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 - 33
Ender's RAMP/SAMP based systems - I

So, welcome back everyone. In the last lecture, we have just started the discussion on different type of Aza enolate, and enamine based alkylation. And, particularly we have started with a chiral hydrazone which is named as RAMP and SAMP which is first invented by Professor Ender's. And, Ender's RAMP SAMP based systems, we are going to discuss in much more detail in today's class.

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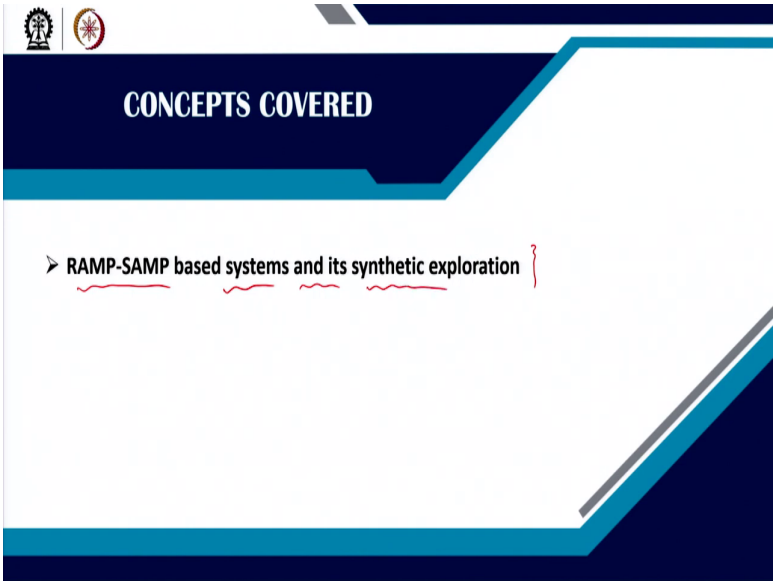

And, particularly this class, the main content which we are going to cover RAMP SAMP based systems, and its synthetic potentials. And, in the last class we talked about how asymmetric induction can be explained with the help of a typical working model.

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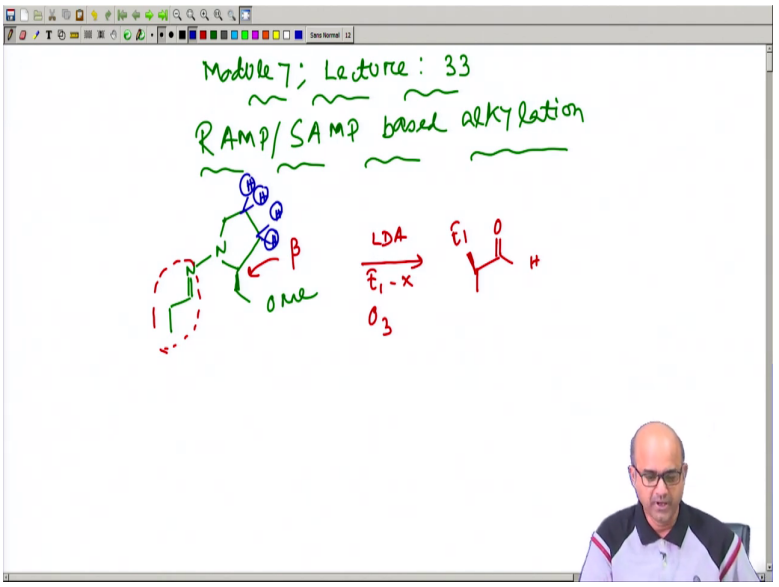

So, in the previous class, we talked about RAMP SAMP based alkylation. And, actually if I have to do a quick recap, we have said that the working model or rule of thumb is something like this. You prepare the corresponding RAMP or SAMP and you write this way. If you write in this way, where your enolate part is this or enolate precursor is this and this is the auxiliary part. Now, the auxiliary part this if is a beta O-methoxy ok. And, then as a rule of thumb what you do? You treat this compound with base and the electrophile is E1-X and then you remove this auxiliary with the ozonolysis.

So, what you are going to get? You we will be getting this corresponding carbonyl compound with this E1 will be the beta. So, this is your straight forward rule of thumb and that you can usually use for the exam purpose. So, if you take OMe below here, your E1 will be below ok. So, these things you are you have to just try to remember and the way it has been explained in the earlier part, we have shown you that this particular 2 methylene hydrogen, because normally, cyclopentane exist as an envelope structure.

And, we have actually drawn a puckered structure of cyclopentane, if you follow the previous lecture. And, this 2 hydrogen methylene bridge actually gives you a little bit of steric congestion and the enolate face can be judiciously tuned up during electrophile approach. So, in this particular auxiliary, this two CH2 group blocks the one face and the enolate attacks the electrophile from the opposite face. So, anyway with this little bit of background information,

we will now try to explore some of the synthetic potentials, how this compounds can be synthetically manipulated.

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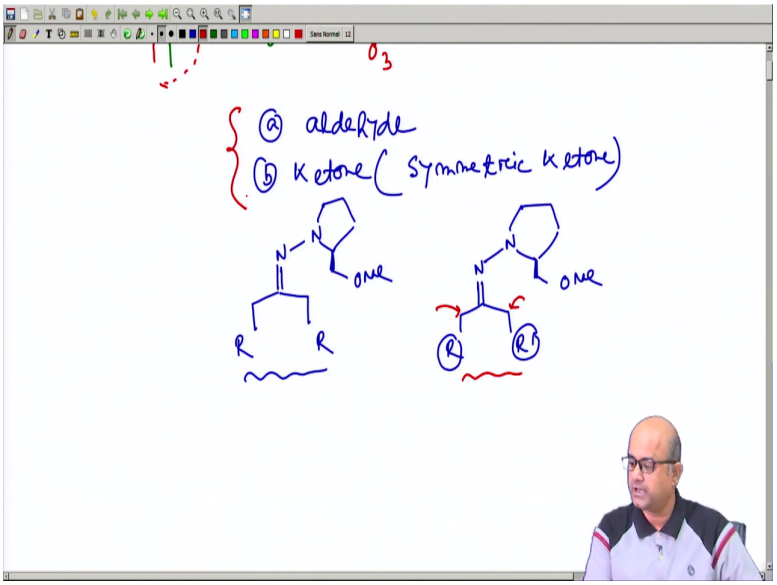

Now, normally in the most of the cases what we will be using? We will be using aldehyde as a precursor, aldehyde and then we will be using ketones. Now, the note of caution is ketones will be always a symmetric ketone. So, this was one of the potential disadvantage for this RAMP/ SAMP method. You will be always using a symmetric ketone something like this. Now, symmetric ketone always you have to use in the RAMP/ SAMP method. If you do not use symmetrical ketone, then the regiochemistry issue will be always there ok.

So, always symmetrical ketones are permitted. Now, if you do not take a symmetrical ketone, let us say you are using this R and this R prime. And, in such cases you will be definitely dealing with a regiochemical feature based on the steric as well as kinetic parameter which controls the kinetic acidity of this 2 hydrogen ok. So, there will be alkylation either here or here ok and this is a real problematic for RAMP and SAMP.

So, normally in RAMP and SAMP always symmetrical ketone was preferred, we always take.. ok; that kind of regiochemical preferences we can actually control through a different cyclic ketone. We will be talking about those cyclic ketone little bit later on. So, now, most of the substrates which will be using are basically based on aldehyde and symmetrical ketone for synthetic utility of this RAMP/SAMP based asymmetric hydrogen based alkylation.

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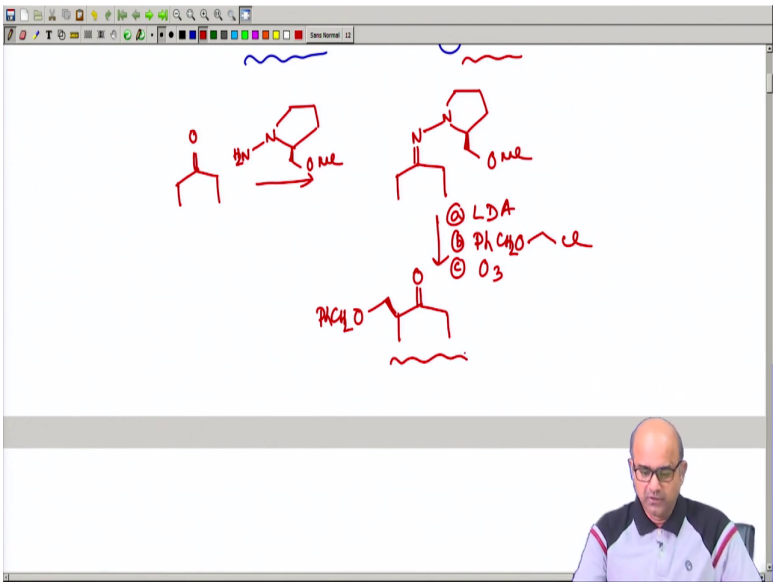

Now, let me talk about its simple system a diethyl ketone. Now, this diethyl ketone this is very standard example taken from the literature. And, this diethyl ketone was used as the precursor for the enolate alkylation with using this enantiopure hydrazone. So, first definitely you will be getting the corresponding chiral hydrazone which you can isolate this compound and this is your main precursor.

Here regiochemistry does not matter because both the things are symmetrical. Now, the way I have written you basically can write that what will be the electrophile. The electrophile was first was a base, the electrophile which was chosen is a BOM- chloride; BOM-chloride is Ph CH2 O CH2 Cl, benzyl oxy methyl chloride. So, you can easily see that the way it has been written, we can apply the rule of thumb as this OMe is beta, the electrophile will attack this carbon and this will be also beta.

So, fine you can just write this. The BOM means you will be having a Ph CH2O and then next step you basically do an oxidative cleavage that will give you a ketone. So, you can simply get this compound. This should not be any problem and this is actually served as an intermediate and for some reduction this is of natural products. So, there are few more examples which probably we will be trying to discuss in the subsequent lecture.

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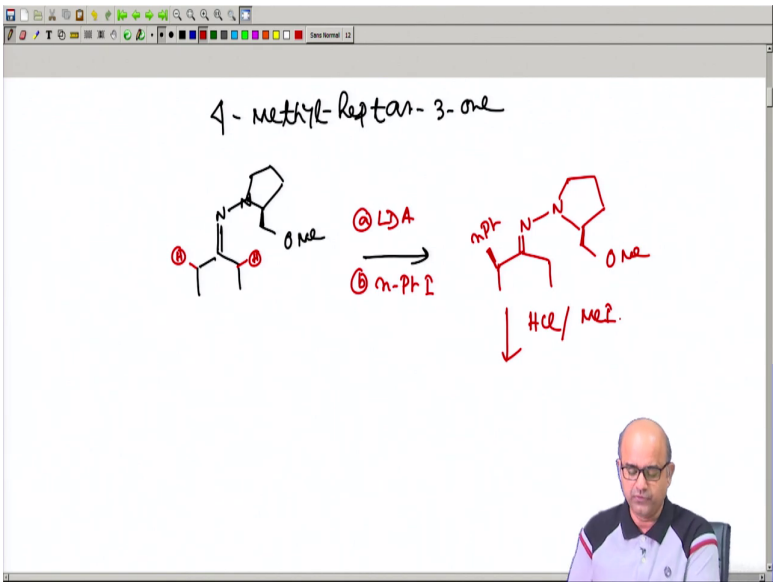

And, next we will be talking about the synthesis of one such intermediate, which is also another chiral intermediate, I just put a name; probably that does not give you that much importance is 4 methyl heptane 3 one. Anyway, this name does not give you that much sorry weightage. Now, eventually here also symmetrical ketone compound was taken and the symmetrical ketone compound was first you prepare the corresponding chiral hydrazone derivative with one of the RAMP or SAMP depending on your choice.

And, then this is the best way to write that what asymmetric center when you are trying to create, what would be the absolute configuration. So, the reported procedure was first you have to use LDA as a base fine and then n-propyl iodide as the electrophile, the symmetrical ketone. So, definitely you can in principle remove any of this hydrogen, does not matter. As for the working model is concerned, we will try to remove this hydrogen and then we will be just writing like this, this will be your auxiliary.

So, we can write everything as it will be OMe. This is the n-propyl, now we will have a beta connection n-propyl. So, everything is fine then you can actually do the typical cleavage of this carbon nitrogen bond. And, here it was done by HCl and methyl iodide treatment which is a hydrolytic cleavage. And, normally if you do this hydrolytic cleavage, you will try to get this compound this and this and this will be your n propyl means this, this.

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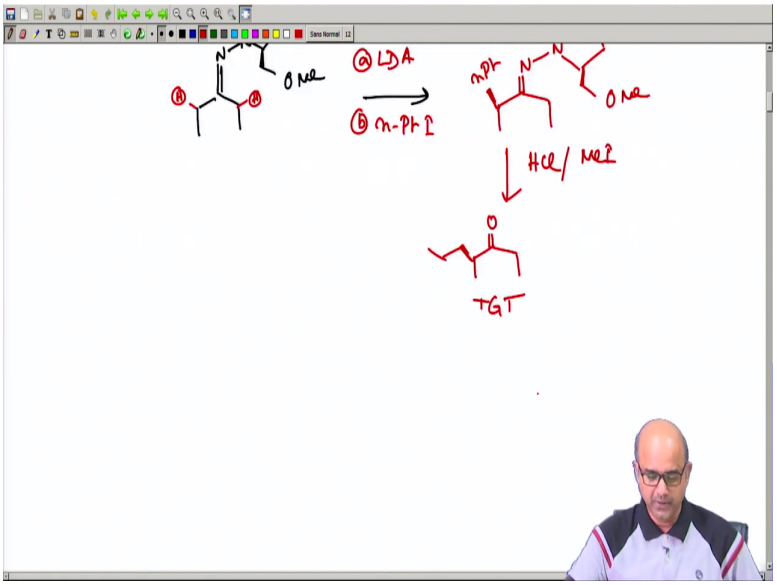

So, this compound is your 3-methyl- 1-hept -4 methyl-1-heptanone. So, 1 2 3 4 5 6 7, 4 methyl-1-heptanone. This is the asymmetric synthesis of this particular compound. Now, such synthetic strategies you can do it quite easily.

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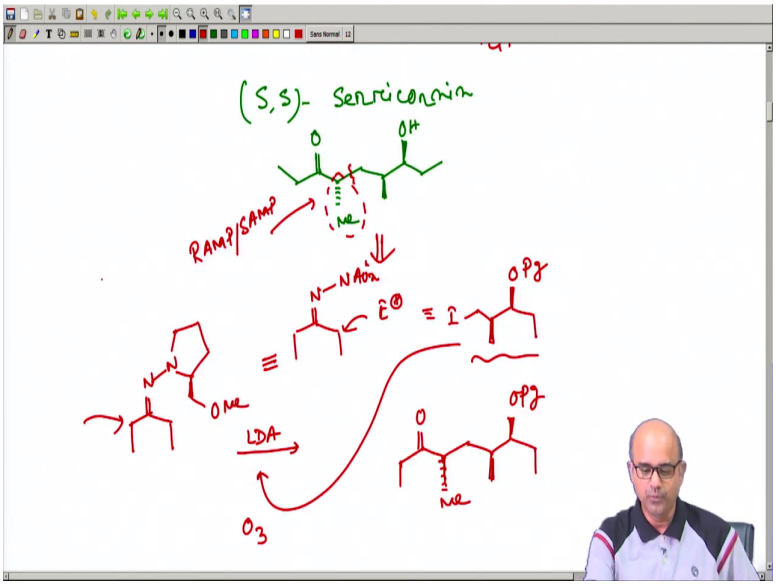

And next we will try to use the synthesis of a target molecule which is a natural product whose name is S, S serricornin. We will try to do a little bit of retrosynthesis of serricornin. Now, serricornin structure was ……let me first draw the structures and then how you can use this RAMP/SAMP based hydrazone based alkylation that we will be explaining. This and there is a OH here, there is other functional groups.

Definitely, we will be not going to talk about its complete synthesis and particularly for serricornin how it was reported in the literature, we are not going to discuss it. But, particularly this stereo center was seeming to be fixed by our RAMP/SAMP based methodology. So, let explain then how it was done and as this will be your alkylating portion and you can actually try to take a symmetric kind of ketone. So, this part is ethyl, this part is ethyl ok.

So, this will be your N auxiliary means the chiral part. So, your electrophile will be coming here. So, this will be your electrophile. So, now, you can write what could be the electrophile. So, you can see this bond you are going to be disconnected. So, you can have to take an electrophile which already contains this pre-existing stereo center. The free hydroxy group was not recommended, that probably need to be protected it with some protecting group, depending on your choice you can take the protecting group and rest of the thing……..

So, if this could be your electrophile, you can complete the synthesis by applying the normal working model. Now, let us see how we can do it. So, what we will be now you using as a starting material, you the symmetrical ketone ok. The based on the stereo center you actually choose the which RAMP or SAMP you have to use. So, we use this one and by working model if you take this as a precursor LDA and this will be your electrophile, you have to use this electrophile.

And, then definitely after that you just cleave with ozonolysis and actually you will going to get this, this, this part is the ketone and this part is your methyl. And, then you write in actually we have written in a wrong way. So, just you can do the absolute configuration mapping. This will be your below methyl and this will be your CH2 these things, this methyl. This protecting group you have to remove -Opg and then you can complete the synthesis.

Now, what I am trying to say normally if you follow the rule of thumb, this will be your alkylating part. So, you can just rearrange or redraw the compound. So, if you put a carbon electrophile bond here, you can redraw the entire thing. Now, this is once you deprotect the -Opg, this will be your serricornin which is the natural product which was obtained by this method.

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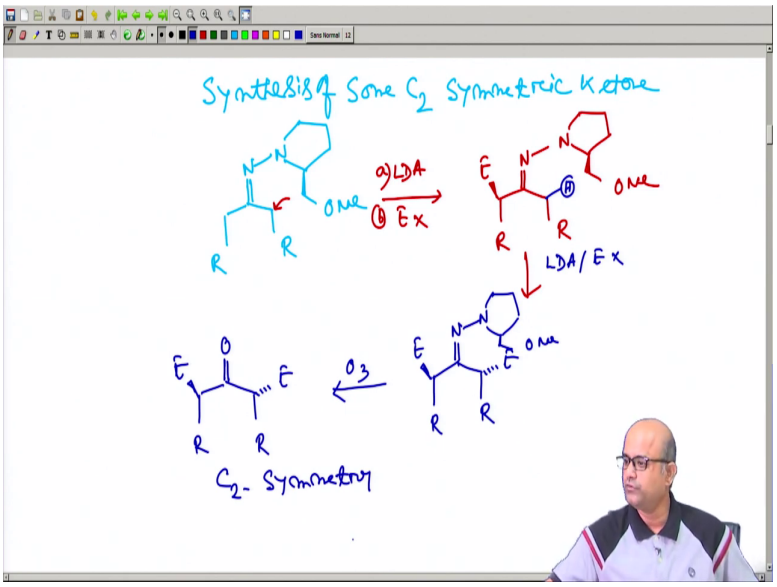

Now, synthetically there are other ways or you can synthetically manipulate. And, we will try to use this RAMP /SAMP technology for such a strategy for synthesis of some C_2 symmetric ketone. Some C_2 symmetric ketone you know can be synthesized by using RAMP/ SAMP based technology. Now, initially you choose symmetrical ketone, as I am saying that symmetrical ketone was a prerequisite for this RAMP/ SAMP base method.

Normally, if you take an unsymmetrical ketone, you will be having difficulty. So, you take any of such symmetrical ketone with a RAMP/ SAMP based thing. And, then what you do? You now you can see that if you choose this compound little bit judiciously or same auxiliary you can keep, you can do an alkylation here first and then once this alkylation once done, this carbon will be sterically crowded.

So, this hydrogen will now kinetically more acidic and you can abstract this hydrogen, this the auxiliary remains same. But so, let us do one by one. So, first you treat with LDA and you react with an electrophile E-X. So, according to the working model, what we have seen here. This will be your R, this will be your R. Now, E will be here ok fine.

You do not cleave the auxiliary. So, you keep everything as it is, this OMe. Now, if you follow the rule of thumb, we have drawn in this way; that means, this way. But, now this hydrogen will be now abstracted. You can redraw it, but in the rule of thumb if this is beta, now here will be you get the alpha alkylation. So, you do a second round of alkylation with LDA and same electrophile because you are trying to mate a pseudo symmetric molecule.

So, now what we will be getting? You get this will be your R, this will be double bond N with everything remains as it is, your auxiliary part. This already you made and the second one you actually make this ok R. So, now, you have to remove the auxiliary, just you can do an oxidative cleavage. So, now, you can see you actually get this R, this E and this R. Now, this kind of compounds are constitutionally symmetrical, but they have a nice C_2 symmetry.

So, such C_2 symmetry based carbonyl compound you can do a double alkylation, but one after one. This level of sequential alkylation you can make and you can create a C_2 symmetric based target molecule. This was quite nicely or judiciously done by this way.

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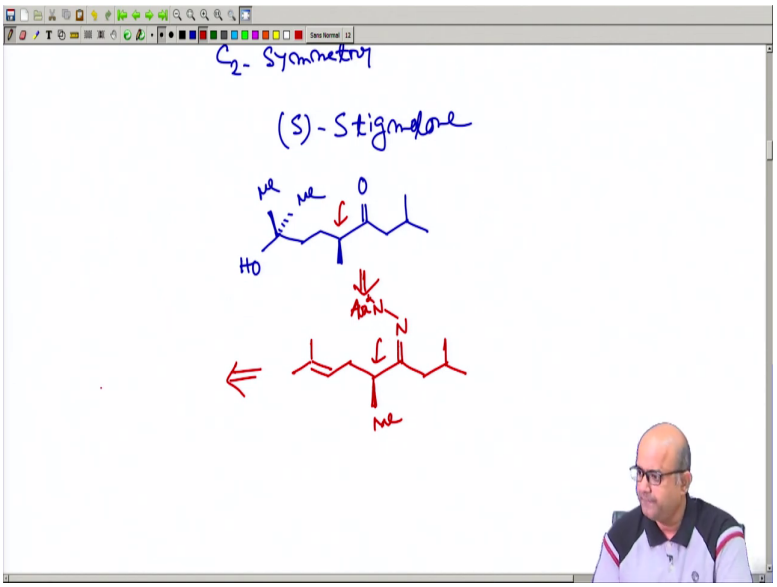

Let us try to use some of the more synthetic exploration and we will next try to use for the synthesis of a natural product whose name is stigmolone. It is a pretty small natural product. It does not contain that much stereo centers. This is a tertiary hydroxy compound containing component at the end. You have a gem dimethyl group, you have a 2 CH2, then you have a methyl.

And, definitely as you can see this methyl we can construct through the, this compound is stigmolone. And, we are talking about this particular stereo center which you can make through RAMP /SAMP based technology. So, what usually was preferred, the retro OH actually this was something like preferred in this way. This auxiliary choice is yours.

Now, you can just see that this terminal double bond can selectively be undergoing a hydration…… with a Markovnikov type of hydration, you get this tertiary alcohol. Now, how you can create this ketone? With this now this was the particular stereo center you can create from RAMP /SAMP. This can be definitely done. Let me go back little bit, we will just try to use a different piece of paper and or in the digital board.

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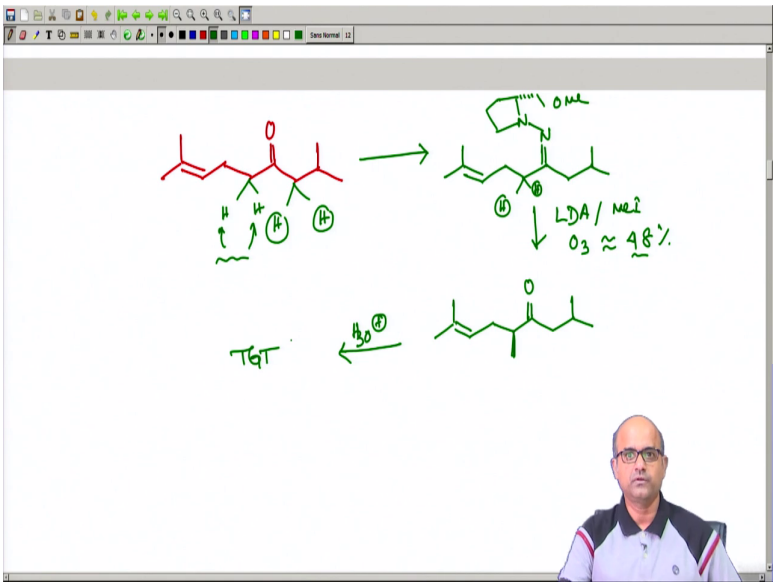

So, now you try to take a compound which seems to be having this structure. Now, definitely this compound is a non-symmetrical compound, that was one of the point in this synthesis. But, still for this compound, the idea was probably this isopropyl group seems to be little bit bulky. So, you do have a regiochemical issues, but when this kinetic acetate is coming for this compound, you do not have such things you basically have a CH2 and here you have a isopropyl group. So, definitely probably this hydrogen seems to be kinetically more acidic ok.

So, this can be picked up though this was definitely not recommended because, you might have a regiochemical issue. Now, we will explain. So, first you take this compound and first you convert it to corresponding hydrazone, the chiral hydrazone which you need to make. So, this hydrazone the drawing will be this and if you try to take the rule of thumb, we have drawn it like this.

Now, as I am saying that you will just try to do the alkylation at this part, but definitely regiochemistry will be a big issue ok. So, LDA electrophile will be ……..your methyl iodide fine and then followed by you do a ozonolysis, but the point is the yield was 48

percent. So; that means, that definitely the other regioisomers or alkylation also taking part here.

So, the desired stereochemistry which is needed by us, definitely you get one thing; means this CH3 CH2, then you get this one. And then you try to; obviously, the other alkylated product also you will get, because the yield is only 48 percent. Rest is absolutely simple, you just do a Markovnikov hydration with $H3O^+$ and you get your target molecule. This seems to be quite doable and you can actually complete the synthesis with a very short span of time.

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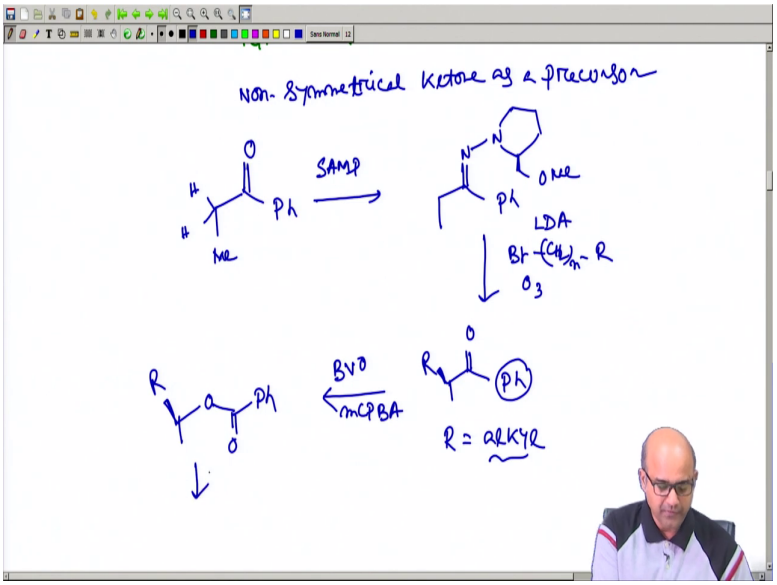

Now, there will be some other synthetic manipulation for such compounds or this kind of RAMP /SAMP based alkylation strategies. We already earlier said that non-symmetrical ketone is not a good precursor, non-symmetrical ketones. But, it is sometimes you can also use this non-symmetrical ketone as a precursor. Earlier, we said that these compounds are non-symmetrical ketones are not good precursor.

But, try to remember non-symmetrical ketone with two sites available for abstractable hydrogen. But, if some ketones are there where you do not have any abstractable hydrogen like phenyl, then this is basically like a symmetrical ketone. Because, always the hydrogen will be abstracted from this one, this is the only available hydrogen ok. So, now, let us use this kind of compounds could be potentially very good substrate ok, for such thing.

So, here you just try to use your RAMP or SAMP any particular hydrazone. So, you take Ph and CH 2 Me, then you write the drawing required for our working model so, this OMe. Then, now electrophile choice probably you choose some electrophile, let us say you take a typical electrophile like Br and CH2 whole something n-R. I am just trying to give you a different synthetically experience, that how you can manipulate this compound.

Now, definitely you can say that once you do an alkylation with LDA followed by this and followed by you do a ozonolysis. So, these all three you have to do it. So, what you will get? You actually get this, this will be ketone, this will be Ph and definitely this as it is above. So, you will get a R, completely this R group ok, fine. Now, you can see that this is a non-symmetrical ketone.

And, if you try to do a Baeyer Villiger oxidation now, with a mCPBA as an oxidizing agent, this phenyl group seems to be a better migratory aptitude if this R is kind of an alkyl. So, earlier we said that R is alkyl. So, definitely and Baeyer-Villiger rearrangement, retention of stereo genic center took place. So, this stereo genic center will remain as it is. So, now, you can eventually find that this will be your R and oxygen will migrate towards the O CO Ph. So, definitely you will to get this compound.

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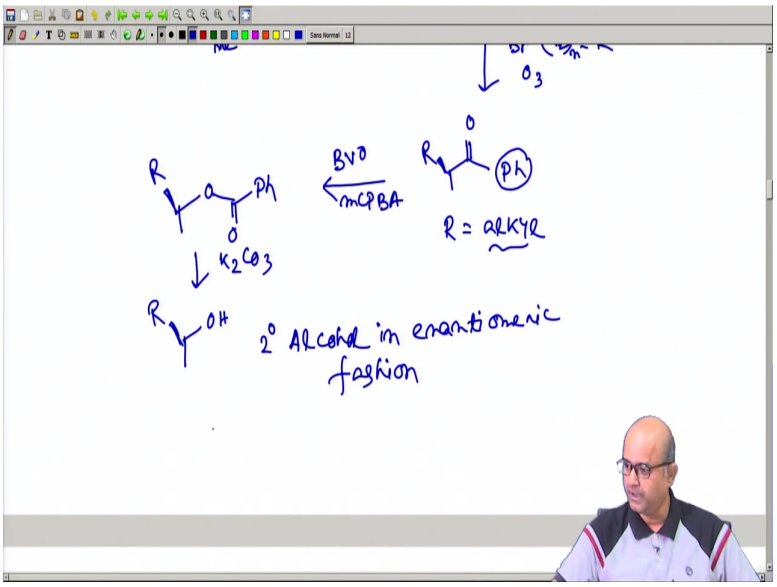

Now, this compound is what? This component is simple benzoate ester, this compound is benzoate ester. And, you actually can simply do a hydrolysis by potassium carbonate and actually you will get a secondary alcohol starting from this Baeyer Villiger thing. So, this

kind of 2 degree alcohol, secondary alcohol in enantiopure fashion, in enantiomeric fashion. You can actually create it by using a RAMP /SAMP based technology.

But, RAMP SAMP based technology, it basically gives you an enolate or (Refer Time: 26:27) enolate alkylation. Latter, that you have to do a Baeyer Villiger oxidation by potentially keeping the fact that the electron deficient oxygen migrates towards the particular phenyl group ok. And, this was usually a good way of accessing secondary alcohol. And, actually such methodology was being used for some macrolide synthesis though we are not giving these things in little bit detail.

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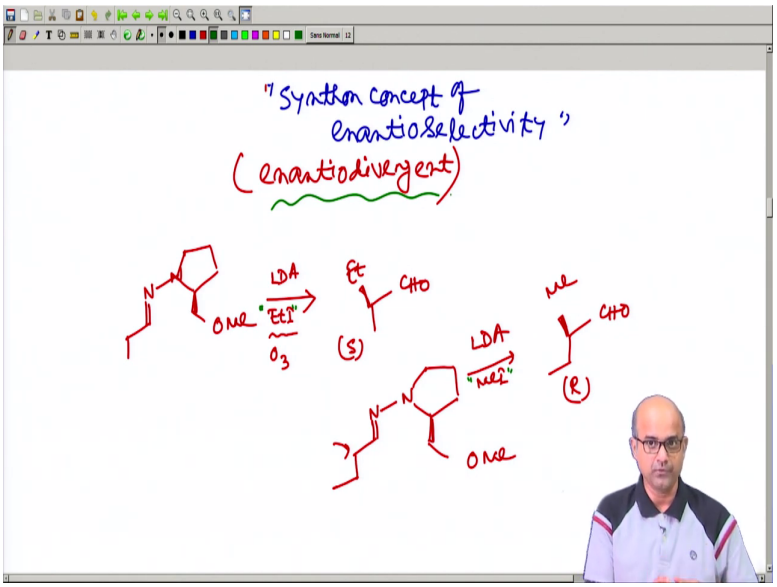

We will just quickly try to close this today's lecture with a new concept which already we have explained in the earlier part synthon concept of enantioselectivity. Now, what does it mean? It means that by using a same auxiliary you can actually access both the enantiomer of the target molecule, its enantio divergent concept. And, this was usually we earlier used for the Meyer's oxazoline pathway, you have seen that how two reagents have been sequentially added and you can actually do it. Now, let me try to get these things in a way. So, first we just take example.

So, you take this, this and this as your first auxiliary, I mean this particular. So, this is a 3 carbon CH3 CH2 CHO, you just did a SAMP based hydrazone thing. Now, you react with LDA and as an electrophile, I will be using ethyl iodide, will be now quite clear the first we are adding ethyl iodide. Now, what will be our new stereo center, the stereo chemistry as

OMe is above will be just ethyl will be above, then you will be removed with ozone. So, what will be then our final compound configuration? This will be there, this will be CHO, this will be ethyl fine.

Now, let us say by using the same thing, how you can synthesize the enantiomer of the compound. Now, for doing this one, for the other enantiomer you actually have to take a little bit of different a different precursor. Now, I am trying to do it in this way. Now, this compound the normal carbon is 1 2 3 ok. So, this here I have taken an actually a butanol backbone 1 2 3. Now, the same auxiliary we have used.

Now, what I am doing? I am doing it with LDA, but now we are using a methyl iodide as an electrophile. Now, methyl iodide means you will be now getting a new carbon electrophile bond here. So, first write this, this, this, this is the original one ok and then see methyl. Now, say this compounds on this compound, if you now try to write the absolute configuration, this is S same compound and this is R.

So, what causes the entire enantio divergency? The choice of reagent. In one case we add ethyl first, one case we add methyl first. Actually, this is a basically a normal C4 backbone or C3 backbone. The first case we took a C3 backbone, we add a C2 electrophile ok, that gives you a S-2 methyl butanol. The second case it says C4 backbone, you add a C1 electrophile.

So, the final product is a C5 carbon backbone. So, this was just a synthetic pathway starting from a same auxiliary with same enantio preference, just changing the synthon of the starting material you can create or you can access both the enantiomer. So, in principle this is enantio divergent concept and if you remember in the earlier when we talked about Meyer's oxazoline, we actually literally use the similar kind of strategy where by changing the reagent sequences, you can create both the enantiomers of a gamma lactone 5 membered lactone by using a same oxazoline.

This is nothing new in terms of the strategy considered. But, the main thing is you have to choose the synthon in such a way, you can control its original thing. So, we will discuss few more things in the subsequent lecture. And, then we will be coming with new synthetic exploration of Ender's RAMP and SAMP based alkylation, what are the potential disadvantages we have discussed. Because, we see that in many times if you have a symmetrical compound, this is the only limitation. Non-symmetrical usually it gives you a little bit less yield and less stereo control.

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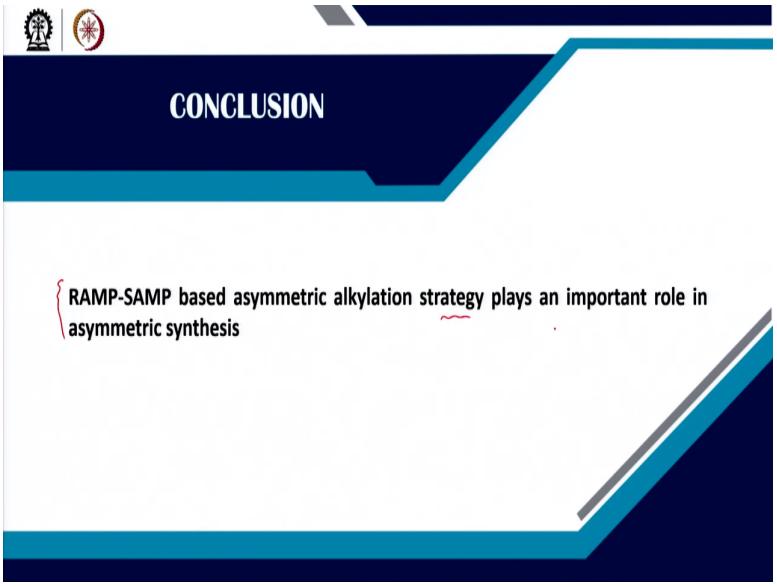

So, finally, as a concluding remark for today's lecture, you can see that RAMP/SAMP based asymmetric alkylation strategy seems to play very important or significant role in the field of asymmetric synthesis. As this strategy is very much powerful and you can create a large number of chiral intermediates with a specific stereo center and you can judiciously control the stereo center.

So thank you, we will discuss more things in the coming days.