Advanced Transition Metal Organometallic Chemistry
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Module - 10
Lecture - 46
C-Heteroatom Coupling: Hydroamination

Welcome to this course on Advanced Transition Metal Organometallic Chemistry. We have been discussing C carbon-heteroatom coupling reaction. In this context, in our previous lecture we had looked at C-N bond forming reaction, particularly with respect to amination of arene. Now, as had been mentioned in the last lecture that C carbon-heteroatom bond forming reactions usually are formed by 2 approaches.

And all both of these approached require drastic conditions and both of these approach also is challenging to perform. And these 2 approaches had been nucleophilic aromatic substitution reaction which requires drastic conditions as well as nucleophile addition to unsaturated alkenes and alkynes which also is very challenging in absence of any catalyst. Now today, in that pretext we had spoken about palladium mediated C-N bond forming reaction and that, how that helped in carrying out all these amination of aryl reaction under conditions which are more mild and not that drastic and also more applicable in terms of the breadth and the depth of the chemistry is concerned.

We have looked into aryl amination reaction in details, not only from the mechanistic point of view but also its broad spectrum of applicability in the previous lecture. Today, we are going to take another example from the second approach that we had just mentioned about that being addition reactions through alkenes and alkynes. And in that context, we are going to be talking about this hydroamination reaction.

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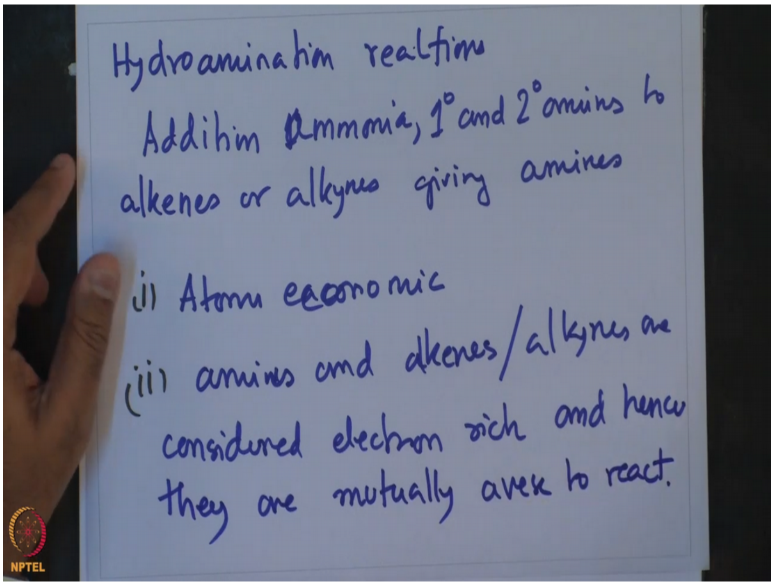

Hydroamination reactions

Addition Ammonia, 1° and 2° amins to alkenes or alkynes giving amines

i) Atom economic

(ii) amins and alkenes/alkynes are considered electron rich and hence they are mutually avers to react.

Hydroamination reactions is nothing but addition of ammonia or primary or secondary amines to alkene and alkynes, addition of ammonia primary and secondary amines to alkenes or alkynes giving, yielding amines. Now, this reaction has significant interest, not only it arises academic interest, but also it arises industrial interest. And this is primarily because of the fact that this reaction is an approach that is atom economic, that the reaction is atom economic, which means that there is no side products produced.

And this, so, this is the atom economic approach to formation of amines. And that is why this is of industrial importance, that they would really love to have a method in which they can make amines without producing any byproduct or any waste material in the process of making this amine. And hence, the atom economic reaction helps in the cause. The other challenge as I said is also very academic in nature in the sense that, these amines and olefins or alkynes all the reacting substrates are, all of them are very electron rich entities.

And hence, they are averse to mutually react. And as a result, this hydroamination reaction indeed is very challenging. However, the landscape changes as one moves from a non-catalytic to catalytic reactions using transition metals. Then, the metal cast catalysed hydroamination reactions however are feasible and can also be performed in a mild conditions.

And that is why transition metal catalysed hydroamination reactions have been pursued vigorously with the intent of developing preparative methods for producing amines which are not only convenient but also environmentally benign in the sense that there is no waste material produced in the large-scale synthesis of these amine reagents. So, in general, so drawback has been that, these hydroamination requires drastic conditions in absence of the catalyst.

However, the advantage is, if one can be made to do so that this reaction is atom economic as well as, this amine, amines and alkenes or alkynes are considered electron rich. And hence, they are mutually averse to react. And hence, normally, as I said that hydroamination reaction requires drastic conditions or there are catalyst which limited applicability and high cost. So, in this context bis Cp titanium dimethyl is an excellent catalyst for inter and intramolecular hydroamination of alkynes.

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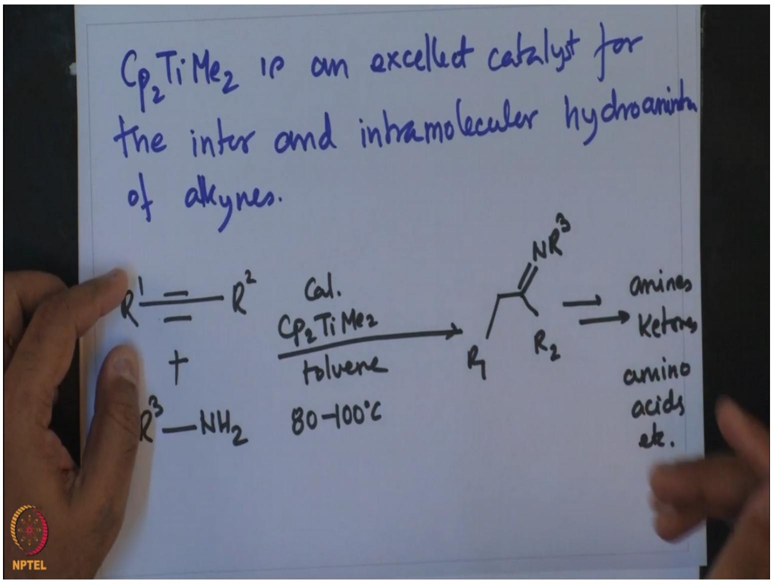

Cp_2TiMe_2 is an excellent catalyst for the inter and intramolecular hydroaminatn of alkynes.

Bis Cp titanium dimethyl is an excellent catalyst for the inter and intramolecular hydroamination of alkynes. And this is illustrated in the equations below. For example, the alkyne R 1, R 2 + R 3 NH 2 in presence of catalyst Cp 2 titanium dimethyl toluene 80 to 100 degree centigrade, provides this hydroaminated product, R 1, R 2, NR 3 which under further conversion gives amines, ketones, amino acid, etcetera.

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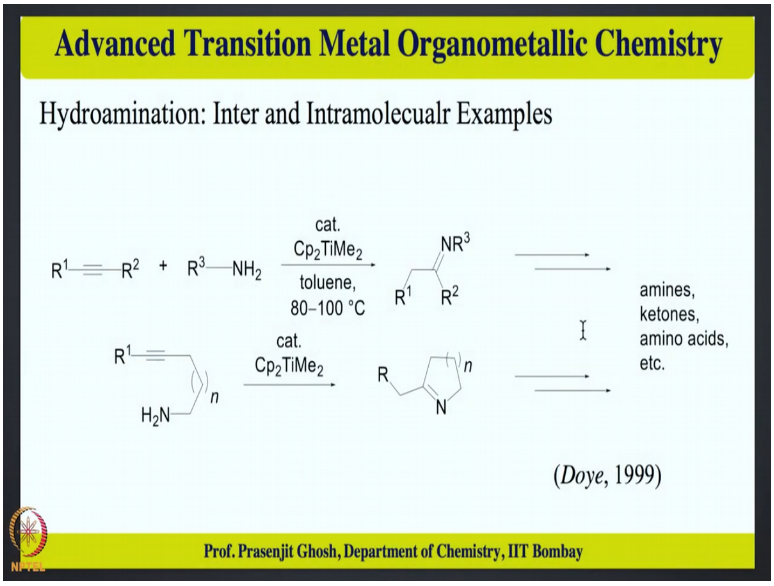

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Hydroamination: Inter and Intramolecualr Examples

(Doye, 1999)

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So, here one can see that this is a case of intermolecular hydroamination where NH is adding against the double bond to form this imine compound that can finally be converted to amine by deduction hydrolysis ketone or amino acids, so on and so forth. So, there are not only the example of intermolecular hydroamination there are well known examples of intramolecular hydroamination.

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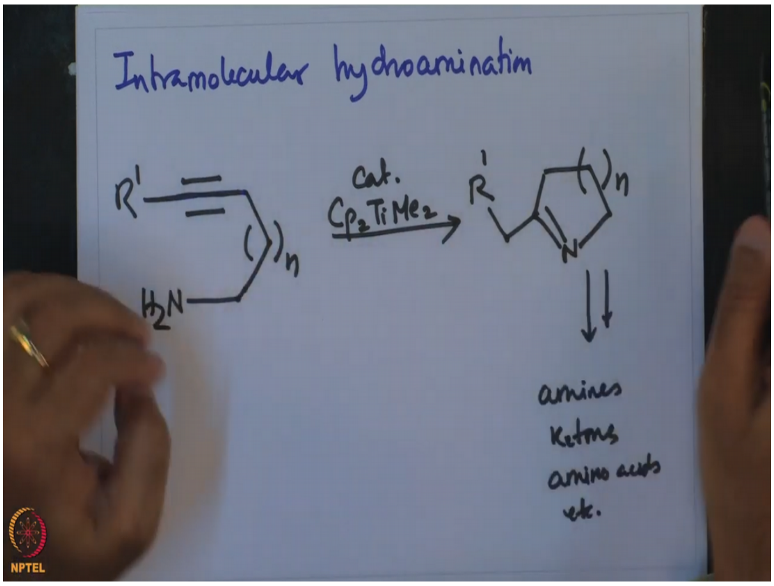

Intramolecular hydroamination

So, the example of intramolecular hydroamination using this same bis Cp titanium dimethyl catalyst is given over here. R 1, n, N H 2 catalyst Cp 2 titanium dimethyl giving N, n, R. So, this is a, this NH adding across this alkyne in a intramolecular fashion which again can be converted to amines, ketones, amino acid and etcetera. So, what it shows that these hydroamination when catalysed using a transition metal can be used to convert in a very effective manner to various amines, amino acids, ketones and other useful reagents.

So, having seen the utility of a catalyst in bringing about the activation barrier or bringing or making the hydroamination reaction facile, to be practiced within the laboratory conditions. Now, we are going to be interested in looking at the catalytic cycle for this particular hydroamination reaction. So, the active species for this hydroamination reaction for this titanium bis cyclopentadienyl titanium dimethyl is a titanium imido species and that is generated by reaction of titanium bis Cp titanium dimethyl with this amine. So, this is, the catalytic cycle is best illustrated in the following example:

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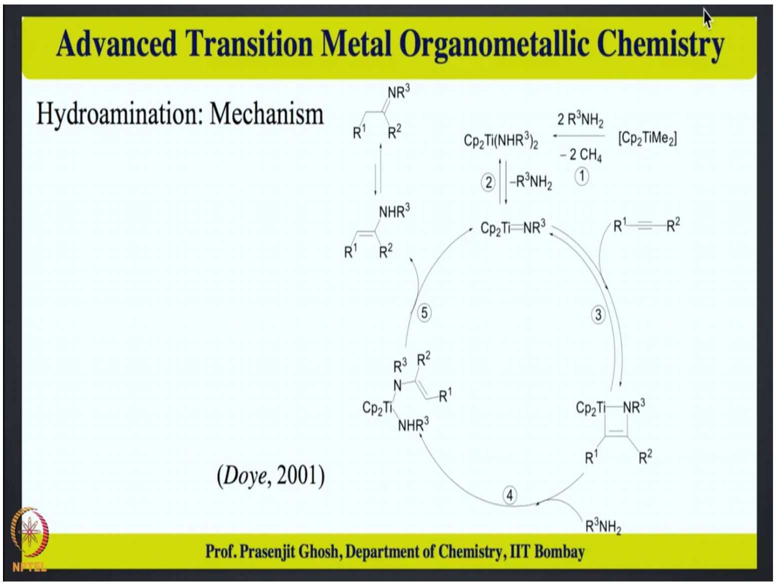

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Hydroamination: Mechanism

(*Doye*, 2001)

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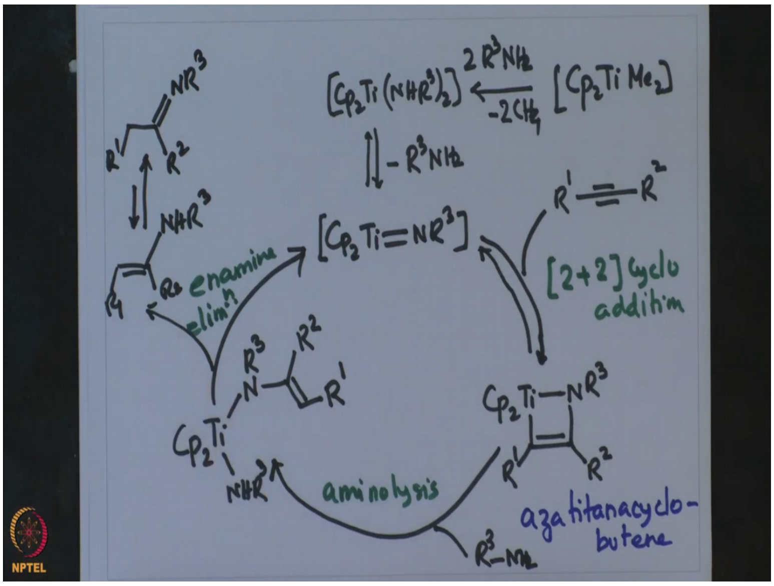

When this bis Cp titanium, Cp 2 titanium dimethyl, when reacting with R 3 2 2 of R 3 NH 2 which, this NH and methyl will eliminate methane to give this compound Cp 2 titanium NH R 3 whole 2. That will eliminate 1 molecule of R 3 NH 2 to give the active species which is bis Cp 2 titanium NR 3. This is a imido species. Now, this imido species undergoes reaction with the acetylene R 1, R 2 in a 2 + 2 cycloaddition to give the product Cp 2 titanium NR 3 olefin R 1, R 2.

So, this addition happens in a 2 + 2 cycloaddition fashion to give this cyclic 4 membered metallacyclobutane kind of species. So, this intermediate is popularly called as asa titano titana cyclobutene, azatitanacyclobutene. So, this is aza, titana, cyclobutene. So, this species then reacts with another molecule of the amine R 3 NH 2 to give this amine attacks. And then, this cyclobutene ring opens up to give Cp 2 titanium, N R 3, R 2, double bond, R 1, NHR 3.

So, what really happens is that one of the proton then leaves this titanium carbon bond upon coordination of amine over here. And then, this carbon gets protonated with the amine proton giving this CH over here and the nitrogen. So, this ring just opens up from this titanium carbon bond. And this process is called aminolysis. This elementary reaction is thus called aminolysis.

Subsequently, elimination from this titanium amido bis amido amine species which is a simple elimination enamine elimination step in which enamine is N amine is eliminated to give R 1, R 2, NHR 3 that is in equilibrium with R 1, R 2, NR 3 giving the imine product. So, here we see is that a very nice catalytic cycle. And, 1 interesting thing about hydroamination reaction is that the catalytic cycle consists of 3 elemental steps elementary steps.

The first one is this 2 + 2 cycloaddition followed by aminolysis in presence of excess amine. And third is a amination elimination reaction eliminating enamine as the product and reataining back the retinium imido species. So, this catalytic cycle is by far different from the other catalytic cycles which we had been discussing so far, in which there were 4 elementary steps and 2 of them were oxidative addition, reductive elimination.

The other 2, coordination insertion or coordination deprotonation, so on and so forth. So, here we see that this hydroamination reaction indeed proceed by a different catalytic mechanism in which it involves 3 elementary steps. And catalyst does plays a important role in carrying out this challenging catalysis. Now, the scope of this reaction was subsequently extended in performing this reaction under asymmetric condition.

Now, one can sort of gauge the utility or advantage of using hydroamination reaction under catalytic condition by comparing it with the fact that typical addition of ammonia to ethylene happens only at 190 degree centigrade at 900 pressure. So, it is that difficult reaction.

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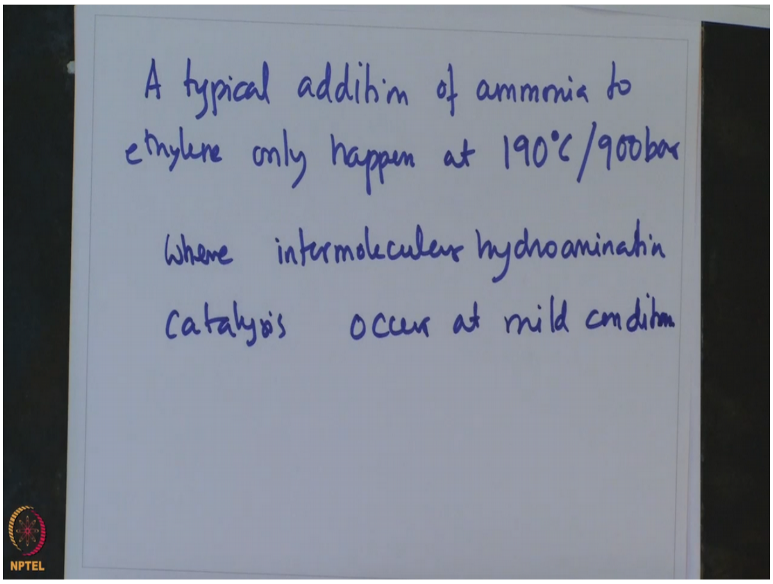

A typical addition of ammonia to ethylene only happen at 190°C/900bar

Where intermolecular hydroamination catalysis occur at mild condition

A typical addition of ammonia to ethylene only happen at 190 degree centigrade 900 bar pressure. So, this is that how much drastic a condition is required just to add ammonia to ethylene in absence of the catalyst, whereas intermolecular hydroamination catalysis occur at mild condition. Now, as mentioned that the scope of the reaction has been extended to carrying it out in a under asymmetric conditions. And asymmetric hydroamination reaction has been achieved at a ambient condition, that is at room temperature, using Noyori catalyst.

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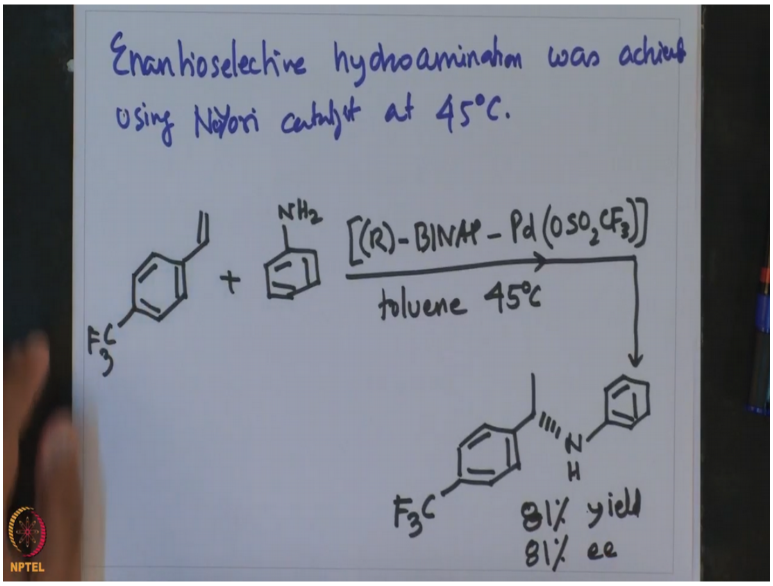

Enantioselective hydroamination was achieved using Noyori catalyst at 45°C.

Was achieved using Noyori catalyst at 45 degree centigrade mild temperature. And this is a beautifully illustrated by the reaction discussed over here. + amine giving R BINAP Pd O SO 2 CF 3 in toluene 45 degree centigrade giving this hydroamination product C F 3, N H Ph in high yield 81% yield and high ee 81% enantiomeric excess. So, this is indeed a breakthrough in which these hydroamination reaction has been performed in an enantioselective fashion. And that too at very mild condition of 45 degree centigrade.

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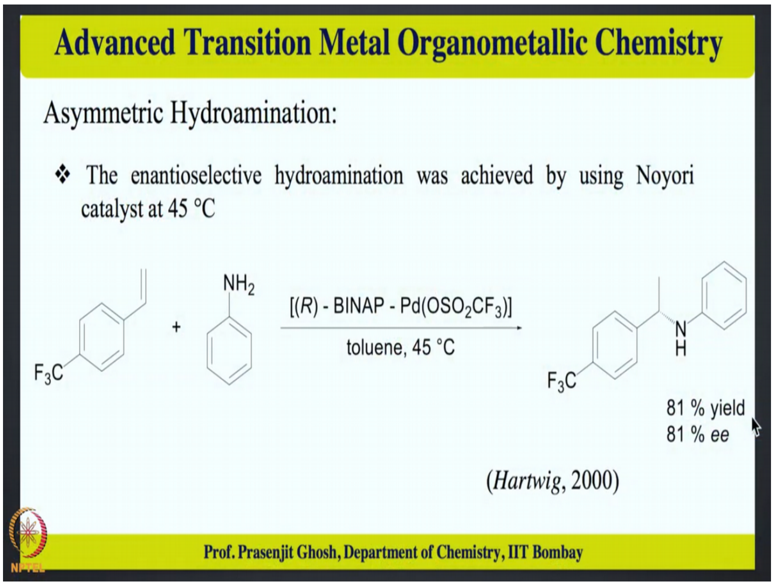

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Asymmetric Hydroamination:

- The enantioselective hydroamination was achieved by using Noyori catalyst at 45 °C

(*Hartwig*, 2000)

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And with this I would like to conclude today's discussion on hydroamination reaction. And before we move on to other kind of carbon-heteroatom bond forming reaction. Now, to summarise, what we had seen is, we had seen the challenges that are often associated with hydroamination reaction. And that is because of the fact that both the amines and the olefins or the alkynes are extremely electron rich entities which are mutually averse to reacting each other.

And this can be a typically gauged from the fact that the addition of ammonia to ethylene occurs, can only occur at a very high temperature of 190 degree centigrade. And at a pressure of about 900 bars. So, which sort of explains that how difficult it is for this amines and electron rich entities like amines and alkenes or alkynes to react. Now, given the scenario there are a lot of advantages to come out of this approach, in the sense that if it does react this reaction is completely atom economic without the production of any kind of byproduct waste materials.

And as a result, this approach is quite important from industrial point of view. Now, so, this hydroamination of alkene and alkyne is indeed a problem which is of both academic as well as industrial interest. Now, this has been cleverly solved using a nice demonstration of the concept of a catalysis using transition metal complexes, how the catalytic reactions overcome the inherent difficulty associated with the mutually reacting substrates.

And this has been clearly observed in case of a titanium hydroamination catalyst which is of the formulation bis cyclopentadienyl titanium dimethyl which can carry out both intermolecular as well as intramolecular hydroamination of alkynes to give the corresponding imines. And that can be finally converted to amines or ketones or amino acid, depending on the conversion one takes reserve to.

We have also taken a look at the catalytic cycle for this hydroamination reaction as mediated by bis cyclopentadienyl titanium dimethyl precatalyst. And what we had seen that, the bis cyclopentadienyl titanium dimethyl precatalyst initially reacts with 2 equivalents of amine to give the bis amido titanium complex which loses 1 amine to make the titanium imido complex which is the active species that initiates the catalytic cycle.

In particular, the catalytic, in the catalytic cycle, the alkyne reacts with the titanium imido species in a 2 + 2 cycloadditon to given an azatitanacyclobutene macrocycle to which then undergoes aminolysis using the extra the large excess of amines that are present to give titanium amino imino amino imido species that undergoes elimination to give inamine which finally rearranges to gives the imine.

So, this is a nice demonstration of catalytic cycle. Also, what noting as we have discussed while during the catalytic cycle, that this hydroamination catalytic consists of 3 steps, the first one obviously is the 2 + 2 cycloaddition, second one is aminolysis and third one is the elimination step. And this is quite different from the other catalytic cycles for C-C or C-N coupling reactions that we have spoken about, which consisted of 4 catalytic cycles and 2 of which obviously involved reductive elimination and oxidative addition.

We have also seen that the scope of the hydroamination reaction can be extended to be able to carry out asymmetric hydroamination under mild condition at a temperature as low as 45 degree centigrades, producing the desired enentioselective products in high yield and high enantiomeric excess. So, with this, I would like to conclude at our today's discussion on hydroamination reaction. And we are going to be looking at other kind of carbon-heteroatom coupling.

And we are going to move on from C-N coupling that we have been discussing in the form of amination of arenes and hydroaminations to another famed C-B coupling which is hydroboration reaction. This also is an addition reaction similar to the hydroamination reactions that we have been discussing so far. So, with that, I again thank you for patiently listening to me in this lecture and I look forward to take up this topic on hydroboration reaction in bit more, in quite detail as we meet next time. Till then, goodbye and thank you.