Principle of Organic synthesis
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Lecture 25
Reagents Containing Phosphorus

Welcome you all to principals of organic synthesis. So far, we have studied C-C and C-N bond formation of aliphatic substrates, organometallic reagents, electrophilic/nucleophilic aromatic substitutions, reactions of diazonium salts and molecular rearrangements.

In this lecture, we will study the reagents containing phosphorus, which is a new chemistry. Reagents containing phosphorus are important molecules, which find broad utilities not only in organic chemistry, they also have broad applications in agriculture, medicinal and material sciences.

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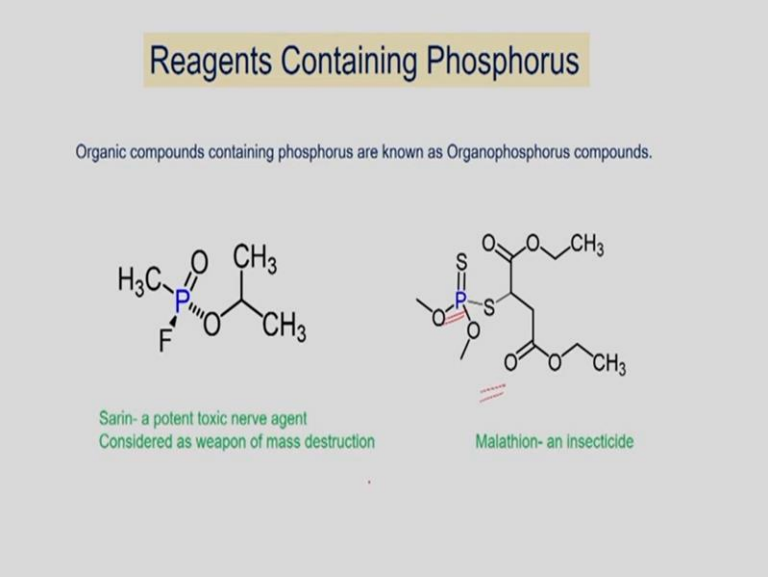

For example, the first compound is a potent toxic nerve agent and considered as weapon of mass destruction, while the second compound is used as an insecticide in agricultural science. We also use the second compound to kill mosquitoes.

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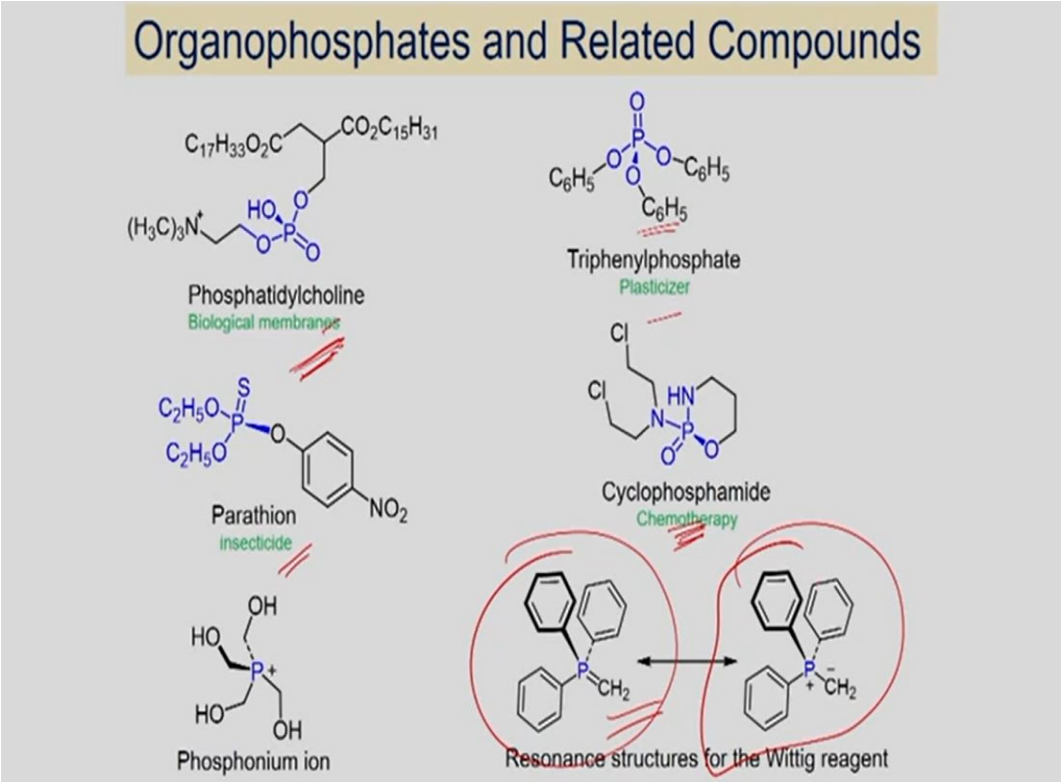

Here are some organophosphates and related compounds that are important in medicinal, biological, agricultural and chemical sciences. Phosphatidylcholine is the biological membrane, triphenylphosphate is the plasticizer, parathion is the insecticide and cyclophosphamide is used in chemotherapy, while ylide and phosphonium ion are utilized in organic synthesis.

In this lecture. we will focus the use of phosphorus reagents in the organic synthesis.

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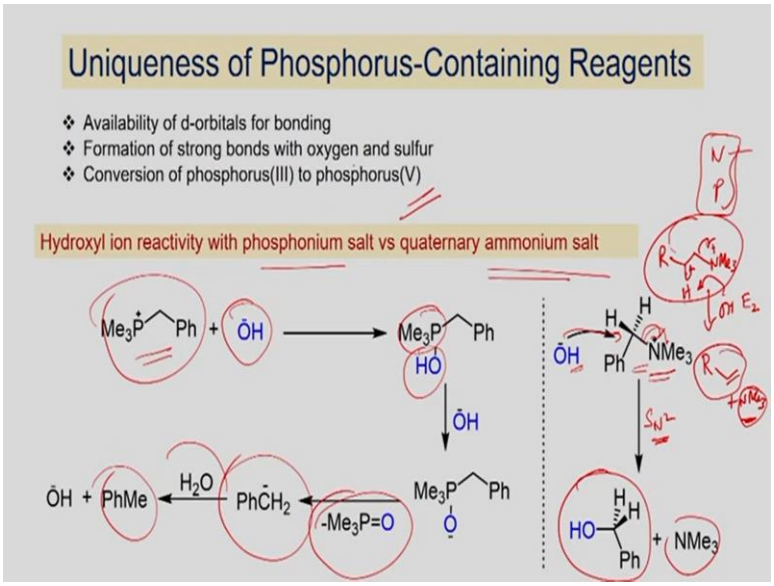

Here is the uniqueness of phosphorus containing compound. If you look at nitrogen and phosphorus, both are in same group. However, they differ in the reactivity. This is because of the availability of *d* orbital in phosphorus for bonding. For an example, let us see the reaction of benzyltrimethylphosphonium ion with hydroxide ion. The phosphonium ion makes bond with the hydroxide, which further converts to trimethylphosphine oxide and benzyl carbanion. Whereas benzyltrimethylammonium chloride with hydroxide ion leads to S_N2 reaction at the carbon to give benzyl alcohol and trimethylamine. Further, if you remember the Stevens rearrangement, where we have seen that quaternary ammonium salt converts to alkene and amine with hydroxide ion vis E2 elimination. Phosphorus has thus unique reactivity compared to nitrogen although both are in the same group.

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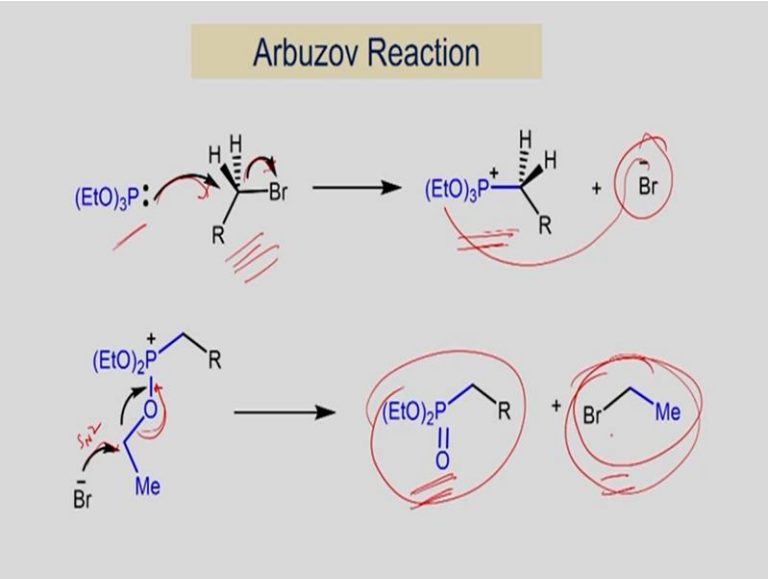

Let us look at the reaction of alkyl halide with triethyl phosphite to produce alkyl phosphonate, which is known as Arbuzov reaction. Tiethyl phosphite as nucleophile undergoes nucleophilic substitution with alkyl halide to produce the phosphonium salt. Halide ion as nucleophile undergoes the nucleophilic substitution to furnish alkyl phosphonate.

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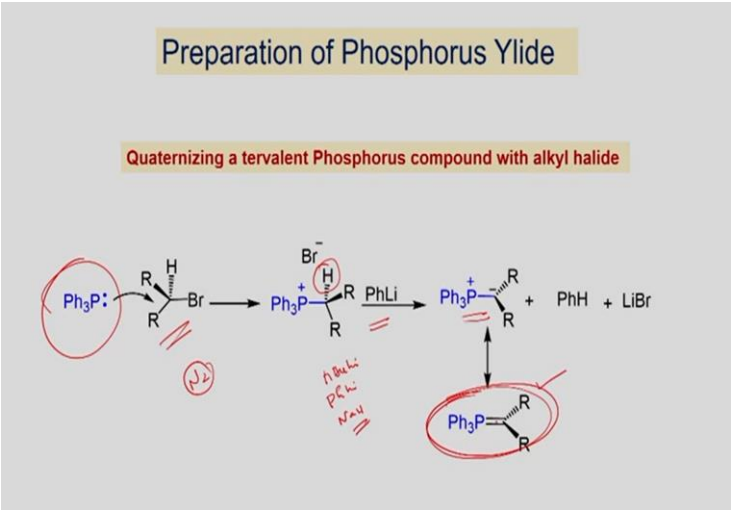

Here is the preparation of the phosphorus ylide. Triphenylphosphine reacts with alkyl bromide to form the phosphonium salt, which with phenyllithium undergoes deprotonation to produce triphenyl phosphonium ylide.

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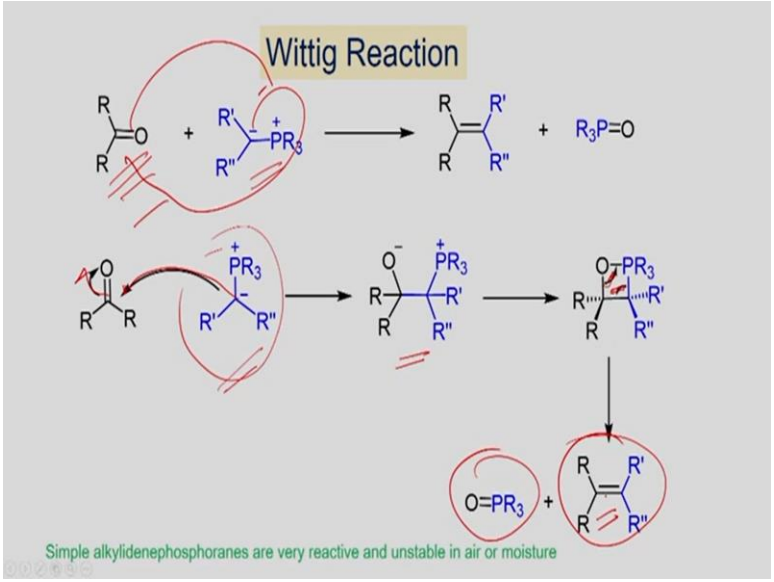

Here is the reaction of phosphonium ylide with aldehyde as well as ketone to produce alkene, which is the Wittig reaction. First, the ylide with aldehyde or ketone produces betaine, which then converts to oxaphosphetane. Elimination gives the alkene along with triphenylphosphine oxide.

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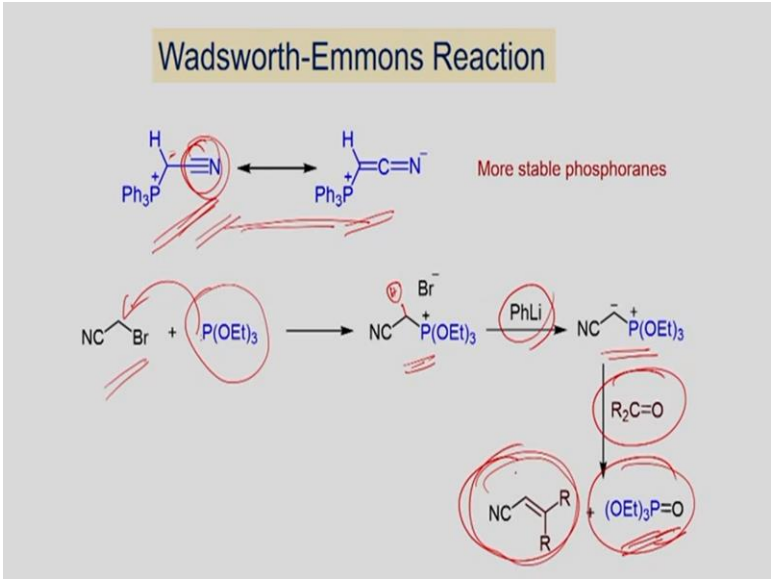

The phosphonate stabilized carbanion can be reacted with aldehyde as well as ketone to produce alkene. This is a modified Wittig reaction. In contrast to the phsophonium ylide, phosphonate

stabilized carbanion is more nucleophilic but less basic, and can be alkylated. Further, unlike the phophonium ylide, the dialkylphosphate salt byproduct can be removed by the aqueous work up. For example, nucleophilic substitution of triethyl phosphite with bromoacetronitrile produces the phosphonate. Deprotonation using phenyllithium gives phosphonate carbanion, which adds onto the aldehyde or ketone to produce predominantly E-alkene.

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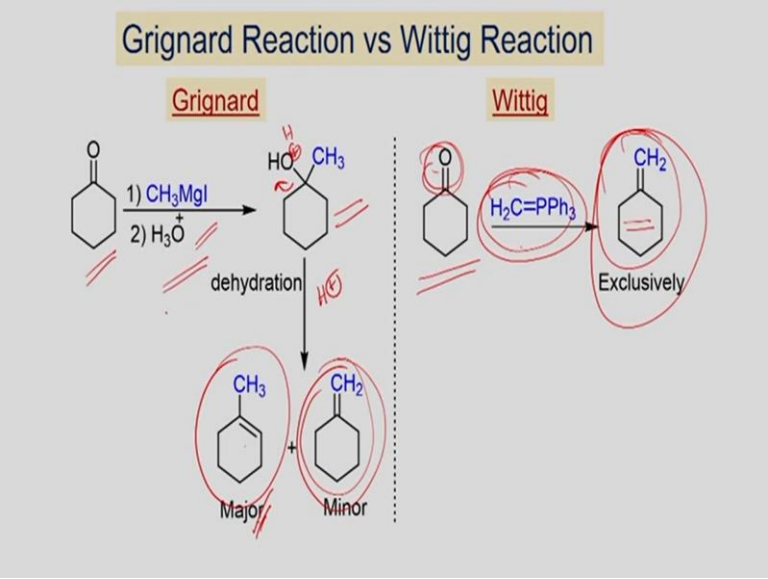

Traditionally, Grignard reaction followed by acid catalyzed dehydration is used to prepare alkene. For example, cyclohexanone with MeMgBr gives the 1-methylcyclohexanol, which leads dehydration using acid to produce 1-methylcyclohexene as the major product. On the other hand, Wittig reaction selectively produces methylenecyclohexane as the product. Thus, Wittig reaction plays a crucial role in synthetic chemistry.

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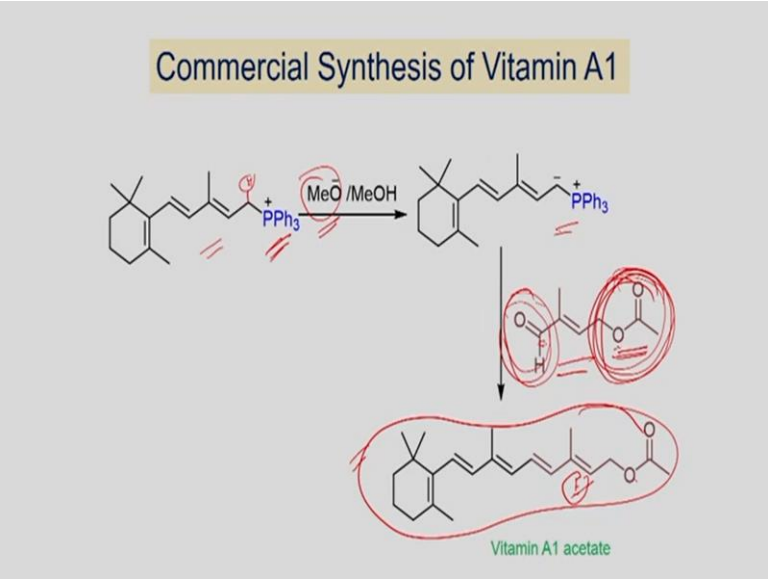

Let us look at the synthesis of vitamin A1. Deprotonation of the phosphonium salt using methoxide produces the ylide, which reacts with α,β-unsaturated aldehyde bearing ester group to produce vitamin A1 acetate. In contrast, we will not be able to use the Grignard approach as it can react with acetate group also. Thus, Witting reaction provides a powerful synthetic tool for the double bond construction.

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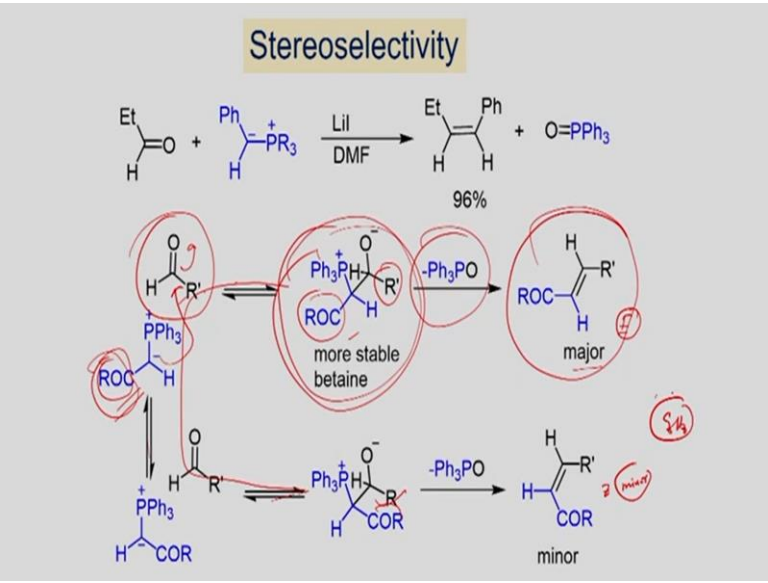

Now, let us look at the selectivity. In non-polar solvent like benzene, stabilized ylide reacts with aldehyde to produce the reversible betaines (*threo* and *erythro*). The more stable *threo* betaine produces *E*-alkene. Thus, the reaction of stabilized ylide produces mainly *E*-alkene.

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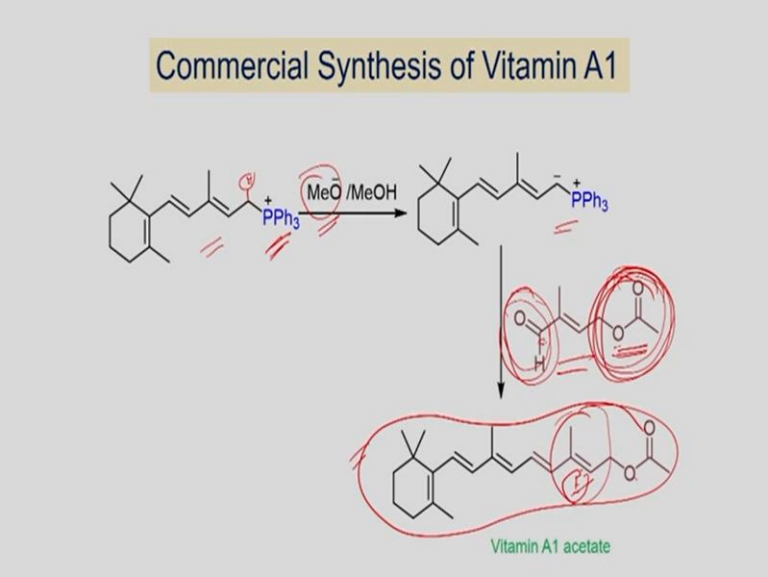

For an example, here, the stabilized ylide with aldehyde produces *E*-double bond.

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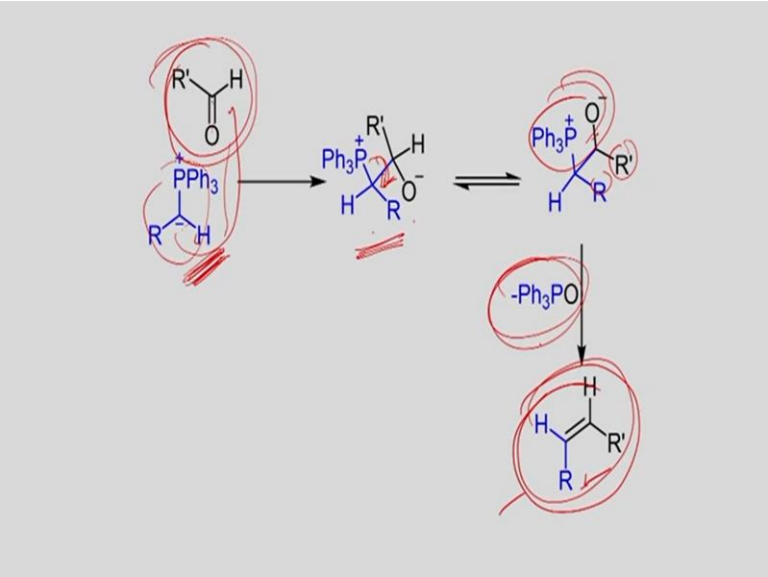

On the other hand, the less stable ylide, in polor solvent, reacts with aldehyde to produce *erythro* betaine, that rotates to oxaphosphetane, and elimination take place to produce *Z*-alkene. In this reaction, the betaine formation is irreversible. Thus, the less stable ylide in polar solvent reacts to produce *Z*-alkene.

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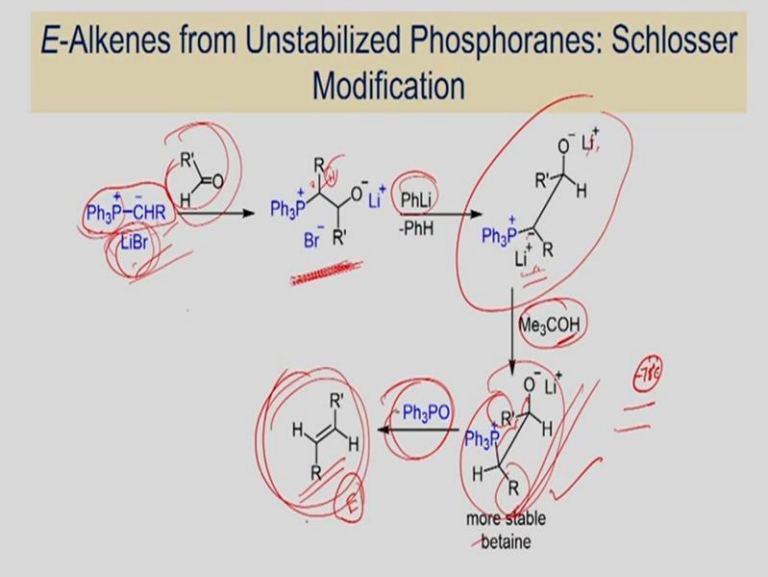

Just we have seen that the stabilized ylide favors the formation of the reversible betaines and the more stable *threo* betaine converts to *E*-alkene, whereas the less stable ylide forms irreversible *erythro* betaine that converts to *Z*-alkene. Schlosser modified the reaction of the less stable ylide using PhLi that converts the *erythro* betaine to *threo* betaine and then elimination occurs to produce *E*-alkene. Thus, the stereochemistry of the alkene can be controlled.

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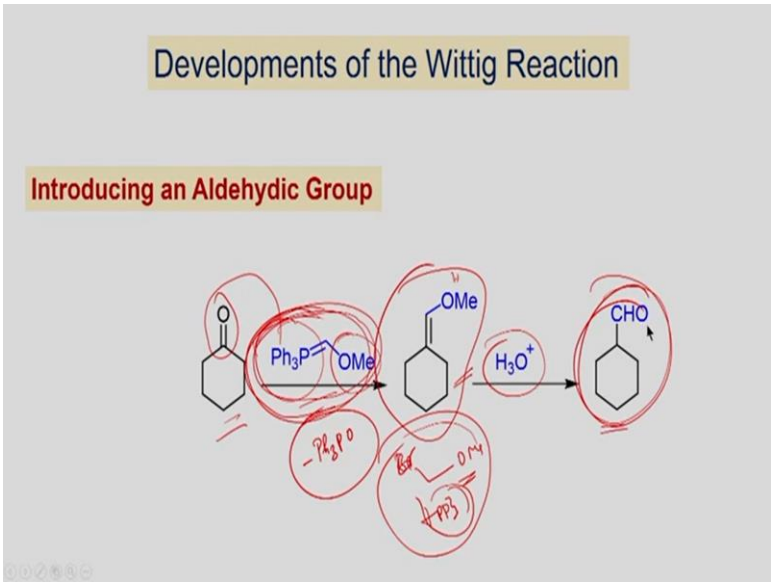

So far we have seen the use of Witting based reactions for the formation carbon-carbon double bond. Here the transformation of cyclohexanone to cyclohexanecarboxaldehyde is shown. Reaction of bromomethyl methyl ether with PPh_3 gives the phosphonium salt that deprotonates using base to give the ylide, which with cyclohexanone gives (methoxymethylene)cyclohexane. The latter on hydrolysis yields the aldehyde.

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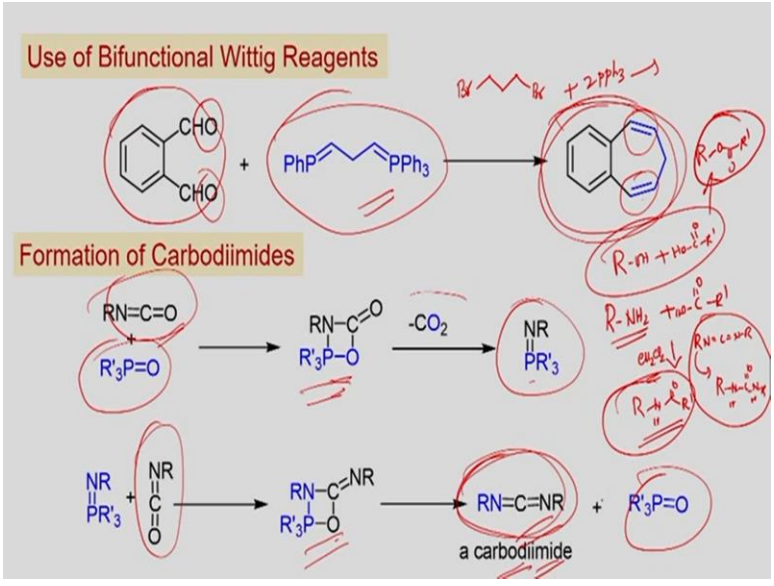

The first example involves the use of double Witting reaction for the conversion of the phthalaldehyde to bicyclic compound. The second example shows the use of Wittig reaction for the transformation of isocyanate to carbodiimide. Reaction of R_3PO with isocyanate gives the [2+2]-cycloaddition product, which loses CO_2 to give phosphanimine. [2+2]-Cycloaddition with isocyanate gives the cyclic compound that undergoes elimination to give carbodiimide, which finds broad utilities in peptide synthesis as the coupling agent for the peptide bond formation between amino and carboxyl groups.

So far we have seen the Wittig based reactions for carbon-carbon double bond formation. Now let us look at the use of triethyl phosphite for the organic transformations.

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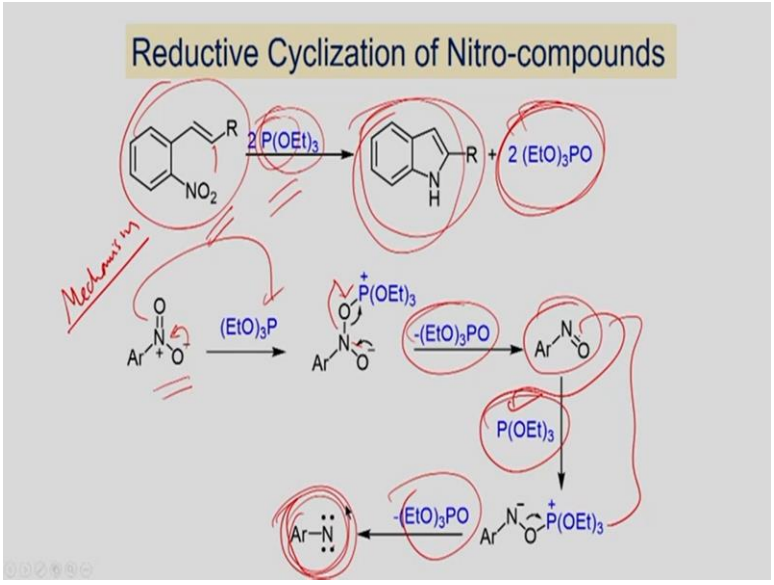

Here 1-nitro-2-vinylbenzene converts into indole using two equiv of triethyl phosphite via nitrene intermediate. The nitro functional group is converted to nitrene by triethyl phosphite and the cyclization occurs. During the reaction triethyl phosphite is converted to triethyl phosphate. As you can see here, the lone pair of phosphorus adds to the nitro group and converts to nitroso group. Which further reacts with another equiv of triethyl phposphite and converts to nitrene, which undergoes cyclization with the vinylic double bond to produce indole.

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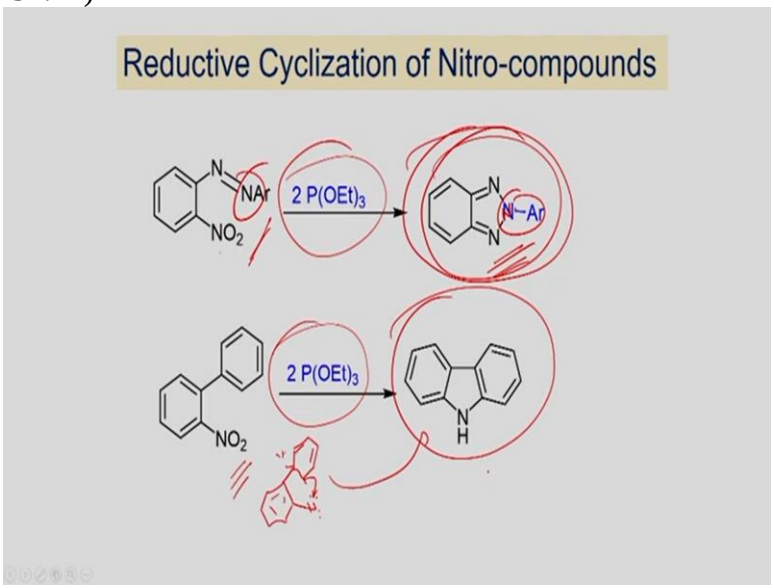

Let us look some more examples on the transformation of nitro group to nitrene and application for the construction of nitrogen based heterocyclic compounds. Here the first example shows the reaction of 1-nitroazobenene with two equiv of triethyl phosphite to produce benzotriazole. Likewise, the second example covers the transformation of 2-nitrobiphenyl to carbazole. In these reactions the nitro group is converted to nitrene and the cyclization occurs.

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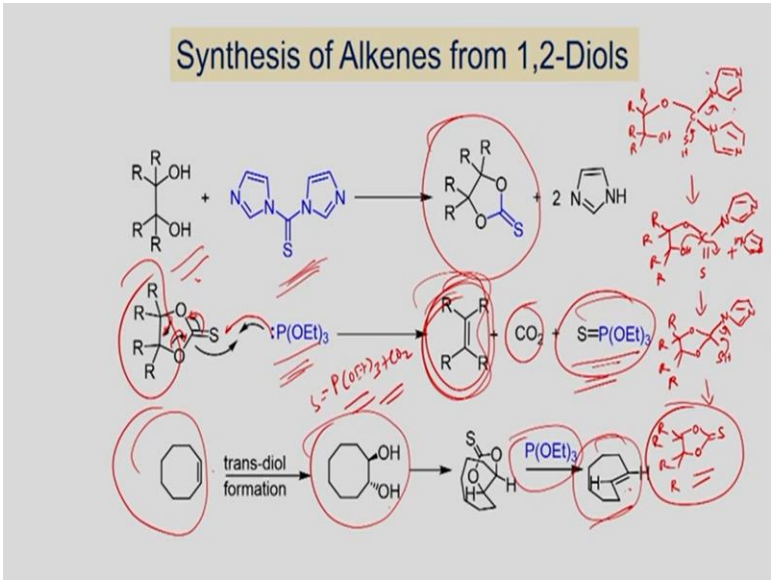

Here the transformation of 1,2-diol to alkene is shown. It is a two steps reaction, and the diol undergoes addition reaction with thiocarbonyl diimidazole to produce thiocarbonate. Which

reacts with triethyl phosphite to produce alkene. The reaction is stereospecific. For example, *trans*-1,2-cyclooctanediol can be converted to *trans*-cyclooctene.

We have seen two types of reactions using triethyl phospite for organic transforamtions. Now let us move to the use of phosphines.

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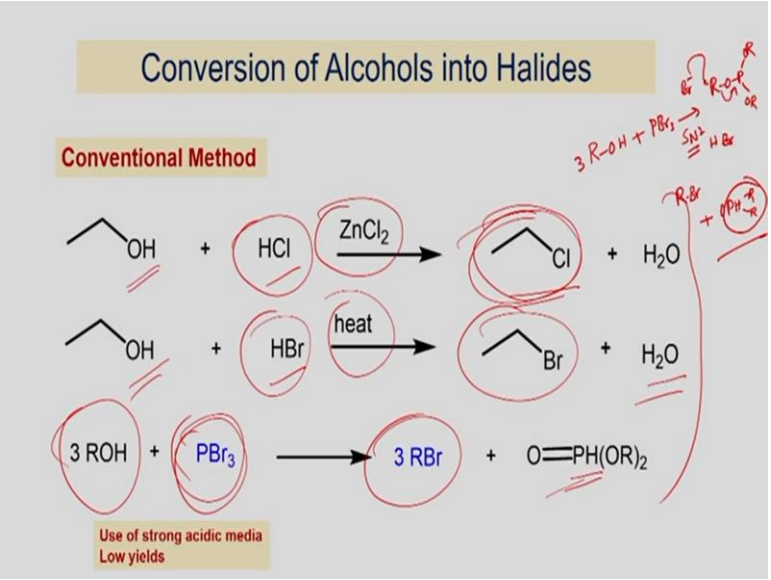

Here is the transformation of alcohol to alkyl halide. For example, traditionally, ethanol is converted to ethyl chloride using HCl in the presence of $ZnCl_2$. Similarly, ethanol reacts with HBr under heating to produce ethyl bromide. Alcohol also reacts with phosphorus tribromide to produce alkyl bromide. The latter method can be used for the transformation of 3 equiv of alcohol to alkyl bromide with one equiv of phosphorus tribromide. However, the yields are moderate due to strong acid conditions. Development of effective methods are essential to carry out the reaction under mild conditions.

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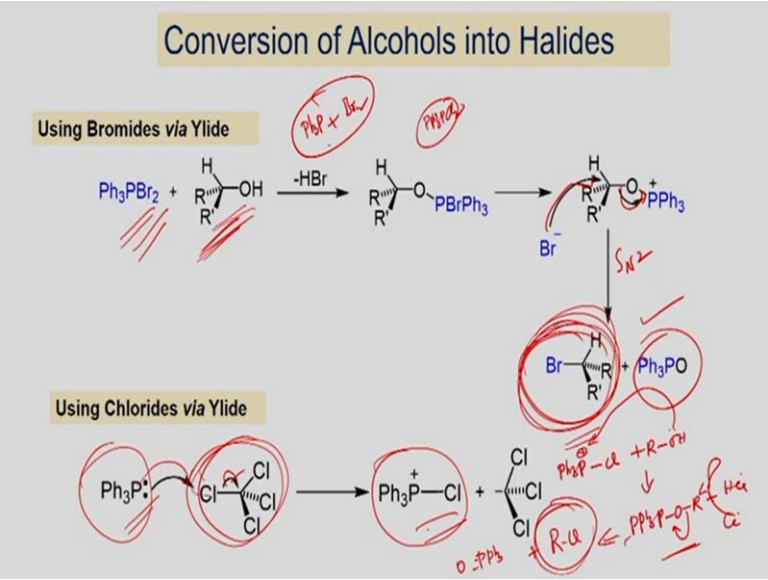

Here improved method is shown for the conversion of alcohol to alkyl halide using phosphonium ylide. For example, triphenylphosphine with bromine gives the ylide, which reacts with alcohol to produce oxyphosphonium salt, which undergoes S_N2 reaction with bromide ion to produce alkyl bromide. Similarly, phosphonium chloride can be made from triphenylphosphine and carbon tetrachloride. The ylide can be reacted with alcohol to convert to alkyl chloride. These reactions provide effective synthetic methods for the transformation of alcohol to alkyl halide under mild reaction conditions in high yields.

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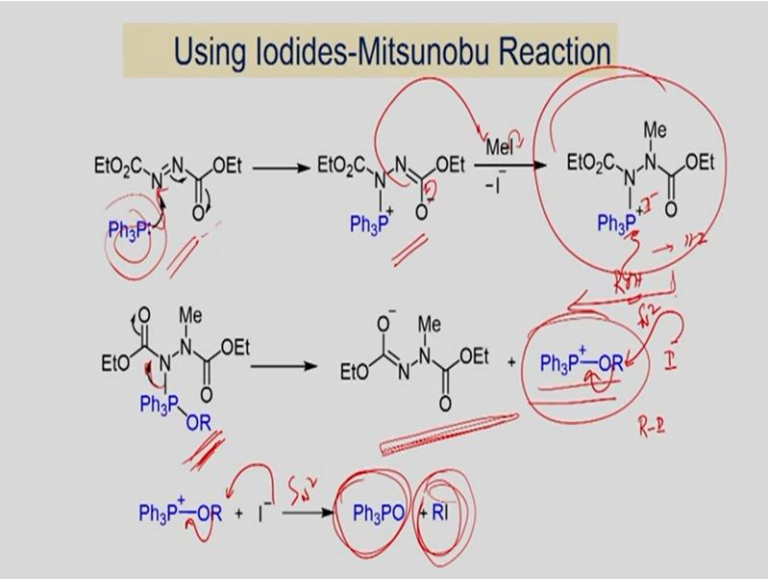

In the previous slides, we have seen the transformation of alcohol to alkyl bromide as well as alkyl chloride. Now let us focus on the preparation of alkyl iodide using Mitsunobu reaction. PPh_3 activates DEAD via addition reaction, which undergoes S_N2 reaction with methyl iodide to give phosphonium iodide. Alcohol as nucleophile undergoes substitution onto the phosphonium ion to yield oxyphosphonium ion. Iodide ion leads to S_N2 reaction to produce alkyl iodide, which is one of best method to make alkyl iodide.

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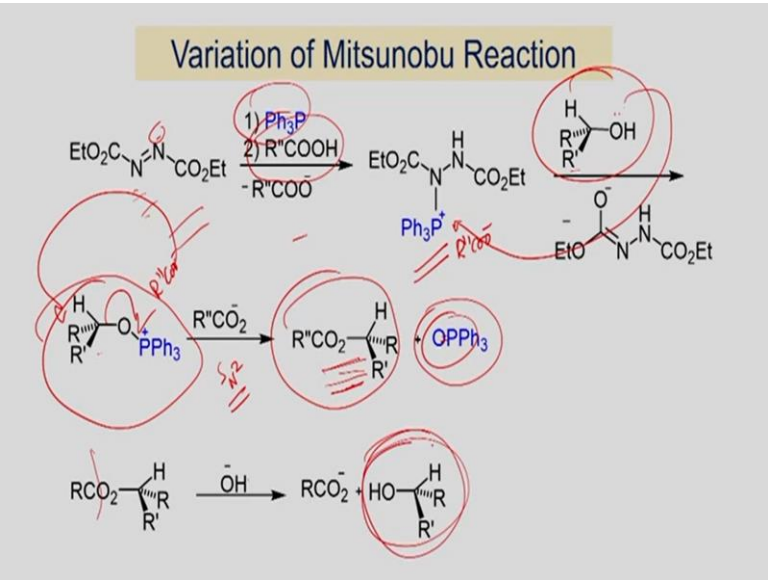

Mitsnobu reaction also provides powerful synthetic tool to invert configuration of chiral compounds. As we have seen in the previous slide, triphenylphosphine activates the DEAD via addition reaction. The alcohol leads S_N2 reaction with the phosphonium ion to produce oxyphosphonium ion, which undergoes S_N2 reaction with carboxylate ion. Hydrolysis of the ester provides the alcohol with inverted configuration.

So far we have seen the reaction of alcohols with phosphorus reagents to convert to alkyl halides as well as inversion of the configuration,

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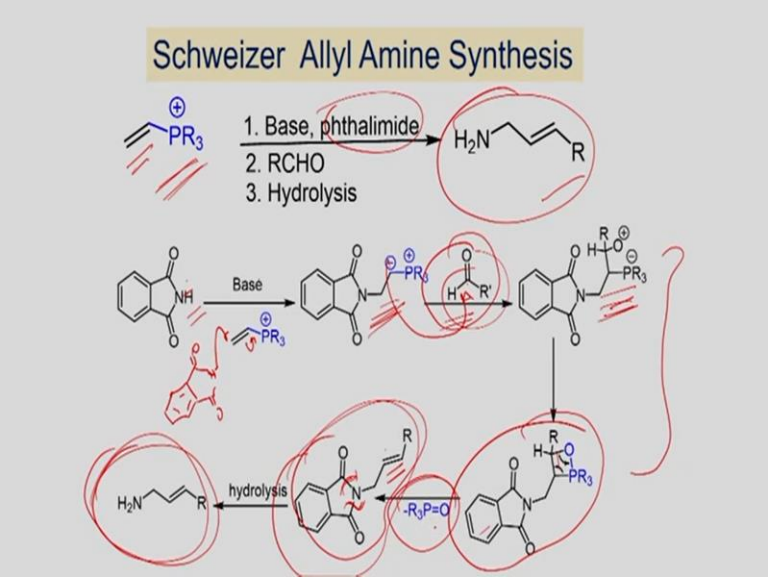

Now let see the use of vinyl phosphonium salt for the construction of allyl amine. Deprotonation of phthalimide and addition to vinyl phosphonium ion gives the ylide. Which undergoes addition reaction with aldehyde to give the betaine. The formation of phosphetane and elimination produces the allyl phthalimde, which on hydrolysis gives allyl amine. This is an effective synthetic tool for the preparation of allyl amine under mild conditions with high yields.

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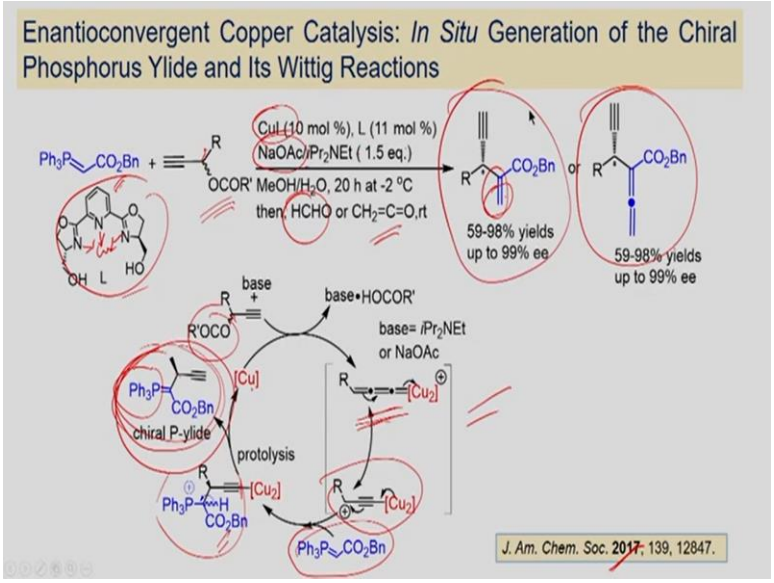

Efforts are also made on the use of chiral phosphorus yield for enantioselective reactions. For example, chiral copper(I) complex with propargyl ester forms propargyl cation, which undergoes addition with the stabilized phosphonium ylide to produce chiral phosphorus ylide (*in situ*), which is trapped with HCHO or ketene to give the methylene or ketene derivative with excellent enantioselectivity.

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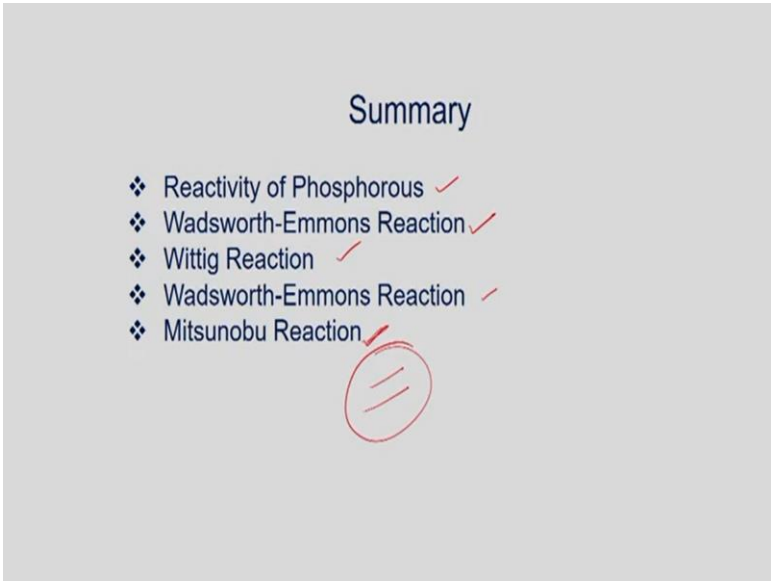

In summary, in the first part of the lecture, we have seen the role Wittig reaction for the formation of carbon-carbon double bond. Then, we have seen the utilization of triethyl phosphite for the transformation nitro group to nitrene and its application for construction of the nitrogen heterocycles. We have also seen the role of triethyl phosphite in the transformation of 1,2-diol to alkene.

We have seen the use of phosphonium ylide for the transformation of alcohol to alkyl halides. These are mild reaction conditions for the transformation of alcohols to alkyl halides with high yields. Then, we have seen the Mitsunobu reaction, which affords powerful synthetic tool to invert the configuration of alcohol. We have also seen the application of vinyl phosphonium salt for the synthesis of allyl amine.

At the end, we have seen an example for the *in situ* generation of chiral phosphonium ylide for the enantioselective synthesis. Thus, phosphorus compounds have broad utilities in organic synthesis. With this we conclude this lecture, thank you very much.