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So, the next topic we gonna to take up is Alkylation of Enolates. So, we have already looked at it briefly in some of the previous discussions that we have had. So, in principle we know that ketone, when you add a base, for example when you add a strong base like LDA that can pick this up and you generate the enolate. So, this is something that we have looked at.

Now, one important point here is that when we add a strong base such as LDA or NaNH$_2$, butyl lithium, and so on. They are quite strong bases that one could use and these actually make this an irreversible process. So, this process that we are looking at becomes irreversible that means that the enolate formation is something that does not go back to form the carbonyl compound.

So, if you adjust the reaction conditions carefully, you know if you let us say you go to low temperatures and so on this can have a very significant population in the solution. But now, you can also do the same process by dealing with or by resorting or using bases which are not as strong. So, for example, you can use you know, amines and so on, which have lone pair of electrons, so this can happen. But this is going to be some sort of equilibrium.

So therefore, when you use a weak base, this deprotonation occurs to some extent, and depending on the pKa of the base, you know, the pKa of the conjugate acid of the base, if it is comparable or lower to this carbonyl compound, then you end up getting an equilibrium. So, this is basically an incomplete enolate formation.

So, case number 1 is when you have a very strong base such as LDA, NaNH$_2$, KNH$_2$, butyl lithium and so on. And the case number 2 is when you have a weak base, which can react with a carbonyl compound, but it does not produce the enolate completely. So, these are important for us to understand, because later on in this lecture, we will look at methods to control these kinds of enolate formation.

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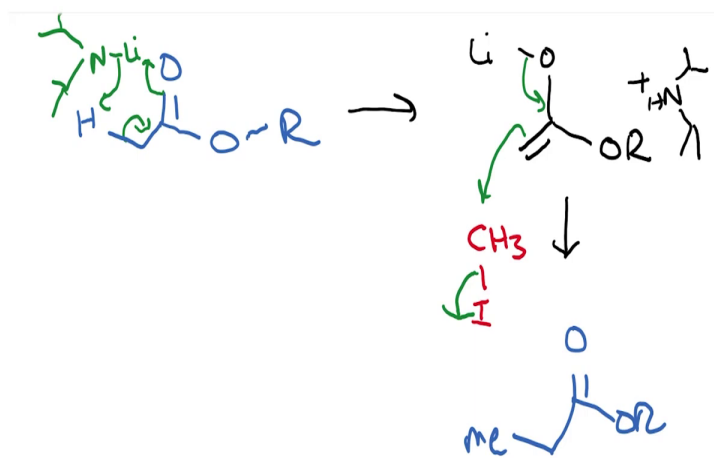
Especially when you have a couple of choices for enolate formation. And I would like it to go along a particular path. So, now let us quickly look at some examples of alkylation reactions. So, the example that maybe we can start with is with this ester CH$_3$C=OOR and you have hydrogen here. And now let us say we use LDA and now there is an abstraction of this hydrogen and you end up forming irreversibly as we discussed, this enolate of the ester, and N, N-di-isopropyl amine.

And now the next step can occur where you have methylation. And this attacks here, and this attacks here, and let me just draw out the methyl iodide properly. So, this is CH$_3$I, this is kicked

out and the product that you get is methylated ester. So, this is a classic method of alkylation of esters. And I am just going to give you a couple of more examples so that we can understand the range of reactions that can occur.

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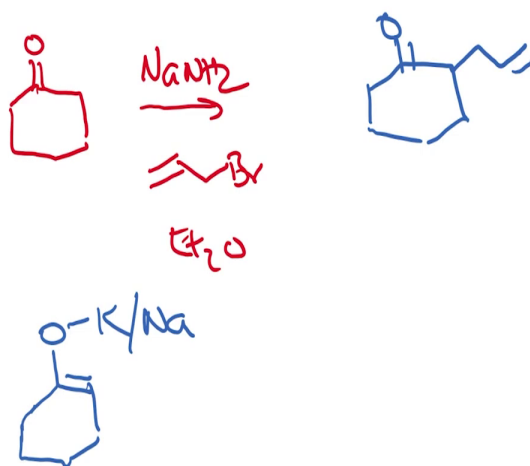
So, let us say I start with cyclohexanone and add NaNH$_2$ and then allyl bromide, diethylether and the product that I get is this. So, basically these are potassium or sodium or Na enolates and they can be generated by using the corresponding potassium or sodium salts. Now, so ketones and esters are fairly straightforward to react with.

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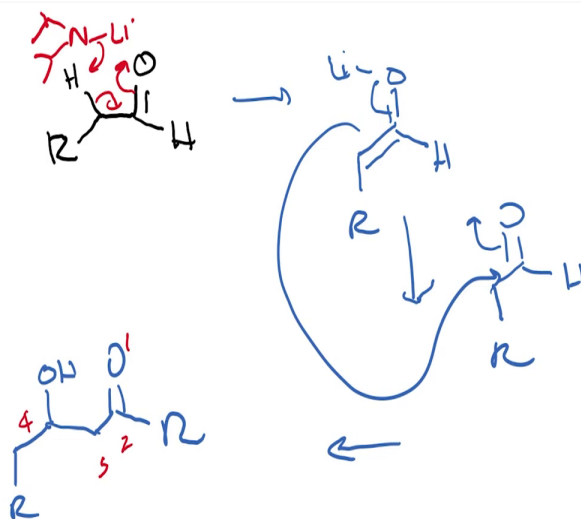
The problem really starts, the complications really start when we start doing alkylation of aldehydes. So, we touched upon this in the previous lecture as well, but alkylation of aldehydes using LDA while in theory can occur, if you start with this kind of compound, you know, you have (iso-propyl)$_2$NLi, this principle, this kind of a reaction can occur and give you the corresponding enolate. The only problem that we face frequently is that the aldol reaction, whereas reaction with itself dominates.

And after you do the work up, you end up getting the aldol product. So, this is, you know you get a mixture of this aldol product, and whatever alkylation of whatever that you need to do. So, this is 1 2 3. So, the bond between carbon 3 and carbon 4 is what is possible. So, aldol condensation basically competes with alkylation, even at -78ºC.

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Specific enol equivalents
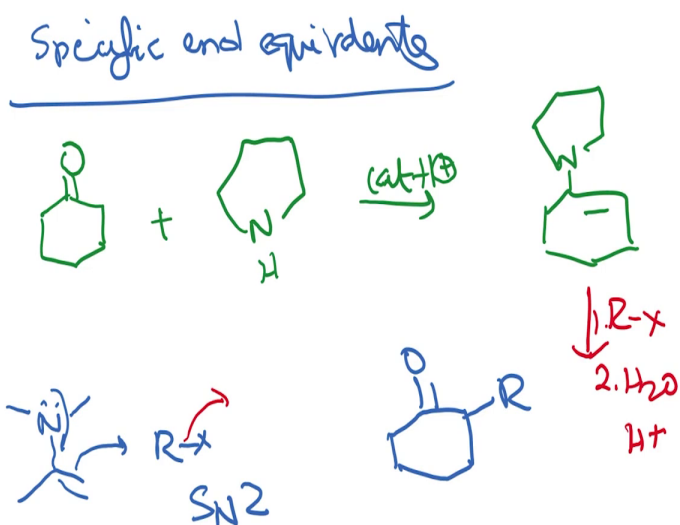
So, we normally do not use LDA conditions for basically alkylation of aldehydes. And also keep in mind that if you want to do a cross-aldol reaction, you still cannot do it at -78°C, because self-condensation is going to compete. So, we have already looked at this previously. So, one of the strategies is to use specific enol equivalents. And these specific enol equivalents can be used with several ways, we will start with the enamine formation.

So, we already know that, you know, once you add, let us say you take, there is just an example. But once you take cyclohexanone, and you add a secondary amine in the presence of catalytic H^+, you know, we have already looked through the arrow pushing mechanism for the formation of such enamines, so I am not going to repeat it.

But what you can do at this stage is that you react this with RX number 1, and number 2 is you do H_2O, H^+ and get the corresponding alkylated product. So, the mechanism of this reaction is something that we have previously looked at, but very briefly, I am just gonna draw out the key step, this is your enamine. Now, the key step here is the reaction with RX. So, if you notice that in the previous example, and as well as this example, the main mechanism of alkylation or substitution is actually S_N2. So, many of these reactions are going to follow all the same rules that we have studied or same patterns that we have looked at with S_N2.

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NO SELF-CONDENSATION

MILD

COMPATIBLE   Functional

groups
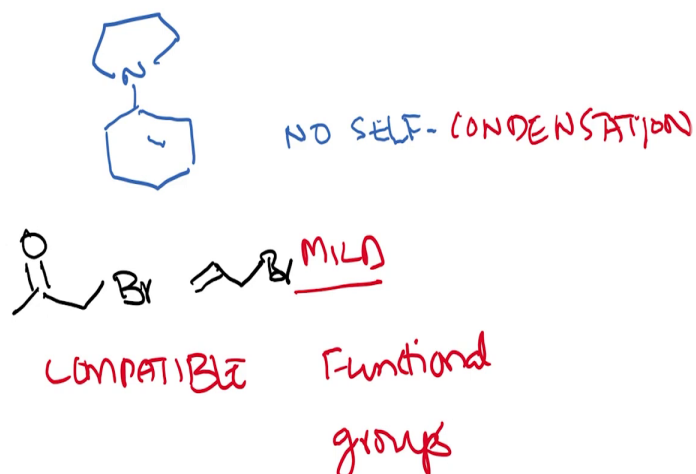
So, the advantage of using these kinds of enamine chemistry to do these kinds of alkylation reaction are that number 1, with enamines, the reactivity of enamines is quite low when compared to aldehydes, or ketones and so no self-condensation. So, this is advantage number 1 and second one is that it is a very mild method. So, you know it is compatible with or potentially compatible with many functional groups. So, this is very useful because when we use harsh conditions such as LDA and so on, you can have multiple reactions occurring in a complex molecule.

So, some of the other electrophiles that can react with such enamines are, you know we already looked at alpha-bromination of ketones you can react it with this, it can react with Br and so on. So, I will not go into further details because we have already looked at several examples and also when we looked at aldol condensation we were also looking at the several examples of this.

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Aza-enolates
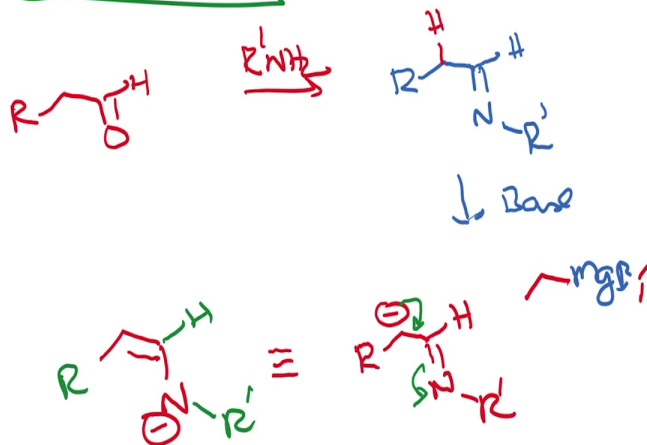
So, now the next method which we have already looked at is to generate Aza enolates. So, the Aza enolates are again a very useful method and the way we do this is starting with an aldehyde, you react this with $R'NH_2$ and you know, I am not gonna draw the arrow pushing mechanism but you will agree that this kind of product can be formed.

And now to this you add a strong base, for example you can add a LDA or you could add butyl lithium or Grignard reagents and any of these I want to pick up this proton and you end up getting the carbanion, which is nothing but is a enolate. So, as you can imagine the Aza enolate is more reactive compared to the enamine and it attacks as a much better nucleophile. And when this Aza enolates are reacted with, just draw it out on the next page.
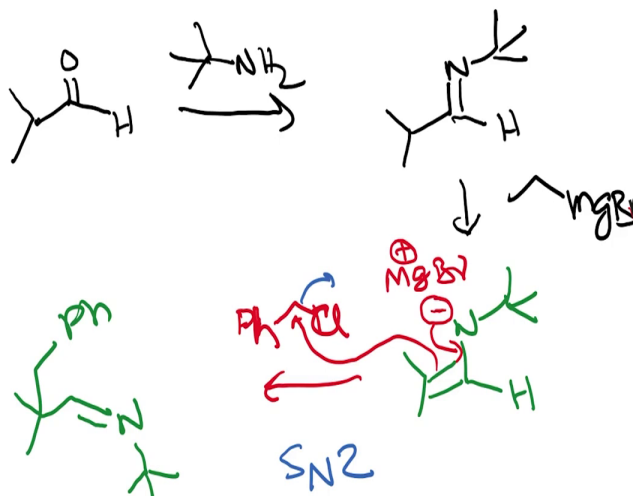
So, the example that I am going to look at is I start with this aldehyde and first react it with tertiary butyl amine and we end up getting $(CH_3)_2CHCH=N(C(CH_3)_3)$ and then we add a let us say C_2H_5MgBr or $RMgBr$ and the product here or the intermediate here that is formed is the Aza enolate. And now you can react this with electrophile such as benzyl chloride, and then you have Mg^+Br, you could also have a covalent bond over here, depending on the nature of that intermediate solution.

So, you are gonna be able to kick the chloride out. So again, this is like an S_N2 reaction. I would urge all of you to go back and look at your basics of S_N2 reactions and so that you can get familiar with it. Now, when you hydrolyze off this in aqueous acid, you get the product which is the corresponding aldehyde.

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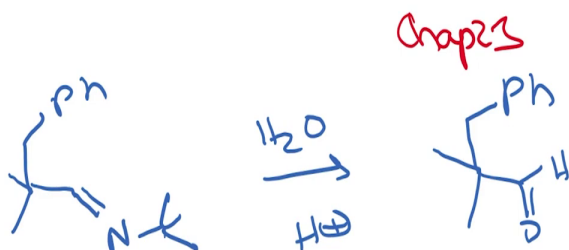
So again, I am not going to, go into the mechanism of this reaction, but this is something that we have looked at. So, you start with this and then you add H_2O, H^+ and the product that you get is the aldehyde. So therefore, in order to do alkylation on aldehydes the preferred method is to be able to generate the Aza enolate and then react it with an electrophile. So, we already looked at some examples about how to generate the Aza enolate. So, please go back to your textbook and this is of course, discussed in chapter 23 in Clayden. So, please go back and look there are several examples of this alkylation reactions in the textbook.

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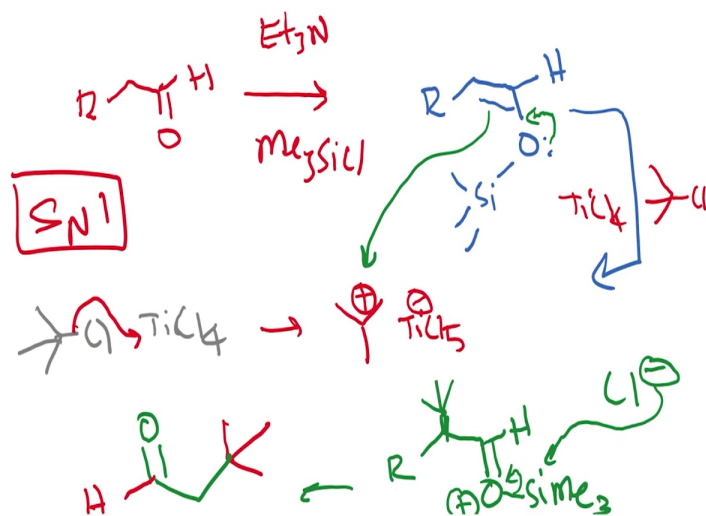
The next major way to actually go forward to alkylate aldehyde is the way we have looked at previously which is generation of the silyl enol ether. So, if you start with an aldehyde such as this and react it with triethyl amine, Me_3SiCl the product that you get is the silyl enol ether and, you know, this is actually this carbon silicon bond is going to, or this carbon oxygen bond, I mean there is no, there is always going to be presented the other side also just drawing this out in this method.

And silyl enol ethers as you know, are very stable, they can be isolated, and so on. So, the reaction of, you know, silyl enol ethers you may recall, requires a Lewis acid, which has titanium tetrachloride. And, you know from the electrophile standpoint, we typically use electrophiles that require Lewis acid, for example. So, the kind of electrophiles that we look at are hindered electrophiles, sterically hindered electrophiles that can, in principle form carbocations. So, let me just qualify my statement.

So, let us say I start with this tertiary butyl chloride. And when we expose this to $TiCl_4$, you know, what we could expect is the attack of this $TiCl_4$, and you produce this kind of a carbocation with the counter ion as $TiCl_5^-$. So, this carbocation now is well set to react with the silyl enol ether. And you know presumably, the reaction goes with this kind of a mechanism. And you end up with a product which is going to look like this.

And the rest of the mechanism is identical, pretty much to what we have studied in the past, so you end up with the double bond, and positive charge, and then chloride ion which is being produced here, will attack and give you back the aldehyde. So, the product that you get is basically C double bond O with an alpha-position contains a tertiary butyl group, this is the new tertiary butyl group that is formed and this is an aldehyde.

So, keep in mind that this kind of silyl enol ether method works very well with the electrophiles that can in principle react through an S_N1 type mechanism. Whereas, the previous examples that we looked at are with S_N2 type alkylating agents. Now, the last method, which we are going to look at, is to use β-dicarbonyl compounds.
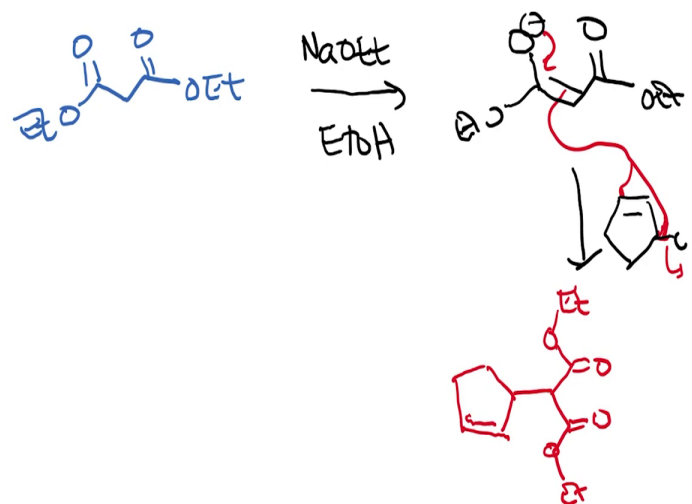
We have already looked at it in the previous discussion. So, you start with something like this, diethyl malonate and you know, you generate the enolate by adding something like sodium ethoxide and ethanol. And we already discussed that the ester since you are doing it in ethanol, and sodium methoxide is going to react and give you back the ester, so you might recall that. So, we are now gonna react this, with this enolate EtOCO⁻=CHCOOEt. And now, let us imagine that we react this with something like chloride over here.

So, this can either attack on this carbon or it can attack on this carbon, the product would be the same. You end up C double bond O OEt C double bond OEt. And this is now bound to a 5-membered ring. And you may recall that in the previous discussion, I had mentioned that we could sort of convert this, bis-carbonyl compound or this 1, 3-di-carbonyl compounds to a mono carbonyl compound.
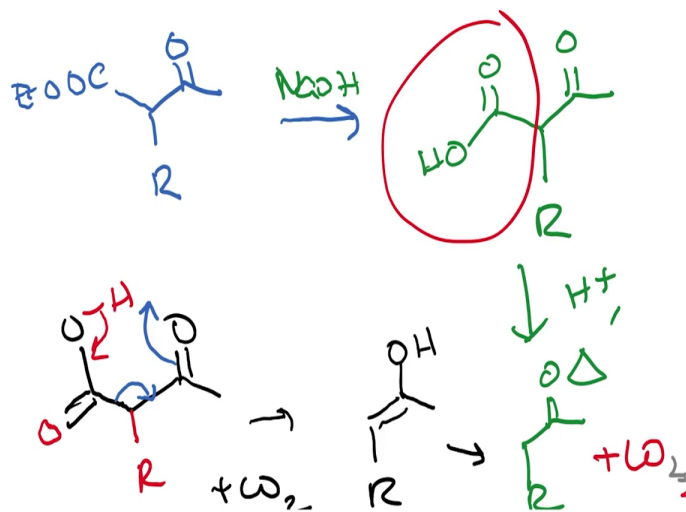
And I am going to just outline how that can be done. So, after you do the alkylation reaction COOEt, let us say we reacted with this kind of ketone, and that is R here. So, what you could do is, this is a very old-fashioned technique, it works really well it gives excellent yields, but what you do is you hydrolyze off the ethyl ester, and you end up with this carboxylic acid. So, here is your main intermediate. And now, when you add H^+ and you heat, there is a decarboxylation reaction that can occur which basically cleans off this carboxylic acid.

And it gives you CO_2. So, let us look at very briefly the mechanism. So, you have $CH_3C=OCHRC=OOH$, just drawing it a little differently so that it is easy for us to see this. So, this is the hydrogen, this is the oxygen. So, now when you add acid and heat, the kind of mechanism that can occur or the kind of arrow pushing that occurs that we propose is the following, this carbon-carbon bond breaks and you get the corresponding enol is the product and CO_2, which can tautomerize to give you the ketone. So, this is a very, very useful method.
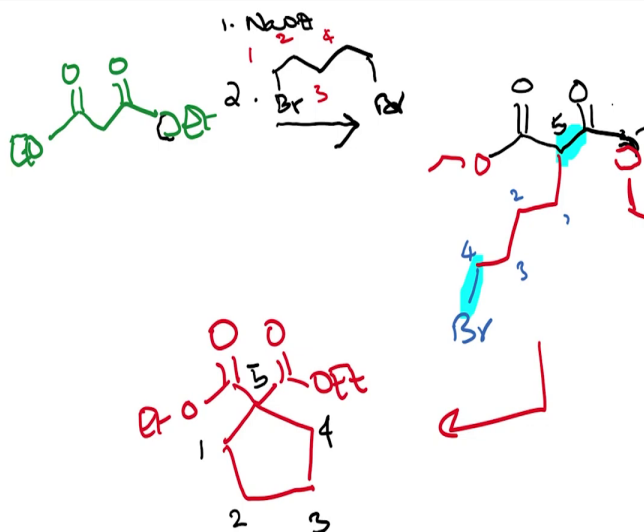
Going forward because literally, although you are losing molecule of CO_2 in this reaction it is a very, very selective reaction. So, you can actually control the outcome very nicely. And again, this is a reaction that requires S_N2 type conditions. So, the last example that we look at is this, 1, 3-di carbonyl compounds allow you to make a cyclic compound as well because if you react this with the compounds such as this, so you now, the first step is obviously, reaction with NaOEt and then you add in this di-bromide, so you can end up with OEt, so this is 1 2 3 4 and then you have the bromide so through the enolate formation.

And then the second enolate can be generated and subsequently you have reaction at the, so this is the second enolate and this can react with this carbon bromine bond and you are going to get a 5-membered ring. So, I will just re-number these carbons 1 2 3 4 and that is the fifth carbon. So, this is 5, 1, 2, 3 and 4, you can also make a 4-membered ring using this process.
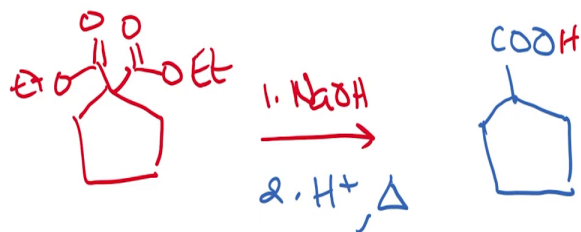
And then the interesting thing that you could do is that once you have this kind of a COOEt CO OEt, first step is reaction with sodium hydroxide and then the second step is H^+ and heat, you can do a decarboxylation reaction and end up with corresponding carboxylic acid which can of course be further transformed, if you want to.

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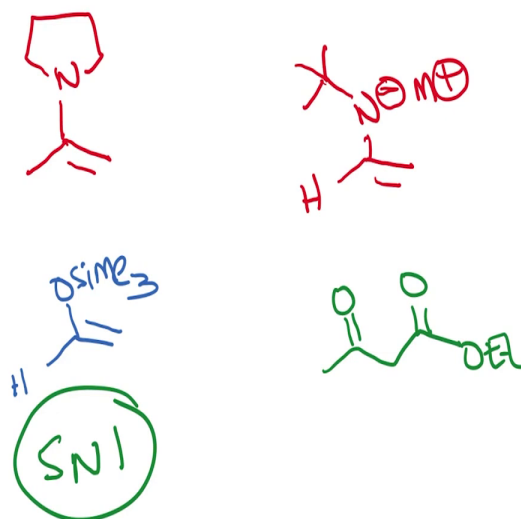
So, to summarize here, there are three important methods that we can use. The first one in addition to direct enolate generation. You can generate the enamine, the second one is further

generate the Aza enolate. So, what we need to do is we need to start with primary amine for example, you generate the Aza enolate which is looking like this or it could be a covalent bond also.

And the next method is to use the trimethyl silyl ether that we are quite familiar with. And the last one is to use a 1, 3-dicarbonyl type compound which can then be easily deprotonated and reacted with. So, this is the one that goes through an S_N1 type reaction because addition of the corresponding titanium tetrachloride or Lewis acid is going to generate the carbocation. So, these are the major methods by which one could do alkylation of enolates. The methods are quite similar to the ones that we looked at with aldol reaction.