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 - 08
Aza-Enolate alkylation
Lecture - 36
Coltart's cyclic carbamate hydrazone and its exploration

So, welcome back. So, in this particular module 7 and lecture 36 seems to be the final lecture in continuation with the earlier discussion. We will mainly talking about this Coltarts cyclic Carbamate based hydrazone and its exploration.

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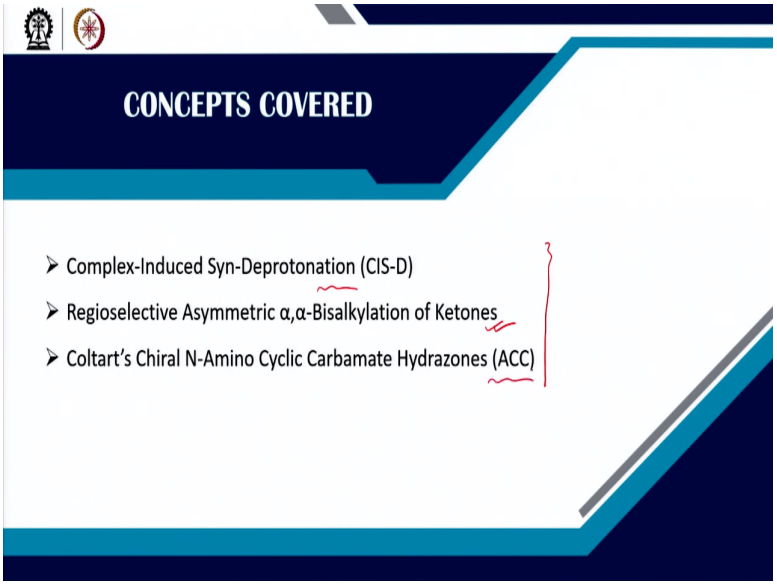

So, the main content which we are going to cover based on these three concepts. We will talking about complex induced syn deprotonation which seems to be unique feature for this Coltart's ACC based hydrazone. How regioselectivity can be achieved with this particular type of hydrazone? And, how synthetically you can manipulate this Coltart's asymmetric cyclic carbamate hydrazone?

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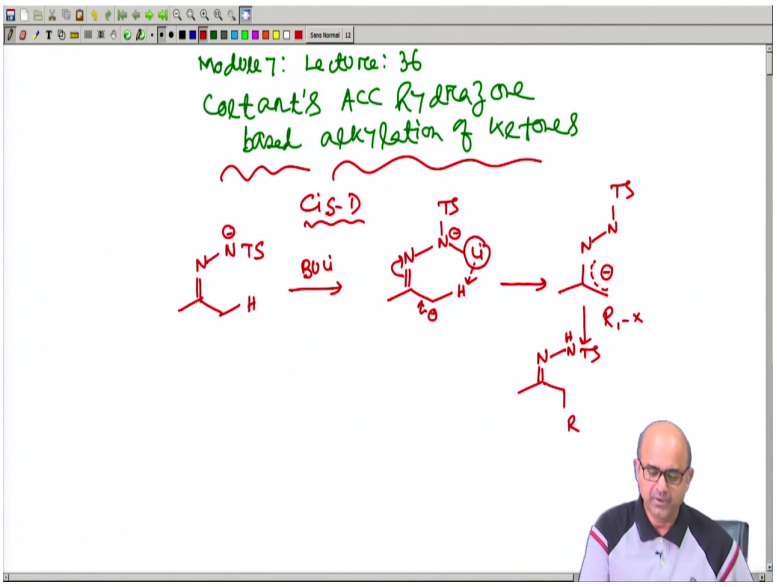

So, we are discussing this Coltarts ACC hydrazone based alkylation of ketones. Normally, last class we talked about a new concept CIS-D which seems to be abbreviated from of complex induced syn deprotonation. Now, normally such syn deprotonation if you check, it was already known for the Shapiro or similar kind of reaction.

Now, what is exactly happening in the syn deprotonation? If you take a Shapiro kind of reaction where a N….. N minus Ts was usually used or N, N, H, Ts now initially your butyl lithium or any base was used. And, what it does? It actually first give you a N, then N TS and then lithium is there and this lithium seems to be your coordinating or it tries to give you a coordination with this close proximity hydrazone which seems to be the alpha of this imine, ok.

So, now initially if you try to think about on the similar concept this is going to be you get a nitrogen as well as carbon centered negative charge. And then your NTs was there. So, because once you abstract this thing, it will be trying to give you this ok. Now, then further alkylation or suitable electrophile which later on we can do it and then you get this CH2 or N, H, Ts.

So, this is usually happening in typical Shapiro kind of reaction, but Shapiro kind of reaction you will actually get rid of this tosyl amine. Now, similarly this was the complex induced means complex initially you form say N minus Li and this Li. Now, here if you try to get a carbonyl or other some coordinating group which also in close proximity.

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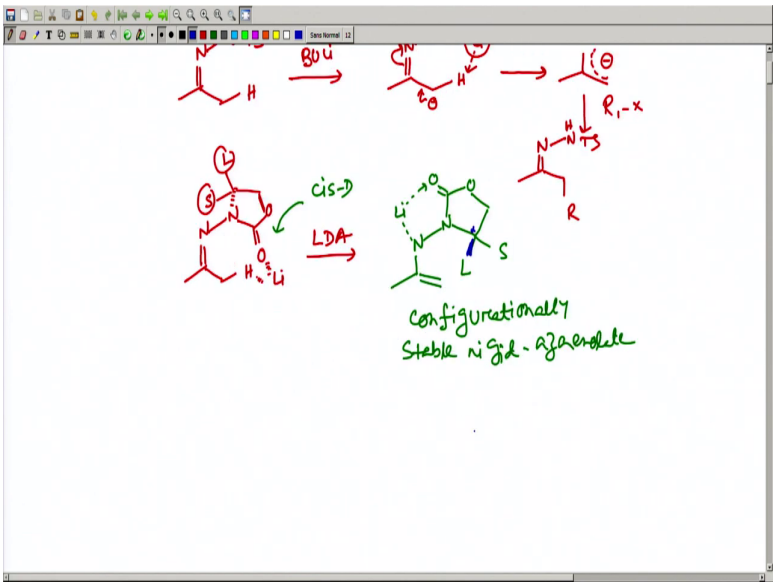

Now, originally the Coltart system which was principally if you can write let me draw in this way. So, you have a typical imine system now here you do a cyclic part and the earlier slide which you have drawn the complex camphor derived thing we are just trying to give you a with a large group is a small group.

We just abbreviating is that this and then you have a C double bond O you have a carbamate. So, this is the simplified version of this Coltart's system. Now what I am trying to say that this carbonyl initially coordinates with the lithium of the any base. And then it is also in close proximity of the hydrogen because that is going to be picked up.

So, you treat with base as I said and this is the CSI-D fact which is operating here the complex induced syn deprotonation. So, normally what will be happening? You basically get the corresponding aza enolate ok. Now, this aza enolate once you get you are actually you write this the cyclic hydrogen part. Now, this nitrogen now becomes a negative and lithium is here now the beauty of this system is the C double bond O. Now, this entire part it having a carbonyl group.

So, this again can rotate around this thing so that the coordination might be possible. So, earlier we have kept in this way the large group and small group. Now, eventually this initially this large now comes here and the small now comes here. Now, you have a rigid cyclic chelate. So, this configurationally stable chelate was the main the important factor for the stereo controlling element configurationally stable rigid aza enolate.

So, this rigid aza enolate seems to be the main factor. Now, here the stereo center of this particular carbon is fixed. So, if you have a large group above now you can easily see that the enolate this face the top face is not available ok. So, means that the bottom face you can actually the electrophile can approach. So, this was the main thing which you are going to talk. Now, let me try to give you a little bit of more pictorial representation in different way.

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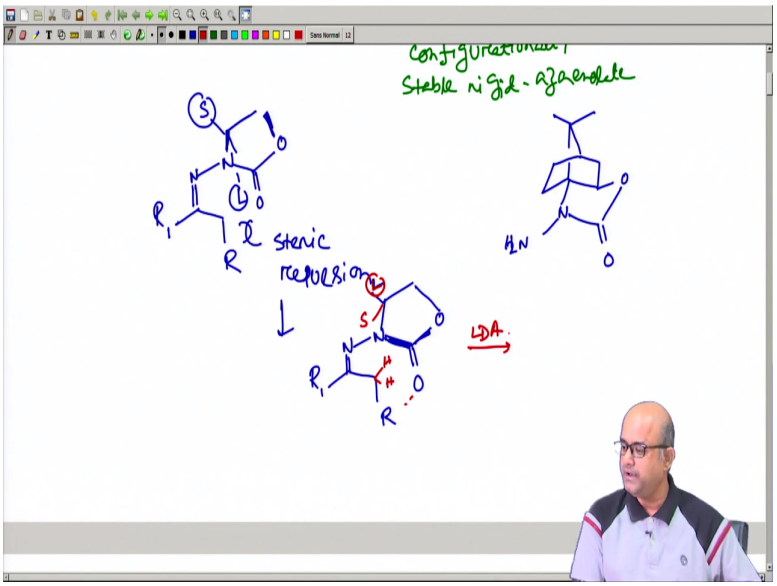

Let us say we try to take a compound which is non symmetrical we said the regio chemistry was a big issue. So, R1 this CH2R ok. And then initially you have this N. So, first you put it like this that you have a carbamate is there because you are always trying to put the carbonyl in the same close proximity of this thing. So, I have just written this and you have a small group here and you have a large group which also try to be here in this way.

Now, if you write in this way probably this large group which was the gem dimethyl group in the cyclic hydrazone. We can eventually write this cyclic hydrazone once more that will serve our purpose. So, this is the cyclic hydrazone we are talking about. So, N this H2 N CH double bond O. So, this part we are talking about. Now, this large group means the entire bulky bridged part ok. Now definitely, if you have this kind of thing you definitely have a steric crowding here, ok.

So, a L group is trying to be reorient itself in a different way. So, there is a steric repulsion. Now, this steric repulsion probably will force the typical of this compound to a rotate. Now,

we can just try to write in this way the double bond N. This N and then this will be the above part the C double bond O.

And this O naturally such thing was very much difficult to understand in the drawing part, but if you have a model that will be quite clear, but here this is the L group and this is the small group. So, now, it is quite steric free. Now, in this case this will be now take part in this hydrazones are there. So, your CIS deprotonation will be now taking part with LDA treatment.

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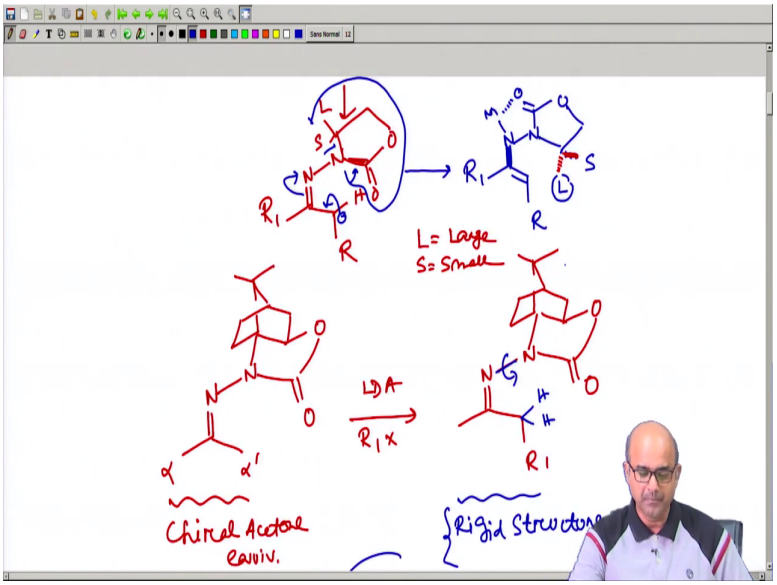

So, LDA treatment the moment you have this CIS-D, CIS-D means you just try to take this compound this R1 this R and you have this hydrogen, double bond N your N C double bond O O and this ok.

So, you have a large you have a small. So, syn deprotonation now takes. Now, the moment you have a syn deprotonation means you trying to get your minus here. So, this minus we will now switch over to this here and you give you N minus. Now, this N minus moment you get a N minus here, that will again try to give you a further coordination. Now, this coordination means the carbonyl will now again rotate.

So, let me now try to rotate the carbonyl. This will be your single bond now and this will be the typical aza enolate kind of thing your N. You have a metal ok or lithium this N ok. And then you will find that this will be N C double bond O with an oxygen and this. Now, this

absolute stereo center will be,,,,,,,,, I mean whatever stereo center you have taken that will remain as it is. So, it could be the L and could be S ok.

Now, see this rigid chelation we are talking about, now this is quite clear. So, with this enolate the L group is the larger group which now focus that the enolate alkylation is not possible from the top face it will be from the bottom face or if you take the other enantiomer where this will be above and this will be below. So, this choice is depending on which enantiomer of this initial carbonyl compound you choose.

So, L is a large substituent and S is a small substituent. Now, normally this gives you a pretty good stereo control. Now, here as I am; as I am trying to give you a little bit more emphasis……. we just try to do it few things on a different aspect. So, let me try to draw the compound it is a simple acetone kind of compound you then write the cyclic hydrazone part this ok.

So, this is N, this is O, this is C double bond O. So, initial acetone does not create any problem. So, first you do a normal LDA. So, (Refer Time: 13:53) this is alpha, this is alpha prime. This is a chiral acetone equivalent you can think about or acetone equivalent ok acetone equivalent. Now, first you take R1 X. Now, moment you create R 1 X you get this as a R1. The auxiliary part was remaining similar. The regio chemical feature now you have to explain in terms of CIS- D; and there are some prerequisites which you have to take care.

Now, you may argue that this nitrogen bond can freely rotate. Now, here this is the first prerequisite that this particular nitrogen bond it rotation is restricted. So, this is more or less conformationally pretty rigid, and such rigid structure its actually have been proven from the corresponding X-ray structure that once you make this first alkylation the compound its frozen in this conformation ok. So, this N nitrogen N N bond if it can rotate it can actually go to that side.

But it is not going to be rotated. So, initially this was the main pre assumption for successful exploration of this model, now once this CO. So, means that this CO carbonyl and this more substituted hydrogen is always on the same side. So, this was the initial pre assumption

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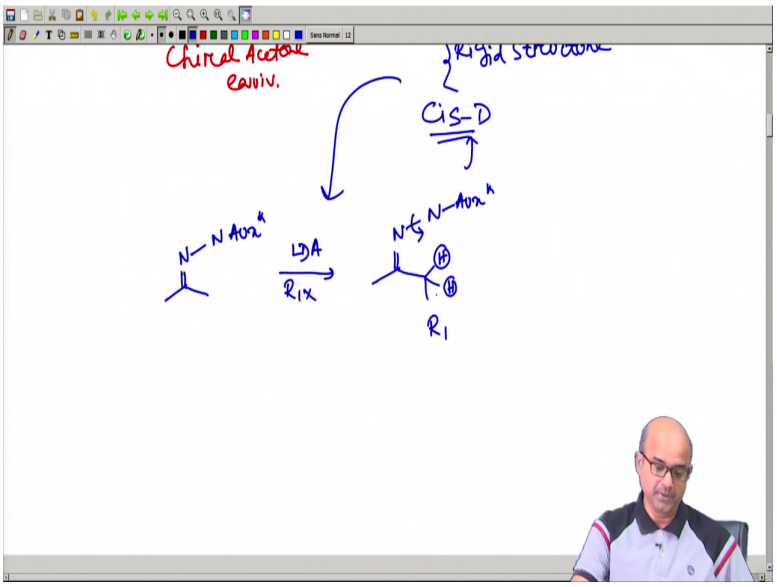

So, this presumption you need to be take care and this is our CIS-D assumption, the complex induced CIS deprotonation. Now, once you do it means once your initial assumption was done, then what you are trying to do? You are actually next going to be abstract the hydrogen which is there ok.

Now, this thing you can next explain the working model which you have just now talked about. So, initially to avoid this complex thing you can now simply write a cyclic carbamate based on the C double bond O with the group like a L large as well as small.

Now, initially hydrazone abstraction will give you a minus here that will give you an imine enamine tautomerism and puts a negative charge on nitrogen, fine. Now, this nitrogen we will now then focus that this entire auxiliary around this N carbon bond and this bond can rotate, but this N-N bond cannot rotate. So, this was definitely. So, within this framework the entire of this portion is going through little bit flexible or rotate, then that basically puts you the CO and the N minus with the metal on the close proximity.

So, a rigid chelate can form; now by this rotation the large group and S group. So, large group is mainly the bridge dimethyl containing group it has to be now orient on this part. Now, this orientation actually enforces or give a message to the enolate or electrophile can now approach from opposite to the large group. So, this was the main idea of this entire system which we are going to talk in terms of this Coltart's asymmetric hydrogenation sorry asymmetry alkylation.

Now so, eventually if you can now try to try to rationalize the entire thing that you take a chiral sorry this normal auxiliary not the RAMP/SAMP. This N-N auxiliary was always fixed you first take a LDA with R1X and you get this R1. Now, this is the single hydrazone you actually get because this N-N bond rotation is not allowed is frozen. Now, and this actually give you the second round of alkylation based on the kinetically controlled…….. this kind of hydrogen seems to be not kinetically acidic because of sterically crowded.

But still as the auxiliary carbonyl was induced in the complex induced syn deprotonation that basically gives you the regio control in the overall pathway. So, anyway this was a bit complicated, but we can expect a very good asymmetric induction for the entire system. So, now, let me try to talk about few things which we can discuss with the help of such compound. So, we will just trying to give you a bit application oriented thing

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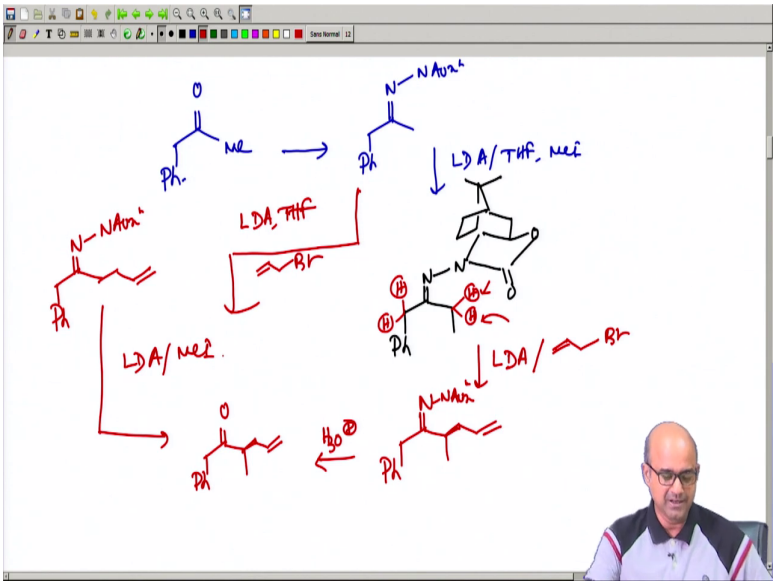

So, take a compound like this PhCH2CO methyl. This was a simple compound and then this compound you just fused sorry you put the auxiliary part as there. Now, in this case it was absolutely no problem this is the kinetically more labile hydrogen there is no stereo chemistry involved.

So, you just do a LDA, THF methyl iodide. So, now, the next part was crucial because now what you get? You get Ph you get this you get this; and now here you get N, this N and then you can write the entire auxiliary part. This, and then you have now your N C double bond O, this O, and this O. Now, what I am trying to say that this is the single hydrazone you will get

it now in this way, this two hydrogens are not available because they are not in the close proximity of the CO.

Because you get always a single hydrazone from this. Now only hydrogens which are available is basically either this or this. So, this you can eventually now control the second round of allylation with a let us say LDA and allyl bromide, now the moment you do it you can just do the asymmetric alkylation with the help of this.

Now, this stereo control will be depending on which auxiliary you choose. This auxiliary you just remain it and then you simply try to hydrolyze with this aquas acidic workup you can actually get PhCH2C double bond O with methyl with this allyl thing.

Now, the beauty was the actually the stereo control of the different enantiomers you can created by taking the same auxiliary. Now, if you take the auxiliary here, let me try to do a similar kind of reaction. So, with this auxiliary you first do a LDA, THF. Earlier, we have added methyl iodide here first you add allyl bromide. So, if you add first allyl bromide what you are going to get? You get Ph, you get CH2 C double bond N. This entire Coltart's auxiliary and then you get CH2 CH2 this compound.

Now, take this compound and add LDA with methyl iodide, now see everything will remain more or less similar, but the asymmetric induction what you are going to get.

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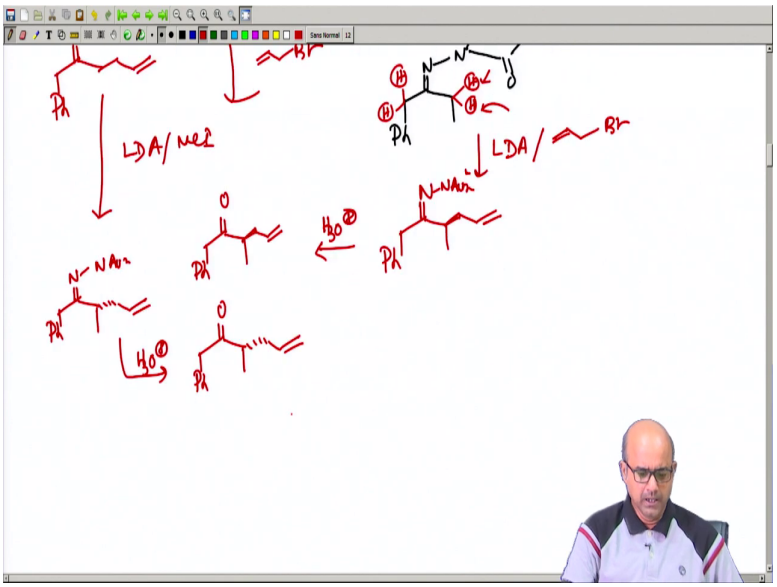

Because typically in the synthon concept. So, N this N auxiliary and then you have your methyl iodide you are adding. So, you can actually the get this and this, this thing. Now, after hydrolysis. So, this arrow was wrongly given, this actually will be coming up to this ……sorry yes.

Now, you just do the hydrolysis. So, you get PhCH2 C double bond O methyl. So, you can actually get two enantiomers two enantio divergent way by controlling the reagent sequences. This is usually done very nicely now such Coltart's asymmetric cyclic hydrogen based compound you can actually do couple of synthetic exercises.

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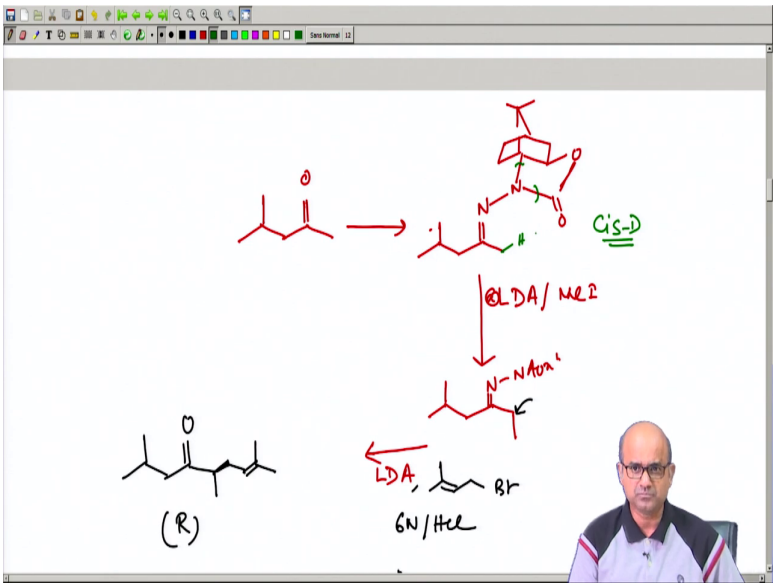

And one such synthetic application of CIS-D, now or synthetic exploration we will try to do it. So, initially if you take a ketone like something like this. And this ketone actually you can create by taking simple acetone or you can actually make this ketone by using taking acetone with this auxiliary fused.

And then add an isopropyl iodide, that is a different issue. Now, take this ketone and then react with your Coltart's cyclic thing in this, Coltart's cyclic thing means you just have to have a single hydrogen that was the beauty of the system and then you have O you have C double bond O you have O.

So, with these things now if you can see these are basically non symmetrical ketone ok non symmetrical ketone. Now, this first part you try to use this ketone and then if you take this

compound and let us say you do a first round of alkylation LDA methyl iodide. Now, this part is still fine because the kinetically this will be more labile. So, eventually you can do the first round of kinetic alkylation here ok.

So, LDA methyl iodide will give you this, this, this we write double bond N, N auxiliary and then you have a CH2, CH3. Next, you can just the earlier one which you have did you can use another round of LDA. Now, here the again the main duty was basically as it is frozen in this thing this hydrazone we will be abstracted. So, the point was that CIS-D was initial precursor what you prepared that basically controls the regiochemistry.

So, here now LDA, and then the electrophile next electrophile which you are which you are choosing is the prenyl bromide; and then you can just remove the auxiliary with 6 normal HCL or other part. So, then you have this C double bond O your methyl and here is the stereochemistry now coming into picture.

So, we will get this particular compound. Now, if you try to create the other enantiomer you just change the sequence of the reagent as I said by the synthon concept. So, you can do the if you take this compound this compound probably is the R isomer in this thing.

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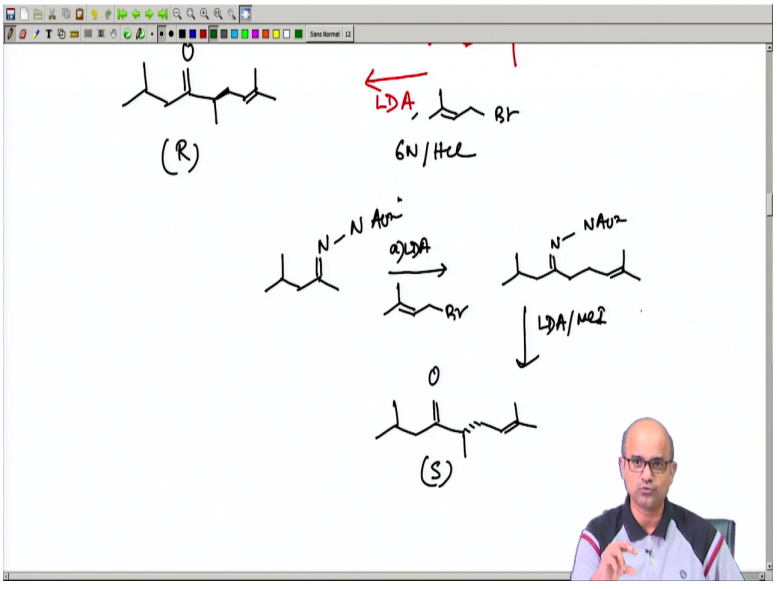

If you want to make the S compound this also can be quite possible you just take the same auxiliary N the Coltart's auxiliary and then you take these things. So, what you do first? You

react with LDA and first you add prenyl bromide. So, first you add the prenyl-bromide means this your auxiliary was this part the CIS-D will give.

So, CH2, again CH2, CH2, CH2, then you have this and this. Now, here now use the second round of LDA and methyl iodide. The second round of methyl iodide means you can now control the entire thing. And you eventually end up with the S isomer of the initial compound means this and you get this. So, it is more or less synthetically synthetic manipulation you add one reagent first another reagent second in the other case you add reagent second reagent in the first step and the first in the second step.

So, this kind of synthetic manipulation you can easily do, but the main advantage of this Coltart's method which we are trying to explain in the sense that the regiochemistry was the main governing factor in the entire case. And particularly this CIS-D, the CIS-D was the eventually the governing factor. The complex induced CIS-D deprotonation which probably is not happening in case of other cyclic hydrazones or like ramp samp based method hydrazone you it always end up with the regiochemical choices.

But this case, the initial starting hydrazone was frozen to a one conformation and that basically gives you other competing things you can simply omit. And then particular this complex inducing syn deprotonation gives you the regiochemical chemical control. And for the then the cyclic part of this hydrazone contains two bulky group one large one small mainly the large group which is a breached GM dimethyl group that basically controls the stereo chemical outcome.

You have to also take care of the typically what I am trying to say the cyclic rigid chelate. Once you abstract the hydrogen through cis deprotonation the normally this cyclic carbamate has to rotate little bit not around the N-N bond, but after the nitrogen bond is there it can eventually rotate through this either this or this and that basically forces the large group and the small group in the close proximity of this enolate.

And that gives you the stereo control in this thing, but anyway Coltart's cyclic hydrazone was definitely useful method, but it is a very complex method and conceptually very nicely designed. So, there are few applications which for the time being I am basically omitting because we are running out of time. We have four hours remaining in sorry 4 lectures remaining in the entire course. And finally, the remaining the 4 lectures we are trying to cover some new concept mainly the phase transfer catalysis in the asymmetric alkylation.

We will spend one lecture for the memory of chirality which is basically nothing but a self regeneration of stereo center in the amino acid derived enolate alkylation. And we will also talk about little bit of organocatalytic asymmetric alkylation in one lecture. And then at the final lecture we will just try to give you with all the concepts in a single lecture in a condensed fashion and then we will conclude.

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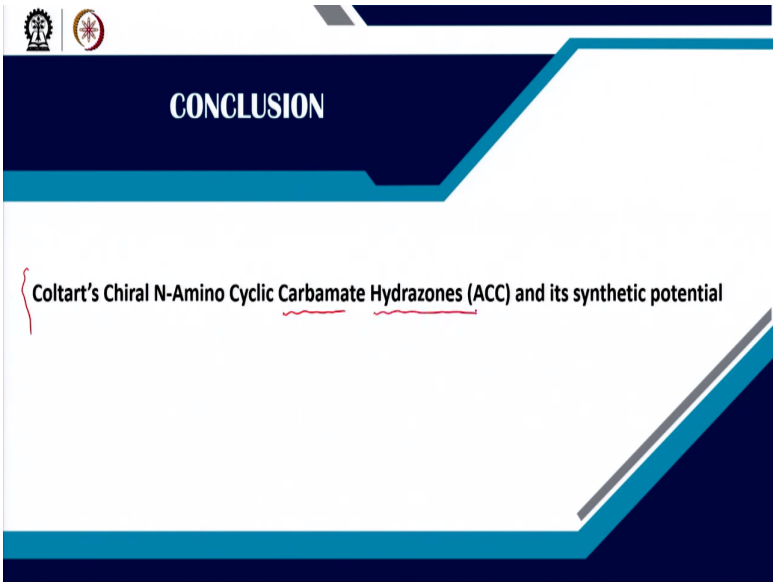

So, as a concluding remark you can see that Coltart's chiral N amino cyclic carbamate hydrazones and its synthetic usefulness……. probably this particular cyclic carbamate hydrazones is little bit advantages in terms of regiochemistry than the Enders well known RAMP-SAMP based method. So, we will try to give you a concluding verdict that cyclic carbamate hydrazones developed by Coltart is very novel and very innovative in its conceptual design.

Thank you. We will talk about the remaining 4 lectures in subsequent days.