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 - 10
Seebach's SRS principle and related systems - III

So, welcome back students, so in continuation with the earlier lecture. Today we will be talking about lecture 10 mainly and in this module, module 2 we are basically discussing Enolate alkylation of several carbonyl species and mainly we started with Seebach's SRS system.

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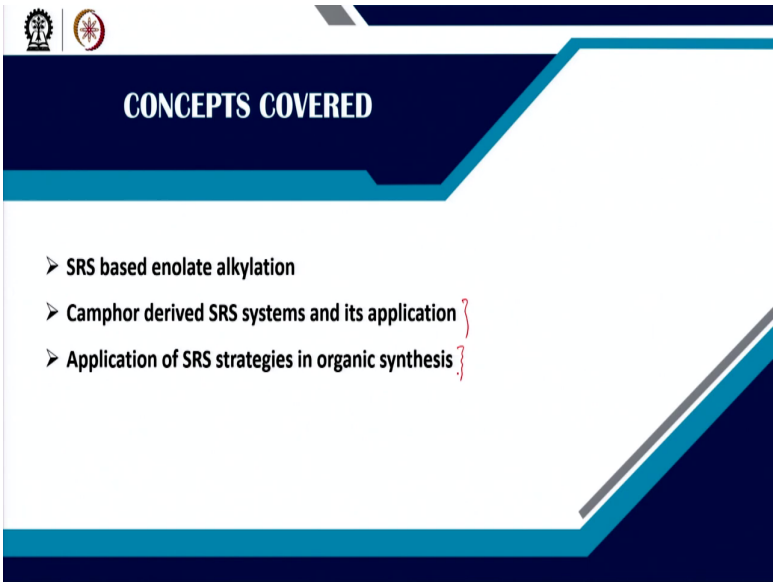

And today in this module in this lecture we will be trying to give you final touch of the SRS based enolate alkylation. And particularly rigid camphor derived SRS system will be trying discuss. And then few application of SRS based strategies in organic synthesis we will be talking about.

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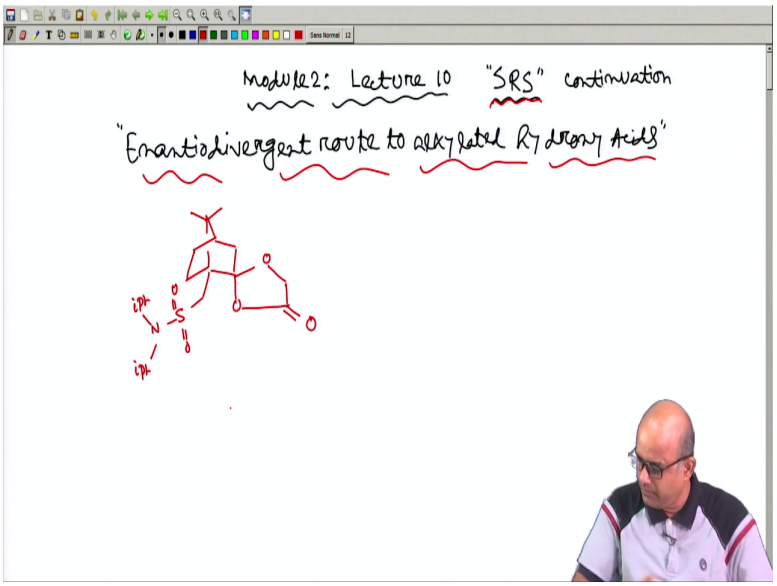

Welcome back students, so in continuation with our discussion today we will be talking about lecture 10 in module 2. And particularly we are discussing this SRS concept and today we will be talking about a little bit of different kind of system which is mainly based on a rigid camphor based framework.

And we will be starting with a new concept called enantiodivergent route to alkylated hydroxyl acid. Now enantiodivergent route means with the help of this SRS system you can basically access both the enantiomer of the target molecule. Now before going to the detail thing, let me try to draw the structure of the parent system,

Now this kind of parent system having a rigid camphor framework I will be later on explaining through the help of model. And this is the part where this type of ketone or lactone basically is framed ok. And now in this part you have a sulfonamide this kind of compounds can easily be prepared…… they are basically you can easily can prepare those.

So, this could be your compound one of the compound.

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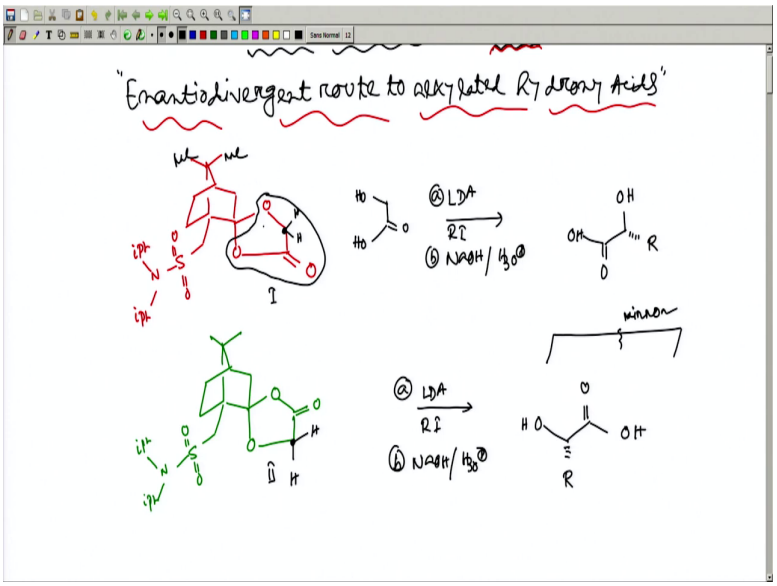

And in another compound, I will let me scroll down little bit which is another similar kind of camphor based framework, but the relative positioning of this thing the glycolic acid part. Now this part is usually your glycolic acid which we have explained the structure of glycolic acid in the earlier lecture, everything else remain similar ok iPr iPr.

So, this part actually is your glycolic acid ok glycolic acid. So, glycolic acid is what CH 2 OHC double bond OOH, it is a hydroxy acid. So now, see you take both the compound and write compound 1, compound 2 which is covalently attached with the camphor framework. Now you do the similar kind of reaction, so basically you treat with a base like LDA you treat with RI as the electrophile, same thing here.

Now what is the basic differences between compound A and compound 2? The basic difference is in this CH2 both the compounds has a CH2 part, but see the connectivity of the top CH2 and the bottom CH2 is different and actually this CH2s are enantiotopic in nature. Why? I will explain little bit later.

Now see both the compounds if you try to treat with LDA means you will be generating the enolate. Now enolate the face the top face seems to be blocked by this bridged methyl group ok, so and then after this attack. So, alkyl group always attack from the bottom face and then finally, if you do a hydrolysis simple base mediated hydrolysis followed by aqueous workup, what we will get I will just write this part.

The OH C double bond O, alkyl group comes from the below so this and this is your OH, so you get this enantiomer. Now in this case similar thing happens in this case also the electrophile will attack from the below that is absolutely no doubt ok, but how you can visualize. So, OH this part is there and then you see here is your R. So, R and this is your C double bond to OH.

Now these compounds are what? These compounds are basically enantiomer or mirror image isomer to each other; this is the mirror image isomer. So, this is the point that by using two different SRS based auxiliary system, now I will be coming to the working model.

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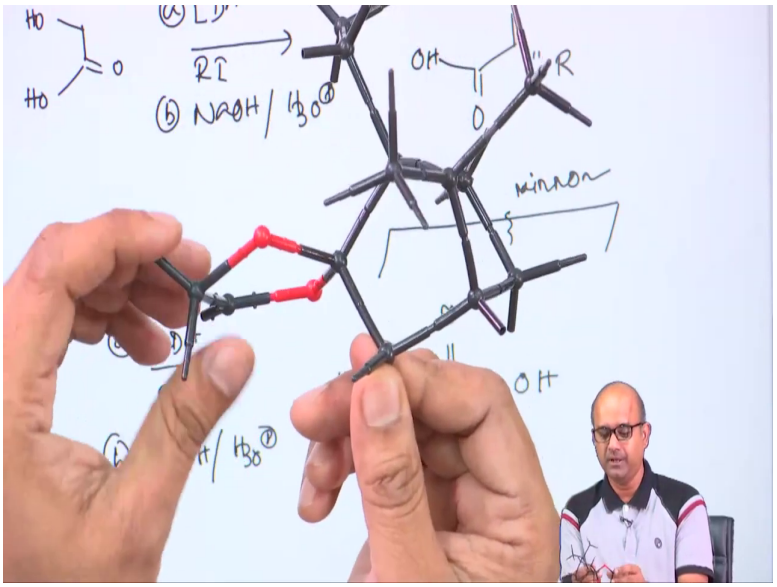

If you can see that this compound the core structure is the bridged rigid camphor unit and this is your two methyl which I have shown. Now this the way I have shown is a cyclohexane chair form of the camphor unit, this part is the sulphonate part S double bond to N. Now here is your oxygen CH2 CO and O.

So, this is basically which compound this is your top compound number one compound. So, you abstract any of this hydrogen generate the enolate and then you see the top face is blocked by this two bridge methyl. So, electrophile will attack from the bottom face of this enolate.

In the other one you can basically try to also reconstitute the thing you just do a different kind of connectivity and then that also you can simply explain that you get other enantiomer.

Now, it is very easy to say now we have to go to the really real working model how these compounds are prepared.

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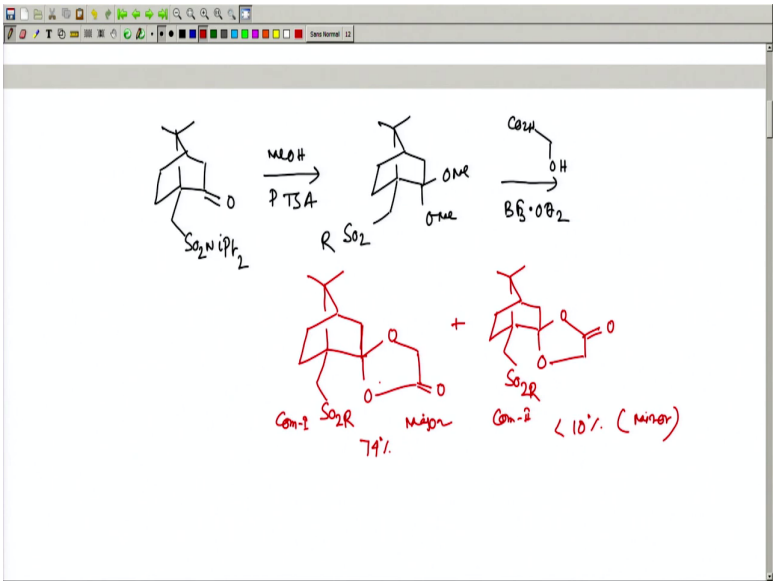

The starting material for preparation of this SRS derived glycolic acid derivative was this camphor derived double bond O CH2 So two N-iPr, this compound is commercially available even if you can make it in your lab. So, first you treat these compounds with methanol in camphor sulfonic acid or PTSA thing.

At the very beginning you actually get the carbonyl compound of camphor which forms the diacetal, this was simple the sulfonyl group we can just write So 2 R. Now here you treat this compound with glycolic acid which is what Co 2 H and then you have a CH2 OH the glycolic acid ok. And you treat with a little bit of Lewis acid BF3.OEt2 whole twice.

And then found that in this reaction mixture we will use a different colored pen, after this reaction is done you actually will end up with two of this auxiliary which in the last discussion. We have talked about let me try to draw the auxiliary, this is our compound one in the earlier slide.

You get this as a 74 percent ok plus you get the other one the compound 2 as a minor one you get as a very less amount and the amount is eventually pretty less, but you yes OCH 2 OCH2 yeah this will be this one. So, you actually get this compound less than 10 percent.

So, this one is your major product and this one is a minor product. Now such product distribution you can also explain that why you get this compound one as a major and compound two as a minor. But you will try to remember both the compounds will be useful for us both the compounds will be useful for us.

Now coming to the reaction mechanism what is usually happening here.

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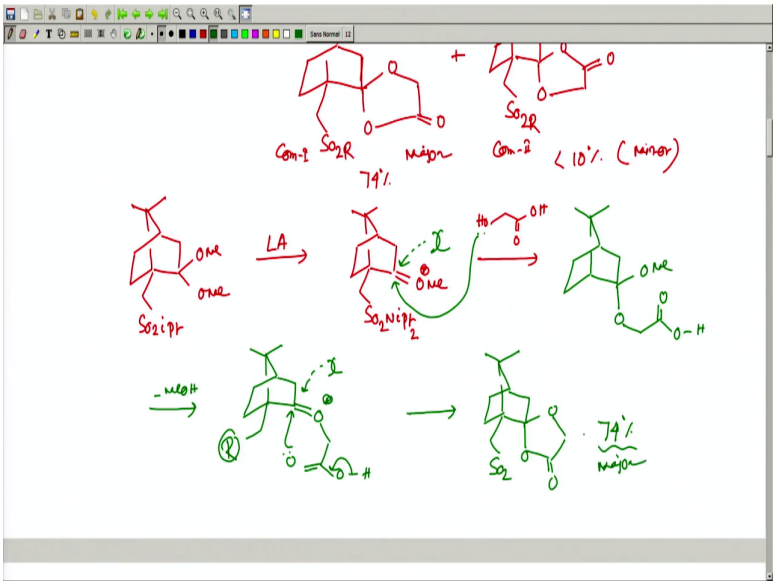

You first try to make the initial part the mechanism will be has to be little bit shorter version. So, I will be trying to be little bit just brief as I can. So, initially you have this OMe both the OMe, OMe. So, first with the BF3.OEt2, coordination or any Lewis acid what is going to be happening one of the methanol seems to be knock down this will be So 2 N isopropyl actually anyway I just try to you can make it N iPr for whole 2.

And then initially first you get one oxonium ion of this kind of thing ok. Now this oxonium ion once you treat later on the glycolic acid which is this structure. So, now, this glycolic acid this is basically coming to attack at this thing, because this is the less inner side because the top face. Now this compound can attack from either this face or this face, but this face seems to be blocked mainly due to these two gm dimethyl.

So, eventually what is going to happen? You now try to. So, first this OMe is there and initial attack took place from the hydroxy group thing O CH2 C double bond OOH. So, things are kind of pretty much settle down. Again the Lewis acid is still there, so another molecule of

methanol will be eliminated, the moment you get another molecule of methanol eliminated you get another oxonium ion.

And this oxonium ion, now we will be having again a structure this O plus this, this, this and this. Now see again the similar kind of attack will take place you can write it in this way like this with this thing again the attack will be from the below face, because the top face attack will be strictly hindered. And the sulfonyl part is there I just write it R big R.

Now see once this will be done this will be your major product or the compound one which we have already talked about So 2. And see there is the oxygen this is the oxygen and then you have your compound which is this will be your C double bond O CH2. So, this is the 74 percent product you get in the major one.

So, you can definitely explain that how this major isomer you are going to get.

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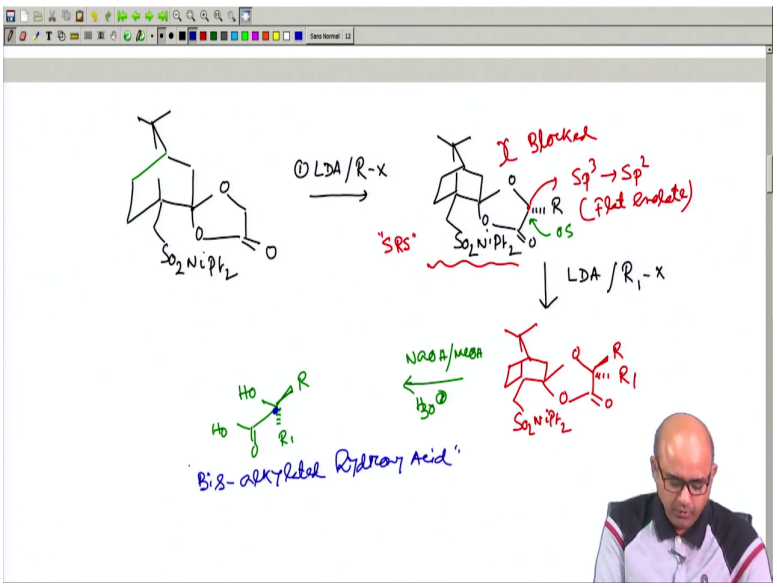

The moment you get the major and minor isomer your next part will be just doing the simple alkylation.

So, let me again come back to the alkylation part. So, try to draw the major compound which just now we prepared, but the minor compound also can be useful as we talked about the minor compound will give you other enantiomer. So, So 2 N iPr whole 2 and now you get this O…… O fine, so this is our major compound. And then you can basically try to use different.

So now, initial compound this is your permanent geo center though this is not a SRS at this point. But first you try to do then LDA and react with Rx one equivalent of LDA and Rx. And the stereochemistry of the product will be mainly governed by a bridge dimethyl group. So, it will be always attacking from the opposite of the bridge diameter elbow this is as simple as that.

So, it will get O O this this this this is the ketone and you see this will be the opposite again. You can do the hydrolysis, but if you do not do the hydrolysis let us say you do not do the hydrolysis. You can further you can do a second round of alkylation. So, LDA and then you treat another electrophile R 1 x.

Now again from this Sp3 after the enolate you basically get a trigonal Sp2 fine. So, means a flat enolate the flat enolate and; that means that basically once you have a flat enolate the electrophile will try to approach from the opposite face of this gem dimethyl group. So, top face attack is blocked, it is blocked it always.

Now, what will be you will be basically getting you will be getting this this this part remains as it is the structure remains as it is. Now see O, this O this this this double bond O. So now, the R will be forced to adapt the beta and R1 will be alpha. Now the second case this particular case will be a SRS principle, because this kind of things will be your SRS principle because the initial compound which you are having now it is an original stereo center.

And this the camphor part is your temporary stereo center ok. Now fine you can eventually try to do the hydrolysis part of the hydrolytic removal. So, NaOH was usually used NaOH methanolic solution followed by acidification with HCl or other things. And then what we get you get R 1 as this this is R and then your CO2H and this is OH.

So, you can see alkylated double alkylated hydroxy acid you can eventually get. So, you can actually create a bis alkylated hydroxy acid and those hydroxy acid could be quite useful as a synthetic intermediate.

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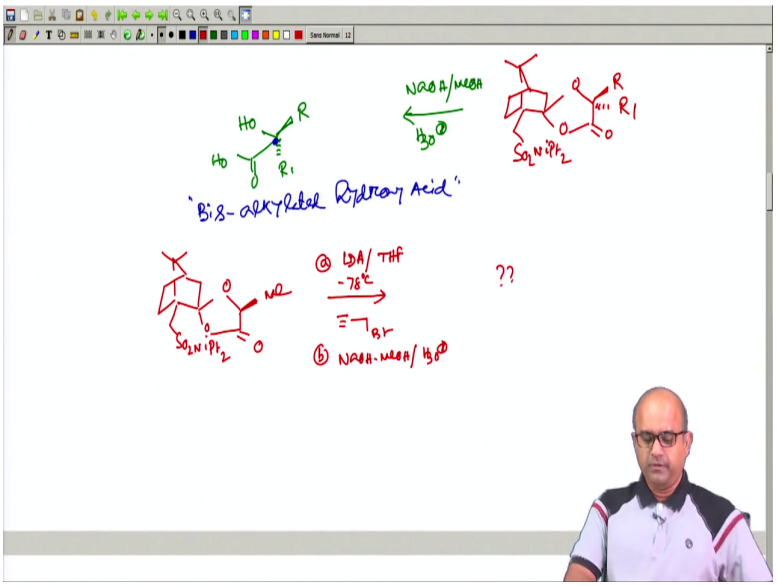

Now let me try to give you a small problem based on this one.

So, first I write the parent compound this this So 2 N ipr whole 2 and then let us say you do this this and then. So, already the methyl stereo center was given, it is a pure SRS system this is the original stereo center this is the temporary stereo center fine.

And what reaction conditions was given to you LDA THF solvent minus 78 degree centigrade and then they have used propargyl bromide as the electrophile. So, propargyle electrophile you can simply have used it and then it was used sodium hydroxide in methanolic solution and then you react with H_3O^+. So, predict the product.

So, it should be simple and you can eventually try to do it.

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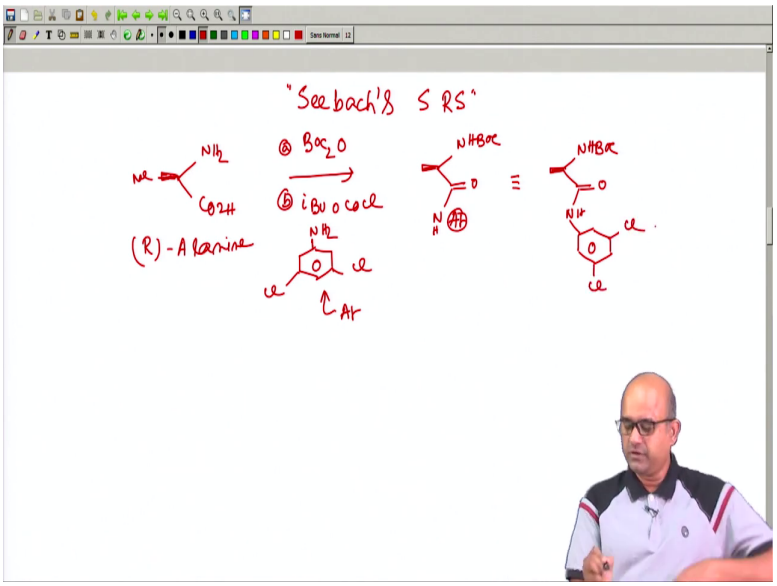

Now, let us go back to couple of other original SRS system which was again devised by professor Seebach.

So, Seebach's SRS we actually talked about simple oxygen containing system, but there is other system where amino acid can also be synthetically manipulated to use as a SRS precursor. So, first I will be using such system where a simple amino acid like alanine was used. Now this is a naturally occurring amino acids which is R alanine, I mean amino acid was used alanine.

Now, see with this series of reagent conditions I just try to use, I first protect this amine group as a Boc anhydride by Boc protection. And then I then use a isobutyl chloroformate to protect the another amine, not another amine you basically try to react with this 3, 5 this ok.

Let me first see what is happening and then isobutyl chloroformate was try to give you. And then we react to with this thing. So, initially what is happening this while explaining this NHBoc. So, one of the hydrogen is replaced by the Boc this carboxylic acid first gives you a mixed anhydride this is chloroformate and this this anhydride is reacted with this nucleophilic 3, 5 dichloroaniline.

So, what we will be now getting you're basically getting an amide thing with a aryl part. So, this is the aryl part this is the aryl part NH aryl. So, eventually the entire structure will be this

methyl NHBoc C double bond O NH and then you write the aromatic part which is the 3 and 5 Cl. So, you just abbreviate it is aromatic part ok.

Now, this compound just scroll down little bit.

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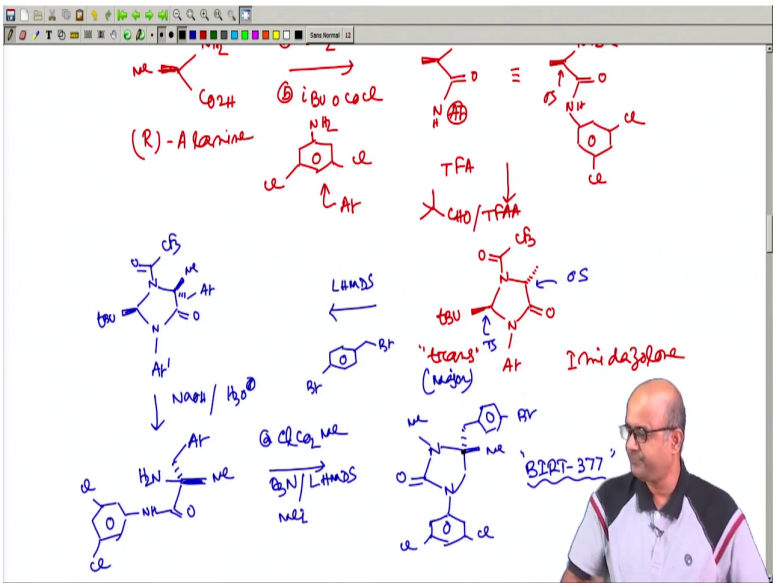

This compound was now reacted with trifluoroacetic acid followed by the original compound pivaldehyde was reacted.

Now, you will see that original stereo center is this ok and you have a temporary stereo center or transient stereo center which will be now generated. Now we will write this compound in this way. Now in the case of oxygen in the earlier part we have seen that this oxygen usually gives you a cis compound. Now here you can just try to write in this way this is the aryl part ok, this is the tertiary butyl part ok.

And this N it is usually N CO CF3, because how this is getting converted later on you react this molecule with trifluoroacetic anhydride. Now this kind of compound is named as imidazolonone or imidazolone. Now this imidazolone the major diastereomer was the trans one, we will explain it why this is trans one.

In case of oxygen it is cis, but in case of nitrogen it is becoming trans. Now this is the original stereo center and this is your temporary stereo center fine. And trans is the major product we will explain these things later on and actually transcend says both you can control with the help of judicious substitution choice ok.

So, first here we will be treat this treating this compound with LHMDS and we will be using some electrophile and this electrophile was taken as a specific electrophile like 4-bromobenzyl bromide because this compound was chosen mainly due to specific target structure. Now as you can see that the temporary or transient stereo center having a tertiary butyl group above.

So, definitely the aryl group has to be below. So, finally, what product structure we will be getting this methyl will be then forced to go above this will be your aryl group means the 4-Bromobenzyl bromide group, the carbonyl is here this is another aryl part the 3, 5 dichloro thing.

This is your tertiary butyl part and this is your N CO CF3. So, you can simply hydrolyze the entire thing you can simply hydrolyze the entire thing let me try to do the hydrolysis. So, in this case you are actually trying to hydrolyze with sodium hydroxide followed by acidic workup and you are getting the original stereo center of this alanine this methyl. You have this part is the aryl part coming from 4-Bromobenzyl bromide.

And then you have this Co this NH and you can simply write the 3, 5 dichloro part this Cl this Cl and you have a amine here. So, basically what happened the alanine is getting alkylated and see the original stereo center was basically coming back ok. So, self regeneration of stereo center is happening and this compound was just subjected to a few extra functional group based conversion, first you treat with this chloromethyl formate.

And then try to react with triethylamine followed by LHMDS and then react with a methyl iodide. I will just explain what is happening here, once I draw the product structure. So, you will actually be getting a cyclic imidazolone which is a biologically active a target molecule, where everything remains as intact this is the aryl part which also is very important this and this part you have this methyl and this part is your 4-bromobenzyl bromide.

Now, this compound is named as BIRT-377 is used in the medicinal chemistry field is basically acting as a protein antagonist ok. Now this compound is a biologically target molecule and if you now see the reaction the original stereo center was remain intact it is it was not touched. And what is happening, basically you are just trying to make this free amine to chloroformate and then doing the condensation and then the other amine which is basically methylated.

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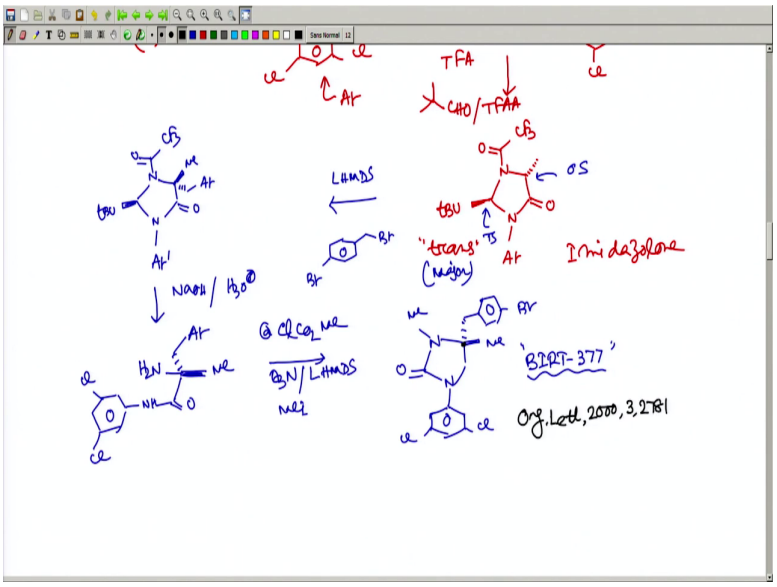

And such application of this SRS strategy was very recent. It was reported in a very well known Journal Organic Letter in 2000 which is and having a page number 2781. So, such things will give you.

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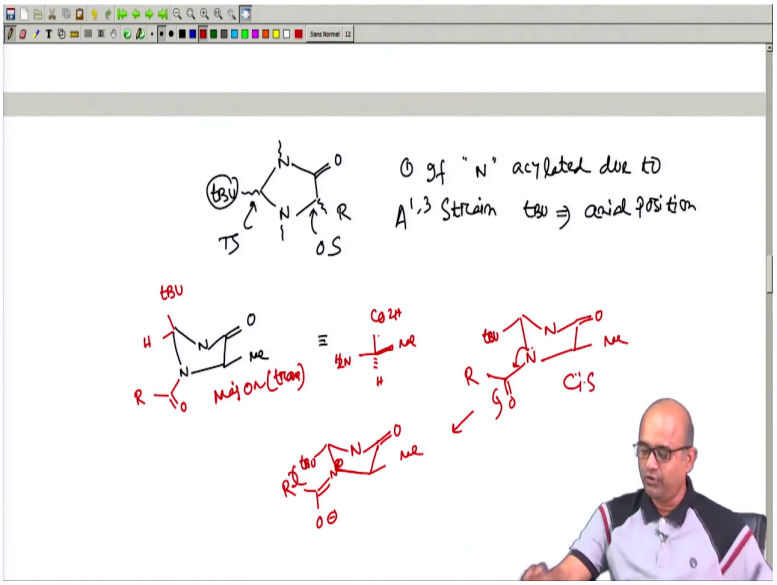

Now what question you might ask that if you have this kind of imidazolone compound like imidazolone. And this imidazolone whether it could be cis whether it could be trans, now this part is your tertiary butyl. Now this is very important concept that what will be the major product now there is a two point I will just try to write, if this nitrogen I mean one of the

nitrogen is acylated. Acylated means you have an acyl group coming or joined with the nitrogen then due to allylic 1, 3 strain.

I will be explaining how this is coming, allylic 1, 3 strain. The third butyl group third butyl group occupies an axial position. Now axial position means we will now explain, how it is happening. Now let us say this stereo center is the original stereo center ok and this is your temporary stereo center.

So, fine let me now try to put the compound, is it basically a five-member ring, so five member rings are envelope in nature that all of us know. So, you basically will be having this kind of envelope structure this is your already methyl. So, means that the parent compound where from we generate this compound is methyl is this way this is your NH 2 and this is the hydrogen and this is the CO2 H fine.

So, basically one enantiomer of the alanine. Now see if the N the finally, this N if you are trying to put a acylated CO R ok. Now then in this case the tertiary butyl group actually occupies a pseudo axial position, now why? Now, if this is the preferred or the major.

So, means this is what this is basically trans isomer, trans isomer. Now why cis is not the major one? Means that if now you try to put the tertiary butyl group in the equatorial position. Now in this case C double bond O R and let us put tertiary butyl group as an equatorial position. Now the amide due to the amide resonances this due to amide resonances this system now, it is basically kind of a having an allylic 1, 3 strain.

Let me explain I guess all of you know the allylic 1, 3 strain if you do not know just check. So, this N will be now plus and you have a double bond amide resonances O minus R. So, this tertiary butyl group will now give you a very severe interaction if it sees.

So, only for that region the trans will be mainly major.

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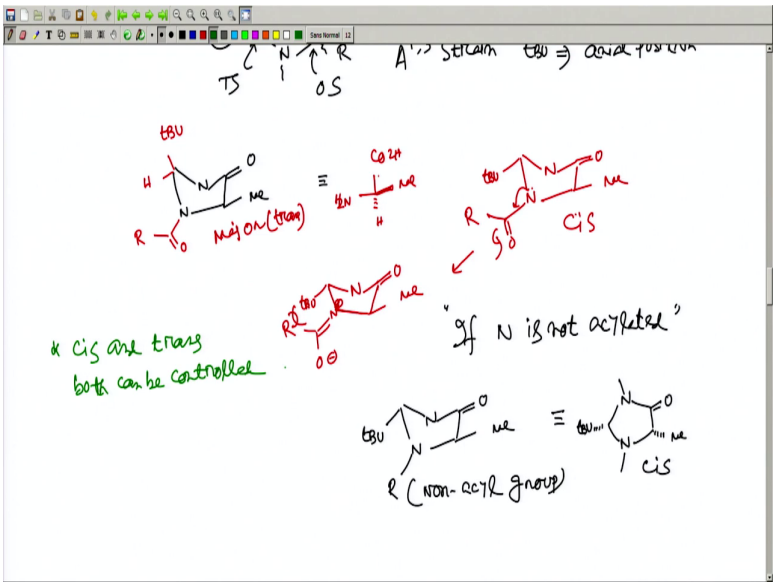

But there is another point if N is not acylated, if N is not acylated. There are two factors the first factor if N is not acylated, sorry if N is acylated then you have a trans as a major. If N is non acylated means this way, then basically cis will be the major same like the oxygen one.

So, this case N this this this means C double bond O the original methyl is equatorial and now this N R. So, R is a non-acyl group non-acyl group and in this case you will find that tertiary butyl group seems to be equatorial. So, then this will be now will give you a cis kind of compound.

So, this is you can write it like cis orientation. So, cis and trans in both the cases can be controlled. So, you can eventually you can write the cis and trans both can be controlled and the choice remains on you and you can eventually try to control the entire geometry. Now we will just try to give you a little bit of application purpose just for couple of one interesting fact.

Now you can eventually solve this as a problem kind of thing.

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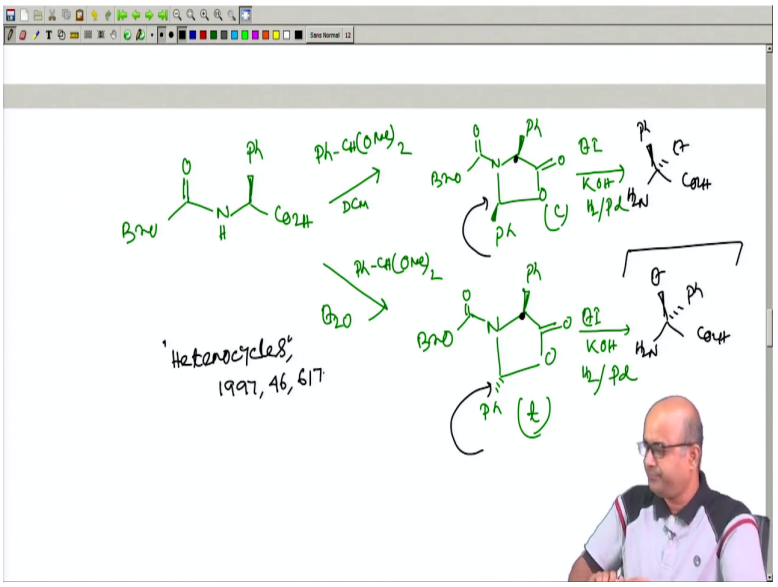

So, take this phenylglycine derivative, where this is a phenyl ring and this is a CO2 H. This is basically a phenylglycine derivative and this compound was reacted with actually a benzaldehyde acetal ok and same thing reacted here also.

Eventually this case as I am trying to let me explain, the N is already kind of acylated, so N is already kind of acylated. And then if N is acylated you actually can get cis as well as trans. And we will try to explain or try to just see what is happening. So, this is the cis one in one case you get cis and trans also you will get, trans also you will get, trans also you will eventually get and actually this is kind of more of like a solvent dependent.

So, you can find in one case the dichloro methane will give you this cis one and this case if you try to do this reaction in diethyl ether you get the trans one. So, this is trans and this is cis and then finally, you can simply try to write or add some external electrophile ethyl iodide, in this case also ethyl iodide then you do simple hydrolysis by KOH to remove the oxolane.

And the moment you remove the oxolane the next will be the this removing of this severe group by hydrogen palladium this is also by hydrogen palladium. So, the original stereo center is this this part. So, original stereo center and this is your temporary stereo center.

So, temporary stereo center means in this case, so phenyl is above. So, this phenyl is above, so ethyl will be below fine. So, you get this compound H2N CO2 H the alkylated amino acid.

In this case the controlling part is this phenyl ok this phenyl is below, so ethyl will be above. And this will be here H 2N CO2H. So, basically you will get the mirror image enantiomer.

The reason for this solvent dependent thing seems to be not very clear. But eventually both the things you can explain and this was reported by Dr. Seebach in a well known journal heterocycles in 1997 as a volume is 46 page number is 617.

So, we will be mainly just try to give you few homework kind of thing.

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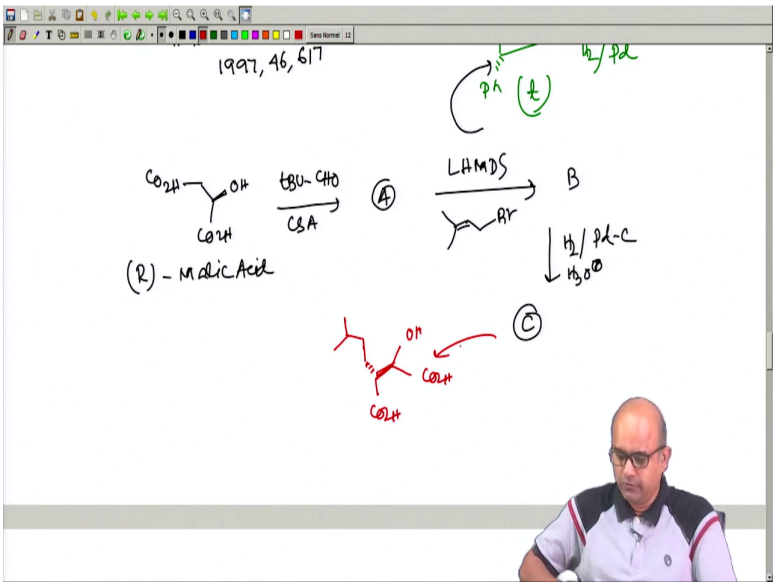

So, let us say I give you some alpha hydroxylated acid which is a malic acid with this structure as a malic acid which is R malic acid just try to do couple of homeworks. So, to get a better view of this entire problem.

This pivaldehyde react with camphor sulfonic acids it forms the compound A, so write down the structure of compound A. Second, a LHMDS and electrophile is the prenyl bromide fine and then. So, number B and then C, you write hydrogen palladium charcoal followed by aqueous H_3O^+ write the structure of C.

So, you can eventually try to write, if I try to give you a hint I will draw the structure of C and then you can complete probably the synthesis. So, this will be the structure of C basically it will be alkylated malic acid and CH2 another CH2 this this. So, this is the structure of C.

So, please you can think what could be the A and B.

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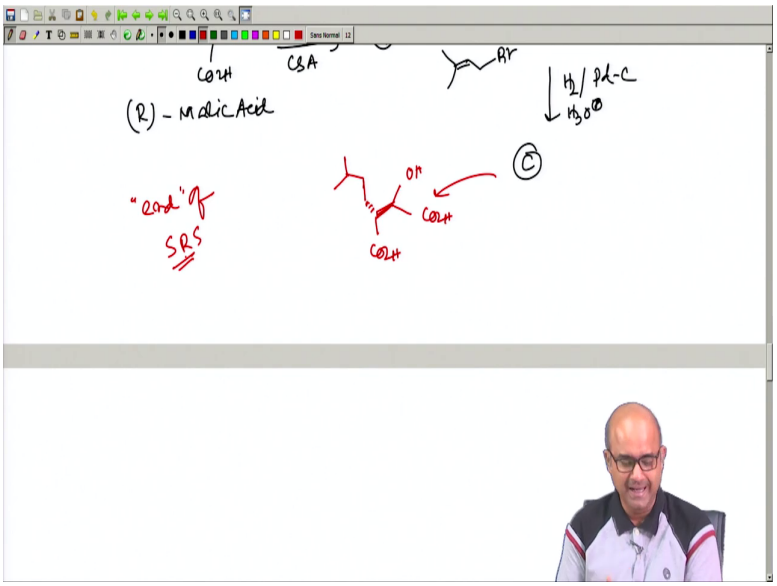

So ok, with this probably we will be trying to give you at the end of this SRS strategy ok end of SRS. Anyway we will be again continuing other discussion or other similar systems in the subsequent section, but SRS seems to be ending at this point.

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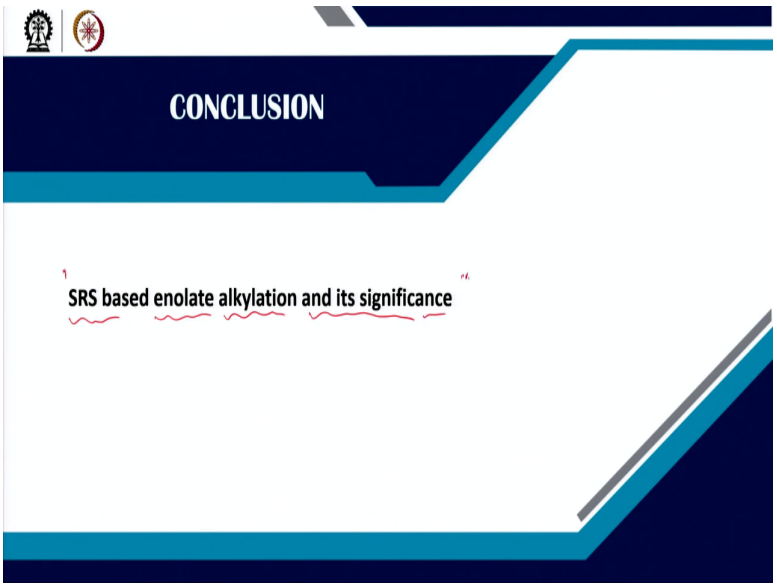

So, finally, at the end of this lecture you probably can say that SRS plays a very important role in enolate alkylation of couple of systems like alpha hydroxy acid, even amino acid derivatives. You create a temporary stereo centers with the help of a bulky ter butyl aldehyde

or pivaldehyde and this ter butyl groups the main role is to control the stereo center in the incoming electrophilic alkylation ok.

And so we can say that it plays a very important role and it can be used in various application purposes as we have also seen couple of examples. So thank you we will see you in the subsequent classes.