Mechanisms in Organic Chemistry
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Lecture-30
Trapping Intermediates: Part C

So welcome back. We are now nearing the last 2 weeks of this class. And so far we were looking at experiments to determine reaction mechanisms. So, in the last class we had looked at how we can trap reaction intermediates to understand the mechanism. So, we had looked at traps for anions. So logically if you have anions, something which is electrophilic, would be a good trap for the anion. For cations you would need something which has nucleophilic.

A lot of times solvent is used because solvent is nucleophilic and it is in a large excess. So, it ensures that your intermediate is actually trapped. Towards the end we had looked at traps for radicals.

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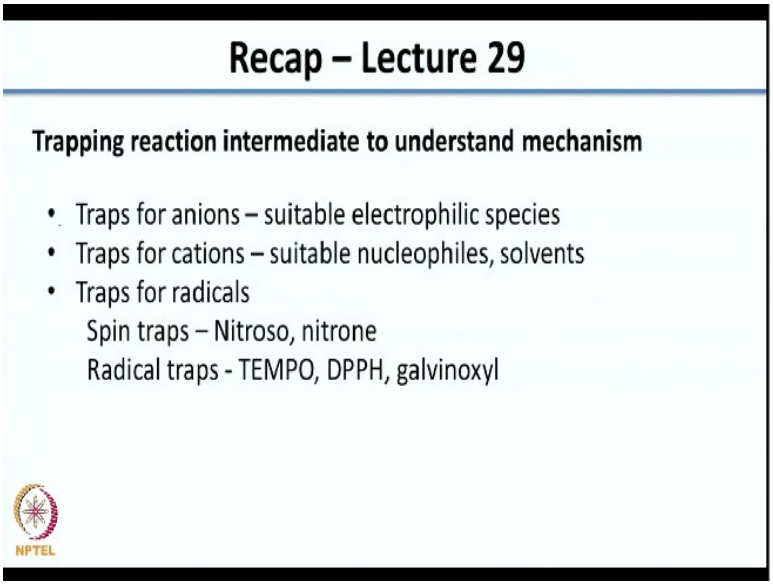

And in radicals there are 2 types of traps. One type of trap quenches the radical, so these are called as radical traps. The other type of trap retains the spin or the radical nature and these are called a spin traps. So in spin traps, we had looked at nitroso and nitrone compounds, which could be used to generate a new radical, which has long lived because it is more stable. And in

the radical traps, what you use is you use a stable radical, which will react with your reaction intermediate radical to form a quenched or neutral species.

So we had looked at several examples of radical traps. Now in today's class, what we will do is we will look at trapping of other intermediates that cannot be classified as carbocations, carban ions or radicals. One classic example is trapping of benzyne.

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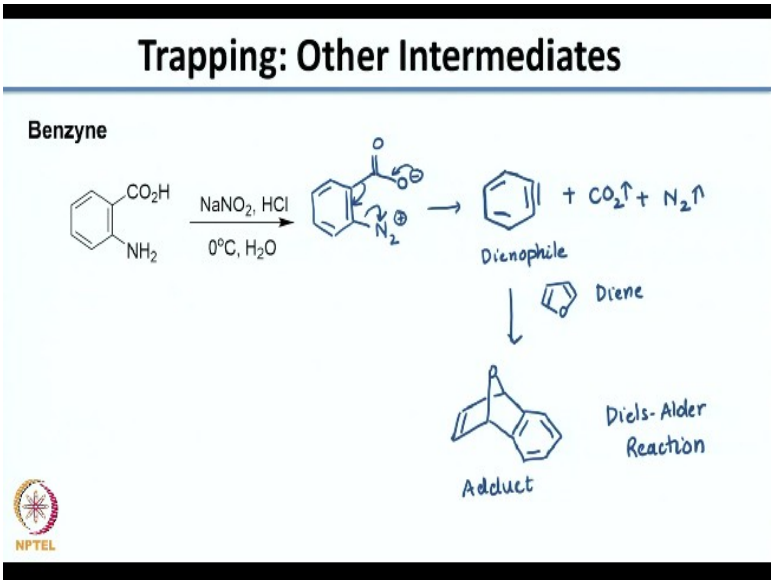

So we had seen the benzyne intermediate earlier when we were looking isotope labeling. So here is another method to generate a benzyne. And how this reaction works is quite interesting. So if you have this molecule, so when you do the diazotization reaction, so you have a aromatic amine here, what is the product that you will form? Hopefully you have gotten the answer right. So you will generate the diazonium salt.

Now once you generate this zwitterionic intermediate, you can then imagine these electrons coming in and forming the benzyne. And once you form the benzyne, you would need to figure out a way to trap the benzyne. Now this reaction is very very facile because the other by products are gases, and these gases will go away. So the reaction is highly favorable to the right where you generate the benzyne, and you have these gases going away.

Now once you generate the benzyne, it is a highly reactive intermediate. So you need a good reagent to trap the benzyne. And benzyne, we have studied is an intermediate when you look at

nucleophilic aromatic substitution reactions, but benzyne is also a very good dienophile for the Diels-Alder reaction. So if you react this with a highly reactive diene-, you will be able to form the Diels Alder adduct and what has been used to trap the enzyme is furan.

So the adduct that you form would be, so this would be the adduct that you form. Now, given the fact that this is a Diels-Alder reaction, so you have you are diene and you dienophile, looking at the structure of the adduct you know that the intermediate formed is a benzyne. So, this is a nice method for you to figure out that the benzyne intermediate was actually formed. Otherwise, it is so reactive that it is very difficult for you to isolate the benzyne.

And this example also shows you a very elegant method to generate the benzyne. Now, we will look at application in biology. So as usual, we were looking for all experiments, how one can use these simple principles to even understand biology. So, let us see how we can use this concept of trapping in biology.

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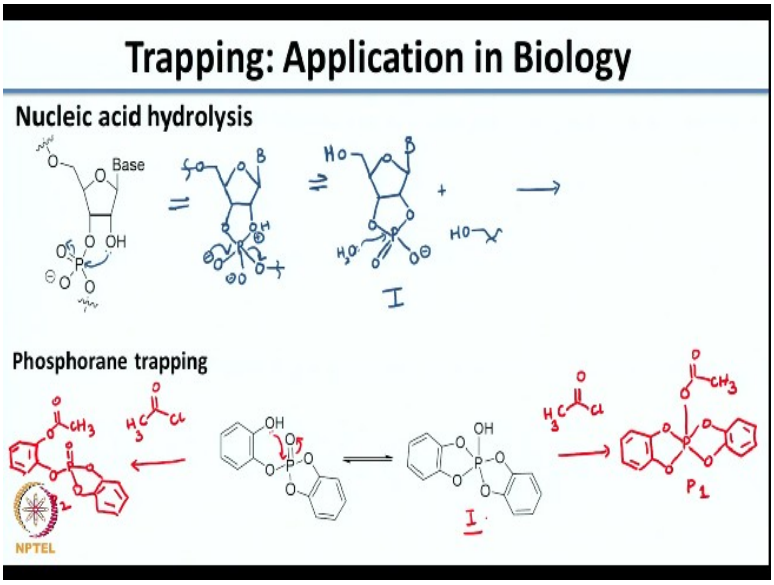

So shown here is the structure of a polynucleic acid. So it is a repeating unit and this is a polymer I have just shown you one monomeric unit of the polymer. So, this is an RNA structure. So, the mechanism for its hydrolysis has been proposed, where you can draw the arrows from this neighboring hydroxy at the 2 position and it gives you this intermediate. I will just write this as B and here you have the rest of the.

So, here you see that the sugar polymer backbone is still intact. So, I can then imagine this electron coming back in and kicking this out to give you another intermediate structure. So, I am not showing the proton transfer steps. So, I have shown the free OH here, because it has hydrolyzed that linkage. So, you have this + the rest of the, a similar unit will be there on this side. So, this intermediate would then react with water to give you your final hydrolyzed products.

Now, what is the proof that you have this intermediate forming? This sort of a cyclic intermediate? Now in order to prove that, a clever experiment that was done was where a model system was used to understand nucleic acid hydrolysis. Now, in the RNA you have this OH group at the 2 position, which helps in formation of this cyclic intermediate. So to mimic that the model system that was chosen had an OH group right next to the phosphoester here.

So, you have this OH group right next to the ester linkage. So, if you have this OH group, one can imagine a similar mechanism, where you can visualize, you can visualise this lone pair coming in to give you the intermediate shown here. Now, what a scene is if you just use the model system, you are not able to isolate this intermediate. So, what was done was in order to isolate this intermediate the reaction was done in the presence of acetyl chloride.

So, in the presence of acetyl chloride, what was found was that both of these intermediates interacted with the acetyl chloride. So, the product that was formed would be the corresponding O-acylated derivatives. Now, once this acylated derivative is formed, it is not very easy for this to go back to your starting compound. So, what was seen was in both these cases, the corresponding acylated products were isolated.

So, the fact that this product could be isolated, I will call this as $P_{1,}$ indicated formation of the intermediate I. So, this is a very simple method by which one can indirectly show formation of the intermediate I by trapping it as the acetyl adduct. So, once you form the acetyl adduct you know that you have formed this particular cyclic phosphorane intermediate in this mechanism and indirectly this was used to ascertain that during nucleic acid hydrolysis such an intermediate is actually formed.

So, these were examples of how you could use trapping agents to get some insight into the nature of the intermediate. Now, there is another slight variant to this. One can think of varying the reactant a little. So that you can actually trap the intermediate in some form or the other. So, here you are not adding a trapping agent, but you are by clever design modifying the reactant so, that indirectly you can say oh this intermediate was formed in the reaction.

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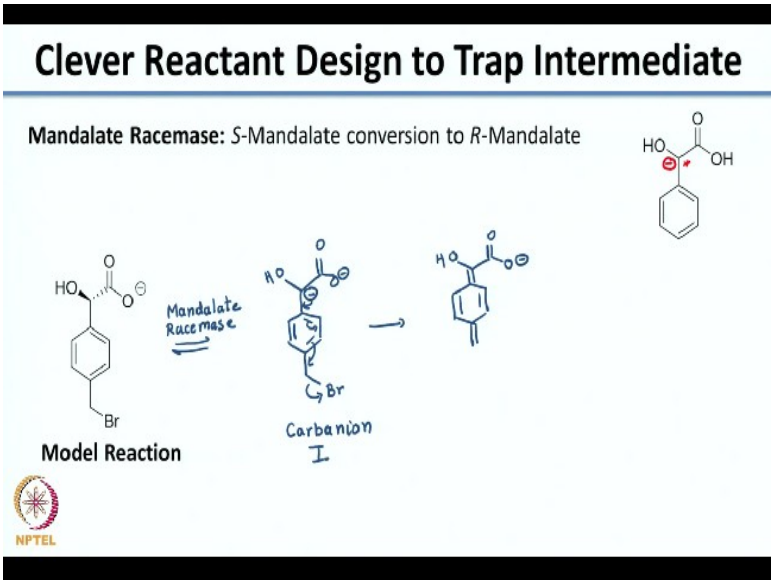

So, one example is understanding the mechanism of mandalate racemase. So what mandelate racemase does is, it converts S- mandelate to R mandelate. So, this is the structure of mandelic acid and the chiral center is here. So, what the enzyme does is, it converts one enantiomer to the other enantiomer and what is proposed is that it goes via a carbanion intermediate. Now, as we have seen this is not very stable for you to isolate.

So, how do you actually know that the enzyme goes via a carbanion intermediate? So, one clever design was using a slightly modified reactant. So, here the reactant used instead of mandelic acid was a derivative where at the para position, you have this CH_2Br group. So now I want you to think if you have the CH_2Br group and say you generate the intermediate carbanion here, what would happen? So I repeat the question.

So, now you have chosen a clever model substrate, now in the model substrate you have the CH_2Br group. So, what I want you to think of is once you generate the anion intermediate, what

will happen to the reactant? You can press the pause button and try to work out the answer by writing the mechanism. So, let us see if you have this answer correct. So, here let us assume that in the presence of the enzyme.

So, this reaction is carried out in the presence of the enzyme mandelate racemase. So, your substrate reacts with the enzyme and what you get is this intermediate carbanion. Now, once you form this anion, this is in conjugation with the aromatic ring. So, this is a hint I am giving you. If you did not get the answer earlier, now, think of drawing the resonance structures possible for this and trying to push the arrows starting from the carbanion into the aromatic ring.

So, what will you get? So since you have a very nice living group here, what will happen is you will get the elimination product. So, once you form this elimination product, indirectly you know that you have generated the carbanion intermediate. So, this is a very nice method where one can use a model reactant to trap a particular intermediate. So, this shows you a very nice example of how the reactant was modified to give you insight into how an enzyme works in biology.

Now, there are other experiments that one can do to gain insight into the nature of the intermediate and one such experiment is the competition experiment.

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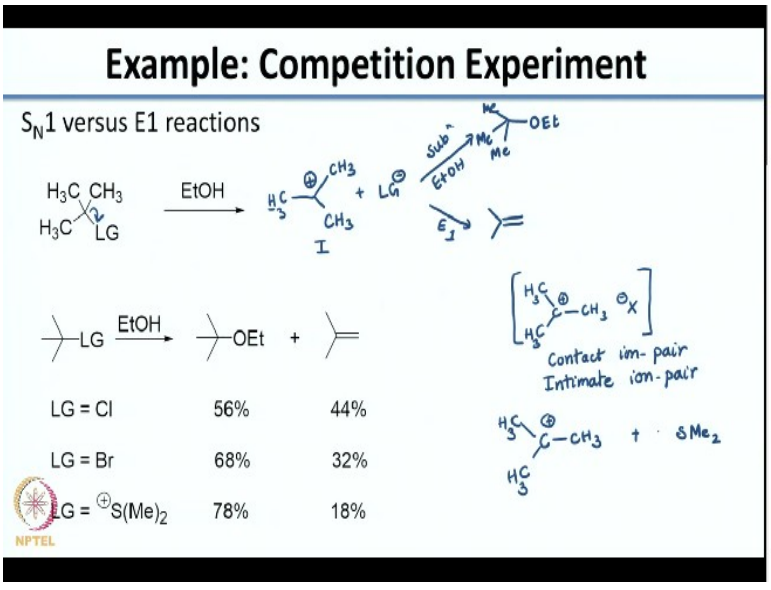

So, competition experiment is a slight extension of what we have studied so far with trapping reagents. So what happens just as the name suggests, competition means you have something competing with the other. So, in this case, you have a reactant, which forms the intermediate . You add 2 traps. So, now, you have a competition between trap 1 and trap 2 to form 2 products. Now, depending on the ratio of product 1 and product 2 you can gain insights into the nature of I.

So, the tapping experiment that we had seen earlier, the same concept is actually used here, except you are putting 2 traps. So that you can compete. So, these 2 traps can compete with each other. So, just to give you an example, now, you have studied the mechanism of S_N1 and E1. So, shown here is a substrate. I want you to write the products that you get, if you do the S_N1 reaction on the substrate or if you do the E1 reaction. So, quickly press the pause button on your screen and go ahead and write these 2 mechanisms.

So, let us see if you are able to write the mechanism. So, in the S_N1 or the E 1 the first step is you have the leaving group go. So, what you generate is the carbocation plus the leaving group. Now, after this it can undergo substitution or elimination. So, if it undergoes substitution, the product that you get would be, in this case your nucleophile is ethanol. So, the product you get would be OEt. Again, I am not showing the proton transfer step. If it undergoes elimination,

so, the E1 mechanism, what you would end up getting this in this case, you would have this product being formed because now what will happen is you will have a proton being abstracted from any one of these hydrogens to form the corresponding double bond. So, these are the 2 products that are possible. Now, if you look at it based on the standard textbook mechanism that you have studied so far, the rate determining step is formation of the carbocation.

So then what you would see is you should be generating the same intermediate irrespective of which leaving group you use because we have studied that this first step is the rate determining step. So irrespective of whichever leaving group, you would end up generating the same carbocation. So once you generate the same carbocation, if your nucleophile is the same, which is ethanol, in this case, one would assume that you would have the same extent of substitution or elimination, irrespective of whichever leaving group you choose.

So just to repeat, you are generating a carbocation irrespective of whichever leaving group you choose. Now once you generate the carbocation, it can undergo either substitution or elimination. So what I am saying is if you have the same nucleophile, the extent of substitution and elimination should be technically the same. So here is what was observed. So here, the leaving group was varied and what you see is the ratio of the products actually changes.

So in the case of Cl and Br, what you see is that you have quite a bit competition between the substitution as well as the elimination, whereas when you have a charged leaving group, what you see is that you have a greater extent of substitution. Now this would be confusing right because I just told you that once you generate the same carbocations, so in all these cases you generate the same carbocations, you have the same nucleophile, then why do you see this difference?

So what this gives you a hint is that the leaving group seems to be important in this particular reaction. So in this case, what is seen is, the leaving group plays an important role. This is not true for any S_N1 or S_N2 reaction, it depends on the nucleophile you are using, the solvent you are using and the leaving group. In this case, you see similar behavior between Cl and Br, but with the charged leaving group you see a different behavior.

So now how do you explain this mechanism? So how you can explain this is. Shown here, I have shown you the carbocation intermediate and the counter ion for that separately. Now, you can imagine a scenario where once you have the carbocation formed, you can have the X^-actually in close proximity to this carbocation. So it is not fully solvated as I have shown in the scenario above where it appears that both these species are independently in the reaction mixture and fully solvated.

Here, what I am saying is they are still in very good contact with each other. So, these are called as contact ion pair, intimate ion pair. Just as the name suggests, it indicates that they are still very much close to each other. So, if they are very much close to each other, now, when your

nucleophile comes, it will not be able to immediately access your electrophilic center. So, what you see is in the case of Cl and Br you see a competition between elimination and substitution.

That is because it still exists as this ion pair. Now, as you can see, Cl would probably form a better ion pair as compared to Br because it is more electronegative. So, what you can see is the competition is more in the case of Cl. In Br you have a larger extent of substitution as compared to elimination. Now, what happens in the third case? So when you are leaving group is charged, so, what you have is you generate a neutral species once you form the carbocation.

So, once you form the carbocation you generate a neutral species unlike the other cases where you were generating a charged species. So, once you generate this neutral species, it does not have as much as an affinity for the carbocation as compared to the earlier cases. So, you do not form an intimate ion pair and you see a greater extent of substitution. So, very simple competition experiment here was able to tell you what is the nature of the intermediate.

So, in the first 2 cases the intermediate is a contact ion pair or an intimate ion pair whereas in the third case, it has more of a carbocation nature. So, this shows you how you can use a competition experiment to figure out the nature of the intermediate. Now, there is the reverse of this. So, imagine that you take 2 reactants, which can form the same intermediate. So, initially, you are taking the same intermediate and trapping it to give 2 products.

Here you are starting with 2 reactants which will form the same intermediate. Now, this can be used to figure out the nature of the intermediate because if you design the reactant such that they will give whatever is the same proposed intermediate, you know that you will get the same product irrespective of the reactant because the intermediate is common. So, this method is called checking for a common intermediate.

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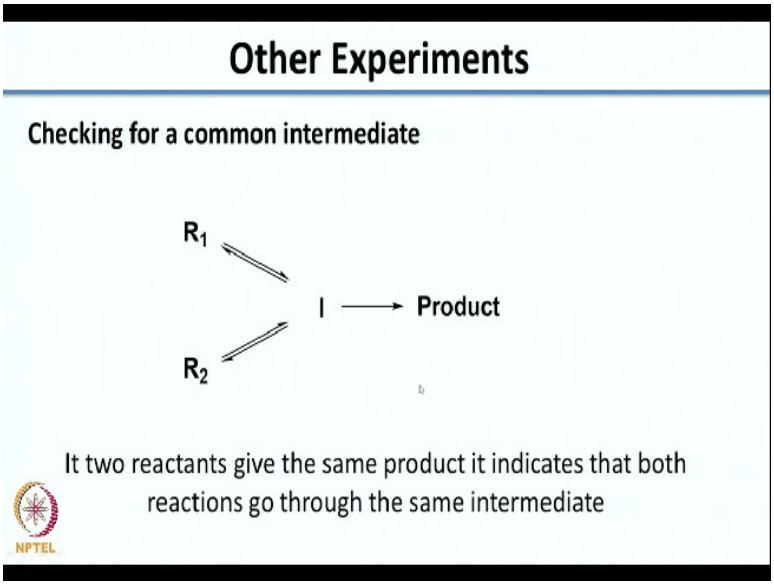

So, as you can see, you have two reactants forming a common intermediate, hence you get a common product. Now, let us see 2 examples as to how this can be used to figure out the mechanism.

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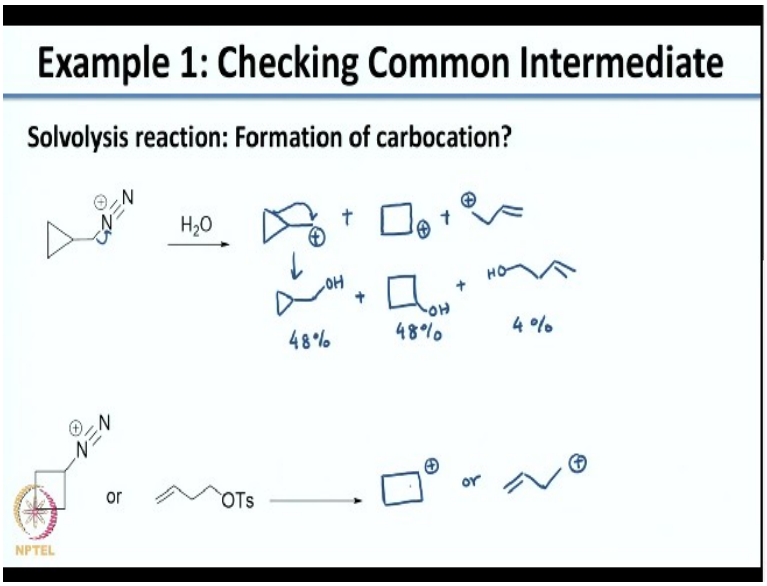

The first example is a solvolysis reaction. So as we have studied solvolysis earlier, it is a reaction where your solvent is also involved. Your solvent is acting as a nucleophile in this case. So, now, what was probed is, in the substrate shown above, are you actually forming a carbocation or do you have direct displacement of the solvent which is water? So, can you write both mechanisms, one where you form the carbocation and the other where you have a direct displacement?

And the second question is, when you form the carbocation, can it rearrange to give you other carbocation. So, again, I repeat once you form the carbocation, can it rearrange to give other species. So press the pause button and write out the mechanism. So, let us see if you are able to write the mechanism. So, if this generates a carbocation, so you have loss of nitrogen. So, this would be the carbocation that would be generated.

So, can you get other carbocation by rearrangement of this carbocation? Let us see if that is possible. So one ways if I push an arrow going to this carbon here. So, what I generate would be a 4 membered ring and the new carbocation here. Another thing you can think of is you can think of pushing the arrow such that instead of pushing it at the carbon, you form a new bond here. So this cyclopropane ring opens up to give you a new bond here.

And the product that you would get would be or rather the new intermediate to get would be so, this would open up and you will get possibly all of these leading to product. So you can probably form this product, this product and this product. So if it goes via the carbocation one would see all of these products. Now does this actually take place? So what is seen is that you observe all these products.

Now we were talking about checking a common intermediate. So now suppose I use these 2 reactants. So these 2 reactants now I am starting with taking cyclobutane with a diazonium salt attached or we are taking the open tosylate. Now both of these would generate the corresponding carbocation or, now these carbocations are similar to what we had seen in the first example and they can again rearrange.

So you can draw all of these resonance structures starting from any one of these. Correct? So I can still draw from the cyclobutane. I can get the cyclopropyl with the exocyclic carbocation. I can also generate the open carbocation starting from cyclobutane. So, I can generate all of these carbocation, even if I start with the other 2 reactants. So now, how to actually understand whether this is taking place?

So, if I do the reaction in the presence of water, what is seen is that I get an identical distribution of products. So, I get 48% of both of these cyclic products and the acyclic product in 4% irrespective of which reactant I use. I can use the cyclopropane, cyclobutane or the open compound acyclic compound. In all cases, I get the same product distribution. So, what this tells you is that, indeed the carbocation is formed which can rearrange to give you 3 different carbocations which lead to 3 different products.

So this is a very nice example of how you can use 3 different reactants to check for common intermediates. So before I go, in the next class, what we would be doing is we will be looking at another example for checking the common intermediate. So I will just leave you with the reaction that we would be looking at.

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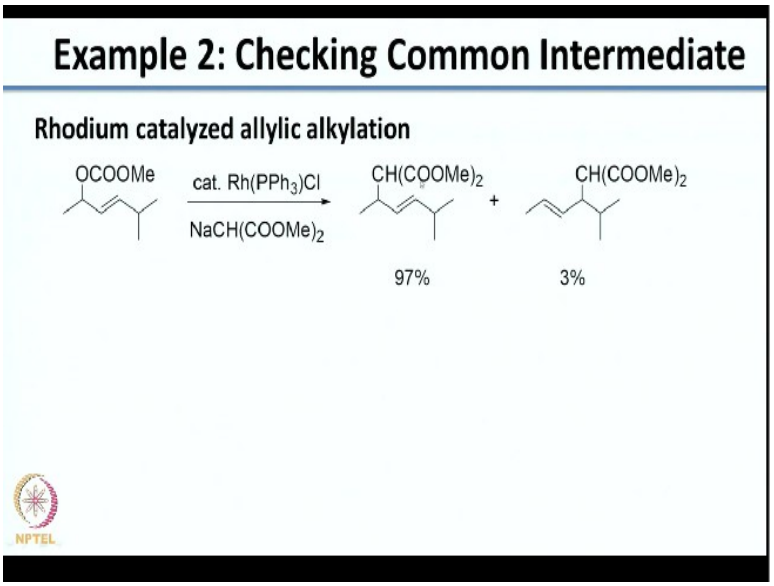

The reaction we would be looking at is a rhodium catalyzed allylic alkylation. So this is your allylic group and you are alkylating at this position. So the product distribution you get this 97:3. So what we are going to see here is what is the nature of this intermediate and how you can use this method of checking for a common intermediate to figure out the nature of the intermediate. In the meanwhile, you can try to work out how this reaction works. Thank you and see you in the next class.