Introductory Organic Chemistry II
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Indian Institute of Science Education and Research, Pune
Module 03
Lecture 23
Nucleophilic Addition Reactions and its Stereochemistry

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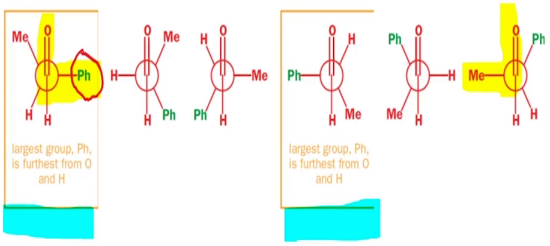

So, in the previous lecture, we looked at the various conformations that you would be interested in, for developing a model with, and these conformations are the ones which have the groups which are perpendicular to the carbonyl. And so, we do them out, there are six of these conformations. So, here is the phenyl ring, which is perpendicular to the carbonyl. And there are various other sort of similar conformations.

And from this, we sort of deduced that the two important ones are the ones where the largest group is farthest from the carbonyl. So, it is important to note in this model that, just to understand this whole framework under which we are operating, there are many several models which account for the selectivity that we observed.

So, if you remember, we are trying to develop a model that helps us rationalize the 3:1 selectivity that we get in the nucleophilic addition reaction. And so, one of the models is this, so this model sort of tells us that, you need to place the group, the largest group perpendicular to the carbonyl.

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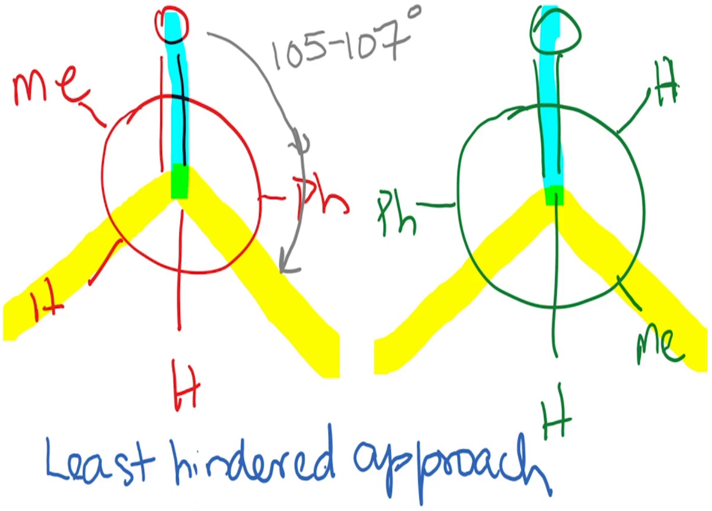

So, as a general model, what we need to look at is, we draw out these two structures here. So, that is, one is this where you have the C=O here, the hydrogen here, the phenyl ring was over here, methyl was here, and H was here. And the other conformation was the following where you had C=O. I think by this time, you are getting quite familiar with drawing out these various conformations.

And so, according to the model that we are trying to develop here, the important conformations are these. And wherein the largest group is perpendicular to the carbonyl. And now, what we need to sort of figure out is, we already know that the attack of the nucleophile on the carbonyl, so this is your C=O, it does not occur at 90 degrees. So, that we already know.

And so, the attack happens at 105 to 107 degrees, so depending on which source you follow, this is called the Burgi-Dunitz's angle. And it ranges from 105 to 107. So, this is kind of the angle at which your attack is going to happen. Now, let me just draw this out, so this is the Burgi-Dunitz's angle, which is 105 to 107 degrees, if you look at Clayden, the book refers to it as 107 degrees.

And if you look at the other sources, it says about 105 degrees. So, this is the sort of range that we are looking at. So, this is the angle of attack. So, we know all of this because we have developed the framework based on the main parameters that help us understand this angle of attack. So, now how do we account for the difference in reactivity?

So, the difference in reactivity can now be attributed to the one which has the least hindered approach. So, I will repeat, so the attack that has the least hindered approach is the most favourable or the least energetic.

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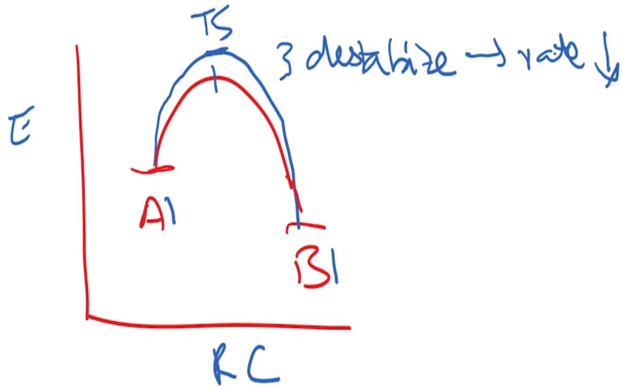

So, just to put this in perspective, let us look at the reaction profile. Let us say A goes to B. Now, if you want to look at something like here is the transition state, so energy-reaction coordinate. So, let us say I go now and make another analog, A1. And if anything, that results in an increase in the transition state energy. So, let us say I am going through this pathway to give me B1.

Now, this difference in energy is going to destabilize the transition state, in which case the rate is going to be going down. So, anything that destabilizes the transition state is going to result in reduction of rate. Anything that stabilizes the transition state, or removes the hindrance to the reactive centre, is going to result in a decrease in the transition state energy, which results in an increase in rate.

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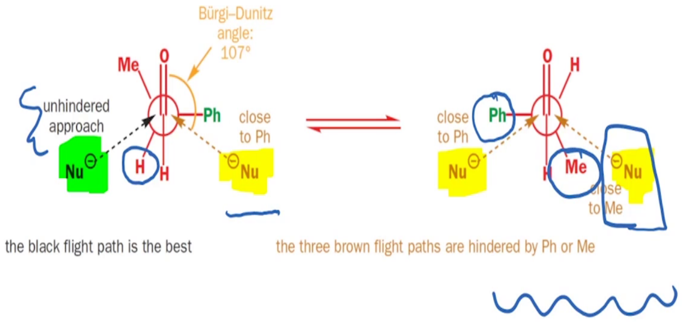

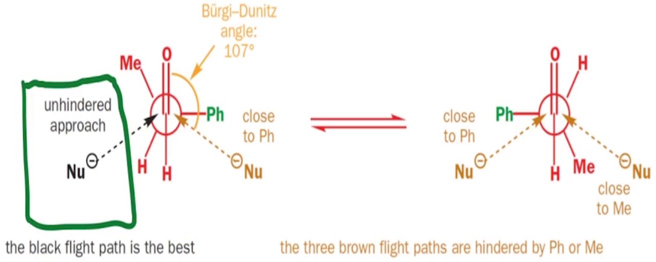

So, now coming back to the picture, I am just taking this out from Clayden, so that you guys can go back and refer to it. So, therefore, these are the major paths that we are looking at, in which the nucleophile can attack. And now, among these four paths, what we can sort of try and understand is that this nucleophile can attack from here; this conformation it can attack from here, it can attack from here.

So, these ones that are highlighted yellow versus the one that is highlighted in green, there are differences. So, here in this, let us start from the right. So, here in this path, for example, the methyl group is quite close and therefore, this path maybe slightly hindered or you can assume that it is going to be unhindered. Similarly, here, you have a very large phenyl group on this position, and so the attack at 107 degrees is going to be disfavored.

So, in this particular conformation, both the attack paths or trajectories are going to be hindered. Whereas in this, you have a situation where the phenyl ring is close to the nucleophile attack, just like the other case, but you have a situation where you can have an unhindered approach. So, the unhindered approach is because of the presence of the hydrogen here over the, in the other case, the methyl.

So, therefore, among the various trajectories that are possible, you have a situation in these four compounds, in these four conformations, you have a situation where a particular path is most f, and which is this. So, let us try and understand this model a little better now. So, you have the nucleophile attacking here from the unhindered side, as we described in the previous lecture. Now, what are the products that are going to be formed.

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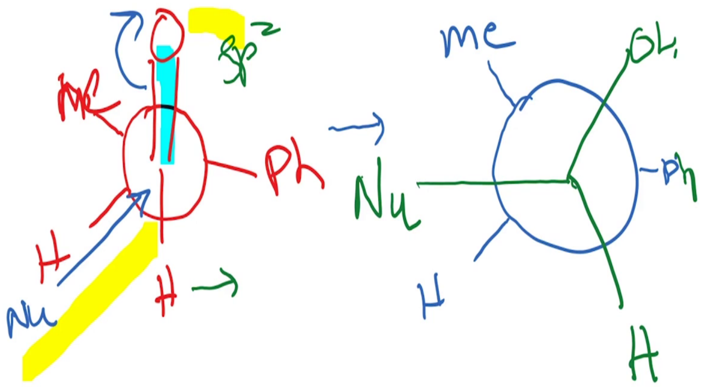

So, this is going to be an exercise that we need to understand or to pay attention very closely. So, if you draw out this conformation, the most important conformation, then you have a phenyl here, hydrogen here, and methyl here, and the nucleophile is attacking from here, as we described it. And so, if you push the arrows, then you get the following compound, which is shown here, they have the same ring in the back.

So, keep the back carbon the same and do not make any changes to this. And now, in order to draw the front carbon, we need to look at it in a slightly more careful way. So, what happens in this process is that this carbonyl bond is going to break. And this carbonyl bond was sp^2 hybrid, and now it is going to become sp^3. And so, since the nucleophile, is attacking from this direction, the C=O is going to move here.

So, you are going to have, just to simplify things, I am just going to draw it like this, the nucleophile is attacking from here, the nucleophile is here, the OH is going to be here and the hydrogen is going to be over here. So, this sort of pushes the two groups, that is a C=O and the C-H it is going to be pushed in this direction, the carbon is going to assume sp^3 hybridization. Now, this is the general model that we are going to follow. And this is the model that we are going to use to understand the outcome.

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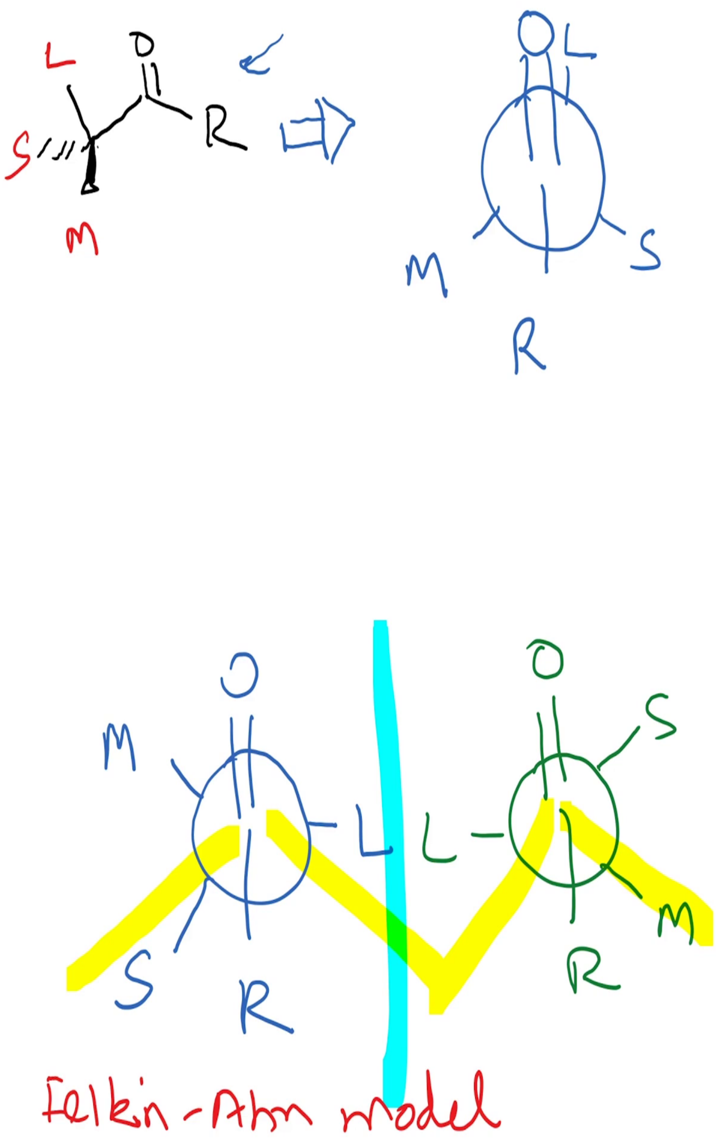

But now, in order to generalize this, the way forward is that when you have a carbonyl compound, such as this RC=O, with three different groups, let us say you have a small group, a medium group, and a large group that is large, small, medium. Now, the strategy moving forward is to look through this C double bond O R group and draw this out in the following way, which is the Newman projection, C double bond O R, and exactly the way you draw it, the large group is always going to be on top.

And now from looking at it from here, the small group is going to be on the right and the medium group is going to be on my left. So, this is how I would draw this. But this is not the important conformation. In order for us to understand the model better, we need to be able to draw it out in two special conformations that is the first one is this C double bond O R, where the large group is perpendicular.

And now you need to rotate the previous conformation that I had drawn and draw out the correct ones. So, this takes a little bit of practice. So, I would urge all of you to go back and try out some of these methods for rotation and so on. So, that you get familiar with this. So, you have these two conformations, and these are the two conformations that are going to be important.

And now, the question is, which of these two is going to be more reactive. So, I just want to remind you, once again, we are not looking at populations of conformations, we are looking at which conformation is more reactive, and according to this model, the more reactive one is going to be giving you the major product. So, now we know the Burgi-Dunitz's angle and so the nucleophile is going to approach from here or from here and so on.

So, all of this is already known to us. So, I am just recapping this. So, as a general model, this is the one that is used to understand nucleophilic addition reactions on carbonyl compounds. So, this model is called the Felkin-Ahn model. So, this is the most reasonable and well-studied model which helps us understand additions to carbonyl compounds. And so, therefore, and also it has been figured out using a lot of experimental data. And so, therefore, this model is the one that we would recommend that you follow to predict the major product.

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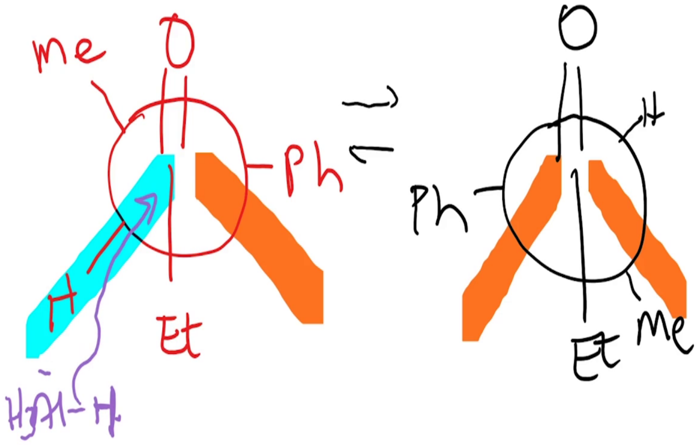

Now, going back to the example that we started with, where we found that we were getting one particular major product, the conformations, I am going to draw it over here which is C double bound O, Et, phenyl, H, Me. So, this is one of the conformations, I would urge you to go back and work this out. And this is the second one, C double bond O, Et, phenyl over here. And you have hydrogen, and methyl.

And so, keep in mind that these are in equilibrium with one another. And, given these two conformations, we now need to understand what is the most favourable attack trajectory. So, the way we would project forward is that clearly, this attack is not very favoured because of the methyl group, this one is not going to be favoured because of the phenyl ring, the same situation over here.

And therefore, the most favoured one is the one which I am drawing in blue. So, now, if we consider that lithium aluminium hydride attacks from this particular trajectory, and now the product that you will get, which I am just going to draw it as hydride that is the way we write it as H_3AlH^-, and so this is the one that is going to attack from here.

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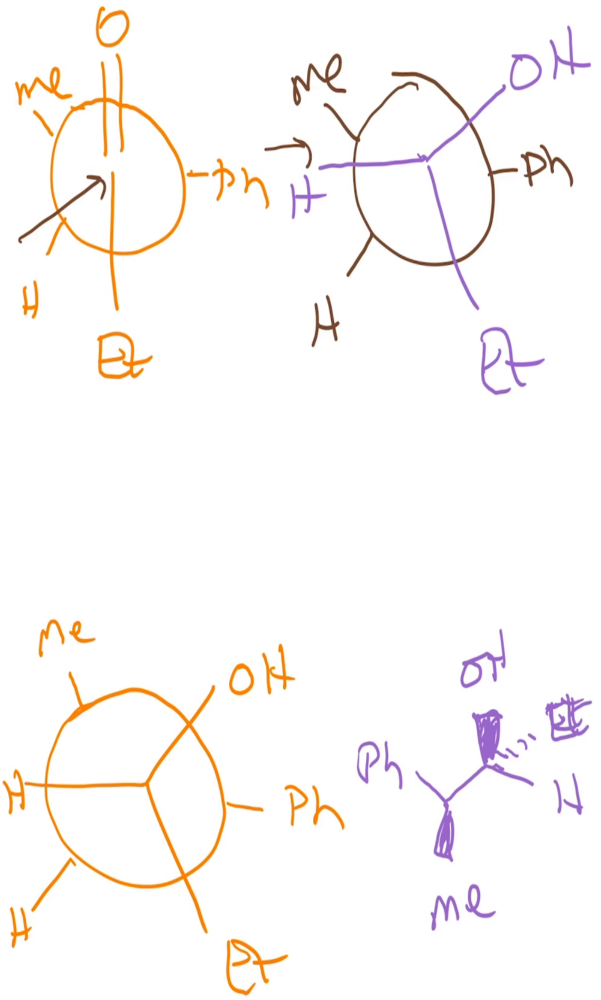

So, the product that we will get is, start with this C double bond O, Et is here, phenyl is here, methyl is here, hydrogen is here. And so now as we discussed the hydride is going to attack from here. And so, once this attack happens, immediate product that you are going to get is this, keep the back carbon the same. And now, we need to correctly write out the front carbon. So, this is OH, H and Et.

So, this kind of a conformation has to be drawn in the correct sort of projection. Let us look at it a little bit closely. So, you have OH, Et, and H. And the three substituents in the back remained the same. So, you have methyl and hydrogen and so the way we would redraw this is in the following manner. So, the way we would redraw this is that we would keep the phenyl ring in the back.

And so, now, if the phenyl ring is in the back, then the methyl is coming towards me and the hydrogen is going into the plane of the board and then you have the hydroxyl group that is going to be over here and the ethyl group is going to be the back. So, this is the conformation or the product that we would expect. And now, if you go back and check the major and minor products from the previous lecture, you will find that this was the major product that was formed.

So, therefore, the Felkin-Ahn model is a very powerful model to help us understand the experimental outcome. And this model has been developed using very rational methods, which is, we start with giving out that the largest group is perpendicular to the carbonyl, which is a reasonable thing to propose because the eclipsing interactions are going to be minimal in that conformation, then we go to and invoke the Burgi-Dunitz's angle, which was again experimentally derived. And then we also use high level computational calculations to support the model. And, therefore, the Felkin-Ahn model is perhaps the very reasonable and rational and consistent model that helps us understand the outcome of these kinds of attacks.

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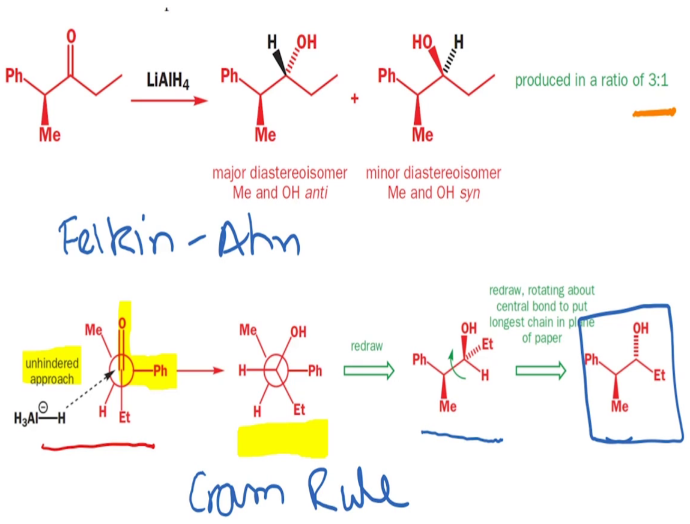

So, let us just now quickly recap. So, when we want to explain the formation of a product, in this case in the ratio of 3:1, so we want to develop a model. And the model that we want to use we prefer to use is the one which is the Felkin-Ahn model. And the Felkin-Ahn model basically has very important characteristics and that is the large group is going to be perpendicular to the carbonyl.

And when you draw out this kind of conformation, you will find that there are two conformations, and there are four possible modes of attack. And among these, the unhindered approach, which is shown here, is the most favored. And that is going to give you the corresponding product and we also looked at how to draw this product. And this allows us to sort of redraw it and you get this final product. Now, as I mentioned here, this is called the Felkin-Ahn model.

Now, there are other models, which are developed based on just completely based on the observation, that is, you get this ratio of major to minor, and you can develop a model which does not have a clear logic to it, but still accounts for the formation of the product. And one of those models is called the Cram Rule, or the Cram model. Now, the Cram rule is very interesting, because it is one of the earliest developed rules in this field.

And it is a very powerful rule and it works very well. But the problem with any such rule is that there is no rational basis for us to consider this. And so, the Cram's rule has fallen out of favour among scientists, and therefore we do not need to discuss it. So, Clayden says, explanations and clear logical thinking are more important than rules. And you must be able to account for and predict the reaction of chiral aldehydes and ketones using the Felkin-Ahn model. So, we would prefer to use the Felkin-Ahn model.

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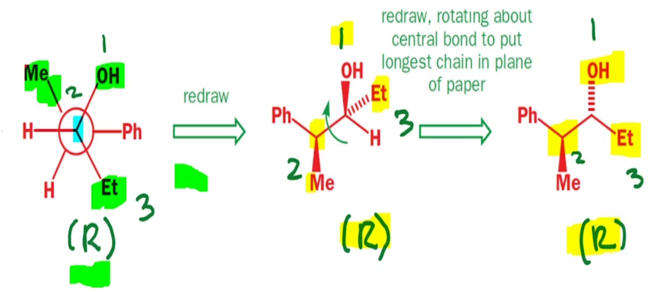

And there is a little bit of confusion I see in the conversion of this product to the corresponding structure drawn as shown on the right. So, if you have any confusion, the best way to sort this out is actually, since there is going to be an enantiomer that is going to be formed, you can assign the absolute stereochemistry. So, what I have done is, I have just tried to assign the stereochemistry of this carbon over here.

And here, the OH gets priority number 1, the carbon in the back gets priority number 2, ethyl get priority number 3, and of course, hydrogen is priority number 4. And so, if I look at it from here, from this side, now, it is going to go in the clockwise direction, and therefore, I have this assigned as R. Now, when I am drawing the next structure, whatever method you follow to draw it, the absolute stereochemistry will remain intact.

And so, I go back and assign the stereochemistry for this product here. And this is priority number 1. And this carbon here is priority number 2, the ethyl group is priority number 3, and of course, hydrogen is priority number 4. Now, when I look at it, with the hydrogen pointing towards me, it is clockwise, and therefore, it is R again. And lastly, we will do the assignment of stereochemistry for this final structure over here, this is again, taken from Clayden.

And so here again, OH, this carbon over here, and ethyl, this is 1 2 3. And so, this is anti-clockwise, but since the hydrogen is pointing towards us, this becomes R. So, when you are in doubt about what the structure that is formed, it is best that you assign the stereochemistry and make sure that the stereochemistry is consistent.

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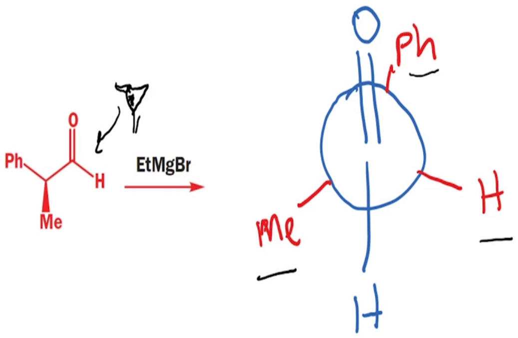

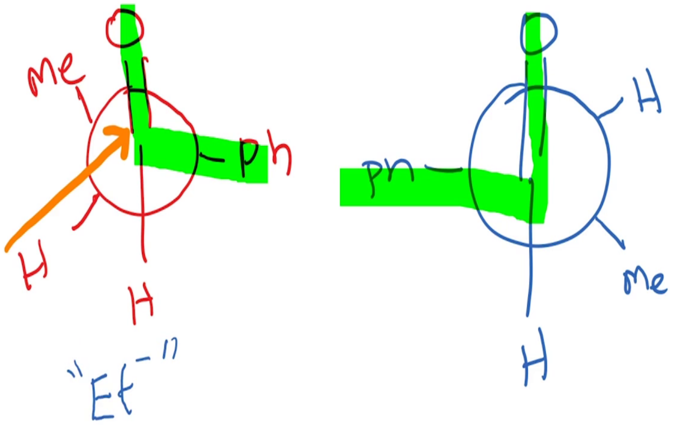

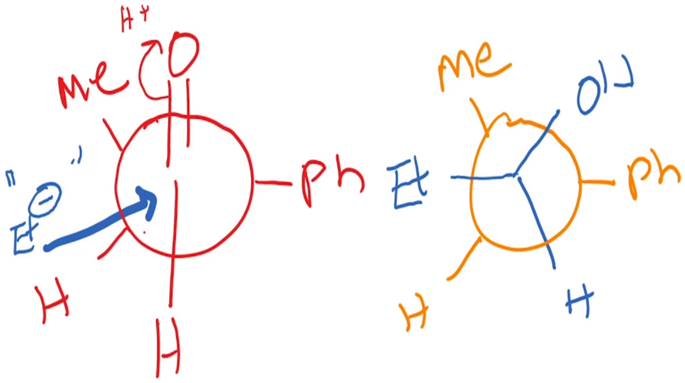

Now with this, let us move on to one more example, which is the addition of Grignard reagent. We will look at Grignard reagent later in the course. But all of you must be familiar that this is a carbon-based nucleophile. And so, when I look at the structure, I know at the carbonyl, what I want to do is, as we looked at in the example I just placed myself over here, and look from here, so the carbonyl is on top, and the hydrogen is below.

And now, if the way I have drawn it, the phenyl ring is eclipsing the carbonyl, hydrogen is on the right, and methyl is on the left. So, then what I do is I move on and draw out two different conformations wherein the largest group is perpendicular to this. So, I am just going to draw this in this following manner. I think you guys need some practice. So, you should go back and draw these for yourselves.

And what you will find is that these are the two major conformations. And when you look at these two conformations, we have attack, which is favoured as shown in this orange arrow, which is going to come here. Now, the attack of the nucleophile as shown here. So, nucleophile here is “Et$^{-“}$ and I am putting this in parenthesis because it is not really Et^{-} its EtMgBr.

But nevertheless, if Et^{-} attacks from here, then this carbon-oxygen bond is going to break and you can push electrons here and give O^{-} which is going to pick up a proton from somewhere and pick up this and become OH. So, this is going to be the structure of the compound that is formed.

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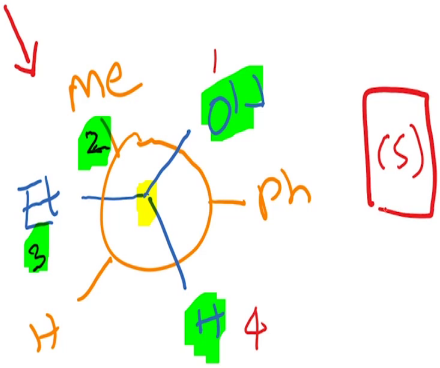

Again, this is all worked out in Clayden and so, you can go back and look at it, but just so that we follow the correct convention that I discussed, let us now assign the stereochemistry. So, for this carbon over here, the priority number 1 is OH, priority number 2 is the carbon behind, priority number 3 is the ethyl group, and priority number 4 is hydrogen.

And now, if I assign the stereochemistry. So, if I have to look at it from this direction, then the hydrogen is remote to me and then it is an anti-clockwise direction and so I am assigning this S. So, again please go back and double check this and make sure that you are getting the answer correctly.

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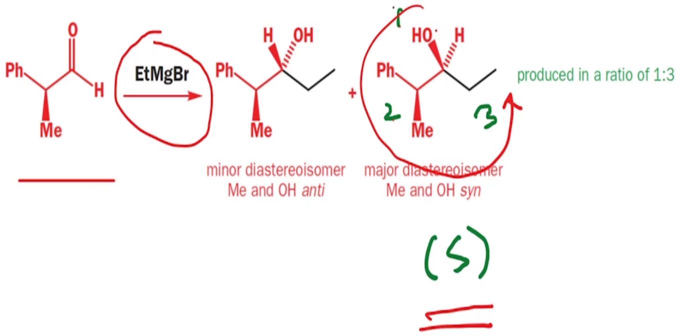

And based on this, what I would predict is that the major product that is going to be formed is the S compound as shown here. So, again, I would when I convert this to the corresponding compound, you again want to double check that it is S. So, there is 1 2 3 and so this is going to be anti-clockwise.

And so therefore, the assignment of the stereochemistry is S. So, to answer the question, when this compound reacts with ethyl magnesium bromide, it forms a mixture of two compounds and the major diastereomer according to the Felkin-Ahn model is predicted to be S at this center.