A Study Guide in Organic Retrosynthesis: Problem Solving Approach
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Lecture – 06
Tf/Fg/SM based strategy and its exploration

Welcome back. So, last week, we have basically discussed the end part of the our retro quiz. And from subsequent week, we will be now covering the strategical guidelines or basic guidelines which we will take you through a virtual tour of that how different kind of complex or simple molecules can be made and what are the essential guidelines to be followed. May be follow standard textbooks like to (Refer Time: 00:47) the very old books, we will find couple of strategies like one gb disconnection, two gb disconnection disconnection, for 1,2 dicarbonyl, 1,3 dicarbonyl, 1,4 dicarbonyl, we are now to make those kind of things in a those things are basically complicated.

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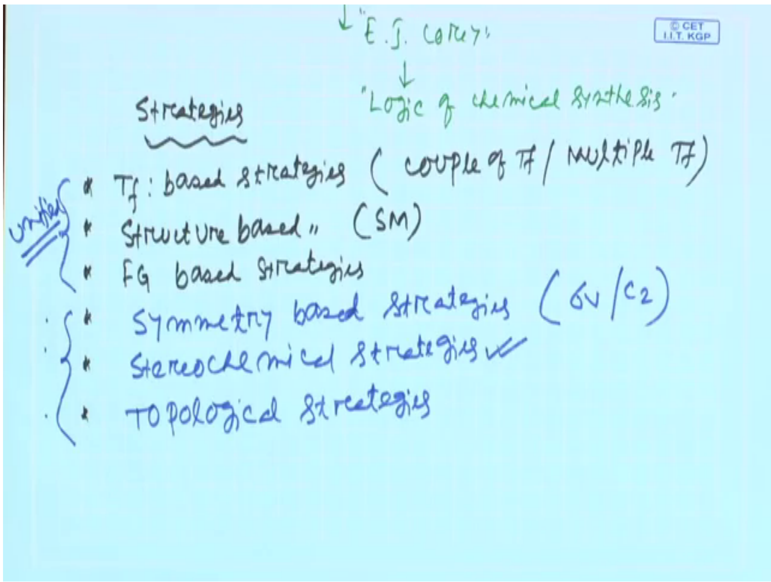

"E. J. Corey"
↓
"Logic of chemical synthesis"

Strategies

- Tf : based strategies (couple of Tf / multiple Tf)
- Structure based " (SM)
- FG based strategies
- Symmetry based strategies (σv / C_2)
- Stereochemical strategies ✓✓
- Topological strategies

unified

So, what we are trying to do we will follow standard processor E. J. Corey model. Now, E. J. Corey in his book the logic of chemical synthesis which we have shown in the earlier slide; this logic of chemical synthesis of the Corey has pointed out couple of strategies which are basically very general strategies and should be followed I believe should be followed by all the practicing organic synthetic chemist as well as student and that makes our life quite simple.

Now, those strategies are basically as I going to write it down strategies are mainly figured or main focused on six different points. What are the six different points? The first one we already talked about few times transformation base strategies. It means that you have to think about transformation which is the key transformations, your path way could be a single transformation base strategies or sometimes it happen you combine couple of transformation together or you can say multiple transformation together. Now, the prerequisite for this kind of strategies is you have to have quite sound knowledge of the transformation you are dealing with, I need to quite see over what is the exact mechanism so that (Refer Time: 02:47) chemical issue as well as stereo chemical issues could be adjust properly.

So, then next strategies is which will going to figure is called structure based strategies. Structure based strategies is basically similar kind of strategies which is abbreviated as SM strategy or starting material based strategies means that starting material was known to you or giving to you. Remember the retro quiz we have given some starting materials, but essentially we said that this is either a starting material base strategies or a functional group base strategies or transformation group base strategies.

The third strategy which will be trying to give you a idea is called FG base strategies or functional group base strategies. Now, in my personal opinion, the above three strategies transformation sub structure based or starting material based or FG base strategies can be combine together can be combined together and can be called as a unified strategy or one strategy unified, this can be unified. But eventually for the sake of simplicity will be trying to give a brief emphasis on all the strategies, for transformation base strategies, we will pick up some unique transformations and what are the retros you can think about. And structure based means the starting material is available to you functional group means is a functional group additional or inter conversion. The remaining three strategies are very unique.

And the remaining strategies next strategies will be talking about number four is symmetry based strategies. Now, symmetry it is basically the we are talking about symmetry elements on a given molecule. And normally for symmetry based strategies are very important and the two symmetry element either sigma v or c 2 played an important role for a synthetic path wave design. So, we will be trying to spend little bit time not extensively, but out main focus throughout this entire course work will be based on transformation based strategies, structure based and functional group based strategies. We will try to put more emphasize on initial top three strategies which is said is kind of a amalgamation. And all three strategies are basically to in principle similar. So, we will try to have that strategical disconnection at the very beginning and extensively.

The fifth one is again very important the stereo chemical strategies means that whenever your molecule have some asymmetric center normally does have. If you talk about compressed target molecules, they essentially are having (Refer Time: 05:38) chemical lead gains functional groups. Remember last week we talked about some of the molecules which is having continuous eight stereo center we say stereo octtered. So, many of the compressed in general products have multiple steroes centers and this strategies is very important. But eventually we might not discuss it extensively and probably a specific course called asymmetry synthesis will be the helpful. We will try to give you a flavour then only strategies.

And finally, we will talk about the topological strategies or strategies which will give you a idea for topological distant molecule. I said topology means a cyclic connectivity it will have a complex thermocycle structure complex hetro cyclic structure then what are the essential guidelines, what are the essential rules to make those molecules will be discussing. So, entire initial discussion will try to cover this three transform base strategies, structure based strategies, FG based strategies. And then in later part we will talk about this two strategies individually. Sometimes, this will happen these three strategies when you talking about as there is no well defined boundary separation, probably transformation based strategies you can fit into the structure based strategies or vice versa FG based strategies you can fit into the T f based strategies or vice versa. So, these three strategies there is no clear cut boundary, but this three strategies having clear cut boundary with them.

So, we will next continue our discussion on this top three strategies which basically says that either transformation based strategies, structure based strategies or functional group based strategies. Well as I said out main discussion will be a problem solving approach. So, we will pick up individual problems for each strategically point discussion.

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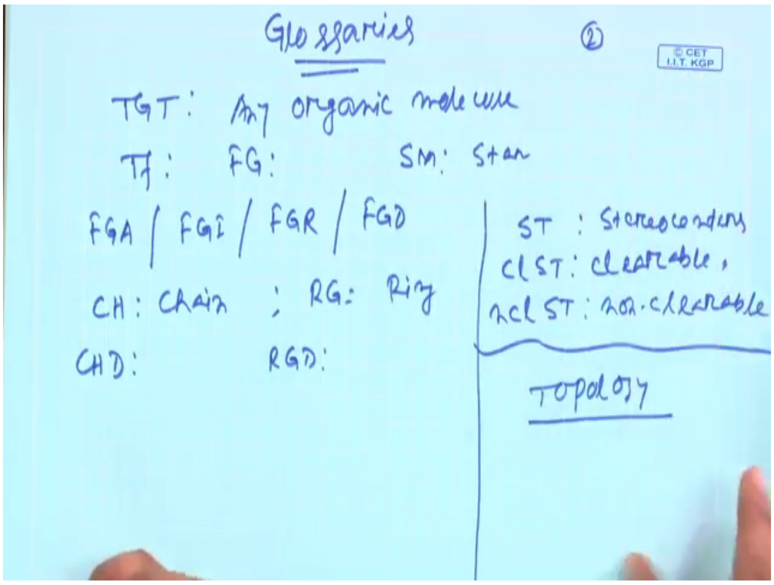

Glossaries ②

TGT: Any organic molecule

Tf: FG: SM: Stan

FGA / FGI / FGR / FGD

CH: Chain ; RG: Ring

CHD: RGD:

ST : Stereocenters

Cl ST: clearable,

ncl ST: non-clearable

Topology

So, before that we will again recapitulate or refresh your memory for some of the glossaries. Glossaries means the terminologies which we often use often will be using in this entire discussion. We say TGT is a target molecule, any potentially any organic molecule could be a target, any organic molecule. Transformation is T f, FG is functional group, SM is starting material these are abbreviated form, starting material or precursor. Then you can call it different terminologies FGA - functional group addition, FGI - functional group inter conversion, FGR - functional group removal, FGD - functional group disconnection so on. So, CH stands for chain, RG stands for ring so the abbreviated form. If you have say CDD means change this connection if you have RGD you can say ring disconnection. So, those are the abbreviated form ring disconnection and you can use it.

For stereo chemical strategies, there are two terminologies will be using ST stands for stereo centers. We said Cl ST, Cl stands for clearable stereo center. Now, what does it mean it means that by a synthetic operation if you can create a stereo center which you can explain logically means you can clear the doubts that is called clearable stereo center. Ncl ST means non clearable stereo center it something happen that your essential chemical logic says that this two synthetic is very difficult to create by the existing chirality of the molecule or the ligand or the chiral catalyst you will be using probably it might pose the problem. And in those cases sometimes it can regard as a non clearable stereo center, but non clearable does not essentially mean that these stereo centers cannot be created, it can be created. So, this is the terminologies.

And then a for topologically driven strategies we will be having some more terminologies and that is basically focused on the ring structure. We will be discussing those strategies when we talked about those particular strategies.

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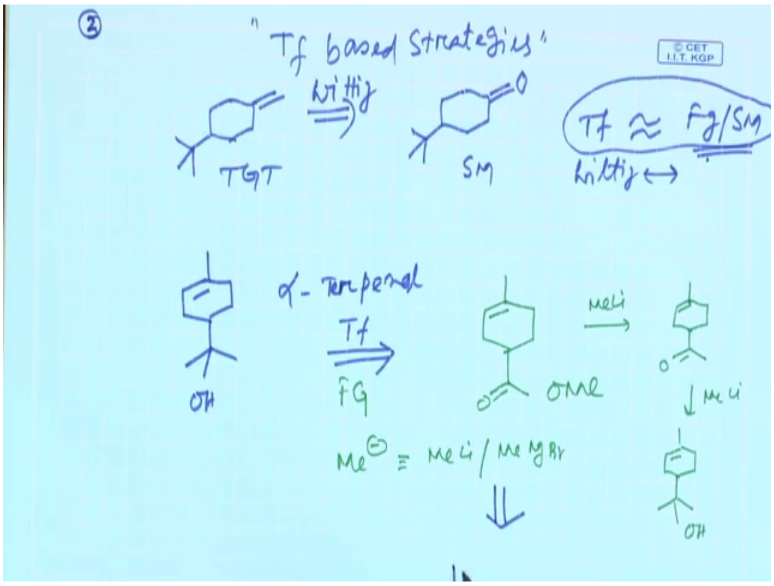

So, let us focus our initial thing on transformation based strategies as we will be discussing. So, transformation based strategies, the basic guideline or basic understanding is you need to be familiar with many transformations many transformations. Simple thing, very simple very classical things, I have given you target molecule, I did not give you a structure, I did not give you a this is a target molecule I did not give you a starting material. But essentially if you can go aware to a retro you can say that this molecules, I will be making from a this kind of reaction.

Now, what is a reaction, the reaction is I said Wittig reaction. So, this is called a Wittig transformation based strategies. Essentially by seeing the molecule you start doing a visual communication, it is very important as I said now Visual communication that basically gives information that Wittig reaction can be applied on this starting material. Now, let see how transformation based strategies and FG based strategies are interlinked I said T f based strategies will be discussing and at that point starting material would not be giving, but [FL]. We can say that this is the transformation based strategies you do a Wittig reaction. It is a Wittig transformation.

Now, I say that this is a target molecule starting material was giving to you. So, by seeing the starting material, it is instantly will be coming to your mind ok this is the Wittig reaction which will be applied to the starting material and that will give the product. So, this is the link thinking. First functional based group thing or the starting material based things, you just see the structure of the starting material or the final functional group of the product and then try to correlate that is why transformation based strategies or functional group based strategies or starting material group based strategies are basically interlinked through common thread.

In principle, you basically cannot distinguish it provide that you are doing some very unique transformations which is not very usual those cases it place a clear distinct role. So, for this transformation based strategies, we will try to focus on initially we will talk about some simple problems how it can be dealt with up. And then in between we will try to do a multiple transformation based strategies means we give a target molecule and then a starting material which can be basically thought of that this starting materials can lead you to this product through a multiple transformation based approach. So, you do a Michael reaction like, Robertson arrogation in a double transformation based approach you do a Michael as well as (Refer Time: 13:49) combine together.

So, let us start the initial proceedings. The initial target molecule, which I have chosen or I was giving to you as a problem is a simple molecule. And this molecule if you remember is a introductory section we talked about this molecule is a alpha terpineol which is a aroma compound was (Refer Time: 14:17) by Prof. Parkin fine. So, alpha terpineol we said we will doing a transformation based disconnection. Now, you see the structure is having an cyclohexene structure it is a hanging append it, this hanging functional group which is a tertiary alcohol functional group one end it is having a methyl things. Now, this at transformation functional group starting material both are interlinked, so initially probably you have to go through a different approach or different idea. If we disconnect initially by this way, it could be a functional group based approach as well as transformation based approach.

Now, how I said a if you have ester molecule, ester unit, ester functional group, you react with a methyl nucleophile now what are methyl nucleophiles methyl nucleophile are basically nothing is a methyl lithium or methyl graviner. Now, based on your chemical knowledge, if a methyl grignard attack on a ester one equivalent you will get a ketone first. Then if you excess the ketone will further attack to give you a alcohol which is required. So, first you attack this to methyl lithium or methyl magnesium bromide one equivalent initially you will get this ketone you use further and then basically you will get the this OH this is known to you fine.

So, now this is our next target. So, now, this retro is basically functional group based you can call or you can call transformation based, as a result nucleophile addition of a nucleophile on ester functional group. This retro this retro is the purely transformation based approach.

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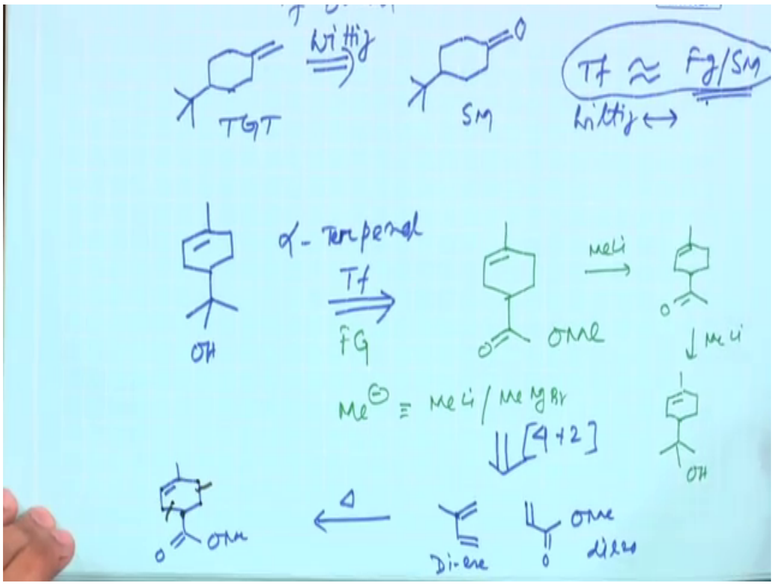

And here you can basically do a simple which is already discussed earlier a 4 plus 2 cycloaddition approach or a (Refer Time: 16:43) based approach. Now, see this a diene this diene, this dienophile and then you do a 4 plus 2 thermal reaction you will basically get the intermediate which was earlier discussed to you. So, the disconnection basically where are the new bonds are basically you are making you are making a new bonds here, and you are making a new bonds here, so that basically gives you one, two, three, four, four carbon. So, which is coming from this diene, and you are having a two carbon dienophile one and two that gives you a 4 plus 2 - 6 unit six carbon framework and then rest of the things are pretty simple. So, this should be a your guiding principle that just once you see the structure, you make it out.

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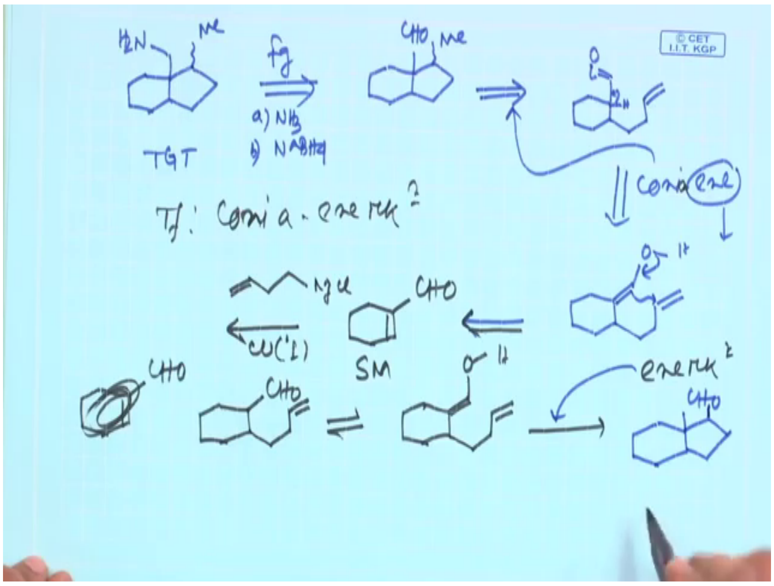

The initial one is pretty simple. We will now next go to a little, but complex system which is the structure is will be bring the structure. And see the structure this compound is having a bicyclic structure, this is our next target molecule. Now, as you said we will try to follow a transformation based approach. So, we will try to design or try to strategically disconnect the molecule by following a transformation which is known to us. If it is not known to us we will discuss the mechanism and we will talk about this. Now, if you see this molecule this molecule have only a active functional group CH 2 N H 2. So, initial disconnection will be doing that how you can make this amine.

So, best disconnection probably a functional group based approach if you have a aldehydes, you can condense with the ammonia you get the amine, and then you reduce this amine with sodium cyanoborohydride to be at the final product. So, the reagent which is required for this forward pathway is a ammonia and then sodium borohydride is it clear?

The next transformation which I am saying or next retro will be the very crucial one. And then try to figure it out the next retro. Next retro is the main key thing in the entire pathway. And if you do not know this particular retro, you might have a difficult time, but that is why to know this exact transformation so I have giving you the sources you go to the (Refer Time: 19:52) or you go to the organic reaction portal. And you try to access those portals to get to a I mean to know the idea there what are the name reactions in those website.

Now, this particular reaction which you said is named as conia-ene reaction which is basically the transformation will be applied here. Now, what exactly the reaction is this reaction is basically reaction where this reaction is basically you have this ineligible hydrogen here which basically makes it enol, is not it? So, having this OH and then you having this is a principle is a ene reaction. Now, try to figured it out what is ene reaction, ene reaction is normally basically a hydrogen migration through a sigma and pi network, it is basically will be reaction is something like this. So, this hydrogen basically migrates from this enol to the right hand side of this molecule. And you say kind of a pericyclic reaction where proper orbital overlapping is the main criteria. As we are not discussing the mechanism you can basically try to find it out what is a ene reaction is called ene reaction, ene reaction is a very important reaction.

Now, so once this ene reaction was done you can basically next try to figure it out what could be your starting material. Now, see the starting material where now trying to put it out something like this. Now, starting material was not giving to you earlier we said the approach is purely transformation based, but the main drawback is that until unless you know this transformation or this conia-ene reaction is very difficult is conia-ene reaction. So, the transformation which is the main highlight here is conia, conia-ene reaction is the main reaction which we are using here.

So, now, we move to the forward synthesis you start with this material what we need to do we need to put this alkyl appendage. Now, this is alpha bit unsaturated compound. So, you a simple grignard kind of thing with a copper to make it a 1, 4 things copper one. So, what will get you will basically get a this bonds would not be there. So, you basically have a one force things you basically have CHO fine so which is now analyzable and then your conia-ene reaction will takes place. So, you have this conia-ene reaction as I said conia-ene reaction and then you will get the product which is this bicyclic thing with a methyl here is a methyl here fine.

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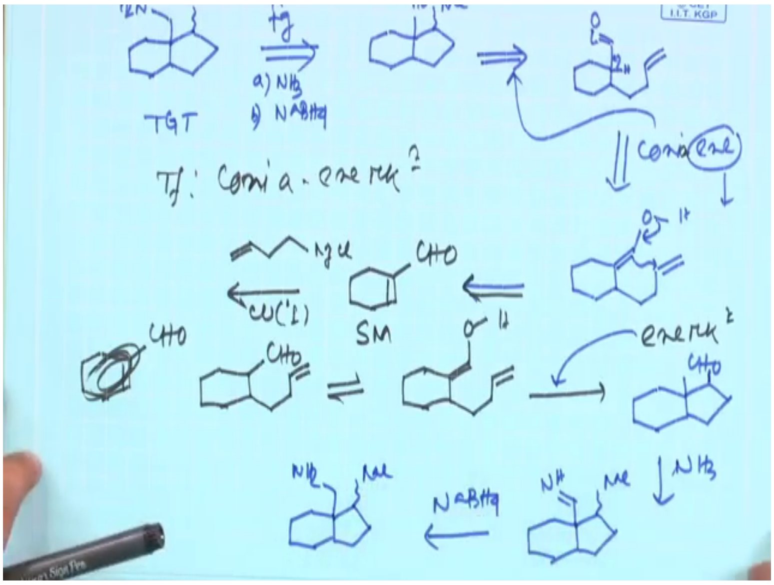

Now, what you need to do next the CHO, you have to convert to CH 2 N H 2 I said condense with ammonia first. So, you will basically get amine fine. This amine you can reduce it with sodium borohydride to yield you the corresponding yield you the corresponding amine. Now, here there is also other way you can do it. Once you of aldehydes, you can convert the correspond aldehyde to amine by different ways.

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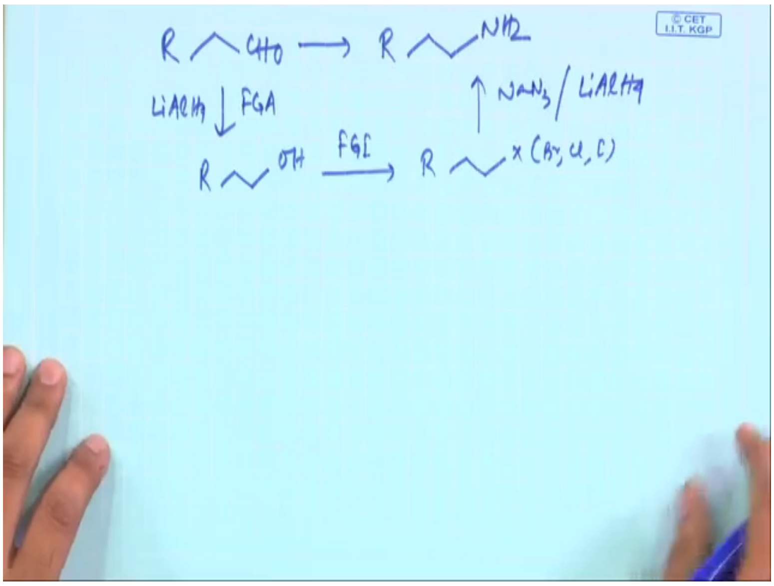

Let us I will try to give you a something else that how you can convert this kind of aldehyde to the corresponding amine. One of the reaction we talked about is a this make the amine and do a reduction reaction. You can also do other things you can do a FG addition functional group addition by reducing it to lithium aluminium hydride. So, what will get, we will get a primary alcohol. So, next you need to convert the primary alcohol to amine. A simple functional group inter conversion by how you can convert this alcohol to corresponding hallow means bromo, chloro, iodo etcetera. You can next do a reaction sn two reaction by sodium azide. Once you convert this bromo to azide, you do a simple lithium aluminium hydride reduction or there are other reductions which is very important transformation named as Schrodinger reaction, we will talk about little bit later on. So, in principle a aldehyde functionality can be converted to corresponding amines as I said particularly this problem.

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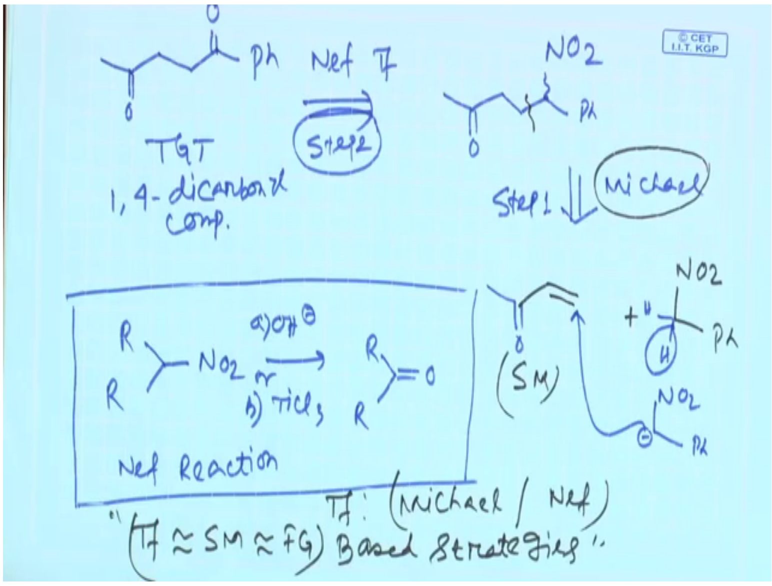

So, our next problems is basically we will a talk about a similar kind of compound, where try to discuss some unique transformation our next target. Now, next target as I said this target if you see it is a 1, 4-dicarbonyl compound dicarbonyl compound. So, 1,4- dicarbonyl compound, so we will put a very unique transformation that probably is not known to you I am not sure we will do a transformation name as Nef reaction or Nef transformation.

Now, Nef transformation basically it gives you a reaction where a nitro space is can be converted to corresponding ketone by reacting with either a strong base OH minus or even you can do a titanium trichloride based reaction. Now, you said the Nef reaction you just give a search in this corresponding website (Refer Time: 27:08) to know the mechanology detail, but the retro of the transformation is this kind of transformation. Now, so we will be use in a Nef transformation now if you know the Nef transformation is very easy so the next retro. Next retro is absolutely simple your standard Michael based retro. So, you disconnect in this bond and then see where is in this benzyl nitro species.

Now, know that this benzyl nitro species is this two (Refer Time: 27:46) extremely acidic as this benzyl as well as electro (Refer Time: 27:51) is attached to it. So, you can easily abstract this photon by base. So, you will basically get a carbonyl, this carbonyl is undergo simple Michael addition reaction. So, this is the transformation is a Michael transformation. And then once you get this, you do a Nef reaction. So, combination of transformation we have used it here. What are those which are basically Michael and Nef. So, it is a both transformations have been used in a combination and then you get the desired product.

So, the information probably Michael all of you know Michael all of you know. Now, definitely you may ask that whether this compounds can be this targets can be made in other wise; obviously, it can be made, but probably this is a economically viable or step economically means we are trying to reduce the step you say. This is basically a six step reaction we will do a Nef reaction first, two step reaction you take methyl phenyl ketone starting material take benzyl nitro species is put a base do a Michael reaction first one step, step one step one. Then you do a Nef transformation Nef for detail mechanism of Nef you go to the website which I have told to you and Nef reaction basically give this kind of transformation it have a nitro compound subject to OH minus base or titanium chloride we will get a carbonyl compound.

So, if you know the Nef reaction this is your step two, step two, and then you can basically figure it out that will coming to the final compound. So, target is known to you only thing is you have to have a small information about the transformation and that is the main duty of transformation. But definitely this transformation based strategies you can combine to functional group based strategies also basically similar this retro you can also discuss in terms of functional group based disconnection you say we have 1,4-dicarbonyl compound. So, I will do a disconnection based on this which is this is a Michael disconnection.

Now, Michael as all of you know a carbonyl will attack. Eventually if the starting material is giving to you I said make this compound from this starting material methyl phenyl ketone. So, initially you can think about let us do a simple Michael and then if you know the Nef, you can do it; if you do not know the Nef you have to a other pathway. So, the take home message the transformation is equivalent to starting material based strategies is equivalent to functional group based strategies. So, all the strategies are basically almost similar, and we will be talking about those strategies that is why together transformation starting material FG all the three strategies will be talking about in a combination.

So, in the next class, we will be giving you more examples of transformation based strategies. So, till then goodbye have a good time.