Advanced Transition Metal Organometallic Chemistry
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Lecture – 36
C–C Cross Coupling Reactions: Allylic Alkylation

Welcome to this course on, Advanced Transition Metal Organometallic Chemistry. We have been discussing an interesting topic which is CC cross coupling reactions, these are palladium based cross coupling reactions and one of the famous recent reactions to have won the Nobel Prize and also had made an elaborate journey from the confines of laboratory to the large-scale industrial usage.

So, this cross coupling reaction has gained its prominence particularly because of several reasons that first and foremost is that, in these palladium mediated cross coupling reactions that there is no possibility of forming the homo couple product, only the 100% exclusive cross coupled products are formed and that palladium is tolerant to very many functional groups as a result of these palladium mediated cross coupling reactions has a large scope of substrate variation, secondly these palladium does not have any toxicity issues which may cripple the large-scale usage of metal mediated catalytic reaction, reaction.

And third, an important factor which goes in favor of palladium is that the Palladium is way to cheaper even though it is an expensive metal but it is relatively a comparative way to cheaper than the magic metals of catalysis like rhodium iridium and platinum. So all of this has tilted the balance in favor of palladium mediated cross coupling reactions and it has really lived up to its promise in the sense that it has shown tremendous utility in various facets of organic synthesis where these reactions have been used extensively.

We have dwelled upon these cross coupling reactions in detail in the previous lecture, and we are going to be talking about some more about it before we go to allelic alkylation reactions.

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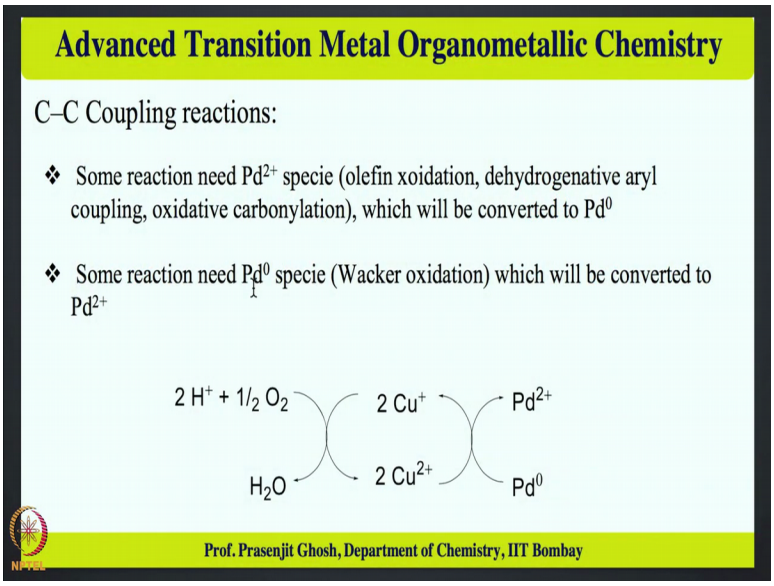

Now as was discussed in the last class that palladium mediated cross coupling reaction, sort of proceeds with palladium 0 which is the active species and even though the Palladium2 precursor is used and these palladium 0 active species is formed from the palladium2 plus active species in presence of some base like phosphine which converts palladium 2 to palladium 0 which then enters the catalytic cycle.

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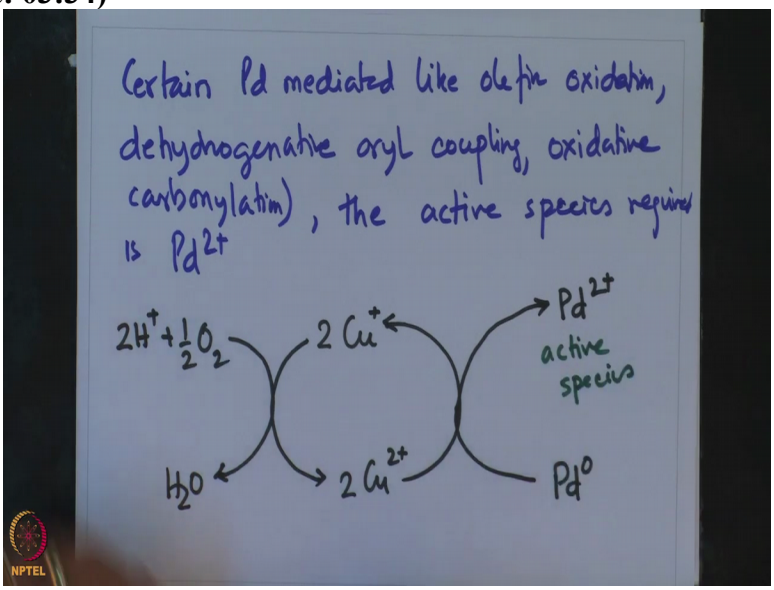

However for certain reactions like olefin, oxidation palladium mediated reaction, like olefin oxidation dehydrogenative aryl coupling, oxidative carbonylation, that the species, the active species, required is palladium 2+, so this is kind of different from that in other cross coupling reactions where palladium 2 precursors gets converted to palladium 0, whereas in reactions like

olefin oxidation dehydrogenative aryl coupling or oxidative carbonation that if species required is actually palladium 2+ and that gets converted to tell them 0 during the part of the reaction.

And these is achieved by putting a separate metal which will convert palladium 0 to palladium 2 so as a part of this and for example in Wacker reaction, copper 2 copper 1, a redox couple, is used to generate palladium 2+ which is used for this reaction.

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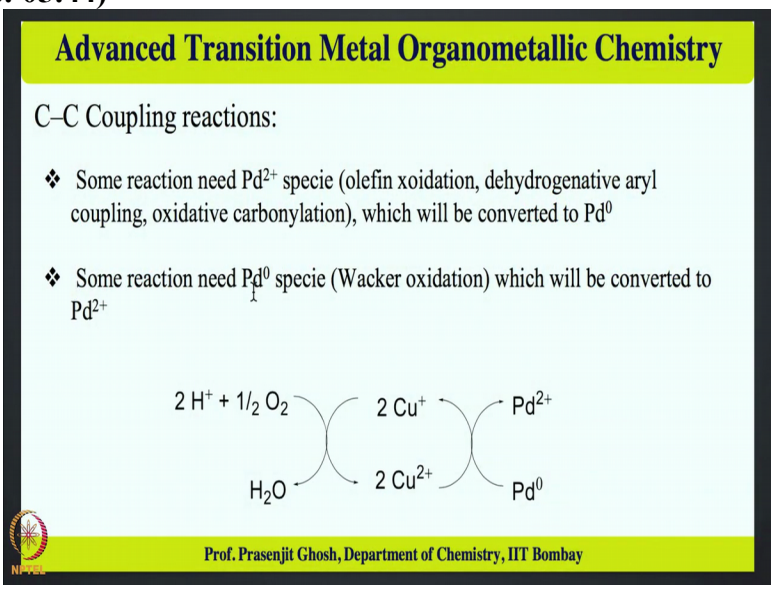

I am going to illustrate this with this beautiful example where this copper 1 copper 2 shuttle plays a prominent role and that can be seen over here, 2Cu+ reacting with 2H+ + 1/2 O2, generating H2O and 2Cu 2+, now these 2Cu 2+ would then oxidize palladium 0 precursor to give the active species plus 2 in the following way. Palladium 0 to palladium 2 + and then copper 2 would get reduced to copper 1, and palladium 0 would get oxidized to palladium 2 and then this palladium 2 would be the active species required in this catalytic cycle.

So, what we, what we see, is that for palladium mediated cross coupling or palladium mediated CC bond forming reactions, there, certain reactions require palladium 0 as the active species like cross coupling reactions and certain reactions require palladium2 as the active species and for those there is an additional copper2, copper 1 couple is required, and these are mainly used for Wacker reaction, oxygen, olefin oxidation.

We have dehydrogenative aryl coupling or oxidative carbonylation reaction. So we are going to be discussing all of this reaction in bit more detail and to begin with let me just talk about allylic alkylation reaction.

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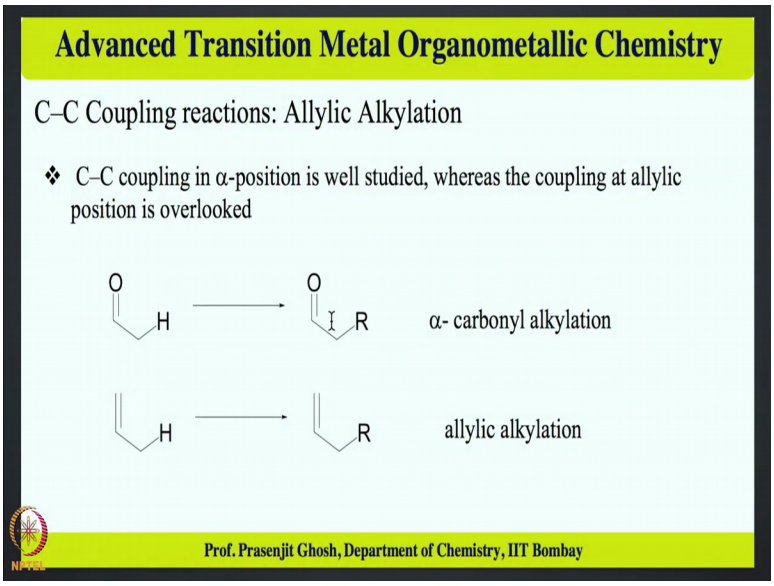

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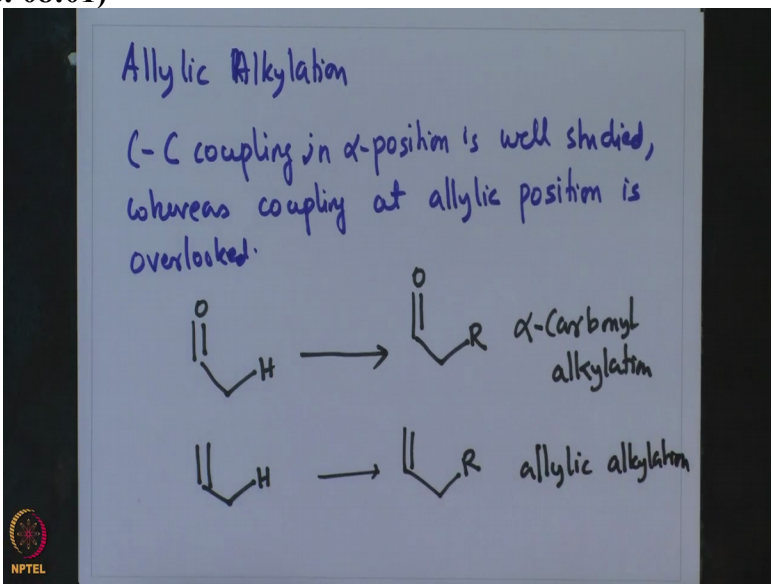

Now, this allylic, now CC coupling reactions, in this context, it is worth noting that, CC coupling reaction, in alpha position is well studied, whereas coupling at allylic position, is overlooked. Let me illustrate this with the following two example, for example, for the compound, this hydrogen getting converted to an alkyl group, this is called alpha carbon in alkylation, whereas allylic protons getting converted to an alkyl group is called allylic alkylation reaction.

So, these aryl calculation reaction is a sort of less studied to that extent and we will to start looking at this allylic alkylation reaction, where does allyl alpha position of the allyl group, this hydrogen gets replaced by an R and we are going to proceed by looking at the mechanism in which this reaction works.

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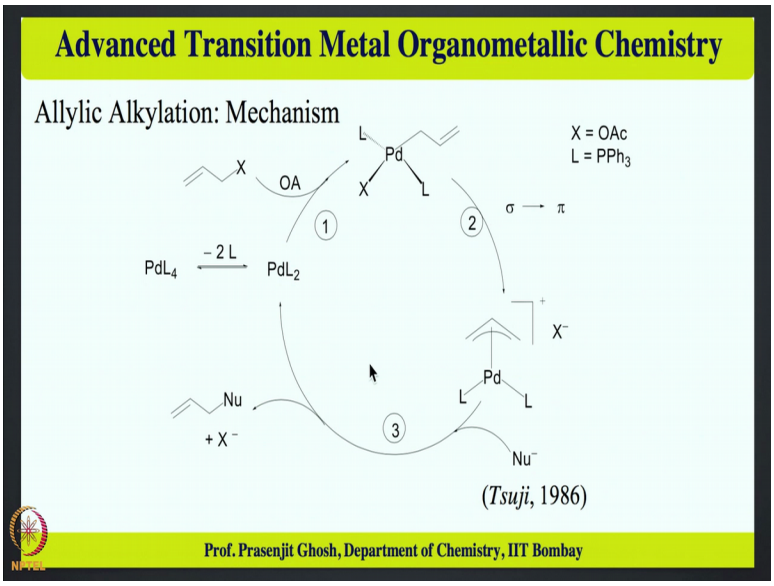

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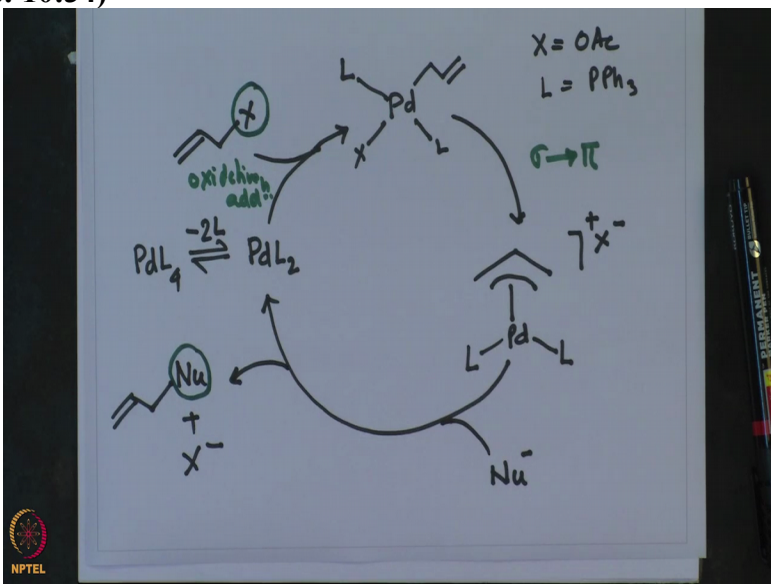

Now to begin with a palladium 0 species like PdL 4 in loses 2L to give the Pd coordinatively unsaturated PdL 2 which reacts with allyl halide in a step which is called oxidative addition, to give the oxidant oxidatively added product. Now this oxidatively added product where X is OAc acetate and L is PPh3, then oxidative values product then undergo a Sigma Pi type re-arrangement of the type shown over here.

To give Pd, allyl Pd L L+ X-, so over here this sigma bonded palladium allyl has become eta 3 bound PI bounded allyl ligand, and this X has dissociated to become an un coordinating counter and the step three then involves addition of nucleophile which goes and attacks with the

generation of the substituted product plus X-, along with regeneration of L 2 which then enters the catalytic cycle.

So, overall the reaction is such that, these X moiety over here, is replaced by this nucleophile Nu and at the allylic position the way it is shown. So, this is the nice reaction and that these also proceeds by three step, one involves, this oxidative addition followed by Sigma Pi rearrangement and followed by the nucleophilic attack re-routeing in formation of this allyl position getting the nucleophile and along with the recent regeneration of palladium 0 species.

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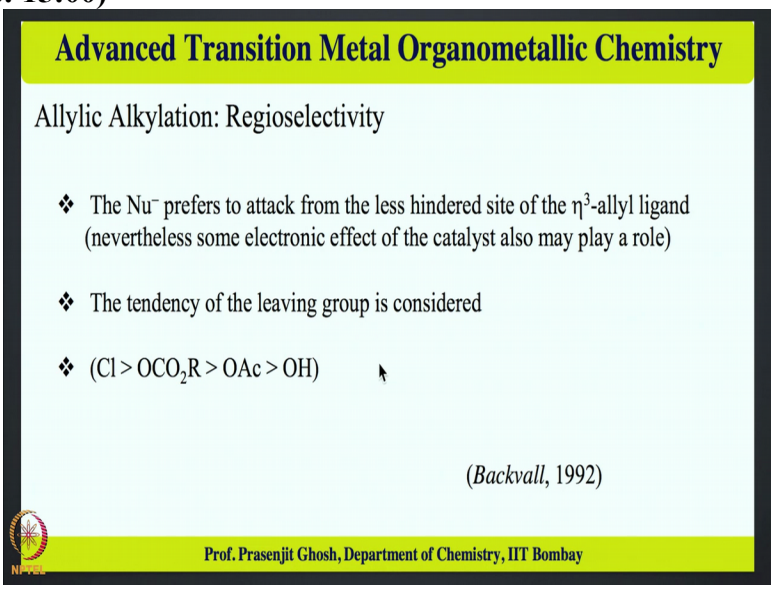

Now, this nucleophile, now it is important to look into the steps of this reaction and this nucleophile prepare to attack from the less hindered side and that is very nicely elucidated in case of cyclic substrates.

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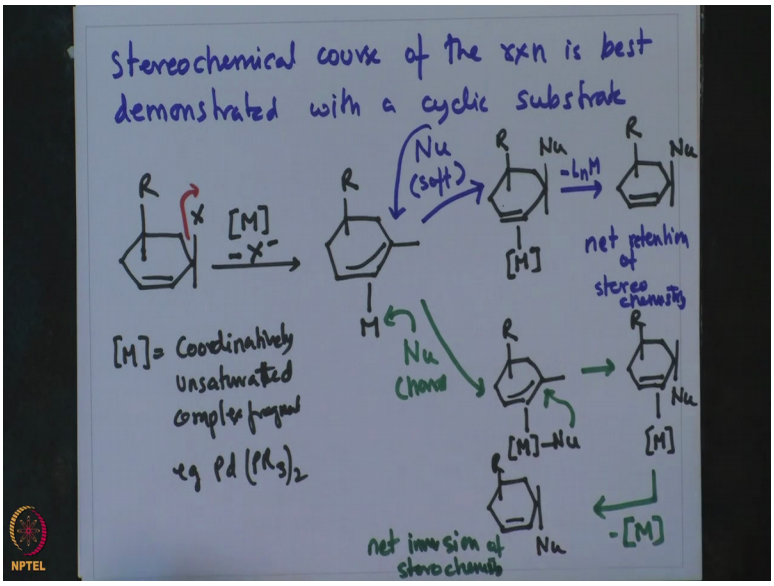

So, stereochemical course of the reaction is best demonstrated with a cyclic substrate and this we are going to show it for this set of cyclic substrates, where this is schematically shown as R X M and -X, M equals coordinatively unsaturated complex fragment, natively unsaturated complex fragment example Pd PR3 whole 2, then that undergoes attack from a nucleophile. So this reaction attacks the X, leaves, giving rise to these allylic metal complex X leaves, takes minus stimulise to these allylic metal complex of the type this, and this may be, illustrated by;

Now, to this when a nucleophile which is a soft nucleophile attacks, then attacks happen from the less in that side, giving rise to this compound which is a Nu R and that eliminates L and M to give this compound Nu R. So what is interesting over here if one compares with the initial RX structure, that this is net retention of stereochemistry. Now in case of hard nucleophile, when a Nu is hard, then hard nucleophile attacks at the metal and our different reaction proceeds.

Now in this case the metal stays bound to a Nu and then the nucleophile now attacks from the bottom part of the ring, resulting in, the nucleophilic addition to the ring, which is Nu, R, M and this eventually will lose M, to give the corresponding compound, which is, this and if one were to compare the stereochemistry of RX with our nucleophile, this is net, this is net inversion of stereochemistry.

And so this is a interesting example where one can see that the stereochemical course of the reaction in which the attack will commence, dependent, depends on, what kind of nucleophile that one uses and what is seeing that in case of soft nucleophile the attack happens for the, from the exo side, from the further side and as a result of which net retention of stereochemistry is

observed and this is shown in the blue by the blue arrows or the pathway depicted by the blue arrows and these proceeds in case of the soft nucleophile.

However the scenario is different when the nucleophile is a hard nucleophile and in this case the hard nucleophile instead of attacking at the alpha allylic position, attacks the metal, and first binds to the metal and then the metal bound nucleophile does one additional step in which the nucleophile attacks from the bottom of the, from the endo side, resulting in the net inversion of stereochemistry from its starting point, so this is a beautiful example which elucidates or explains the kind of stereochemistry that is observed and which is dependent on the type of nucleophiles arrayed.

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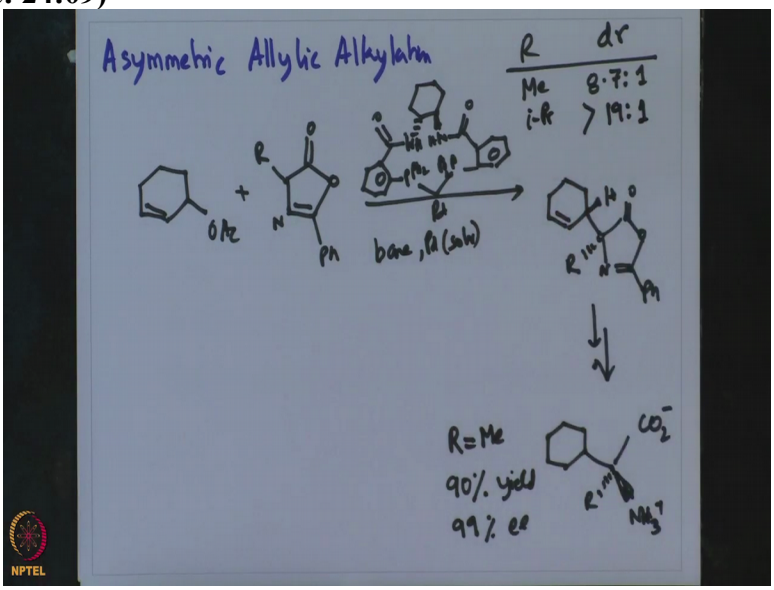

Now we are going to also look at another interesting form of this allylic alkylation and this is a symmetric allylic alkylation and in this case there is this 2 compound one is as shown over here, OAc reacting with the black tone substituted and it uses big chiral catalyst shown over here, PPh2, PPh2 and both of this bound to palladium base and salt dissolved, now this gives to this allylic alkylation product hydrogen P 8 R. So that is too many carbons which after work out, would give the following, MNR thrice, R equals methyl and 90% yield and 99% ee.

So, this is a very useful method in generating this amino acid containing a cycloxyl group and before this final work up the diastereomeric ratio that was observed as for R, R equals methyl, these to ratio was 8.7:1, for these two chiral atom or when R becomes isopropyl, this even becomes 19:1, so this is a nice demonstration of how the influence of R can tilt the formation of

the product favored formation of one diastereomer over the other, and how allylic alkylation has been exploited by using this chiral catalyst.

So, with these I would like to come to conclusion of today's lecture. Today we had started by looking at the various kind of catalytic cycles, to begin with, and what we had seen that in the most commonly observed palladium palladium cross coupling reaction, the catalytic cycle initiates with that species ring palladium 0 whereas in certain other reactions like olefin oxidation as well as dehydrogenative aryl coupling or oxidative carbon relation palladium 2, is the active species and that has been achieved by coupling it to a shuttle a copper 2 copper 1 shuttle in presence of air which dioxygen is converted to water.

We had then moved on to look into allylic alkylation reactions and despite alpha alkylation has been quite studied allylic alkylation remains kind of less explored and what we see that these allylic alkylation reactions, proceeds in three steps the first obvious of course is a oxidative addition Sigma Pi rearrangement followed by the elimination nucleophilic attack giving to the eliminate elimination of the alkylated product.

And then the regeneration of the Palladium 0 species. What we had discussed further is that the stereo chemistry of this allylic alkylation reaction is best illustrated for cyclic substrates and for which we had seen, that if the nucleophile is soft, then the attack at the allylic position happens from the exo side, resulting in the net retention of configuration whereas for hard nucleophiles the nucleophile first go and attack the metal center and then carry out an endo attack reason resulting in net inversion of stereochemistry.

Lastly we had also looked into one example of asymmetrical allylic alkylation and what we had seen that this is quite an effective and useful method for preparing amino chiral amino acids with high yields and high antae selectivity and also we saw that for an intermediate species before workup, one can tilt it to its favored by increasing the bulk on going from aryl methyl to aryl isophyl and the diastereomeric ratio changes from 1:9 to 1:19, that is almost double.

So, with that I would like to conclude today's lecture, now we are going to be taking up another very interesting about this noble prize award winning cross coupling reaction, the heck reaction in particular, in the next class and that will be taken up in the next class and I thank you for being with me in this class and I look forward to take up a coupling in the next class, in much more detail. Till then good bye and thank you.