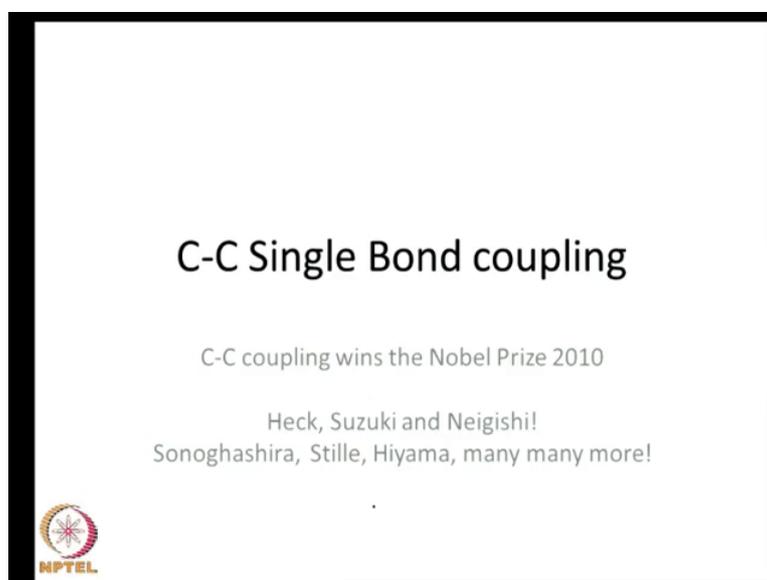


**Introduction to Organometallic Chemistry**  
**Prof. A. G. Samuelson**  
**Inorganic and Physical Chemistry**  
**Indian Institute of Science, Bangalore**

**Lecture - 24**  
**C-C Single Bond Forming Reactions**

In organic synthesis, you very often want to combine two different fragments either through a single bond or through a double bond.

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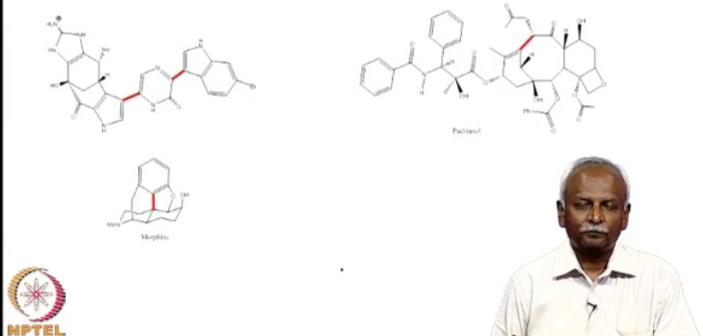


In today's lecture we will look at options where we can combine two organic fragments through a carbon-carbon single bond. In fact the problem is so important that solution to this problem was awarded the Nobel Prize in 2010. At least some of the processes, which brought about carbon-carbon Single bond coupling in a very interesting and normal way. Now, the three people who won the Nobel Prize are Heck, Suzuki and Neigishi, but there are many, many more who have contributed to this area and we will look at time permitting. We will look at some of the processes which are useful in bringing about a carbon-carbon single bond coupling.

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## Synthesis of complex molecules

- C-C coupling is the key to making complex molecules in a convergent manner.



The slide displays three complex molecules with newly formed C-C bonds highlighted in red. The molecules are labeled as follows: a large polycyclic aromatic hydrocarbon (top left), a complex bicyclic system labeled 'Faldaf' (top right), and a complex bicyclic system labeled 'Mupirocin' (bottom left). The NPTEL logo is visible in the bottom left corner of the slide.

We will start with some of the examples where these have been used. Here I have shown for you on the screen three different naturally occurring molecules. These molecules are important as drugs. They have been useful for the treatment of various diseases and surprisingly the synthesis of these molecules in the laboratory. So, that they can be synthesised readily and administered to is patients critically dependent on some carbon-carbon bond forming reactions. These carbon-carbon bonds are shown in red in these molecules and you can see that if one develops, interesting methods or green methods to couple the systems together. Efficiently you would have achieved the goal of the goal which in this case the synthesis of the molecule.

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### The Problem Defined

- C-C coupling ←
  - C· Coupling of radicals ←
  - C<sup>-</sup> and C<sup>+</sup> ←
  - C-C and C-X metathesis
- C=C coupling ←
  - Trimethylsilyldiazomethane TMSCHN<sub>2</sub>
  - Wittig (Organophosphorus chemistry)
  - Metathesis
  - ICH<sub>2</sub>ZnI
  - Tebbe Reaction



So, the problem essentially boils down to making a carbon-carbon coupling reaction. And it can be generalised to say that there can be two different ways you either couple them through a double bond or a single bond. And today's lecture as I said it is for a single bond coupling and you can couple them when they are two radicals. This would be if the two fragments are two radicals they would lead to indiscriminate coupling reactions, where there will be homo coupling and hetero coupling other fragments.

You can make this more specific by combining a cation and anion in which case the cation will react only with the anion and not with itself. So, homo coupling would be avoided in this process. You can also have some metathetical reactions a single bond metathesis reaction and this is something, which would be valuable, and we will consider this a little later.

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**Negishi C-C coupling Matrix**

	R-CH <sub>2</sub> -X	R-CH=CH-CH <sub>2</sub> X	RCH=CHX	ArX	R-C≡C-X
R'-CH <sub>2</sub> -M-Y	↻				
R'-CH=CH-CH <sub>2</sub> -M-Y	→	✓			
R'CH=CH-M-Y					
Ar'-M-Y				↓ Ar'-Ar	
R'-C≡C-M-Y				R'-CC-Ar	R-C≡C-C-R'



So, let us take a look at some carbon-carbon bond coupling reactions. The first person who systematically examined this process is Negishi. So, this coupling metrics that I have written for you is the matrix that was originally defined or written down by Negishi. And he says that this is the way in which he systematically approached the problem.

He took two fragments and for convenience we have written it in such a way that the... If we have an alkyl fragment and that is R-CH<sub>2</sub>-X which is functionalised. You can think of a metal fragment which can be generated from the same R-CH<sub>2</sub>-X in which case it will be R-CH<sub>2</sub>-M-Y. Coupling of these two would then lead to a molecule R-CH<sub>2</sub>-CH<sub>2</sub>-R and that would be in this product cell.

So, similarly you can couple two allylic fragments. And that would give you this. You can also couple the allylic fragment with the alkyl fragment in which case we would write the product and the cell, which is indicated here. So, you can have a matrix of coupling reactions and this would be useful from making bi-rails and these are indicated here. You can also couple alkynes alkenyl species.

So, R-C triple bond C and this would give you a conjugated triple bond C coupled products as we have written here R-C triple bond C-C triple bond and R dashed. So, you can have R-C triple bond C-C triple bond C and R dashed. So, you can imagine

all the products written down in this matrix. These will have to be coupled using various metals.

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### Historical Development

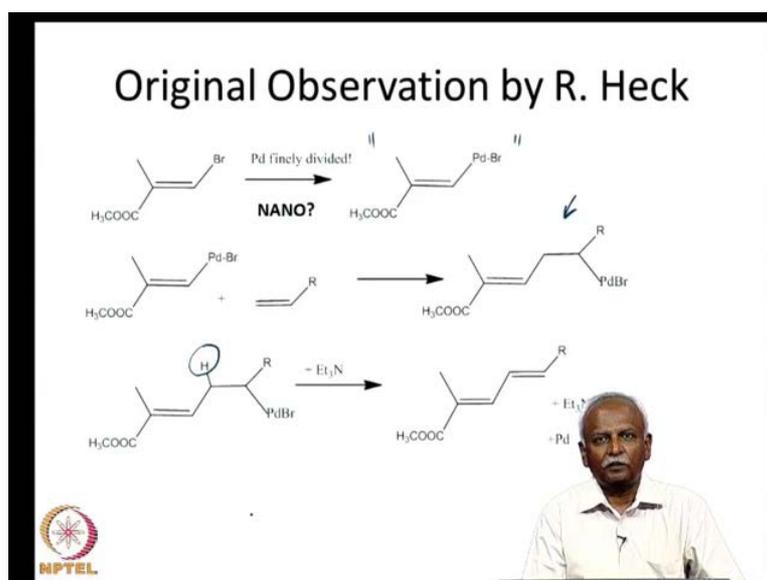
- Kharasch (Grignard)
- Heck (palladium) ←
- Tamura and Kochi (copper) ←
- Kumada and Corriu (nickel)

NPTEL

Let us backup little bit and talk about the historical development of this process. It was not Neghishi, who originally developed carbon-carbon bond coupling processes. It was in fact a problem that has been tackled for long time. There are reactions were Grignard reagents have been coupled together. They could be oxidised with copper, copper two plus salt, there is this crash coupling and the situation really became or problem was taken up more seriously after Heck found out that palladium was able to carry out some very interesting reactions

At the same time Tamura and Kochi have looked at copper, cuprate couplings and these are also important. But it was the work done by Kumada and Corriu with nickel based coupling reactions that caught the attention of the Neghishi. Neghishi took that reaction and started investigating or developing that reaction in greater detail.

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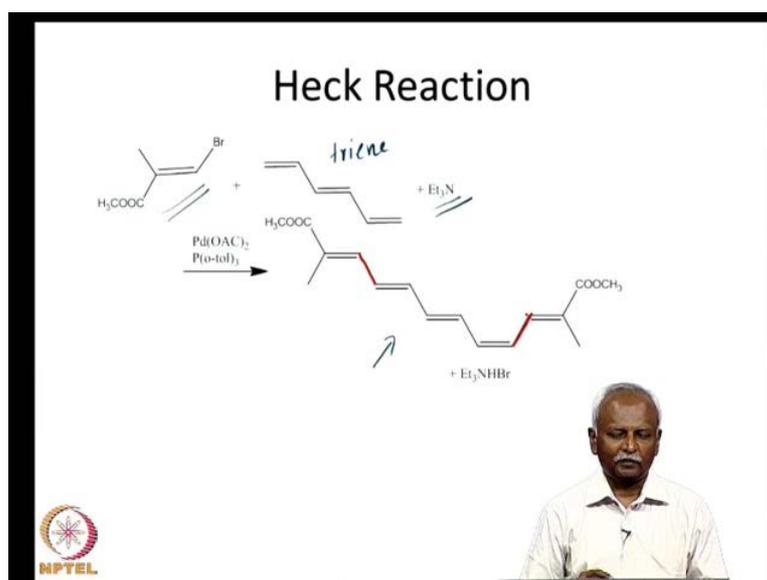


The original observation at the time or the turn of the birth of organometallic chemistry in the nineteen, late nineteen fifties and early nineteen sixties was observation made by Heck. He observed that if it took finely powdered palladium, finely divided palladium if you generate the reactive form of palladium and reacted with an ally or a vinyl bromide. You could in fact generate a palladium, organo palladium compound, which is reacted as if it had the palladium between the carbon bromine bond. And this compound could add onto olefins in order to generate organo palladium species, which I have pictured for you here.

Simply put you have a sigma carbon, sigma carbon palladium bond, which now adds onto the double bond and that is how you get this intermediate. And because this intermediate has got this hydrogen here, which can be eliminated in the presence of the base like triethylamine you would eliminate and form these diolefins.

So, if you took a vinyl compound you would end up with a diolefins. Essentially you have in the process you have eliminated a molecular H B R from these two species together in the presence of palladium. In the presence of finely divided palladium. So, what is pictured here is a stoichiometric reaction. The question that you can ask now in hindsight is that, was that palladium that was used by Heck and nano palladium? Now, there is a lot of interest in nano catalysis and it is possible that the palladium that was used by Heck was in fact in the nano regime in terms of size.

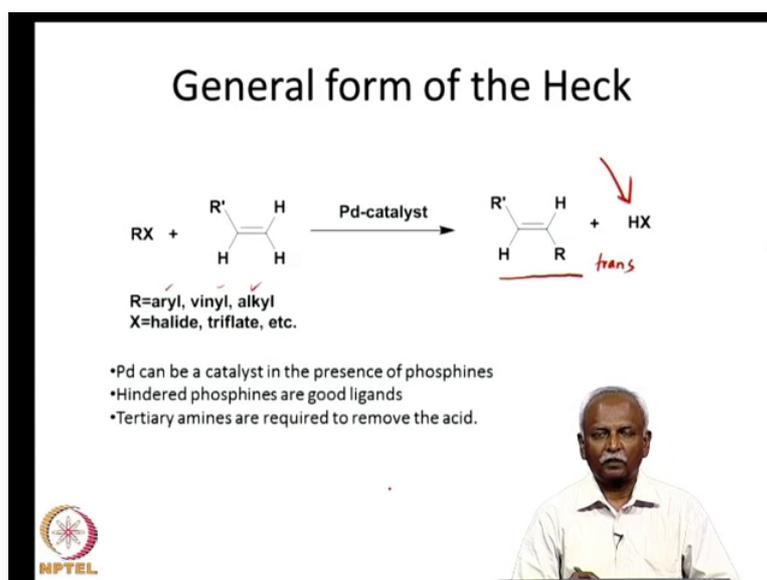
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But whatever it may be Heck's original contribution in this at this critical juncture was the fact that he converted this reaction to a catalytic reaction. This original reaction that I described to you was done in a stoichiometric fashion. Now, he found out that if you use palladium acetate and a phosphine in the presence of a base like triethylamine. You can in fact couple the vinyl bromide that we have here these two species can be coupled to give you... If you couple it on both ends of this triene. This is a triene. And if you couple it with both ends you will get this molecule.

So, you can couple both ends of this triene to get this rather complex pentane. But notice that I have deliberately written this reaction in such a way that this particular coupling has been done in a trans fashion. This carbon-carbon bond has been formed in a trans fashion, whereas this carbon-carbon bond has been formed in a cis fashion. So, it is possible using the Heck reaction to form both trans and cis couplings. This is in fact a disadvantage very often you would get mostly the trans compound, that is the thermodynamically more stable compound and that is what you would isolate in the reaction mixture. But at the same time this is a disadvantage for the reaction.

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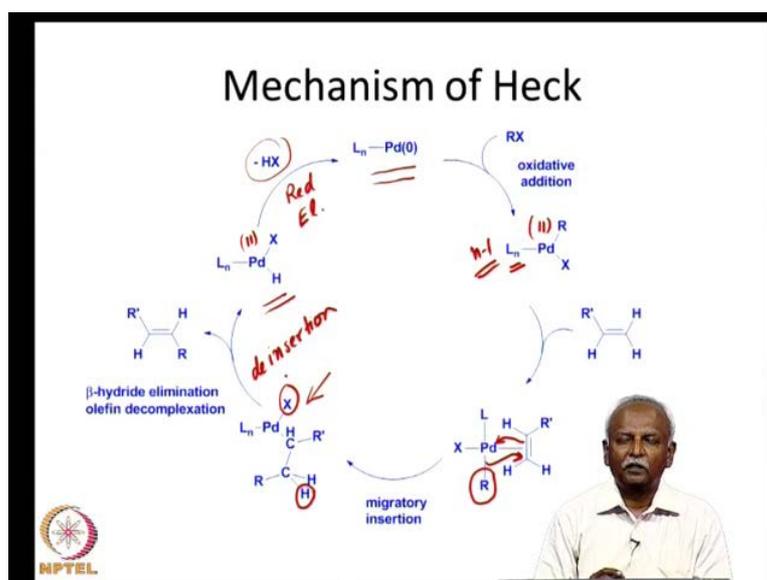


So, in the general form if you write out all the substrates that are capable of undergoing the Heck reaction here are the compounds that have been used you have RX and olefin and the R can be either aryl vinyl: or an alkyl component. So, all of them are capable of forming the palladium alkyl species or palladium aryl vinyl species.

These add onto the olefin in such a way that you form a substituted olefin. Notice here that the substituted olefin I have written it in the trans form in this case also, but other products should also be written. Now it turns out that because eliminating a molecule of the H X you should have another atom or another hydrogen atom present on this olefin. Only then you would end up with the Heck reaction.

So, the x group itself can be a halide or a triflate. It only has to be a good leaving group, which can add onto the palladium to form the organo palladium species that we talked about. So, palladium can then be made into a catalytic this reaction can be made into a catalytic reaction in the presence of phosphine. That was again found out that if you have hindered phosphine then they are good ligands in the turnout to carry out reaction more efficiently. Similarly, if you have tertiary amines they are the best in order to remove this acid that is found acid that is found can be removed readily and efficiently if you have a tertiary amine.

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So, let us take a look at the mechanistic aspects of this reaction now. This is the familiar catalytic cycle that is written for the Heck reaction. Initially, you have the palladium 0 species, which in the reactive form would react with an alkyl halide or a vinyl halide or an aryl halide and undergo oxidative addition. The number of ligands that we have specified here can go from  $n$  to  $n$  minus 1 during this process. It can also remain the same or it could lose more ligands.

And as the reaction proceeds so here I have carried out oxidative addition. This oxidative addition gives you now palladium two species. This palladium two species coordinates to an olefin and you end up with a vinyl species or an alkyl species, which is adjacent to an olefin. So, this can now carry out an insertion reaction and in such a way that you end up with an alkyl organopalladium complex which is pictured here. Such that you this insertion reaction gives you the two  $R$  groups attached to this vinyl group that the olefin that we started out with.

You should have this hydrogen in the carbon, which is away from the olefin carbon, which takes on the  $R$  dashed. So, now you have, you have two hydrogens on the olefin and one of them can be eliminated. It is in general the hydrogen which is and, which is in the beta position next to the palladium. So, now if you eliminate  $H$  and  $X$  the two atoms, which are rounded off. So, you could end up with a palladium  $HX$  species, which would rapidly eliminate palladium.

This is also palladium two you have only carried out a migratory insertion and the de-insertion. So, this is the de-insertion step in which the olefin, which was initially added on had one R group and the olefin that is de-inserted has got two R groups. And you have only added and subtracted a ((Refer Time: 15:01)) you added a vinyl group or an alkyl group and you have subtracted the HX group. So, that you end up with a palladium two species and this palladium two species loses HX reductive elimination. This is a reductive elimination step and that gives you back palladium 0.

So, the cycle is completed and you end up with palladium 0 compound. This is stabilised again with ligands such as triphenyl phosphine tri alkyl phosphines. Now this whole catalytic cycle is efficiently carried out only by palladium. That is a uniqueness of palladium no other metal has been able to supplement palladium in this whole process.

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### Limits to the reaction

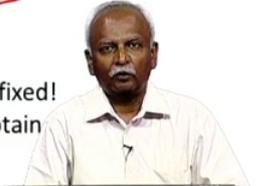
- X should be a good leaving group
- Alkene should have one hydrogen!
- Should not be overcrowded

$$\text{RX} + \begin{array}{c} \text{R}' \quad \text{H} \\ \diagdown \quad / \\ \text{C} = \text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{H} \end{array} \xrightarrow{\text{Pd-catalyst}} \begin{array}{c} \text{R}' \quad \text{H} \\ \diagdown \quad / \\ \text{C} = \text{C} \\ / \quad \diagdown \\ \text{H} \quad \text{R} \end{array} + \text{HX}$$

R=aryl, vinyl, alkyl  
X=halide, triflate, etc.

trans

- Stereochemistry of the product is not fixed!  
Both *cis* and *trans* products can be obtain

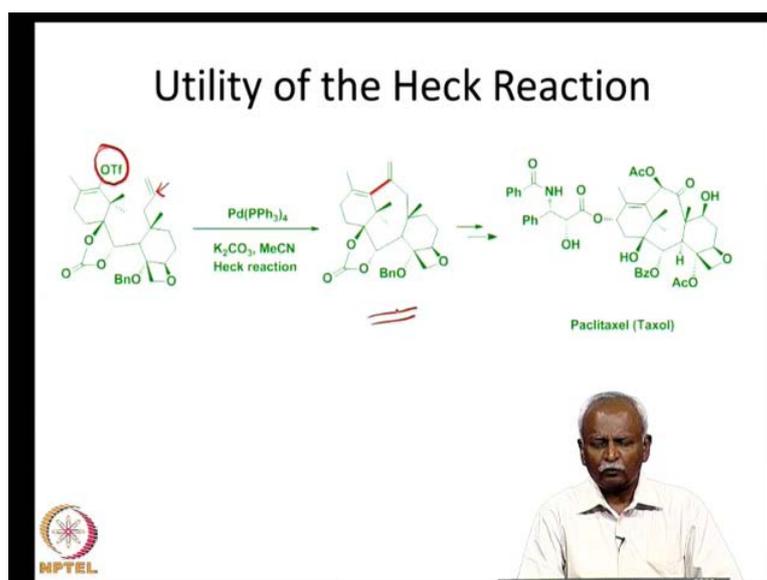



There are limits to this reaction. X has to be a good leaving group which is obvious because if you want to have a oxidative addition then the rate would become the first step would become extremely rate limiting effects is not a good leaving group. The alkene as I mention because you eliminate HX it should have a hydrogen. And the olefin that you originally carry out the Heck reaction with should be reasonably sterically free.

If it is overcrowded with say, three alkyl groups on the olefin then the reaction becomes extremely sluggish in fact you may not get a Heck reaction at all if you have all three positions on the alkene which are substituted by alkyl groups or vinyl groups. So, you need a minimum of one-hydrogen that is technically true, but no hydrogen is on the olefin the better it is.

Now you have the limits to reaction to find. You also have one very important limit and that's the fact that the stereochemistry of the final product is not fixed. And you can have both cis and trans products, which are only the trans product, is given here because that is very often the major product which is found. That is why this reaction is still a useful action you can have a carbon-carbon coupling very efficient carbon coupling which is useful.

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So, here I have for you the taxol synthesis, which utilises the Heck reaction, and you will notice that the carbon-carbon bond, which is formed, indicated in red. And the leaving group is that triflate and that is what I am circling in, circling in the original molecule. The and the height and the place where it is adding on is the vinyl position between adding it onto his right here. And that gives you because of the ring size it gives the single product and becomes the key step in the taxol synthesis. In one of the synthesis that utilises the heck reaction.

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**Negishi C-C coupling Matrix 1970-1980**

	R-CH <sub>2</sub> -X	R-CH=CH-CH <sub>2</sub> X	RCH=CHX	ArX	R-C≡C-X
R-CH <sub>2</sub> -M-Y	■	■	■	■	■
R-CH=CH-CH <sub>2</sub> -M-Y	■	■	■	■	■
RCH=CH-M-Y	■	■	■	■	■
Ar-M-Y	■	■	■	■	■
R-C≡C-M-Y	■	■	■	■	■

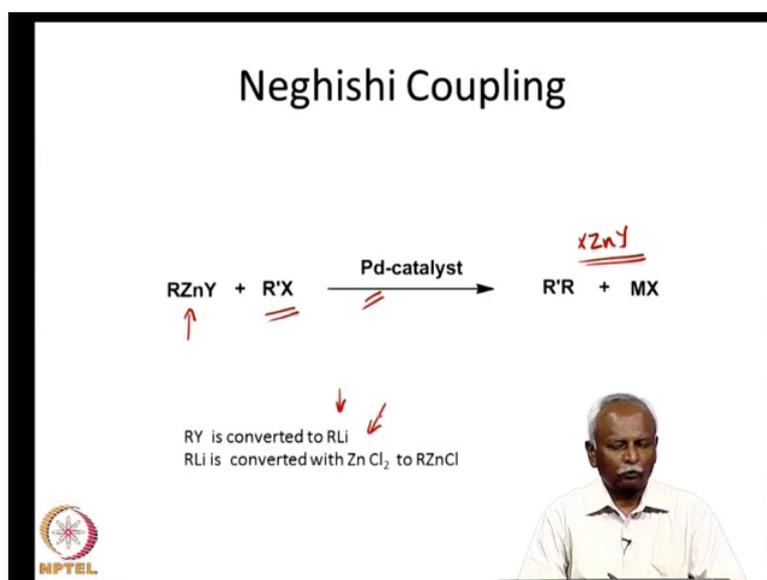
↑

 Zn, B, Mg, Al, Zr, Si, Sn, and perhaps Cu

So, you can see that the Heck reaction has been a useful reaction and that this time around the late nineteen sixties the Negishi started investigating the coupling matrix which we talked about earlier. His investigation was a fairly systematic investigation. And he found that if you combine two different metals palladium as a catalyst and a stoichiometric amount of a couple of molecule, which is indicated in this column.

If you have a stoichiometric amount of this metal alkyl and palladium as a catalyst is you can carry out a variety of reactions very easily. In fact in his early, in the early stages he had investigated quite a few of the metals, but then he found that zinc was a unique metal. And the zinc was unique and it was good because the zinc have the capability of the capacity to do reaction stereo specifically. He claims that is a key factor, which makes the Negishi coupling in fact one of the best couplings that is known the literature.

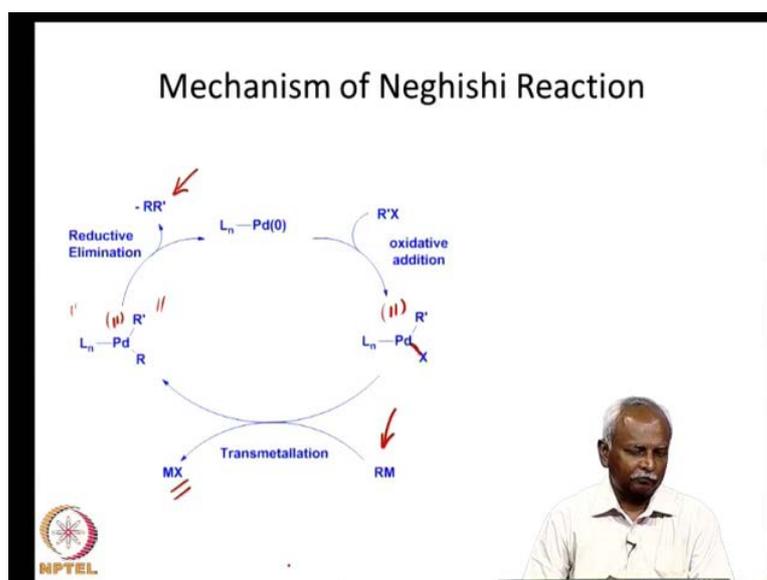
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So, the Negishi coupling which most, which is mostly developed and popularised by Negishi involves a zinc alkyl zinc organozinc compound. Which is reacted with an organohalide and this leads to a coupling reaction where X and Y is eliminated. So, X Z and Y is eliminated in this process and you have palladium only in catalytic amounts.

But we should note at this point that the organo zinc species could utilise is very often synthesised through organo lithium species. So, first you have to make a reactive lithium species and then the are alike is converted or is it is transferred to the zinc using zinc chloride to RZ and C. This is in fact the most efficient way of carrying out the Negishi coupling.

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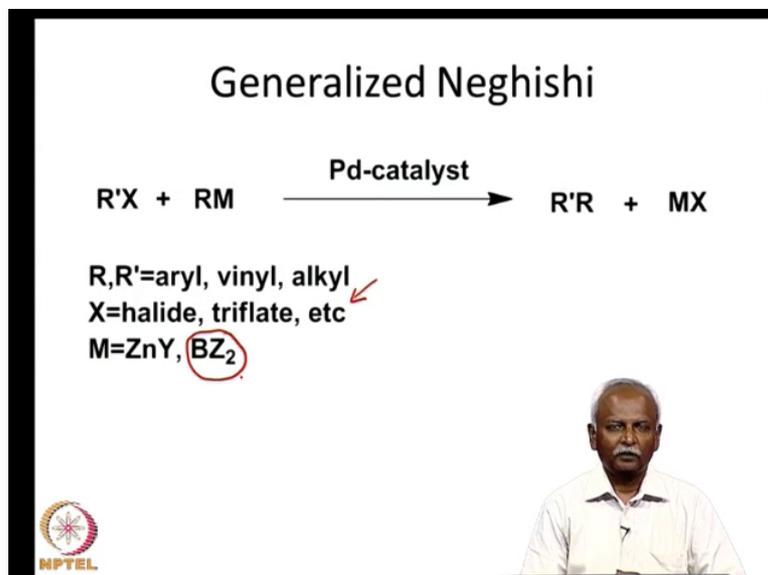
So, let us take a look at the mechanism of the Negishi coupling now. And let us look at the differences between the Negishi coupling and the Heck coupling. The first step is identical what you are doing is carrying out oxidative addition between an R dash X to palladium so that you get a palladium two species. So, this is a oxidative addition. And then you have a palladium X bond. This the palladium X bond which I am marking for you in bold and red colour. And this palladium X bond can be converted into palladium R bond where the R is coming from zinc.

So, if I have a zinc coordinated zinc alkyl or an aryl this aryl can be transferred to the palladium and MX can be eliminated. So, you eliminate MX and generate, now you generate diorgano palladium complex. And this diorgano palladium species is capable of undergoing reductive elimination. So, that you end up with the palladium 0 species and coupled product. Notice that you do not form you do not have a migratory insertion reaction there insertion reaction was one which was a key step in the Heck reaction.

Here you carry out a trans metalation reaction, which involves conversion of palladium X bond to palladium R bond. And so, the nature of the metal, which is indicated by RM, is crucial in how this whole reaction proceeds. And Negishi popularised the zinc version of this reaction and later on we will see that Suzuki who

popularised the boron, where M is boron variety of the reaction is also a useful alternative.

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So, the generalised Neghishi reaction in fact involves a whole range of a aryl vinyl or alkyl groups in either RX or RM. So, it is extremely versatile reaction and the X group you can use the transmit the oxidative addition can be halide or triflateas I mentioned earlier that step is in fact common to both Heck reaction and the Neghishi reaction and the Suzuki reactions well. So, you just need a very good leaving group on the X group.

Now you need to do a trans metallation and the trans metallation can be done with a zinc Z and Y. That what is given here is a generalised the generalised initial reaction. Later on we will see that the Z2 or boron with two electronic groups is what was developed by Suzuki. To give credit Neghishi was the first one who reported the Boron reaction also he had tested the boron, but it was popularised and made more useful by Suzuki were by numerous examples that he demonstrated later on.

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**A genealogy of Pd-catalyzed cross-coupling**  
Ei-ichi Negishi \*

- Journal of Organometallic Chemistry 653 (2002) 34/40

This paper describes a very brief history leading to the birth of the Pd-catalyzed cross-coupling, its birth in the mid-1970s,

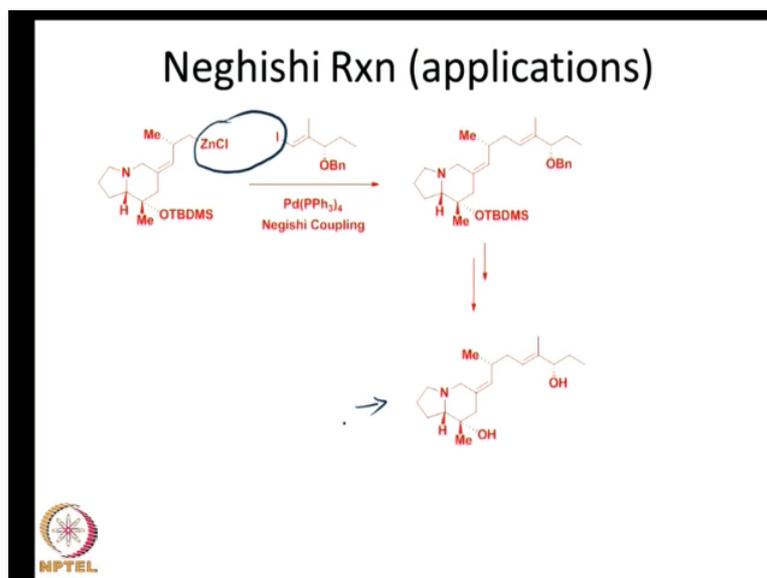
- (a) the development of the Pd-catalyzed cross-coupling with organometals containing Zn, Al, Zr, and Mg (the 'first-generation' Pd-catalyzed cross-coupling) in the 1970s,
- (b) seeding of the Pd-catalyzed cross-coupling with organometals containing Sn, B, and Si (the 'second-generation' Pd-catalyzed cross-coupling) in the late-1970s, and <sup>“Zn”</sup>
- (c) further developments in the Negishi's group in the 1980s.



So, it is interesting that the Negishi is in fact written a historical introduction to this palladium catalysed cross coupling reaction. And the... In this paper, which was published in journal of organometallic chemistry. He describes the development of the palladium catalysed cross coupling reactions. He notes that zinc aluminium and zirconium and magnesium also were used extensively in nineteen seventies.

It was a later on it was tin boron and silicon were in fact taking second place in the carbon-carbon coupling reactions and it was Negishi's group which popularised in the nineteen eighties most catalysed varieties which now holds one of the key ranks in the carbon-carbon coupling process.

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So, let us take a look at one of the applications of the Negishi reaction here you have this coupling between these two units that is. So, you can see that Zn Cl can be eliminated and you can have this key coupling reaction, which leads this natural product, which is shown here. So this is only possible because you can have a very clear stereo specific reaction between these two fragments, and it can be accomplished within each coupling very efficiently by simple palladium catalysts.

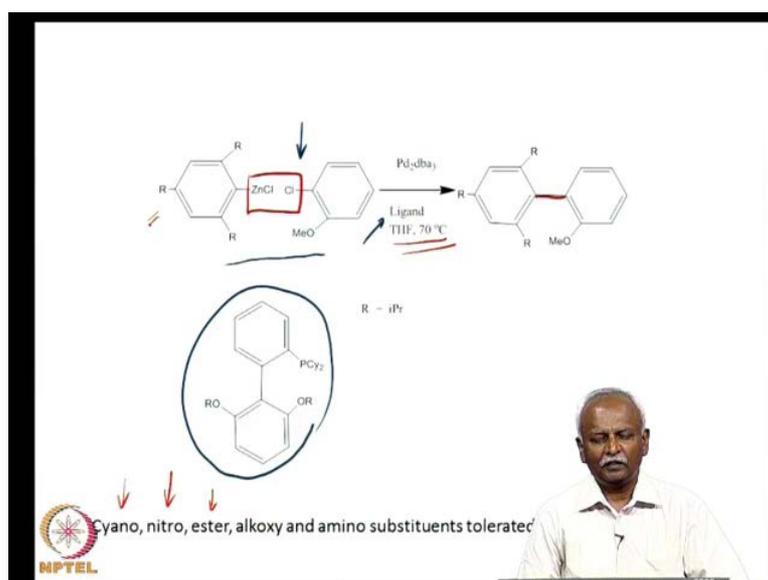
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### Low catalyst loading & Hindered substrates

An Extremely Active Catalyst for the Negishi Cross-Coupling Reaction  
Jacqueline E. Milne and Stephen L. Buchwald\*  
J. AM. CHEM. SOC. 2004, 126, 13028-13032

So, what is interesting is that many times you need an extremely active catalyst for the Negishi coupling cross coupling reaction. And many people have come forward to design new catalyst for the Negishi cross coupling. Because if you have an alkyl halide like alkyl chloride then the oxidative addition becomes more difficult and you need an active catalyst. And it is being shown the people like Buchwald in this paper which is shown right here.

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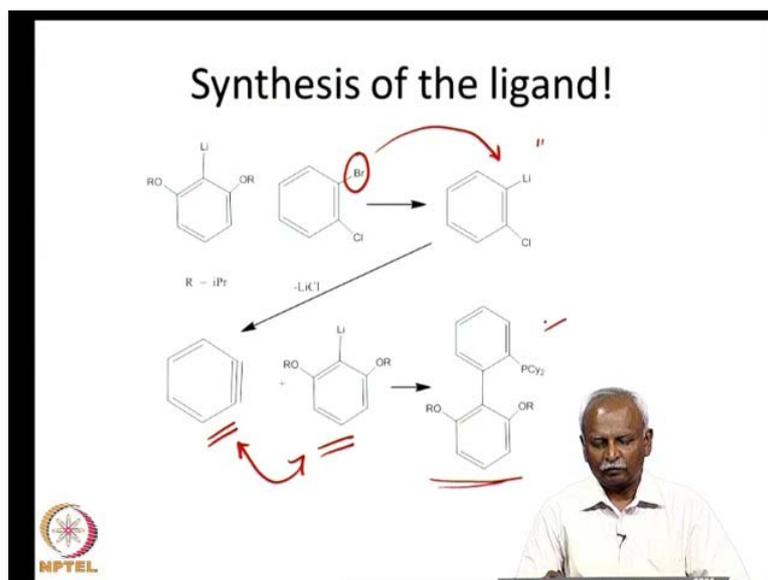


That you can have efficient coupling with hindered phosphine. The phosphine that he has developed recently is pictured here. This is the ligand and which will, which will enable which is, which will add to palladium 0. Palladium 0 itself in this particular instance is introduced conveniently in the form of dibenzylidene acetone complex. Dibenzylidene as stone complexes palladium and keeps it palladium 0 and this is a convenient way to store palladium 0 and added to the reaction mixture.

So, the ligand used is highly hindered and they have shown that you can even activate aryl chlorides, which are reasonably unreactive under normal Heck or the Negishi reaction conditions. Here you can see two very hindered molecules, which are coming together and forming a new bond, which we will highlight for you here. This is the new bond formed and you have eliminated zinc chloride from this reaction mixture efficiently at reasonably mild temperatures.

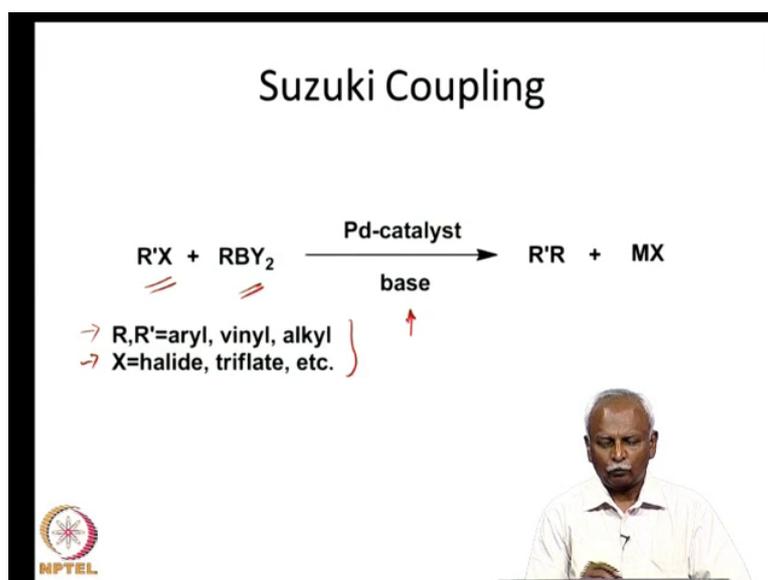
This can be, this can be made possible only because you have this very hindered ligand. And in this reaction a variety of very different functional groups are tolerated. So, you can have a variety of groups which are present in the aryl moieties and ester alkoxy or even an amino substituents stop tolerated the in this whole process. So this makes it a very extremely versatile useful coupling process.

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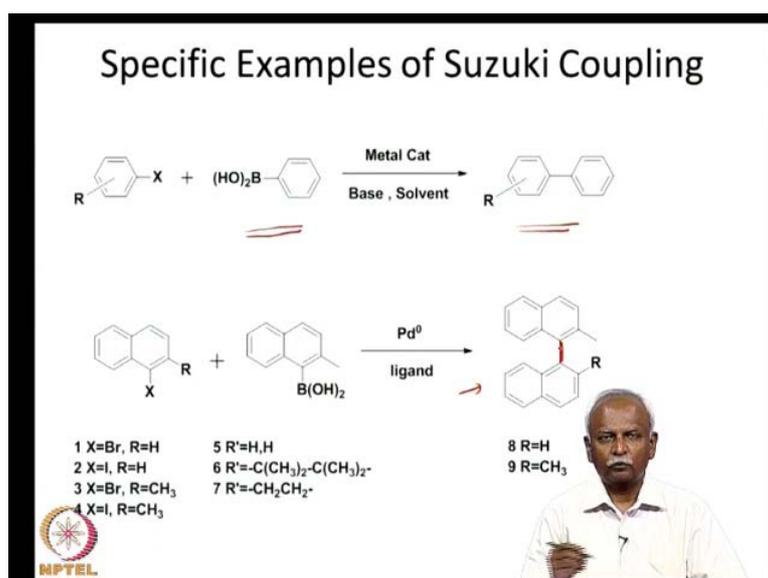
It is interesting to see the ligand synthesis in this particular instance it goes through organolithium molecule. And the worked transpires is that the lithium molecule initially forms benzyne and that intermediaries is through replacement of this bromine with a lithium. And as exchange of B R and L I and it is the same molecule with adds onto the benzyne which then gives you this coupled product. So this addition would lead to addition of these two molecules would give you phosphine, which is extremely useful.

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So, let us take a look at the Suzuki coupling now. The Suzuki coupling as I mentioned earlier is a coupling between an alkyl halide and the boron compound. Alkyl halide or oxidative as to the palladium and the boron is a trans metalation agent. And the scope of reaction is given here once again you need a good leaving group and that remains constant at consistently that remains an essential component of this reaction and you need you can have alkyl vinyl or aryl species.

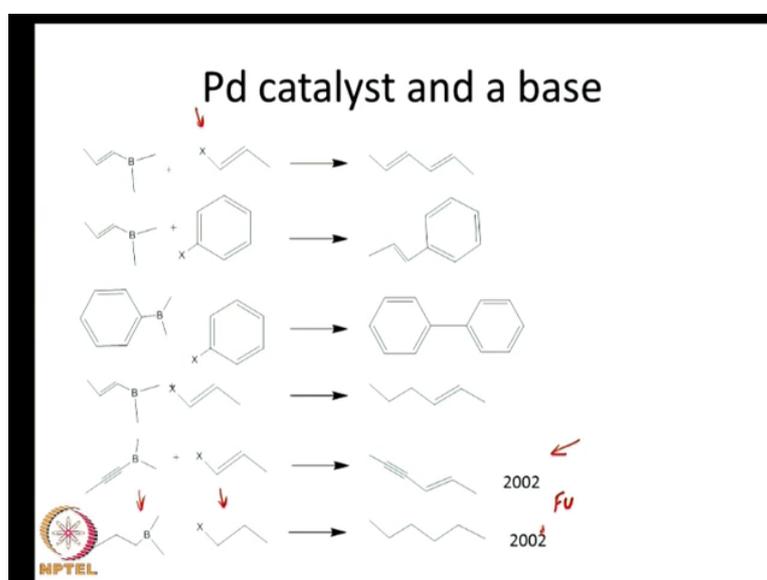
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That the requirement for a base in this reaction, which I have been shown here, is also a key factor in this reaction. You need a base small to carry out the action. Now a variety of examples are given in this transparency once again have given you the coupling of two hindered arene molecules, which can be carried out by arene O.

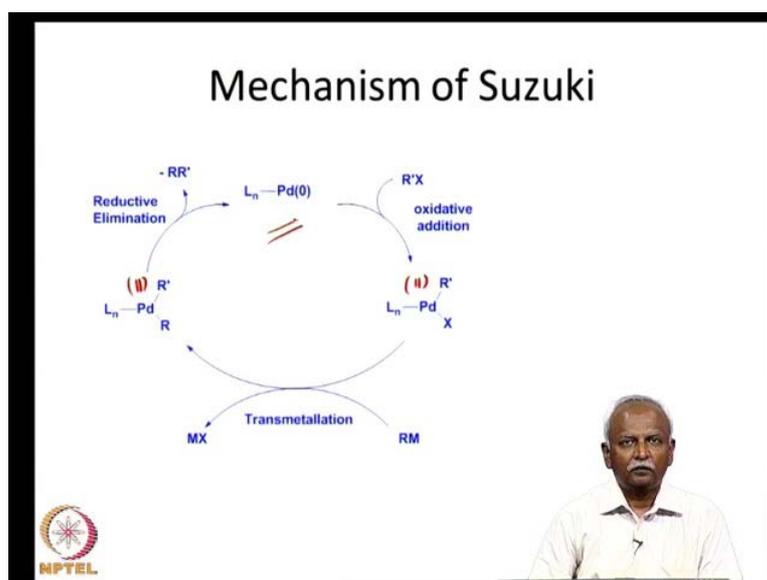
The simple boronic acid, which can be coupled this is, this is an example which would couple two different aryls to give you an arly. And this reaction so efficient that it can couple naftali group also. If you have these molecules are axially chiral around this bond and that is how we can make chiral compounds if you have a chiral ligand.

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So, let us take a look at the palladium catalyst and the link, let us take a look at a variety of Suzuki reactions which are, which are possible. And in the presence of the palladium catalyst and the base you can combine this whole set of molecules which are listed on my left. Two different molecules either allylvinyl or an aryl can be combined with a variety of boron containing compounds. Now, towards thousand and so it was possible to combine even alkenyl species with a vinyl species. And in 2005 it was possible to carry out the combination of alkyl boron with an alkyl halides. This is carried out by a Fu this was done in 2005.

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So, let us take a look at the mechanism of the Suzuki reaction now. Suzuki reaction is also very similar to the Negishi reaction. So, the Suzuki and Negishi fall into the same category of reactions, where you have an oxidative addition to give you the palladium 2 species, which undergoes trans metalation.

The trans metalation step is one where you either use a zinc species in the case of Negishi and in the case of Suzuki you use a boron containing compound. The palladium 2 species di organic palladium containing compound where the two carbon palladium bonds. This undergoes reductive elimination in order to give you palladium 0 species.

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## Suzuki Coupling

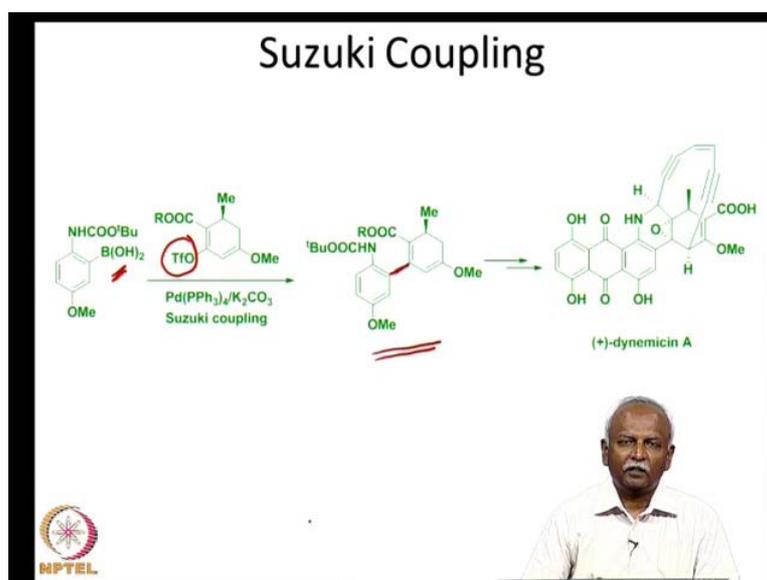
- Aryl - Aryl bond formation.
- Pd(II) or Pd(0) catalyst precursor, Phosphine ligand, Pd(0) actual catalyst.
- Aryl iodides, and bromides work, chlorides are unsuitable
- Chlorides can be used if ancillary ligand is very electron donating.



It turns out that the variety of Suzuki couplings that can be carried out are fairly large and so you can form mostly aryl bonds that would be used for significantly. You can use a palladium(II) precursor or it can use a palladium(0) precursor. The precursor is a very often reduced in situ ((Refer Time: 33:16)) if it is a palladium(II) so, the active form of the catalyst is still palladium(0), but you can use a phosphine which can reduce to palladium(0).

Now, you can use bromides iodides and iodides are very good for oxidative addition, but you can also use chlorides under some conditions, but under normal conditions of Suzuki coupling chlorides are extremely reluctant and they do not work they are not suitable. If the ancillary ligand that you use the L group is extremely electron donating then you can force Suzuki coupling to work and that has been carried out also by people like Fu and Stephen Buchwald.

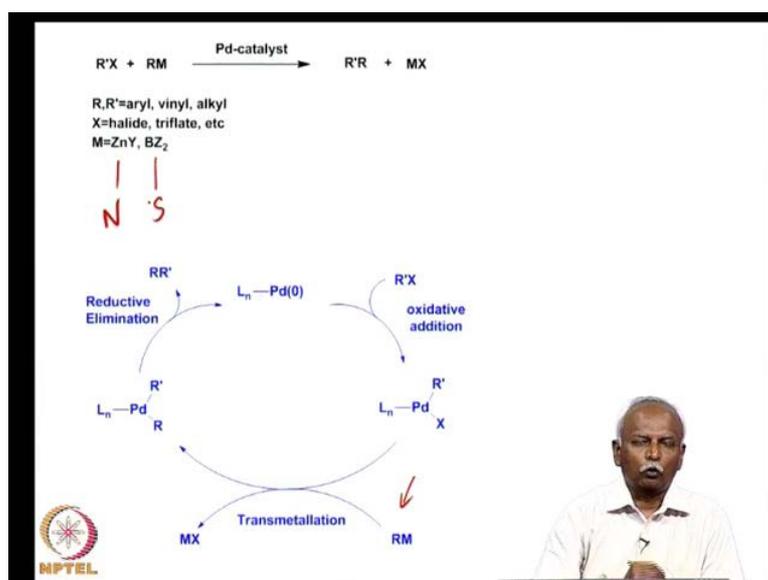
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Now here is a key reaction and there in the synthesis of a drug molecule dymenicin and this again has been carried out by a Suzuki coupling that has been, that has been done. And this case I am going to mark it for you again in a different colour so that you can see the bond that has been formed.

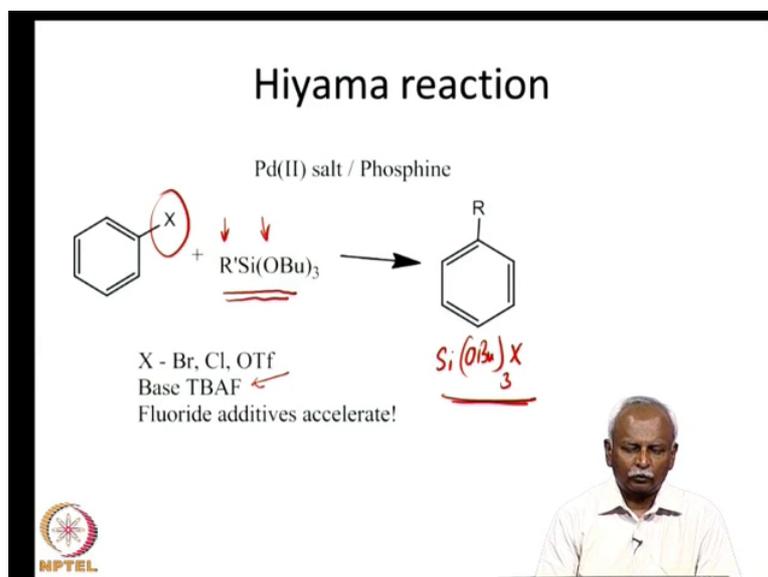
Here is a boron containing compound and here is a triflate that was eliminated from using palladium to give you an oxidative added intermediate. And that couples with the arene to give the key intermediate which would then be converted into dynamic. So all three coupling reactions the Heck reaction the Negishi reaction and the Suzuki coupling reaction have been used for the synthesis as key steps in the synthesis over variety of organic drug molecules. So they have become extremely popular.

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And there are in fact similarities between the between three, but as I mentioned to you between the Negishi and the Suzuki there is very little difference. It is only the trans metallation reagent that becomes a different when you go from Negishi to Suzuki. For Negishi you use zinc for Suzuki you use the bore.

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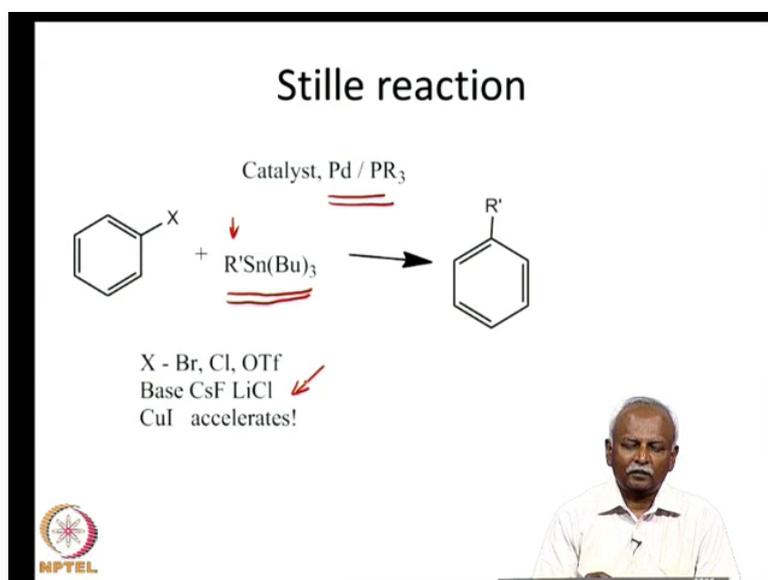
So as I was telling you in interaction it is possible to you do the trans metallation with a wide range of substrates. So after forming the palladium 2 oxidatively added product that product can trans metallate it because it has a P X bond and the trans

metallation can be done with any electro positive element. And so it is just depends on what is available and here is variant of this two coupling reactions that talked about. This is called the Hiyama reaction where you have a silicon substrate, which does the trans metallation.

Notice here that silicon has got three electro negative groups of these are not the ones, which are transferred to the palladium it is only the R group, which is less electro negative that is one which is trans metallated to the palladium and the excluded from the palladium is transferred to the silicon. So what would be eliminated is a Si OBU thrice. And X would come from the group which was present on the aryl molecule which oxidative he added palladium.

So here there is an interesting variation and that interesting variation is the fact that you can use that its ((Refer Time: 37.07)) ammonium chloride as an additive. And that seems to the increase of accelerate the reaction PD X can also be used as the base for removing the compound that this formed.

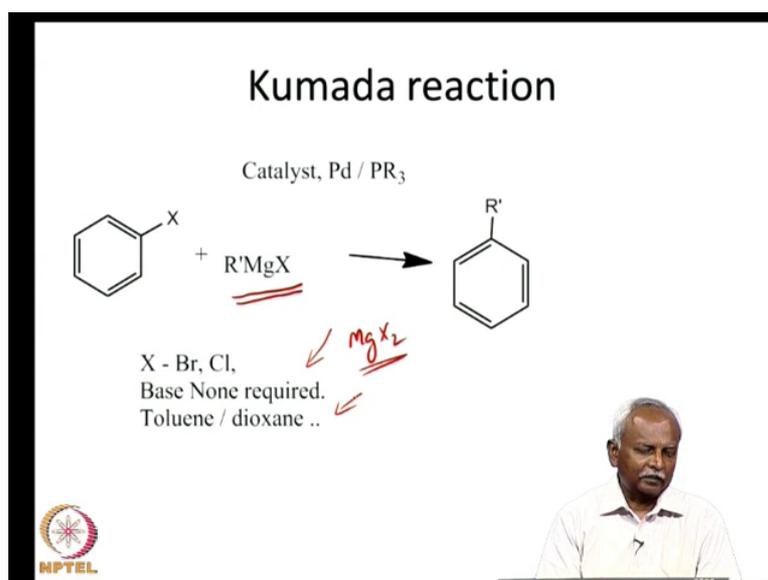
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So, there is a, there is another variant which is stille reaction this stille reaction has also been an extremely popular variant of this type of reaction. And again palladium and phosphine are essential and it adds on to the vinyl or aryl, halyid. And here you end up adding active compound, which will transfer this R dash group onto the palladium. And once again you see that this reaction is a small variation.

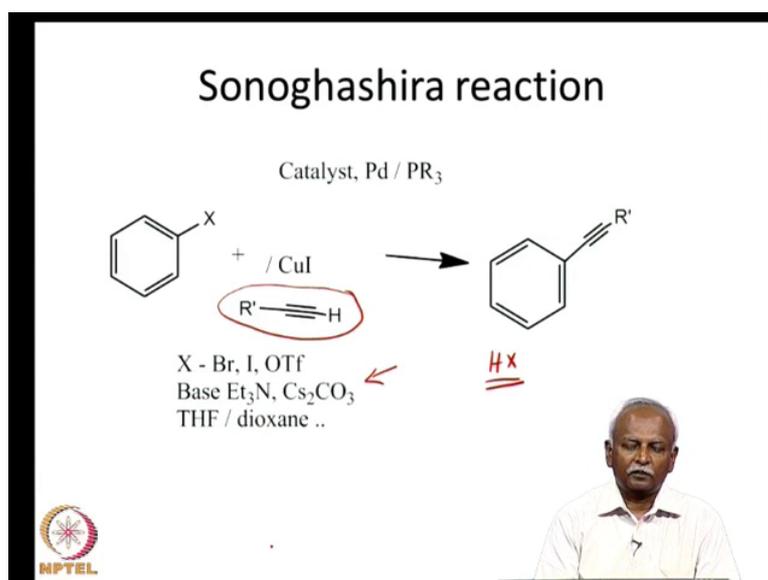
You can accelerate this reaction using copper iodide. The base that can be used a simple metal salts which will promote the removal of the tin from the reaction medium. So, the reaction proceeds in the forward direction. So, the stille reaction was also developed around the same time, but still the Suzuki became a lot more popular because of its extensive use, extensive tolerance of a various functional groups and its efficiency.

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Here is one more example which is using a Grignard reagent the Grignard reagent is a, is RMg any RMgX. The only advantage of this reaction is that there is no base that is required in this whole process. MgX<sub>2</sub> is removed in this reaction and you can do the reaction completely in the absence of the base. If you have a base sensitive reagent then this would be a suitable way of carrying out this coupling reaction. The reaction is usually carried out in toluene or dioxin.

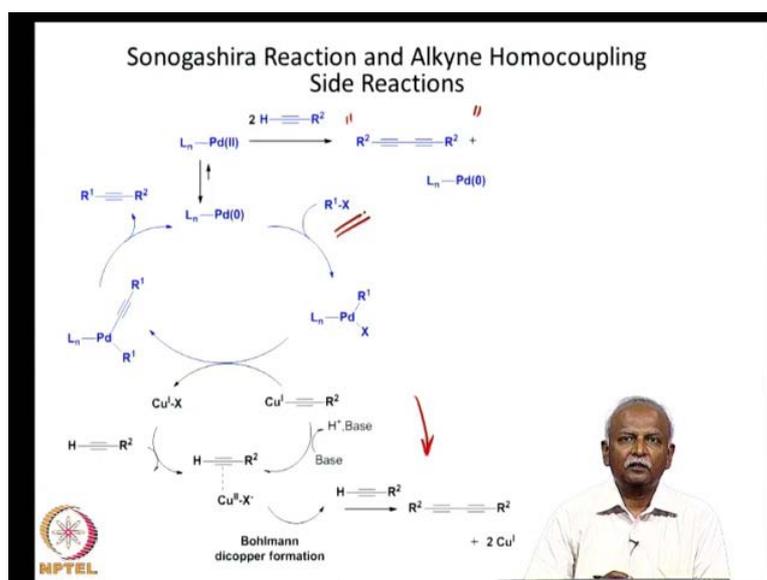
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Another variant, which is extremely popular, is the Sonogashira reaction. The Sonogashira reaction varies in the fact that you can now use an alkenyl substrate. And the alkenyl substrate just adds on exactly in the same fashion you removed an HX so you need a base.

You removed a HX so you need a base and the base is very often a triethylamine or a trialkylamine or an inorganic solid base like caesium carbonate. And this leads to the formation of the coupled product and extremely high yields and this is once again a good substitute for this for the type of reactions we have been for Negishi and this Stille reaction that we have talked about.

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And the Sonogashira reaction suffers from one drawback that is a fact that in it there are situations where you can have a homocoupling of two, of two of the alkenyl species can be homocoupling to give you the dialkenyl species which is pictured here. So this is a disadvantage and so one has to suppress that. Usually the addition of copper is to supposedly to transfer the alkenyl substrate directly onto the palladium. And so it leads to another complication which is the alkenyl species that is formed with copper can also do coupling reaction. And that gives you the dialkenyl species as well.

So, you can see that the Sonogashira coupling although it is quite popular can lead to some complications depending on how reactive organic organocopper species is present or organopalladium species is capable of doing the homo coupling reaction. But nevertheless it can be used for coupling and reactive RX with the alkaline. And with elevation of HX you would lead to new carbon-carbon bond between the alkaline species and the RX.

(Refer Slide Time: 41:43)

SC Activating Aryl Chlorides

- Trialkylphosphines (most electron donating)
- Sterically demanding ←
- Why??
  - Oxidative addition to M(0) centre is rd.
  - low coordination no. supported by large phosphines

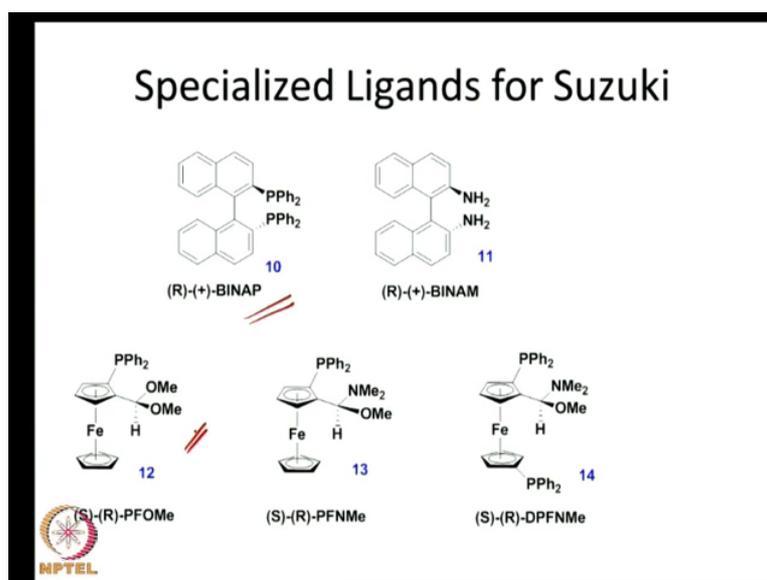
NPTEL

The slide features a video inset of a man in a white shirt speaking, positioned in the bottom right corner. The NPTEL logo is located in the bottom left corner of the slide frame.

So, I mentioned to you earlier that the Suzuki coupling is not efficient if you have an aryl chloride. And it is been possible to use very electron deficient, very deficient electron, very electron donating tri alkyl phosphine. When you are also sterically demanding which means if they are bulky tri alkylphosphine then they are very good and they can in fact activate aryl chlorides. This is a deficiency in the Suzuki coupling reaction that I mention, but it can be turned around and it would be possible to do this in the case of a phosphine, which are electron donating.

Now, the first step is a mention to you is an oxidative addition. So if the metal centre has got a great amount of electron density it would be possible to carry out the oxidative addition reaction. Usually the oxidative addition will become with determining if the halide or the chloride, if the halide is reluctant to carry out oxidative addition. And one should also remember that the presence of a sterically demanding phosphine leads to a low coordinated species on the palladium. And low coordinated species it is the advantage for carrying out a oxidative addition because oxidative addition usually requires a low coordination number on the palladium 0.

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So, that is how it is possible to have a very efficient Suzuki coupling reactions. It has been applied for Suzuki coupling specifically with chiral ligands and will with these ligands later on also later talk about chirality transfer. These are a variety of chiral ligands, which are very popular in the literature. And these ligands have been used for Suzuki coupling.

Here the ligands of the pictured although it's difficult to put them on the same transparency you can remember that binam which is actually a chiral molecule. And extremely popular for chirality transfer has got two phosphorus atoms and the ferrocene based molecules which have got a also named actually chiral have got a single phosphorus ligand on the ferrocene molecule.

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### Assymmetric Suzuki Coupling

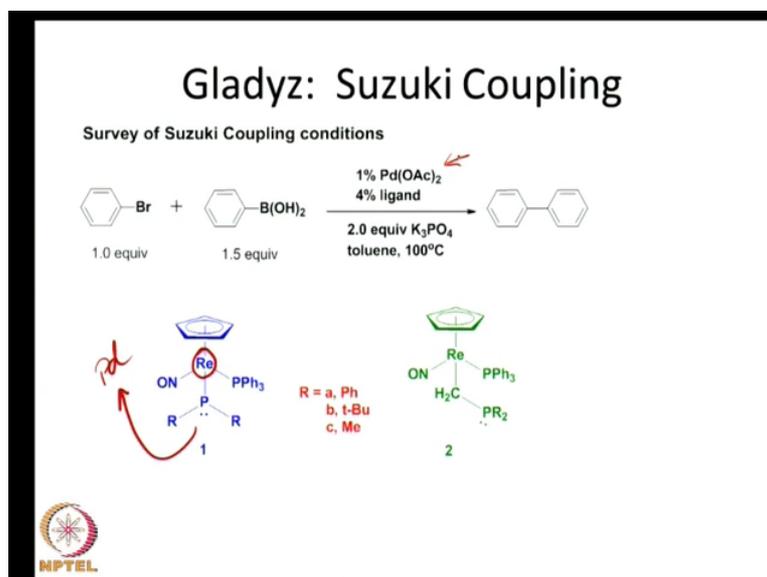
Assymmetric Suzuki coupling

Ligand	Product	Time/h	ee %
13	R-(-)-8	19	63 (44)
10	s-(+)-8	19	25 (55)
14	s-(+)-8	19	4 (73)
11	8	19	0 (9)
13	R-(-)-9	6 days	85 (50)
14	s-(+)-9	9 days	17 (13)



So, these two are extremely popular and it been shown to carry out a symmetric Suzuki coupling and this Suzuki coupling can be done with an asymmetric excess which are fairly large. So, the advantage as I mention to you is the fact that you can carry out these reactions with un activated aryl chlorides.

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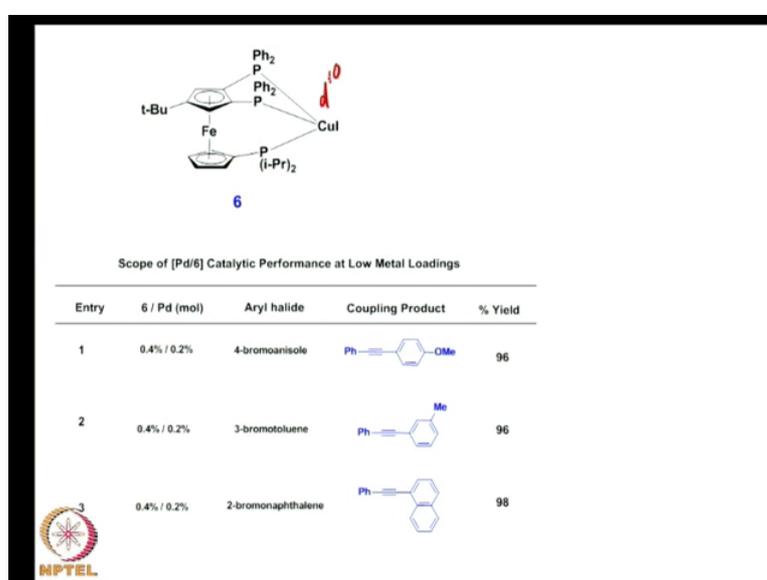


So, here is another example and that example comes from the group of Gladyz. And they have carried out very efficient Suzuki coupling reactions by aryl coupling reactions using the interesting concept. And that interesting concept is a fact that. If

you have a very electron donating group on the phosphorus and that phosphorus will be able to give electron density to the palladium very efficiently.

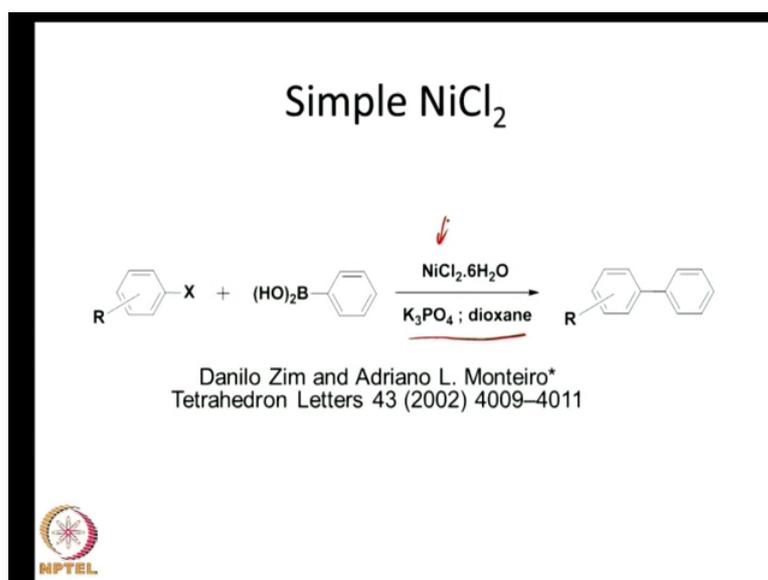
So, here is a phosphine which is attached to palladium and the palladium is a coordinative saturated and also electronically saturated centre. So, because of this you can transfer electron density to the phosphorus and the phosphorus in turn transfers electron density of the palladium. And makes this reaction very efficient with one more per cent of palladium and with four per cent four equivalent ligands with respect palladium you can now carry out the bi aryl coupling very efficiently.

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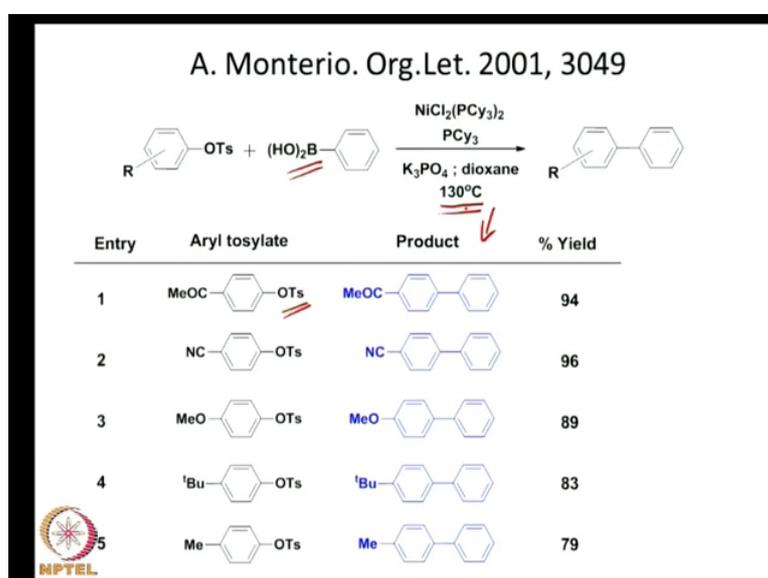
So, this scope the importance of these reactions is a fact that you can have blue metal loadings. And here is another example where the phosphorus is coordinated to a d ten system. So this is a d 10 system, which is a electron rich and this is attached to the phosphorus and that makes the coupling reaction very efficient and this can be done with blue metal loadings.

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So up to now we have talked about a variety of reactions that palladium has been used as the key reaction for carrying out coupling. Now and in recent years in two thousand and two it has been shown by a Monteiro that it is possible to carry out this reaction efficiently with nickel chloride where the only disadvantage is that this reaction has been done in the presence of an inorganic solid base and dioxane, but the advantage is a fact that you have simple nickel chloride as the starting material. And the price difference between the nickel and the palladium would be enormous. So it is possible to carry out these reactions very cheaply it is exactly the same reaction as a Suzuki reaction.

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coupling that we talked about only thing is now we are doing it with nickel, it is nickel which is a 3D transition element.

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**NiCl<sub>2</sub>·6H<sub>2</sub>O- catalyzed Suzuki cross-coupling of 4-bromoanisole with phenylboronic acid**

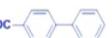
Entry	Ligand	Conversion (BrPh%)	Yield (PhPh%)	Time/h
1	1a	100	93	2
2	1b	100	97	0.5
3	1c	100	96	96
4	2a	100	90	24
5	2b	76	57	168
6	PPh <sub>3</sub>	100	95	1
7	P( <i>t</i> -Bu) <sub>3</sub>	100	97	0.5
8	No ligand	66	59	168



Now, let us take a look at these are reactions, which we can do as across coupling with a variety of areans the reaction, the yields are extremely good. As I mention the only disadvantage seems to be the fact that you have to, you have to carry out the reaction at a fairly high temperature.

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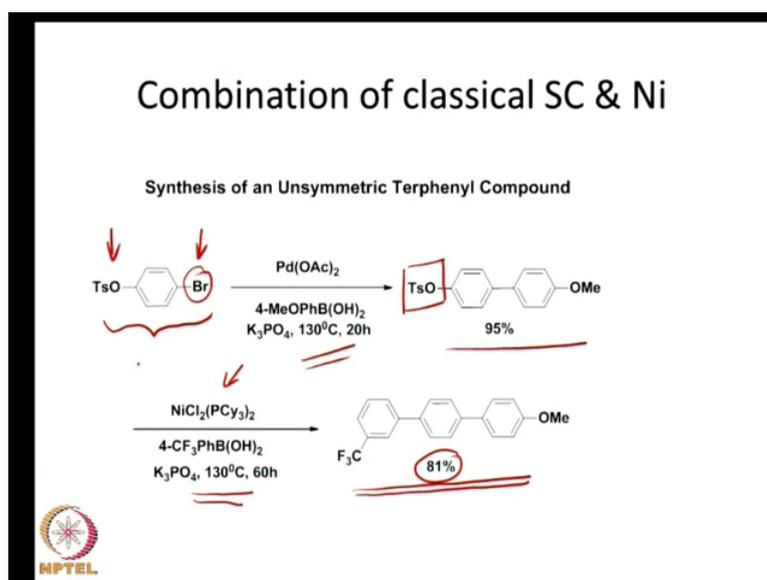
**Danilo Zim and Adriano L. Monteiro\***  
Tetrahedron Letters 43 (2002) 4009–4011

Entry	ArX	ArB(OH) <sub>2</sub>	Biaryl	% Yield
1				65
2				74
3				61
4				87 (85)
5				76 (72)
6				67 (61)



So, bi aryls are synthesised readily using nickel coupling.

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And one advantage is that you can couple it can now combine it with a classical Suzuki reaction. Because one reaction needs a higher temperature than the other one can be done with the tosylate the other one needs a bromide. So, here is a reaction where the substrate, which has got two leaving groups one is a bromide another is a tosylate. So with the palladium the bromide reacts very readily and you can have the coupling reaction between a boronic acid substituted methoxy substituted boronic acid and that gives you a single compound where the tosylate is unreactive. So, the tosylate here has been a unreactive.

You have a substrate, which is capable of undergoing reaction on either end. Only bromide is reacted with the palladium and with the nickel at slightly harsher conditions. You can see that the coupling can be carried out in the trans-position that is tosylate now leaves. And that gives you a three a tri aryl if you will and that is been done with an overall efficiency of nearly eighty one per cent so that is an excellent, transformation from this simple di-substituted arene to give you a tri aryl molecule.

(Refer Slide Time: 51:33)

### Ferrocene /Arene Phosphines.....

- Shih-Yuan Liyu, Michael J. Choi & G. C. Fu  
– MIT, USA.

R = H  
Me



So, many of these molecules have got phosphine attached to the ferrocene that again is probably because the ferrocene has got an eighteen electron. And iron centres that are electron rich and that in turn can pump in electron density onto the phosphorus, and that in turn can push it onto the palladium and making the palladium and making the palladium more reactive. ((Refer time 52:00))so, ferrocenearenephosphines I have mentioned you have been developed by Greg Fu.

(Refer Slide Time: 52:11)

### G. C. Fu et al. Chem. Comm. 2408, 2001

Suzuki reaction of an unactivated aryl chloride: triarylphosphines as ligands

Entry	Ligand	% Yield by GC after 24 h <sup>a</sup>
1	1	37
2	2	87
3	3	8
4	PPh <sub>3</sub>	<2

Average of two runs



And the this here is a chloride which usually unreactive under the reaction conditions with palladium. And you cannot carry out this reaction this carbon-carbon coupling reaction easily because you have to act with chloride, but because the ligand and that they are using is extremely electron rich with the ferrocene centre, you are able to carry out this reaction efficiently. And as much as eighty seven per cent yield has been achieved in this reaction.

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### To Summarize

- C-C coupling is a key reaction in organic synthesis
- Transition metals are essential in many cases
- Pd is the key element to carry out the key step.



So, let me now summarise what we have talked about today, what we talked about is the is that key reaction in organic synthesis. In many of the drug molecules you need to couple two different fragments, so that in a convergent fashion you can synthesize of fairly complex molecule. And during this process you either need to carry out carbon-carbon coupling a single bond coupling or double bond. And the transition metal turns out to be the key factor and so far there are very few reactions, which will not use a transition metal of key coupling reaction. And interestingly palladium turns out to be a the key element in many of these processes. So much so that the chemical engineering news article recently has the title. The most important element inorganic chemistry is palladium.