A Study Guide in Organic Retrosynthesis: Problem Solving Approach
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Lecture – 07
Tf/SM/Fg based approaches to solve some basic problems

So, welcome back. We will basically continuing the discussion on transformation based strategies. And as we said this transformation based strategies, functional group based strategies and starting material based strategies are similar. So, we will try to overlap all the three strategies together. And we are basically continuing the transformation based strategies, but some of the strategies I mean the transformation based strategies will be also overlapped with starting material as well as.

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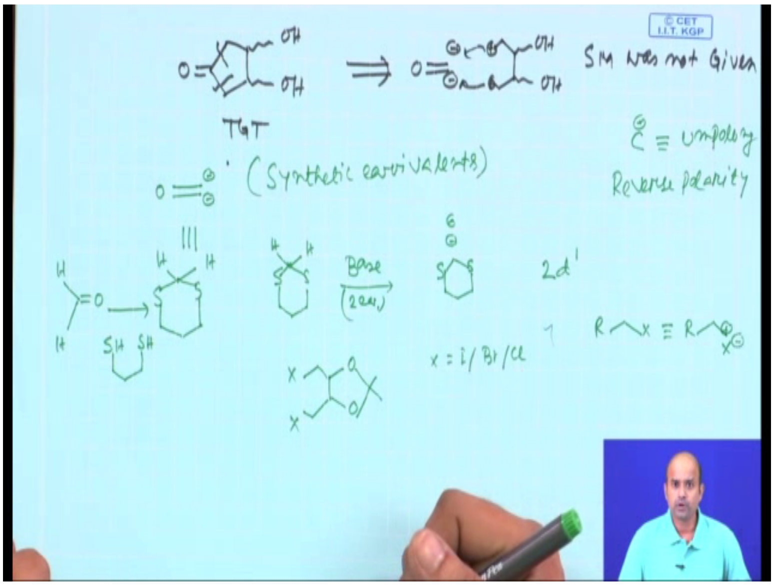

The next problem which is basically I am initially trying to draw the target molecule is it dihydroxy based cyclopentanone, this is the target molecule. I have not given the stereo chemistry here, this hydroxy can be up, can be down, but eventually that is not our main concern here. So, the target molecules was given to you. The starting material I have not given, starting material was not given. So, as I am discussing about the transformation best strategies, normally we try to avoid to give the starting material fine. Now, eventually if you try to do a disconnection for this molecule, we will do a disconnection something like this and let us we will try to figure it out.

When putting two negative charge here by doing a disconnection something like here by doing a disconnection something like here. And then you say that if you have a compound something like this as a intermediate as a CH 2 plus and CH 2 plus means that if you are having a positive charge at both the end, it can be connected to this double negative charge basis. And the main thing is you have to think about some species which will give you a doubly charge negative carbonyl compound.

This species we will be covering in detail when we talk about synthetic equivalents. Synthetic equivalents are basically nothing they are basically charge species, imaginary species which is in reality may not exist, but we have to think about that those species are where the charge have been given. And reality we all know that carbon negative charge seems to be the polarity has been reversed, and this species are normally named as umpolung species where the usual charge on carbon seems to be positive it has been reversed. It is called umpolung as a Greek name or reverse polarity. We will try to explore how this kind of species will give you a suitable disconnection.

As I said this kind of species you in reality you would not get it. So, we have to think about some chemical compound which will yield you this compound or this species. This 1, 3-dithiane of formaldehyde. So, if you take a molecule of formaldehyde, formaldehyde is what is a this compound react with 1, 3-dithiane which is a thermal compound the aldehyde will react and will give a 1, 3-dithiane species. Now, 1, 3-dithiane as a unique property, if you take this 1, 3-dithiane and react with base this hydrogen are extremely acidic, it reacts with base two equivalent and normally that will basically give you a double anion here.

Later we say that this kind of species are named as 2 d 1 species, d 1 d stands for donor and two means it is a doubly donor and one stands for one carbon is basically one carbon you need one carbon. So, based on this retro, you can think about the left hand side will be this one coming come one here dithiane. Now, coming to the right hand side, if you have a compound something like this x stands for iodo or bromo or even chloro means that this CH 2 Cl any alkyl halides you can potentially write it like R CH 2 plus and x minus. So, means that this iodo species are potentially viewed as a electrophile and this is a neutrophile.

Now, why this three alcohols have been protect it, because sometimes you need to do a protection group chemistry because alcohols are normally not very good functional group to keep as intact. Based on the region conditions like acidic condition of basic conditions, they may not stable. So, we have to have starting material something like this, we will now figure it out how the starting materials can be prepared.

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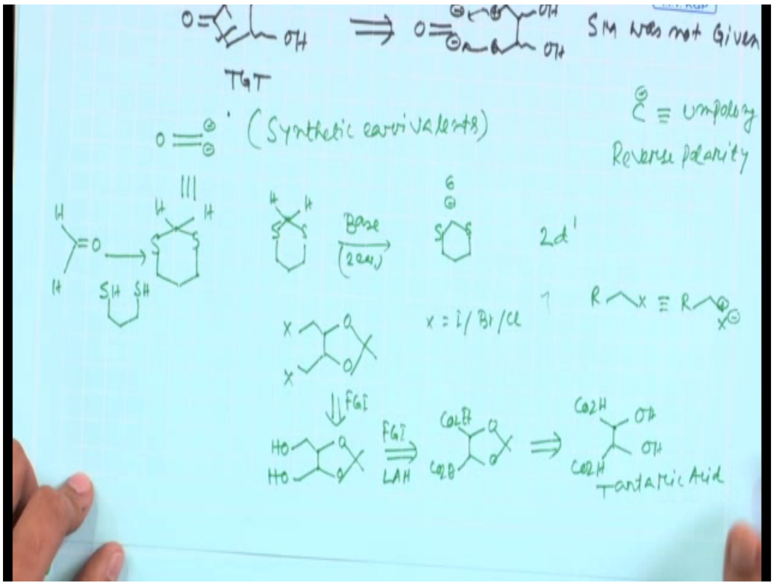

So, if you have a compound like this you can do a both the alcohol we can convert to corresponding iodo. And now do a again retro this retro is basically based on functional group inter conversion, where both the iodo has been converted to corresponding iodo both the alcohols. And now this retro is a if you have diester, you can do a functional group interconversion through normal reduction like lithium aluminum hydride. And now you see that this starting material is basically a simplified starting material, which is a very cheap starting material name is tartaric acid. It is a commercially available and very cheap starting material raw fixed stock.

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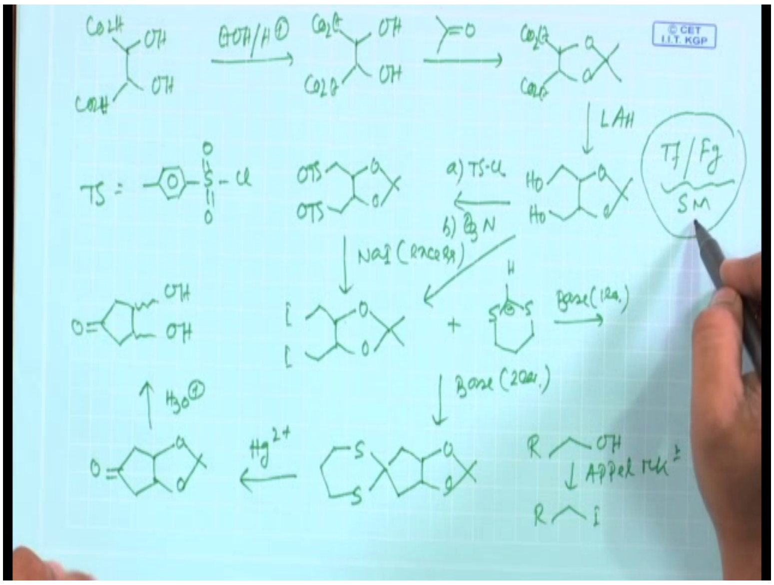

So, if you would now try to do the forward synthesis, we start with tartaric acid. Let us say we start with tartaric acid first these are the ester acid groups. So, do a esterification reaction double esterification and that will give you Co 2 E t Co 2 E t. And you have a free alcohols the free alcohols need to be protected. If it is possible you can do a production in a single step for both the alcohol yeah this is a possible, you treat the compound is acetone. Now, acetone will react to the free alcohols will give a compound named as acetonide is a basically a ketone formation. So, your ester part remain same.

Now, you convert it to LAH, the corresponding diol. So, we will basically get this things. Now, our sequence demands that both the free alcohols, they need to convert to corresponding iodo. Now, that you can do it by several ways, I can initially doing it a multistep way, you convert the corresponding alcohol to corresponding tosyl, tosylate by reactionate tosyl chloride, and you need a base like triethylamine. So, what will get you get a ditosylate OTS OTS. What is TS, TS basically stands for this is a tosyl chloride paramythia sulphur chloride.

So, you OH attacks here and give you OTS. Now, what is it good living room as you know. So, now, threat this OTS with sodium iodide excess will give it to you the corresponding diodo species, this diodo species now basically acting as a double electrophile. Now, you react with your 1, 3-dithiane you can do a stepwise reaction because you need to react with two electrophiles subject to base first one equivalent. So, it will be abstract one of the hydrogen here to give you a carbonyl. Now, one of this iodo will attack here. Next step you replace another hydrogen by another equivalent of base react with another iodo.

So, finally, if you treat with two equivalent of base as I said two equivalent of base and treat this things with this iodo, what will get you basically get this part will remain same get this compound. Now, you need to remove this dithiane which is normally done with Hg 2 plus a mercury treatment, and then you will get back to your original ketone which is required. And finally, you remove this hydroxy protection by treating with aqueous acidic workup you will get the target molecule with this free OH. So, you see the entire transformation is basically based on a umpolung alkylation.

Now, I said umpolung means reverse polarity will be discussing this umpolung in detail when you talk about synthetic equivalence. Now, see the entire forward pathway, start with tartaric acid, we will first do the double esterification this free acid, then you react with esters with lithium aluminum hydride. And eventually the free alcohol need to be protected as acetonide. You are here then you do a double displacement OH 2 tosylate followed by sodium (Refer Time: 12:12) give the diodo. Now, you can directly do a one step transformation from alcohol to iodo. This transformation if you are not familiar is fine, but you can directly do the like this kind of reactions, you can transfer directly alcohol to a corresponding iodo or any highlights species by reaction named as appel reaction.

Now, appel reaction if you are not familiar is fine, if you are familiar is also. Now, if you are not familiar go to the scene syc-archive website to exactly know, what is the reagent condition, but eventually will be discussing it. And once you make this double iodo, you react with this 1, 3-dithiane of formaldehyde stepwise that two hydrogen need to be abstracted you generate the doubly charge species and react with these double electrophile to get you the final product. And then basically you need to be protect this (Refer Time: 13:17) production group.

Now, eventually this is a nice demonstration of transformation based approach as well as functional group based approach. And now if I give you the starting material tartaric acid, this whole strategy can be a combination of transformation based approach, functional group based approach as well as starting material based approach. That is why

I say the both the three approaches of the initial three approaches transformation, functional group and starting material can be combined in a single operation that is why I will be discussing all these three strategies together.

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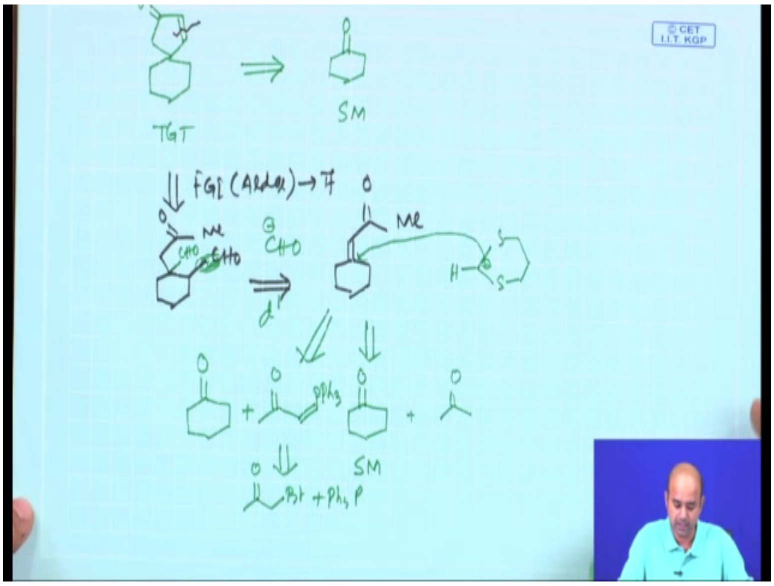

Let us talk about a very simple target molecule. The target molecule is having the structure is a spirocycle compound is a spirocycle compound. Now, this spirocycle for the sake of simplicity here we are discussing transformation based approach is fine, but for your better understanding, I have given you the starting material also. I said you have to make this molecule starting from a cyclohexanone, this is your target molecule and your starting materials. As I said all the three transformation base static and functional group based and starting material based can be combined together.

Let see how it works. So, initial target was this one. Now, if you see this molecule having alpha beta unsaturated ketone part here. So, we will do a retro here. And then you will see that a simple function of inter conversion will give you this particular compound. See if you have a aldehyde, you can do intramolecular aldol here aldol dehydration. So, this basically the transformation is aldol. So, this is the transformation we are talking about fine. And then you basically need to make this compound. Now, this compound you can make by numerous ways, but one of the ways I will be trying to give it to you if you have something like this. We said is basically this structures will be wrong actually the aldehyde should be here is a spirocycle compounds. So, aldehyde should be here.

Now, next disconnection what we said if you having some species which is a CH O minus, CH O minus just now we talked about is a umpolung species. We say d 1 species d 1 species means it can donate, and one means stands for a single carbon. Now, if you a alpha beta unsaturated ketone which is michael acceptor and remember last discussion if you have a species something like this you can do a michael directly here come to this compound. There are other ways also we can do it, but fine this is simple one and then this starting material you have to correlate with it comes from a cyclohexanone which is starting material given to you. The cyclohexanone you have to make a this kind of compound is a very straight forward, you can do it by a sample aldol reaction also you can do, you can take a acetone do a aldol here, but eventually that path way might lead you some mixture of compound because acetone can undergo self aldol reaction something like that.

But if you do a other pathway, so if you can follow other pathways there are better ways. So, take a starting material cyclohexanone and then if you react with something like this, I said a you do a Wittig reaction you do Wittig reaction. Now, these Wittig elite can essentially be generated from a mono bromo acetone and triphenyl phosphine will give you wittig elite. So, this Wittig transformation you can do starting from this starting material, now let us go back to the forward synthesis.

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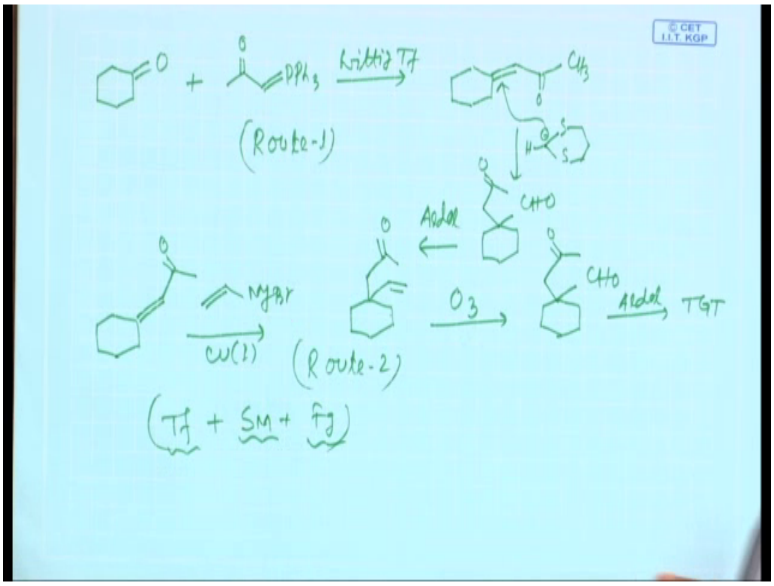

To start with the cyclohexanone react with this Wittig elite. So, this is the Wittig transformation which you must be aware of. This Wittig transformation will now give it to a the alpha beta unsaturated things, is a michael acceptor. Now, we will be the reacting this 1, 3-dithiane species where you picked up one hydrogen and generate a carbonyl, it is umpolung. Now, it will basically attack here, and then you remove this 1, 3-dithiane. So, then you will get and a CH O.

Now, basically what will give next is your aldol transformation, simple aldol and then you will be coming to the final product. This is the another way. Another you can do it. Let see you are having the cyclohexanone, you have already converted this to the corresponding compound the same compound. I said you have to introduce a aldehyde here. What will do we will try to do a vinylmagnesium bromide reaction in presence of copper to make it 1, 4. You see this compound undergoing this particular reaction and will give you a vinyl thing here. And what you need to do we need to convert this vinyl to aldehyde which is you already discuss you can do by (Refer Time: 20:05) or oxygen (Refer Time: 20:07) any of the oxygen (Refer Time: 20:09).

So, then you will be here, and will be aldehyde. So, it is a same compound can be retro synthetically disconnected by two different os, even you can think about many otherwise. Now, there are two routes as I said is a route one where you can do a umpolung nucleophilic addition to introduce the aldehyde which is require for the aldol reaction, you can also do a vinyl (Refer Time: 20:42) addition in 1, 4 fashion then you can do a be oxygen (Refer Time: 20:48). So, both the os are quite possible and depending as I said depending on a resources if your lab having vinyl grignard, you can do this one. If you lab is having umpolung, so proper resources at proper time is essential and you need to take care of those aspects when you design a pathway.

You see that what are the chemicals available in your lab then you design the pathway. So, both the path ways are quite useful, and ot will give you the target molecules through a aldol dehydration, you get the target molecule. So, now, if you go back to the entire pathway is basically a combination of a transformation based approach, a starting material based approach as well as functional group approach that is why we are discussing three pathways in a combinating fashion. Transformation means you are having a Wittig kind of reaction, you are having a michael based reaction starting material the cyclohexanone was giving to you.

So, now, you design based on the starting material what are the reactions available to cyclohexanone to reach to the target molecule. And then functional group as I said functional group means if you having alpha beta unsaturated ketone which is very familiar for michael type of a reaction. So, in that way you can basically choose your appropriate pathway. So, transformation, starting, material functional group all are in action here, so that basically gives you a nice demonstration that how a suitable target can be retro synthetically disconnected to give you the simplified starting materials from the simplified starting materials, you can now design your overall pathway.

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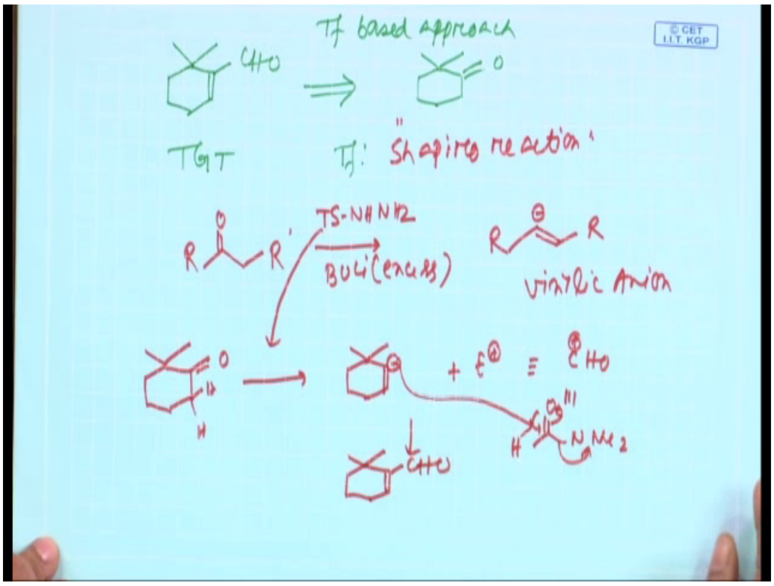

The next reaction is a single transformation based approach, but let us give the target. I said the target molecule is something like this; starting material was available to you I have given the starting material. And I said this is a single transformation based approach, this is a transformation based approach, it is a one step reaction. So, normally a one step reaction. Now, until and unless you are quite familiar with this transformation is difficult. The transformation what will be now targeting is named as Shapiro reaction. Now, Shapiro reaction is very useful reaction and if you see the original reaction of Shapiro reaction, you see the Shapiro reaction was based on a ketone which is having alpha hydrogen and it was reacted with tosyl hydrogen in presence of a excess base either butyl lithium or methyl lithium. And the initial intermediate which have been generated which was not isolated is a vinylic anion is a vinylic anion. So, the disconnection based on Shapiro transformation always think about you can generate a vinylic anion.

Now, our retro demands that if you have a starting material something like this is a ketone, and having alpha hydrogens here that is why the this alpha side we have blocked intentionally. Then you subject to this Shapiro reaction. Now, Shapiro reaction mechanism as I said you can go through it or in the starting material we will be finding it. Now, see the disconnection will be giving you a vinylic anion here. So, you have vinylic anion. Now, what you need to do you just need to react with some electrophile. So, what are the electrophiles, electrophiles demand that you need a cho plus electrophile means a electrophile should be a CHO plus is a normal priority it is not umpolung polarity. So, this species can be coming from a DMA or dimethyl form amide. So, what you do you put this reaction here and normal reaction of a carbonyl compound NMe 2 will go off and then you basically get a this CHO. So, this completes the synthesis and it is based on a single transformation which is very useful is named Shapiro reaction.

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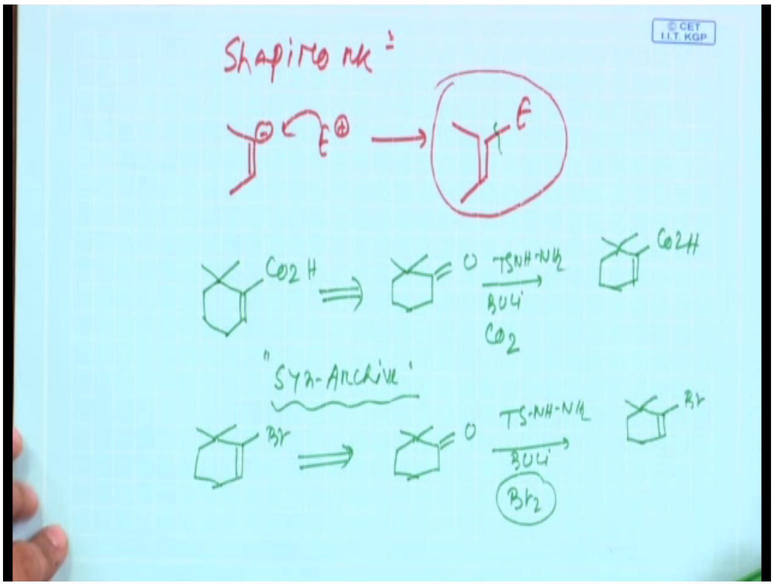

So, Shapiro reaction, if I now give a retro synthetically disconnection Shapiro reaction, you can say that Shapiro reaction normally will give you a vinylic anion. And this vinylic anion can be quenched to it suitable electrophile based on you. So, the final pathway is something like this. So, any possible intermediate or any possible target if it is having this kind of structure, you can disconnect like this, E stands for electrophile.

Let us having a similar kind of problem I said I want to make you this compound. So, you do Shapiro reaction by taking the same starting material the cyclohexanone based compound where one side alpha these are absent. So, subjected to tosyl hydrogen butyl lithium excess, there will give you the final species. And then the electrophile you can quench with it carbon dioxide that will basically give you the final product CO 2 H. The Shapiro reaction is a potentially very useful reaction and please I am referring all of you to go to the Syn-Archive website which was given to you in the last couple of weeks back the lecture have talked about Syn-Archive website. You can access the website you can go to the website and you can check the mechanism of Shapiro reaction. Shapiro reaction will be very useful for making this kind of compounds.

Even other compounds like if you have you need to make a vinylic bromide. So, what you do you take this starting material react with tosyl hydrogen butyl lithium. Now, what you need, you need a bromine as a electrophile. So, you can just react with simple molecular bromine and then finally, you can end it up with a vinylic bromide. So, Shapiro reaction basically gives you a vinylic functionalization when you have a ketone adjacent to some alpha hydrogen definitely otherwise if you have both the alpha hydrogens are free, then you have a retro chemically issues.

So, normally as Shapiro reaction is a very good disconnection of this kind of compounds and we will find the Shapiro reaction was one of the potential important reaction based on the Shapiro reaction many problems have been framed out in the GATE exam as well as NEET exam. So, Shapiro reaction is a potentially very useful reaction and will be finding the Shapiro reaction is the very useful reaction. So, we will try to give you more examples for transformation based approach in a subsequent weeks. So, please go through the Syn-Archive website, try to get a glimpse of Shapiro reaction and what exactly tells, and then Shapiro reaction based retro synthetic problems will be giving you in the assignments then you can solve those assignments and you can find it out how useful the Shapiro reaction could be.

So, we will see you in the next week, till then goodbye.