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 - 03
Enolate alkylation of several carbonyl species
Lecture - 15
Evans oxazolidinone and related systems - V

Welcome back everyone. So, in this module which is supposed to be the final module of lecture 15 we will basically be talking about Evans oxazolidinone and related systems and its exploration in organic synthesis.

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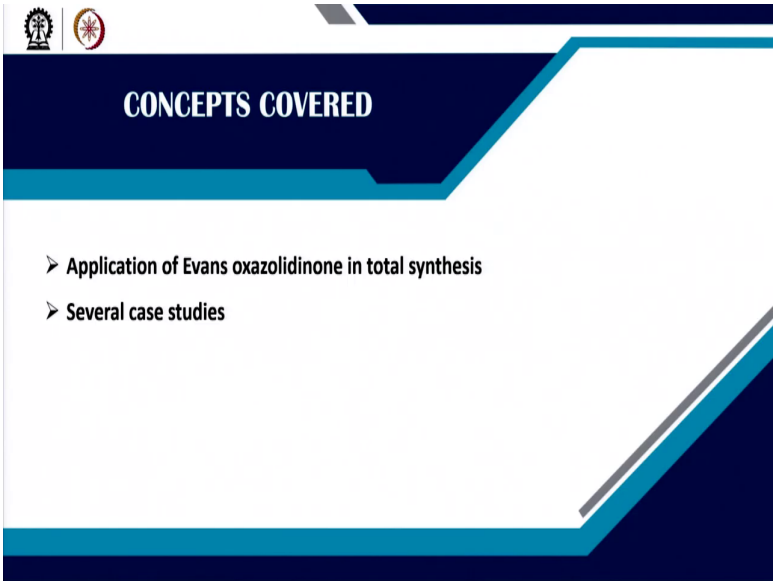

We will mainly discuss couple of case studies through a problem solving approach and how such intermediates can be used in synthesis of some value added product.

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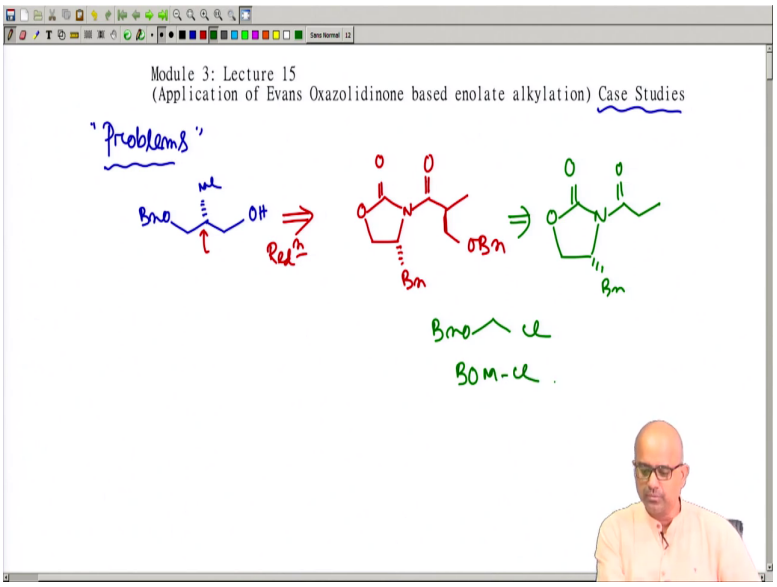

So, today in this module, which is module 3 and lecture 15 most probably the last lecture of this module, I will be trying to discuss couple of problems as well with Evans oxazolidinone based enolate alkylation. So, we will talk about the different case studies ……..let us start some of the problems which have been taken from relative literatures, literature references. We will try to analyze in a different way, let first try to draw the target structure which you want to make.

Now, if you initial first target was this molecule, if you see the structure of this is basically a 1 ,3 propane diol derivative and this stereo center we want methyl should be having this absolute configuration. Now, let me try to do the retro which you probably seem to do in a different way. Now as Evans oxazolidinone based thing was we need, so let me try to do in this way, any group you can basically choose; so depending on your choice. Now you have a benzyl group here OBn ok.

And you need to think that this CH2OH this CH2OH is basically coming from this oxazolidinone cleavage. So, the reductive cleavage you can think about ok. So, based on this, let me try to draw the structures. So, if you can think about something like this, this is basically the compound we are looking for once you do a reductive cleavage so, reduction. Now, this CO will give you a CH2 OH. Now, these two compounds are having same absolute configuration once you cleave it ok.

Now everything matches perfectly because you have a Bn and now what could be your electrophile? That is the most important part the way it has been written, it seems that if this Bn is basically below the CH2 OBn ok, its above now, fine. We will try to write in a normal oxazolidinone which you now need ok. So, Bn is this and if you can now take this compound everything matches very perfectly fine.

Now, what will be electrophile? So, electrophile will be BnO CH2 Cl this fine is basically a benzyl oxy methyl chloride. This compound is named as BOM chloride, similar like MOM chloride. And this is acting as a very good electrophile. So, similar kind of approaches with help other reaction conditions we have not written basically you need a reductive cleavage means in the forward pathway what you need.

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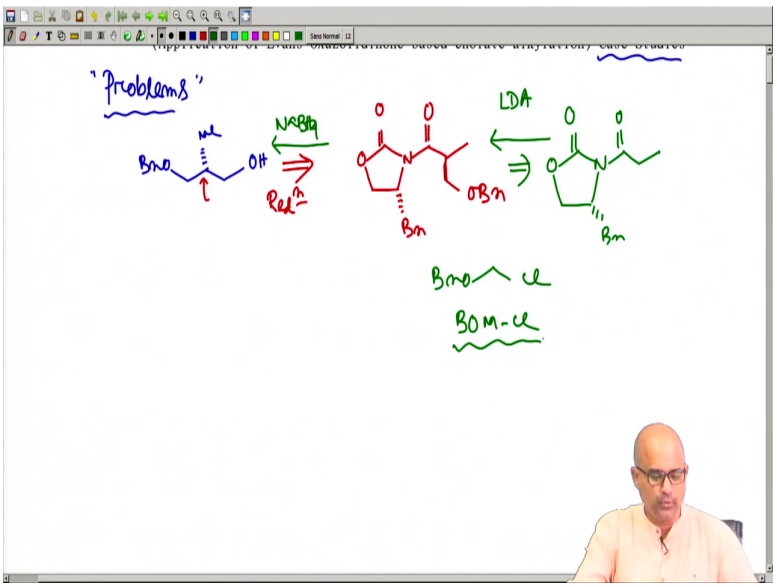

You actually need a reducing agent sodium borohydride or lithium borohydride and in this way basically you will try to use a normal base like LDA and solvent like THF or TH of HMPA and you need an electrophile something like this ok. That is the a very standard way of doing it.

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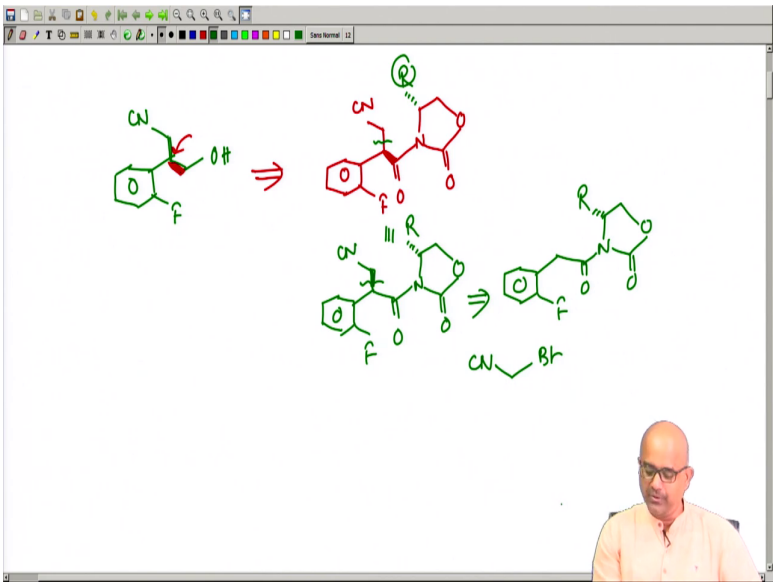

Try to do the next problem in the next problem what target let me first try to write draw the target at the very beginning.

So, then you can actually retrosynthetically we can cut or draw the molecule and then you can think that which could be the potential starting material have a CH2OH and we have a CH2 Cn here as a potential target structure. Now, if you see the absolute configuration, you can basically do the CIP. So, this CH2 OH is above the plane ok and this is the (Refer Time: 05:09).

Now, let me do the retro again on the similar way. Now this is CH2 OH, it means that this part we are trying to access from the auxiliary after reductive cleavage. So, by with this idea in your mind you just can try to draw the auxiliary based thing. Now, put the CH2 CN in the similar way, and then here as it is beta you put this beta ok. Now here you need to put the auxiliary fine.

And then, this is N this, this, this O; this is the auxiliary. Now where there is a fine catch, catch in the sense the CH2 CN it seems to be the coming from the electrophile ok so, but we have not we keep kept it on a plane ok. So, you need to do little bit rotation by keeping the absolute configuration similar, but by doing this you actually can just try to put the alkyl group here ok.

Now, this alkyl group is basically below. So, it means that I mean I have drawn it because I know the answer ok. Now, you can eventually try to write the absolute configuration of this compound, just by keeping the absolute configuration same. So, it will be basically give you these things ok. Now, I just did the simple carbon-carbon single bond rotation is free.

So, I took that liberty and this component this component is basically same. It means that the idea was very simple as R is below CH2 CN, if it has to be electrophile it will be coming from this. Now, how this compounds this compound you can create basically what you need? You basically need to oxazolidinone which is F, which is this and which is. So, this oxazolidinone if you can create everything is fine.

Now what could be the electrophile? You do this disconnection here. It means that the electrophile could be something like this. CNCH2 Br…… this is very well known electrophile and this is a commercially available actually ok. Now this compound you can use as electrophile.

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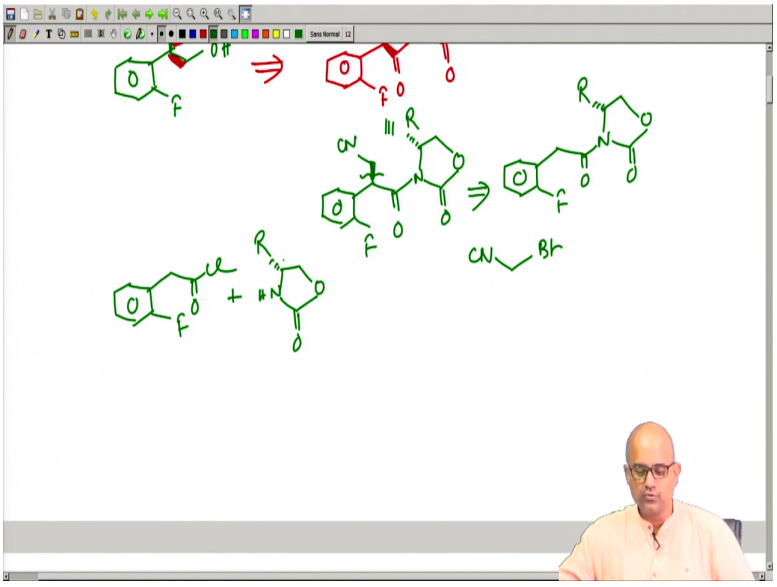

Now, rest of the synthesis seems to be pretty simple. So, what are the starting material you need? You actually need a starting material with this F with this CH2CO Cl and then, the auxiliary or oxazolidinone which you need it is basically this.

So, this is your oxazolidinone this is a starting material and rest of the part is pretty much similar, you can usually do it. Let us do it a little bit complex thing where retro might not be very suitable, but let us try to do it in the forward pathway.

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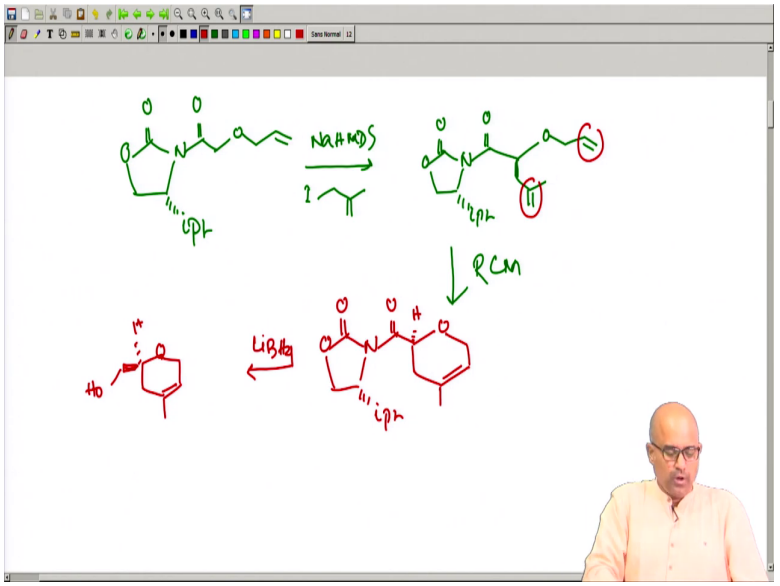

We have a system where this oxazolidinone its having derived from the valinol isopropyl group is there ok. And this part is having this kind of structure sorry; I did a mistake, so this will be deleted because you have to generate the enolate ok.

So, you will be this CH2 O and this is actually glycolic acid derivative ok remember if you remember in the previous few classes ago, we talked about this glycolic acid derived enolate alkylation. So, treat with base like NaHMDS fine, and this I this methyl double bond C, the isopropyl is below so, this will be above. So, very simple straight forward you can just apply this enolate alkylation method and you will be getting this and you will be getting this fine and CO then this will give you the O allo……. ok.

Now, this part is fine everything. Now, next there is a reaction which is named as ring closing metastasis reaction, which you some of you might be knowing it this olefin and this olefin undergoing ring closer with the expulsion of another molecule of ethylene actually and actually what will be happening you get a six-member ring. So, if you are not familiar with ring closing metaphysic just have a look and then with this thing you actually get a ring closing product.

You actually get this ring closing product with the double bond is so this beta. So, I put hydrogen is an alpha. So, this is the same thing, and now if you can remove the auxiliary this simple by reduction by lithium borohydride you can actually get a six-member intermediate with these things as a major product. So, such a small ring compounds in enantiopure fashion.

You can actually create and this is actually serve as an intermediate for a natural product though I am not going to give you the name, because that seems that gives you little bit complicated scenario; because the natural product structure is pretty much complicated. Similarly, you can apply the same strategy let me just try to give you a home assignment kind of thing.

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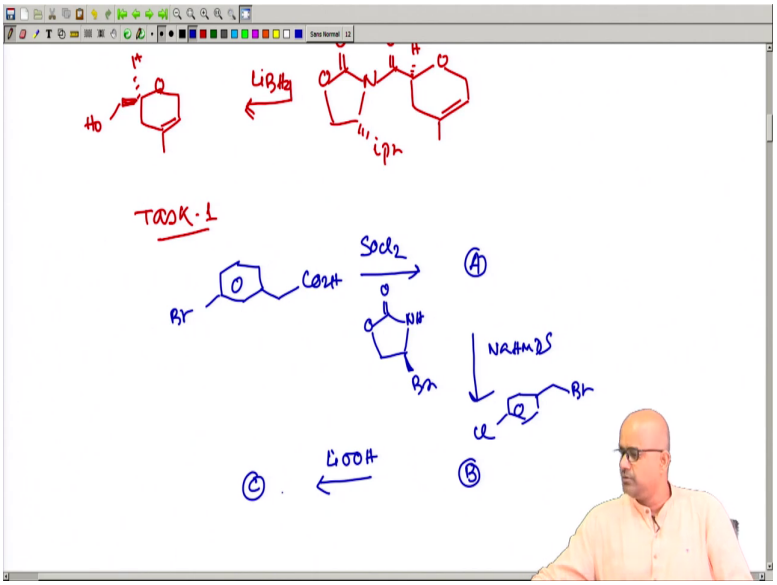

So, that also give you that idea that you can which you can try in your home task 1. So, let us start with this acid, which was meta bromo phenyl acetic acid you just try to condense with this first convert this corresponding acid chloride, and then take this oxazolidinone derived from the phenylalanine in all ok.

So, you know what you are going to get. So, you get A fine. Take compound A as a starting precursor ok. And next what will be trying to do you basically react with NaHMDS as a base fine and then the electrophile which seems to be interesting the 4-chloro benzyl bromide ok.

So, take this electrophile you get B you have to predict the absolute configuration take compound B as with u and treat with lithium hydro peroxide, you get compound C. So, what

is your task? You have to identify compound A compound B and compound C and this is basically taken from another literature synthesis report for a drug like molecule ok. You know you can just try to do this synthesis as a home assignment kind of thing.

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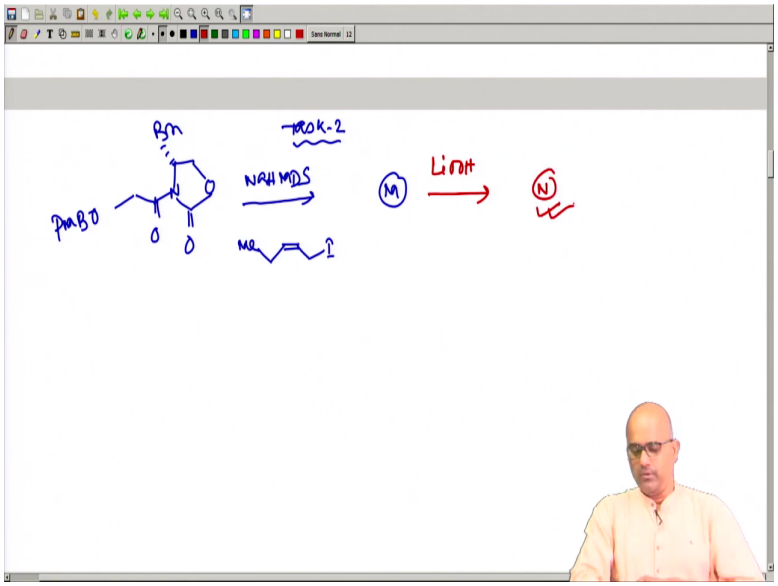

Let me try to give you another home assignment also this is more or less very simple let me first write the structure, then I will as oxazolidinone, so I write task 2 is oxazolidinone and here you are having a CH2 sorry let me just remove these things. So, it will basically give you a PMBO……. PMB is a basically protecting group. So, with this compound and then the stereo controlling element is the alpha benzyl group.

So, this oxazolidinone in your hand the reaction which is going to do if first with NaHMDS as a base followed by you react with this kind of Z allylic iodide, the first step. So, what will give you get compound M let us say, and then take this compound and also react with this lithium hydro peroxide and you will get a compound N. So, we have to definitely identify compound N and you can simply do it how to get this compound; a similar kind of problem analysis if you can do it.

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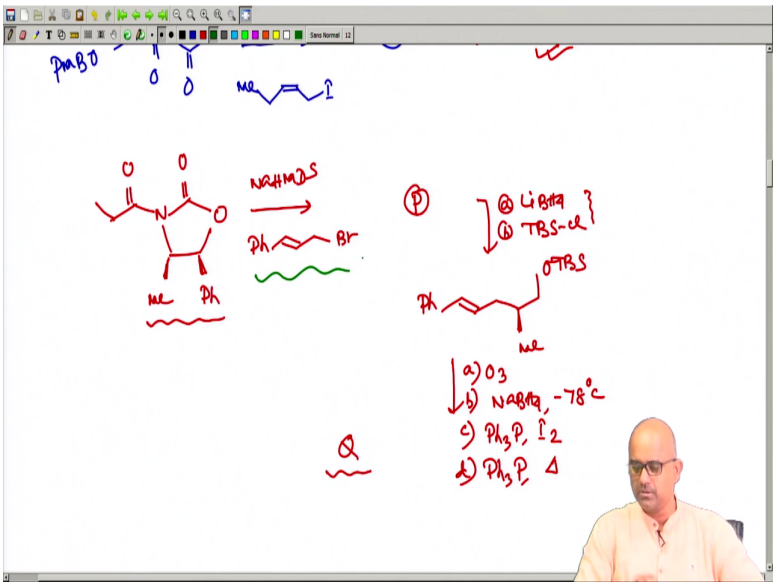

We will try to take another problem; we might be solving it which is a very simple one, but more you solve more efficiency you earn or you gain. So, this structure was little bit different which is basically a 1, 2 amino alcohol derived auxiliary both the auxiliaries have same sense of chirality. Because, this is the point of remember that, you if you take a methyl alpha and phenyl beta that could be typically disastrous choice.

Because, if one group is below one group is above the electrophile has a choice to make and then it will be definitely difficult for them, but in this case as both the groups are beta the steric crowding basically blocks the beta face. So, alpha face is more accessible ok. Now, in this case you take simple sodium NaHMDS which is the base cinnamyl bromide a E cinnamyl bromide was chosen as an electrophile ok.

So, you know what will be you will be getting means. So, you can just write down the compound, you can take it as a let us say P ok. Now, with this P in hand you do a reductive cleavage by lithium borohydride ok. Now means basically you will be getting an alcohol. And then you treat this compound with TBS chloride which is tertiary butyl dimethyl silyl-chloride. I will draw the structure what we will get after this reaction.

You have to basically predict the course of the reaction what is forming actually. So, you have to predict the structure of P first, then this structure was given, but you have to explain this region does what? This region does what? Ok. With this compound in hand the first thing is

the enolate alkylation by Evans method this is the main crucial thing. Second ozonolysis is the first reagent, and then the second region is sodium borohydride at low temperature.

ozonolysis basically means that you are cleaving the double bond and then you are getting the aldehyde that could be reacted, c, you are treating this compound with Ph3P iodine means a apple condition and d is again treating with rifenyl phosphine in reflux. So, you have to predict what is the structure of compound Q is very simple you can actually do it and the main idea was how you can control the enantioselective alkylation at this stage.

Rest of the state things are very much similar no need to bother you can eventually try to do it.

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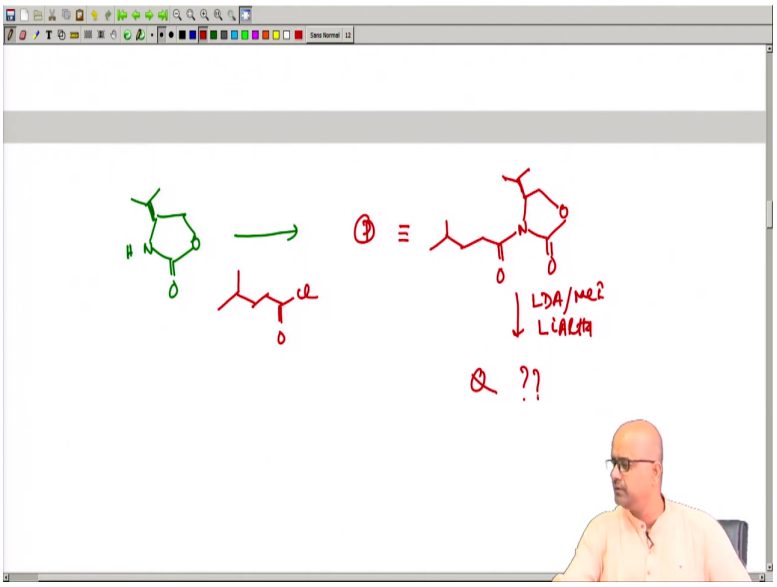

Now, similarly let try to give you another problem. So, this all these problems were basically based on Evans oxazolidinone based auxiliaries and there are very nice reviews available in the literature, though it will be sometimes it will be difficult for you people, but still if you are interested you can just go through it ok.

Now, for this compound this is the auxiliary which we are talking about. Now, this auxiliary was reacted with an acid derivative this acid derivative let us say you are taking an acid chloride. So, you know what could be the product. So, means that the P will be now this, this, this, this CO and this is your auxiliary.

Now, will be fused O this CO is a very simple I mean just I have drawn it for normal practice ok. And then you react with LDA methyl iodide as the electrophile and then, cleave it with lithium aluminum hydride. You know what could be the product fine. So, this will be very simple. This will be very simple and you have to predict.

Let us say structure Q, what could be the structure Q? So, this or the usual way the synthesis was done for various compounds in this Evans oxazolidinone methods. Now, sometimes there is complex compounds also can be synthesized and other compounds can be synthesized for a typical study.

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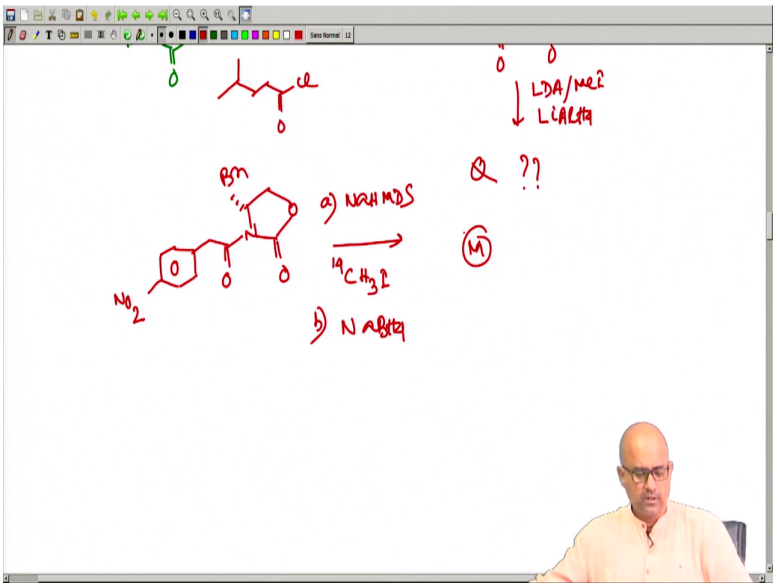

Let us say very interesting compound can also be synthesized I just try to give you the very brief outline.

Now, this kind of nitro 4 nitro phenyl acetic acid was reacted and you I mean you know that what kind of auxiliaries you can choose. So, you can choose it and then this compound was taken and it was reacted with NaHMDS ok and reacting with the electrophoil which is having a radioisotope level methyl iodide with 14 carbon ok carbon 14 ok.

And then step b, it was reacting with sodium borohydride. This means that this compound was basically used for a radio label purpose and they used a design drug molecule with a 14C isotope level ok. Anyway, we are not going to talk about this part, just you synthesize this

molecular hormonal structure you can just keep the structure as a you can how you can solve it.

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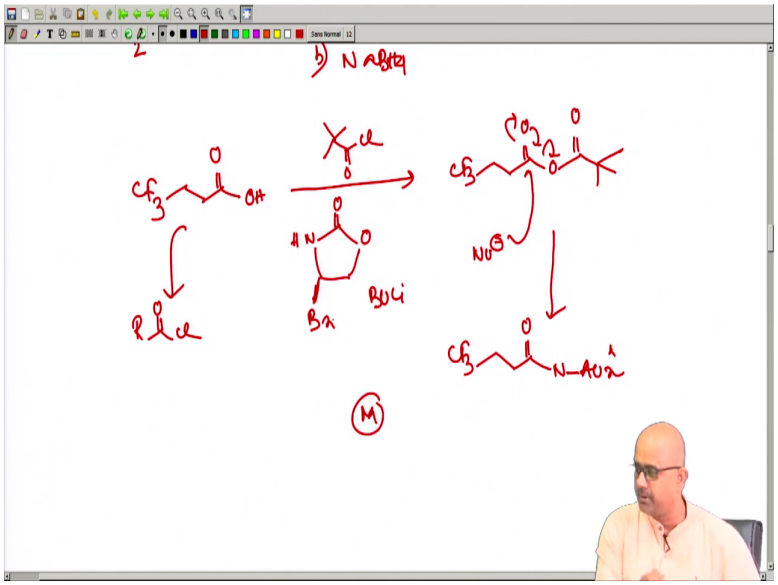

Similarly, I will just give you another problem a CF3 containing compound, means a CF3 containing carboxylic acid ok. So, these things you react with simple oxazolidinone this oxazolidinone which now will be trying to react this NCOO these things.

Now, actually carboxylic acid we said that normally carboxylic acid was usually how you can condense with this oxazolidinone. The best way to do it initially was to convert this carboxylic acid to acid chloride fine. But as it provides sometimes they are difficult to handle. So, normally what people do, they actually take this acid and react with pivaloyl chloride.

Now, pivaloyl chloride means a tert butyl CO CP (Refer Time: 23:21). Now what happens in the pivaloyl chloride basically you get a mixed anhydride. So, you get CF3 CH2 C double bond to OC double bond to this, this, this. This mixed anhydrite, now you have this oxazolidinone nucleophile. Here you treat with oxazolidinone and a butyl lithium. So, it becomes N minus Li plus. Now this nucleophile actually attacks here ok.

And this is attacking this goes this goes and this finally, goes up and. So, this is the now the standard state for our way, replacing with the acid chloride with a mixed anhydride method and then what we will get you get CF3, you get CN and then your oxazolidinone part, the

auxiliary will be fulfilled now. So, you have to predict what could be the final initial compound you get after this reaction ok.

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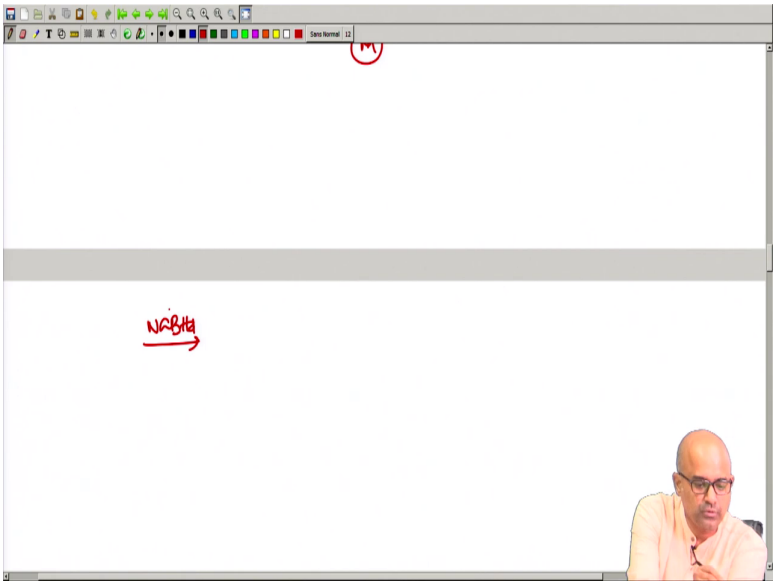

And then your next part is the enolate alkylation or that is very simple. So, you treat with sodium borohydride sorry is not sodium borohydride, you have to do the alkylation first.

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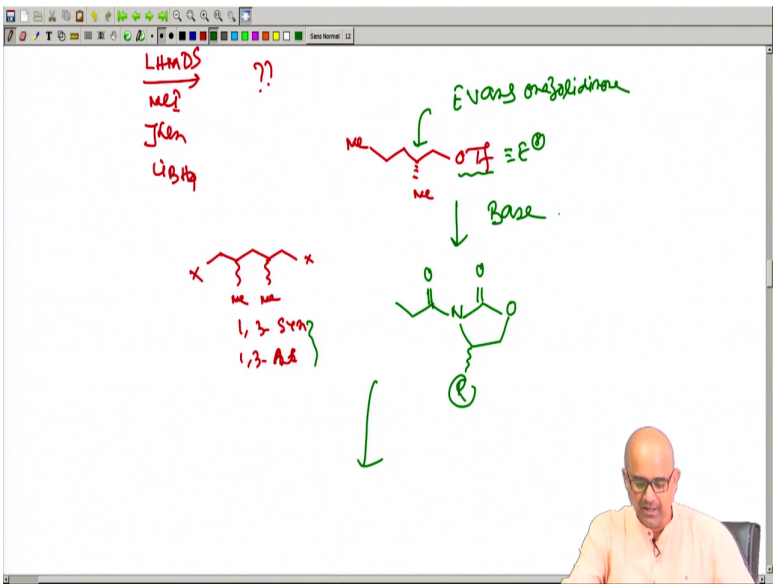

So, alkylation you do it by the condition was similar you treat with LHMDS take an electrophile like a methyl iodide and then you react with lithium borohydride. So, then you have to predict the product.

So, this thing is absolutely simple and now in the previous 2, 3 classes earlier we actually discussed something which is very important that we said that, you actually can predict or you actually can make a 1,3 syn dimethyl or 1,3 anti-dimethyl kind of compound by using this. So, this methyl and this methyl you can make 1,3 syn and you can make 1,3 anti. Now, how you can proceed let me give you a very simple problem.

So, let us start with a normal compound, this ME and let us say this, this, this ok. Now the basic question was how you can fix this stereo chemistry? How you can fix? So, we have to use a Evans oxazolidinone method. So, this center if you can fix it, now take this as a electrophile as is having a good leaving group fine. So, with this compound in your hand, now what you do you take the very simple Evans oxazolidinone based compound like this ok. Now, the choice of this group was very crucial ok.

So, first you make the methyl which is seems to be alpha or beta by one round of Evans oxazolidinone. Second round, choice of this was important, if you take one group here which is beta that gives you alpha here, if you take alpha that gives beta here. So, basically 1,3 syn and 1,3 anti both you can generate. Now, what is the exact reaction procedure on a similar way this is a electrophile. So, this is your electrophile, this is your substrate. And you treat with a base; normally LHMDS or something.

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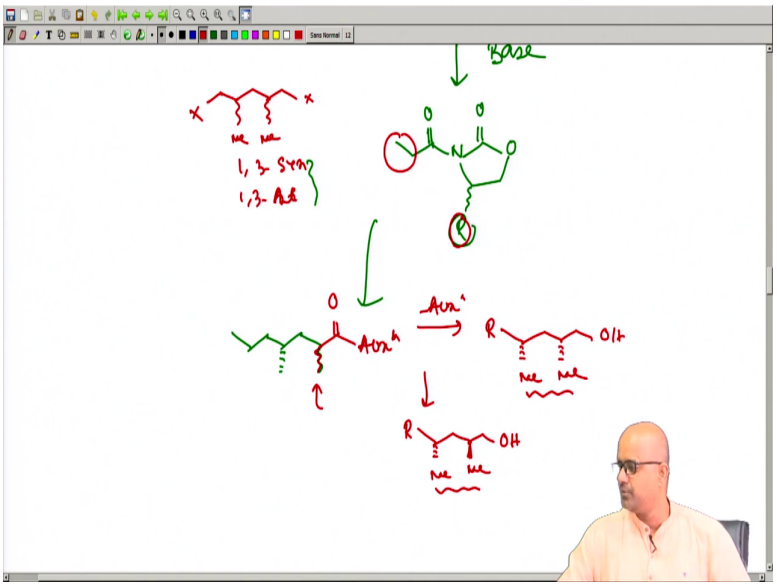

And the moment you do the reaction what basically will be happening with this, this, this. Initially, you are having this typical methyl is below which is your starting point ok, and then you get is alkylation. Now, this methyl which is actually this one so, this one is your this one fine and then you are having this auxiliaries CO auxiliaries.

Now, you see this control you can do it depending on the auxiliary you choose it here or the stereo center in this point. So, both syn and both anti you can eventually create. Now, you can just remove the auxiliaries you can just remove the auxiliaries, and then that basically will give you a compound like this methyl let us say you can create this methyl CH 2 OH. So, this is seen or even you can create anti.

So, in principle, all the possible combinations you can actually create. Now, such a kind of 1,3 syn and 1,3 anti was very common feature in the polyketide structure, you will find such structures in the many natural product.

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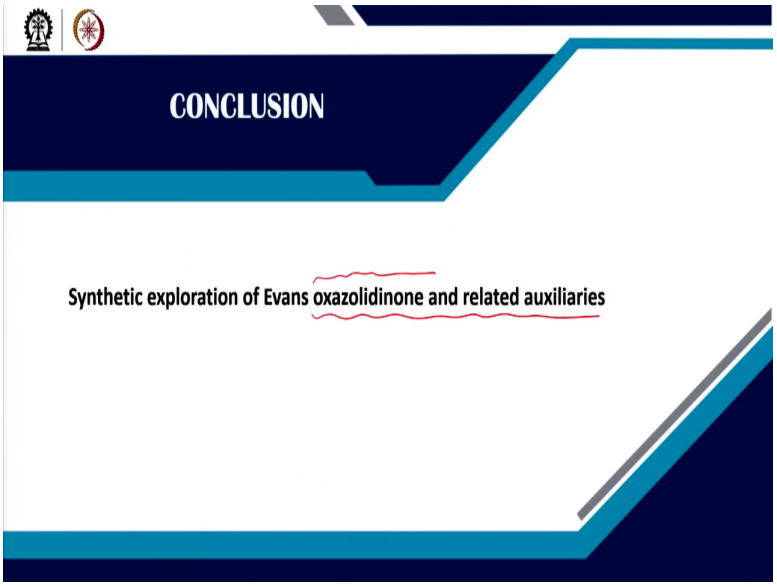

As a concluding remark since the last half an hour or so, you can you have seen that Evans oxazolidinone based auxiliaries have tremendous application in several synthetic problems.

And particularly nice I mean by designing a suitable auxiliary, you can control the absolute stereochemistry through a properly designed pathway and such synthetic experiences are valuable tools in today's scientific community. So, with these things we would like to conclude today and.

Thank you everyone we will see you in the subsequent lecture.