Advanced Transition Metal Organometallic Chemistry

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Module - 9
Lecture - 42
C-C Cross Coupling Reactions: Sonogashira Coupling

Welcome to this course on Advanced Transition Metal Organometallic Chemistry. In the context of our discussion on a variety of palladium mediated C-C coupling as well as cross coupling reaction, we have covered allylic, alkylation, Suzuki coupling, Heck coupling, Stille coupling. And moving further on, we are going to take up another interesting coupling which is Sonogashira coupling followed by Hydrocyanation reaction in today's lecture.

Now, in our earlier lecture, we had observed that various palladium mediated cross coupling reaction follow similar catalytic cycle consisting of elementary steps like oxidative addition, transmetallation, cis-trans isomerization and reductive elimination. So, immaterial of different cross coupling reaction mediated buy palladium, this catalytic cycle containing the above mentioned elementary step sort of remain the same.

Now, one of the hallmark of palladium mediated cross coupling or coupling for that matter, is the fact that this chemistry is quite stable in under aerobic conditions that it can be performed in presence of air. The exclusion of air which is so common for many organometallic transformation is not required for this palladium mediated cross coupling reaction. And hence, this is what make this palladium mediated reaction so popular among chemist in general.

Now, another aspect of this cross coupling reaction is of course the high selectivity, the low toxicity and also functional group tolerance, broad substrate scope and lastly a palladium is not immensely expensive as compared, when compared to other magic metals of catalysis like rhodium, iridium and platinum. Now, with a similar story unfolds in case of Sonogashira coupling too.

Sonogashira coupling sort of more air sensitive coupling of copper acetylides with aromatic halides of electrophiles which is popularly called as Stephens-Castro coupling and requires aerobic conditions. So, Sonogashira coupling sort of removes the challenges of that reaction and helps the reaction proceed under mild aerobic conditions. So, this is in another way, Sonogashira coupling can be seen as a revised version of a very air and moisture sensitive Stephens-Castro coupling of copper organyls and organic electrophiles under mild conditions.

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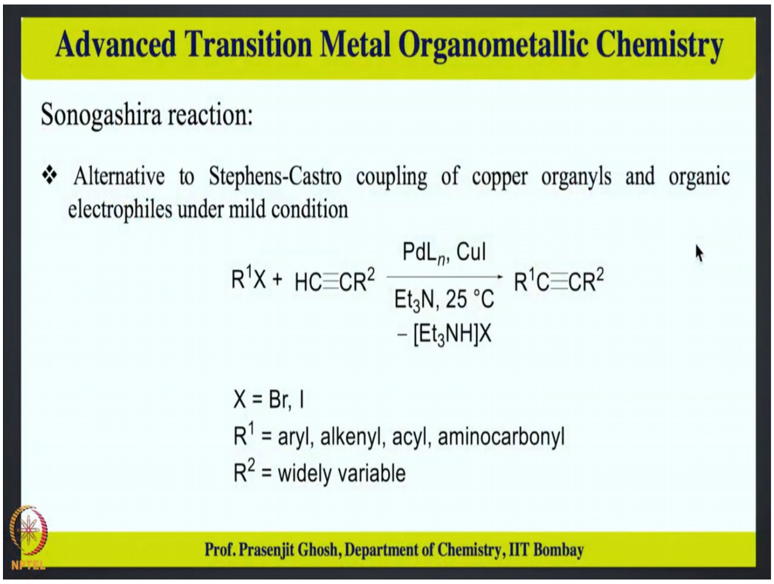

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Sonogashira reaction:

- Alternative to Stephens-Castro coupling of copper organyls and organic electrophiles under mild condition

$$R^1X + HC\equiv CR^2 \xrightarrow[\substack{Et_3N,\ 25\ °C \\ -\ [Et_3NH]X}]{PdL_n,\ CuI} R^1C\equiv CR^2$$

X = Br, I

R^1 = aryl, alkenyl, acyl, aminocarbonyl

R^2 = widely variable

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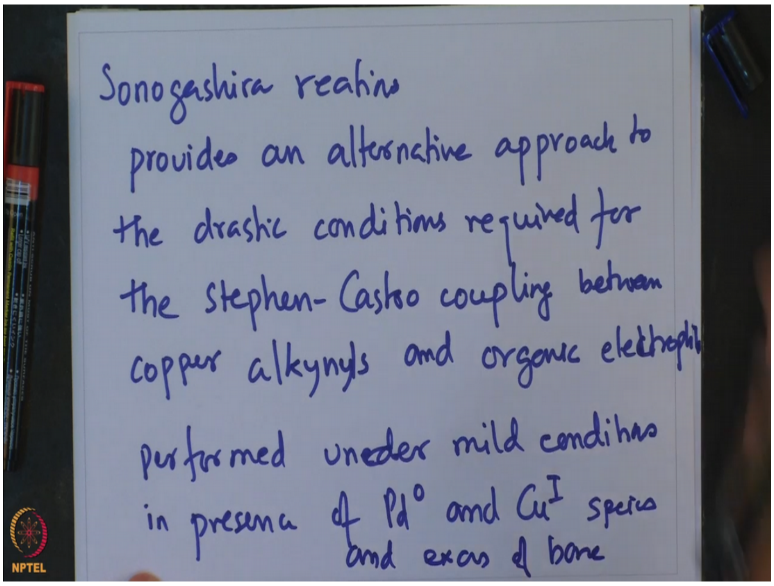

Sonogashira reaction

provides an alternative approach to

the drastic conditions required for

the Stephen-Castro coupling between

copper alkynyls and organic electrophi

performed under mild conditions

in presence of Pd^0 and Cu^I species

and excess of base

So, in short, one can say that Sonogashira reaction provides a alternative pathway to Stephens-Castro coupling of organic copper organyls and organic electrophiles by being able to perform the reaction under mild conditions between copper alkynyls and organic electrophiles. So, alternative approach. And these are done under mild conditions in presence of mild conditions, in presence of palladium 0 and copper 1 species and a base. So, this can be illustrated using this chemical equation.

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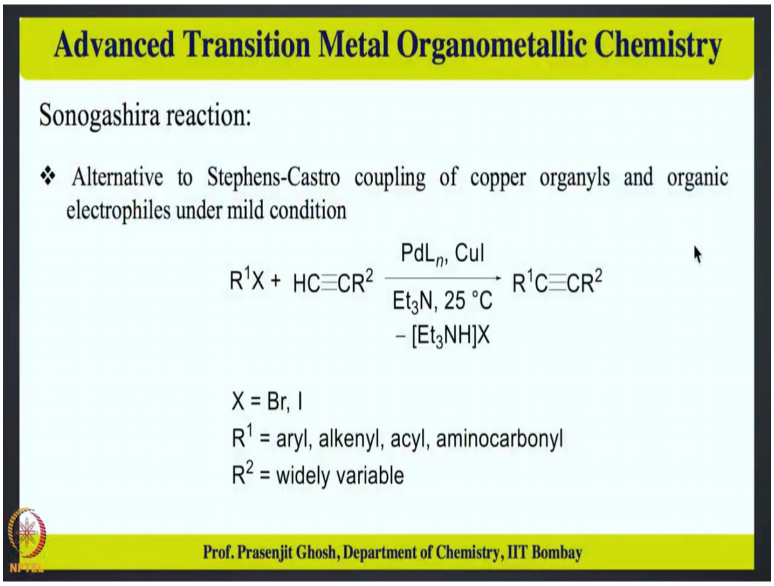

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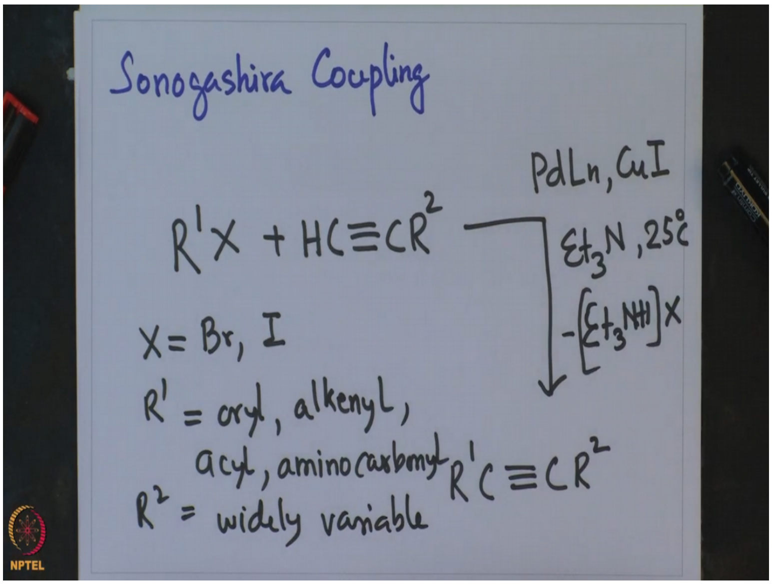

Sonogashira Coupling

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As shown over here, Pd Ln Cu iodide triethylamine is the base at 25 degree centigrade, really mild condition, which eliminates this salt of protonated triethylamine and give the corresponding alkyne. So here, once this coupling between these R 1 X organic electrophile, where R 1 is cationic. And then, this copper, salt of this terminal acetylene or so where this alkenyl moiety couples with R 1 to give R 1 C triple 1 CR 2.

So, X can be bromide, iodide; R can be aryl, alkenyl, acyl, amino carbonyl. And R 2 is widely variable. Any variation would do. So, what is seen over here that this Sonogashira coupling really provides a very mild alternative to very challenging Stephens-Castro coupling of copper organyls with organic electrophiles that require stringent conditions in terms of exclusion of air and moisture.

So, from that prospective, Sonogashira coupling is something which has brought the Stephens-Castro coupling out of stringent anaerobic conditions to ambient aerobic conditions, where such useful coupling can be taken place. Now, this as we had discussed earlier, is similar to what we had observed for other cross coupling reaction.

What we saw that this air and moisture stability of this cross coupling reaction, also its functional group tolerance is what it makes this palladium medium mediated cross coupling reaction in general so special and also advantageous to other kind of coupling reactions that involve let us say Grignard, lithium or lithium reagents which require strict exclusion of air and moisture.

So, this ability to perform this Sonogashira reaction or coupling reaction under mild condition is what makes this reaction so special and also makes them so popular among organic synthetic chemist. So, let us now take a look at the mechanism or the catalytic cycle of this Sonogashira coupling. As mentioned earlier that most of the or almost all of the cross coupling reaction follow similar sets of catalytic cycle in the sense that they all have similar elementary steps like oxidative addition, reductive elimination, transmetallation or cis-trans isomerization.

And that is no different even for Sonogashira coupling. And we are going to sort of take a look at how this reaction catalytic cycle proceed. And then compare the same with its most common analogue which is Suzuki coupling or Stille coupling which also proceeds by similar catalytic cycle. So, to start with, you know one sees that it may be a palladium 0 species, palladium 0 species of the type Pd L 2.

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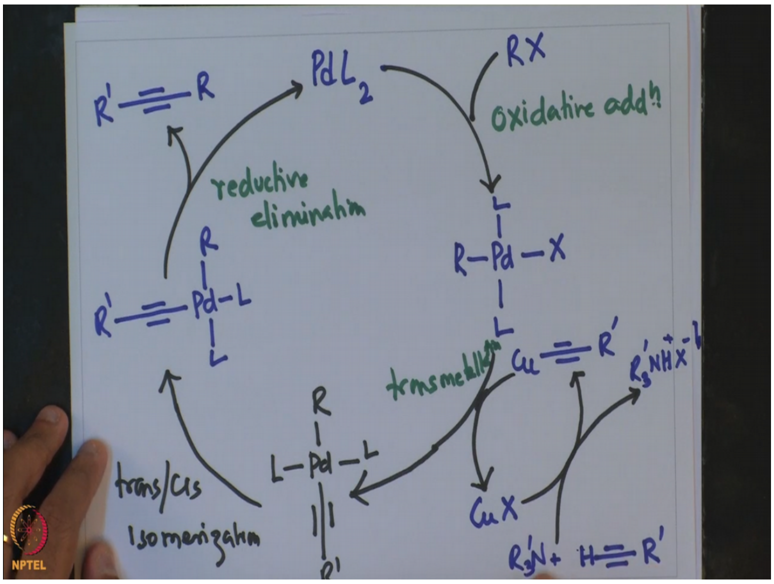

Now, this is the initiating species. And this palladium 0 species then undergoes oxidative addition of RX. And this process is called oxidative addition; to give this palladium R, Pd, L, L, X. This palladium bis L 2 R X then reacts with copper acetylide. And the copper acetylide is formed from terminal acetylene in this following sequence of reaction. Terminal acetylene + R dashed 3 N and copper X.

So, this amine now abstracts proton to give R N 3 R dashed 3 N H + X –. And in turn, this X is also abstracted and in turn copper becomes cationic. And then this acetylide stabilises on copper to give copper acetylide species, which then goes and attacks this palladium bis R species and replaces this X to give copper X. And one forms Pd, R, R, R dashed, L, L. And this undergoes cis-trans, trans-cis isomerization to give the corresponding cis isomer Pd, L, L, R.

And that under reductive elimination to give the corresponding acetylene or cross coupled product. Now, this step is this reductive elimination step. And this one is this transmetallation step. So, what we see is that, this is kind of similar to what has been observed in case of Suzuki and Stille coupling. And that it has the 4 elementary step: 1, 2, 3, 4. And that gives the finally cross coupled product.

Apart from palladium which undergoes the catalytic cycle in a palladium 2 palladium 0 couple there is another additional couple which involves copper X going to copper acetylide. And this also undergoes the coupling in terms of the transmetallation. However, the oxidation state of the copper does not change. It stays as copper 1 all the way. In 1 time, it is copper acetylide and in other time it is corporate halide. And this just goes on in a cyclic fashion as the terminal acetylene get consumed by the base.

So, now this is a nice catalytic cycle and this also resembles the other 2 catalytic cycles that we have discussed, like the Stille coupling and like that of the Suzuki coupling and the cyclical pathway is almost same in the Sonogashira coupling as well. Now, having said that Sonogashira coupling can be used for a lot of purposes in organic synthesis and they are used for making natural products like antibiotics, wherever there is a possibility of having a ene-yne ligand scaffolds, lene ene-yne scaffold. So, to illustrate this, that applications of Sonogashira coupling;

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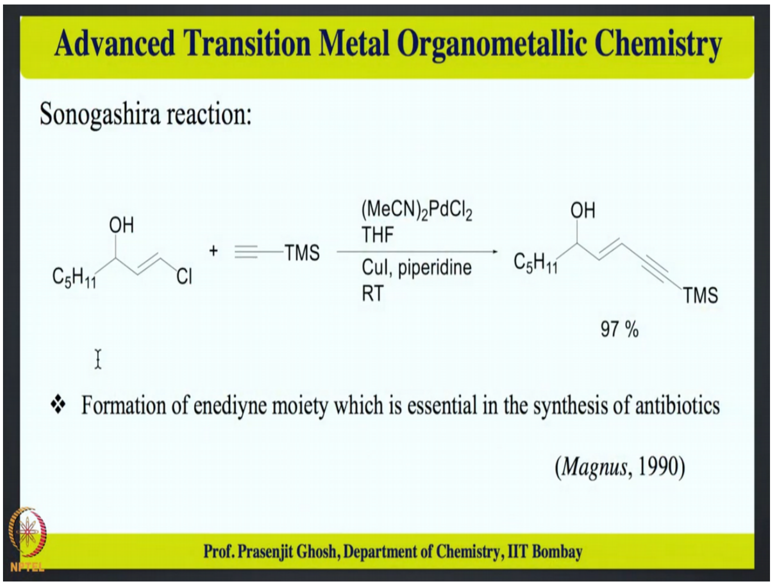

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Sonogashira reaction:

❖ Formation of enediyne moiety which is essential in the synthesis of antibiotics

(*Magnus*, 1990)

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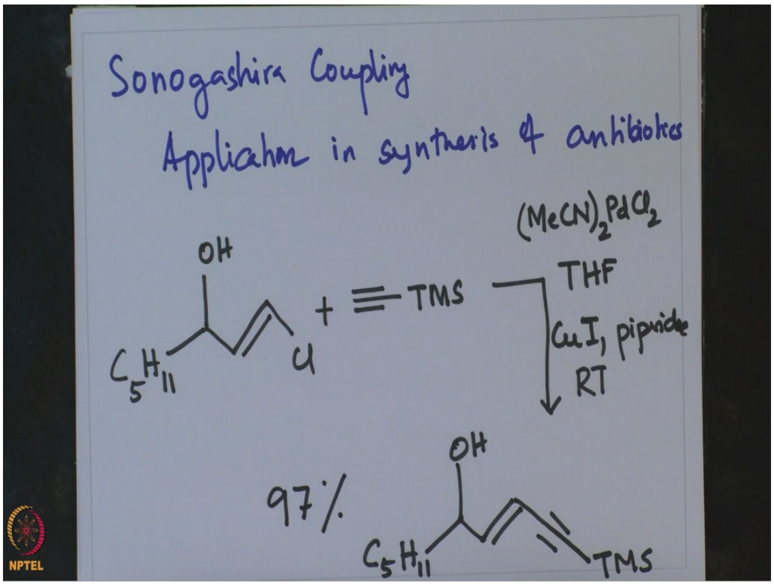

Sonogashira Coupling

Application in synthesis of antibiotics

Application in synthesis of antibiotics. Now, this is nicely illustrated by the reaction given over here. C 5 H 11, OH, Cl + TMS acetylene if in presence of Me CN whole 2 Pd Cl 2, THF, copper, iodide and piperidine at room temperature giving OH, C 5 H 11, TMS. So, this is a nice example where this in dine, ene-yne, this is ene this is yne. This ene-yne framework is constructed right by coupling between and alkene and the acetylene.

So, it is one of the advantage of beautiful approach of this Sonogashira coupling is that, it involves a direct splitting or direct stitching of a acetylene with that of an olefinic halide, so that this ene-yne framework can be conveniently synthesised. And the convenience of this synthesis can be gauged from the yield of this reaction which is extensively extremely high, about 97%.

So, what this underscores is the fact that Sonogashira reaction provides a very smooth direct approach to these ene-yne frameworks. And that is successfully used in synthesising many natural products. And the one that is discussed over here, that could be synthesised very efficiently in 97% yield as is shown over here. Now, the scope of this Sonogashira coupling is not limited to just forming conveniently the ene-yne framework, but also its Carbonylative variant is also known. By that, I am going to illustrate this with a beautiful example.

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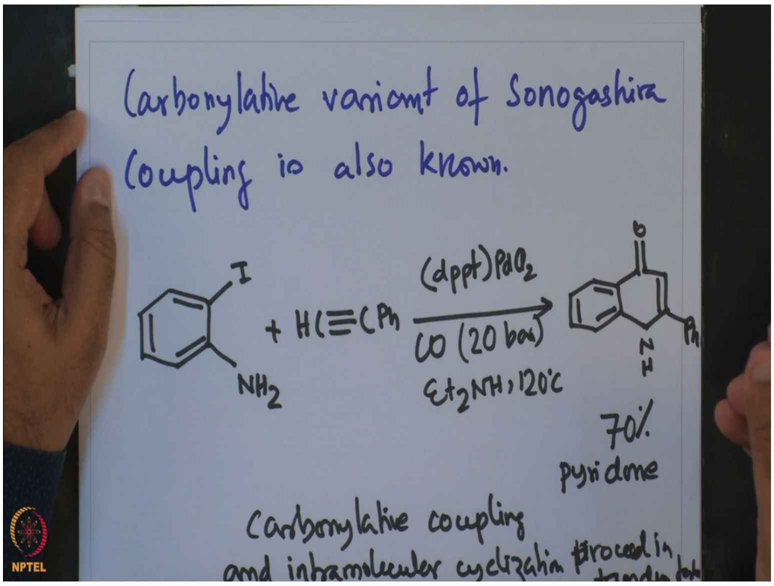

Carbonylative variant of Sonogashira Coupling is also known.

Carbonylative coupling
and intramolecular cyclization proceed in

So, Carbonylative variant of Sonogashira coupling is also known. And this beautiful example involves performing Sonogashira coupling in presence of carbon monoxide and have been used in the synthesis of peridone as is shown over here. So, orthoiodoaniline with phenylacetylene in presence of dppf Pd Cl 2 under CO at high pressure, 20 bar pressure, in presence of diethyl amine at 120 degree centigrade give this bicyclic compound peridone in 70% yield.

Now, this reaction consist of 2 parts. The first one is the Carbonylative coupling and the second part obviously; first is the Carbonylative coupling to form this CO acetylide moiety. And then, obviously is, the next part is this cyclisation, intramolecular cyclisation that proceed in tandem fashion. So, what one sees is a beautiful example in which one can extend the scope of this Sonogashira reaction in terms of providing the Carbonylative variation, variant Carbonylative coupling of Sonogashira reaction, followed by intramolecular cyclisation to produce this peridone in 70% yield.

So, one of the hallmark of Sonogashira reaction can be seen from this utility and that these can be extended to produce bicyclic compounds that involves attending reactions. Not only this Sonogashira coupling it is also a special kind of Sonogashira coupling as performed in presence of carbon monoxide. At high pressure it gives Carbonylative coupling followed by intramolecular cyclisation to produce this peridone bicyclic compound in a tandem fashion in high yields 70% yield.

So, with this I would like to conclude today's discussion on Sonogashira reaction. As mentioned in the beginning of the talk that we had been discussing Sonogashira reaction in the context of palladium mediated C-C cross coupling reaction, particularly with regard to the other more popular cross coupling reaction like Suzuki reaction, Stille reaction that had been discussed in the earlier context.

So, what we see is a similar story unfolding in case of Sonogashira reaction too. Obviously, Sonogashira reaction along the same line provides a more convenient direct approach for constructing ene-yne, ene double bond and yne framework; can also under mild conditions and which have been used for making various scaffolds of natural products, which are in great demands in the world of organic synthesis.

And also, we had seen that this coupling mechanism for Sonogashira coupling resembles very much what we had observed for Suzuki and Stille coupling that it has 4 elementary steps. They involve oxidative addition, transmetallation, cis-trans isomerization and reductive elimination. Also, there is another interesting thing is, apart from palladium which is required for the palladium mediated cross coupling reaction, there is also another second metal involved which is copper 1.

And this copper 1 is also present in a catalytic fashion as it does a couple between copper halide and the copper acetylide moiety. We have also seen the scope of the Sonogashira coupling can be extended to Carbonylative coupling and followed by intramolecular cyclisation that gives this bicyclic compound. So, a beautiful scope for chemistry is represented in form of Sonogashira coupling and the corresponding applications of such coupling that we have discussed.

So, with this I would like to conclude today's discussion on Sonogashira coupling. And we are going to take up another interesting topic of Hydrocyanation reaction in the next lecture in this overall topic of C-C bond forming reaction. I thank you again for patiently listening to today's lecture. And I look forward to being with you in the next lecture when we take up this new topic of Hydrocyanation reaction as a part of C-C bond forming reaction. Till then, goodbye and thank you.