A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture – 22
Fg based Strategy

So, welcome back students. We are basically discussing functional group based strategies and last class or last week lecture we have talked about how different skeletons can be disconnected through a functional group based approach and I said that a key transformation is always essential to find it out. You need to find it out the key transformation which is basically very essential.

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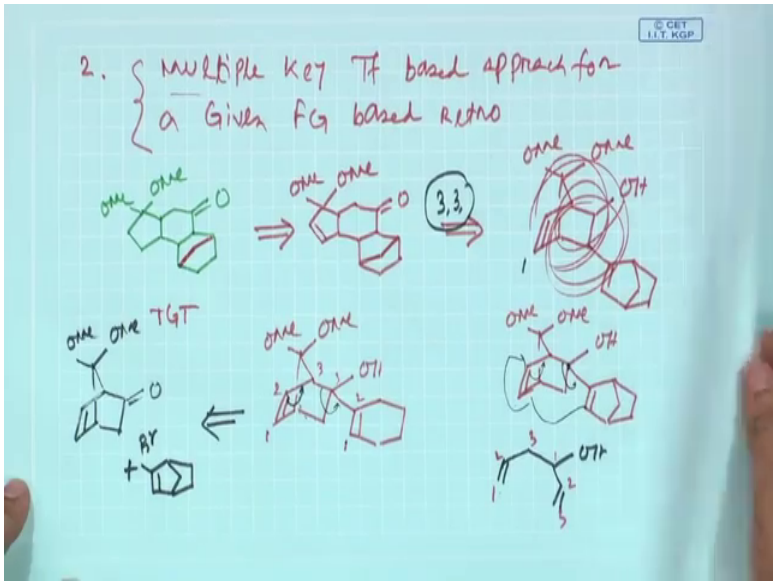

Now today will be talking about the second point which is, how you can use multiple key transformation based approach for a given functional group based retro. Now, initially when you basically discussing the functional group based strategy we said there are 6 guidelines which we will follow. The first one basically functional group based skeletal disconnection, where we said that you have a skeleton given to you in your target molecule and you just try to disconnect the skeleton through a single and uniform key transformation.

Here we trying to follow the similar pathway, but I will try to explore if there is a multiple key transformation is available. So, means that the target molecule essential will

be little bit complex here, where you need to find the doubt more than one key transformation will be needed, but definitely we are trying to do a skeletal disconnection. The initial problem which has given to you for this set, it is a basically completes a carbocyclic skeleton and there are having 4 different ring. Let me first complete the structure and now you will find that this compound here is having another bridge structure, this is a bridge structure. So, 5 member ring 1, 2; this is 6 member ring and in between the 6 member ring you have a bridge unit.

Now, essentially once the target structure was revealing to you or target structure is known to you and I have not given the starting material definitely as I said this is a complex phenomena, complex scenario where you can definitely think about that where from to start and now, I will first try to do the retro based on simple functional group addition elimination they need try to correlate or try to connect how this things can be created. Initially, I said that we will do some hydrogenation here, eventually you may ask that sir, why this hydrogenation was the first step you have chosen? Now, as I said definitely the logic must be there, but that visualisation probably experienced people can think about and these experienced people when they are doing this retro they found that probably hydrogenation will give you some interesting skeletal disconnection.

Now, next skeletal disconnection what I am trying to figure it out is the most crucial part in the entire pathway. We say it if you have a structure like this and then this structure has been envisioned that you basically do a sorry the structure was little bit wrong. So, we will try to do the right structure again. As I said that target is pretty complex sometimes small mistakes do happen and I am sorry for that, but eventually the entire structure was bit complicated. So, now is correct. Now, what is it? I say if you having a tertiary alcohol of this structure and now you try to figure it out this structure is basically nothing, but it is a 1, 2, 3. I mean this a pi network on the left hand side; this is another pi 1, 2, 3. These two pi network basically is trying to have a, so, 1, 2, 3, I write 1, 2, 3, this I write 1, 2, 3.

Now, this basically fits into the perfectly a sigmatropic rearrangement based transformation. Now, once this in the real sense once the transformation was done basically what we do, you come here and then this comes here and then particularly this things comes there, on this back of this bond. So, this particular visualisation is little bit difficult until and unless you are quite know or quite sure, as you place try to do this

practice in your home for this particular transformation. As you are dealing with little bit complex system you please try to figure it out that, now I said is a 1, 2, 3 and then it is a 1, 2, 3. So, what I am basically this comes this a direct connection for this with this; this 5 bond comes here and this comes here. Now, you are basically getting a pi bonds here which is now a enol. Now, this enol basically tautomerase this to give you this ketone and this particular pi bond is basically which is the pi bond which is now generated here. So, is a clear case of 3, 3 sigmatropic rearrangement reaction and that is in real practice that how this structure can be correlated to this target molecule.

Now, this is very difficult, definitely is difficult. You need to practice couple of times in your home to coming from this structure to this structure. So, fine now, once we have this particular structure your next thing is will be how you can make this molecule. This probably you can think of making this molecule by a simple carbonyl addition reaction if you having this carbonyl and you are having this bridged bicyclic vinylic bromo compound as your electrophilic or sorry is a nucleophilic you can just exchange this bromine with a magnesium or lithium you create the corresponding vinylic Grignard species reacted here.

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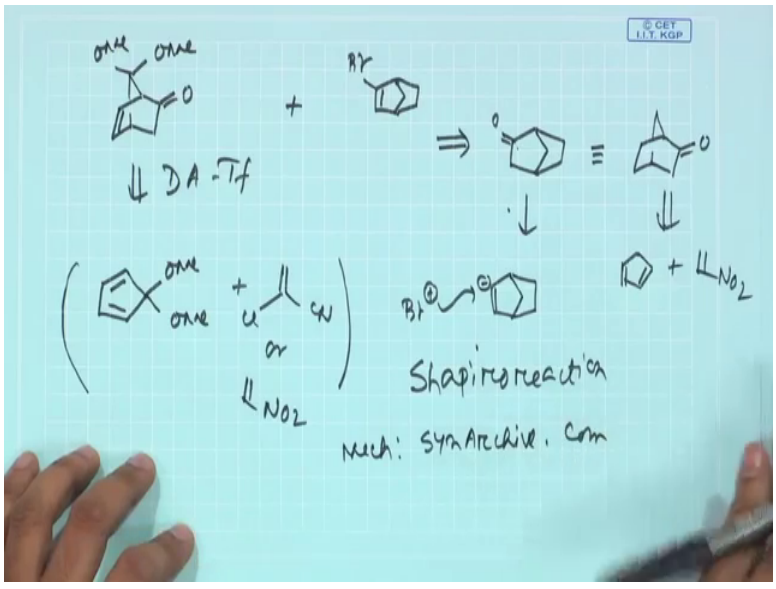

But, nevertheless how you can get that.

But, nevertheless how you can get that target molecule or how you can access this intermediate also. So, the intermediate now is basically, this intermediate as well as this

intermediate. This intermediate will be saying that now a deal stellar transformation is very useful. So, we say you do a dil cellular with this dimethoxy cyclopentadiene with a standard dienophile something like this or a nitro methane this is already discussed in earlier slides.

Now, this compound you can again think about doing a dil cellular reaction definitely. Let us say, if you having a compound like this. This compound is basically nothing this compound is this compound. Is not it. So, means that now how you can prepare this compound this compound is absolutely. You take cyclopentadiene with similar kind of dil cellular reaction and do hydrogenation that will basically give you. Now, from this to this from these to these basically you need to convert this compound with a vinylic species something like this which you can basically easily react with a bromine amine to get a vinylic bromide. Actually this reaction in principle can be done by a reaction named as shapiro reaction. We have not discussed with the shapiro reaction, but probably shapiro reaction is a very useful reaction. Again, if you were looking for the mechanism go to synArchive dot com naturally remembered. In the latter part of our discussion we will talk about some of the specific reactions.

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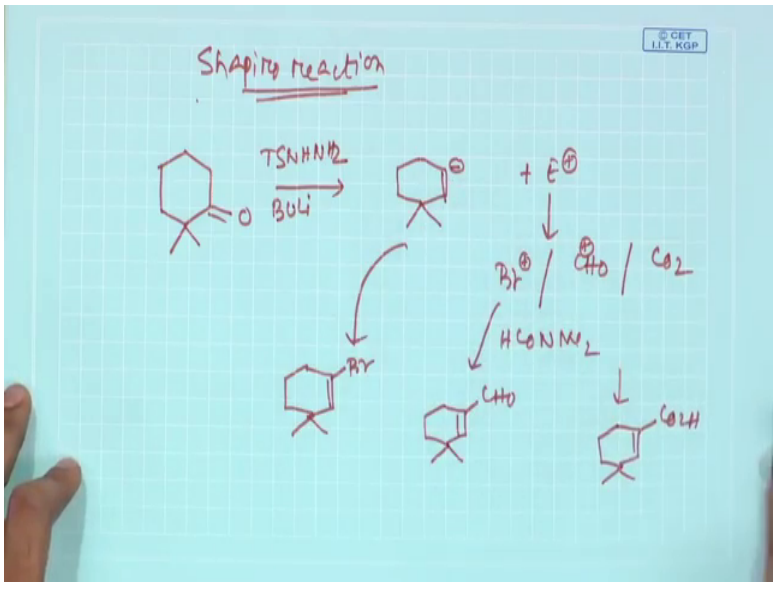

now shapiro reaction is very useful shapiro reaction I will.

Now, shapiro reaction is very useful. Shapiro reaction I will just now give you the disconnection. Shapiro reaction is a very useful reaction and the particular in terms of if

you having some compound like this you can easily convert this compound to this minus. Now, this minus basically can be quenched by varieties of way with several electrophile. The electrophile could be anything, it could react with simple bromoniamine, it could be CHO plus, could be other electrophile like carbon dioxide.

So, basically, if you react with bromine it will give you a vinylic bromo species. It will react with a dimethylformamide to give you a corresponding aldehyde. It will react with carbon dioxide to give you corresponding carboxylic acid. Shapiro reaction what exactly was used we used a tosylhydrazone and then treat with a access base butyl lithium that basically gives you a vinylic anion. The mechanism as I said we probably might have discussed it, I do not remember exactly, but please go through the earlier slides if it is not discussed you can just go through the synArchive dot com to find the mechanism in detail and remember probably in the couple of next lecture, we will be talking about some specific transformation based a synthetic approaches were you can find.

So, if you now come back to the original problem where you have started you will find that this particular retro we started with a very complex molecule. See this is a very complex molecule is started. The only thing is no starting material nothing was available, that is the really tough. We said that a 3,3 sigmatropic reaction was the key reaction which was performed to this intermediate. Now, I said that please make a practice in your home that how this intermediate or this structure is undergoing sigmatropic rearrangement to give you this one. This basically a simple bond breaking and bond making the arrow shifting I have shown you this things is connected to this and this bond is going to be chopped down you make a new double bond here. So, is not easy, but is not difficult also. So, you have to do it and once you have done it, then you can find that there are 2 intermediates we are talking about and particularly that transformation which we basically looking is a combination of several multiple transformation.

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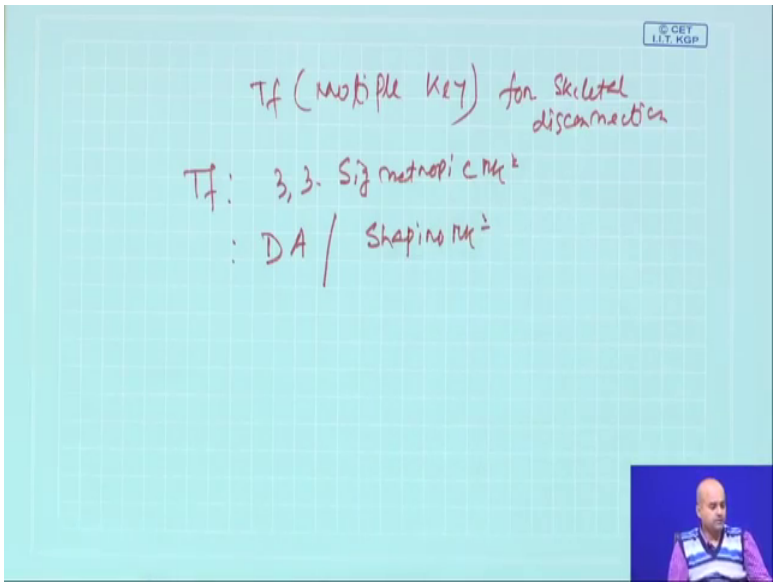

So, now if you see the transformation which we use is based on multiple transformation, multiple key transformations for a skeletal disconnection. Transformation what we basically used a 3, 3 sigmatropic reaction, then we used couple of dil cellular reaction to access both the intermediates, then also we said a Shapiro reaction was used very useful reaction. So, in this way several different kind of multiple transformation based approach can be used to construct a core structure of the given molecule. We remember this kind of multiple transformation based strategies also we have discussed it when you talked about transformation based strategy. So, in principle this multiple transformation based functional group based keys skeletal disconnection it is similar you can just think about combination of using a multiple transformations and how the target molecule was assembled in a efficient way.

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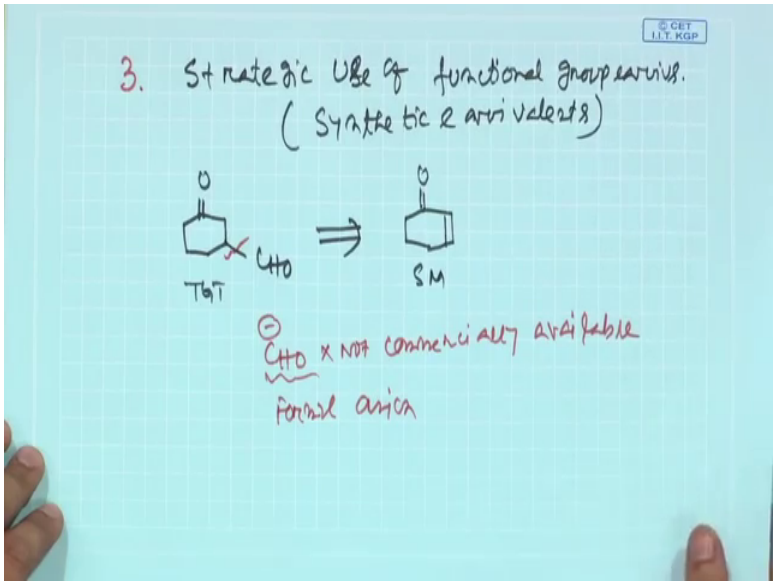

The point-3 in the functional group based strategies, now we will try to explore something different. We will be calling it strategic use of functional group equivalent or synthetic equivalents. Functional group equivalents and now it termed this group as synthetic equivalents. We will explain what the synthetic equivalents are. We will try to give you a simple target and actually if you recollect the earlier lectures we have already discussed this strategy by several reactions. We say it the target molecule is a this compound starting material was this now, basically the retro which we are talking about is a if you having a CHO minus species or this functional group species which is nothing in reality is a umpolong species can be constructed through a different way, because, this is not a commercial available.

Now, this particular species is called a synthetic equivalents or functional group equivalents of a formyl anion, this is nothing is a formyl anion. So, if somehow you are having a formyl anion in your disposal you can basically do this carbon – carbon bond formation. Actually probably all you know that where from this formyl anion can be generated, but this is basically we talked about strategic use of functional group equivalents or synthetic equivalent.

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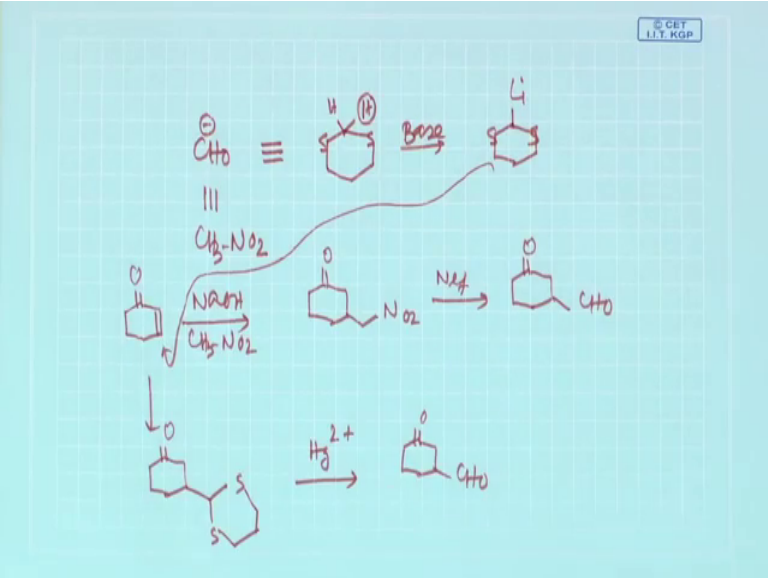

Now, what is this is basically says that, this formyl anion it is synthetic equivalents and it can be generated from a 1, 3 dithiane species of formaldehyde or formal this anion also can be generated from a nitro methane. Now, come to the real system what we initially proposed, which is cyclohexanone. First take a base sodium hydroxide and react with nitro methane. Nitro methane will basically generate the anion and it will undergo Michael addition.

Now, Nef reaction we have already talked about Nef reaction. This reaction now will give you CHO. So, what is this? So, nitro methane can be a potentially considered as a synthetic equivalent of a formyl anion. Same way, you can basically pick up both this acidic hydrogen or one of the acidic hydrogen to replace with a lithium species. Now, this lithium can undergo a 1, 4 attack here. So, this will attack in the 1, 4 fashion to basically give you right and then you basically just treat this with a mercury and you get a CHO. So, this also a this formaldehyde dithiane is also a synthetic equivalent of a formyl anion.

So, our next couple of problems you will basically based on this kind of concept where you can strategically choose a functional group which is realistic can be envisioned or can be constructed through some potentially synthetic equivalents which are in principle is commercially not available, but are very valuable synthetic intermediates.

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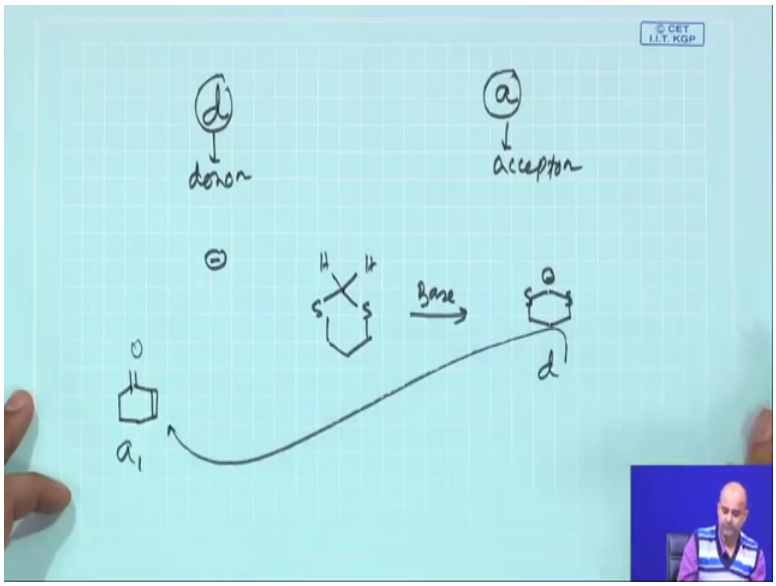

Now, before we talk about this things we will try to give you examples of or explanation about 2 terms d and a. We might have explained it couple of times earlier, d stands for donor and a stands for acceptor. Actually, we are planning to give you a in depth analysis of synthetic equivalent, little bit later on at the end of our main lecture then you can try to talk those things in detail. Donor means that whenever you have a negative charge in the synthetic equivalent it can donate it is electron to a electrophile and acceptor which can accept the electron.

Now, in that that category your formyl anion, 1, 3 formyl dithiane when you react with base it basically gives you a carbon ion, this minus. Now, this minus is basically nothing is d 1 species, d means stands for donor and 1 stands for 1 carbon. This basically gives you 1 carbon. An acceptor are similar, very well known acceptor is something like if you having a compound like this. So, this is a acceptor which can accept a donor. This basically is a Michael acceptor. So, this acceptor and this a donor which can react.

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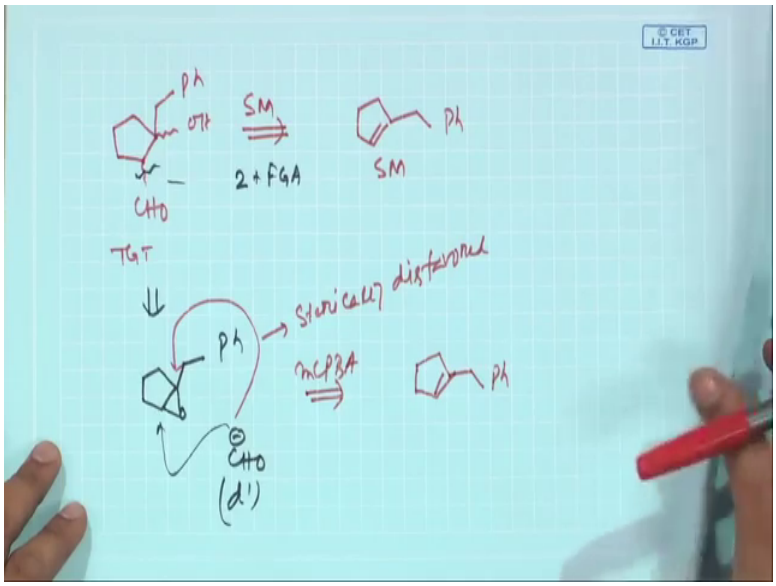

So, one of this next problem which you basically deals with a compound whose structure is something like this. We set a target molecule which was given to you having structure like this. Now, the target was given to you. The starting material was also given to you. The starting material I say is having this structure. So, now, if I closely analyse the functional group content only functional group which was added here, it is this CHO. So, this is basically a double bond adding a CHO and a OH. So, is a 2 functional group which was added in the starting material to give you the target molecule.

Now, do the retro in a very classical way. I say if you having these epoxyte and you are having this formyl anion as a 4 (Refer Time: 23:43) nucleophile or a d 1 species. Now, I say this electro this epoxyte can attack either this way as well as this way. Now, definitely the red path which is sterically less favoured or sterically disfavoured because it is having a bulky benzyl group in this carbon, but this carbon does not have any such steric crowding, so, epoxyte opening with always prefer from the less in that site.

So, now, you can correlate that if you have this starting material you just make this corresponding epoxyte through a mCPBA epoxidation your job is done.

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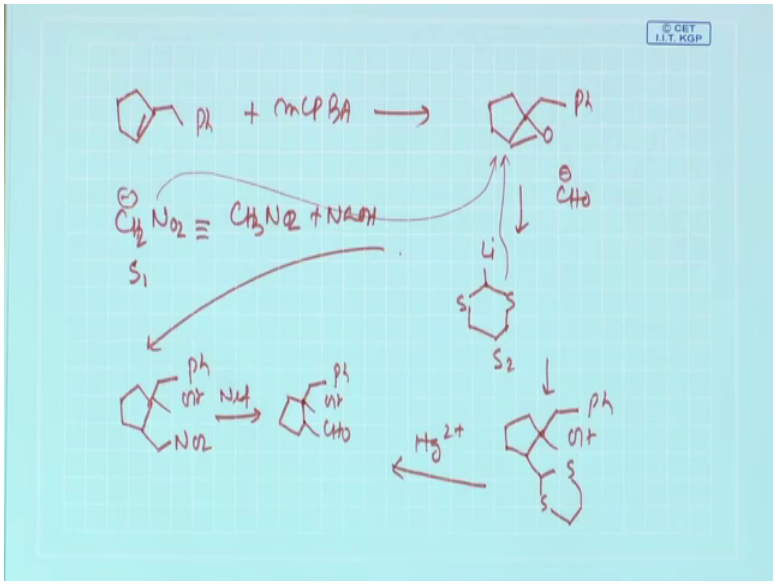

So, for the forward pathway it is as simple as that to start with the corresponding olefin react with mCPBA, you get the corresponding epoxyte, then CHO minus now as I said CHO minus is not commercially available, it is not in the bench or the rack you can get it. So, basically you react with either nitro methane plus sodium hydroxide which basically give you way CH 2 minus NO 2 or take a this formaldehyde umpolung, one equivalent with lithium. So, any of this either synthetic equivalent S 1 or S 2 can be basically reacted either this carbon mainly this carbon as well as this carbon. So, what basically you will get, in this case you will get OH, CH 2 NO 2 and this case we basically get your entire dithiane part.

Next, is you do a Nef reaction here to compute the synthesis. Here, you do the same thing by Marker immediated cleavage. So, basically what you expect that you can use strategically 2 reagents at parallel step, both the reagents can serve as a formyl anion pre cursor. Both the reagents like nitro methane and anion generated here and this 1, 3 dithiane formaldehyde lithium species cannot serve as a formyl anion equivalent and the initial retro it was purely based on a functional group based approaches. And, the key reaction which is said is a umpolung addition on a electrophilic epoxyte and obviously, the stereo chemistry of the epoxyte has a clear cut role in the entire pathway.

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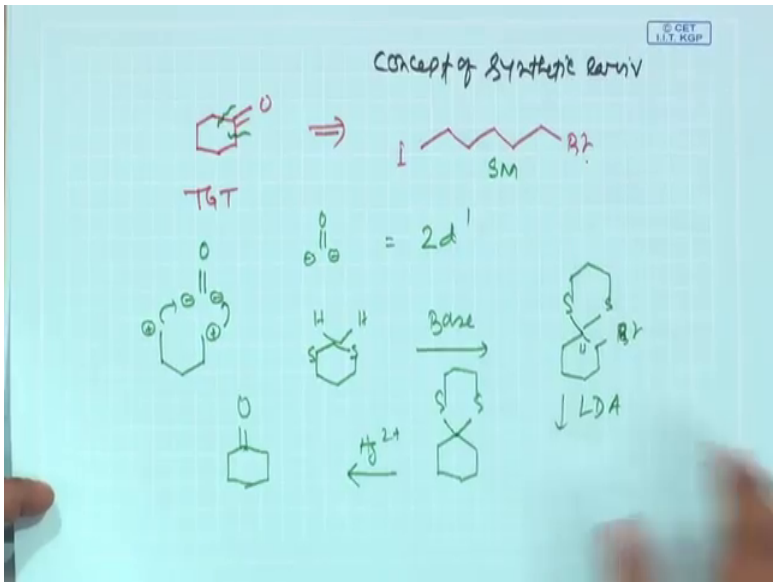

Next, 2 – 3 minutes, I will just trying to explain a I say it target molecule was given to you a cyclohexanone and then you now starting material was also given to you 1 2 3 4 5 Br. I said a this C 5 dehalogenation species was given a starting material. Now, we are basically discussing the concept of synthetic equivalents. Now, this compound is starting material is a having a only carbonyl functionality and based on this things if you try to disconnect here and here what basically you will get? You basically get a doubly charged species and this double electrophile.

So, means that, if you now disconnect this way that this minus react here this minus react here. Now, this particular species which I have now drawn here is named as a 2d 1 species. Now, d stands for donor, 1 for 1 carbon and 2 for doubly negative that there is 2 negative charge. Now, if you try to correlate to this C 5 synthetic which is have been double positive charge this is the starting material; the starting material one end having iodo, one end having bromo. So, now, what exactly you basically will be doing this synthesis, you first take the formaldehyde 1, 3 dithiane react with one equivalent of base and react with this iodo or bromo any of this iodo is supposed to be more reactive. So, first you react with this entire thing and you get this compound this bromo, this hydrogen remains here you react with a one equivalent of base. Further that will generate the anion and you then make the carbon – carbon bond and you cleave with Hg 2 plus, that will basically give your or complete the synthesis.

So, in principle synthesis by using this synthetic equivalents are very fantastic. The only point is you have to be quite sure that which bond you are going to be disconnected and what are the synthetic equivalents we are mainly focused on. Now, mainly the synthetic which are very popular will try to disclose in this particular lecture and then the final part we may discuss of the very unpopular synthetic equivalents, but synthetic equivalents like this formyl anion which can be sub as d 1 species as well as 2d 1 species is very useful, very popular. And, mainly we will try to focus on this kind of umpolung synthetic equivalents in our next couple of lectures where we talk about the functional group based strategies.

So, till then good bye have a good time.