Advanced Transition Metal Organometallic Chemistry

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Module - 8
Lecture - 38
C-C Cross Coupling Reactions: Suzuki Reaction

Welcome to this course on Advanced Transition Metal Organometallic Chemistry. We have been talking about an important application of organometallic chemistry, particularly the C-C coupling reactions and more specifically about the C-C cross coupling reactions. Over the last few lectures in this topic we have looked into a variety of C-C coupling reactions. Started with allylic alkylation reactions, followed by heck coupling.

And today we are going to take up another very important coupling reaction which is Suzuki coupling reactions. Now one of the hallmark of this C-C coupling reactions or the success of the C-C coupling reaction is that of palladium. Now, palladium has brought in a lot of advantages to this coupling reactions particularly with respect to obtaining a highly selective cross-coupled products as opposed to homocouple products or the air and moisture sensitivity.

Palladium is not that sensitive to air and moisture. So, they are easy, more easy to handle. And also palladium can be tolerant to many functional group being a late transition metal not too very electron deficient like early transition metals. So, they are by and large inherently more tolerant to a variety of functional groups which is sort of a, makes way for a much broader substrate scope study.

And a broader and gives a broader acceptance to this application of this reaction. palladium also is does not have much of toxicity issues associated with it compared to other metals. And palladium is so active in such cross coupling reactions that they are required in very minute amount. And that is why the toxicity issues are even far less prominent in case of palladium. And last but that not least palladium maybe bit expensive as compared to first (()) (02:44) metals.

But with respect to the magic metals of catalysis like rhodium, iridium and platinum there is a lot of breathing space in terms of the expenses, as palladium is not as expensive as them. So, all of these factors contributed to the success of palladium mediated cross coupling reactions. And what we had seen that in this gamut of cross coupling reactions, there are variety of cross coupling reactions depending on the type of nucleophiles or reagents people use.

And in that context, we had looked at Heck coupling in the previous class. And then, also another allylic alkylation reaction in the class previous to this. And today we, in that same spirit, we are going to take up another very interesting reaction and also reaction that has found large scope and utility which is Suzuki coupling reaction.

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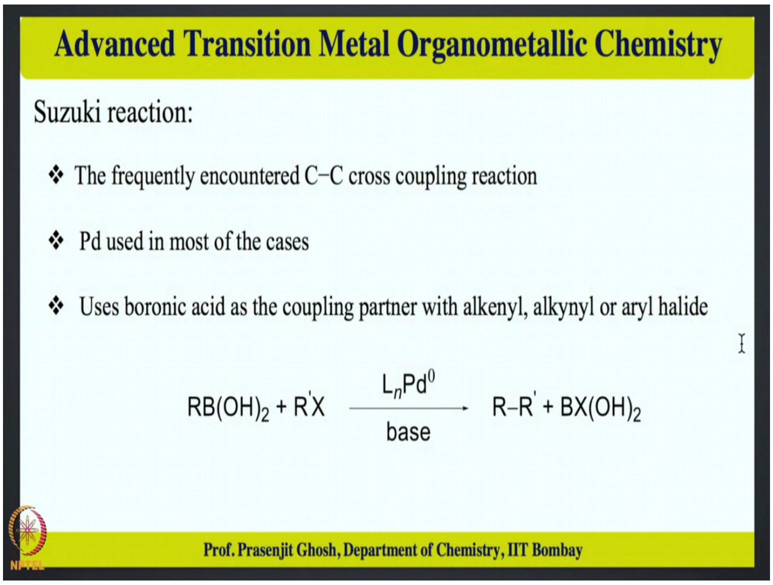

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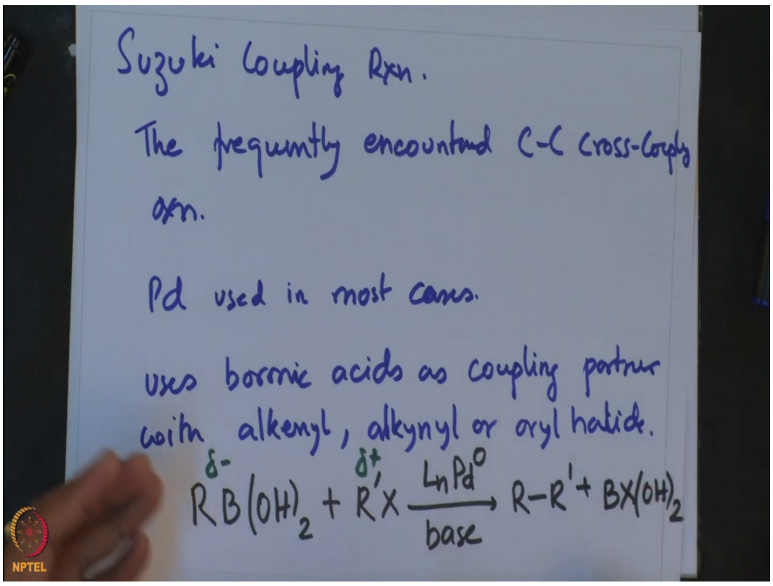

As the name suggests, this was indeed named after professor Suzuki, Akira Suzuki who had first observed this reaction happened. And that is why this reaction has been named after him. And the beauty of this reaction is that this is frequently encountered in C-C cross coupling reactions. So, one of the heavily used reaction till date. So, this is the Suzuki reaction and this frequently encountered C-C coupling reaction.

So, among various cross coupling, Suzuki is quite popular or probably among the few most popular coupling reactions that are known till or that have been used till date. Suzuki definitely falls in them and that is why they have again a huge popularity and huge user base. Then palladium is used in most cases. However, there are few examples where some other metals can have been reported for Suzuki type cross coupling reactions.

However, as compared to palladium their foothold, is footprint is much less. So, palladium by and large is the accepted metal for, or accepted one and only metal for a Suzuki type cross coupling reaction. And another interesting thing about Suzuki reaction is Suzuki cross coupling reaction use, uses boronic acid or boron base nucleophilic reagents, organoboron reagents as coupling partners with various halides.

So, that is a characteristic of Suzuki that it uses boronic acids, organoboronic acids as coupling partner with alkenyl, alkynyl or aryl halide. And the reaction in generic form is given as R B OH whole 2 + R dashed X Ln Pd 0 in presence of a base giving R, R dashed + B X OH whole 2. So, there the coupling happens between this R of boron and R dashed of halide. Now, one of the key reason for success of Suzuki or any of this cross coupling reaction arises from the, stems from the fact that this coupling really happens between a electrophile and a nucleophile.

So, R dashed is the electrophile because R dashed is bound to X. So, there is a partial positive charge on the R. And this R on the boron is a and in presence of base, it becomes anionic. And so, there is a partial negative charge on boron. As a result, the expected or the conventional product which would arise from here is R R dashed. And the possibility of 2 R which are del negative carbonides nucleophiles combining is completely suppressed.

And on the same line the positive of 2 electrophiles or 2 R dashed mutually a coupling to give the homocouple product is also suppressed. So, if one looks at this reaction one can see that this is an interesting strategy where by electrophile and a nucleophile abound to 2 different reagents couple to give exclusively the cross couple product. And that has been the strength or hallmark of Suzuki reaction which has a sort, which has propelled it to tremendous success that it has seen in recent times.

Now, having said that we are going to sort of look into this Suzuki coupling. And the reason for its being so successful is more details. And one of the reason in this discussion comes to the fact that these boronic acids are very convenient reagent to handle as they are air and moisture sensitive and thermo sensitive compounds are relatively inert.

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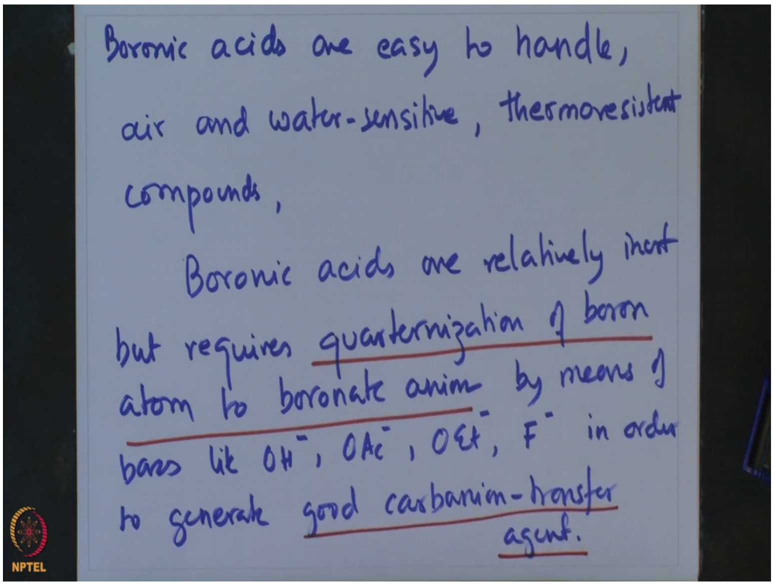

So, that is another advantage in favour of Suzuki, that boronic acids are easy to handle, air and water sensitive, thermo resistant compounds which sort of means that they do not decomposes easily upon heating. And as a result, they are relatively inert. boronic acids are thus, are relatively inert. However, requires quaternization of the boron atom to boronate anion. But requires, quaternization of boron atom to boronate anion by means of bases like hydroxides, acetate, ethoxide, or fluoride in order to generate a good carbanion-transfer agent.

So, this actually is the key point behind the success of Suzuki reaction, because just simple boronic acids by themselves would be miserable in carrying out this cross coupling reaction with this aryl, alkenyl or alkynyl halides. However, the presence of base makes the boronic acids to boronates. And then, the nucleophile present on the boron becomes more nucleophilic enough to carry out this cross coupling reaction.

So, this is indeed a key element, this quaternization of boron with boronate anion is a very key step for generation of good carbanion-transfer agent. So, this actually is a important finding by professor Suzuki himself. He was working as a postdoc in the laboratory of professor H. C. Brown who is known for his boron chemistry and also has been awarded Nobel Prize for like you know, propagating the cause of boron for his boron chemistry.

However, professor, what professor Suzuki had noticed that working over there, what that presence of base is fundamental or crucial to the propagation of Suzuki reaction. So, this is indeed a very important discovery which or observation which led out to immense discovery in terms of this Suzuki cross coupling reaction. So, having said that we are going to look at the coupling of pathway of Suzuki reaction.

Let me illustrate this using a catalytic cycle I had been doing for other, various other kind of coupling reactions. So that one can get a feel for how the reaction proceeds. But not only that, one can also compare the catalytic cycle of various cross coupling reactions. And then, you would have an idea as to what are the similarities and the dissimilarities in various kinds of cross coupling reactions.

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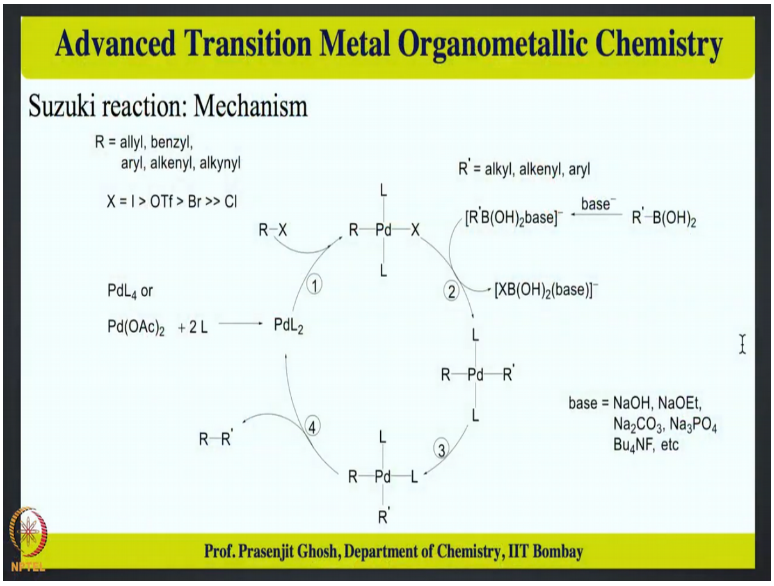

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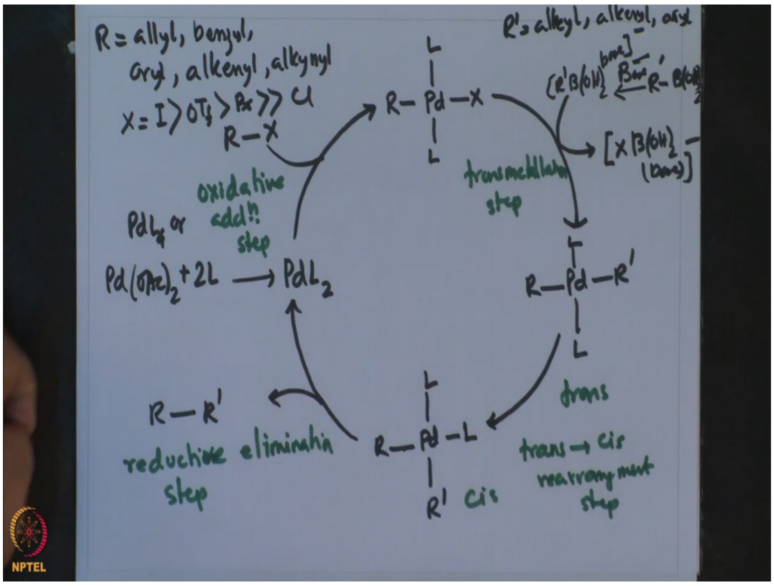

So, you know usually the starting precursors are just palladium acetate you know, Pd O Ac whole 2 + twice L. Sometimes it can be palladium tetra coordinative tetra L 4. That sort of reduces palladium to palladium 2. A palladium L 2 and palladium 0. And then, to this, first step is the oxidative addition where R X is added and R can be allyl, benzyl, aryl, alkenyl, and alkynyl. And X can be iodine, OTf > and bromide much much facile than chloride.

So, this first step is the oxidative addition step in which the palladium 0 undergoes oxidative addition to give this palladium 2 complex. And so now, palladium 0 over here has become palladium 2. And then, this boronic acid which is R B OH whole 2, R dash B OH whole 2 in presence of a base gives base – gives this adduct R dashed B OH whole 2 base –. And R dashed can be alkyl, alkenyl or aryl.

So, this R dash B OH whole 2 base – then enters the catalytic cycle to produce. So, R dash B OH whole 2 base – then reacts with R, L, L, X to give X. So, this X gets replaced by R, B OH whole 2 base –. And this step 2 is called the transmetallation step. And as a result, one forms this palladium complex bound to R, R dashed, L, L. Now, this complex further isomerizes to give the cis complex where one gets Pd, L, L, R, R dashed.

So, this is sort of a isomerization from trans to cis isomerization reaction. And subsequently once these are in cis this position to each other, then the final reductive elimination occurs giving rise to this cross couple product R R dashed. So, this step is called the reductive elimination step. And when the reductive elimination step happens, when palladium 2 bring goes back to palladium 0 and this step is thus as I said earlier, this is called trans to cis rearrangement step.

So, thus one sort of a cis that this involves a full catalytic cycle where palladium 0 species is formed, then it undergoes oxidative addition giving the oxidative addition product followed by transmetallation where the nucleophilicity of the boronic acid is increased by the addition of the base to make these R dashed boron base hydroxo base – anion which then undergoes transmetallation.

And this X is replaced by R dashed form the boron reagent. And then, this undergoes another additional step where it undergoes cis-trans rearrangement and followed by the final step which involves reductive elimination giving these desired cross coupled products. So, as mentioned earlier in our discussion that this the success of Suzuki reaction arises from this boronic acids being easy to handle, are stable, moisture stable.

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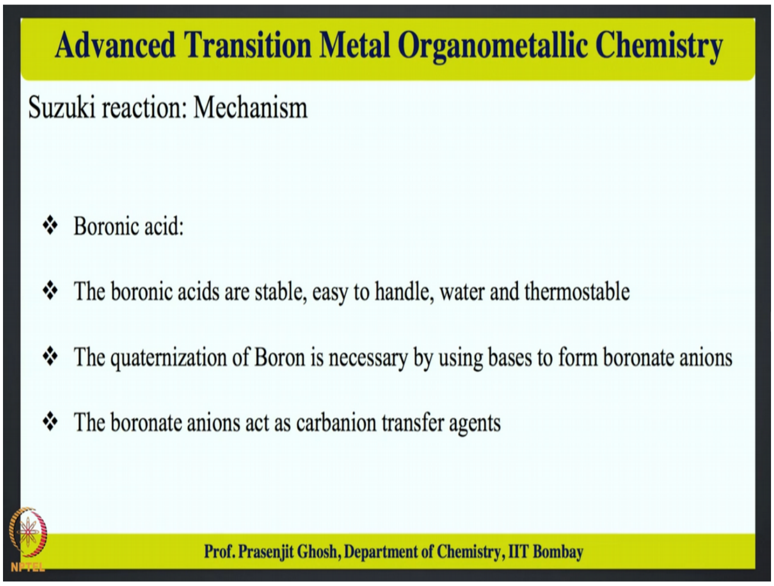

Then, you know they are also not inert, relatively inert, easier to handle and requires quaternization of the acids. And then, the other important thing about Suzuki is in addition for the easy use of the boronic acids. And the other important thing is that Suzuki reactions are tolerant to various functional group which is also important in increasing the substrate scope of the reaction.

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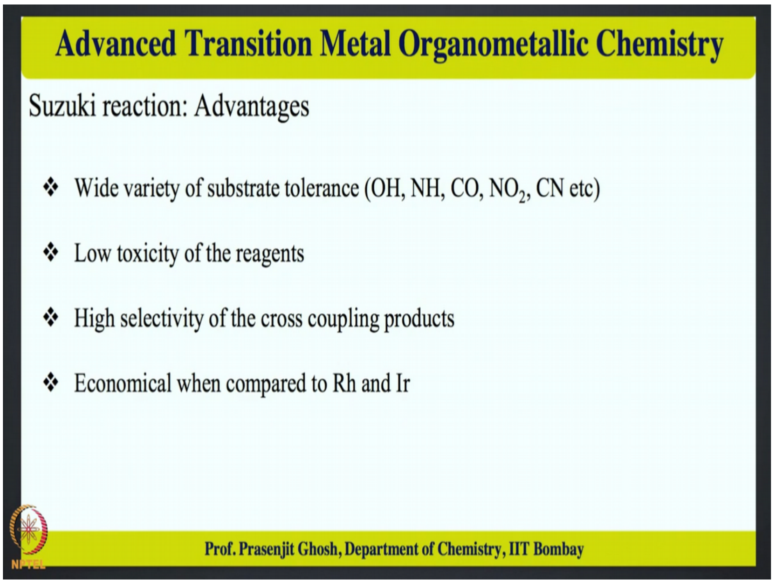

So, advantages of Suzuki is primarily is that boronic, 1 is boronic acids are easy to handle, air and moisture stable, air and water stable. The second thing is a functional group tolerance. For example, OH, NH, CO, NO 2, CN, etcetera. So, this gives a wider substrate scope. The low toxicity of palladium of boronic reagents as well as palladium, low toxicity of reagents. Then high selectivity in a cross coupling product and also economical when compared to rhodium and iridium.

So, all of these makes Suzuki a extremely successful in a variety of cross coupling reactions. Now, having seen the beauty of these Suzuki coupling reactions in terms of their applications as well as in terms of their catalytic cycle, we are going to shift gear and look at the various methods of synthesising this boronic acid reagents. Now, one has to realise that the success of Suzuki coupling would also be very much dependent on the accessibility to the boronic reagents.

So, one needs to know that if these reagents were to be easily synthesised, then obviously their further applications in Suzuki reaction would be very much facilitated. So, from that perspective, we are going to look up the various synthetic routs that are available for preparations of organoboron reagent.

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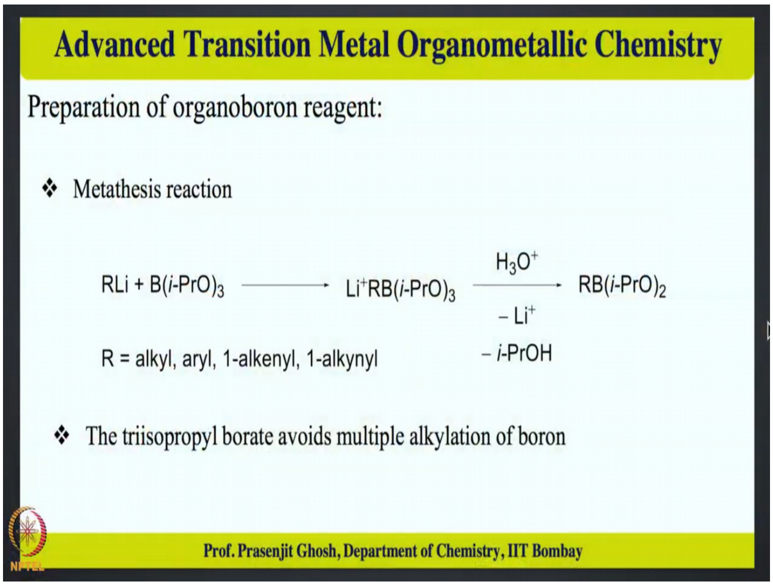

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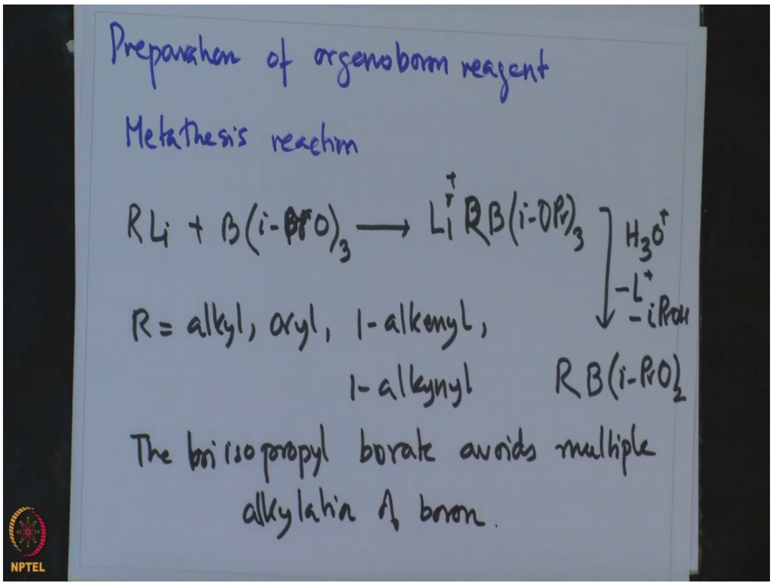

So, now the first and foremost is the metathesis reaction. The organoboron reactions can be prepared by metathesis reactions that involve reaction of R Li with B triisopropoxy boron giving the lithium + R RB i O Pr 3, that in presence of water – lithium planinus i Pr OH gives this R boronic ester i Pr O whole 2. So, R can be alkyl, aryl, alkenyl and alkynyl. And these, the use of triisopropoxyl borate avoids multiple alkylation of boron.

The triisopropyl borate avoids multiple alkylation of boron. So, with this, I would like to conclude today's lecture. In this lecture we have taken up a very important reaction in terms of its application and this is this much popular and much famed cross coupling reaction, the, in particular the Suzuki coupling reactions.

What we had seen that one of the, we have seen that the main reasons for success of Suzuki reaction is the air and water stability of the organoboron reagents, their low toxicity, their functional group tolerance, extremely high selectivity and also being economical as compared to other expensive catalysis metals like rhodium and iridium. So, all of these have contributed to the success of palladium mediated Suzuki cross coupling reaction.

We have also looked into the catalytic cycle of Suzuki cross coupling reaction in today's lecture. And what we had seen that, over here also, the catalytic cycle starts with a palladium 0 species which is formed from palladium 2 precursors by reduction in presence of the basic medium. And then, the second step is oxidative addition of organohalides onto this palladium 0 species to give the palladium 2 species.

The next step is the transmetallation reaction where in which the organic moiety in the organoboronic acid gets transmetallated onto palladium. Now, one of the important requirement for the transmetallation from organoboron reaction, organoboronic acid is the requirement of the quaternization of the boron atom in presence of base which sort of enhances the nucleophilicity of the organo, organic ligand attached to boron.

So, that is a important discovery I must say, which has a, helped propelled a Suzuki to its success that is currently being observed. So, after the transmetallation step comes a simple rearrangement step which is sort of rearrangement of a trans dialkyl palladium compound to a cis dialkyl palladium compound. Now, once the rearrangement has happened, then the final step obviously involves reductive elimination giving rise to palladium 0 species and the desired cross coupled product.

We have also seen that the successes of Suzuki reaction also is very much dependent on the accessibility of boron boronic organoboron reagents. And from that perspective we were discussing the various synthetic methods available for preparing organoboron reagent. In this context, the first and foremost reaction obviously is the metathesis reaction that involves reaction of organolithium compounds with boron tripopoxide isopropoxide to give the lithium salt of organoboron isopropoxide which under hydrolysis gives this organoboron bis isopropoxide compound which is extremely good as a reagent for Suzuki coupling reaction.

So, with this I am going to conclude today's discussion on Suzuki reaction, a bit more is remaining on Suzuki reactions which will be taken up in the next class in which we are going to look at some more methods available for preparing this organoboron reagents. And also, we should see in more details the application of this Suzuki coupling in some organic synthesis in different aspects of including synthesis to highlight the importance of Suzuki coupling and the reason why it has become the number 1 cross coupling method among the various cross coupling method that exist today.

So, with that, I thank you again for patiently listen to me in this class and the more of Suzuki, more of discussion followed by the another Stille coupling, another cross coupling reaction that awaits you in the next class which will take up in the next class. So, with that, I thank you again and I look forward to take up this topic of Suzuki and other cross coupling reactions in detail in next class. And till then goodbye and thank you.