Introductory Organic Chemistry II

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Module 06

Lecture 43

Aldol Reactions: Specific Enol Equivalents - Part 02

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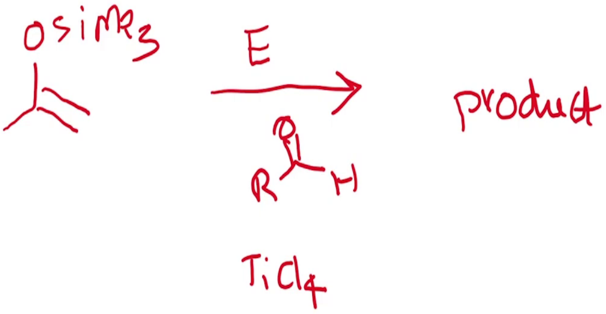

So, welcome back to the discussion on specific enol equivalents. So, what we have done so far is we have used, for example, base like LDA which is a very strong base and which can irreversibly produce the enolate as the way to control the generation of the enolate. So, the principle that is applied here is that we go to low temperature and generate an enolate and then allow it to react.

The second strategy is to produce what are known as silyl enol ethers. So, we can make $CH_3C(OSiMe_3){=}CH_2$, and these are stable, and isolable compounds. So, you make this compound, and then you react it with your electrophile. And the electrophile here is the let us say an aldehyde. And I know we need to add Lewis acid like TiCl4 and this gives you the product. So, this is the second major way in which we use specific enol equivalents. So, keep in mind, we are discussing about how to control aldol reactions.

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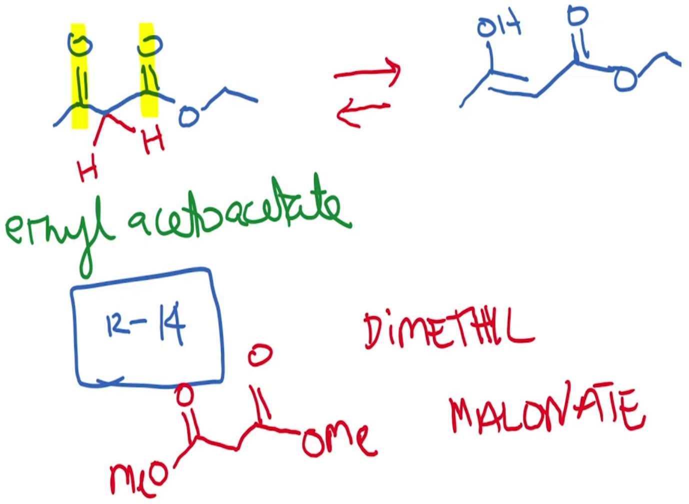

The third way to control aldol reactions is to use a base, which is so basic that there is no competition. So, this is historically one of the most important developments maybe about 40-50 years back, and it is one of the oldest enol equivalents, which is ethyl acetoacetate. So, this is ethyl acetoacetate. So, this is really, really cheap, and it can be bought in very large quantities.

And so, it becomes a very easy accessible starting material to do many reactions. The thing about ethyl acetoacetate is that, when you put this in a solution, we have the possibility of enolization, and because we have two strongly electron withdrawing groups on this adjacent position, this has a very strong tendency to form the enol. So, therefore, you know this is a very useful compound, because it is already present in the enol stage pretty much, when you want to do the reaction.

So, when you are adding an aldehyde for example to this, there is no competition, the aldehyde does not enolize as well as this compound. So, the pKa of this ethyl acetoacetate is pretty low. And it is usually around 12 to 14 maybe even closer to 11 sometimes, depending on what substitutes are there next to this. And the pKa of traditional aldehyde is somewhere between 18 and ketone is about 20 and so on.

So, there is a sufficiently large difference between the pKa of this type of compounds and the aldehyde or ketone that we wanted to react with. And therefore, their competition is less. So, these types of compounds, which are known as ethyl acetoacetate, and you can also use another compound which is known as dimethyl malonate. So, basically, there is malonic acid, and you can add OMe, so this is dimethyl malonate.

So, this is also damn cheap, we can buy this in clearly large quantities, and it becomes a very useful way to do reactions. We will be discussing about alkylation reactions at some point. And these types of compounds will show up again, at that point.

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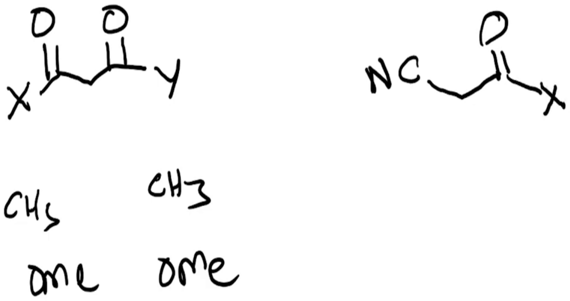

So, now let us get back to this discussion. The idea here is that, both these types of specific enol equivalents, which have the general structure like this, so they can be X and Y, X can be methyl, OMe, and so on. Y can also be methyl, OMe, or OEt, or any of the other compounds. We have also looked at previously that you can have a cyano compound, the cyano component, the adjacent proton is quite acidic. So, you can have this type of a compound and this is also highly acidic, these types of compounds. And so, these are generally very useful as enol equivalents.

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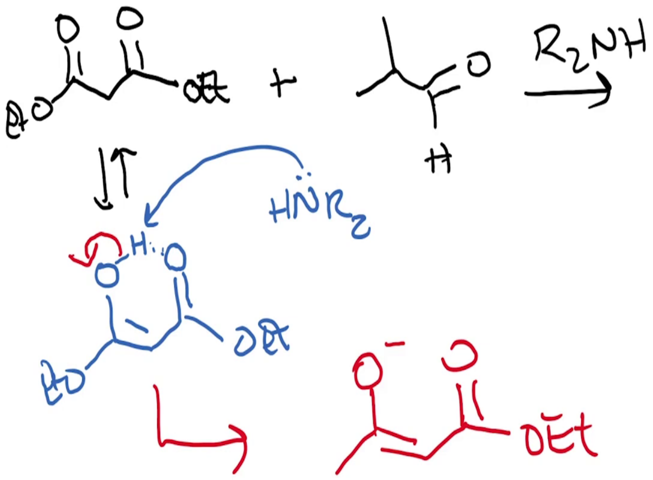

Now, how do we do the reaction? The way we do the reaction is we take the example that I am going to take is with diethyl malonate, OEt, OEt and react it with an aldehyde. And add a base, the base that we add here is let us say general structure is R_2NH. And the first step we can imagine is that this is going to be in equilibrium with the corresponding enol. And one of the reasons why this enol is very stable is because of this intermolecular hydrogen bonding.

And so, this base here, NHR_2 can come and abstract this hydrogen. And this can give you the enolate that we are looking for, or normally that we generate. So, keep in mind that amines are extremely, although they are good bases, but they are quite weak compared to LDA by which we use for the other reaction. So, this is pretty mild conditions that we are going to use. So, this is the first step.

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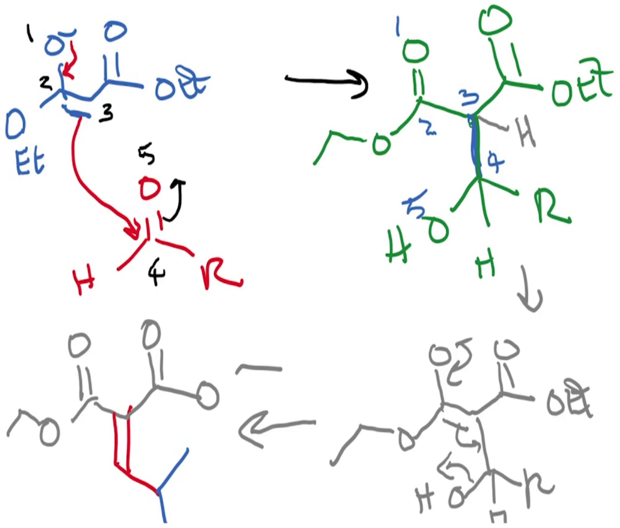

Now, I will take this to the next page and rewrite this. So, you have $EtOC(O^-)=CHCOOEt$, you know how to generate this. Now, in the next step, this has to react with the aldehyde. So, what we can propose is that this goes here, this is a traditional aldol type reaction. And I am just going to number this in the traditional way that we use 1, 2, 3, 4, and 5. So, there is a new double bond between atom 1 and atom 2.

And now, this remains the way it is OEt. And you have OH, and you are have R, and you have H. So, to complete, to do the numbering is 1, 2, 3. And this is the new bond that is being formed between carbon 3 and carbon 4, this is 4, and this is 5. So, this is exactly the way we want it to be. And the rest of the mechanism would be pretty identical.

Since this has one more enolizable hydrogen over here it can produce the corresponding enolate again, you have O minus, OEt, I am not drawing out the arrow pushing mechanism for the formation of the enolate. I think you guys are quite familiar with it by now. R H, now this comes in here, this moves here, and this is kicked out.

So, C double bond O, OEt, C double bond O, OEt, and there is a double bond and R. So, this is usually the final product that is formed, and here R is isopropyl. So, we can just erase this and write it as isopropyl. So, this is another important way to use this as a enol equivalent for controlling aldol reactions. And it is a historically very important method, people use acetoacetic acid or they use malonic acid.

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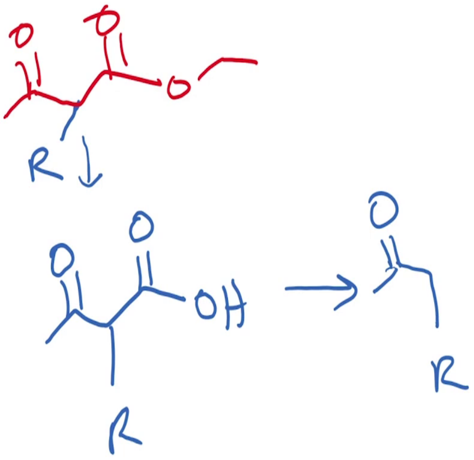

And there is another reason for this. The other reason for this is that there is a very nice way in which you can do what is known as a decarboxylation reaction after you do the reaction, so we will take this up very soon. So, you can convert this, you can do the ester hydrolysis, let us say you add a group R to the ester hydrolysis.

And you get this carboxylic acid over here. And then under certain conditions, this loses CO_2 and it produces the corresponding product CH_3COCH_2R. So, we will take this up at some point later in the course. But suffice to say is that these 1,3-dicarbonyl compounds are really important as specifically enol equivalents.

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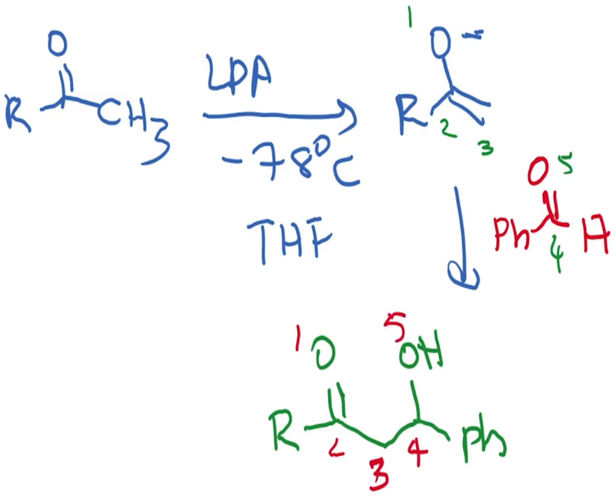

So, what we are going to look at is additional ways of generating specific enol equivalents. So, what we have done so far is we have taken for example, ketone and reacted it with LDA at minus 78 degrees centigrade and we generate the enolate, $RC(O^-)=CH_2$ and then we will look at this a little bit in detail later.

But then what you do is then you add the, this is typically carried out in solvents like THF and then you add your aldehyde or electrophile over here, we will look at later that you can also carry out alkylation reactions using this kind of strategy. So, you will end up with RC=O $CH_2CH(OH)Ph$. So, this is just to keep our numbering system 1, 2, 3, 4, and 5. So, that would be 1, 2, 3, there is a carbon-carbon bond formed between 3 and 4 and this is number 5. So, this is pretty straightforward and this is something that we have already looked at.

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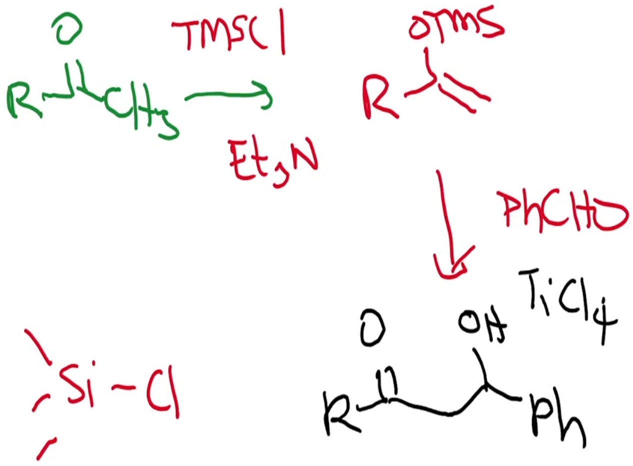

The second strategy is to make a stable system which is what is known as a silyl enol ether. So, you add TMS chloride which is nothing but $SiMe_3Cl$ and then you add a mild base like triethylamine and you make this TMS ether and then you react this with the aldehyde like for example benzaldehyde. And you may recall that just adding benzaldehyde is not sufficient, you need to add Lewis acid such as titanium tetrachloride and you end up with this product.

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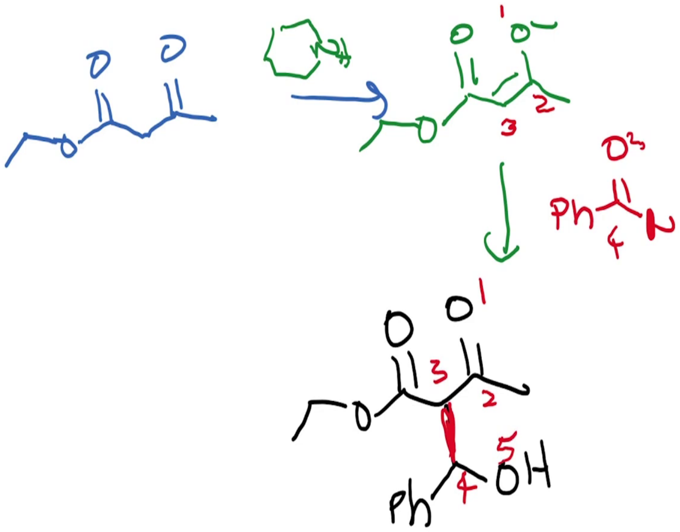

So, the third important method that we looked at was to use what are known as 1,3-dicarbonyl compounds. And essentially, these are compounds where you have no choice in enolization and you get very stable enolate once you add a mild base. So, the base that you add here is something like this can be added, piperidine or pyridine or piperazine and you regenerate the enolate, EtOCOCH=C(O^-)CH_3 and then this is then reacted with the aldehyde that we are interested in and you get the corresponding product which is EtOC=OCH(CHOHPh)C=OCH_3.

So, just to remind you about the numbering 1, 2, 3, 4, and 5, so the numbering is still the same 1, 2, 3, 4, and 5, so the bond between carbon 3 and carbon 4 is the one that we are formed. So, these are all the major ways in which we generate specific enol equivalents as far as ketones are concerned.

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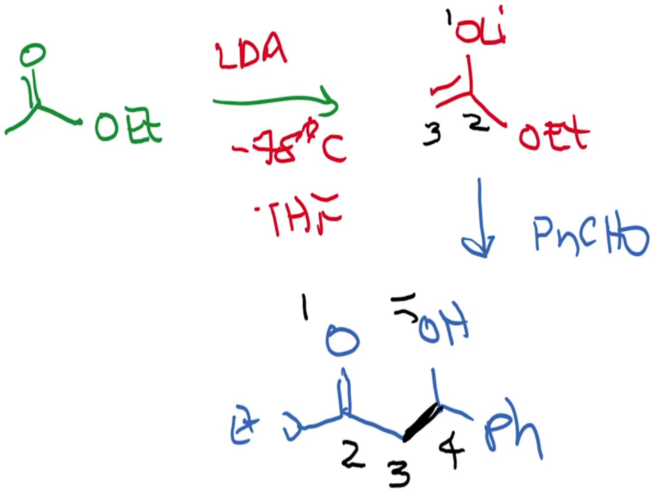

Now, we already know that esters, which are let us say, we take an ester such as this, these are virtually very similar to ketones. So, one way in which you can generate the enolate from the ester is the same strategies that you use for ketones, so LDA, minus 78 degrees centigrade and THF and you generate $CH_2C(OLi)OEt$ and this is then further reacted with an aldehyde such as benzaldehyde and the chemistry is the same, you end up with $EtOC{=}OCH_2$ $CH(OH)Ph$. So, just to complete the numbering, this is 1, 2, 3, and the aldehyde is 4 and 5. So, this is 1, 2, 3, 4, and 5. So, this is the new bond that is formed. So, esters can be treated very similarly to ketones and you can produce the same sort of intermediate that is produced.

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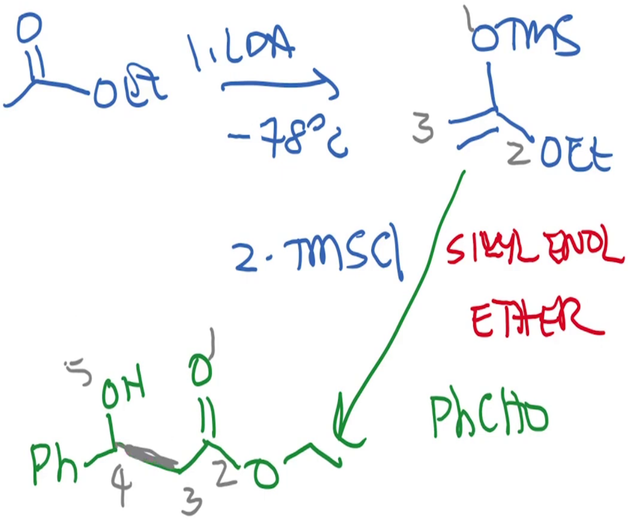

Now, the next method is to go to generate the silyl enol ether, which also can be done. So, if I start with $CH_3C=OOEt$, and then I react this with, I might need to use a little bit of a stronger base here sometimes, and so the base that I would use here is LDA, and minus 78 degrees centigrade, this is step number 1. And step number 2 is to add TMSCl and so the product that you are going to get is $CH_2=C(OTMS)OEt$.

So, this is your silyl enol ether of the ester. So, this is the silyl enol ether of your ester. Now, what we need to do is you add your benzaldehyde, PhCHO, and you get this as the product. So, here again, let us just keep the same numbering 1, 2, 3, so this is 1, 2, 3, this is the bond that is formed, this is 4 and this is 5. So, these are pretty straightforward reactions for us to carry out.

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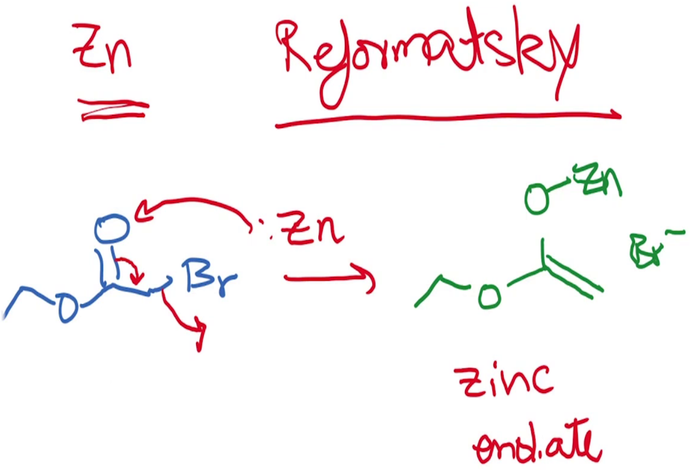

But with esters, there is a very powerful method and very, fairly mild method that can be used to generate enolates, and these are enolates that are derived from zinc. Zinc is used in this reaction, and this reaction is called as the Reformatsky reaction, and it is a fairly powerful reaction. So, the way we would do this reaction is to take an α-bromo ester. So, this is the α -bromo ester and then you react this with zinc. So, zinc being a metal is actually a source of electrons.

And it can add a pair of electrons to the carbonyl. And one of the ways in which to consider this is because the carbonyl can move, the pair of electrons from the carbonyl can move and kick out this bromide. So, this kind of reaction can in principle occur. So, the product of this first step is a new bond between oxygen and zinc.

And this carbon-carbon double bond now becomes a single bond and this carbon-carbon bond which used to be a single bond is now becomes a double bond and Br^- is kicked out. So, this is nothing but a zinc enolate. So, I think we have looked at you know, α-bromo ketones and α-bromo esters can be easily synthesized from readily available starting materials. So, making this compound is really easy. And then you just add some zinc, and you produce a zinc enolate. So, it is a fairly mild process, you do not need to use a strong acid or a strong base to generate the enolate. And therefore, this reaction is quite popular.

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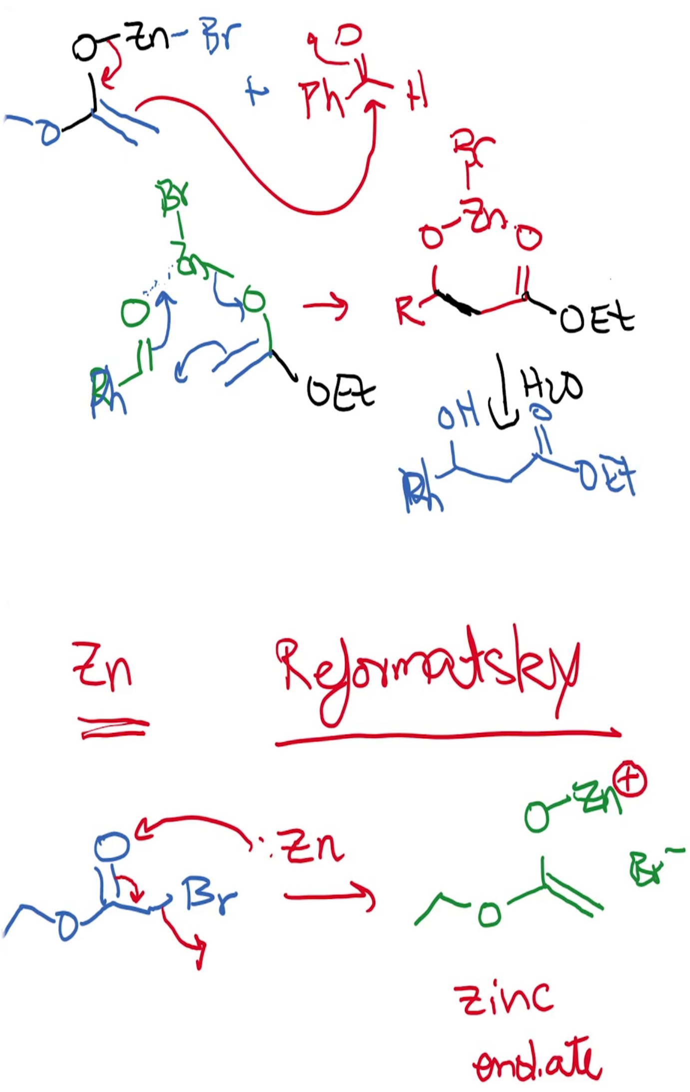

Now, once you generate this enolate, this can then be reacted with an aldehyde or a ketone. Let us look at the reaction with an aldehyde as an example. So, this is your zinc, I am very sorry, I think I missed out a positive charge on the zinc. So, there should be a positive charge over here. And now Br minus is going to act as the counter ion. So, we can write this out as Zn-Br.

And here is your enolate. And here is the remaining part of the ester. So, you can react this with an aldehyde and the example that we are going to look at is benzaldehyde as always. Now, the chemistry is the same, so it just moves here, attacks here and kicks this out. And you can also draw this in a cyclic transition state. So, the way we would draw this is the following R C double bond O, and here is your O-Zn-Br, and this is the enolate.

So now, you can imagine that there could be a coordination between oxygen and zinc. And this weak bond is going to bring these parties together. And then you have the rearrangement, or the pushing of electrons. And that is going to give you the product that you are looking at, which is R O Zn. And now, this becomes a weak bond between this, there is a new carbon-carbon bond that is formed here, and this is OEt.

So, you can imagine that there is a ethyl group over here, maybe I should just erase this and redraw it, just that part of the screen does not show up well sometimes, and so my apologies for that. And this is the new bond that is formed, the carbon-carbon bond and subsequently you can hydrolyze this reaction to give you the final product, which is this in our case is a phenyl ring. So, the phenyl ring is here, $PhCH(OH)CH_2C{=}OOEt$. So, this is a really, really nice method to do the aldol reactions with esters.

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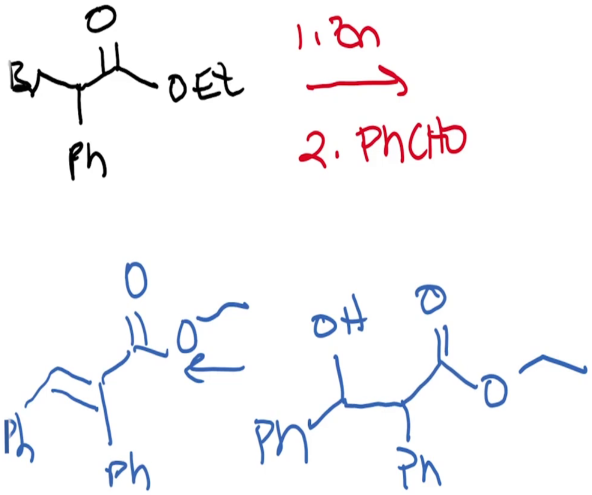

Now, let us look at an example before we proceed, so the example that we are going to look at is the reaction of (add structure)with this and this is going to, when you react this with zinc. And number 2 is PhCHO, and the product that you get is PhCH(OH)CH(Ph)C=OOEt. So, of course, this can subsequently eliminate to give you the ester. And you might even end up with a mixture of cis and trans isomers.

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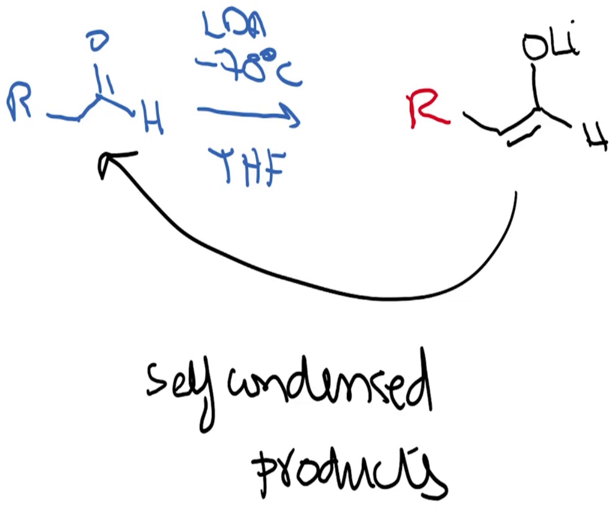

So, the last major topic in generating specific enol equivalents is with the aldehydes. We have looked at generation of silyl enol ethers from aldehydes previously. So, that continues to be a very good method. The problem with using LDA for example, is that even at -78°C with LDA for example.

We see a fair amount of self-condensation that happens, so you do produce the enolate as ketones do, like ketones, aldehydes also produce enolates, but the problem with these kinds of enolates are that they are quite reactive and then they react with itself and they produce a significant amount of self-condensed products. So, therefore, use of LDA with aldehydes is generally not preferred. Because even at -78ºC they do a fair amount of self-condensation.

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So, the alternate method that is preferred is to use silyl enol ethers like I just mentioned, so you take this kind of and aldehyde, react it with triethylamine, Me_3SiCl. And so then, the product is generated as RCH=CH(OTMS). And this is quite stable. I mean, you could isolate these compounds and then react this. So, the example that I am going to give you is cross-condensation reaction, that is going to make it obvious as to why we would need to use this.

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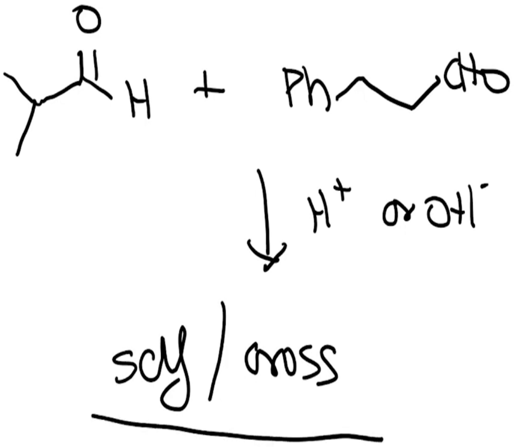

So, for example, if I start with this aldehyde and react it with and add a small amount of acid or base. What happens is that you get, like several products that are formed, which include self-condensation, cross-condensation, and so you really get a mixture of these products.

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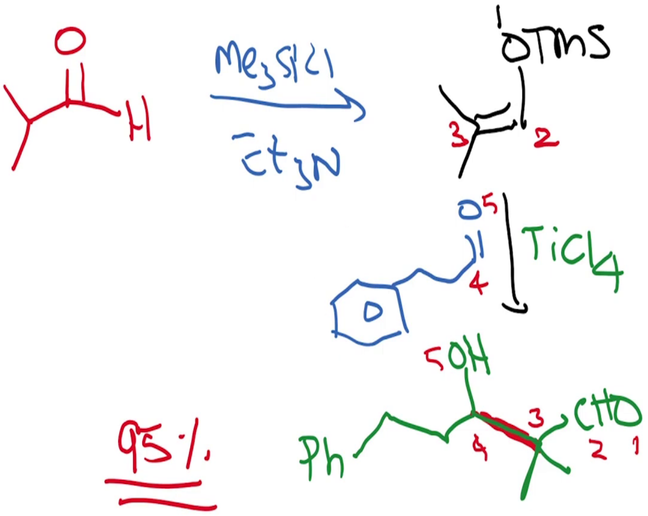

But by using the silyl enol ether method, what we could do is we could now control which kind of compound that we would want. So, for example, if I start with this aldehyde and I want to generate the enolate from this. Then, what I do is first produce the specific enol equivalent. And keep in mind, we cannot use LDA. So, we would use Me_3SiCl in the presence of triethylamine. And the product that is formed is $(CH_3)_2C{=}CH(OTMS)$.

Now, we can then go ahead and react it with the aldehyde of choice, which is this. And keep in mind that this reaction does not go unless you add a Lewis acid, like titanium tetrachloride. And the product that is formed is $PhCH_2CH_2CH(OH)C(CH_3)_2CHO$. So, just to recap here, this is 1, 2, 3, and this is 4, and this is 5. So, we keep the same order, that is 1, 2. 3, this is a new bond that is formed between, this is 4, and this is 5.

And so, this yield of this product is 95 percent, the isolated yield of this compound. So, it is a fairly powerful method. And now, in your free time, what you can do is you can do the reverse reaction, that is first generate the silyl enol ether of this and then react it with this and write out the product that is formed.

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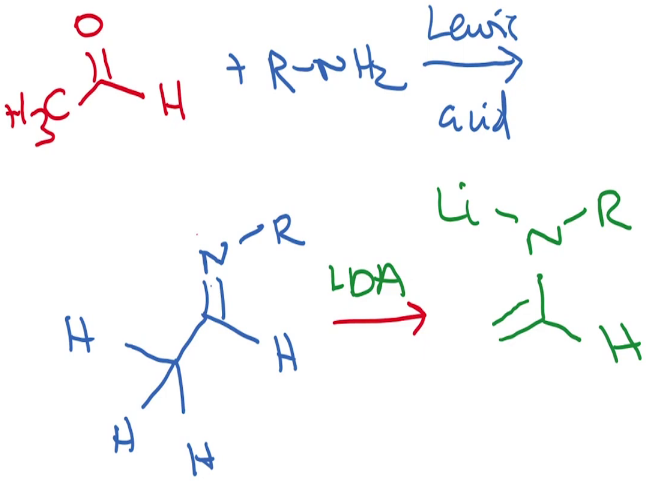

Now, there are other methods that we could use, you may recall that with aldehyde, we can generate imines. And so, imines are very useful intermediates, I mentioned it while we were discussing that topic, so let us revisit this. So, let us say we take acetaldehyde, and react it with RNH_2. And we can do this in the presence of a Lewis acid. And this we have already looked at, so I am not going to spend much time looking at the mechanism.

So, let us say this is the kind of product that we expect. And now, we have three hydrogens that are present next to the imine. And just like this carbon-oxygen bond is electron withdrawing, and you can produce an enolate, the carbon-nitrogen bond is also fairly activated towards deprotonation. So, if you add a strong base, such as LDA, so the advantage of using imines are, that imines are fairly much less reactive compared to aldehydes.

And so, you can produce an Aza enolate, which is fairly stable when compared with the aldehyde. So, the product, I am just going to write out the product, and then we can look at the mechanism. So, this is the Aza enolate that is produced. And now, this Aza enolate is in a position to react with an aldehyde. So, before we go ahead, let me just quickly write out the mechanism of this reaction.

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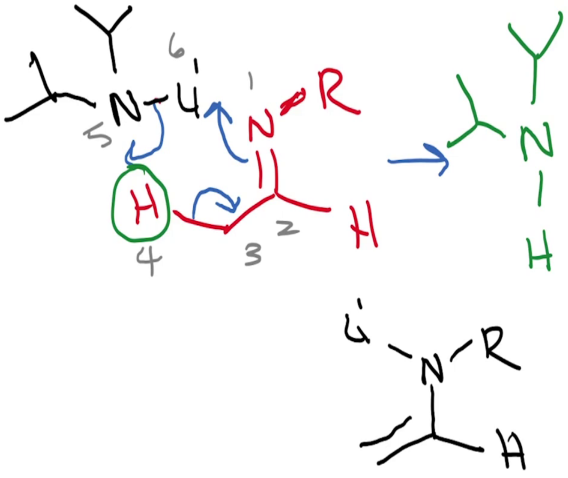

So, the way LDA is going to react is that this is LDA, which has two isopropyl groups, and it has the lithium over here, and here is your imine, and this is the hydrogen, that is going to be abstracted. So, the bond between nitrogen and lithium is broken. And then you have this moving here, and then this moving here.

And so, what this produce is, let me just number this, so that it is easier for us to follow. I will start with this 1, 2, 3, 4, 5, and 6, so it is nice 6-membered ring transition state that we would be producing. And so, if I keep track of the arrows, so nitrogen is here, and this is my LDA, the isopropyl groups are still here. And now, there is a new bond between this hydrogen and this LDA. So, now LDA has become diisopropylamine.

And now, there is a new bond between this nitrogen and lithium, so I am just going to draw this as N-Li, and so this double bond is broken. So, this double bond becomes a single bond. And this carbon-carbon bond between 2 and 3 now becomes a double bond. So, that is the double bond here and the hydrogen remains intact and R remains intact. So, this is the sort of the arrow pushing mechanism with an intermediate or a transition state that we could envision. And these Aza enolates can now react quite nicely.

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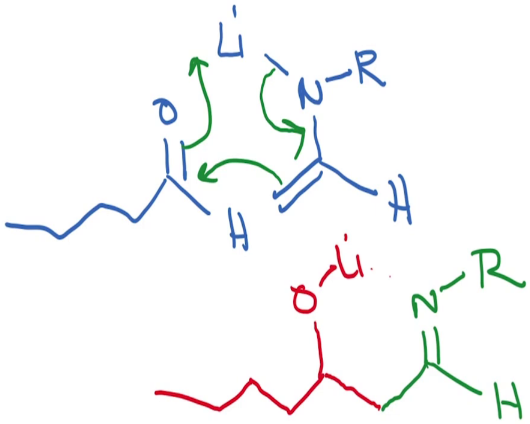

And I am just going to redraw the Aza enolate, and so this is the double bond, there is the hydrogen for the aldehyde and this is R. Now, if I react this with an aldehyde such as this. Now, again, you can draw a nice 6-membered ring type of intermediate, this goes up here. And the product that is produced, I mean a product that is formed is C double bond N, this R remains the way it is, this becomes a double bond, the hydrogen remains here.

This is the carbon-carbon bond for this. And this is the new carbon-carbon bond that is formed, there is an oxygen, lithium is now bound to this oxygen, perhaps there is some weak interaction over here and the rest of the carbon chain remains this way.

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And now, when you work this up with water and a little bit of acid, the product is formed would be the aldol product. And under acidic conditions, you can expect that it will dehydrate and give you the α, β -unsaturated compound with the rest of the molecule over here. So, all of this of course, is available in Clayden. So, I would really urge you to go back and read the chapter on this very carefully and understand the reactions quite well.