A Study Guide in Organic Retrosynthesis: Problem Solving Approach
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Lecture - 10
Tf/SM/Fg based strategy and its exploration

Students welcome back. So we are basically discussing different strategies for a proper Retrosynthetic pathway of a given target. And, we have talked that transformation based strategies, starting material based strategies, and functional group based strategies are basically similar they are overlapping. And we are explaining these things with several examples. So, as I said throughout this course work, we will try to pick up many more examples or many more problem based approach. And during this whole process you will come to know many transformations which is, might be known to you, but how to explore those transformations that you have to use it.

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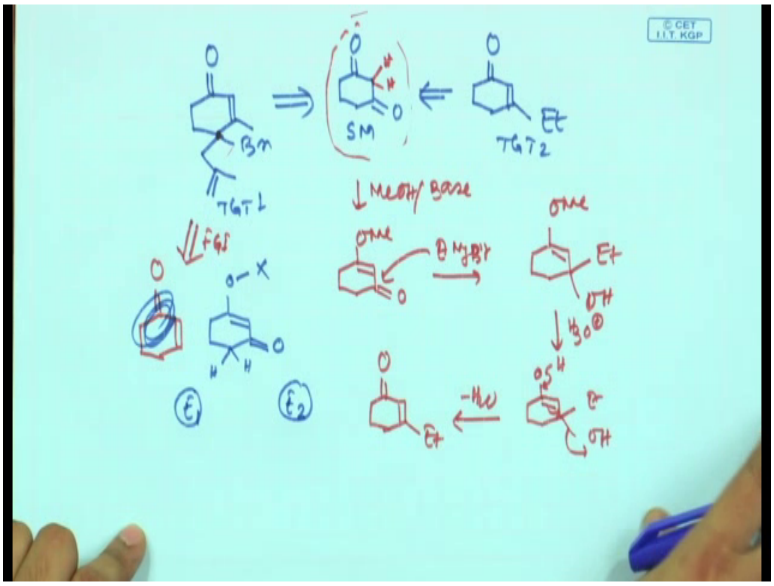

So now, we will basically continuing the discussion on the same thought. We will trying to provide you a problem, which is based on similar kind of transformation based as well as you can think of functional group and other things. I have given you or rather I will give you 2 targets: the left hand side this molecule which I am drawing it here and as well as I will try to give you another target this from a same starting material. I said you have to make this targets starting from Cyclohexane 1 3 diode. So, these are your targets this is the starting material, this target 2, target 1 target 2.

Now, remember in the very introductory session, we talked about something which is called divergent synthesis. This is a classic example of divergence synthesis, where you start from a single starting material and you can access both the targets. So, we will initially try to finalize the target 2 because which seems to be a little bit simple. Target 2 is 3 ethyl Cyclohexanone, the starting material provides the Cyclohexanone 1 3 Cyclohexane ion.

Now, if you do a close, analogies are will find that one of the carbonyl compound in this starting material was not there is a final target. So, somewhere down the line you have to play with one of the carbonyl functionality and you have to introduce a ethyl group. And eventually what essentially you will try to do, we will do a forward pathway. As you know that one side Dicarbonyls are very good analysable compounds, you can simply put if methanol and a base to make this compound as this.

So, this is the initial Enol ethers, which you can easily access. Now see, one of this carbonyl group will be not remain in this final target and you have to introduce a ethyl group; so ethyl magnesium bromide, probably the preferred nucleophile, which you can think of attacking here. And if you do such reaction this reaction basically we have discussed earlier in a different way, now you will get a tertiary alcohol. Now, next what you need to do? You basically need to do a allyl magnesium kind of things. So, the double bond will migrate and you get a Ketone there.

Now, I said this is a phenyl methyl ethyl. Phenyl methyl ethyl this is a normally very unstable if you put a little bit of acid they will basically try to hydroids, and will give you this compound. Now, this compound is what? This compound is basically enole. So, enole have a instant tendency to totamorise to the parent ketone, but in this case you do not simple totamoraisation it will also followed by a elimination of a water molecule and will basically get the target 2 which was initially asked.

Now we saw the reaction, this reaction is basically nothing; you are fine tuning out of this 2 Dicarbolic compound, one of these carbonyl was basically making inert through a suitable protection, is basically kind of protection and this protection is only possible as you are having a symmetrical Dicarbolic compound with a active Methylene group. This active Methylene group, this active Methylene hydrogen is responsible for the instant analyzation.

Now, coming to the second target that will be little bit of difficult, is not difficult in the sense, but eventually for second compound you need a similar kind of group; here we need a methyl group not ethyl group. In addition at this into the methyl group you need a quaternary carbon means all carbon quaternary. I say methyl sorry it is a Benzyl; you need a math allyl group, this group as well as the ring group. So, do a very conversional retro by a functional group inter conversion, and you will be coming to a structure which we have say, it is a wrong structure we drawn here we will be just coming to a typical something like this, if you can have a compound like these. And then you can try to figure it out, this is the out of this 1 3 Dicarbonyl compound, we have selectively manipulated 1 and then this is now we having a active Methylene group and then here you want to put 2 electrophile in a successive manner E 1 and E 2. nNow what are E 1 and E 2? E 1 will be this Benzyl group and E 2 will be this Methylene group. And then you can do the similar kind of step which we earlier did for target 2.

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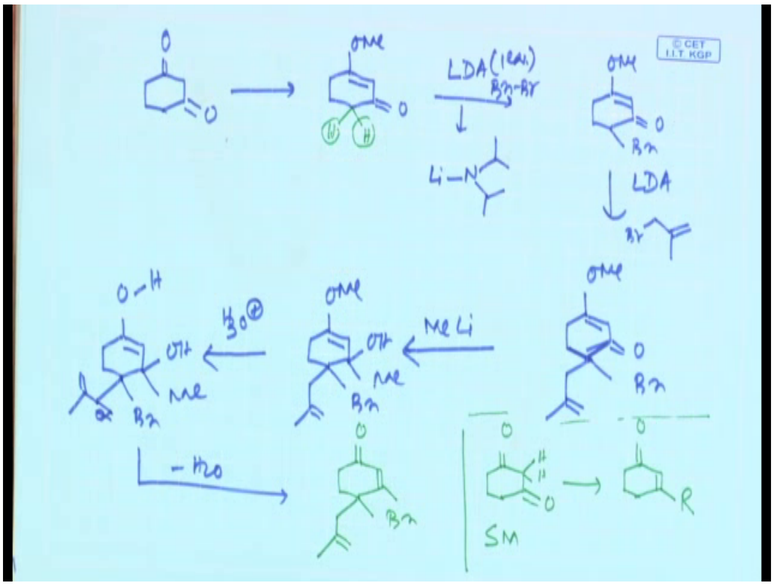

So, your synthetic experience will again start from this parent Dicarbonyl, you just do the initial analyzation and that will basically give you this compound. Next we said, out of this 2 carbonyl you have selectively protected 1. So now, what you do? You put a base LDA, now what is LDA? Do you know the structure of LDA? LDA structure is nothing is a lithium Diisopropyl amide this structure, Diisopropyl group, lithium amine and it is a amide.

So, now you putting a LDA, means 1 equivalent of LDA and the first electrophile you are putting benzyl bromide. So, you will basically get this o m e, this ketone and this benzyl group, will be need to put another electrophile, inform the form of this Methylene group. So, you do another round the alkylation with LDA and then you see, you need to put the another round of electrophile who structural be this, this, this and you do the successive round of alkylation all together, you basically have a ketone and then 1 is benzyl and 1 is the math alyl.

So, now you almost came close to the final structure. The target molecule, you basically need a methyl here. So, what to do? Similar thing, you react with methyl lithium to get the methyl introduced in the proper place remaining part all remains similar with your benzyl.

Now, basically will do the similar kind of thing vinyl ethyl hydrolysis, just exposure to mineral acid, your vinyl ethyl would be hydrolysed and then it tends to analyse followed by water elimination. Rest of the molecules will remain sorry rest of the molecules will remain similar and your benzyl. So, do a water elimination, then you get your final target. Your methyl is here, your benzyl is here. So, this is a final target.

Now, this kind of transposition what you can, in reality you can expect basically what you are doing? You are doing a starting material or using something like this? Now, final outcome of this product is basically you are getting this kind of compound that is it. Very useful transformation, where the allylic double bond is basically kind of migrating or transposed, means from one place to another place.

The initial allylic bonds, which have been generated by this analyzation is here. Then after Grignard addition, that Grignard making the c-c bond, now we have the trick is, if you want to after this fine initial protection, you can use this methylene groups for your alkylation part. So, the entire trick is that you have to basically fine tune the chemical reactivity of the starting material and then you can basically do the mode of reaction which you want to do, want to carry out.

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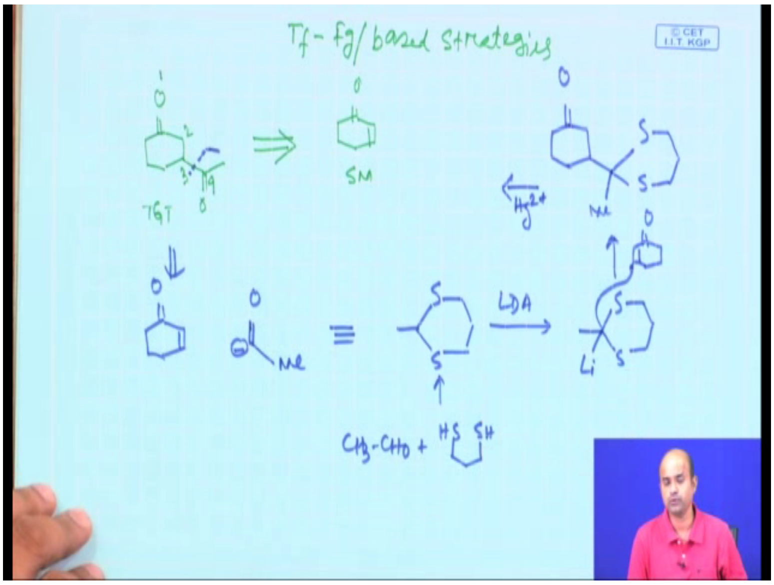

So, next will try to figure it out a combination of a functional group base strategy as well as transformation based strategy, we said basically this strategy is are overlapping. So, we will be trying to discussing with as many as example as you can. This target is pretty simple target, we have a target something like this and we will provide you the starting material, I say you prepare a 1, 2, 3, 4, 1, 4 Dicarbolic compound by using Cyclohexanone as a starting material.

Now eventually, if you do a very conversional retro, you will do a retro here and that will basically give you a Cyclohexanone as a Michael acceptor and you need a species, which is a basically Umpolung species, is a d 1 Umpolung d 1, is a d 1 species. Now, is it as you discuss this species can, be easily generated from 1 3 Dithaion chemistry of acetaldehyde.

So, what you do? You take acetaldehyde, react with 1 3 Dithaion will get this 1. Fine, you now treat with LDA. So, LDA what will do? It will basically replace another acidic hydrogen with a lithium. So, this lithium species is now active, is acting as a nucleophile and react with cyclohexanone the starting material in a 1 4 fashion.

So, you will basically get, fine, next step is only remaining. You have to remove this 1 3 Dithaion group, that you can do by H g 2 plus. Now this is very straight forward, this is a absolute straightforward there is no hidden tricks or techniques.

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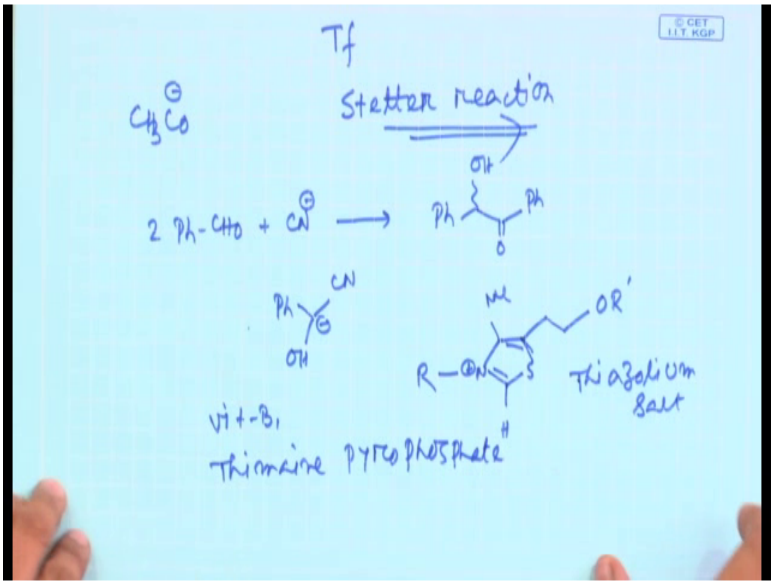

Sometimes, do I will ask you, that whether is there any direct reaction you can think for doing this transformation, means is there a way you can generate this kind of Umpolung species in c 2, I mean in reaction mixture, answer is yes. This is single step transformation is known, which is known as reaction. Now, Stetter reaction is a very useful reaction, now what exactly was done in the Stetter reaction.

Before going to Stetter reaction I will try to explore something else. All of you know the Benzoin condensation reaction, in which a Benzaldehyde, 2 molecular Benzaldehyde is reacted in the presence of cyanide to give you a compound name Benzoin. Now, Benzoin reaction basically goes through a mechanism is similar like Umpolung mechanism, this kind of species is in reality has been generated and this basically attacking to the other molecular Benzaldehyde.

Stetter reaction, basically a biochemical version of Benzoin reaction normally was proposed and this kind of stetter reaction or this kind of transformation is known in the living system for long time and particularly vitamin B 1 or thiamine analogue has been known for long time to catalyse those kinds of reaction. Now, this is a thiazolium nucleus, where nitrogen and sulphur is present and you are basically having a acidic hydrogen in this portion, which is flanked by nitrogen and sulphur. Now, this kind of thiazolium species are basically named as thiazolium salt, they are commercially available. Now, vitamin B 1 it is name is thimaine Pyro Phosphate. Vitamin B 1 is also known to catalyse this kind of reaction by exactly the mechanism similar to Benzoin conventional mechanism.

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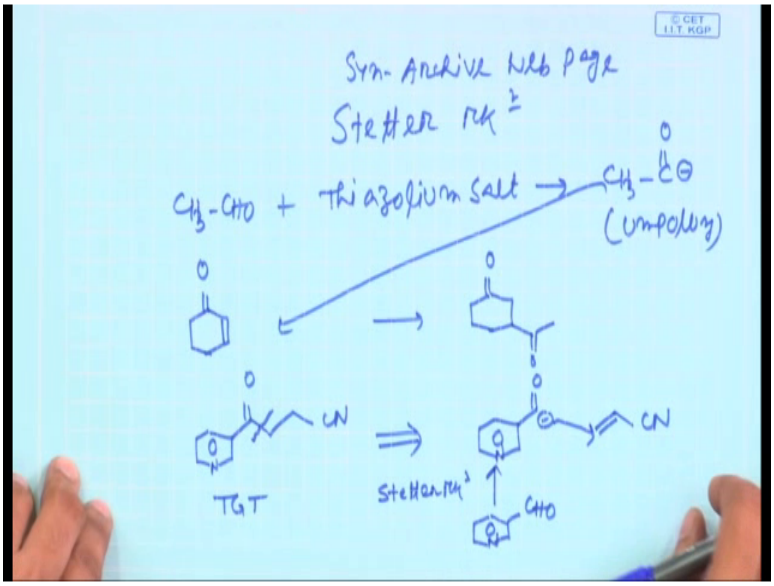

So, I will urge all of you to go through the mechanism of Stetter reaction or even if you just go through the syn archive, syn archive web page to know the detail of Stetter reaction. The disconnection for Stetter reaction is very state forward, you react acetaldehyde as in our case with these thiazolium salt, just know we talked about thiazolium salt.

You will basically generating a species CH 3, C O minus and this is the active species or the Umpolung species which will now react with the Michael acceptor which was given to you. So, the solution was very nicely handled by a name reaction called Stetter reaction. Now, usually all this kind of 1 4 Dicarbolic compound you can synthesise by using Stetter reaction. I will try to give you another very interesting example. I said I want to synthesise this target molecule by using Stetter reaction.

Then as I said Stetter reaction is a good platform, is a good way to generate Umpolung carbonyl Nucleophile. So, you can just disconnect this molecule as this, now this part you have to formulate that as a Michael acceptor, you can use Acrylonitrile. So, you start with your 3 pre period in Carboxaldehyde, as a parent Aldehyde, exposed to Thiazolium chloride or the Stetter reaction condition.

Now, this reaction condition will make sure this species will generate and then it attacks to Michael fashion and then basically will get the target molecule. Now, Stetter reaction is very important reaction as I said and hopefully you will try to explore them it is mechanism, but eventually from the mechanistic perspective is similar like Benzoin condensation.

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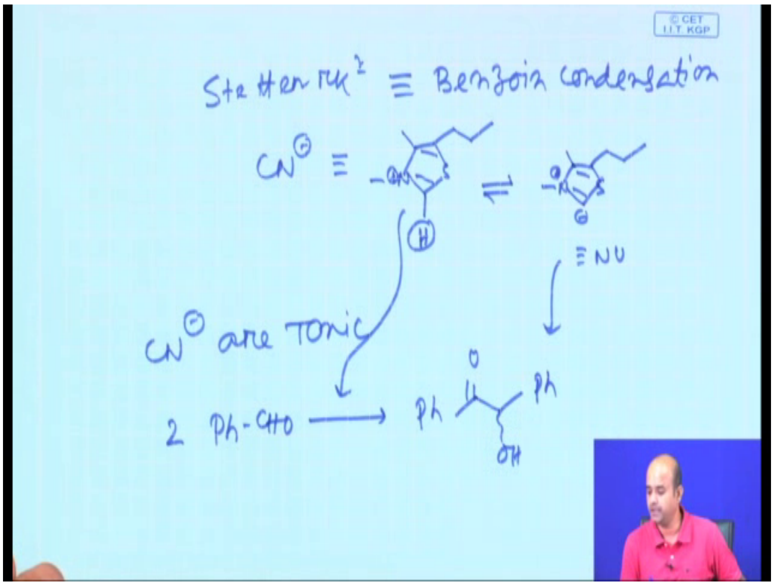

So, I will write it down. Stetter reaction mechanism is similar like equivalent to Benzoin condensation that will basically give you a hint. If you remember the mechanism of benzoin condensation, then this mechanism will be very similar, accept that in Benzoin conversation you are having a cyanide species, in Stetter reaction you are basically having a thiazolium species, which is a 5 member nitrogen and sulphur containing compound is having this kind of core structure and then you will having a active acidic hydrogen, which is basically mainly replaced to generate you a Carb anion or a Nucleophile and this is the basically the main active species act as a Nucleophile and this is the real Nucleophile, this Nucleophile basically the next attack to different conditions.

So, eventually in the sometimes your instructor in the lab will tell you that can you a synthesized Benzoin without using cyanide because that all of us know that cyanides are toxic, toxic chemical and they have a potentially health effect. So, your answer will be definitely yes, we can do it, if I use this thiazolium thing. So, you can use 2 equivalent of Benzaldehyde with this thiazolium thing and you can basically get a sufficient quantity of Benzoin by using this thiazolium solved mediated Benzoin condensation and that is also very nice way to think about different transformations.

So, this Stetter reaction I am sure all of you have not studied yet, but is very useful way to do, to synthesise 1 4 Dicarbolic compound.

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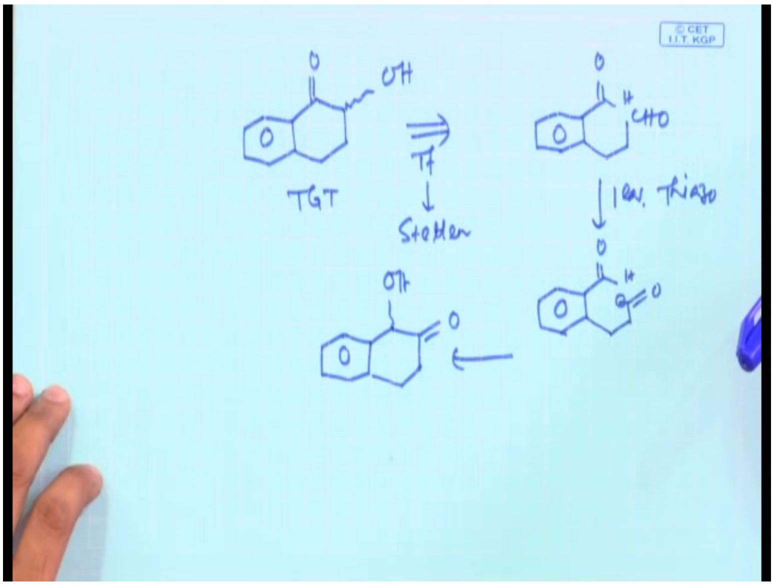

Even some cases, if I say I will give you a target molecule something like this and I said you have to use a Stetter kind of reaction, the prerequisite is you have to use a Stetter transformation, the answer will be definitely yes, the only thing is you have to use a intra molecular version, so you need 1 2 3, 1 2 3.

So, basically you have to first take this aldehyde and eventually you make sure that which aldehyde will react. It does not matter, if you take this aldehydes is starting material 1 equivalent of thiazolium chloride, thiazolium salt and then you can generate 1 of this Umpolung let us say I am generating this Umpolung thinking that aliphatic aldehydes are much more reactive than the corresponding aromatic aldehyde, but if this aldehyde has been generated as your main carbon ion you get a different product, it is not the real target which were looking for, in that case basically you will be getting a this product is not it.

So, basically you can either think of using aliphatic aldehyde which is divisible much more reactive or otherwise you can think of using aromatic aldehyde as the main reacting partner and you can fine tune the reactivity are to get a good amount of alpha Hydroxy Ketone, which is basically similar like a Benzoin kind of compound and Stetter reactions are very important reaction for carrying out this kind of things. So, next will be trying to something else and eventually as I said Stetter reaction, Stetter reaction is a very good platform to give you something else, would try to figure it out some other problems based on this kind of transformation, this is a similar problem.

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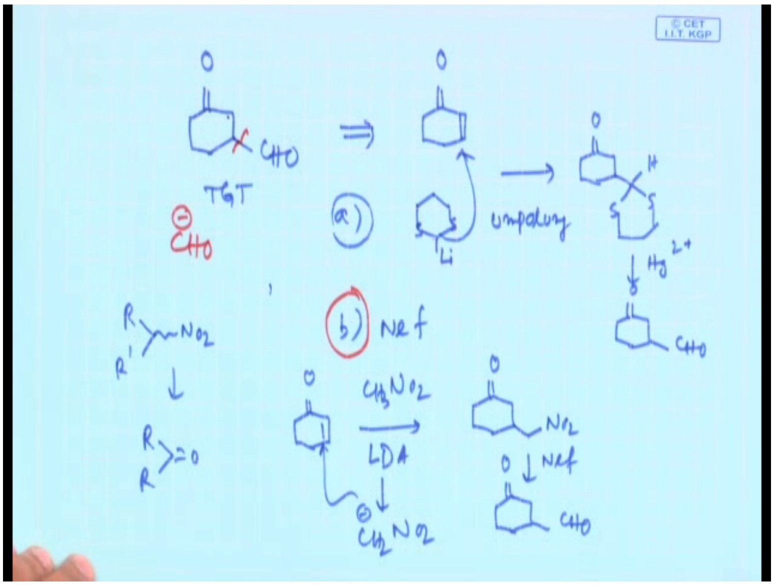

If I give you target molecule this, but starting material have not provided, starting material let us say, I am giving you this, then what will approach, same line, same way down the line you can think of, you can basically take 2 different routes, you can take the original thayl route, which is basically this route, you can do it. So, what you need to do? You basically need to take a monolithic reds species as a Nucleophile or a Umpolung species, then you can react with this in a Michael fashion and then you can remove the dithiane protection. So, dithiane protection basically you can remove and that will give you the target molecule, eventually there are other ways, try to remember we have talked about reaction called Nef reaction.

So, in this case Nef reaction I said the disconnection you will be something like this. You have a nitro compound that will be converted to the corresponding Ketone compound. So, what will be approach, you take this starting material Cyclohexanone, react with nitro methane, nitro methane's are and with a base. A nitro methane as known to generate this carbon ion from this things you react in a Michael fashion, basically you will be getting CH 2 No 2 and then do a Nef reaction you will end up with this product.

So, this was the beauty of a different strategically useful transformation. For a single target you can choose different pathways as evidence from this particular 2 strategies, one is the Umpolung based strategies and another is the a powerful transformation, which is known as Nef transformation, but the main bottom line is both the case is, we do a disconnection based on a CH o minus or the Formyl anion species, which needs to be generated and which will be attacking to the Michael acceptor in a 1 4 fashion.

So, no matter whether it is a 1 3 Dithaine chemistry or it is a Nef chemistry, the final target can be achieved with extremely efficient way. As I said choice is yours to pick up the right pathway depending on the resources which is available with you.

So, probably if we will just continue our discussion throughout this session and will be back in next week, till then have a good time.