A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 53
Stereochemical Strategies (Contd.)

So, welcome back students we are basically discussing the first guideline of classical resolution or stereochemical based strategies.

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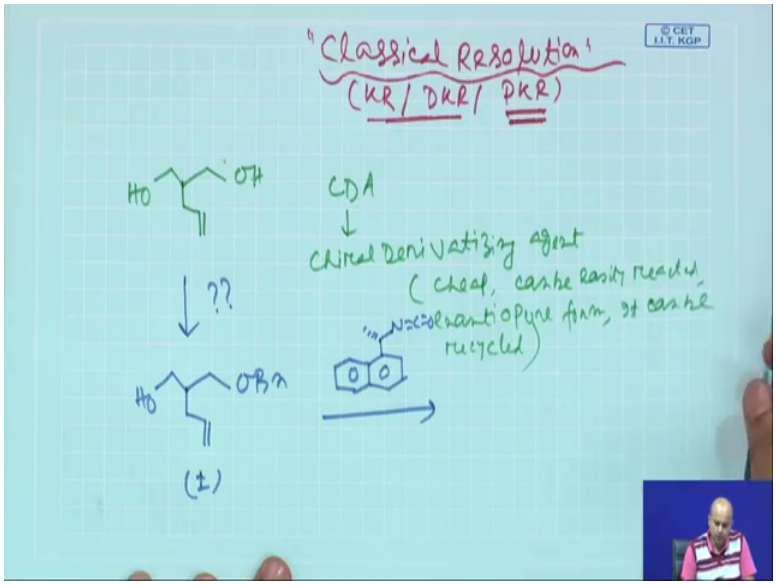

And we said that we have to follow certain instruction in the stereochemical strategies, our initial point is classical resolution, which basically includes kinetic resolution, dynamic kinetic resolution, parallel kinetic resolution, etcetera and we mainly focused on KR and DKR.

DKR we have not talked about it is not basically essential at this point to know detail about the PKR. In classical resolution there are very this reason is very powerful, and till today many industry follow this classical resolution method. I will probably try to give you a case studies, where classical resolution was done through a technique, which is now named as CDA.

Now, CDA basically stands for chiral derivatizing agent. It basically means that, if you having a racemic mixture; you react with the racemic mixture to a chiral derivatizing

agent through a covalent bond formation. Now, this chiral derivativizing has in must be very cheap commercially available and it can be easily derivatized, it can be easily reacted easily reacted, it must be available at enantio pure form; so those are the certain pre requisite you need to maintain and the final point is it can be recycled, if you can recycle it there will be also extremely important.

So, now, what I am saying I will give you a particular pro chiral compound and I said we initially convert this compound to a racemic mixture. Now, this reaction, we have discussed in detail in the earlier lecture, so please go through it. Now this compound initially is pro chiral, you do a desymmetrization to get racemic mixture it is fine. Now what you say? I am saying that, now while I will be reacting this compound with a chiral derivatizing agent.

The chiral derivatizing agent what was commercially available is this iso cyanide. Now, before we talk about this reaction you need to know how isocyanates react with alcohols.

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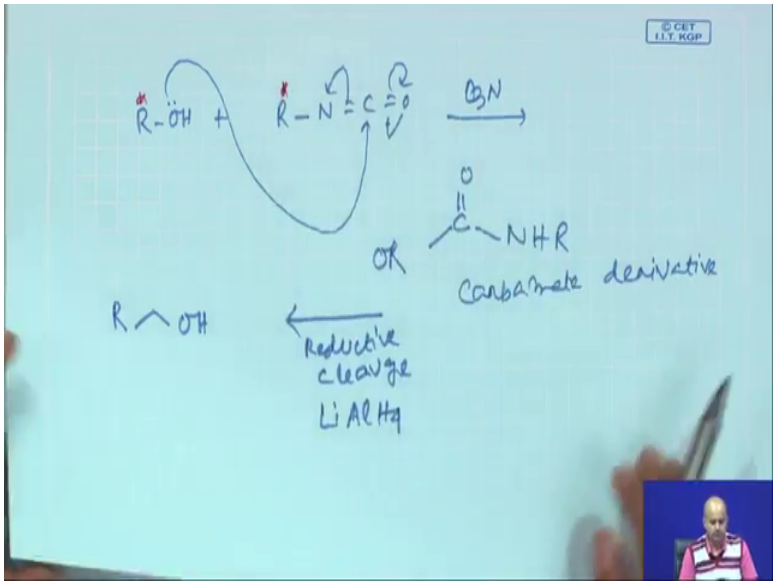

Isocyanates are basically compounds having this structure. So, if you react isocyanate with this alcohol, in presence of a very mild base like trisilylamine this alcohol nucleophile attack to this carbonyl ok. Then this carbonyl backfire it gives a these things.

So, basically you will now get; this is nothing a carbamate it is called a carbamate derivative carbamate derivative say carbamate derivative. Now carbamate derivative you

can basically cleave the corresponding carbamate derivative to get back your original alcohol back the normally you can cleave this carbamate.

Now, this carbamate is basically ester, you can keep this carbamate through reductive cleavage reductive cleavage like, simple you react with lithium, aluminum, hydride to get back your alcohol as it is.

So, this is the way you can basically react, now what I am saying that; if you are having a chiral alcohol or racemic alcohol and you have this part here. So, now, we will start working on the real problem which was given to us.

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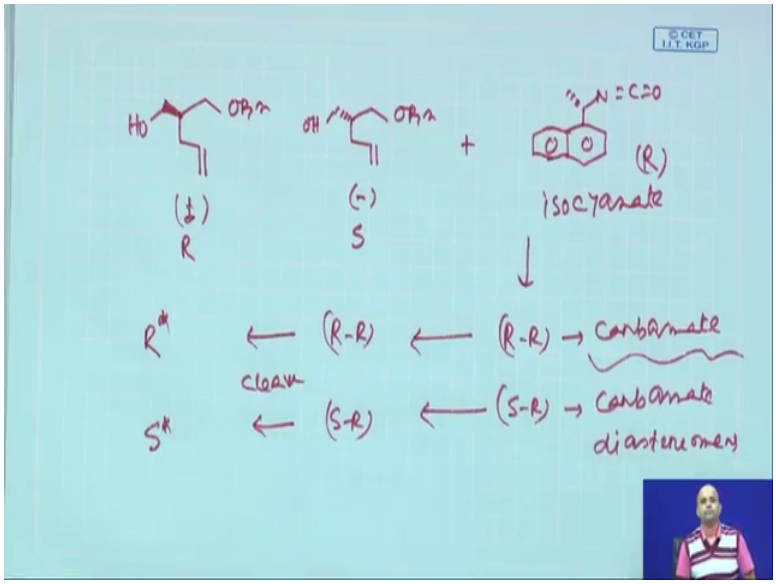

So, I am saying that you are having this compound as well as you are having this compound these two are basically enantiomer.

So, you are having this plus or c plus this is minus 2 enantiomers. Now this or you can say R and S, now this compound next is reacted with a chiral derivatizing agent, which is a chiral isocyanate chiral iso cyanate. The similar way this isocyanate is chiral; so means let us say it is having a R absolute configuration. So, if both the enantiomers reacts in the equal fashion you will get a R-R carbamate you will get a R-R carbamate and you will also get a S-R carbamate fine.

Now, these two compounds are disasteremer these two compounds are disasteremers. So, you can easily separate them out. Disasteremers are having different physical properties all of us know, so these two compounds now basically you can easily separate.

Now, what you need to do? You basically cleave the cleave the chiral remodeling agent. So, now, you get pure enantiomer of R and pure enantiomer of S. So, this is the very standard text standard protocol of a physical kinetic resolution it is not a kinetic resolution in two sense is basically now taking the two enantiomers reacting in a similar fashion through a chiral derivitizing agent chiral derivitizing agent and then the kinetic resolution If you see kinetic resolution, now I try to give you a example; normally we would not go very detail, which is a kinetic resolution if you are having a racemic mixtures say having this particular compound this and it is mirror image.

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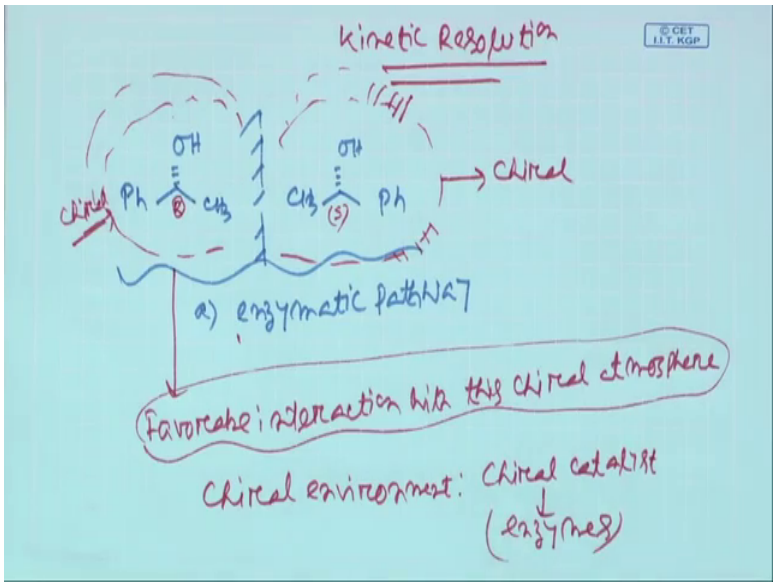

So, both compounds are there; there are basically mirror image isomer. I am saying their rate has to be substantially differentiated.

Now, there are many ways you can we can do the kinetic resolution, probably the best way people are now using a in geometric pathway. Now, initially if you follow the kinetic resolution strategy we said that this enantiomer have similar kind of functional group attachment except the stereo orientation in space.

Now, if we create a chiral environment chiral environment throughout both the in enantiomer then you put some extra groups extra groups, so these groups are basically chiral. Now the only difference is the groups are chiral around the enantiomer. So, now, this enantiomers are basically in diastereomeric environment, it means that this enantiomer is having R or S I am not sure, but just perhaps simplified thing I am giving you the R this S.

Now, I am saying that this both the enantiomers have been put in a chiral environment. Now as their stereochemistry differ in the stereo genic center, this chiral environment is similar. So, basically is in again CDA. So, now, they react in a or they can kind of interact it with this chiral atmosphere and I am saying that in case of CDA both the enantiomer reacts, but here one enantiomer has favorable interaction one enantiomer has favorable interaction with this chiral environment favorable interaction with this chiral atmosphere or chiral environment.

Now this favorable interaction makes you that one of the enantiomers will be reacting in a faster rate compared to the other enantiomer. So, basically enantiomers both the enantiomers are put in a chiral atmosphere and then through diastereo selection is basically diastereo selection, you are getting the kinetic resolution.

The slow reacting enantiomer would not be having a favorable interaction with this chiral environment. Now this chiral environment basically can be created mainly chiral environment, which is essential for this thing it is mainly created by chiral catalyst or chiral reagent.

Now, out of this chiral catalysts enzymes have been now very effectively use used for this kind of resolution, then these resolutions are now termed as EKR or enzymatic kinetic resolution, but definitely we are not going to discuss these things in detail here, because this is beyond our scope, so we will try to bypass it.

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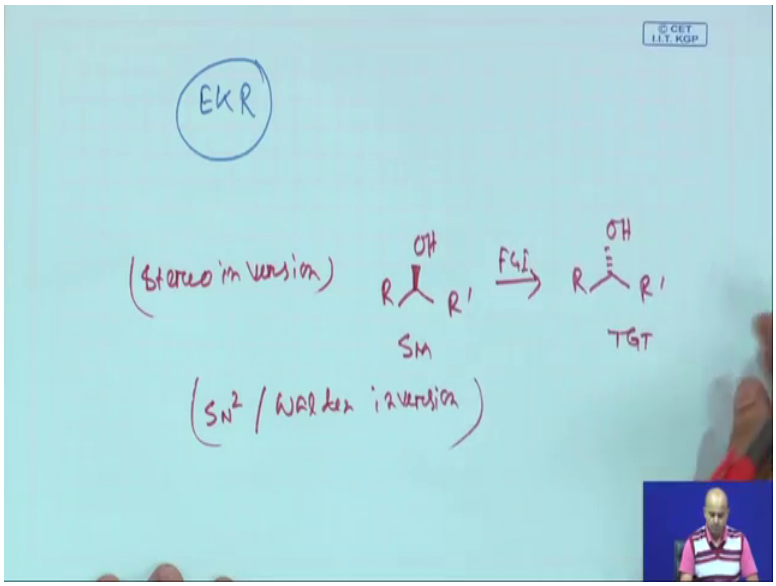

Now, in the case of kinetic resolution he always says that there is a another process, which is named as stereo inversion. Now what is stereo inversion? Stereo inversion means that if you are having a stereo center you; if there is a way you can invert the stereo center depending on your need I am saying you are starting material is this which is the easily available.

Now, your target molecule is this. So, can you do a simple inversion by a FGI, this is the very classical technique very classical technique probably the best solution is; you can simply do way SN 2 inversion or a Walden inversion, which was done earlier it was still followed it was still followed.

Now, let us talk about a similar kind of reaction where, which probably we have not heard about or if you know it still you can have a more information.

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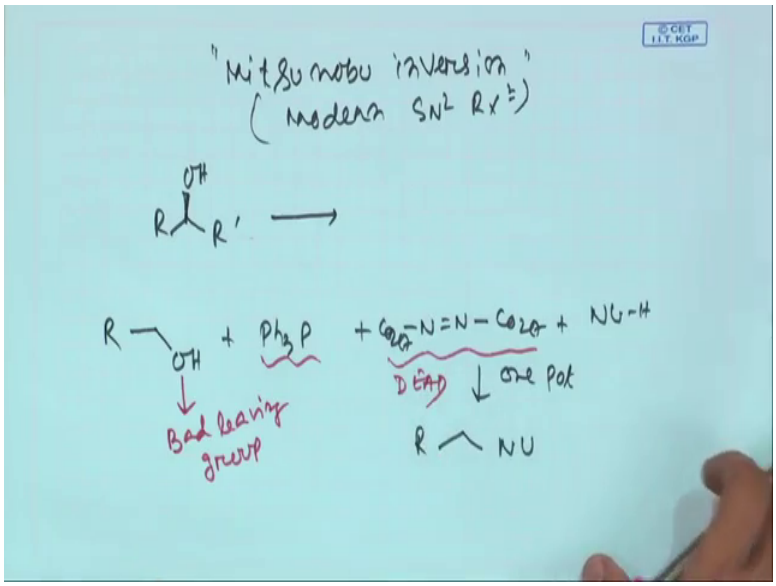

We are talking about a reaction, which basically named as “mitsunobu inversion” it is a named reaction it is called a modern SN 2 reaction.

Now, this reaction is very important in terms of; if you are having a stereo center you want to invert the stereo centers mainly your strategy is basically focused, if you are having a alcohol containing stereo genic center ok. Now alcohol continue stereo center the mitsunobu reaction is very important and now what exactly in mitsunobu reaction was done; mitsunobu reaction you basically I just tried to give you a schematic thing.

You have a alcohol, you mix the alcohol with triphenyl phosphene and a reagent abbreviated as that N double bond CO 2A CO 2A and you react with a nucleophile, so that you basically get a this compound. This is a one pot reaction one pot; all the components are makes together and you can get this compound.

Now initially problem associated with this simple one for substitution by alcohol is very difficult, because we are always says that alcohol are good bad leaving group, alcohol are very bad leaving group; that is why in the standard textbook of SN 2 reaction is always says that this alcohol are converted to tosylate or mesylate, then you react with a suitable nucleophile.

Now, here what we did we reacted with triphenylphosphine and a reagent may abbreviated as dead diethyl azodicarboxylate. Now, what exactly this dead and triphenyl phosphene does?.

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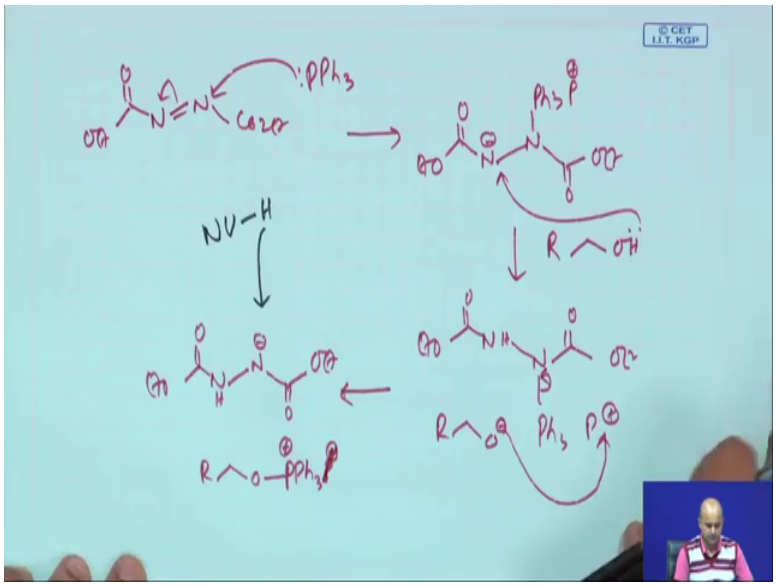

Now initially it was this diethyl azodicarboxylate and this triphenylphosphine basically react. This phosphorus lone pair attacks here and basically give you a negative charge on this nitrogen, which is definitely stabilized by this electron withdrawing of this adjacent theotivity.

So, this is the initial step, which basically happens. Now we have your substrate as a alcohol as well as you are having this any nucleophile. Now if your substrate; now having alcohol say that this can give you the acidic hydrogen through this nitrogen. So, the nitrogen now is basically quenched this negative charge will basically give you N with this tri phenyl phosphine and alcohol now become R CH 2 O minus fine.

Now, this RC H 2 O minus will now react this is also a good necrophile, this is basically react to this phosphine, and now this phosphorus nitrogen bond we will now try to cleave. And then again it we will put a negative charge on this nitrogen, which is stabilized through this electron withdrawing and what you will get you basically get a this spaces oxygen phosphorous spaces.

Now, oxygen and phosphorus are having a very strong bond energy. Basically is it should be right like this O PPH 3 plus is a very strong bond energy. Now this N minus is there, now what happened; if you are having a nucleophile which basically donates this hydrogen to become a this NH CO 2A NH CO 2 A and it gives you a NU minus in addition you are having a R CH 2 OP plus PH 3.

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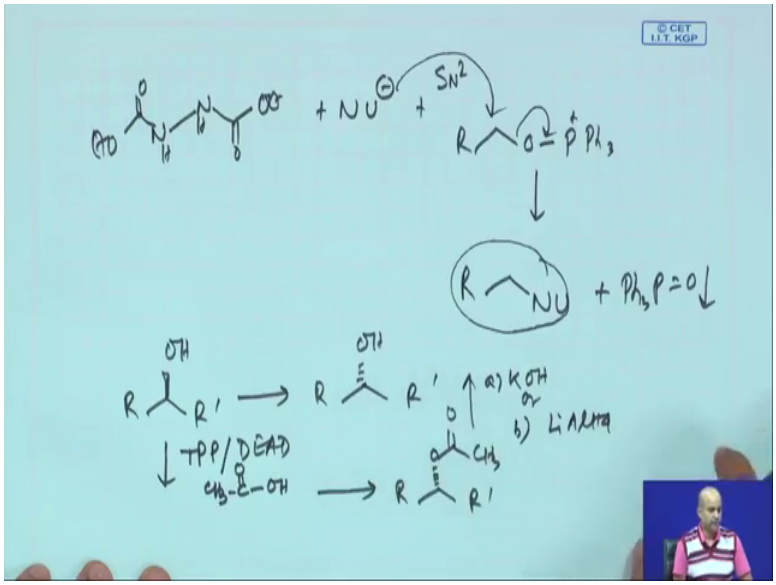

Then this nucleophile attack through a backside attack of this carbon oxygen bond and gives you a phosphorus oxygen bond. So, phosphorus oxygen bond is much more energetically favorable. And then basically you get R CH 2 NU plus triphenyl phosphine oxide as a byproduct, which is comes the solid. So, in reality you basically get these things and this is your SN 2 step, which is your mitsunobu inversion.

So, the problems which have now trying to address, if you have a compound something like this; how you can invert this alcohol? The best way to do is mitsunobu reaction, you react with triphenyl phosphene react with dead, but what about the nucleophile you simply cannot take an equivalence of water, definitely OH minus those are that may be a good nucleophile, but OH minus a harsh condition.

So, try to take a nucleophile, which may have a tendency to donate it is hydrogen also, because if you follow the mechanism you need a hydrogen source to quench this nitrogen. If you take acetic acid or benzytic acid as a nucleophile, initial step basically

what will give get after the first inversion; you get a acetate here. So, acetate is acting as a nucleophile.

Now, you just do way alkaline hydrolysis or you can do a reductive cleavage by lithium, aluminium, hydride you get your product here. So, this is absolutely simple and you can basically complete the stereo inversion or stereo mutation process based on these. Next we will try to do a problem, which is exactly based on this.

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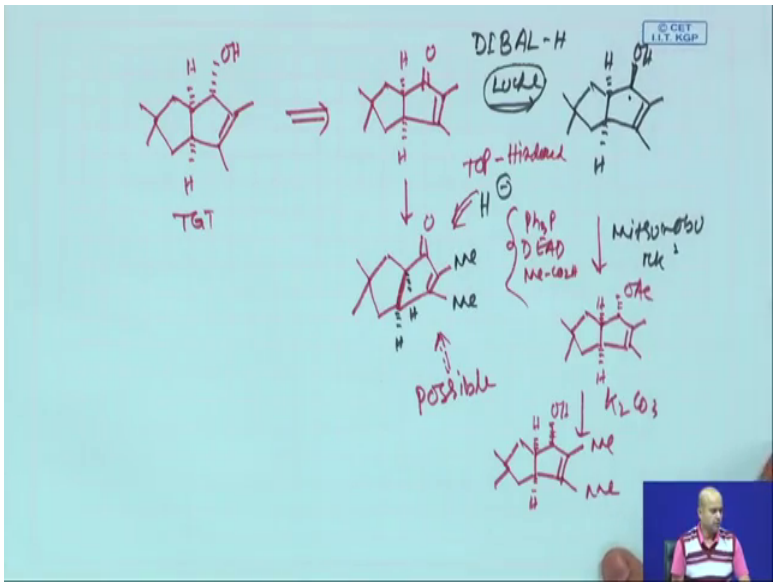

The problem which was next given to you a bicyclic compound has given the bicyclic compound has given the stereochemistry at the stereo chemic center was having this structure. Now, this is your target molecule, the starting material which was given to you is this alpha beta unsaturated ketone. Now from the very beginning it looks a simple, if you say that ok; we can do a simple luche reduction it can be done.

But in reality is not that simple. If you try to do this or try to draw this compounds conformational behavior in the ground state you will find that this compound, it a reality it exists as this kind of structure. So, this kind of structure basically means that this compound is kind of tilted the hydrogens are below hydrogens are below the plane, it basically like this two cyclopentane ring is like this and your hydrogens are below; so you have this compound.

So, now you are trying to do a simple hydride, addition you see that hydride. Now it is compound is like this and the missiles are top. So, top face is basically blocked top face is blocked. So, hydride has to come from the bottom face. So, if you now do a simple luche reduction you will basically able to get the compound, which is not the required compound, which was desired you basically get this compound right.

So, initial hydride addition from the top face the top face is hindered top face is hindered, but the bottom face the or the below face is possible. And this is basically due to the structure, which I have shown is basically kind of this structure; so makes that as the molecule is kind of folded the entire top face is blocked.

So, now if you do this reaction you get this product, but this is not the target; so what you need to do? Now basically you can use the mitsunobu reaction, which will be coming into place. So, now, initial your luche reduction or any sterical actually in principle luche probably want feature because luche is a very it gives you a small hydride source.

Now, if you can do a reduction with a pretty bulky reagent like dibal, which having a spherically bulky hydride. In case of luche probably you get both the diastereomers one is to one that probably once are; now if you do a dibal reduction you get only exclusively this product, but then you need to invert the stereo centers here. Now, in the last part we discussed that, we can invert the stereo center by the stereo universal process through a mitsinobu reaction mitsinobu reaction.

So, what do next do? You do a mitsinobu reaction you do a mitsinobu reaction the same reagent condition and then you do the hydrolysis acetate hydrolysis. So, now, basically you get your product back this OH which is the target molecule was drawn. So, mitsinobu reaction the region conditions will be using triphenylphosphine, you will be using dead and you will be using acetic acid as the main reagent.

So, these things in combination will give you the initial inverted acetate, then you follow the hydrolysis that will basically give you the complete story. So, kinetic resolution, dynamic kinetic resolution and stereo mutation, stereo inversion will basically covered a little bit and a few examples have been have been provided.

Now, the next point in the stereo chemical strategies will now try to cover substrate directed approach.

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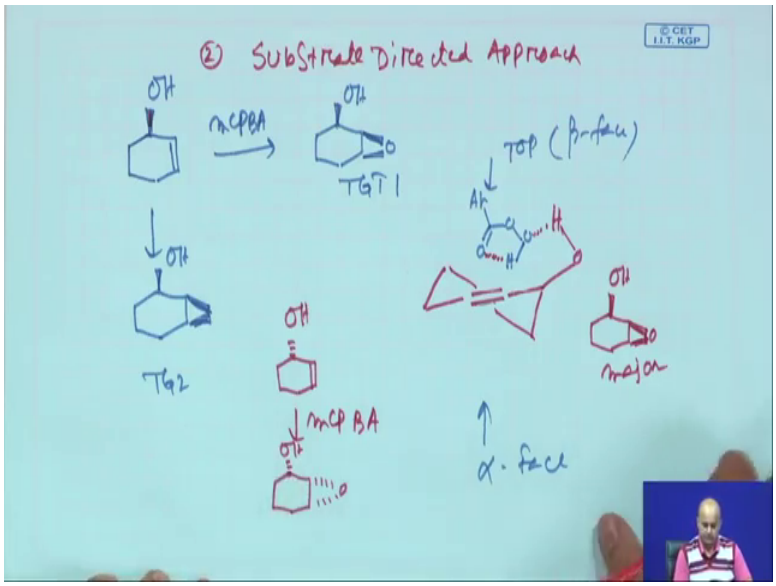

Now, where we will straight forward go to some I will assign some problem to you and say that I will be having this particular compound from this I will I want this to target. So, you are having this cyclohexane based compounds and I will be needing this target 1 and target 2.

The one is epoxide one is cyclopropane, but if you closely analyzed the stereochemistry of this hydroxyl group was the governing factor means that whatever stereo chemist the hydroxyl group is having; the final product has same stereo chemical orientation, if it is beta this is also beta, this is beta, this is beta. So, means that you have to devise some reagent or some reagent system for that stereo chemical information was preserved or this stereo chemical information directs the incoming reagent to attack from this one only.

Now, we first talk about the initial example. Now for the initial example, if you draw it is ground state conformation is basically a half chair formed and half chair formed the OH is above. So, basically the pseudo equatorial; now this pseudo equatorial basically you can write like this is the initial starting material.

Now, see the starting material is having a pi bond, where two phases are available: the top phase or the beta phase and the bottom phase is the alpha phase this is done. Now, the reagent I am saying that you use the reagent mCPBA which is very known epoxy

rising agent or electron deficient epoxyrizing agent. The mCPBA I will now draw the structure; I will put Ar; Ar is your basically this aromatic things is basically meta chloro

So, you now put Ar C double bond O, you are having this oxygen another oxygen and then H. Now, what happened this pseudo equatorial or the beta phase OH will try to have a hydrogen bonding with this electron deficient oxygen of this meta chloro per benzoic acid been doing acid; it could have a inter intra molecular adiabatic is something like this.

So, the whole region system will basically through this intra molecular hydrogen bonding, it will try to approach from the top face. As this OH is pseudo equatorial it is not pseudo axial, if it has to be pseudo axial the mCPBA will coming from this bottom phase. So, this was the; now your epoxidation will take part from this bottom phase and we will find that that product distribution, which was given here you will basically get the this is as a major poem this has a major product major product or main product.

Now, if you have this compound like this epoxide for this alcohol, then you do mCPBA the same analogy you will get the alpha epoxide get the alpha epoxide you get the alpha epoxide. So, depending on the substrate stereochemistry you can basically control the epoxidation reaction. The second case you are having a similar kind of system, where basically you do a Simmon Smith reaction you have to do it.

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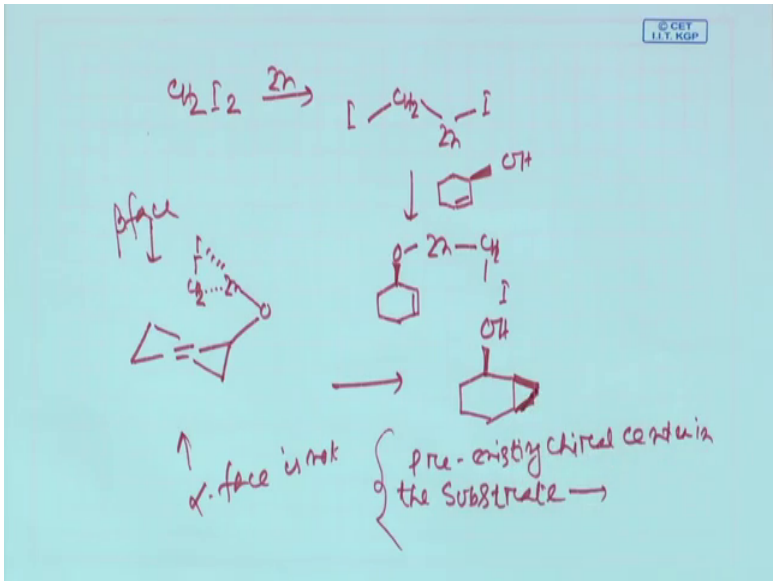

Now, simmon smith reaction we say it is the reagent system is CH 2 I 2 and you react with a zinc, it is basically will give you a zinc carbamate spaces, who structure is I CH 2 ZN I this carbamate. Now initially this carbonide reacts with this alcohol, which was a starting material and basically gives you this kind of O ZN CH 2 I.

Now, this intermediate you can basically again write it in the similar pseudo equatorial way your O your ZN, then basically you are having this your CH 2 and then you are having this iodie, which is also having a zinc coordination. So, now, the beta phase the beta phase is more accessible the alpha phase is not alpha phase is not accessible.

So, in this case also if you trying to do this reaction you will basically get this O H and this CH 2. So, this is the and the induction was pretty good; the advantage is you are not using any chiral reagents already chiral catalyst, your substrate is having pre existing chiral center substrate is having pre existing chiral center pre existing chiral center in the substrate that basically dictates the whole thing.

And then this kind of substrate directed studio control is absolutely important, you will find many examples and particularly for cyclic substrate the control is absolutely good, because cyclic substrate has this well defined conformational behavior. We will keep on continuing this discussion in the next lecture, till then you have a good time and good bye.