A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 36
Fg/Tf/SM Based Strategies (Contd.)

So, welcome back student so, we are basically discussing a combination of different strategical viewpoints and we set that functional group based strategies, transformation based strategies, functional group transformation and starting material based strategies, you can always couple together to access medium sized target molecule.

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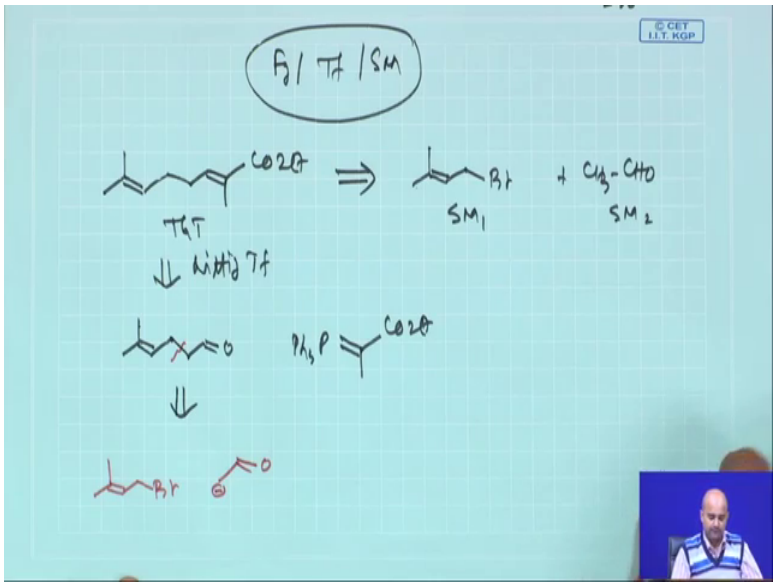

Now, here the first problem which will be analyzed in this lecture the structure is this compound. Now, this compound, if you see, it is a alpha beta unsaturated ester and starting material was giving to you the starting material I will be giving to you and I said you use this compound and as well as acetaldehyde as a starting material. So, target molecule is this your starting material 1 is this starting material 2 is this now let see where this acetaldehyde and this compound can be coupled to give you this part will initially analyze the standard retro path way by formulating this kind of things.

So, CH 2 CH 2 CH 2 CH 2 if you have a aldehyde something like this and if it is possible you can do a Wittig transformation is very much possible and we say the Wittig things will be using this kind of elite. Now, this intermediate if you now count the carbon

is having this part is coming from this part 1, 2, 3, 4, 5, 1, 2, 3, 4, 5 and remaining part is basically your acetaldehyde.

So, now, we can say that this can be in principle disconnected by this way, that you take a acetaldehyde anion is a acetaldehyde anion CH 2 minus and then you react with this electrophile. So, basically you need to do a alkylation on acetaldehyde, normally acetaldehyde alkylation is not very well known not very well known means acetaldehyde is usually like alkylation is often called about ketones.

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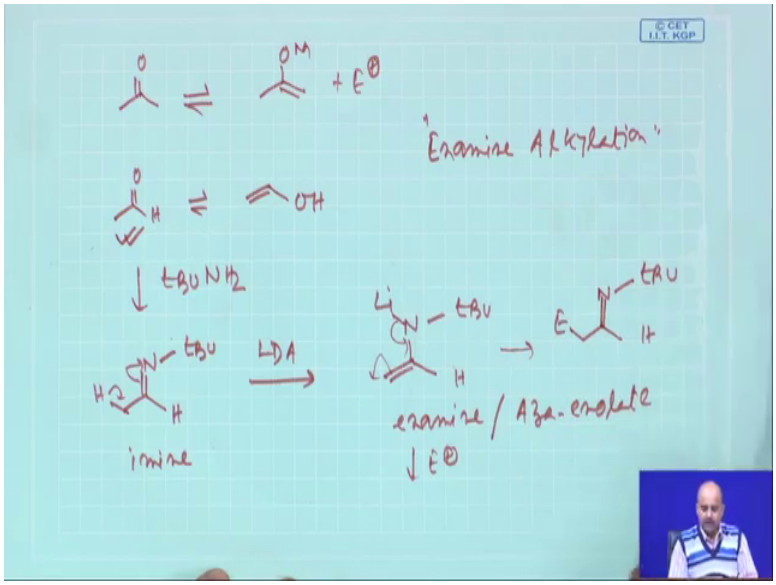

Ketones can be easily alkylated you can generate the enolate very easily by this metal and do the alkylation over this electrophile. Now, acetaldehyde it is a tricky situation acetaldehyde probably will definitely analyze and will give you a vinylic alcohol.

Now, vinylic alcohol is very unstable so, normally this compound will always try to be in this form this keto form in more most of the time. Now, here we will be using a particular strategy named as Enamine alkylation I am sure probably we have talked about this strategies earlier when we talked about Stork enamine methods. Now, Enamine alkylation for this compound like this acetaldehyde is very useful so, what initially was done you treat this compound with some primary amine and initially you find that this acetaldehyde reacts with this primary amine through a condensation reaction to give you imine.

Now, this imine when you subject it to base imine are basically equivalent of ketone so this acidic hydrogen will be now picked up acidic hydrogen will be now picked up and this imine will be now converted to a enamine. We will basically gets this N Li so, imine now converted to enamine.

Now, enamines are basically nothing these are Aza enolate, the word is Aza enolate method we have already discussed earlier, but again this Aza enolate is very interesting. Now, this Aza enolate if you react with a electrophile this see this things will again come back to react here and basically will give you this N tertiary butyl will remain here and will give you CH 2 E imine back. Now, you can hydrolyze this imine to get the corresponding aldehyde back.

Now, compounds like acetaldehyde as I said which are not very easily analyzable you can initially convert this acetaldehyde to its corresponding imine, which I have just explained in the earlier slide.

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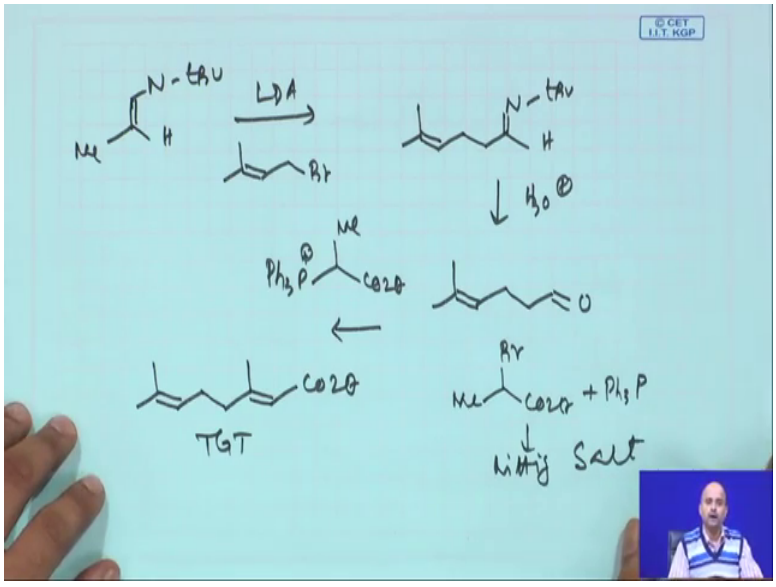

So, now, you react with LDA and instantly put this electophile which is phenyl bromide, now see once this phenyl bromide you can use first you will get this one and then this imine can be easily hydrolyzed to H 3 o plus you can basically generated this compound, which is nothing a acetaldehyde which have been alkylated with phenyl bromide. So, now, we are very close now we need to do a Wittig reaction with this particular elite or

the salt you do this Wittig reaction which seems to be pretty much straight forward and you come to this target molecule.

This Wittig salt can easily be generated this Wittig salt by using this bromo compound with reflaxing with triphenylphosphine which will be giving this required Wittig salt, this way this enamine alcohol is very useful and you can combine it with this particular electrophile were use the prenyl bromide. So, try to continue the similar strategy.

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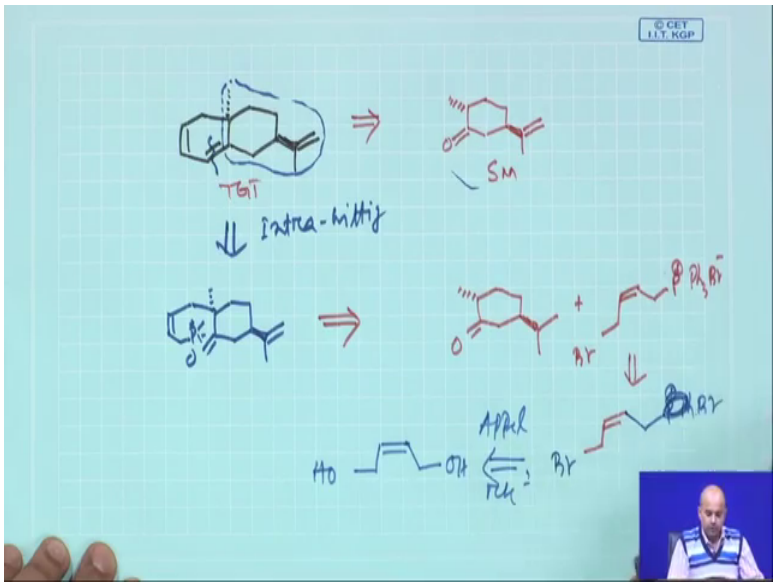

Next we will analyze another problem so, more problem you solved your ideas will be coming out. So, you need to solve as much problem as you can the starting the target was basically this conjugated line. The starting material which is also give it here I said this compound this compound starting material. Now, if you now do a skeletal analyses as I said this skeletal remains same, the right hand side skeleton of this molecule was remain similar in starting material fine, only thing is next you need to do something.

So, what I now initially propose that you will keep it this way and we say as this ketone group is there will do a Wittig kind of olefination, if it is possible here a P plus and other things. So, be Wittig reaction to basically a intramolecular Wittig reaction to make this olefin so, we all often use inter molecular Wittig, now will be using a intra molecular Wittig now you say the how you can get this Wittig salt or Wittig elite.

Now, you say if you having a if you now disconnect the original starting material with this particular, yes it is quite possible. So, this starting material is known to you and this starting material probably you can make it by basically corresponding, this compound with you can easily met from this compound by apple reaction apple reaction. So, now, start the forward synthesis and how the synthesis can be achieved.

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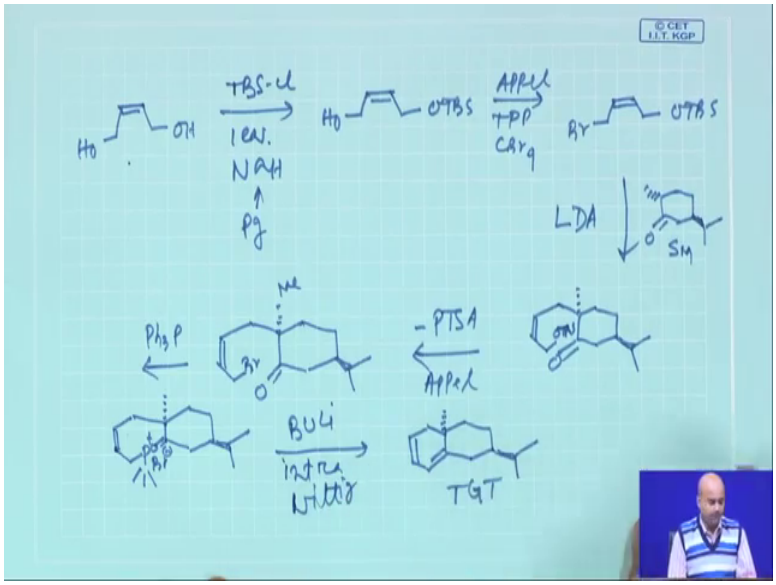

So, initially I said you are having these alcohol you do a double apple reaction or you can do a single apple reaction probably we will do a step watch thing or so, that no regiochemical issue is coming in between. So, we will do a simple protection first we do a TBS provide protection one equivalent by Magdugal's protocol so, then you get a OTBS CH 2 H O fine, now do a apple reaction apple TPP and CVR 4 basically get the OTBS CH 2 B r.

Now, here react your starting ketone and take this as a electrophile generate the enolate from this thermodynamically more stable enolate anole and then you do the alkylation OTBS. So, now, basically remove this TBS with PTSA that will give you the alcohol then you do this apple again apple again. So, now, what will basically get this B r double bond O will remain here, do this missile you put this things now here will reflox with triphenylphosphine to get the corresponding Wittig salt and we say this Wittig salt will be P plus this PH 3 was not written here due to space problem and then you find this compound ketone is there you are having this things.

So, this structure probably you can easily write it out now will be subjected to a base butyl lithium and do a intramolecular Wittig to a intra molecular, Wittig this intra molecular Wittig will now close the ring will give you this product so, this target was basically achieved by using this as this main starting material. So, what transformation we have used we mainly used a the couple of interesting transformation who use a protecting group best transformation we protect a hydroxy group. We do apple reaction to convert hydroxyl group bromide, then we do a thermodynamically controlled alkylation, we revoke the protecting group we do a one down of the apple further to come to the bromo, you convert this bromo to the corresponding phosphonium salt then you close the ring by a intra Wittig. So, we basically combined couple of transformations together and then you can access the particular target molecule.

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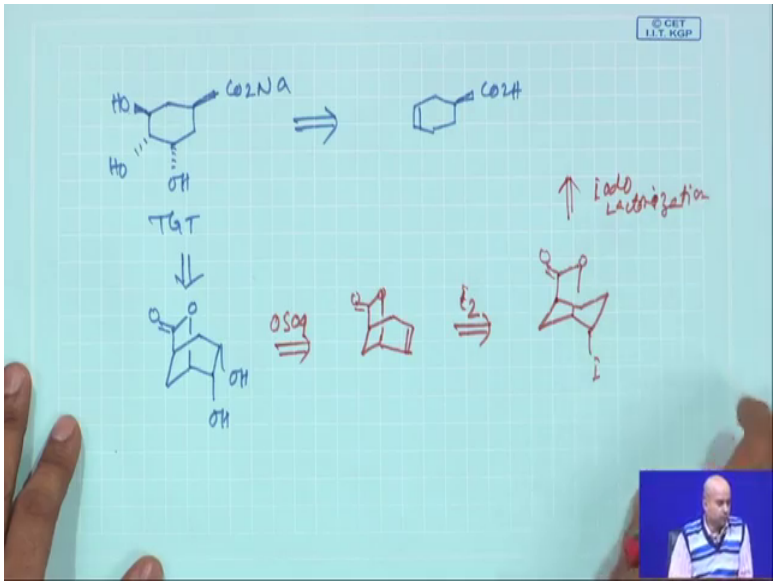

Next we will try to analyze the very simple problem probably the last problem in this class, but let us try to analyze it this is a carboxilate acid salt and three hydroxyl group is there on the Cyclohexane subject. A related stereochemistry was also given starting material which was given to you is a this starting material Cyclohexane carboxylic acid. Now, we will say the retro which I will be doing now will try to write the Cyclohexane ring in a different way and then we say that this compound can easily be made if you having a this lactone which you can easily opened up through sodium hydroxide.

Now, see the latest stereochemistry this C O 2 is above this OH is above so, this is 1 3 relationship 1 2 3, if they make a lactone which looks like this and then OH is below OH is below. So, if you have this lactone you can open it up now how this below OH you can basically introduced, we basically propose that if you have a double bond here. The hydroxylation by a osmium tetroxide will takes plate takes place from the bottom phase as top phase is blocked by this lactone ring and then we try to figure it out that this lactone, this particular iodo lactone can give you this olefin by simple E 2 elimination. Now, this iodolactone can be constructed by from this carboxylic acid through a iodo Lactonization. So, now, we will analyze the forward path and how this things has been done.

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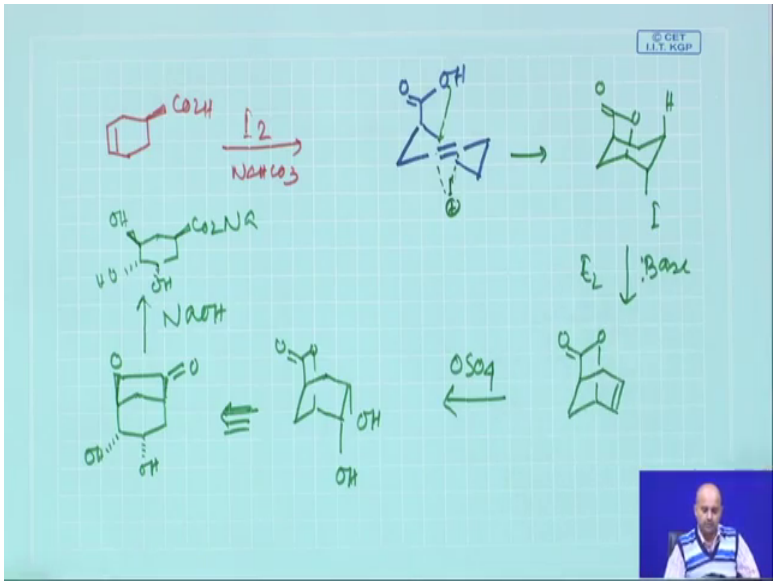

We first write this starting material in the two dimensional form then say that this compound is subjected to the iodine and sodium bicarbonate the standard condition of iodo Lactonization. We write this compound in a half chair form to give you little bit structurally structural viewpoint, now initially this iodo Lactonization will be formed in this way. Basically, have this iodinomide here this CO 2 H minus will attack to this double bond from the below side and then you now though we are not talking about stereochemistry in detail.

But in principle you will get this kind of because if it attacks here this axial this iodo now comes here it is basically 1 to n type, the attack s n 2 type of attack it comes in a

backside attack. So, give you this compound now it is having a hydrogen here it is having a hydrogen here so, base n type (Refer Time: 19:16) arrangement E 2 elimination nicely takes part. Now, if this E 2 has to be taken place the ring will not be now chair it will be again half chair kind of things that is what you put the half chair lactone. This half chair this axial this axial locks the top phase.

So, now you use the osmium tetroxide the this was now OH now comes from the bottom. So, this compound is basically nothing, but if you can write it in a two dimensional stereochemistry it is OH here, it is oh here, it is O it is C double bond O. Now, what will you to do basically hydrolyze this compound with sodium hydroxide, sodium hydroxide will be acting as a base and it will touch the lactone ring and it will hydrolyze this lactone this corresponding carboxylate salt it is the target molecule.

So, we will see the what are the transformation we use to access the entire thing we said that transformation we used a iodo Lactonization starting from a tri cyclohexane carboxylic acid we do a iodo Lactonization. The stereochemistry part was has to be taken care because initial iodo Lactonization you forms the iodinenamine, initial starting material we assume a halfchair kind of confirmation. Hydroxyl comes from the backside gives you a dihexyl thing and then this lactone is basically now having a sees both the CO 2 H and O H are sees to each other. You put a base now iodone and hydrogen now in 1 to n type (Refer Time: 21:35) arrangement you get a new pie bond.

(Refer Time: 21:40) mediated a iodoxidation you get this OH, OH here now which is basically nothing that related to stereochemistry this O and CO both are above the plane and this OH are below the plane. Now, you hydrolyze it to sodium hydroxide you can basically end up with this particular compound.

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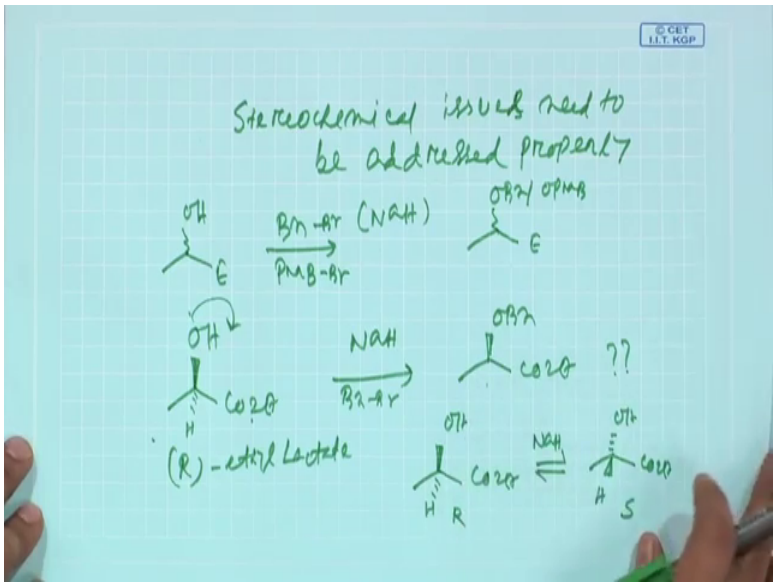

So, there are many similar kind of reaction, but try to try to figure it out that as stereo chemical issues, if there are stereo chemical issues which need to be addressed you have to be taken stereo chemical issue, issues need to be addressed properly how and if your molecule has some stereo center you need to be think out very carefully and probably we can earlier we have talked about that if you having a free hydroxyl group you can immediately protect this hydroxyl group as its benzyl or PMB ether very easily. Now, I am saying that you just read treat this compound with benzyl bromide or PMB bromide react with a base sodium hydrate you can immediately get is O benzyl or O PMB which is the very good protecting method.

Now, group E we have not specified what kind of group is this now I say I am giving you a compound whose structure is this, is basically a ethyl lactate and next stereo center is given is a 1 2 3 hydrogen is on backside. So, this compound is R so, this R ethyl lactate now I am saying that if you react this compound with sodium hydrate and benzyl bromide will you get the same benzyl ether. Now, I my answer is no because sodium hydrate seems to a strong base the hydrogen which is available here is adjacent to a carbonyl group. The sodium hydrate it picks up this hydrogen fine, but in addition it may pick up this hydrogen also.

So, basically this hydrogen can be picked up and this stereo chemistry of this particular centre may get changed, you will basically getting a ephemeralization of this particular

centre there is absolutely serious issue needs to be considered. If you treat this molecule with strong base like sodium hydrate you will find that this things basically ephemerides to give it the an ensumers. So, this compound if it is R this compound is S so, under the reaction condition the ensumers are basically dynamic equilibrium. So, if you start with R you might get this product, but this centre might be inverted; so, in those cases, we need to find out a relative mild protecting group condition where the benzyl or other groups can be protected.

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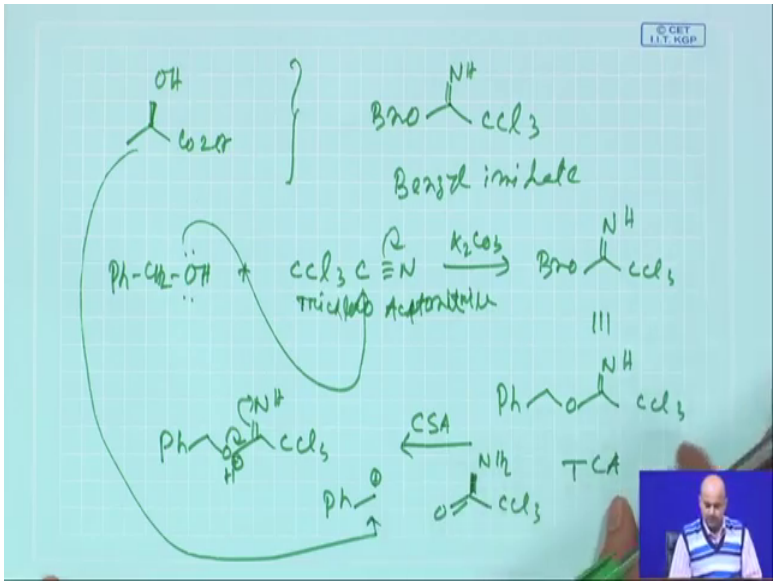

This was we did not discussed earlier when you talk about protecting group chemistry and I thought we will be discussing while we discuss the functional group strategies.

Now, this case will basically using a reagent whose name is benzyl imidate, benzyl imidate or PMB imidate is a pretty mild reagent which you can easily prepared by reacting with benzyl alcohol with trichloroacetonitrate. The unit pretty mild base like potassium carbonate to generate this enolate generate this imidate so, what happens this basically reacts here and initially will give you this imidate.

Now, this imidate whose structure is basically Ph CH 2 O double bond NH ccl 3, it keeps in presence of a pretty mild acid like camphol sulphonic acid and it exists as a its first basically a kind of protonated. The first kind of a kind of a kind of protonated and then it will give you a simple benzyle kind of cation with this things like this oxygen is now shifted to give this things protonated.

So, basically you will get ccl 3 CO NH 2 which is basically trichloroacetamide and this compound name is trichloro aceto nitrile. So, now, as this benzyl cation is free now if you react with this cation it will basically react under this condition and will give you a benzyl protected thing.

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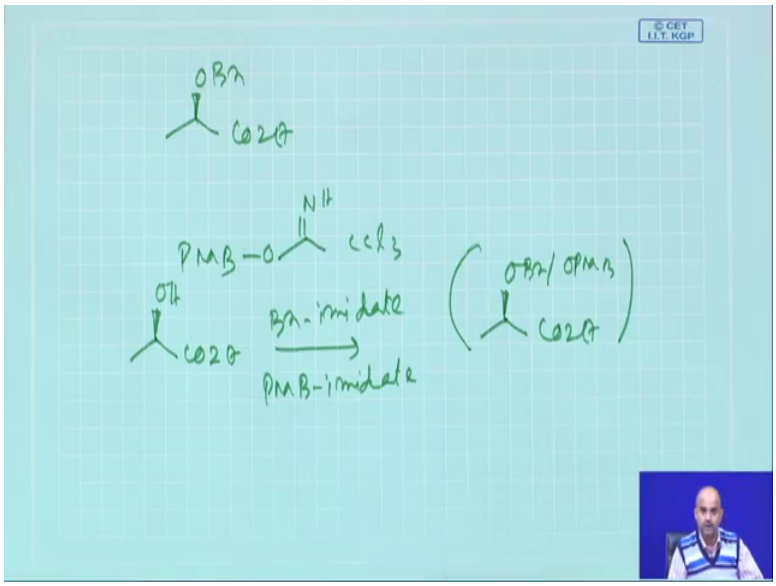

Similarly, you can also create PMB imidate whose structure is also similar like this so, if now you have to tackle some issues that wherever you having a acidic hydrogen which is mainly possible if you have a electro withdrawing group. Then you can easily protect this hydroxyl group where this benzyl and PMB ether by using benzyl imidate or PMB imidate. So, base condition you have to avoid it to suppress the ephemeralization.

Now, very efficiently you can protect this hydroxyl group as its benzyl and PMB ether with absolute ease and the stereo chemical information will be retained. So, next class we be talking about a particular this aspects and I will based on this information will formulate our next problem which is again basically a combination of starting material functional group and transformation based approaches. So, till then have a good time and good bye.