Introductory Organic Chemistry - II
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Lecture 50
Regioselectivity of Alkylation Reactions

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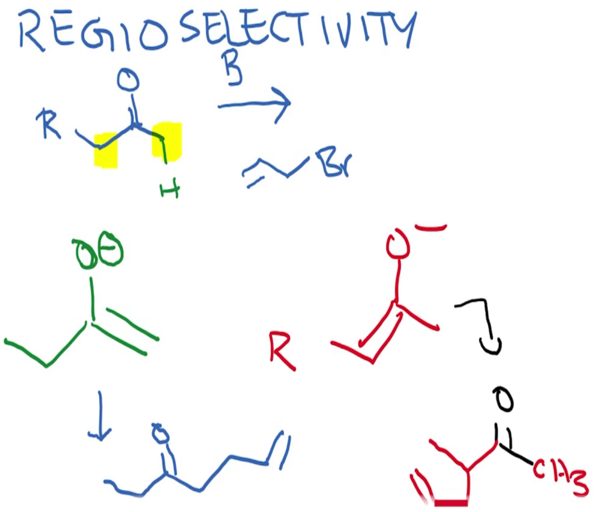

So, the next concept that we want to look at is regioselectivity as far as ketone reactions are concerned. So, if we have a ketone such as this, and when you generate the enolate there are two enolates that are possible. So, one is this, let us say hydrogen is picked up, then you end up with this enolate else you end up with this kind of a enolate. So of course, you have the cis-trans isomerism also has an issue here. You know, we will look at that in the coming semesters. Right now, assume that the problem that we are looking at is only between picking up this hydrogen versus this hydrogen.

So now, clearly, if alkylation occurs, let us say with allyl bromide, you end up with a mixture of two compounds. And this is quite normal, that if you do not have any other conditions, you usually end up with a mixture of two compounds. So, this is a huge problem that we face when we look at enolate alkylation reactions. And so, there are some good ways to address these problems.

And that is what we want to look at. So, you will end up with this type of compound. So, if this gets this enolate this formed, you end up with this product. If this enolate is formed, you end up with this product. So, the reactant here is basically allyl bromide or something like that. So, the problem is called Regioselectivity problem. And so, this is something that we are going to discuss in this lecture.

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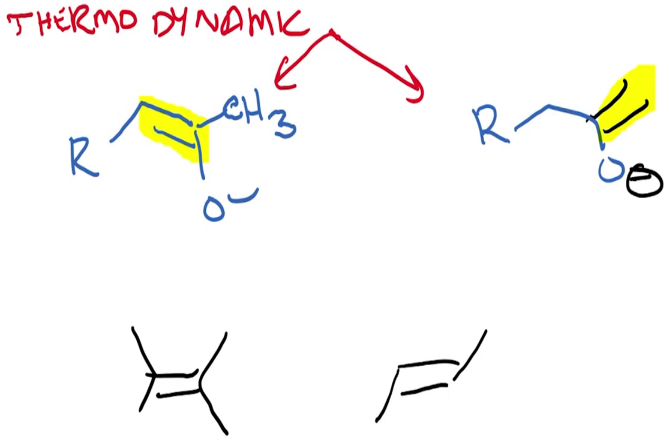

So, the first way to think about this is if we can you know form something that is going to be more stable, since we are quite used to stability as a factor. So, let us say, I have a choice and if I am able to produce this kind of enolate versus this kind of an enolate. Now, looking at these similar principles that apply to olefins also apply here. So, when you have an olefin, the more substituted olefin is more stable than the let us say less substituted one.

So therefore, between these two enolates this enolate is considered to be preferred from a thermodynamic standpoint, compared to this enolate. So, if we recall, we have already discussed this concept. So, when you have a choice of formation of these two products, and if one of them is formed, then one of them is considered the thermodynamic product and the other one is called the kinetic product. So, we look at the kinetic product in a short time, but the more stable compound is actually going to be the more substituted enolate.

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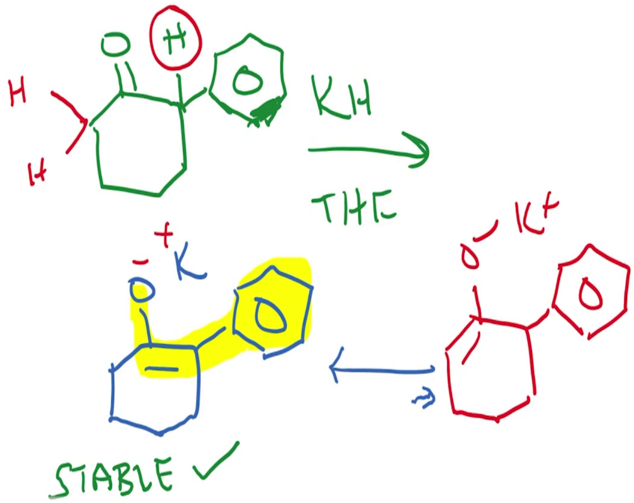

So, having said that, now let us look at an example. And we will see how well this concept holds good. So, let us say we take this ketone with a benzene ring alpha to it. So, when we react this with, let us say potassium hydride, THF. Now again, we have a choice, the choice is between this hydrogen or one of these 2 hydrogens. So, let us look at the enolate that is formed. So, if this hydrogen is picked up, and you end up with the enolate, it is going to look something like this.

So, this is going to be likely it is going to be a O minus and K plus. So, now the other possibility is that you get the abstraction of hydrogen at this position and the final ring continues to be on the right. So, these are the basically two enolates that can be formed. And you can imagine that these two would be in equilibrium, because you are not doing anything to push the equilibrium towards the low temperature or anything to induce any form of selectivity.

So, what one could imagine is that when we start with this ketone, you have the possibility of forming two enolates and it is likely that both these enolates are going to be formed. However, there is one significant difference between this enolate here and this enolate, one is that basically you have an extended conjugated system.

So, based on this concept, one could argue that this is the stable or thermodynamically more stable enolate and therefore, this is actually going to be formed when we do in practice, we do find that this forward reaction is actually not very favored. And you end up with a situation where, you know, the enolate that is formed is actually majorly, this one. So, now of course, if you know react this with allyl bromide or anything, the product that you are going to get would be the one that is reacting over here. So, let me just write that out. So, that it is easy for us to follow.

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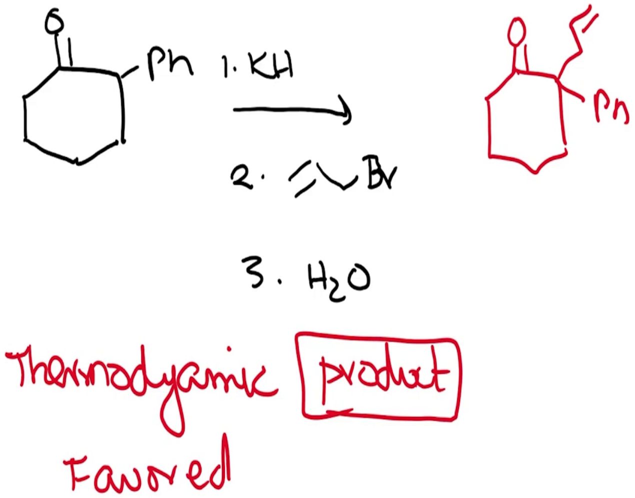

And I will take a slightly different example or maybe use allyl bromide as the same example here. So, number 1 is KH and number 2 is allyl bromide, number 3 is H_2O. So, the product that we end up getting is... So, this tells us that this is under what is known as thermodynamic product or thermodynamic product is favored and by product, I mean, what I actually mean is the intermediate, the thermodynamic the more stable enolate is formed which then gives you the product.

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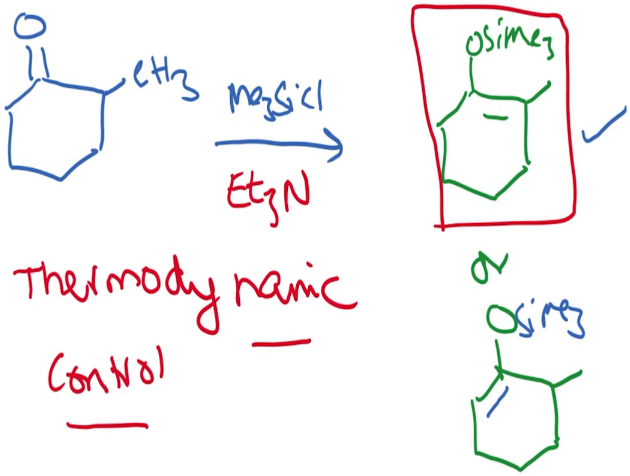

Now, the other way in which we are used to reacting to generate enols is use the trimethyl silyl enol ether. So, when we start with this kind of a ketone, when you react this with Me_3SiCl in the presence of weak base such as triethyl amine. Again, you have a choice here and I can just write that two products. So, when we do this kind of reaction, we observed that the only product that is pretty much formed is this one.

So, this is under excellent thermodynamic control and we exclusively get the formation of this product. Now, so the advantage of using this kind of trimethylsilyl ether is that one can generate the trimethylsilyl ether and then react it and you are going to get only a single product that is going to be form.

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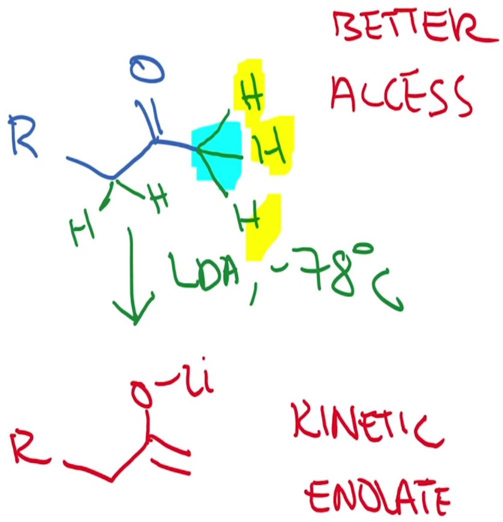

Now, in terms of regioselectivity, how would you do the reaction in a kinetically controlled manner, that is we started, if you remember the discussion is how do we access this enolate. So, the way we would do this is to use conditions, which we are very familiar with, which is LDA, -78ºC, and a solvent such as THF. And what ends up happening is that these hydrogens, now you need to understand that we are at extremely low temperatures.

And so, the temperatures are so low that the populations of molecules that have sufficient energy to cross barriers that we are considering is quite low and even small structural changes, you know the change in the or an addition in the barrier for example sterics can result in a small increment in the barrier, which then becomes inaccessible to most molecules. So, here what is found experimentally is that these 3 hydrogens are far more accessible.

So, they are accessible at room temperature and therefore, they end up being the preferred sites where reaction occurs. So, when we add LDA at -78ºC the only product that is formed is the kinetic enolate. And this ends up giving us the preferred alkylation product which is at the less substituted site. So, just to complete the discussion here…

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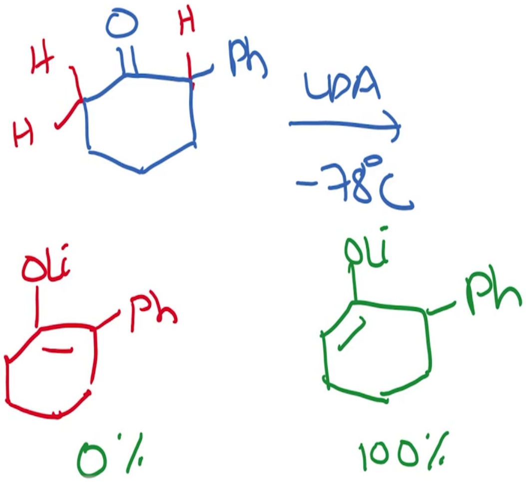

If we start with this product, I mean this ketone, now if you had LDA, -78ºC then based on our discussion this hydrogen is less accessible, these two hydrogens are more accessible and so let me just draw out the two enolates. So, these are the two potentially enolates and so our data shows that this is 100 % formed and there is no evidence for the formation of this product.

So, this is really, really useful. So, when I want to do alkylations at this position then I generate the thermodynamic enolate using potassium hydride or sodium methoxide or some other base at room temperature, so that I can get an equilibrium over here, even better if I want to generate the enolate here, then I actually do the trimethyl silyl enol reaction so that I can exclusively form the more substituted enol.

And if I want the enolate to be produced here, then I react it with an extremely strong base at low temperatures such as LDA and this gives us the kinetic enolate and that is the less stable product. And we have already discussed about kinetic versus thermodynamic in this lecture previously.

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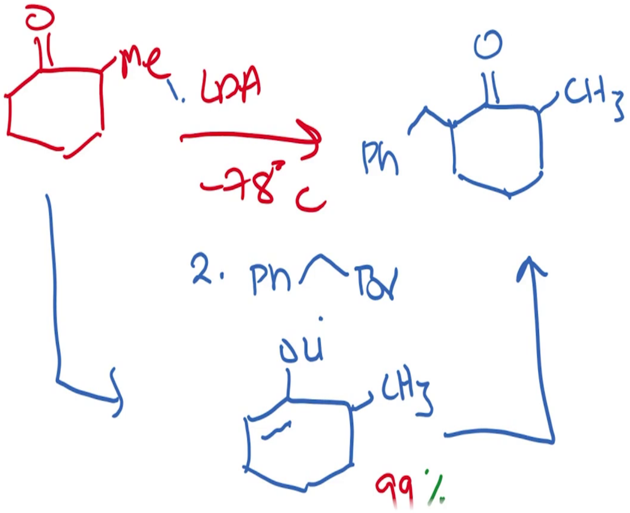

And therefore, we can actually control the outcome of the reaction. Now, let me stop one last example which is 2-Methylcyclohexanone. So, if we add LDA at -78ºC number 1, then number 2 is reacted with benzyl bromide, the product that is formed is this. And so, the intermediate as you know would be the enolate and studies show that this yield of this enolate is pretty much 100% or quantitative and 99% to be accurate. So, this is nearly quantitative and then the alkylation reaction is going to give you the product.

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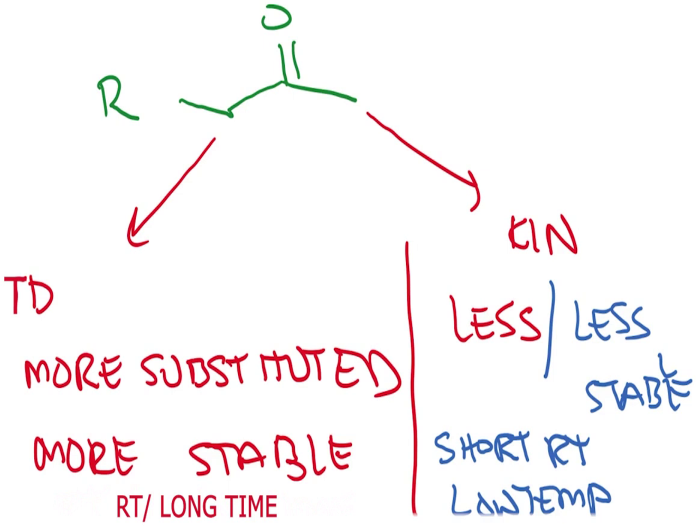

So, to summarize this part of the lecture when we have a situation where you have a competition between two kinds of positions where enolate can be produced. So, this is the thermodynamic enolate and this is the kinetic enolate. So, the thermodynamic enolate is more substituted and more stable. And, you know so one of the ways in which you can actually produce this is to use room temperature or even higher temperature and you react it for a long time basically, you give enough time for the reaction to equilibrate because we are looking at an equilibrium reaction.

Whereas with the kinetic enolate you need to have less, it is basically the less substituted enolate that is formed, it is also less stable. So, if this enolate is produced it is less substituted and therefore it is less stable normally. And we use a short reaction times and low temperatures to produce this kind of enolates. So, we will solve some problems, which are related to this and I hope this will become much clearer as we move forward.