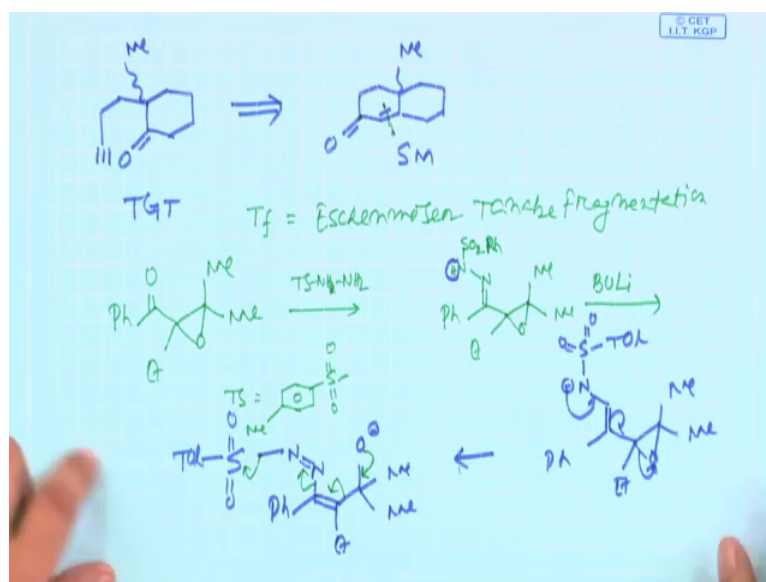


**A Study Guide in Organic Retrosynthesis: Problem Solving Approach**  
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**Lecture - 12**  
**Tf/Fg/SM Based strategies and its exploration**

Welcome back. So, we are basically discussing several strategies for a given target molecule, based on Transformation based on approach, Starting Material and Substitute based approach. Talked about many transformation; today, we are going to discuss about some unusual transformations.

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And but let us first formulate, what is the target structure given to you. I am saying I will give you a target molecular structure is this; this is basically Methyl group, the stereo centre was not specified. Having a CH<sub>2</sub>, CH<sub>2</sub> to CH<sub>2</sub> then, you are having a alkyne functionality; C H<sub>2</sub> CH<sub>2</sub> alkyne. This is a target molecule, the starting material was given to you, the starting material was given to you. And the starting material was a bicyclic compound, this one starting material.

Now, if you count the number of carbon for target molecules, 1 2 3 4 5 6 the rest of the parties remains same. So, this also 6 member. So, the only thing is from this starting material to target, this particular bond; not this basically the cleavage usually takes place here, takes place here. You get a carbon oxygen bonds and a alkyne was generated here;

remaining part remains same. Now here I will try to first talk about a reaction or a transformation which is named as Eschenmoser Tanabe Fragmentation. This is the key reaction which we will be using in our discussion for solving this problem.

Now, this is I am not sure whether all of you know this fragmentation, but it is very unique transformation probably it is not given in many text books, but we first discuss it. Now I will draw a structure and to explain, what exactly this reaction is this reaction is. This reaction is basically a fragmentation of epoxy toxil hydrozone. I am taking an epoxide something like this and then, I am reacting with a (Refer Time: 03:16) hydrogen. What is (Refer Time: 03:18) Hydrogen? This one (Refer Time: 03:21) group as all of us know is a para methyl S O<sub>2</sub> group, this group. And this is NH, NH<sub>2</sub> sorry NH NH<sub>2</sub>. So, initially this carbonyl group reacts with these to give you hydrogen. So, it gives a N NH S O<sub>2</sub> phenyl, this phenyl. Phenyl is basically para tolyl.

Then your rest part is similar methyl methyl all the methyl remain same and a ethyl. So, I have just taken epoxide substituted epoxide to show, how this reaction takes place. This is a fragmentation reaction. Now the condition is this compound is now next subjected to any base suitable base, ductile lithium. Now as you see this ductile lithium will try to abstract this particular hydrogen which seems to be very much acidic due to presence of this nitrogen hydrolysis sulphone group by electron withdrawing. So, fine.

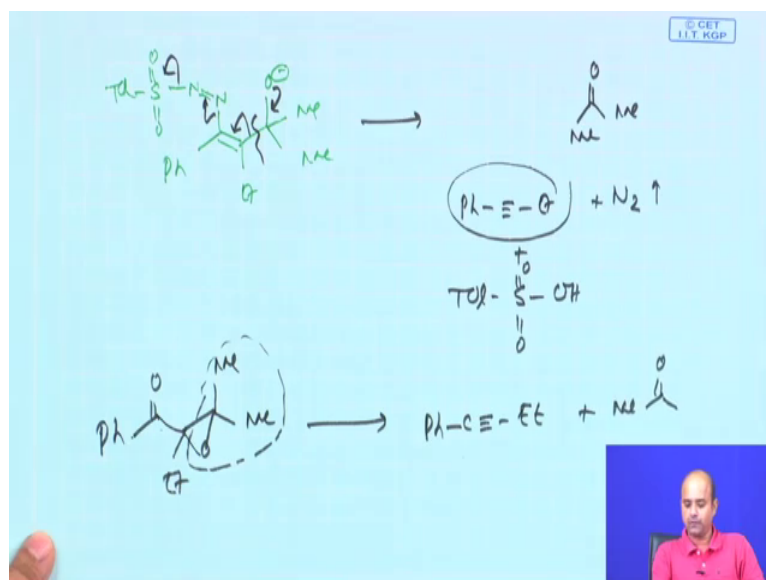
So, this O will be abstracted and you will then get this minus and this S double bond O double bond O and let's say tolyl it means 4 methyl phenyl; the remaining part is all similar. You have a ethyl group here. Here methyl methyl group here. So, after the initial base abstraction you are here. Now this nitrogen, this nitrogen on set idle; this nitrogen we will try to delocalises negative charge and if you see we have a electrophilic epoxide oxygen which can accepts this electron flow. So, flow will be something like this and this epoxide basically will be open, epoxide will be open and what essentially you will get? You will basically get a product; this double bond is now will be created here.

And then you will get this this ethyl group will now here and this epoxide as it is open up, we will get a O minus you get a methyl you get a methyl and then you will get a N double bond N; N double bond N from this and then you have this is S double bond O double bond O and tolyl group, S double bond O and tolyl group. So, this was the main thing.

Now, next step is very interesting; next step a guy just first write it was the next step is happening. As you are having a o minus at one end this o minus also is not a very stable species. So, what we try to do, we will try to like in fragment the molecule in this way. Now this sigma bond will be now has to break and put a triple bond here and then, these basically forces to give a nitrogen spaces to explain and then, this entire sulphonal things will also leave.

So, it is a very interesting reaction and then finally, what will be happen; we will again draw the entire structure as in the earlier intermediate.

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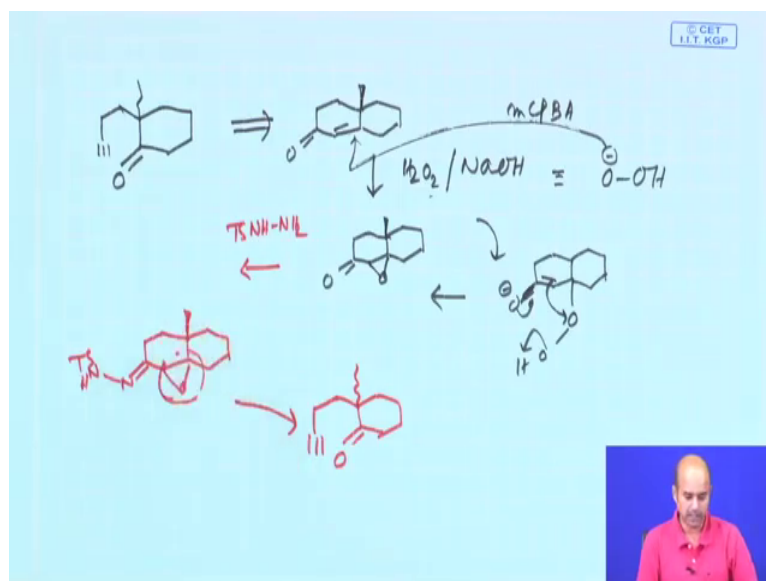


Then we explain how it takes place. This is your thing as I said the fragmentation takes place like this, like this, like this, like this and finally, what you get you basically get from this part, this bond is going to be chop down. You basically get acetone; acetone is this, you get acetone and then, you are getting a alkyne here. So, alkyne means you are basically getting E t and then we are getting a nitrogen as a gas.

And then you are also getting this toluene sulphonial thing probably as O H minus. So, the entire thing is a unique fragmentation reaction, which will basically give you a alkyne as a main compound. Now if you go back to the initial starting material; what we have initially drawn to explain the reaction mechanism, the starting materials this. After the fragmentation, what it gives? It basically gives a alkyne and acetone.

So, basically you get a P h c c E t, you get a triple bond here and these entire part is basically fragmented out as acetone. So, this was the main reaction; now in coming to present context, we have to see, what is the target molecule and what was the main thing? Now see the target molecule the target molecule, I am again drawing it from you, drawing it for you.

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The target molecule is basically a cyclohexanone based compound. This one the starting material was given to you a by cyclic ketone this one.

So, this reaction is nothing, you need to use a intra molecular version of eschenmoser fragmentation. So, first what you need to do? You need to prepare the epoxide. Now that is a very useful reaction, how you can make epoxide of an electron deficient bond. This bond is a linked with a carbonic compound. So, electron deficiency oxygen bond and m CPBA, the reagent for epoxidation of your olefin double bond is also a deficient.

So, how the electron deficient reagent can reactivate different olefin? So, principle is bit difficult. So, in this case you are using a nucleophilic oxidising agent and usually this is not a oxidizing agent; it works in a different way. We use hydrogen peroxide in sodium hydroxide; we are basically generating hydroperoxide anion and this hydroperoxide anion basically attacks in a Michael fashion here to give you all of you know it, but still I am explaining it, basically it will be come here.

Then, it comes here and basically you get a O minus. So, O minus back fires; then, these things comes attack here and you get the corresponding epoxide. Now we say epoxide, we need because we have to do a intra molecular Eschenmoser fragmentation.

Now, you subject this compound to react with profile hydrogen NH NH 2 and you will basically get a double bond N N T S, the epoxide is here. So, the mechanism basically now goes in similar way and only thing is you basically fragment this part out of this thing, out of this molecule and the fragmentation takes place to generate this ketone; generate this ketone and this end will be your alkyne, this end will be your alkyne.

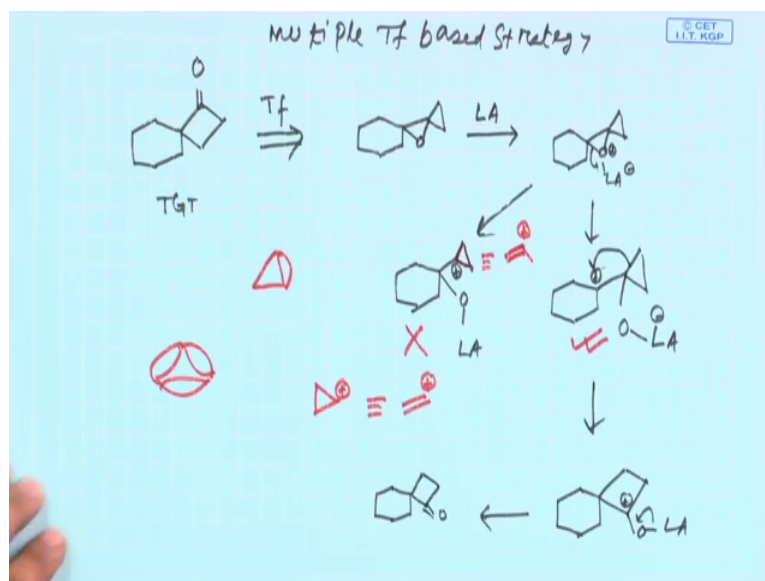
So, now you get it this ketone from this epoxide thing; epoxides as the electronics sink. It can receive the electron which was initially generated at this N H T S at this end, this methyl group remains here and then, you get this as a alkyne; this alkyne is the main product. So, until unless you no more this Eschenmoser fragmentation or Eschenmoser tunnel fragmentation; this whole problem will be very difficult to solve. That is what I am telling this, you need to know very interesting transformation.

And this Eschenmoser tunnel fragmentation is one of the transformations, which you can think of using it through a semi job similar kind of reaction, but the reactions are very compact. You take a ketone alpha, beta unsaturated ketone, make the corresponding epoxide through a nucleophilic mechanism.

As I said hydrogen peroxide N a O H and make the profile hydrogen and then, do the fragmentation that is that exactly what we do here.

So, we will from single transformation to multiple transformation that is basically we are doing.

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Now in the next problem, we will try to figure it out if a multiple transformation base strategies and how it solves one of the problem which we will be dealing next. The target molecule next, which I am giving is a this compound. I see this pyro cyclic compound; it is pyro cyclic compound. 6 member ring, 6 to the cyclobutanone; 6 and 4 member ring the target molecule.

Now, in principle you can solve it through many path ways. The transformation which we will be now pointed out, pointing out is basically known to you is basically known to you, the transformation is basically named as Meinwald rearrangement; Meinwald rearrangement. Now, how it happens? Probably all of you know, as I said if you have this kind of epoxide compound which is unsymmetrical the retro which we solved this arrangement puzzle by using a symmetrical epoxide. Now we say these epoxide were subjecting it to Lewis acid; it will have completely different pathway than the symmetrical epoxide, but initially the coordination is there.

The oxygen is now, basically it will provide that makes carbon oxygen bond to open it up and eventually the choice of carbonium ion formation it is very important, you might have a choice that this carbonium ion is forming as 1 case. In other case, you also have the possibility to form another carbonium ion by opening through this way; under this case you will basically having, forming these carbonium ion.

So, both the carbonium ion in principle can generate, but in reality this will be the most stable carbonium ion. Why? This secondary carbonium ion, this is all secondary, but this carbonium ion is basically having a cyclopropyl thing attach to it. Now cyclopropyl are basically equivalent to a vinylic systems because the due to the pie character in the cyclopropyl ring, in reality cyclo propane ring doesn't have a pie bond.

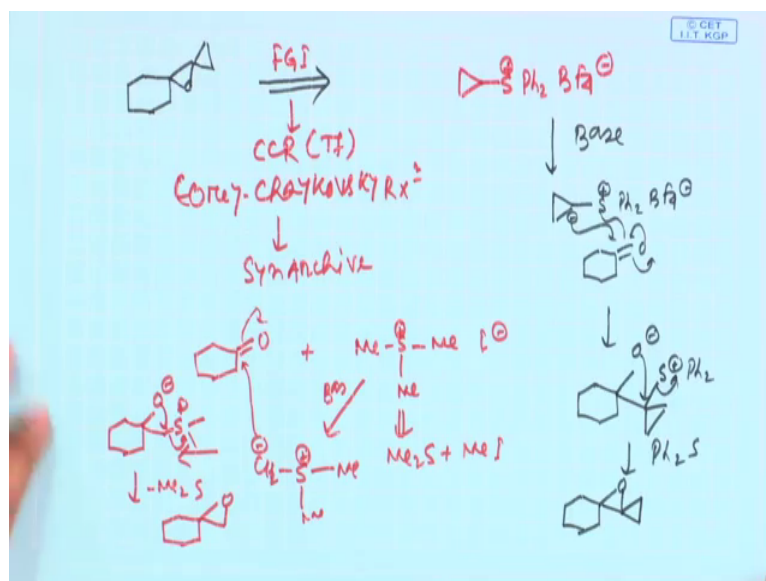
But cyclo propane, if you check the hybridisation is a very strange molecule. In reality it should have a 109 degree bond angle, a standard (Refer Time: 17:38) hydrogen demands, but cyclo prop propyl ring to make it a 3 carbon units, the bonds are normally kind of a deformed. It is basically always having a this kind of banana bond to give you this cyclopropane systems. This is a real cyclopropane picture and as why this cyclopropane a substantial pie character in it; it is like a vinylic system. That's why cyclopropyl carbonium ion is equivalent to vinyl carbonium ion which is absolutely not stable.

So, this carbonium ion won't be stable, you would be having this carbonium ion. So, find this carbonium ion we will now, try to rearrange within this molecular framework and would find a 1 to migration will be still takes place like the way Pinacole-Pinacolone arrangement takes place. So, this is one of the cyclopropyl will migrate; because the cyclopropyl is strain system, the strain releasing factor in the cyclopropyl system is a governing factor. Then once it migrates you are basically give you a 1 carbon extension.

And then you will find this things . So, now, the Lewis acid can go out from this reaction mixture and you will basically get this as a main product. So, this is basically nothing, but a systematic exposure of a Pinacole-Pinacolone type of rearrangement. Eventually, if you are not familiar with this Meinwald rearrangement, you can do it in different way. But our next process will be how to access this epoxide because this epoxide is also you require.

So, next our target will be to access this epoxide which is now required for the Meinwald rearrangement to access the target.

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Now accessing this epoxide will be using a reaction again for a single set of transformation is a FGI based reaction. Now, this transformation is named as Corey Chaykovsky Reaction or Corey Chaykovsky Transformation. And write it Corey, Corey is the famous Egypt Corey, the famous Egypt Corey Chaykovsky reaction. Now, what exactly this reaction is? This reaction very interesting reaction; Corey Chaykovsky reaction you can search in the Syn Archive.

Syn Archive you can just go and search in the Syn Archive, you will find some nice link. In reality this reaction is basically you take a carbonyl compound and react with this kind of sulphonium iodide, this sulphonium iodide can be generated by reacting with dimethyl sulphide  $\text{Me}_2\text{S}$  and methyl iodide. Now, actually what happen? If you would take this sulphonium iodide reacting with a base, you basically have an anion generated from one of these methyl.

And then, this methyl attached to this electrophilic carbonyl; it becomes  $\text{O}^-$ . Now this  $\text{O}^-$ , now basically initially get this,  $\text{O}^- \text{CH}_2\text{S}$  plus methyl methyl. Now this  $\text{O}^-$  now, attack intramolecular  $\text{S}_\text{N}2$  fashion to this carbon sulphur bond. To release this dimethyl sulphide and will give you an epoxide. This is the one way of epoxide synthesis through exploration of Corey Chaykovsky Reaction.

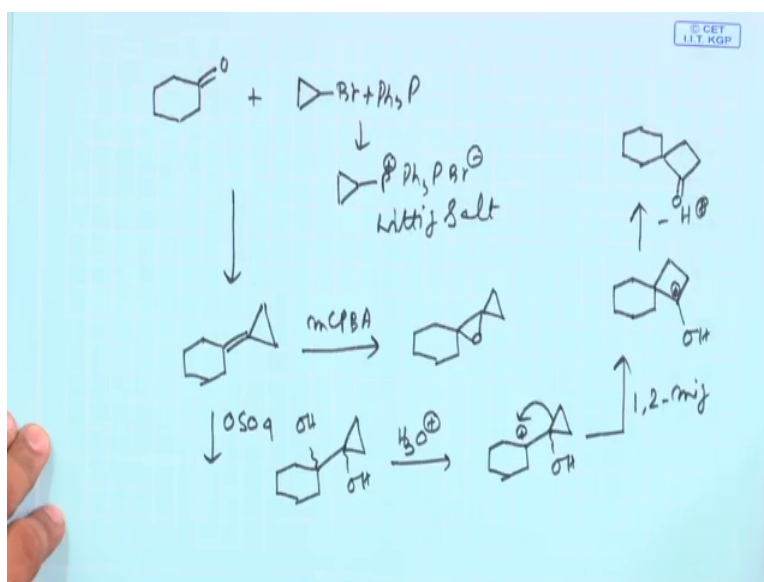
Now, here we will be using a similar kind of Corey Chaykovsky reaction; if you are having a sulphur based reagent, which is commercially available. Anyway, never the less



if you are not familiar with Corey Chaykovsky Reaction then, also you can do. So, you take this compound reacts with a base.

Now, this compound on reacting with base put a minus here S plus P h 2 B F 4 minus cyclohexanone is here. So, minus comes here, go this O minus when back fires it attach to the sulphur. To make it more simple, I will write it O minus then, is your cyclopropyl thing and then your S plus P h 2. So, now, this O minus attacks here and get rid of this Diphenyl sulphide; to get the corresponding epoxy spaces. Now this epoxy spaces you have to use it in this manually rearrangement. As I said eventually if you are not familiar with this Corey Chaykovsky Reaction you can still do it.

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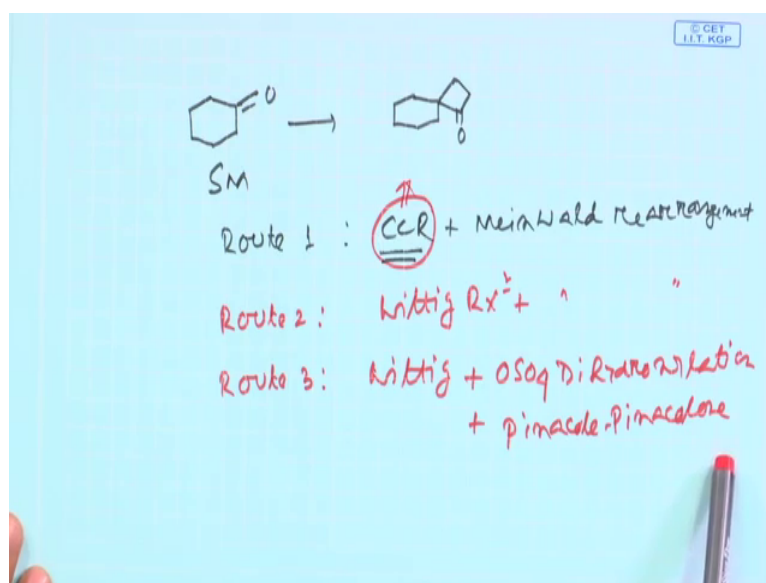


You can still do it, you take this cyclo hexyls thing, you can do a wittig reaction by taking this cyclopropyl bromide, reacting with these triphenylphosphine to get the corresponding P plus P h 3 B r minus wittig, wittig salt.

And next, you react this, Wittig salt, with this cyclohexanone to get the corresponding; this is very simple. Now this things, you can next react with mCPBA that will give you this epoxide. So, this is one way, you can get the epoxide. There are other ways you can if you do a dihydroxylation reaction that also will give the target molecule through a Pinacole-Pinacolone rearrangement.

So, now you do a Pinacole-Pinacolone rearrangement remember the retroquic we talked about Pinacole-Pinacolone rearrangement. So, first the most stable carbonium ion would be generated here. So, initially you will basically generate carbonium ion here, this O H and this now 1, 2-migration will takes place; this 1, 2-migration will basically takes place. This 1, 2-migration and this 1, 2-migration would basically give you a 4 member rings, ring expanded things with your O H and this positive. Now this will lose the H plus to give you the desired target molecule. So, now, you check entire path way there are independent o s we are explained.

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So, where we said, you have starting material is trying to recapitulate the whole thing; starting material the product which was desired is something like this.

So, I said Route 1; Route 1 we have talked about Corey Chaykovsky Reaction plus Meinwald rearrangement, that was one of the nice way and if you know both the reaction you can explore it. And in the way you learn the new reactions called Corey Chaykovsky Reaction, Corey Chaykovsky Reaction. Route 2, you do a Wittig reaction with this corresponding triphenylphosphine basically from the (Refer Time: 26:43) and then a Meinwald Rearrangement. Route 3, you do a Wittig; then, you do a Osmium tetroxide immediate DiHydroxylation; DiHydroxylation, lation and then you do a Pinacole-Pinacolone rearrangement; Pinacole-Pinacolone rearrangement.

So, in principle all these 3 pathway, you can basically try; but probably this reaction Corey Chaykovsky Reaction was not known to you. If you know the Corey Chaykovsky Reaction then, basically you can design this 3 pathway; if your supervisor or your or if your teacher ask this problem, you can basically design 3 different pathway provided that you know this Corey Chaykovsky Reaction.

If you do not know, do not worry; you pick up this Wittig reaction pathway or Wittig as well as (Refer Time: 27:49) pathway and then Pinacole-Pinacolone as I said the choice is yours, but you have to bend down many suitably, a logically driven approaches and out of that depending on your resources, depending on the steps, depending on the yields, you can choose the best possible path ways. So, that should be your main approach and next week also we will try to discuss further more strategies, more problems, more transformation.

Till then, have a good time. Goodbye.