Metal Mediated Synthesis - I
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Lecture – 9
Stille coupling reaction

Welcome back as we were discussing in the last class today we will be discussing the Stille reaction. Stille reaction is the carbon-carbon bond formation reaction where organo halide is used in conjunction with organo tin reagent the moment one is talking about tin reagent there the first problem that comes into mind is how this is going to be industrially relevant because industry does not want to use the tin reagent indeed that is the one and only problem that we have with Stille reaction industry does not like it medicinal chemistry people does not like it, but then why Stille reaction is so popular because it works it works beautifully almost for everything.

So, academician is going to like it academics favorite is the Stille reaction mainly because of the fact every functional group works beautifully usually very little problem is associated with the Stille reaction and therefore, also it is one of the carbon-carbon bond forming reaction which is which had seen most use in natural product synthesis the big molecule synthesis, we see are quite used tool under the Stille reaction condition.

So, today we will discuss the Stille reaction the exemption the example of the Stille reaction as we have said the drawbacks of the Stille reaction is the industrial use medicinal chemistry use is not really viable nonetheless it remained very popular in academia as well as natural product synthesis let us look at Stille reaction.

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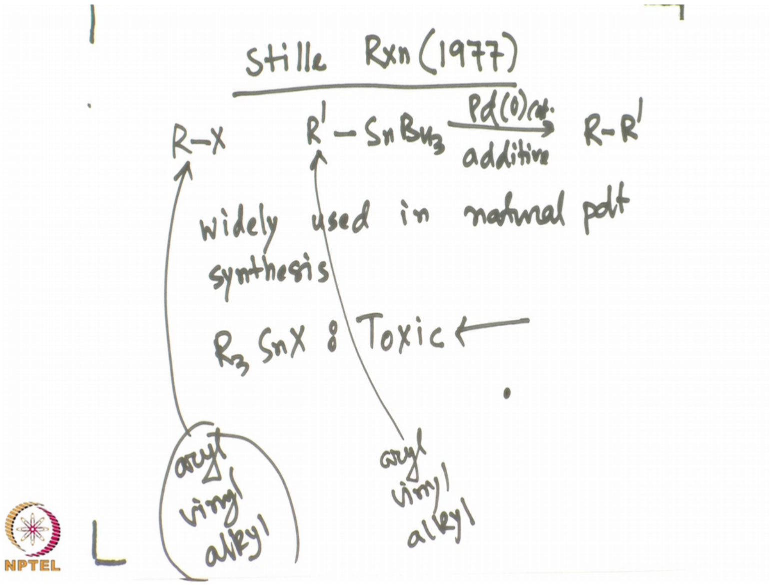

Stille Rxn (1977)

$$R{-}X \quad R'{-}SnBu_3 \xrightarrow[\text{additive}]{Pd(0)\,cat.} R{-}R'$$

widely used in natural pdt synthesis

R_3SnX 8 Toxic ←

aryl vinyl alkyl

aryl vinyl alkyl

So, you have R-X reacting with R prime Sn Bu 3 for a example palladium 0 catalyst in presence of additive we get R-R prime as the product. So, this is very widely used in natural product synthesis natural product synthesis, but R 3 SnX is toxic of course, it is.

So, there is problem in medicinal chemistry problems in industrial use therefore, although this is problematic what we see these R-X could be aryl vinyl and alkyl all different variation that you can think of that is good with these reaction and this R prime over here can be once again good for aryl vinyl alkyl.

So, that is quite interesting and this is this reaction is often air and you know air and moisture stable this reagents particularly tin reagents are air and moisture stable. So, that gives the access or that gives the possibility that it can be used quite widely for academia the reagent we do not have any problem in dealing with we can pretty much use quite under quite normal condition and therefore, the very challenging reaction.

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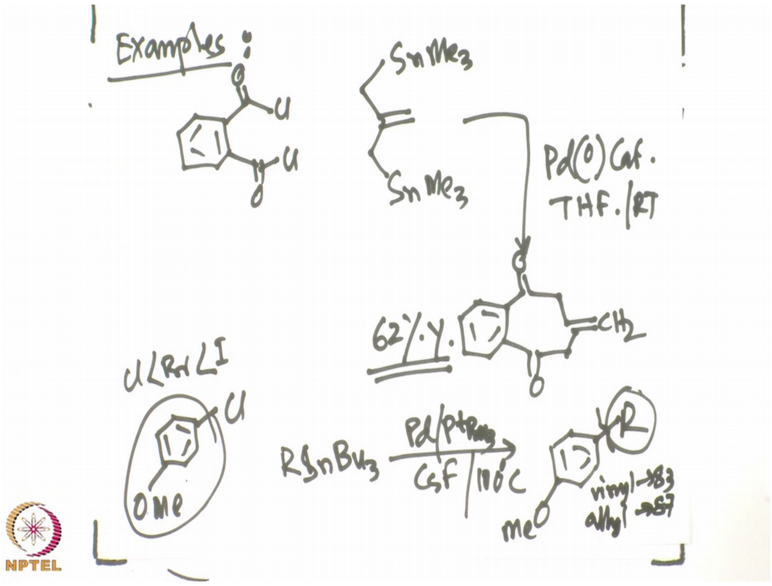

Let us look at one such example where it is a challenge to synthesize the product, but Stille coupling can deliver the product where a di asyle unit is involved examples now we have this chloride dye as chloride and one is interested in using this tin reagent under THF at room temperature even the desired product that is the ketone product die ketone product one could imagine that is beautiful domes demonstration of this reaction.

This again 62 percent yield of the product another interesting point could be of course, if we were to synthesize a product such as these any of these are of deactivating, these coupling partners are very tough one because you have electron rich couple electron rich substituent electron rate as well as aryl chloride as you know the reactivity pattern is iodo is most reactive than bromo than chloro.

If you are reacting it with RSn Bu 3 even this reaction works quite beautifully in presence of palladium peter butyl 3 cesium fluoride under hundred degree c condition we get the desired product for example, here you different R group you can have R if R equal vinyl you get eighty 3 percent yield alile you can get eighty seven percent yield alyl phenyl ninety four in butyl eighty 2 for. So, for this reaction therefore, you have different alkyl partner or different R group ranging from vinyl alyl alkyl aryl all those can give very good yield of the desired product.

Well that is quite interesting irrespective of the coupling partner we get very good yield on the other hand you can take the toughest possible substrate one such substrate we have shown that aryl chloride again the chloride coupling partner are the most difficult one because the oxidative addition is the slowest with aryl chloride on top of that with aryl chloride if one has the electron rich substituent such as methoxy it is even more difficult still under the Stille reaction condition we can get those coupling going in quite good yield and you know under the standard palladium catalysis we can get the product in quite high ratio.

Let us look at some more example of the Stille reaction where we will be able to appreciate the efficiency of such reactions. So, we will look at more example of this RSn Bu 3.

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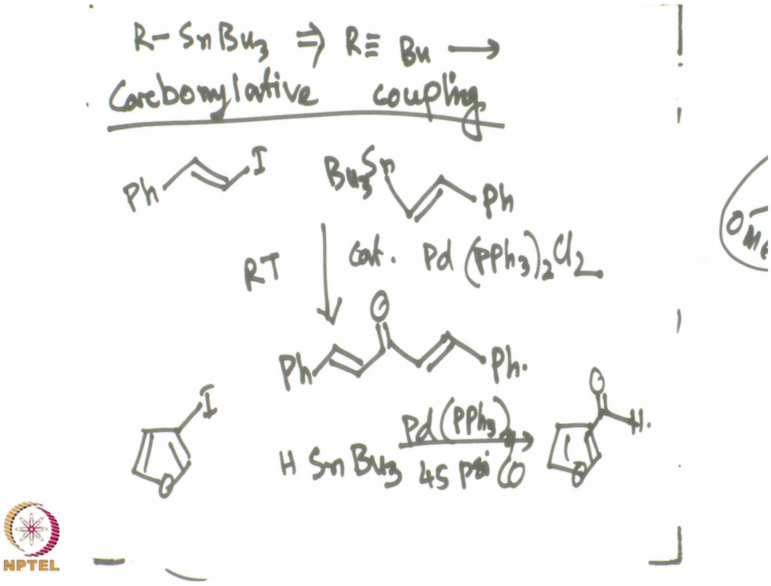

We are using R equals could be butyl usually no choice, but butyl, but anyway carb; let us look at the carbonylative version. Now as we were looking at the Suzuki reaction for Suzuki reaction we have also seen between 2 coupling partner namely aryl boronic acid or any boron partner as well as aryl halide if we are doing this reaction under the co atmosphere we were able to get carbonlative Suzuki the coupling between one coupling partner and another coupling partner there was a carbon monoxide similarly for Stille reaction also we can have 2 coupling partner one is ala halide another is the stin reagent if we are doing this reaction under carbon illative condition; that means, carbon monoxide in presence of it we can get the corresponding ketone product most importantly even both the coupling partners are alkenyl substituted or alkenyl derivative.

Still we can get this product quite efficiently let us look at one such example where we have styrenyl halide reacting with Sn Bu 3 again we have another alkenyl partner we end up getting the product that we are looking for in between the product.

This can be done at room temperature using cattle a catalytic al amount of palladium PPh 3 to Cl 2 well that is again; once again very interesting by this process we can synthesize a ketone any desired ketone can be synthesized by using this Stille coupling you can have di aryl ketone you can have aryl alkyl ketone you have alkyl alkyl ketone you have alkenyl alkenyl keton in between, right another interesting thing could be can you synthesize aldehyde by this method or as it turned out one can starting with alkenyl halide or even aryl halide with a hetero cycle coupling partner and the tin reagent with tin hydride as a coupling partner instead of an alkyne. Now we have a hydride reagent to transfer.

and therefore, we can get the corresponding aldehyde. So, that is once again a very attractive reaction not only ketone aldehyde can be synthesized by utilizing this technique let us look at that we have for example, one of the most troublesome coupling partner is this thio phenyl iodide at 3 position with tin reagent at HSn Bu 3 with palladium tetrakis once again to rescue forty five psi co we can get the corresponding aldehyde well because this hydride is coming from this tin reagent right tin hydride, but that you know tributyl tin hydride reagent that is used. So, what we have just seen that not only ketone aldehyde can be synthesized quite beautifully, let us look at one of the little complicated synthesis which at a glance from the product purpose perspective it could be complicated, but from Stille a perspective this is a simplest reaction of all where.

We will undergo oxidative addition insertion into an unsaturated molecule and finally, coupling with it Stille condition or still tin reason to give the desired product. So, we will see a sequence of events happening to give a desired product which otherwise might would have been very difficult to synthesize under normal normal condition let us look at application further application of such reaction.

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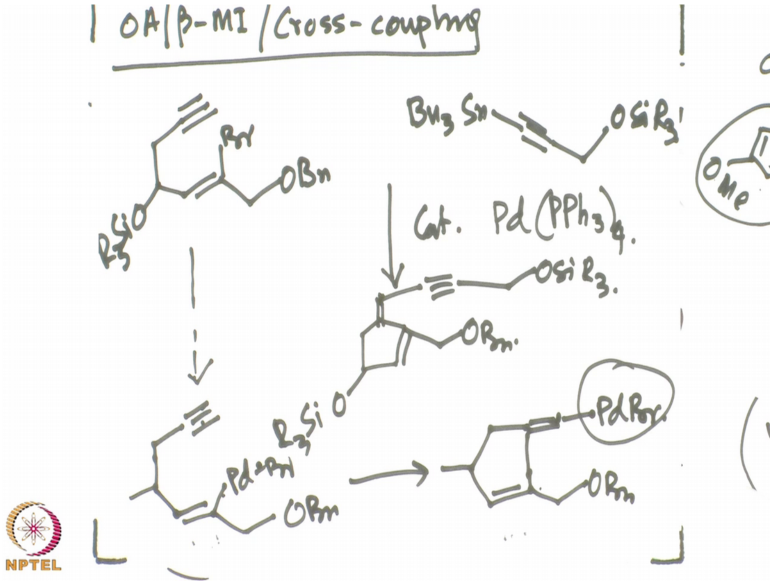

So, oxidative addition beta migratory insertion and cross coupling all are happening in one part at one stage. So, the substrate for this reaction is a little bit decorated one. So, the bromo coupling partner with it o benzyl and you have an allylic alcohol o protected one and you want to react it with Bu 3 Sn; this alkyne reagent well that is of course, and alcohol protected version now what would be the product if you are adding catalytic amount of palladium PPh 3 palladium tetrakis in this case as it turned out this gives you a cyclized product.

So, oxidative addition will occur fast at the alkenyl halide center that palladium intermediate will insert in a beta migratory fashion with the dangling alkyne intramolecular fashion subsequently it will react with the tin reagent. Let us look at the product formation first and then we will draw the mechanism stepwise. So, the product that we get in this case is the one where we have Si R 3 alkynyl and we have ob n and o Si R 3.

So, that is the product formation how is this product formation happening of course, overall you have this alkyne sitting over there the first step would be the oxidative addition oxidative addition into the alkenyl halide oxidative addition over here to give the palladium bromine intermediate and this then insert into the alkyne to give you palladium bromide now this coupling partner at this side.

So, then over here as you can see over here then it reacts with the tin reagent to give you the final desired product. So, that is quite interesting I thought overall for these processes and then therefore, we have a substrate in this case where we have alkenyl halide perfectly positioned in front of an alkyne oxidative addition into the alkenyl halide insertion into the alkyne and subsequently that in C 2 form alkenyl halide will react with the tin reagent to give you the final product.

That is a powerful demonstration of the Suzuki reaction, where sequentially oxidative addition beta migratory insertion and the Stille coupling finally, is taking place overall then what we do have a Stille coupling it works beautifully for academic purpose, but it is not a great choice for industrial purpose because of its toxicity any given reaction you can think of perhaps you can think using the Stille coupling if it is not of medicinal use Stille coupling is used quite beautifully and quite extensively in academia in selective cases in industry also.

It can be used, now let us look at the problems that is associated with the alkyl partner. So, the coupling reaction has a number of problem one such problem is incorporation of alkyl partner either in the form of electrophile or nucleophile during the reaction, let us look at if you have alkyl halide what type of problem one may associate during the reaction and why a desired product formation may be hampered because of the nature of the alkyl halide.

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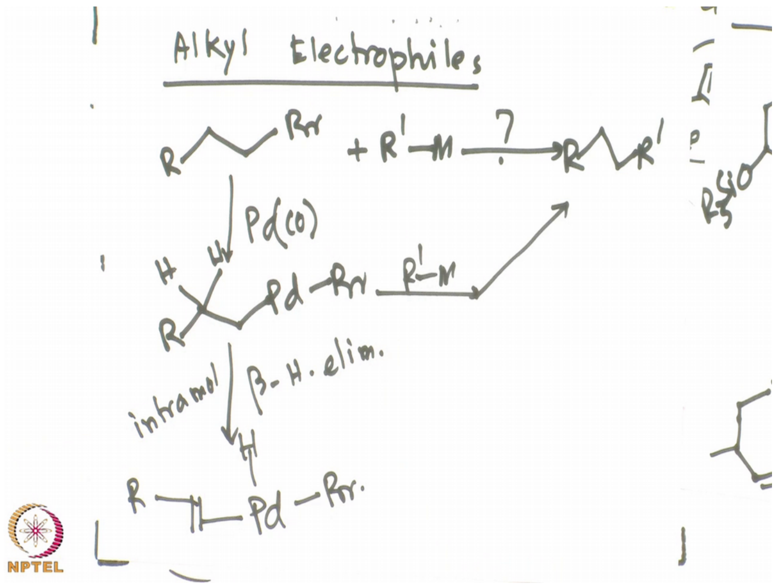

We have alkyl electrophile now alkyl electrophiles for example, if you have alkilil alkyl halide and you want to react with R prime m any catalyst you want to put and you want to get that one the problem the first problem that one associates with this is if it react with palladium 0, it gives of course, the palladium bromide oxidative addition complex, but from the beta position alpha beta-beta position this beta hydride elimination beta hydride elimination that is intramolecular reaction before this one proceeds for reacting with R prime m to give the desired product a side reaction which is intramolecular and that is where it is very difficult to prevent.

Can proceed to give the palladium hydride and bromide right well if that is happening one would expect that corresponding problem of getting the desired product. So, olefin will be formed from this reaction not the desired product or good amount of this beta hydride elimination product can jeopardize the formation of the desired coupling product well this is why we see that al alkyne halide are challenging partner for this coupling reaction.

One way to solve this problem is to discourage the beta hydride elimination of course, you have to have the alkyl partner you want to use the alkyl partner. So, changing alkyl partner to aryl or something else does not solve the problem because you want that desired product in order to do that if one is using a bulkier ligand, then due to see as you see for the beta hydride elimination coordination number the increases but if it is a bulkier ligand already present with the metal center then beta hydride elimination may be discouraged to some extent.

So, this is where a bulky ligand can be good of course, ligand has to be electron rich, but usually phosphine ligands are electron rich enough and therefore, oxidative addition may not be a problem for the phosphine ligand, but the bulkiness can be beneficial for preventing the beta hydride elimination; let us look at those alkyl alkyl coupling between the between alkyl halide and the and the alkyl boronic acid partner.

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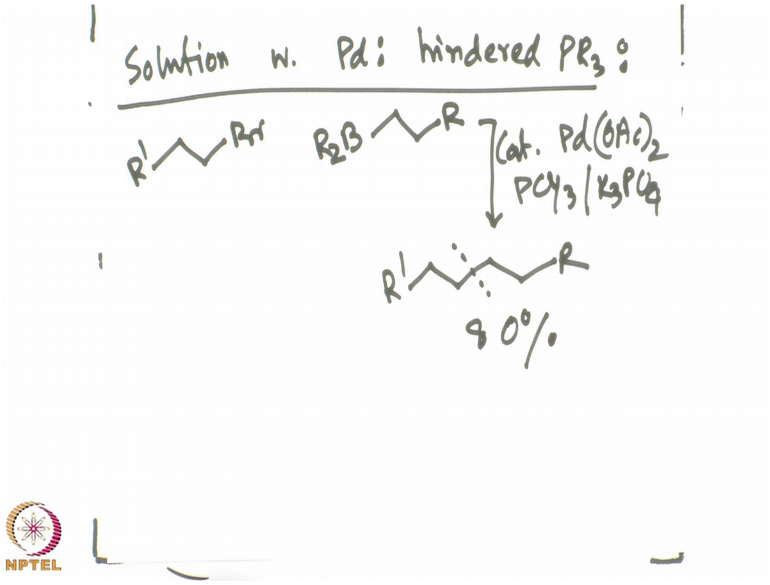

Solution to this problem is the Suzuki reaction solution with palladium and that is using hindered phosphine reagent if you are taking R prime Ch 2 Ch 2 here we have seen the other coupling partner as this one overall if you are reacting it with catalytic palladium acetate in presence of Pcy 3 and potassium phosphate and the base hindered and electron reach this triplane, phosphine, tricyclis, phosphine and hinder and electron is that is crucial and that is why we get the product the alkyl product corresponding alkyl product in very good yield.

Well that is a very good reaction where we see that alkyl halide is used in conjunction with alkyl boron reagent to give you the corresponding sp 3; sp 3 couple product although this is a successful reaction still it remains one of the most challenging problem that sp 3; sp 3 coupling is not really that easy easiest of the coupling partner that one can think of for this reaction many recent developments has solved.

This issue to some extent mainly the very beautiful contribution an important contribution by Professor Greg Fuji's lab which had given not only this coupling aliphatic aliphatic coupling even the asymmetry version of this reaction has been solved quite beautifully, but in by this way this Pcy 3 is good for let us say aliphatic partner, but they may not be or they are usually not good for secondary or tertiary halide because for secondary and tertiary halide we have a whole bunch of other problem to deal with.

A along with this reaction where we see that sp 3 primary center is working the secondary center might will not be happening oxidative addition because it is hindered aliphatic halide may be preventing the oxidative addition because usually oxidative addition is occurring under Sn 2 reaction condition right. So, the backside attack could be problematic. Let us look at one such problem where Sn 2 reaction for oxidative addition is going on and then look at the example with that. So, the previous reaction works well for the primary, but secondary and tertiary Pcy 3 does not work that very well.

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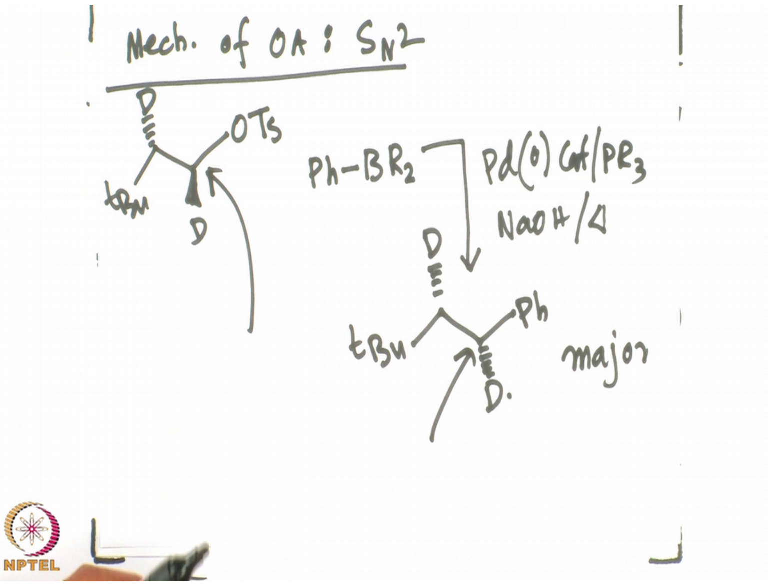

Let us look at one of the example mechanism of oxidative addition usually it is a Sn 2 reaction the type of substrate that we would like to demonstrate for this for to prove that it is a Sn 2 reaction is where you have deuterium labeling into the substrate. So, these are trans to each other and the reagent that is working, where we are interested in is the Suzuki coupling partner aryl boronic acid or aryl boron reagent and in presence of palladium 0 catalytic amount and pr 3 in presence of base such as sodium hydroxide and hit what we get in this case is that butyl phenyl and deuterium; deuterium, you see it is the one which is the major product the stereo center over here as you can see over with respect to here is opposite; that means, this is indicating that this is a this is a Sn 2 reaction that is happening during these cases.

So, what we have seen in this particular example is we have alkyl halide alkyl halide is working with a boronic acid reagent or al aryl boron reagent to give the desired product, but the alkyl partner is having 2 nutriyum one at alpha position the another as beta position we started with the one of deuterium at the alpha position in the product what we see that it is below the plane; that means, a Sn 2 reaction is happening during the oxidative addition reaction because the reductive elimination is usually not going to be it is concerted process it is not going to change the geometry or it is not going to change the stereochemistry at the partner. So, alkyl partnered stereochemistry changing that demonstrates that for alkyl halide it is a Sn 2 reaction.

That is happening with the metal center therefore, one could imagine that it will be problematic for the secondary and tertiary halide to undergo the Sn 2 reaction because backside attack is going to be difficult for secondary and tertiary halide therefore, what we have seen. So, far is although for primary halide these reactions could be possible a coupling reaction could be possible, but secondary and tertiary coupling partner remained.

One of the most problematic issue in the cross coupling reaction or carbon-carbon bond formation reaction in the next class will discuss some of those issue not only that the asymmetric version of those issues and some examples by Professor Greg Fuji lab who has contributed immensely to solve this problem in today’s class. Therefore, we have discussed why alkyl halide each coupling is a is a difficult coupling partner because it gives you the side product in the form of beta hydride elimination.

How to solve it we show we can solve it by having tri cyclohexyl phosphine electron rich bulky phosphine that can give, but it is not a generalized solution for every aliphatic halide because for aliphatic halide it is a Sn 2 reaction condition that is that its predominant for this reaction. Therefore, Sn 2 reaction cannot tolerate secondary and tertiary substrate and thereby we have a problem to deal with in the next class.

We will see how to get around this problem even with this alkyl halide what is the strategy what should be the metal that we should use perhaps not palladium some other metal to use. So, that we can change the reaction mechanism itself mechanism it selves and thereby we can introduce secondary and tertiary halide even perhaps using a chiral ligand can give the stereo center that will be generated during the carbon-carbon formation process we will discuss all those in the next class, till then, you keep reading about this carbon-carbon bond formation reaction bye-bye.