A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture - 39
Fg/SM/Tf based Combined Strategies

So, welcome back students we are basically discussing several mechanistically important transformations. And we are saying that if you are quite familiar with the mechanism of some of the transformation then sometimes it is very easy to formulate a retro synthetic path way. And basically we discussed some unusual transformation and its mechanism and those mechanism based transformation are very important for your exam purpose also.

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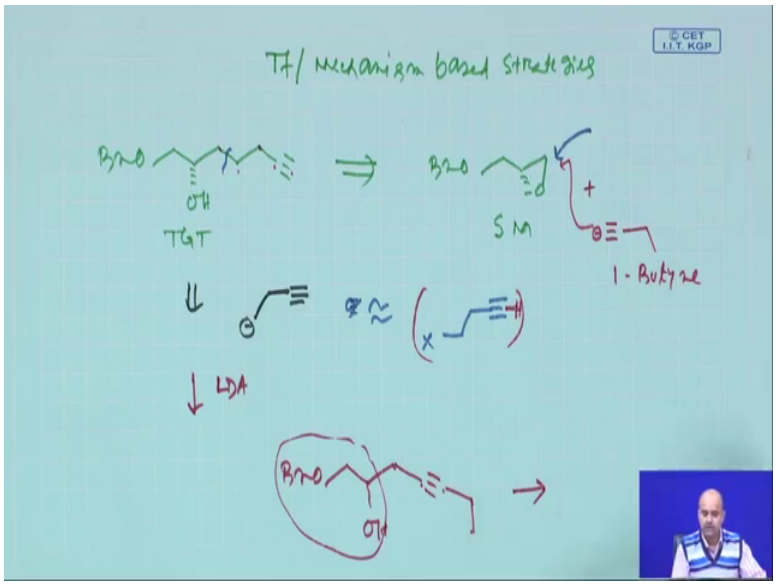

Then also we are giving a highlight or giving a heading that transformation as well as mechanism based strategies. Now the target molecule which I am now given is something like this and I say the starting material will be also given to you; the starting material also given to you. The epoxide stereo chemistry was not that relevant, but the problem where from I have taken it gives the stereo chemistry

Now if you see the target in the starting material will find that something is definitely can be doable and I said that you having a ben benzo benzyl group here, CH 2; CH 2 this epoxide has to be cut down or epoxide has to be generated. So, if some nucleophile you

add it here that will basically give you this. So, what you can think about that this epoxide you can use 1, 2, 3, 4; this CH 2 CH 2 minus; see if something like this CH 2 CH 2 minus you can have in your lab or may this compound is basically nothing will basically equivalent to triple bond CH 2 CH 2 X.

It is basically a homopropargyl kind of bromide or alkyl anything; now I say will be will be giving you something else. As I know I will be not giving you this compound this is not available in the lab. So, why you do not you take this particular compound; this is a basically a acetylene derivatives. So, basically 1 2 3 4; 1 1 butyne; 1 2 3 4; 1 butyne now earlier this particular if you are thinking of using this you said that this compound is having a X here.

X is basically a chloro or bromo and ha how the why you are planning for synthesis, you are trying to convert this compound to corresponding lithium or magnesium spices. So, a negative charge generates here and you will be opening this epoxide that is fine, but you are basically over looking in this carbon you are also having a acetylene hydrogen that extremely acidic.

So, why not trying to exploring this compound with base you might generate the lithiated salt of acetylene also. And then this might also react with this thing; so, basically you were having a regiochemical issues. Now if I say I am giving you 1 butyne you should that say 1 butyne if you use how it can give you the target molecule fine. First for first think about the 1 butyne; I have given to you, you react with a base LDA. So, basically you will be generating the minus here now this minus attacks the epoxide.

So, what product you will be getting? You get the OH here CH 2; now this CH 2 will be having this alkyne ok. So, instead of a terminal acetylene you get a internal acetylene as a product then you are in doubts have your target molecule is having a terminal acetylene and your generated a internal acetylene ok; do not worry this count the number of carbon. This part is fine this part is fine basically 1, 2, 3, 4, 5; 1, 2, 3, 4, 5; so, number of carbon is absolutely same.

Now I am saying I am saying that can you think of some reaction so, that this internal alkyne can be rearranged to a terminal alkyne means that I am saying that you just transfer this internal alkyne to a terminal end just by this and this. So, basically this internal alkyne has to travel 2 carbon extra from this part to this part.

So, at is it looking very interesting and particularly these reaction is possible.

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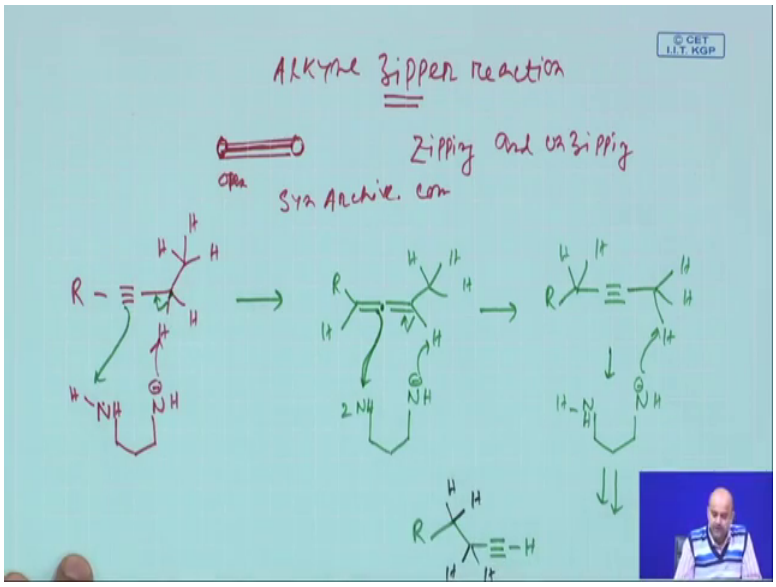

And this reaction is particularly named as alkyne zipper reaction; zipper reaction. Now in zip; zip basically you remember zip is basically the zip which you use normally you zip up, zip down. So, you are having something like this frame work, you are having some button and this button is going through this way; so zip is opened up and zip is closed. So, now, what is this zipping? Zipping means that you are opening and closing through this particular instrument or this particular link; so, once it comes this side; the zip is opened once it come this side; the zip is closed, so we call zipping and unzipping.

Now, this same terminology was used in a reaction named as alkyne zipper reaction. Now for the detail mechanism you can refer to syn archive dot com, but we will be also talking about the mechanism how this reactions takes place?. So, I am saying you are having this alkyne this, we are drawing the hydrogen here which seems to be extremely acidic alkyne; so, you are having alkyne CH 2; CH 3. Now I am saying the I will be giving this alkyne to a strong base; the base name is kappa what is kappa? Kappa is basically 1 3 diamino propane and you can use it with this potassium salt 1 3 diamino propane and potassium hydrate you can use.

Now, initially this 1 3 diamino propane is NH minus and H plus with this things; this is basically extremely basic. It abstracts this acidic hydrogen of one of this alkyne; now this alkyne is having a CH 2 and this methylene seems to be pretty acidic. And this by this

methylene once it acidic what it does? It is basically abstracted by this base and it gives you a alene kind of thing and these end, when it gets the electron it abstracts this hydrogen of this 1 3 di amino propane.

So, initial step you are basically having this aline; this is basically a alene the remaining part are similar. So, now this part is becoming your this way now; the this same base remains here, the same base will try to do the same thing again; it will abstracts this hydrogen again. It try to put the minus again on this double bond to generate the alkyne and then this particular alene center carbon will now take this proton; sorry this here this comes in entirely this way yeah. So, is basically this things will be now abstract the proton.

So, now you are having this R 2 hydrogen one is the initial step, one is the second step you will be getting here. So, the initial triple bond is here; it is now zips to one carbon right to a alene intermediate. So, triple bond now becoming 2 double bond of alene on the left hand double bond is now becoming a single bond and the right hand double bond now becoming a triple bond to this hydrogen abstraction.

So, basically this alkyne has shifted to one carbon right; now basically what we are what you are getting? You are now getting hydrogen, hydrogen, hydrogen. So, this methelyn comes in the left and these triple bond comes in the right. So, basically this alkyne is now zipping through out this acyclic chain; the same things basically operates again with this same compound, even have this NH 2 or this kappa and this NH minus. So, it again abstracts the photon; the same mechanism does operate and eventually what you will get? You basically get R CH 2 this is to comes here and then you get these alkyne at the extreme end.

So, 2 methylene; so, initial compound you are having 2 methylene at the right hand side and you have a internal alkyne. Now this 2 methylene have shifted towards the R and the terminal alkyne sorry internal alkyne now moving to extreme right is basically the zipper reaction.

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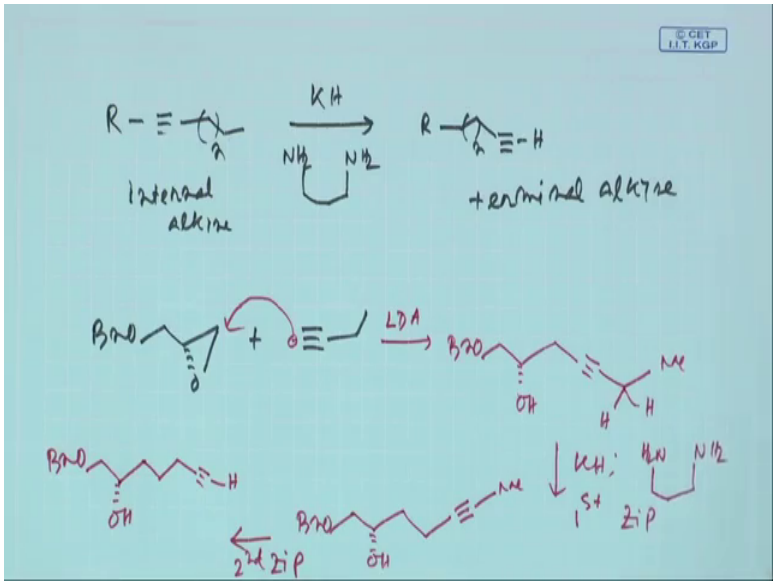

So, in retro synthetic terminology a zipper reaction basically is something like; this if you having a CH 2 n here; you treat with potassium hydrate and 1 3 diamino propane and it basically unzips like this n and at the extreme end you get this alkyne. So, a internal alkyne alkyne was transferred to a terminal alkyne that is why we called it the alkyne internally has been zipped to a terminal position. Now coming to our problem which was given to you; I said initially we have given this epoxide and I say you react with this epoxide; with this compound.

So, initially open up this epoxide trough a base like LDA will give this minus here this minus will attack to this. And you basically will be getting this OH CH 2 CH 3. So, now here the scene is ready for the zipping; so, first KH and 1 3 di amino propane. Now see the zipping will be taking place and it is a O B n basically have 1 OH here now see this CH 2 will be now linked to this CH 2. So, there will be CH 2 CH 2 and then will be having a methyl.

There will be another zip; so, I called this is as a first zip; there is a second zip. So, zip will be continued till the internal alkyne is converted to the terminal alkyne. So, BnO; BnO now will give you this CH 2; CH 2, CH 2 this is having a CH 2 H. So, this CH 2 also now coming CH 2 CH 2 CH 2; now the zip will be stopped. So, zip will be continued till there is a no more methylene left in the ring. So, first zip second zip; there

is a n number of zip possible and this zipper reaction is very useful in terms of synthetic I mean synthetic potential.

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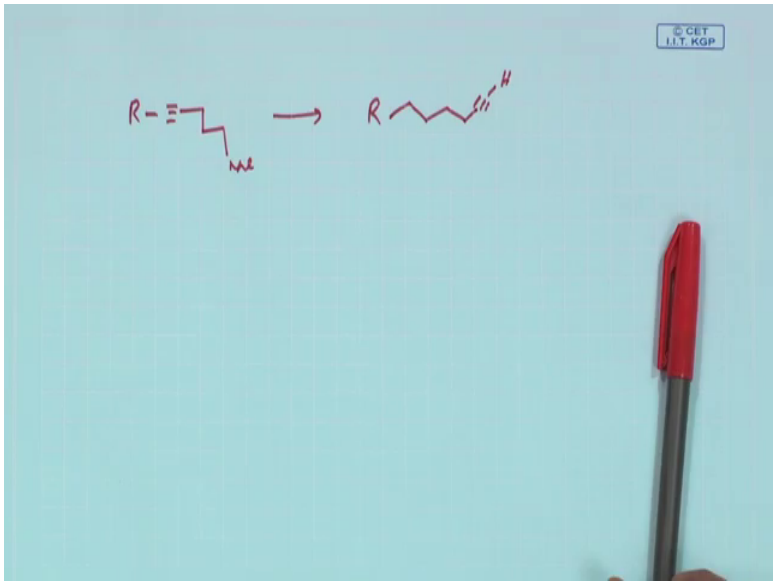

So, internal alkyne like this is often converted to a terminal alkyne; terminal alkyne ; now the terminal alkyne you can basically you can do different kind of reactions, they can be easily converted to the corresponding (Refer Time: 15:04), you can do whatever chemistry you want. So, this zipping is absolutely absolutely very useful and that gives you pretty a nice synthetic useful reaction.

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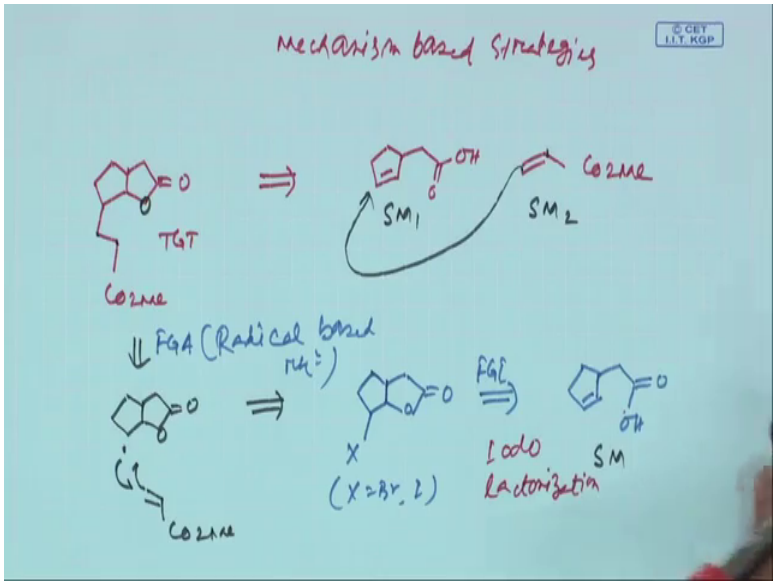

So, next one we will try to give a similar mechanism based strategies ; mechanism based strategies. And the problem which was now given to you, the target structure is having this; this is the target structure. Then I say the I will be giving you the particular starting material I say the initial starting material which I gave it to you is having this carboxylic acid. And then I also give you a compound like methyl acrylate; now if you see closely the carbon network almost remain similar you have a oxygen here; carbon network remains similar you have a one starting material, you have second starting material.

So, which seems that somehow if this carbon you can link this particular alkylate sorry this methyl acrylate; you get a 2 carbon thing 1 2; this 1 2. Now eventually initially you need to construct this ring with this help of this carboxylic acid oxygen. So, I will now draw this retro; in little bit different way and I say if somehow its possible for you to generate a radical here, this radical shall undergo reaction with these ethyl acrylate through simple radical radical coupling or radical olefin coupling.

Now, this chemistry we have already explained to you earlier that how you can generate radical; if X is bromo and iodo I said if you treat this compound with BU3SnH and AIBN; you can get radical here ok. So, in particularly redundant functionality we have talked it. So, now, which I am saying that now your almost close and I say if you have this compound, you can easily generate this.

Now this is basically a you can think about a simple FGA through radical based reaction; radical based reaction; a this is kind of a FGI functional group inter conversion. Now, so your starting material is there now what you can think about you have to introduce a iodo here and this oxygen also should be in a 1 2 position with a iodo.

Then if you try to do a iodonium ion to this olefin; you can form a iodonium ion then you can visualize at this carboxylic acid can act as a nucleophile. And to cleave this iodonium ion to close this ring to give you a lactone and this iodine now comes here; so this reaction is we also talked about is a iodo lactonization reaction. So, only thing is what you need to do? You basically need to know the mechanism of the inter transformation.

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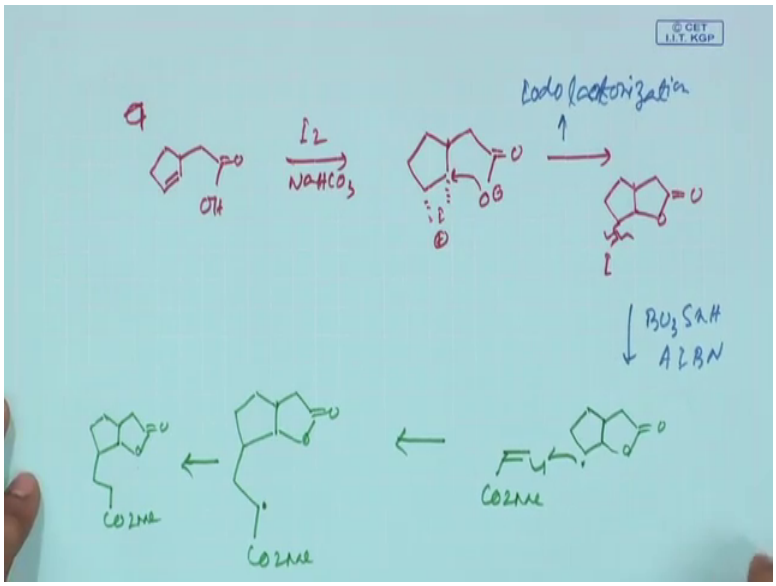

So, now, sorry now start with the starting material which was given to you. First iodine and sodium bicarbonate was used. So, initially iodine we basically get the iodonium ion fine and then as bicarbonate is there you having these O minus here. Now this will instantly undergoes nucleophilic opening of this iodonium ion. So, what you will get? You get this O and this I.

It could be iodolactonization, it could be bromolactonization whatever you can do it; this is basically a iodo lactonization reaction. Now I am saying this iodo compound can be easily cleaved through BU3SnH, AIBN. This heterolytic bond cleavage is possible and what you are getting? You will basically get a radical here; get a radical here is not it?.

Now, I say this radical can easily be reacted as another starting material is giving you a ethyl lactate. This radical usually reacts through this double bond and you get a CH 2; CH 2 Co 2 m e; you get initial dot here this radical. Now this is this radical is definitely stabilized by the captodative effect of this CO 2 m e group; CO 2 m e; group. Now you are having solvent or BU3SnH; which can abstracts the hydrogen and then you basically get the final product.

The final product structure was given to you CH 2 CH 2 CO 2 m e that basically closes your synthesis. So, with in this particular synthesis what have the things we have seen?.

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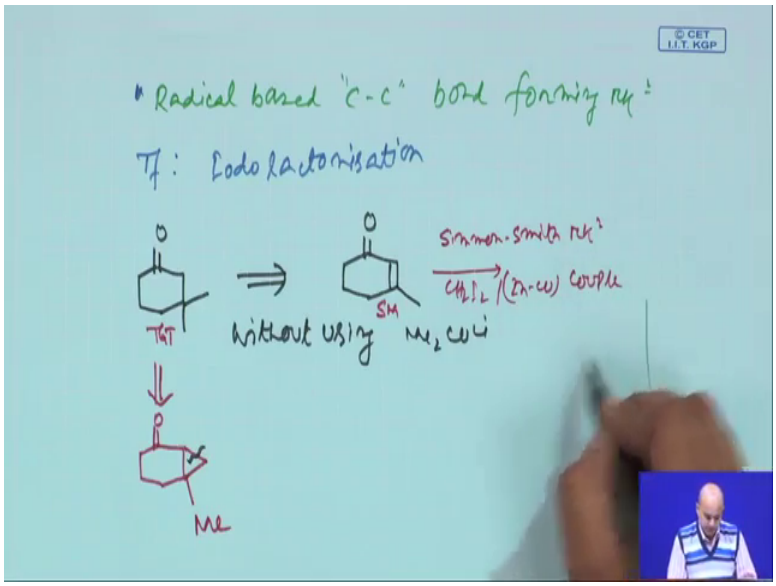

We have seen that that a radical based carbon carbon bond forming reaction is very important bond forming reaction; we have used it. And then also we use our earlier reaction the transformation iodo lactonization which we have used it.

Then similar kind of thing now I will be try to explode a very simple problem. I say you have to make this compound starting from a this compound without using; without using m e 2 C U LI or without using the Gilimer's condition. Now then you are thinking that this is a rits bit difficult how can do it because 1 4 Gilimer is the normal way and you can use it I said ok; do not get confused.

The target was given I said this one, starting material was given this one. So, you need to think about something; so, I say is it possible? hm You said that sir you are making a cyclopropane kind of thing and then how you can peep this cyclopropane ah? So, now, cyclopropane I basically as I said there are a strand ring, this is absolutely strand ring the cyclopropane ring is absolutely strand and they often behave like a normal olefin; they are more of pie character then the usual sp 3 hydro carbon.

So, I say if you can open this thing here then it is a absolutely possible. So, first your starting material was given here, you do a simple Simmon Smith reaction which is known to you CH 2; I 2 zinc copper couple right. So, basically what you get here? We will explain in the next slide.

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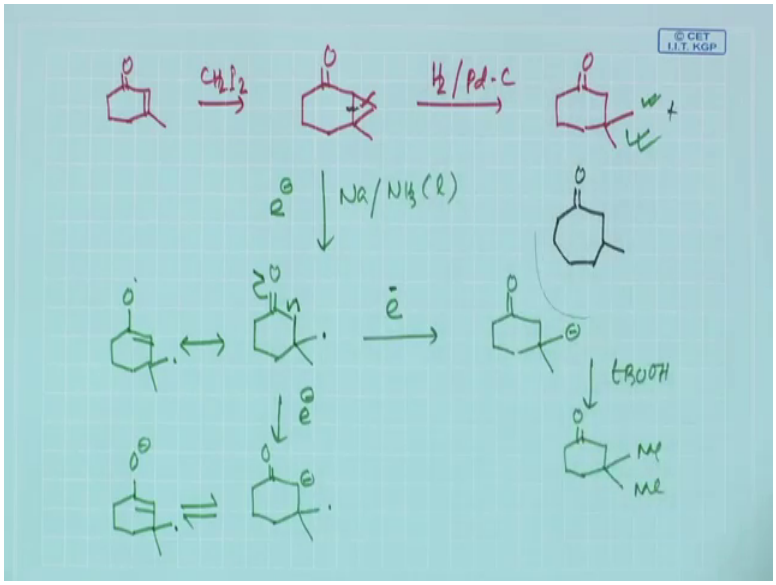

So, first you get this compound do a Simmon Smith reaction or even you can do a carbin addition. So, Simmon Smith you will basically get now this cyclopropanes are absolutely a strand molecule and they often behave like a more of pi more of pi olefinic unsaturation. In principle you can basically cleave this compound with hydrogen palladium charcoal.

Now palladium charcoal what it will give? It can cleave here as well as it can cleave here. So, you basically can get this compound this compound as well as your ring might be extended. I mean if you cleave this way also that also you can get the corresponding 7 member thing, you can get the 7 member things also. So, now, as I said our DR molecule is this I should that say other way to cleave this.

So, now all of you know that sodium liquid ammonia is basically the birch condition; the birch condition. So, now, birch condition you will basically getting a single electron; now this single electron we will try to cleave this cyclopropane to a radical pathway. Now if you see how these things will be, it basically cleaves this particular bond and will give a dot here give a dot here ok. Now you say the dot on this carbon is a is basically stabilized through these captodative effect of particularly this carbonyl compound.

So, its the radical was somehow kind of stabilized; somehow kind of stabilized. This is the main thing that is what, now you can also have this radical cleavage here to get the cyclo hepto heptane also. Now you see if you have this radical which can cleave from

particularly this thing; you get a CH 2 dot here. Now sodium liquid ammonia will give you another electron; so, basically it will give you this minus or even this particular point, you can now have a tertiary butanol which will now act as a proton acceptor and you get this methyl.

Now, this thing; this particular radical which is now generated here this also can initially be a hydrogen. And now this is absolutely stable if you have a this carbon ion; this also can be easily will give you the corresponding enolate which you now pretty well known. This step wise; now this particular radical can again accepts this another electron to give you the hydrogen.

So, in these way you having a electron this way basically you can cleave this particular cyclopropane and cyclopropanes are always strand intermediate they can easily cleaved; the only thing is the birch reduction mechanism we should be quite familiar of. And it can be you can basically make both the molecules either this one as well as this one; depending on the reaction condition and if you have to make this one probably you can try using this without the Gilmen, Gilmen definitely you can do, but I said if you if you try to avoid the Gilmen; you follow this path way and this will give you a nice access of this particular dimethyl thing.

So, we will try to continue our discussion in the mechanism based strategies and I will come back in the next lecture till then good bye.