Advanced Transition Metal Organometallic Chemistry
Prof. Prasenjit Ghosh
Department of Chemistry
Indian Institute of Technology - Bombay

Module - 9
Lecture - 43
Hydrocyanation Reactions

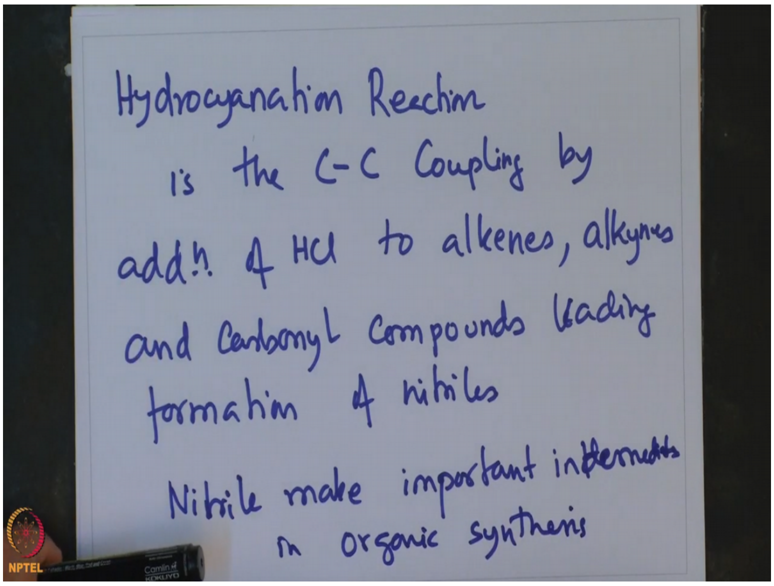
Welcome to today's lecture on Advanced Transition Metal Organometallic Chemistry. We have been discussing interesting topic which is C-C bond formation reaction using organometallic reagent, particularly the palladium mediated C-C coupling as well as cross coupling reaction. Now, to begin with let me say that the C-C bond formation is a powerful reaction in the domain of organic synthesis because C-C bond formation leads to construction of many important frameworks or target molecules that one needs to synthesise.

So, C-C bond formation is a integral part of organic synthesis and that is why the reaction is of prime importance. Now, what is more important than ever is the fact that this C-C bond formation is performed under catalytic fashion using this palladium mediated C-C cross coupling reaction. Now, being catalytic in nature, only a small amount of catalyst is required to produce or construct many many C-C bonds in a design planned and design fashion.

And that is what underlines the powers of organometallic catalyst in homogenous catalysis. So, in that context, we have seen that C-C cross coupling reaction has mediated by palladium compounds is indeed a powerful strategy for constructing a variety of scaffolds. Now, in this discussion we have touched upon this palladium mediated various C-C bond forming reactions, starting from allylic alkylation to the cross coupling reactions like Suzuki, Heck, Stille, Sonogashira and so on and so forth.

And today, we are going to move on from palladium to another metal primarily nickel. And that we are going to be discussing in the context of hydrocyanation reaction. Hydrocyanation reaction is C-C coupling by addition of HCN to alkenes.

(Refer Slide Time: 03:05)



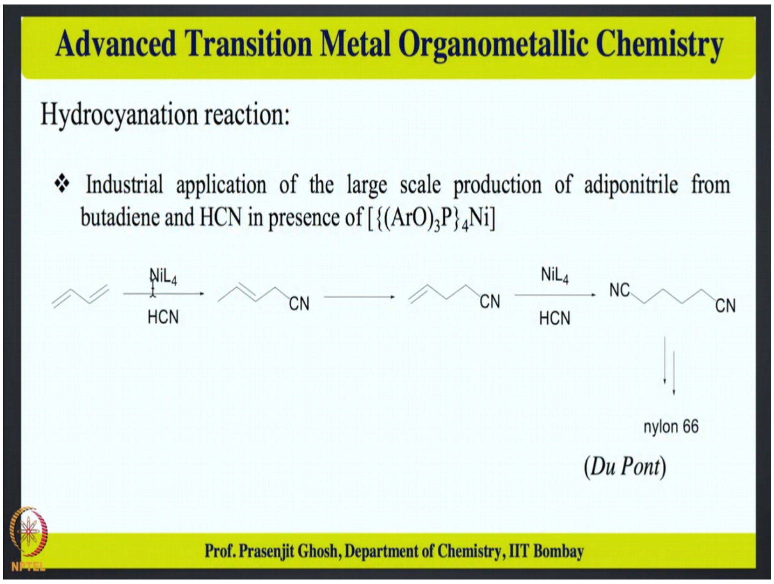
Hydrocyanation Reaction
is the C-C Coupling by
addn. of HCN to alkenes, alkynes
and Carbonyl compounds leading
formation of nitriles
Nitrile make important intermediates
in organic synthesis

Is the C-C coupling by addition of HCN to alkenes, alkynes and carbonyl compounds, leading to formation of nitrile. Now, and nitriles are important intermediates to many types of organic compounds. Nitriles make important intermediates in organic synthesis. So, it can be a sort of thought of, these nitriles can give access to a very many different compounds because modification of cyano groups to other functionality broadens the scope of the reaction.

For example, a cyano group can be converted to amine or acid and other functionalities by using different reagents. And that sort of enhances or extends the scope of this hydrocyanation reaction. So, in that way, hydrocyanation is a very utility oriented reaction which is found its application in industrial scale processes. And one such thing is the large scale production of adiponitrile from butadiene and HCN that further is used for the preparation of nylon 66 by DuPont.

So, this is a beautiful example of bench to industry translation of this chemistry where hydrocyanation reaction is used for preparing the substrate for producing nylon. And nylon has great utility in fabric and other applications in society.

(Refer Slide Time: 06:24)



Advanced Transition Metal Organometallic Chemistry

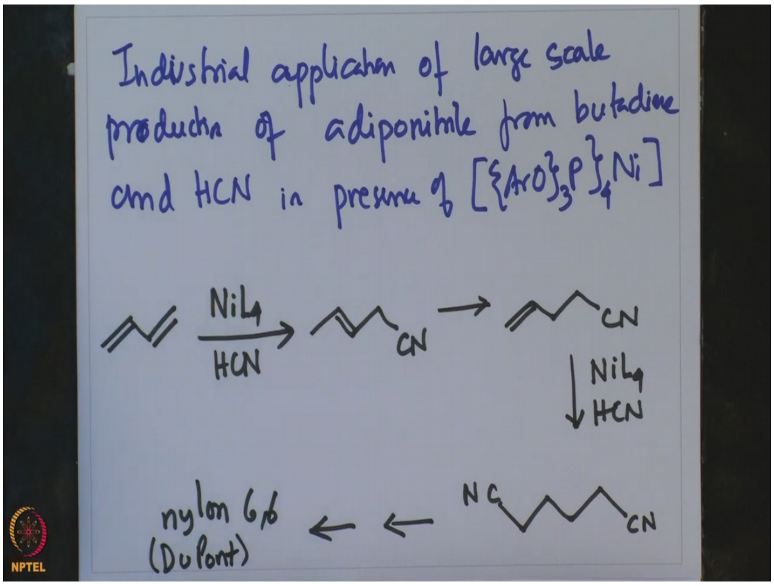
Hydrocyanation reaction:

- ❖ Industrial application of the large scale production of adiponitrile from butadiene and HCN in presence of $[\{(ArO)_3P\}_4Ni]$

(*Du Pont*)

Prof. Prasenjit Ghosh, Department of Chemistry, IIT Bombay

(Refer Slide Time: 06:32)



Industrial application of large scale production of adiponitrile from butadine and HCN in presence of $[\{ArO\}_3P\}_4Ni]$

nylon 66
(DuPont)

So, let me just illustrate this with this beautiful example; industrial of large scale production of adiponitrile. Adiponitrile is 1 4 dicyanobutane which is a monomer for producing this nylon 66 from butadiene and HCN using a nickel catalyst. This is also a kind of deviation from the theme of reactions that we had been looking at, all the reactions, applications that we have looked so far involved using a palladium as the catalyst.

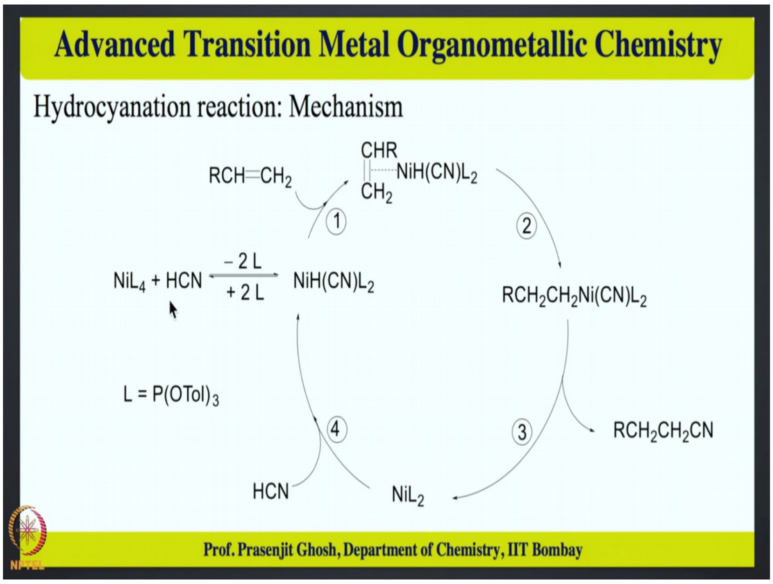
But here is an example where the nickel has been used in, as a catalyst for such a important transformation. And the reaction is beautiful example is given by the sequence of reaction shown here; Ni L 4 + butadiene. And this Ni L 4 is this catalyst phosphorus triaryloxy tetra phosphine nickel in presence of HCN undergoes the first hydrocyanation. Now, this addition is a 1 4 addition instead of 1 2 addition.

And as a result of this, 1 4 addition over here and here, 1, 2, 3, 4; what we see that, there is a migration of the double bond from the terminal to the middle. So, this, this and this is a 1 4 addition where cyanide adds in the 1 terminal. Then followed by isomerization to give a terminal alkene which then again reacts with Ni L 4 HCN subjected to hydrocyanation to give adiponitrile CN, CN.

And that after several transformation is given, gives nylon 6, 6. And this was a process discovered in DuPont. DuPont has a rich history of discovering lot of organometallic catalyst. And this is one such example where it uses a nickel catalysed organometallic reaction to produce something which has large scale utility as fabric or fabric materials for various purposes.

So, this nylon is one of the synthetic fabric known for its strength and durability and which was also used in lot of applications lately. So, this is a beautiful demonstration of hydrocyanation which has been used in a large scale for producing the adiponitrile that is a reagent for synthesising this wonderful material nylon 6 6. And this process was erupted by DuPont. Now, let us look at the mechanism of this hydrocyanation reaction.

(Refer Slide Time: 12:07)



Advanced Transition Metal Organometallic Chemistry

Hydrocyanation reaction: Mechanism

$NiL_4 + HCN \underset{+2L}{\overset{-2L}{\rightleftharpoons}} NiH(CN)L_2$

$L = P(OTol)_3$

$RCH{=}CH_2$

①

$CHR{=}CH_2 \cdots NiH(CN)L_2$

②

$RCH_2CH_2Ni(CN)L_2$

③

RCH_2CH_2CN

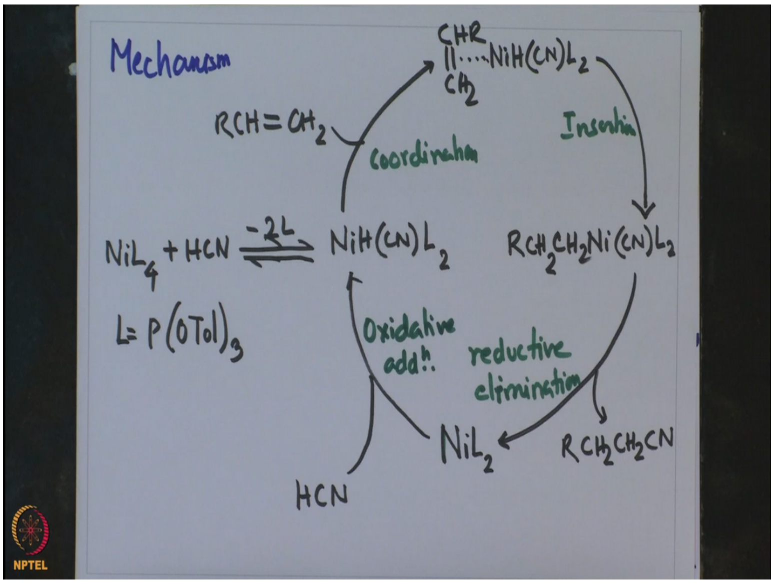
NiL_2

④

HCN

Prof. Prasenjit Ghosh, Department of Chemistry, IIT Bombay

(Refer Slide Time: 12:14)



And now, the active species for this reaction is a nickel 2 species which is obtained by addition of HCN on to nickel 0 Ni L 4 species. Ni L 4, L is para ortho tolyl phosphine. O, O-tolyl phosphine. Ni L 4 + HCN loses to L to give Ni H CN L 2. That, then reacts with the olefin RCH double bond CH 2 to give CHR, CH 2. This is a coordination of olefin to Ni H CN L 2. This reaction is first activation of olefin by coordination to nickel followed by insertion of this olefin into the nickel hydride bond to give this species, nickel alkyl species of the type R CH 2 CH 2 Ni CN L 2.

And then is this reductive; so first is the coordination insertion. And the next is reductive elimination to give R CH 2 CH 2 CN. This step is reductive elimination to give Ni L 2. And this Ni L 2 undergoes oxidative addition to HCN to give this Ni H CN L 2. So, this is again the oxidative addition step. Now, at this point, what we see is the beautiful cycle that involves again the 4 elementary step oxidative addition, reductive elimination, olefin coordination and then olefin insertion into a nickel hydride bond.

Now, at this point I would like to draw a conclusion of this nickel catalysed hydrocyan compression of this nickel catalysed hydrocyanation reaction with the palladium catalysed C-C cross coupling reaction catalytic cycles that we have discussed. And what we see that, they the common feature is, the both contain 4 elementary steps that is similar over there as well as here. And of the 4 steps, 2 steps are common for both.

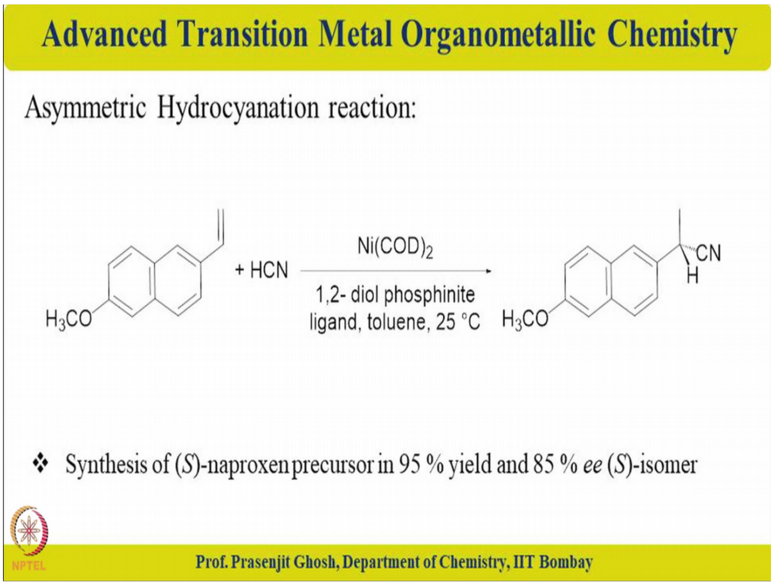
For example: the palladium mediated cross coupling reaction also had 2 elementary steps that were, oxidative addition, reductive elimination as well as nickel mediated hydrocyanation reaction also had similar 2 steps of oxidative addition and reductive elimination. However, the other 2 step in the palladium mediated cross coupling reaction were different from the other 2 step of this nickel mediated hydrocyanation reaction.

And this, for example, for palladium mediated cross coupling reaction, the other 2 steps were transmetallation and cis-trans isomerization reaction. Whereas, these counterpart or these 2 different step for the nickel mediated hydrocyanation reaction is olefin coordination followed by olefin insertion. So, what we see is a catalytic cycle with 2 of the 4 elementary steps being different in case of the nickel mediated hydrocyanation reaction as opposed to the palladium mediated cross coupling reaction.

So, this is a beautiful example. And in this case what has been found that lewis acid catalyses these hydrocyanation reactions. And this happens by coordination at the cyanide ligand. Now, the scope of this hydrocyanation reaction we had seen is already used for large scale production of nylon production of the substrate that is used for producing the nylon. But also, it has been extended in other directions particularly in a asymmetric catalysis.

And a asymmetric catalysis. And in this context a beautiful elegant work has been reported by Rajan Babu who has developed chiral phosphine ligand from sugars for use in asymmetric hydrocyanation reaction.

(Refer Slide Time: 19:22)



Advanced Transition Metal Organometallic Chemistry

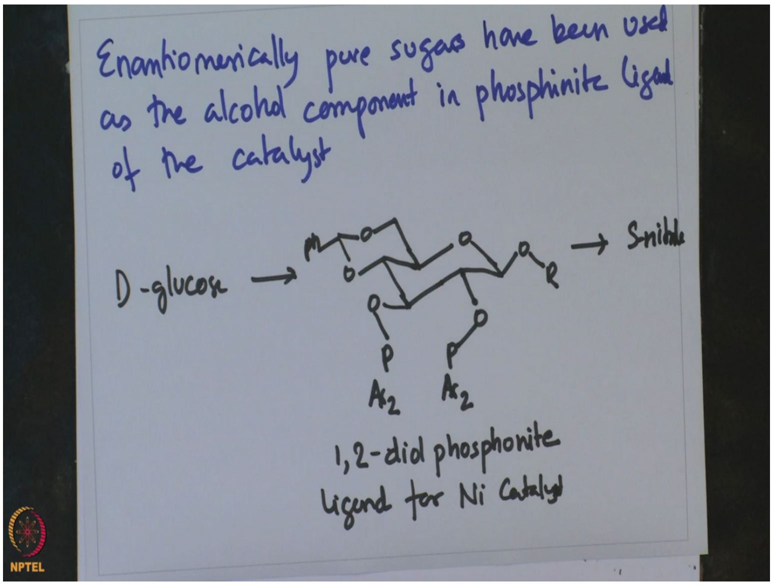
Asymmetric Hydrocyanation reaction:

- Synthesis of (*S*)-naproxen precursor in 95 % yield and 85 % *ee* (*S*)-isomer

Prof. Prasenjit Ghosh, Department of Chemistry, IIT Bombay

This is indeed a very elegant work by Rajan Babu when he was a DuPont pursuing this reaction. I will illustrate this with this beautiful example in which;

(Refer Slide Time: 19:37)



Enantiomerically pure sugars have been used as the alcohol component in phosphinite ligand of the catalyst

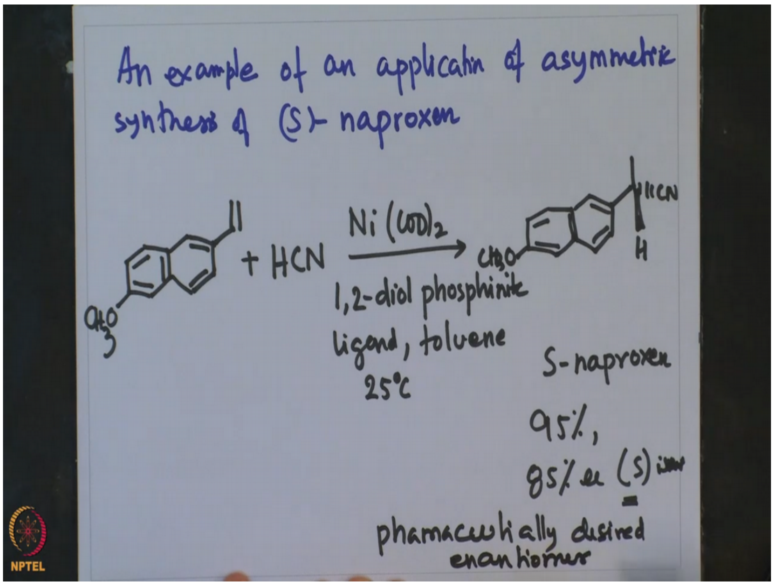
1,2-diol phosphonite ligand for Ni Catalyst

Enantiopure, enantiomerically pure sugars have been used as the alcohol component in phosphinite ligand of the catalyst. And then, chiral catalyst that which have been used for carrying out this hydrocyanation this reaction in a enantioselective fashion. And this is beautiful concept where instead of using organic moiety, organic compounds as a ligand for organometallic catalyst, here, this concept involves use of natural sugars, enantio pure sugars as making the scaffold, ligand scaffold for this chiral hydrocyanation catalyst.

And which would then be used, subsequently used for carrying out this hydrocyanation reaction in a enantioselective fashion. So, a beautiful demonstration of chemistry where this concept of sugars which is something more of a biological molecule found in biology is being used as a ligand scaffold for making organometallic catalyst. And then, to carry out enantioselective synthesis in organic chemistry.

So, let me illustrate this beautiful example in which this sugar based phosphonite ligand for this catalysis was synthesised. So, it started with D-glucose was converted to 1, 2 diol phosphonite Ph, O, P, Ar 2, O, P, Ar 2, O, R. So, this is called 1, 2 diol phosphonite ligand for nickel catalyst. And this would give S nitrile in the corresponding catalytic transformation. And let me just illustrate the application of these 1, 2 diol phosphonite ligand prepared from sugar by Rajan Babu for asymmetric synthesis of a precursor in naproxen.

(Refer Slide Time: 24:12)



An example of an applicatn of asymmetric synthess of (S)- naproxen

S-naproxen
95%,
85% ee (S) isomer
phamaceutically desired enantiomer

An example of an application of asymmetric synthesis of S naproxen. Now, this is beautifully illustrated in this compound CO O CH 3 + HCN in presence of nickel COD. And the ligand which was discussed earlier, 1, 2 diol phosphinite ligand toluene 25 degree centigrade gives this compound O CH 3 CN H. And this is S naproxen 95% yield and 85% ee of the S isomer. This is the pharmaceutically desired enantiomer.

So, the important is this S isomer is the also the one which is pharmaceutically desired; pharma enantiomer. Now, with this, I would like concluded today's discussion on hydrocyanation reaction. Let me just summarise what has been discussed in today's class. We have started looking at hydrocyanation reaction in the context of our discussion of various types of C-C coupling and cross coupling reactions.

And this is the first one of the nickel that we have taken up after we have discussed a large number of palladium mediated cross coupling reactions like Suzuki, Sonogashira, Stille, Heck, allylic alkylation reactions. And then one of the importance of hydrocyanation reaction is that this is HCN addition to unsaturated compounds like alkenes, alkynes or carbonyl compounds leading to the formation of nitriles via C-C bond forming reactions.

Now, nitriles being a very important or intermediates to various other functional groups which can be readily converted to various other functional groups, provides access to a large body of important synthetic targets. And as an example of such accessibility to large a variety of molecule, we took up this example in which, which was used in industry, this, the utility of hydrocyanation reaction on butadiene giving rise to this adiponitrile which was then subsequently converted to nylon 6, 6 in the, in our industrial scale.

So, this indeed is a big application of hydrocyanation reaction. Another interesting thing about hydrocyanation reaction is the fact that, this is a nickel catalysed reaction as opposed to the palladium catalysed C-C cross coupling reactions we have discussed. We have also looked at the catalytic cycle of hydrocyanation reaction. And what we had seen that this nickel catalysed hydrocyanation reaction proceeds with an active species which is nickel hydride cyano bis ligand.

And 1 important homonality of this nickel catalysed hydrocyanation reaction is that it has 2 4 elementary steps in its catalytic cycle. And the 2 of the steps like oxidative addition and reductive elimination is quite similar to the 2 of the 4 steps of palladium mediated cross coupling reactions which were also the oxidative addition and reductive elimination.

However, the other 2 remaining steps for the hydrocyanation reaction which is olefin coordination and subsequent insertion is however completely different from the palladium mediated other 2 steps of the cross coupling reaction where it was transmetallation followed by cis-trans isomerization reaction. We have also seen a beautiful example of an elegant work of Rajan Babu who had used the concept of making 1, 2 diol phosphonite ligand using natural enantiopure sugar as a ligand scaffold for making the nickel based catalyst.

And then, which was successfully employed in synthesising this pharmaceutically desired S isomer of naproxen by hydrocyanation of this 1, 2 diol phosphonite ligand. A beautiful demonstration of a concept with regard to this hydrocyanation reaction. And this also shows the power of organometallic chemistry in general, the organometallic catalysts in particular, particularly in the domain of homogeneous catalysis.

So, with this we are going to stop today’s lecture. And we are going to see much more burning example of such powerful demonstrations of organometallic complexes in catalysis in subsequent examples that we take up in remaining lectures. So, I again once again thank you for patiently listening to me in this lecture. And we are going to take up carbon heteroatom coupling, another interesting coupling.

So, we had been looking at C-C coupling. So, we are going to move on from C-C coupling and go into the area of C-heteroatom coupling, carbon heteroatom coupling in the subsequent lecture and see how organometallic compounds make a difference to this extended applications of, extended new applications of a variety of bond forming reactions. So, with that I would once again thank you for patiently being with me in this lecture and I look forward to being with you discussing carbon heteroatom bond formation in the next lecture. Till then goodbye and thank you.