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 - 05
Enolate alkylation of carboxylic acid derivatives
Lecture - 22
Meyer's oxazoline based alkylation - II

So, welcome back everyone and today in this module which is module 5 today will be lecture 22. And we will basically be discussing Mayer's oxazoline based alkylation which we have started just in the previous week.

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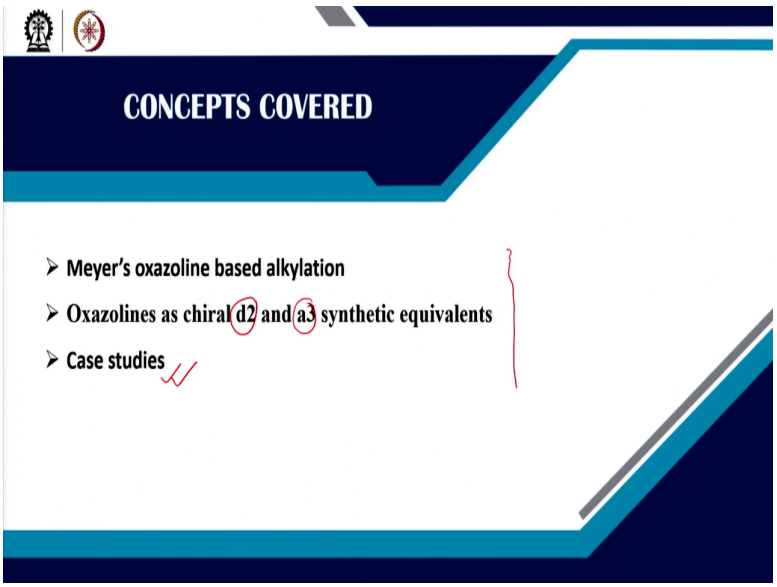

And in this particular lecture the main content which we will be going to cover the basic principle behind oxazoline based alkylation. And particularly we will try to focus on oxazoline as chiral d2 and a3 synthetic equivalents and some of the potential case studies for asymmetric alkylation based on Meyer's oxazoline. And how synthetic chemist used those methods of for making several enantiopure chiral molecules.

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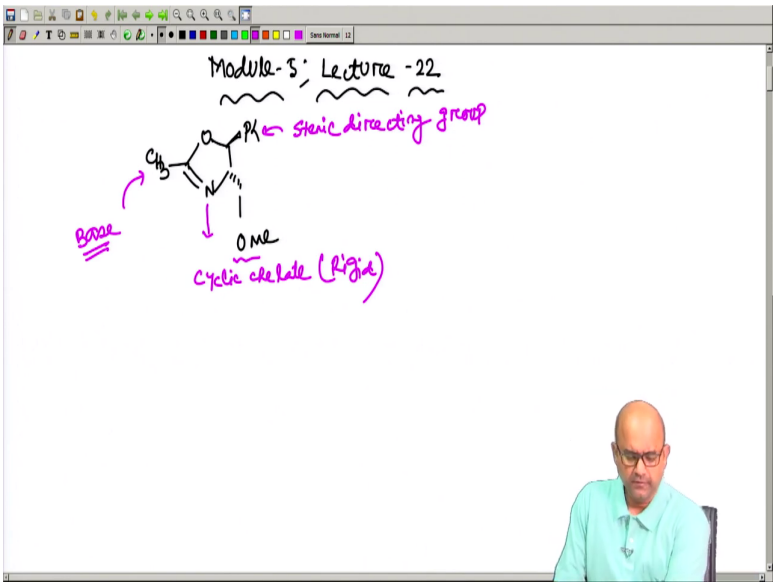
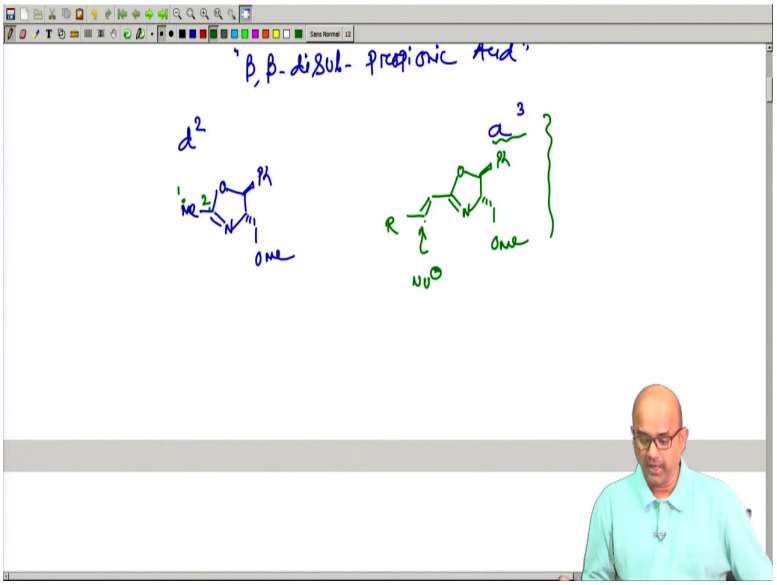


So, we are basically discussing asymmetric synthesis of several enantiopure alkylated carboxylic acid with the help of Meyer's oxazoline. And in the previous class we said that Meyer's oxazoline basically the core structure or the framework is having this structure. And where we have discussed that this phenyl group, this phenyl group acting as a steric directing group.

So, alkylation usually took place from the opposite of this bulky phenyl group and this OMe and this nitrogen they basically help in chelate. So, you get a cyclic chelate which is rigid in conformational behaviour and then you abstract the hydrogen from this acidic proton through base and you generate the enolate. Let us say we will be trying to give you couple of extra things that how you can synthetically manipulate this Meyer's oxazoline.



So, at the very beginning we will discuss about a particular synthesis of beta beta di substituted propionic acid. Now, this seems to be interesting because in the last class we also talked about that Meyer's oxazoline can be act as a properly substituted Meyer's oxazoline can be act as and like d2 acceptor sorry d2 donor and some oxazoline act as a3 acceptor ok. Now, d2; d2 means you basically need a oxazoline where you will have a acidic hydrogen and you abstract the proton. So, this kind of oxazoline in principle they will be acting as a d2.

So, this is number 1 carbon and this is number 2 carbon ok 1 and 2. If you have an alpha beta kind of oxazoline which in principle can act as a Michael acceptor and if you see their structure this will be something like this. So, these compounds may not be act as a direct enolate precursor, but they can be a very good substrate for the Michael type of addition you see nucleophile can easily attack here.

So, let us explore some of the a3 activity that how you can prepare. Now, once this nucleophile attack here what you will get after this you get a 1 2 3, it was a hydrolysis. So, these compounds are nothing, but a beta substituted propanoic acid through Michael reaction, but usually this reaction is not a enolate reaction, anyway, this thing we can just discuss.

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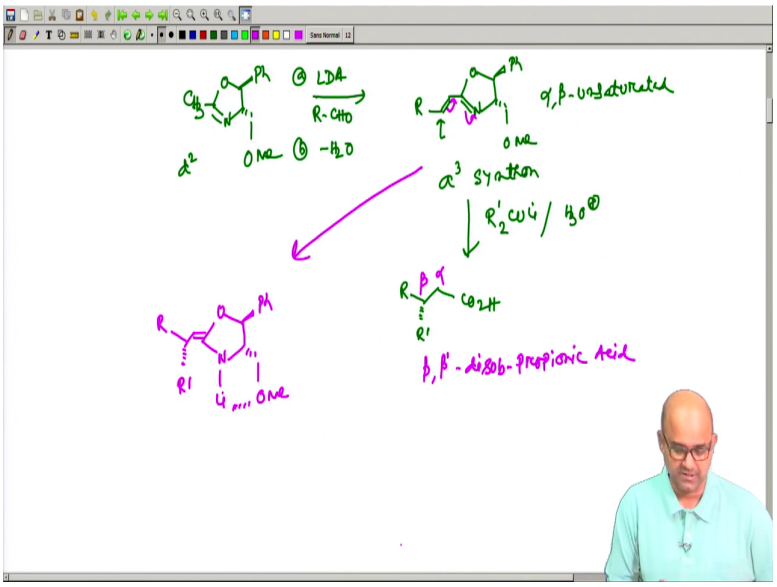

So, first you take this oxazoline which is a very well known oxazoline which you can easily prepare from acetic acid or its derivative. So, first you need to prepare the corresponding alpha beta unsaturated oxazoline means starting from a d2 oxazoline you have to prepare a3 oxazoline. You just do an aldol reaction ok number 1 and then you do a dehydration reaction and this dehydration followed by water sorry, this aldol reaction followed by dehydration will give you this oxazoline.

Now, this oxazoline the structural framework remains same, and now as this is an alpha beta unsaturated carboxylic acid derivative you can easily figure it out that this could act as a Michael acceptor a3 synthon ok. Now, in this compound you can eventually add some nucleophile; the nucleophile could be your choice, you can simply add a Gilman type of nucleophile R2CuLi. Now, once you add it you can see that this is a flat trigonal sp2 hybridized carbon, where the nucleophile is going to attack and definitely though this phenyl is little bit remote, but still it can give you enough stereo control.

So, what you will be getting the new carbon R prime bond will be below just opposite to your phenyl ok. And then you can eventually after that you can just do the hydrolysis. Now, you can see what you get this is basically 1 2 3 propionic acid. This is alpha carbon and this is beta carbon; so, beta beta di substituted propanoic acid. So, this actually you can get beta beta di substituted propionic acid. Now, such compounds you can easily prepare with the help of

Meyer oxazoline, but as I said these this are usually not the enolate alkylation it is a Michael addition.

Now, such thing you can also explore in a different way, let us say you first do the Michael addition. So, the moment you do the Michael addition initial Michael thing means this ok and then you can eventually generate the enolate with this. So, now you can see you have this, you have this you have this, you have this omi o me and the lithium the chelate forms now this is the enolate ok. Now, this enolate you can have a different structural features, how?

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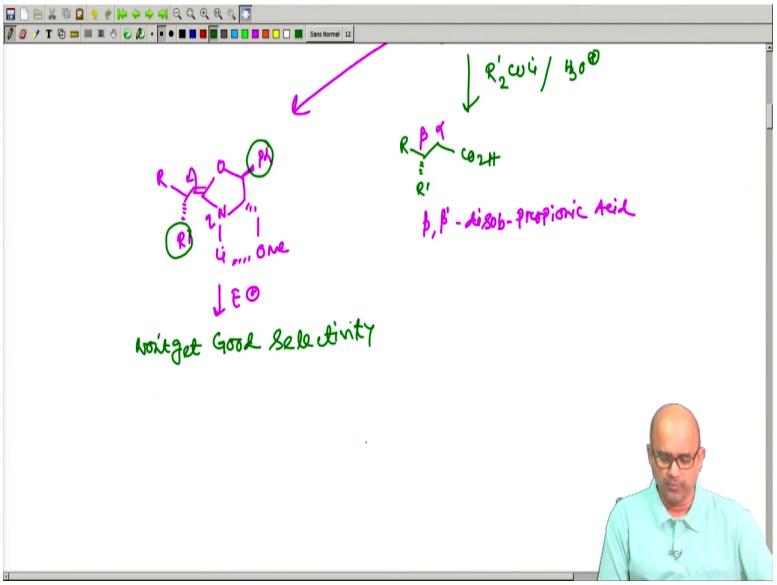

Now, the moment you try to have a further electrophile if you want to attack some electrophile, you can see that this electrophile can now attack on this carbon. But, this carbon will be having now adjacent a beta, sorry alpha is prime group and as well as beta phenyl group; so, selectivity might be a big issue. So, you probably would not get good selectivity you would not get good selectivity; normally, this kind of enolate alkylation and Michael addition is not used in tandem fine. Still you can just use that beta beta di alkylated propionic acid in a good stereo control way.

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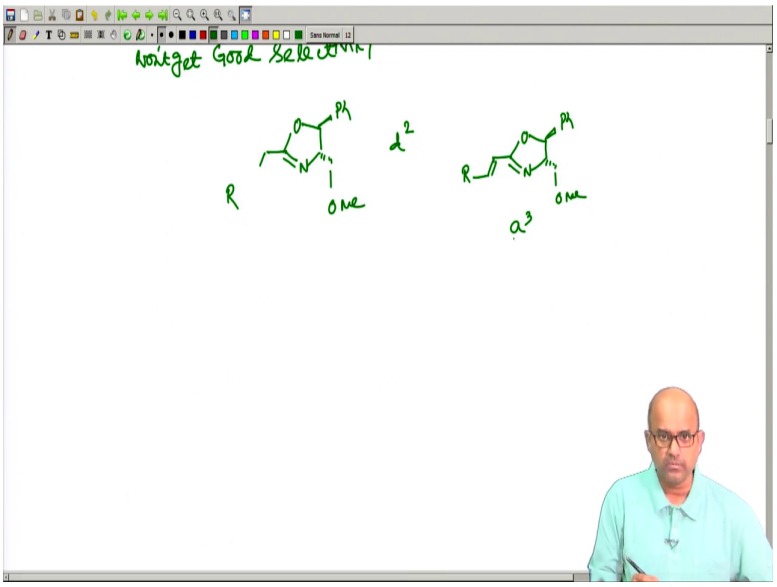

Now, we will try to give you a little bit of different aspects, but before that again we can write the same thing, which you are going to explain in repeated times that this kind of oxazoline you can just regard as a d2 synthon. Because this contains a two carbon unit and if you have a structurally alpha beta unsaturated oxazoline, which you can simply regarded as an a3 or acceptor synthon ok; so, d2 and a3. So, these two concepts will be mainly tested for several application purpose of many of the enantiopure intermediate

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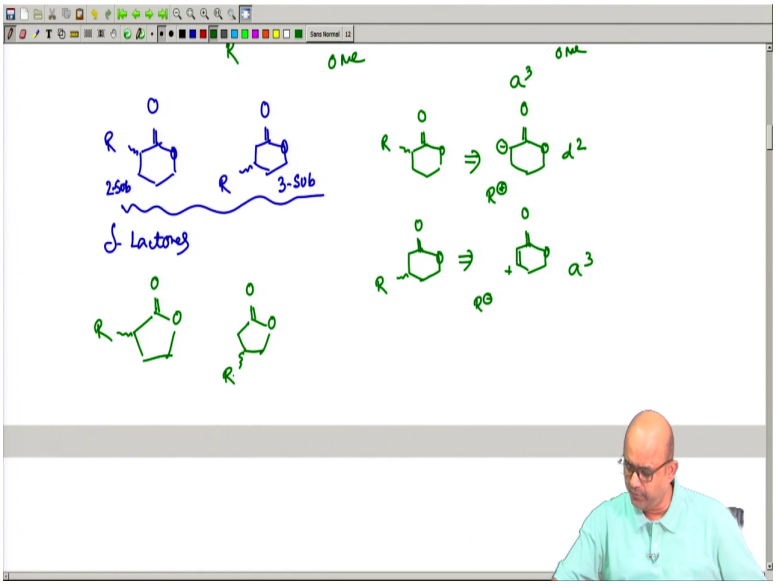

Now, let me try to use that principle for trying to give you some of the potential general target molecule which you can prepare. We actually can prepare several delta lactone derivatives with a substitution at the two position and also we can prepare these things. So, now, these compounds are what? These compounds are substituted delta lactones and such delta lactone frameworks are present in many of the natural products.

So, this is basically a 2 substituted delta lactone and this is a 3 substituted delta lactone. Now, if you check these compounds very carefully what you can find that the initial compound means that 2 substituted part probably you can try to do a retro analysis through this way, that if you have a minus here ok and you add a electrophile. Now, what this means this basically means a two carbon synthon this more or like a d2 ok.

For the second compound the three substituted one you think in similar way, but here if you try to do a Michael type of addition with that this could be your plus and R could be your minus. Now, see this basically act as an a3 synthon. So, this these two precursors we are actually visualizing in terms of d2 as well as a3.

Now, let us see how such compounds you can easily generated, even you will also can make the delta lactone as well as you can by applying the same thing. You can also prepare corresponding gamma lactone with both the enantiomers you can access depending on which auxiliary or which oxazoline you choose ok. Now, we will try to give you a general overview for both the compounds ……ok.

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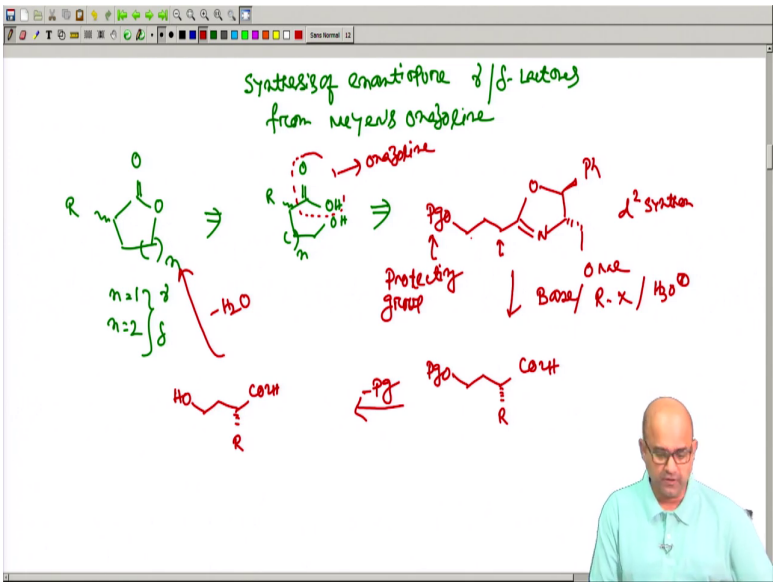

So, let me write the title in such a way that we want to achieve synthesis of enantio pure ok. Because you want to make pure enantiomeric form enantiopure gamma or delta lactones lactones from Meyer's oxazoline based Meyer's oxazoline ok. Now, just probably we can give you a very general outline and that could serve you a brief idea or overall guideline.

So, let me first take any of this thing will take a, this part here. Now, if I put a n here if n equal to 1 that could be your gamma lactone if n equal to 2 that us your delta lactone right. So, you can basically choose what precursor you want to choose it now let do the lactone. Now, lactones are what lactones are basically hydroxy acid if you do a dehydration, you can eventually try to get it.

So, let us say if you are having a compound something like this where you can do a dehydration reaction you can easily get it. Now this compound this carboxylic acid will be now viewing as this part will be coming from the oxazoline ok. So, this is the main structural view point you have to do it. So, now, let me complete the remaining step what you want to have it; so, if you now have a oxazoline something like this where this Pg stands for a protecting group.

So, what this protecting group does is basically protect the free hydroxy group which you require at the final step for the ring closing for the lactone synthesis. Now, see this compound seems to be a d2 synthon ok why d2 synthon you just wanted to create a new carbon carbon bond at this point ok. So, you just put the base and your electrophile in form of RX ok then what you are going to get you are going to Pgo this and then let us say you put a R ok. And after the hydrolysis aqueous workup you will get this CO2H.

Now, see you just remove this Opg; so, you can just write you can remove the OPg depending on which protecting group you choose you apply the suitable condition for removing the protecting group. And then if you will get a hydroxy and you can actually get the corresponding R CO2 H, now this you can just do the ring closing.

As I said the number of carbon chain is pretty important, because here depending on the size of the ring is it delta or it is gamma you can choose the corresponding ring. Now, how the starting auxiliary or starting oxazoline you can synthesize it.

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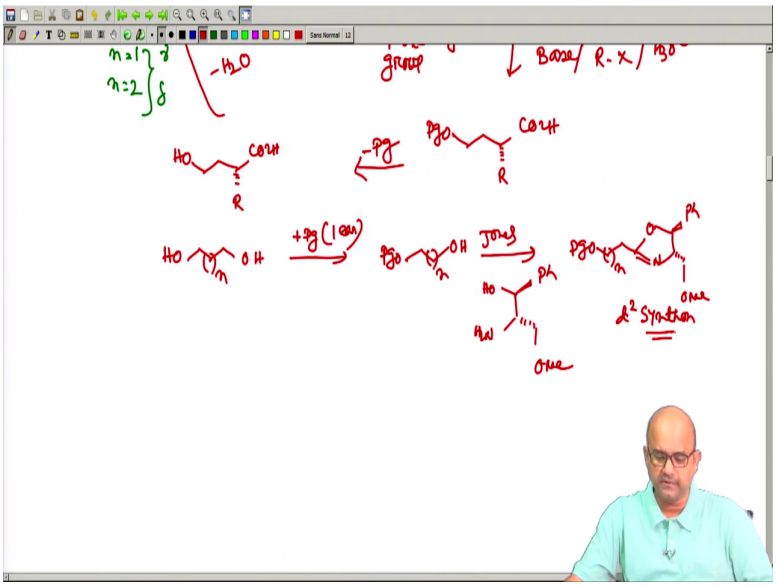

For this part you actually start with corresponding 1 n propanediol may be 1, 3 or 1, 4 depending on which ring you want. So, first you do a mono protection this is very simple you use a one equivalent of protecting group, the protecting group could be a TBS or TMS, could be a MOM, could be a benzyl, could be a para-methoxybenzyl and then.

So, once you do the protection the one end is protected and other end is free. And this free hydroxyl group you just oxidized to corresponding carboxylic acid through Jones oxidation. And then you eventually add this amino alcohol which is your Park-Davis amino alcohol which you can easily get.

So, by applying this chemistry you can now easily get your oxazoline and then this oxazoline you can actually choose the as a main precursor. And you can just write n depending on number of carbon which you need now this is your d 2 synthon. Now, if you want to make the three substituted compound, for three substituted compound your strategy should be little bit different.

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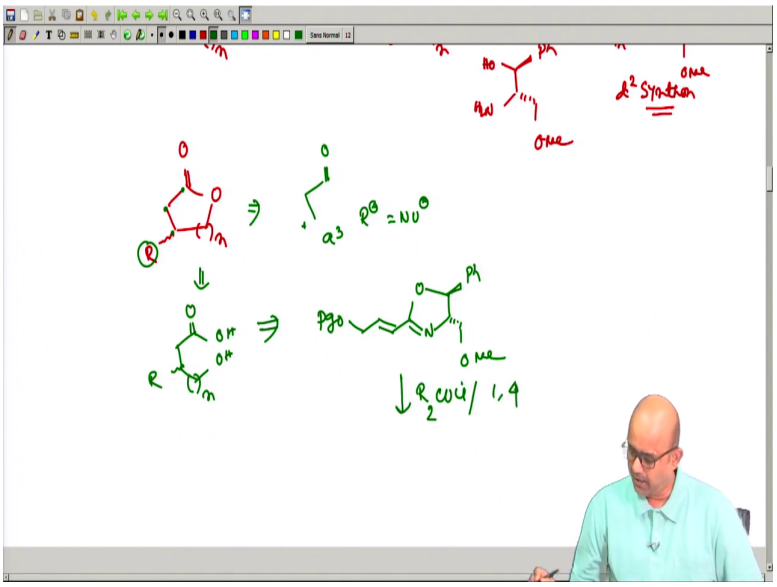

For three substituted just you write this here is your R ok. So, now, you can easily see that the number of carbon is now 1……. 2 and 3. So, basically this will basically we are talking about a species something like this which is a plus is an a3 acceptor and your R minus as a nucleophile. So, you can just use the corresponding alpha beta unsaturated oxazoline for the Michael type of reaction.

So, here also you can easily prepare this compound let me try to do the retro little bit. So, in this case we will be something like this and then you have one carbon away you have this CO2H lactone. So, basically you want to have the corresponding hydroxy group; so, you can put a n if you having a gamma lactone n will be 1, if you having a delta lactone n will be 2. Now, your oxazoline part you can now fix it according to the similar kind of strategy; so, for you check it this will be your oxazoline structure.

Now, this is your alpha beta unsaturated oxazoline and now see the number of carbon if you count 1 2 3 4; so, we are basically talking about a gamma lactone. And so, in this compound you please add a R or R prime whatever substitution you require you just add a R2 Cu Li means a Gilman type of nucleophile to make sure the reaction goes through a 1 4 fashion ok. So, R2 CuLi and this will give you 1,4 fashion and what you will going to get you actually just…….. 1 minute.

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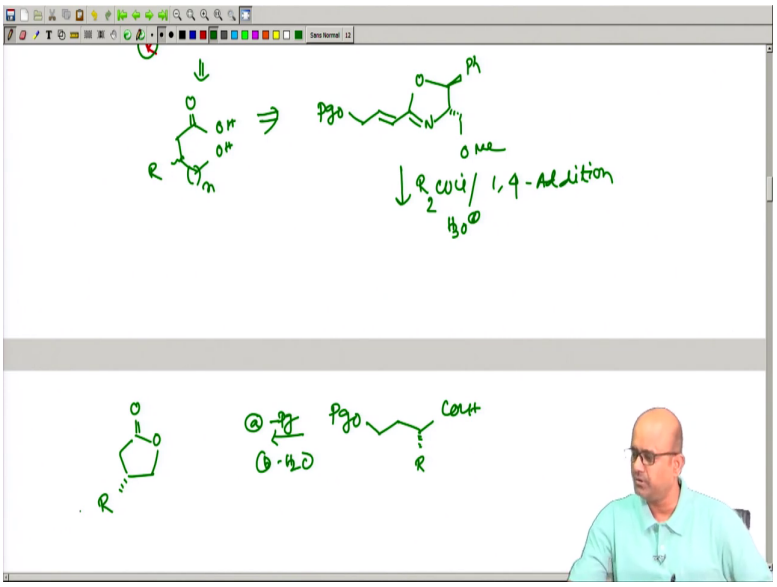

You will get the corresponding Pgo this will be now, will be this R,2 or other substitution. And then if you do a corresponding hydrolysis to remove the oxazoline part just by H_3O^+ treatment; so, you get the corresponding carboxylic acid. You remove the protecting group and then you do the dehydration reaction to close the ring. So, what we are going to get you will eventually get the corresponding this one or if you take the other oxazoline you get the other enantiomer. This seems to be pretty much simple and doable.

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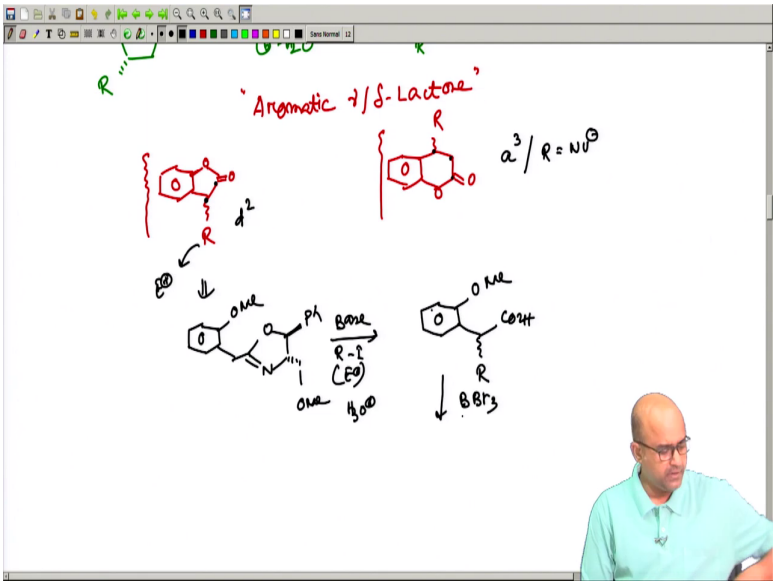

Now, in extension of such methodology you can also use to access several aromatic gamma as well as delta lactone precursor in enantiomeric precursor. Now, the structural features let me first draw their structural features usually such aromatic gamma or delta lactone also you will find in many of the natural products and their structure is the first one is a gamma lactone ok.

And the second one it is definitely the delta lactone which is having a 6-member ring unit and here you get R C double bond OO. Now, if you analyze these structures very carefully these are basically nothing in the earlier case, we have this gamma lactone which you have prepared. So, now, the first case you see the initial carbon is a carbon is number 1 and this is number 2; so, you need a two carbon unit.

So, basically you can just regard as the d2 synthon ok and R could be your electrophiles. In this case this is 1, this is 2, this is 3; so, it can be simply regarded as a, a3 synthon and then your R could be a nucleophile; so, by applying such strategy you can easily make those molecules. Now, eventually let me go through how you can make those molecules in a quick way.

So, for the initial compound like this if you probably try to apply or take a precursor something like this, I will just take a methoxy group. The methoxy group main idea was it is kind of a protecting group with the, this hydroxy or the phenolic OH……. ok. Now, rest of the part is all similar depending on which enantiomer of the lactone you want.

So, you choose it and then you take this compound, you use base ok and then use your alkyl iodide as an electrophile fine, and then you do the H_3O^+ treatment. So, what basically you will get? You will get your OMe which is a phenolic group as a protected this thing you create a new carbon R electrophile bond the oxazoline is hydrolyzed fine. And then next part is very simple you just remove the omethoxy group by usually a Lewis acid treatment BBr3 and then you do a dehydration reaction.

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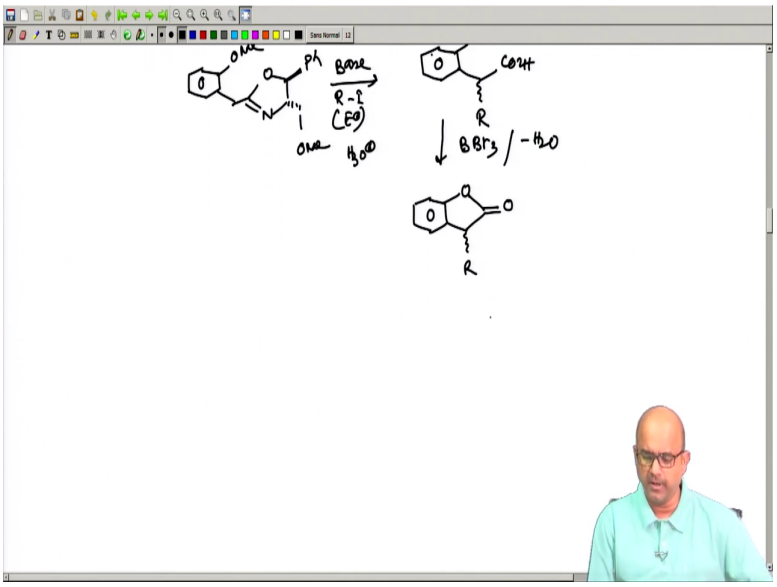

So, that basically fetch you the corresponding lactone unit in a, we will talk about few more application when we do some problem solving analysis. But for the time being we will try to explore couple of other things for the Meyer bicyclic lactone. And normally this Meyer's sorry this Meyer's oxazoline.

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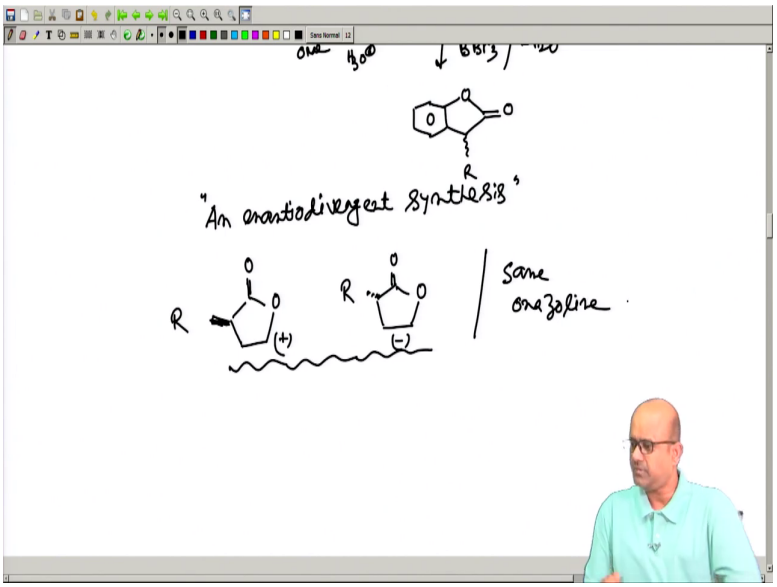

Now, this Meyer's oxazoline you can also use as a enantio divergent synthesis for same precursor by using same chiral auxiliary. Now, this kind of enantio divergent process is very important in the sense that, you no need to use two different auxiliaries you can just use a

single chiral auxiliary, but your sequence of the reaction should be differ. So, both the enantiomeric gamma lactones or even delta lactones you can prepare. If this is plus it could be minus both the compounds you can prepare by using a same oxazoline. Now, quickly let me finish through this then probably we will come to end

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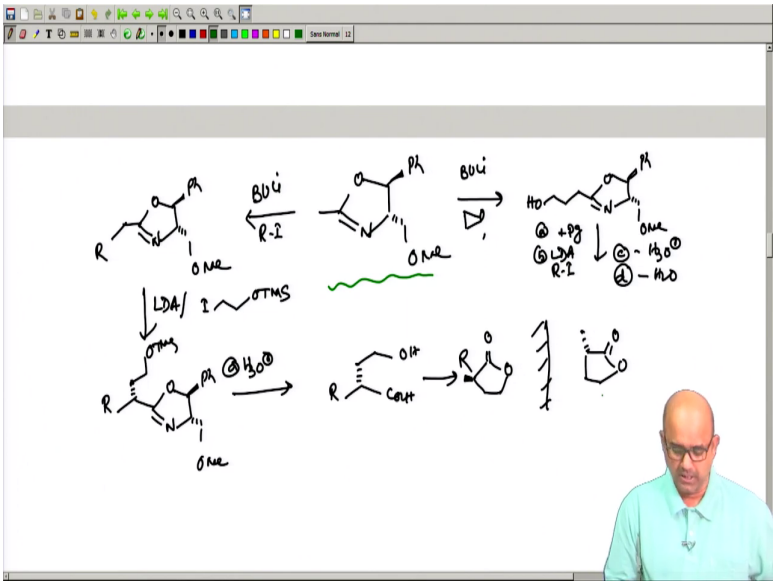

Now, for this one as we are talking about initially, we start with the parent oxazoline a single oxazoline ok; so, this is our main oxazoline. So, first what we do it; so, let me first try to do an initial reaction BuLi with RI. Now, this there will be no stereo center generation; so, you basically have a R because you are not creating any stereo center ok; everything remains similar, follow the reaction pathway carefully you will get the answer ok.

Now, the second case now you apply a base LDA, and now the electrophile is such that you have a, I you have a CH2 OTMS. Now, why this TMS you basically need to have a protecting group; now, if you can check it your R is here you have a new carbon thing bonds. So, CH2 CH2 OTMS fine and your remaining oxazoline everything is as it is.

So, just you can first hydrolyze the oxazoline, and in the H_3O^+ if you have an acidic medium the TMS group also will leave. So, if the TMS group leaves you can basically get R this OH and CO2H upon dehydration this compound will actually give you this one. Now, for the second one, second one what we did we start to the same oxazoline for the other enantiomer we just treat with butyl lithium and do a two carbon extension with simple epoxide generated from ethylene ok. Now, and then so this will basically give you a, OH epoxide opening this

part will remain similar. You first protect this OH as TMS fine number 1 then do the alkylation LDA with R iodide, then what you do remove the oxazoline $H_3O^+$and then followed by minus water.

Now, you check it you can you are actually will be getting the other enantiomer. So, this is really beautiful because you can access both the enantiomeric compound just by using a different sequence of reagent. Now, see in the first case you add the two-carbon little bit later and in this case you add the two carbon unit at the very beginning. So, this is a purely reagent control addition on the same sense of chiral oxazoline to access both the enantiomeric delta gamma lactones through enantiomer divergent pathway. We will discuss remaining things in subsequent days.

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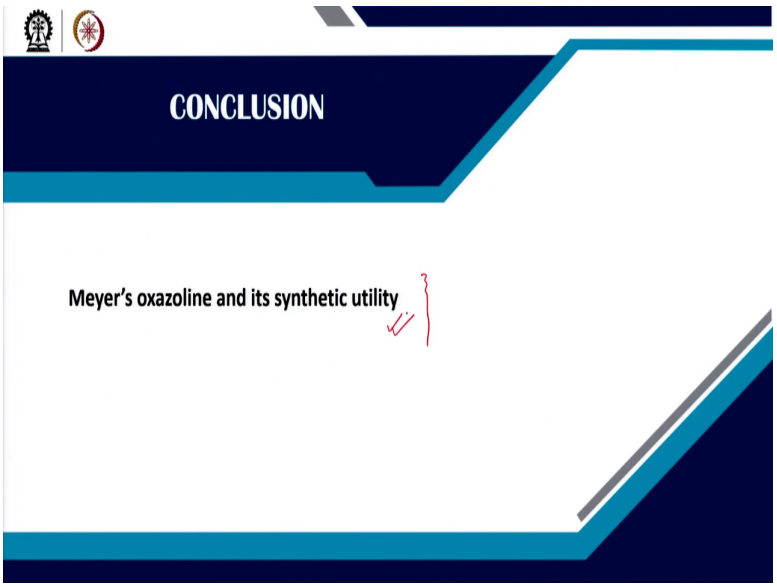

So, the concluding remark, we can say that Meyer's oxazoline based chiral auxiliary plays a very important role in the field of asymmetry synthesis. More precisely on enolate alkylation and you can create different enantiomeric version of chiral carboxylic acid through enolate alkylation.

Thank you , we will see you in the subsequent lectures.