Essentials of Oxidation, Reduction and C-C Bond Formation. Application in Organic Synthesis

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Lecture - 40
Asymmetric Hydrogenations and Reductions Using Rhodium and Ruthenium Derived Chiral Catalysts

Hello and welcome you all for today's class. We will briefly go through the last lecture's points, main points like we discussed the few aspects of the dihydroxylation of olefins.

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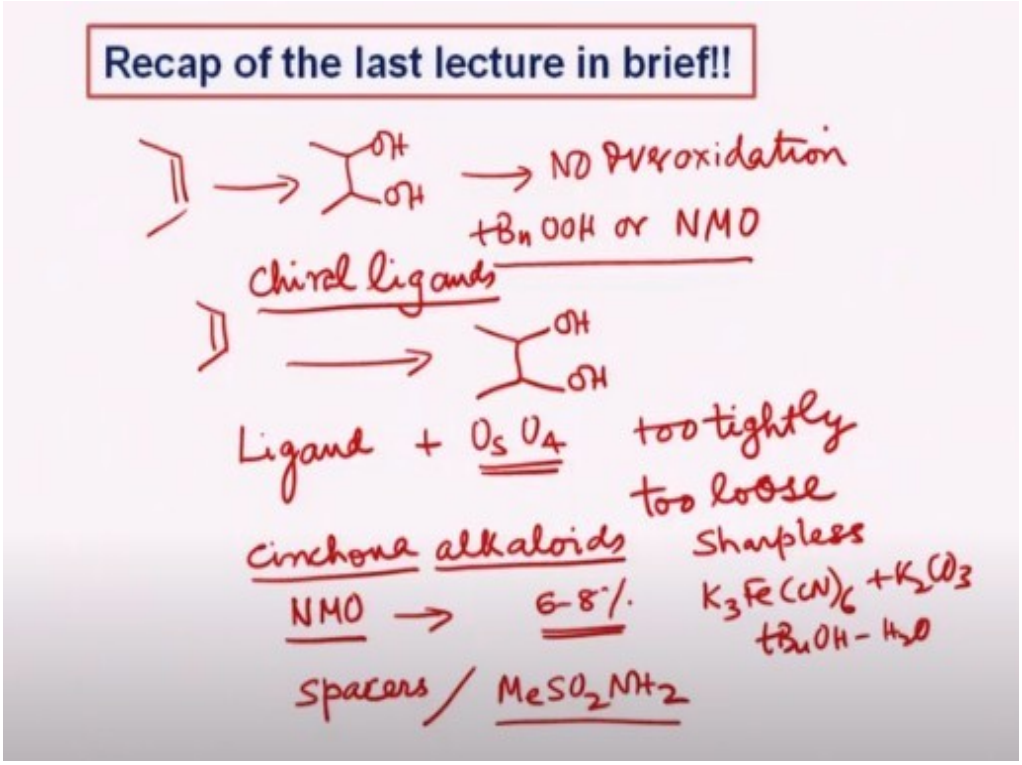

And towards the end, we saw that it is important that we need to have the co-oxidants which allow the dihydroxylation to take place without over oxidation. So there should be no over oxidation. For that purpose we saw that the use of tertiary-butyl hydroperoxide or NMO was utilized and it has become very popular as far as the dihydroxylation of osmium tetroxide is concerned.

And then it was found that we can also make use of the chiral ligands. The chiral ligands such as pyridine based molecules can allow the dihydroxylation to take place and the enantiomeric purity was found to be reasonably good, but not very high. So then it was found that the complex between the ligand, which is the chiral ligand and the osmium tetroxide OsO4 should not be too tight, it should not be too tightly bound.

Neither it should be too loose. In either case, there should not be any advantage because if it is too tightly bound, then we have to use a large excess of the ligand. And if it is too loosely bound then

of course the enantiomeric purity will be low. In that respect, it was found that cinchona alkaloids were a good compromise between the two and it was used for the purpose of dihydroxylation by Sharpless.

And initially, although the NMO was used, it was found that the NMO leads to the optical purity of the dihydroxylated molecule being low in some cases, as low as 6 to 8%. And therefore, it was not the best choice. So the Sharpless introduced K3FeCN6 and potassium carbonate in tertiary butanol water as a good source for the re-oxidation of the osmium tetroxide based byproduct which is osmium VI.

And therefore it is water soluble and therefore the hydrolysis of the osmium VI, which is ligand bound occurs faster and then regeneration of osmium VI to osmium VIII also occurs with this. Then of course we saw the spacers were used and which led to high enantiomeric purity of the product and also it was found that in the case of the tri-substituted olefins, the use of methyl sulfonamide also give high enantiomeric purity and the rate of the reaction was also high.

So these are the various things that were seen. And now we look at the reduction of the different types of organic molecules in an asymmetric fashion. If you recall, we had discussed the Nobel Prize to be given for oxidation and reduction. So the oxidation based work was awarded a Nobel prize to Sharpless and the reduction based Nobel Prize was given to two people, William Knowles and Ryoji Noyori.

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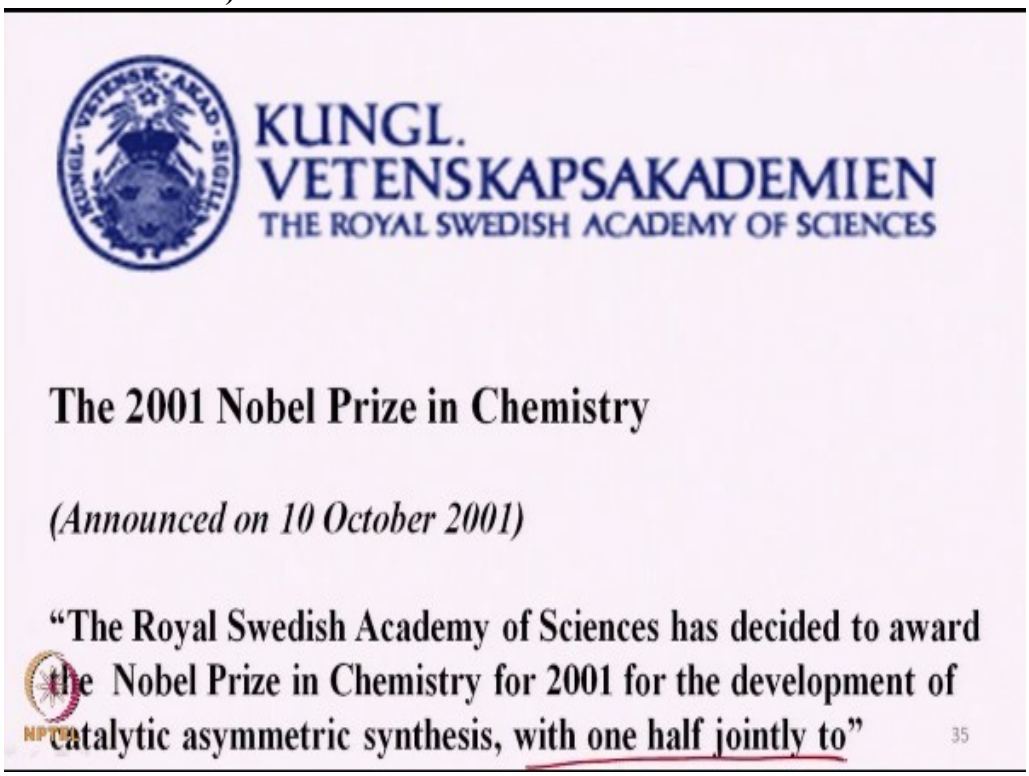

So if you look at it once again, so the 2001 Nobel Prize was given one half, jointly two as you can see it here.

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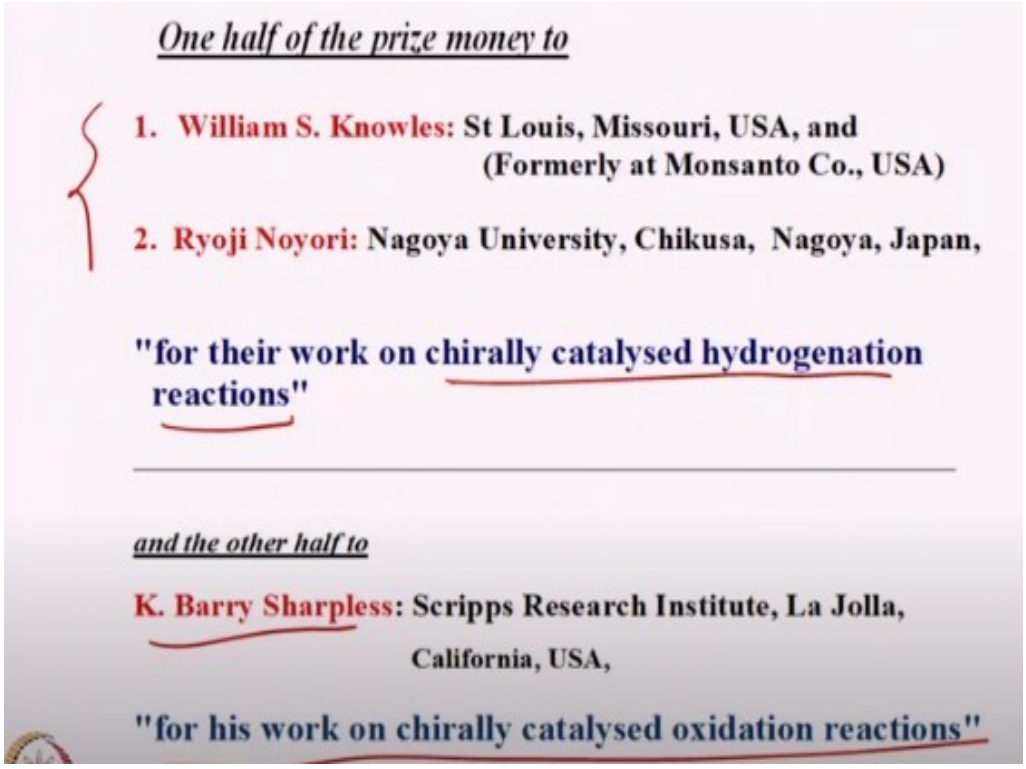

One half was given to K. B. Sharpless above whose work we have already discussed for both catalytic, asymmetric epoxidation and dihydroxylation and the work of William Knowles and Ryoji Noyori for chirally catalyzed hydrogenation reactions and of course many other reductions by Noyori especially, were given the Nobel Prize for 2001.

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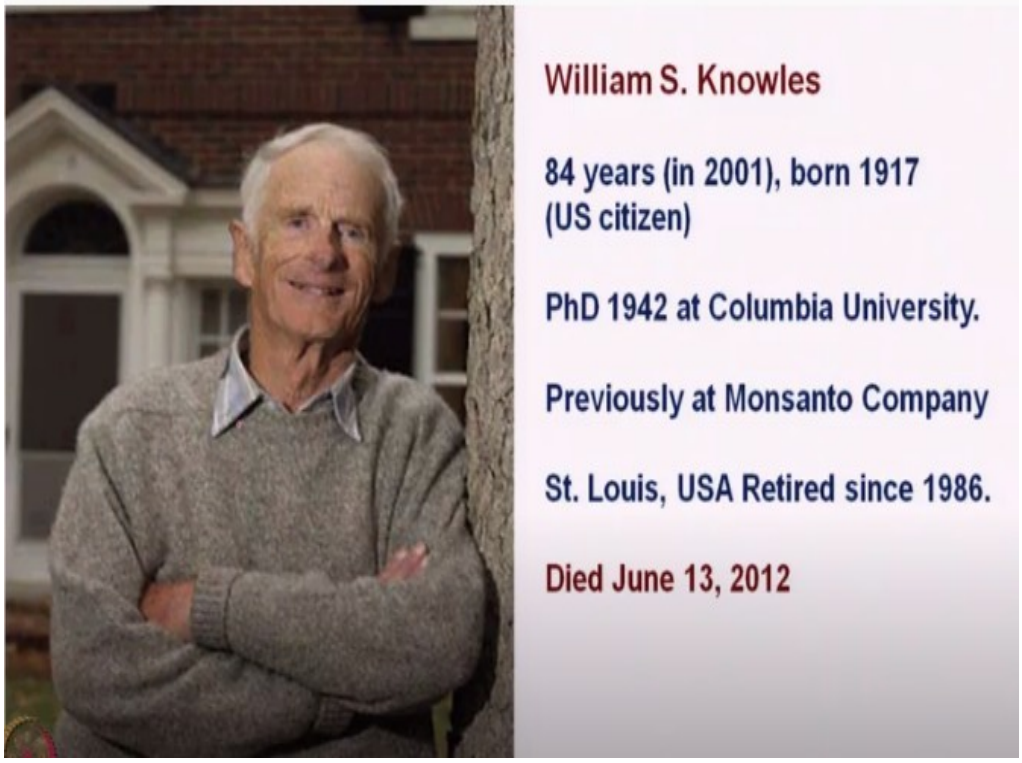

So we will not get into the details of these now.

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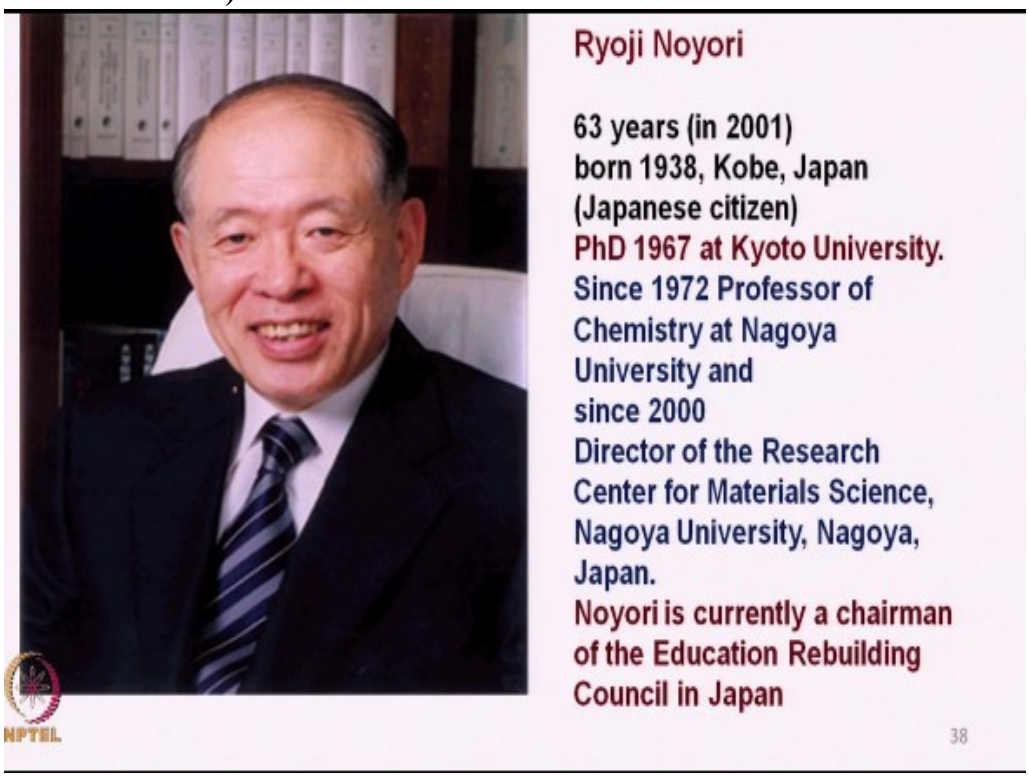

And these are the two people who did the reduction part of it. So now we will look at their work.

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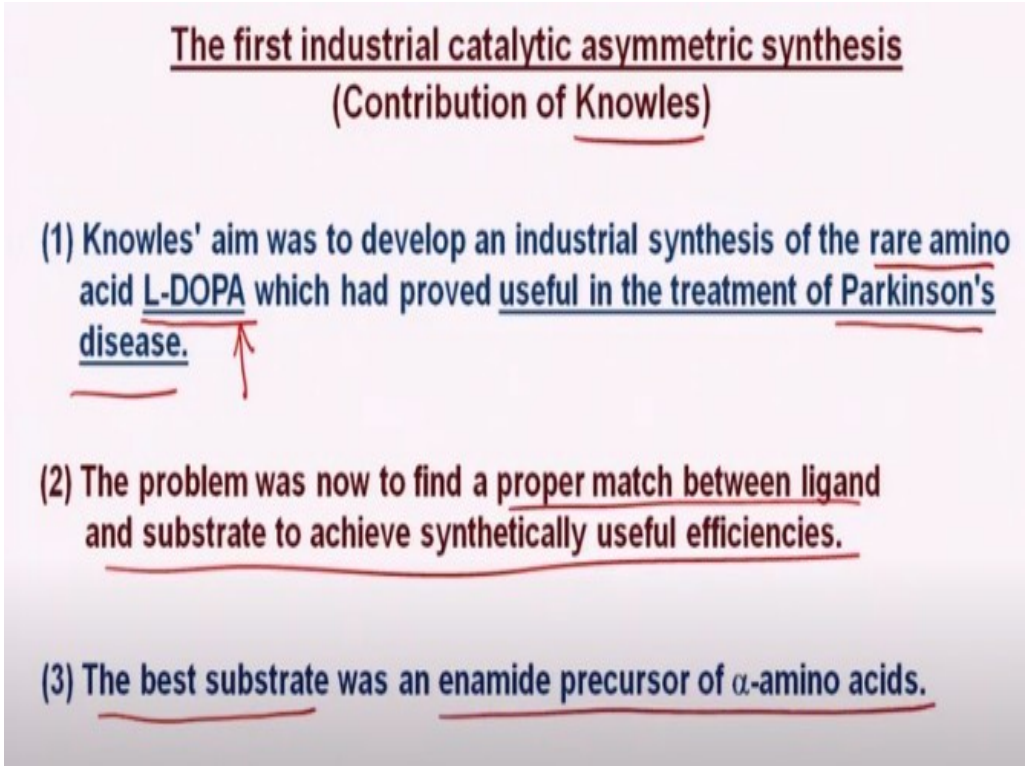

The first industrial catalytic asymmetric synthesis was actually done by William Knowles. William Knowles, who was working in a company like Monsanto company in United States and his aim was to get the synthesis of L-DOPA, which is useful in the treatment of Parkinson's disease in as high enantiomeric purity as possible.

If you recall, we had discussed that that whatever optically active molecule that we need to use as a medicine should be in that particular optically pure form, because the other enantiomer could be not useful at all. So the first industrial synthesis of this rare amino acid L-DOPA was actually done by the contribution of William Knowles.

And basically, he spent a lot of time to find a proper match between ligand and substrate to achieve synthetically useful efficiencies. And it was found that the best substrate was an enamide-precursor that led to amino acids. So the hydrogenation of such molecules was the main purpose for William Knowles' work.

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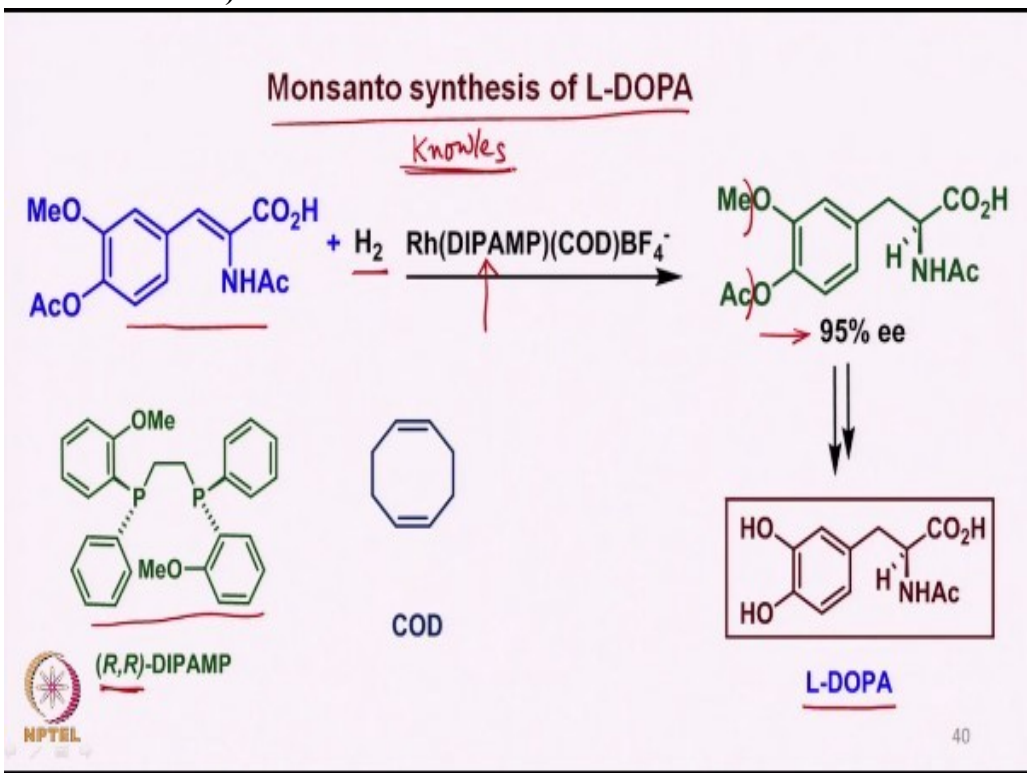

This is what is the enamide which was hydrogenated in the presence of this particular rhodium complex and where the chirality comes from this DIPAMP, which is in this case is R,R configurated and that gave the hydrogenated product as 95% enantiomerically pure and which led eventually for demethylation and deacetylation.

And then you get the corresponding L-DOPA, which was optically pure and that is how the first synthesis which is named as Monsanto synthesis was basically done by William Knowles. And that is the reason why he was given the Nobel Prize for his work.

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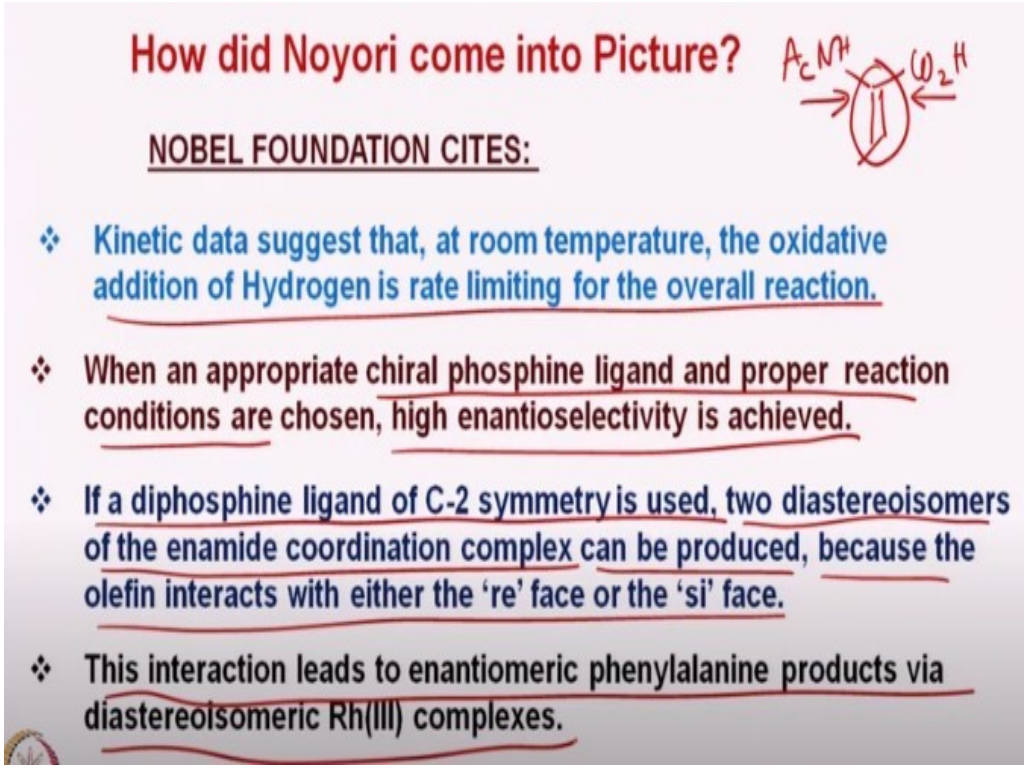

Now how did Noyori come into picture? So the Nobel foundation cites the kinetic data suggests that at room temperature the oxidative addition of hydrogen is rate limiting for the overall reaction. So this was just of the various kinds of work that Noyori has done it. It suggests that this is what is the rate limiting step. When an appropriate chiral phosphine ligand and proper reaction conditions are chosen, high enantioselectivity is achieved.

This is what the Noyori has really addressed it. If a diphosphine ligand of C-2 symmetry is used, the two diastereoisomers of the enamide coordination complex can be produced, because the olefin interacts with either the re face or the si face. So if we have this enamide, which is what we are seeing it in the case of William Knowles' work and obviously when the attachment of the hydrogen occurs from either side, we are basically trying to induce a diastereomeric transition state.

And then the two of them should be differentiated, two of them should have a large gap and then we can get the corresponding enantiomeric purity through diastereoisomeric transition state. So this interaction leads to enantiomerically pure phenylalanine products and of course various kinds of diastereoisomeric rhodium complexes have been utilized for a large number of asymmetric reduction work. That is where the Noyori came into the picture.

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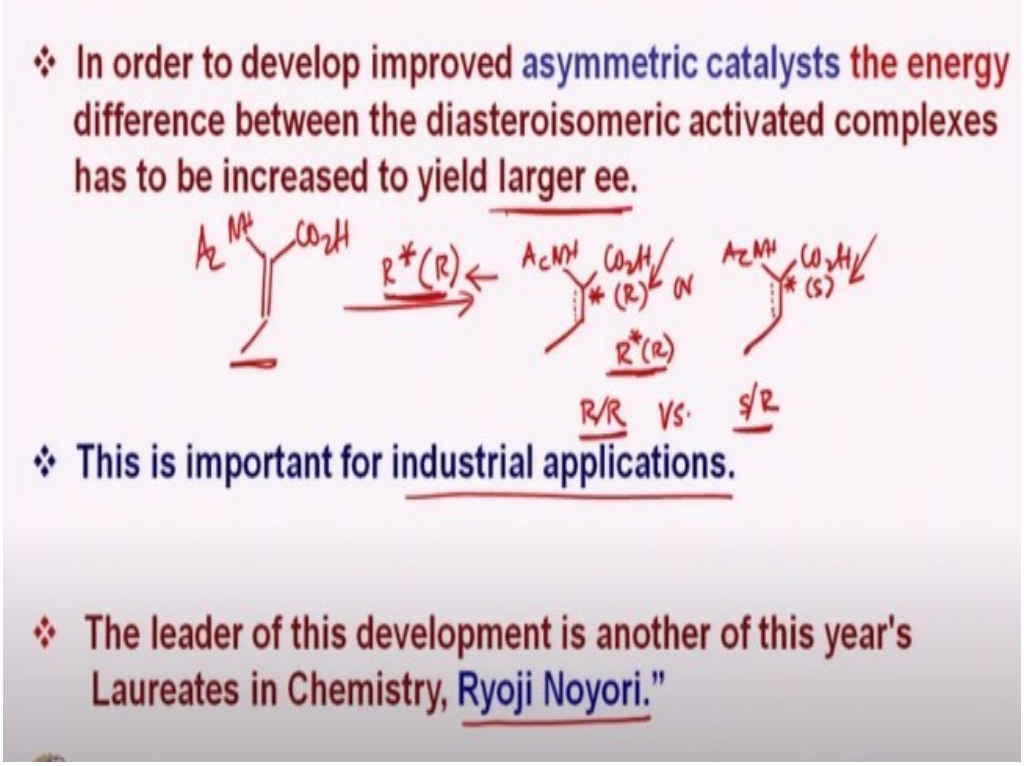

So in order to develop improved asymmetric catalyst the energy difference between the diastereoisomeric activated complexes has to be increased to yield larger enantiomeric purity or enantiomeric access. So as I said that, if a double bond, say for example the same double bond as we saw in the case of Knowles work, if this comes in contact with optically pure ligand where say you have an R star and which has say R configuration.

If that comes in contact with this, then there are two possibilities. One is that you have a possibility of having this particular asymmetric center being generated as R or you have a possibility of this asymmetric center being generated as S. And in the transition state when the double bond is still there, and the asymmetry is being induced here the ligand which is present having an R configuration, should give us R,R as a diastereoisomer.

And this one should give S/R as diastereoisomeric transition state. So these are the two different diastereoisomeric transition states that will form when the ligand modified hydrogen comes in contact with the double bond which is prochiral. And there are two possibilities. One R configuration to come and the other S configuration to come.

And if the ligand has say for example only one asymmetric center and has R configuration which is 100%. So we are basically looking at this R/R versus S/R as two diastereoisomeric transition states. And the larger the gap energy difference between these two diastereoisomeric transition state will be the larger will be the enantiomeric purity of the molecule that we get at the end of the reduction.

So this is what is important for industrial application. And such a large gap was basically addressed by the work of Ryoji Noyori, who introduced several different kinds of ligands and several different kinds of catalysts for making the high enantiomerically pure reduced products.

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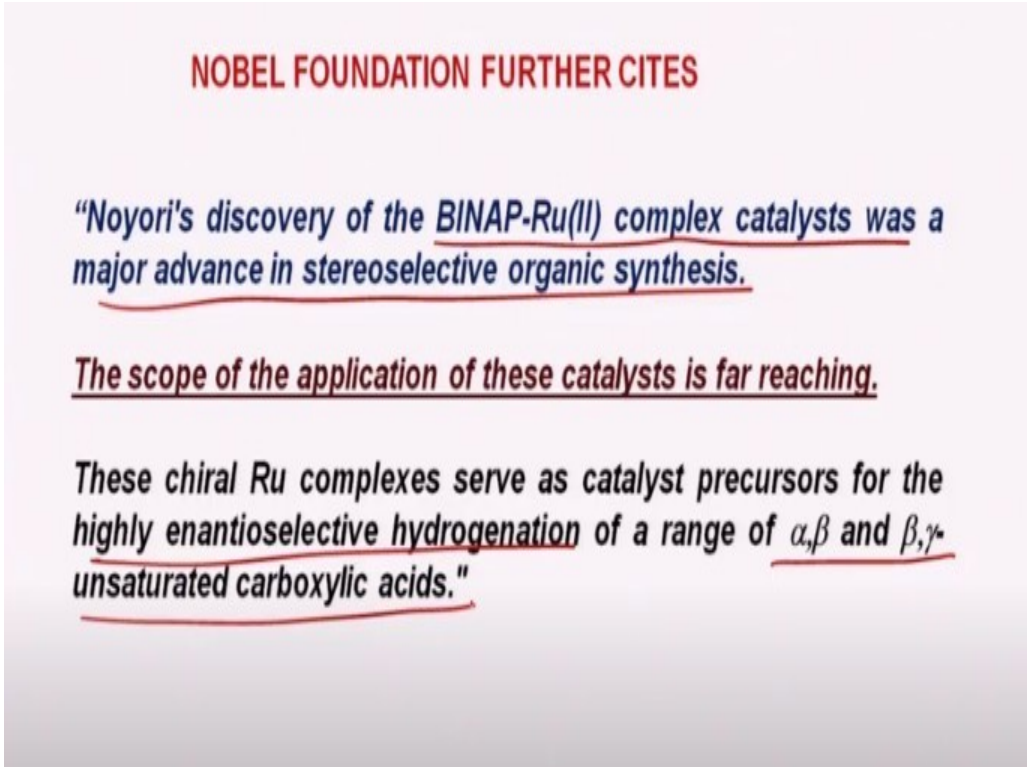

So Nobel foundation further cites, Noyori's discovery of the BINAP-ruthenium complex catalysts was a major advance in stereoselective organic synthesis. The scope of the application of these catalysts is far reaching. These chiral ruthenium complexes serve as catalyst precursors for the high enantioselective hydrogenation of a range of alpha, beta and beta, gamma unsaturated carboxylic acids. So this is how the Noyori's work was basically cited by Noble foundation.

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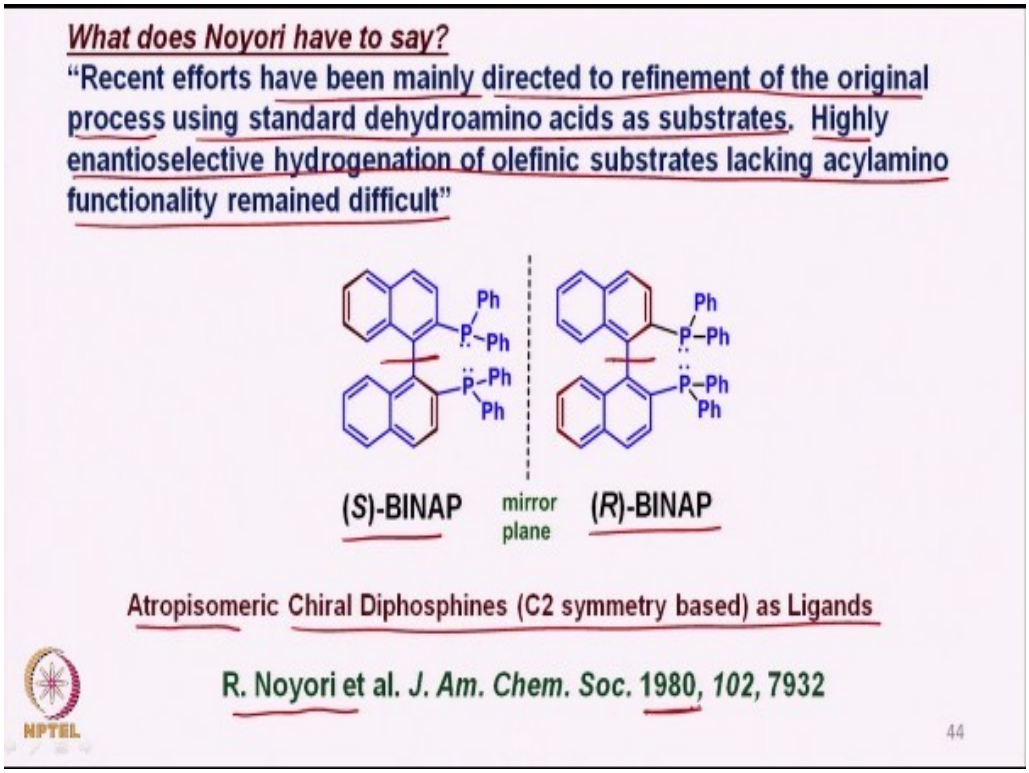

Now what does Noyori have to say? Noyori says that recent efforts have been mainly directed to the refinement of the original process using standard dehydroamino acids as substrates, basically enamides. And highly enantioselective hydrogenation of olefin substrates lacking acylamino functionality remain difficult. So the kind of substrate that was used by William Knowles was found to be good for the preparation of L-DOPA.

But then Noyori also looked at the hydrogenation of other double bonds, which were lacking the acylamino functionality. That is and of course during the process he developed, introduced the (S)- BINAP and (R)-BINAP to atropisomer based chiral diphosphine ligands. And of course, they are C2 symmetry based ligands.

And these are the two which were basically introduced by Noyori in 1980 and for which he really did a lot of work to get to the highly enantiomerically pure different types of molecules.

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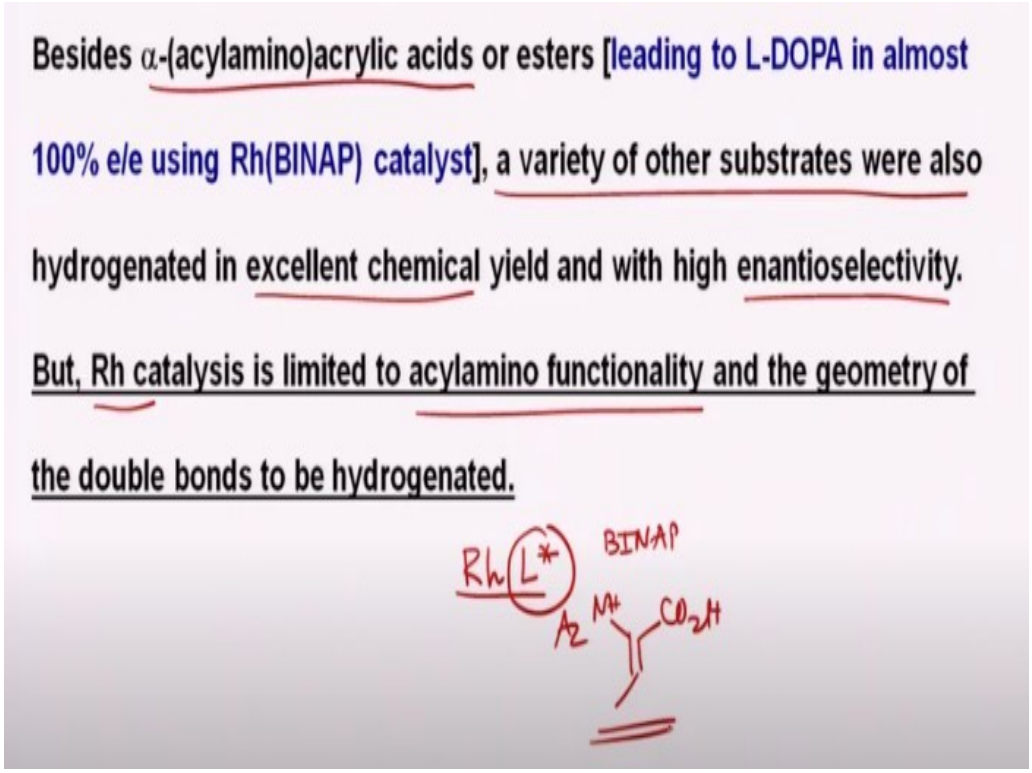

Now besides alpha-(acylamino)acrylic acids or esters leading to L-DOPA the same enamides, which we have talked many times, the a variety of other substrates were also hydrogenated in excellent chemical yield and high enantioselectivity. But then the rhodium catalyst is limited to acylamino functionality.

Basically, rhodium based the catalysts having different ligands, particularly the kind of ligands that Knowles used or the BINAP were used. And therefore, the molecules were hydrogenated, where this enamide type which were very useful for the synthesis of L-DOPA. But there were, these rhodium catalysts were not particularly useful in some other context and therefore Noyori developed many other catalysts and ligands to overcome this and apply new methods for the reduction of different types of molecules.

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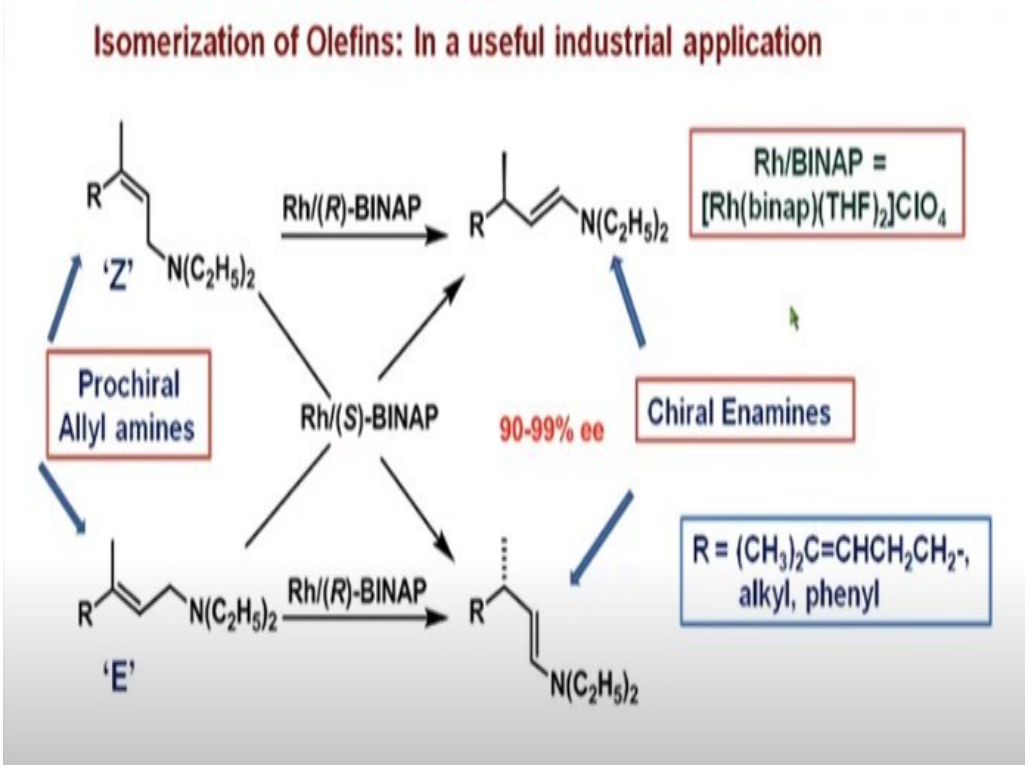


Now rhodium based catalysts using different BINAPs have been utilized in the isomerization of certain olefins and they have been used in the industrial application for the synthesis of a variety of important optically pure molecules.

For example, if we start with a prochiral allylamine of this type, where the double bond geometry is Z and reacted with this rhodium catalyst, where the BINAP has R configuration, then the enamine that is observed after the isomerization of this particular double bond is of this kind, where the absolute configuration is as shown.

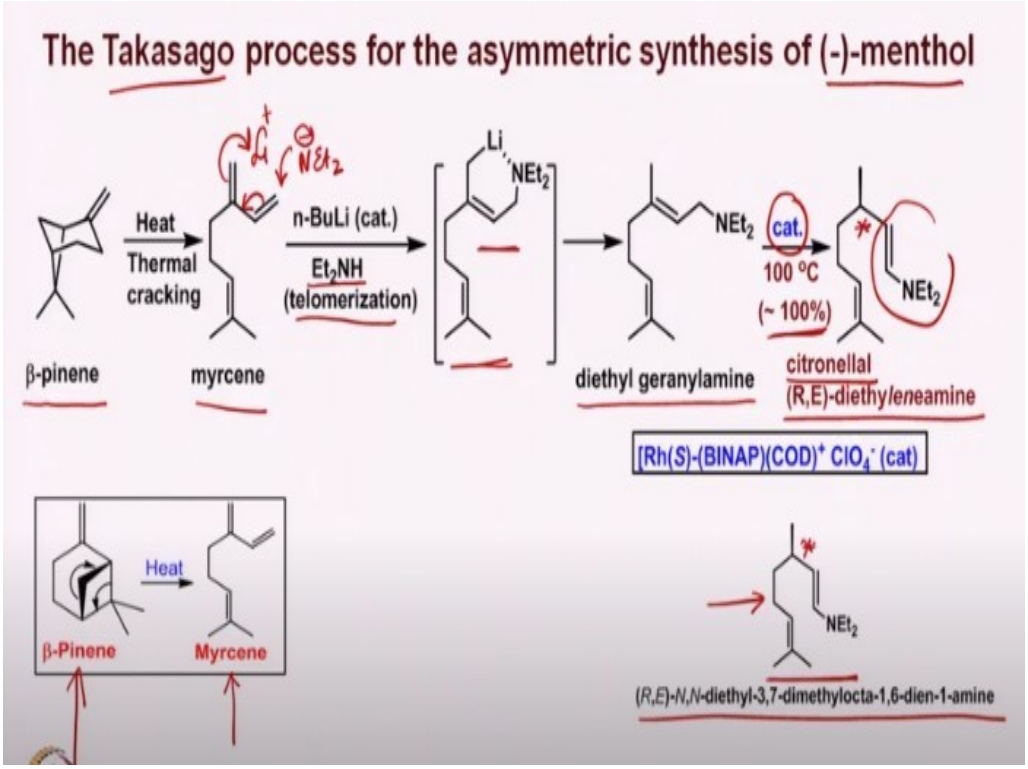
Now the same prochiral allylamine, when it is reacted with the same rhodium based catalysts, but with different BINAP, that is now (S)-BINAP, then what we get is this kind of chiral enamine in which the absolute configuration of this asymmetric center is opposite to that of what we observe with (R)-BINAP.

Now if we change the geometry of the prochiral allylamine from Z to E and react with the same rhodium catalyst, but with (R)-BINAP then what we get is the chiral enamine of this kind with the absolute configuration of the asymmetric center being as shown here, which is opposite to what was observed here.

Now the same allylamine when it is reacted with the same rhodium catalyst, but now with (S)-BINAP as a chiral ligand then what we get is this type of chiral enamine. What it means that when we start with a prochiral allylamine of a specific geometry of the double bond and reacted with a particular rhodium catalyst with a (R)-BINAP we get a chiral enamine of certain absolute configuration.

And with the same allylamine when it is reacted with the rhodium catalyst having a BINAP of opposite configuration, then we get the chiral enamine of opposite configuration. So these type of chiral enamines have been utilized in the synthesis of a variety of important compounds, which are optically pure. And the optical purity has been found to be in the range of 90 to 99%.

As one can see that the R group here has a lot of scope. For example of this kind of allyls or phenyls and various kinds of substitutions can be utilized. So it is an easy method for converting a prochiral allylamine to chiral enamine using rhodium based catalyst and a BINAP based chiral ligands. **(Refer Slide Time: 20:00)**



Now this has been utilized in the synthesis of menthol by a company called Takasago who basically have used the process developed by Noyori. So in that process we start with beta-pinene which of course can be written up in this way also. And if we do the thermal cracking the way I have shown here the arrow, it breaks and it forms myrcene. This is what the myrcene is.

So you start with beta-pinene and heat it and get the myrcene and then butyllithium is used along with diethylamine. It stops at this particular stage. It does not undergo further polymerization or oligomerization. It stops at this particular place as you can imagine here that if suppose lithium plus comes in here, then of course, you have chelation like this.

Or the coordination of the lithium plus with this and the butyllithium that n-Bu minus takes a proton from the diethylamine and this diethylamine then attacks on to this and one can stop it at this stage because of the chelation between now nitrogen and the lithium plus and then that undergoes the formation of this diethyl geranylamine, which then in the presence of a catalyst, which is what is the different catalysts and undergoes isomerization in a catalytic asymmetric fashion.

And then we get enantiomeric purity which is almost like 100% enantiomerically pure molecule and we get the enamine, corresponding enamine, which is what is known as citronellal (R,E)-diethyleneamine or this is the correct IUPAC name of this particular molecule. So basically starting from beta- pinene one has come all the way to here where this particular asymmetric center is generated and then enamine is formed.

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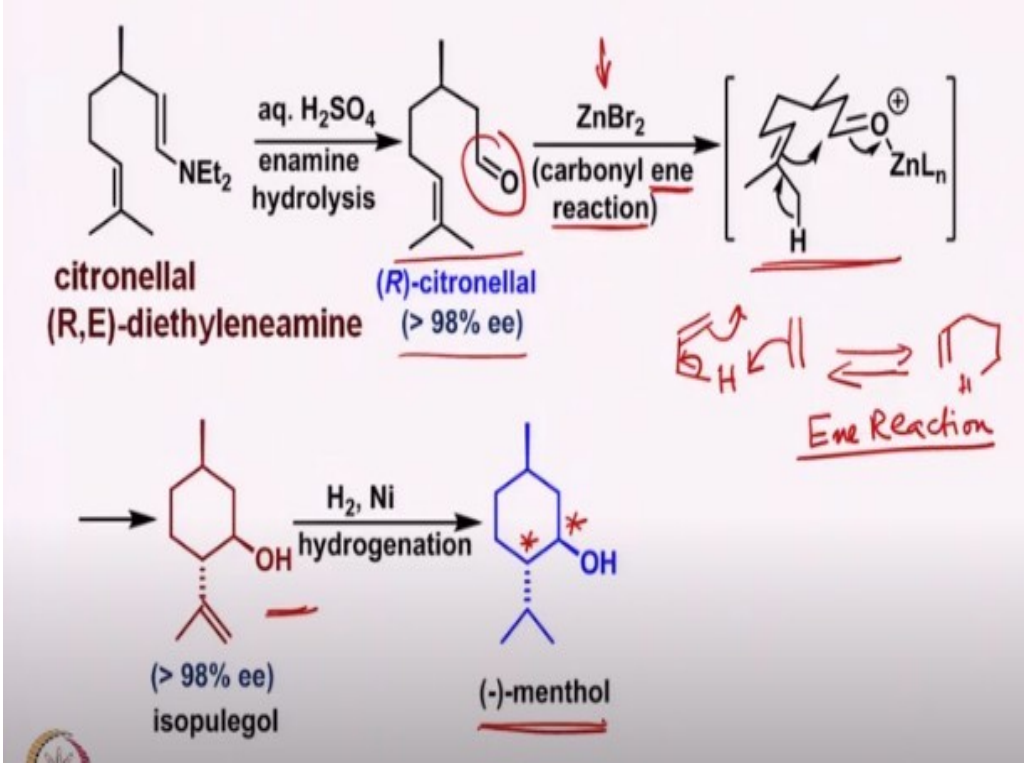

Now this particular enamine can be hydrolyzed and we can go to the corresponding optically pure which is more than 98% enantiomerically pure (R)-citronellal is formed, this is the aldehyde. And when zinc bromide is used, this undergoes what is known as carbonyl ene reaction. The ene reaction we will discuss later on more in detail.

But if suppose you have an ene and an olefin here like this, then of course, that undergoes upon heating or under some metal catalyzed reactions to form basically a molecule like this. So this is in equilibrium, this is called as ene reaction and that also can be done using an aldehyde which is what is known as carbonyl ene reaction.

And therefore, in the carbonyl ene reaction when a Lewis acid like zinc bromide is used, zinc bromide coordinates with the oxygen of the aldehyde and then we have this type of proton transfer and that leads to the formation of the corresponding alcohol. And this alcohol which has now a double bond because of this ene reaction can be hydrogenated.

And of course now during the process, we have basically formed menthol. So this is how the menthol's synthesis has been reported by Takasago Company in Japan where the reaction or the process has been borrowed from the work of Noyori.

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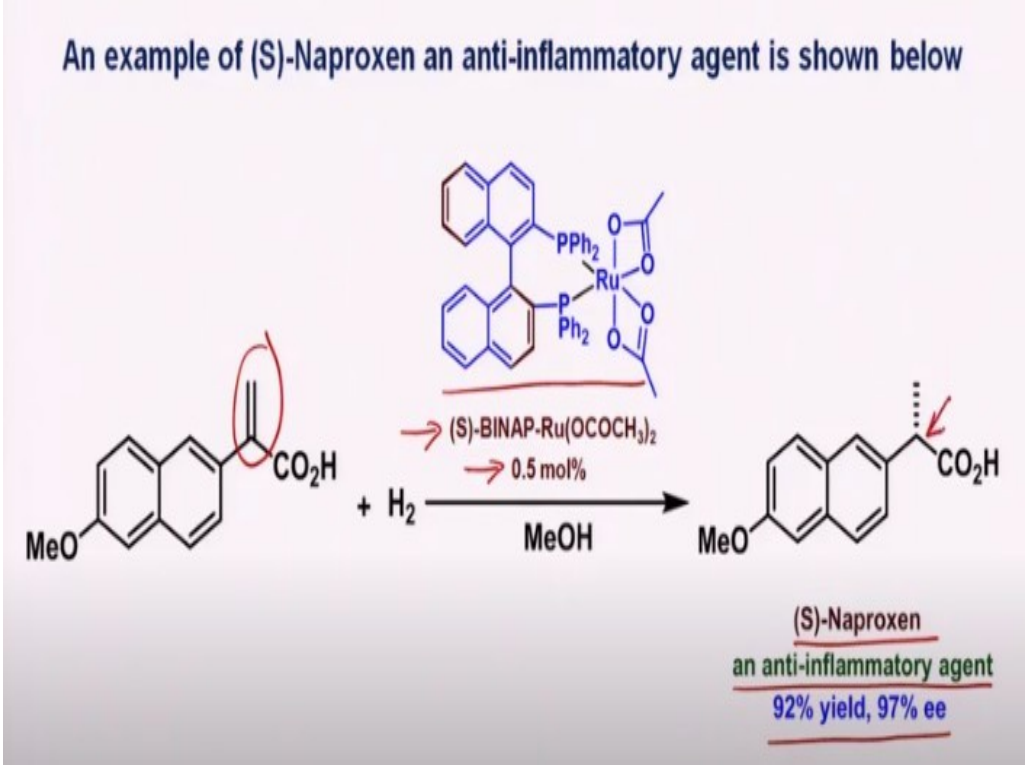

Now another non-enamide or non-acylamino based chemistry is the synthesis of (S)-Naproxen, which is an anti-inflammatory agent which is formed in 97% enantiomeric purity and 92% yield where this particular kind of ruthenium complex was used by Noyori, where only 0.5 mol% of this was used. And that led to the hydrogenation of this by using this (S)-BINAP based ruthenium complex and that led to (S)-Naproxen in a high enantiomeric purity.

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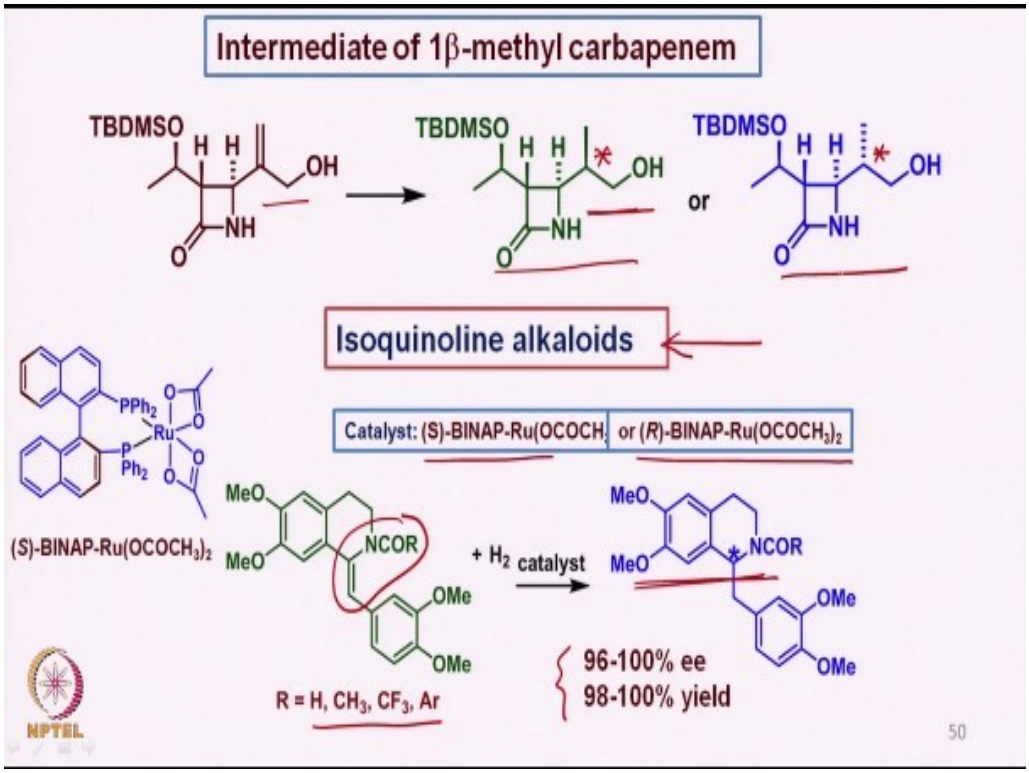

Likewise these BINAP based catalyst this or this have been used for the conversion of this allylic alcohol to this particular saturated alcohol or this saturated alcohol they are enantiomers of each other. So any one of them can be made depending on which one one uses, either (S)-BINAP or (R)-BINAP. And likewise this type of double bond also can be hydrogenated and yields.

And enantiomeric purity are as high as 96 to 100% and 98 to 100% with different types of substituents that have been found. So these alkaloids of isoquinoline type of alkaloids, which are very useful can also be synthesized and then this carbapenem antibiotic type of molecules can also be prepared in optically pure form.

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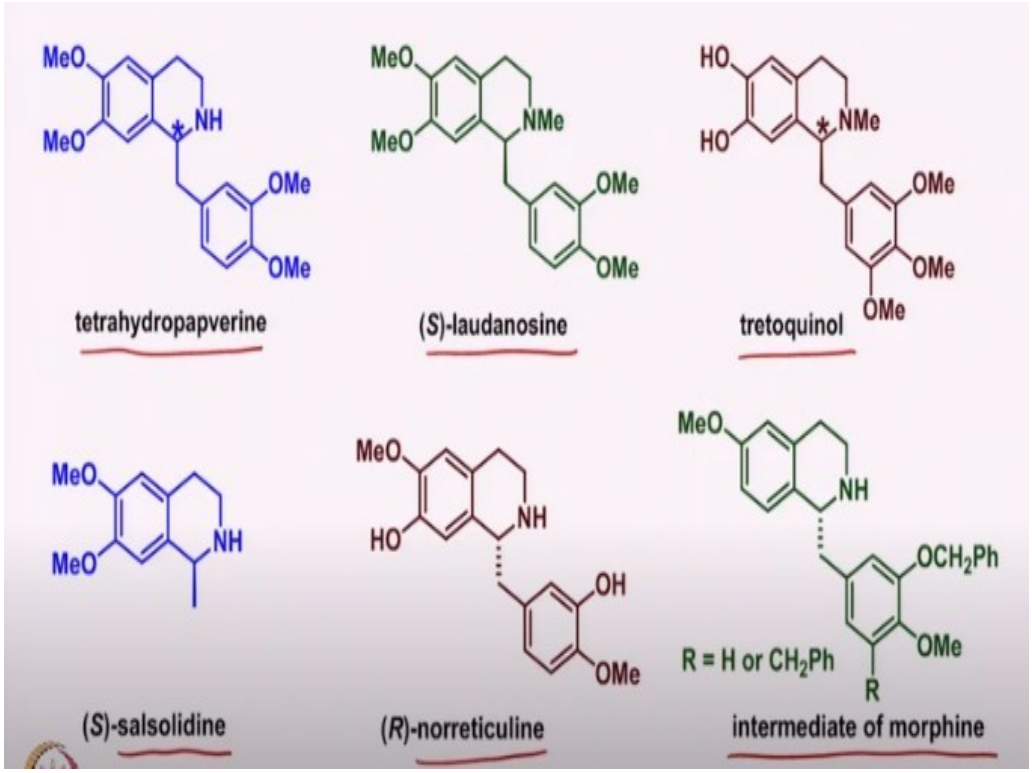

As one can see that different **tetra** this isoquinoline type alkaloid tetrahydropapverine, laudanosine, tretoquinol or salsolidine, norreticuline or morphine type of molecules intermediates, they all have been synthesized by the work of Noyori's hydrogenation reactions using the catalyst based on BINAP.

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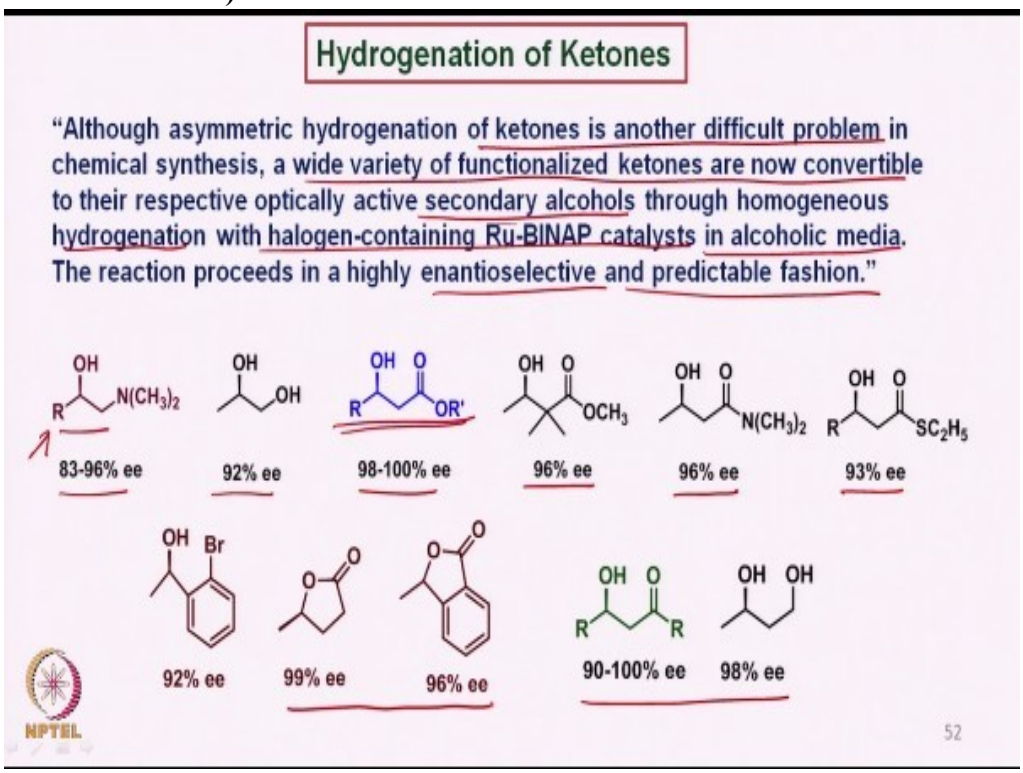

Now this ruthenium BINAP catalyst also has been used for the synthesis of different types of ketones. So although asymmetric hydrogenation of ketones is another difficult problem in chemical synthesis, a wide variety of functionalized ketones are now convertible to the respective secondary alcohols through homogeneous hydrogenation with halogen containing ruthenium BINAP catalyst in alcohol media.

The reaction proceeds in high enantioselective and predictable fashion. This is what is important and as I have shown here, different types of molecules as you can see depending on R enantiomeric purity between 83 to 96% such as this 92% here and if this kind of molecule is to be obtained, the enantiomeric ratios range from 90 to 100%, for example 96% .

96%, 93% and of course different types of other molecules in which one can get the enantiomeric purity as high as 90 to 100% or 98%. And the reactions can be used for the preparation of this kind of lactones also.

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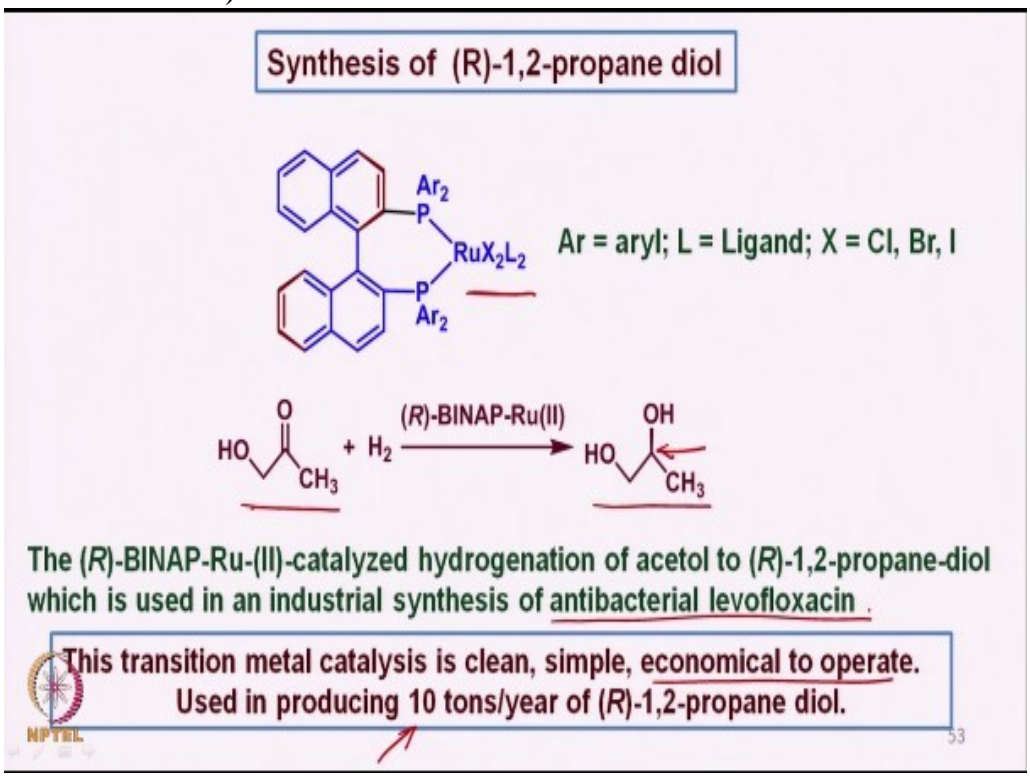

Now this particular hydroxy ketone which is again a prochiral ketone and this particular ruthenium complex has been utilized in the synthesis of this 1,2-propane-diol having R configuration here. Now this particular molecule is very useful to prepare using this protocol and economically it is easy to operate and its preparation has been shown to be useful for producing 10 tons of such a molecule per year by using these catalysts.

And therefore, it is very commendable that such a reaction can be done on a catalytic fashion. And this is basically an intermediate for the synthesis of antibacterial levofloxacin and therefore, it is of high commercial utility.

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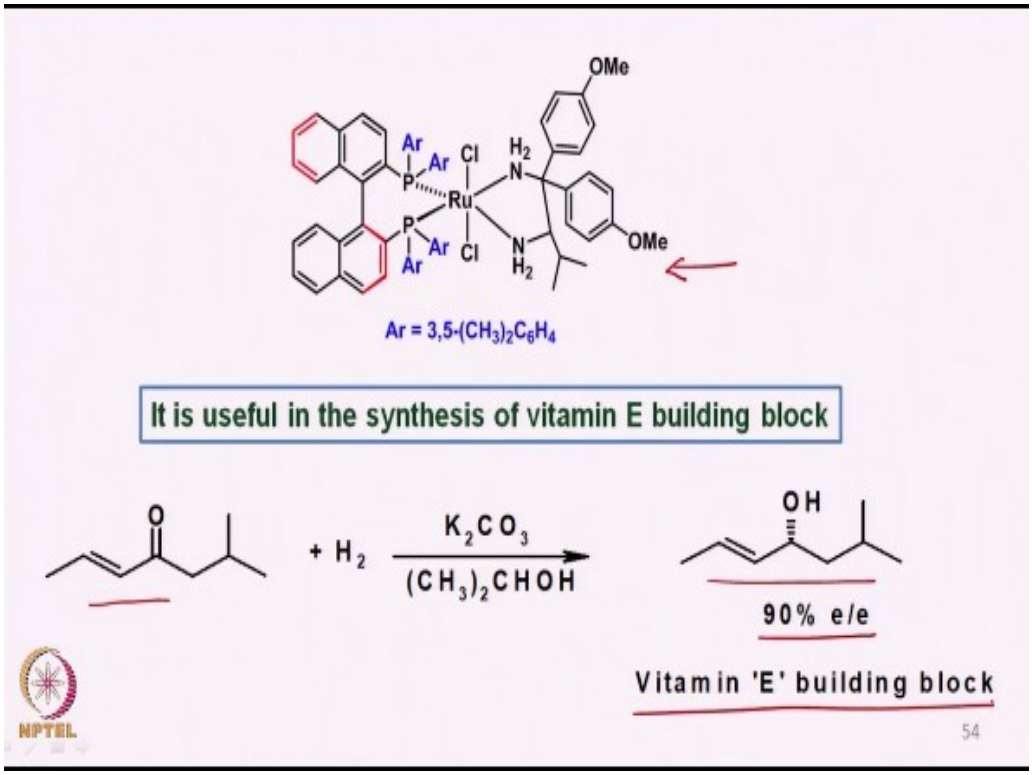

Now this particular molecule has also been used as a catalyst in the hydrogenation of this enone to the corresponding allylic alcohol and as you can see that it is not a hydrogenation of a double bond, but it is a reduction of the ketone and it gives the corresponding allylic alcohol in 90% enantiomeric purity, which is a building block for the synthesis of vitamin E.

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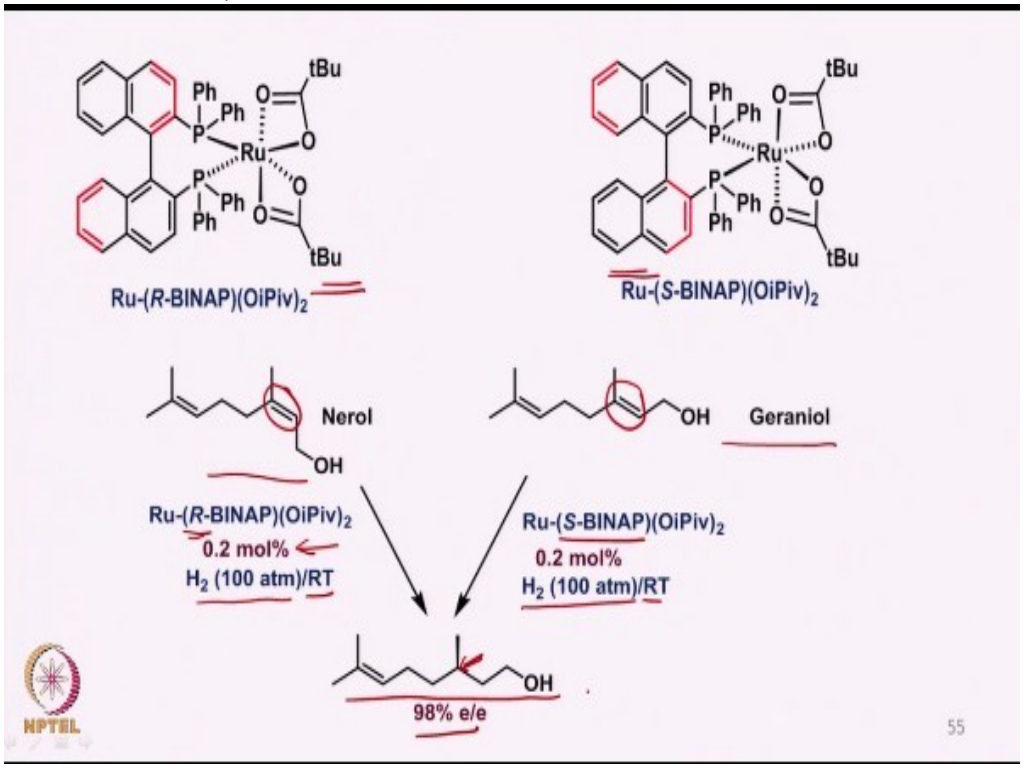

Likewise, nerol and geraniol can be converted into the corresponding alcohol where there is a hydrogenation of the allylic alcohol part and using these types of ruthenium catalysts. As we can see that only 0.2 mol% of the catalyst has to be used with the hydrogen at 100 atmosphere pressure at room temperature. And if we start with this and use (R)-BINAP we get this molecule.

And the same molecule can be obtained by inverting the geometry of the double bond from nerol to geraniol and use (S)-BINAP and we get the same molecule with same enantiomeric purity and same configuration. And therefore, both nerol and geraniols can be converted to this using different (R)-BINAPs or (S)-BINAP type of thing.

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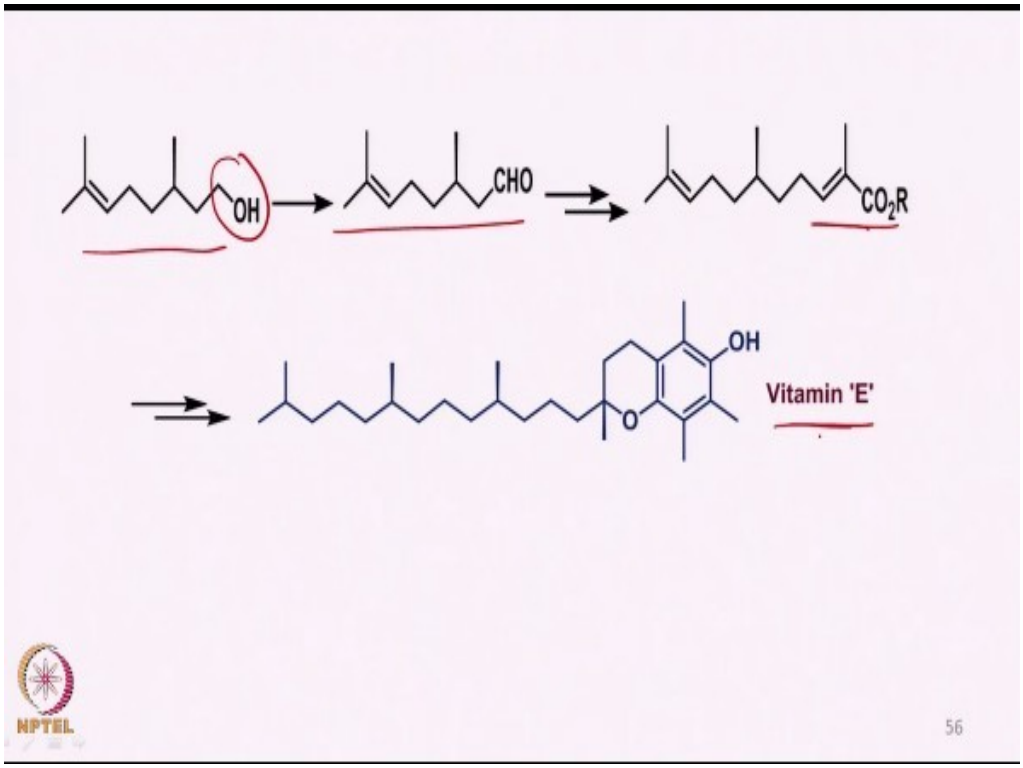

And this particular molecule has also been utilized in the synthesis of vitamin E via this oxidation of the CH2OH to the corresponding aldehyde followed by Wittig reaction and a few more steps to go to vitamin E. So these are the various applications and utility of the hydrogenation reactions and reductions of ketones that have been developed by using rhodium and ruthenium based catalysts and BINAP ligands as chiral ligands and also some other ligands developed by Knowles.

And therefore, the work was given the Nobel Prize. So we will stop it at this stage today and take up some other aspects of asymmetric reduction next time. Till then you can study these things which are told today and look at it and generate questions which you can ask me later on when there is a live interaction or post me whenever it is needed. Till then, bye and thank you.