

Advanced Transition Metal Organometallic Chemistry
Prof. Prasenjit Ghosh
Department of Chemistry
Indian Institute of Technology - Bombay

Module - 8
Lecture - 39
C-C Cross Coupling Reactions: Suzuki Reaction

Welcome to this course on Advanced Transition Metal Organometallic Chemistry. We have been discussing various types of C-C cross coupling reactions. These are reactions which are important with respect to the applications of organometallic chemistry. And they are one of the first and foremost examples of utility of this a great field of organometallic chemistry. So, these by and large can be thought of as ambassadors of organometallic chemistry as far as the applications are concerned.

And in among the various ambassadors or various applications of organometallic chemistry that exist, C-C cross coupling reaction definitely falls among the most notable ones. With regard to our discussion on the C-C cross coupling reaction, what we had observed so far that there are a variety of cross coupling reactions which falls under the gamut of C-C cross coupling reactions.

However, despite the diversity, the communality that lies between them and among them is the mechanism that they exhibit while carrying out the cross coupling under the desired name. So, in that key context, we have looked at 3 different coupling reactions. First, we started off with allylic alkylation reaction. And then, we have also taken up Heck coupling. And in the previous class we have been discussing about Suzuki coupling reactions.

Now, with refer to Suzuki coupling this I had mentioned in the previous class that this by far is the most popular among various cross coupling methods that are available out there. And the, and we were sort of discussing about the reason behind the in tremendous popularity of this Suzuki cross coupling reaction. In that context, what we had seen that the popularity of any laboratory reaction sort of lies in the ability of that reaction to transcendent the confines of the 4 walls of the laboratory and see its occupied space in the larger greater utility space in terms of a large-scale synthesis or synthesis of fine chemicals or industrial applications.

So, from that perspective, what we had seen that Suzuki indeed had made a mark of its own and the reason behind them is that the reagents that Suzuki uses, for example the boronic acids, they are quite easy to handle and also not very air and moisture sensitive. Actually, they are air and moisture water stable. So, much of the chemistry can also be done in benign solvents like water and also thermo stable.

That means that they do not decompose at much, at a higher temperatures which are conducive for the cross coupling reaction. Apart from that, we had also observed that the Suzuki reactions is involving palladium or functional group tolerant which gives them a large separate separate scope in terms of the utility. They are also not very toxic neither the boronic reagents nor palladium is known for their toxicity issues.

And hence, they do not have any like reservation being used in larger scale and scope. And lastly, palladium is by and large by from quite economical as compared to other expensive magic metals of catalyst like rhodium and iridium. And all of these help propelled palladium mediator cross Suzuki coupling reaction to where it is today in terms of popularity, name and fame.

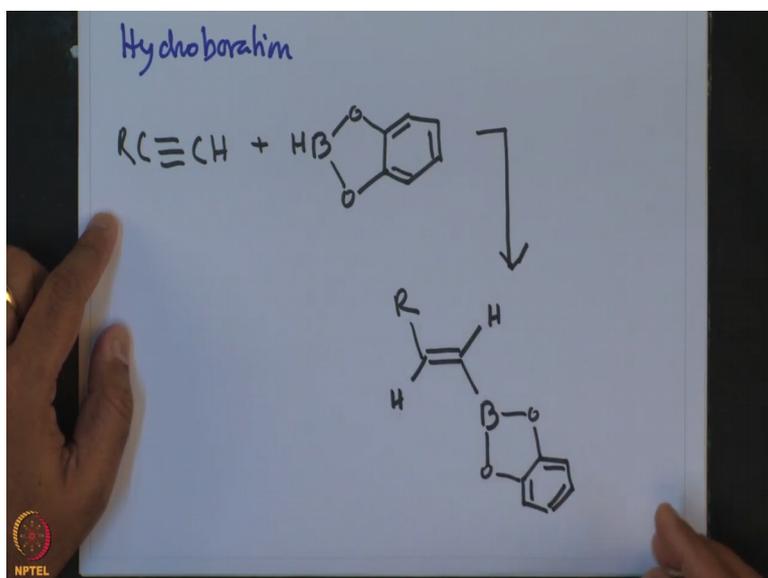
Now, we have also looked in the catalytic cycle of the Suzuki reaction in the last class. And we had seen that this basically involves a palladium 0 species formed from a palladium 2 precursor in presence of the base. And then, the first step elementary step involves the oxidative addition followed by transmetalation. Transmetalation requires quarternization of the boronic reagent in presence of a base, because that would influence the nucleophilicity on the boron.

And then, there is a trans to cis rearrangement which sort of deditions. The next step which is reductive elimination to give the cross couple product and regenerate back the palladium 0 species. Now, with continuing further on this discussion on palladium based or this Suzuki reaction, we had also observed that the success of Suzuki would be very much dependent on the accessibility of organoboronic reagents.

And then, we had focused on various methods available for synthesizing this organoboron reagents. So, in this pretext we are going to, we had discussed the metathesis reaction which is quite common in preparing organoboron reagents by the reaction of lithium organolithium

reagents with boron triisopropoxide giving the organoboron bis isopropoxide reagent which is, it can be used for the, for Suzuki. There are 2 other methods available for this preparation of organoboron reagents. And the next one that we are going to be discussing in this lecture is hydroboration reaction.

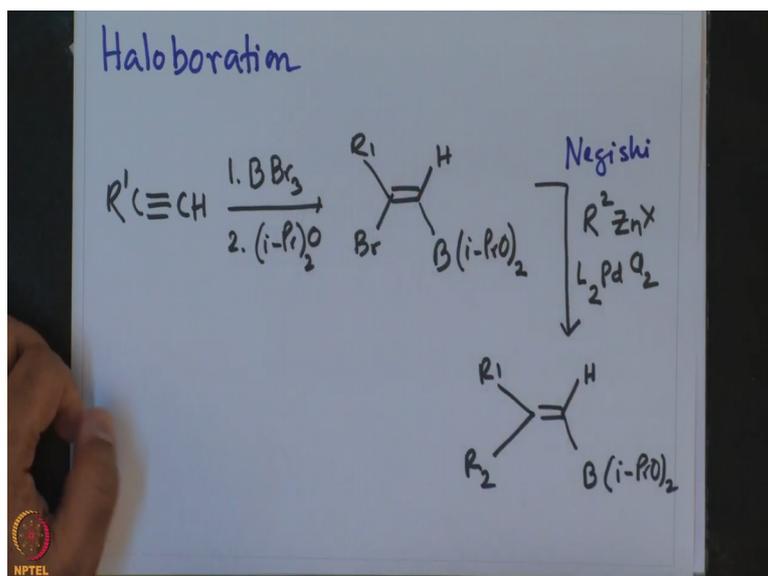
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Hydroboration, the example of hydroboration is best illustrated by this reaction of funtaminanal kind with boronic ester of the type shown over here. Now, this hydroboration gives the desired boronic ester of the type. Please note that this B H is adding against this alkyl to give the hydroboration product which is a very useful reagent for the subsequent cross coupling reaction.

So, a trans olefin is obtained through hydroboration and hydroboration like metathesis also provides a useful access to organoboron reagent. Apart from hydroboration, haloboration is also a useful synthetic protocol for preparation of organoboron reagents.

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And this is best illustrated by another reaction which is also, that it also involves a terminal kind which is R dashed CH which reacts with B Br 3 and isopropoxide ether to give the halo boronated product R 1, H, Br and Boron or with bis isopropoxide. Now that, when treated with organozinc reagent R 2 Zn X in terms of palladium compound Pd L 2 Pd Cl 2. Then, one can see this bromide getting replaced with L L R 2, R 1, R 2, H, B i Pr 2 Pr O 2.

Now, this a very interesting organoboron reagent in which there is R 1, R 2 and H. So, there are 2 interesting thing about this organoboron reagent. The first one obviously is this trans halo bromo organoboron reagent, the trans one. And the second obviously is the reaction which involves replacing this bromide with another alkyl group by R 2 Zn X organozinc and in front of L a palladium 2 complex.

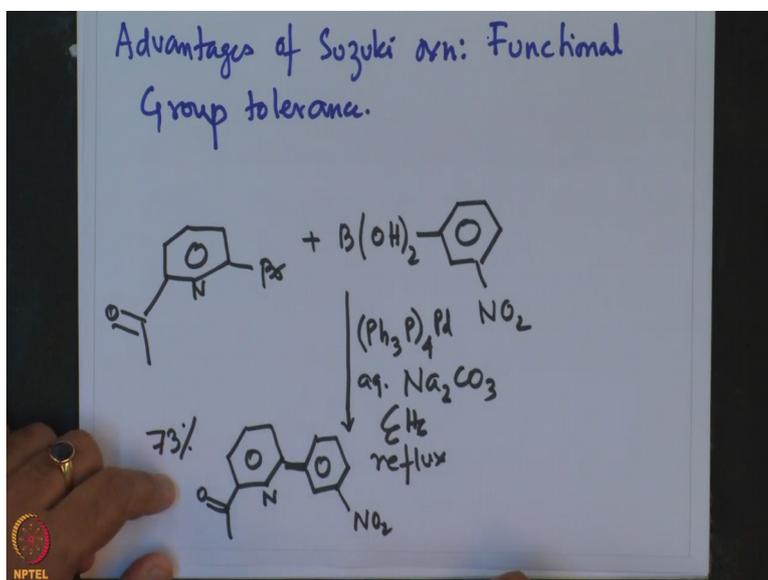
Now, this is exactly similar to the kind of coupling that we have been talking about. And this is a, this particular coupling is called Negishi coupling. And this Negishi coupling involves reaction of zinc organozinc reagent with this boron. So, what we see that another cis palladium mediated cross coupling reagent like Negishi coupling has been invoked to prepare organoboron reagent for Suzuki coupling.

So, this cross coupling reaction about this sort of tells us has a tremendous application. And which can, not only go in making a, the various cross coupling products but also it can be used, this cross coupling reaction can be used to make reagents for cross coupling reactions. So, here what we see is that Negishi coupling being used to prepare organoboron reagent which is a reagent for Suzuki cross coupling reactions.

So, tremendous applications of C-C cross coupling reaction, the, some beautiful examples of chemistry that is being played out over here, that we see that Negishi coupling being used to prepare organoboron reagent. And this organoboron reagent would subsequently be used for Suzuki cross coupling reactions. So, wonderful demonstration of coupling chemistry that we see that highlights the beauty, applicability and the generality of this cross coupling reactions.

And also sort of underscores the importance of the discussion that we are giving it to this particular topic. So, we are going to now take a look at some of the applications of Suzuki cross coupling reactions in terms of their applicability. And the first one that we see is the functional group tolerance.

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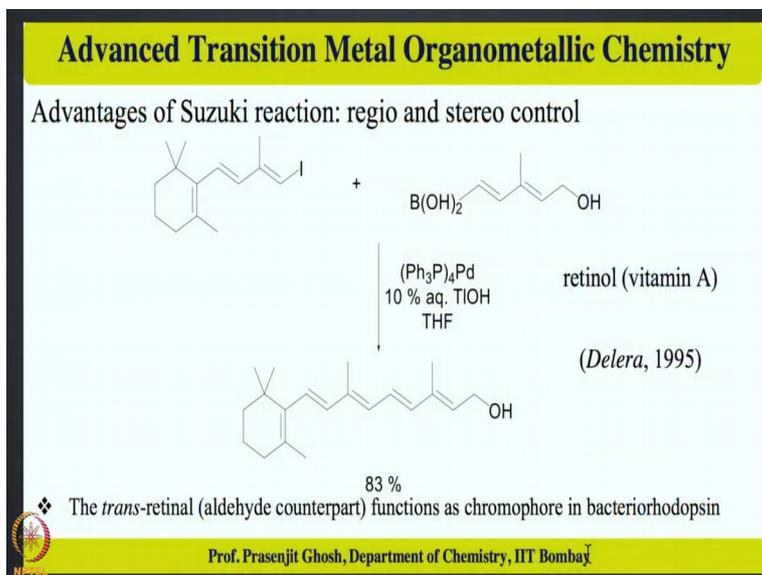


Now, this is best illustrated by this beautiful reaction which involves substituted pyridine. Bromine containing a keto group reacting with, also containing a nitro group in presence of tetraphenyl phosphine palladium. There is a palladium 0 complex, palladium is in 0 oxidation state in which aqueous sodium carbonate, benzene under reflux condition produces this cross couple product in 73% yield.

So, it is a definitely one of the high yielding reactions that we see in which the functional group over here, nitro group and or a ketone group does not affect the catalyst. And indeed, the cross coupling reaction occur at very high selectivity or very high yield. So, this certainly highlights the importance of Suzuki with regard to its functional group tolerance that this functional group on this reagents or the substrate does not really affect the catalyst.

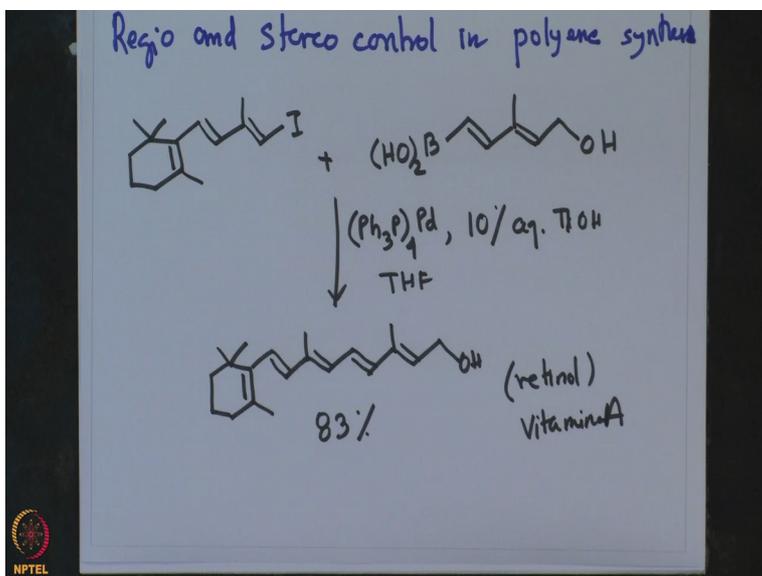
The next reaction in this that we are going to talk about is regio and stereo control in a polyene synthesis.

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So, that is also an interesting advantage of Suzuki. And this is sort of demonstrated in polyene synthesis.

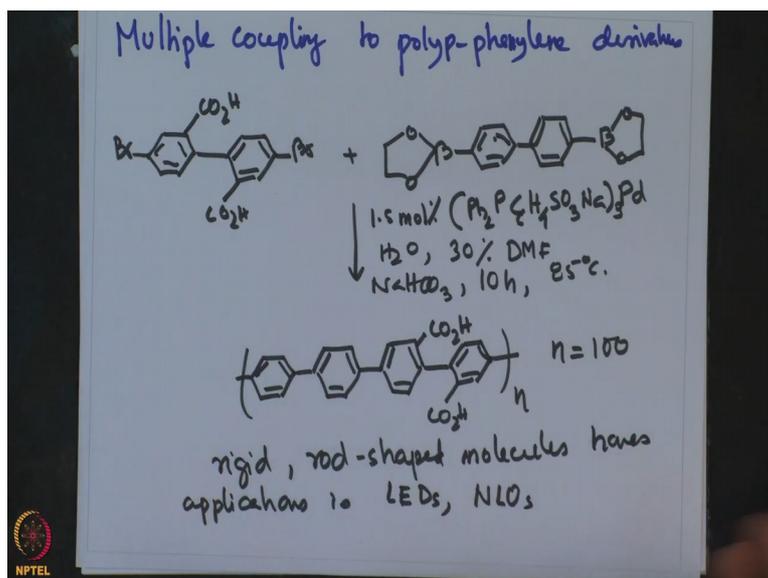
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So, regio and stereo control in polyene synthesis. And this is best illustrated in this beautiful reaction, this tetra substituted olefin conjugated the way it is shown + A which whole to B OH. This in presence of tetraphenyl phosphine 10% aqueous thallium hydroxide I think. THF in gives this polyene; this is a retinol vitamin A 83% yield. So, what it shows that, here is a nice control over the regio chemistry in synthesis of this retinol vitamin A.

And that, in this case exclusively the trans product, the desired trans product is obtained. So, Suzuki sort of because of its selectivity and also high generality high yield access to very complex natural product is obtained through this method which sort of again highlights the importance of regio and stereo control that has been achieved using Suzuki in polyene synthesis. Coordinating further we are going to take a look at another interesting reaction which is multiple coupling to poly paraphenylene derivatives.

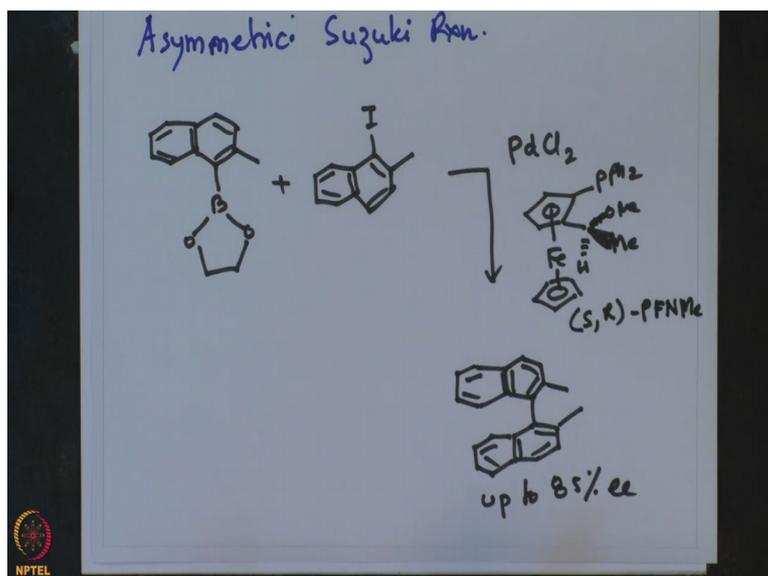
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Paraphenylene varied derivatives. This is a sort of illustrated by this beautiful example CO₂H + boronic esters, that in 1.5 mole % Ph₂PC₆H₄SO₃Na whole 3 palladium water 30% DMF sodium bicarbonate and 10 hours 85 degree centigrade gives this desired product. This polymeric product is a huge product with n = 100. So, this is a really large molecules. And these rod shaped molecules, these are rigid rod shaped molecules, have widespread applications in LEDs light emitting diodes, NLO nonlinear optical applications.

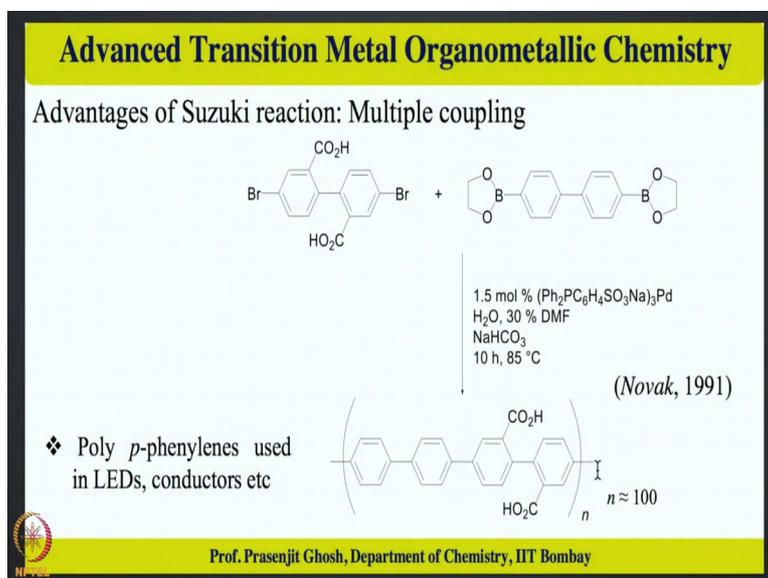
And with this, one can see that these have, can be prepared in water also. So, this is a interesting demonstration where multiple coupling of Suzuki has been achieved to produce this material of interest particularly of interest to LEDs and NLOs where huge amount of coupling about n = 100. So, at least maybe for these I think 2 couplings, 1, 2, 3, so, maybe 300 such Suzuki couple to get a polymeric compound like this that can be achieved. So, this again, once again highlights the importance of Suzuki cross coupling reactions. We are going to take a look at a asymmetric Suzuki reaction.

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That is also an important application of Suzuki reaction in chiral catalysis and one can see that these can also be done to give binaphthyl compounds of the type shown over here. So, this is the boronic ester iodide with the methyl. Then, in presence of PdCl_2 and a ferrocene based chiral auxiliary which is O Me methyl H and P Ph 2 gives this binaphthyl compound in a ee upto 85% ee. So, that is highly a selective and this catalyst is called S R P F N Me. Okay. So, this also is a beautiful application of asymmetric Suzuki catalysis.

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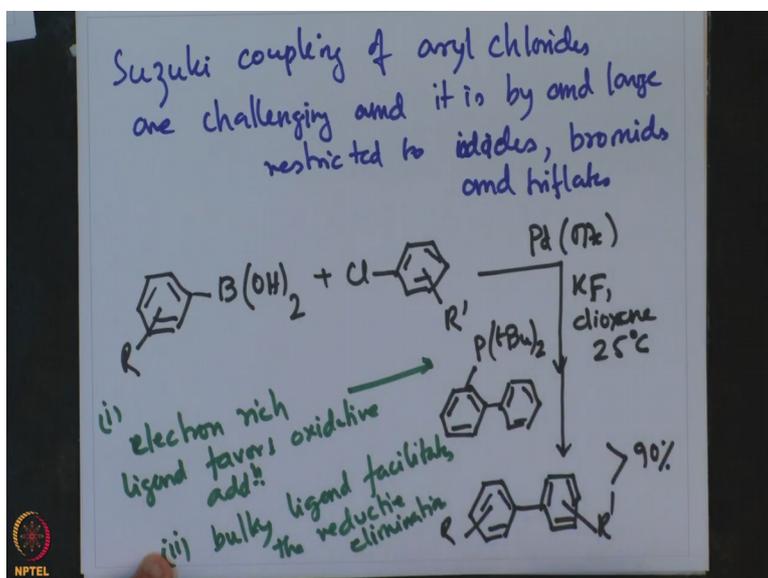


And then, another important highlight of Suzuki reaction is that you know, it can be extended to a aryl chlorides because you know aryl chlorides are very cheap and readily available. Then the bromides and the iodides which are expensive. So, one of the important criteria for Suzuki to be acceptable is that the Suzuki cross coupling should be applicable across the board and in fact should also work with the aryl chlorides.

Now, one of the reason other than being aryl chlorides being cheap, one of the challenges in such a Suzuki coupling extending to aryl chlorides is, even though the chlorides are cheap and readily available, the carbon chlorine bond is much more stronger, way stronger than carbon bromine bond in aryl bromides or carbon iodide bond in aryl hydrides which is even weaker. So, the challenge sort of goes up as one goes moves on from iodide to bromide to chloride.

And this has been solved in an elegant way by Buchwald, professor Buchwald who successfully reported the Suzuki coupling of aryl chlorides. And this is illustrated in this beautiful example given over here.

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So, Suzuki of aryl chlorides are challenging. And it is by and large restricted to iodides, bromides and triflates. So, actually, in that sense chloride is the new block in town and that was first reported by Buchwald in which they could couple the aryl chlorides in a facile manner using a beautiful catalyst, elegant catalyst. And we are going to talk about it as boronic acid + aryl chloride in palladium acetate K F dioxene.

And also another remarkable feature is that this was achieved at room temperature, so at 25 degrees. So, that indeed is a great feat in itself. And this was achieved by a specially designed legend which is extremely bulky the way it is shown one can say. And then, I will elaborate the reason for using a bulky ligand for the success of this aryl chloride coupling t Bu whole 2. And that gives the desired coupling in above 90% yield for many substrates.

So, one of the reason for this is a, that this ligand which is phosphine, a strongly electron donating ligand, electron rich ligand, makes the metal palladium more electron rich, favours oxidative addition step. So, if the catalyst is more electron rich, then the oxidative addition, the cleavage or activation of aryl chloride bonds become easier. That is the first and the strategy that has been used.

And the second strategy is that a very bulky ligand has been used. And this bulky ligand facilitates the reductive elimination step. So, what one can sort of right now see how this aryl chloride coupling which is a very challenging coupling for Suzuki have been achieved at room temperature by exporating 2 elementary step. The first obviously is the oxidative addition step and that has been solved or that has been overcome by putting a very electron rich ligand which will make the metal centre electron rich.

As a result, the metal will put electron density on the sigma star of aryl chloride bond. And then, facilitate the oxidative addition. So, the first elementary step is facilitated by the electronics and the sterics which this very bulky ligand is used, would facilitate the third step or the last step which is the reductive elimination step of the Suzuki coupling. So, one can see that in this Buchwald report reference that both the first step and the last step has been exporated by sterics and by electronics and sterics respectively.

As a result, a very convenient coupling of aryl chlorides with yields > 90 degree could be achieved at room temperature. So, this also is a fine demonstration of the power of chemistry or how a proper chemical understanding of the catalytic process might help improve a catalytic cycle that is beautifully demonstrated over here. So, with these I would like to conclude our discussion on Suzuki coupling.

And as we had seen in this lecture, let me just summarise that we had looked into the reasons as to why Suzuki is the popular most popular coupling reaction and to that what we found that these Suzuki is popular for several reasons like low toxicity, high selectivity, less thing and also easy accessibility of the organoboron reagents. And what we had seen that this oroganoboron reagents can be prepared in multiple way.

And then, we had looked into the applications of Suzuki coupling in total synthesis, particularly we had looked into examples, where polyene where it was synthesised in regio

and stereoselective fashion. Then we have also looked at a synthesis of organic application materials like LEDs in terms of again poly polymers which could do multiple coupling. We have also seen its use in synthesis of natural products and asymmetric coupling as well as its extension to take up this challenging coupling of aryl chlorides.

And also, we have seen an example of it functional group tolerance. So, with this I would like to conclude our discussion on Suzuki coupling one of the most important coupling in C-C cross coupling reaction in today's talk. And I am going to take up the Stille coupling in more details with regard to our discussion, palladium mediated cross coupling reaction in the next class. So, till then thank you again for patiently being with me in this class and I look forward to discuss take up this topic of Stille coupling with you in the next class when we meet. Goodbye and thank you.