Reagents in Organic Synthesis
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Lecture 22
Pd Based Reagents in Organic Synthesis

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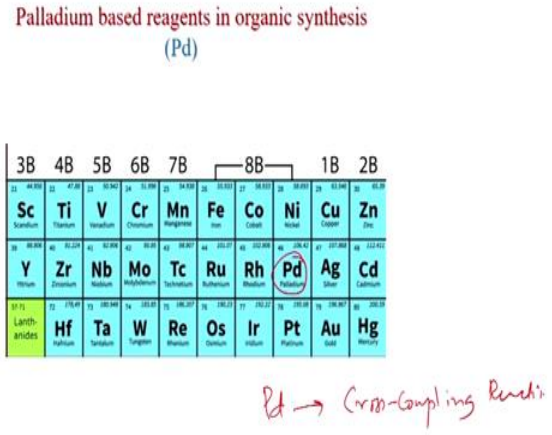

Welcome again. Today, we will discuss palladium catalysis. And you know palladium based reagents in organic synthesis - these are present in every lab and this is very useful for cross coupling reaction. So, if you see the periodic table, this is palladium. Palladium is in the same group with nickel and it is the same row with ruthenium, rhodium. So palladium very useful for cross coupling reaction. C-C bond formation happens.

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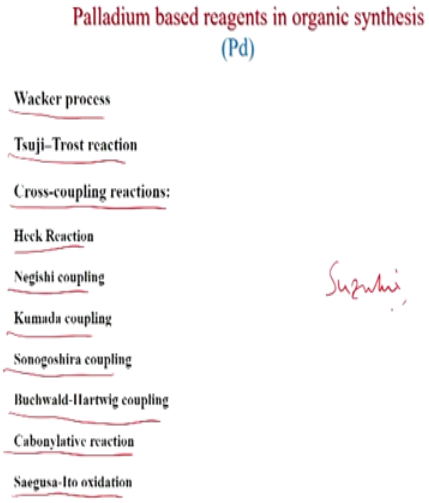

So today's lecture, we will first discuss Wacker process. Then we will discuss Tsuji-trost reaction. And we will discuss different cross coupling reactions like Heck reaction we will discuss, like Negishi coupling, Kumada coupling, then Sonogoshira coupling. We will see Buchwald-Hartwig coupling which is amine formation. Carbonylative reaction with carbon monoxide that also we will discuss. And Saegusa-Ito oxidation to generate enone from saturated ketone that we will discuss. And some coupling reactions like, Suzuki coupling we already discussed earlier, so it will not be discussed here.

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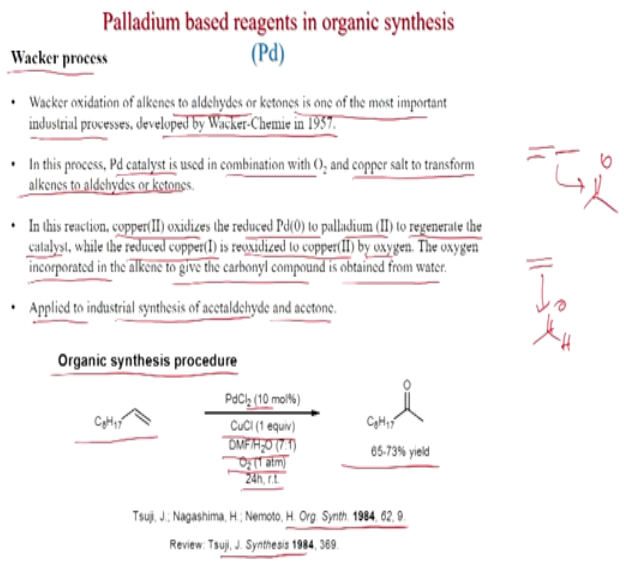

So, Wacker process first we will discuss. And Wacker is the name of a company. So Wacker oxidation of alkenes to aldehydes or ketones is one of the most important industrial processes developed by Wacker Chemie in 1957. In this process, palladium catalyst is used in combination with oxygen and copper salt to transform alkenes to aldehydes or ketones. That we will see depending on the Markovnikov and anti Markovnikov addition. In this reaction, copper(II) oxidizes the reduced palladium(0) to palladium(II) to regenerate the catalyst, while the reduced copper(I) is reoxidized to copper(II) by oxygen.

The oxygen incorporated in the alkene to give the carbonyl compound is obtained from water. So this is very important. The carbonyl group which is coming in that's - that oxygen is coming from water. And this method has been applied to industrial synthesis of acetaldehyde and acetone. Suppose, if you do reaction from ethene, then you get acetaldehyde. And if you do reaction with propene, then you get acetone.

So this is the organic synthesis procedure that if you react suppose 1-decene with palladium chloride 10 mole percent, copper chloride 1 equivalent. This is cuprous chloride 1 equivalent. Then, DMF water is 7:1, so water should be present. Oxygen 1 atmosphere and 24 hours, we will get this ketone in 65 to 75 percent yield. This is the organic synthesis, the review and another review also synthesis 1984, same year by Tsuji.

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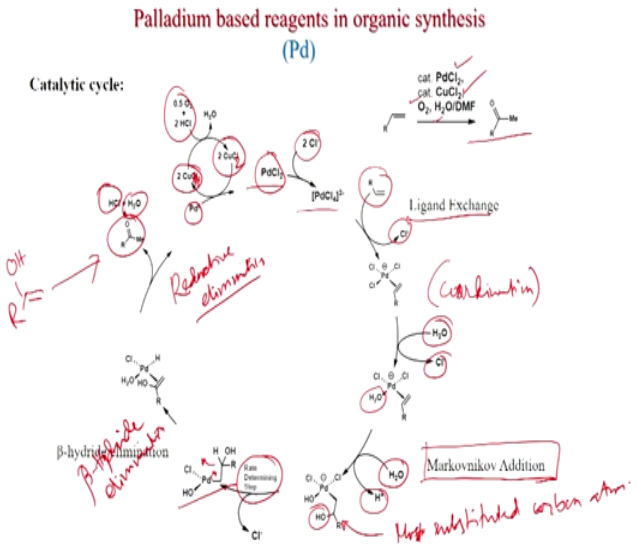

So, what could be the mechanism for this reaction here? So alkene goes to ketone here with catalytic palladium chloride, copper chloride, oxygen, water, DMF. And the catalytic cycle will first involve the 2 Cl^-, as to $PdCl_2$, so the more ligand will come. And now the ligand exchange will happen. So, olefin will exchange with this Cl^-, one Cl^- will eliminate and this coordination will happen: coordination of the olefin to the palladium because olefin has electron cloud.

Now, water will come. First, water will do a displacement of Cl-, so again ligand exchange will happen and water will be here, connected with palladium. And now another molecule, water will come and do an addition to this species. So the rule will be Markovnikov addition and in this process you will see this OH is from the water and in this process 1 H^+ is eliminated. And you see this attack happen to the most substituted carbon atom.

After that, Cl^- will be dissociated from here to generate this neutral compound. This is the rate determining state. And now the elimination will happen. So this elimination - this is the beta hydride elimination, beta hydride elimination. So, this hydride will be taken by palladium and now this you get enol which will be coordinated with palladium. And after that reductive elimination will give you ketone and palladium(0).

Ketone, HCl, water; so this is reductive elimination and this enol, so enol we know, enol after tautomerization, goes to the ketone that is the keto-enol tautomerization. And in the process you

get HCl, water also. And this palladium(0) will be reoxidised to palladium chloride. So, there is a mistake here, this should be $CuCl_2$ and this should be CuCl. So this is CuCl. CuCl with oxygen HCl is converted to $CuCl_2$.

And that $CuCl_2$ is oxidizing palladium(0) to palladium chloride and itself getting reduced to CuCl. So, this CuCl that is the role of oxygen to oxidized CuCl to $CuCl_2$ and palladium is getting oxidized to palladium chloride by $CuCl_2$. So this is the overall mechanism of this reaction. And the importance of regioselectivity is Markovnikov addition that we will see. Sometimes anti Markovnikov product can also be obtained.

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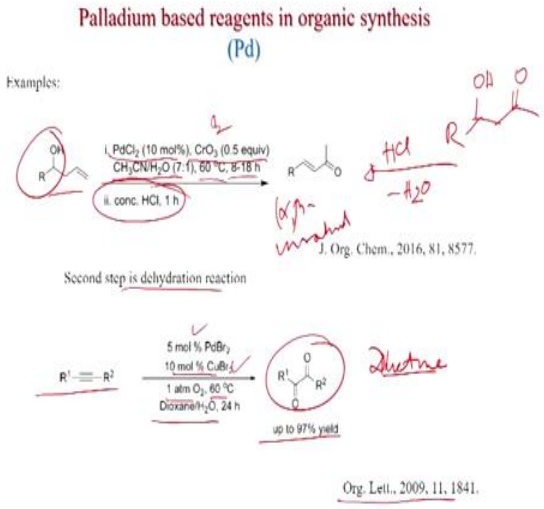

So some examples: suppose if you can take secondary alcohols with an alkyl group that is the terminal olefin and under this condition palladium chloride 10 mol%, chromium trioxide, that is the oxidant here instead of copper chloride, and acetonitrile:water 7:1, 60 degree centigrade, 8 to 18 hours. Of Course, this should be under oxygen atmosphere, or in presence of air. And after that you treat with concentrated HCl, so what happens you get first this 1 - beta hydroxy ketone. And beta hydroxy ketone, if you treat with HCl, then water gets eliminated and you get this alpha beta unsaturated ketone.

Second step is the dehydration reaction – so this is also the same mechanism the Markovnikov addition is happening. This was published in JOC, JOC 2016. Now, if you treat an alkyne;

alkyne also under this condition goes to diketone. Suppose 5 mol% of palladium bromide, 10 mol% copper bromide, 1 atm oxygen, 60 degree centigrade, dioxane and water, you get this diketone upto 97 percent yield. So, this is also an important reaction to convert alkynes to diketone. This was published in Organic Letters 2009.

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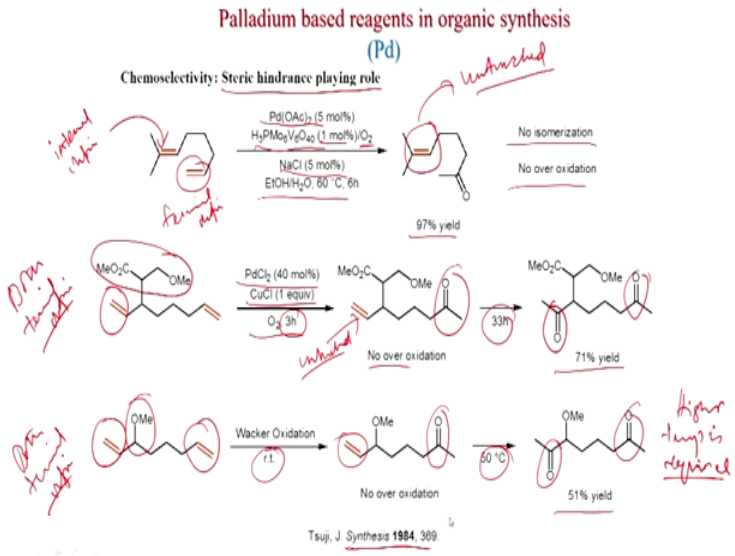

Now we will discuss chemoselectivity. Suppose if a substance has 2 olefins; now which olefin will get oxidized and which olefin will react in the Wacker process- that we will see. And there the steric hindrance is playing a role. Suppose if you think about this substrate. Here an terminal olefin - this is internal olefin. So this is internal olefin and this is terminal olefin. So the internal olefin, steric hindrance is there.

So, now terminal olefin is only reacting under this condition - palladium acetate 5 mol%, this molybdenum catalyst 1 mol% oxygen, sodium chloride 5 mol%, ethanol and water. You get this one and this double bond is untouched. So this is very important that regioselectively you can give this product in 97 percent yield. Here also no isomerization and no over oxidation. Now, if you think both the terminal olefin, both terminal olefin and in this case this olefin is close to this substituent and the other, this olefin is quite far.

This double bond is quite very far from substrate and when you put palladium chloride 40 mol%, copper chloride 1 equivalent, oxygen only 3 hours, if you give then this ketone is formed. This

double bond is untouched so this is very important which is sterically less hindered that is getting oxidized. Now, if you put the reaction for more time; like 33 hours then you get these diketone both double bond getting oxidised to the carbonyl group. And you get these 71 percent yield. So, if you start for shorter time, then you will get the selective oxidation. On the other hand, for longer time, you get the diketone.

Also if you see, here also both terminal olefin and here also, this olefin is close to this methoxy substituent. Just methoxy also can give a selectivity. So this is very sensitive reaction and with this terminal olefin is quite far. So, you can see when Wacker oxidation room temperature under the standard condition. In room temperature, you get only this ketone. So that double bond which is far from the methoxy getting reacting.

And you get this ketone with having double bond. Now, if you do the reaction at 50 degree centigrade then you could get this diketone. So, higher temperature, higher temperature is required for the reaction of the sterically hindered olefin. So, either you need longer time or you need higher temperature for the diketone synthesis. This was published in Synthesis 1984.

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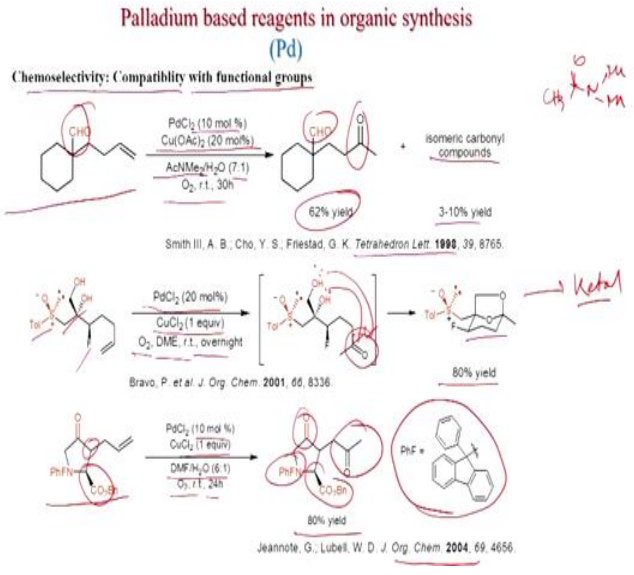

Also we will see the chemoselectivity compatibility with functional groups, like this substrate if you see there is a terminal olefin and aldehyde motif is there and with condition - palladium chloride 10 mol%, copper acetate 20 mol%, AcNMe2 - this is solvent - N,N- dimethylacetamide,

water 7:1, O_2 atm, room temperature for 30 hours; you get this keto-aldehyde. And this aldehyde group is untouched under this condition, also some isomeric carbonyl compound, 3 to 10% yield and this product is obtained – 62% yield.

This work is published in Tetrahedron Letter in 1998. So aldehyde, we know, this is very prone to oxidation that did not react under this condition. Also, if you see this compound, there are many; chiral center is there, sulphoxide, diol and fluorine and this is the terminal olefin and with Palladium chloride 20 mol%, copper chloride 1 equivalent, Oxygen atmosphere, DME, room temperature, overnight. You get this ketone first.

And what happens, this ketone in situ reacts with diol because you can see nicely six membered ring will form here. And this is another 5 membered ring. This ketal is formed because this 2 oxygen; OH is reacting with the carbonyl group and you get this ketal in 80 percent yield. Also if you see, this compound there is also chiral center; here also, this is stereogenic centre, and under this condition Palladium chloride 10 mol%, copper chloride 1 equivalent, DMF, water 6:1, oxygen atmosphere room temperature condition ; you get this ketone.

And these groups are untouched or not disturbed in this process. And PhF is the protecting group. Here, you can see the structure of PhF, that is the amine was protected and this product is obtained in 80 percent yield. And this work was published in JOC 2004. So we can see that different functional group can also be tolerated in the Wacker oxidation process.

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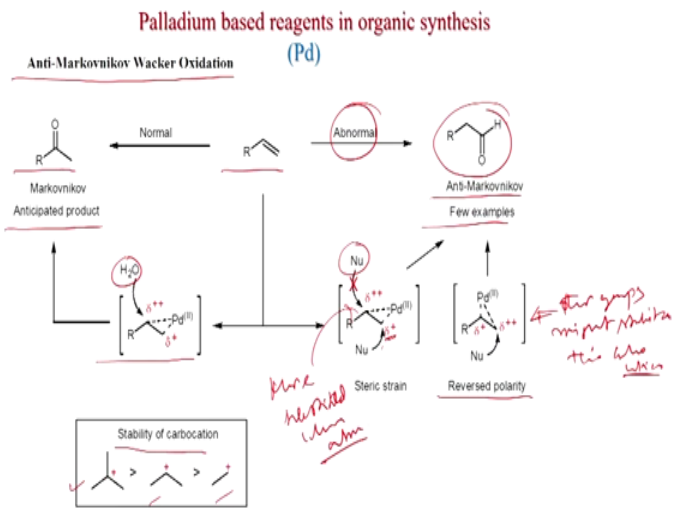

Now we will see anti Markovnikov oxidation. So far we have seen that Markovnikov addition happens and if you have a terminal olefin you get the ketone. Now we will see, if you have terminal olefin via anti Markovnikov addition you get an aldehyde. Like this is the olefin, this is the Markovnikov product, the ketone normal, that whatever you have seen. Now from the abnormal cases, you can get the aldehyde. That mean the water attacks here - this is the anti Markovnikov and few examples are known.

So, what happens in normal cases, whatever we have seen that this kind of carbocation intermediate will form and more stabilized carbocation that is the more substituted that is here, that is the Markovnikov addition. And water will attack to the more substituted carbon atom that is how you get the Markovnikov product and this is the stability of carbocation. We know that tertiary is more stable than secondary, secondary is more stable than primary.

Now in the anti Markovnikov cases, what will happen? So anti Markovnikov cases one possibility will be that the nucleophile might face the steric hindrance because this is the more substituted carbon atom. There the steric effect might be there. If the neighboring group is bulky then this nucleophile may not attack the centre. Instead it can attack to the terminal carbon because there also might be little delta plus.

It is also coordinated with palladium. Another thing the reverse polarity that also might be possible. Suppose, if you generated terminal carbocation which is stabilised by other olefin or other groups, the other groups might stabilize this carbocation. So, that we also, we will see. And that case, you can also get anti Markovnikov product.

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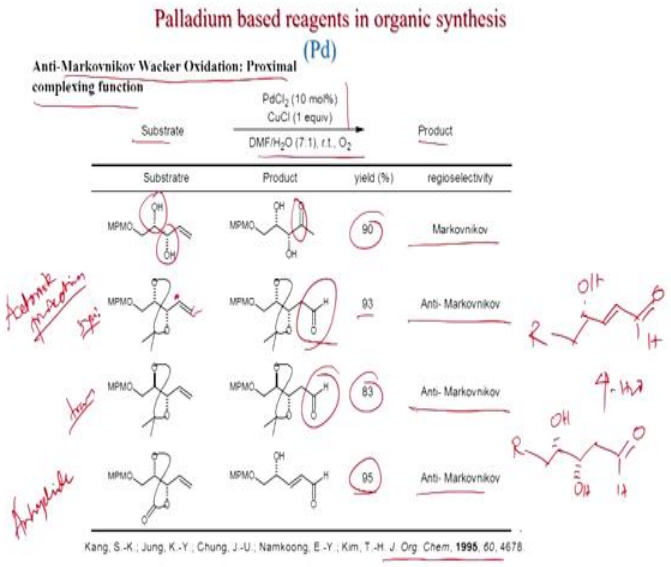

So we will see the anti Markovnikov Wacker oxidation proximal complexing function. So substrate giving product with the standard condition; Palladium chloride 10 mol%, copper chloride 1 equivalent, DMF, water 7:1, room temperature, oxygen atmosphere. Now, if you see the substrate - this is syn diol and a terminal olefin is there. Now, if you put under standard condition, you get 90 percent yield of this ketone. And that is the Markovnikov addition. Now, if you put this diol protection, so this is called acetonide protection, acetonide protection, that is the reaction with acetone if you do.

That is diol will be protected. And once it is protected, the aldehyde is formed. That is the anti Markovnikov product. This is obtained 93 percent yield. So, what happens after the protection? This carbon atom feeling steric effect and that is why the nucleophile can not attack. So, water cannot attack to this and instead it is attacking to this terminal carbon atom. Not only this is syn, this is the trans so this is syn. This is trans.

Trans cases also you will get anti Markovnikov products though yield got reduced to 83 percent but here selectivity is good. That is the terminal carbon atom is reacting with the water and you get the aldehyde. Also, if you have a anhydride, so this is anhydride. This diol is protected anhydride. In this case also the aldehyde is formed. So what happen, the aldehyde is formed and this anhydride maybe getting hydrolyzed.

And what happen, the aldehyde whatever is formed that is eliminating water and you get this alpha beta unsaturated aldehyde. So, this is very important that whenever you have a steric effect at the internal carbon, then the terminal carbon atom will react. This was published in JOC 1995.

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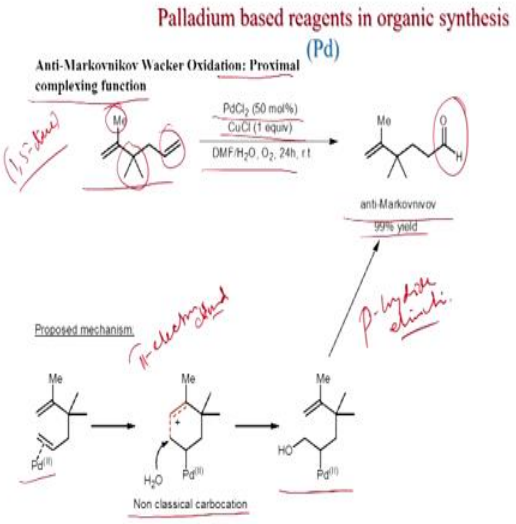

And this is also a diene if you see this one; now you see the proximal complexing function. So if you see this diene, this is actually 1,2,3,4,5. 1,5 diene and there is a quaternary centre here and this is a methyl substitution. And interestingly, with palladium chloride 50 mol%, copper chloride 1 equivalent, DMF, water oxygen atmosphere, room temperature 24 hours, you get the anti Markovnikov 99 percent yield. So double bond is only reacting, this double bond is not reacting, this bond is also reacting at the terminal carbon.

So, this is quite interesting what is happening. Now if you see the mechanism, proposed mechanism that this bond, this double bond will react with palladium because there the methyl substitution. So, this will be less sterically hindered and now this carbocation will be stabilized

by this pi electron cloud. So the pi electron cloud of the olefin is stabilizing this carbocation. And that is why this is called the non-classical carbocation is formed like this. The electron cloud will delocalize here. And now water attacks to this centre and you get this intermediate and after elimination, of course, you get the beta hydride elimination. You get the aldehyde.

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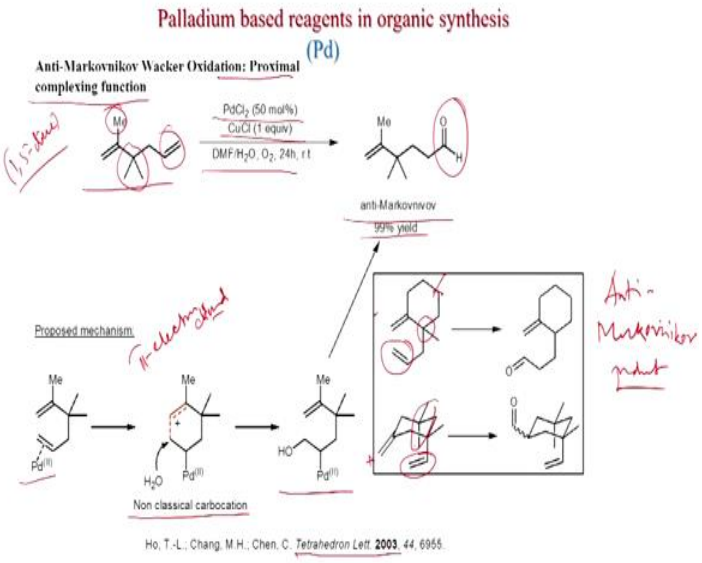

So, we will see some more examples. Suppose if you see this diene, here also quaternary centre is present and this is the exocyclic olefin. And this olefin is little bit far. And this olefin is reacting in anti Markovnikov fashion because here also this carbocation will stabilized by this double bond. Now, interestingly, if you put 2 methyl groups here, what happens this substrate? Now, this double bond will face some steric repulsion because there is a methyl group here.

So the nucleophile will not attack to this double bond. Instead it will react to this exocyclic olefin and here also the terminal carbon atom will react because here also the non-classical carbon atom will formed and you get the anti Markovnikov product.

So both cases you get anti Markovnikov product that is the aldehyde is forming. But 1 case, this double bond is reacting and another case, this double bond is reacting. So, this is very important; the steric effect is playing a very role. And if there is a non-classical carbocation formation, if there is another olefin which can stabilize the carbocation then you can get this anti Markovnikov product. And this work was published in 'Tetrahedron Letter' 2003.

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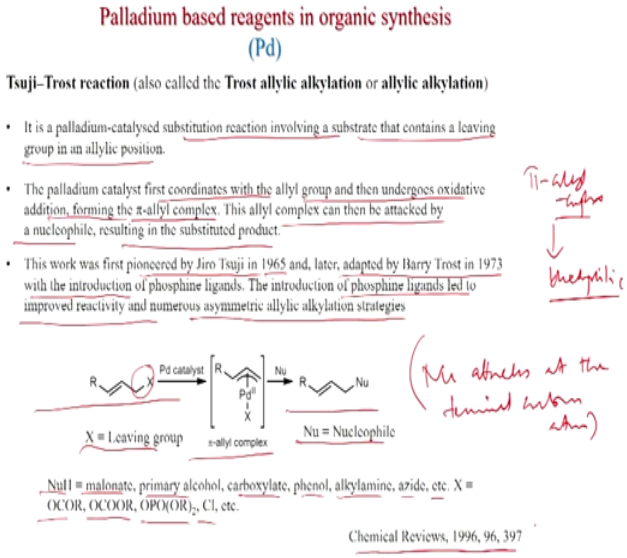

Now we will see a different reaction which is Tsuji-Trost reaction also called the Trost allylic alkylation or allylic alkylation. It a palladium-catalysed substitution reaction involving a substrate that contains a leaving group in an allylic position. The palladium catalyst first coordinates with the allyl group and then undergoes oxidative addition, forming the pi-allyl complex.

So, this is very important and this pi-allyl complex, that is electrophilic. So, different nucleophile can react. This allyl complex can then be attacked by a nucleophile resulting in the substituted product. This work was first pioneered by Jiro Tsuji and later adopted by Barry Trost in 1973 with the introduction of phosphine ligands. The introduction of phosphine ligands led to the improved reactivity and numerous asymmetric allylic alkylation strategies.

So, this is the overall reaction. If you have this allylic substitution X here; which is leaving group and when you put palladium catalyst then this pi-allyl palladium complex is formed and this X comes to palladium and now nucleophile comes and you get this product and you can see here the nucleophile attacks at the terminal carbon atom. So this is very important. And also the olefin is regenerated.

So X is leaving group, Nu is nucleophile and now different kind of nucleophile can used - malonate, primary alcohol, carboxylate, phenol, alkylamine, azide, etc. X is equal to OCOR,

OCOOR, $OPO(OR)_2$, Cl, etc. So different nucleophile and different leaving group can be put. And this was published in Chemical Reviews 1996.

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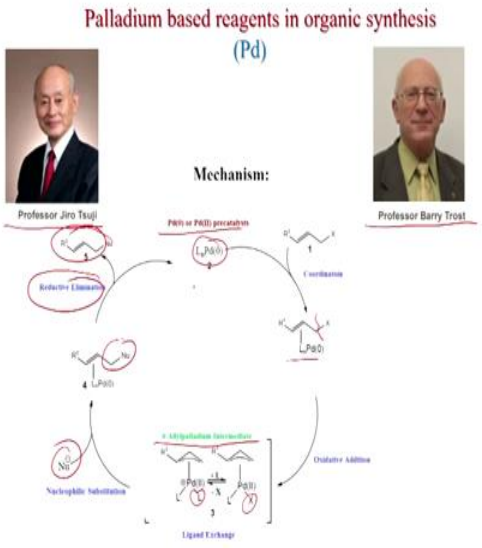

So there are the scientists who who developed this reaction. This is Japanese scientist 'Suji' and this is American scientist 'Barry Trost'. Now, we will discuss mechanism of this reaction. So you can use palladium(0) or palladium 2 precursors. And now this palladium(0) will be in coordination with this double bond first. And after that the oxidative addition will take place. And this bond will, of course, break and the X will come to the palladium and there might be ligand exchange also. That ligand can remove this X to get this one.

So, overall a pi allyl palladium intermediate is formed. And as I have told that this is electrophilic, so a nucleophile can react. A nucleophile react such that you get this nucleophile attack from the terminal carbon and you get this intermediate which after reductive elimination get your olefin and palladium(II) becomes palladium(0) here. So, this is the reductive elimination.

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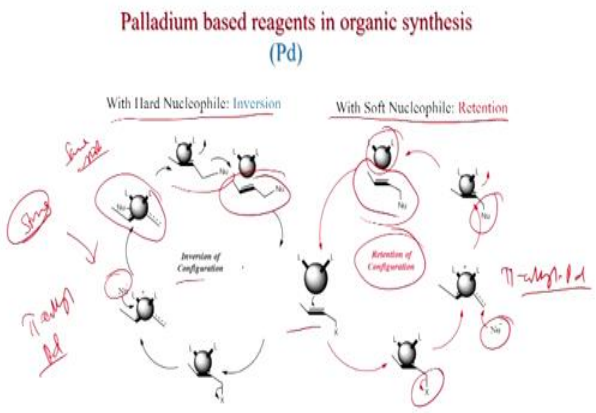

Now we will see that if you have chiral compounds in which soft nucleophiles can retention and hard nucleophiles will get inversion. So it is very interesting. What is happening, so if you have a this substrate, then this palladium ligand interacts, coordinates and then this pi allyl palladium is formed. So, this pi allyl palladium. And what happens in case of soft, if it is soft then these does not want to interact with palladium. So, what happens, it wants to stay away with palladium. So, it reacts from the side where the palladium is present. So it ultimately it is reacting with the same side where X was there.

So that is why it is reacting opposite of the palladium, that is the same side of X and you get this one. Then after reductive elimination you get this and this is the product ultimately retention of the configuration happens. So, now in the hard nucleophiles you get inversion. So, what is happening here: here also the coordination and then the pi allyl palladium is forming, pi allyl palladium. Now, because this hard, so hard is, hard means, this is also strong.

So, strong nucleophile that wants to interact with the palladium because palladium is a charge; positive charge is there. So that wants to interact with palladium. So, ultimately what happens, it came from the same side of palladium. So same side and that is why ultimately it is opposite side of X, so ultimately you get an inversion. So this product is formed where the nucleophile is

coming from the same side of palladium, ultimately you get an inversion. Thus the inversion of configuration happens.

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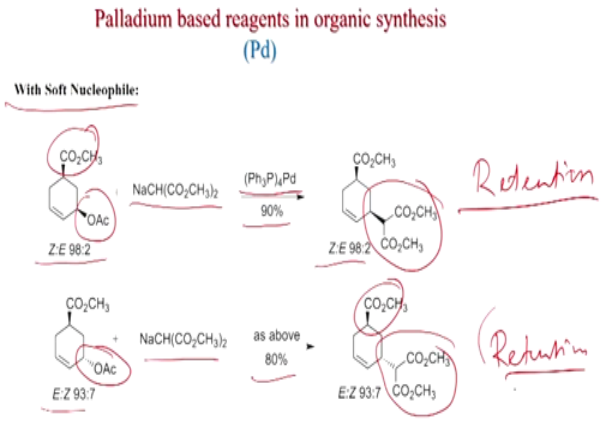

So this kind of reactions we will see by examples with soft nucleophiles, suppose this chiral substrate if you use and with Z E, this is the syn actually, syn is more 98:2. And we react with this malonate with tetrakisdiphenyl phosphate palladium, you get 90 percent yield of this product. And if you see, it is coming from the same phase of acetate. So, this is retention and you get this product in 98:2.

Now, if you react with this one, E Z that is a trans one and where O acetate is down now with 93:7 ratio with same malonate if you use and same condition you get little less 80 percent yield. But the stereochemistry is opposite now. Whatever earlier products with this one, so here also retention is happening. So independent of whatever other stereochemistry is not affecting. It is the aceto - stereochemistry pi allyl palladium intermediate and there the reaction; that is very important for the retention of the stereochemistry.

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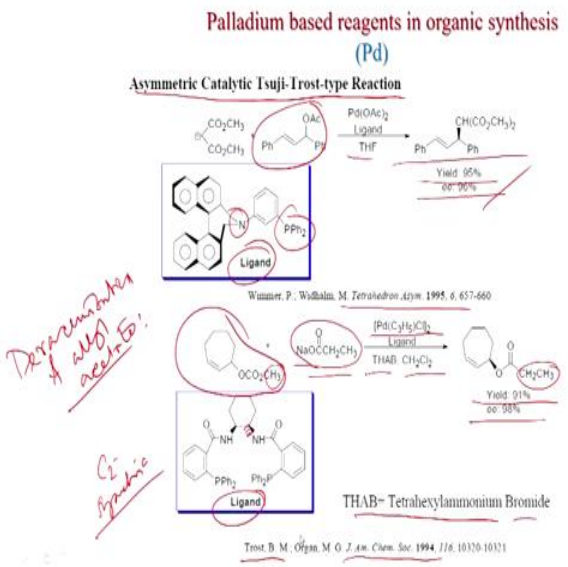

Asymmetric catalytic Tsuji- Trost type reaction is possible. Suppose here, this is secondary acetate and this is malonate with this ligand. You can see there is a phosphine and amino group is there. With palladium acetate ligand because this phosphine nitrogen is bind with palladium and THF solvent you get this product. The malonate group come at the same carbon as acetate was there and you get 95 percent yield and 96% ee. Though this pi allyl palladium will be symmetric does not matter which carbon because it will be symmetric but you get high yield and high yield, this was published in Tetrahedron Asymmetry. Not only malonate, you can use some acetate motif also.

And with this ligand, so this is a mistake, this should be - down. So this is actually C2 symmetry. So this is chiral ligand C2 symmetry, if you make a trans here, then it will be C2 symmetry and if you react with this; acetate seven membered ring allylic acetate. And it you react with this then you get this product. So this acetate only methyl is going to ethyl but almost same thing. So, that is why this is called Deracemization, Deracemization, Deracemization reaction.

Deracemization of allyl acetate. So this is very important. You react with this catalyst, ligand THAB is additive, tetrahexylammonium bromide, dichloromethane solvent, you get 91 percent yield. So this is very efficient and 98 percent enantioselectivity. So a racemic is converting to a

chiral compound with this ligand and palladium catalyst. So this is reported by Barry and Trost in JACS 1994.

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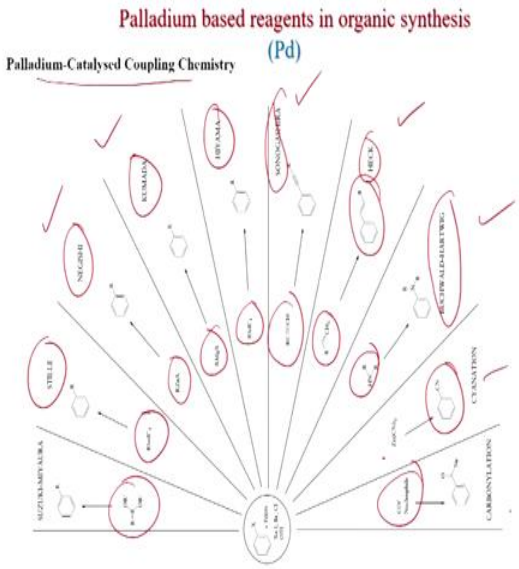

Palladium catalysed coupling chemistry. So, now we will discuss different palladium catalysed coupling. So, Suzuki Miyaura that we have already discussed when boronic acid, if you use the stille then Stille, this also we have already discussed. Negishi, if you use the zinc, then you get Negishi. So this will discuss today. RMgX Grignard then it will be Kumada. This also we will discuss. $RSiR'_3$, Hiyama, this we will now discuss.

Triple bond alkyne if you use then Sonogashira this also we will discuss. And olefin, if you get if you react, then you get substituted olefin. This is Heck reaction, we will discuss. Amination, this is Buchwald-Hartwig amination we will discuss. If you use the Cynation formation, that is also cyanide we will not discuss. This we will discuss - carbon monoxide nucleophilic carbonative reaction we will discuss.

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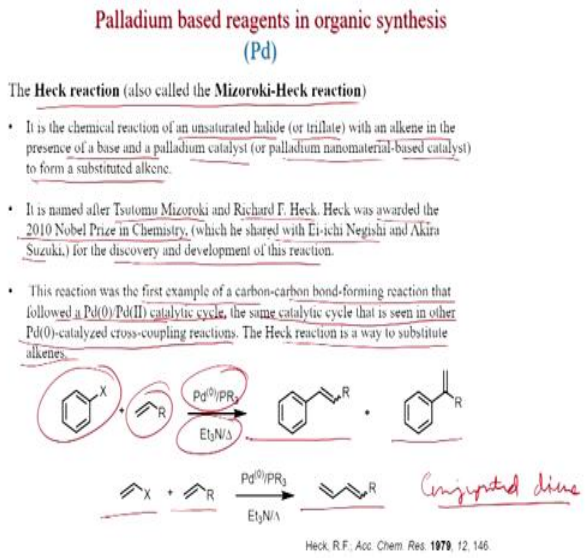

So, first we will discuss 'Heck reaction' - and the Heck reaction also called the Mizoroki-Heck reaction. It is the chemical reaction of an unsaturated halide or triflate with an alkene in the presence of a base and palladium catalyst or palladium nanomaterial based catalyst to form a substituted alkene. So alkene is converted to an substituted alkene and it is named after Tsuruko Mizoroki and Richard F. Heck. Heck was awarded the 2010 Nobel prize in Chemistry which he shared with Negishi and Suzuki, of course, for the discovery and development of this reaction.

So, Heck first discovered the reaction and that is why it is called the Heck coupling. This reaction was first example of carbon carbon bond forming reaction that followed a palladium(0), palladium(II) catalytic cycle. So, this is very important. The same catalytic cycle that is seen in other palladium(0) catalyzed cross coupling reactions. The Heck reaction is a way to substitute alkenes.

So, this is the reactions. Suppose you have a aryl halide, we have a olefin with palladium(0), phosphine, triethylamine base. You can get 2 olefin products. One is the normal, another is the isomerized. So 2 olefins can be formed but we will see the regioselectivity issues. And if you have vinyl halide and an olefin, then you get conjugated conjugated diene that also is possible with heck coupling reaction. So, this is the Account of Chemical Research; full story is there, 1979.

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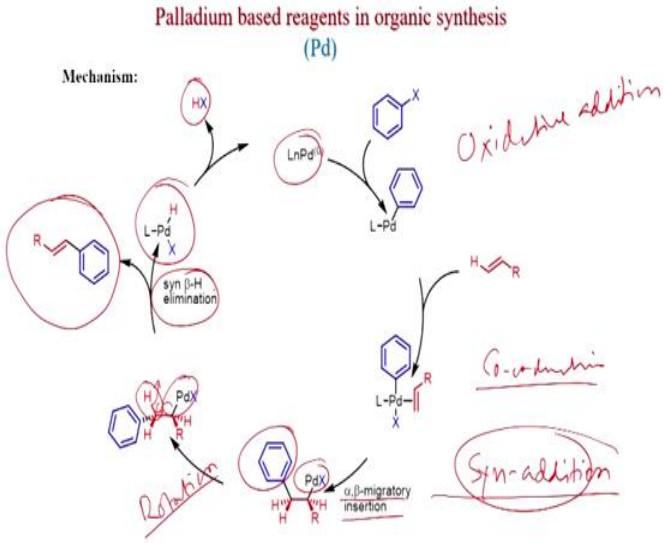

So what could be the mechanism? So here also the palladium first reacts with the aryl halide. And this is oxidative addition. And now your olefin will interact with this palladium because this palladium is charged now. So the olefin will do a coordination. And, this is very important - alpha beta migratory insertion will happen.

So, now your, so this one will add to the double bond and this is also very important. We will see the regioselectivity issue later but first what we want to see this aryl and palladium - it is coming from the same side. So this is syn addition. So this is very important. This is syn addition is happening. So this - it is from the same side. Now what will happen - you have to give a rotation because if you want to take a hydride, it should be from the same side of palladium.

So, if you give the rotation, then phenyl will be down and one hydrogen will be the same side of palladium. So this is rotation. And after that rotation only, the elimination, beta hydride elimination will happen. So, like this, hydride will be taken by the palladium and you get this olefin and this is formed which after reductive elimination is from the HX and LnPd(0). And this palladium 0 again react in the, with the aryl halides. So this is the overall reaction. If you see these two things very important - syn addition and syn elimination. That we will see.

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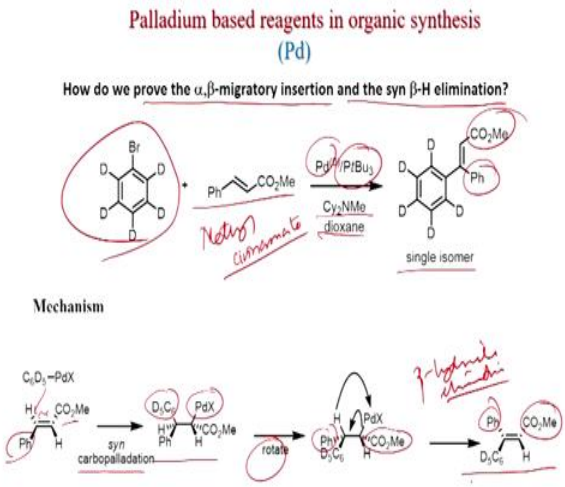

So what is evidence, that how do we prove that alpha beta migratory insertion and the syn beta hydride elimination is happening? So if you put this - methyl cinnamate with this deuterated bromobenzene. Now this is trans orientation. After this coupling, palladium(0) tributyl phosphine is the amine dioxane solvent.

You see now in the product, this phenyl and CO_2Me are on the same side. So this is single isomer is forming. So what could be the mechanism. And this is a prove that the addition syn elimination will happen. So first if you see this cinnamate, we can draw like this also. This meaning trans is there, phenyl is this and this is down. So this is trans. Now syn carbopalladation will happen.

And like this palladium is going here reacting. You get this. And here, now you have to give a rotation because palladium in the same side as this. So, hydride has to bring the same side that is why you have to give rotation. And now if you give the rotation, then what happen, the Ph comes from the same side of the CO_2Me. And after the elimination, you get this. So the Ph and CO_2Me is on the same side after beta hydride elimination and reductive elimination, of course, you get the palladium(0). And this is the product.

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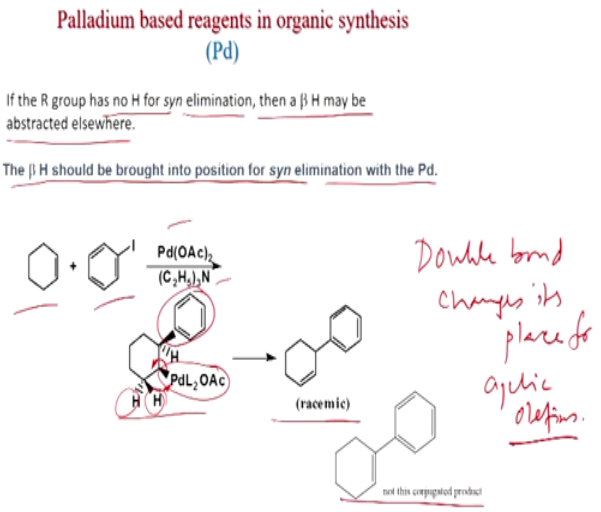

Also, if the R group has no hydride for syn elimination then a beta hydride may be abstracted elsewhere. If you want to generate an olefin, of course, you need a hydride. And that beta hydride should be brought into position for syn elimination with the palladium. Suppose, if you react iodobenzene with cyclohexene in this condition with palladium acetate, triethyl amine, then you get this one.

And you can see for cyclic structure we cannot give rotation, like earlier we have given. So what happens, this phenyl and this palladium is on the top side of the same phase. So, this hydride cannot bring to the same side. So what happens? There is a neighbouring carbon where the hydride, one hydrogen, of course, in the same side. So you get this olefin. So olefin is now not with this conjugated.

So this is racemic, of course. You get this product, so not this conjugated product. Not here, where the original. So what happens double bond changes its place. So double bond changes its place for cyclic system, for cyclic olefin. And this tells that the syn elimination is very important.

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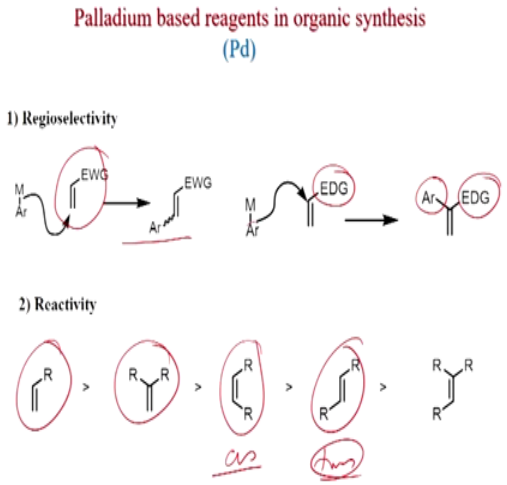

Now we will see regioselectivity issue. Of course, this is a nucleophile kind of a thing and if you have a electron withdrawing substituent then the reaction will happen here. The aryl will be here, and you get this product. On the other hand, if a electron donating group is present on the olefin then the Ar will come on the same carbon where the same electron donating group is present. Reactivity, monosubstituted olefin will react, then the di-substituted olefin then the - this is 1-1 di-substituted, this is 1-2 di-substituted. This is cis, this is trans and then tri substituted. So steric repulsion or steric effect will control the regioselectivity issue.

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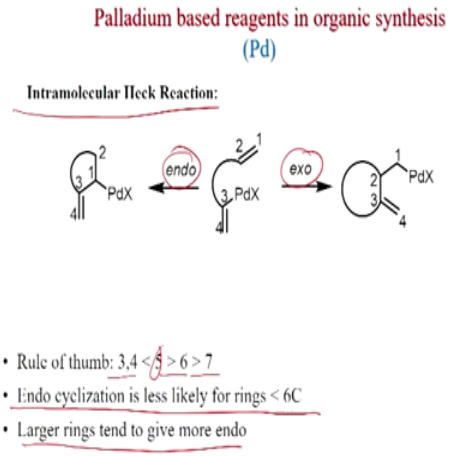

Now good additives - suppose this is the standard reaction. You can get two products. And palladium - it can be $Pd_2(dba)_3$. So this is also Pd(0). $Pd_2(dba)_3$ so this is the - dba: Ph, Ph - this is dba. Also palladium acetate can be used. This is Pd(II) and Pd(0) - triphenylphosphine palladium, ligands, triphenyl phosphine, tertbutyl phosphine 1:1, palladium phosphine.

Solvents - dioxane, DMF, acetonitrile: Base – triethylamine, cesium carbonate, inorganic base can also be used. This is Dicyclohexylmethylamine. So, now, we will discuss intramolecular Heck Reaction. So, so far we have discussed is intermolecular. Now intramolecular; if the vinyl halide or vinyl triflate and the olefin, in the same molecule to couple then you can get a ring. And now depending on endo and exo cyclic cyclization, you can get two different rings, of course.

Now what is the selectivity rule? Rule of thumb is that if you generate a 5 membered ring, that formation process will be faster than 6, that will be faster than 7. Also 5 will be faster than 3, 4. And endo cyclization is less likely for rings less than 6 carbon. For larger rings only, endo cyclization is possible. So for higher than 6 or 6 cyclization, the endo is possible otherwise you have to make exocyclization.

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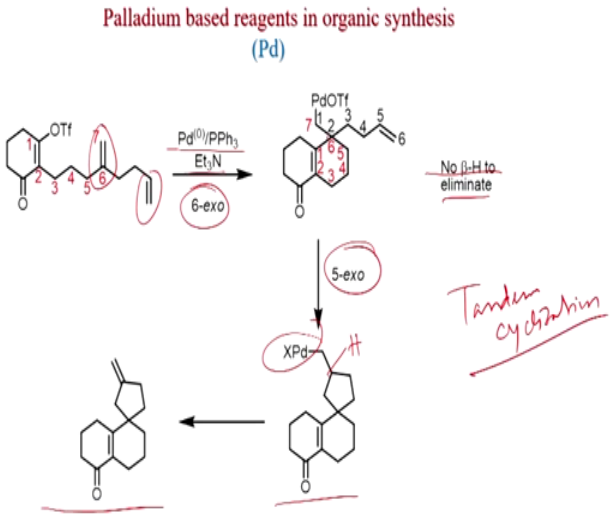

So some examples you will see. So if you see this substrate - here the vinyl triflate is there. Here is olefin is present, here is olefin is present. And if you count here, this carbon if you consider - 1, 2, 3, 4, 5, 6 - now 6 exocyclization will happen. With this catalytic system, triethylamine, and you get this 1. Now if you see, this intermediate, here no beta hydride is present because this is now quaternary.

So again it will cyclize. Now if you see, this 1, 2, 3, 4, 5 - so now again 5 exo-cyclization will happen you get this intermediate because 5 member ring is form here. And now if you see this one, there is a beta hydride to eliminate. And that will eliminate to give a olefin. So this will be the ultimate product. So this is tandem. Tandem cyclization.

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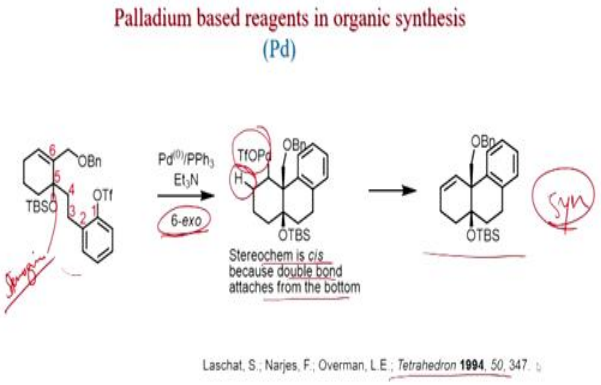

Also if you see this one - intramolecular version - this is a triflate - aryl triflate. Here is a olefin substituted is present. Now if you see the count 1, 2, 3, 4, 5, 6 - so this is also 6 exo is possible. 6 exo - also the stereochemistry is cis. Because this is a stereogenic, stereogenic and the addition will make a stereogenic centre. And this stereochemistry will be cis because the double bond attaches from the bottom. Because this one, if you think it is in the bottom then it will attack from the bottom also. So it does not want to change its side.

So it will be the syn orientation. Now your palladium is here now; but if you see this, this is quaternary carbon, so hydride is present in the neighbouring carbons and it is always like cyclic system. Here the elimination will happen and you get the double bond here. This is the product. This is syn. The stereochemistry is syn. Research published in Tetrahedron 1994.

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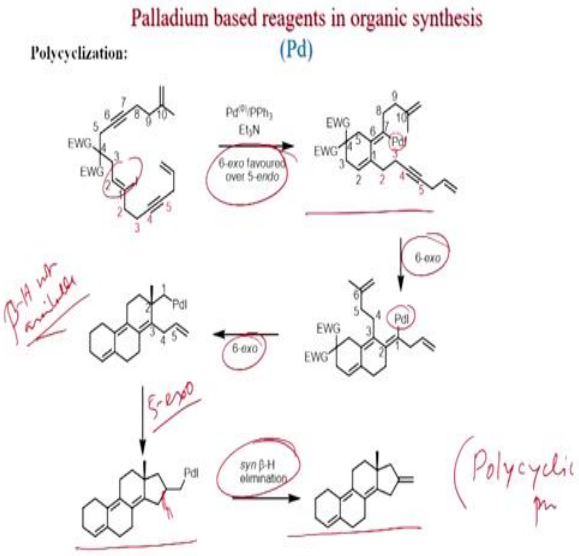

If you see this substrate, there are many triple bond and double bond is present. This is the vinyl iodide and if you see this triple bond - this is 1, 2, 3, 4, 5 but we need a 5 endo which is not possible. But if you see this carbon - 1, 2, 3, 4, 5, 6, so 6 exo is possible, 6 exo favoured than 5 endo and with this palladium(0) triphenylphosphine triethylamine you get first this intermediate. The palladium is now here. Now, again if you see, this is 1, 2, 3, 4, 5, 6. So this 6 exo again is possible.

So, after 6 exo, this carbon they are now palladium. Again we will do cyclization - 1, 2, 3, 4, 5, 6. Though there is a hydrogen here, but it will further cyclize because the allene will form but that process will be slower compared to the 6 exo cyclization, 6 exo cyclization will happen. This one will form but here also the beta hydride is not available, beta hydride not available. So what will happen, this again will cyclize so 1, 2, 3, 4, 5 , so again 5 exo.

So again 5 exo, so 5 exo you get this 1, this intermediate. And if you see this intermediate, there is a hydrite, of course, here this carbon and syn beta hydride elimination you get this product. So this is very important. If you have a substrate with many double bond and triple bonds, then depending on the 6 exo that is the Baldwin rule, 6 exo, 5 exo, many cyclization is possible and you get a polycyclic product. So this is polycyclic product.

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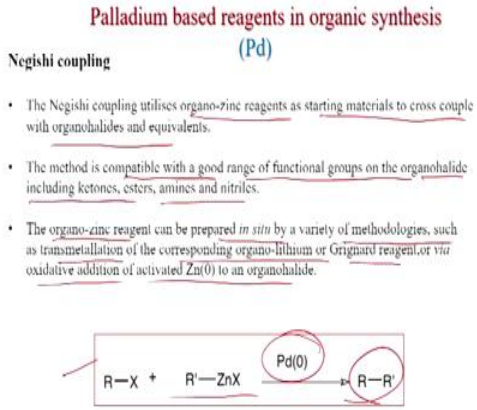

Now we will discuss Negishi coupling. So Negishi coupling utilizes organo-zinc reagents as starting materials to cross couple with organohalides and equivalents. This method is compatible with a good range of functional groups on the organohalide including ketones, esters, amines and nitriles. The organo-zinc reagents can be prepared in situ by a variety of methodologies, such as transmetallation of the corresponding organolithium or Grignard reagent or by oxidative addition of activated zinc to a organohalide. So, this is the overall reaction - and halide and then zinc compound palladium catalyst you get this cross couple product.

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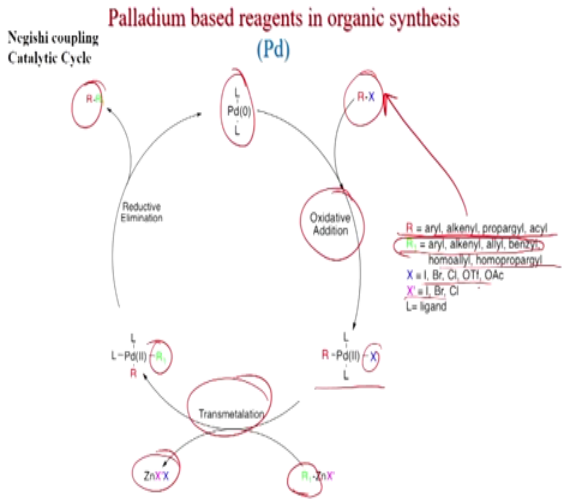

So what is the mechanism? So here also the oxidative addition will happen first with the aryl or vinyl halide to get this. Now the transmetallation will happen. So this is a nucleophile R1 that will make a substitution here. So X will be eliminated and X will react with zinc now. So ZnX'X will form now and the R1 is now with palladium.

So this process is called transmetallation and after the reductive elimination you get the couple product RR1 and you get the Pd(0). So R can be, that is the halide can be aryl,alkenyl, propargyl, acyl. R1 that is the Zn(I); this can be aryl, alkenyl, allyl, benzyl, homoallyl, homopropargyl, etc. So broad range. X can be different: iodo, bromo, triflate, acetate. X dash also iodo, bromo, chlorine and L is ligand.

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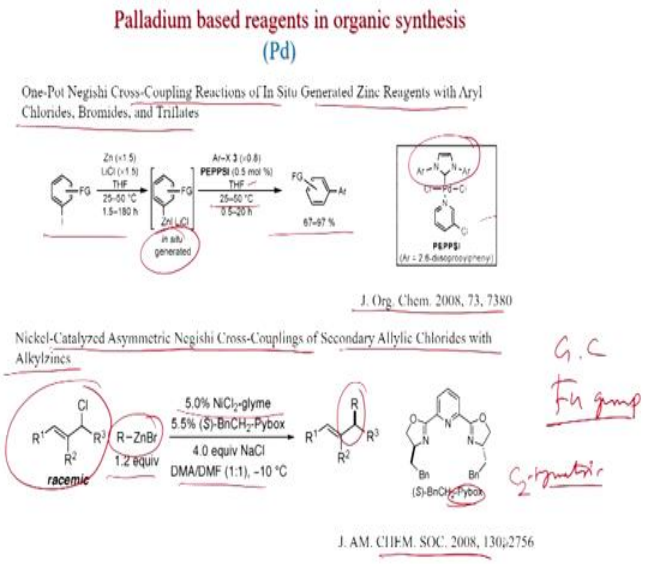

So one-pot Negishi cross coupling reactions of in situ generated zinc reagents with Aryl, bromides, chloride and triflates we will see now. So this is the in situ generation with zinc, lithium chloride, THF you get this zinc complex. And now react with aryl halide, PEPPSI - PEPPSI is a N-hetrocylic carbon palladium is there, that is the catalyst now. THF solvent 25 - 30 degree centigrade you get this cross coupled product 67-97 percent yield and this was reported in JOC 2008.

Nickel- catalysed asymmetric Negishi cross coupling of secondary allylic chloride with alkylzinc. So this is the reaction, this was developed by Fu I think - Fu group - G. C. Fu. So, if you have a secondary allylic chloride which is racemic and now if you have a zinc bromide R-ZnBr, 1.2 equivalent, 5 mol% of nickel chloride glyme and this C2 symmetric Pybox; so this is C2 symmetric, this is the Pybox. This coordinates with nickel and this cross couple product you get in very high yield as well as the enantiomeric excesses. This work was published in JACS 2008.

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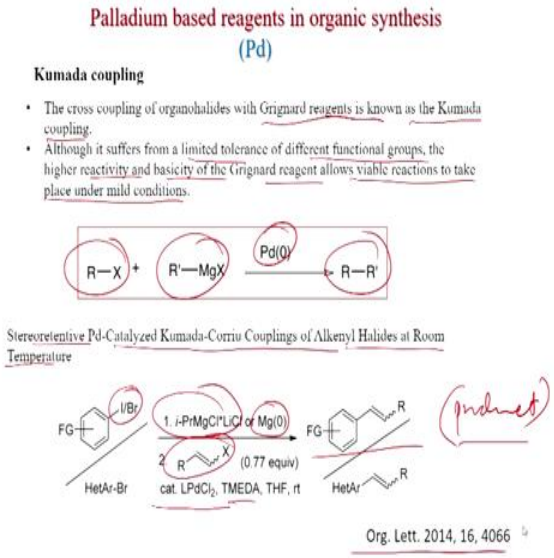

Now we will discuss Kumada coupling. So the cross coupling of organohalides with Grignard reagents is known as Kumada coupling. Although it suffers from limited tolerance of different functional groups, the higher reactivity and basicity of the Grignard reagent allows viable reactions to take place under mild conditions.

So this is very important. Grignard can do many side reactions but it is also high reactive. So, if you have an aryl or vinyl halide then the Grignard with palladium(0) will give the cross coupled product. And now we will see the example - stereoretentive palladium catalyzed Kumada-Corriu couplings of alkenyl halides at Room temperature. So this is an example - the in situ generation of Grignard from the iodo bromobenzene with this one.

If you put this one or magnesium then the Grignard region is formed. Now if you react with vinyl halide, vinyl triflate with the palladium catalyst - this is the base, then you get the cross coupled products. So this is the product. And you get this product in high yield. It was published in Organic Letters 2014.

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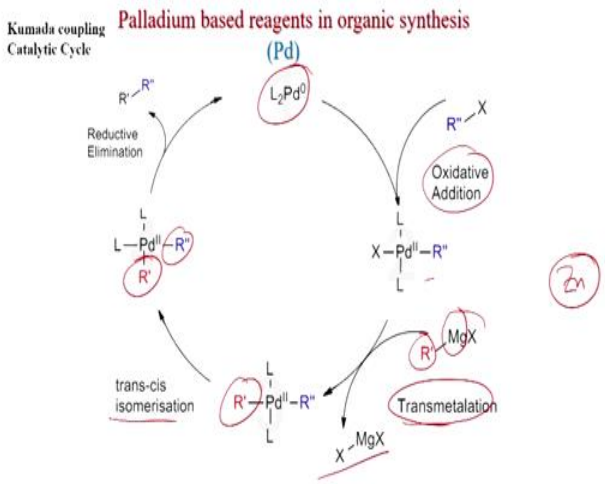

Now we will discuss the mechanism. The mechanism is same like Negishi coupling. Here also the oxidative addition will happens and the transmetallation; earlier we have zinc Negishi but Kumada coupling this is the magnesium Grignard. Now transmetalation will happen – R' is nucleophile reacts with the palladium and this is the byproduct. Now trans cis isomerisation will have to happen, so they will be close to each other. After the reductive elimination you get this product and you get your Pd(0).

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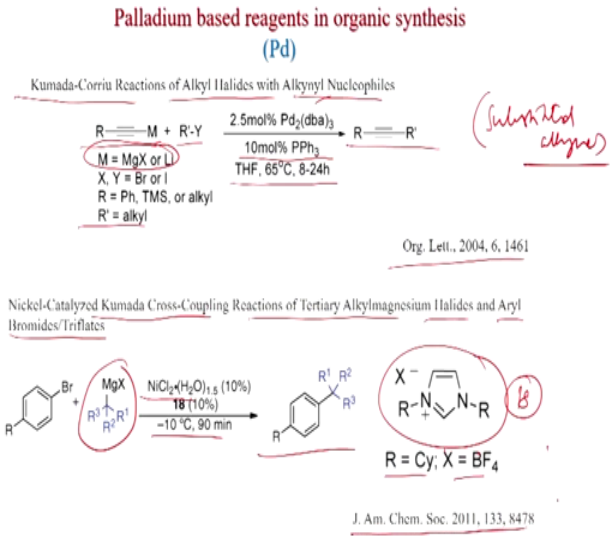

So, some examples - Kumada Corriu reactions of alkyl halides with alkynyl nucleophiles. This is the alkynyl Grignard or lithium reagent and with R'Y; R' is here alkyl and 2.5 mol% of $Pd_2(dba)_3$, 10 mol% of triphenylphosphine, THF at 65 degree centigrade, you will get this internal alkyne or substitution. So, substituted alkyne is formed. This was published in Organic Letter 2004.

Interestingly, if you have a Grignard reagent with a tertiary carbon atom, that case also the reaction will happen. This Nickel catalysed Kumada cross coupling reactions of tertiary alkyl magnesium halides and aryl bromides or triflates. And for that you have to use nickel catalyst and this imidazolium salt is 18 the number here, so imidazolium salt and -10 degree centigrade 90 minutes you get this cross coupled products in good yield. So, R can be Cy here, in this catalyst and X is equal to BF_4. So JACS 2011, 133, 8478 this was published.

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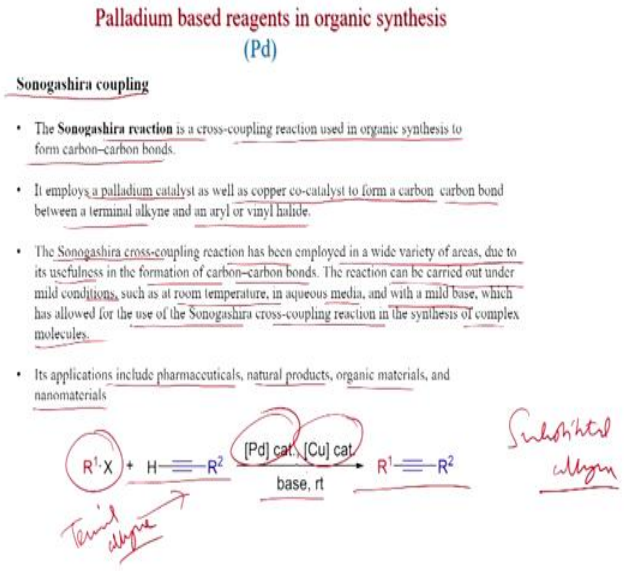

Now we will discuss Sonogashira coupling. So Sonogashira coupling, in this process you generate alkyne. So we have seen that Kumada coupling also alkyne and Grignard you can get the triple bond but simple alkyne you can use in Sonogashira reaction. Sonogashira reaction is a cross coupling reaction used in organic synthesis to form carbon carbon bonds.

It employs palladium catalyst as well as copper co catalyst to form a carbon-carbon bond between a terminal alkyne and an aryl or vinyl halide. And the Sonogashira cross coupling reaction has been employed in wide variety of areas due to its usefulness in the formation of carbon carbon bonds. The reaction can be carried out under mild conditions, such as at room temperature, in aqueous media, and with a mild base, which has allowed for the use of the Sonogashira cross coupling reaction in the synthesis of complex molecule.

So, this reaction is very important. And its applications include pharmaceuticals, natural products, organic materials and nanomaterials. So this is the reaction; you can use an aryl halide or vinyl halide and then an alkyne. So this is very important generally the terminal alkyne, so terminal alkyne if you use then you get substituted alkyne. This is Sonogashira reaction. And you need palladium catalyst as well as copper catalyst, copper is required to activate the - this hydrogen. So the copper acetylide will form. And base is required.

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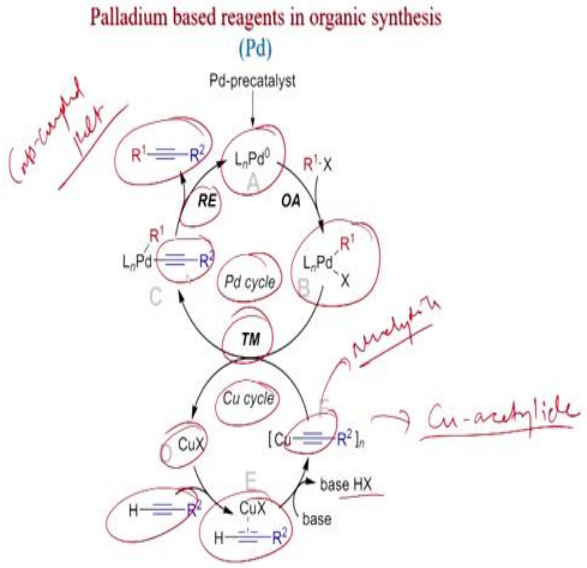

So what is the mechanism? So this is mechanism as I told. The copper react with the triple bond, alkyne for the coordination and then the copper acetylide. This is copper acetylide is formed with base - base takes up the HX. And this one react with this one. After oxidative additive, so this is the transmetallation. Earlier we have seen zinc, magnesium now we will see copper.

So, this is a nucleophile. This nucleophile - this attacks to the palladium now and you get this one after reductive elimination. You get the alkyne, that is the cross coupled product, cross couple dproduct and the palladium you get which will react again under oxidative addition. So, two catalytic cycle is present: one is copper cycle, another is palladium cycle. So copper main role is the - to make copper acetylide from alkyl.

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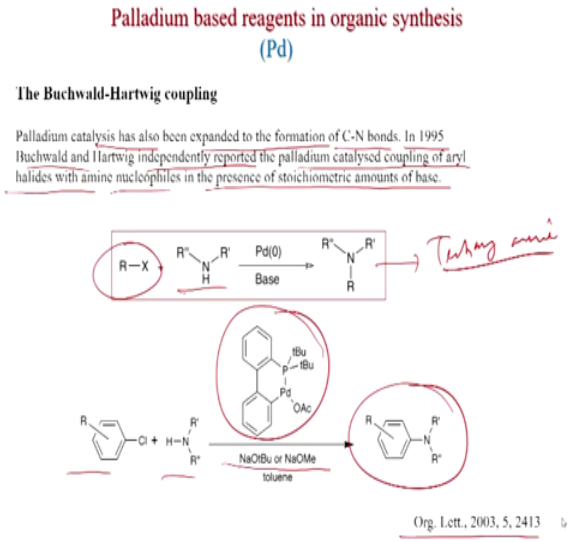

Now we will discuss Buckwald-Hartwig coupling. Palladium catalysis has also been expanded to the formation of Carbon-Nitrogen bonds. In 1995, Buckwald and Hartwig independently reported the palladium catalysed coupling of aryl halides with amine nucleophile in the presence of stoichiometric amounts of base. So this is the reaction - R-X, this is secondary amine you get a tertiary amine product.

And this is an example, if you use a chlorobenzene and a secondary amine with this catalyst. So here palladium phosphine is present, Sodium tertiary-butoxide or Sodium methoxide base, then you get this tertiary amine. And this work was published is Organic Letter 2003.

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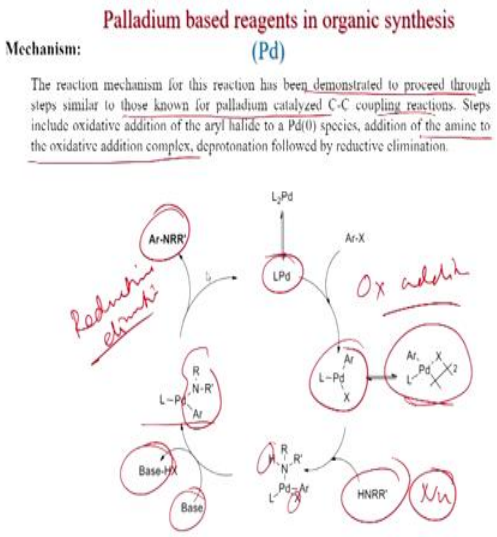

So, what is the mechanism? The mechanism is same, that the oxidative addition will happen like palladium catalyzed coupling reaction. So this is oxidative addition; oxidative addition is happening like earlier. This can be like this also. And now the amine comes. So addition of amines to the oxidative addition complex. So this addition is happening here. So amine is nucleophile; nucleophile it is reacting to the palladium and now this HX will eliminate.

So, if you base, then the base HX will eliminate and you will get this intermediate. And after that you get reductive elimination of this so the amine is reacting with the aryl group; reductive elimination will give you the amine and your catalyst back. So, this is the overall reaction.

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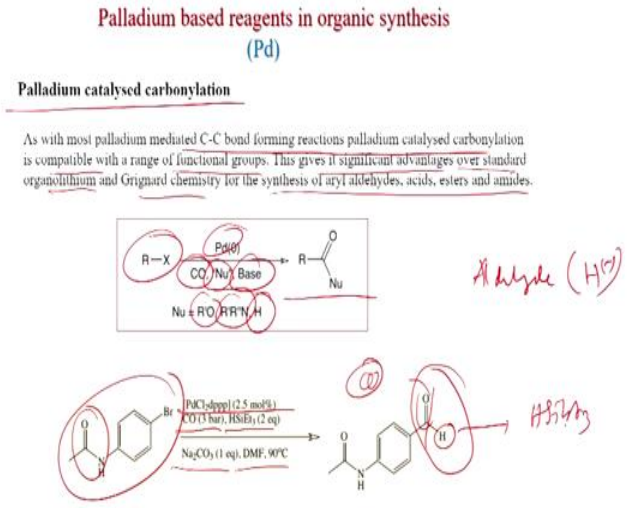

Now we will discuss the palladium catalysed carbonylation reaction. So carbon monoxide can also be incorporated in the palladium catalysis and different nucleophile can be used so the amides esters can be obtained. Palladium catalysed carbonylation is compatible with a wide range of functional groups. This gives it significant advantage over standard organolithium and Grignard chemistry for the synthesis of aryl aldehydes, acids, asters and amides. So this is the reaction: RX with palladium(0) carbon monoxide nucleophile and base you get this carbonyl compound. And depending on the nucleophile you get different carbonyl compound like OR', that is ester.

If you have amine, then you will get a amide. If you give H^-, then what will happen - aldehyde. So aldehyde will form when there is a H^- that example we will see. Suppose if you have this one is bromobenzene and the substitute is present and this catalyst is $PdCl_2dppp$ and with carbon monoxide 3 bar - this is the hydride source - triethylsilane and this is the base sodium carbonate, DMF, 90 degree centigrade. This bromine is displaced with aldehyde molecule. So now this CHO is there. So carbonyl is coming from the carbon monoxide. This hydride is coming from $HSiEt_3$.

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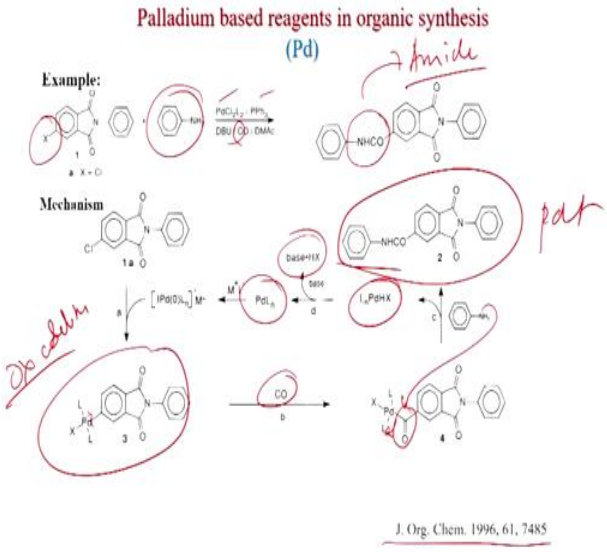

So this is another example - like here phthalimide with substituent is there and there the amine is the nucleophile and carbon monoxide of course is present there with ligand triphenylphosphine as the base, then you get the amide. So this is the amide. So what is the mechanism. So mechanism is same. The oxidative addition happens here as you have seen the oxidative addition done.

And now carbon monoxide will attack to this one. Carbon monoxide actually inserts this bond; palladium carbon bond and carbon monoxide is present here now. Now a nucleophile will react to this activated intermediate. Like this your palladium will eliminate to generate this and, of course, you will get your product here.

This is product and this is the catalyst become like this. Now with base, HX will, base HX will take up and your palladium catalyst will be regenerated. So, this is the overall reaction and this publication JOC 1996. So this very important depending on the nucleophile you get different carbonyl compound like amide, esters, aldehyde.

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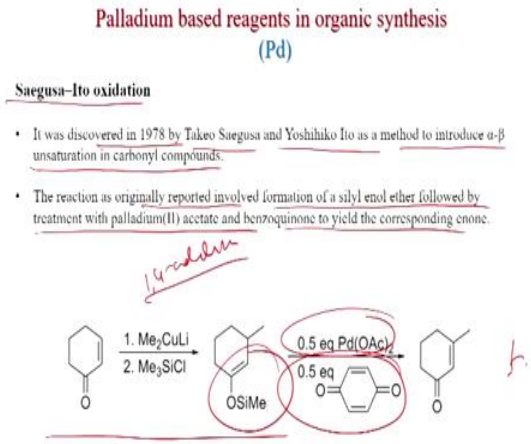

Now we will discuss another oxidation - Saegusa Ito oxidation. This is process is for the conversion of saturated carbonyl to unsaturated carbonyl. So it was discovered in 1978 by Takeover Saegusa and Yoshiko Iko as a method to introduce alpha beta unsaturation in carbonyl compounds. The reaction as originally reported involved formation is a silyl enol ether followed by treatment with palladium(II) acetate and benzoquinone to yield the corresponding enone. So this is important that cuprate first add to the 1,4 addition followed by enol silane formation to get this, enol silane. And now if you put palladium acetate 0.5 equivalent and this is oxidant 0.5 equivalent para-benzoquinone to get enone.

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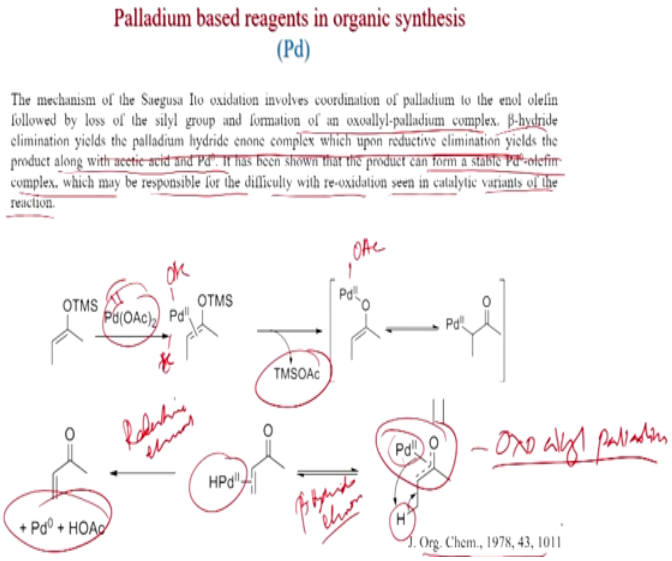

So mechanism is there; the palladium acetate reacts first coordination. Remember here palladium is (II) is present. And after that here two acetate are there: one acetate will eliminate like TMSOAc. Here now one acetate. Now this oxygen will coordinate with palladium. First oxoallyl-palladium complex will form.

So, first this one will be equilibrium with this one. So this is called an oxoallyl palladium, oxoallyl-palladium. So in the oxoallyl-palladium, this palladium is interacting with this oxoallyl species. Now, what will happen, this palladium will see this neighbouring hydride. So what happen the beta hydride elimination will happen, beta hydride elimination and what happens after a beta hydride elimination, of course, you get a double bond.

Now your hydride is going the palladium and double bond is generated, of course, after the reductive elimination, reductive elimination. It generates reductive elimination is the product along with acetic acid and palladium(0). It has been shown that the product can form a stable palladium(0) olefin complex which may be responsible for the difficulty with re-oxidation seen in catalytic variants of the reaction. That is why stoichiometric amount of palladium is used generally. And this was published in JOC 1978.

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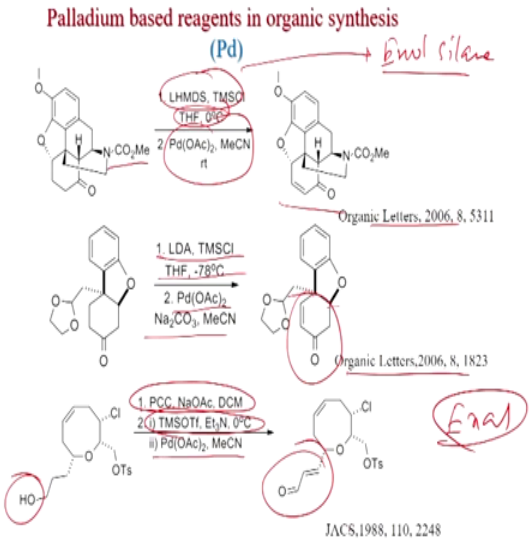

So we will see some examples. Here suppose saturated ketone is there- 6 membered ring and many; this is complex structure. Many functional groups are present here. Carbamate motif is there and under this condition first you have to make an enol silane with LHMDS, TMS chloride, THF 0 degree centigrade. So you make an enol silane and then you put palladium acetate, acetonitrile at room temperature you get the enone in high yield. This was published in Organic Letters 2006.

Also if you see this structure, here also a carbonyl compound is there. Similarly, LDA, TMSCl to generate enol silane, THF at -78 degree centigrade, palladium acetate, sodium bicarbonate, Acetonitrile you get this enol because this hydride elimination will be difficult that is why the less substituted carbon atom, there the hydride delivery is happening. This was published in Organic Letter 2006. And this is a larger ring.

Here, the alcohol you have to oxidise is PCC to generate the aldehyde and the aldehyde then you make a enol silane with TMSO triflate, trimethylamine and with palladium acetate acetonitrile you get the alpha beta unsaturated aldehyde. This is called enol. So enoas as well as the enols can be generated by the Saegusa Oxidation method. This was published in JACS 1988.

So today whatever we have seen? First the Wacker process we have seen. The Wacker process - a terminal olefin generally converting to ketone or aldehyde. Ketones are forming, that is the normal product Markovnikov pathway. On the other hand, aldehyde can be formed when there is steric effect at the substituted carbon atom or there is a non classical carbocation formation we have seen that the olefin, external olefin stabilising the carbocation then you can get anti Markovnikov product.

Then we have seen the Tsuji Trost allylation. Here the allyl X, where X is a leaving group and nucleophile can be, soft nucleophile as well as a hard nucleophile. So soft nucleophile we have seen the retention of stereochemistry, hard nucleophile the inversion of stereochemistry. Also asymmetric versions are possible with chiral ligands. Then we have discussed different cross coupling reactions.

Heck cross coupling; here the syn addition and syn elimination is very important. So cyclic systems, the cyclic olefin, the double bond has to isomerise that we have seen. And then we have seen the Negishi coupling; here the zinc are used and Kumada coupling; the Grignards are used. So Grignard, the alkynyl Grignard can be used for the generation of substituted alkynes. And Sonogoshira coupling we have seen.

There the alkynes can be used; the terminal alkynes, palladium, copper cocatalysts method to catalytic cycle are there to generate the substituted alkyne. Then we have seen the Buchwald Hartwig amination. Here the amine has to be used and you get the aminated product. Then we have seen the carbonylative reaction where carbon monoxide is used with external nucleophile. Depending on the external nucleophile you can get ester, amide, as well as the aldehyde.

And lastly we have seen the Saegusa oxidation. It converts saturated carbonyl to unsaturated carbonyl via enol silane and stoichiometric amount of palladium acetate is used. And this method we have seen can generate also enals that is the alpha beta unsaturated aldehyde as well. Thank you.