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NATIONAL PROGRAMME ON TECHNOLOGY ENHANCED LEARNING

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Organometallic
Chemistry-I
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Module No. 4

Lecture No. 18

STEREOSELECTVE HYDROGENATION REACTIONS

Welcome everyone today we will discuss on stereoselective hydrogenation we would like to specifically go about the molecule where we can get the stereoselective. And then how the hydrogenation reaction can be utilized to generate with the steroselective. For example, all of us are aware of the fact that there exists a number of naturally occurring amino acids right, nearly 20 of them right.

Now if you want to synthesize any unnatural amino acid or the other isomer of the amino acid which is not naturally occurring what are the techniques that you can use that is one of the way to solve these or to get this compound is to really do the hydrogenation reaction. So stereoselective hydrogenation that first we will discuss with the rhodium catalyst.

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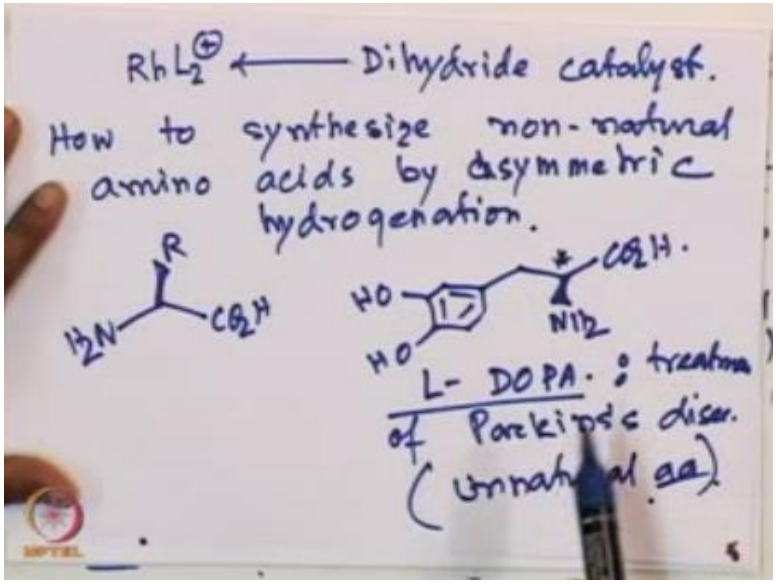

Of course, the catalyst that we will be discussing today first is the rhodium L_2^+ that is the one which is the dihydride catalyst okay dihydride catalyst this is the one we will be discussing and you know of course, the topic would be how to synthesize first we will discuss how to synthesize non-natural non natural amino acids amino acids by hydrogenation, asymmetric hydrogenation okay. That existed number of number of important molecule first of all you know let us try to look at the general formula of amino acid, this is the general formula general substrate for non natural amino acid.

And of course another one very popular is the L-dopa, L-dopa is the one where you have NH_2 and CO_2H. So this is going to be your L-dopa and this is the one which is used for treatment of Parkinson disease as you are aware of Parkinson disease and this is the one which is an unnatural one unnatural amino acid. So you can understand that it is very, very important to synthesize this molecule because this is the only good drug.

Let us say for example for Parkinson disease, there are a number of target molecule where you need an asymmetric center like this where I think hydrogenous and asymmetric hydrogenation comes to rescue and this is one of the more really a broader reaction a reaction which is more

reliable for asymmetric synthesis okay and we will discuss today briefly about the asymmetric synthesis how for example your L-dopa can be synthesized by asymmetric synthesis.

Let us try to look at that the starting material of course you need to have is the one with olefin let us say for L-dopa case corresponding olefin where the asymmetric center is there if you can have the corresponding olefin then you can expect to get the essential hydrogenation reaction.

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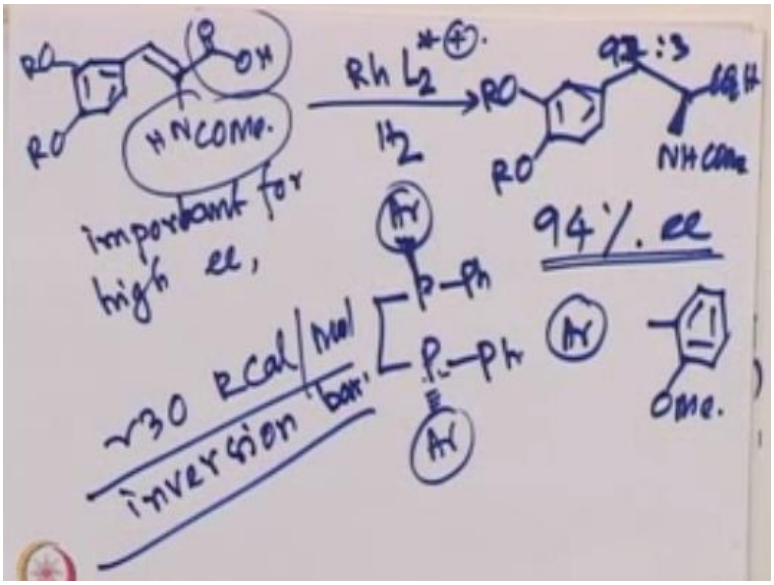

Let us try to draw this overall this substrate where this over or protected maybe and then you get the double bond this is your precursor and you need perhaps NHcome because these are the one which will be important both these groups will be important for high enantio selectivity important for high enantiomeric excess right enantiomeric excess so this in this particular case the amide binds to rhodium and of course acid will bind to rhodium both of them are coordinating therefore these are the one which will coordinate with the olefin or help guide the olefin to the metal centre overall if you have a asymmetry catalyst.

So there is no centers which will direct which whether Rh product will be forming at the center so therefore you need in ligand which is which is chiral so chiral ligand is required and you will

get the hydrogenation to give let us say for example you are the one going to synthesize the l-dopa by this method so this is going to be up in NHcome and CO2H right now for particularly for this case you 94% ee with a phosphine ligands this L2 you can have like you know previously we have seen two different triphenylphosphine was there as L2 you can have one substrate.

Let us say for example these are ethylene Phosphine diphosphine ethylene diphosphine where one of the group is aryl group another is final then again another group will be the aryl group another is final now this aryl group this array almighty the one over here can be the one for example particularly for this 94% ee in the literature it is going to be this one so why one thing as you can see in this example that the corresponding olefin is taken along with a by coordinating you know auxiliary which will coordinate or which will help direct the olefin to the metal centre but there is no asymmetric induction in the substrate itself.

So you start with an a chiral substrate or then there is no chiral center in the substrate you need the stereo induction in the form of the ligand now the ligand is going to be very important for the rhodium as use as you know for Schrock Osborn response catalyst specifically it is a these coordinating ligand in this particular case we have this ethylene diphosphine okay dpp e type of ligand diphenylphosphino it ethane ligand where the phosphine is substituted by two phenyl ring one is going to be your aryl ring another is another is going to be the simple phenyl ring this is a chiral or pure enantiomeric excess will be they are completely irrelevant, in this particular case we know that this aryl group is going to be in the one which is ultimate oxy one and this gives very good EE up to 94%, 94% means the ratio is basically 94:2 right.

So now sorry this is 94% EE that that means it is a 97:3 so this product is 97 and the other product is 3 overall you get the 94% EE, so the one up this air this group is up is 97% and the three percent you get where this is below, now this is a very good EE which is acceptable another thing which is important that these phosphines has the rotation inversion barrier nearly 30kcal/ mol.

This first thing has inversion barrier 30 kcal/ mol this inversion barrier is good enough to get this product in pure form but term inverse and barrier right but if you get the corresponding amine for example nitrogen over there and this will not get give you an enantiopure these di-amine because the inversion barrier is so little that you will not be able to get for the nitrogen if these two are nitrogen you will not be able to get the compound in enantiopure form, okay.

So what we have learnt right now is very simply if you have a di-phosphine ligand, okay this di-phosphine ligand can have the chiral center okay at both the phosphine center and therefore it can be acting as a bidentate ligand for the rhodium for example for shock cause bone catalyst which is the origin of stereoselectivity in your hydrogenation reaction now if you take for example any oily film where you can potentially generate the stereo center.

Then you can you can expect by suitable having suitable R group or aryl group on the first thing you can you can get a decent enantiopure metric excess in this particular case we have seen the dopamine l-dopa synthesis or precursor for l-dopa synthesis which is the corresponding olefin we start with and we get very good EE such as 94% EE another substrate we can briefly discuss is of the sweetener as part in. That is again thus corresponding starting material is required and for the for example as part time as you may know.

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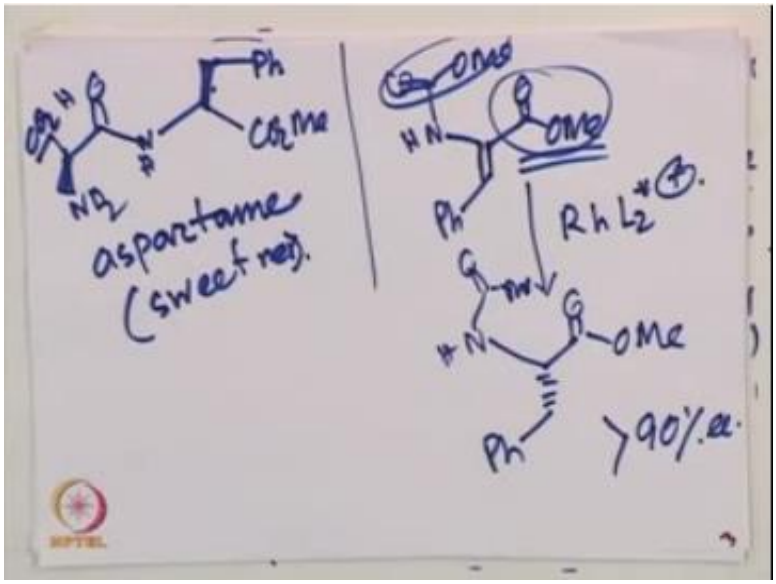

Is the one where we have this you know Co_2 any over here and Co further NH_2 over there Co_2H now this is as patent this is artificial sweeteners right now you can get for cost for synthesizing this you can have a precursor where you have this you know the coordinating unit is your CO2 OMe unit along with this CO Me unit leads these both these unit will help you doc the metal center perfectly so that only one pace of this double bond is available for hydrogenation reaction in this particular case you will end up getting the product with a corresponding hydrogenation product with greater than 90% ee right.

This is with again rhodium l2 plus right this is with rhodium l2 plus okay so what we have seen so far in this case is you know of course you will have NCO Me along with it but we have seen over here the a Spartan synthesis which is a sweetener okay we get we can we can have quite easily and as patent corresponding starting material with the double bond can be hydrogenate stereo selectively to give you the very good ee right so Shrock Osborne catalyst as we have seen so far it is very good for a symmetric hydrogenation reaction it indeed industrially a number of hydrogenation reactions are done.

With the Shrock Osborne catalyst of course you have to choose the right phosphine ligand if so to speak the diphosphine ligand to promote high level of enantio selectivity we have seen the example of aspartame and thel-dopa synthesis now we will see if how you have a directed dash to your selective hydrogenation reaction okay next topic briefly we will discuss Directed Diasteroselective hydrogenation reactions.

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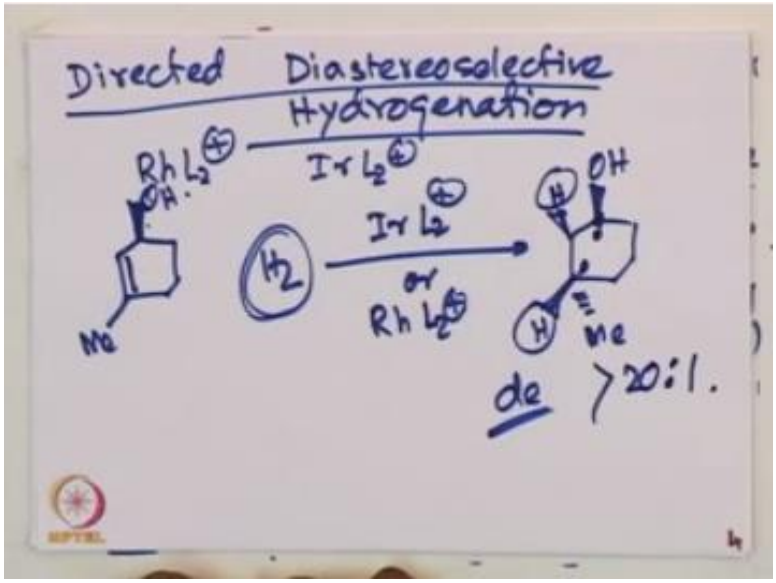

You now of course the good catalyst for very for this purpose is always going to be again going to be your Shrock Osborne catalyst or even the rabtree's is catalyst right these can be using quite good effect the directed dash through selective hydrogenation usually mean that you have a directing group into the substrate itself which is chiral center for example over here this is the one which will which will be useful so you have the hydroxyl above the plane in this case okay, and you want to add hydrogen to it for example with IrL2+ which is again scrubbed ridge catalyst or you can take RhL2+ which is again Schrock-Osborn one catalyst overall in this case you are going to get the hydrogen addition from the same plane as you are having the hydroxyl.

So hydrogen will be above the plane that this is the hydrogen that is coming from here these two hydrogen and the methyl group will be below the plane and diastereomeric excess in this case

because there are two centers this one and tha tone so these are going to be diastereomers the products are going to be diastereomers, diastereomeric excess in this case is going to be 20:1, okay.

Now so this is a very again it is a directed diastereoselective hydrogenation reaction and it is very important reaction because you have a cyclohexene moiety which is substituted by methyl and you know with respect to that methyl you have at the β position there is a hydroxyl group which is above the plane if you have that substrate you can have with either with let us say Schrock-Osborn catalyst or will or your on your cavities catalyst you can promote asymmetric hydrogenation and on this on the substrate where the both the hydride adds sink to the hydroxyl group which is on the top of the plane in this case both the hydride will be added from the top of the plane to give you the diastereomers, diastereomeric excess found to be quite efficient if you will see particularly in this case.

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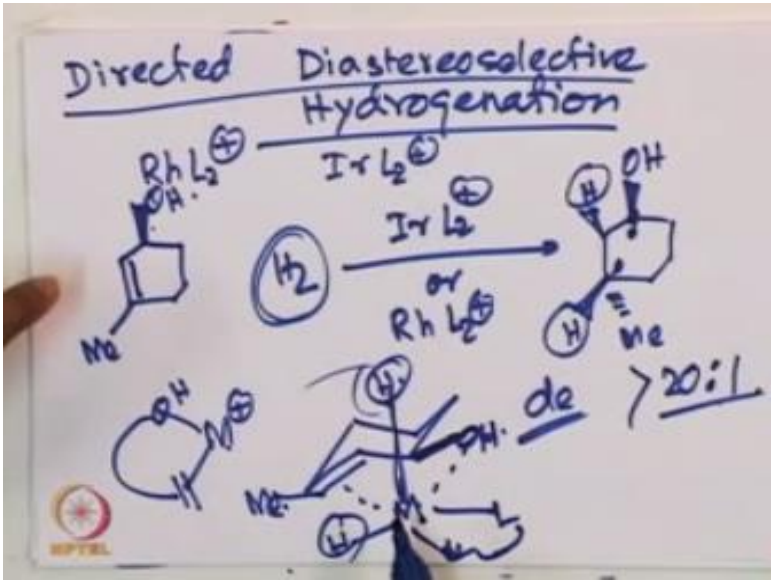

We have 20:1 diastereomeric excess of course the binding to the metal side if this is the rhodium or iridium center if your hydroxyls over there it binds more of like this and then of course over here β migratory insertion occurs here hydrogen adds that is why hydrogen addition from up

sight indeed you know this is the site which is inner by the hydroxyl group. If you want to draw in a little bit more understandable fashion you can have something like you know hydroxyl up and methyl will be let us say over here so the way it would be attaching to the metal centre will be like this and the hydride is over here and then hydride is over here your this by coordinated ligand is over here.

So in this model as you can see hydride has only one way to add that is from the top phase, so the same phase where the hydroxyl is there the same phase the olefin will be hydrogenated so both the hydride will be coming from the top phase so this is what is called directed hydrogenation so this hydroxyl group is directing the hydrogenation reaction, so the bigger migratory insertion is taking place at a site where you have the hydroxyl group is directing from it.

And this particular example we will have seen that a hydroxyl group is directing the hydrogenation reaction and we are getting a particular product if hydroxyl is up then corresponding hydride which are adding is from the same plane right, now the question is if still let's say you have a hydroxyl up above the plane and you want to have hydride addition or the hydrogen addition from below the plane because you want to have the other das trauma how can you get that.

Simply you know the answer to such question is since hydroxyl is directing and the hydride is adding to the same plane from where the hydroxyl group if it is above the plane it is hydrides are adding from above the plane if it is below the plane hydrides are adding from the below the plane so to prevent that if you convert the hydroxyl group into the corresponding alkoccy or some bulky OR group then it is more of a streak hindrance from that side and therefore of course it will not be that much coordinating therefore the directing ability will be somewhat loss and acting as a more of a streak hindrance.

Since let us say if the OR group is instead of hydroxyl you have a wire loop and that is on the top now the hydride addition will be from the bottom side let us draw that one okay.

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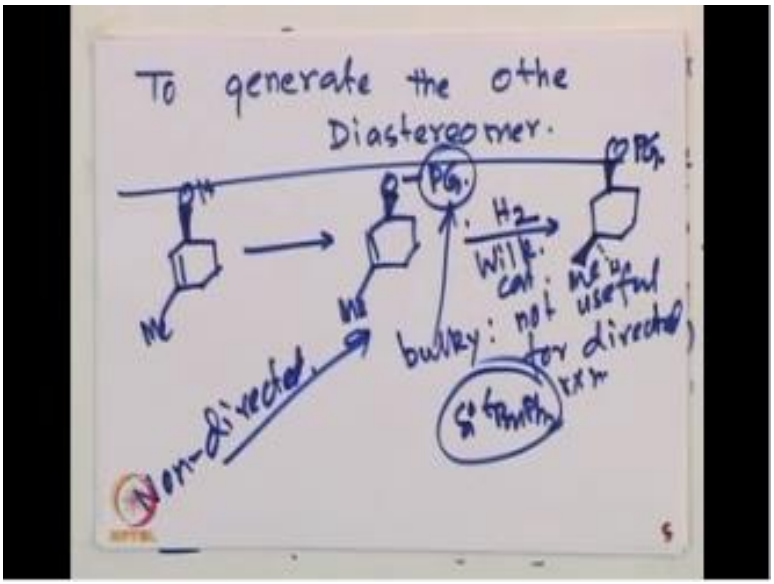

So to generate the Diasteromer what we will need to have is instead of the hydroxyl let us say we were having the hydroxyl from top okay and we are having the hydride from top as you have seen in the last place now what you need to have is a protecting group opg of course still hydroxide on the top O protecting group if you have that now what you have is this is a bulky group okay.

So this is bulky therefore not useful for useful for directed reaction directed reaction and let us of course what the protecting group could be you could have silyl protection silyl tar-butyl life in 9 protection and so on of course and then you can have the hydrogen gas let us say for example Williamson catalyst Wilkinson catalyst you can use now instead of methyl below you have the methyl up, because hydrogen edition is going on from the below side so hydrogen from the below just opposite to what you have seen in the last class okay.

So this is not directed anymore, this is not non-directed okay no directed hydrogenation you get, of course rhodium and iridium are good for directed one, and Wilkinson catalyst for the non directed one. so what in these two examples what we have seen, that in the last example as you

as you remember in the last case, we have the hydroxyl, hydroxyl which is directing and therefore method is coming down, and hydride is coming up, hydride is coming up.

So hydroxyl up, the hydride up methyl down, the one we have discussed right now with a protecting group, methyl is up of course these alkoxy is up, or and then hydrogen is adding from downside. So what we need to cases we have seen in the first place hydroxyl is acting as a directing room, okay and therefore thus from the same plane where the hydroxyl is so the one we have drawn hydroxyl from the top lane.

So the hydride addition happen from the same plane, as you have also shown by the drawing that how the hydride is adding from the same plane, and therefore both the hydride will be above the plane, and the methyl is going to be the below the plane, but in the next place when hydroxyl group is now protected with a protecting group, such as the slide protection with it with a bulky substituent on the seal-oil, group then what we have seen is it is no longer a directing group it is more of acting at the steric bulk.

And therefore the if it is on the steric bulk is on the top, and then if the hydrogen addition will be from the down side, or the below side and therefore methyl is coming at the topside, and there you see this is the way you can get both the dash to your mark, AZ as you may need and for the one with the protecting group, your simple milking some catalyst which is going to be the best one, and actually it is the cheapest one among the stock Osborne and the Iridium catalyst that is the crab dredge catalyst.

But of course for the directing group you were, directing group assisted hydrogenation one you have struck husband catalyst or the or the crab tree is catalyst as the be stone okay, we will stop here today ok I hope you will keep reading more about this from various books, and till then you keep studying we will see you in the next class thank you.

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