Course on Stereochemistry
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Mod08 Lecture 37
Asymmetric Induction: Nucleophilic Addition to Chiral Carbonyl Compounds (Contd.)

Okay, welcome beck to this course on stereo chemistry, right now we are towards the end of this course, almost towards the end, we were discussing, now the dynamic stereo chemistry and under dynamic stereo chemistry, we have come to the what is called symmetric synthesis asymmetric synthesis sometimes also called asymmetric, because the synthesis is carried out by induction of some group or some center. So it is sometimes called asymmetric induction, okay.

Now last time we have seen what are the different type of reactions stereo specific reactions, stereo selective reactions and we have gone through the definition. Now asymmetric synthesis, I have also defined, but I have also made a comment that nowadays this stereo selective synthesis and asymmetric synthesis are continuously used as if they are the same.

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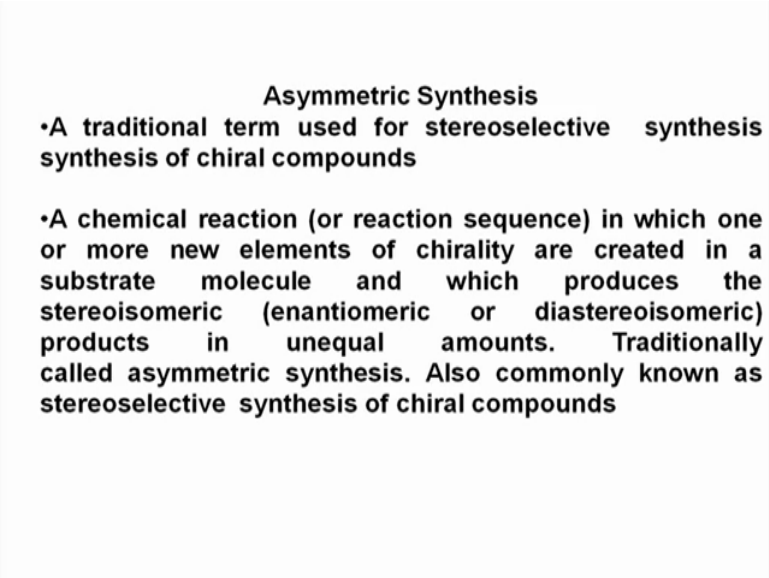

There are slight differences, when the stereo selective synthesis is meant to form a chiral compound. When a stereo selective synthesis sorry, ((()))(1:37) it is repots the synthesis of achiral compounds if it leads to the synthesis of a compound in chiral form then that is called that is a stereo selective synthesis. This is also called in traditionally it was called stereo selective synthesis, but it falls under the broad category of asymmetric synthesis. So again I

repeat that whenever you are making a compound and you see that the end of the end result of your reaction is that you are making a compound in chiral form in one chiral form, then we say that you have achieved the stereo selective synthesis, but that is same as saying that you have achieved what is called an asymmetric synthesis.

Now asymmetric synthesis is the basically the broader term and the definition again I repeat, last time I told that if you are generating an asymmetric center in a chemical reaction and if, so that should lead to the formation of either R or S. if one of the configuration predominates in the reaction that means, it is pre-dominantly produced then we say that we have achieved an asymmetric synthesis.

So in a molecule if you are generating a chiral center and if you generate the chiral center in one enantiomeric form then that is called asymmetric synthesis. Now in this definition you see that it says that a chemical reaction or a reaction sequence, it may not be achieved through one chemical reaction, it may be achieved through a series of chemical reactions, in which one or more new elements of chirality are created, in a substrate molecule and now we are brought negative little bit, we are not sticking to only one center. There may be several centers that are created in the molecule in the substrate molecule and which produces the stereo isomeric products.

Now if it is only one center that will produce enantiomeric product. If it is if you are producing multiple chiral centers then the products will be diastereomeric and if these products are produced in unequal amounts then that is called an asymmetric synthesis, but as I said also commonly known as stereo selective synthesis of chiral compounds.

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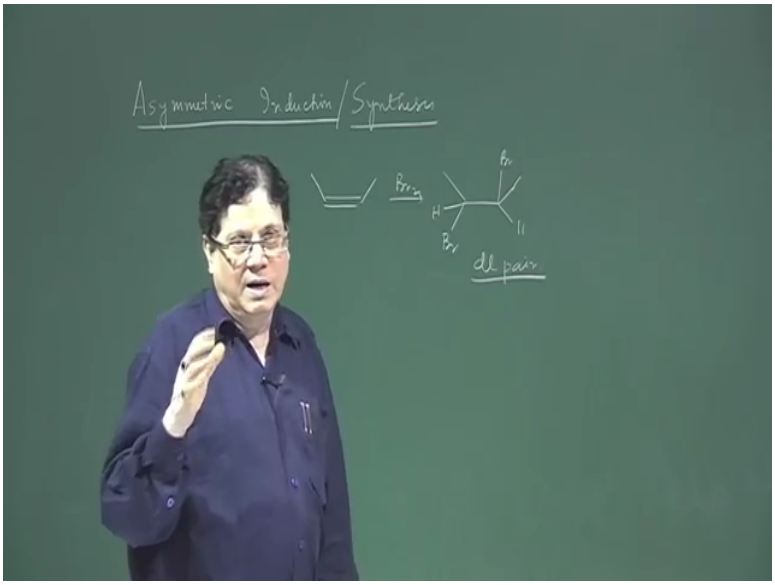

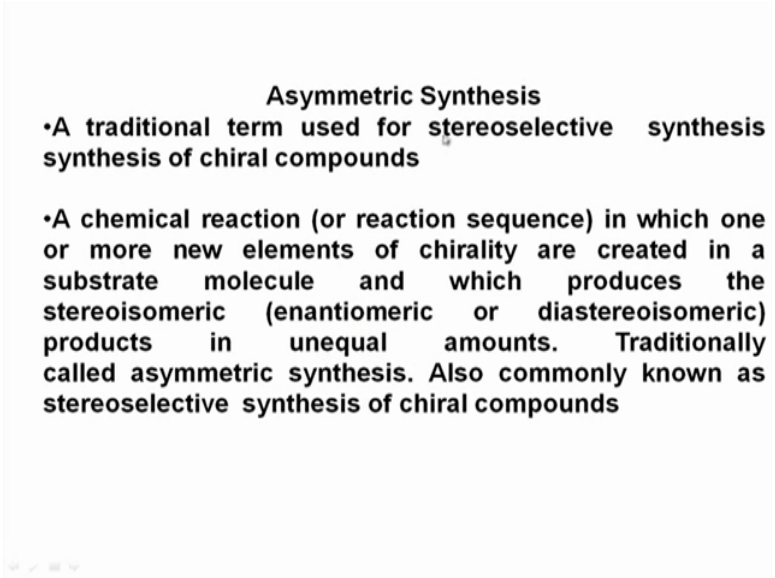

Now stereo selective synthesis has too many ends (())(4:02), one is that addition of bromine to a double bond that is also stereo selective, but that does not produce any that produces only dl-mixture, okay and so chiral compound is produced, but that is produced as a dl-mixture. This is also stereo selective reaction, but this does not fall under the category of asymmetric synthesis. When you can make the compound in one chiral form, or partially pure chiral form then that will be called a stereo then that stereo selective reaction will fall under the category of asymmetric synthesis, I hope it is clear. Stereo selective reactions leading to the production of chiral compounds falls under the category of asymmetric synthesis, okay, but asymmetric synthesis is a general term that whenever you make a center chiral center or a series of centers and if they are produced lead to stereo isomers in unequal amounts then that is called an asymmetric synthesis.

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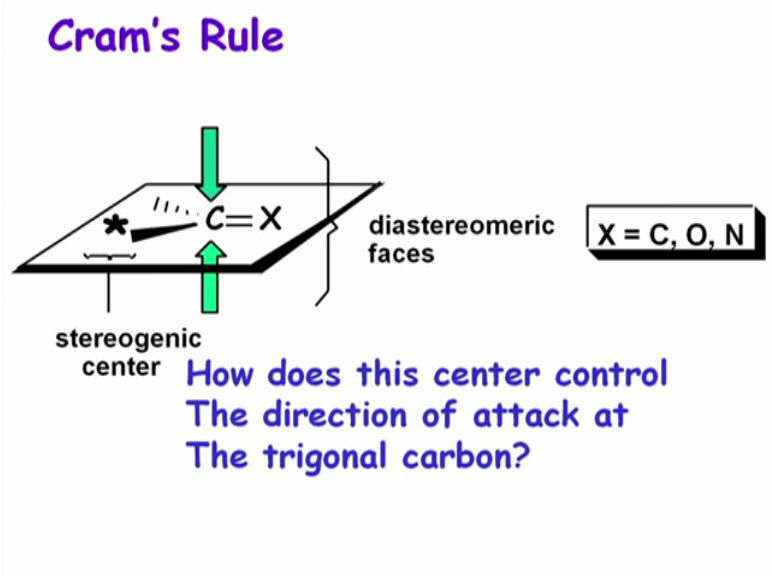

Now asymmetric synthesis, I told you that what is the basis of asymmetric synthesis that the molecule that the transition state leading to the product has to be diastereomeric, otherwise the rate of formation of the two isomers will not be different, because what you aim at is that the rate of formation of the diastereomers should be different then only you can get different products, different amount of products, okay. If the transition if the activation energy is happen to be same then it will lead to a racemic mixture. So the target of asymmetric synthesis is to make the gap between the transition states for the two diastereomers or further two ultimately it may lead to enantiomer, but the gap of the diastereomeric transition state, the transition state has to be diastereomeric and when either you are leading to enantiomer ultimately or diastereomer that does not matter, the reaction has to go through diastereomeric transition state and the bigger the difference the greater will be your success in asymmetric synthesis.

Success means the diastereomeric excess that means the excess of one diastereomers over the other or the enantiomeric excess that is the excess of enantio one enantiomer over the racemic form of the mixture they will be of higher value, okay. Now I give you here that how to make this one way of making diastereo selective, diastereomeric transition states is to have a built in chiral center already. If you have any built in chiral center and which is in a particular form R or S then what happens the transition states that will be generated by the approach of the nucleophile to this, suppose the X is oxygen to the carbonyl carbon will be diastereomeric to the transition state which is obtained when the nucleophile approaches from

the bottom side okay. So now you have two different transition states. So there is a possibility that the two isomers will be formed in different amount, okay.

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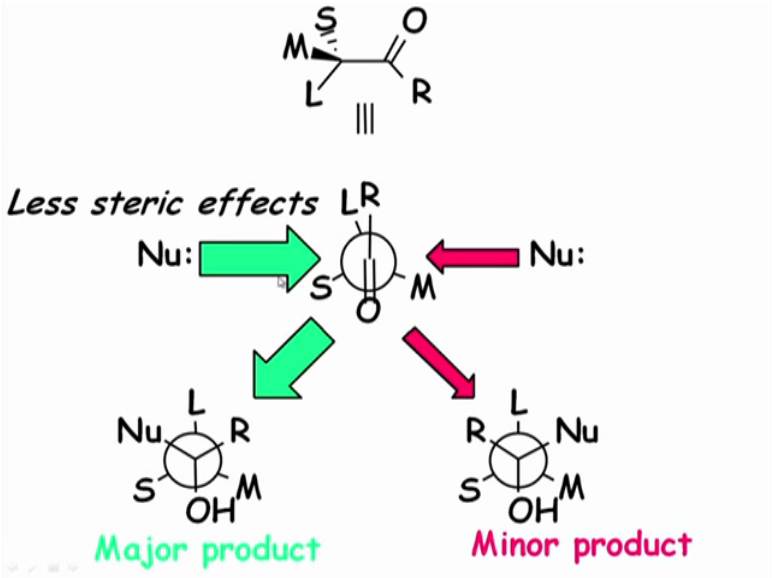

Now there are how do you consider is which one will be the major product can we predict and I gave you certain rules that yes there are certain scientist who have tried to predict that what will be the major product if the substrate if the substrate configuration is known that means if the chiral center that is already pre-existing is known. Now in the in the here, I have also introduced one term that is induction asymmetric induction, see whenever this reaction takes place whenever you are having a nucleophile to this carbon, because of diastereomeric transition state and if the transition state happen to be quite different in energy then you will get one compound in much excess over the other and we say that this and this is due to the fact, why it does happen, because it is due to the fact that this carbon center is present.

So we say that this carbon asymmetric carbon is having an induction on the asymmetry that is generated on this carbon. So that is why this is also called asymmetric induction. So induction of an asymmetric already present asymmetric group on an on a carbon which is becoming asymmetric during the reaction. So this is also called asymmetric induction. So induction takes place, so that means two different isomers that will be created from here, addition of nucleophile will be of different proportion, okay. Now as I said that which one will be more which one will be less? There are certain set of rules. One set of rules was given by cram D.J cram and according to him that if the, see there will be three groups apart from this carbonyl attached to the stereogenic center.

Now this is only true for a system where the carbon is adjacent alpha to the when the carbonyl is **is** alpha to the or the stereogenic center is alpha to the carbonyl, okay then only this rule is applicable. If it is little bit far away then this rules does not hold. So we are only is sticking (())(9:44) for the compounds where there is an alpha stereogenic center attached to a carbonyl system and what it says that this will take a preferred conformation where the oxygen will be flanked by the small and the medium group and that puts the large group eclipsed with the R group that is the other group attached to the carbonyl and now according to cram that if that the nucleophile approaches preferentially from the side of the smaller group and so if this approaches preferentially from the side of the smaller group. What will happens the product will be your LSM remains in the same position, only the nucleophile comes and this becomes a nucleophile this is the OH and that will be the R, R will be shifted on this side, okay and while it comes from the opposite side that means which is not the preferred one, so you get the other isomer.

These are (())(9:44) So these are the by the way two diastereomers, So we have diastereomeric excess or you have what you had achieved is a diastereo selective reaction and this diastereo selective reaction is due to asymmetric induction by this chiral carbon, okay. Now this is what is crams rule.

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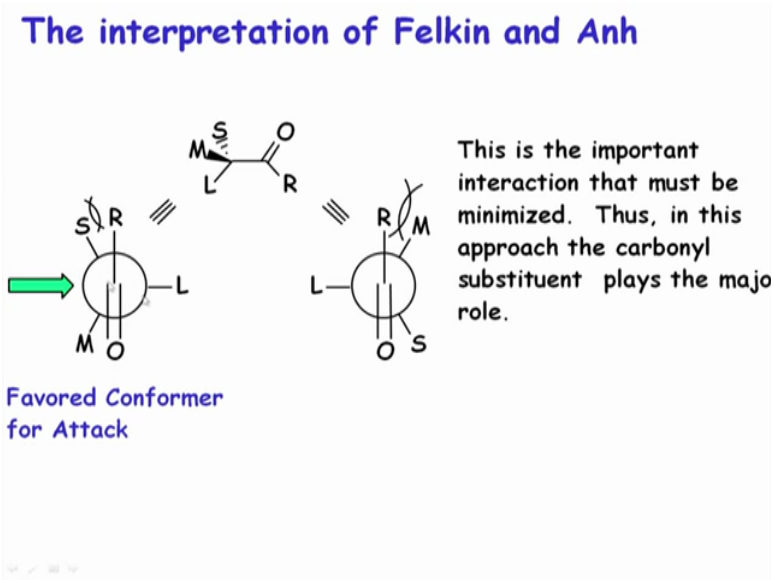

Now there are other rules, felkin and Anh, they differed from cram. They said, the actual preferred conformation is one where the large group is perpendicular to the orthogonal to the carbonyl group and that is that is a preferred one. So if you have the same compound. So according to felkin and Anh, so we have to put the large group perpendicular to the carbonyl

R axis okay. If you take a fisher projection Numan projection and then what happens you are left with S and M and see the this is equivalent to this. How do you know, because the carbonyl is placed on the top? So what we have to do, you just see the on seeing from this side what is a direction of motion as you go from L to M to S. So that is clockwise, so L to M to S.

Once you put L you know this is M, this is S, because that should be clockwise. So that is the easiest way to consid this, you do not have to think much. If you put the carbonyl then just see from this side and what is a sequence as you go from L to or the direction as you go from L to M to S and this is the, see there are two possibilities. Now L can be orthogonal on this side also, but that puts the aim on the right in front of the R. So this is the, because of more steric hindrance here. So this will be less favored and this will be favored conformation.

So now the carbonyl, now the nucleophile attacks here on this molecule and the OH goes there and the nucleophile comes here, I told you about the barge donage principle that the nucleophile actually approaches around 107 degree, which is closed to the actual angle after the once a reaction takes place when the carbon changes the hybridization from 100 from sp2 to sp3. So that is the barge donage trajectory, okay. It should actually approach from around 107 degree like this, okay. So carbonyl will remain almost in the same position only the R will shift here and the nucleophile will come here. So that is felkin-Anh model.

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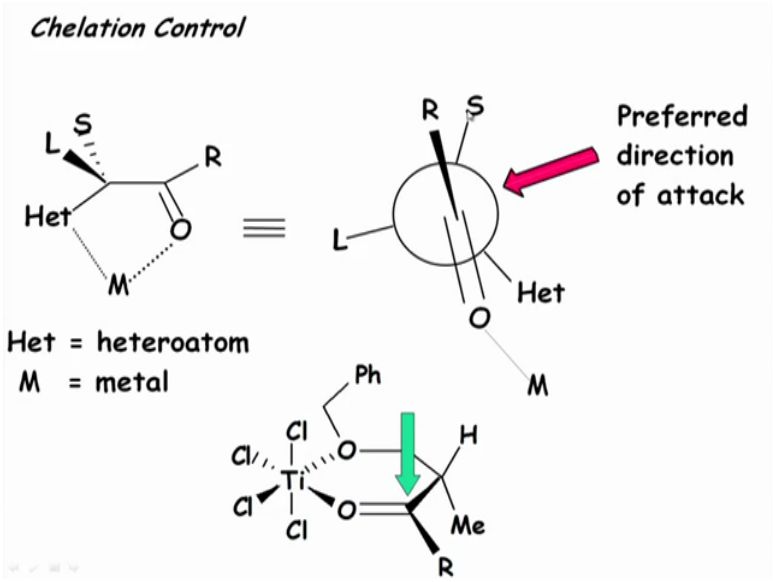

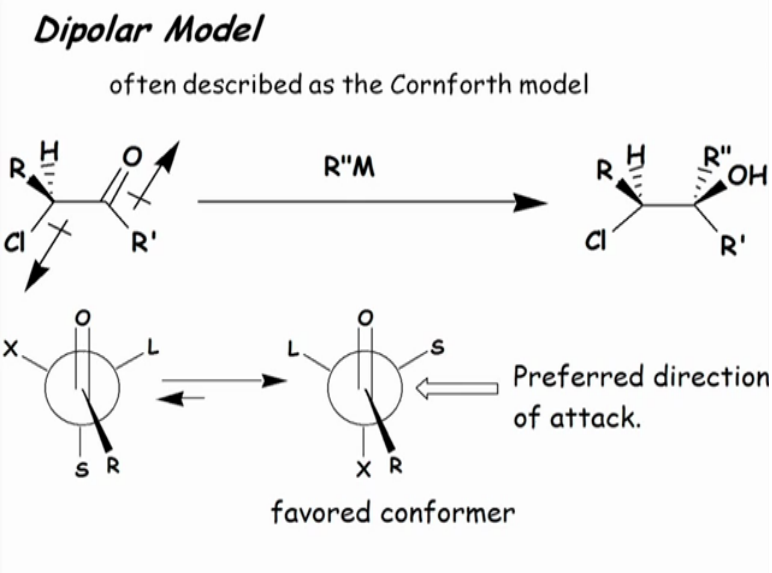

Now there may be systems where the both the rules are not applicable as per the earlier system, see if you have a system where there is a dipolar group a chlorine where is a this is called a dipolar models. So already there is a dipole that is the carbonyl and suppose the next adjacent carbon that means the stereogenic center has chlorine. So now if you have a chlorine, so what happens these two dipoles will tend to be tend to be aligned in an anti-fashion and that gives the most stable conformer, okay. So this is what is crams model. So cram said that crams model. So earlier cram said that L should be opposite to the carbonyl, but now according to this model X should be opposite to the carbonyl, in order to have less repulsion.

So ultimately if that is the case then wherever be the S from that side the nucleophile will attack and you will get the product, okay. We will do some problems now, to show the application of this. So this is also called Cornforth, I think this was given Cornforth improve crams model in this dipolar system. In case of felkin, the same thing is there, if you actually try to apply felkins model on this according to felkin that if there is a earlier felkins model we see we have seen that the large group has to be placed orthogonal to the carbonyl.

In case of the halogen, which is a polar group, so we have to put the, so they have modified their hypothesis and said that the chlorine or if there is any dipole like this then that dipole has to be placed orthogonal to the carbonyl. So in that case the large group is not the dominant factor. It is the polar group which takes the which takes the orthogonal position to the carbonyl, okay. Interestingly, both the models they lead to the give rise to the same products.

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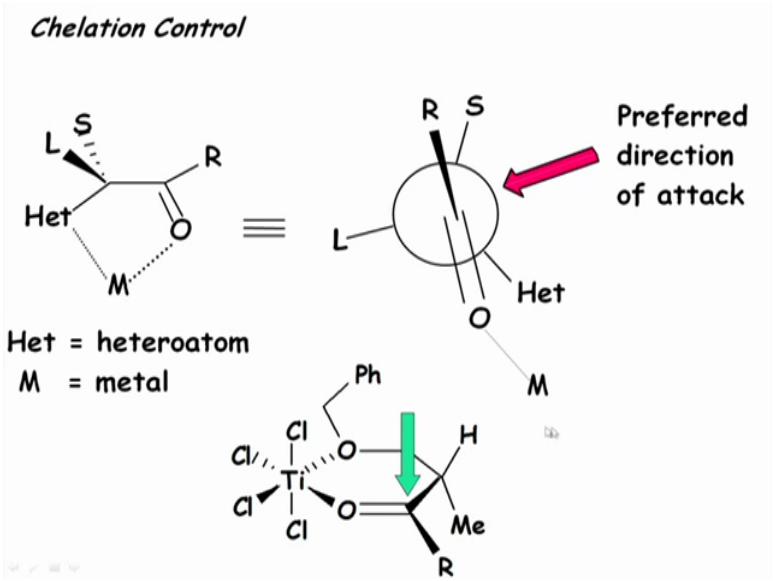

Now another system or another situation that can happen that in the chiral center you have a hetero atom and which is in a position to form a chelate complex chelate complex when the reagent approaches, because many of these reagents are like methyl lithium or metal mediated reagents like methyl lithium, butyl lithium or titanium compounds. So in that case what happens your hetero atom even if it is by the whether it is large or small or medium, you have to place it syn to the carbonyl so that this chelation is possible, okay.

So now if you transfer it to the crams model, so in this crams model modified cramps model which is called crams chelation model. So what this is a carbonyl, in the original cram L should be opposite to the carbonyl in the polar dipolar system the dipole should be opposite that polar group should be opposite to the carbonyl. In case of groups which are able to form chelate like the hetero atoms then the hetero atom should be syn to the carbonyl and if that is the case then whatever conformation you get that the nucleophile will come from the side of the small group. So this is an example which is not drawn according to the numan, but this you can say that there is a center which is chiral center and there is carbonyl and then you have CH2OH.

So in this case obviously this titanium reagent will form a complex in this direction and now you have the small group here on the top and the large group comparatively larger group at the bottom. So the nucleophile will approach from the top face, okay. So this is an example of that crams chelated model okay.

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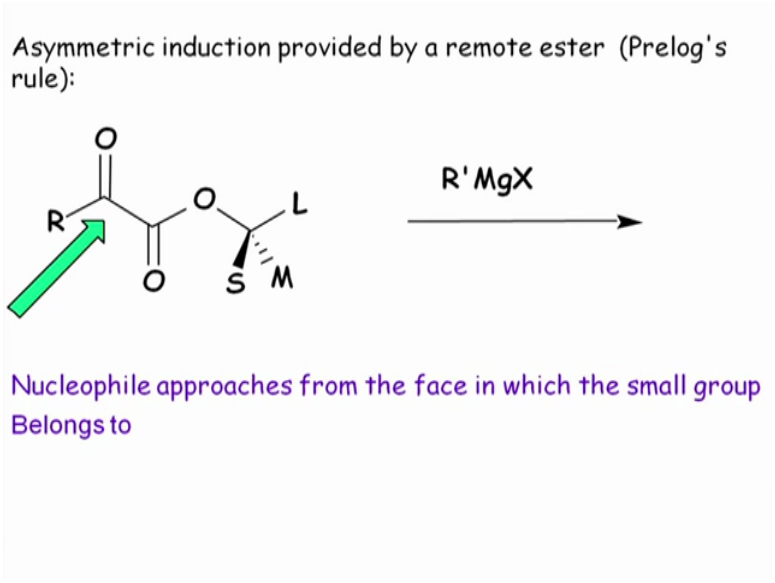

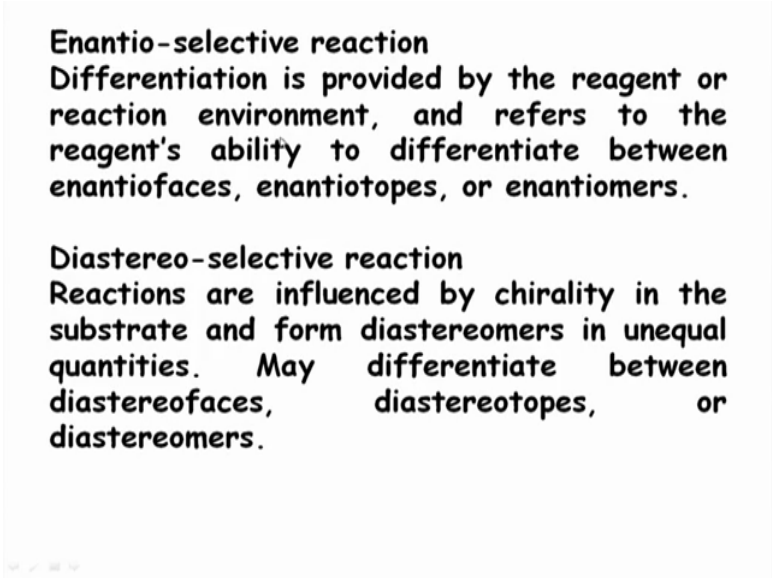

Finally, there was another system, I told you that crams model is applicable to systems where carbonyl is alpha where the stereogenic center is alpha to the carbonyl system, where the stereogenic center is alpha to the carbonyl system. Now you can have a system where the reacting carbonyl is quite far away. Interestingly, in this molecule. Now this is by the way is a compound which is derived from, this is called if R is equal to phenyl that is called phenyl glyoxalic (())(18:17) acid or you can say it is an alpha keto-acid in general an alpha keto acid and if you make an ester with an alcohol. So you get an ester linkage and a pure carbonyl linkage and whatever R groups you have. It may be phenyl it may be other groups okay. Initially it was done the experiment was done with phenyl was phenyl. Now what happens even if this chiral center is far away?

Now there is a rule which is call prelogs rule that this molecule is somehow influenced by the presence of this carbonyl and what prolong says that now this molecule will adapt a conformation, in which this carbon and the large group carbon large group bond this bond will be syn to the carbonyl carbon, okay. See there are two carbons carbonyl carbons one is the ester carbonyl another is the plane carbonyl, okay. This is ester carbonyl so what he says that the carbon and the large group bond should be syn to the ketone carbonyl, okay and then if you add a grinder (())(19:31) region suppose R dash MgX then you have now two other groups, small and medium. So the grinder (())(19:39) reagent will now approach from the side of the small group. This was called the prelogs rule, we have heard of Prelog, because (())(19:47) Prelog, Prelog is a very famous well known stereo chemist and he was awarded the Nobel prize for his work on stereochemistry, including all these things.

So Prelogs rule where he started and this Prelogs rule became very important, because earlier days it was very difficult to know the configuration of naturally occurring compounds, I told you the naturally occurring compounds, exist in one enantiomeric form. So if we have a chiral alcohol, so it was a tough job at that time to know the configuration exact configuration of the alcohol, whether it is in the R form or in the S form, because the rotation I said rotation has no connection with R or S. So it was Prelog's rule, which was applied. So if you take the alcohol make this alpha keto-ester and then do the (())(20:41) reaction and see what is the end product of this and if you can analyze the end product then if you do backwards, finally you can get the configuration of the alcohol. So we will do all this will all this in this in this lecture, okay.

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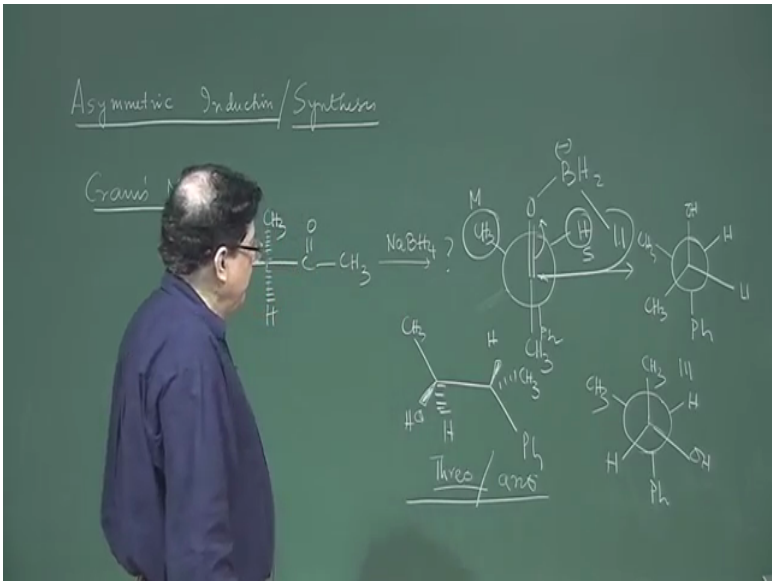

So let us do, because unless you do problems, these things will not be clear okay. First we will see the crams application of crams model. So crams the normal model, the first model that was given by cram, suppose we do one problem we take a compound, which looks like this and this was reduced with sodium boro-hydried. The question is what is that major product okay. What is the major product? So how do you do it solve it? Only the first thing you do you have to draw a numan projection, okay put the carbonyl and then the here is the methyl. So it is a methyl ketone, okay and then you have to put the bigger groups the biggest group that is the phenyl, which is anti to the carbonyl, because this is not a case of chelation, this is not a case of polar substituent, so you can apply the crams normal model, okay and then you have two groups methyl and hydrogen.

Now this methyl is actually it is written in Fischer projections. So this methyl is alpha. This hydrogen is also alpha and this phenyl is beta. So now if you look from this side you can tell that the methyl phenyl methyl hydrogen that is actually going in a clockwise direction and you have drawn the numan projection such that this carbon is at the top. So same thing will be maintained. So you have phenyl then methyl will go into this side, sorry not here, methyl will be on this side and hydrogen on this side. So that is the, because your phenyl methyl hydrogen is in clockwise direction, okay and then, so once you have fixed that. So this is your the preferred conformation.

Now you know that your nucleophile, see which is suppose the boro-hydried we have said the boro-hydried complexes with this and then it approaches from the side of the smaller group. So this is the small and this is the medium. So preferential attacks takes place from the side of

the medium group. So now what you get is your bottom three groups remain the same the methyl, the H and the phenyl only thing you have to do some changes in the. So that is OH, this is methyl you have to follow the barge donage principle. So carbonyl remains almost in the same position pushing the methyl here. Now question is what is this compound?

so you can, so this is the major product that is you can stop here, but if you want to know whether it is threo-erithrow (())(24:14) that you can work out by putting the threo-erithrow (())(24:20) in the zigzag conformation, threo-erithrow (())(24:23) has a problem, I told you that in the Fischer projection you have threo-erithrow (())(24:29) nomenclature, which does not match with the zigzag conformation, okay.

So let us or you can now you can say syn and anti that will be actually better. So in syn and anti what you do you have to place the carbon chain in the opposite in a zigzag fashion okay. So put this methyl here, the phenyl there and the OH , so first check the methyl here then OH there and H here and the other the phenyl remains at the same position. So hydrogen and this is methyl. Now you see that if you draw a zigzag conformation. So basically the methyl then this and the phenyl. So this is phenyl, this is methyl and then you have this is the seen arrow. So in methyl you have when you look you have OH to the right, so OH to the right and H to the left and in the phenyl you have H to the right.

So you have H to the right and your methyl is to the left that means alpha. So that means you are getting this is in in the books it is say that this is a threo compound we can say this is the threo, but means this is the zigzag nomenclature, okay. So that is the main chain, so threo or you can say, this is the anti- conformation that you get, okay. So that takes care of this crams normal model.

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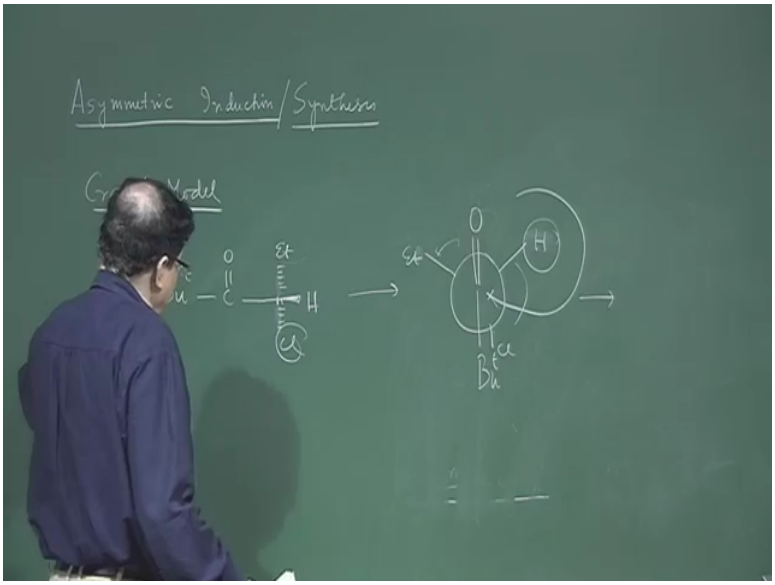

Now if you take if you take the chelation model**,** suppose or the so suppose I have this tersary butyl CO and then hydrogen ethyl and chlorine, okay. So the way to do it, I will not do many problems, I will just do it the way to do it is that you have to see from that side. So the carbonyl goes there, butyl goes there and now the chlorine is on the bottom, you have to put the chlorine at the bottom, because that is a polar, you have to use the polar model. So other two groups will be here.

The other two groups and again I said that better, see what is the directionality if you go from, suppose I go from chlorine then I come to hydrogen then I come to ethyl. So that (()) (27:30) I have to see from this side and that makes chlorine hydrogen ethyl clockwise. So chlorine hydrogen ethyl clockwise, okay. Chlorine, hydrogen, ethyl, so I am seeing it from this side sorry, this is very this is chlorine hydrogen ethyl that is anti-clockwise. So I have to put the anti-clockwise, hydrogen ethyl again I repeat I see from this side. So first it is chlorine then, I come to hydrogen and then I go to ethyl. So that is anti-clockwise, so this anticlockwise you maintained and this is the preferred conformation. This is the small group. so now the nucleophile will approach from the side of the small group and you can I am shure you can get to the product, only careful you have to be careful while converting this into the Fischer okay, I was almost making a mistake. So this chlorine, hydrogen, ethyl is anticlockwise. So chlorine, hydrogen, ethyl you have to make anti-clockwise.

So if you follow that then there should not be any problem. So likewise you can do the chelation model everything. So if you know how to draw the convert one form into the other, I think situation will be handle much in a easier way, okay. So we have seen that this

asymmetric induction how does it control the stereochemistry of compounds where stereochemistry of compounds. It is very specific group of compounds where the carbonyl is present adjacent to a stereogenic center. This stereogenic center then induces asymmetry while the nucleophile is delivered on to the carbonyl, okay.

And the next session we will try to work out the Prelogs rule we will do some examples on Prelogs rule. How the absolute configuration of alcohols can be obtained with the use of this rule and by the way, before the advent of extra crystallography these Prelogs rule was becoming very important in solving natural products structures and stereochemistry. Thank you.