Metal Mediated Synthesis - I
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Lecture – 7
Kumada coupling reaction

Hello welcome back. So, Todays class will continue discussing on the Cross Coupling Reaction or so to speak the Carbon-Carbon Bond formation reactions. In the last class, we have seen the generalized mechanism for the Carbon-Carbon Bond formation reaction. The named reactions there are plenty of it, in these domain. So, to speak lithium and magnesium as a transmitter relating reagent would be called Kumada reaction. Boron as a starting material or Organo boron reagent, if it is used for these Carbon-Carbon Bond formation reactions. This that is usually called the Suzuki reaction. If it is tin that is Stile reaction. If it is silicon that is the Hiyama reaction or if it is you know as we said zinc, it is Nikiski reaction.

So, all these reactions are the one, which forms the basis for the difficult Carbon-Carbon Bond formation reaction that one would like to achieve. The generalized mechanism that we have discussed, we have incorporated Palladium 0 to 2 plus catalytic cycle. Now as we also discussed that, that mechanism is not going to be the case for everyone or every metal. Sometime its radical reactions most importantly sometimes when we do have the, you know nickel as a catalyst. Then we have radical reaction in place. We today, we will see the transmetallation reaction little bit.

How transmetallation reaction is occurring? We have discussed the oxidative addition as the first step, then, the transmetallation; then the reductive elimination for the process. Today, we will just briefly look at the Transmetallation process and then, start discussing mainly about the Kumada coupling in short. Let us look at the transmetallation process.

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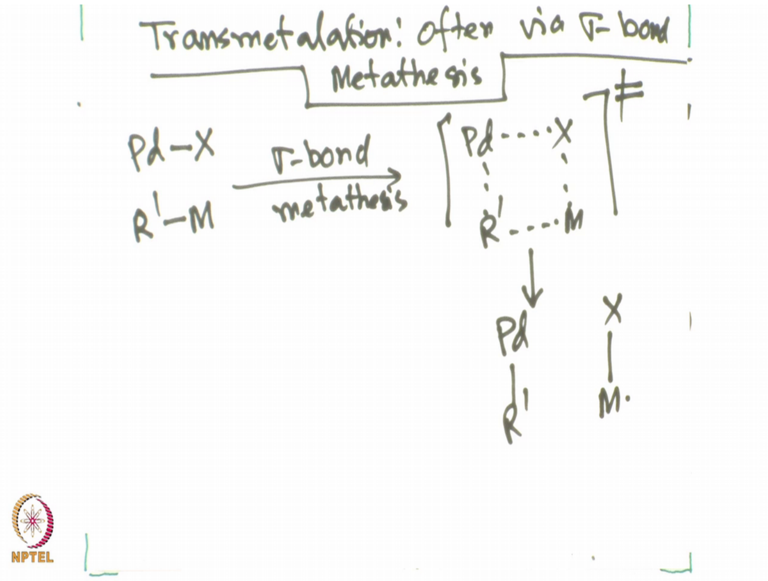

Transmetallation often, this is often happening via Sigma bond Metathesis, which is interesting; quite interesting.

I would say often via Sigma bond Metathesis. What you have here is Palladium X and the transmetalating reagent or R M right, R prime M for example. Sigma bond Metathesis usually will give rise to the Palladium metathesis; Palladium X and R prime. This is the 4 central mechanism or Sigma Bond Metathesis Mechanism. That would be involved in the transition state and we have Palladium R prime and exchange of partner XM.

Now substituent effects usually for example, oxidative addition if you are looking at oxidative addition substitutes and has a lot of importance in the process. Overall if you look at, if we have an electron rich substituent on oregano halide, we have a slower reaction. If we have a statically bulky substituent in the oregano halide reagent, then, also we have a very slow reaction.

On the other hand, if the living group is Iodole, that is more facile over brome than chloro and you know the reactivity pattern of the aryl halides are also quite interesting and their electronic properties would matter a lot during the processes.

Let us look at again, the properties of oregano halide that would be important for these Cross coupling reactions. Substituent effect for Ar X organ halide reagent. Well, more electron rich aryl will be having a slower reaction.

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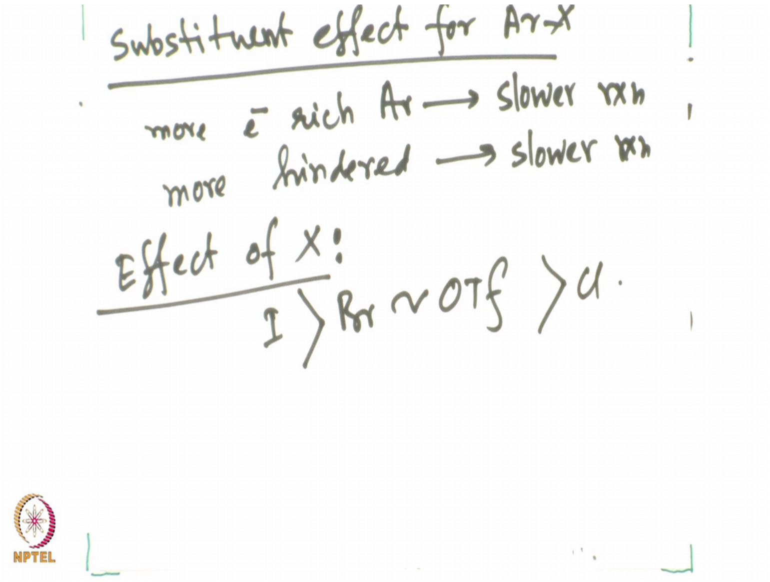

Substituent effect for Ar-X

more $\bar{e}$ rich Ar → slower rxn

more hindered → slower rxn

Effect of X:

I > Br ~ OTf > Cl.

The opposite, also to definitely true; electron deficient aryl halide will be giving faster reaction; more hindered the reaction is terichally it is challenged reactions or so then, we have a slower reaction and effect of X that is oregano halide. What type of oregano halide, halide you have; effect of X is usually iodize is more reactive than bromo, which is similar as OTf and then the chloro. So, this is an interesting reaction pattern and we would say the reactivity pattern can be a consistent or is consistent with the oxidative addition at the oregano halide reagent.

Let us try to look at each of these Carbon-Carbon Bond formation reaction in little bit more detail. We again, we will give try to give a overview and then, will discuss few of these things in more detail. Today, we will start discussing about the Kumuda coupling. Again, Kumada coupling is the one where organ lithium or oregano magnesium reagent is used for the Carbon-Carbon Bond formation reaction. Let us look at the Kumada coupling in little bit detail and then, some of the example we would like to discuss as well.

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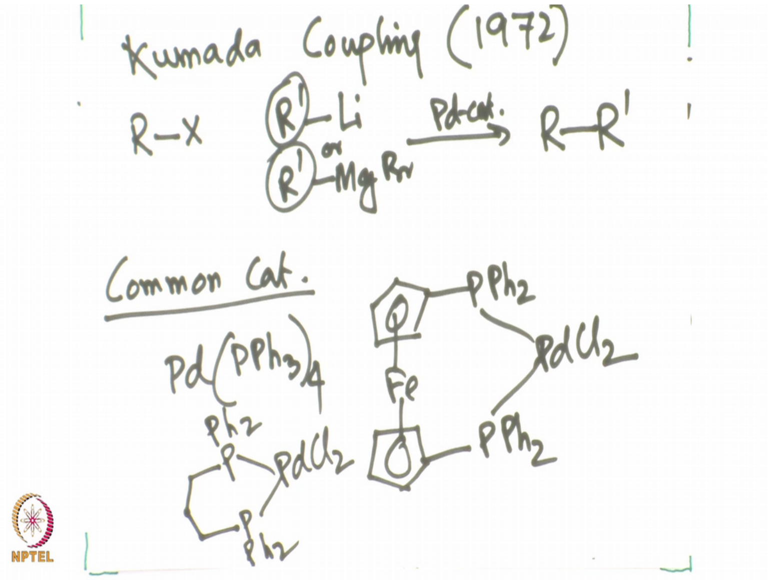

So, Kumada coupling, it is discovered in 1972; that is one of the Golden Era, I would say RX are lithium and or R Mg Br of course, or R Mg Br any of these. In presence of Palladium catalyst would give you R R prime. This is the R prime one of those R and R prime will become utilized. The common catalyst, that is used or the one which is usually known as Palladium tetrakis or Palladium tetrakis triphenyl phospene that is usually referred as Palladium tetrakis or we do have dp pf as the reagent as well or the Ligand for Palladium and we do have PPh 2 dp pf is PPh 2 reagent. This is the Ligand and Palladium chloride is used for this purpose.

Also, we can have dpp as the Ligand for the Palladium and we do have Palladium chloride this different Palladium chloride that can be used for these processes. Now for the Kumada coupling reactions or for any of these Carbon-Carbon Bond formation reaction, we know that usually although, we need a Palladium 0 as a catalyst, but we start with Palladium 2 that is quite interesting. So, what is usually thought or has been proven by now, that initial starting material although is Palladium 2; Palladium 2 is generating Palladium 0 very rapidly under the reaction condition. So, the real active species is Palladium 0 that is undergoing oxidative addition with aryl halide or oregano halide reagent.

But the starting material is let us say for example, Palladium chloride or Palladium acetate these are Palladium 2. So, there must be a very good mechanism by which the Palladium 2 reagents are forming these Palladium 0 reagent. But, what is wrong with Palladium 0, as a starting material ball; usually Palladium 0 itself cannot be very cannot you cannot buy it from the commercial stores except when you have a very good stabilizing ligand with the Palladium 0. For example, Palladium dba pd 2 dba 3 or Palladium dba or other Palladium 0 reagent, where you have ligand, a ligand associated with it by virtue of the ligand being very good donor; you know displacing that ligand with your desired ligand, that is usually phosphine ligand becomes challenging or it competes with the phosphine bindings.

So, therefore, you know extra ligand you usually donot want to have during your a Palladium catalysis that can hamper your real catalytic cycle. So, the idea usually that is found to be very general is you start with Palladium 2 under the reaction condition in C 2, it will form Palladium 0 rather rapidly, some cases when it is slow then there could be a problem. But otherwise, Palladium 2 to Palladium 0 formation happens in presence of often the starting material that you need to use for the Carbon-Carbon Bond formation reactions. We will discuss one of the method by which the Palladium 2 is converted to Palladium 0 in C 2. Therefore, Palladium 2 is used as the material for these Cross coupling reactions.

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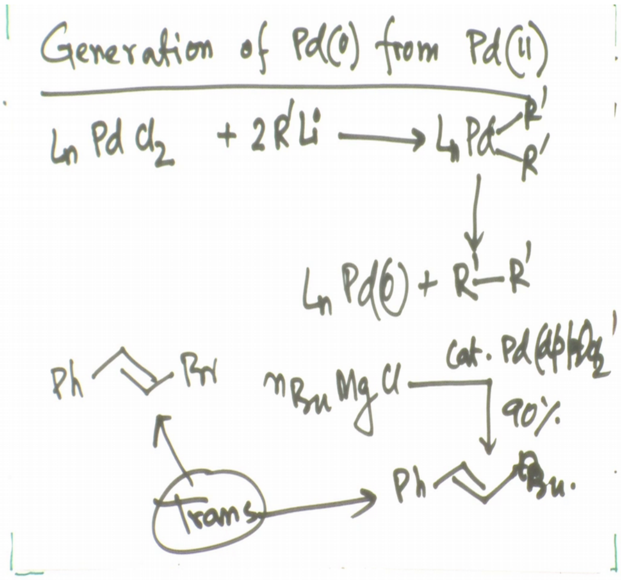

Generation of Palladium 0 from Palladium 2, of course, there exist several mechanism by which this happens. This is just one of the mechanisms a specific case Palladium chloride. Let us say we are using Palladium is in plus 2 oxidation state that is not of our interest; we are interested in Palladium 0. So, what happens if you are doing the Kumada coupling with oregano lithium reagent? If you are using let us say 5 percent palladium. So, nearly 10 percent oregano lithium reagent will be required. This is used, this is where we see that little bit excess of oregano lithium is used. Let us say 1.1 equivalent, that 0.1 equivalent will be utilized for Palladium 2 to Palladium 0 formation.

And often we have Palladium 2, R and R prime that is what is expected, you know from here. Let say the this you have R prime from here; you will get R prime and R prime, this is a side product when and it is forming in very less amount and in the process what you get Ln Palladium 0. That is the one, which you are interested in. So, what you have seen right now is Palladium 2 the starting material is converted to Palladium 0 in presence of sacrificial organo lithium reagent. Organolithium reagent in any way, you are going to use for your Kumada coupling reagent. Some part of those organo lithium reagent will be utilized for Palladium 0 formation. That is usually true for almost every Carbon-Carbon Bond formation reaction by utilizing the sort of Cross coupling reaction.

One of the reagent will be helping some time base, combination of base a little bit of oxygen or air or moisture; sometimes, other oregano, boron reagent and so on. In any way, one way or the other one need to form Palladium 2 to Palladium 0; because Palladium 0 is the one you are interested in that is the real active site, active species. You donot want Palladium 0 to be directly used from the market because Palladium 0 is stabilized with a ligand which is usually difficult to get rid of from the Palladium 0 site.

Now that is one of the method. Let us look at some of the example of these Kumada coupling reactions. One of the example that is easier for this, styrinyl bromide for example, in Butyl Magnesium Chloride. So, if you are using Catalytic amount of Palladium dp pf chloride you get 90 percent yield of the product which you might be interested in. In butyl in over here, this is trans geometry both in the starting material, both in the product; that is very interesting.

Both the starting material and the product will have the same geometry, that is one of the key factor one would look for the starting material and the product formation. If you have a transolefin, you know alkenyl halide if you are starting with, if it is having trans geometry, will you get trans or a mixture of cis and trans or cis? The answer for the Kumada coupling for example, it retains the geometry. So, if you start with trans you get the trans. Well, to demonstrate this point, if it one can utilize a mixture of cis and trans and selectively the one that is more reactive will be giving the product first; the other one which is less reactive can give the product next.

Let us look at one of those examples where we have 2 starting material; one is trans in trans geometry another one is in cis geometry and then you are reacting that with the in under the Kumada coupling condition and then, what is the product formation during these processes?

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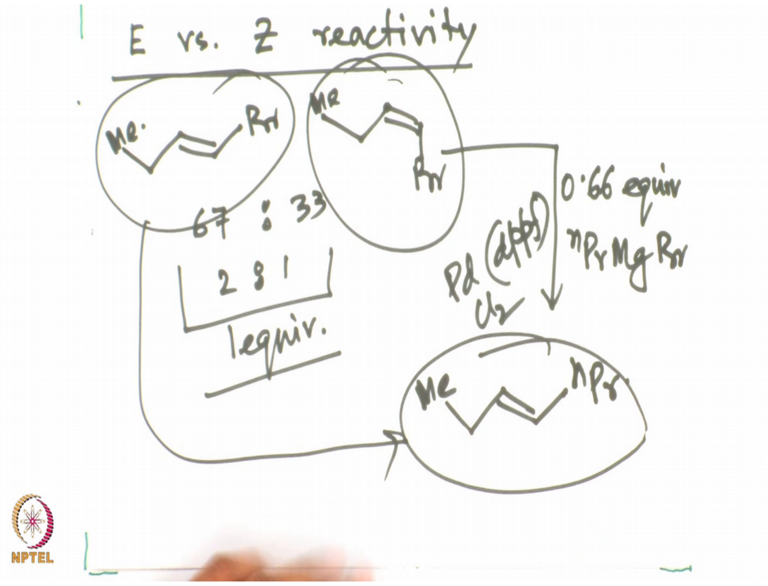

So, we are looking at E versus Z or Z selectivity is reactivity pattern. The starting material we are taking first is the one, where you have a trans geometry and the corresponding other one is there let say, you take 67 isto 33; that means, you know 2 isto 1 category; you are taking 1 equivalent of it. Total you have these 2 reagent in one equivalent, but one of them in 67 is and another is 33 equivalent or 0.67 and 0.33 equivalent and if you are reacting this with 0.66 equivalent; that means, you know if it is 2 is to 1 you are taking 2 equivalent of in propyl Magnesium Bromine.

So that means, you are going to do the Kumada coupling in presence of the Palladium catalyst specifically let us say dp pf dichloride if you are taking. Now, what is observed in these cases is, you get C, since you have 2 is to 1 and 2 equivalent of the organ magnesium reagent and you get, you know the one of the product only selectively you get the trans product that is more reactive. So, 2 equivalent reacting with or 2 is to 1 the 0.66 equivalent or 0.67 equivalent reacting with 0.66 equivalent of n propyl Magnesium Bromide to selectively give this product in trans geometry and the. So, thus this starting material is selectively 100 percent converted to the product this reagent.

Although similar only it is the cis one is not reacting at all for the product formation reaction. Now that is quite interesting, because you know when even when you have a mixture still you can phase out the one you want based on their reactivity. So, the geometry is const you know geometry is retained during the Kumada coupling reactions. It is, although it is a mixture of trans and cis, there is no mixture of product formation as long as you have the controlled delivery of the Organo magnesium reagent or Grignard reagent, if you are using in a very selected amount.

Now this Kumada coupling is very good right as you see that it is it can it can maintain the stereochemistry, it is a very good approach. But the problem well, one would expect that you are using Oregano lithium reagent, you are using the Grignard reagent as the coupling partner. This reagent are very reactive and they are notoriously reactive towards functional group.

So, therefore, functional group compatibility is an issue that is the major drawbacks of the Kumuda coupling. Although it is a great reaction, but if you have too many functional group Ester, Ketone, you know different other Aldehyde and other sensitives as Cyanide, other sensitive functional group you could run into danger. Because under the reaction condition, those functional group can also get affected by this oregano lithium or oregano or this you know magnesium or the grignard reagent that you are using. So, one has to be careful about the Kumada coupling.

Now next we would like to briefly discuss about the Suzuki reaction; see each of these reactions we can discuss hours after hours, because there are lot of advances being made. A lot of problems being addressed first of all identified and then, addressed and these are truly why the oregano metallic chemistry is considered very highly in modern synthetic chemistry. Let us we are trying to keep it brief maybe will come back to these discussions once again in greater detail. Let us look at briefly the Suzuki reaction.

I think it is one of the most promising and one of the most popular reaction at this point of time and it is very truly perhaps one of the most referred chemistry by chemists and non chemists alike. Let us look at the Suzuki reactions.

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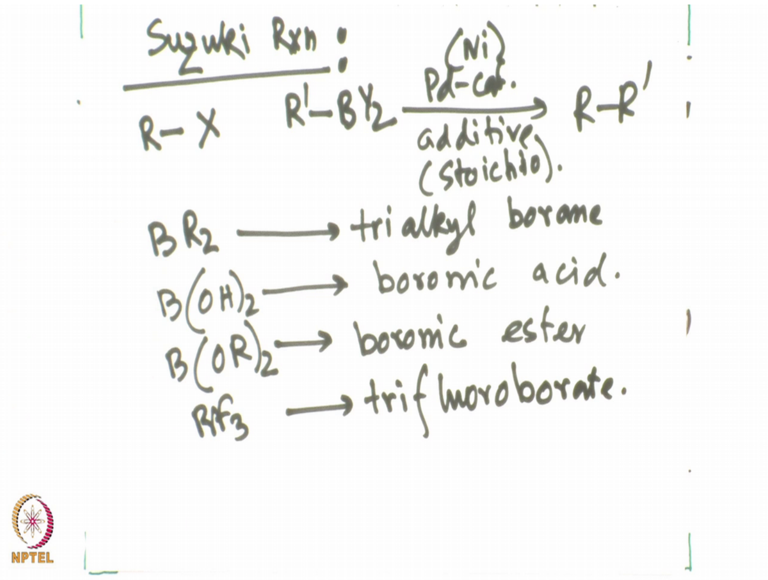

So, the reagent what is used oregano halide once again and organo borane reagent or boron reagent BY 2. Now, Palladium catalyzed is used sometimes also Nickel, sometimes Nickel. Additive stoichiometric additive are used. Usually stoichiometric additive are used Palladium catalyzed reaction stoichiometric used and the you form R R prime if it is a BR 2; that means, tri alkyl borane, that can also be used as the sapling sufficient or you know suitable coupling partner for this Suzuki reaction. If you have a boron nic acid, this is boronic acid; that is one of the most famous one that is used. If you have boronic ester, that can also be a suitable partner for these sort of reaction. Boronic ester, if you have aryl trifluoro borate, usually, called Mulandarets; tri fluoro borate that can be also used as the coupling partner for these reactions.

So, there are many different oregano borane reagent that can be used for the Suzuki coupling reaction. But invariably usually, they end up giving the product quite nicely. How one would get the trans metalating reagent in pressure or trans metallation in presence of the oregano boron reagent is one of the areas people have studied and it is now quite well understood, you need a base, you need a nucleophile for this oregano borane reagent to be participating in to the transmetallation step.

Once again, oxidative addition will be the first step. Then trans metalation and then, reductive elimination for this Carbon-Carbon bond formation reactions. Let us look at the trans metalation utilizing oregano borane as the material and how they might will be involved during the processes.

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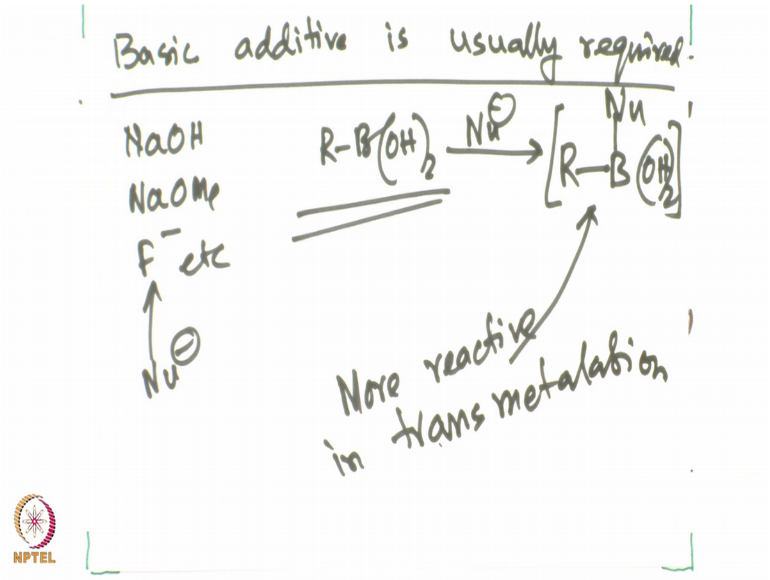

So, Basic additive is usually required. The Basic additive could be your Sodium Hydroxide, Sodium Methoxide, Fluoride etcetera. These are called usually Nucleophile, let us say we can call them and it is reacting with oregano borane reagent for example, organic oregano boronic acid; oregano boron acid reacting with Nucleophile to give R B. This Nucleophile Hydroxo 2. Overall, this is more reactive in trans metalation; the resultant species becomes more reactive in transmetallation; then, compared to this oregano boronic acid or any oregano borane reagent.

That might be used for the process. Now that is quite interesting because oregano boronic boron usually itself is not that much good for trans metalation, but when you have a nucleophile such as base Sodium Hydroxide, Sodium Methoxide, Fluoride anything you want, once you add that; then, it becomes a much better trans metalating reagent by which this transmetallation reaction can proceed. And therefore, product formation can be viable, what is also important to understand that these reactions are quite useful not only you know a aryl and aryl coupling which is usually the case or usually most widely studied or on Suzuki reaction where you have let say aryl halide reacting with an another aryl boronic acid to give you aryl aryl.

That means, by aryl fragment that is I think is quite well understood or quite well explored, the one which are little bit problematic could be the Alkenyl halide one where you have this alkenyl halide reacting quite efficiently for this Boronic acid reaction as well or the Suzuki reaction. Let us try to look at one such example where as sp 2 carbon of course, alkenyl halide is reacted with alkenyl boronic acid or boron reagent to give you the Carbon-Carbon Bond formation between the 2 alkenyl centers.

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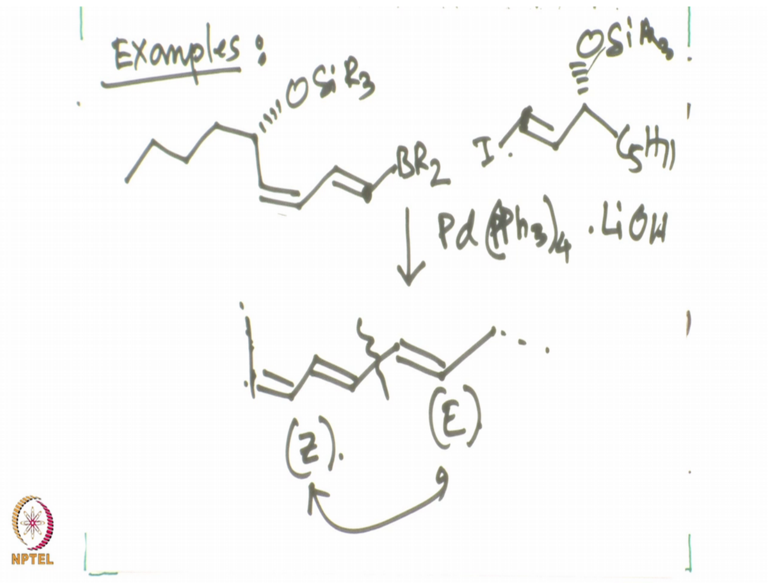

Let us look at the examples, we have let us say protected alcohol and organo boron reagent and we have this alkenyl halide. For example, over here to give you these again both the partners are sp 2 carbon center and these are alkenyl; these are considered as the coupling between these sp 2 and these sp 2, where it is alkenyl and this is also a conjugated one along with the alcohol. You know you have ally alcohol as well and over here ally alcohol protected as well. From here on, you can get in presence of Palladium tetra case, you can get the desired product that is quite amazing I would say, because the overall the product formation.

So, this is your new bond and of course, this is E geometry and this was the Z geometry over here as from the starting material the same geometry is retained. Of course, the rest of the things can be as it is. So, what you see in this particular product, what is most important for this 2 particular starting material is these are having a particular geometry both on the halide and at the boronic acid reagent. But irrespective of the geometry you see in the product formation both the geometry are retained, as they are in the starting material you get the same thing in the product formation that, I think is quite amazing and you can perhaps take almost at this point almost any sp 2 sp 2 bond formation can be done by almost any, I mean not definitely.

Everything there are limitation existing limitations are plenty, but most often, what you may need this is the reaction perhaps to go for and the geometry of the starting material could be retained. So, with this, would for todays class will we would like to summarize that we have discussed the Kumada coupling reaction with plenty of with some example and also we started discussing the Suzuki reaction with some very very attractive example. We did not discuss way too many of the other bi aryl coupling formation because those are very very well known.

The one which are more difficult or the one where alkenyl halide and alkenyl your organo oregano borane reagent are involved of course, you know sp 3 sp 3 carbon center could be another approach or another difficult coupling partner. Indeed those can also be done by these by this Suzuki reaction. Anyway, but the problem with the Kumada reaction as you discuss it is a very good reaction, you know geometry of the starting materials can be retained. But since we are using for Kumada reaction oregano lithium or oregano magnesium reagent, therefore, there is a danger of having the sensitive functional group being attacked under the reaction.

So, that cannot be Kumada coupling cannot be reliable part, reliable reaction under a condition where many functional group are there. On the other hand Suzuki reaction what is important is it is usually can tolerate quite a wide variety of functional group. Even the geometry of the starting materials retained and a lot of other beneficial features we might will be, we will be discussing in the next class. And maybe we will come back again in a much broader way to discuss most the more of the efficiency and the drawbacks of these reactions individually.

Till then, we will see you in the next class. Keep studying this Carbon-Carbon Bond formation reaction. Bye-bye.