Advanced Transition Metal Organometallic Chemistry
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Module - 9
Lecture - 41
C-C Cross Coupling Reactions: Stille Coupling

Welcome to this lecture on Advanced Transition Metal Organometallic Chemistry. As a part of our discussion on C-C cross coupling reaction, we have discussed Stille coupling in great detail in our last class. We have noted that Stille coupling is quite popular, particularly because of its, the mild condition in, under which the reaction is performed, its functional group tolerance and also because of the scope of the reaction.

What is important is the fact that the scope of the reactions can be extended to even producing ketones if the reaction is performed, the Stille coupling is performed in presence of carbon monoxide. as well as if the acyl group chloride is directly coupled with organotin reagents, then one can get ketones. And then, another important aspect of Stille coupling is the fact that it uses organotin compounds.

And these are mixed tin organyl compounds. That means, there are 2 different kinds of tin organic moieties that are attached in this reagents. However, only 1 of the 2 undergoes this coupling reaction. We have also discussed in great depth the elementary steps in Stille coupling catalytic cycle. And what we had seen is that the Stille coupling catalytic cycle consists of 4 steps.

The first involves oxidative addition, then there is a cis-trans rearrangement, followed by transmetallation and then subsequently reductive elimination. Now, the transmetallation step is the rate determining step in Stille coupling. And unlike what we had observed for this Suzuki reaction where the quarternization of the boronic reagent occurs prior to transmetallation in Stille coupling, and for the quarternization that the base is required in the Stille coupling.

No such thing take place. And it is a sort of the rate determining step for the overall coupling reaction, this transmetallation step. This transmetallation step proceeds in a concerted pathway through a transition state, leading to the formation of palladium bis organyls containing 2 different kind of organyl moiety R 1 and R 2 which sort of is formed through in this method in a cis orientation that largely undergoes this reductive elimination.

Now, we are going to be discussing a bit more on Stille applications of Stille coupling in today's lecture. And then, we are going to take up another very interesting coupling which is the Sonogashira coupling. So, we are going to be talking about asymmetric Stille coupling in bit more detail.

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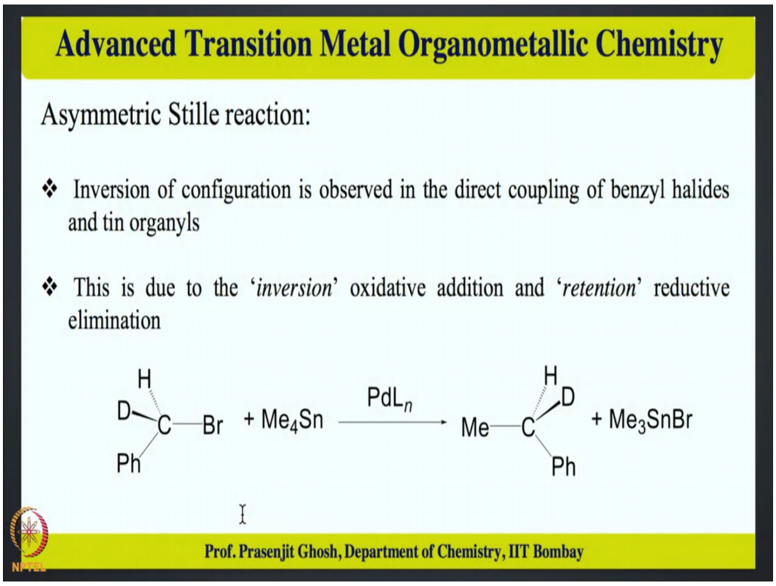

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Asymmetric Stille reaction:

- Inversion of configuration is observed in the direct coupling of benzyl halides and tin organyls
- This is due to the '*inversion*' oxidative addition and '*retention*' reductive elimination

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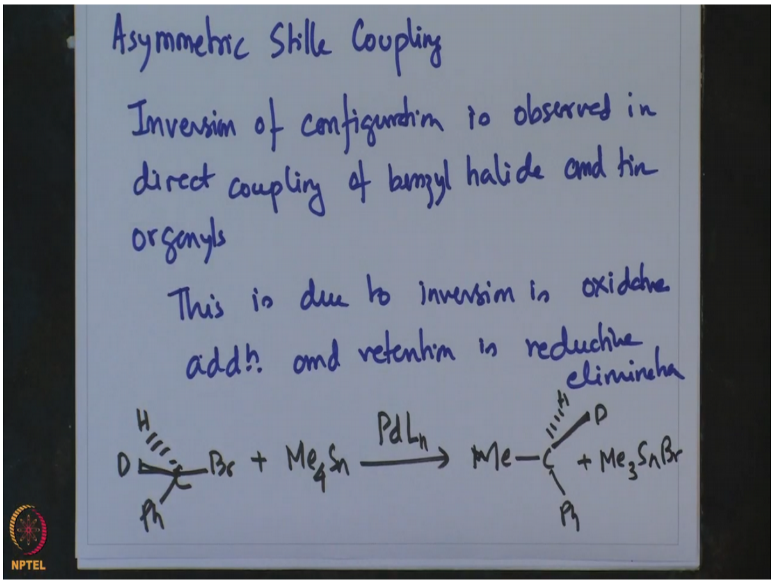

Asymmetric Stille Coupling

Inversion of configuration is observed in direct coupling of benzyl halide and tin organyls

This is due to inversion in oxidative add^n and retention in reductive elimination

And in this case, inversion of configuration is observed in the direct coupling of benzyl halides and tin organyls. And this is explained by, this is due to inversion in oxidative addition and retention in reductive elimination. So now, if one sort of analyses this in bit more details that, if there is inversion in the first step of oxidative addition and subsequently the last step there is retention. So, overall it would be inversion of configuration.

Indeed, that what is has been said over hear, that there is a overall inversion of configuration during the direct coupling of benzyl halide with tin organyl. Now, we are going to sort of explain that in bit more details through this equation Br + Me 4 n Sn, Pd L n giving Me C D H Ph + Me 3 Sn Br. So, clearly one can see that this has undergone an inversion of configuration.

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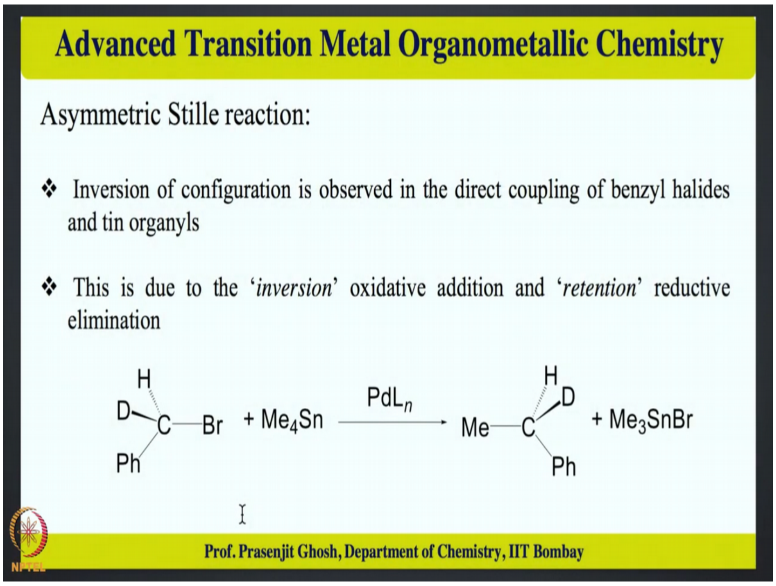

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Now, another interesting thing is that coupling of aryl bromide with tin allyl compound is, proceeds with allylic rearrangement.

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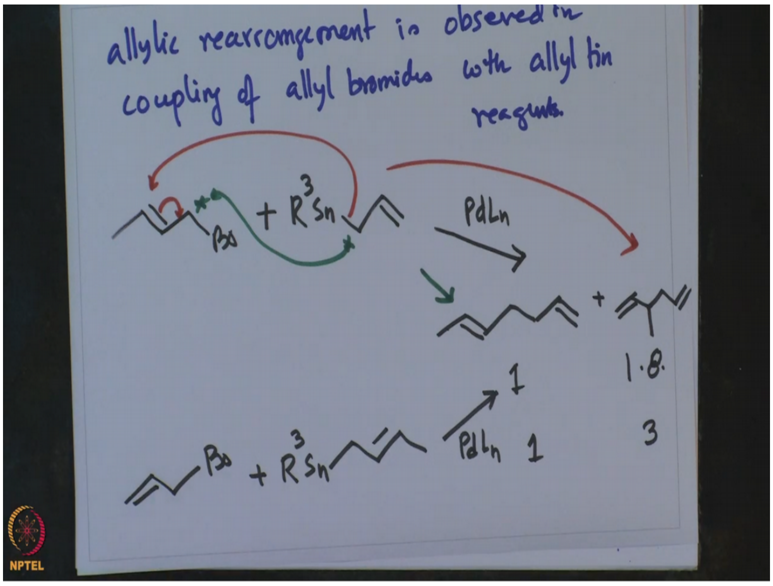

allylic rearrangement is observed in coupling of allyl bromides with allyl tin reagents.

Allylic rearrangement is observed in coupling of allyl bromides with allyl tin reagent. So, the reaction is best illustrated as over here. Br + R 3 Sn, this would give the following compound. So, here the coupling is observed between this and this moiety which is over here, followed by this, that is the expected product. And the rearranged product is; now the ratio of this is 1:1.8. Now, if 1 2 does the reverse, whereas it starts with the allyl bromide and this moiety on the tin, the reaction would thus be this + R 3 Sn.

This, all this requires palladium coupling Pd Ln. Then, one gets the ratio of the main product which is 1 and then the rearranged product 3. So, what one sees that it does gives the rearranged product. The rearranged product is obtained by the attack the of this allyl tin reagent on the other thing and other distant carbon. So, let me just explain how the coupling; if the coupling happens between the unrearranged product, this attacking straight over there.

Then, the overall product one gives gets as shown is the normal product. And if the attack happens at the distance carbon this, then one would get the rearranged product. As a same thing is observed in this case, if the attack happens in the distant carbon, then one would get the rearranged product as well as this. And one sees that such kind of rearrangement as well as normal coupling, both can be seen in terms of coupling of allyl bromides with allyl tin compounds. And the ratio varies from 1:2 to 1:3. So, this shows the significant amount of rearrangement that happens.

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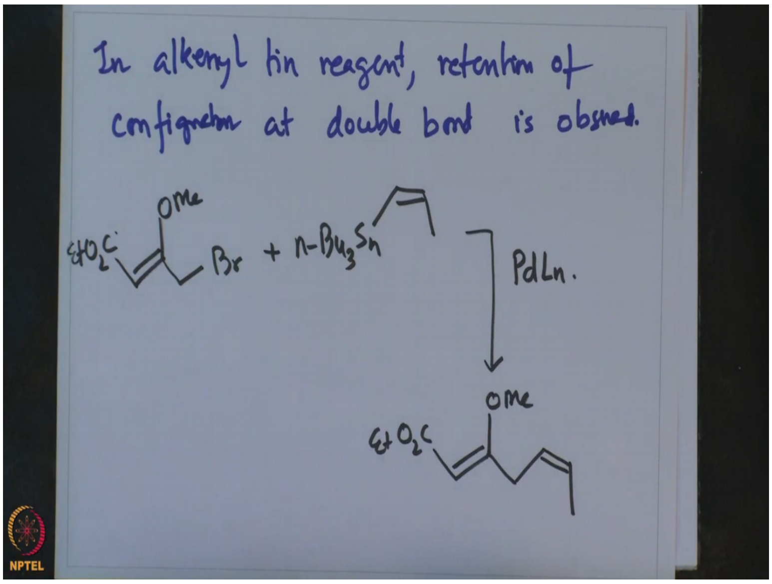

In alkenyl tin reagent, retention of configuration at double bond is observed.

Now, another important aspect is that it, in alkenyl tin reagent, retention of configuration at double bond is observed. And this is best illustrated by the equation over here; OMe, C O 2 Et, Br + n Bu 3 Sn. And this is alkenyl, so, this is a Sp 2 carbon bound to the tin in presence of palladium Ln produces the expected compound. So, this is the carbon. And over here, this is alkanyl carbon gets attacked, giving this compound. So, this is a cis olefin and in the end a cis confirmation of the olefin is preserved. Another interesting example of applications of Stille coupling is seen in Carbonylative coupling.

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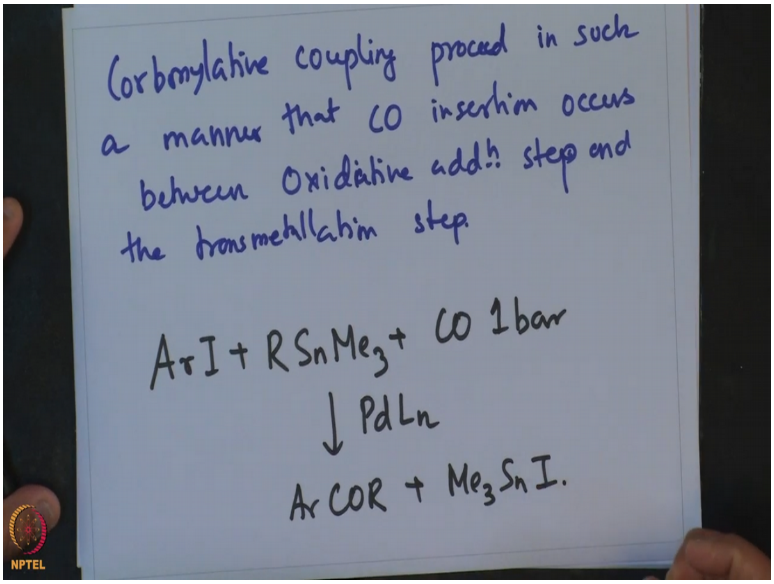

Carbonylative coupling proceed in such a manner that CO insertion occurs between Oxidative addn. step and the transmetallation step

$$ArI + RSnMe_3 + CO \text{ 1 bar} \xrightarrow{PdLn} ArCOR + Me_3SnI.$$

Carbonylative coupling where one makes ketone through Stille coupling, proceeds in such a manner that CO insertion occurs between oxidative addition step and the transmetallation step. Now, this is a interesting observation because the oxidative addition step sort of activates the electrophile and then the transmetallation step where the second nucleophile comes and that forms the adduct.

So, CO insertion proceeds in between that. So, it is sort of migratory insertion of CO onto the metal alkyl bond after the oxidative addition step has taken place. And this is successfully used in preparing various forms of ketone. So, one such example is given over here. Aryl iodide + R Sn Me 3 + CO 1 bar, giving palladium L and n and Ar COR + Me 3 Sn I. Another, if, another interesting thing is that not only organotin reagents can be used for this Carbonylative coupling.

Tin hydride can also be can be used for Carbonylative coupling and one can end up getting aldehydes in place, instead of the ketones that are obtained in Carbonylative coupling reaction. So, this also is another important scope for scope of variation for this Stille coupling. We had seen that Stille coupling can give ketones. Now, we also see that Stille coupling can also give aldehydes.

And in such cases where it gives aldehydes instead of organotin reagent, tin hydride reagents can be used. So, this is a very interesting observation which sort of extend the scope of Stille coupling to towards the formation of aldehydes.

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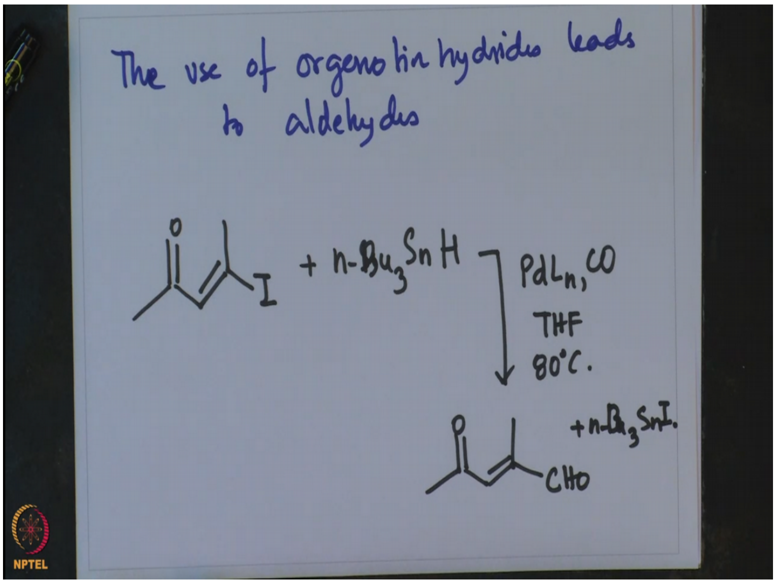

The use of organo tin hydrides leads to aldehydes

So, the use of organotin hydrides, leads to aldehydes. So, this is quite intuitive, because if it were organotin reagents, then under Carbonylative coupling one would get ketones and that one such example we have discussed about. But if one starts with tin hydride, that also can undergo similar reaction and gives the corresponding aldehyde. And this is best illustrated in the example given over here.

Halide + tin hydride in presence of Pd Ln CO THF 80 degree centigrade, then 1, the CO and H will add over here. The one end up getting CHO + N Bu 3 Sn I. Now, so this sort of gives a broad scope of applicability for this Stille coupling, where one can see that, one gets not only the ketone but also one can get aldehyde if tin reagent hydride, tin organotin hydride is used for the Stille coupling.

We are going to discuss a bit more about Stille coupling and look at the disadvantages of the Stille coupling. The main disadvantages of the Stille coupling is the high toxicity of the tin reagent.

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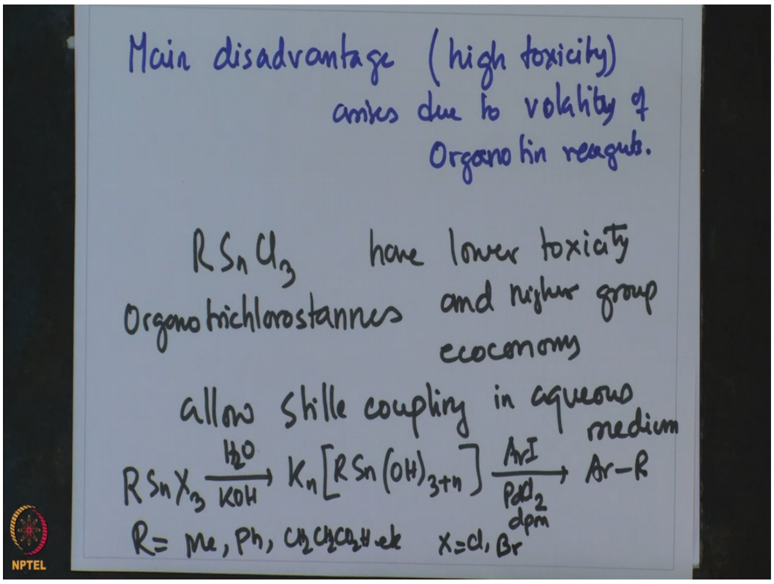

Main disadvantage (high toxicity)
arises due to volatility of
Organo tin reagents.

$RSnCl_3$ have lower toxicity
Organotrichlorostannes and higher group
ecocomony

allow Stille coupling in aqueous
medium

$$RSnX_3 \xrightarrow[KOH]{H_2O} K_n[RSn(OH)_{3+n}] \xrightarrow[PdCl_2\ dpm]{ArI} Ar-R$$

R = Me, Ph, $CH_2CH_2CO_2H$ etc X = Cl, Br

Main disadvantage of Stille coupling is high toxicity of organotin reagents. And this is particularly because some of the organotin reagents are also volatile; arises due to high volatility of organotin reagents. And so, one way out of this is to move away from organotin reagents and organotrichlorostannes of the formula R Sn Cl 3. These are organotrichlorostannes are have lower toxicity and higher group economy.

And one of the advantage of this is, they allow Stille coupling in aqueous medium. This is indeed a great breakthrough in the sense that one can move away from this toxic organotin reagent and tri organotrichlorostannes, where there is only 1 aryl organic group on the tin. And this compound has lower toxicity also higher group economy, because there is only 1 group that gets transferred via transmetallation to the coupling.

And also this facilitates reaction being performed in more, much desired aqueous medium. So, this indeed is a breakthrough in terms of circumventing the limitation or that arises due to high toxicity of organotin reagent. And suitable compounds can be developed that makes this organotin reagents to be performed in aqueous water. And one such example is given by over here, R Sn X 3 in H 2 O KOH H 2 O gives Kn R Sn OH 3 + n.

That with aryl iodide and Pd Cl 2 dpm; that is the ligand; give the corresponding Stille couple product. R can be methyl, phenyl, Ch 2 Ch 2 CO 2 H, etcetera. X can be chloride, bromide, so on and so forth. So, what one sees that Stille coupling can be even performed in water and one can use reagent like R Sn Cl 3. So, with this I would like to wrap up our discussion on Stille coupling.

What we had seen in today's lecture is we had looked at the various reasons for which the Stille coupling is so of useful. And then, looked into various applications of Stille coupling that involved asymmetric Stille coupling. We have looked into cases where inversion of configuration happened. And then, we have looked into alkenyl Stille coupling where there was retention of configuration at the double bond was observed.

We have also seen that the scope of the reaction can be extended to carry out this coupling in presence of carbon monoxide to give this ketones. And if one uses the tin hydrides and do this Carbonylative coupling reaction, then one can even produce aldehydes. We have also seen that major limitation for Stille coupling obviously is the high toxicity issues that are associated with organotin reagent.

And this is primarily due to the high volatility of this organotin compound. And one can move away from this toxicity issue to a great extent, if one uses the organotin trichloride, or oreganotrichlorostannes reagent which have much lower toxicity, higher group economy. And also the main advantage of using this reaction is that, they allow the reaction to proceed in aqueous conditions.

We have discussed a general reaction which allows this. One thing to summarise that in Carbonylative coupling, the CO insertion happens in the step after oxidative addition and before transmetallation reaction. So, this is an additional step that is observed in Carbonylative coupling. So, with that let me just summarise the different facets of Stille coupling before and concluded this topic on Stille coupling.

So, what we had seen that Stille coupling is quite effective primarily because it is performed under mild conditions, under aerobic conditions, can also be carried out for wide variety of substrates, functional group tolerance and which are also similar to what has been observed for Suzuki and other things. And one thing about Stille coupling is that the reaction scope can be extended not only for making this cross coupled product, but also towards producing ketones as well as aldehydes.

And also, the reaction can be performed in aqueous medium by using organic tri tin trihalides. Though these are certain advantages of Stille coupling, we had also seen that Stille coupling can be used for carrying out the challenging coupling with aryl chlorides. If one were to use the logic of bulky electron rich phosphine ligands, the similar to the logic that was used in performing the same under Suzuki conditions.

So, with this, I would like to conclude today's discussion on Stille coupling. We are going to take up this Sonogashira coupling in bit more detail when we meet in the next class. So, with this let me conclude today’s lecture and I look forward to being with you in the next lecture when we take up Sonogashira coupling in bit more details. Thank you.