**Molecular Rearrangements and Reactive Intermediates in Organic Synthesis**

**Prof. Santanu Panda**

**Department of Chemistry**

**Indian Institute of Technology, Kharagpur**

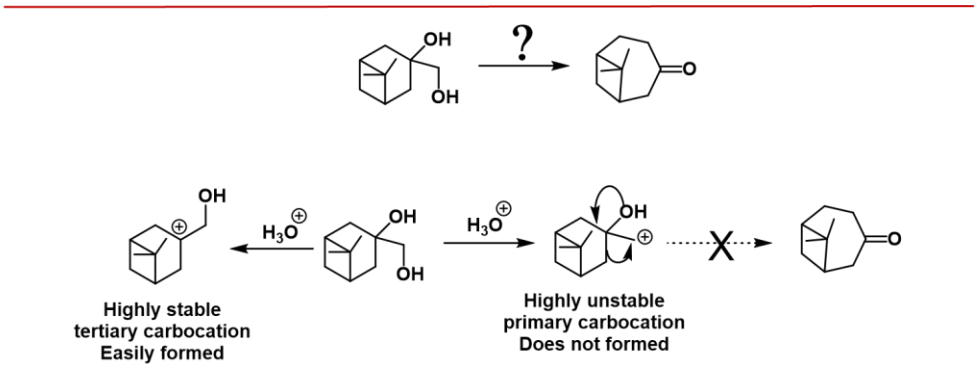
**Lecture 04: Carbocation**

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. So, in the last couple of classes, I was talking about the carbocation rearrangement. I taught about Wagner-Marwin shift in the last class, I taught about the pinacol–pinacolone rearrangement. In the today's class my plan to teach about several other carbocation rearrangement. So, let us start today's class with the contents I am going to cover for today. So, I am going to start with the Semipinacol rearrangement and I am going to show you what is the important of Semipinacol rearrangement.

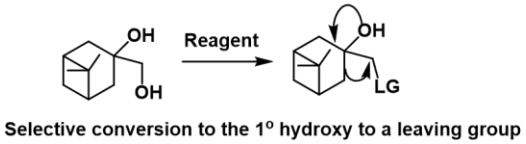
And then I am going to talk about the you know Tiffeneau-Demjanov rearrangement, I am going to talk about the Meyer–Schuster rearrangement, then the Baeyer-Villiger rearrangement. So, in the last class if you remember I was talking about the pinacol–pinacolone and always I try to tell you that the carbocation going to form there which will be more stable. That means if you have a two different place you have alcohols then the water elimination is happening where your more stable carbocation is generated. But now suppose from this particular compound if I want to get to this particular compounds.

So, if you try to look into this problem, first thing is, okay, you have a vicinal diol, you might think, oh, sir, what about putting, you know, acid? As soon as you put acid, you will generate a more stable carbocation here. From there what is going to happen there might be a 1,2 so there is two hydrogen here, so there will be only possibility of hydride shift, it can generate little bit of aldehyde. And then the other way that there is you can generate you this particular carbocation which will be highly unstable, so it will drive the reaction towards the more stable carbocation. So, now you cannot able to form this particular compound through this method. So, now the idea is that how to selectively from a primary carbocation means how to selectively get rid of this OH to make a carbocation on this particular carbon. If you can able to make the carbocation very easily then there will be a 1,2 to shift which I have mentioned here which can give it to your target product. So, that is going to bring you to the Semipinacol rearrangement where the idea is you try to convert this OH to a leaving group. selectively you have to convert this

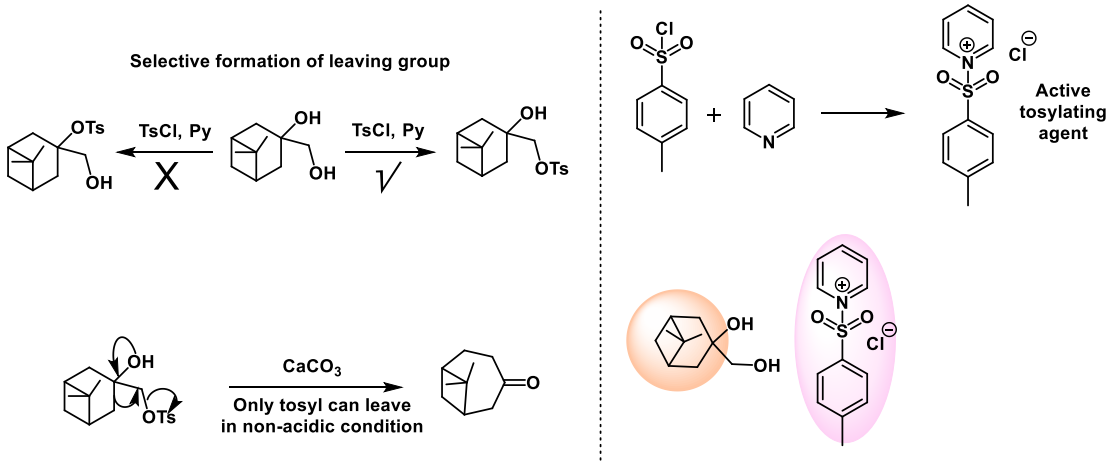
primary alcohol to the leaving group that will allow this1,2-shift happening to the corresponding you desired product you want.




**Solution?**

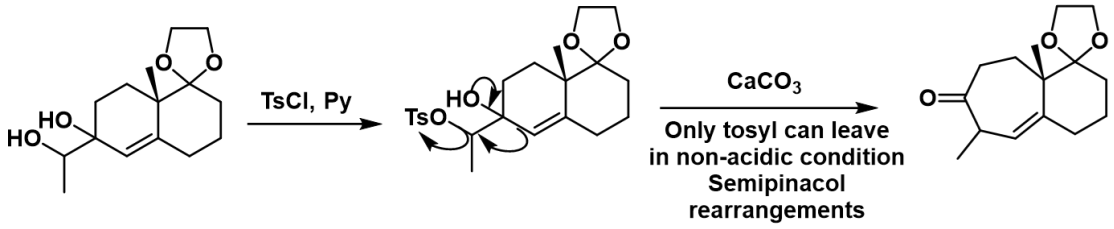


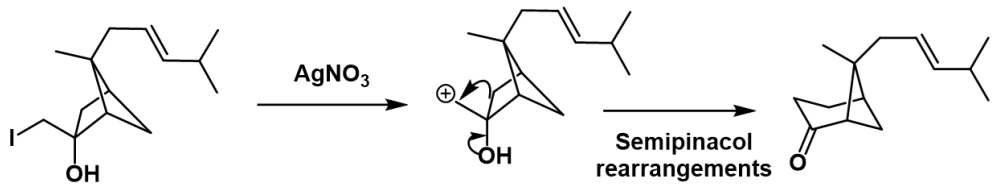

So, this can be done using this pyridine and tosylchloride. Now, if you use tosylchloride and pyridine I think you guys already know about this form these acylating agents pyridine react with this tosylchloride.



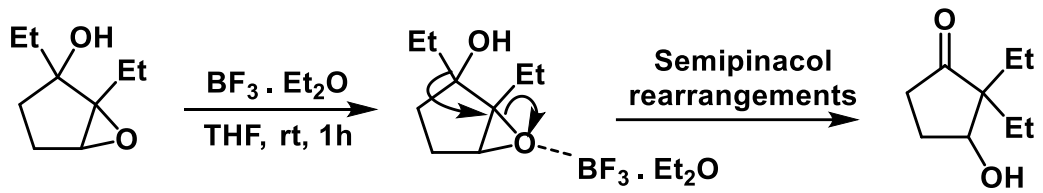

So, now what is happening if you use this tosylchloride with this vicinal diol this is a tertiary this is a primary. So, primary will form very fast this product will be obtained. So, now, once you have this particular compound once you treat with this calcium carbonate. So, in absence of any acid this will go for this 1,2-shift, it will give this particular compound.

So, this is the beginning of the semipinacol rearrangement and there are lot more example I am going to bring some of them here. Again, there is a scenario where you have a tertiary alcohol versus a secondary. So, in previous slide we have a tertiary versus primary here tertiary versus secondary. Again, if you use this tosylchloride pyridine it will form selectively in the secondary. Again the major is the steric effect due to steric it will go to the primary or secondary not the other hydroxy group. Now once we treat with the calcium carbonate is go for this ring expansion. Now, there is a important thing here. In this particular stage, there is two different place can be get expanded. It can expanded through this side where you have this alkyl chain or it can goes through this side where you have this vinyl group. Now, again I told you this expansion of this 1,2-shift. Wherever groups is going for 1,2-shift, we will have some sort of a delta positive and this vinyl group able to stabilize the delta positive more compared to this alkyl.



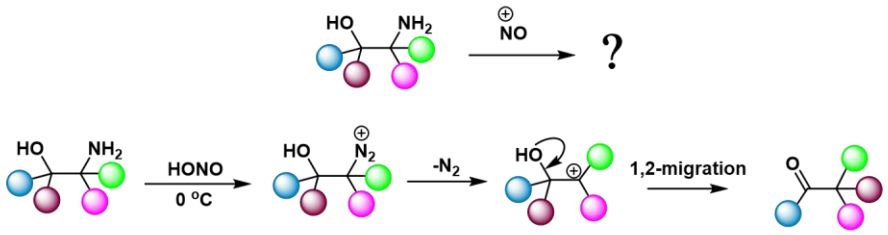

that allow you to get the vinyl group. So, this part of this ring will participate 1,2-shift that will allow formation of this product. Again, there is another example here if you have this primary iodo-compounds in place of silver nitrate it can form this corresponding positive charge that will allow this want to shift. here to form this particular compound through semi pinacol reagent. You might find in the exam or in the practice question that in the same compounds if you use a pinacol reagent you will get one product, if semi pinacol reagent you will end up getting other product.




There is another example here. So, this is a epoxide. I told you before that if you treat epoxide with a Lewis acid $BF_3$, what is happening here? There is formation of a delta

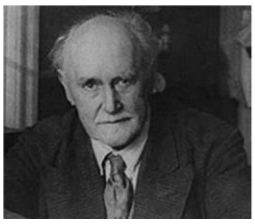
positive charge in this carbon or there is a carbocation formation happening in this carbon. So, that will allowing this ethyl shift here. So, this is coming here ethyl group is migrating here forming this compound. You might be asking this question sir why this is ethyl shift is happening why not this alkyl shift? Now the question is once you go for alkyl shift what is happening? As soon as you go for alkyl shift here instead of going for then you will have a ethyl and a OH which will be ketone. But the major problem what you going to encounter here you are making a 4 member ring from a 5 member ring. So that is not going to be a favor you are making more strain ring that is why this is not going to happen the reaction will goes through this pathway. So, this is about the semi pinacol, again there are more example for you to practice.

So, then we are going to introduce this Tiffeneau-Demjanov rearrangement. Again, the idea is same very similar to the semi pinacol, but the idea is you are using a different approach to generate this carbocation. So, this you know reaction was discovered by this Russian chemist the Nikolai Demyanov, he discovered this reaction in 1901. So what is happening that now instead of this 1,2-vicinal diol you have this amino alcohol. Once amino alcohol treats with the $HNO_2$ it forms the corresponding diazo compounds here and now there is a $N_2$ getting released to form this corresponding carbocation. And, now if there is a carbocation and now it is very similar to the pinacol pinacolone and you guys have already learned about that in the previous lecture.




The Tiffeneau–Demjanov rearrangement (TDR) is the chemical reaction of a 1-aminomethyl-alkanol with nitrous acid to form an enlarged ketone.

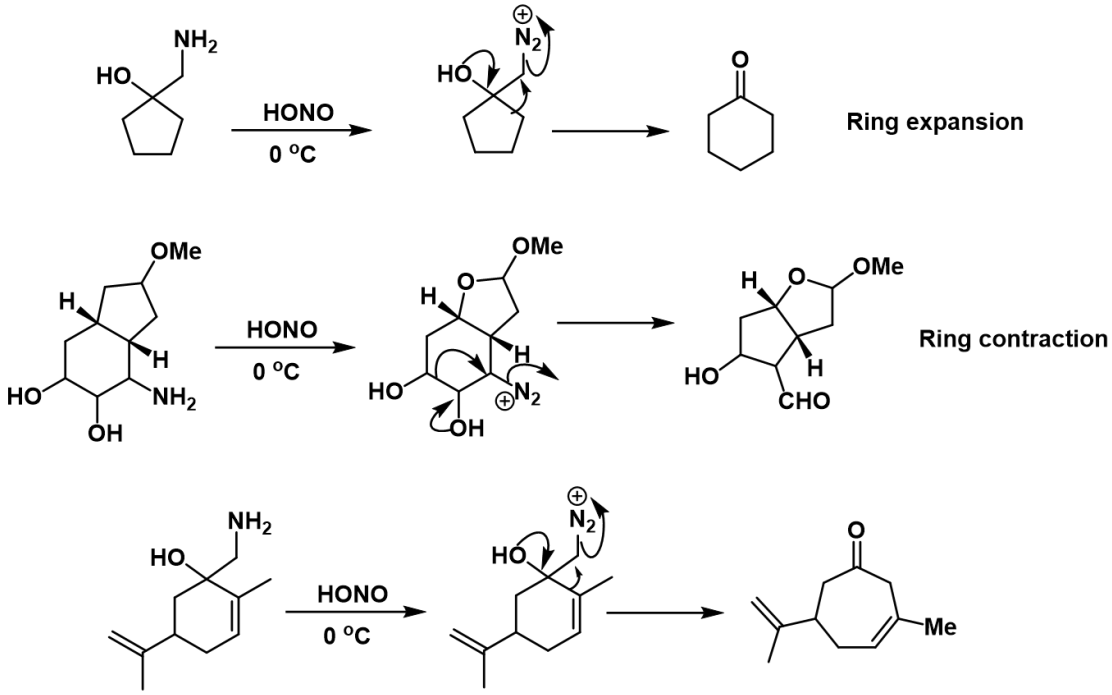
Russian chemist Nikolai Demyanov discovered this reaction in 1901



So, that will allow this 1,2-shift happening from here to here to get to this corresponding product. Again from amino alcohol you are ending up getting to the corresponding carbonyl compound. So, this is the end product.

So, now we are going to learn some of the examples. So, here I am going to show you some of these examples in terms of ring contraction or ring expansion. First thing is if you have this type of amino alcohol where this $NH_2$ group is attached with the $CH_2$ group

and that is not attached in the ring. In that case what we observe? We observe ring expansion. What is happening? First it forms the $N_2^+$ that will get rid of $N_2$, formation of carbocation and allow this ring expansion to happen to form this cyclohexanone. Now, if it is happening that both hydroxy and amine is actually the substitution in the ring, then what is going to happen in that case you will form the $N_2$. So, that will eliminate, so, there will be minus $N_2$ to generate a carbocation that will allow a ring contraction to form this particular product. So, that means, if you want to go for ring expansion versus ring contraction you can use this technique as well.

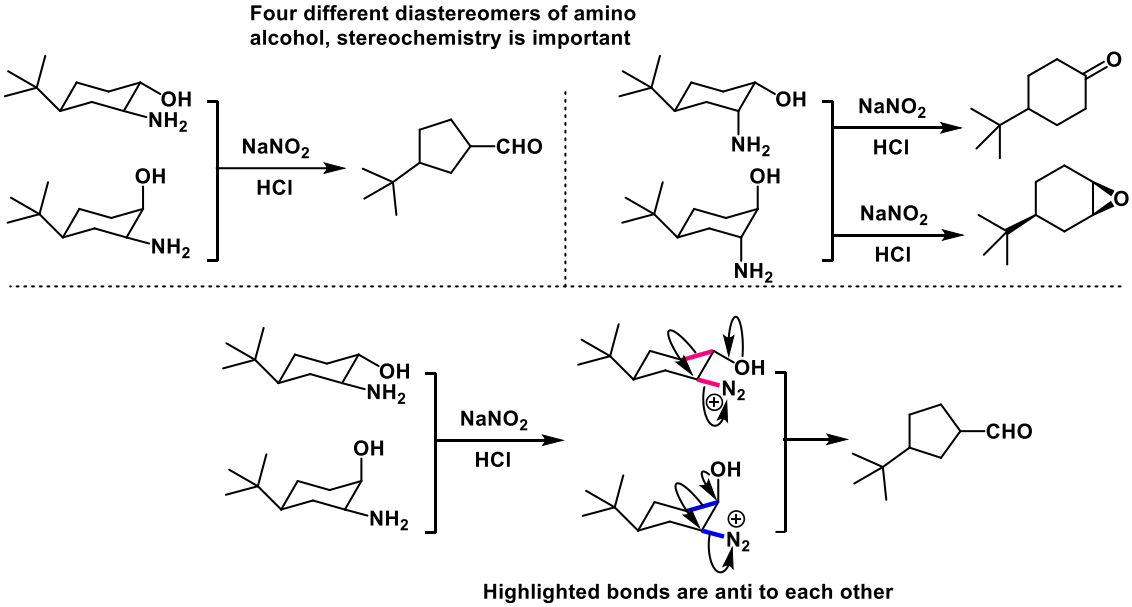



There is another example of ring expansion where you can see this is not in the ring substituted. So, this is $CH_2$, $NH_2$ which can form this $N_2^+$. Now, it will allow this want to shift here to form this expansion product. And again, here there is a two possibility here you can expand the ring can be expanded through this. or through this. Now, which side it will go? It is going through this side because the cases you have this side you have a this vinylic group. So, that is going to stabilize the carbocation and that has a migrating aptitude will be higher. So, that is why you end up forming in this particular product.

So, now I am going to talk about this particular rearrangement if you Demjanov rearrangement with an example of a cyclohexane where you have a tert-butyl group here in this position and then you have amino alcohol. So, this can end up forming. So, if you put this tert-butyl group in the equatorial position you lock the particular conformation. Now, you have four different diastereomer here there is two here and two here. So, now,

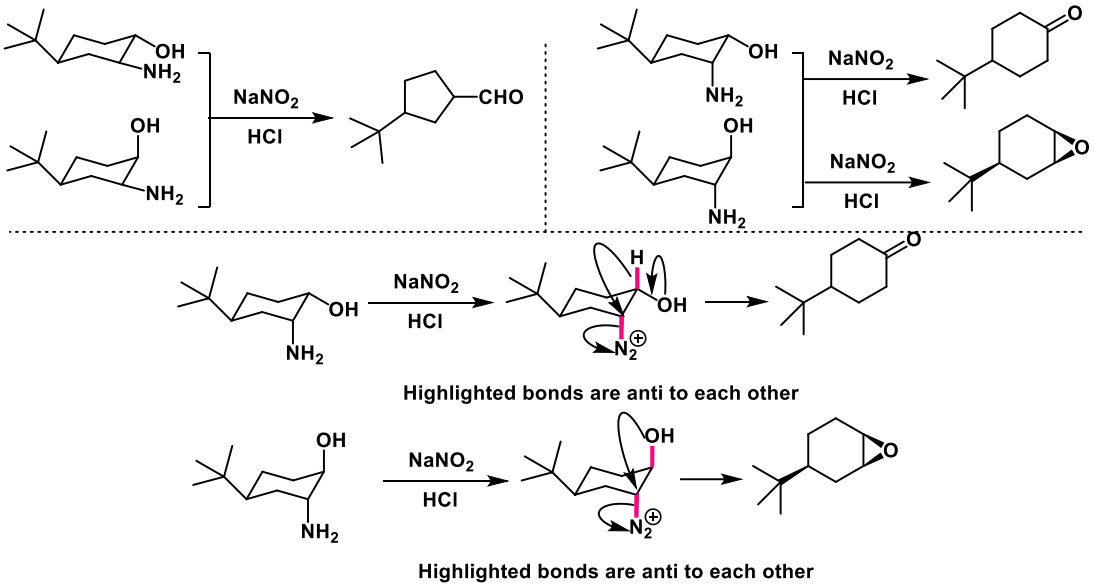
these four different diastereomeric amino alcohol once treated with $NaNo_2$ and HCl it will end up forming different products.

So, now, we trying to understand what is happening why they are formed different products here. First thing we know that once we use this $HNO_2$ it will form this $N_2^+$. So, the most important thing is once you form $N_2^+$, which groups is going to get migrate. As I said this migration going to happen only if you put σ*. So, there is a σ*-orbital and there is a σ-bond which is going to migrate. So, this σ and σ* has to be antiperiplanar. So, this antiperiplanar arrangement is very important because only then it is possible that the σ-bond can give electron to the σ*-orbital. And then what is going to



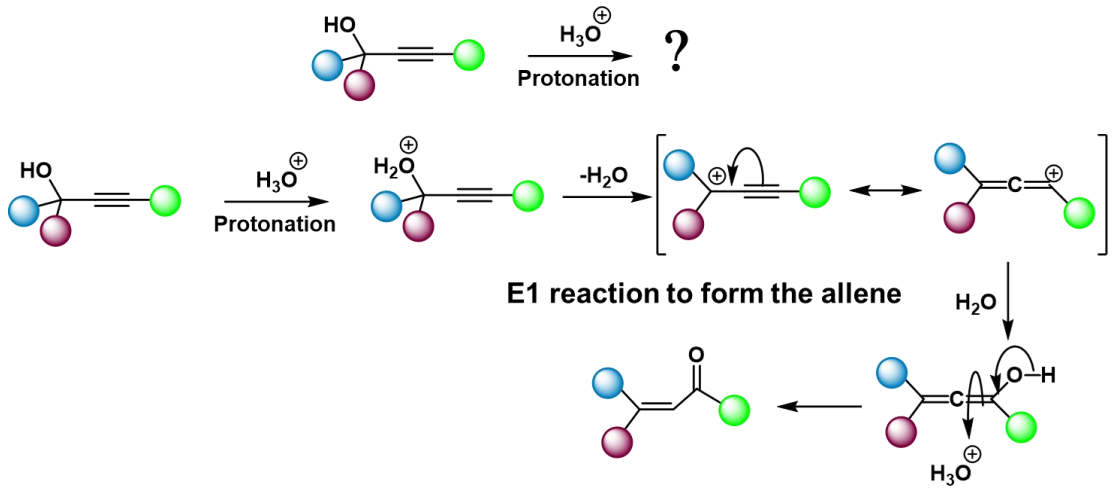

happen once this migration is happening now you can this -OH can give lone pair to form this corresponding aldehyde. So, both of this compound that can end up making to the same product because in both the cases there is a possibility of this σ to σ* donation and so this σ going to shift here to form this product.

Once we start with the other set of compounds the other set of diastereomer what is going to happen here.? Again, first thing is this amine going to form the $N_2$. Now, once it is form $N_2$, now you can see you have this σ* here. And if you think about anything antiperiplanar to that, then only this hydrogen is ready here, this C-H bond. So, now what is going to happen? Instead of this σ-bond donation, this C-H bond going to give electron density here, which end up forming this corresponding carbon compounds.



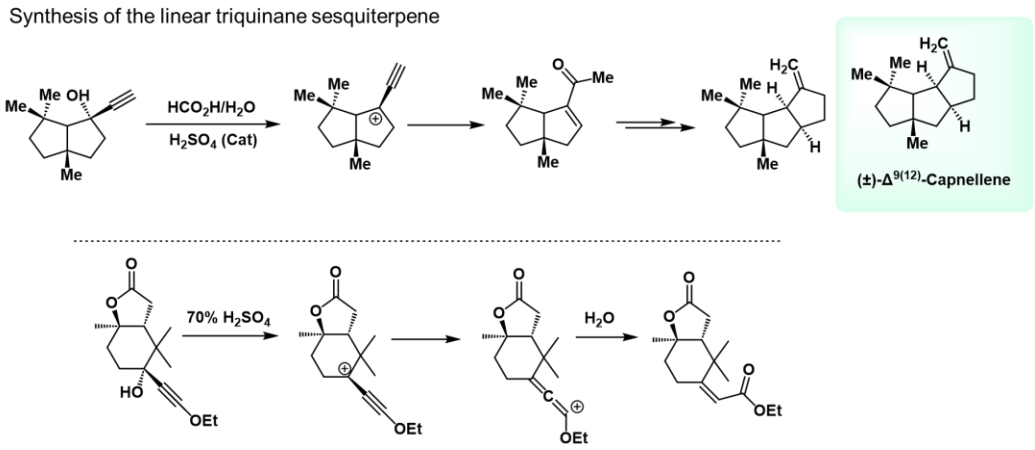

But in other cases, if you have both are diaxial, if both are diaxial then what is going to happen? It is going to form this $N_2$ that means, now in this σ*-orbital this oxygen lone pair can give electron density here that can form this corresponding epoxide. So that means you can see that the logic remains same that you have to find out which group are oriented in the antiperiplanar fashion. That group or that σ-bond can only participate or there is a hydrogen it can participate there to give the σ* -bond of this C-H σ*-bond electron cloud or if there is an oxygen which can give this lone pair to form this corresponding epoxide.

So, now I am going to move it to another important reaction called Meyer-Schuster rearrangement. So, this is another reaction where this carbocation is forming in the propargylic alcohol.

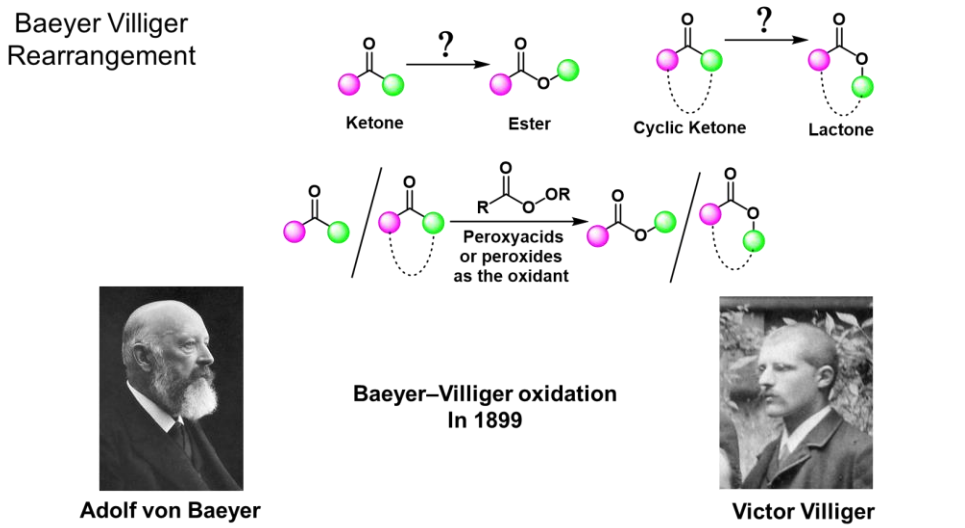


So, if you start with a propargylic alcohol which is secondary or tertiary. So, this alcohol can be a secondary or tertiary. Once you treat this with acid, what is going to happen? It can form the α,β-unsaturated carbonyl compound. So, this α,β-unsaturated carbonyl compound will form. So, how it is happening? It first forming this particular carbocation after elimination of water. Now, it will go for a resonance to form this allyl carbocation which will attack by water. Now it will be going to form this corresponding α,β-unsaturated carbonyl ketones.

So, let's go through some of the examples here. So this is one example here where this is a particular case. We can see this is a propargylic alcohol which will form, which will get protonated. Then it will be going to form this allene and once you form allene it will be going to get attacked with this water which will form this particular compounds. Once it will form that they are it can be no further transformations to get to the corresponding natural products. There is another example here we have another propargyl alcohol here you can see. Now here also you can see you can form this corresponding carbocation. Now you can see there is this type of allene carbocation will form, but here we have a -OEt group. So, the water is going to attack here and which going to end up forming an ester that means,

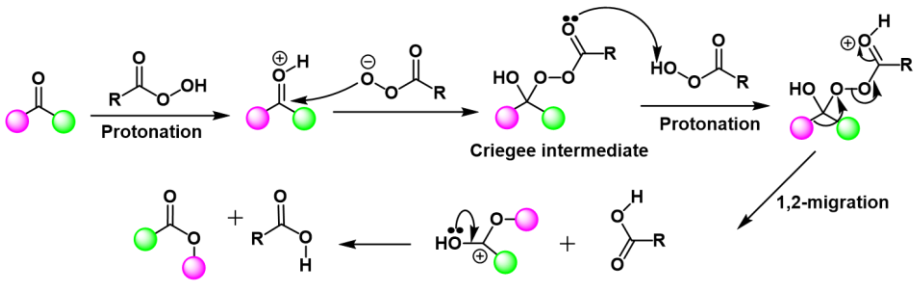



depending on the substitution here you can end up making corresponding ketone or corresponding ester.




So now I am going to move it to another very important reaction called Baeyer-Villiger oxidation or Baeyer-Villiger rearrangement. This reaction was discovered by Adolf von Baeyer and Victor Villiger. They discovered this reaction that if you take a carbonyl compound treat with peroxyacid or peroxide as a oxidant, it will allow to formation of the corresponding esters. So, let us try to understand this reaction that what is the mechanism of this reaction.

First thing is the protonation, after the protonation this compound getting attack here to formation of this intermediate which is called the Criegee intermediate. After that what is happening? After that there is a protonation happening in this position here, then there is a most importantly this 1,2-shift. So, this group is which attached with this carbon getting migrated from this particular carbon to corresponding where it is happening it




**Factors Controlling 1,2-migration**

- Primary stereoelectronic effect
- Secondary stereoelectronic effect
- Migrating ability of the groups
- Steric effect of the groups

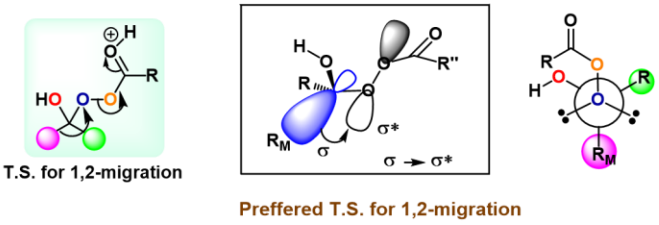
migrates in to the corresponding oxygen. So, there is a carbon to oxygen migration happening 1,2-migration is happening which finally, end up you giving to the corresponding ester. So, first we are going to learn couple of thing about this reaction, first we are going to learn the primary stereoelectric effect, we are going to learn the secondary stereoelectric effect, we are going to learn about what will be the migrating ability of the groups and then the steric effect of the groups as well.

So, let us start with the primary stereoelectric effect. So, let us try to understand this reaction into the little bit with the orbital picture. So, what is happening here? So, one important thing this reaction is that when this reaction is happening this oxygen-oxygen bond and in the peroxide and the group going to get migrate has to be anti-periplanar. So, this is this anti-periplanar thing is very important. What is mean by that it is saying that this particular thing here this oxygen-oxygen and this particular migrating group you can see they are literally are actually antiperiplanar orientation.

**Primary stereoelectronic effect**

Refers to the necessity of the oxygen-oxygen bond in the peroxide group to be antiperiplanar to the group that migrates

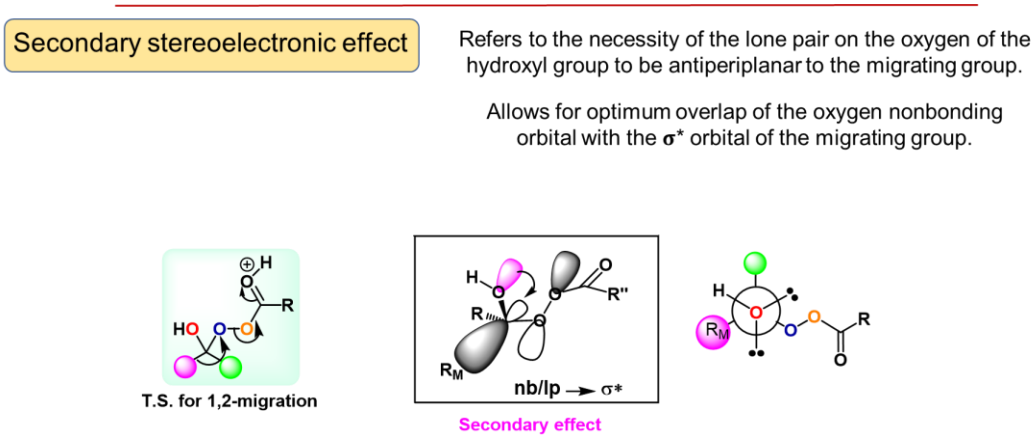
Facilitates optimum overlap of the **σ** orbital of the migrating group to the **σ*** orbital of the peroxide group



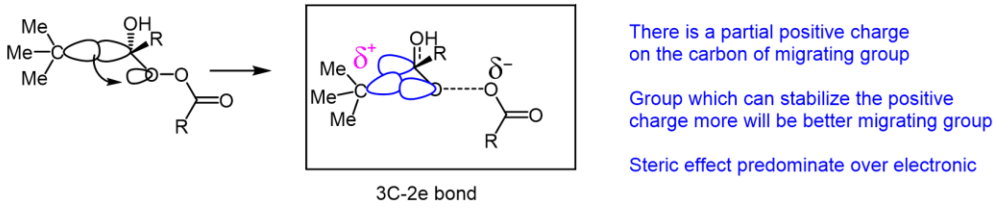

So, if it is antiperiplanar then what is going to happen? Then this σ-bond electron density of this migrating group which is attached with this carbon going to get transferred the σ-electron to this σ*-orbital of this oxygen. So, that will allow these 1,2 migrations to take place. We can see from this also that they have to orient such a way that this σ*-orbital can be accessed from this σ-orbital which is here. So, this is called an antiperiplanar orientation. So, this is about the primary stimulating effect, what about the secondary?

So, there is another important thing that after formation of this alcohol. So, this alcohol also do some important role here. So, alcohol has a lone pair. So, now alcohol lone pair can give electron density to this σ*-orbital. So, there is a σ*-orbital of this migrating group. So, this migrating group also have a σ*-orbital which is this. Now, receiving electron density from this lone pair or the nonbonding orbital from the oxygen. So, that electron donation can also going to help you this reaction. So, again we are said that they have to be orient such a way. So, that this is possible. So, that so, that the oxygen now

can able to oxygen lone pair can able to give to this σ*-orbital which is oriented here. That is the σ*-orbital of this bond and there is this lone pair which can able to donate.




This is called the secondary effect. And now we going to going to answer the another very important question that what will be the migrating aptitudes for different groups. So there is two important thing one is the stereoelectronic effect another is the Turing effect. So what is happening you are breaking this corresponding σ-bond here and which is going to give electron to this σ*. So, in the transient state what is happening this it is forming again this there are three orbital and two electron bond formation happening here. You can see this is 3 center 2 electron bonds here. So, there is a partial positive charge on the carbon which is getting migrating. I put here this, tertbutyl group here. If the tertbutyl group is migrating there is a, so there is a bond breaking happening when this group is getting migrated. So, this is going to carry a delta positive charge. That means, which group can stabilize the delta positive charge more that can have a more migrating capacity. more migrating aptitude. But there is also some steric effect that

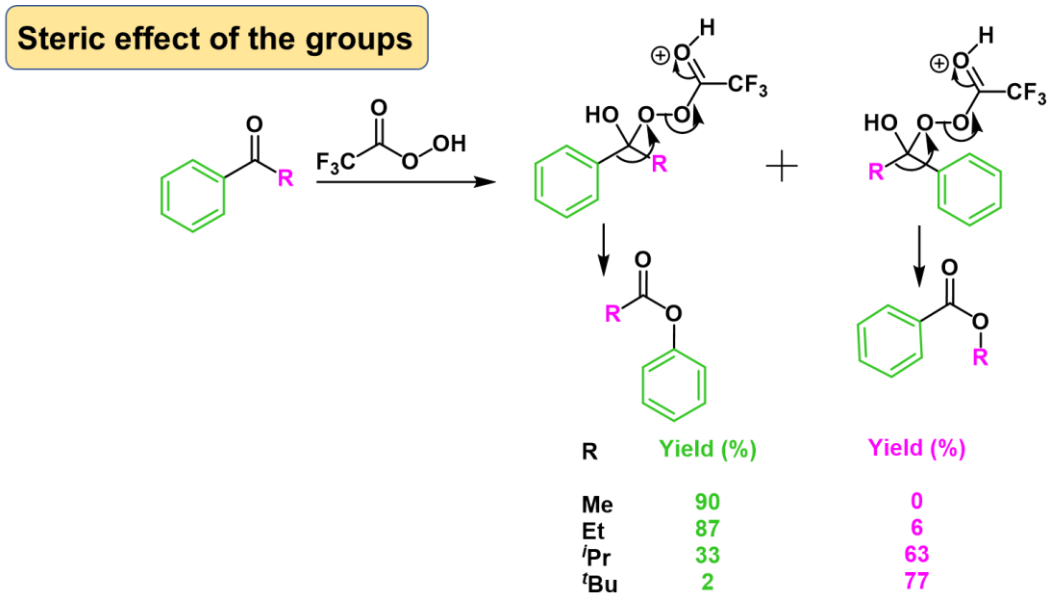



The relative migratory aptitudes are:

H > 3°-alkyl > cyclohexyl > 2°- alkyl > benzyl > aryl > 1°- alkyl > methyl

is also important sometimes the steric effect also predominate over the electronic effect. In general, so, there are it is very difficult to generalize, but in most of the cases these are the what are followed, but there are also some cases what are change based on the different other effect as well.

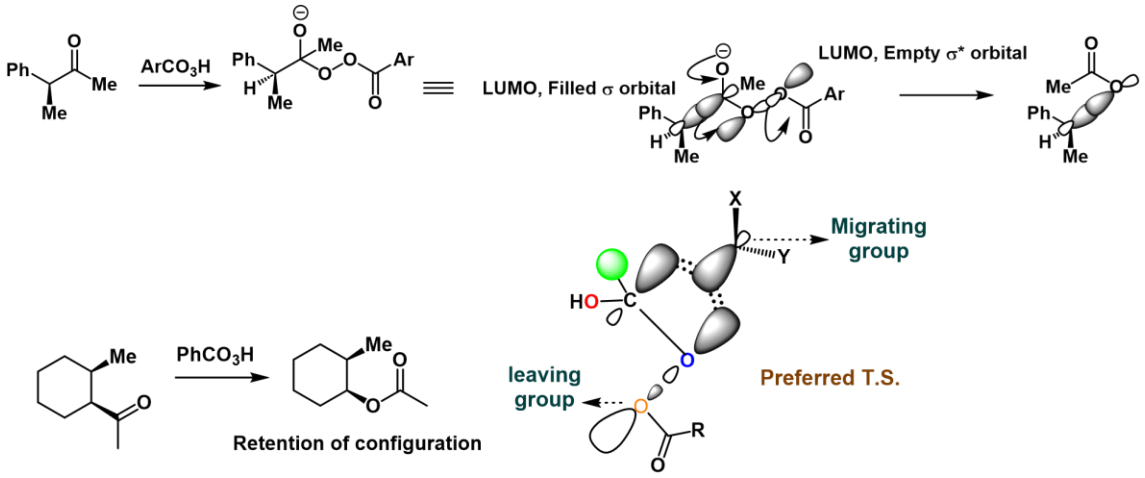
So, let us start with this simple example here, if you have, we have different type of acetophenone derivatives, here we are changing different group in this acetophenone from we are going from methyl to ethyl to isopropyl to tertbutyl.




| R | Yield (%) | Yield (%) |
|---|---|---|
| Me | 90 | 0 |
| Et | 87 | 6 |
| $^{i}$Pr | 33 | 63 |
| $^{t}$Bu | 2 | 77 |

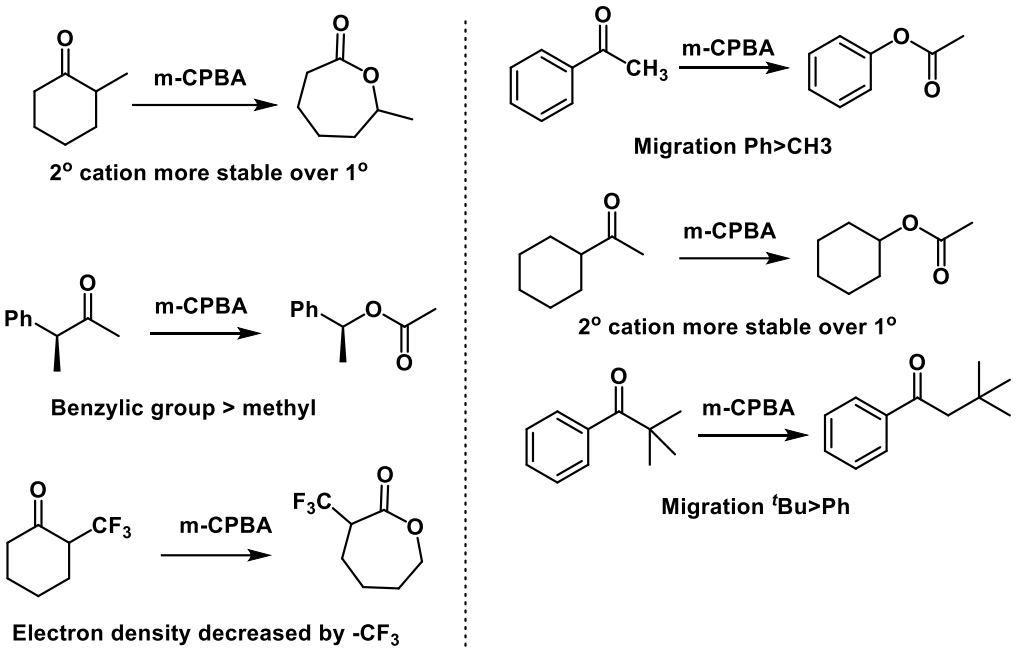
So, what we are increasing in the in one side we are increasing the steric effect, we are increasing their size, other side we have a phenyl. So, once it is forming this corresponding Criegee intermediate, now there is two possibilities, either the phenyl can migrate here or the R group can migrate here. which is here. So, that can form this particular product if phenyl migrate it will form this product. So, what you observe that once R equal to methyl we are seeing 90 percent yield of phenyl migration. So, I think there is 0 either there will be 10 or this number will be 100. and then there is a 87 is to 6. So, what is happening that if you have ethyl, if you have a propyl butyl slowly what is happening this value is getting decreased and slowly we are seeing this value is getting increased. So, once you come to a tertbutyl group now a better migrating aptitude compared to a phenyl. So, we know that phenyl can the benzylic things can stabilize the phenyl can stabilize the corresponding charge, but again the tertbutyl is getting migrated ok instead of phenyl here. So, here so that means, the steric is also playing important role

here.



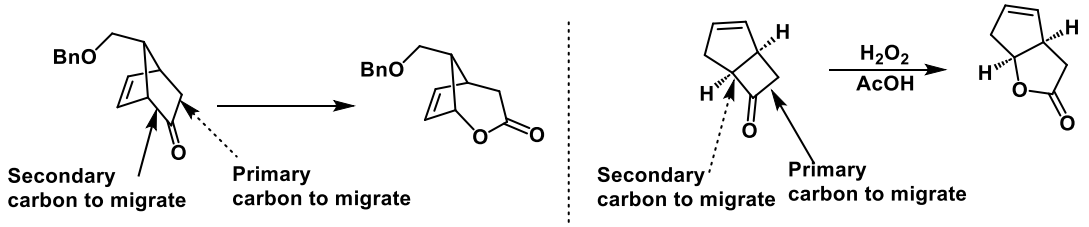

Now, if you have a chiral center here does the chiral center remain same there is a retention happen or inversion happen. What is actually happening there is a chiral center remain retention there is no change happen on this chiral center. Because if you see here in this intermediate there is nothing happening in the chiral center only thing this bond is getting broken and it is migrating here which you can see from this particular tangent state. So that means in the final product also you see this the configuration remain same what you started with. So, you can see some example here that the configuration remain same as you started with.

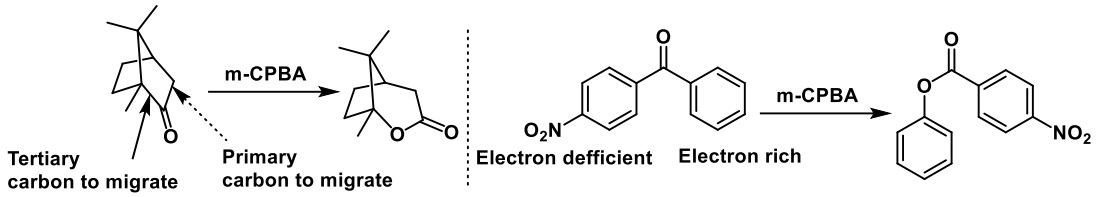
So, here some of the examples here that if you treat with m-CPBA this compound what is happening there is two different possibilities. You know once you make this Criegee intermediate here now you have to think about what are the two different site which site can again stabilize the carbocation more. You can clearly see this will be the winner having a secondary versus a primary. So, it will form this product. Again I talk about this product here you have a methyl one side you have a benzylic another side. So, if you have a benzylic then the benzylic will have a better migrating aptitude because the benzylic carbocation will be get more stabilized. Again, if you have a $CF_3$ one side and this you do not have a electron withdrawing group on the other side. Then the side which you do not have electron withdrawing group will be they will be the winner forming this particular product. We have learned about this that if you have a methyl versus phenyl then you can end up here once you put a NaOH this can goes to corresponding phenol. So, this is a very important things that how do you convert acetophenone to phenol in in one shot ok. Again the phenyl is a better than $CH_3$. Again we have example here methyl versus cyclohexyl again the cyclohexyl




is the winner. And we have shown you that if you have a phenyl versus terbutyl then the terbutyl migrate first then compared to the phenyl. So, there will be oxygen here. And then there are some other example here you can see there is a two possibility on this particular carbon because now once you attack with the parasite now this side can be migrated or this side can be migrated now this is a secondary so there is a so there is a major possibility of this side getting migrated to forming this product so once you are trying to solve this thing problem in the exam you should look into this Again there is a very similar scenario here there is a secondary versus a primary scenario. The secondary is getting winner to form this particular compound here ok. So, that means, what is happening that we have to when you are when you are trying to understand this type of reactions try to think about that in the Criegee intermediate which particular site has a more possibility to migrate that will have that will migrate first.

As I said you that that reaction not only done with you know m-CPBA, I told you at the beginning you can use $H_2O_2$ and acidic acid you know that also do the job well ok. Now, we come back to show this is a very important example here. So, after this is getting attacked and this is forming this corresponding Criegee intermediate with m-CPBA, what is happening now you can think about there are two different side here ok.

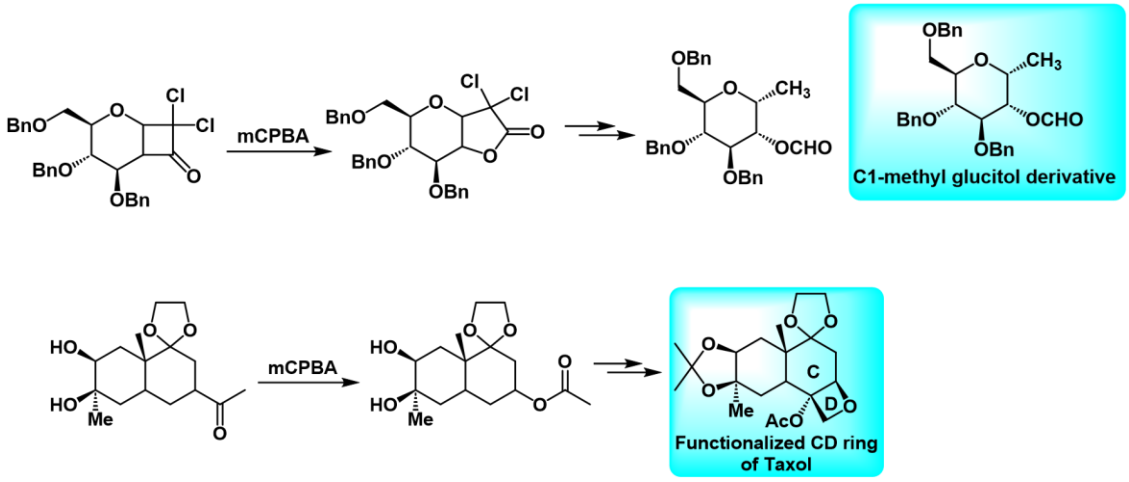




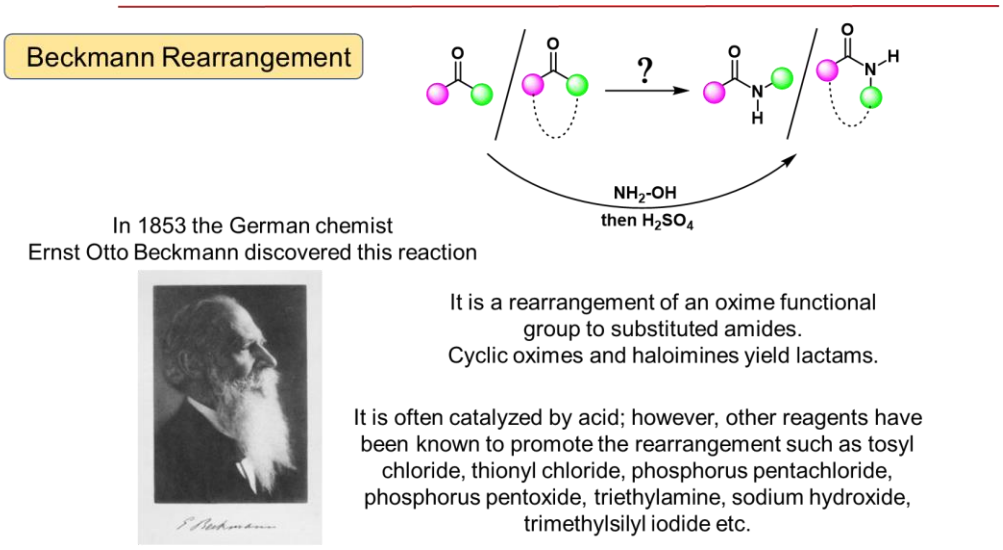

So, you can migrate from this side or you can migrate from this side. ok. So, what we are observing here that the migration happening from this side only. So, this is because you can see this is a tertiary carbon to migrate versus this will be a primary carbon to migrate that is why what is happening that is ending up to this particular product ok. And now we have a scenario where you have a electron deficient phenyl and there is no and that is only phenyl. So, if you have a only phenyl versus electron deficient one what is going to happen there is one which is electronically deficient cannot migrate because I told you that there will be a delta positive charge. So, that delta positive charge cannot get stabilized with that. So, that is why you will observe that the phenyl group is going to get migrate here to form this compound.

And then there will be another very important example here. So, these are the example which is applied for synthesis of very important molecule. So, I try to bring this example here because you might find similar questions in your exams or in your practice you know question as well. So, once you try to see there is m-CPBA is given into the problem, now you try to look for that, what you have learned from m-CPBA, that if you have a double bond in the compound, it will form epoxide, that is, that we know.

Suppose you do not have a double bond here in this molecule, correct, we cannot see a double bond here. So, that means, what is the possibility here? If you do not have a double bond, then you look for a carbonyl group there. If you have a carbonyl group, then we know that m-CPBA is going to get protonate, then going to get attacked. But now, once it is getting attacked, it has a possibility that which side is going to get migrated, you know, this side or this side. Because we know that if it is going to migrate from this side, it will

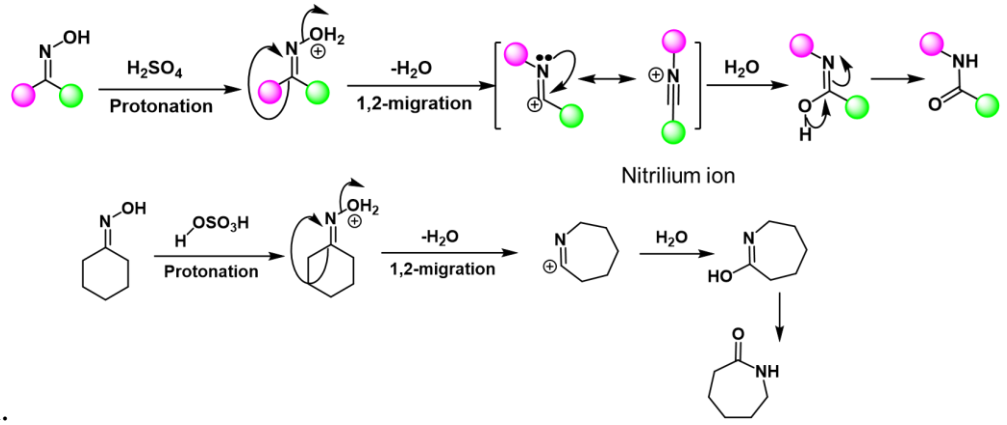



going to form a completely different product versus if it migrates from the other side. okay because that that connection will be completely different so you can see there, what is happening we end up seeing the migration happening from this side not from this side because you have two chlorine which are electron withdrawing that is why it is going to form these particular compounds and after several steps it can form these particular compounds There is other example here you have this example here you have one carbonyl group here one m-CPBA will be attacked. This is comparatively easy here because you have a methyl versus a cyclohexyl and we all know that the cyclohexyls will have a better migrating group compared to a methyl group. And then after that it can form this Cp ring of the taxols.



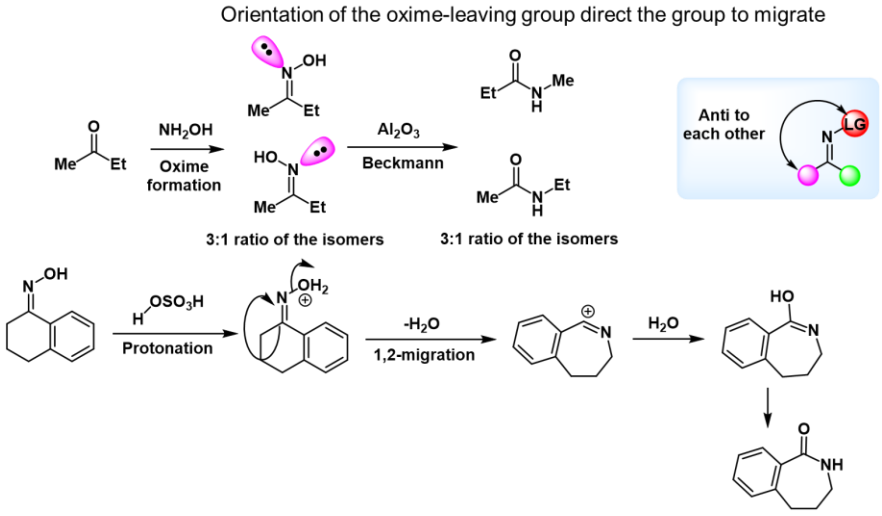

So, now I am going to talk about another important rearrangement reaction called Beckmann rearrangement. So, what is happening in the Beckman rearrangement in the before that I am going to talk about this was discovered by Ernest Otto Beckman discover these reactions. So, what is happening here once you treat with this carbonyl compound

with hydroxylamine then the oxime functional group to substituted amide. So, from oxime is forming oxime which is going to convert to corresponding substituted amides. So, this is a very important reaction that the reaction has in a lot of importance because not only it goes to amide if you have a cyclic oxime it forms corresponding lactams ok. And it often catalyst by acid you can see it often we use acid, but there are also example where we used some sometimes in tosyl chloride, thionyl chloride and other things as

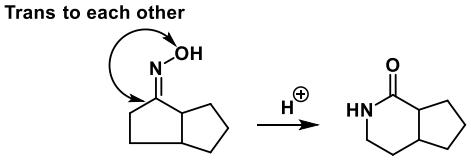


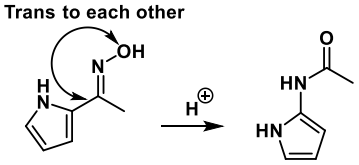

well.

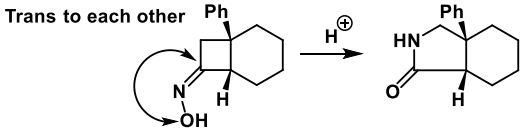
So what is happening? First step is the protonation of this. once the first thing your formation of this corresponding compound for us once you form this now what is going to happen the acid going to get in protonate in a release of water allow this one to shift so now the important thing is this 1,2-shift happen only they are in the transposition they only participate in this 1,2-shift to form this corresponding nitrilium ion once you form this nitrilium ion the water attacks here which finally goes to the corresponding amide And if you have a cyclic one then you end up you know making to this very important compound here ok, which can apply to the to the polymer industry. So, now, in case of intramolecular also is forming this after forming this it can protonate after the protonation what is going to happen is going to go to the corresponding nitrile and then water attacks to the corresponding product



Here are some example what I am going to show here that after the oxime formation here that is very important that if you are forming oxime and these two groups are not very different in the size if they are different in the size there is a possibility formation of particular oxime but if it is not very much comparable then they makes a three to one ratio but once you treat for the Beckmann rearrangement it end up the corresponding amide in the same ratio as well what i am trying to mean that it does not matter what a oxime you form once you form this oxime it will going to get this methyl going to migrate because the one which is trans to that alcohol is only going to get migrate So, that means here the corresponding the ethyl going to get migrate in this case and here you have a corresponding you know methyl going to get migrate. We have a example here we are showing here intermolecular example where it can goes for this formation of this corresponding compounds which can attack with the water. So, corresponding nitrile which get attack with water to corresponding amide here.




There is some other example I am going to show you. So, you should look for here. In the previous case, you look for primary versus secondary versus tertiary. Here, you look for, you know, which one is trans to it. Here, this particular skeleton is trans to it. That is why, this side is getting expanded, okay, to forming this corresponding product. Again, you can see here, this group is trans to it, not this one. So, if this is the trans to it, this is going to get migrated to forming this product. here you have a scenario here that you form this corresponding oxime now you have a two different scenario you have it can migrate from this side or it can migrate from this side. So, what you observe that it is getting getting migrated from this side which is trans to it. So, you have to understand that trans side only getting migrated not the secondary versus primary you cannot compare that ok.

So, that is all about the Beckmann rearrangement. So, I think we have learnt very important thing we have learnt the Semi-Pinacol rearrangement here, we have learnt about the Tiffeneau–Demjanov rearrangement we have learnt about the Myers-Quester rearrangement. We have learned about the Bayer viliger and finally, the Beckman

rearrangement. So, these are very important topic there are these in reference book you can go through the Clayden and you know Carry Sandberg and other books. thank you for listening I am going to see you guys in the next class.