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 - 07
Aza-Enolate alkylation
Lecture - 35
Ender's RAMP/SAMP Coltart's cyclic carbamate hydrazone, Ellman's sulfinamide and related systems

So, welcome everyone. In continuation with the earlier thing, this lecture 35, we will try to conclude the Ender's RAMP-SAMP, and then we will mainly discuss this elements sulfinamide and related system is a very small a portion. And then, we will try to spend little bit time for this Coltart's cyclic carbamate based hydrazones and its exploration in enolate alkylation mainly Aza-Enolate alkylation.

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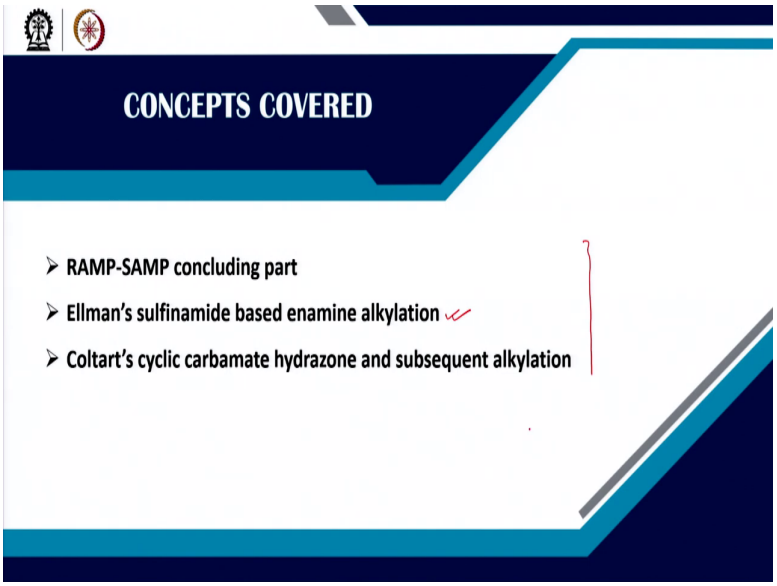

So, what we are trying to discuss? The main content here RAMP-SAMP, the concluding part. Ellman's sulfinamide based enamine alkylation. And then, we will give you a subsequent introduction of Coltart's cyclic carbamate hydrazone and it is exploration.

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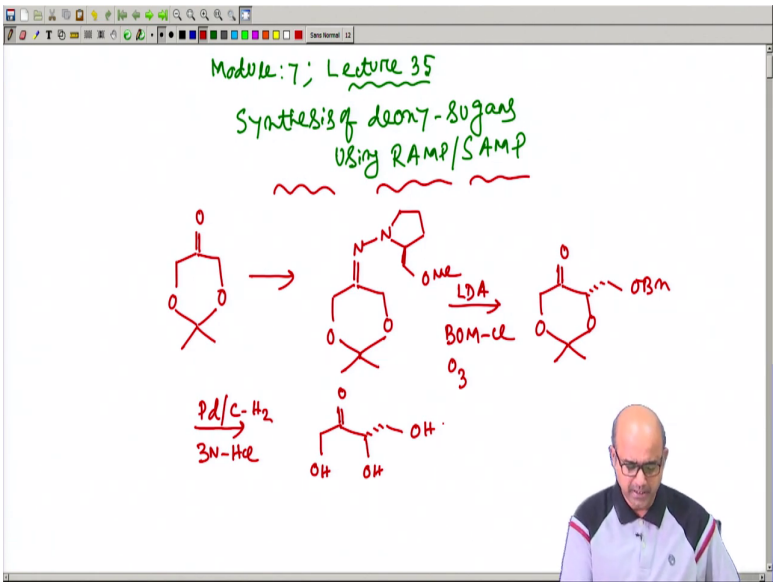

So, today in this module, we will be mainly talking about synthesis of deoxy-sugars using RAMP-SAMP and then we will talk about something else.

So, in the last class, we talked about this di-hydroxy acetone which can be act as a potential precursor. And then, this compound if you trying to fuse with the corresponding RAMP-SAMP derivative, this can actually give you a very good precursor for several deoxy-sugars. We just try to give you a brief outline how such compounds were made.

So, initially, this RAMP-SAMP based compounds you take and then you alkylate with a base or followed by your BOM chloride, the benzyl-oxy-methyl chloride or other sources. Now, then you cleave this thing, the hydrogen part with the ozonolysis. So, what you are going to get? You will be going to get this, this acetonide protected here, and here you will be getting this O-benzyl. Now, means you are creating an oxygen containing thing.

Now, with this thing in your hand, actually this OBn group can be removed by reductive de-benzylation, ok. And then if you remove this acetonide part with HCl mediated hydrolysis you can actually create it, this OH, this also an OH and then this CH2OH. So, this is a kind of a deoxy-sugars.

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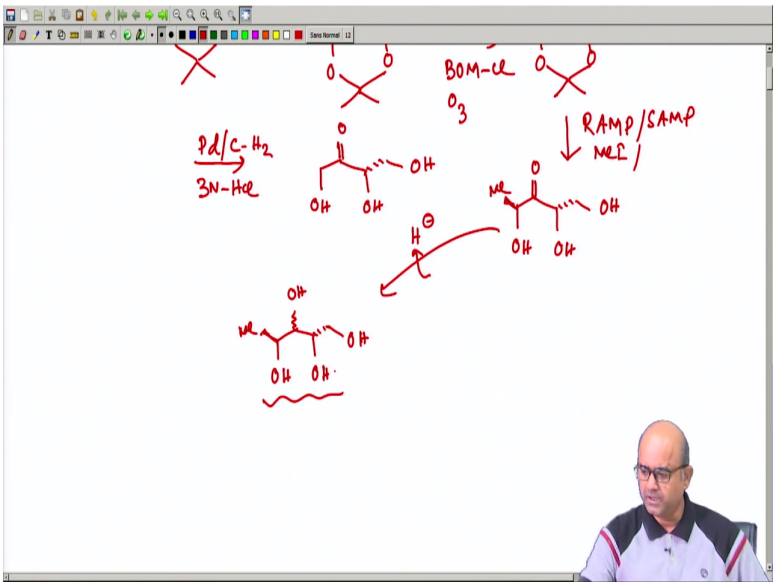

In addition, you can actually further synthetically manipulate here; you fuse with another RAMP-SAMP based thing. And then you can alkylate on this particular carbon which is now kinetically more acidic.

So, you can use a simple electrophile like methyl iodide and then follow the same thing. So, finally, what we are going to get? You get OH here, you get this CO, you get a methyl or another group depending on which auxiliary you choose and then you get OH and you get CH2OH. So, this kind of poly-hydroxylated compound you can actually create.

Now, then you can also create something else. Once you take this compound, this carbonyl group selectively you can reduce. So, this carbonyl group addition with H minus you can do it in asymmetric fashion or even substrate controlled carbonyl addition which you can create.

And then you are trying to get this stereo center you have already created, and here this OH you can actually create either alpha OH or beta OH, depending on which asymmetric induction methods you are doing it or substrate directed reduction. So, you could get a typical poly-hydroxylated compound which are normally termed as deoxy-sugar. So, this kind of deoxy-sugars with the help of RAMP-SAMP methods, you can usually create.

So, higher order of deoxy-sugars also you can create.

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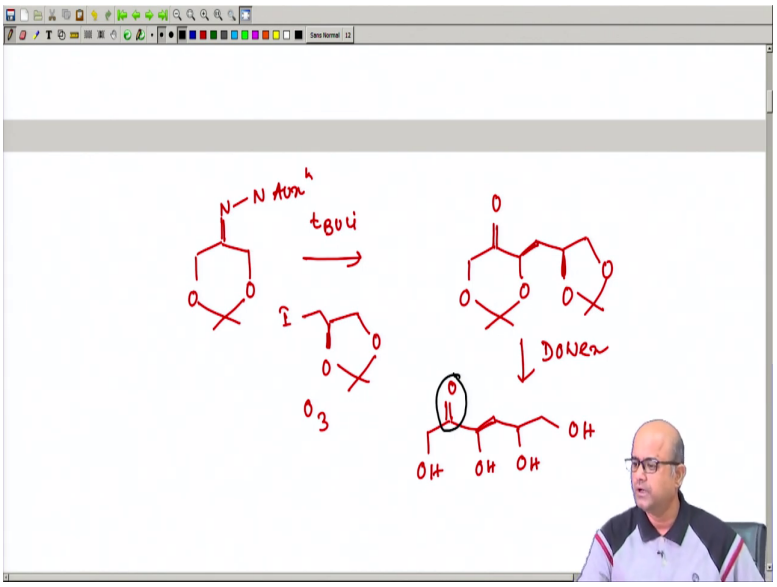

If you follow a similar kind of strategy means, you take a corresponding N auxiliary means your hydrazone and take the same di-hydroxy acetone where it is protected as an acetonide. And the electrophile seems to be important, you choose an electrophile which already contained some oxygen functionality, something like this.

Now, once you do this followed by ozonolytic cleavage, you are actually going to get this O, these things, and here you now create these things. You have now this both this acetonide, you can actually remove with strong ion exchange resins like dowex or normally acidic hydrolysis.

So, what we are going to get? You get a this OH, this OH, this, and this OH, this OH. Now, count the number of carbon 1, 2, 3, 4, 5 ,6. So, this kind of actually deoxy hexoses, ok. Because one of this carbon does not contain oxygen.

Now, this carbonyl, this particular carbonyl you can actually selectively reduce, ok. So, you can create particular specific deoxy-sugars by using this methodology, this RAMP-SAMP based techniques.

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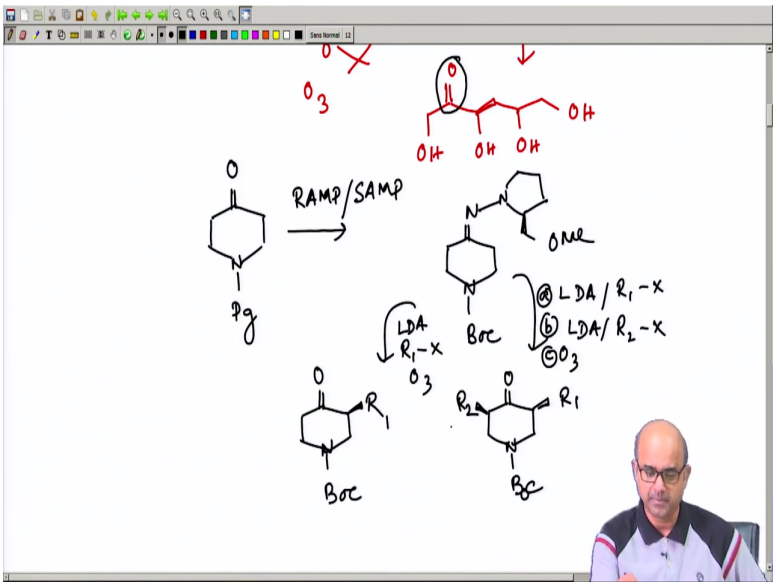

Some of the other methods which might be quite useful for cyclic, heterocyclic compound synthesis for that you can choose a piperidone based starting material.

Now, this nitrogen usually protected as a suitable protecting group. Now, it means that here we are talking about a cyclohexanone analog with a nitrogen at the 4 position. You can selectively alkylate here as well as here, ok.

So, what you are trying to do? You can actually create a RAMP-SAMP based hydrazone, ok. So, means you will initially condense with any of this hydrazone depending on your choice and then you do the alkylation.

Now, a symmetrical thing. So, you can treat with base LDA, and let us say R1X and then you do the ozonolytic cleavage. So, first thing, you will get this ketone, this N, this Boc, and you will create a particular carbon carbon bond, if the R1 is a carbon containing electrophiles.

Now, this is a mono alkylated piperidone derivative. And this carbonyl group now you can selectively reduce. This carbonyl group you can selectively reduce. So, you can get a further functionalization of this carbonyl group.

Now, here you can do a double alkylation, means you can first do not do the ozonolysis, put R1X followed by, if you, so let me write like this LDA…. R1X, the first round of alkylation. The second round of alkylation, you can actually create here. So, another round of alkylation

you will get R2X and then you do the ozonolytic cleavage in the next condition. So, you can actually create this R1 and this kind of compound.

Now, the stereo center, you can create by judiciously choice of the particular RAMP or SAMP. And then this carbonyl group you can obviously, then reduce.

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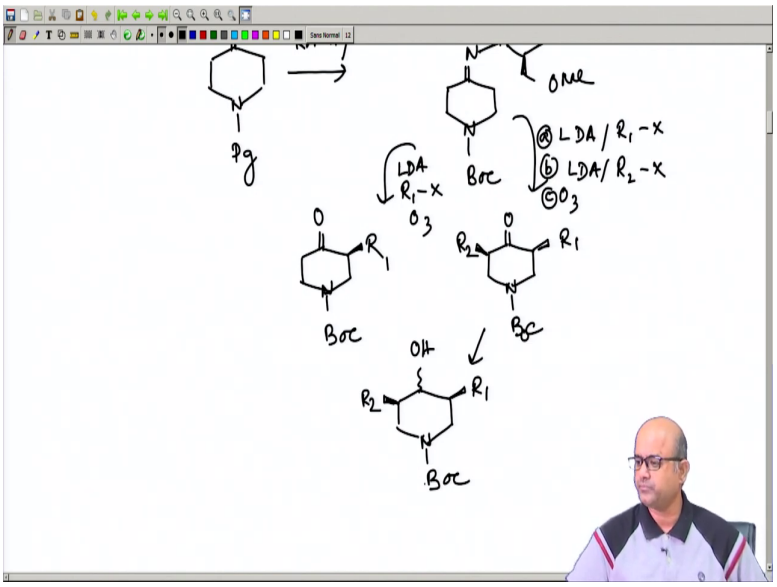

You can obviously, reduce the carbonyl group with specific stereocontrol and you will have a different functionalize piperidine compound. This Boc group finally, you can remove, and you can end up with different functionalized compound. Such synthetic exercise was quite judiciously you can do it.

We will just try to end up with this RAMP-SAMP based technology with one particular synthesis of a natural product.

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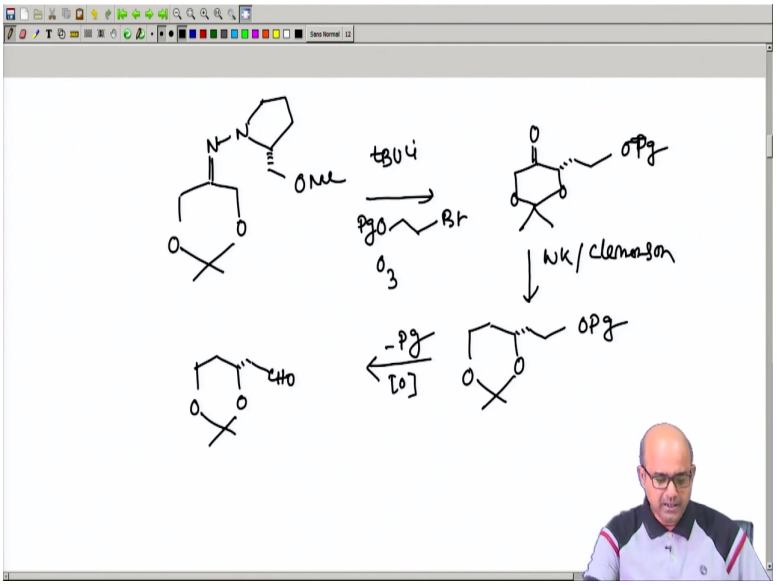

But we may not give you the entire detail. The starting material was a di-hydroxy acetone derivative which we already explained. You take any of this RAMP or SAMP, here I took this particular compound and then you react with tert-butyllithium and electrophile was you choose a protecting group with a two carbon electrophiles at.

Then you do a hydrolytic cleavage with ozone. So, what basically you will be first getting…. This stereo center will be created, your oxygen will be here, to methyl group, gem-dimethyl group and then you can get your OTBS or O protecting group. We have not mentioned what kind of protecting group.

Now, here this carbonyl you can reduce or deoxygenate by normal reaction like Wolff-Kishner or Clemmensen. So, these things we already know which we have studied. And once you do it, you will find that deoxygenation thing was there. So, what I am trying to say that, you can actually synthetically manipulate these compounds in different way.

Now, for one of this particular synthesis which we are talking about, now this pg, you can remove you can remove the pg. And you can oxidize this 3 hydroxy group with a simple oxidizing agent. So, that basically will give you this O and will give you CH2, CHO, CHO.

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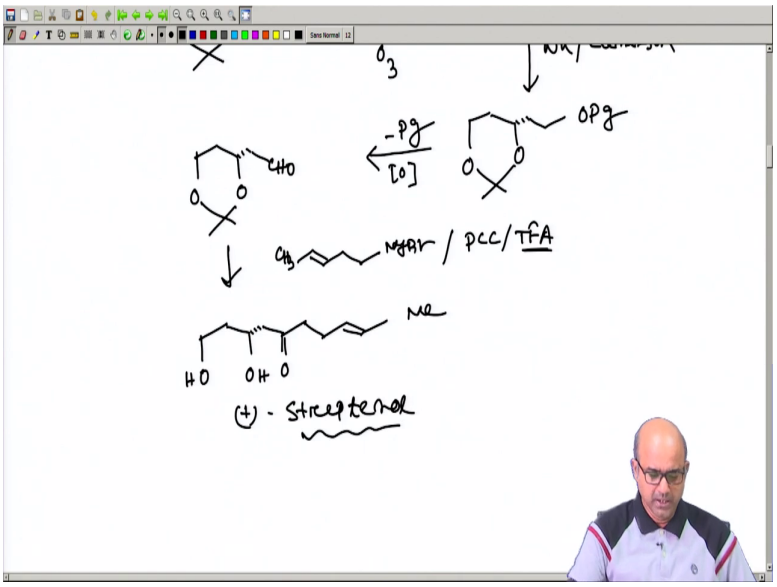

And then this compound was later on the reacted with a simple Grignard at this point. Now, this Grignard, the structure was this and then CH2-MgBr. So, you react with the aldehyde with this Grignard followed by a PCC oxidation, and then you remove this acetonide with trifluoroacetic acid.

Now, what that will provide you? That will provide you OH here, give you a OH, fine. And then here CH2. You get the Grignard. Then, once you get the Grignard, you get a secondary hydroxyl, that is oxidized with PCC. So, C double bond O, and then you have this CH 2, CH 2 double bond methyl, and then finally, you with TFA, you actually remove this acetonide group.

Now, this compound is a natural product whose name is streptenol. So, usually this RAMP-SAMP based methodology was often used or it is used very frequently for the synthesis of some of the natural products which we have just now talked about.

Now, so we will be not a considering this RAMP-SAMP based methodology for the further discussion. We will send you some assignments in the NPTEL platform. You try to solve the assignments.

Now, we will be trying to give you a little bit of this sulfonamide and how this sulfinamide can be used of an enolate precursor; sulfinamide.

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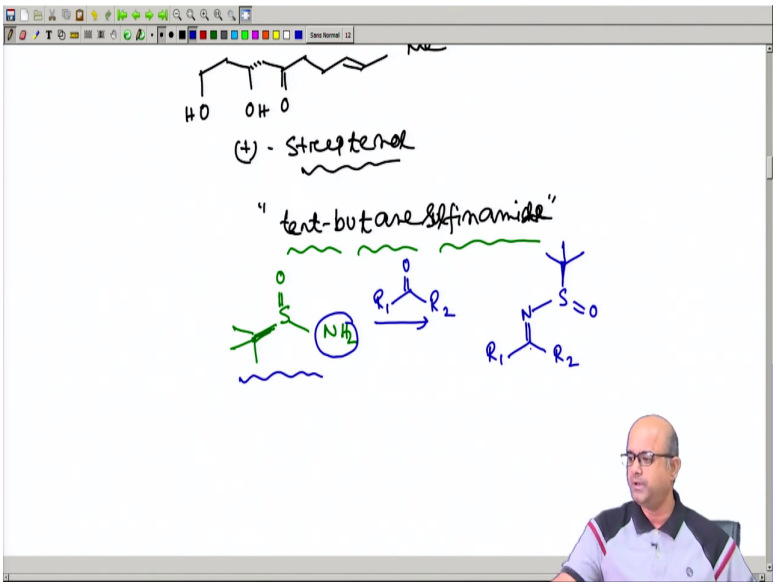

This sulfinamide was actually the first, sulfinamide was invented by Profsessor Jonathan Ellman of University of California, Los Angeles. And this structure of this sulfinamide we will be now talking.

This actually contains a sulfur stereogenic center, and this chiral sulfinamide actually is commercially available. It contains a bulky tertiary butyl group at one end. And this NH 2 is acting as the imine forming agent. So, initially what was happening, you react this sulfinamide with the carbonyl compound R2.

And what we are going to get? You get this, you get this, you get the corresponding sulfinamine, S double bond O and your tert-butyl. So, this chiral sulfinamide is commercially available and you just do it.

Now, here this R1 and R2, if they contain say abstractable hydrogen you can just abstract those hydrogen through base. And then, by similar way the imine enamine alkylation which you have earlier explored you can do it.

Now, let us go to a few example of this sulfinamide.

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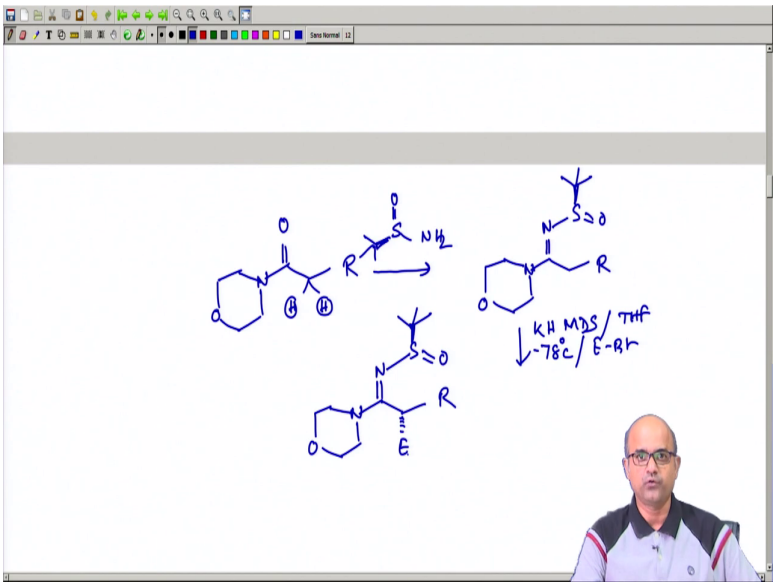

And normally this this sulfinamide was one such sulfonamide where a one portion of this ketone was this morpholine part and then this was this kind of ketone was taken.

Now, this kind of ketone was judiciously chosen because the one part does not contain hydrogen. So, basically it is a non-symmetrical ketone, but the there is no regio chemical issue, only this hydrogen will be abstracted by the base, ok.

So, now you react this sulfinamide, this this this ketone, with this corresponding tert-butyl sulfinamide which was this. And then what we are going to get? A simple imine derivative of this compound. And then this imine derivative you can actually selectively alkylate, S double bond O the tert-butyl group, this bulky tert-butyl group as you are taking a enantiopure sulfinamide that acting as a, this tert-butyl group acting as a chiral controlling agent.

So, you treat with the base, KHMDS, and then with a THF by the solvent, temperature was usually pretty low. So, kinetic deprotonation we are talking about and then electrophile your, E-Br. And usually, you will find that this gives you a stereo controlled enolate alkylation. And this part was there your N, S double bond O. I will try to give you the mode of asymmetric induction, and this R. Obviously, you will try to get a E.

Now, tert-butyl group being the beta, this will be the alpha because that is a very straight forward way to memorize the entire thing.

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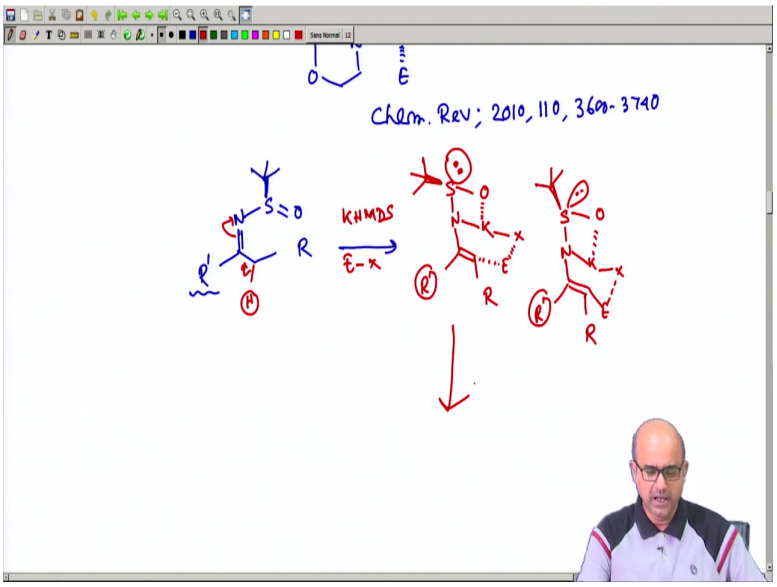

Now, if you are trying to get more insight of these things, a chemical review paper written by Professor Jonathan Ellman, we might be helping you. This was reported in 2010; and page number is, I think just 1 minute. Yeah, it is a 3600 to 3740. So, 140 page detailed review was written by Professor Ellman.

Now, let me talk about the asymmetric induction part, how it is, how it is happening. So, initially you will see that this is a CH2R, and this group I will write something else like R prime which does not contain a hydrogen. This group does not have hydrogen, ok.

Now, you have a N, you have your sulfinamide which you form sulfinamine and your tert-butyl, this, this, this, ok. So, with the help of KHMDS as a base, the KHMDS seems to be the base. And usually it has been found out that this kind of transition state and you add an electrophile EX.

So, first this hydrogen is going to be abstracted. Once it is going to be abstracted you get a N minus here, ok. Now, this N minus; which, this part is R prime, the other group which does not contain any hydrogen and then you have a this N. Now, this N may contain a metal because you have a KHMDS. So, may contain a potassium, fine.

And then with this thing you have a sulfur. With this sulfur you have a chirality, this tert-butyl group, and definitely you have a oxygen here, ok. And you have a sulfur-lone pair which we did not talk about earlier.

Now, this oxygen actually also coordinates with this potassium, ok. Now, we have a EX. Now, EX means usually once this electrophile supplies this E of this alkyl group, the X has to be reacted with this potassium. So, KX you can write, and then this is your electrophile path, and this is the enolate which is going to be react.

It is a more of like a 6 member chair form, but that drawing would be little bit complicated, in the sense that you are also considering an oxygen which is coordinating with these things.

But, ok if you want to prefer a chair form that also you can do it. But such chair form may not be that much well-defined chair, X; and this is your electrophile. Yeah, it looks like a, looks like a more oblique electric chair. And then you have a sulfur, your oxygen, here the K thing, and your this tert-butyl group, and the sulfur-lone pair is there.

So, this kind of geometry was usually proposed.

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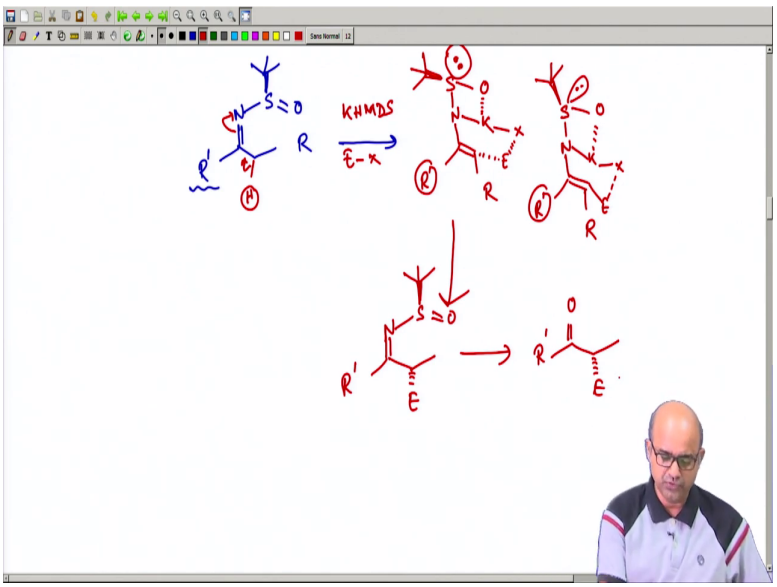

And once you do this alkylation, ok once you do this alkylation as we have already said, so the alkylation was done with S double bond O, this sulfur chirality remains. The, this group R prime which does not have hydrogen. So, the regiochemical issue is not coming and you have a carbon electrophile bond which has been nicely created.

Now, then definitely you can you can treat this compound with a, (Refer Time: 22:58) do a hydrolysis kind of thing and that can give you a simple alkylated product like this, R, C double bond O, this and this.

Normally, the sulfinamide was never, I mean not that much explored for the enolate alkylation. Usually, it was used for some other purpose. The imine can be reduced chiraly to give you an amino derivative or those kind of component. But still there are few examples where this alkylation also can be used.

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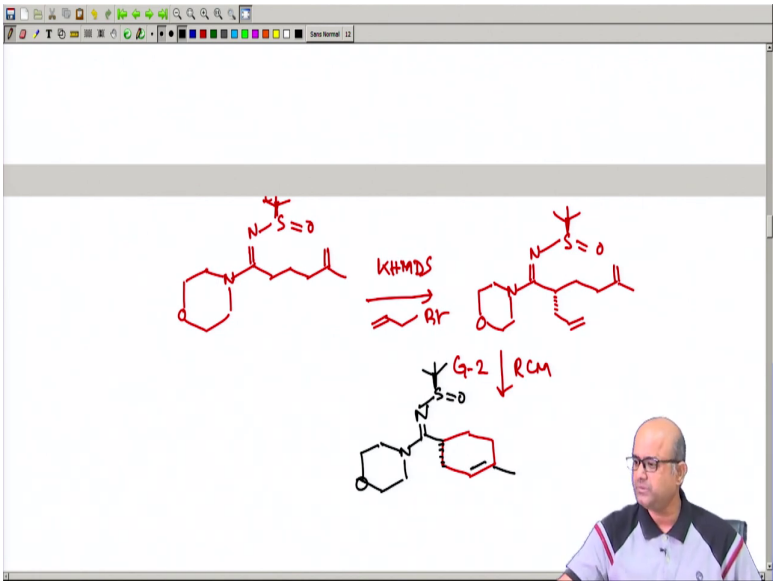

Now, one such example was pretty nicely explained for synthesis of a ring containing compounds or particularly a natural product. We will just try to explore how this was done.

So, initially you take this corresponding morpholine based sulfinamide. This is the tert-butyl sorry; this is the tert-butyl part, this and this, ok. And then, you try to take an alkyl group which will contains some hydrogen, fine. And then, you react with a base KHMDS which was usually used. And then allyl bromide was used as electrophile.

The choice of allyl bromide, I will explain why it was done. Because they wanted to make some ring containing compound through ring closing metathesis reaction.

Now, initially this thing was there, you have this sulfur, and then you sorry, I have that will be a nitrogen. So, I did a mistake, ok. So, N, then S double bond O, and your tert-butyl group this was there. And then, you will see that this allyl group electrophilic alkylation took place and you have this, this, double bond Me.

Now, this two things now, you can actually do a ring closing metathesis reaction. So, once you do a ring closing metathesis reaction with Grubbs-II catalyst, you can actually create a

cyclic part. So, this will be your 1, 2, 3, 4, 5, 6. You can actually get a 6 member ring where this particular stereo centre at, this point is fixed and then you can have your this imine part which is there, which I am not elaborating. And then, here you have this thing.

So, such synthetic manipulation with this cyclic part, you can actually do it very nicely. And then, this sulfinamide is already there, double bond O, that sulfinamide you can later on cleave in different way. So, such sulfinamides may not be that much significantly explored in the enolate alkylation, but there are few examples.

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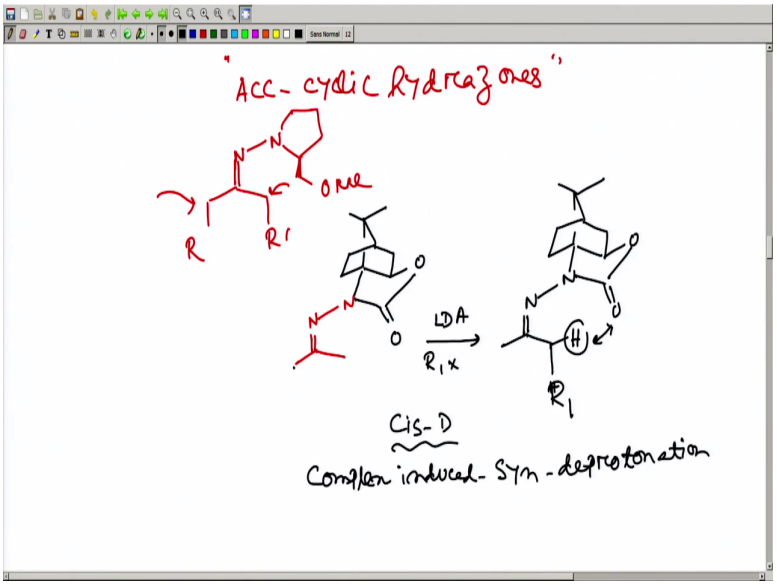

Now, next few minutes will be actually trying to give you a different flavor that, talk about, we will be talking about ACC cyclic hydrogen. And we have earlier discussed that if you are dealing with a non-symmetrical ketone through RAMP-SAMP method, we are talking about a non-symmetrical method in the RAMP-SAMP method.

If you have this, if you have RAMP-SAMP thing, and we say that RAMP-SAMP based thing was not very selective you can actually can have an alkylation here, you can have a alkylation here. So, regio-chemistry was definitely a big issue. But for, to avoid this problem a cyclic hydrazone was eventually visualized. Now, such cyclic thing we will now try to explain.

Now, this cyclic thing was a camphor based compound which was derived by Professor Don Colter. And he was trying to use such acyclic sorry, cyclic carbonate based derivative. And it has been found that if you have, like this is fine, this is a basically normal acetone where both

the compounds you can actually abstract the hydrogen. Final, you do a, take this compound and treat with first LDA, R1X.

Now, initial R1X will be coming this methyl double bond N, CH2, R1, CH2R1 and there are hydrogens, ok. Now, the beauty of such system was, this system, there is a pre requisite that always this auxiliary will be fixing on this particular position. So, normally this rotation around this nitrogen-nitrogen bond was not possible. Usually, it is a pre-requisite for such cyclic system.

Now, once you try to do this you can again draw this typical compound by featuring out its entire structure. And this particular carbonyl was helping. Now, this carbonyl actually if you can write in a different way. We just write this is a R1, and this could be the hydrogen I am sorry, yeah, this could be the hydrogen.

It was anticipated that this carbonyl might play a proximity effect to enhance the kinetic acidity. Now, reality this was sterically more congested hydrogen because it contains say R1. But as the main prerequisite was the cyclic carbamate hydrazone will be frozen in this conformation, the ground state, because restricted rotation around this N-N bond makes it the CO and hydrogen in close proximity.

And such carbonyl induced deprotonation, we are now trying to call it as a phenomena which called CiS-D. Now, CiS-D protonation which basically means that complex, C stands for complex, i stand for induced, complex induced S stands for syn, and D stands for deprotonation. Now, such complex induced syn deprotonation will be occurring.

Now, the beauty is, in this case no matter what kind of structural features you to give it to non-symmetrical, then definitely the more substituted carbon, more substituted carbon, it is possible to pick up the hydrogen. And this complex induced syn deprotonation you can actually do it.

Now, the moment you abstract the second hydrogen, the electrophile actually will approach from this. And then, this entire chiral auxiliary will actually control the phenomena.

Now, the C double bond O, in addition with this complex induced phenomena, it also helps in the chelation because once this proton was picked up from here, it becomes minus. So, this comes a N metalated here. This N lithium and this CO again form a rigid chelate.

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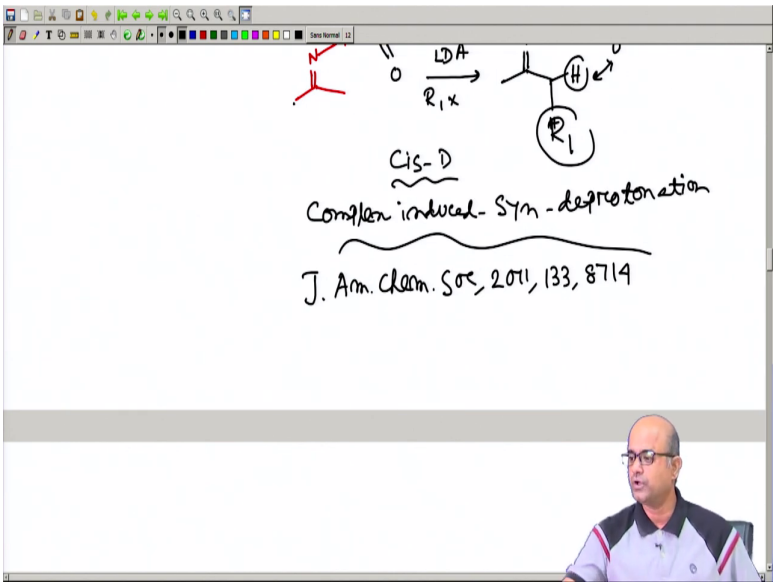

Now, such a nice proof of concept was first reported by Professor Don Coltart in a JACS Paper in 2011. This was kind of very new phenomena which overrides the regio-chemical preferences of the usual RAMP-SAMP based technology. In the normal RAMP-SAMP based technology, we do not get such regio preferences.

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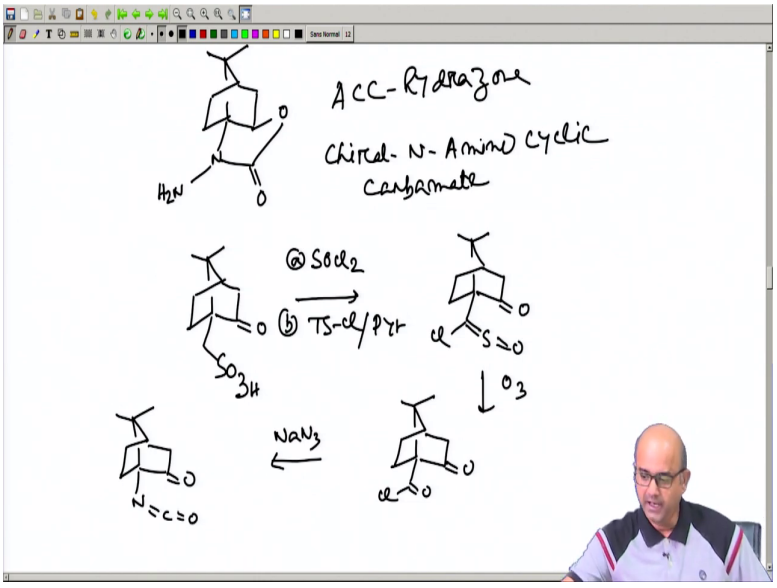

Now, such compound was usually not commercially available, but you can even make in the lab from the corresponding camphor derivative. So, the compound structure was something like this. It is a modified form of a hydrazine derivative with this structure.

And this is the ACC auxiliary. ACC auxiliary the name stands for the ACC auxiliary, we call it ACC auxiliary, which basically stands for chiral, chiral is the usual adjective the N amino, you see the N amino, ACC the cyclic carbamate ACC hydra zone hydrazone. So, this was the cyclic part, cyclic carbamate C double bond O N O.

So, such cyclic carbamate based hydrazone was first actually pointed out by, I mean first pointed out by Professor Don Coltart. Now, how these compounds are made? This compound was not, I mean is basically easy to make actually such compounds. You can easily make.

Let me just quickly go through how to make this compound. You can make you can easily make this compound from camphor sulfonic acid which seems to be commercially available. You take this thing, the camphor sulfonic acid which is commercially available or even you can make it from the corresponding camphor.

So, take this compound, first you convert this sulfonyl group to a sulfonyl chloride by associative treatment. And then, you treat tosyl chloride followed by pyridine that will actually give you a rearrangement, base induced rearrangement for the mechanism. You can just search in the original paper, otherwise you can we will discuss once we have some clarification. So, initially, you get this kind of ketene type of intermediate which contains the sulfur.

Now, this was cleaved with ozone. And that basically gives you one carbon less, this acid chloride CoCl. Now, this acid chloride you treat with sodium azide for a Curtius reaction. And this Curtius reaction basically give you a which probably all of you are familiar, acyl nitrate which actually rearranged to isocyanates, this N double bond C double bond O.

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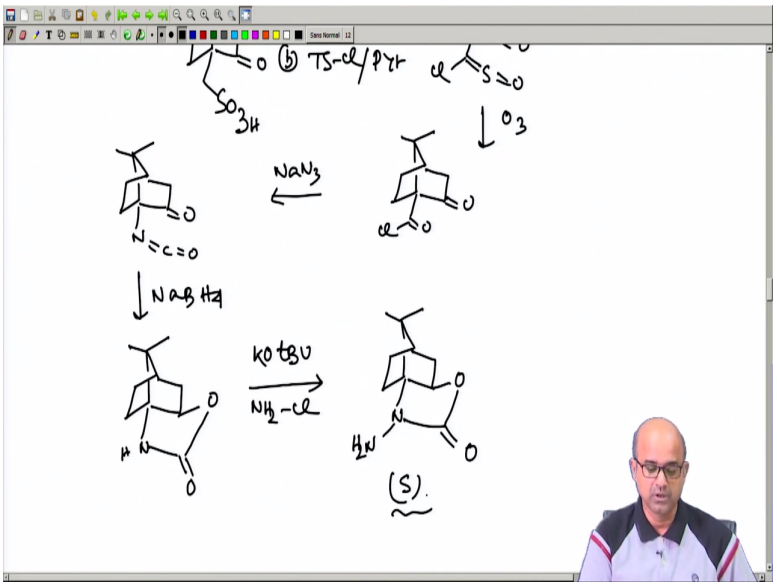

Now, this N double bond C double bond O, this isocyanate, you can actually now reduce with sodium borohydride. You can reduce sodium borohydride.

Now, sodium borohydride will come from this bottom face because top face is blocked by this gem-dimethyl group. Once you get the corresponding OH, immediately this OH will react with isocyanate in the intramolecular pathway.

So, what will you get? You get this O, and here you have N H, this C double bond O, and this. Now, the final part was really good, this NH was reacted with potassium tertiary butoxide with N minus and then simple ammonia derivative NH2Cl, just by SN2 reaction you can actually get the corresponding ACC based hydrazone.

So, probably in the next class, we will talk about how this hydrazone was synthetically manipulated for the asymmetric alkylation and what is the mode of asymmetric induction we will discuss in detail. So, both the isomers you can create. So, this is your S compound. You can also create the R compound, from the, starting from the R camphor sulfonic acid.

So, we will discuss more things on this ACC on this Coltart's ACC based hydrazone and how you can employ these compounds for the asymmetric, regioselective alkylation of non-symmetrical ketone.

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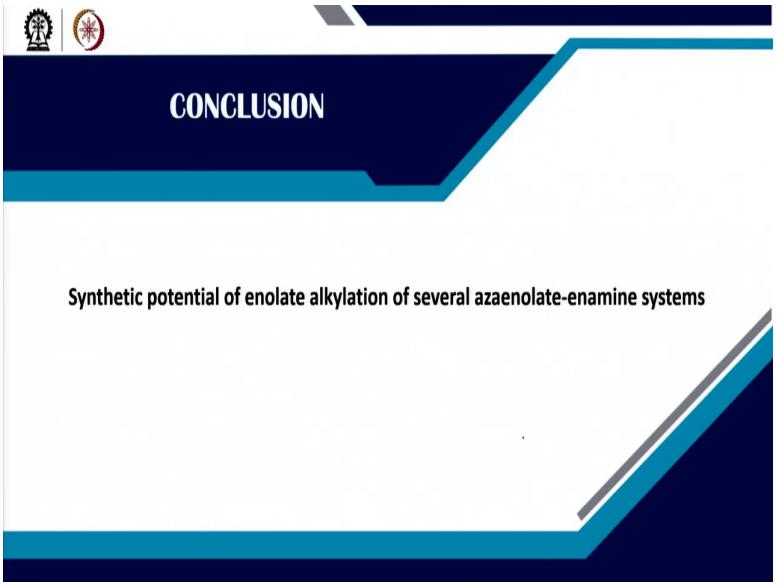

So, as a concluding remark. We can say that synthetic potential of this enolate or more specifically aza-enolate alkylation is very useful tool in the organic synthesis, which you are going through this particular this module 7. We will discuss the remaining part in our next module. And then, we will conclude the entire discussion.

Thank you all.