Course on Stereochemistry
Prof. Amit Basak
Department of Chemistry
Indian Institute of Technology Kharagpur
Mod08 Lecture 36
Asymmetric Induction: Nucleophilic Addition to Chiral Carbonyl Compounds

Okay, welcome back, we have just seen the definitions of stereo selective and stereo specific reactions and asymmetric synthesis, okay and in true sense, they are all different, but in reality what happens. This stereo selectivity is now most often clubbed with asymmetric synthesis. So if an asymmetric synthesis, the actual asymmetric synthesis definition that whenever achiral center is converted into a chiral center and if you get one configuration in excess over the other that is asymmetric synthesis, many scientist call it that, it is a stereo symmetric synthesis that you are making one stereo isomer more over the other, okay.

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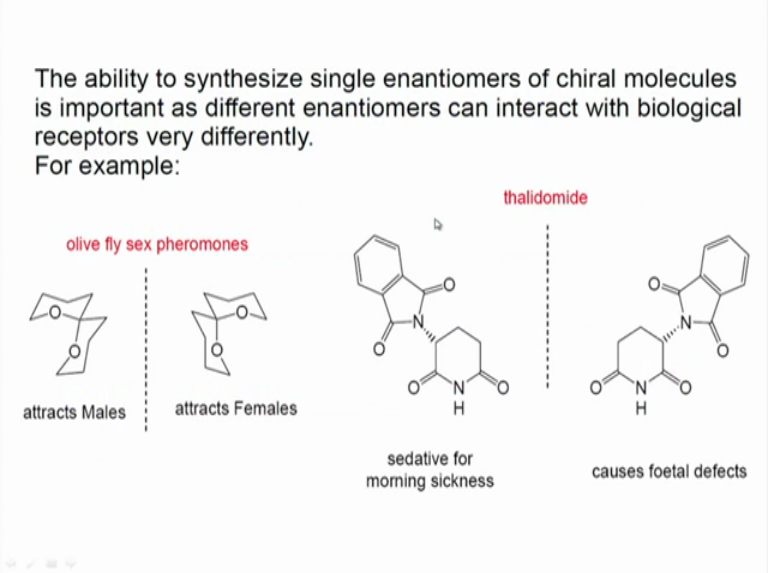

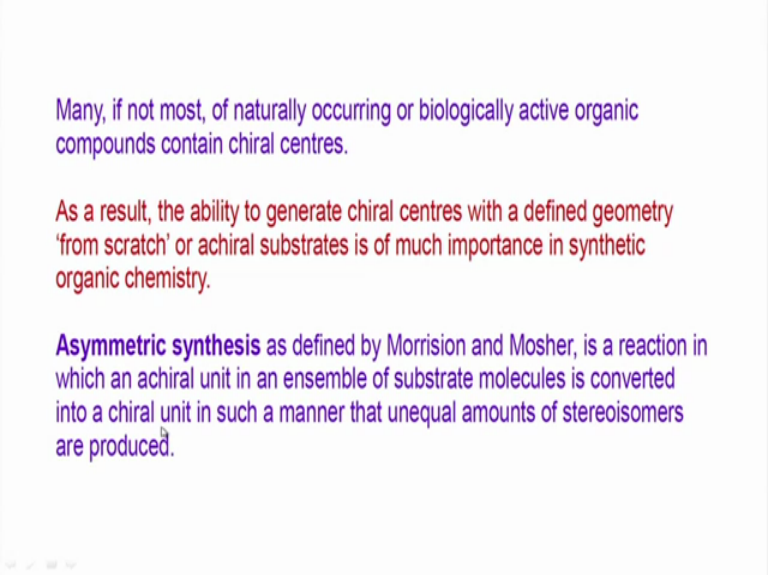

Now, I will just show you few slides to impress upon you that again, upon the importance of this asymmetric synthesis and the definitions are also included here, see what you should know that most of the naturally occurring compounds that we see, in our daily life, most of the naturally occurring or biologically active organic compounds, they contain chiral centers and nature makes it, this makes this creates this chiral centers only in one configuration with a define geometry and the question is that means nature has the ability to make compounds or to make asymmetric synthesis of highest order. So whenever we take get menthol or drugs like anti-malarial (())(2:06) like quinine, synchronine whatever compound you call, they are mostly chiral and if it is chiral that is obtained in one enantiomeric form and that is the beauty of nature and you have to symmetric synthesis is, I have given you the definition that a chiral achiral unit is converted into an chiral unit. So that is one textbook definition, but I gave you that one chiral center have define this unit as a chiral center and convert achiral center converted to a chiral center, in unequal amounts, that is called an asymmetric synthesis.

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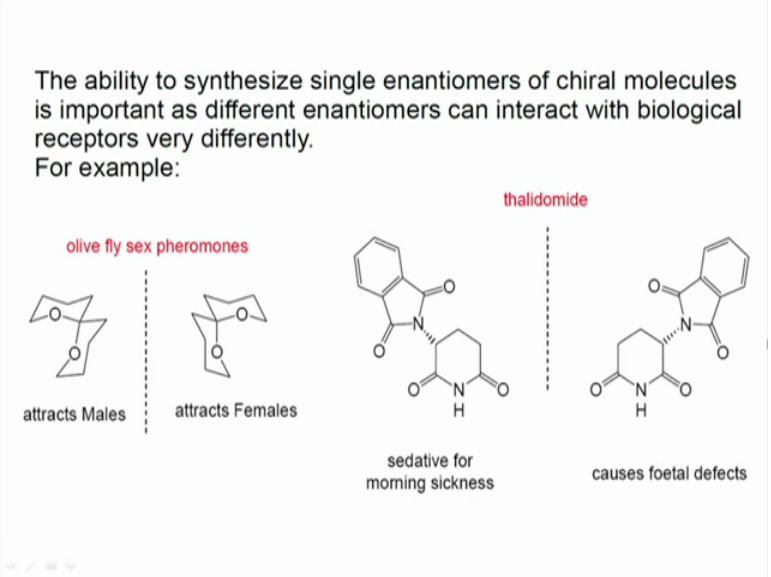

Now asymmetric synthesis why is important, I again a code some examples that there are molecules which are artificially made like this compound. This is these are called the (())(3:04) pheromones means they can attract the counter the to the opposite partner, but when you take the mirror image of this molecule this attract males and this attracts female. So only there is a difference in the stereochemistry. This is the mirror image of this one. So one enantiomer if it is present in the body then that then the males feel an affinity towards the animal, which is secreting these type of compound. On the other hand females, have the affinity, this affinity if someone if some animal is secreting this molecule. So you see the just a difference in stereo chemistry can have different biological activity can discriminate between to opposite people, male and female.

Similarly, there was one drug. This is a man-made drug thalidomide, this name was thalidomide and the structure is shown here. This was sold in the 1960s as a plus minus mixture that means as a racemic mixture and it was given to it was given to pregnant mothers, okay. The pregnant mothers who are likely to have child very soon. So those that was, now what happens? This was given as dl-mixture at that time; drugs were all given as racemic mixture unless they are naturally occurring, because natural products are all chiral.

So the synthetic drugs where usually made the laboratory. They are all prepared in the dl-form, because dl form is a easier ones to make. If you want to make it in the optically pure form then

you have to do an asymmetric synthesis. An asymmetric synthesis will cost you more, because your design has to the more circle and more chemically intensive. So the cost was higher if you want to have only optically pure of this or that.

So the drug companies just to cut down their cost they were introducing that dl-pair, thinking that they will have the similar kind of effect, in the body, but the what happen thalidomide was made was meant to have sedative action, for morning sickness, which was the usually the pregnant women suffers, but what happen? This is the molecule which this with this configuration that has the sedative effect. The other compound the mirror image has the causes foetal defects that means it is called teratogenic compound, which causes birth defects.

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And what happen the babies that were formed, from mother who are taking this thalidomide. The babies were borned with deformed (())(6:02) deformed legs and this is one of the greatest tragity in human history that and that brought us to the importance of chirality in pharmaceutical industry, I told you in the beginning that chirality is very important in pharmaceutical industry and this was the turning moment in the history of drug industry when drug industries realized that in order to sell a drug, you have to have a you have to first know that the effects of the plus compound and what are the effects of the minus compound, it may so happen that the plus compound is the one which is giving the required effect and the minus compound is toxic then you have to give the drug as a chiral drug.

There are many examples today of chiral drugs like anti (())(6:59) drugs, (())(7:01) like the anti-Parkinson drug that is called L-doper (())(7:06) like levocetirinine is another one an anti-allergic drug. So there are many such drugs, which are now sold as only the in one in the actual active chiral form. So asymmetric synthesis has become at very important area in pharmaceutical industry who are making drugs okay.

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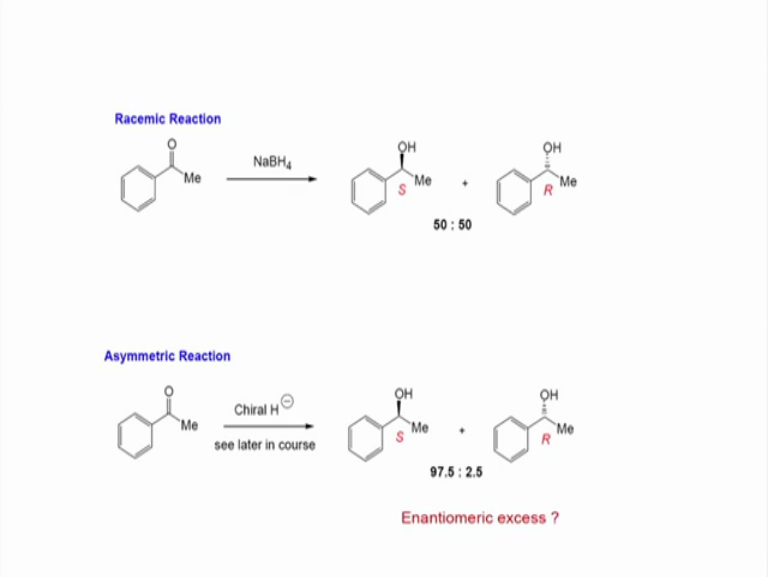

So as I said that if you have a ketone where there is a methyl and a phenyl I gave an example of ethyl and methyl. If you reduce sodium boro-hydried you get both R and S, because the transition state leading to the S compound on the transition state leading to the R compound. They have the same energy and so the activation energy for the two processes are same. So they will be formed in the similar rate and ultimately it will be 50-50 mixture. So this is a symmetric synthesis not asymmetric synthesis.

On the other hand, if you have an aldehyde, if you have the same ketone phenyl methyl ketone or aceto-phenone that is commonly known as and if your reducing agent is not chiral is not boro-hydried is a chiral hydride source that means it is boron, which was attached to attached a chiral group here. So may be all the hydrogens are not present, may be because you need only one hydrogen of the boron to reduce the carbonyl to the alcohol. So maybe you have one boron, boron connected to one hydrogen and the other groups are basically chiral groups and in only one chiral configuration. If that is those are call chiral boron reducing agent. So if you use that

compound chiral boron reducing agents then what happens the transition states, because in the transition states, it is the complex, the boron is complex to the carbon, so that complex we immediately make a chiral will involve chirality make the molecules chiral, okay and then when the hydrogen comes and produces a new chiral center they are formed in unequal amounts okay.

So actual result is when it is used in it is not said which chiral boron agent is used, but a chiral hydride. These are hydride transfer agents chiral hydride transfer agents is used and you can get, these two alcohols in unequal amounts. So the experiment that was done here was that S compound was obtained in 97.5 percent and 2.5 percent is the R compound. So now you know what is enantiomeric excess. The enantiomeric excess will be 95. It is the difference between the two, okay excess again I repeat, it is the enantiomer percentage of enantiomer in excess of the racemic counter-part, okay.

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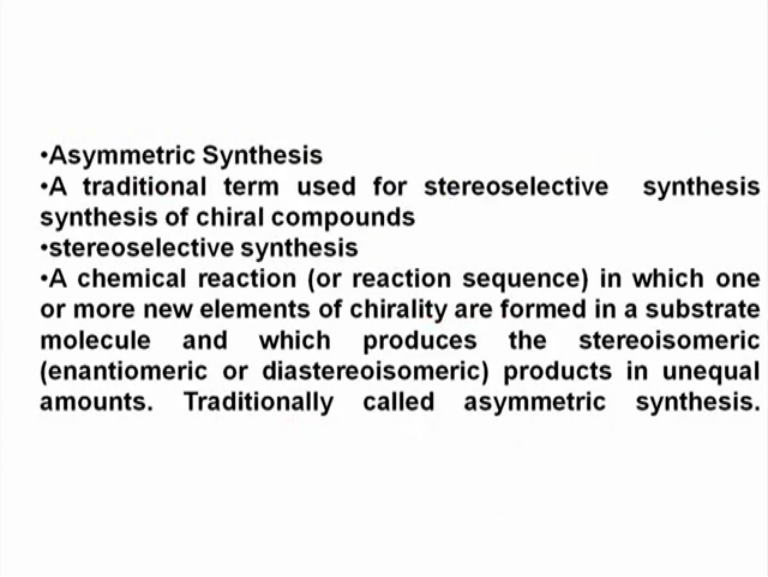

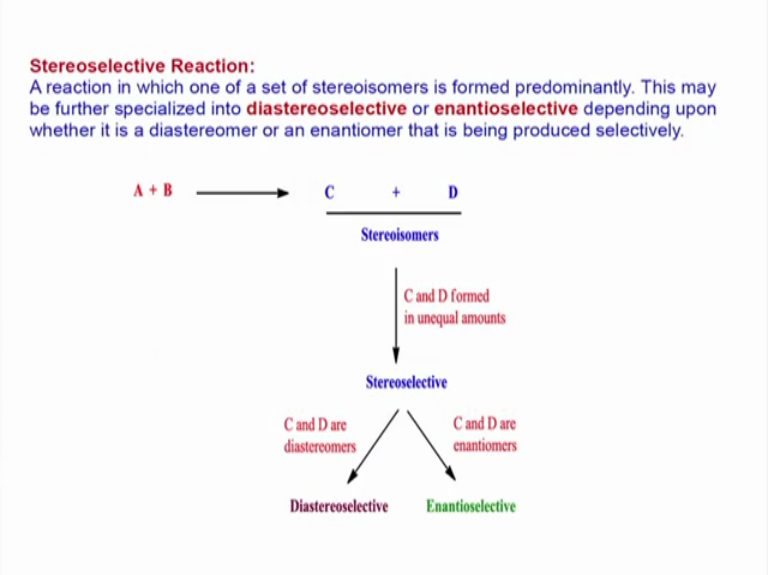

So this is the start of the asymmetric reaction, I have already told you about the selective synthesis.

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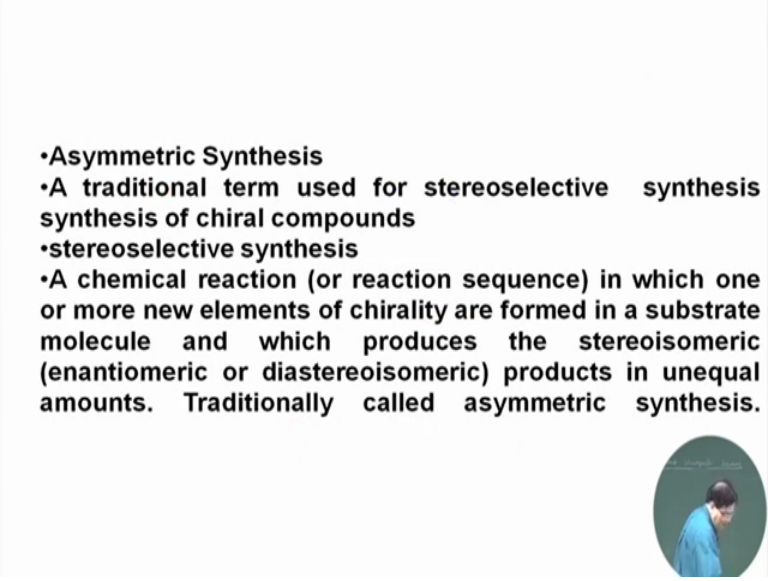

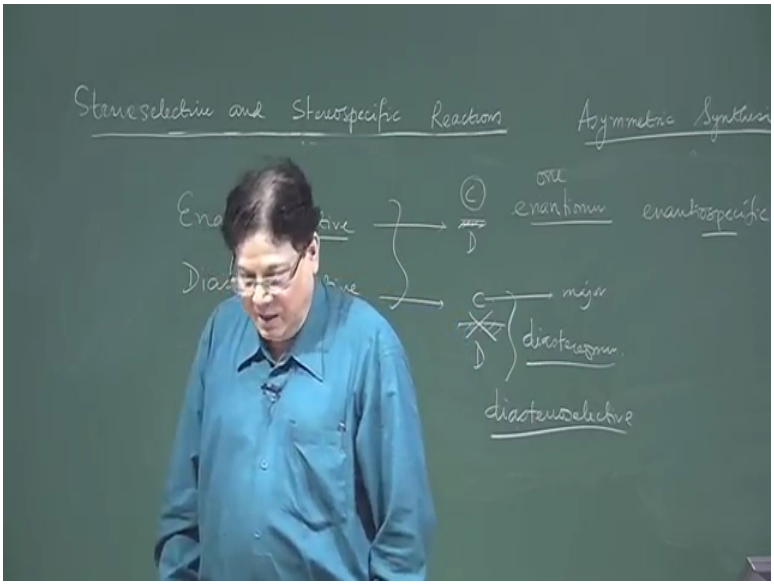

Now in asymmetric synthesis, there are again two terms, one is enantio selective reaction and the other is diastereo selective reactions okay. So if your product suppose the products that are obtained possible products C and D are linked by the enantiomerism that means C is the mirror image of D and if you get only C then that reaction will be enantio selective, because you are getting one enantiomer over the other. If it happens to be that C and D are not mirror images. They are diastereomers and you get only one in major amount, suppose C is in major amount then that will be called diastereo selective reaction, okay. So depending upon the relationship of the products, you can call them as enantio specific or diastereo specific or diastereo selective or enantio sometimes specific is also called, but better term is, because specificity is reserved for the configuration of the starting material. So is better that you use this enantio selective and the diastereo selective.

So here this is a diastereo selective reaction if you get one diastereomers over the other and if you get one enantiomer in excess over the other then that will be called enantio specific, okay. Now remember when we started with a carbonyl chemistry, I said that if you take a flat carbonyl with two adjacent hands and none of the hands are chiral, then what happens, the nucleophile which is also suppose not chiral when it comes, then it generates transition states which are enantiomeric in nature and that is why the rates of formation of both R and S compound will be same and you get 1 is to 1 mixture

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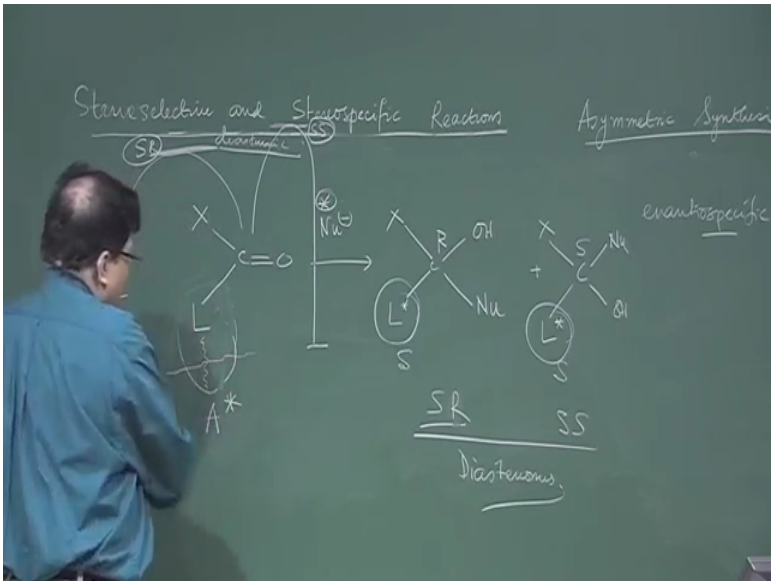

However suppose a molecule already has a groups which is chiral which has got a chiral center, in one particular configuration if you can get it and suppose this is another group R. So now this molecule is **is** not chiral here, but overall it is a chiral molecule, because it has got a chiral center somewhere is L, okay and suppose this chiral center whatever is present in L is having an S configuration, I think better make it another group say X, in S configuration, okay and you now add the nucleophile, okay. So the nucleophile will add to it, this is one possibility I am drawing the 3 dimensional structure just a rough sketch. So this is one possibility and the other is the nucleophile on this side and OH on the other side, okay X and L star remains okay.

Now suppose now this is still S**,** because we have not touched the chiral center of L. what you have done is a created a new chiral center, okay you have created a new chiral center. Now there is a possibility that there will have configuration, suppose sequence I did not know what is a nucleophile, but suppose we have a sequence order here such that this becomes R, so then this has to be S, okay. If this is R then this is S, I am not giving any priority order, suppose this becomes r, the priorities are such that this carbon becomes R then this carbon will be become S, okay.

So what is the two products are SS and S sorry, SR and SS. what is the relationship between these two product? The relationship between these two products are diastereomers, okay and that implies that this is going into the two products, the RS or the SS, because these are

diastereomers. So these two will be also diastereomers, because the transition states if you take the mirror image of this transition state to the and the other transition state mirror image one transition state and try to compare with the other transition state, it is not possible, because you will have one configuration which is always S.

So taking the mirror image of one transition state you have to make this R, but that is not possible, because this is fixed S. so the transition states now you have will be diastereomeric that is why I gave different (())(15:30). Why these are diastereomeric, because you have already a prefixed predefined configuration for which you do not have any mirror image, in this transition states. This transition states always have this SL, L as the S and then if I write it this way that this will be S and if the configuration that is being generated is R then this will be SR and this will be S that this is relationship is diastereomeric.

So the principle of a symmetric synthesis as I tell told you earlier that you have to go through diastereomeric transition state. So if you go through that diastereomeric transition state you will get selectivity or you will get the asymmetric asymmetry that you desire, okay. So asymmetry can be obtained in various way one is the molecule already having a chiral center that is one way, the other is that you use the reagent, which is chiral then also, because in the transition state the nucleophile is involved and if the nucleophile has a particular configuration. So then the configuration is fixed you cannot have the enantiomeric mirror image then you have to have diastereomeric mirror image, okay. So the other possibility is the nucleophile can be chiral. There is third possibility that there are, if it is catalytic reaction, some reactions are can be catalyzed then the catalytic the catalyst can be chiral that what happens in biological system that why natural products are chiral. Why all natural products nature mix or chiral, because nature uses enzyme which are chiral catalyst.

So whenever a reaction is done via a chiral catalyst then also you can get asymmetric induction or asymmetric synthesis you can achieve asymmetric synthesis, okay. So there are these are the three most important ways, either you use already a prefixed at already an attached asymmetric center or you can have a chiral nucleophile or you can have a chiral catalyst or sometimes what happens that if you should do not have any asymmetric center, but what you do you temporarily attach a chiral center into it, okay temporarily attach a chiral center unit and then do the reaction then also, the transition states will be diastereomeric, because of this chirality of this A okay.

And then after the reaction, once the as the asymmetry degree of asymmetry is achieved then you can take this A of and get the original target compounds okay. So that is another way. So if the starting compound is not chiral you attach some chirality in the molecule and then do the reaction, okay and get the diastereomeric transition states or you can have chiral reagent as I said or you can have chiral catalyst okay, sometimes chiral solvents also can induce asymmetric asymmetry in the reaction, okay.

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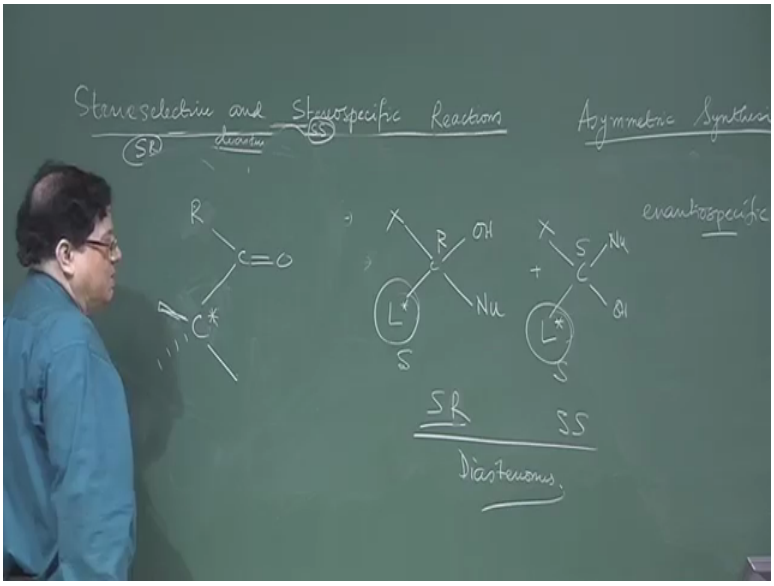

Now let us take the cases where there is a carbonyl and the carbonyl is attached to a carbon, which is having a chiral which is a chiral center, okay. So chiral center means there are three groups here and there is R group here. Now if you want to do a reaction, say boro hydride reduction or a magnesium or RMgX addition methyl magnesium bromide addition then you are passing through a diastereomeric transition state. So you will get the alcohol (())(19:31) boro if it is a boro hydride then you will get an alcohol if it is methyl magnesium bromide then you will get a tersary alcohol , but the question the fact is that you are going through a diastereomeric transition state, because you have a chiral center here, which is fixed.

Now there are certain rules, which can tell you which compound is going to be obtained in major amount. So now let us take this inspect what I am saying, I am taking a carbonyl compound, see this is my carbonyl group and there is a group attached any group I can attached, suppose carbonyl in one hand, there is a symmetric group, okay and the other hand, the there is a

attachment of a carbon, which is chiral, because the this is red, this is white and this is a different group. So this is a chiral group chiral center, it is a carbonyl and carbonyl has other hand, okay.

Now you are doing a reaction, suppose a boro-hydried addition on to this carbonyl so the boro-hydride has the possibility the hydride can come from this side or hydride can come from this side. The question is which side you will be preferred. Now there are certain set of rules to decide upon that, okay. What are these set of rules? So that we will discuss now, okay.

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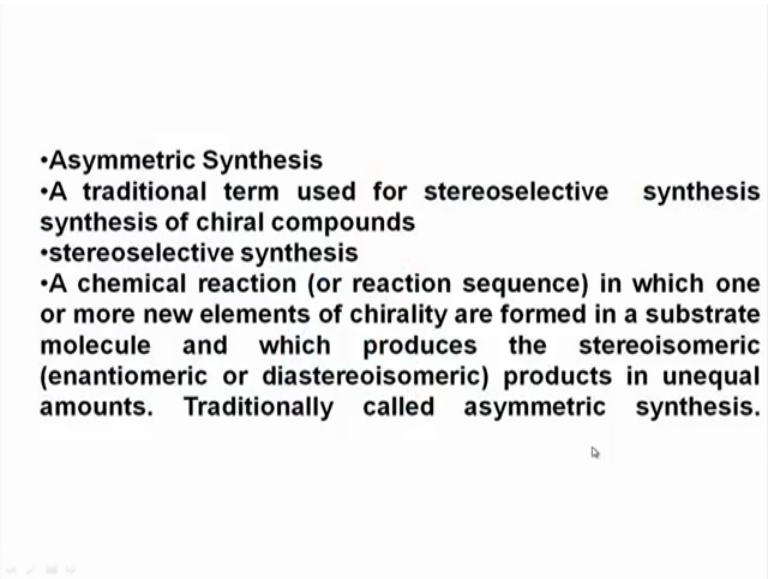

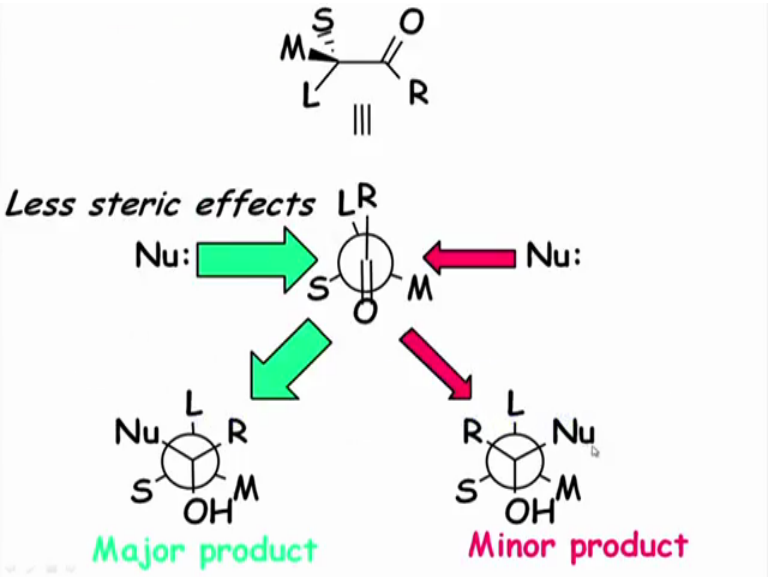

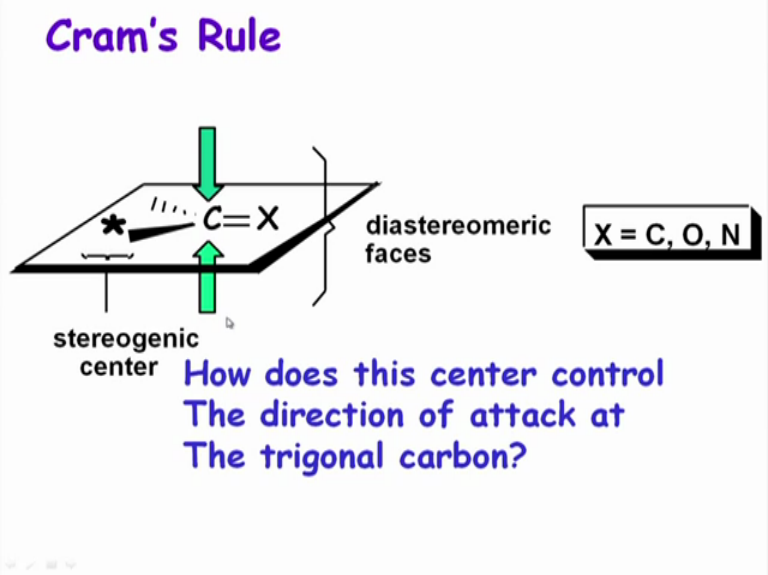

The first is, see this is a situation that what I am saying that you have a carbonyl group, but this rule is the very general it could be X could be carbon also that means you are adding a nucleophile on to a carbon that happens in a mical (())(21:23) type addition C double bond C usually nucleophile does not approach, it approaches only when there is another electronegative group further down. So if it is carbon, that means it is in a mical (())(21:37) type addition or if it is oxygen, it is 1,2 carbonyl addition addition of a on toward 1,2 carbonyl system or if it is nitrogen then it is addition on the emine (())(21:48), okay. So whatever I am taking about the carbonyl the same rule applies for carbon that means double bond as well as for the (())(21:58).

Now let us see what is the problem, the problem we are defining is that, there is a group which has got a chiral center here, stereogenic center that is a common that is a modern name. Now there are these two possibilities, the nucleophile can come from the top or can come from the bottom and so these two faces are no longer enantio topic. They are diastereo topic. Why, because the products the way to do is that products, obtained from these additions are diastereomers. So the faces are diastereotopics, okay or the other way around that if there is a chiral center already attached, the faces becomes diastereotopic okay, but for easier understanding you can say that the products that are obtained from it are diastereotopic. So the faces are diastereotopic are diastereomers, so the faces are diastereotopic, okay.

If they are enantiomers, the products then the faces are enantio topic, but the same ray-psi concept is still there that means if this is one, if this is two, if this is three then that is the that is

1,2,3 that means that goes in a clockwise. So the top one is the ray and the bottom one is the psi, okay. So this is the seen arrow now. Now so question is which face will be favoured that was the our problem.

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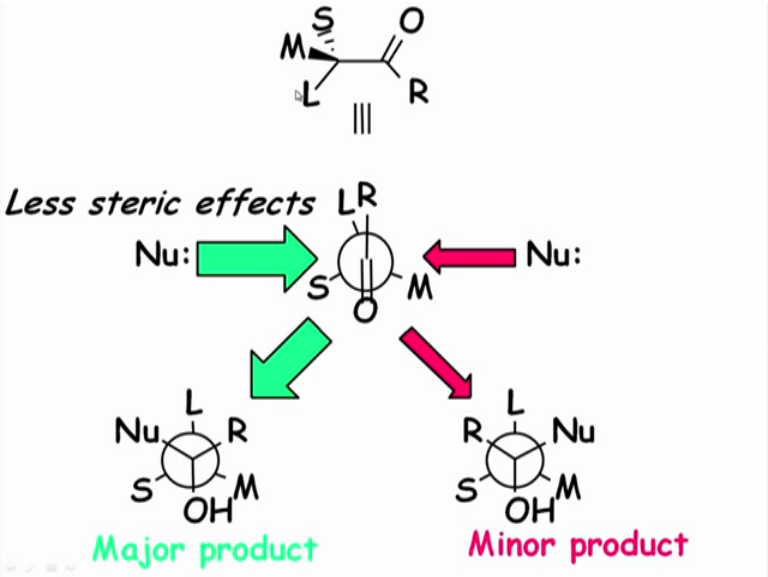

So now let us break down this carbonyl attach the alkyl the groups attached to this carbons. So our problem is that we have carbonyl system where this is R, do not have any chirality here, but the next other half other hand, next carbon is a chiral carbon. So it has got three additional ligands. Now out of these three ligands, one will be this is now the pure steric the size, the steric size of these groups. So one will be small another will be medium and another will be large.

Suppose this is a case that there are three groups. So one is small this is large, suppose and suppose the white is the smallest and the red is the medium one. So you classify these three groups, which are attached to the stereo genic center as large, medium and smaller, then you try to figure out that what is the preferred conformation of this molecule, see this is there is this free rotation happening in this molecule free rotation. So as the free rotation is happening that means, it has got different types of conformations. So which conformation is preferred and according to Cram the conformation that is preferred that will give the give the major product that will react in a particular fashion and that will give the major product.

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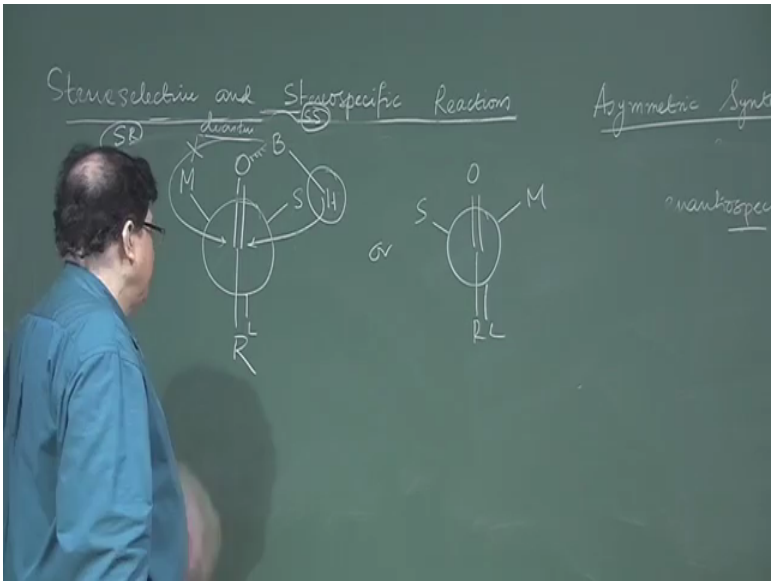

So according to Cram, if I go to the board, according to Cram, this is the simplest the first rule that came out, of addition to a carbonyl adjacent to a chiral center, okay. So according to cram that you have conformation, which is most stable is the one where the carbonyl has another group that is R where the next carbon that means the chiral carbon, the large group is anti to the carbonyl. So if that be the case, then there will be a small group, suppose on the right side that of course, depending upon the chirality of that center, but suppose this is the case that, it has got a conformation like, this S M L or you can have another S M L okay or depending on the chirality again, I say that you can have the other also, R L S here or M there, okay, but for a particular compound you will have only one set I will go through the example.

So the most preferred conformation will be this or this one again I repeat this is that depends on the chirality of the stereogenic center, whether L M S will be anticlockwise or L M S clockwise that depends on the configuration of the chiral center, but this is the preferred conformation where the carbonyl the other way to say, the carbonyl is flank (())(26:27) between the small and the medium, okay. So once it is fixed like that then the boro-hydride, suppose I am doing a boro-hydried reduction. So boron is complex to the oxygen and then it has got the hydride. So the hydride will now approach the carbonyl from the side of the small R group and it will this the hydride could have approach from the side of the medium group, but he say according cram that this approach is not favoured, the approach which is favoured is the hydride or the nucleophile

here, hydride is the nucleophile that is the that approaches from the side of the smaller group. So if that happens that means OH will be on this side and hydrogen will be on this side, okay.

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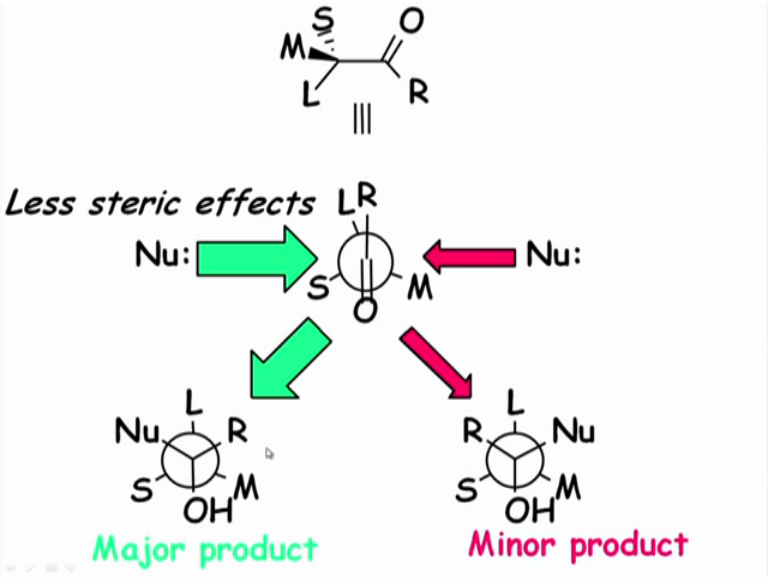

So let us go to this example, which is writurn here, in the on the slide, okay. So this was my compound and if you try to draw the correct numan projection, keeping the carbonyl flank between the small and the medium you should not make any mistake which side will be S which side will be M. So the way to do it, now is the carbonyl is the actually the front carbon, okay front carbon that means if you look from this side, so you see the L M S is in a from this side, again I repeat. If you look from this side, the L M S looks clockwise okay. So whenever you put these groups L M S that should be in a clockwise fashion, L M S that means you are on the correct path okay, again I repeat carbonyl is on the top. So you have put the carbonyl at the top, so the L M S while viewing from this side you maintain that whatever the directionality of L M S. So that that is maintain here L M S is like that. So this is a correct conformation of this and the carbonyl is flank between S and M. so according to cram, now L is anti to the carbonyl.

So now the nucleophile will approach from which side, from the side of the smaller group, okay. So the from the side of the smaller group. So this will be, now according to barge donage principle, the hydride should approach at an angle of 107 degree. So it will approach, an angle like this in an angle like this**.** So it approaches from an angle like this. So if that happens then R goes to the right side. So this is the nucleophile and this S M L remain at the same position, only

when the nucleophile comes from this side, the oxygen goes to the nucleophile comes from this side, the R moves to the right side, OH remains at the same position, because it was 107 degree. So only slight deviation only slight adjustment, this CO bond has to do. So it is almost at the same position. So this is OH, this is M this is S and this is L and that is R.

So now you can, if the nucleophile approaches from this side then the R will be on the left side, okay. So that is the difference. So these are the two diastereomers possible, but the major product is the obtained when the nucleophile approaches from the side of the small group. So this is what is called the classic crams rule, incidentally Donald j. cram, he gave that rule, he receive Nobel prize later on for some other work not this stereochemistry work.

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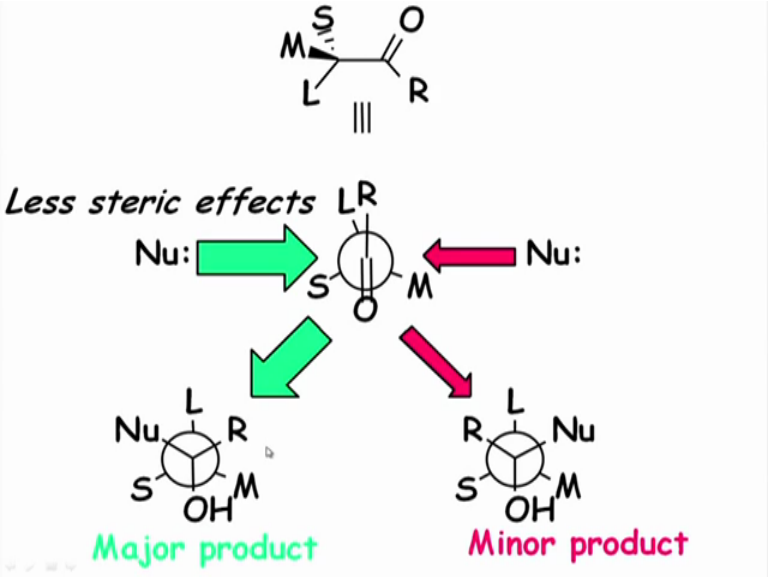

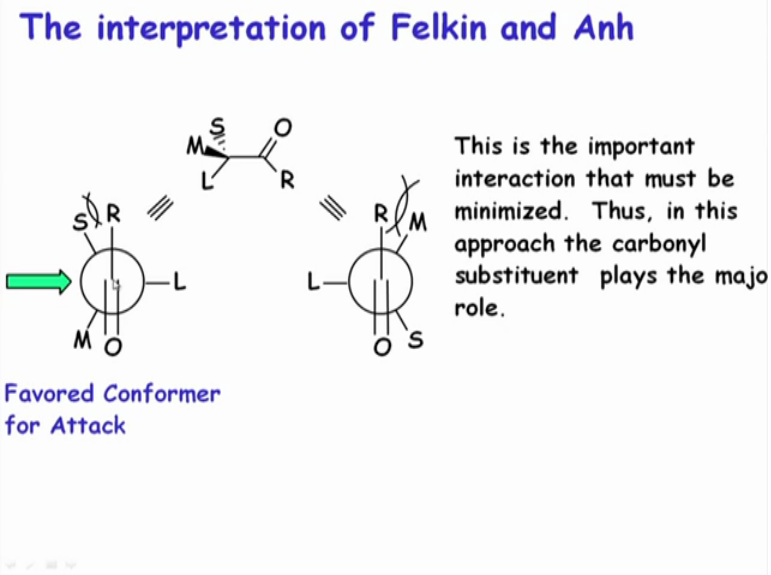

There are other interpretations other rules, which can also explained, the formation of this as the major product and we will end up with this. This is the other model which is call felkin-Anh model. In the Felkin-Anh model, they differ from the cram model in the sense, that they said that the preferred conformation is not the that the carbonyl is flank between the small and the medium group. Here, this says that the large group has to be perpendicular to the carbonyl. So the large group has to be perpendicular to the carbon. So this is L then and then you have to maintain that what I said from this side L M S is clockwise. So that you maintain L M S is clockwise. So this is one configuration, but the large group can be on this side also. So you rotate by 180 degree bring the large here and the medium here goes there and the small comes here.

Now between these two, which one is, here it is there is RS interaction where the interaction between R and the S group, the small group and here it is R and the medium group. So obviously (the) this one will be the more stable one. So now the nucleophile will approach from this side opposite to the L group. So it will approach from this side and from the side of the small group that means according to the barge donage (())(31:47), so it comes from an angle of this 107 degree and the product, I do not know the product is not writurn (())(31:54) here and the product will be from if we have to just put the nucleophile here and the OH almost at the same position and R goes in the opposite direction, okay. So this is what is call felkin-Anh model, I think next day we will we will do this in more elaborative fashion.

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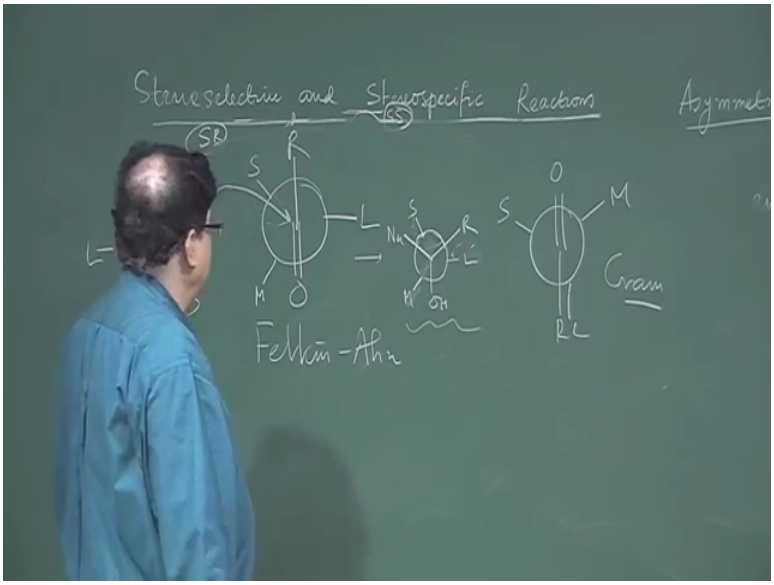

So according to cram, this is a situation, this is the preferred conformation, this cram model and according to Felkin felkin-Anh model, so you have to place this that the carbonyl is this. This is R then L is here, M is here and S is there and not the other way, other way around means L is on this side and then what happens you have introduction between R and medium. So L medium and S, so this interaction will be there. So that will not be there. So this is the favoured conformation.

Now the nucleophile approaches as per the barge donage (())(33:08) trajectory and then carbonyl almost stays here. So the product that will be obtained is, so R will move out now. So this is OH, this is R. This is the nucleophile and then you have the S, you have the L and you have the M. so just slight you can just move it little bit to eclipse all these. So S is somewhere here, okay somewhere here M is here and L is there, okay. That means if you rotate it S will eclipse nucleophile, M will eclipse OH and L will eclipse R.

It is a same product remind you these are the same product as the cram product, but this is a better approach than the better approach later on this is supported by quantum mechanical calculation. So now many people prefer the felkin-Anh model and not the cram model. We will discuss some other systems, uh some other tricky systems where the cram had do extend his model or felkin also had to extend his model, the earlier model was based on steric size of L M and S, but later on they found that if one of the groups is a polar group or if one of the groups can

chelate (())(34:34) complex, so the carbonyl then the whole thing falls apart this model falls apart. So to change the model and accordingly draw the preferred conformation and get the correct product, okay. So we will do it that in a next class, thank you.