A Study Guide in Organic Retrosynthesis: Problem Solving Approach.

Prof. Samik Nanda
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture – 55
Stereochemical Strategies (Contd.)

So, welcome back students we are basically discussing concept of Enantio divergence.

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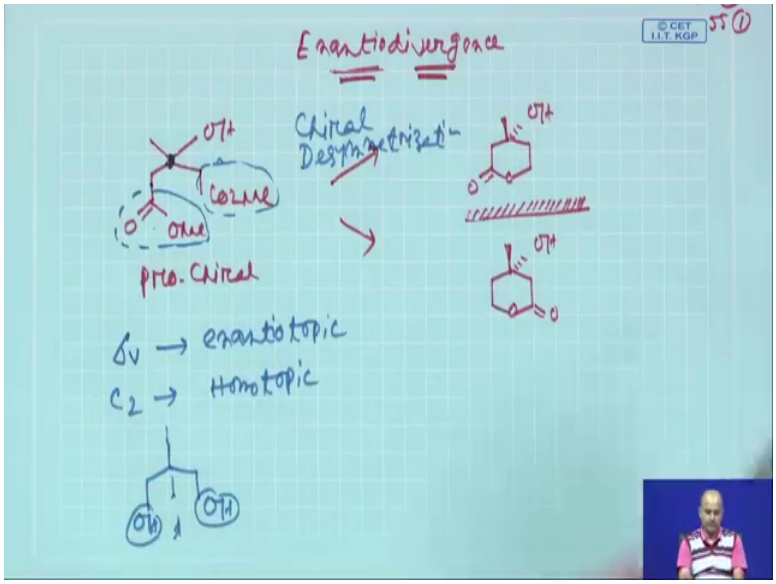

And we said that desymmetrization and divergence are very much while linked together and if you are thinking about a desymmetrization of a pro chiral entity that basically leads you to divergence. Now normally we will try to give you a similar kind of problem in our next assignment and here we will give you a compound which is this compound this compound I say you have to convert this compound to both the enantiomers of a this product which is basically nothing, but a lactone 6 member lactone. Now if you say this compounds are basically mirror image isomer or enantiomers.

So, what in reality you need to think about the initial starting compound is a pro chiral compound it is a pro chiral compound means that this C O 2 C O 2 m e and this C O 2 C O 2 m e is enantio topic. Now for your sake of simplicity if the topicity was not covered or not properly taught to you so you just remember that if the molecule is having sigma v the similar kind of group having enantio topic behaviour if it is having c two symmetry

these groups will be homotopic will be explaining this C 2 symmetric and homotopic little bit later on.

Now, if the compounds are having a, I mean one compound like compound like this if it is having constitutionally symmetrical part and you have a sigma plane you can say that this O H and this O H are enantio topic to each other. You can consider through a symmetry element consideration or you can do a substitution pattern which is also evolution standard stereo chemical textbook

So, now I am saying that is a you having a pro chiral compound the assignment was given that you need to convert it to a 2 enantiomeric lactone, but the [vocalized noise] initial reaction basically you have to do it a chiral desymmetrization reaction which will lead you to the divergence..

Now also the point is two of the functional groups are basically similar so it means that this part is remains fixed the central part is remain fixed and then you are basically targeting one reacting site at first keeping this, but intact and another sequences you trying to do this part first, this part later on.

So, basically right hand first left and second left hand first right hand second that basically gives you two enantiomer enantiomers are what right hand and your left hand handedness.

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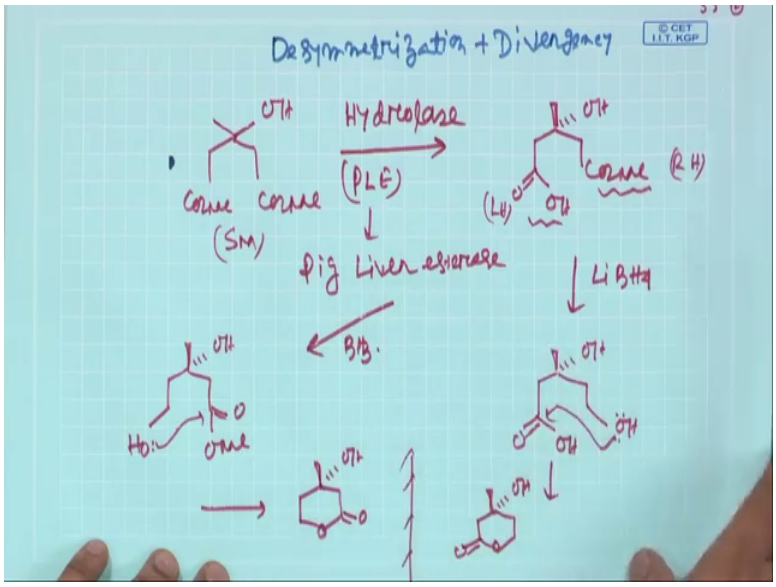

So, now based on this information we will try to analyze this particular problem the starting material is C O 2 C O 2 m e C O 2 C O 2 m e. Now I say for this kind of chiral desymmetrization you need to put them in a chiral environment and this chiral environment basically we happen to talked about, but probably one of the chiral environment is given by a enzyme named hydrolase.

Hydrolase are enzyme which basically hydrolys hydrolyze the ester bonds we are not going to discuss about very detail in the mechanism this in hydrolase is abbreviated as P L E which is named as pig liver esterase which have been isolated from pig liver it is a very nice enzyme and it can gives you it can basically give you a out of this 2 enantio topic group one of one of the enantio topic group is hydrolyzed and it basically get you will you can get this particular enantiomer as a main product main product only this enantiomer because hydrolysis of this group only if it hydrolyzed this group you get the other enantiomer.

So, now once you get this compound now have to think about the divergence the divergence can only be created if you think about first during the reaction here keeping this part intact you get one enantiomer now you do this reaction first. So, now, we will be trying to do it you are having a carboxylic acid here you are having a carboxylic ester here now both the carboxylic acid and ester have a little bit different reactivity pattern.

So, initial case if you react with a metal hydride like lithium borohydride not metal hydride basically borohydrides the borohydrides are mild a reducing agent and they are normally known to reduce the corresponding ester group not the acid so acids would not be touch and you basically get this compound ok.

Now, this compound will give you after this simple lactonization will give you one of this lactone whose structure is fine. In second case as I said first we start with the ester in the other route where you have to create the divergence you need to touch the acid first now acid how can I reduced in presence of ester.

The best reagent is boren boren t h f or boren diboren. Now boren basically if you go to a standard textbook boren first react to this carboxylic acid to give you the acyl boren complexes. So, it substantially enhances the electrophilicity of this carboxylic acid then hydride transfer takes part from this boron and is basically reducing the carboxylic acid

to give you the primary alcohol. Now, you see it is almost you first case you do the right hand side reaction and another case you do the left hand side reaction.

So, now here if you now close the ring it will react in this fashion and then what will get you get this now what are they those compounds this compounds are mirror image enantiomer. So, both the enantiomers you can get starting from a single static material.

So, desymmetrization coupled with divergence is achieved so this desymmetrization is coupled to it divergence that is what we are discussing the desymmetrization plus divergence now this dissimulation basically mirror plane differentiating reaction fine. So, we will keep on talking about this divergence and how this two enantiomers of same product can be usually synthesized from a single starting material. Next we will not give you I said desymmetrization can be of two type.

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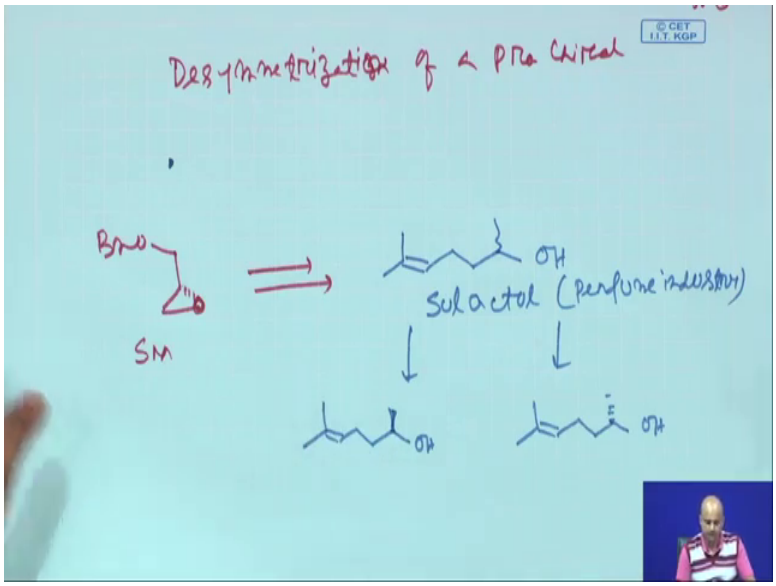

Normally we always talk about desymmetrization desymmetrization or of a pro chiral assembly. So, means molecule is not exactly chiral now in and that will also give you the divergence.

Now, here the next problem, which I am giving to you are having this epoxyte I am saying that convert this epoxyte to both the enantiomers of the target molecule this. Now this compound is a natural product is named as sulactol. Now sulactol this is basically used in perfume industry it is say having very nice smell perfume industry is often used.

Now mean 2 enantiomer means you basically need to make both the enantiomers like this as well as this clear. Now we will now try to explore how this things has been done eventually here if you can see the starting material has already wants stereo centre ok. So, this particular chirality will lead you one of this enantiomer definitely by some f g I.

Now for other enantiomer definitely you need to invert the stereo centre by some means to get the other enantiomer. Now if you now count the number of carbon you basically 1, 2, 3 is the main backbone this 1, 2, 3, you basically need to introduce this extra carbon backbone. So, now we will try to do the retro because retro was our main focus.

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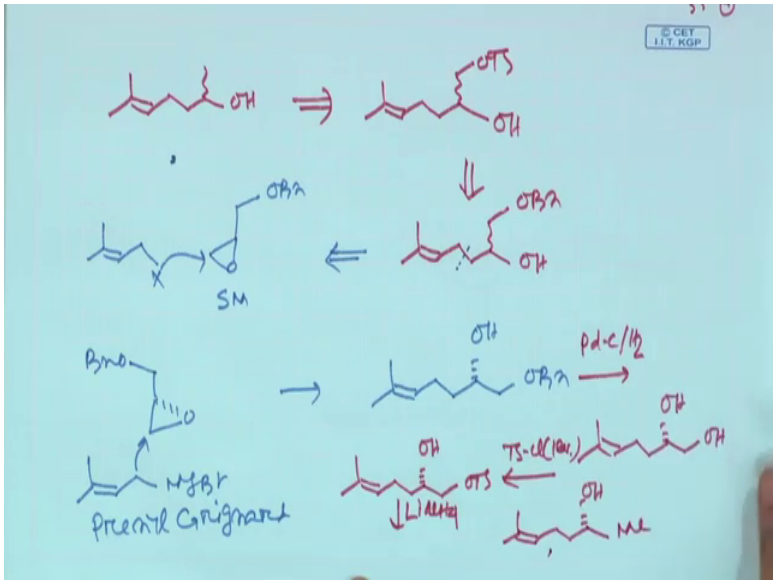

So, what we try to do we will try to do the retro for simple without talking about the enantiomer. Now I am saying that if you have this kind of compound you can easily do a lithium aluminium hydride reduction to convert the C HO 2 O T S to methyl fine.

Now this the starting material was given we need to figure it out how this starting material was basically coming and then we are saying that this O H is coming from this O B N this OBN ok. Now try to analyze this bond if you cut means that you put a this epoxyte here and you react with some nucleophile something like this. So, if it attacks here it opens up to give you this compound.

So, this starting material is here and now we start with the chiral starting material which was given to you starting material which was given to us is this and then you react to it a

Grignard reagent which is very easily available. So, named as prenyl Grignard it is a prenyl bromide and prenyl Grignard reagent it can be easily prepared this prenyl Grignard will open the epoxyte in a less endured site and basically first you get this O H O B N very simple.

So, we will continue the synthesis what you need to do you need to convert this benjile to tosylate. So, what you do you just do a deep benjilation by palladium charcoal hydrogen and you get this O H C O 2 h fine. Now you are having a primary alcohol secondary alcohol primary alcohol reacts faster one equivalent of tosyl chloride you can basically get this O H C O 2 O T S. Now just do a lithium aluminium hydride based reduction or reductive removal of this tosyl group. So, you get 1 enantiomer of sulactole that was one enantiomer.

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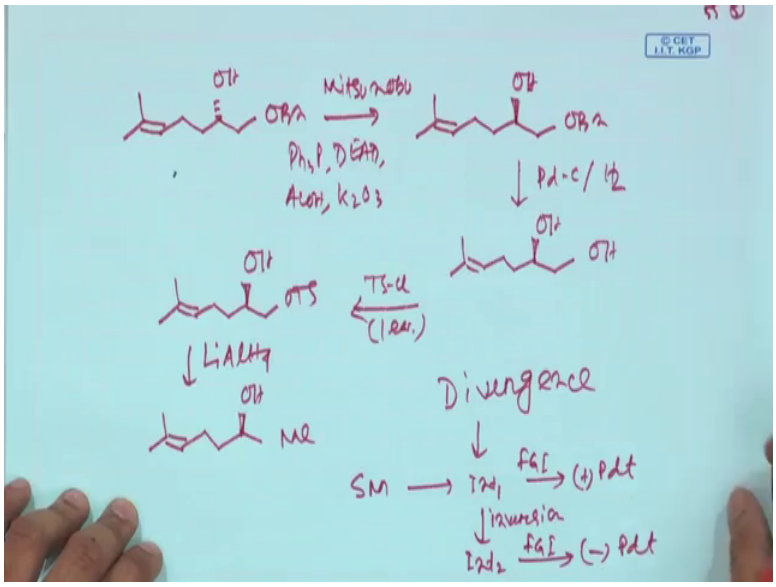

Now if you now see it initial opening of this epoxyte will give you this intermediate whose structure. Now I am again drawing because for the other enantiomer you need to do similar things now I say I want to convert this enantiomer to this t d o inverted enantiomer now the answer is there already have discussed it you can simply do a mitsunobu inversion by a mitsunobu reaction.

So, take triphenyl phosphine diethyl as you di carboxylate, acetic acid followed by potassium carbonate that will give you the inverted thing. Now the same thing you do palladium charcoal hydrogen you will basically get this O H and this primary then you

react with one equivalent of tosyl chloride, 1 equivalent you get O H primary is reacted you are simply reacting with lithium aluminium hydride I will find that this will now complete the synthesis. So, book other enantiomer of sulacto also can be made.

So, the divergence basically now here can be easily created divergence can be easily created from same starting material the pathway you have all already said you have a intermediate you do a F G I you get the product one enantiomer plus product. Now here I said this intermediate if it is possible you do a inversion osteo mutation you get another intermediate which is inverted.

Now do the same sequence of F G I to complete the synthesis so this studio of studio mutation was very important and you can basically try to think about this kind of reaction in a in a numerous pathway.

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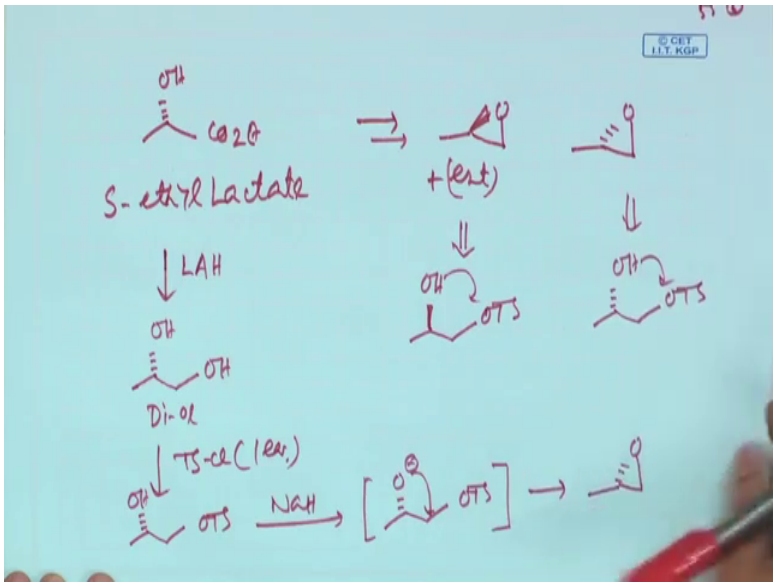

We will try to do similar kind of exercises by taking a very simple example I am saying I will give you this compound which is basically nothing S ethyl lactate this is easily available starting material which is naturally occurring even you can call this as the chiral pool. Chiral pool will discuss little bit later on I am saying that for this compound what you need to do you need to prepare both the epoxyte of this compound both the enantiomer of this compound. So, this is one enantiomer say plus enantiomer and the other enantiomer which also you need to prepare this. So, this is now we have to think it how you can do it.

Now, if you do the retro for both the enantiomer probably a retro for this enantiomer will be like you do something like this and then put a o t s here that will basically you will be o minus doing o minus and that will ring closer and similar case if you can get a compound like this you can basically do a intermolecular S N 2 without disturbing the stereo centre and the chirality which is given here is this. So, now, how to correlate I am saying ok.

Let us do this lithium aluminium hydride reduction first so which will simply give you this O H C O 2 O H diol. What is the diol now this diol is basically having a primary hydroxy secondary hydroxyl so reactivity is basically differences.

So, you react with one equivalent of tosyl chloride and then so what you get you get this O H C O 2 O T S this is intermediate. Now you treat this intermediate is sodium hydride. So, this will basically will give you a O minus and C O 2 O T S which is now intra molecularly react to this primary centre it will give you this O.

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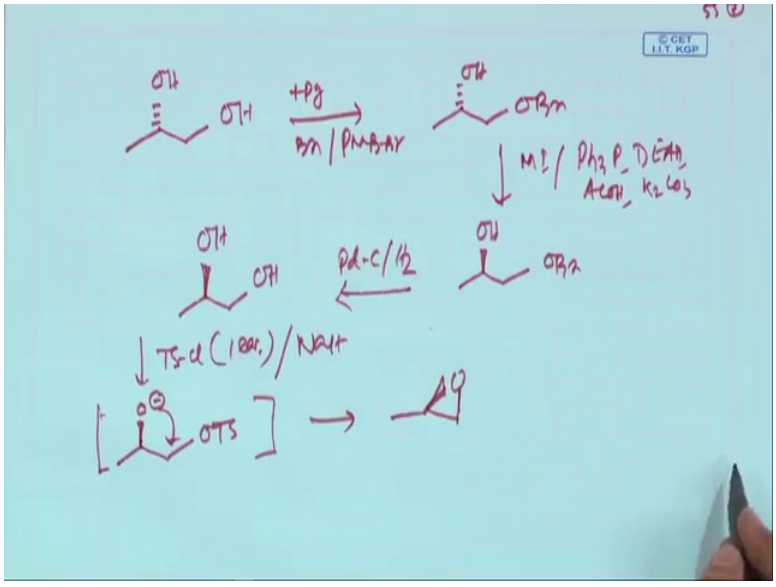

Now for the other enantiomer probably you need something else as I said you probably need to invert the stereo centre. Now this inversion is required something else basically you have a pre hydroxy group. So, probably the base two ways first protect this hydroxy group now base protecting group for this kind of things.

So, basically protect with benzyl or P M B as the protecting group benzyl bromide P M B bromide. So, first let us do the protection let us say benzyl then same like sulactol problem you do the mitsunobu inversion M I by using triphenyl phosphine your dead, acetic acid, and your potassium carbonate for acetate cleavage.

So, basically you get now this compound benzyl removal is easily done by palladium charcoal hydrogen and then basically you get this O H. Next is your diol so tosyl chloride one equivalent the stereo centre basically now is not touched that is why there is no inversion.

So, here tosyl chloride followed by one equivalent of sodium hydride then you see this intermediate will now react you get the epoxyte which is desired. So, this way the divergent can easily be created, easily be created.

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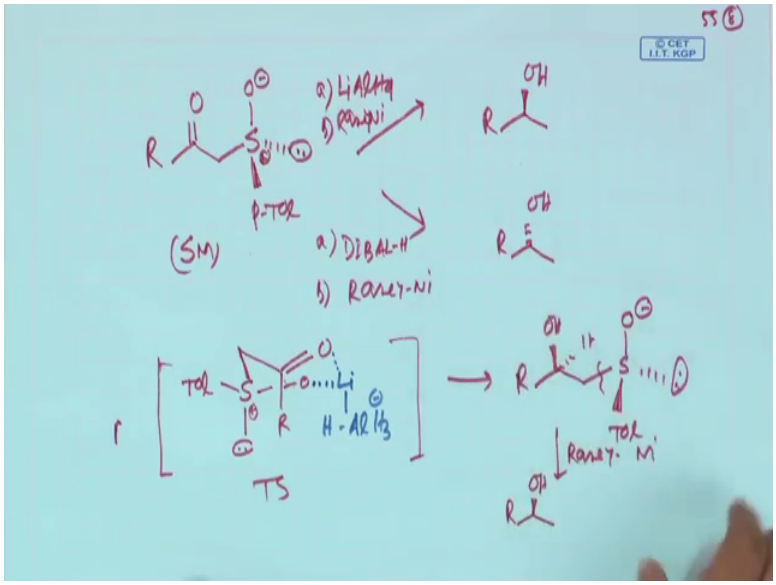

The next particular example will be a little bit not little bit complicated is a similar kind of thing this example of substrate directed divergence here will give you a starting material the starting material is having a sulfoxide basically and the sulfoxide we say sulphur sulphurs are chiral sulphurs stereogenic so this is your lone pair, so this is a chiral sulfoxide.

Now what is it I say that the starting material was this one and the 2 divergence you have to be create you have to make this compound as well as this compound. This component

this compound actually I will now give you the reagent system the first case the reagent was lithium, aluminium, hydride and I give Raney nickel to remove Raney nickel to remove the sulfoxide bond.

The second case the hydride donor is little bit different instead of a di l a h you is a bulky hydride donor and the remaining part is Raney nickel. Now this is a very nice demonstration of substrate directed chemistry. So, initially what I will right we first take the variant sulfoxide or the which was written here.

Now, the sulfoxide you can basically write in 2 different conformational picture this is the lone pair. So, I will try to write the sulfoxide in a will say your R is here and then the sulfoxide oxygen is here initial case I am saying lithium aluminium hydride.

So, lithium is small and then we assume that probably lithium coordinates with the sulfoxide oxygen as well as its carbonyl thing and your aluminium hydride is here here so this is the transition state for this sulfoxide and lithium aluminium hydride this way the sulphur particularly this you can write it S plus S plus the chirality remains basically similar.

Now as this is basically a chelation this hydrogen where from it will attack this will absolutely be attacking from this part or this back side of this carbonyl it will basically attack from this backside of this carbonyl to give you way to basically give you a product where the hydrogen I will now write from the back side keeping the sulphur thing remain intact the paratol will which was the beta or above the plane your lone pair is below the plane ok.

So, I am forcing that hydride in this way if it is close transition state it would attack the hydride from this from this bottom phase put you the alcohol here now your Raney nickel which is we already explained Raney nickel is known for carbon sulphur bond cleavage through this way you basically get the one enantiomer which is drawn here ok

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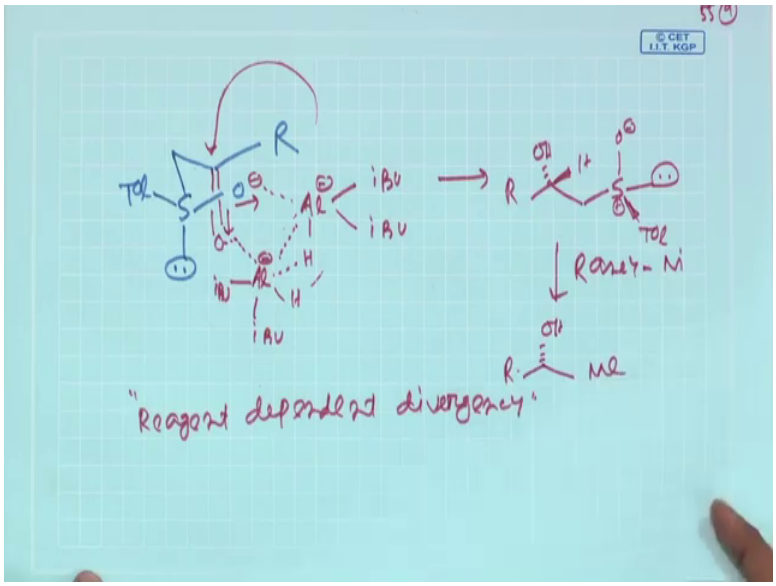

Now, in second case you are having dibal dibal is very bulky reagents. So, now what will happen the initial sulfoxide you can simply draw the same way as you drawn earlier ok. Then the carbonyl now probably it has to be rearranged in different way because the dibal is a sterically bulky probably coordination was now not possible.

So, now, in this case the carbonyl the carbonyl carbon and this sulfoxide is o it will basically aligned in a anti way to have this dipole dipole repulsion in a minimum fashion because this is also electron withdrawing, this is also electron withdrawing. So, this dipole dipole trying to repulse that is why you have a anti alignment.

So, this is the main thing and then you probably have a coordination here with this aluminium; aluminium you are having this hydride and then this bulky isobutyl group isobutyl group. And you can also basically figure it out this aluminium might might coordinate with this electrophilic carbonyl, but is a bit difficult or you can have a dimeric dimeric dibal which also can be quite possible you can have a put a aluminium this H sorry this H with this extra hydrogen you have this isobutyl isobutyl and then this aluminium may coordinate with this carbonyl thing it was just a basically speculation. Now this one minus l minus you have this hydrogen.

Now this hydrogen it to it there is no other way it has to attack from this top, it has to attack from this top. So, in this way now if it is attacked the same way you basically get

the. So, the basically the carbonyl phase in one case attacks from reface one case attack from psi phase that basically dictates the whole stereochemistry.

So, now your remaining part all are similar your tolyl group your sulfoxide lone pair s plus now you are doing a Raney nickel treatment, Raney nickel cleavage which basically give you this O H methyl. So, basically by a choosing 2 different reactions which are fundamentally react in a different way you can basically create the divergency. This is purely a reagent dependent divergency reagent dependent divergency and probably this kind of reagent dependent divergence.

Here very popular because it start with a same starting material and you subject to a simple a chiral reagent you do not use the chiral reagent you have a existing chiral centre in from the sulfoxide it is basically substrate directed approach in one case the hydride has been delivered internally, one case hydride is from externally delivered kind of thing and so that basically gives you the divergency.

So, probably we will try to continue this divergency concept for few more example or will give you some assignments which you can solve at your own and then we will try to have a clear cut concept how this divergency helps you to create 2 enantiomeric product of same compound starting from a same starting material. So, we will try to focus some of the aspects in the next lecture of the stereo chemical strategies till then have a good time and good bye.