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

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Lecture - 34
Asymmetric Synthesis: An Introduction

Hello everyone. I welcome you all for today's lecture. What we did last time, we would look at it in very brief.

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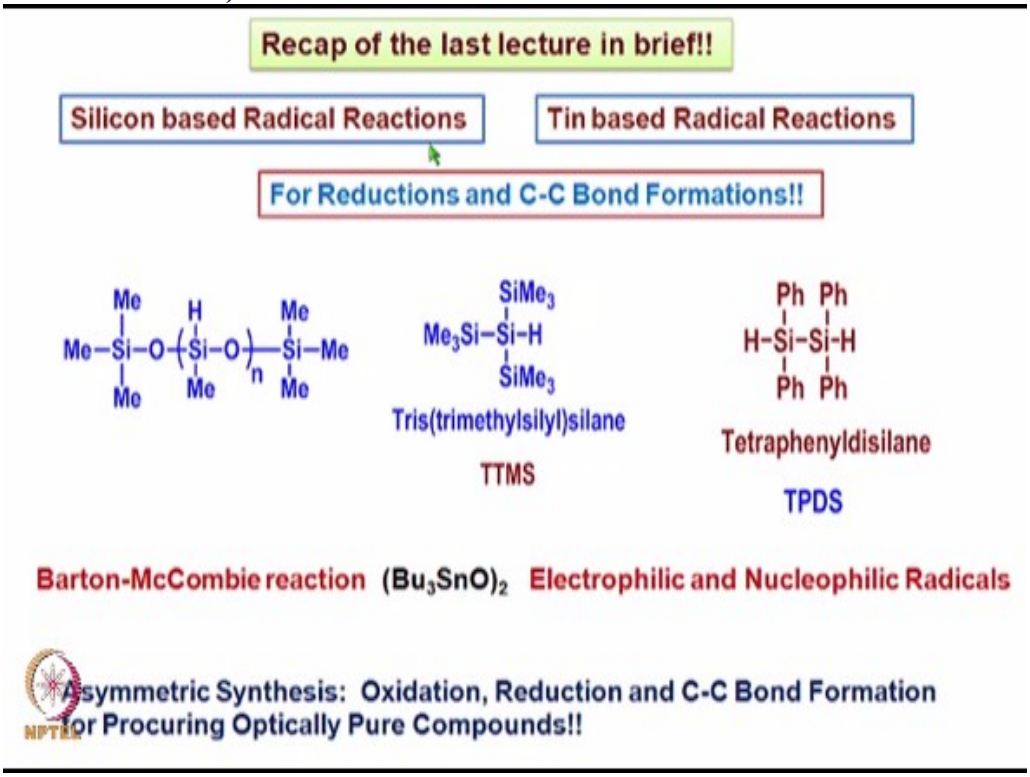

We discussed the various aspects of tin based chemistry and also silicon based chemistry, particularly for reductions and C-C bond formation utilizing radical mediated reactions. Of course, we used the PMHS, which is polymethylhydrosiloxane. Then of course tris(trimethylsilyl)silane TTMS and tetraphenyldisilane that is TPDS in various kinds of reactions.

And we saw how they can be substituted in place of the tributyltin hydride. Then we also looked at the Barton-McCombie reaction. And we also discussed the utility of catalytic amounts of tributyltin oxide using n-butanol as a solvent and of course phenylthionocarbonate based substrates.

Then we looked at the reactivity of various kinds of electrophilic and nucleophilic radicals and we compared them that how they could be utilized in different ways. Now we will now look at the asymmetric synthesis, where we will be taking examples from oxidation reduction and C-C

bond formation to procure optically pure compounds and various aspects of these can be very much useful in organic synthesis.

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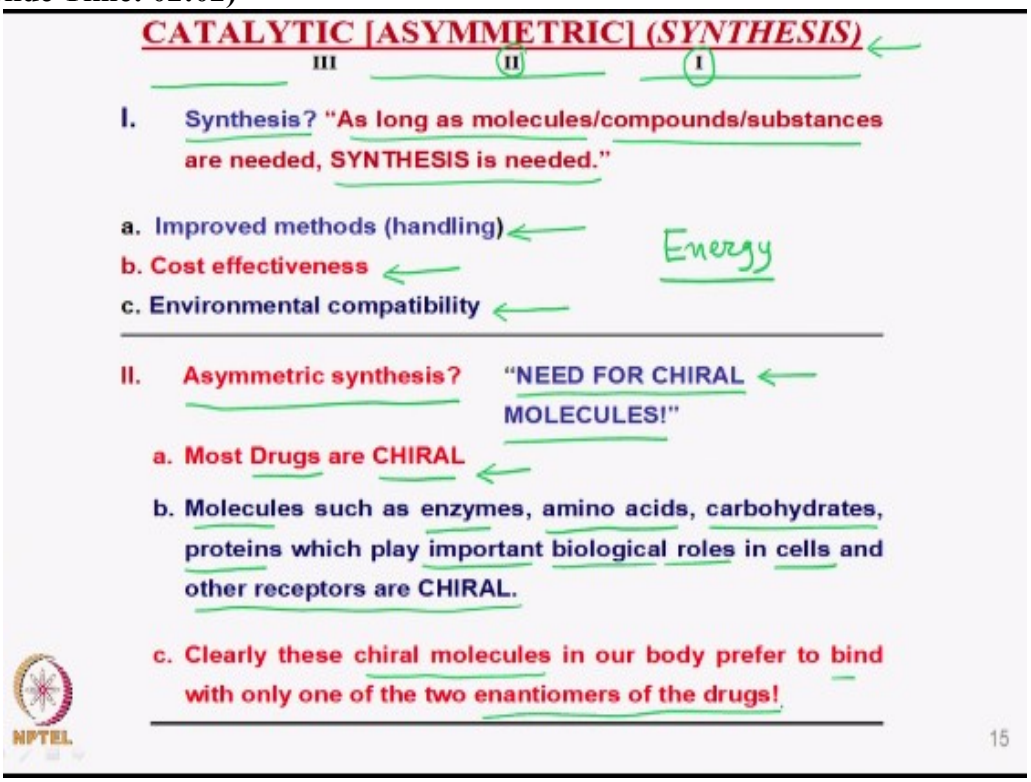

So we have the catalytic asymmetric synthesis as eventually the final goal. First and foremost is that we need synthesis to be done. Now why do we need synthesis?

As long as a molecule is required, as long as molecules, compounds, substances are needed for different purposes for whatever for as drugs or as materials or for any other purpose or food matter, whatever substances or molecules or compounds have to be made, and if they are not naturally available, then of course synthesis is needed. Now when we carry out the synthesis, the improved methods have to be developed.

There has to be a continuous effort or approaches to improve methodologies to make those molecules for which synthesis is needed. And therefore, this is a continuous process of improvisation of methodologies to get the molecules. At the same time the cost of the process is important because that will affect the price of the product.

So we also have to introduce methodologies or improvisations have to be done, which are also cost effective. At the same time, the process which requires handling of different reagents and solvents and byproducts which are formed they all have to be entirely environmental compatibility. Of course, we also have to worry about the energy aspect of it.

That means, if the reaction requires too much of energy, either at high temperature or at low temperature would also affect the cost and the entire process could be little more difficult to carry out. So this is regarding the synthesis part of it. This is how I have written here as 1 and the

second thing is that, it should be asymmetric. That means, we need the molecules as chiral molecules.

Obviously, if there is no chirality in the molecule, then we need not worry. But many of the molecules which are important, especially as drugs are chiral, and therefore it is very important that worry about the asymmetric synthesis that is the synthesis leading to chiral molecules, chiral means optically pure molecules.

Now the most drugs are chirals. Molecules such as enzymes, amino acids, carbohydrates, proteins, they all play very important biological roles in our body, in cells and all other receptors are also chiral. Because we have hormones, we have proteins, we have lipids, we have carbohydrates, obviously, all of them are basically optically active, optically pure and therefore, we need optically active molecules as drugs.

So the point is that such chiral molecules which are biological, which play biological roles prefer to bind with only one of the two enantiomers of the drugs and therefore, it is very important that these molecules have to be synthesized in optically pure form as high optical purity as possible. Now if one looks at the history of the asymmetric synthesis, one of the first things that comes on into the mind is thalidomide.

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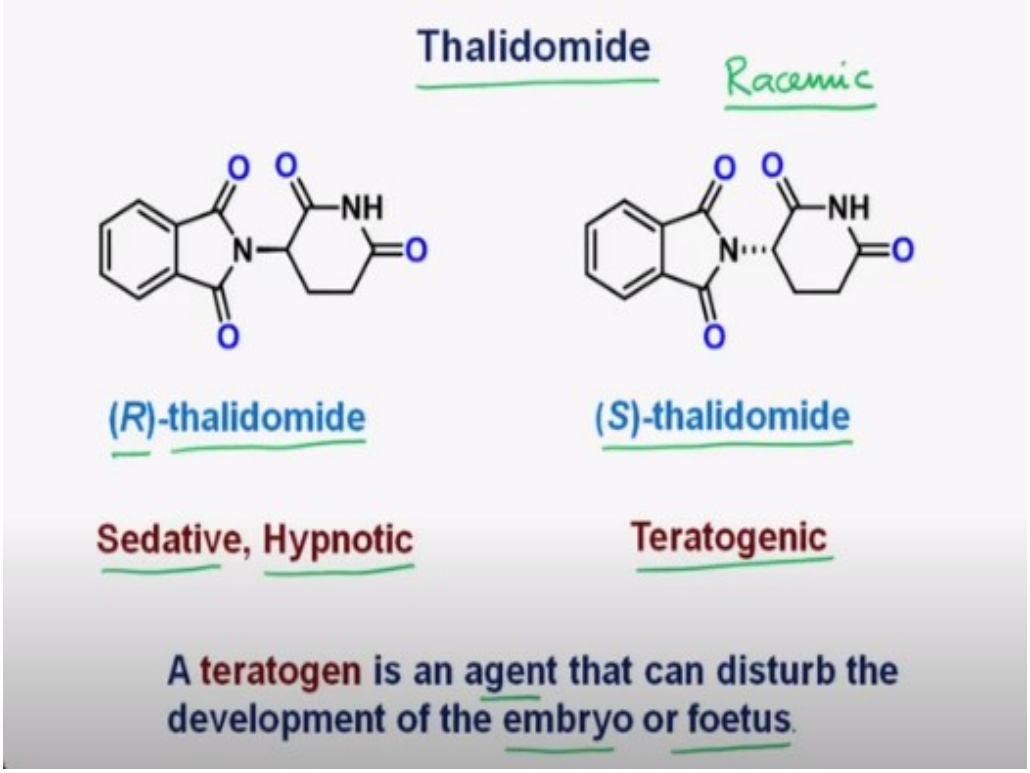

Thalidomide was having problems when it was introduced. When it was first introduced, it was introduced as racemic molecule. And it was later on found out that only (R)-thalidomide is sedative or hypnotic, which is what used to be given to the ladies who were pregnant, and who had morning sickness. And in order to avoid the morning sickness, this thalidomide was given.

And since it was a racemic, thalidomide it also had the other enantiomer, which is (S)-thalidomide, which was found to be teratogenic. And teratogen is basically an agent that disturbs the embryo or the foetus.

And that is how, when the thalidomide tragedy took place, in the late 50s, or early 60s, it was that the children who were born to the mothers who took thalidomide as a drug, many of them would, were found to have various kinds of deformities, because the embryo or the foetus was affected by this particular enantiomer.

So it is very important that the drugs need to be looked at very carefully, from the point of view that which particular enantiomer is useful and which is not. We can also see many other examples in which one enantiomer behaves differently than the other.

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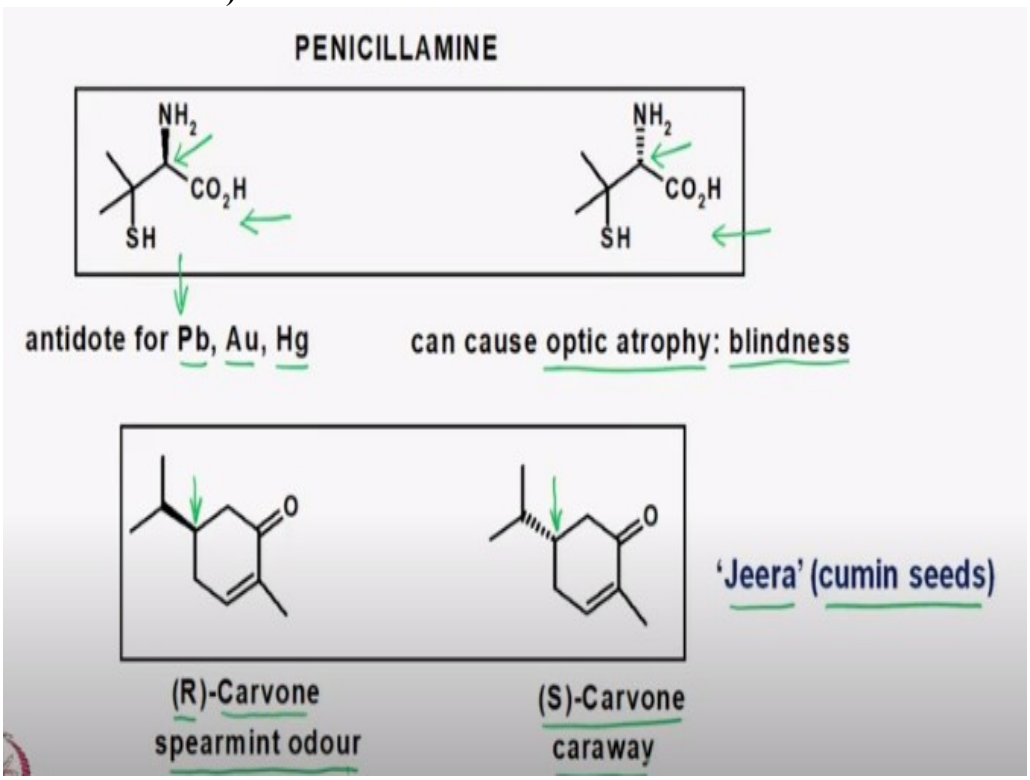

For example, this penicillamine here, as it is shown here has one asymmetric center and this is its enantiomer. So this particular enantiomer which is shown here is an antidote for lead, gold and mercury poisoning. On the other hand, this other enantiomer can cause optic atrophy, atrophy that is blindness. So we can see that if one takes racemic drug, obviously you have 50% of this as a drug, which is not useful.

In a similar fashion, for example if we take carvone molecule if this is having one asymmetric center here, and its enantiomer is this one. So if we look at (R)-Carvone, this particular carvone, it has spearmint odour. It is having a particular mint type of odour. On the other hand, if we take the (S)-Carvone it has cumin seeds, which is called in Hindi, jeera or caraway type of flavour.

So you see the flavour or the odour becomes different if the two enantiomers are taken. So it is in order to have a proper odour, we have to take only one enantiomer.

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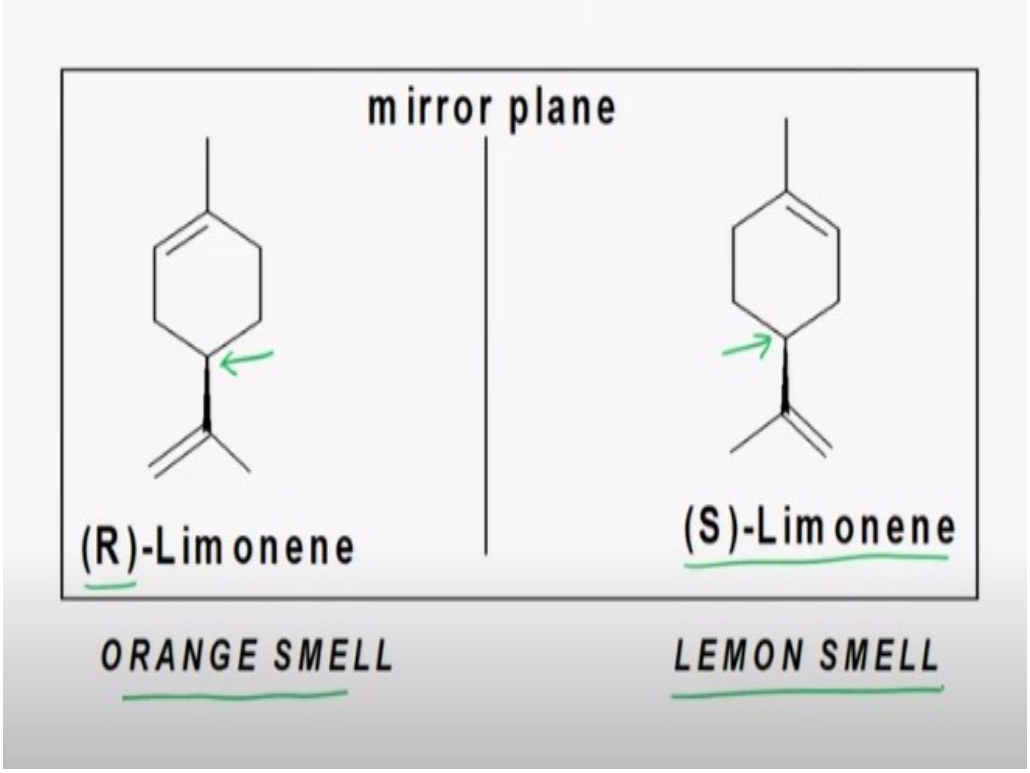

Similarly you have limonene which is what having this asymmetric center and there is a mirror plane and then this is the mirror image. So this is an (S)-limonene and this is (R)-limonene. Then we can see that the (R)-limonene has orange smell, whereas, the (S)-limonene has lemon smell. So you have odour, you have smell.

All these things or the flavor, they are different, because our receptors are also made up of optically active substances. So different optically active molecules or the enantiomers behave differently to the receptor and react differently and accordingly the effects are felt.

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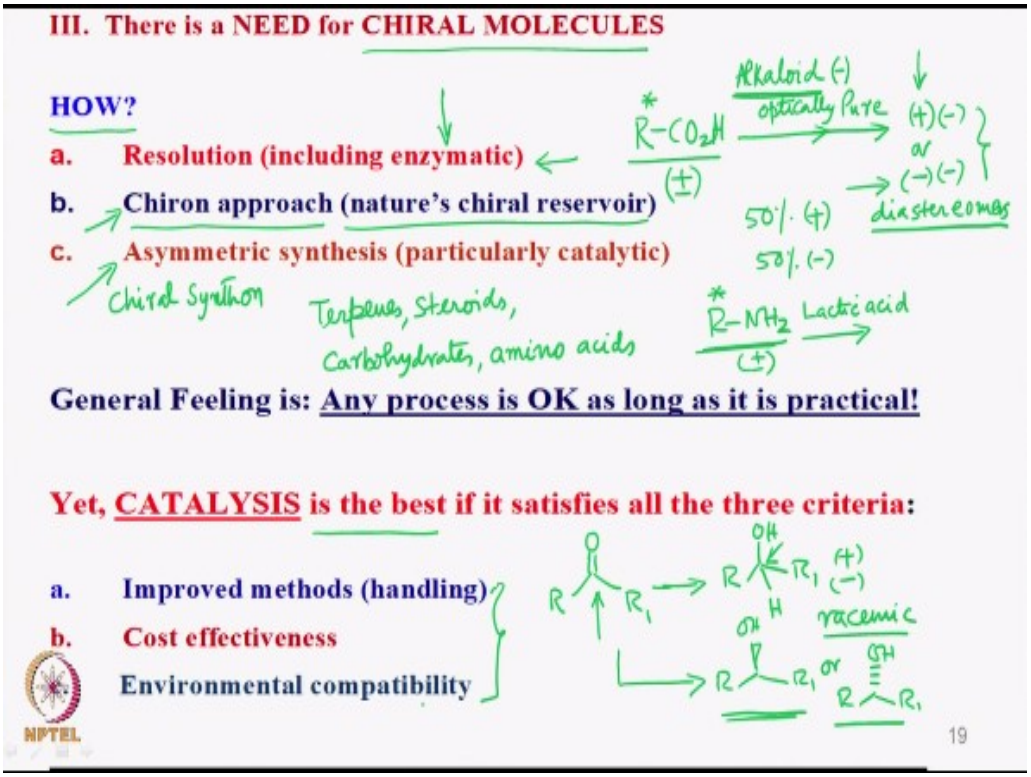

There is a need for chiral molecules. Obviously, as we discussed, there is a need. Now how do we carry out and how do we do the preparation or synthesis or making of such chiral molecules.

It is understood over a period of time that if you have to carry out the synthesis of a very important drug molecule or any other molecule of interest, which involves several steps, and it is better that the chirality is introduced as early as possible in the synthesis so that we do not generate too many diastereomers later on.

What I mean is that suppose if a molecule contains three asymmetric centers, so the first one has to be 100% optically pure to start with, so that we can keep on getting better diastereoselectivity as we proceed further. Of course, we have to choose the reactions accordingly. Now there are several ways, I have shown here three ways is that how you could do the preparation of these optically active molecules.

One of the ways is to do the resolution. That means if we have say an acid, which has an asymmetric center here and there is a carboxylic acid and if this particular molecule is available as racemic, then we use an optically active base so you have an alkaloid, naturally occurring alkaloid or any other molecule, which has a kind of basic character with nitrogen.

And if this is optically pure, then of course, we can then carry out what is called as chemical optical resolution. So if we can resolve it, so one can get plus or minus as a salt, this is an acid and alkaloid is a base. So we can get this as a salt in which say for example, if the chirality of this is minus, so you have plus and minus and this and minus minus these are the two diastereomers.

And they can be separated by say for example recrystallizations and then eventually, you can sort of purify in such a way that the alkaloid can be taken off and then the plus acid or the minus acid can be separated. So we can start with a racemic acid and do the chemical resolution and get 50% of the plus and 50% of the minus enantiomer.

Likewise, one can also do that we can take say you have an R-amine, you have an amine here and now it is basic and this has an asymmetric center, but this is available as racemic and then you can use say you have a optically active acid, any other like for example, lactic acid, which is available as optically pure. Then we can do the similar type of resolution, because that they will give the salt which can then be resolved.

And we can get the amine as 50% plus and 50% minus separated out. We can also do that via enzymes and there are ways of doing enzymatic resolutions also. So there are different enzymes which are available. Now there is something called as chiron approach. We can, so once we have got this particular say amine or acid or any such molecules in optically pure form then we can carry out a synthesis.

The second one is called chiron approach or chiron approach whichever we use the chiral nature of the molecule which is available from nature. For example, there are different types of terpenes, there are different types of steroids; terpenes, steroids or you have alkaloids or say acids like for example tartaric acid, lactic acid or many different types of acids, amines or some hydrocarbons, which are small in size and have one or two asymmetric centers, carbohydrates or amino acids.

So one can have a large number of such optically active molecules and from there we can prepare what is called as chiral synthon. So chiral synthon means chiral synthetic intermediate. So you have chiral synthon, which means that you convert any one of these optically active naturally occurring small molecules and convert that into a synthetic intermediate or an intermediate which could have multiple reactivity.

So this is how one does make use of what is called as chiron approach or chiral synthon approach. The third possibility is of course, asymmetric synthesis. What asymmetric synthesis means is that if we have a prochiral say compound, so you have a say you have R and R 1. So this particular carbon is a prochiral carbon. And if we carry out say reduction or C-C bond information at this stage, so we can introduce the chirality into it.

And once we suppose you have H here, then this is known asymmetric molecule, it can exist in both the forms plus or minus. So if we do not have a proper procedure, we would get the reduction in leading to a racemic molecule. But we cannot proceed with racemic molecule and therefore, the reduction needs to be giving a particular enantiomer say for example, this enantiomer we want and or this enantiomer we want.

So if our procedure or our method is that this or this is formed in 100% optical pure form then of course, we mean that we have a nice asymmetric synthesis of converting a prochiral compound into an optically pure form. In this case, there are several ways by which one can do and the problem is that if it is not a catalytic version, then it turns out to be very expensive.

So catalysis is the best way of carrying out this kind of conversion where prochiral compound is converted to optically pure form. It helps in meeting all the requirements that we can think about it. It has to be. One has to aim at meeting the requirements of improved methods handling cost effective environmental compatibility, and as I said the energy also.

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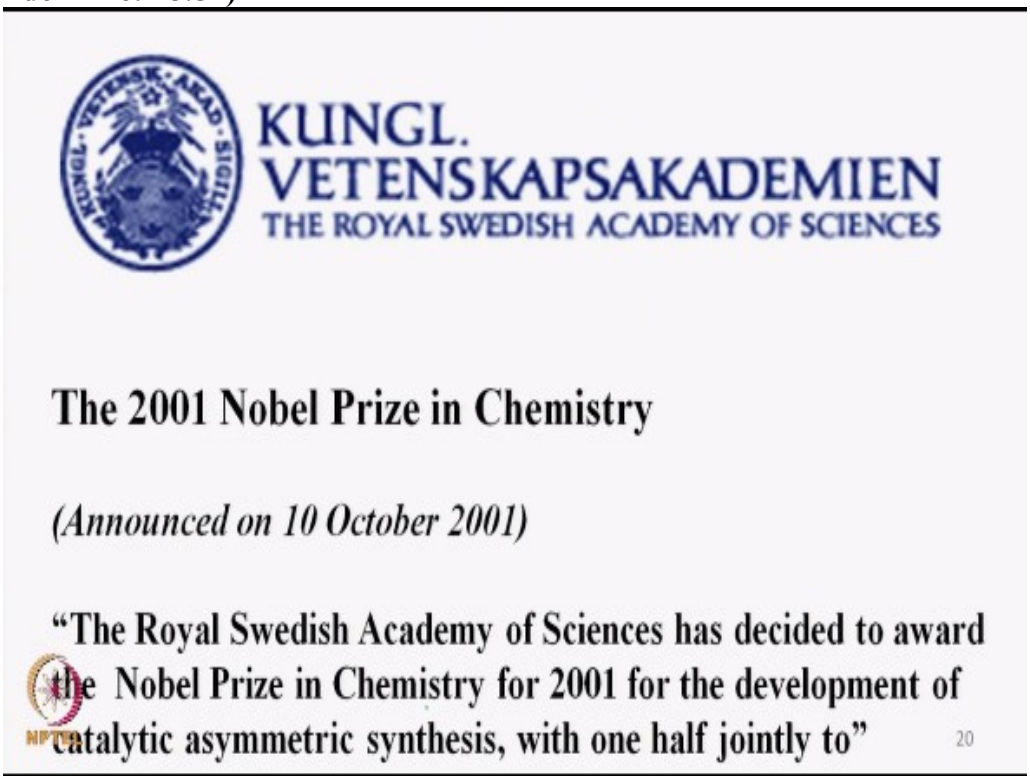

So one can now look at with this background, the Nobel Prize which was given in 2001 for the development of catalytic asymmetric synthesis. So these reactions or the asymmetric synthesis is basically known for a long time.

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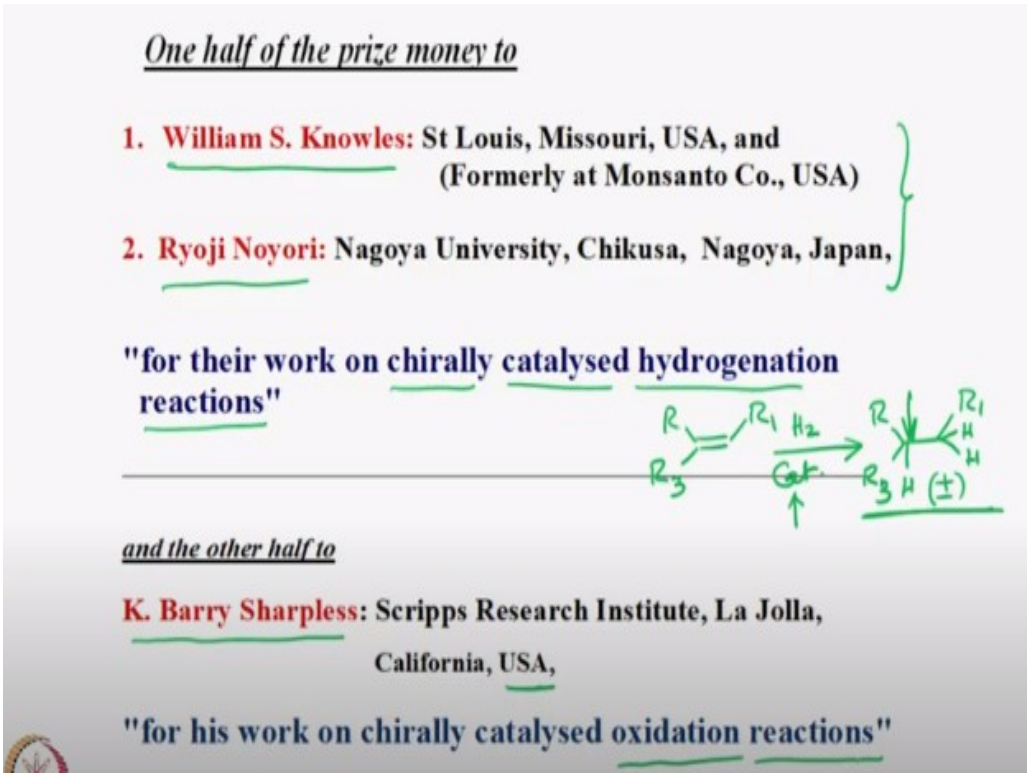

And it was first given, the one half of the prize money was given to William S. Knowles from United States and Ryoji Noyori from Japan for their work on chirally catalyzed hydrogenation reactions. So you have say you have a molecule like this and you have a substituent on this in such a way that it could lead to the formation of a molecule like this here. And of course, you will have two hydrogens here.

So this is the carbon which is now getting an asymmetric center. So this is a prochiral double bond and if we do hydrogenation and you have to use a catalyst. And if this hydrogenation is used in such a way that it does not have any possibility of inducing asymmetry. That means, if there is no chiral handle, so it will give a racemic molecule.

But if we have the catalyst in such a way that that allows only either the plus or the minus enantiomer to be formed in the major amount then of course, it is called as chiral catalyzed or chirally catalyzed or asymmetric hydrogenation reaction. So these two gentlemen, they shared the Nobel Prize for developing the chiral hydrogenation reaction.

The other half was given to K. Barry Sharpless also from United States for his work on chirally catalyzed oxidation reactions. So these people got for the reduction and he got for the oxidation reactions of type, which are extremely popular and useful in organic synthesis.

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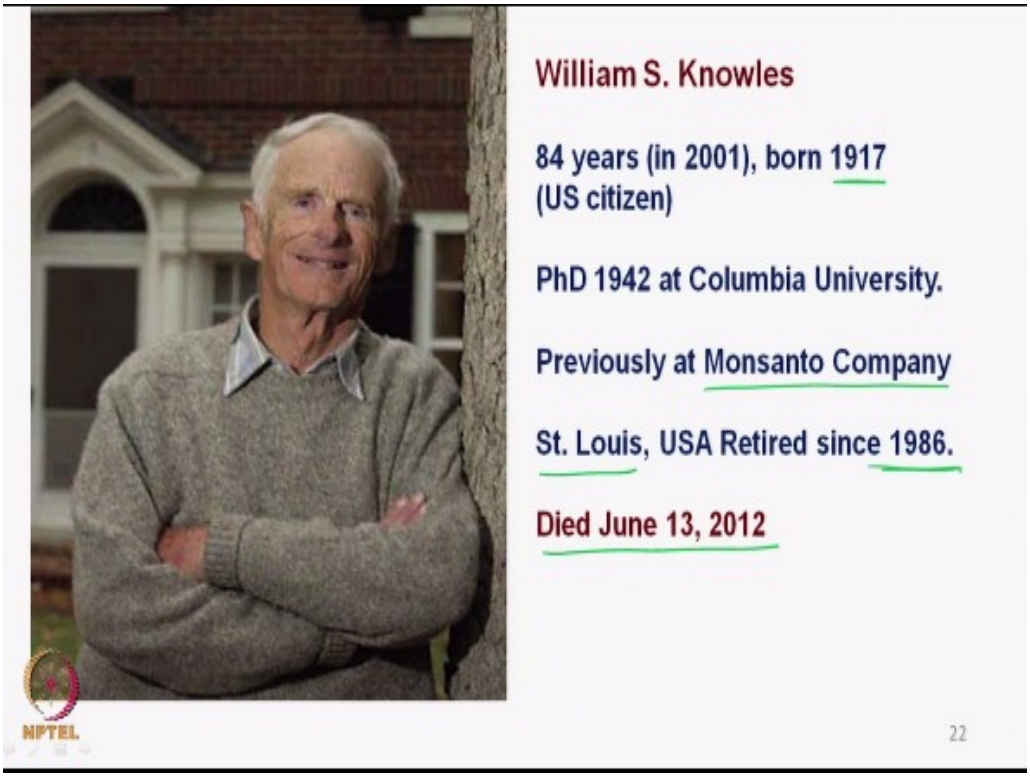

This is the William Knowles, who was born in 1917. And he got the Nobel Prize in 2001, as you can see and he passed away in June 13, 2012. It is interesting to see that after his PhD he was working in a company, a Monsanto company and of course, retired from 1986.

It indicates that you can also work in a chemical company and carry out research which is of very use to the mankind and also be recognized as William Knowles was recognized for his work on catalytic hydrogenation.

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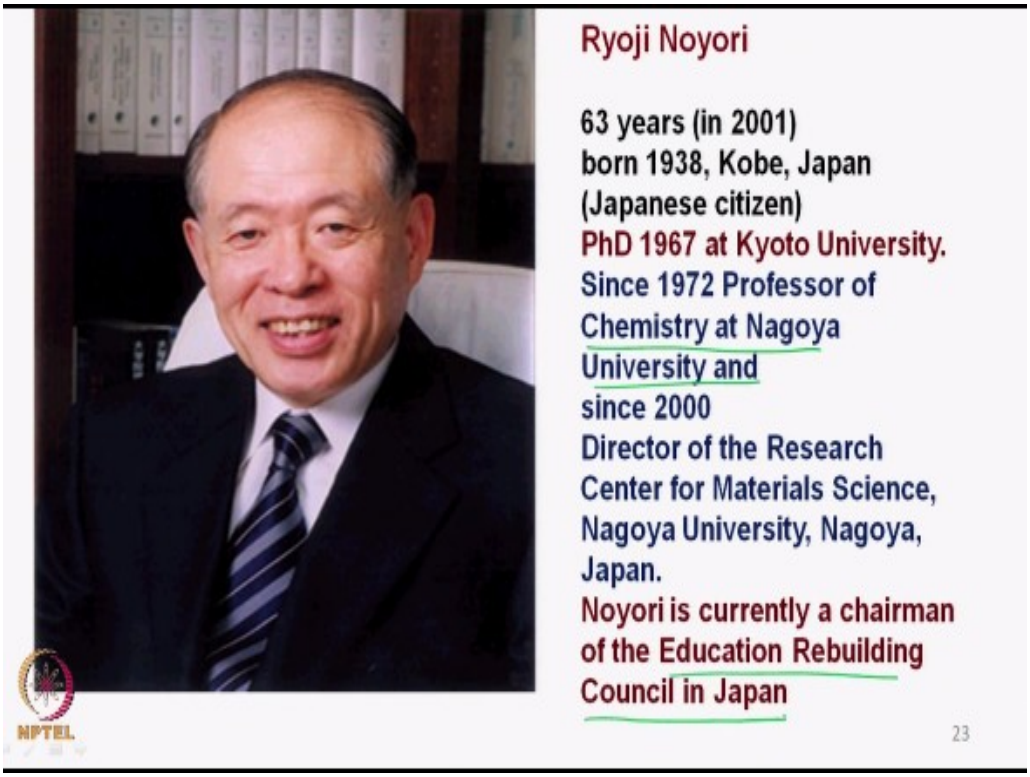

Noyori was a professor at Japan in Nagoya University here. And of course he has done lot of work not only on this hydrogenation reaction, but a large number of different reduction. And he is chairman of the education rebuilding Council in Japan.

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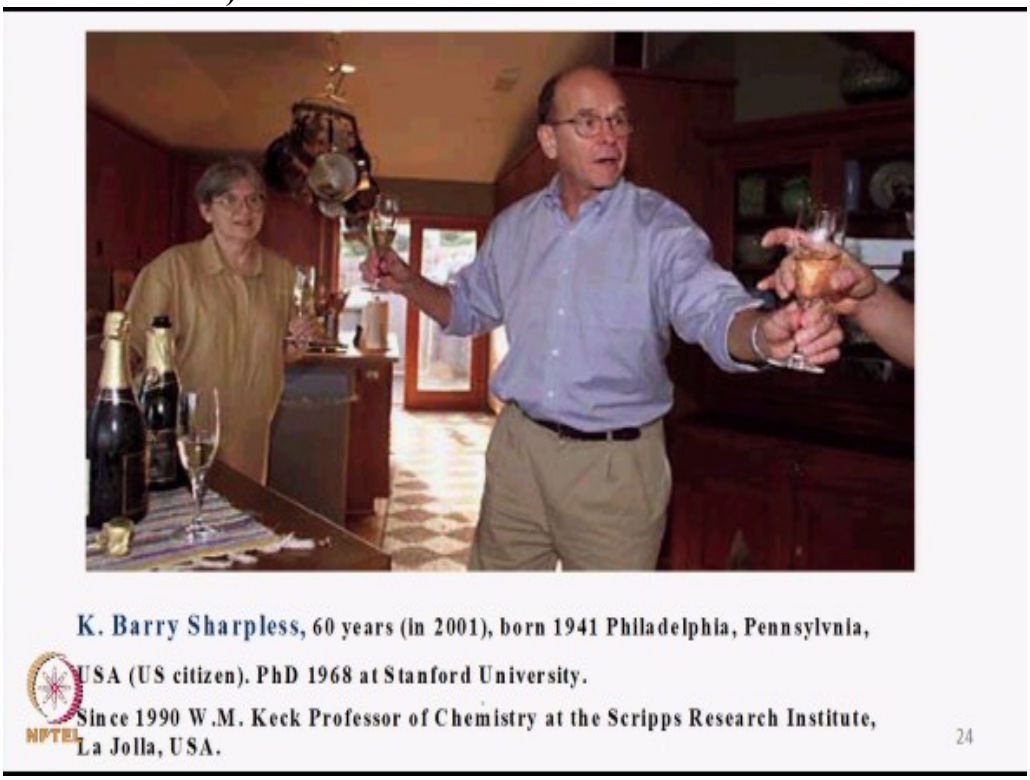

And Sharpless was at Stanford University. He did PhD at Stanford University and now he is at the Scripps Research Institute in United States in San Diego. So he did a lot of work on the oxidation reactions.

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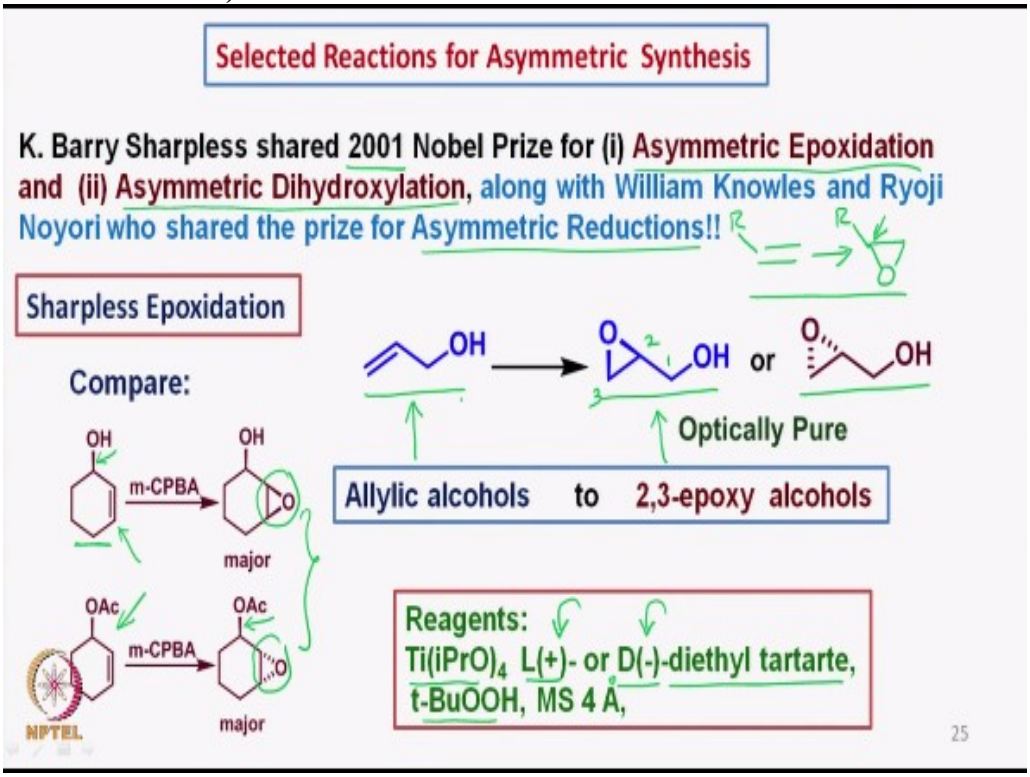

So we would look at it one of the first reactions or a few selected reactions of asymmetric synthesis. As I said that Sharpless shared the 2001 Nobel Prize for asymmetric epoxidation and asymmetric dihydroxylation along with Knowles and Ryoji who did the reactions of asymmetric reduction type. So what is Sharpless epoxidation?

If we look at the epoxidation reactions, normally what we consider is that we take a double bond and then we use any para acid and of course, we get the corresponding epoxide. If we have a possibility of say, you have an R group here, then of course we have R group here. So this particular center becomes an asymmetric center.

So if we have the possibility of epoxidizing such olefins to epoxides, then we can have a very easy possibility of getting this epoxide as optically active molecule at the beginning of the synthesis on a very large scale. What Sharpless did was the epoxidation of allylic alcohols to this epoxy alcohols, 2.3-epoxy alcohol. So you have allylic alcohols and these are 2,3-epoxy alcohols here.

So you have 1, 2, 3. So this is how 2,3-epoxy alcohols are formed. So if we start with a prochiral allylic alcohol, we have a possibility of getting two different types of epoxides. And what Sharpless has done is to develop a method where simple allylic alcohols can be oxidized to the corresponding epoxy alcohols with reagents like titanium, isopropoxide L+ or D- diethyl tartarate, tertiary-butylhydroperoxide in the presence of molecular sieve's, which is 4 angstrom.

Now this protocol or this combination of reagents allows epoxidation to take place in such a way that the two different epoxy alcohols can be obtained by the choice of which L+ or D- which diethyl tartarate is used for the reaction. It can be compared to some extent by the fact that if you take a simple allylic alcohol like this, which has a beta OH configuration then epoxidation takes place from the beta side.

And this is because of the meta-chloroperoxybenzoic acid has a hydrogen bonding with the hydrogen of the OH, that is how it happens. On the other hand, if we do not have that hydrogen present and we carry out the epoxidation with meta-chloroperoxybenzoic acid then it is the steric factor, which allows the oxidation to take place on the opposite side of the acetate configuration.

So these are just some diastereoselective epoxidations. But for that you need the molecules to be optically pure. But the Sharpless has developed this method of getting these epoxy alcohols with predictable geometry starting from prochiral allylic alcohols. So we will stop it today at this stage and we will take up in the next class, how this Sharpless epoxidation can actually be carried out, what exactly is the mechanism.

And once we have got these epoxy alcohols as optically pure molecules, what is the use of it and how these molecules can be utilized for further synthetic transformation. So we will see you next time. Thank you and bye.