Reagents in Organic Synthesis
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Organic Peroxides

Key words: Bayer Villiger oxidation, Sharpless epoxidation, Application to natural product synthesis

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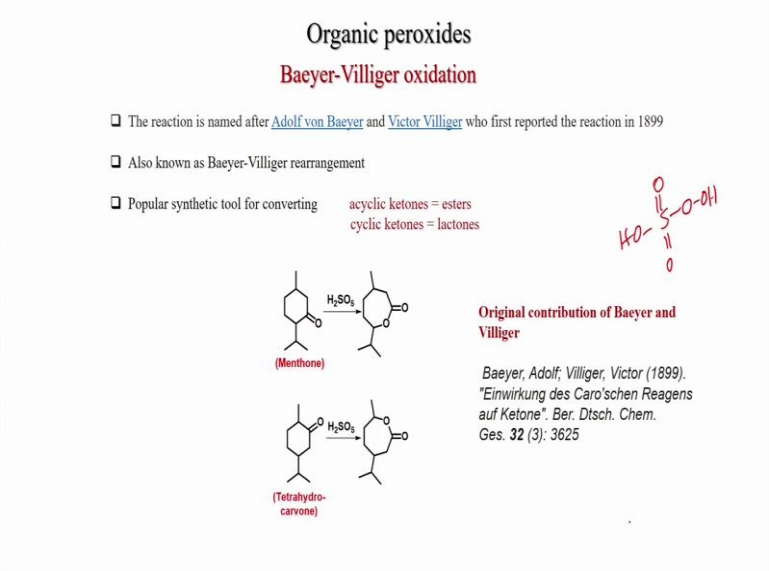

Welcome again. Today we will discuss organic peroxide mediated reactions. First we will discuss Baeyer-Villiger oxidation reaction and then we will discuss Sharpless epoxidation. So Baeyer-Villiger reaction, this reaction is named after Adolf von Baeyer and Victor Villiger who first reported the reaction in 1899. It is also known as Baeyer-Villiger rearrangement and popular synthetic tool for converting acyclic ketones to ester and cyclic ketones to lactones. This was the first report by Baeyer and Villiger.

This was menthone and when they treated with persulfuric acid whose structure is like this. So with persulfuric, mono persulfuric acid they converted menthone to this lactone. As you can see here the more substituted carbon atom migrated to get this lactone. And also they converted tetrahydrocarvone with treatment with same acid, they got this lactone. Here also, the more substituted carbon atom that contained a methyl group has migrated. So after this discovery many applications and options are studied.

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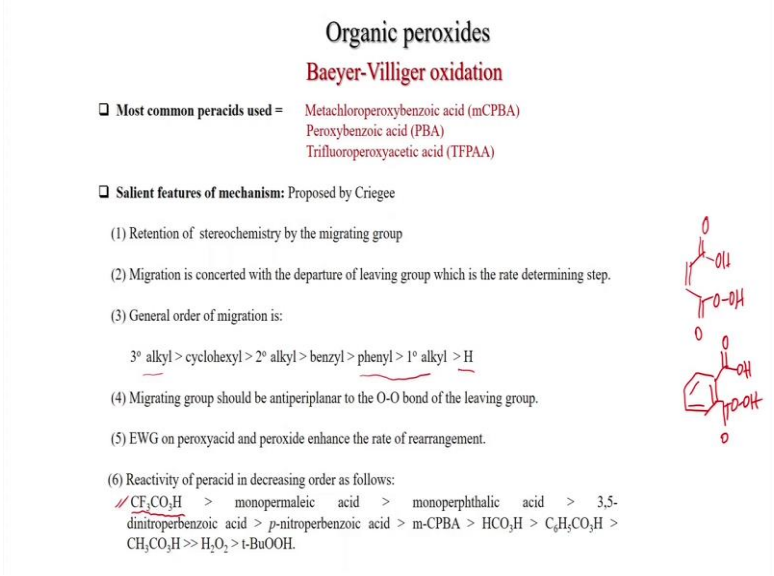

Most common peracids used were metachloroperoxybenzoic acid or metachloroperbenzoic acid mCPBA. Peroxybenzoic acid, also Trifluoroperoxyacetic acid is very commonly used. And salient features of the mechanism which was proposed by Criegee, here the retention of stereochemistry by the migrating group; that is very important. If there is a chiral center, that stereochemistry is retained during this reaction.

Migration is concerted with departure of leaving group which is rate determining step. So there is a leaving group which is ultimately becomes acid. So metachoroperoxybenzoic acid become metachlorobenzoic acid. That is the rate determining step. And general order of migration is 3 degree alkyl. So, more substituted alkyl migrated more than cyclohexyl, 2 degree alkyl, benzyl, phenyl and 1 degree alkyl. So this is important. Phenyl migrates more than 1 degree alkyl and lastly hydrogen is there. Migrating groups should be antiperiplanar to the O-O bond of the leaving group. This is also important. This we will discuss in detail later.

So here also the migrating group and the O-O bond of the leaving group that should be antiperiplanar. Electron withdrawing group on peroxyacid and peroxide enhance the rate of rearrangement. So if there is electron withdrawing group on the peroxyacid, then its reaction is much faster. So reactivity order of peracids, so trifluoroperacetic acid, this is trifluoroperacetic acid, this is the most strongest in this Baeyer-Villiger rearrangement. Then monopermaleic acid whose is structure is, this is monopermaleic acid, then monoperpthalic acid.

So this is monoperphtalic acid then 3,5 dintroperbenzoic acid, para nitroperbenzoic acid, metachloroperbenzoic acid, this is peroxyformic acid, then perbenzoic acid then peroxy acetic acid, hydrogen peroxide and tertiary butyl peroxide. So with trifluoroperoxyacetic acid this will be, rate will be much faster.

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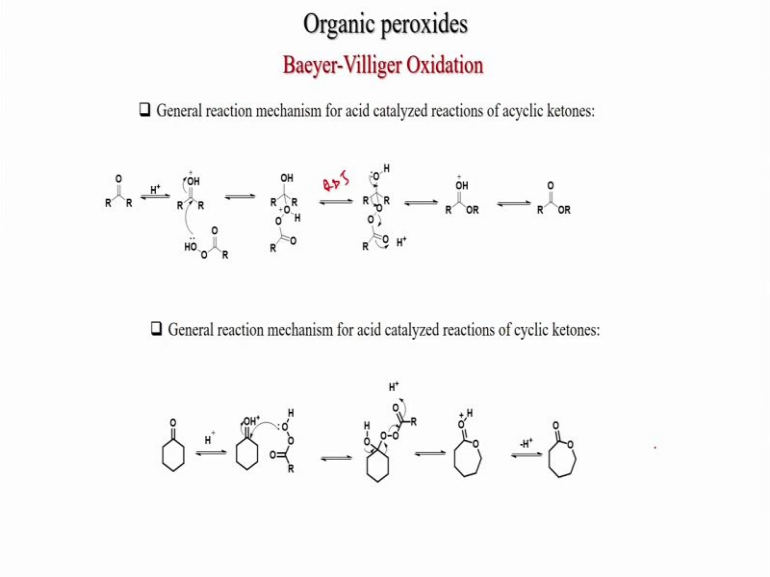

And we will discuss now the mechanism. So general reaction mechanism for acid catalyzed reaction for acyclic ketones, here the ketone is first protonated by the acid and then the addition take place to the carbonyl molecule, activated carbonyl molecule to get this hemiester. And this reaction which is the rate determining step, this is the rate determining step. Here what happens?

This migration happens and this O-H is becoming carbonyl and then one group is migrating. It is attacking to the oxygen and this is leaving group. So this is a conjugate base of the acid, or acid is the leaving group here. And then you get the protonated ester and after the protonation you get the ester. So a ketone is becoming ester in the Baeyer-Villiger reaction. This is very important because esters are very useful structures and for acid catalyzed reaction of cyclic ketones this is similar mechanism.

The cyclic ketone also gets protonated to get the oxonium ion and then the peracid reacts 1, 2 fashion to get this hemiacetal peroxy compound and then the rearrangement will take place. So this will go to carbonyl and then one group will attack to the oxygen and this will leave.

After that this lactone will form. For cyclic ketone you get the lactone, protonated lactone which after deprotonation gives the lactone, so this also very useful compounds.

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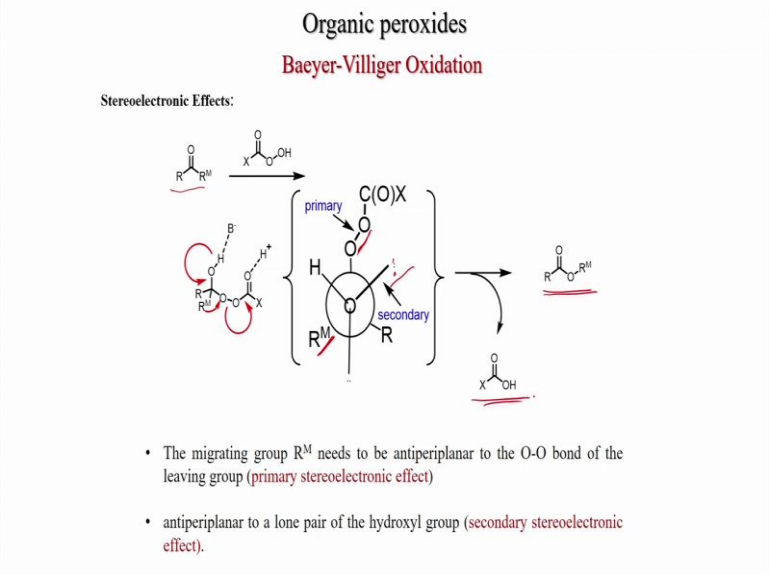

This is also; we just told, so the antiperiplanar orientation is very important. The migrating group and the O-O bond, it should be antiperiplanar to each other and this is the primary stereoelectronic effect. So here if you see that this is the ketone where, R^M is the migrating group and if you treat with this peroxyacid then you get this intermediate peroxy hemiacetal intermediate and here this rearrangement happens. So this becomes carbonyl and this attacks oxygen and this leaves.

Now if we draw like this, Newman projection and if you see on the oxygen and carbon bond, oxygen and down side is carbon bond is there, so oxygen has one hydrogen and two lone pair and R^M will be drawn like this, R^M, R and this, so this carbon has three substitutes, R, R^M and oxygen here. Because C-O we are looking at that bond. Now R^M, R and O-O they will orient like this way, that R^M and this, this and this is antiperiplanar to each other. Also there is a secondary stereoelectronic effect where the lone pair, one of the lone pair and R^M, so this lone pair and R^M, they are antiperiplanar to each other also.

So this is very important, the stereoelectronic effects determine the antiperiplanar orientation of Baeyer-Villiger oxidation and then you get the ester in this case and you get the carboxylic acid. So peracid becomes to carboxylic acid and ketone is becoming ester. So this is very

understanding that one oxygen is going to the carbonyl compound giving it here and one oxygen is liberated so that the peroxyacid is becoming to the carboxylic acid.

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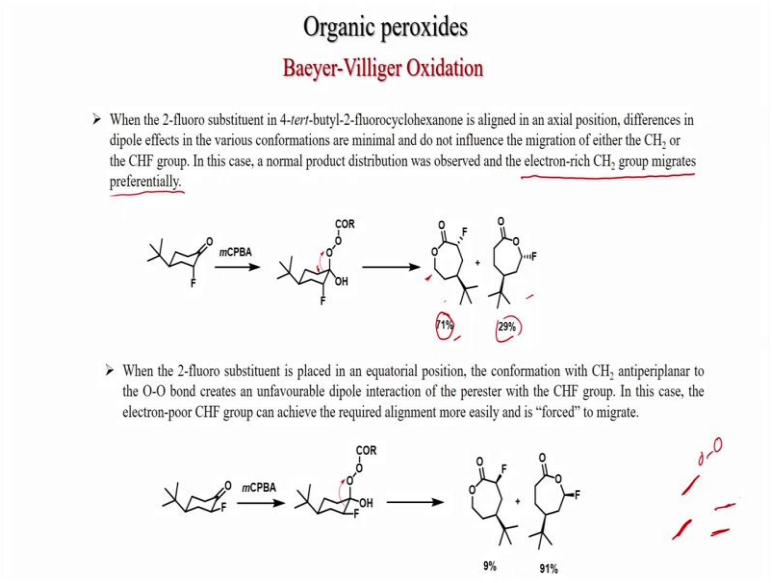

And this stereoelectronic effect can be understood by using this substrate, tertiary butyl cyclohexanone where there is a fluorine atom at the alpha-carbon of the ketone group. So when the fluoro group is in the axial orientation, difference in the dipole moments in various conformations are minimal. Because this fluorine, you can see this is quite far from the carbonyl group. So the stereoelectronic effect is quite low here. Difference in dipole moments in various conformation are minimal and do not influence the migration of either the CH_2 or the CHF group.

In this case the normal product distribution was observed and the electron-rich CH_2 group migrates preferentially. So here just the electron with the effect of C H F is working because there is no such stereoelectronic effect, the dipole effect is not dominating factor here. Here the electron withdrawing group is migrating less. So you get this migration more and that is why you get 71 percent this product, where this group you can see, this group, this carbon has attacked the oxygen and when this carbon attacked then you get this product. So this you get 29 percent.

Now if you, if you put now the fluoro group in the equatorial position what happens? Now the CF dipole is close to the carbonyl and anything you add, this dipole will affect. So the

dipole-dipole interaction will be important in this case. So the conformation with CH_2 antiperiplanar to the C-F unfavorable dipole interaction on the perester with the CHF group.

Because if you want to attack now, CF, this one is closer compared to the axial which was far so there will be some effect on this dipole. In this case the electron-poor C H group can achieve the required alignment more easily and it is forced to migrate. So this one is migrating more, this one because you can see, if this and antiperiplanar will be this one. However when this group migrates, then this and this, so in this case what happens, if this group migrates then what happens, this carbonyl group goes down because to get the antiperiplanar and then it will be more interaction with the C F bond will be there.

But when this migrates, then the O-O will be quite far from the C F bond. So here, this is very interesting, here you get this carbon atom attached to the fluorine, that migrates and you get this product more and this is less. So here when this group migrates then problem is there. Then this interaction of O-O bond because this comes closer to the C-F bond, that interaction is more.

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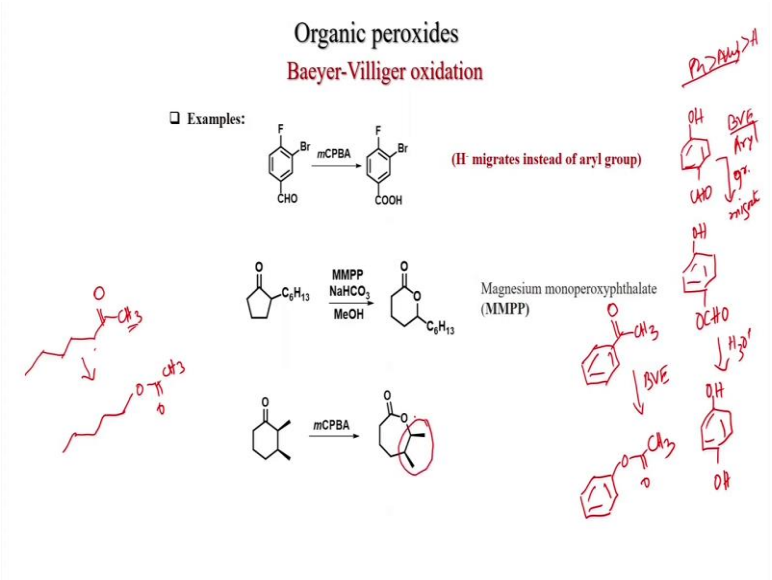

Here are some examples. So this is fluorobromo benzaldehyde, 4 bromo 3, 4 fluoro 3 bromo benzaldehyde. If you do mCPBA oxidation, that is the Baeyer-Villiger oxidation, so you get this acid. So H minus migrates instead of aryl group, this is important. Earlier we told that Ph migrates more than alkyl, more than hydrogen. But here hydrogen migrates because the aryl

group is electron withdrawing. There are two electron withdrawing substituents. So that is why it is not migrating, only H minus migrating here.

However when you treat this one, here what will happen? The aryl group will migrate. And you will get this compound and this after hydrolysis will give this compound. So here aryl group migrates. Here aryl group migrates compared to the aldehyde. Similarly if you do here this Baeyer-Villiger epoxidation, similarly if you use the acetophenone what will be the product here?

As I already told that phenyl migrates more than alkyl. So here phenyl group will migrate. Then you get this compound. So here, a cyclic ketone, cyclopentanone and with a 2-substituent cyclohexyl group is there. This Baeyer-Villiger condition was magnesium monoperoxypthalate and sodium bicarbonate methanol condition you get this product lactone where this more substituted carbon atom is migrating. So this is always, suppose this one, here what happens?

Here also, this is the more substituted, this is primary, this is secondary. So you get this component. And this is a chiral cyclohexanone, 2, 3 dimethyl cis- two dimethyl cyclohexanone, this under mCPBA condition it gives the lactone the more substituted carbon atom migrate, also these groups, chiral groups are undisturbed.

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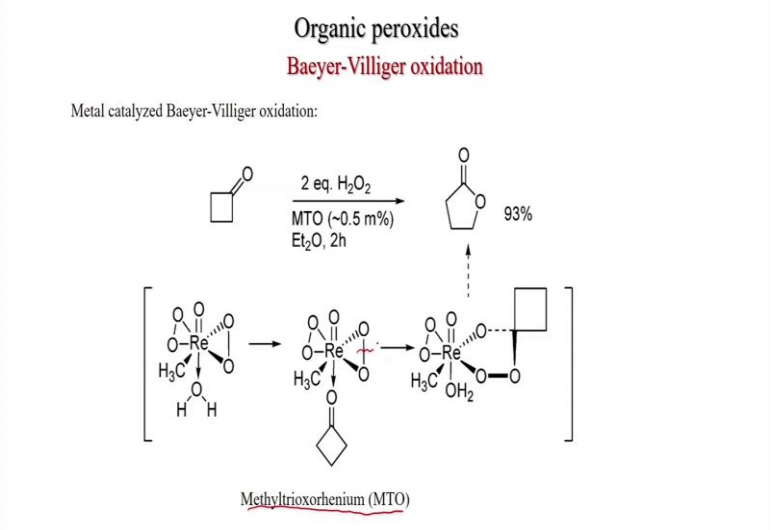

There are many reports also on metal catalyzed Baeyer-Villiger oxidation. So here, the idea is that you can use stoichiometric amount of hydrogen peroxide and you can use metal oxide like here methyl trioxorhenium, rhenium is a transition metal. So under this condition you can get cyclobutanone to butyrolactone, 5 member lactone is formed in very high yield.

So what happens, this complex rhenium, this is the methyltrioxorhenium complex. This binds with cyclobutanone first, there is a co-ordination happens and now this bond, this peroxide bond gets breaks and this attacks to the carbonyl and ultimately this after, this cleavage you get the butyrolactone and this become carbonyl, I think. That is becoming again, the peroxide is forming from the H_2O_2. So catalyst is regenerated again and again by H_2O_2 here.

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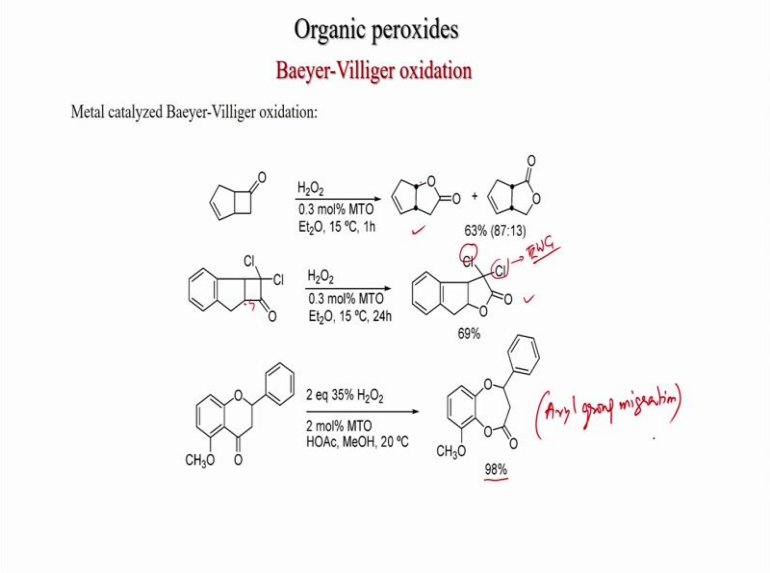

This strategy was applied to other substrates like here, bicyclic compound was converted with that MTO 0.3 mole percent H_2O_2 and you get this lactone. Also there is two mixture products, 87 is to 13, overall 63 percent yield. Here the more substituted was the major, this was the more substituted so this was the major 87 percent.

Here the tricyclic compound was also treated under this condition and this compound was formed. Here though this was the quaternary center but two electron withdrawing groups are there. So groups containing electron withdrawing groups, migration will be much slower and that is why this group is migrating; this carbon is attacking to the oxygen. So you get this product. Here a chroman compound was used, carbonyl group is there. Under this condition

also here you get selectively this product where the aryl group, so this group, aryl group migration. So aryl group is migrating more than this CH_2 group.

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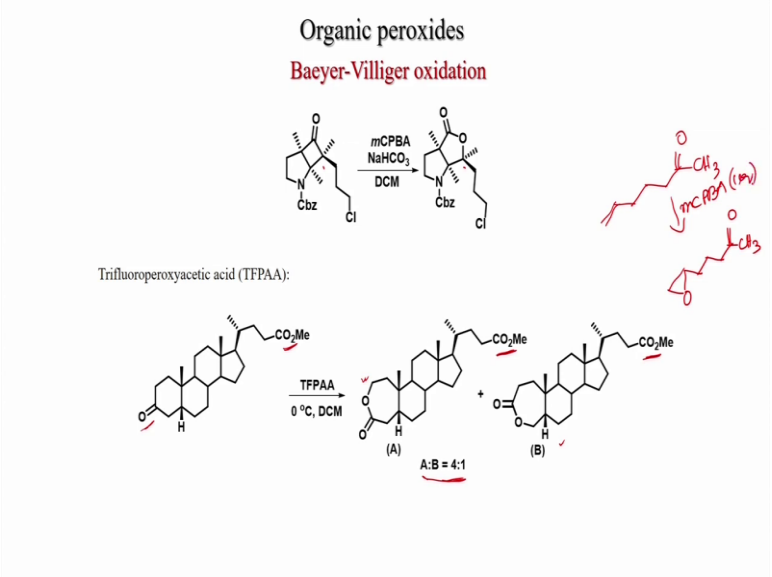

This reaction also was applied in different natural product synthesis. Here a complex structure was used where many chiral center is there and under this condition mCPBA, sodium bicarbonate, dichloromethane, you get these products selectively without disturbing any chiral center. So this lactone is forming and this stereochemistry is retained in the product. Then trifluoroperoxy acetic acid was used for the steroid derivative and here a carbonyl and ester group is there, and under this condition, the ester group is, stays, ester group does not react under this condition and only the carbonyl group reacts to get the lactone.

And here two products are formed, 4 is to 1 ratio, one, when this group migrates, that is this product is forming, that is the major; and this one migrates slowly might be due to the steric reason because here the chiral center is there and that is why might be the slower. So this compound is major and minor. So another thing I just wanted to tell that if you have a compound with a double bond and carbonyl and if you treat with mCPBA, what will happen? So if you treat with mCPBA, it has been found the epoxide will be formed fast. Baeyer-Villiger oxidation is slow process.

So if you use 1 equivalent mCPBA then you can get selective epoxide. So only thing, epoxidation with m CPBA is much faster than carbonyl to ester conversion. So when you treat here only selective epoxidation is formed.

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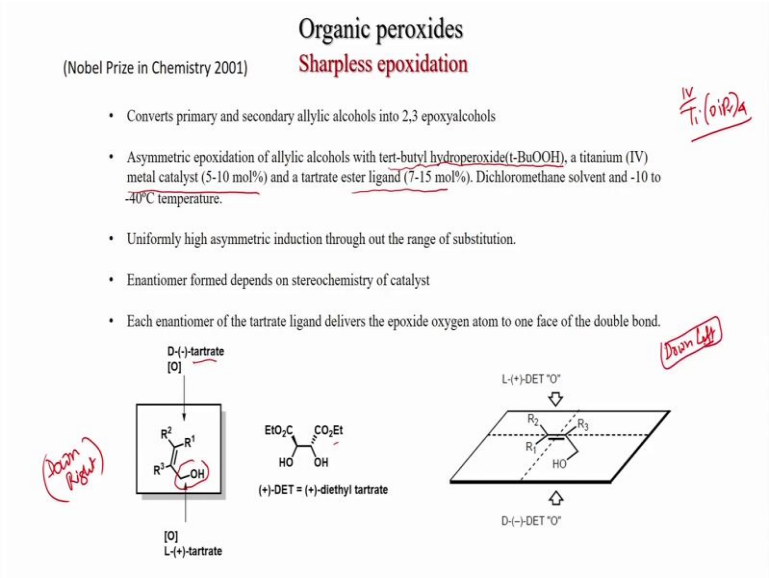

Now we will discuss Sharpless epoxidation. As we know Sharpless, Noyori and Knowles, they share the Nobel Prize in 2001 for the discovery in asymmetric catalysis. Sharpless got mainly because of his epoxidation and oxyamination that is the dihydroxlation reaction. So today we will discuss Sharpless epoxidation. This is mainly primary and secondary allylic alcohol into 2, 3 epoxyalcohols.

Asymmetric epoxidation of allylic alcohols with tertiary butyl hydro peroxide, so this is the peroxo compound, tertiary butyl hdyroperoxide, a titanium IV metal catalyst 5 to 10 mole percent and generally titanium isopropoxide is used, titanium IV and tartrate ester ligand, tartrate ester means it is, should be D or L tartrate, Okay chiral, ester ligand 7 to 15 mole percent so there is slightly more amount of the ligand compared to the metal catalyst. And dichloromethane solvent was used and minus 10 to minus 40 degrees temperature you can use.

Uniformly high asymmetric induction throughout the range of substitution, it is possible to get high asymmetric induction. Enantiomer formed depends on stereochemistry of catalyst. So catalyst determines the stereochemistry. If you use, different compared to D if you use the other L, then you get the other stereochemistry of the product. Each enantiomer of the tartrate

ligand delivers the epoxide oxygen atom to one face of the double bond. This is very important. The facial attack happens.

As you can see, so if you draw allylic alcohol like this way and if you closely look at this, this CH_2OH group is drawn on the right, down right. So the double bond will be drawn such a way that the CH_2OH group will be downside and it is right, it is right side. Then what will happen, then D minus tartrate like the ethyl layer will react from the top face and plus tartrate will react from the down face. And if you draw the alcohol, allylic alcohol, suppose if you give a rotation then what happened?

The CH_2OH group comes this side. R^2 goes to that side. R^1 goes to this side. R^3 goes there. So this CH_2OH group we can tell, it is down left. So this carbon is down, this is dropped down, down left. Under this geometry the plus will react from the top face and the minus will react from the down face.

So this is very important to determine the product structure, the epoxide product structure. So this is very important. If you draw right side, down right then minus will attack from the top face and vice versa. And if you write like down left then the plus will react from the top face and minus will of course react from the down face.

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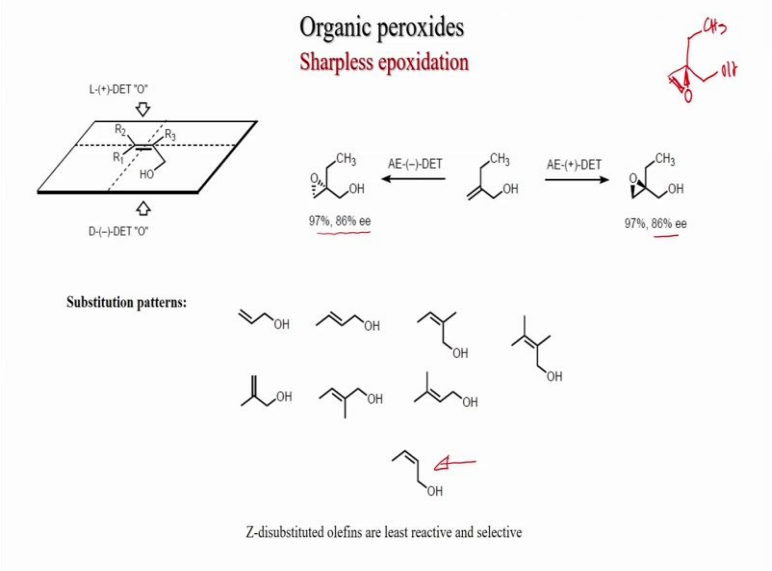

And this is again, this what we discussed that this substituted allylic alcohol can react and when this orientation then plus will react from the top face, and minus will react from the

down face. And if we draw like this compound, so if you see this compound, what happens? This is down carbon if you draw like this and this is left side. So the plus will attack from the top face.

So this way we can see this compound. So plus will give the epoxide from the top face. It gives 86 percent ee. And minus DET, it gives reaction from the down face, as you can see here, the down epoxide is forming and it is giving 86 percent ee. This epoxide can be written like this also. There is no harm.

Substitution patterns, there are different substitution patterns is there, like mono substituted, di-substituted, tri-substituted, tetra-substituted, this was 2, 2 di-substituted, this is tri-substituted, this is also tri-substituted and this is Z di-substituted. So Z di-substituted olefins are the least reactive and selective. So if you have a Z-disubstituted like this allylic alcohol then the reaction is very sluggish and also less selective.

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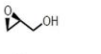
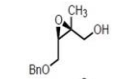
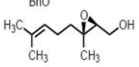
Organic peroxides

Sharpless epoxidation

product	Ti(%)	tartarate(%)	°C	h	yield (%)	ee (%)
	5	(+)-DIPT (6.0)	0	2	65	90
	5	(+)-DIPT (7.0)	−20	3	89	>98
	4.7	(+)-DET (5.9)	−12	11	88	95
	10	(+)-DET (14)	−10	29	74	86
	5	(+)-DIPT (7.5)	−35	2	79	>98
	100	(+)-DET (142)	−20	14	80	80
	5	(+)-DET (7.4)	−20	0.75	95	91

Here are different substitutes are there with different substitution. As you can see, only simply allylic alcohol is there. Plus DIPT, so this is CO_2 isopropyl. Okay, so this is the CO_2 group, O H group here and this compound gives 90 percent ee of the product. When phenyl substitution is there then the ee enhances to 98 percent. When there is a one carbon atom of the olefin is di-substituted then also you get high enantioselectivity. Also the reactivity is very good, 88 percent.

When there is a cis-alcohol now, this is the cis, sorry cis-olefin is there then that case you get the ee is lower, 86 percent. And when, when there is tri-substitution but this is still trans, the more substituted phenyl and CH_2OH group they are trans, so you get 98 ee. However when there is cis, so this is the CH_2OBn and CH_2OH, they are cis to each other, and so the ee is lower, 80 percent. And this is very important, when you have the other olefin and this olefin so allylic olefin only reacts under this condition and this double bond is unreacted. And also you get 91 percent ee. So this is geraniol.

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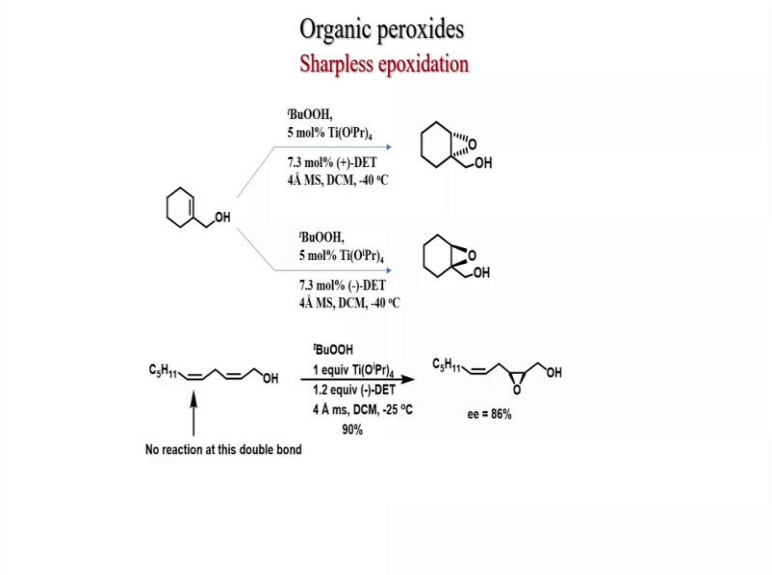

Surely this compound can be seen, that with 5 mole percent titanium isopropoxyide, 7.3 mole percent plus DET, 4 Angstrom molecular shieves, DCM, minus 40 degrees Centigrade, it will give the minus, epoxide will be from the down face. Because here we have drawn like this, down right, so this was the right side and now the plus, DET will come from the down face. Similarly if you use the minus DET under the same condition, 5 mole percent titanium isopropoxide, 7.3 mole percent minus DET, you get the top, the epoxy group comes from the top side.

This is a conjugated diene as you can see. It is very important. The conjugated diene is there and under this condition this double bond is unreacted. And you have to use more equivalent here, one equivalent titanium isopropoxide, 1.2 equivalent of minus DET, also 4 Angstrom molecular shift, dichloromethane minus 25 degrees Centigrade, under this condition only you get this alcohol. Since this is Z, the enantiometer selectivity was slightly low, 86 percent.

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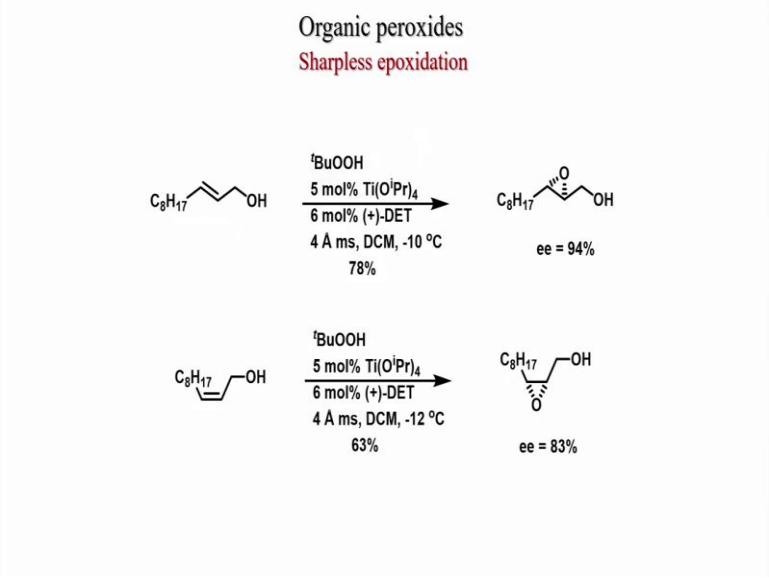

This cis-trans can be also explained by the same compound, the trans isomer and the cis isomer. So trans isomer with 5 mole percent titanium isopropoxide, 6 mole percent DET, 4 Angstrom molecular shift, dichloromethane minus 10 degree Centigrade, it gives this compound because we have drawn the right side. So plus will come from the down face and you get 94 percent ee. And when the cis-allylic alcohol was employed under the same condition, here the ee, the same alcohol is, means from the down face only but the ee is only 83 percent.

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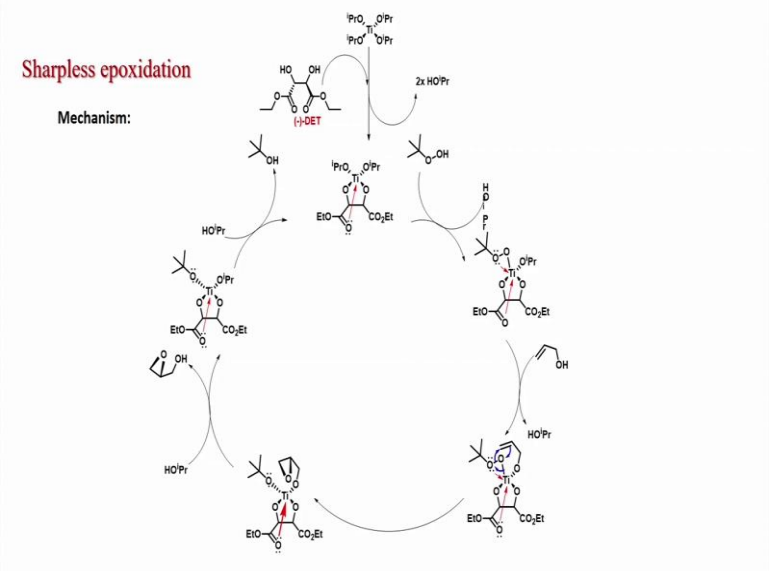

So what is the mechanism of Sharpless epoxidation that we can discuss. So first step, minus, here minus DET, diethyl tartrate is employed and titanium isopropoxide is there. So first what

will happen? This substitution reaction will happen. Two isopropanol molecule will eliminate and you get this titanium tartrate complex. So this is very important.

Titanium metal comes with the ligand. Now the metal center is chiral. So now a tertiary butyl hydroperoxide again will attack to titanium and another isopropanol, this is isopropanol, isopropanol molecule will eliminate, you get this compound where the extra binding of this oxygen and this ester oxygen is also possible to titanium. After that, since one isopropoxide is there, another substitution from the allylic alcohol will happen. And this will eliminate another molecule of isopropanol, and your substrate is now bound with the titanium.

So here you can see a ligand is bound with titanium, your peroxide is bound to the titanium, and your substitute is bound to the titanium. So all three are bound to the titanium and now this desired expoxidation will happen because this metal center is in the chiral environment. So the facial selectivity will happen and you get here, from the top face only and you get the, after treatment of the isopropanol, isopropanol will come, which was eliminated will react now here now after this desired reaction happens then you get your product and this is the derivative which is formed.

Here one isopropoxide is there, and now again one isopropanol will react, so it will join the tertiary butanol and this is the pre catalyst that is the formed. So titanium ligand complex is formed. So here we can see this, your ligand and titanium are getting regenerated. Only your peroxide is getting to the tertiary butanol. So that is why the peroxide we need the stoichiometric amount. Other things we can use in the sub-stoichiometric amount, titanium catalyst as well as the ligand.

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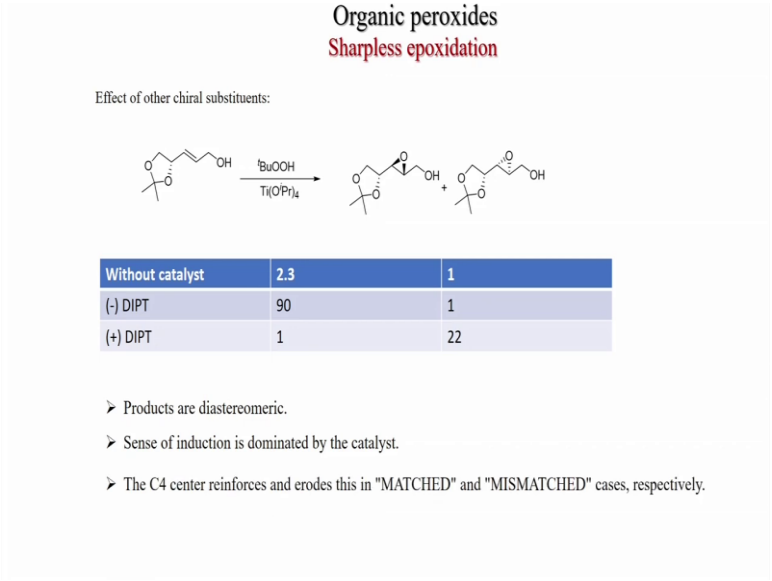

Effect of other chiral substituents, so this is a chiral compound where the chiral center is there far from this and allylic alcohol motif is there and tertiary butyl hydroperoxide and titanium isopropoxide condition you get these two products which are diastereomeric to each other, because there is one chiral center and another chiral center is here. So you get two diastereomeric products. Now since there is already a chiral center, the chiral center also can influence the geometry of the products and this was observation that when you use without catalyst, then you get this measure, 2.3 is to 1.

So this was 2.3 and this was 1, this was the ratio. And when we use minus DIPT, then it becomes 90 is to 1. So this gets dominated more. So this is actually MATCHED case. So here you get 90 percent and it is 1 percent. And now plus DIPT, you get 1 percent this and 22 percent of this one. So that means here the catalyst is operating but this was a MISMATCHED case. So that is why you are getting slightly less ratio. So what are the features of this, products are diastereomeric, sense of induction is dominated by the catalyst, so catalyst is controlling.

Catalyst can reverse also, see here 2.3 when you use plus DIPT, that time you get the, this one is the major. The C4 center reinforces and erodes this in MATCHED and MISMATCHED cases respectively. So in this case, reinforces because, already without catalyst this was the major, so catalyst reinforces that is why you get the better ratio of the major product. And this case, it is erodes so this MISMATCHED case.

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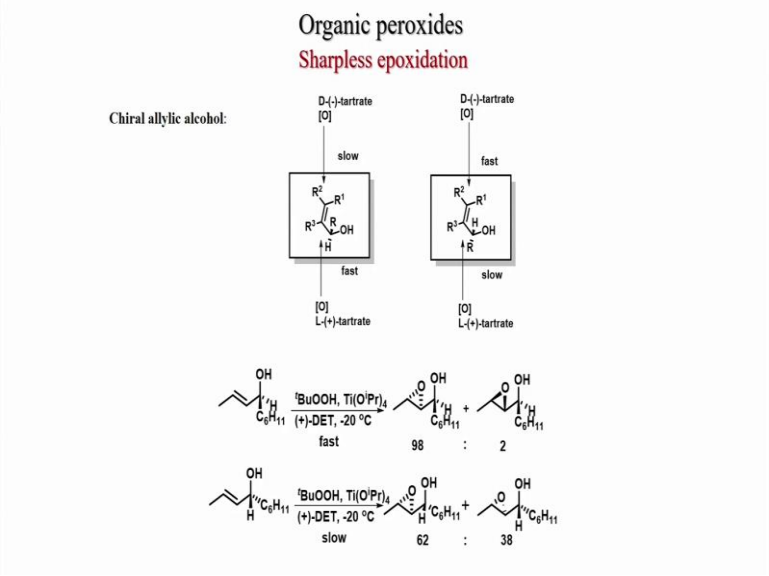

Now chiral allylic alcohol, so if the chiral center is present on this CH_2OH what we have seen so far, there is no substitution. Now if your chiral center is here, so here if there is substitution and if we CH_2OH group, that CHOH group if we draw in a plane, then what happens, the R group that is the substitution either, we can draw up or down. So this will be one chiral compound where R is up and this is one chiral compound where R is down. Now the question is whether the reactivity will be different or not.

Earlier what happened, we have the plane and both side were equally possible. Now here, suppose in this case the top face is blocked by R. So as you know that if we keep CHOH in the down right side, then minus tartrate reacts only from the top face. Now minus tartrate reaction on this one will be slow because the top face is blocked. And minus tartrate under this orientation can react only from top face. So this reaction will be slow because the top face is blocked by the R group. On the other hand if you see the down face, down face hydrogen is there. So it is no, like earlier it was no problem because substitution is on the top side it is blocking so down face it is open.

So the reaction with plus tartrate will be much faster. Similarly if your chiral compound is such that the R is down. R is down then what happens, in this case top face is not blocked. So there is no problem of minus tartrate at all. So again I am telling, when we draw like this way, down right side then only, then only minus tartrate can react from the top face independent of substitution. Now even if the substitution is there the reaction from the top face will be fast

but down face by plus tartrate will be slow because down face in this case is blocked by R group.

This is an clear example of this compound, chiral secondary, allylic secondary alcohol if you see, there is a cyclohexyl group is there and if we draw like this way, the OH group in the plane and this is up down, so in this case the top face of the substrate is blocked. And plus DET, plus DET means this one will, can react from the down face. So this reaction will be very fast if you give the plus DET and if you give the down epoxide and this epoxide is the minor case, from the top face. So this reaction will be much slower. Now if we have a plus DET and same DET we did not change but we changed the alcohol now, the alcohol, this cyclohexyl group now in the down case, down side. So this is the case.

And if you use same DET, plus DET so what will happen? If your DET is fixed your structure is fixed, so what will happen? It has to react from the down side only but the reaction will be slow. So the reaction is slow and you do not get much selectivity. Here 62 and 38 percent, so this is down and this will be actually up. So these two products are formed but the ratio is not good; here 62 percent you get and 38 percent. So in this case, there is an option, the plus DET to react from the downside. But here the downside is blocked so that is why the reaction is much slower and you get mixture.

So this idea was extended, that chiral, that kinetic resolution. So kinetic resolution is a condition, reaction condition where 50 percent of the starting material reacts and 50 percent of the starting material does not react. So this was the idea that if you have racemic alcohol, whether one enantiomer reacts and another enantiomer does not react. Because as we have seen that if plus DET is there, if you have a specific alcohol then the reaction is one case is fast, one case is slow. So this idea can be used in the kinetic resolution, when you start with racemic alcohol.

So as you can see if you draw like this way, the left side, alcohol is there. Now what happens, the top face is blocked and plus DET this reaction from the top side, because when we draw CHOH in the left side, then plus will attack only from the top face but this will be slow. On the other hand when R is down then this will be much faster. So this, two alcohols, when this is the racemic alcohol, the racemic alcohols are there. Because racemic this is 50-50 percent.

So 50 percent that means this isomer, this alcohol will react much faster with DET and this will be much slower. So this will be unreacted and this will give the chiral epoxide. And this rate can be, k relative can be calculated by reaction of k fast by k slow if we divide. Here the products are diastereomeric as we have seen earlier. Using this Sharpless mnemonic contact between C 1 substituent R, so here and the catalyst predicts the slow-reacting isomer.

So if we know the facial orientation of R, we can tell which side is blocked and whether attack will be slow or fast. With the exception of Z-disubstituted allylic alcohols, K relative is generally greater than 25. So if you have substitution then it has been found except Z-disubstituted allylic alcohols, k relative greater than 25. And when k relative is 25 the ee of unreacted alcohol is essentially 100 percent at 60 percent conversion. So this tells, if k relative is equal to 25 or higher than 25 then there the kinetic resolution is possible and high enantio selectivity for both, alcohol and the unreacted alcohol and the epoxide products can be obtained.

Allylic tertiary alcohols are not successfully epoxidized on the Sharpless condition because when there is both side, if there is a substitution here also, then both face will be blocked so the reaction will be much slower. So generally allylic tertiary alcohols are not successfully epoxidized under Sharpless condition. Some extra factor may combine for high selectivity like di-substituted olefin is more reactive than mono-substituted olefin, the k relative around 1000. So di-substituted olefins react much faster than mono-substituted olefins because of the electronic nature.

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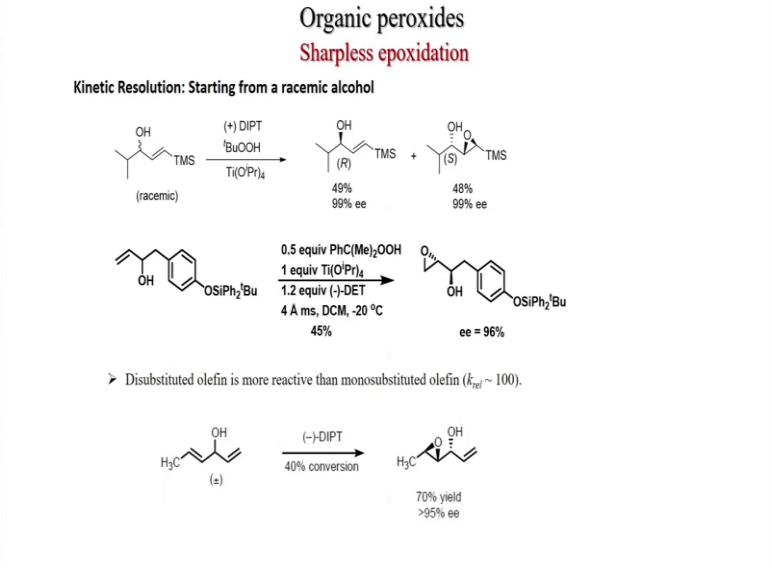

So this is an example of kinetic resolution. This is a chiral allylic secondary alcohol. This is racemic. And here this orientation is on the other, so you have to draw, if you want to draw the epoxide we have to draw properly. And this CHOH we have to draw in plane, and this will be above or down the plane.

And under this plus DIPT tertiary butyl hydroperoxide and titanium isopropoxide condition you get this product starting material, R starting material, R alcohol is unreacted under this condition and 49 percent ee you can get, 99 percent enantioselectivity and S alcohol only epoxidized under this condition. So this clearly tells one isomer is reacting and other isomer is blocking one face so that plus DIPT cannot come to react. So that is why, this on the R alcohol the reaction is not happening.

In this case here one equivalent was used another secondary alcohol, here one equivalent titanium isopropoxide and one special peroxide was used. 1.2 equivalent minus DET, 4 Angstrom molecular shift, dichloromethane minus 20 degree Centigrade you can get 96 percent ee and 45 percent yield. That means the other minus alcohol unreacted, that one did not epoxidized under this condition.

This is an example that is what; we told that di-substitute olefin is more reactive than mono-substituted olefin. Here is an example. So if you start with this racemic bis allylic alcohol, this one, but if you see this substitution here, this is mono-substituted but this double bond is di-substituted. Now under minus DIPT condition and if you stop the reaction at 40 percent then you see only the more substituted olefin has reacted. So this gives the epoxide and this is, this double bond unreacted. So 40 percent conversion, on the 40 percent, 70 percent you get the product and 95 percent enantio-selectivity you can achieve.

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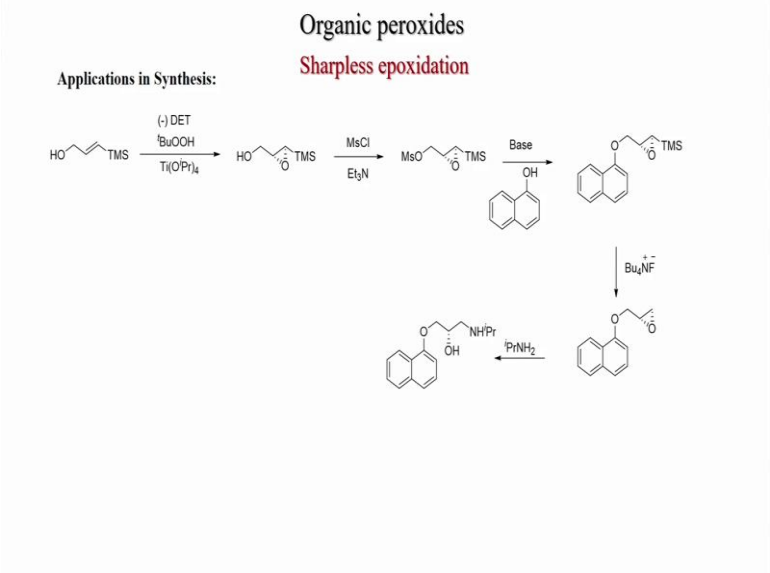

The Sharpless epoxidation was utilized in many natural product synthesis because you get the epoxide. Now epoxide can be opened and also the allylic alcohol that can be converted to aldehyde and then Wittig reaction, hydrogenation, many reactions can be carried out and the functional group you can enhance, you can put different functional groups and you can get many complex structure. So this was an application.

So here this olefin, allylic alcohol was TMS substituted olefin here is there and this also allylic alcohol. So under this condition this gives the down side, minus DET condition, so here we have to reorient this compound so that we can predict, we have to draw like this, stop, sorry, down left or right side, then we can predict, minus DET. So if we right side then minus DET comes from the top face.

And then you can get this epoxide, and after protection of the alcohol you get the mesityl, this is methane sulphonyl chloride, o-mesyl compound, sorry o-mesyl. And now treated with 1 naphthol under basic condition the OH reacts here, the mesyl group and substitution reaction happens and then you get this compound. Then this TMS group was deprotected with tetrabutyl ammonium fluoride to get the epoxide and this epoxide then opened with isopropyl amine, because as we know the S_N2 reaction on the unsubstituted, on the terminal carbon will be much faster than the internal carbon and less substituted carbon the attack will happen and that is why you get this amino alcohol.

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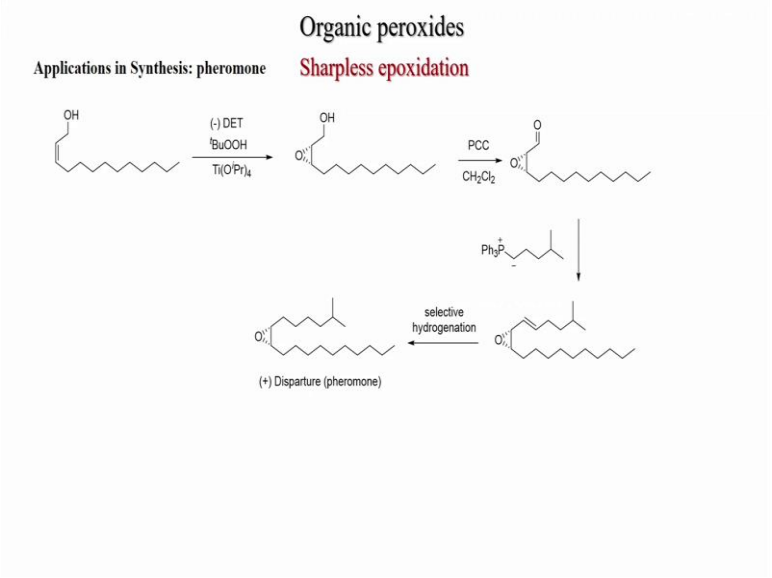

Also it was applied in pheromone synthesis. Here however cis-alcohol Z olefin was used with a long chain hexyl group is there and here also it is very difficult to predict but if we reorient, rewrite the molecule then we can tell the minus DET, if it is from the right side it will come from the top face and you can get the epoxide. Here the enantio-selectivity might be slightly lower because this is Z olefin and now PCC oxidation will give you aldehyde. PCC we have already seen, pyridium chlorochromate without affecting the epoxide you get the aldehyde, then the Wittig olefination will happen with this light and here actually you get the cis-trans mixture.

Then selective hydrogenation will be carried out to hydrogenate the double bond and you get only the epoxide which is called plus Disparture which is a pheromone. So this strategy can be applied in other cases also. So if you have the allylic alcohol epoxide then the alcohol can be oxidized to the aldehyde and then the Wittig reaction and then hydrogenation will give a saturated C-C bond and we can get many more structures.

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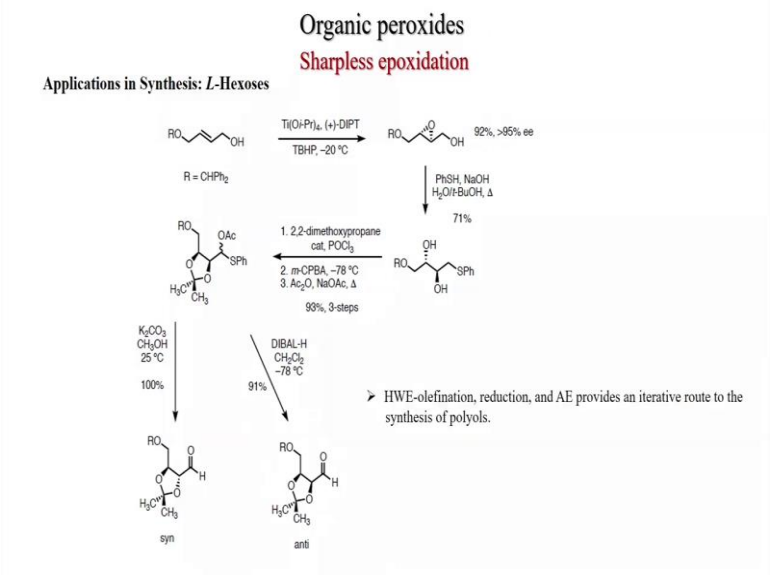

Application in synthesis L-Hexoses, so here this was the starting material. Di-substituted olefin is there and you get, because this is trans so you get high enantioselectivity and, plus DIPT because we have drawn on the right side, lower right so what will happen, the plus will attack from the down face so you get the epoxide like this.

Then thiophenol under basic condition was treated, so this pine rearrangement happens. This alcohol reacts here and terminal epoxide will form here and now the thiophenol will react at the terminal carbon of the epoxide to get this diol. After 2-2 dimethoxy propane we can rewrite this. This was zig zag conformation.

If you do like this, then this alcohol will be cis and you will get the ketal protection. After that the mCPBA you get the sulphur oxide here and then acidic anhydrous sodium acetate, this is Pummerer rearrangement you can get this acetate. So what happens here sulfonium, carbon double bond sulfonium bond is formed and after that the acetate reacts there and you get this compound.

This compound can be converted to potassium carbonate, methanol condition. Here the oxygen is also rearranged to get the same compound. With zig zag it will be syn actually and in DIBAL condition you get the aldehyde. Horner-Wadsworth-Emmons olefination, reduction and asymmetric epoxidation provides an iterative route to synthesis of polyols.

So this compound can be easily obtained. This allylic alcohol from the aldehyde, first you have to do Horner-Wadsworth-Emmons oliefination. You get $CHCO_2Et$ and that DIBAL reduction will give you the allylic alcohol and Sharpless asymmetric epoxidation will give this epoxy alcohol.

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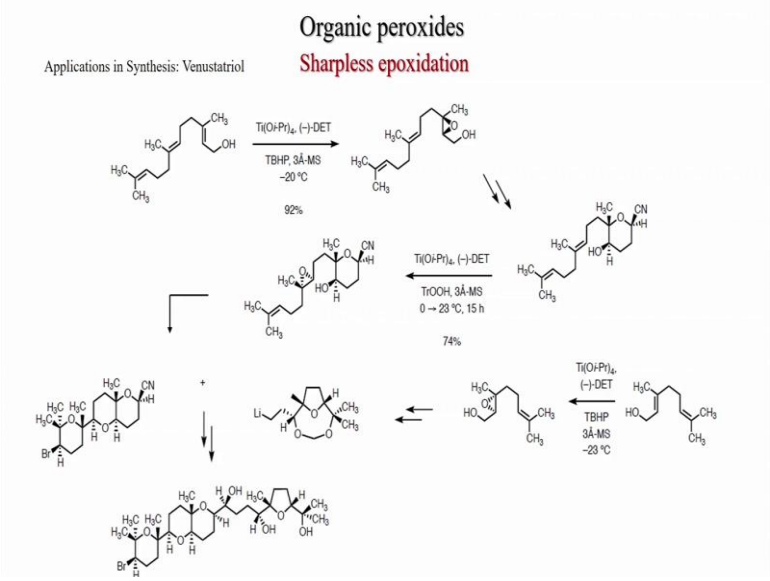

Another application is Venustratriol. Here this farnesol was employed as the starting material and as you can see the ethyl CH_2OH group on the right side, so minus DET comes from the top side and you get this epoxide written like beta top side. And now this epoxide can be converted to this tetrahydropyran motif and then again another Sharpless epoxidation condition can be employed though there is no allylic alcohol but this CH_2OH group might help to coordinate titanium ligand and then you can get also selectivity with the epoxide from the downside and this, after many steps this can be converted to this bromo compound. Another cyclization happens here.

Also the geraniol was converted similarly with titanium isopropoxide minus DET and since this was left, down left side so minus DET will come from the down face so this down epoxide is there and this can be converted in many steps to this one. Here OCH_2OH is there, acetyl motif and then this reaction happens. So here you can see this nucleophile, this is electrophile cyanide after reaction you get carbonyl and that can be reduced to alcohol. You can see this is the alcohol here. This is diastereoselective reduction might be, and this bond was broken and you get the two alcohol here, tertiary alcohol and secondary alcohol.

So oxidation where cyclic ketones are converted to lactones and acyclic compounds converted to esters and we have seen the migrating group is antiperplanar to the O-O bond which is leaving and this migrating group also can also predict the 3 degree alkyl is more than 2 degree alkyl than phenyl than 1 degree alkyl.

And Sharpless asymmetric epoxidation of allylic alcohols we have to draw in proper orientations so CH_2OH group, if it is in the down right side, then minus DET will come from the top face and plus DET will come from the down face. Similarly if it is drawn down left side then plus DET will come from the top face and minus DET will come from the down face. And after predicting this geometry we can write the epoxide structure.

Also we have seen that if there is a chiral center on the alcohol, carbon center then the facial selectivity will happen because then one face will be blocked and we have seen that the chiral alcohol, if it is R or S isomer under plus DET one will be selected when it is MATCHED case and other will not form the product or it will react slowly. And this, this was exploited in kinetic resolution experiment where racemic alcohol, racemic secondary alcohol was converted, one isomer to the product and other enantiomer in the starting material. Thank you.