Course on Stereochemistry
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Mod08 Lecture39
Facial Selectivity and Examples of Asymmetric Synthesis

Welcome back , last time we were discussing, the stereochemistry of addition of nucleophile to a carbonyl in an acyclic system first, which is attached with an alpha stereogenic center and we have covered the crams rule, the different kinds of rules like crams rule then felkins rule the to predict the major product that is formed. We also have gone through the Prelogs rule and that is a remote induction kind of thing, but that was very helpful in identifying the configuration of an alcohol where the stereochemistry is not known at the alcoholic center.

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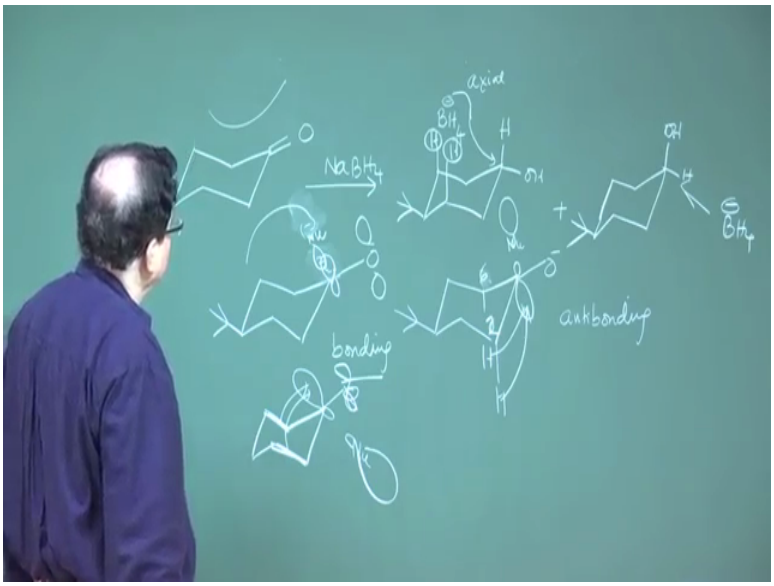

Now then we went on to the cyclohexanone system and we gave one more model in cyclohexanone that is the Ceplak model, so if we take tersary butyl cyclohexanone then what happens, if we treat with sodium boro-hydried then there is the major product formed is the axial alcohol is a equatorial alcohol and not the axial alcohol, remember the equatorial alcohol is formed by the axial approach of the boro-hydried. So the boro-hydried approaches from the axial face, to give the equatorial alcohol, okay and to get the axial alcohol, the boro-hydried

approaches from the apparently more sterically accessible equatorial side. So here this hydrogen comes from the boro-hydried. So that is approaching from the equatorial face.

So there was lot of problems in explaining this reaction, the stereo selectivity of this reaction and finally what happen, because (there is there are) this steric factors which is bother in people that this hydrogens should offer steric hindrance to the approach of the boro-hydried and this reaction is called steric approach control, because it is not product stability controlled and as I told you, it is an exothermic reaction. So you have to consider both the reactant and the substrate at the same time, okay. So that gives you this that you have to involve the boro-hydried as well as the carbonyl.

So when boro-hydried approaches, there is this the steric hindrance expected from the hydrides. now we will later on felkin gave a very good model, which is a which is based on the stereo electronic effect , the stabilization of the transition state, see when the nucleophile approaches from this side, so then if there is there is the anti-bond. If you consider the anti-bonding of this interaction, the carbonyl goes like this. So this orbital will now interact with a nucleophile orbital and that will give two seen arrow, one is bonding another is anti-bonding, sorry (when you) when there is bonding then the nucleophile orbital will, this is the bonding seen arrow and in the anti-bond seen arrow, because they are in opposite face.

So what will happen that the nucleophile will have the orbital towards the back and this orbital also will not try to face each other? They will be posing and there will be a small lobe on the front side okay. So this is the anti-bonding seen arrow and in anti-bonding seen arrow what happens now, at put the tersary butyl, because you want to stop the flipping that is the locking group. In the anti-bonding seen arrow, these hydrogens are almost aligned to this anti-bonding empty anti-bonding orbital of the carbon nucleophile bond and that undergoes hyper conjugative stabilization from electron donation from the hydrogens, so axial hydrogens at C2 and C6, okay at C2 and C6. In this case if you draw that is from the approach from the axial face. If it approaches from the equatorial face then the diagram will be that the anti-bonding lobe will be bigger on this side, the nucleophile is here.

The nucleophile lobe is like this anti-bonding and this is the oxygen lobe okay. So now what is happening that the only orbital that can donate here is this carbon-carbon bonds okay this

carbon-carbon bond and that is much poorer electron donor than C-C bond is much poor electron donor than C-H bond. So ultimately the major product is the approach from the axial face leading to the equatorial alcohol. So that was the status at that time then people started arguing that this may not be an ideal system to test Ceplaks hypothesis. Ceplak what he said that the transition state is stabilized due to electron donation from adjacent bonds to the anti-bonding to the incipient that means the forming anti-bonding orbital.

So now what was the criticism? The criticism was that, because the cyclohexane the two faces are not identical**,** okay. This equatorial face is geometrically not same as the axial face, because axial face you have these axial hydrogens, but in equatorial face you do not have those. So they are not the offering the same type of faces to the to the approach of the hydride. So that may not be an ideal system to really convince that ourselves that the Ceplak model is correct.

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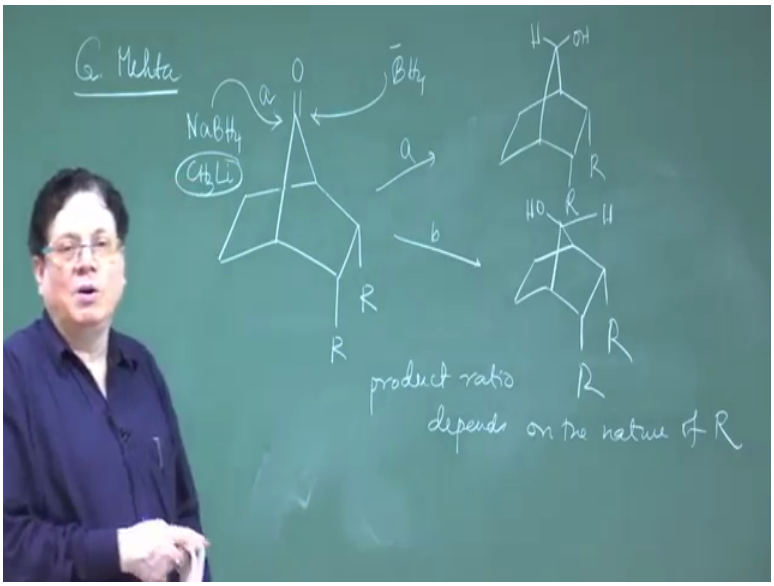

So in that case what we need to do is to take a carbonyl system where the both the sides are facially symmetrical, the both the faces are facially identical, okay like if you take a bicyclic system like this. This is by the way called a (())(7:21) system a nor bornan (())(7:28) system and if you put a carbonyl here okay. Now what happens? Now this is perfectly symmetrical, so if the nucleophile comes from this side or this side for a carbonyl addition, you get the same product, because you do not have any other substituent in the system, but what happens here? This face

the face this face is geometrically same as the other face, okay. So in that case you cannot say that there is kind of steric differences in the approach, of the nucleophile to the carbonyl, okay.

Now what you do? You put some substituents here, suppose I put a substituents R and R, okay. Now what happens the faces geometry are same, because these R groups are not interfering with the faces, because they are pointing downwards. So if the faces are identical, now the question is, now what happens? First of all if you do a sodium boro-hydried reduction, suppose or a methyl lithium addition, okay. So what are the products if sodium boro-hydried you get, so you get either this OH and H that means the H is approaching the boro-hydried is approaching from this face? So that is path a. So if the boro-hydried is approaches from the path b that means from this side boro-hydried then what happens? Then you get the, okay this R1 has to be R has to be there otherwise this products will become identical.

So now you have OH on this side and H on that side, R will be here and R will be there. So these are the products make sure that what I am saying that is right. So this is the path b for methyl lithium, it is the same. So I just exclude the methyl lithium. If the methyl lithium methyl comes from this side, so you get OH on that side. If the methyl comes from that side the OH on the left side it similar. So argument will be same. The question now is which one is the major product?

Now this is a work done by Professor Goverdhan Mehta, the famous organic chemist in India. So he wanted to he was a far believer of Ceplak model and then, but because Ceplak had lot of criticizes, because of the two unequal faces of cyclohexane. So he studied this nor bornan (()) (10:17) system nor bornanone and where the two faces are identical. Now what happens that what is the major product? That was the key issue. So what he found that the product ratio depends, on the nature of R groups okay, R groups can be two types either electron donating or electron withdrawing, okay. So that is a first thing that it depends on the nature of R. So how does it depend?

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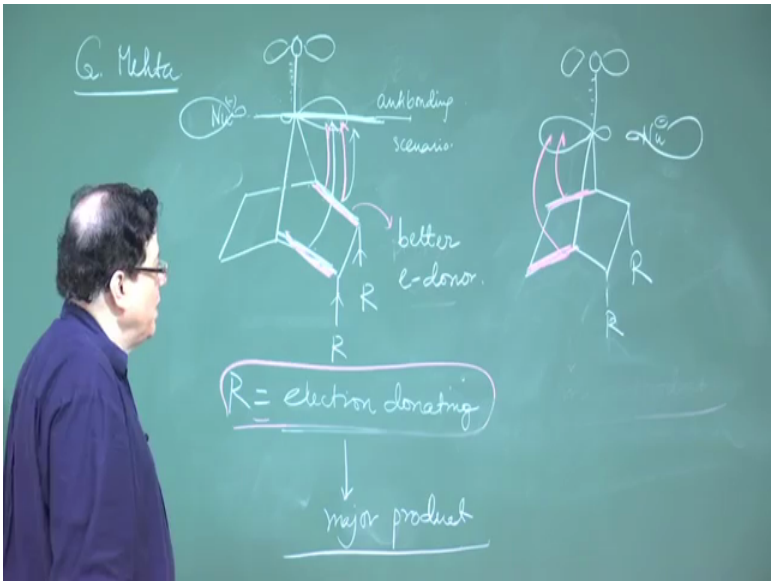

Now let us draw the orbital picture like what Ceplak did that when the nucleophile, in this case boro-hydried, okay approaches from this side the anti-bonding orbital will be, so that will be elongated, now that will be brocken little bit okay. So the anti-bonding orbital of this carbon nucleophile bond will be have a bigger lobe on this side and the smaller lobe on this side and this is empty. This is the anti-bonding say seen arrow, okay. Now if you look at this geometry, this line of the axis of this of this orbital that is not exactly parallel, but they are not also orthogonal. Their angle is not that much. So there is a possibility that these bonds, this is actually in the middle of this two bonds is in the middle between the two bonds. So that those two carbon-carbon bonds now can they donate to this orbital, okay.

On the other hand if it is on the if it is attack take if the attack takes place from the other side. So then what happens? You have, so that is the nucleophile. So there will be small orbital and there will be bigger orbital. Now these are the bonds**,** which are going to which are going to interact with the with this empty orbital. So these are the bonds, which are going to interact with this orbital earlier, these are the bonds, which are going to interact with this, okay. So question is which interaction? We know carbon-carbon donation is much less, but that is in comparison to the carbon-hydrogen. So if it is a carbon-carbon different type of carbon-carbon then we can make a comparison okay, remember there is R here and there is R here.

Now if R is electron windrowing then this will be a poorer donor. This C-C bond will be poorer donor, okay, because it is electron withdrawing, so it will not allow the carbon-carbon electron to interact with the empty anti-bonding orbital. On the other hand if R, so that means in that case we can expect that means we in that case, this is a better donor than this one. This one is a better donor than this one. So in that case this will lead to the major product, provided R is electron withdrawing that is important point. If R is electron donating now, so if R electron donating now so let me change it to electron donating exactly opposite situation will happen.

Now what will happens if R is electron donating then this will be better donor, because there will be more electrons pumping into this carbon-carbon bond say by inductive effect, suppose these are way these are methyl, suppose alkyl groups then that will happen and then this will be a better electron donor. So if it is a better electron donor, now this will happen, this stabilization will be more with respect to this stabilization. So in that case, this will be the major product, okay. So this is a very nice example of the validity of the Ceplak model when the nucleophile attacks to the carbonyl, okay.

So we are not going into other examples, because this is a as I said this is a foundation course, but up to this point is okay, I think for you guys' it will be easier to understand up to this point, okay. So if a problem is given on nor bornanone you can easily explain from which side the nucleophile will come that depends on the remote effect of this R groups. This is remote see the attack is taking place here and these R groups are quite far away, okay.

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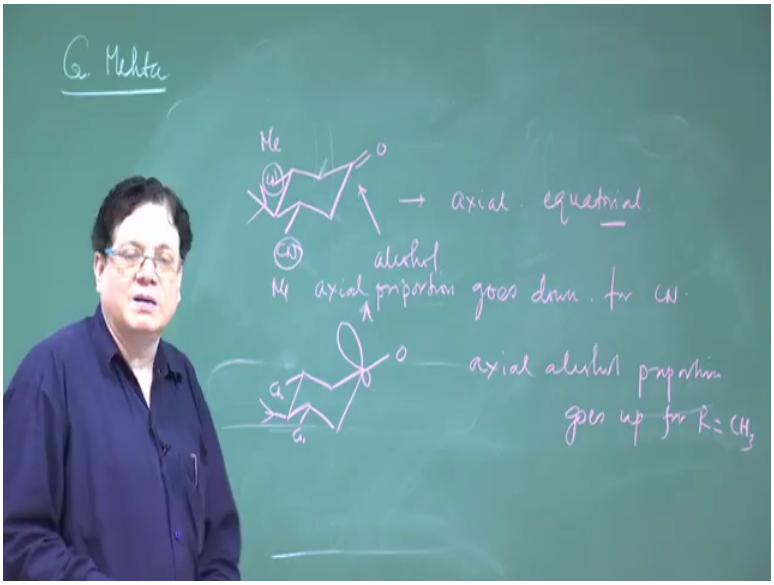

Now the same thing, I did not mention, the similar thing happens in Ceplak model that cyclohexanone also, see in cyclohexanone, we know that the equatorial alcohol is obtained in a is obtained in a predominantly amount. Now that whatever be the ratio of the axial and equatorial alcohol axial is to equatorial, we know that the equatorial is predominantial that is true, but that ratio can be partout (())(17:02) if you put remote substituents like here if I put substituents not here, so if I put substituents here, suppose cyanide.

If I put cyanide then this carbon-carbon bond, because of the electron withdrawing group of cyanide that becomes even poorer donor to that anti-bonding orbital. So in that case the equatorial the axial alcohol will be even less axial alcohol proportion goes down**,** I hope this is clear, because now if you look at the transition state. So now the for the axial alcohol the nucleophile has to come from this side. So you have a bigger orbital on this side that is a anti-bonding orbital and now, because of the presence of the cyanide, this is much worse than a simple carbon-carbon bond.

On the other hand if cyanide is replaced by methyl then the proportion the proportion of the axial proportion axial alcohol, I can axial alcohol proportion goes down for cyanide, axial alcohol proportion goes up for R equal to methyl, but do not expect that this will be the major product, what I am saying that the always the equatorial alcohol is a major, but the percentage of axial alcohol is part out, while going from cyanide to methyl, I think that is also an added proof that

Ceplak model is valid, because this type of see other models like felkins model , which actually relied on the eclipsing interaction with the C2 C6 hydrogens that cannot explain this remote functionalization effect, okay. So that is that is more or less all about this cyclohexanone the reduction at the carbonyl that is a big chapter, okay. In the first week we did the acyclic system then we come to the cyclic system.

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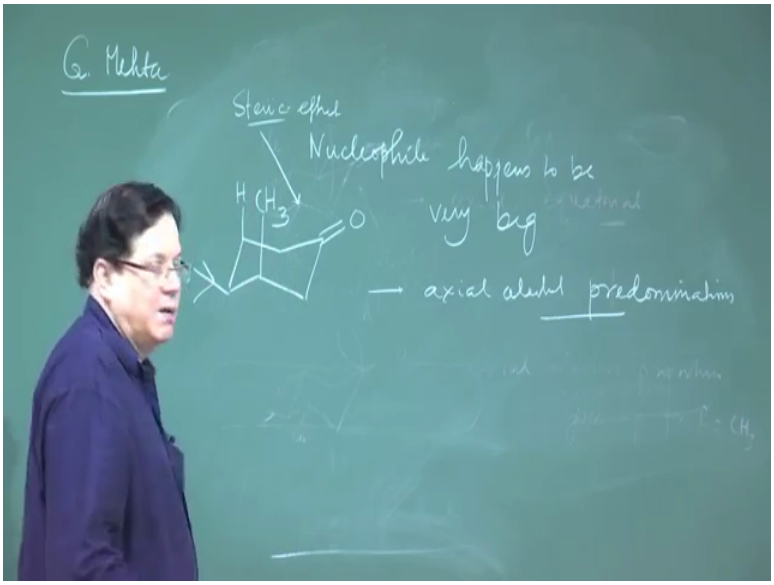

One more point I always want to mention here that if the nucleophile happens to be really very big or if you have, suppose you have a methyl here and the hydrogen. So we have axial methyl and if your nucleophile happens to be very big then the approach whatever stability we are talking about of the anti-bonding orbital all will be washed out by the steric effect. The steric effect, now takes control. It is the steric effect of the approach is too much now, because of the methyl and the hydrogen and the nucleophile is also very big.

So in those cases what happens? It is always think the axial isomer axial alcohol predominates. So keep that in mind, okay. For simple nucleophiles like boro-hydried or for simple alkyl lithium's like methyl lithium. The smallest alkyl lithium the whatever I said that the Ceplak model that they are predominant formation equatorial alcohol stays, but if the if there is a too much steric (())(21:07) either due to size of nucleophile or due to already present axial bulky axial groups then the equatorial approach is favored and the axial alcohol equatorial approach is favored and te product will be axial alcohol mainly, okay.

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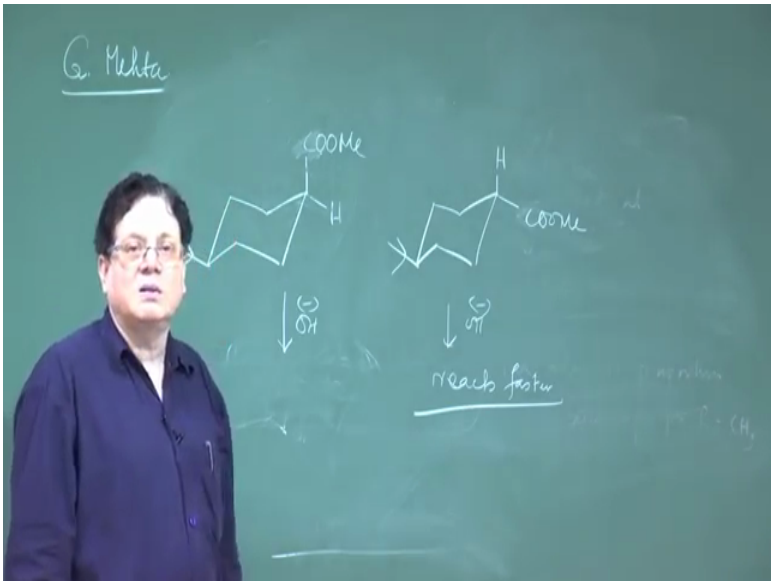

One more point, I think when I told you about this, so steric effect, so there is a continuous contradiction between the steric effect and the stereo electronic effect, okay. So sometimes steric effect wins sometimes stereo electronic effect wins. So that will this evident from these examples. Now remember when we asked for the when we read the rate of oxidation of these two chromic acid oxidation of these two alcohols, our result was that the axial alcohol was oxidized at a faster rate and the reason is that the mechanism is such that they first it forms the chromatoester, but which is a very rapid process and this is not the rate determining step. The rate determining step is the breakage of the chromato-Easter okay and the breakage of the chromato-ester releases the steric strain that is associated with the chromato-esters and these axial hydrogens.

So decomposition of the chromato-ester is the rate determining step and that is why axial chromato-ester undergo faster breakage and that is why ultimately the axial alcohol axial alcohol reacts faster. Interestingly just exactly the opposite effect is there. If you have a ester here CO2Me and an ester here CO2Me. So an equatorial ester verses an axial ester. In this case, what happens if you do, I think this was covered may be the saponification what happens? The saponification rate if you just recapitulation. In this case this reacts faster, because it is the rate determining step which will decide. In the rate determining step, the base attacks and the steric crowding increases and if the steric crowding increases in the base rate determining step, then the

reaction becomes slower. So thus we find a rule of thumb. If the steric crowding increases in the rate determining step, then the rate becomes slower, so that molecule will react in a slow fashion.

If the steric crowding decreases during the rate determining step then that molecule will react faster and that is what is called steric acceleration. The first one is steric retardation, okay.

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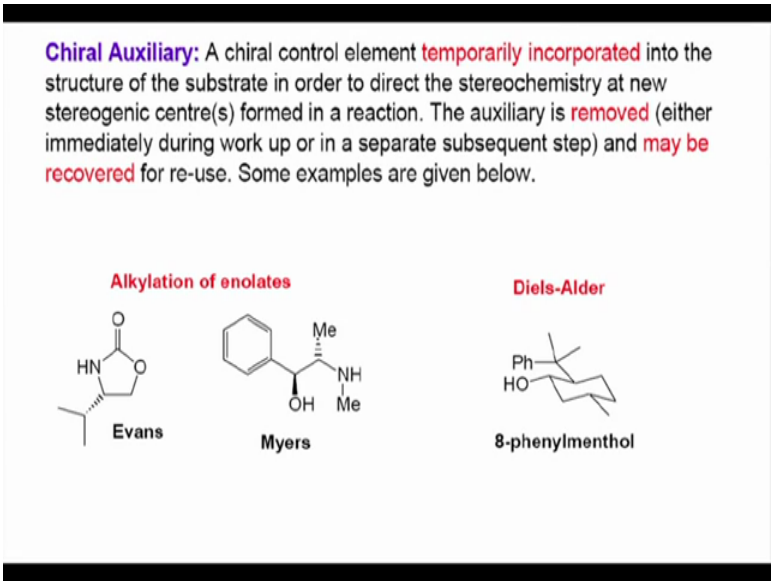

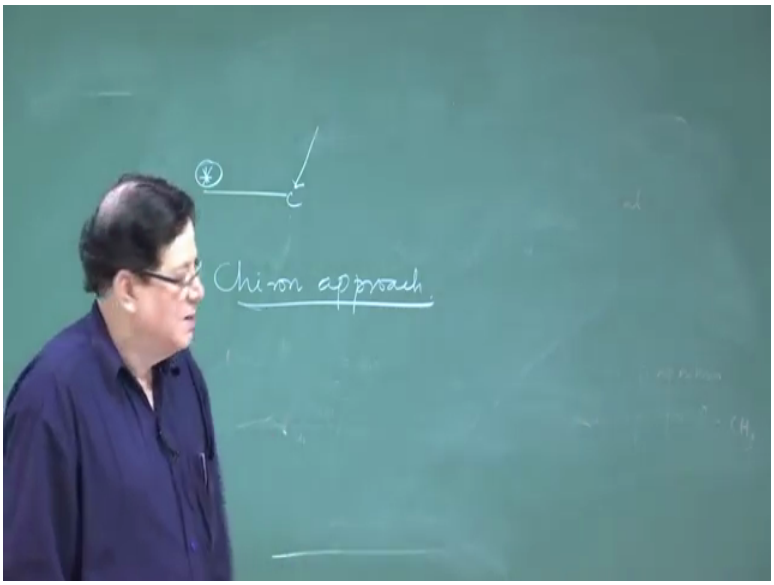

Now let us go through some of the modern developments of asymmetric synthesis, okay some modern development some asymmetric synthesis and I have told you that in asymmetric synthesis what you need to do is , there are several ways to do asymmetric synthesis, one is that

your starting material wherever you are doing the reaction suppose here this carbon, but you have a built in asymmetric center somewhere and that then induces the asymmetry of the controls the asymmetry of the that is generated at the neighboring carbon, okay and that we have seen that where the crams rule have been applied the prelogs rule have been applied. Those molecules already had a stereogenic center built in stereogenic center, okay.

So this is that means you have you start from a chiral molecule and then you start generating chiral center at different positions okay and this is an approach. This type of asymmetric synthesis, because you are getting only one isomer over the other in major amount. So this type of approach is called Chiron approach that means you started with a chiral molecule and then you generate the other carbon and control the configuration that is called the Chiron approach, okay. Then you have. Now there are different chiral materials available in our day to day life from natural products, I told you the natural products are always chiral and some of the natural products are very good Chiron's like sugars, like amino acids okay, because they have built in chiral centers.

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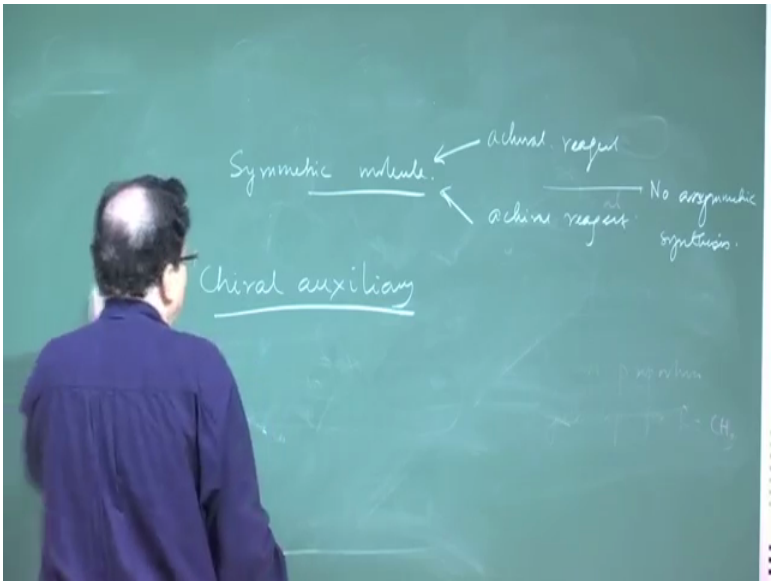

Then comes the chiral auxiliary approach. Chiral auxiliary approach. What is that chiral auxiliary approach is that you have a symmetric molecule. So there is no chiral center present in it symmetric molecule. Now if you do the reaction in a symmetric molecule and if the reactant is also a chiral achiral reagent then what happens if you are generating a new chiral center then the

transition state for formation of the new chiral center will be enantiomeric, because you do not have any built in chirality involved earlier. So here you will not get any asymmetric synthesis. So no asymmetric synthesis that means you will not get any discrimination between the R and the S that is produced.

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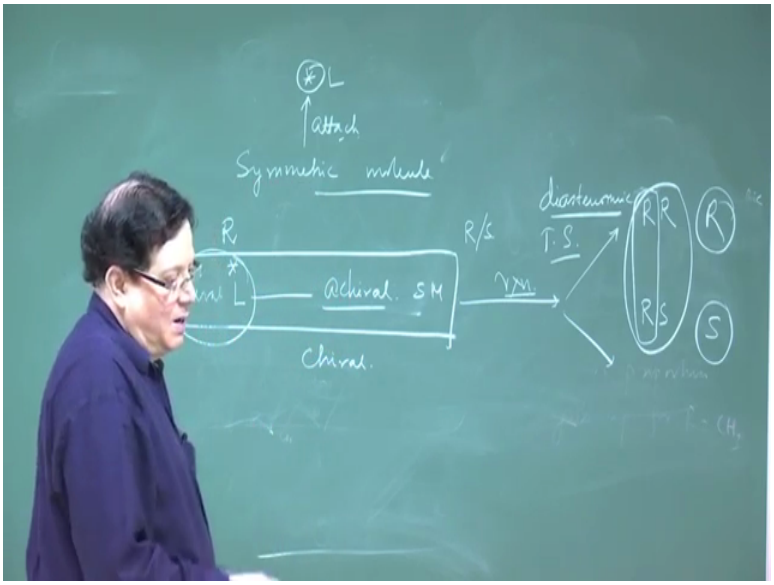

So in those cases what happens? What you do? You attach a, in the symmetric molecule you attach a chiral material a chiral entity, okay achiral entity through a covalent bond and then do the reaction. So now what you have earlier it was a chiral achiral starting material, but once you put a chiral entity L. So whole thing becomes chiral the**.** So now if you do a reaction**.** So you are doing a reaction on a chiral material, so if under particular chirality. This has got a particular chirality. So suppose this is generating achiral center, which has got R or S configuration and your starting chiral entity has a S con R configuration. So your transition states will be diastereomeric, because you are producing now diastereomers R-R and R-S. So if these are diastereomers, so that means you are going through a diastereomeric transition state.

So there is a possibility that you can get enantiomeric excess diastereomeric transition state. So now if there is a sufficient energy gap between the transition state, so you will get one over the other in large excess okay. So this is called chiral auxiliary methods. So you put this extra this chiral entity attach it via covalent bonds to the your achiral substrates and then after the reaction you take it off chop it off. So what you end up is. So if you take this off these R portion, which

comes from the L, see you are left with R and S. So if one of then major, so you get either R or you get either S okay. So this is called the chiral auxiliary method.

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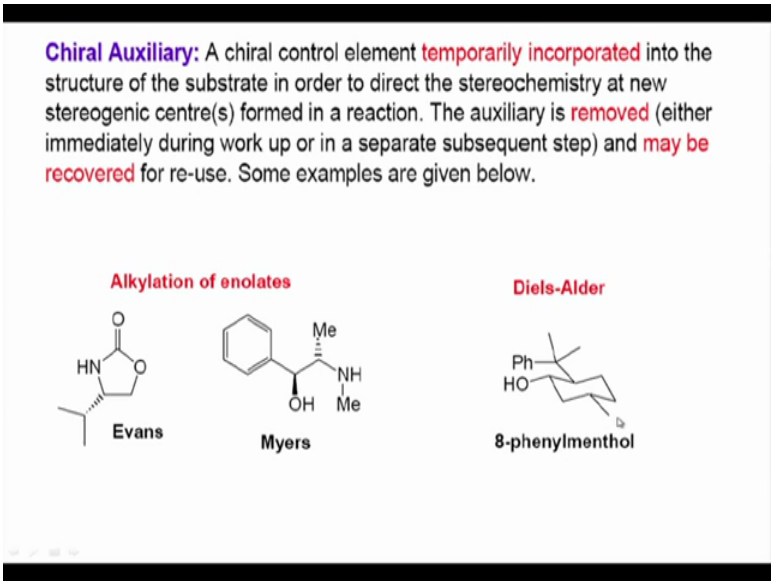

Now let us see here. Chiral auxiliary, it is a what it says, a chiral control element temporarily incorporated into the structure of the substrate, in order to direct the stereochemistry at new stereogenic centers formed in a reaction. The auxiliary is removed either immediately during work up or in a separate subsequent step and may be recovered for re-use, okay. So definition is very clear, I have an achiral system, I put a chiral entity that is the auxiliary do the reaction, this auxiliary now induces the asymmetry when it is generated and after the reaction you take off (()) (30:06) the chiral auxiliary that can be taken some reactions, the chiral auxiliary falls apart during the work up, in some reactions. It has to be taken separately.

Some of the there are plenty of chiral auxiliaries available nowadays. They are made from the amino acids mostly from the amino acids or other natural compounds like, this is obtained from menthol, you can see 8 phenyl menthol is a chiral auxiliary for Diels-Alder chemistry Diels-Alder reaction is a 4 plus 2 cycloaddition. Then alkylation of enolates enolates alkylation that means you are putting an alkyl group alpha to an ester or a carbonyl with a stereo control then also, this type of chiral auxiliary can be used. This is called according to the name the auxiliary scientist name, who has discovered. So they have name the chiral auxiliary like this is called

Evens chiral auxiliary. This is called Myers, this is 8-phenyl menthol, I think this is may be (()) (31:07) chiral auxiliary.

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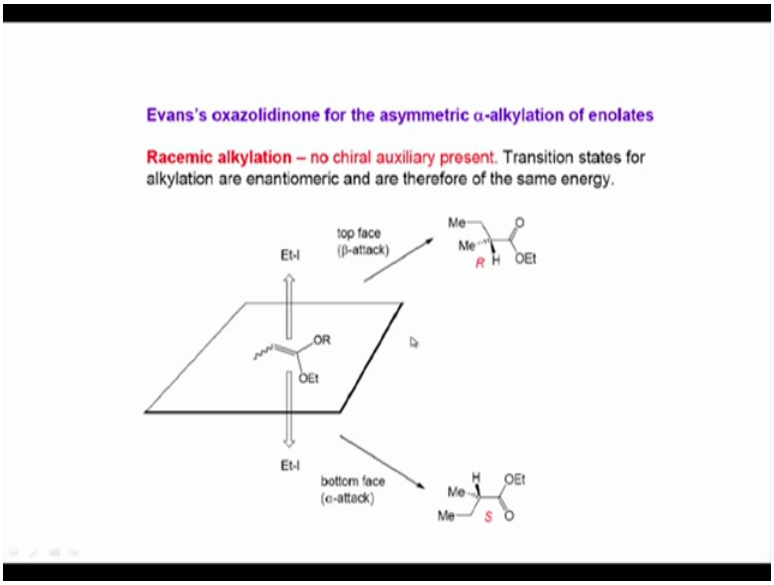

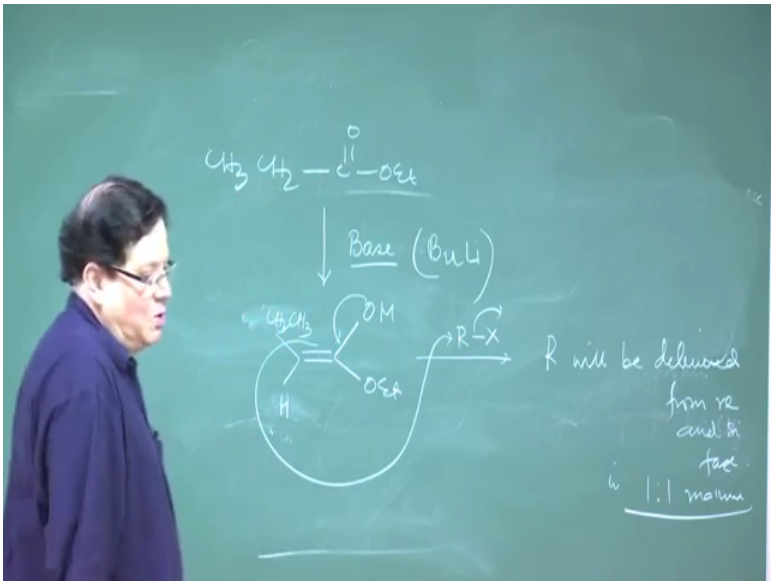

Now what happens suppose, (I have a) I want to alkylate an ester. Suppose I want to alkylate and ester group say I have CH3-CH2-CO-OEt. Now in alkylation what you need to do, you convert it to an enolate? So you have to add a base these bases are like a alkyl lithium reagents and then what happens? It goes into the, so is a usually organometallic reagent say alkyl lithium, butyl lithium suppose. So this will be the metal, so this will be OEt and then depending on the substrate, now you have this. So there are two types of enolates that can be formed, suppose I get

this enolate in predominant amount, suppose I get this one, okay. It also depends on the condition reaction condition, which enolate will be formed. Suppose I get this enolate and then I do the reaction with the alkyl halide. So this comes back and now this comes and attacks the R the X goes out.

Now since I do not have any chirality involved in this system. This is not chiral and the whole system is flat. So what happens? The R can come from the (R can) R-X can come from the top side or R-X can come from the bottom side like your ray face. So you can work out, which is ray face which is psi face okay. So this is your this is one, that is two, that is three, that means this is the this is the ray-psi face and the back side is the ray face. So anyway the percentage of, because these two transition states are enantiomeric or the other way around, since this faces are enantio topic faces. How do you know they are enantio topic faces, because ultimate product is enantiomer? So they are enantio topic faces. So ultimately you will get both the products both this R from the ray side. So R will be delivered from both ray and psi face in a 50-50 manner in a 1is to 1 manner. So you get a racemic compound, okay. So now in order to introduce asymmetry in this reaction. So what you need to do?

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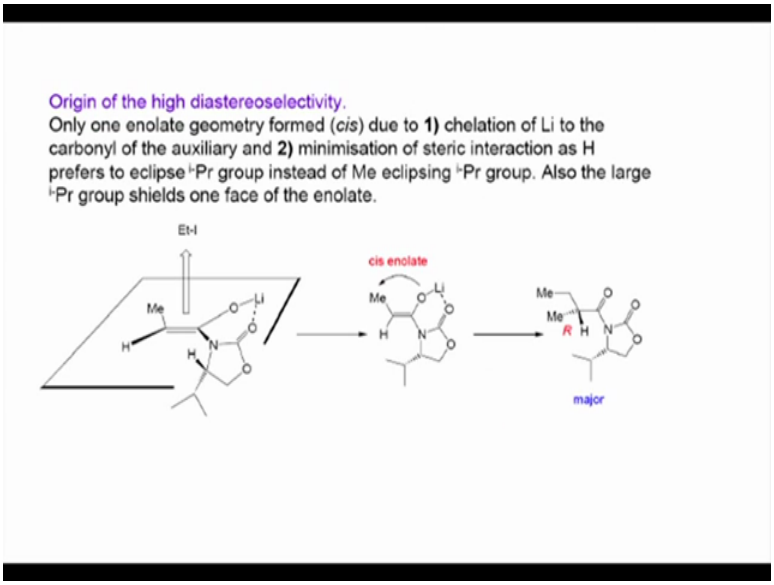

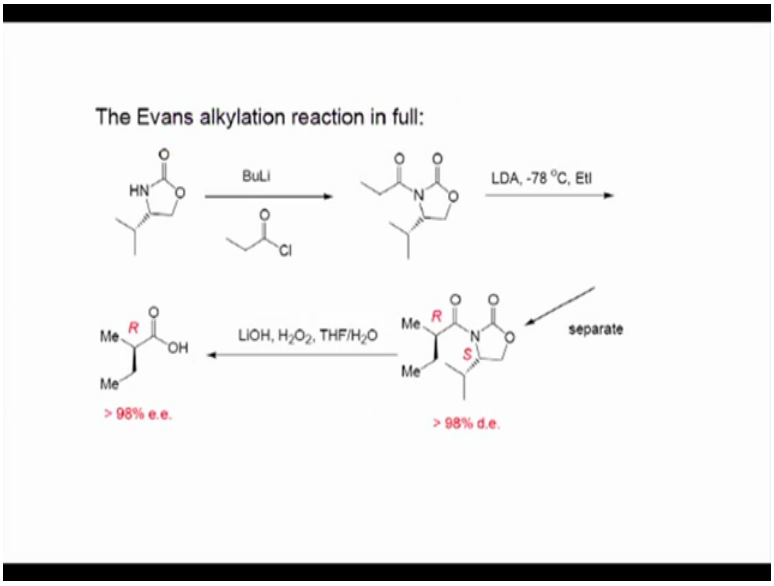

So you need to do attach see instead of OEt you see OEt O ethyl we attach that what I showed the evens chiral auxiliary, you do not need to know what is how do you attach, but it is there in the slide that how do you attach this chirality. So these auxiliaries, so you have this auxiliary put butyl lithium. So this becomes n minus then you put your that alkyl chloride acyl chloride instead of OEt chlorine is a better reactive system acyl chloride. So you get the similar system CH3-CH2-CO and then the auxiliary that Evens auxiliary okay then what you do? You do the LDA minus LDA is another base is called lithium di-iso propyl amide and that forms the anion here and the anion then goes to the conjugation with the carbonyl. So you get the enolate , once enolate then you add your alkyl halide and then do the alkylation that is the whole thing is shown in this slide, okay.

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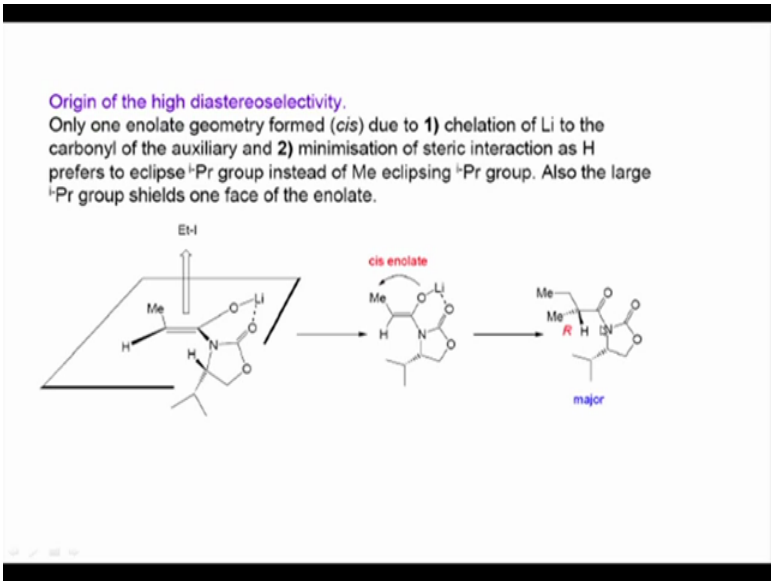

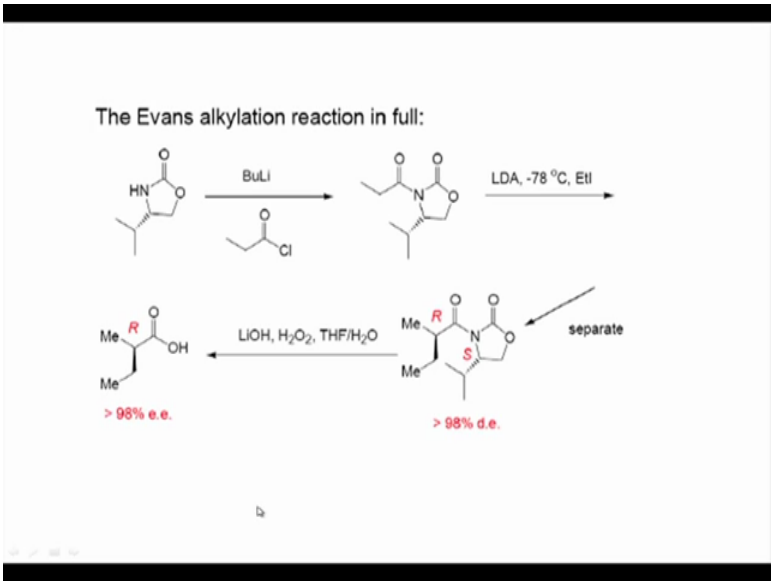

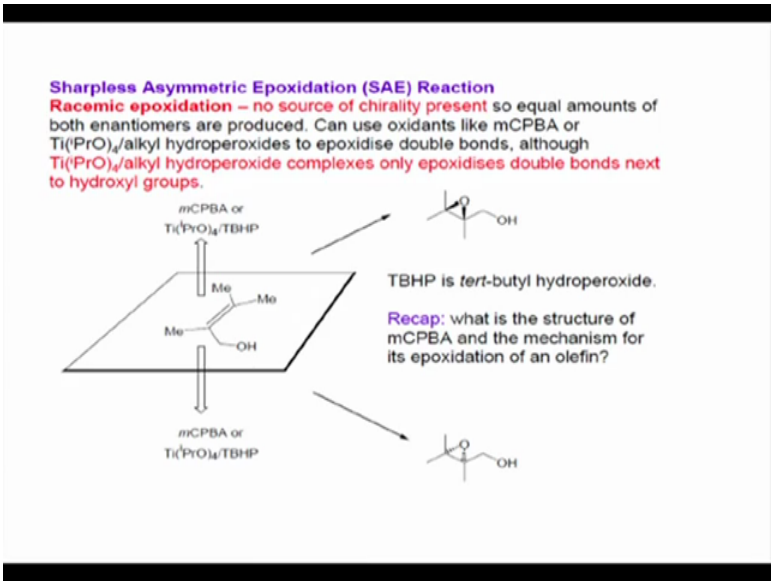

So this is the compound. So usually what happens? This type of enolate is obtained that means the methyl is on this side and the hydrogen is on this side and this is the OLi this is a carbonyl. There is a chelation formed between this OLi and the carbonyl. So that will be directed towards that direction okay, remember this carbon nitrogen bond can rotate. This carbon nitrogen bond is in a position of rotate, but that rotation is restricted, because of the formation of this chelate.

So once that is restricted, now this is the **e** iso-propyl group that is pointing downwards that came from the chiral auxiliary. So that is decided by the chiral auxiliary and the chiral auxiliary that was taken this iso-propyl group is alpha, okay. Now what happens the this big group will stop the ethyl iodide that is the alkylating agent to come from the back side. So it is the front side from which the ethyl iodide will approach, okay.

So if the ethyl iodide approaches from the front side. So this is the other way to see the enolate. So the ethyl will be so that is on the top side. So that is this ethyl and this methyl is still alpha and the hydrogen is beta. So the most important thing is ethyl comes from the top side and that is the product predominant product that you will get. So this is the R compound okay. If you take the other chiral auxiliary into beauty Evens chiral auxiliary is that if you take the other chiral auxiliary where the iso-propyl is beta and the hydrogen is alpha, then you get exactly the opposite compound the S compound. So this is then there are ways to take this up like the earlier slide after the alkylation is done then what you do then you hydrolyze this. These hydrolyze, this is an amide, this is not an amide. This is a urea type of linkage N-CO-CO. So you can hydrolyze

with lithium hydroxide hydrogen per-oxide that was all done by David Evens at Harvard (()) (37:25) university.

So he hydrolyzed it and one can get these carboxylic acids in, 98 percent more than 98 percent enantiomeric excess, see at this point you have to say 98 percent diastereomeric excess, because at this point, the chiral auxiliary is S, if you calculate the if you determine the configuration here. This was one nitrogen. This was the 2 and this is the 3. So apparently, it looks like R, but actually the hydrogen is beta. So this is S and this is R. So now you have the formation of RS and SS. So these are diastereomers out of these RS is greater than 98 percent. So that is why here you have to write 98 percent diastereomeric excess and once you hydrolyze then you have the enantiomeric excess, because now we are handling only enantiomers. So this is the Evens chiral auxiliary method, I will just quickly give you the essence the modern what the status? Evens chemistry is very well used not even alkylation chemistry. It was used in aldol chemistry also; very similar kind of auxiliary is used in aldol chemistry.

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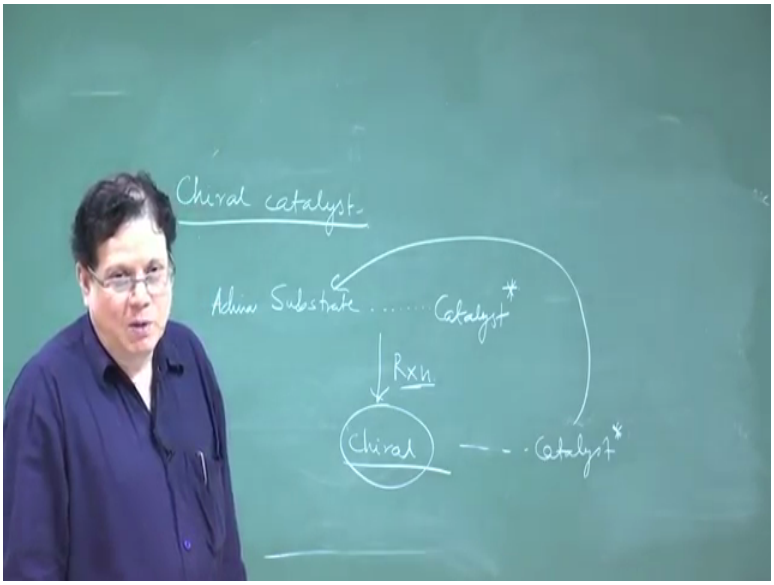

There is a third approach, see Chiron approach then auxiliary approach and there is the third approach that is the chiral catalyst. So what happens here, your substrate achiral substrate forms a complex with the catalyst, but the catalyst is **is** chiral and then the reaction takes place and the catalyst goes away and what you get is a your reaction is such that it gets a chiral center and may be multiple chiral centers in one reaction that is also possible, that is even better, see that is also

again I point out that in a particular reaction, if you can generate one is okay, but if you can generate more than one, in one reaction then that reaction will be will be more acclaimed in the literature, okay.

In fact, this asymmetric synthesis about few years ago may be 10-14 years back people three people shear the Nobel prize for asymmetric synthesis and why this is important, I told you that many of the drugs are chiral drugs and to make those drugs in one enantiomeric form is extremely important, I told you about the thalidomide tragedy and after that people have devoted lot of time in achieving asymmetric synthesis and it was Barry Sharpless and then Noyori and there was a third person, he Noyori, Sharpless and some other person. Now I am forgetting these three shear the Nobel Prize for asymmetric synthesis, okay.

So we have just discussing their strategy was unfortunately, the chiral auxiliary based strategy was not recognized by the Nobel committee, because what happens you have to attach a attach the auxiliary in a 1 is to 1 (())(40:50) manner, okay 1 is to 1 (())(40:53) manner, but if you have a catalyst if you do the reaction, the catalyst attaches to the substrate do the reaction, get the chiral compound out, the catalyst goes out and this catalyst then catalyze the catalyze fresh substrate molecules, okay. So this is basically, the lesson was learn from nature. This is how the enzymes catalyze reactions.

Enzyme takes a substrate, does the reaction and when it does the reaction, it is always stereo it is always stereo selective and it is asymmetric, the reaction is asymmetric and then this goes out, the enzyme is free another molecule comes and then the reaction takes place. So in this way, one enzyme molecule can convert several substrate molecules per second and that is a term which is called turn over number that one molecule of the of the catalyst is turning how many substrates into products per minute, okay or per unit of time whatever is the unit of time. So this has got an advantage that means you can use much less catalyst much below the (())(42:05) amount and today even one mole percent or below one mole percent catalyst has been used to generate to achieve asymmetric synthesis.

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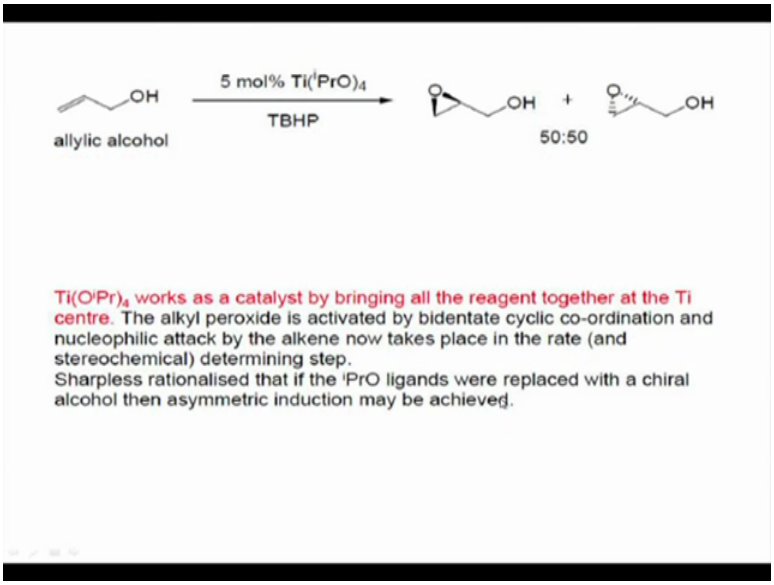

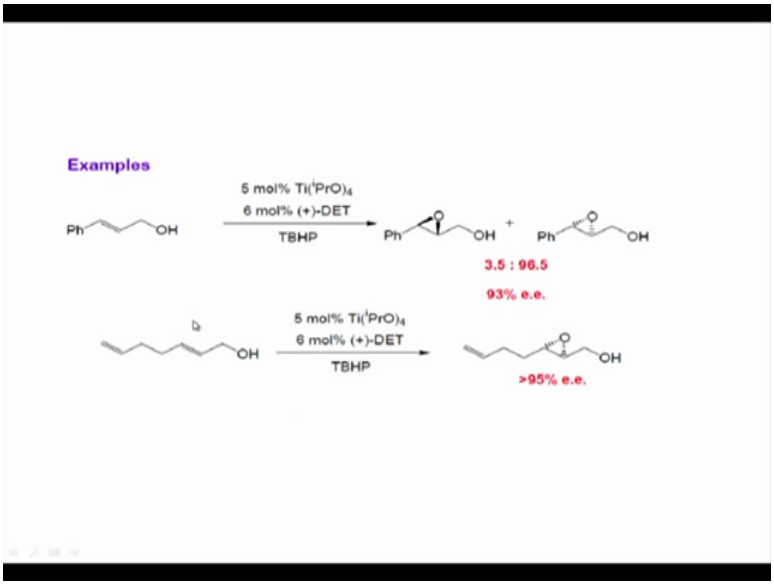

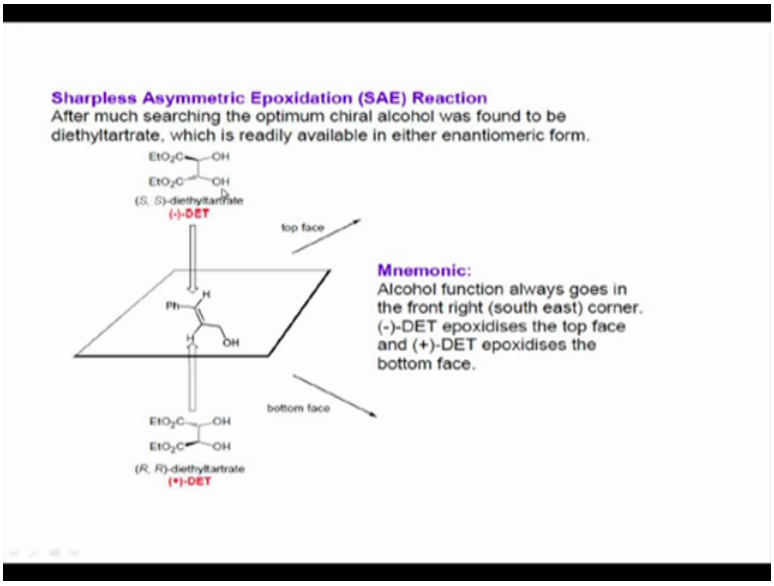

So what is Sharpless epoxidation that is the Nobel prize winning work, you know that double bonds can be epoxidised, okay and the epoxidation can again, the epoxidation is a is a face dependent phenomena that when you form the epoxide, either the oxygen the epoxide can be formed from the top side or from the bottom side, okay. Now there are reagents to do, so usually you get plus minus mixture 50-50 plus minus mixture of the epoxide. So when you when you do the reaction epoxidation, suppose with MCPBA metachloroper benzoic acid or there is another reagent which is called titanium iso-propoxide alkyl hydro peroxide like butyl T-butyl hydro peroxide then these double bonds are epoxsized. One difference between T-butyl hydro peroxide and titanium iso-propoxide combination is that. It only epoxidises compounds, which are allylic alcohols. So there must be a OH here and then CH2 then a double bond okay.

Now sharpless saw this reagent that this reagent is able to epoxidised the double bond. So what it did, see if you again I repeat if you take this compound and do the epoxidation with either of these reagents? So what you get the beta epoxide and the alpha epoxide in equal amount, okay, but if you take slight like (())(43:41) this experiment, see if you do if you do not have any chiral reagent, you will, this is T-butyl hydro peroxide you will get 50-50 mixture of this, but what sharpless did that titanium iso-propoxide has 4ligands 4 iso-propyl ligands. So he added this di-ethyl tartrate, which can displace 2 of the ligands in titanium. So form a titanium will be complex now with the iso-propoxide as well as with the di-ethyl tartrate, okay and then when this attaches to the titanium complex, now it is attaching to a chiral titanium complex. So epoxidation now

can be diastereo selective at this stage when it is bound to the catalyst the catalyst goes out and you see which epoxide you are getting.

Now what sharpless observe that if you add minus di-ethyl tartrate and titanium epoxide and the titanium iso-propoxide and T-butyl hydro peroxide all together and the allylic alcohol. So you get discrimination you get either the alpha or the beta epoxide. Now which one you get? There is a mnemonic device mnemonic way to remember that if you use minus this is**.** If you use minus di-ethyl tartrate then the epoxide and if you write the alcohol in this way that means the OH is towards your right and the bigger alkyl group is towards the left of these carbon of the of this carbon then the (())(45:20) carbon then what happens epoxidation takes place from the top face, provided you write this in this fashion and provided it is minus di-ethyl tartrate that you are using as the chiral ligand, okay for the titanium.

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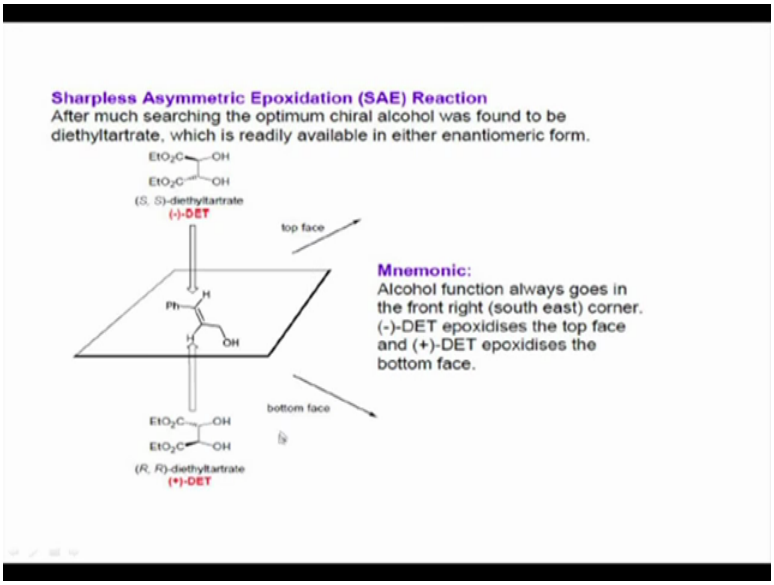

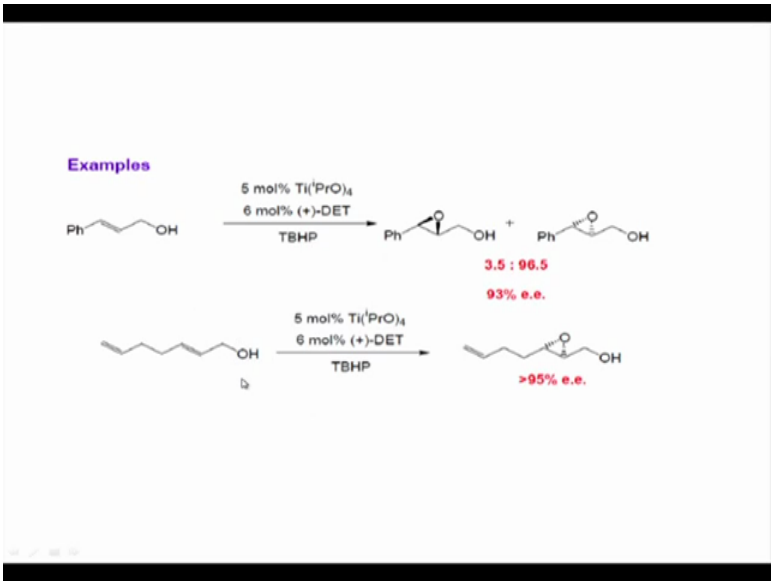

If we use the plus di-ethyl tartrate you get the epoxidation from the bottom face, one example is this, see this is the synamile alcohol. Now synamile alcohol, if you just it is actually retaining the way that was shown in the mnemonic device that basically, if you turn it a little then the phenyl will be on this side then the double bond and then this CH2OH. So in this case if you are using plus, now this they have used plus di-ethyl tartrate, so if you use plus di-ethyl tartrate, what was the earlier result if we use plus di-ethyl tartrate then it is the bottom face let see minus di-ethyl tartrate. They used 6 mol percent plus di-ethyl tartrate and here they used 6 mol percent plus di-ethyl tartrate and here they used 6 mol percent of this is minus; I think there is something wrong here. This is this should be this should be minus di-ethyl tartrate. Because the minus di-ethyl tartrate gives from the top face. So this is the this is minus di-ethyl tartrate and this should not be plus minus di-ethyl tartrate, so that gives the beta compound and this should be plus di-ethyl tartrate not the minus.

So if it is plus di-ethyl tartrate then it will be the alpha epoxide okay. According to the mnemonic device, see you have writurn it in the double bond OH, this fashion, okay and these actually writurn like that only slightly inclined, okay just remember that you have to write this in this fashion if it plus if it is minus then it comes from that bottom in the top face that is beta epoxide. If it is minus di-ethyl tartrate plus di-ethyl tartrate then it gives the alpha epoxide.

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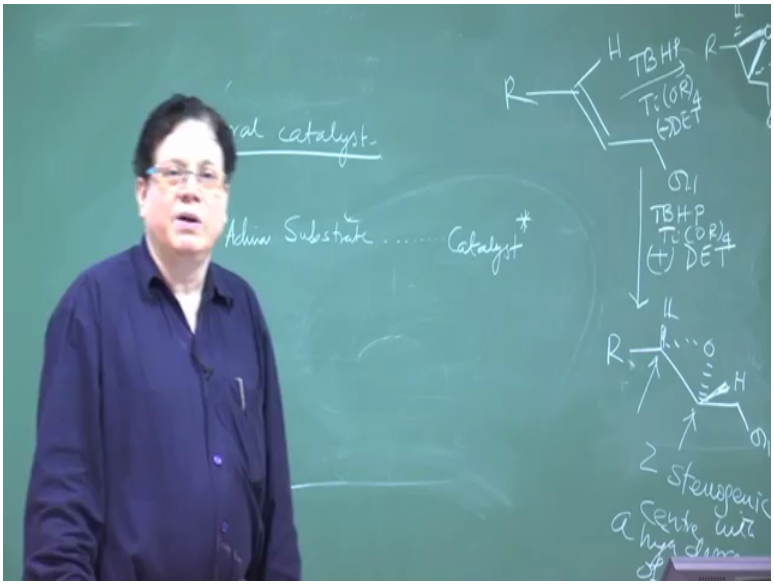

So just to finish up, so what is sharpless method that you write this compound in this? This is your R group, this is the hydrogen and your reagents are if you use reagents are this T-butyl hydro peroxide that is the oxidizing agent then you have the catalyst titanium iso-propoxide, I just write over 4 and you have the di-ethyl tartrate. Now you have this diethyl tartrate can exist in plus and minus form that is optically active forms of tartaric acid. So if you use minus di-ethyl tartrate then, it will be the epoxide will come from the beta face okay. So that is the and if it is plus di-ethyl tartrate, I just want to di-ethyl tartrate want to make clear, because there was something wrong in that slide TBHP T-butyl hydro peroxide and you have titanium iso-propoxide, I just wrote OR 4 then what you get the epoxide is comes from the bottom face. So you have this and this is the epoxide, okay.

This is the hydrogen this is beautiful in the sense that you get very high enantio selectivity and the other thing if you have notice that it creates, 2 stereogenic centers at the same time. So 2 stereogenic centers with a high degree of asymmetry**,** okay. So that is the, so I give you some glimpse of the modern asymmetric synthesis, I just explained you the Evans chemistry and I just told you about the Sharpless chemistry, I did not go into the mechanism how the oxygen is delivered from the beta side.

When minus di-ethyl tartrate that is too complicated for you at this stage, but as you grow older and attain higher stereo chemistry level courses, I think I am shure that will be done, because

there other, I said Noyori also got the Nobel prize by doing the asymmetric hydrogenation and that was also I just excluded from this part that is the part of the asymmetric synthesis in detail is usually a part of the advance stereochemistry courses okay. So we stop at this stage regarding the asymmetric synthesis and next day we will try to that is the last class and we will we will again recapitulates some of the concepts and if something is left behind we will also cover that in the last class. Thank you.