Advanced Transition Metal Organometallic Chemistry

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Module - 8
Lecture - 37
C-C Cross Coupling Reactions: Heck Reaction

Welcome to this lecture on Advanced Transition Metal Organometallic Chemistry. As a part of our discussion on C-C Cross Coupling Reaction in the last class, we have looked into palladium mediator allylic alkylation reaction. And we had observed that carbonyl, alpha carbonyl alkylation reaction, allylic alkylation reactions are less explored. And we have looked into various mechanistic aspect of this allylic alkylation reaction.

Then what we had seen, that this, that the catalytic cycle allylic alkylation reaction involves a palladium 0 palladium 2 shuttle. And that involves 3 steps in which the first involve the initiates with an oxidative addition state followed by a sigma pi rearrangement and then the third step involves the attack of the nucleophile resulting in the allylic nucleophile getting attached to the allylic position along with the regeneration of the palladium 0 species.

We have also looked at how the nucleophile really attack and this was illustrated by looking at a cyclic substrate for which it was seen that for soft nucleophiles the attack happens at the allylic position at from the far end that is from the exo side. Whereas for hard nucleophiles there is an additional step and the nucleophile first goes and attack the metal centre followed by an endo attack on the cyclic substrate resulting in the corresponding product that involves inversion of configuration.

Whereas, for soft nucleophiles it was observed the reverse, that is the retention of configuration. And then, we had also taken a look at a asymmetrical allylic alkylation reaction involving chiral catalyst which could give a this reaction in very high yield and enantioselectivities. So, with that said, we are going to take up another interesting reaction. This is a Heck reaction. And this also involves a palladium 2 palladium 0 palladium 2 shuttle. And also gives this C-C cross couple product. So, let us today take a look at this Heck coupling reaction.

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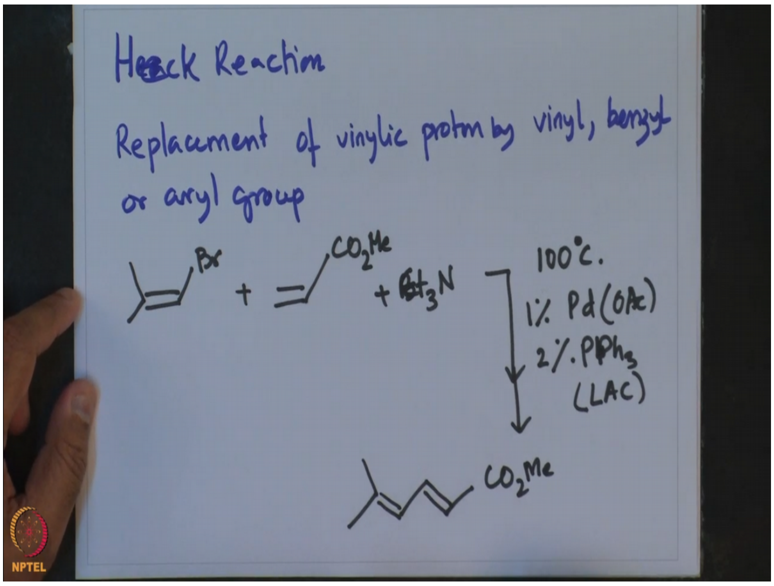

Heck Reaction

Replacement of vinylic proton by vinyl, benzyl or aryl group

And this reaction is illustrated by the replacement of vinylic proton, of vinyl, vinylic proton by vinyl, benzyl or aryl group. And this is shown over here. This vinyl boride reacting with this ester in presence of this, which is triethylamine at quite higher temperature, 100 degree centigrade in presence of 1 mole % of palladium acetate and the ancillary ligand being phosphine which is in 2 mole %.

This is under ligand assisted catalysis condition or LAC condition. Now, LAC condition means that, the catalyst active species which is palladium bisphosphine is formed in situ from the 2 precursors, 1, that is palladium acetate and the palladium and the triphenylphosphine during the course of the reaction. And then the active species source formed then carries out this catalysis.

So, this is called a ligand assisted catalysis or under LAC condition. The corresponding, the Heck product obviously is the coupling of these aryl vinyl bromide with this vinylic proton giving rise to the desired product CO 2 Me. Now one sort of sees that usually this desired product is by and large predominantly trans and Heck that is one of the hallmark of Heck coupling that this a trans product is observed.

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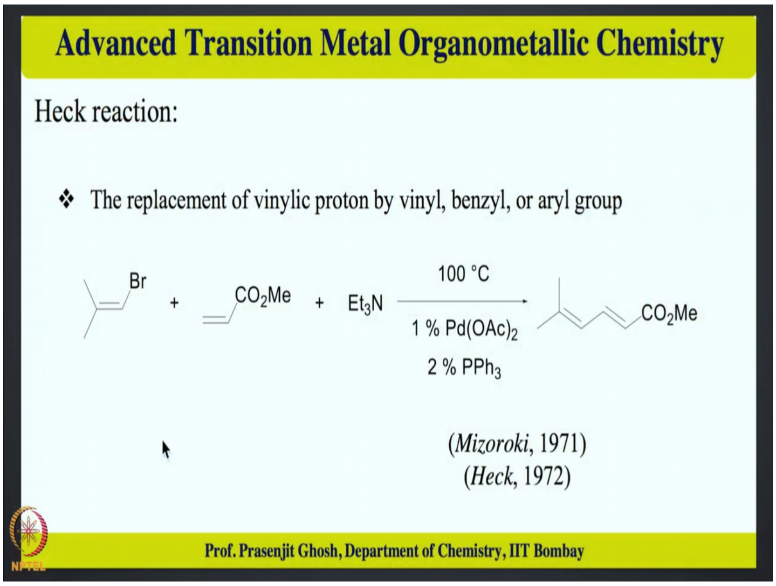

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Heck reaction:

- The replacement of vinylic proton by vinyl, benzyl, or aryl group

(*Mizoroki*, 1971)
(*Heck*, 1972)

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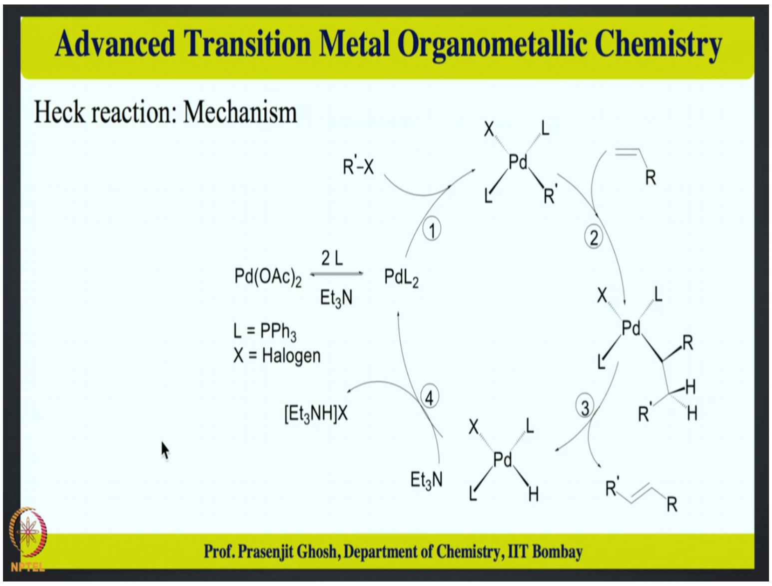

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Heck reaction: Mechanism

L = PPh_3
X = Halogen

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Now, we would sort of start looking at the mechanism. But before we do so, let me just look at the substrate that undergoes this Heck reaction. The substrate which does this vinyl halide, benzyl halide or aryl halide that adds against the vinylic proton of this activated olefin. So, these vinyl halide, or benzyl or aryl groups does not have any beta hydrogen. So, that sort of promotes the reaction in forward direction and not the reverse, that is, that in other words to say, that this will sort of facilitate the oxidative addition step, the first step and not the other way round.

Now, I am going to illustrate these more with the mechanism that we are going to be discussing. And then, we see how this beta hydrogen elimination has been deliberately suppressed in these 3 substrates vinyl, benzyl and aryl substrates, such that the Heck coupling proceeds in the forward direction and the reverse reaction of beta hydride elimination for this substrate does not occur.

As a result, the coupling reactions proceed as desired. So, I am going to illustrate this more convincingly with this mechanistic cycle which will show why this substrate does not undergo beta elimination reaction. So, the pre-catalyst over here is a palladium 2 species, palladium bis acetate.

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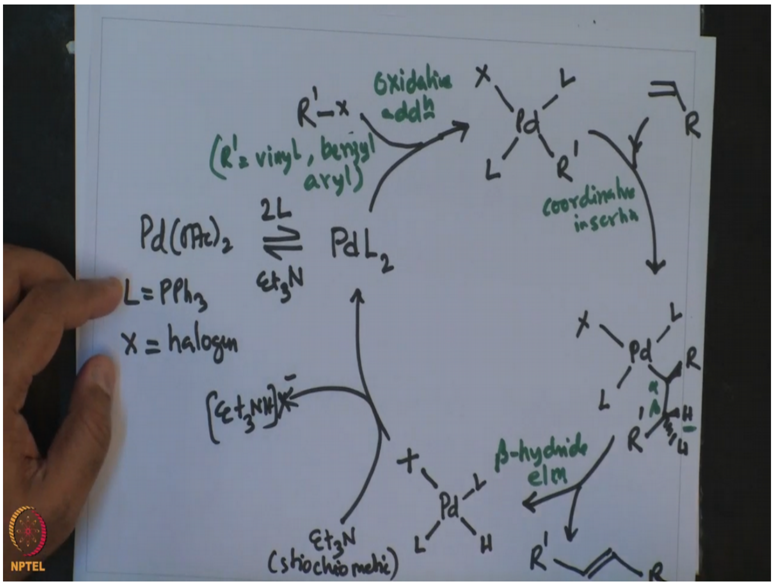

L = PPh 3, X = halogen in presence of twice L Et 3 N giving palladium 0 Pd L 2 Species. Now, this reacts with R dash X and undergoes this oxidative addition. And this R dash X are vinyl, benzyl and aryl group which does not have a beta hydrogens. As a result of the reverse beta hydrogen elimination does not occur. And this give rise to the palladium 2 species R dash. Now these reacting with this olefin which has a vinylic hydrogen.

And this olefin then coordinatively inserts into the palladium R dashed bond. This is kind of coordination insertion chemistry going on over here to give the complex which is palladium L, L, R, H, H, R dashed. So, this is a coordination insertion into palladium alkyl bond. Now, one thing that the, one has to remember that these R dash X are the substrates which does not have beta hydrogen.

As a result, once the oxidative addition occurs, it cannot decompose through beta hydride elimination mechanism. So, it can only move forward. And when it move forward, then the olefin undergoes coordinative coordination insertion into the palladium R dashed bond. And this gives rise to this coordinative insertion reactions of the olefin to this species which then undergoes a beta hydride elimination as shown over here.

So, this is the beta hydrogen and this undergoes beta hydride elimination to give this trans olefin which is a desired Heck product. And this method, this step is called beta hydride elimination. And this step is called coordination, coordinative insertion of olefin into palladium R bond, palladium alkyl bond. So, once this beta hydride elimination happens, then the desired Heck product along with the formation of palladium hydride is observed.

Now, the palladium hydride in presence of base, will picks up this proton and halide to give back this palladium 0 species. And this is a stoichiometric reaction. So, this is a interesting cycle containing a 4 elementary step. The first obviously involves the formation of palladium 0 species from palladium acetate in presence of phosphine. And then, the palladium 0 species then undergoes a oxidative addition with R dashed X, R dashed can be vinyl, benzyl, aryl group.

Once it has undergone oxidative addition, it has become a palladium 2 species, then the coordinative insertion on the palladium R dashed bond with the olefin sort of occurs coordinative insertion followed by beta hydride elimination leading to the formation of the desired product which is the olefin, substituted olefin along with a palladium hydride complex, which went through with triethylamine regenerates back the palladium 0 with the elimination of HCL.

So, this is by and large the established mechanism in which this unique cross coupling of in Heck reaction proceeds. So, this coupling reactions has a effect on the counter anion. And the effect of the counter anion is a sort of elucidated by the following experiments.

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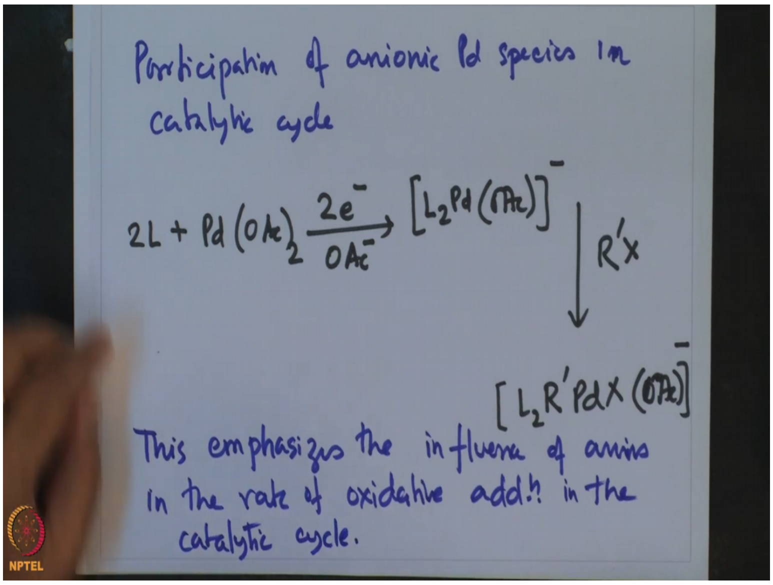

Participation of anionic Pd species in catalytic cycle

$$2L + Pd(OAc)_2 \xrightarrow[OAc^-]{2e^-} [L_2Pd(OAc)]^-$$

$$\downarrow R'X$$

$$[L_2R'PdX(OAc)]^-$$

This emphasizes the influence of anions in the rate of oxidative addn in the catalytic cycle.

So, participation of anionic palladium species in catalytic cycle. And this is a sort of illustrated by the following example, twice L + Pd O Ac whole 2 in presence of 2 electron and O Ac – gives this L 2 Pd O Ac – which then reacts with R dash X to give the oxidative addition product; R 2 R dashed Pd X O Ac in –. And this emphasises the influence of anions in the rate of oxidative addition in catalytic cycle.

So, this emphasises the influence of anion in the rate of oxidative addition in the catalytic cycle. So, this is an interesting example. Another seminal study has been done to see the effect of the solvent and how the reaction proceeds in the polar and non-polar medium. Now, this has been examined after the first step where the oxidative addition reaction has taken place and that how the solvent influence kicks in over here.

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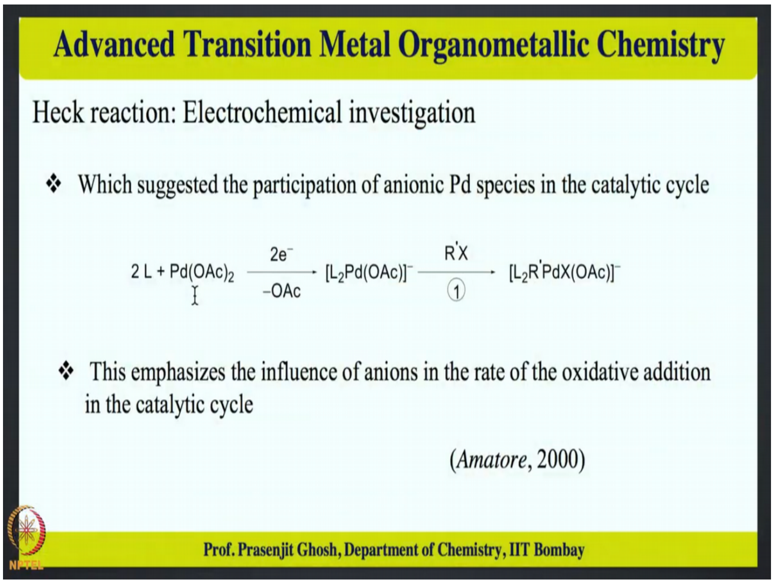

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Heck reaction: Electrochemical investigation

- Which suggested the participation of anionic Pd species in the catalytic cycle

$$2\,L + Pd(OAc)_2 \xrightarrow[-OAc]{2e^-} [L_2Pd(OAc)]^- \xrightarrow[①]{R'X} [L_2R'PdX(OAc)]^-$$

- This emphasizes the influence of anions in the rate of the oxidative addition in the catalytic cycle

(*Amatore*, 2000)

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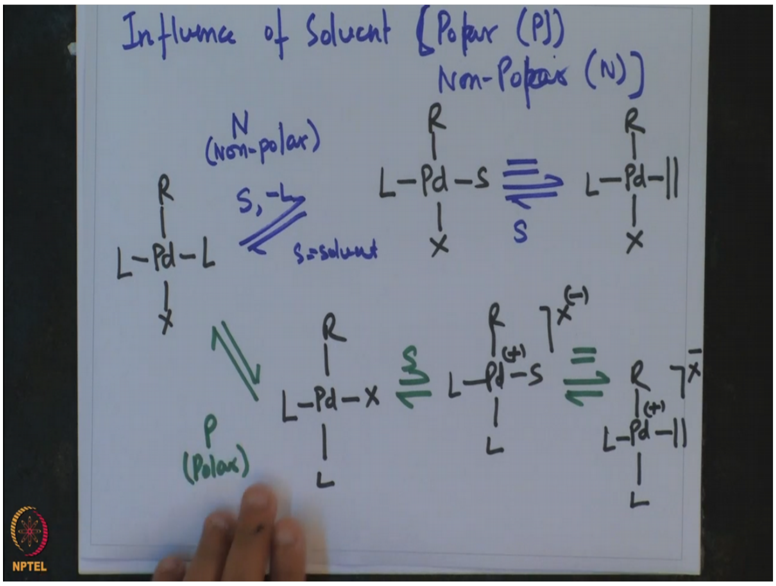

So, we are going to see that how the solvent polar P or non-polar N effect the catalytic cycle. So, after the oxidative addition has taken place, the product of the following intermediate has been isolated L, L. And this is R, X. Now, in presence of non-polar solvent N or non-polar medium. This is in equilibrium with in presence of solvent S loses the L. S = solvent. So, one of this L is lost.

And then, a solvent goes and occupies its place to produce this intermediate L, Pd, S, X, R. And then, this further adds to the olefin in presence of solvent to give this product which is L, Pd, olefin, X, R. However, the reaction proceeds in a different direction in presence of polar or polar medium in which this sort of space undergoes a rearrangement which is shown over here, from trans it becomes cis R, R X now has become cis with L. And then, in presence of a solvent S, this X dissociates.

And solvent goes in to give this product which is L, Pd, S, L, R + and X –. And that, in presence of olefin gives the corresponding product which is L, Pd, olefin, R, L and X – and Pd +. So, what we see, as seen from the green line over here is that, in the polar medium actually he helps dissociate X and X stays in the counter anion. That sort of first gets occupied by the substrate followed by this olefin.

Whereas in a non-polar X medium, this dissociation of Pd X is suppressed, as well as X remains. And one of the neutral molecule S is replaced by S followed by the olefin. Now the subsequent step however is the insertion of this R into this olefin and that is a concerted mechanism.

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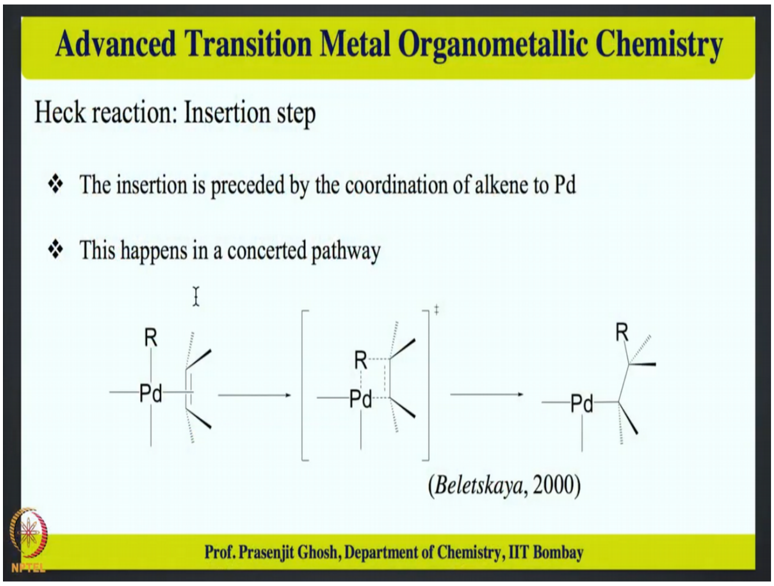

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Heck reaction: Insertion step

- The insertion is preceded by the coordination of alkene to Pd
- This happens in a concerted pathway

(*Beletskaya*, 2000)

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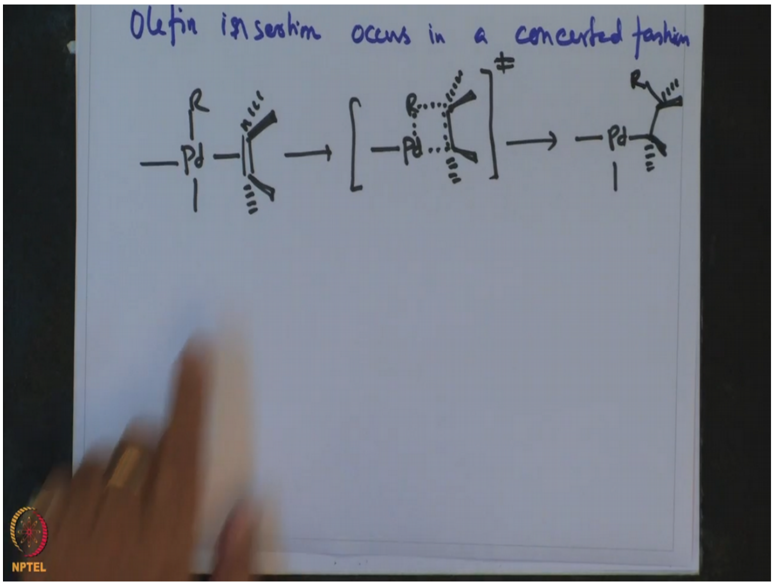

Olefin insertion occurs in a concerted fashion

Olefin insertion occurs in a concerted fashion and is explained in the way as it is shown Pd, R. Olefin, it goes by a transition state which is Pd, R. And then, finally going back to Pd, R. So, this is a concerted process.

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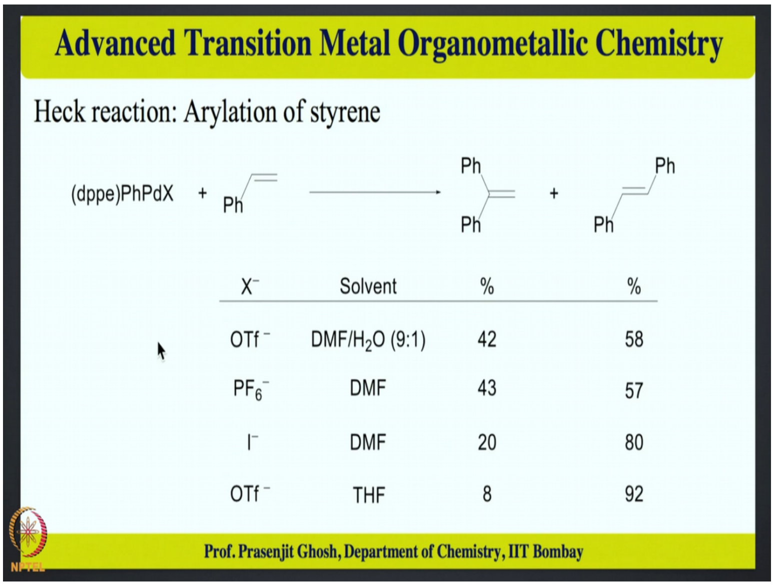

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Heck reaction: Arylation of styrene

X^-	Solvent	%	%
OTf^-	DMF/H_2O (9:1)	42	58
PF_6^-	DMF	43	57
I^-	DMF	20	80
OTf^-	THF	8	92

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And what one can see is that this polar pathway has a detrimental effect in regioselectivity. So, what we saw that non-polar versus polar.

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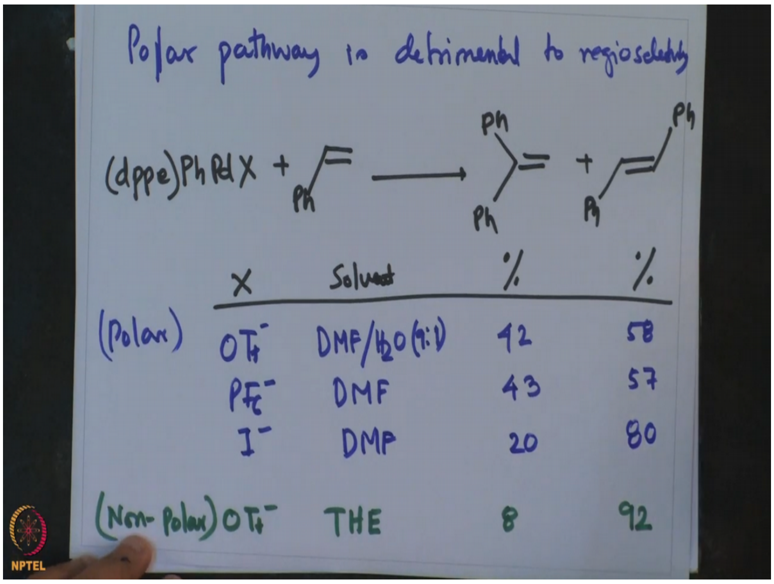

Polar pathway is detrimental to regioselectivity

	X	Solvent	%	%
(Polar)	OTf^-	DMF/H_2O(9:1)	42	58
	PF_6^-	DMF	43	57
	I^-	DMP	20	80
(Non-Polar)	OTf^-	THF	8	92

So, what we saw that polar pathway is detrimental to regioselectivity and this is illustrated by this beautiful example where the reaction is done after the oxidative addition dppe Ph palladium X. So, that means the first oxidative addition has taken place. And then the olefin is kept styrene. And then, there are 2 kinds of product, one is this versus the desired trans carbene. So, what one sees that, depending on the X solvent % formation of this product, % formation of this product;

What one sees that when X is OTf, one does the reaction in DMF which is polar medium water 9:1. Then one gets the ratio of 42:58. Whereas, the same OTf, the same reaction OTf when done in THF which is a non-polar, this is non-polar. And OTf this is polar medium which is non-polar, then one gets ratio of 8:92. So, one sees the selectivity increases. Similarly, for other anion like PF 6 – in DMF, again it is a polar medium shows 43 to 57.

I –, again in polar medium DMF shows 20 to 80. So, in terms of selectivity obviously it is seen that the non-polar medium gives rise to this trans product in higher syllable selectivity. And we had seen how the anions get dissociated in the polar medium as opposed to the non-polar medium.

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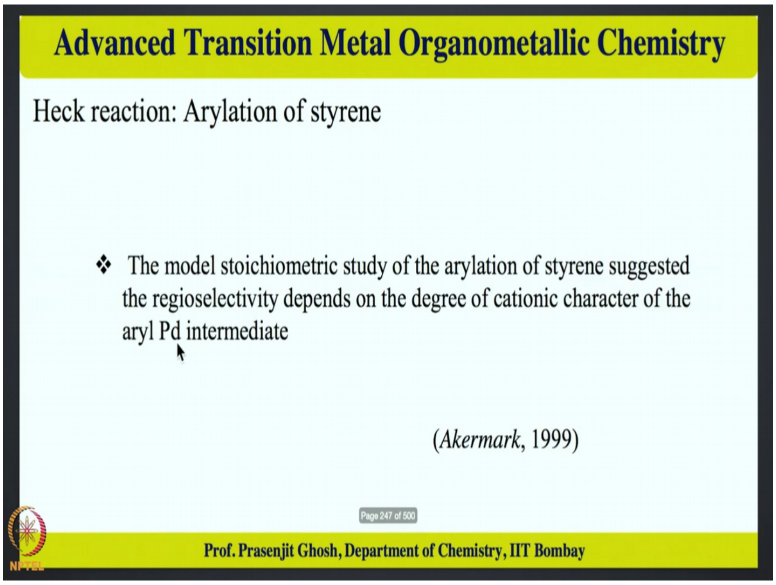

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Heck reaction: Arylation of styrene

- The model stoichiometric study of the arylation of styrene suggested the regioselectivity depends on the degree of cationic character of the aryl Pd intermediate

(*Akermark*, 1999)

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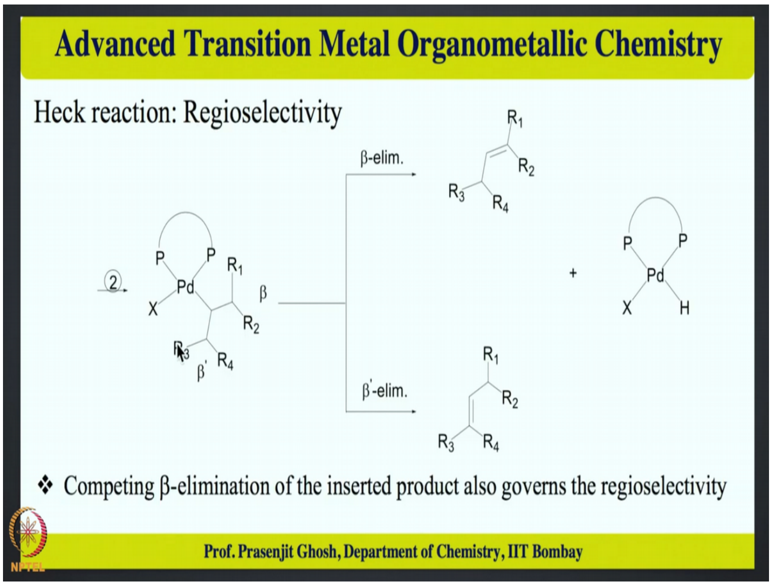

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Heck reaction: Regioselectivity

- Competing β-elimination of the inserted product also governs the regioselectivity

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And lastly there is this beautiful example of seeing this beta hydrate elimination which has, which usually takes place after olefin coordination insertion has taken place. And this is beautifully illustrated by the following compound.

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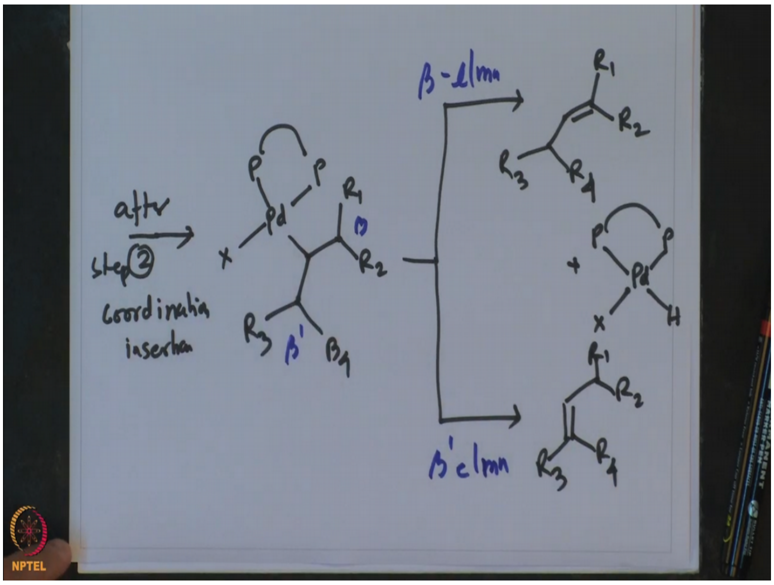

So, this is after step 2 that means a coordination insertion. Then one forms this type of complex Pd, P, P and R1, R2, R3, R4. So, this hydrogen is beta and this is beta dashed. And what if one sees that this will go beta elimination to give the product which should be of this type R3, R4, R1, R2 + the palladium hydride complex. And would undergo the beta dashed elimination to give the following olefin R3, R4, R1, R2 and then along with this.

So, this can be easily identified based on which olefin is formed. Once this olefin is characterised, that will give insight and to how this reactivity is governed. So, with that I would like to conclude today’s discussion on Heck coupling reactions. And what we had seen that in the beginning we had looked at the mechanistic cycle for the Heck coupling. And what we had observed that this Heck coupling proceeds by 4 elementary steps.

First involves, and it involves palladium 0 palladium 2 couple. The first reaction obviously is this oxidative addition followed by this olefin coordinative coordination insertion followed by the beta hydride elimination. And then, last step involves the conversion of the palladium hydride species to palladium 0 species. We had also seen that the anions do have a significant impact in this Heck coupling reactions.

And we had observed that this anion sort of stay coordinated to the palladium intermediates and keep it anionic. And hence, the reaction proceeds as desired. Lastly, what we had also seen that the reaction proceeds slightly by 2 different mechanisms in polar vs non-polar solvents. And in polar solvents the halide, palladium halide gets further dissociated and solvent remain coordinated. And also we had observed that in such a scenario the selectivity of the Heck product goes down in polar medium as opposed to non-polar.

And one can also look at the pathway in which the beta elimination which happens after this coordination insertion of the olefin. That sort of provides a insight into the regio chemistry of the Heck coupling reaction. So, with these we have done a full circle on the Heck coupling, as started from its the scope of the reaction to looking at its catalytic cycle, the mechanism and then try to understand the different product it produced under different conditions through sort of get a idea on the depth and the breadth of this fantastic coupling reaction.

So, I again thank you for patiently listening to me in this lecture. And we are going to take up another very interesting cross coupling reaction. The again the noble prize award winning Suzuki coupling, the much awaited Suzuki coupling in the next lecture. And I look forward to being with you to take up Suzuki coupling in more details are in introduce this coupling and discuss in details in the next lecture. Till then, goodbye and thank you.