Principles and Applications of Enolate Alkylation: A Unique Strategy for Construction of C-C (sp3 - sp3) bonds in asymmetric fashion

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Module - 02
Enolate alkylation of several carbonyl species
Lecture - 08
Seebach's SRS principle and related systems

Welcome back everyone. So, today we will be talking about this module 2; and mainly we will be trying to discuss couple of interesting things, where our main focus will be Enolate alkylation of several carbonyl species in asymmetric fashion. And, today we will be talking about Seebach's SRS principle and related system.

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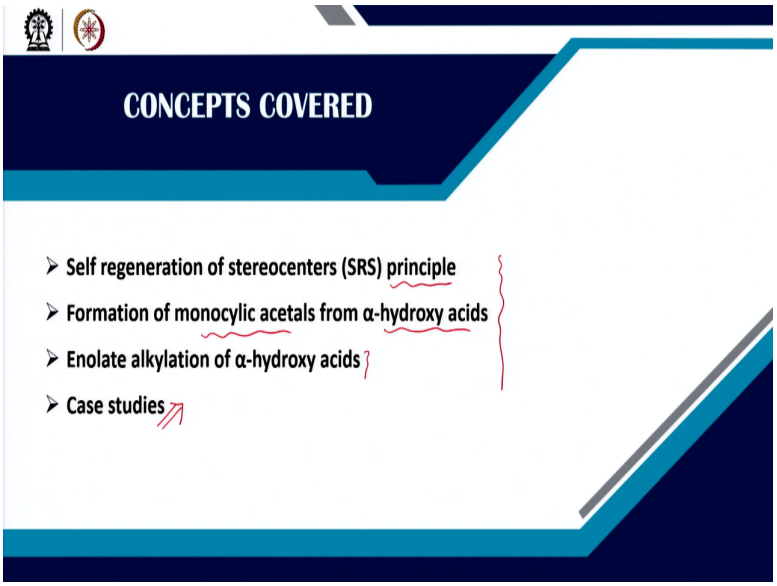

Main topics which will be covered today what is SRS system, its conceptual analysis and particular principles behind this. And, how you can generate different monocyclic acetals or dioxolanes from alpha hydroxy acid and how we can regenerate the stereo centers through enolate alkylation. And, mainly couple of case studies we will be covering and this work was mainly pioneered by Professor Dieter Seebach.

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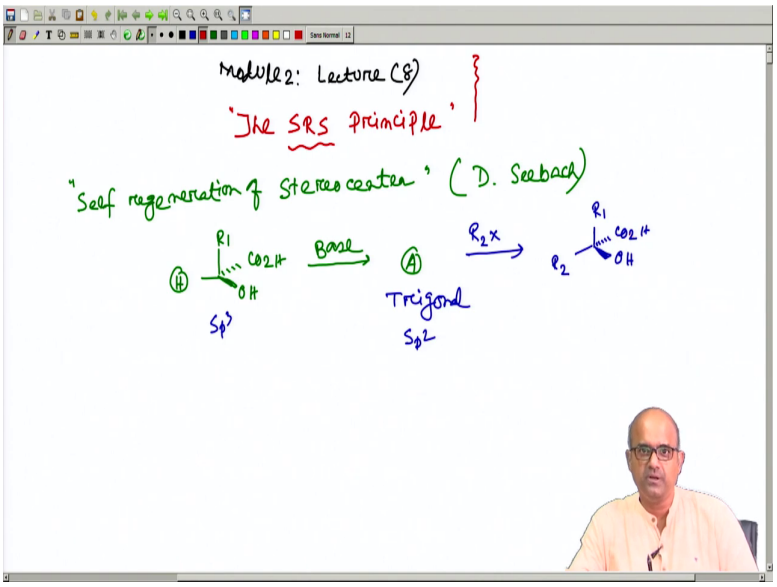

So, today we are going to talk about our module 2 …..but new lecture, lecture 8 and particularly in this lecture we will be talking about the SRS principle. SRS is a very a unique principle which actually stands for Self Regeneration of Stereo center. And, this is one of the very important concept in the enolate alkylation and this particular concept was used since long ago.

And, this was first coined by Professor Dieter Seebach and who actually pioneered in this concept. And, with this help of this particular concept what you can do, you actually can alkylate a couple of interesting compounds which already having a pre-existing chiral center. Let us, as a proof of concept, I am trying to talk about a very simple compound which is an alpha hydroxy acid.

Now, this alpha hydroxy acid the moment you try to generate the enolate this hydrogen will be abstracted. So, the stereo center will be lost ok and you basically get an intermediate which is trigonal. So, this trigonal intermediate means a flat sp2. So, from sp3, you get sp2 ok and eventually if you now try to react with an electrophile as a R2 x, you will find that you will definitely trying to get the alkylated product. But, what about the stereochemistry of this particular center?

Professor Seebach pointed out that this is possible whatever stereo center was the having in the parent compound that can be regenerated, that is what it is called self regeneration of stereo center. You see the original compound hydroxy was beta, CO2 is alpha in the parent

compound in the final compound, OH is beta, CO2 is alpha. Now, how to make this thing feasible?

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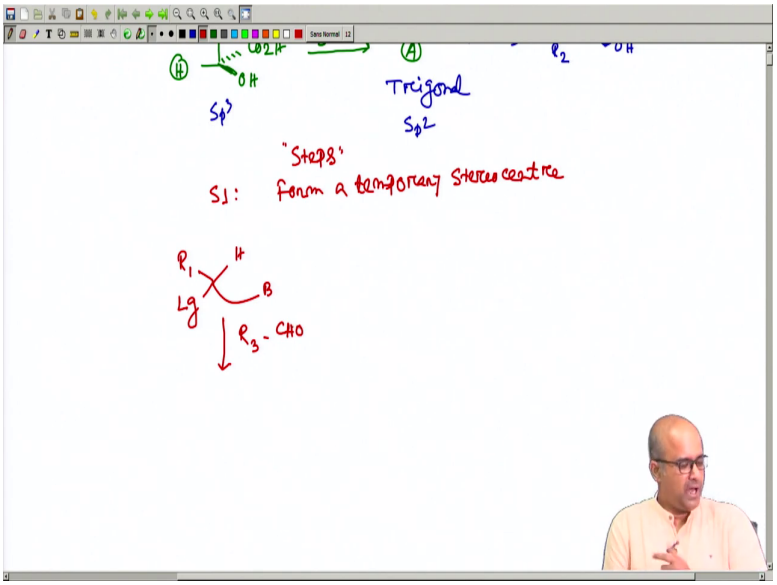

There are couple of steps in designing a ideal SRS system. What are the steps? Step 1, you first form a temporary stereo center and means that the initial compound having a stereo center which is going to be destroyed during the enolate generation. So, first you form a temporary stereo center ok.

Now, how to do that? Usually, what is happening you take the hydroxy acid and the hydroxy acid you can eventually try to write something like this, that you put a leaving group or something like this and then you have two different reacting components ok. Now, how to make this temporary stereo center? You actually trying to react with other reacting component and this is basically you can covalently react with an aldehyde which is having a bulky group this R3.

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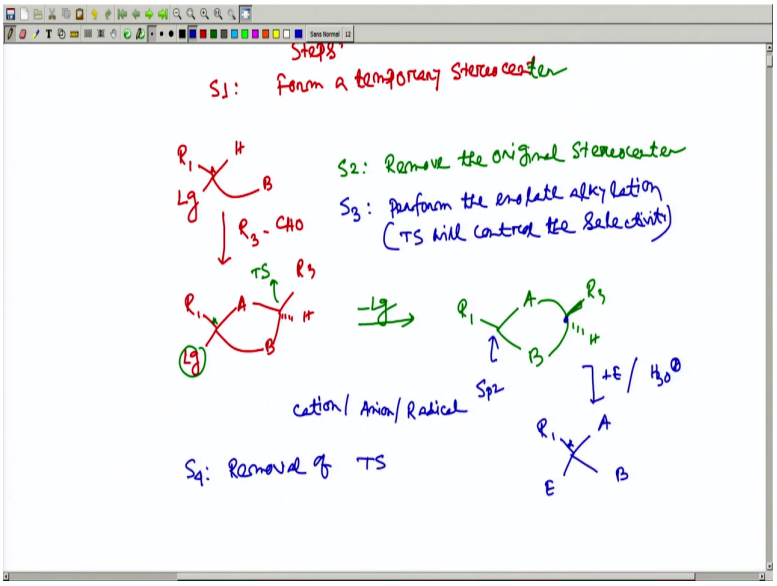

So, initially you now this; so, R1 means the existing stereo center your this. So, R1 with this Lg is the leaving group which is basically the hydrogen kind of thing. Now, you form a temporary stereo center. Now, how you can do it? This A and B are basically atom ok and then you can connect these things with a R3 and H. So, this is the original stereo center in the molecule.

Now, you are forming a temporary stereo center. So, this is called the temporary stereo center fine. Now step 2, step 2 remove the original stereo center because, you have to remove the original stereo center once you are abstracting the hydrogen to generate the enolate. So, this can be easily done and just you can remove these things as a to have a homogeneity in the spelling.

So, it is the significant moment means you are trying to remove the original stereocenter means you are trying to remove this Lg which is a hydrogen by a base. So, now, what we are trying to get? You basically get a trigonal system with A B, with a this and you have a well-defined temporary stereo center which you can create it ok. Now, this is now becoming a sp2, this now become a sp2.

Now, this sp2 could be an anion even could be a radical based center also, even a cation also; we did not write the cation. But, as we are interested on the anion alkylation; so, we will be talking about this thing. Now, step 3 what it does? Now, you perform the alkylation. In our case if you are trying to use the hydroxy acid, you can do the now the enolate alkylation.

Now, how the stereochemistry will be controlled? Now, see the temporary stereo center, which have been newly created is now the controlling factor.

So, now you can write that the temporary stereo center will control the selectivity, will control the selectivity and then step 4, step 4 is now basically you are trying to do the hydrolysis. So, in the step 4 you first attack the electrophile and then you do the hydrolysis H_3O^+. So, here what will be happening? Your R1 and you have a new carbon electrophile bond and then you basically create the original.

Now, if it happens that whatever stereo center you start with that remains same; that means, that the regeneration of stereo center has taken place. So, in the step 4 what we do? Step 4 is mainly you can say the removal of the temporary stereo center, removal of temporary stereo center. So, conceptually this was usually a pretty good idea and we will now try to explain the real case studies how it takes place ok.

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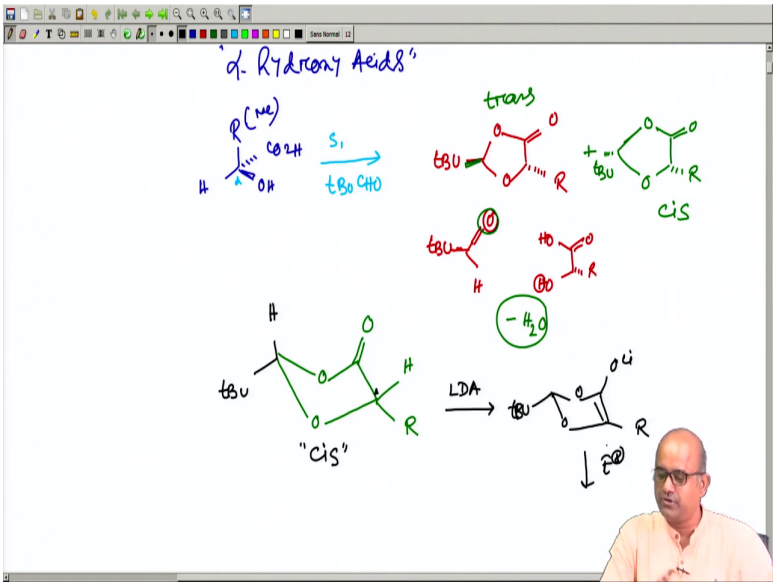

So, for example we now take a very well defined hydroxy acid and actually alpha hydroxy acids are the usual substrate for such SRS based alkylation. Now, let me write an alpha hydroxy acid. The most common example of alpha hydroxy acid probably all of you are familiar with lactic acid. So, let us say this could be a lactic acid, if R is a methyl group.

So, we take a lactic acid fine. Now, this is the original stereo center. Now, next step is step 1. What is the step 1? Step 1 is formation of a temporary stereo center and we are going to react

this compound with pivalaldehyde or tertiary butyl aldehyde. Now, what is going to happen? This pivalaldehyde actually react this is basically nothing, but a dehydration reaction and you get dioxolane type of compound; I will explain how, but the mechanism I may not explain because, is a very simple mechanism.

Now, if you see that this is the parent hydroxy acid R -OH -CO2H. So, one this O is coming from the carboxylic acid and this OH is the hydroxy aldehyde. So, tert butyl tertiary butyl group these things are basically condensed and you get the dehydration reaction. So, if you now try to write this as a tertiary butyl C double bond OH and this is your R, this is your H C double bond to OH, you can now eventually can see that this H ok.

And so, this OH ….H 2 and your ……a water will be simply going out and you get a dehydration reaction which eventually try to takes place in a stepwise, in a stepwise manner ok. Probably we need to for little bit just try to do it yeah, this hydrogen actually will be just there yeah; tert butyl this and this ok yeah. So, this oxygen, this hydrogen is there definitely this oxygen and this hydrogen and this hydrogen yeah. So, that basically gives you a water elimination.

Now, this kind of dioxolane compound you will eventually try to get a temporary stereo center. The point is it could be your trans or it could be your cis, cis means this center is fixed, the parent center. So, you could have a two different diastereomeric compound. Now, we will try to explain which one will be major which one will be minor. So, this will be your cis, this will be your trans. Now, normally such compounds you do have a well defined a conformational bias and these compounds are actually crystalline.

So, let me try to draw their three-dimensional structure which actually is very well documented in the literature and actually can be predicted. Now five-member ring, usually five-member rings are more of like envelope structure ok. So, now, this is the carbonyl compound and this is your initial structure means the R is below. So, R is pseudo equatorial fine. So, this is the parent structure or parent absolute configuration of the given molecule because you start with a enantiopure compound fine.

Now, in this case this if you get this compound, this is your cis compound ok. Now, you can see that as tert butyl is equatorial, you definitely have a cis control, cis control is much more.

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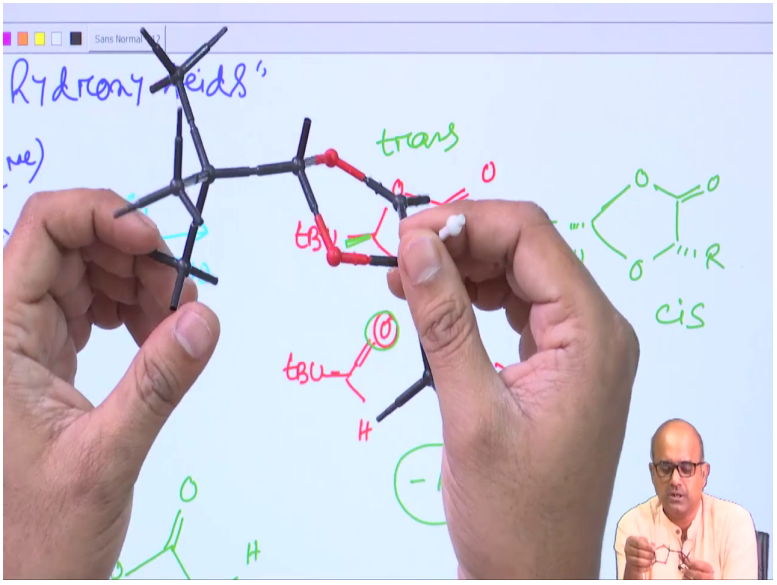

So, now, you can see three-dimensional structure of one such dioxolane which has been generated. And, you see that cis structure which seems to be thermodynamically much more preferable once you try to put the tertiary butyl group which is my left hand side and this methyl is my right hand side. They are basically cis to each other.

Now, cis seems to be much more preferred and this is your methyl, then you have a hydrogen, then you have a C double bond O, then you have oxygen and another oxygen. Now, let us see for clarity you remove this tertiary butyl group and try to put in an equatorial way, sorry axial way. Now, see the bulky tertiary butyl group was pretty bulky and this it could basically try to have a severe interaction with the ring.

So, that is what is not actually preferred always you, yeah if you try to draw in this way see tert butyl is kind of axial, pretty bulky group we try to put in axial way and this is now trans one. So, cis one is thermodynamically much more preferable and you always try to get this kind of structure. So, that gives you a pretty nice demonstration of this kind of cis dioxolane.

So, as we seen that cis dioxolane we just now saw this is the major one. So, now, if you try to generate the enolate from here. So, what we try to do? You treat with a base LDA and eventually the everything will remain as it is. You have this, you have this and then you get this corresponding metal enolate and you actually are trying to get a flat system ok.

Now, tertiary butyl being an equatorial one, next you are trying to have an electrophile which will be approaching to the enolate which will be approaching to the enolate. Now, see the moment you have this enolate alkylation, you can again try to draw the structure of the final product by keeping everything same.

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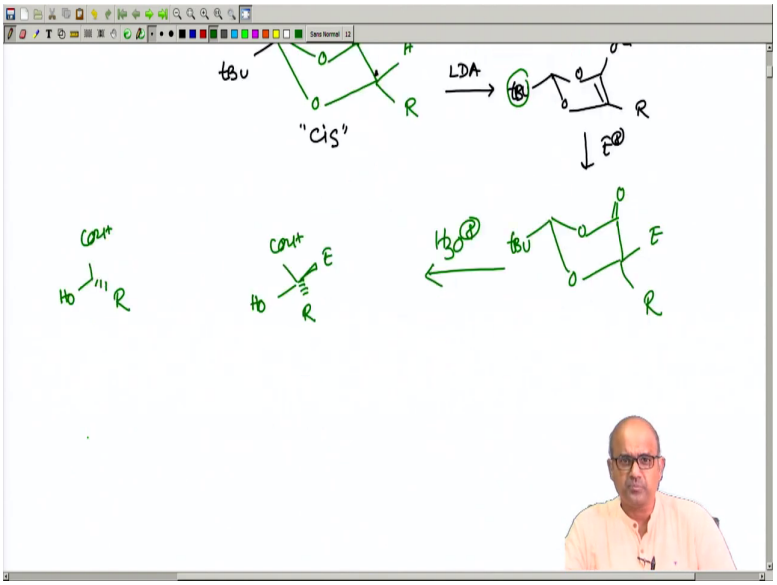

Your tert butyl or the temporary stereo center is there, the carbonyl is now; now you can see as this is blocking the below face, the electrophile has to be approached from the top face. So, your electrophile is here and your R is here. Now, see the original stereo center the R is below, R is below has been regenerated. Now, if you try to do a hydrolysis H_3O^+, now what you will get? You actually get the similar kind of structure, where you can just simply write this is the R, this is the E, this is the CO2H and this is the OH.

So, we actually get a quaternary stereo center. So, just the point is your initial compound which you have taken as a hydroxy acid whose structure is something like this. So, the original stereo center, where R is below has been regenerated by a temporary stereo center. Now, similar approach has been the extended by Professor Seebach and different other coworkers, we will now be trying to give you some case studies.

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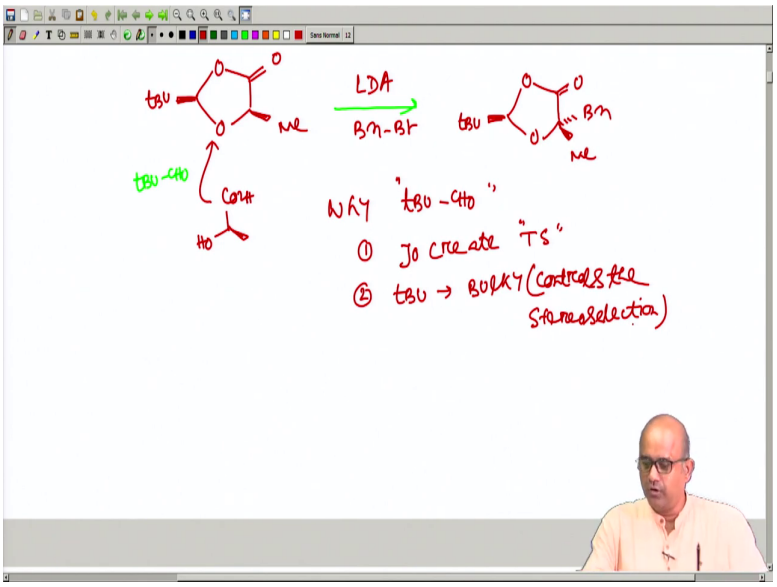

So, in one of the case studies where the initial dioxolane will be probably trying to draw the dioxolane in just normal two-dimensional way. And, as you have seen that the cis form was majority or is a major diastereomer you can see that if you can generate this compound; now how you can generate this compound?

From lactic acid, now lactic acid structure is methyl is a OH and CO2H. So, see lactic acid if you condensed with a pivalaldehyde or tBuCHO, you can actually generate this kind of cis dioxolane. Now, once you generate this cis dioxolane then your definitely your LDA will be there and you can switch over to the electrophile. Let us say you are using electrophile benzyl bromide.

Now, benzyl bromide, benzyl group will be approaching from the opposite to the tertiary butyl group. So, finally, what will be the stereochemistry of the final product? This tertiary butyl is above and C double bond O. So, methyl will be now this and benzyl will be this. So, original stereocenter everything remains same except the benzyl group is now coming from the below.

Now, you might be asking that why tert butyl was always chosen? Why tert butyl aldehyde? Why tert butyl CHO? Now, tert butyl CHO, the main role is actually step 1 to create a temporary stereo center ok, to create temporary stereo center and tert butyl being a pretty bulky group is sterically pretty bulky. So, tert butyl group being pretty bulky, it actually

controls the stereo selection. So, this was also the major factor for choosing tertiary butyl group as a main controlling factor.

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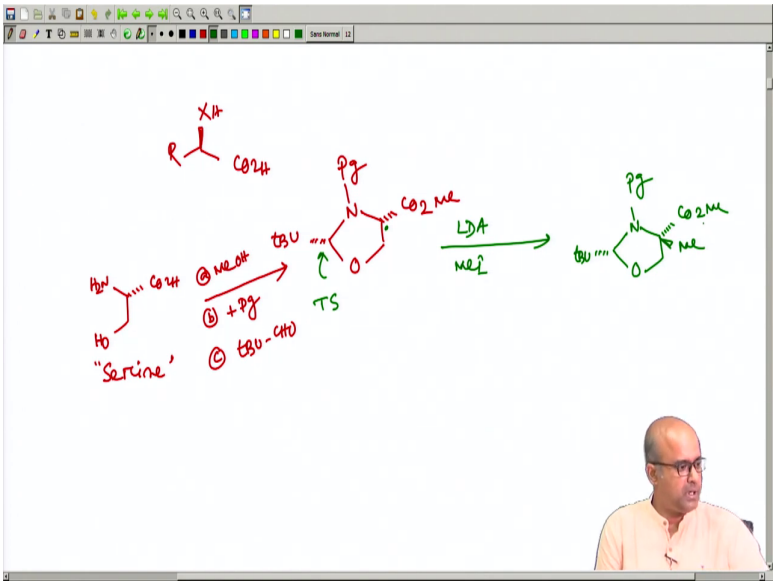

Now, a quick couple of structural survey you can actually do it and not only alpha hydroxy acid; you can eventually try to alkylate other acids also, like you can eventually you can write something like this XH. So, XH could be anything, it could be an amino acid, it could be thio acid something……...

So, let me try to take some other compounds which you which we have generated or which people have been generated. Now, this compound was one of the compound which was prepared from serine by using this method ok. Now, this is basically a protecting group here NPg and this is a tert butyl. How you can generate this compound? All of us know the structure of the amino acid whose name is serine.

Serine is this compound, H2N its serine, serine you can take either D isomer or L isomer. Take one enantiopure compound and what you are trying to do? First you protect the serine carboxylic acid group as its methyl ester. So, you can just treat with methanol and sulphuric acid or diazomethane or something like that then you protect the NH. So, NH should be protected ok. So, means you have a free NH, an NPg and then CH2 H and then you react with tert butyl CHO.

So, this is the original stereo center, this is your original stereo center and this one is your temporary stereo center ok. So, cis compound is generated. Now, what you try to do? You react this compound with LDA ok and then react with methyl iodide. And, then you what we will be expecting to get? You get O, this CO2Me will be there fine, tert butyl group is below. So, definitely methyl will be above NPg.

So, SRS was perfectly maintained because the initial stereocenter remains as it is; CO2H is below, CO2H is below and then this CO2Me is also below. So, this are the usual way to generate a stereo center for this kind of compound. Now, this is not only limited to monocyclic compound, its also can be applied to a bicyclic analog. We will next switch over to a bicyclic analog.

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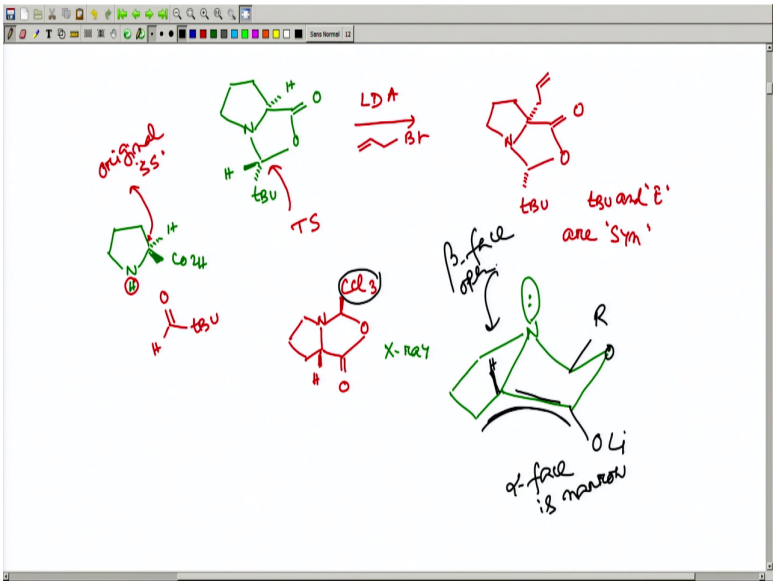

Let us talk about a well defined bicyclic analog and such a bicyclic analog has been actually being synthesized by condensation of a cyclic amino acid which all of us are familiar which is proline. Now, such compound was first generated. Now, how it been generated that we will first explain. So, initial you start with the amino acid which is proline, proline all of us are familiar. So, proline we have been taken.

So, hydrogen is below and this CO2H is above fine. Now, here this is the original stereo center of this compound, this is the original or existing stereo center ok S, Now, you react this compound with tertiary butyl aldehyde. A simple condensation with this NH group and this

CO2H group will basically takes part and now you see you have been created a temporary stereo center in this molecule ok.

Now, what Professor Seebach has been pointed out, that for such compound the explanation for this now we will be trying to react with this compound with a LDA and let us say allyl bromide ok. Now, actually it is in found that such reaction usually gives a selectivity, but the selectivity was actually not governed by the stereo center of the temporary ring only, means now temporary ring is tert butyl which is below ok.

And, this stereo center which has been also generated it is also cis to each other, but in the earlier case we found a different issue ok. Earlier case, we said that tert butyl as it is below the electrophile is coming from the above, but now here tert butyl and electrophile are seen to each other.

Now, this was a bit difficult to understand, but this you can actually understand through a similar kind of analysis. Now, first we give you a background analysis. This background analysis was actually done by Professor Seebach by using a similar kind of compound, where the X-ray structure of this compound was known.

Now, we do not have a clear cut picture how this compounds in their ground state how they actually behave. Now, Professor Seebach first prepare a compound something like this where a proline was condensed with trichloroacetaldehyde. And, this compound X-ray structure was reported. Now, the X-ray structure was reported and it has been found that the X-ray structure as the ring was kind of flat and the pivotal bond around nitrogen and hydrogen. So, hydrogen is above ok.

Now, remember the two in the last two classes we talked about a bicyclic ketones and its enolate generation. So, this nitrogen is basically pyramidalized and this hydrogen is kind of also above; that means, that this part and this part and this part and this part was more of like its tilted towards the bottom side ok. So, this kind of a very roughly drawing of such molecule, which probably you can explain in this way.

Now, in this case as probably you can take a CCl3 is there you can now put a group something like this as a R, which could be tertiary butyl also. You put oxygen here and the moment you generate the enolate, it will be OLi fine. And, now you can see that actually the

it was more or like the similar way, the bottom phase is squished ok and the top phase is more of like open. So, alkylation always occurs seen to the bulky group.

Similar thing happens here, here you have to just draw in opposite way as hydrogen is below. So, now, we can say that the alpha phase for this particular example is narrow or restricted, but the beta phase seems to be more open, beta phase seems to be open. So, in such way you can eventually try to make it a very effective generalization, that generalization basically coming from this picture.

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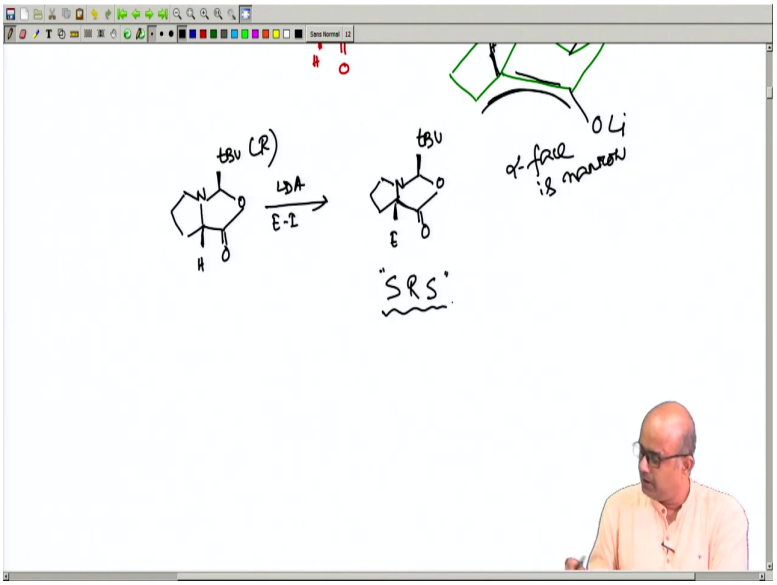

You take the corresponding bicyclic compound ok and then you put this tertiary butyl or other group, pretty bulky group in this way ok. And, then you can see that whatever stereocenter is there in the tertiary butyl group, you actually the alkylation will be trying to give you the final product.

Now the alkylation will be syn to the tertiary butyl group and only decisive factor is the ring stereo center ok. But, definitely the SRS principle is applicable here because whatever you started with, you started with a compound you can see, you start with a compound where this hydrogen is below; hydrogen is below.

So, but you can regenerate the same thing. So, this particular conceptual analysis of this SRS will basically continuing in the next class with more example and more case studies. And, we will try to have a closer look or closer analysis with the help of real systems.

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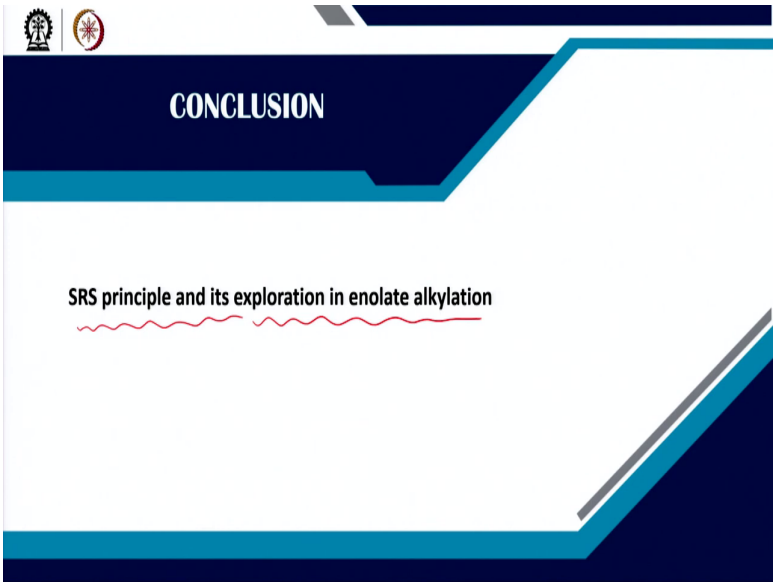

So, as a concluding remarks, we can say that SRS principle is one of the very well defined principle. And, through the concept of enolate alkylation, alpha hydroxy acid or alpha amino acids can be selectively alkylated with regeneration of the existing stereo center.

So, thank you. In the next coming classes we will be talking about more case studies on SRS principles, have a good time.