Advanced Transition Metal Organometallic Chemistry
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Module - 8
Lecture - 40
C-C Cross Coupling Reactions: Stille Reaction

Welcome to this course on Advanced Transition Metal Organometallic Chemistry. In the context of C-C cross coupling reactions, we have been discussing various types of cross coupling reactions. These are mainly the palladium mediated cross coupling reactions, starting from Heck, Suzuki; and today we are going to take up another interesting reactions which is the Stille cross coupling reaction.

Let me reiterate at the heart of this palladium mediated cross coupling reaction, besides the fact that these are highly selective reactions in the sense that they give cross couple products. And that these reactions have a broad applicability in terms of the reagents being tolerant towards various functional groups. As well as this chemistry is much a, more or less a out of the globe box, dry box chemistry.

So, it can be performed under aerobic conditions in open laboratories, as well as palladium does not having any toxicity issues associated with it. These palladium medium mediated cross coupling reactions have are in turn are heat in terms of the popularity and the usage of this chemistry. We had, in that context we had analysed Heck coupling reaction as well as Suzuki reaction in our last lecture. And today we are going to take up another such important cross coupling reaction which is the Stille reaction.

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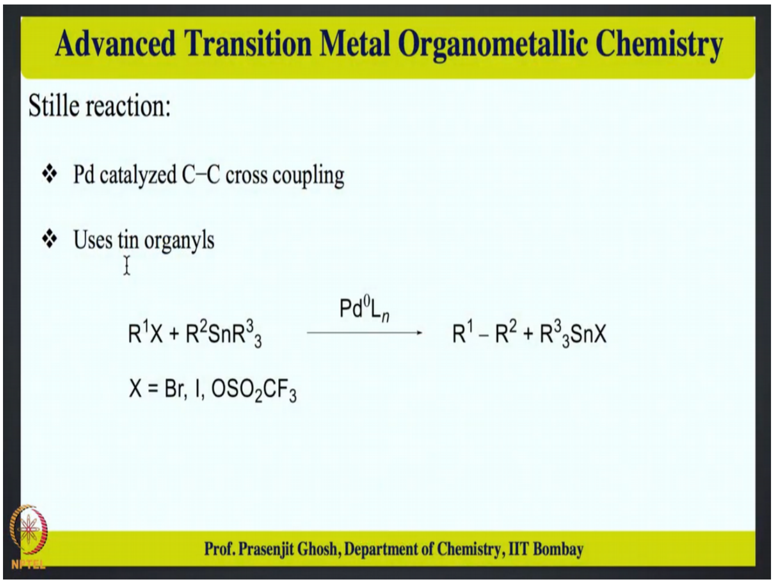

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Stille reaction:

- ❖ Pd catalyzed C–C cross coupling
- ❖ Uses tin organyls

$$R^1X + R^2SnR^3_3 \xrightarrow{Pd^0L_n} R^1-R^2 + R^3_3SnX$$

X = Br, I, OSO_2CF_3

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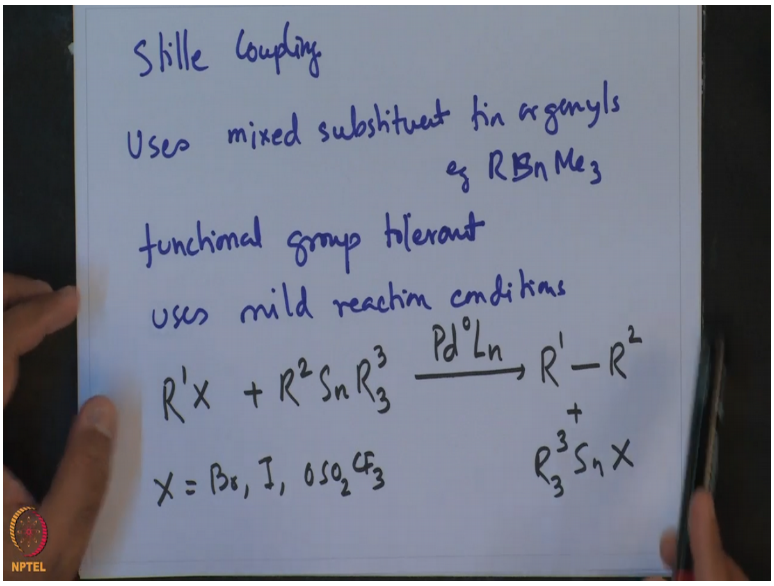

Stille Coupling

Uses mixed substituent tin organyls
eg $RBnMe_3$

functional group tolerant

uses mild reaction conditions

$$R^1X + R^2SnR^3_3 \xrightarrow{Pd^0L_n} R^1-R^2 + R^3_3SnX$$

X = Br, I, OSO_2CF_3

In the Stille coupling, tin organyls are used. And these are mixed substituted tin organyls which are used for Stille coupling. So, there would be, these are organyl compounds of tin. But they may have more than 1 kind of ligand. So, uses, mixed substituent tin organyls. Example: R Sn Me 3. So, there are 2 different kinds of organic moiety attached to tin. And these Stille coupling also is functional group tolerant.

And uses mild reaction conditions. And are used in synthesis of biaryl compounds and also various macrocycles and so forth. So, actually Stille coupling is also one of the preferred method for performing this palladium mediated cross coupling reaction. And the Stille coupling in general is given by this following equation, R 1 X + R 2 Sn R 3 give in presence of palladium 0 Ln giving R 1 R 2 + R 3 3 Sn X where X is an halide like bromine, iodide or triflate O SO 2 CF 3.

Now, 1 thing which is characterised of to note in Stille coupling is, that this organotin reagent though is a mixed substituted; that means it has 2 different kind of organic moiety attached to the tin. Only 1 gets stands for in the cross coupling reaction. For example, in this case R 2 gets coupled, whereas R 3 is stays on the tin. So, it is just transfer of one of the organic moiety from this mixed is tin organyl compound that really happened in the cross coupling reaction.

Now, 1 thing which is common for most of the cross coupling reaction is, as I mentioned earlier is its mechanism. That the mechanistic pathway more or less remains the same immaterial of different kinds of cross coupling reaction. And that why all of these cross coupling reaction are sort of clubbed under 1 platform. Now, that being the case the logic is to solve a particular challenge in 1 cross coupling reaction is equally effective in solving the similar challenge in another cross coupling reaction.

A nice demonstration of that we had seen Buckwald's ligand in the last discussion on Suzuki where Buchwald had used a electron rich bulky phosphine ligand, where in which case the electron richness of the ligand was used to facilitate the first step of the oxidative addition reaction. Whereas the bulky nature of the ligand was used to facilitate the last step, the reductive elimination step of the Suzuki catalysis cycle.

And as a result, when both of these work in synergy, this the catalyst so developed by Buckwald could easily carry out a very challenging Suzuki reaction for of aryl chlorides. Now, the, given the fact that the catalytic mechanism for Suzuki and Stille, the one that we are discussing right now are quite similar. In that case obviously the similar choice of bulky ligand with basic additive can also make the Stille coupling of chlorides possible. So, that is exactly what is seen over here.

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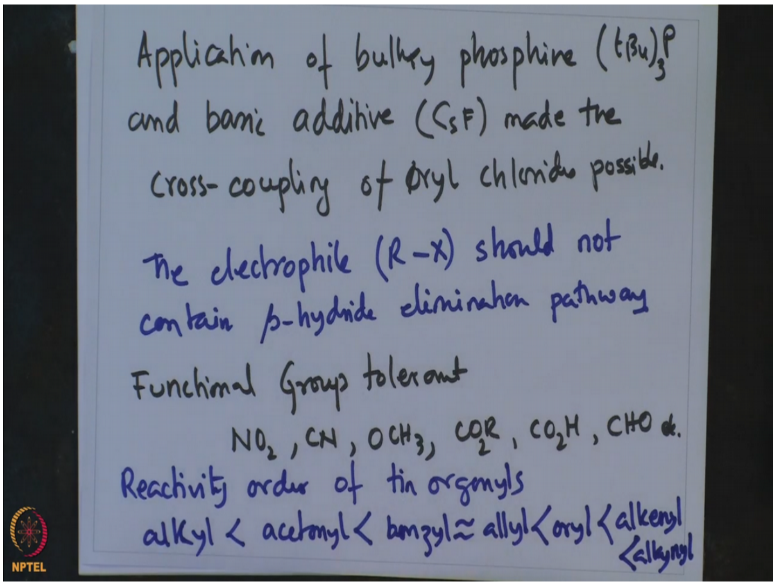

Application of bulky phosphine $(tBu)_3P$ and basic additive (CsF) made the cross-coupling of aryl chlorides possible.

The electrophile (R−X) should not contain β-hydride elimination pathway

Functional Group tolerant

NO_2, CN, OCH_3, CO_2R, CO_2H, CHO etc.

Reactivity order of tin organyls

alkyl < acetonyl < benzyl ≈ allyl < aryl < alkenyl < alkynyl

That application of bulky phosphine like t Bu whole 3 P. And basic additive cesium fluoride made the cross coupling of aryl chlorides possible. So, of these, this was reported by professor Gregory Fu. And this is exactly the same logic which was used for performing the room temperature Suzuki coupling of aryl chlorides. Exactly is the same logic of using bulky phosphine with electron rich bulky phosphine.

It can also be used in performing the Stille coupling of aryl chloride the similar way. Now, 1 important thing is for the Stille coupling that the electrophile should not contain beta elimination pathway. So, these are some of the standard basic requirements of Stille coupling that would provide a favourable cross coupling reaction.

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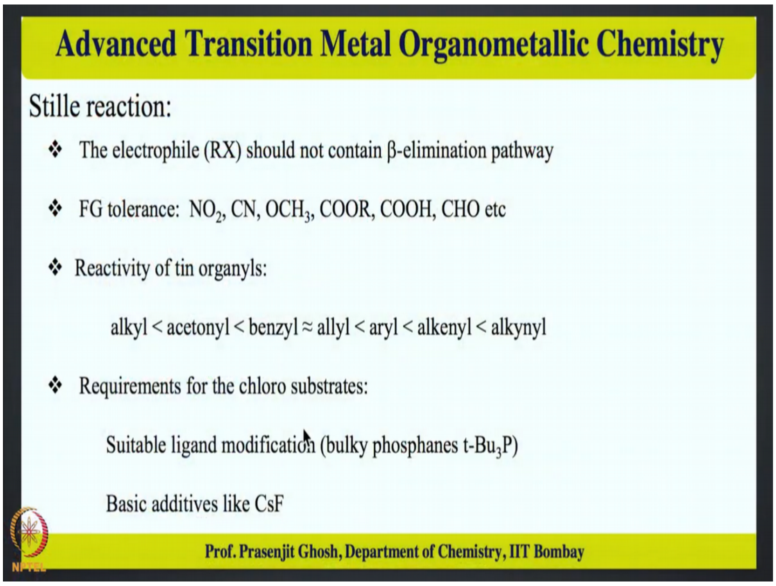

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Stille reaction:

- The electrophile (RX) should not contain β-elimination pathway
- FG tolerance: NO_2, CN, OCH_3, COOR, COOH, CHO etc
- Reactivity of tin organyls:

  alkyl < acetonyl < benzyl ≈ allyl < aryl < alkenyl < alkynyl
- Requirements for the chloro substrates:

  Suitable ligand modification (bulky phosphanes t-Bu_3P)

  Basic additives like CsF

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The primary thing is that the electrophile or R X should not contain beta hydride elimination pathway. And this Stille coupling is obviously functional group tolerant. And for example, groups like NO 2, CN, OCH 3, COR, CO 2 R, CO 2 H, CHO, etcetera are functional group tolerant. Now, in terms of the nucleophile which is a organotin reagents, the following is the reactivity order of tin organyls.

Now, the water is given as alkyl < acetonyl < benzyl which is = allyl < aryl less that alkenyl < alkynyl. So, these are the reactivity order or order for the tin organyl. Now, this strength sort of resembles to the more carbonionic nature of the organyl which is bound to the tin. For example, alkyl is a Sp 3 carbon attached to the tin. But in alkenyl, it is Sp, Sp carbon attached to the tin alkenyl Sp 2, arly Sp 2.

So, what it turns out is the most S character is on the carbon attached to the tin. The more negative charge it, more carbonic or more del negative charge it will accrue. And as a result, it sort of behaves as a better nucleophile in the cross coupling reaction with its electrophilic partner R X. So, the idea is the reactivity of the organ the tin organyls, the organyls which are more negative in terms of electron richness or electron density, they make better nucleophile as opposed to the alkyl ones or the acyl ones which are not as that electron rich.

So, this sort of is quite intuitive in the sense that this indeed in fact is a cross coupling reaction. So, the more nucleophile, more nucleophilic the organic moiety is, the better would it be to couple with the electrophilic count partner which is, which comes form the R X. Okay. So, now, we just had discussed about this, the coupling requirement for the chloro substrates, the challenging aryl chloride coupling.

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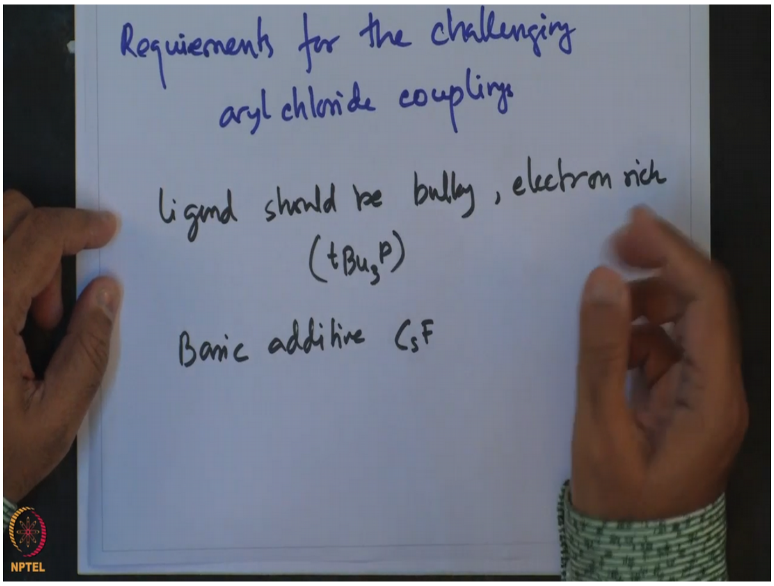

Requirements for the challenging aryl chloride couplings

ligand should be bulky, electron rich (tBu_3P)

Basic additive CsF

The requirements for the challenging aryl chloride coupling is that, for the challenging couplings is that the ligand should be electron rich and bulky, ligand should be bulky and electron rich, write a t Bu whole 3 P. And then the presence of additive like basic additives is required, like cesium fluoride is required for performing the chloro coupling the challenging chloro coupling at a room temperature, chloro coupling under convenient conditions. So, apart from making this C-C cross coupling biaryl, there are other scopes of Stille coupling available. For example, in presence of carbon monoxide ketones are formed.

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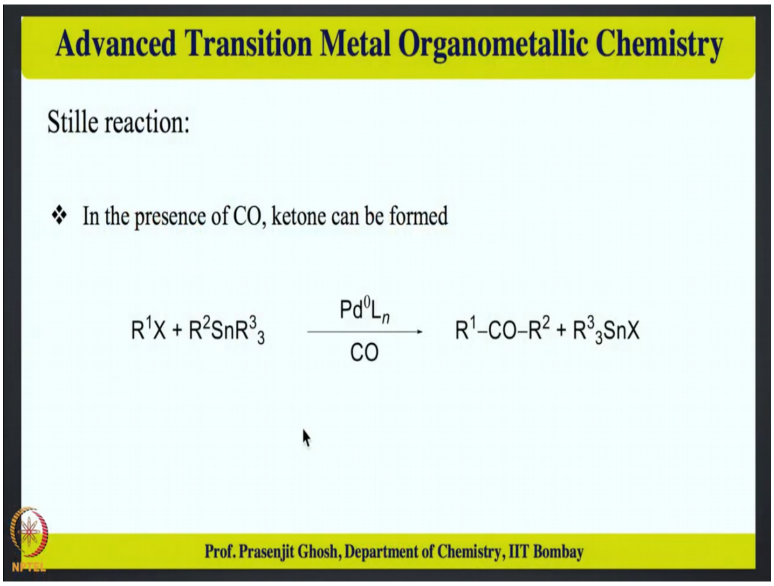

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Stille reaction:

- In the presence of CO, ketone can be formed

$$R^1X + R^2SnR^3_3 \xrightarrow[CO]{Pd^0L_n} R^1\text{–CO–}R^2 + R^3_3SnX$$

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So, we are going to see some of the scope as well as the reactivity of Stille coupling.

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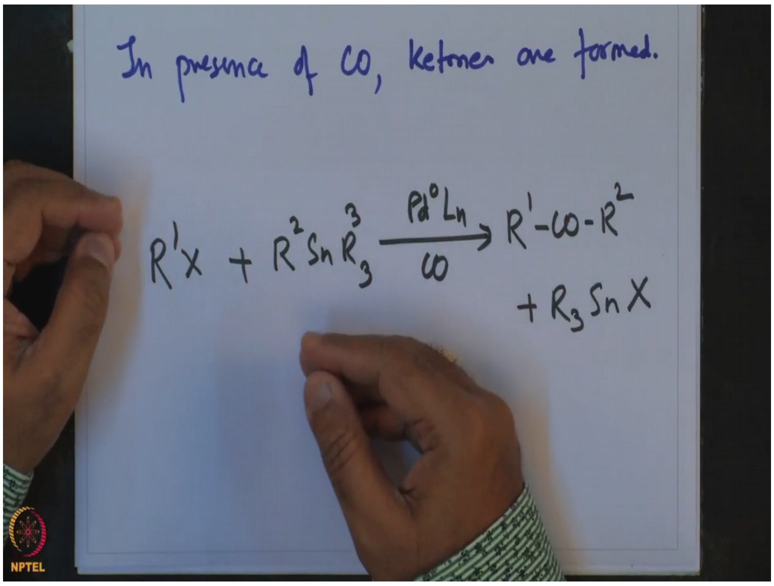

In presence of CO, ketones are formed.

$$R^1X + R^2SnR^3_3 \xrightarrow[CO]{Pd^0L_n} R^1\text{-CO-}R^2 + R_3SnX$$

So, in presence of CO, ketones are formed. So, this is beautifully illustrated by this example in which R 1 X + R 2 Sn R 3 whole thrice palladium 0 Ln carbon monoxide giving R 1 CO R 2 + R 3 Sn X. Now, so, this says that you know, in presence of CO there is a formation of ketone. So, what one can see that the scope of Stille coupling also is quite large that it cannot, not only make the biaryl or C-C coupling but it also can results in a formation of carbonyl compound ketones in presence of reaction being done in presence of carbon monoxide.

Now let us sort of take a look at the mechanism that by which this Stille coupling proceeds, as that will provide an insight into the mode of the catalyst action, as well as it will enlighten us about the similarities and dissimilarities of Stille coupling with regard to the other cross coupling reactions particularly the Suzuki; one that we had discussed in our previous class.

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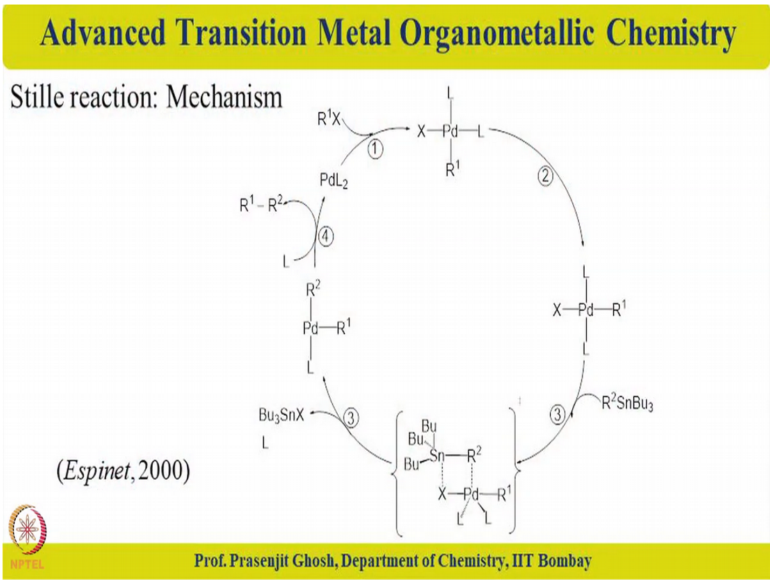

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Stille reaction: Mechanism

(Espinet, 2000)

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The reaction over here to the catalyst precursor is a palladium 0 species which is given by Pd L 2.

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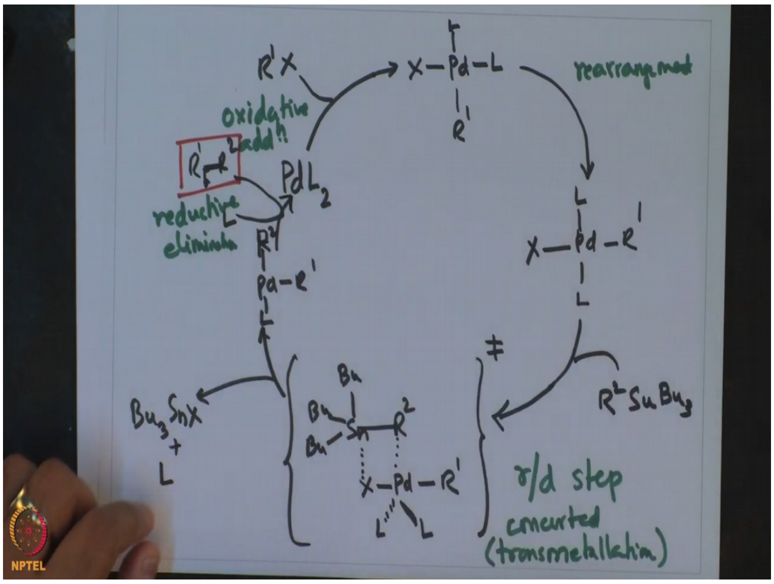

The first is obviously the oxidative addition of R 1 X. So, this is the oxidative addition step to give this compound X, Pd, L, L, R 1. The next step is the conversion of this cis compound to the trans compound similar to what we had seen that cis-trans rearrangement. So, hereby it becomes a trans compound R 1, X. Now, the next step is the transmetallation step. This is a cis-trans rearrangement step.

And the next step is the transmetallation step that occur from R 2 Sn Bu 3. And this goes via concerted pathway through a transition state which is shown over here. L, R 2, Sn, Bu, Bu, via this transition state to give the compound Bu 3 Sn X along with the generation of Pd, L, L 2, Pd, R 1. And this compound in presence of L gives the reductive eliminated product R 1 + R, R1 + R 2. This is the cross coupled product.

So, this step is the reductive elimination step. And the rate determining step of course is this attack of this R 2 on this Pd R 1 X. So, this is the R d step of the reaction. And this step proceeds by a consulted mechanism, pathway as it is seen over here. And this step is also popularly called as transmetallation reaction. So, this in a brief gives a glimpse of how the Stille coupling happens.

First is the oxidative addition, then followed by the rearrangement from a cis to a trans and then subsequently the attack of the rate determining step in which R 2 knocks out this X and produces palladium R 1 R 1 R 2 L and generates, in turn generates Bu 3 Sn X and L. Now this R 1 R 2 already are in cis disposition. So, it really undergoes reductive elimination to give the desired product which is R 1 R 2 couple product.

It is marked in red along with the formation of the starting precursor which is Pd L 2. Now, this is a sort of a similar to what one sees in Suzuki as well, because there are 2, there are 4 step. 1 is oxidative addition, transmetallation, reductive, rearrangement and then reductive elimination. In this case it is oxidative addition, rearrangement, reductive, transmetallation and reductive elimination.

So, basically these 4 step are quite similar to the steps elementary steps that what has been observed for the Suzuki coupling. Now, proceeding further, let us take a look at the some of the examples applicanted, application oriented examples of Stille coupling. For example, it can be used for synthesising ketones in presence of acyl chlorides.

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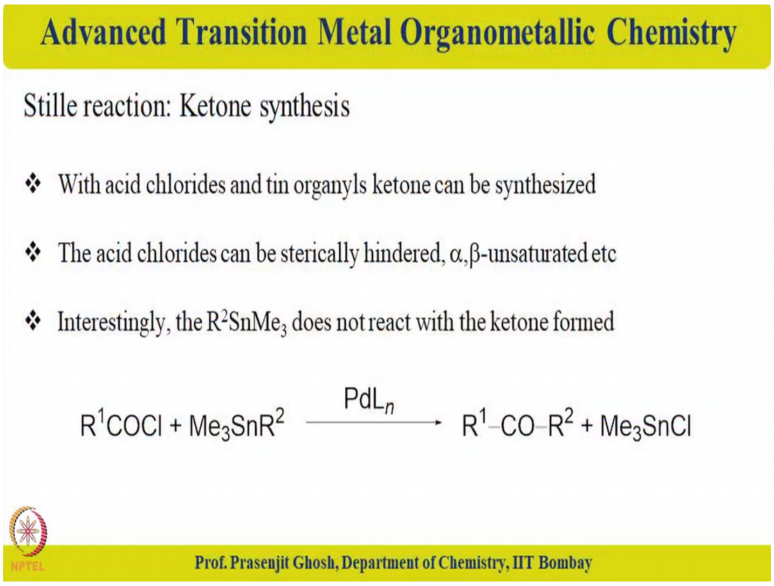

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Stille reaction: Ketone synthesis

- With acid chlorides and tin organyls ketone can be synthesized
- The acid chlorides can be sterically hindered, α,β-unsaturated etc
- Interestingly, the R^2SnMe_3 does not react with the ketone formed

$$R^1COCl + Me_3SnR^2 \xrightarrow{PdL_n} R^1{-}CO{-}R^2 + Me_3SnCl$$

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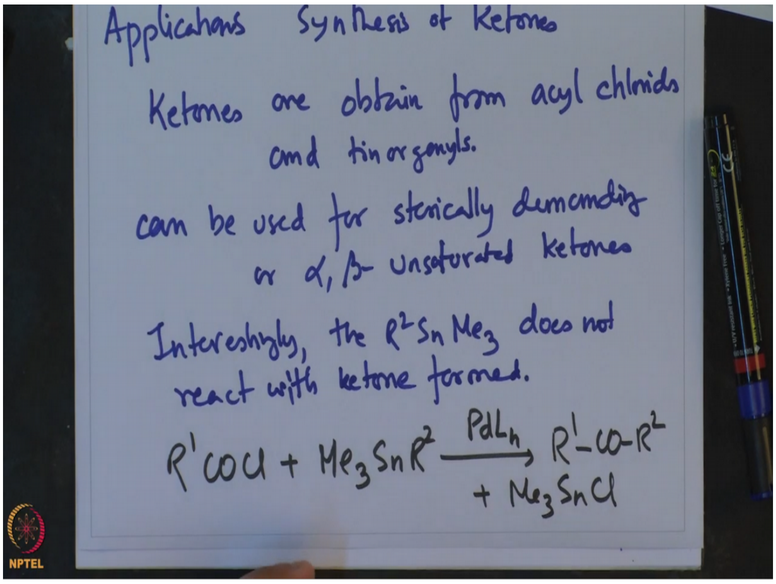

Applications Synthesis of Ketones

Ketones are obtain from acyl chlorids and tin organyls.

can be used for sterically demanding or α, β- unsaturated ketones

Interestingly, the R^2SnMe_3 does not react with ketone formed.

$$R^1COCl + Me_3SnR^2 \xrightarrow{PdL_n} R^1\text{-}CO\text{-}R^2 + Me_3SnCl$$

So, applications of Stille coupling, synthesis is of ketones. So, with acyl chloride ketones are obtained from acyl chlorides and tin organyls. And this can be used for sterically demanding as well as alpha beta unsaturated ketones. So, it is versatile, can be used for sterically demanding or alpha beta unsaturated ketones. And the best thing is that the final product, it does not react with the organotin reagent.

So, quite interestingly, the R 2 Sn Me 3 does not react with ketone formed. And this is given by this equation which is R 1 CO Cl + Me 3 Sn R 2 in Pd Ln giving R 1 CO R 2 + Me 3 Sn Cl. Now, with this I would like to conclude today's discussion on Stille coupling. Today what we have looked upon is the, touched upon is the reason for Stille coupling to be as effective as the Suzuki in the sense that it uses mild conditions.

And it instead of organoboron reagents which are used for Suzuki coupling, organotin reagents are used for Stille coupling. Further more, in Stille coupling, these tin organotin reagents are mixed organ substituted organyls organotin substituents. And of these only one of the substituents gets transferred over to the transitional metal and the other does not. We have also looked into the order of the reactivity of the in terms of the electrophile.

As well as, we have looked at the reactivity of the organotin reagent. And what we had seen that Sp carbon is no more nucleophilic or better performing than Sp 2 carbon moieties which is obviously better performing than Sp 3 ones. And this is in line with the greater S character on the carbon, making it more electron rich as opposed to and that decreases; I am going from Sp to Sp 2 to Sp 3.

We have also seen that in presence of carbon monoxide, the scope of the reaction can be extended from just producing, simply producing biaryls or bialkyls or alkyl allyls. One can also get ketones if the reaction is performed in a presence of carbonyl CO gas. And same thing if the reaction is performed with acid chloride, again one can also get ketones. We have seen the example of it.

We have also looked at the mechanism of Stille coupling and what we had seen that this mechanism is somewhat similar to that of the Suzuki coupling in terms of the presence of the 4 elementary steps which are oxidative addition, transmetallation, rearrangement and then reductive elimination. And the logic you have also noted that the logic which was used to achieve a Suzuki coupling of aryl chlorides was also equally effectively used for achieving Stille coupling of aryl chlorides.

And the logic being the use of electron rich and bulky phosphine based ligands, which the electron richness of the phosphine ligand would facilitate the oxidative additions step. Whereas, the steric bulk of the phosphine ligand would facilitate the last step which is the reductive elimination step. So, with this I would like to conclude today's discussion on Stille coupling and I am going to take up some more applications of Stille coupling to highlight its effectivity in from in various C-C coupling reaction in the next class.

And then I will also touch up on another important C-C coupling reaction which is the Sonogashira coupling. So, with this once again I would like to thank you for being with me in this class and I look forward to discuss more on the Stille coupling and then take up another new coupling which is Sonogashira coupling when we meet next time. Till then good bye and thank you.