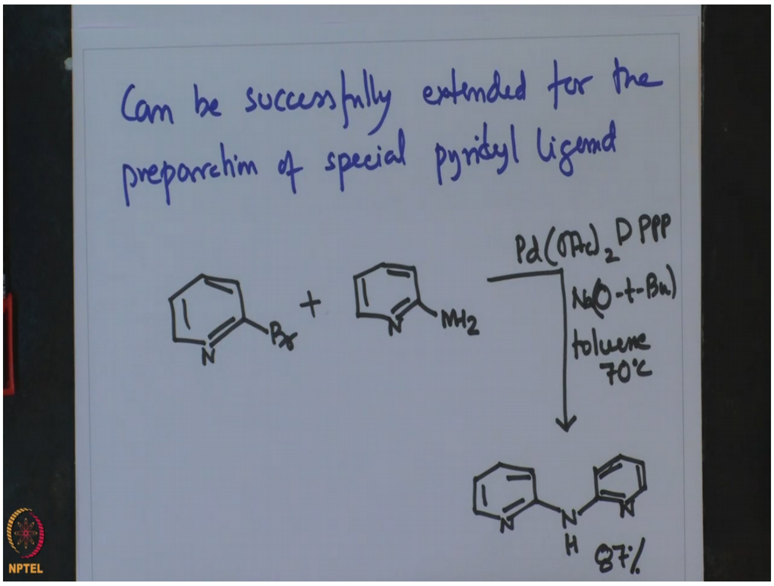

Can be successfully extended for the preparation of special pyridyl ligand

Can be successfully extended for the preparation of special pyridyl ligand as is shown over here. Br + N H 2, Pd O Ac in presence of Pd O Ac whole 2 D PPP ligand sodium t-butoxide toluene 70 degree centigrade to give this ligand N H pyridine in 87% yield. Another important utility of this amination of arene is a transformation of phenol to aniline.

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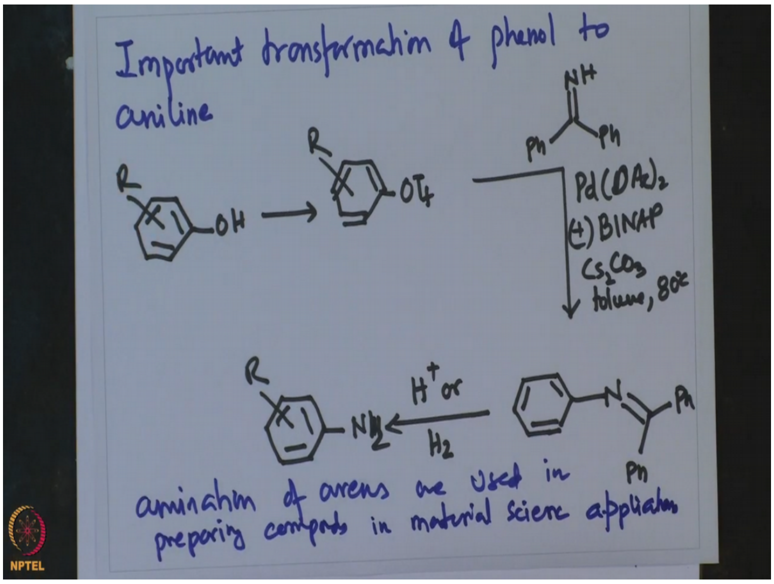

Important transformation of phenol to aniline

amination of arenes are used in preparing compounds in material science application

Important transformation of phenol to aniline. This is a very utility a driven transformation. And this is achieved by converting first phenol to triflates. And then, through a sequence of reaction it is converted to aniline. And this is beautiful illustrated by the example which is shown over here. R, so this is substituted phenol first converted to triflates OT f. And then, in presence of imine Ph, NH, Ph, palladium acetate + minus BINAP caesium carbonate toluene 80 degree centigrade.

One would get the corresponding C-N couple product which in presence of H + or H 2 would give the desired aniline. So, this was also reported by Buckwald in 1997. So, this is a beautiful process in which phenols are converted into amines and substituted phenols are converted to amines. And in the first step, the substituted phenols are converted to triflate. And then, the triflate is subjected to this amination reaction using benzophenone imine with palladium acetate BINAP caesium carbonate toluene to give the corresponding C-N couple product which can finally hydrogenated to give the corresponding amines.

Amination of arenes are used in preparing compounds in material science applications exhibiting electronic and magnetic properties useful. So, in this regard, one important thing to mention is the polyarynils and the polyanilines can be prepared by this arylation of imine in a much more selective fashion. Then it can be done with this oxidative coupling method.

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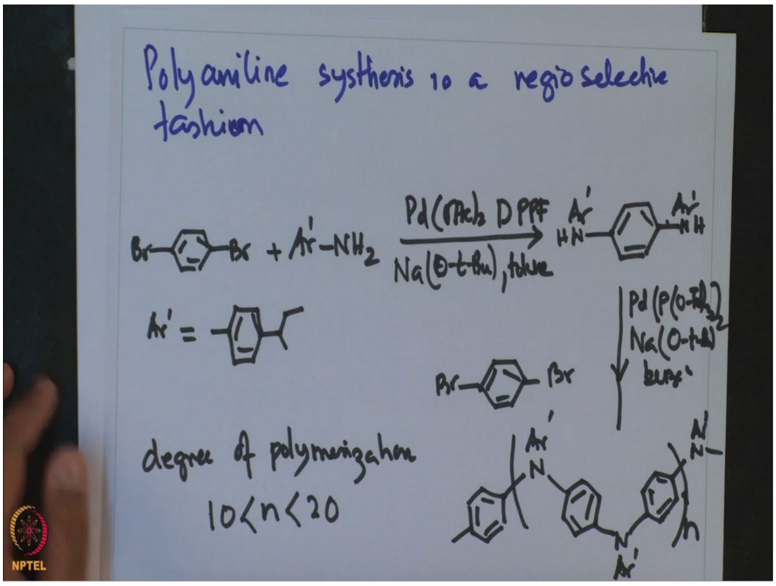

Polyaniline synthesis in a regio selective fashion

degree of polymerization
10<n<20

So, polyanilines synthesis in a regioselective fashion can be achieved by this arylation of amine reaction as opposed to this coupling, oxidative coupling pathways that would not be so selective.

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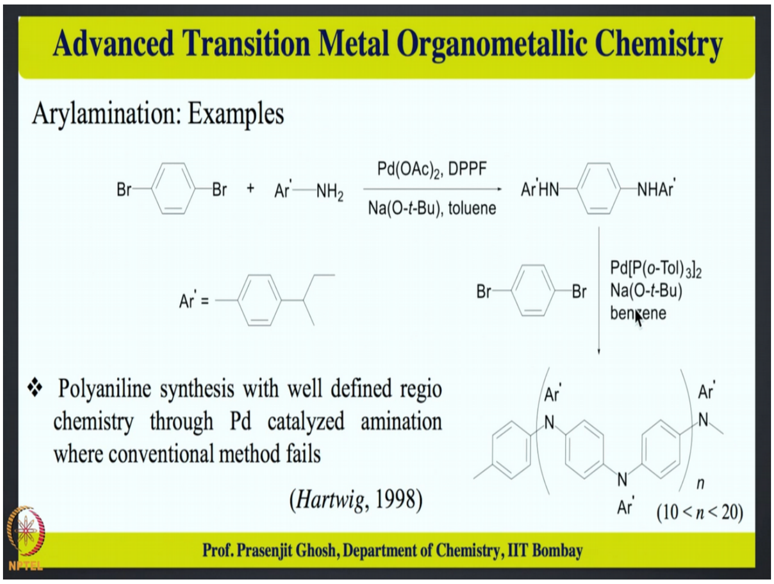

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Arylamination: Examples

- ❖ Polyaniline synthesis with well defined regio chemistry through Pd catalyzed amination where conventional method fails

(*Hartwig*, 1998)

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So, this is beautifully illustrated by the following coupling reaction in which para bromo phenol para tribromophenol + aryl amine with palladium acetate D PPF sodium t-butoxide toluene give this diamine N H Ar. Ar dashed = phenyl, substituted phenyl group as is shown over here. This when coupled with palladium P O tol 3 whole 2 sodium O t Bu benzene in presence of paradibromobenzene benzine Br, Br, gives this desired compound, N Ar, N Ar, N Ar dashed, n.

And this R polymeric material and the degree of polymerisation can vary from n being > 10 and < 20. And also, by varying this bromide, aryl and the aryl bromide and this aryl amine fragment, as well as this dibromide fragment, one can create a large library of this poly aniline compound of different structure and properties. So, the beautiful chemistry is played out over here, where we see that there are 2 C-N coupling happening.

One in the first step where the bis amine substituted amines are made in the benzene ring. And subsequently that is coupled to another aryl dibromide using the palladium C-N coupling. So, this is a wonderful example in which 2 C-N couplings have been subsequently affected to give this polyaniline polymer and in a very selective fashion. And also, the degree of polymerisation is quite large because it goes beyond n = 10 and something around n = 20.

So, with these, we would just conclude our discussion on the utility of arylamination reaction. And what we had today spoken about is 3 important utility of arylamination reactions. What we had observed that, during intramolecular arylamination, one can carry it out in terms of highly enantioselective fashion, where one could obtain ee of about 98%. Then we had also seen that this arylamination can be effectively used to make amino pyridines.

And these are very versatile form of synthesis. And it can carry out this synthesis with ortho, meta, para substituents along with primary or secondary aryl or alkyl amines. We had also seen that this arylamination reaction can be effectively used in preparing pyridial based ligands which are of great importance in this organometallic chemistry. We have also looked upon useful very important application in terms of conversion of phenols to anilines and this also involves C-N bond forming reaction.

Specifically, what we have observed noted that substituted phenols are converted to triflates and then triflates are subjected to this imination reaction with palladium to give the corresponding C-N coupled product. And which can finally be piduced with the hydrogen to give this anilines. So, the real the versatility of this C-L coupling is being played out here. What we had observed, noted this palladium catalysed arynation is produces useful material for material science that exhibit interesting electronic and magnetic properties.

And one such important thing is that of this polyaniline synthesis which is achieved in a very regioselective fashion starting from aryl amine and dibromo benzenes. So, this reaction actually proceeds in 2 steps. The first is a C-N coupling with a palladium catalyst to give the bis amine complexes of arenes which are subsequently coupled with the bromo dibromo arenes to give the corresponding polyaniline product.

The substituents and the fragments, this one, this one as this one may be so chosen that the desired para substituted products can be obtained. The degree of polymerisation for this polyanilines are also quite large, as one can see that the value of n can be > 10 and < 20. So, once again what all of these points do is the depth and the breadth of this arylation of amine reaction that we had been talking about in terms of formation of C-N bond.

And with regard to the utility space this occupy in providing compounds of importance to materials chemistry and other sophisticated applications. So, indeed, to summarise this amination of arenes is a useful method, very powerful method that carry out this C-N bond forming reactions in a stereoselective fashion under mild condition as tremendous breadth and the scope of utility of this reaction.

And also can be used for making compounds which has immense usage in materials science. We have also looked at the catalytic cycle and we had seen that, this is very much similar to that observed for other palladium mediated C-C bond forming reaction except that the 2 elementary steps are different and these are amination of coordination of the amines and deprotonation of the amines.

And the other 2 elementary step which is reductive elimination as well as or oxidative addition or however common for this arene amination reaction. So, with this, we are going to come to an end with this as arylation of amine reaction. And we are going to take up another interesting reactions which is hydro aminations of olefins or alkynes in the subsequent lecture. This hydro amination reactions are also very useful in the sense that they are atom economic.

So, there is atom economic, so, there is no side product or waste product produced as a course of the reaction. The other important challenges of hydro amination reaction is the fact that both the nucleophile and the unsaturated alkenes or alkynes are considered to be extremely electron rich. As a result, they are averse to mutually reacting to each other. And this is where the scope of organometallic catalysis comes in, the power of organometallic catalysis comes in, in making this to seemingly difficult substrate to react.

And react in a meaningful way to produce something which is useful. So, with that, I once again thank you for patiently listening to me in this lecture and I look forward to taking up this new C-N bond forming hydro amination reactions in the next class. Till then, goodbye and thank you.