Lecture – 20
Functional Group (Fg) based Strategies

So, welcome back. So, last lecture we are basically discussing of multiple transformation based approaches and many of the unknown transformations was discussed in a detailed mechanism, mechanistically way.

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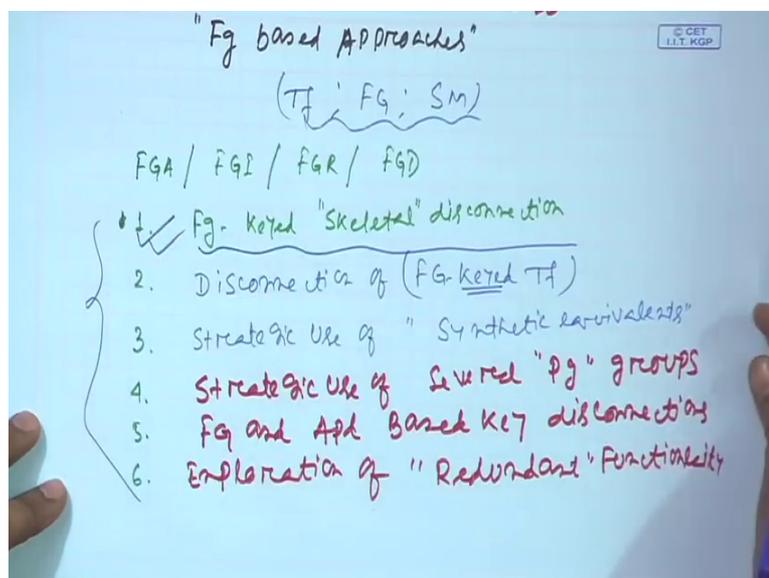
Today, what we will going to talk, we will basically give you a much more emphasis on Functional Group based approaches. We said Functional Groups are basically a eventually a Functional Groups, you can talk about any functional groups like Alde Hyde Ketone Hydroxyl Thiele anything. I will try to figure it out; how functional group based approaches can be useful.

But on the other hand, as I said Transformation, Functional Group and Starting Material, we are discussing in a parallel fashion or a overlapping fashion; because all the strategies which dealing with this 3 are basically interlinked or interconnected through a common thread.

Now, Functional Group based approaches, we already talked about many of the abbreviation, Functional Group Addition which is Functional Group Inter conversion which is Functional Group R, Removal we didn't talk about. But we will say then, is it Functional Group D stands for Functional Group Disconnection. The terminology if you can write there will be many terminologies, but I don't want to make your life bit complicated. So, just forgot about those terminologies; terminologies are basically just for sake of to make your make things little bit complicated.

Now, this Functional Group approaches will try to figure it out or try to focus it out 6 different aspects. I mean our main discussion will be based on the 6 different aspects, so initially will be talking about Functional Group, keyed "Skeletal" disconnection.

It means that if you have a compound, whose structure was given to you and also a Starting Material was giving to you, you try to disconnect the "Skeletal". Skeletal means the skeleton the molecular skeleton, you try to disconnect by taking the help of for the functional group present in that molecule.

So, we will initially, we will talk about these things. The latter part, we will talk about the other things; where, is it we will be doing the disconnection of Functional Group keyed. Key means functional group keyed based on key, keyed transformation. Now actually in principle, we have talked about these strategies. When you talked about transformation based strategies.

So, we will again try to explain these things with more examples. Number 3 will be talking about Strategic use of "Synthetic equivalents". Now Synthetic equivalents will be spending much more time it will be later on, but now as I said for my anion, acetate anion, those of the Synthetic equivalents we have already discussed.

And then, number 4 is very important. We will be trying to explore the Strategic use of several Protecting Groups. We will spend few lectures based on the protecting group chemistry. You will try to have a general discussion. We already discussed what are protecting groups and few protecting groups based transformation have already been talked about. Finally, sorry number 5, we will be talking about Functional Groups and Appendages.

I mean the Appendages are Functional Group which are basically hanging or through a cyclic structure or acyclic structure and Functional Groups and Appendages based disconnection. I mean how Appendage you can insert in a given molecule. In reality, those strategies are already have been talked about with the example. And number 6 or finally, will be talking about a relatively new topic, which was probably not brought yet Exposition of "Redundant" Functionality.

Now "Redundant" Functionality basically means that functional group which is not required in the final structure. But still you need to talk about those groups; because let us say you are synthesizing a hydrocarbons, a target molecules hydrocarbon. Now, hydrocarbon you cannot think of the reaction to means that you have to take a starting material which does a functional group and then, you try to remove that functional group to access you target molecules. That is what the functional group is named as Redundant functionality which is not really present in the final target molecule.

So, you will try to focus our discussion on these 6 topics and as I said we will first talk about number 1 point, Functional Group based Skeletal disconnection.

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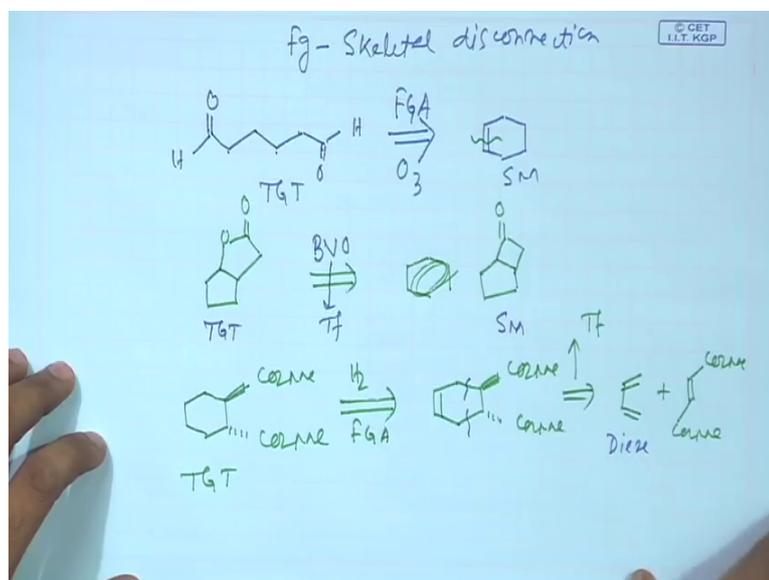
Functional Group based Skeletal disconnection. Now let us talk about very simple things, very simple things. I am giving you a molecule which structure is this, is basically what? 1 2 3 4 5 6, you have 6 carbon network and the end we are having a di

aldehyde, very simple answer. So, what you do? You basically do analysis by a functional group addition. This is starting material.

So, this is a simplified version of a functional group keyed Skeletal disconnection. This is final skeleton and this is the starting material Skeleton. You know that if we do a reductive cleavage sorry oxidative cleavage here you can get this molecule.

This kind of things are basically will try to cover in this functional group keyed Skeleton disconnection. Lets say little bit more fundamental problems, your give it target molecule something like this and if I say the starting material was giving to you, sorry the starting material was basically a 5 member things with a 4 member ring. So, initial is the target; you see the Skeleton of the starting material and the target you just need a ring expansion.

So, what you can think about? You can do a Brevier oxidation and principle you can fit these strategies in the transformation based approach also; because it is a based on brevier transformation. That is what I said, depending on the methods the transformation based, starting material based and functional group based all the approaches are similar; all the approaches are similar. A simple example probably will give you some idea where, this is a target molecule, simple target molecule.

So, you can think about simplified retros by a hydrogenation reaction. But what is this functional group addition and then here, you can think about a transformation based approach from a suitable dyne and dienophile. What is this? Is a transformation based approach. So, Functional Group and Transformation can be combined together and this is also a Skeletal disconnection.

You see this skeleton of the final target molecule, you say, if you can do a hydrogenation on this skeleton will be coming to this target. And then, this skeleton can be disconnected through this through this give you the, so, dyne and the dienophile. So, simplified way you can basically make many interesting features.

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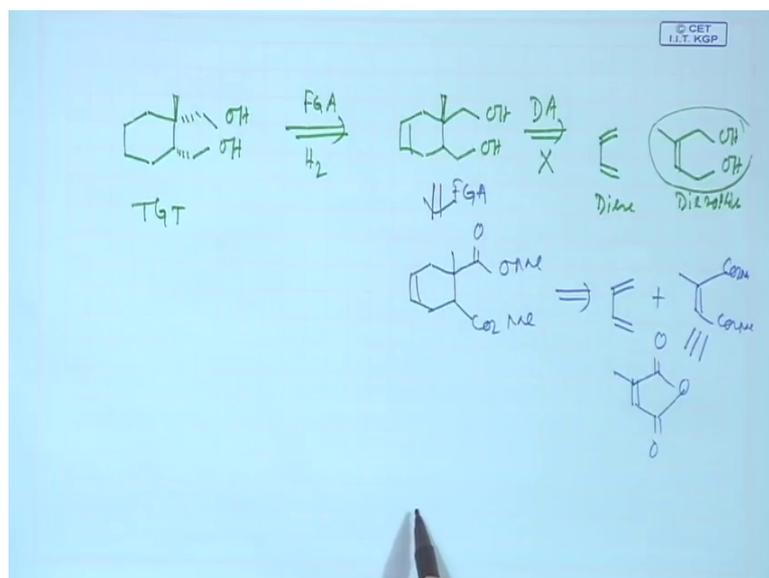
Next, will try to give you a little bit more example and let us see how you can do it. I have given you a target with structure is this. I will just straight wise doing it, where do a FGA by hydrogenation. Then, basically you will be having this compound and then, eventually you can cut this molecule through a Diels Alder way. Now let see if is it is feasible or not. I say will be doing a Diels Alder reaction by using this dyne and this dienophile.

Now, this compound has a dienophile, probably is not a good choice; because this compound does not have a electron withdrawing group. We say dienophiles will be always better, if you have electro withdrawing group attached in it. So, this route might not be feasible. On the contrary if you have a another route, which will basically give you this ester group on a later stage. I mean you can just doing a FGA by reductive method then you can fit it into the Diels Alder pathway.

Now, see your Diels Alder pathway is perfect we are having this dienophile or even you can choose a dienophile something like this. A cyclic dienophile which also will serve have the purpose. So, any one of these dienophile can be used and then, you can do a reduction. A same problem can be also solved in a different way. We talked about inter molecular Diels Alder reaction. But now let us do it in different way.
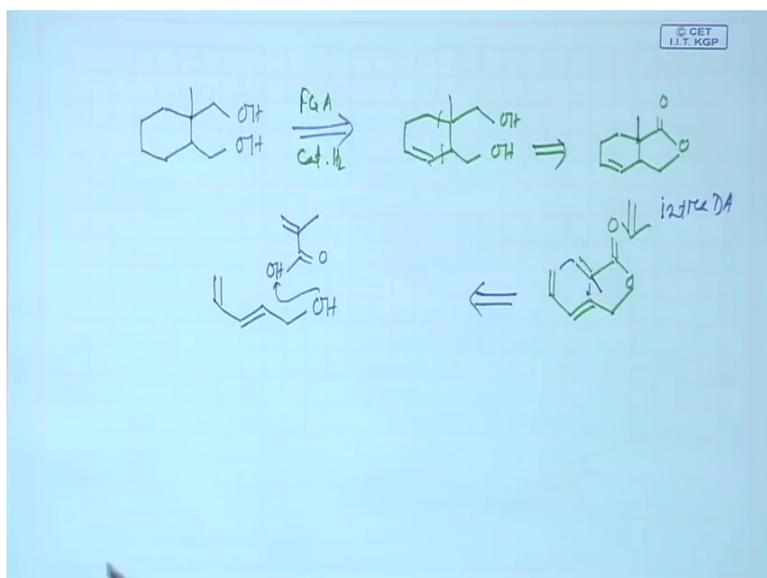
We take the same target, we took the same target and now, we say will be doing a Functional Group Addition through catalytic hydrogenation. But now, the intermediate which have now drawing is bit difficult or bit, bit different.

So, now you basically cannot cut the molecular traditional Diels Alder way. The traditional Diels Alder way, you dyne should be this, this. But here the dienophile position has been changed. Now this is also in principle possible, if you can think about you are having this particular compound, how? You just do a reductive method to come to the ester. Now these things you need to be prepare. Now you see the power of the retro is absolutely fantastic. We are trying to use a intra molecular Diels Alder reaction; intra molecular Diels Alder reaction.

So, we put the methyl here. This methyl, methyl here and as the double bond we have done retro here. We put this double bond here. So, is basically a intra Diels Alder same target. You can figure out a different way. So, now, this 4 plus 2 takes part and how this compound can be synthesized. This compound can efficiently be synthesized by this allelic alcohol and react with this corresponding acid. So, do a stratification reaction where, these things and then do a intra Diels Alder.

So, same Skeleton of the target, but we are taking the Starting Material in a different way. So, in principle this can be also fitted into the Starting Material based approach. So, the power is such that you have to device the whole pathway in such a way, you can fit

into either Functional Group based approach, Transformation based approach, Starting material based approach. So, this is combination of all the things.

Now, will try to explore that the how complex structures can be assembled from simple starting material through a functional group based keyed skeletal disconnection which we said is a point 1.

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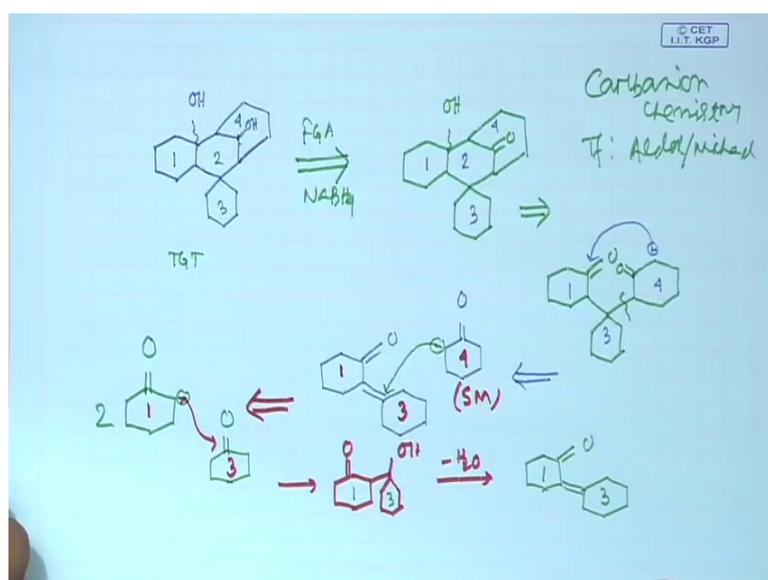
Now this molecule, you I am just drawing the molecule first. The molecule was, if you see the molecule this, molecule is basically 1 ring, 2 ring, 3, ring 4 ring is a target; it look a complex molecule. Cyclohexane, Cyclohexane linearly fused. This Cyclohexane is pyro cycle fused and these Cyclohexane the number 4 is basically bridged with the number 2. You have a bridging things and a OH, but you will see once I do the retro it's it looks very easy.

So, 1st retro, what I am doing it here by keeping everything sam[e] remains same. I will just doing a simple Keto reduction, because out of this 2 hydroxyl this is tertiary and this is secondary. So, tertiary hydroxyl cannot be done by hydride reduction. Only secondary hydroxyl, this is basically functional group addition. If you have sodium borohydrate kind of reducing agent, you put this ketone to come to here.

Now, the remaining transformation is a very interesting. I will cut the molecule now here and draw the intermediate. Then, I will see, I will show you which bond was basically

made. Now the molecule has been simplified. So, basically this is number 1, this is number 2, this is number 3. So, 1 3; now this one, this one, this one basically as a 4; this one is 4. So, what I am doing a basically doing a Aldol type of reaction to close this ring 2, close this ring 2; the molecule was just been written this way.

So, so, that you can have a bridging carbonyl; bridging carbonyl which have been reduced to bridging alcohol. So, this is can be very strategically done. Now will, you will see the power of the retro transformation. Was absolutely brilliant and then, we say will be using these 2 starting material, these 2 starting material.

Now, what bonds you are making? We are basically making this bond. How? Now you see this is, this compound is the alpha beta saturation ketone. We have a Cyclohexanone. So, this can undergo a Michael type addition here. Now once it gives the Michael type addition, this entire cyclohexanone, this is 1, this is 3, this is 4. So, that puts the, this 3 ring as a s pirocycle. So, this carbonion is (Refer Time: 19:22) in the michael fashion; to use the ring 3. So, Cyclohexanone as I said is very commonly starting material. So, you can put is a starting material.

Now, these things, this Michael acceptor you can also easily met by starting from a 2 equivalent of cyclohexanone. How? You take a cyclohexanone, generate the carbonion, react to it another cyclohexanone. So, means that these cyclohexanone you react to it another cyclohexanone. So, this is basically 1 and this is 3. So, you react here and you basically get a then, you undergo simple elimination; simple elimination, simple water elimination will basically give you the Michael acceptor as it was drawn here. So to start with 1, this is 3, this is 1, this is 3.

So, basically interesting, it's absolutely interesting. Starting from a very simplified starting material cyclohexanone so, 4 rings you are making or you are preparing through a common starting material, which is very (Refer Time: 21:06) available cyclohexanone. Now see the retro or the visual communication which were using, but everywhere the chemical logic is quite clear. You start with cyclohexanone, reacting with another cyclohexanone to make this 2 ring, where pick this Michael acceptor.

Now, then another round of cyclohexanone is coming. This carbon ion attacking in the Michael fashion 1 4 fashion. And then, you basically getting this compound, where the

number 3 ring has been fixed as a spirocycle. Then so, basically a complete carbonion chemistry; it is kind of a Carbonion Geonosian and Aldol reaction and Michael reaction.

So, this was a simple carbon ion chemistry, and basically the transformation which you are using is a Aldol and Michael something else. And then, at the end we do a FGA or FGI just by just to reduce the carbon ion compound. So this is simple substrates and of you can say that this approach is basically based on Functional Group based keyed Skeleton disconnection.

We see how the Skeleton of the target molecule try to dissect the skeleton. In our terminology you can say try to disconnect the skeleton through simplified intermediates, but everywhere the chemical logic must be cleared the which transformation will be using.

So, initially sodium borohydrate base reduction. Then, you will do a Aldol type of addition here. Then you have a Michael transformation, simple cyclohexanone and then, this cyclohexanone is linked or dimerized through a Aldol dehydration to give you this Michael acceptor. So, the powerful combination of a transformation as well as Functional Group keyed Skeletal disconnection we are using here to give you a very clear, clear full or idea that how this kind of compounds can be made.

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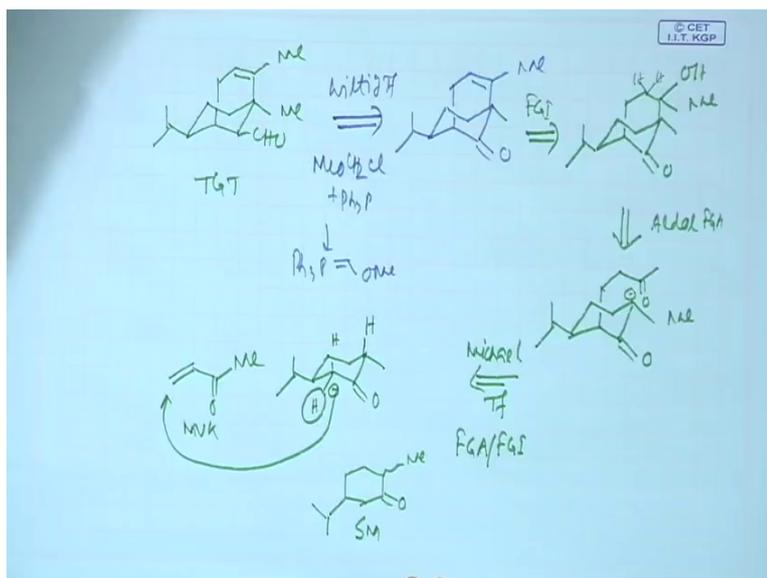
Let us see time permits to discuss another simple molecule which is basically nothing, but a complex carbocycle molecule and the structure is basically here. You trying to analyze this molecule as a functional group based keyed skeletal disconnection. We have drawn the three dimensional structure and if you see the initial skeleton was this one and then, you devise a retro where we said will be using a Wittig kind of reaction is a Wittig transformation.

We haven't discussed that how to do it? But if you remember earlier, we talked about this kind of disconnection you use mom chloride and triphenyl phosphine get the Wittig Ph 3 P double bond OMe, you can use it. We discussed in this retro key quiz.

So, you are basically here and then you do a very straightforward functional group based inter conversion, just by putting all the structures similar. And here, the olefinic unsaturation was thought to be created by elimination of this tertiary alcohol. Now as I said this is a basically keyed skeletal disconnection, we have to simplify the structures and how it can be related to a simple starting materials or now we are trying to figure it out or trying to close the gap. Now you will see its almost done.

So, here what you do we basically do a FGI that is my elimination? This is also similar we assume that this carbon ion will undergo Aldol reaction. So, it is a Aldol FGA, Aldol FGA or a Aldol FGI. Now trying to again simplify the things, we can say that if you have the starting material of these structures of this and you are having these methyl, vinyl, ketone you can basically do it. Now how? This compound is having 1 hydrogen here and 2 hydrogens here.

So, you can basically generate annotate depending on your reaction condition, you put a carbon ion here and this by an abstract use hydrogen. Now this carbon ion will attack in a Michael fashion. Michael fashion you can come here. Basically what are doing? Basically take the skeleton of the molecule and try to coded the simplified starting material. On this starting material is a monocyclohexon on derivative. So, generate the carbon ion try to react with methyl, vinyl, ketone. Then you get a 1 4 addition.

So, this is basically a Michael transformation, Michael Tf. You can say is FGA or FGI, because functional groups are addition or inter conversion. And then once this Michael addition was done, basically get 1 2 3 4 5, 1 5 dicarbonyl compound. And then you see,

this ketone in it's close proximity its having a carbon ion. So, which is basically ready for this Aldol dehydration.

Now, Aldol dehydration once it is done, you basically get this, tertiary alcohol. Tertiary alcohol now will be having only this hydrogen for elimination. Eventually this methyl the hydrogen, but that will give you the exocycle double bond, will get the endocycle double bond here, which is much more stabilized. So, you have this tertiary alcohol which in undergo elimination to give you this product; you simplified starting materials like methyl, vinyl, ketone and you can try to write it out the starting material which is again simple that methyl and a isopropyl group.

So, this is the starting material which you can use in combination and then, you can get a target molecule something like this. This functional group keyed skeleton approaches what we have seen? We have seen that if we have a core skeleton of the giving target you try to disconnect the skeleton, entire skeleton. The starting material was given to you that is fine.

Then you try to correlate the skeleton of the starting material with the target molecule and see what are the connecting transformations will lead you to the given target. And definitely you have to start with a visual communication with a given target and how you can correlate the target molecule with a given structure.

So, 2 examples we have shown the first oxne is a bit complex bit complex, but eventually that will give you a very simple chemical logic come to a simplified starting material. We did not use any high five transformation any sophisticated transformation we use simple carbon ion chemistry. Here also use the simple transformation only thing we used a wittig reaction or to convert this carbonyl to aldehyde, because if you use a Wittig and Hydroboration you have a another double bond here.

So, hydroboration bond you cannot use. So, you have to the direct wittig reaction and then, you try to formulate the chemical logic which is pretty much obvious, you do a Aldol kind of transformation here, simplified it, do a Michael with this starting material and the methyl, vinyl, ketone.

So, will basically continue our discussion throughout this Functional Group based approaches and try to remember these 6 topics will be covering one after another and

eventually, this Transformation base strategies, Functional Group base strategies and this Starting Material base strategy are overlapping things, will sometimes things should be overlapped, but nevertheless that will give you a combined effort to learn many things.

Sometimes if you use some unknown transformation will try to explore it. If the transformations are very common we are not going to discuss it in this forum. So, till then, have a good time and try to study all these lecture notes; go through textbook, go through scene archives and have a good time. Bye.