# Reagents in Organic Synthesis
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## Lecture 17
## P Based Reagents in Organic Synthesis

Welcome again. Today we will discuss Phosphorus based reagents in organic synthesis.

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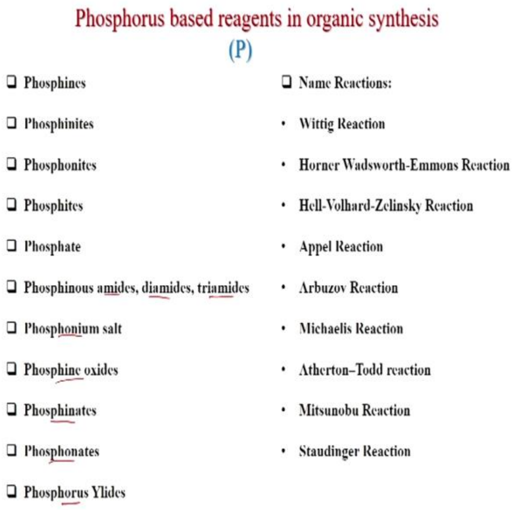

Phosphorus based reagents in organic synthesis

(P)

- ❑ Phosphines
- ❑ Phosphinites
- ❑ Phosphonites
- ❑ Phosphites
- ❑ Phosphate
- ❑ Phosphinous amides, diamides, triamides
- ❑ Phosphonium salt
- ❑ Phosphine oxides
- ❑ Phosphinates
- ❑ Phosphonates
- ❑ Phosphorus Ylides

❑ Name Reactions:

- Wittig Reaction
- Horner Wadsworth-Emmons Reaction
- Hell-Volhard-Zelinsky Reaction
- Appel Reaction
- Arbuzov Reaction
- Michaelis Reaction
- Atherton–Todd reaction
- Mitsunobu Reaction
- Staudinger Reaction

In today's lecture, first we will discuss Phosphines, then Phosphinites, Phosphonites and in the next slide I will show the structures of these compounds. Phosphites, Phosphates, Phosphinous amides, diamides, triamides, Phosphonium salt, Phosphine oxides, Phosphinates, Phosphonates and most of the cases depending on the oxygen atom they are named like this, and Phosphorus Ylides.

And in the Name Reactions, we will discuss Wittig Reaction, Horner Wadsworth-Emmons Reaction which is Wittig variant, Hell-Volhard-Zelinsky Reaction, Appel Reaction, Arbuzov Reaction, Michaelis Reaction, Atherton-Todd Reaction, Mitsunobu Reaction, and last we will discuss Staudinger Reaction.

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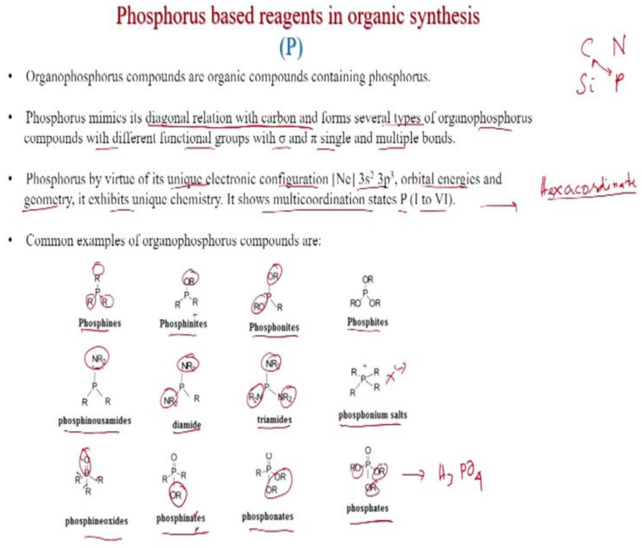

## Phosphorus based reagents in organic synthesis

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- Organophosphorus compounds are organic compounds containing phosphorus.
- Phosphorus mimics its diagonal relation with carbon and forms several types of organophosphorus compounds with different functional groups with σ and π single and multiple bonds.
- Phosphorus by virtue of its unique electronic configuration [Ne] $3s^2$ $3p^3$, orbital energies and geometry, it exhibits unique chemistry. It shows multicoordination states P (I to VI).
- Common examples of organophosphorus compounds are:

So Organophosphorus compounds are organic compounds containing phosphorus and Phosphorus mimics its diagonal relation with carbon. If you remember the periodic table, then Carbon, Nitrogen is their then there is Silicon and Phosphorus. So Carbon has diagonal relation with phosphorus and forms several types of organophosphorus compounds with different functional groups, so its sigma and pi single and multiple bonds.

So like Carbon, Phosphorus also forms sigma and pi bonds. Phosphorus by virtue of its unique electronic configuration and Neon 3 S to 3 P three, orbital energies and geometry, it exhibits unique chemistry. It shows multicoordination states Phosphorus 1 to six. So maximum it can go to Hexacoordinate.

So, it can take up to 6 ligands. Common examples of Organophosphorus compounds are so whatever I told in the first slide, so here are the structures. This is the Phosphines. When 3 groups are present, R groups, and when one R is replaced by OR then it is called Phosphinites. And two OR is present then it is called Phosphonites. So now it common here because there is no Phosphorus oxygen double bond. Only single bond is there, so OR is there once then Phosphinites, 2 OR is Phosphonites and 3 OR is Phosphites.

Similarly, when one NR add to group, that is the amine group is there, then it is called Phosphinousamides. Two NR2 group is present then it is called diamide, and three NR2 groups are present then it is called triamides. And this is Phosphonium salt, there is a positive charge on Phosphorus. So there will be a counter anion, X minus**.** And now this oxygen double bond, Phosphorus oxygen double bond is coming, and first one is phosphine oxides, when 3 R are present along with a phosphine oxide double bond. And now when 1 R is replaced by OR then it is called Phosphinates.

So you can find the difference between this and this. This is called Phosphinates, A is here; and here it is I. Phosphinates and Phosphinites. And here, 2 OR group is present then it is called Phosphonates. And when 3 OR group is present then it is called Phosphates. So these are esters of H3PO4, Phosphoric Acid. So it is called Phosphate.

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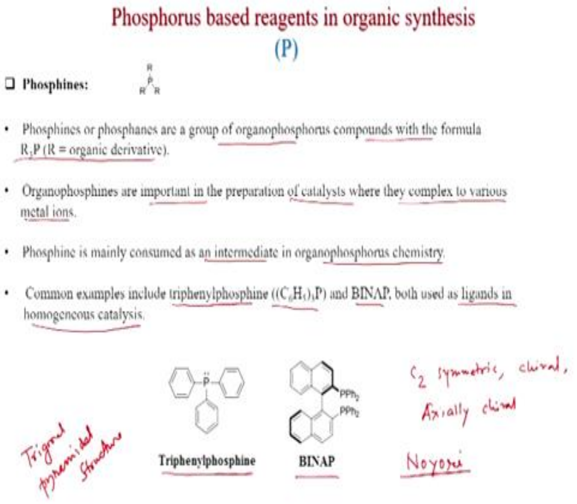

Phosphorus based reagents in organic synthesis

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❑ **Phosphines:**

- Phosphines or phosphanes are a group of organophosphorus compounds with the formula $R_3P$ (R = organic derivative).
- Organophosphines are important in the preparation of catalysts where they complex to various metal ions.
- Phosphine is mainly consumed as an intermediate in organophosphorus chemistry.
- Common examples include triphenylphosphine ($(C_6H_5)_3P$) and BINAP, both used as ligands in homogeneous catalysis.

Now, first we will discuss Phosphines. So Phosphines or Phosphines are a group of organophosphorus compound with the formula R3P. R is equal to organic derivative. Organophosphines are important in the preparation of catalysts where they complex to various metal ions. Phosphine is mainly consumed as an intermediate in organophosphorus chemistry. Also, it is used as catalyst in different reactions Phosphines. Common examples include triphenylphosphine like PPh3 and BINAP, both used as ligands in homogeneous catalysis.

Like this one is Triphenylphosphine and it has Trigonal Pyramidal Structure because one lone pair is present, because of this lone pair it is nucleophilic also. And this is BINAP, this is C2 Symmetric, and Chiral and this Chirality is actually, this is Axially Chiral or Axially Chiral. Axial Chirality is present. And this is used in metal catalysis used as ligands in metal catalysis and first was discovered by Noyori who has got Nobel Prize also. So this Japanese Scientist Noyori, first found this BINAP as useful ligand in asymmetric catalysis**.**

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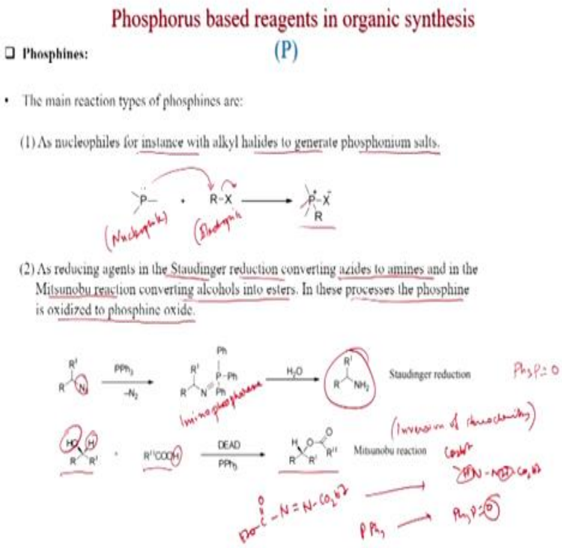

Phosphorus based reagents in organic synthesis

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❑ **Phosphines:**

- The main reaction types of phosphines are:

(1) As nucleophiles for instance with alkyl halides to generate phosphonium salts.

(2) As reducing agents in the Staudinger reduction converting azides to amines and in the Mitsunobu reaction converting alcohols into esters. In these processes the phosphine is oxidized to phosphine oxide.

The main reaction types of Posphines are: As nucleophiles for instance with alkyl halides to generate phosphonium salts. Like here as we told that Phosphorus has a loan pair so this acting as a nucleophile and RX we know this is an electrophile. So what will happen this will attack to here and X minus will liberate**.** So Phosphorus will get a positive charge. Here one group is missing and X minus will be counter anion.

As reducing agents in the Staudinger reduction converting azides to amines and in the Mitsunobu reaction converting alcohols into esters. In this processes the Phosphine is oxidized to phosphineoxide. So, this is the Staudinger reaction here and azides is converting fast to iminophosphorane and next after hydrolysis it is going to amine. So an azide is converting to amine and triphenylphosphine is going to triphenylphosphine oxide.

Also, in this reaction if it is alcohol and carboxylic acid with DEAD PPh3, DEAD is diethyl as diethyl azodicarboxylate. So, this is DEAD. DEAD will convert to this compound and triphenylphosphine will convert to triphenylphosphine oxide.

So, this oxygen is going to triphenylphosphine and ultimately it is going to triphenylphosphine oxides. And you get, this has to do some reaction here and with inverse and the detail mechanism we will discuss later, inversion of stereochemistry is happening here. If you start with the chiral alcohol, then you will get the inversion.

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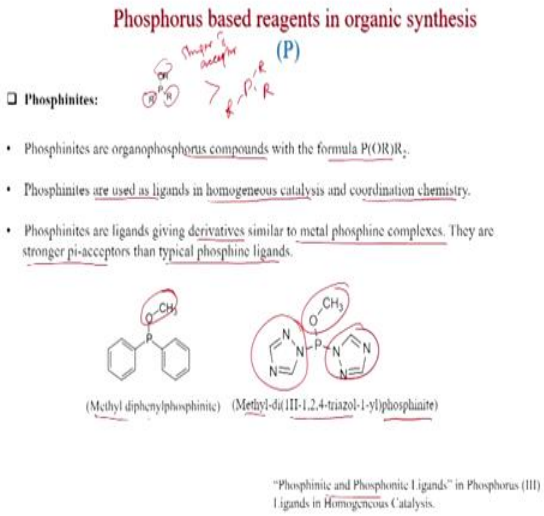

## Phosphorus based reagents in organic synthesis

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❑ **Phosphinites:**

- Phosphinites are organophosphorus compounds with the formula $P(OR)R_2$.
- Phosphinites are used as ligands in homogeneous catalysis and coordination chemistry.
- Phosphinites are ligands giving derivatives similar to metal phosphine complexes. They are stronger pi-acceptors than typical phosphine ligands.

(Methyl diphenylphosphinite) (Methyl-di(1H-1,2,4-triazol-1-yl)phosphinite)

"Phosphinite and Phosphonite Ligands" in Phosphorus (III) Ligands in Homogeneous Catalysis.

Phosphinites as we told that Phosphinites will have two R group and one OR group. Phosphinites are organophosphorus compound with the formula P(OR)R2. Phosphinites are used as ligands in homogeneous catalysis and coordination chemistry. Phosphinites are ligands giving derivatives similar to metal phosphine complexes. They are stronger pi-acceptors than typical phosphine ligands. So they are stronger pi-acceptor, stronger pi-acceptor because of this OR.

Like this one this Methyl diphenylphosphinite here two phenyl group and O1 OCH3 group is present and this one Methyl-di(1H-1,2,4-triazol-1-yl)phosphinite. So 2 triazol motifs are present and 1 methoxy group is present. So they are Phosphinites. And this is the book chapter. Phosphinites and Phosphonite l.igands in Phosphorus l.igands in Homogeneous Catalysis.

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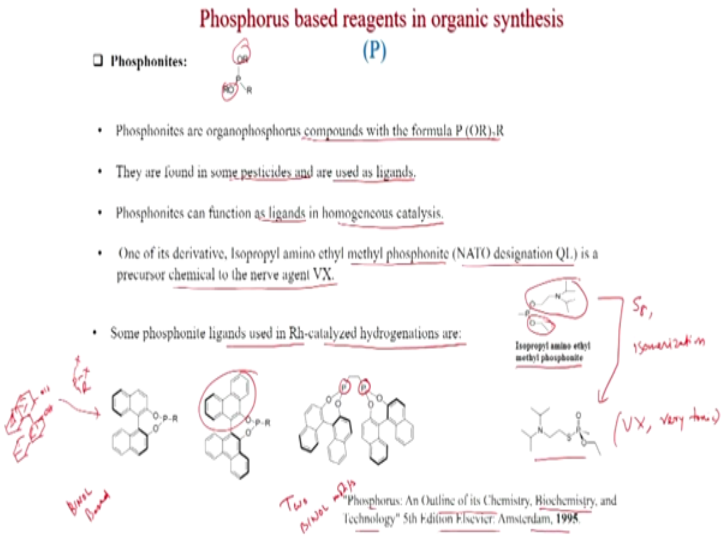

Phosphorus based reagents in organic synthesis

(P)

☐ **Phosphonites:**

- Phosphonites are organophosphorus compounds with the formula P (OR)$_2$R
- They are found in some pesticides and are used as ligands.
- Phosphonites can function as ligands in homogeneous catalysis.
- One of its derivative, Isopropyl amino ethyl methyl phosphonite (NATO designation QL) is a precursor chemical to the nerve agent VX.
- Some phosphonite ligands used in Rh-catalyzed hydrogenations are:

"Phosphorus: An Outline of its Chemistry, Biochemistry, and Technology" 5th Edition Elsevier: Amsterdam, 1995.

Now in Phosphonites two OR groups are present. Phosphonites are organophosphorus comounds with the formula P (OR)2R. And they are found in some pesticides and are used as ligands. Phosphoites can function as ligands in homogeneous catalysis. One of its derivative, Isopropyl amino ethyl methyl phosphonite (the NATO designation QL) is precursor chemical to the nerve agent VX.

So this is the Isopropyl amino ethyl methyl phosphonite, you can see here two OR group is present. One OR group continuing the tertiary amine, and another is ethoxy group and one methyl group is present. So this is Isopropyl amino ethyl methyl phosphonite. And these can be converted. So this is VX, this is very toxic for nerve**.** And this can be converted if you put S8 and followed by isomerization. And this is chiral compound, so this will of course give a racemic, but you can get chiral also. So this compound is very toxic for nerve.

Some phosphonite ligands used in Rh-catalyzed hydrogenations. So this is BINOL based see BINOL based because this you can get from BINOL, OH OH. And if you treat with PX XR2 living group then you can get this. Also this is anthracinol based because 2 anthracene motifs are there you can see here. And this is two BINOL motifs are present and also two Phosphorus atoms are present here. So two BINOL motifs and these are all chiral. So they are used in rhodium-catalyzed hydrogenation and this is this is in book Phosphorus: An Outline of its Chemistry, Biochemistry and Technology 5th Edition Elsevier: Amsterdam, 1995.

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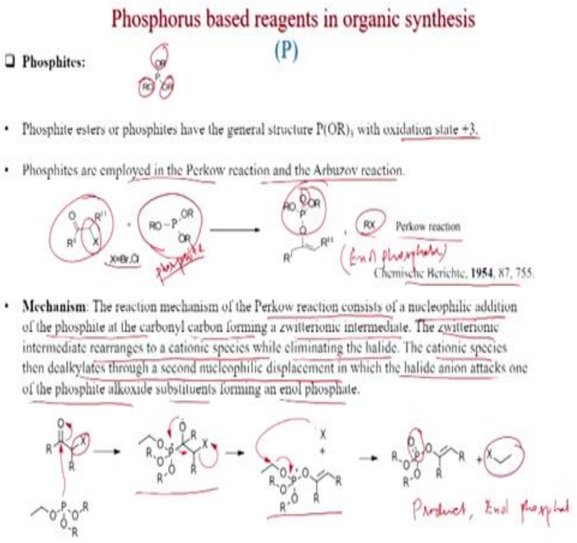

Phosphorus based reagents in organic synthesis

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❑ **Phosphites:**

- Phosphite esters or phosphites have the general structure $P(OR)_3$ with oxidation state +3.
- Phosphites are employed in the Perkow reaction and the Arbuzov reaction.

Chemische Berichte, **1954**, 87, 755.

- **Mechanism**: The reaction mechanism of the Perkow reaction consists of a nucleophilic addition of the phosphite at the carbonyl carbon forming a zwitterionic intermediate. The zwitterionic intermediate rearranges to a cationic species while eliminating the halide. The cationic species then dealkylates through a second nucleophilic displacement in which the halide anion attacks one of the phosphite alkoxide substituents forming an enol phosphate.

Now, we will discuss phosphites. So phosphites will have three OR group. Here three OR group will be present and phosphite esters or phosphites have the general structure P(OR)3 with oxidation state +3. Phosphites are employed in Perkow reaction and in the Arbuzov reaction. So they are employed in special reactions one is Perkow reaction and Arbuzov reaction.

So in the Perkow reaction, as you can see one haloketone**,** one haloketone is treated, X can be Bromine, Chlorine with a phosphite, so this is Phosphite. Then you get Enol Phosphate. So this is phosphate we will discuss later because here a P=O is there so this is a Phosphate and double bond is there so Enol Phosphate. And RX is coming out. So this is Perkow reaction. This was first we put it in chemistry, Chemische Berichte 1954.

So we will discuss the mechanism of this reaction, the reaction mechanism of the Perkow reaction consist of nucleophilic addition of the phosphite at the carbonyl carbon forming a zwitterionic intermediate. So, this is important. The Phosphorus pass as to the carbonyl oxygen. So there is a living group also, but first it reacts to the carbonyl oxygen and forming a zwitter ionic intermediate. So this is the zwitter ionic intermediate. So, this carbonyl become now alkoxide and you see this Phosphorus has a positive charge here.

And now, the zwitter ionic intermediate rearranges to a cationic species while eliminating the halide. So now, this rearrangement will happen because Phosphorus will take this oxygen and this kind of elimination will happen. So you get this intermediate, this also Enol Phosphate. And now, the cationic species then dealkylates to the second nucleophilic displacement in which the halide anion attacks one of the phosphite alkoxide substituents forming an Enol Phosphate. So here X minus is attacking this and you get this Phosphorus oxygen double bond. And this ethyl X is forming. So one of this R is converting to RX. So this is the product Enol Phosphate.

So first, the phosphite reacts to the carbonyl oxygen to generate a zwitter ionic intermediate then it rearranges to a cationic species and then the halide displaces one of the alkyl group and ultimately Phosphorus the oxygen will from, so which is Enol Phosphate.

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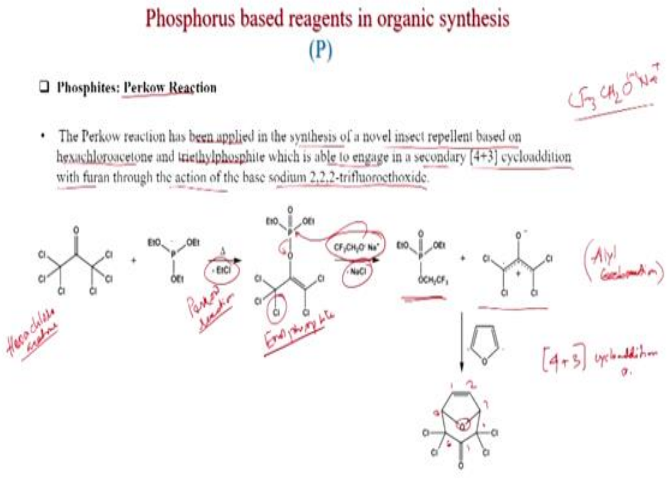

Phosphorus based reagents in organic synthesis

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☐ **Phosphites: Perkow Reaction**

- The Perkow reaction has been applied in the synthesis of a novel insect repellent based on hexachloroacetone and triethylphosphite which is able to engage in a secondary [4+3] cycloaddition with furan through the action of the base sodium 2,2,2-trifluoroethoxide.

Now we will discuss some more of Perkow reaction. The Perkow reaction has been applied in the synthesis of a novel insect repellent based on hexachloroacetone and triethylphosphite which is able engage in a secondary 4+3 cycloaddition with furan through the action of the base sodium 2, 2, 2 trifluoroethoxide.

So, this is sodium, 2, 2, 2 trifluoroethoxide. So, this is the reaction, hexachloroacetone, hexachloroacetone is reacted with triethylphosphite then what happened? This reaction happens this is the Perkow reaction whatever we have discussed now Perkow reaction Enol Phosphate. And one Chlorine is displaced as ethyl chloride.

Now, if you put this enol phosphate with this base sodium 2, 2,2 trifluoroethoxide then what will happen? This will react here and this bond will break. So, you get this side product and after another chloride elimination, you get this allyl carbocation**.** So allyl carbocation is formed after one Cl minus is displacing as sodium chloride, you get this allyl carbocation. And now this allyl carbocation will react in 4 +3 cyclo additions. So here, this center will react to this center, this center will react to this center and you get a 7 monomer ring, 1, 2, 3, 4, 5, 6, 7. So, this is a bridge compound and also this oxygen bridge is present and this is called 4 +3 cycloaddition reaction.

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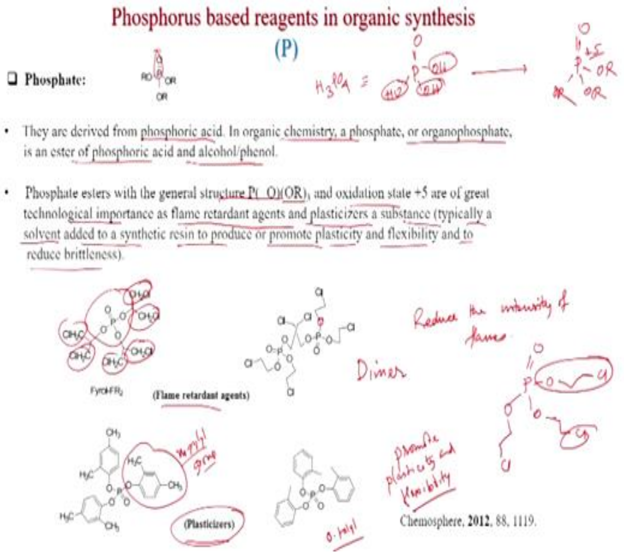

Phosphorus based reagents in organic synthesis

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❑ **Phosphate:**

- They are derived from phosphoric acid. In organic chemistry, a phosphate, or organophosphate, is an ester of phosphoric acid and alcohol/phenol.
- Phosphate esters with the general structure P(=O)(OR)$_3$ and oxidation state +5 are of great technological importance as flame retardant agents and plasticizers a substance (typically a solvent added to a synthetic resin to produce or promote plasticity and flexibility and to reduce brittleness).

(Flame retardant agents)

(Plasticizers)

Chemosphere, **2012**, 88, 1119.

Phosphates have structure like this. So now this will have a phosphoryl oxygen. So P double bond O is present. They are derived from phosphoric acid. In organic chemistry, a phosphate or organophosphate is a ester of phosphoric acid and alcohol/phenol. So this is phosphoric acid H 3 PO4. So, this is structure.

Now, if you displace this OH as OR then you get this phosphate. Phosphate esters with this general structure P double bond OR3 and oxidation state plus 5. So, it has plus 5 oxidation state because three single bond and one double bond is present are of great technological importance as flame retardant agents. So, these are flame retardant agents. So, these reduce the intensity of flames. So they are very useful compound.

Like this one, this is also Phosphate you can see, one phosphorus oxygen double bond and three alkoxy group are present and this group CH2Cl, CH2Cl it contains. So these have some effect on this flame retardant. And also, this is also flame retardant, this is Dimer. As you can see here, one oxygen should be there. As you can see the monomer is this P double bond O, O.

So, they are same this group. OR group is same and here also it is including. So it is Dimer, this also flame retardant. And now they are also compounds with Plasticizers as substance typically a solvent what is Plasticizer? Typically a solvent added to a synthetic regime to produce or promote plasticity and flexibility and to reduce brittleness. So Plasticizers they promote plasticity and flexibility.

So these compounds you can see they are all phosphates, here this alkyl group are present and meta-xylyl group is present and all are same. Here also, ortho tolyl group is present.

So when this CH2 CH2Cl are like this, CH2Cl, are connecting to carbon, this they are and the phosphate then there are some flame retardant. And simple aryl phosphate phosphates like meta-xylyl and ortho tolyl they are Plasticizer. So these are simple compounds which saw useful activities and this you can see in this general Chemosphere 2012, 88, 1119.

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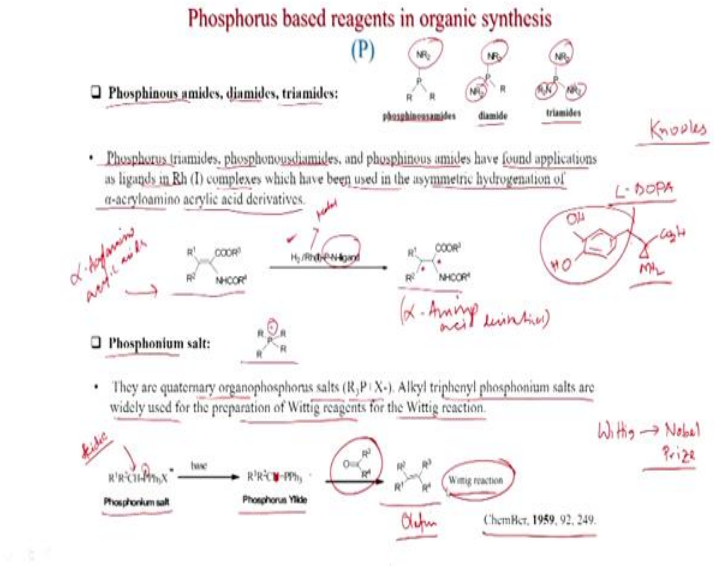

Phosphorus based reagents in organic synthesis

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❑ **Phosphinous amides, diamides, triamides:**

- Phosphorus triamides, phosphonousdiamides, and phosphinous amides have found applications as ligands in Rh (I) complexes which have been used in the asymmetric hydrogenation of α-acryloamino acrylic acid derivatives.

❑ **Phosphonium salt:**

- They are quaternary organophosphorus salts ($R_3P^+X^-$). Alkyl triphenyl phosphonium salts are widely used for the preparation of Wittig reagents for the Wittig reaction.

ChemBer, **1959**, 92, 249.

Now, we will discuss phosphinous amides, diamides, triamides. So of course, they contain this NR2 group which is called phosphinous amide. And when two NR2 is there that is called diamide. And when three NR2 are present that is called triamides. So phosphorus triamides, phosphonous diamides and phosphinous amides, so depending on this number of amine their term is different like this case when triamide is there that is called phosphorus.

When two amides are there that is called phosphonousdiamides and one is there that is called phosphinous. Phosphinous, phosphonous, and phosphorus amides have found applications are ligands in rhodium(I) complexes which have been used in the asymmetric hydrogenation of alpha-acryloamino acrylic acid derivatives.

So this is the substrate you can see a double bond is present, this double bond has to be reduced with hydrogen of course and you need the ligands. So chiral ligand, this is metal and

P-N ligands. So P-N ligand will complex with metal and will do an asymmetric hydrogenation and you get two chiral centers.

And this strategy actually, this double bond hydrogenation to generate this the alpha-acrylo amino acrylic acid. These substances are this and you get this alpha-amino acid, this is alpha-amino acid derivatives. And this strategy was used in the synthesis of L-DOPA.

One scientist name is Knowles, who got Nobel Prize also. He developed this synthesis with this hydrogenation strategy. So, there is a group of 3, 4 dihydroxybenzyl group in the alpha-amino acid and this is called L-DOPA. So this double bond will be here. In this case the double bond is here and the hydrogenation happened in the chiral fashion.

Now, we will discuss phosphonium salts. So phosphonium will have four R groups and will have a positive charge. They are quaternary organophosphorus salts PR3 plus X minus alkyl triphenyl phosphonium salts are widely used for the preparation of Wittig reagents for the Wittig reaction. So these are very useful in Wittig reaction. So this is the phosphonium salt. This is a phosphorus is connected to four atoms and there is a counter anion X minus. Now if you treat in base, what happen this CH, this is acidic because it is connected to phosphorus plus, so it becomes acidic.

Now with base, you can get this Phosphorus ylides. And this hydrogen should not be there. Now, if you treat with carbonyl compound this ylides then you get this product. This is Olefin. So we will discuss detail the mechanism and this is called the Wittig reaction. This published in Chemistry Beriste in 1959, 92, 249. So, Wittig also Wittig scientists he also got Nobel Prize for this reaction. So this is very powerful reaction to generate Olefin from carbonyl compound, this carbonyl compound and it give the Olefin.

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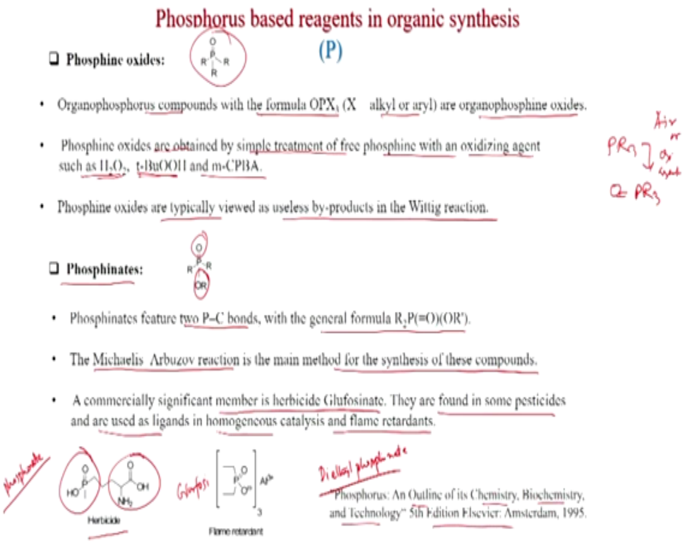

Phosphorus based reagents in organic synthesis

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☐ **Phosphine oxides:**

- Organophosphorus compounds with the formula $OPX_3$ (X alkyl or aryl) are organophosphine oxides.
- Phosphine oxides are obtained by simple treatment of free phosphine with an oxidizing agent such as $H_2O_2$, t-BuOOH and m-CPBA.
- Phosphine oxides are typically viewed as useless by-products in the Wittig reaction.

☐ **Phosphinates:**

- Phosphinates feature two P–C bonds, with the general formula $R_2P(=O)(OR')$.
- The Michaelis Arbuzov reaction is the main method for the synthesis of these compounds.
- A commercially significant member is herbicide Glufosinate. They are found in some pesticides and are used as ligands in homogeneous catalysis and flame retardants.

"Phosphorus: An Outline of its Chemistry, Biochemistry, and Technology" 5th Edition Elsevier: Amsterdam, 1995.

Organophosphorus compounds with the formula OPX3 (X = alkyl, aryl) are organophosphine oxides. So these are phosphine oxides. Phosphine oxides are bi-products in the Wittig reaction. So phosphine oxides are obtained by simple treatment of 3 phosphine with an oxidizing agent such as H2O2 tertiary butyl hydroperoxide m-CPBA.

Also phosphines we told it is very nucleophile. So if you keep in air for long time then this phosphine also gets oxidized to phosphine oxides under air. Also with oxidizing agents like H2O2 tertiary butyl hydroperoxide and meta-CPBA you can convert PR3 to POR3. With this oxidizing agent, also with air or oxidizing agent. Phosphine oxides are typically viewed as useless by-products in the Wittig reactions that we have already told.

Now, we will discuss Phosphinates. So phosphinates with one phosphorus oxygen double bond and one OR group. Phosphinates feature two P-C bonds, with the general formula R2PO OR. And this Michaelis Arbuzov reaction that we will discuss later is the main method for the synthesis of these compounds.

A commercially significant member is herbicide Glufosinate. They are found in some pesticides and are used as ligands in homogeneous catalysis and flame retardants. So this is the herbicide Glufosinate and you can see here amino acid group is present and this is the one P double bond O and one OH. So this is phosphinate. And this has this herbicide activity. And this is the flame retardant. So this is the aluminum complex of this diethyl phosphinate, diethyl phosphinate.

This also you can get, this is book chapter Phosphorus: An Outline of its Chemistry, Biochemistry and Technology 5th Edition Elsevier: Amsterdam, 1995.

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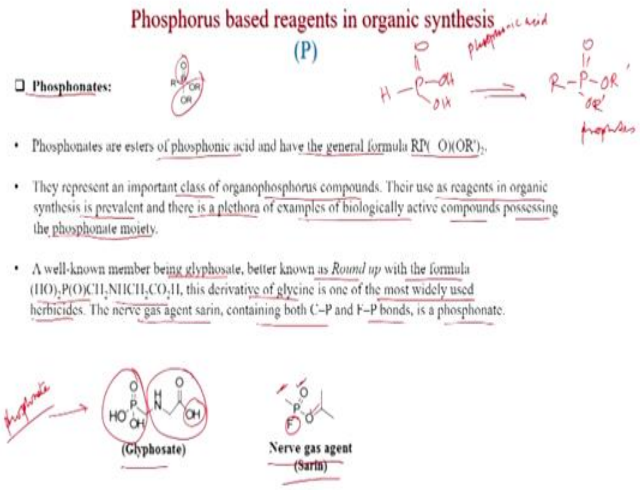

Phosphorus based reagents in organic synthesis

(P)

❑ **Phosphonates:**

- Phosphonates are esters of phosphonic acid and have the general formula RP(O)(OR')$_2$.
- They represent an important class of organophosphorus compounds. Their use as reagents in organic synthesis is prevalent and there is a plethora of examples of biologically active compounds possessing the phosphonate moiety.
- A well-known member being glyphosate, better known as *Round up* with the formula (HO)$_2$P(O)CH$_2$NHCH$_2$CO$_2$H, this derivative of glycine is one of the most widely used herbicides. The nerve gas agent sarin, containing both C–P and F–P bonds, is a phosphonate.

(Glyphosate)

Nerve gas agent (Sarin)

Now, we will discuss phosphonates. So phosphonates will have OR group along with this double bond. Phosphonates are esters of phosphonic acids and I have the general formula RP(O)(OR2). So they are esters of phosphonic acid. So this is the phosphonic acid or phosphorus acid. And this you have to call back to RPO O R dash. So these are phosphonates. These are phosphonates.

They represent an important class of organophosphorus compounds. They are used as reagents in organic synthesis prevalent and there is a plethora of example of biologically active compounds possessing the phosphonate moiety.

A well-known member being glyphosate, better known as a Round up with the formula (HO2)P(O)CH2NHCH2CO2H, this derivative of glycine is one of the most widely used herbicide. So here also another herbicide is there with phosphonate. The nerve gas agent sarin, containing both CP and FP bonds, is a phosphonate.

So this is the Glyphosate. Here you can see an alpha amino acid group is there and this is the phosphonate. So this is phosphonate. Also here, OH is there, so this is acid and this is also acid moiety. So these acid groups are present Glyphosate.

And this is nerve gas agent. As you can see here one F is taking this OR position, so this is also phosphonate because one alkyl group one P double bond O and this is present. So this is phosphonate and this is nerve gas agent.

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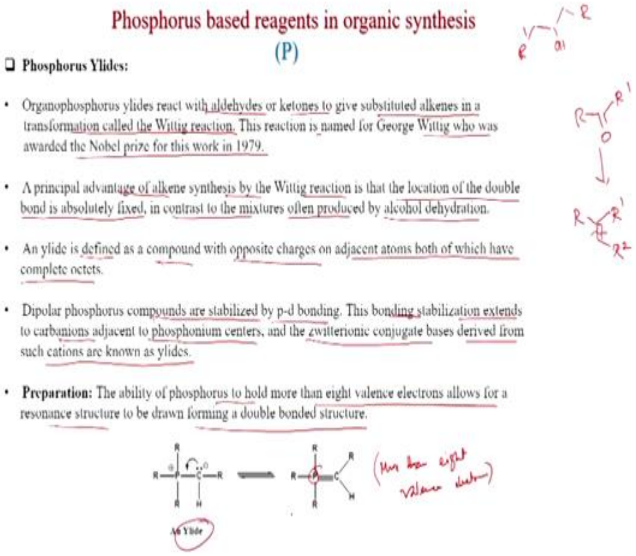

Phosphorus based reagents in organic synthesis

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❑ **Phosphorus Ylides:**

- Organophosphorus ylides react with aldehydes or ketones to give substituted alkenes in a transformation called the Wittig reaction. This reaction is named for George Wittig who was awarded the Nobel prize for this work in 1979.
- A principal advantage of alkene synthesis by the Wittig reaction is that the location of the double bond is absolutely fixed, in contrast to the mixtures often produced by alcohol dehydration.
- An ylide is defined as a compound with opposite charges on adjacent atoms both of which have complete octets.
- Dipolar phosphorus compounds are stabilized by p-d bonding. This bonding stabilization extends to carbanions adjacent to phosphonium centers, and the zwitterionic conjugate bases derived from such cations are known as ylides.
- **Preparation:** The ability of phosphorus to hold more than eight valence electrons allows for a resonance structure to be drawn forming a double bonded structure.

Now, we will discuss Phosphorus Ylides. So organophosphorus ylides react with aldehydes or ketones to give substituted alkenes in a transformation called the Wittig reaction, that we told earlier. This reaction is named for George Wittig, who was awarded the Nobel Prize for this work in 1979. So in 1950’s Wittig developed this powerful reaction and in 1979 he got the Nobel Prize.

A principle advantage of alkene synthesis by the Wittig reaction is that the location of the double bond is absolutely fixed. So this is very important in Wittig reaction the carbonyl group will take a double bond. So this double bond position is fixed actually. In contrast to the mixtures often produced by alcohol dehydration. So if you do an alcohol dehydration then you can get different product because then the Olefin can be from this side also. Then Olefin came from this side, this side, so you get mixtures often produced by alcohol dehydration.

An ylide is defined as a compound with opposite charges on adjacent atoms both of which have complete octets. A dipolar phosphorus compounds are stabilized by p-d bonding. This bonding stabilization extends to carbanions adjacent to phosphonium centers and the zwitter ionic conjugate bases derived from such cations are known as ylides.

So we have seen this phosphonium salts when treated with base when this ylide is generated. The ability of phosphorus to hold more than 8 valence electrons allows for a resonance structure to be drawn forming a double bonded structure.

So this is an ylide and here this more than 8 valence electrons. And phosphorus has the ability, three single bond, one double bond is there, that is why ylide can be drawn like this way also.

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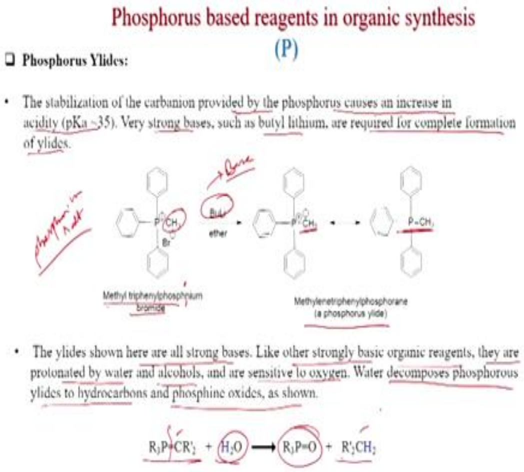

Phosphorus based reagents in organic synthesis

(P)

❑ **Phosphorus Ylides:**

- The stabilization of the carbanion provided by the phosphorus causes an increase in acidity (pKa ~35). Very strong bases, such as butyl lithium, are required for complete formation of ylides.

- The ylides shown here are all strong bases. Like other strongly basic organic reagents, they are protonated by water and alcohols, and are sensitive to oxygen. Water decomposes phosphorous ylides to hydrocarbons and phosphine oxides, as shown.

$R_3P{=}CR'_2 + H_2O \longrightarrow R_3P{=}O + R'_2CH_2$

The stabilization of the carbanion provided by the phosphorus causes an increase in acidity pKa 35. Very strong bases, such as butyl lithium are required for complete formation of ylides. So this is the triphenylphosphnium bromide, this is a phosphonium salt.

Triphenylphosphnium bromide CH3 group this hydrogen now it is acidic, so this can be taken by butyl lithium which is base. So butyl lithium is base here and you get this carbanion, so carbanion and positive charge will make a double bond. So that is what we have seen here. So this double bond can be drawn because phosphorus can take more than 8 valence electron and this is the phosphorus ylides.

The ylide shown here are all strong bases. Like other strongly basic organic reagents, they are protonated by water and alcohols and are sensitive to oxygen. So this is very important, the ylides are unstable in air and moisture because they are basic and reactive, they can be easily quenched by water as well as in air.

Water decomposes phosphorus ylides to hydrocarbons and phosphine oxides, as shown. So, if you put phosphine in water then what will happen? This oxide this bond will keep and you get the phosphorus oxygen bond and R2CH2. So oxygen is taken by the phosphorous and carbon takes a proton here, CH2.

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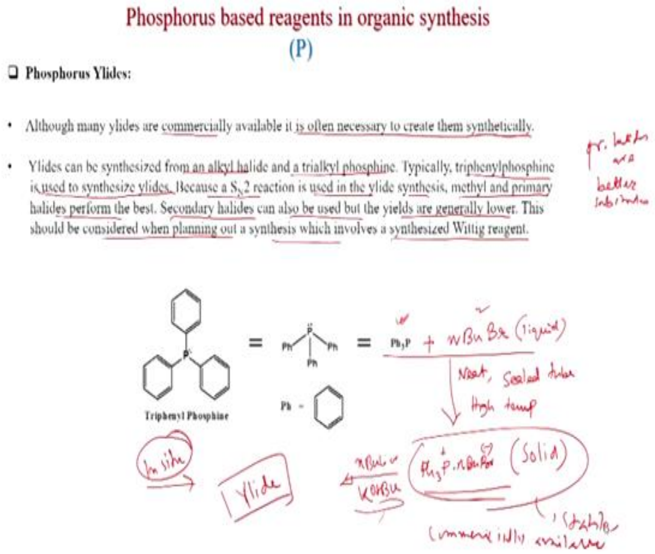

Phosphorus based reagents in organic synthesis

(P)

❑ **Phosphorus Ylides:**

- Although many ylides are commercially available it is often necessary to create them synthetically.
- Ylides can be synthesized from an alkyl halide and a trialkyl phosphine. Typically, triphenylphosphine is used to synthesize ylides. Because a $S_N2$ reaction is used in the ylide synthesis, methyl and primary halides perform the best. Secondary halides can also be used but the yields are generally lower. This should be considered when planning out a synthesis which involves a synthesized Wittig reagent.

Although many ylides are commercially available it is often necessary to create them synthetically. And ylides can be synthesized first from an alkyl halide and trialkyl phosphine. Typically triphenylphosphine is used to synthesize ylides. Because a $S_N2$ reaction is used in the ylide synthesis, methyl and primary halides perform the best. Secondary halides can also be used but the yields are generally lower. So primary halides are better, primary halides are better substrate. This should be considered when planning out a synthesis which involves a synthesized Wittig reagent.

So this is triphenyl phosphine we have seen and you have to react with an alkyl halide generally alkyl bromide suppose n-butyl bromide and this is generally liquid. So what you have to do, these two you can put in neat without solvent or so you can do this reaction, neat sealed tube and high temperature then you get this salt. The salt is formed, so this is solid. After that you have to put the n-butyl lithium or potassium tertiary butoxide strong bases so that you get the ylide.

So these are the steps for the formation of ylides. First you have to generate and phosphonium bromide salts like triphenyl phosphine and alkyl bromide reaction to generate salt and then with the base ylide. And this is generally generated in situ. In situ, this ylide is generated from this salt because they are stable. Stable commercially available, sometimes.

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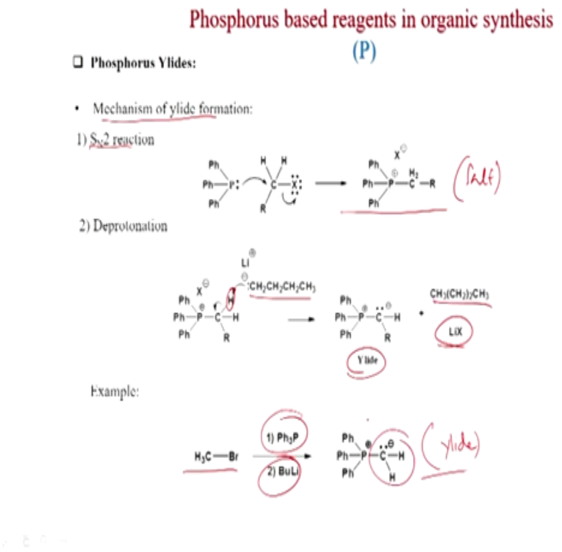

Phosphorus based reagents in organic synthesis

(P)

❑ **Phosphorus Ylides:**

- Mechanism of ylide formation:

1) $S_N2$ reaction

2) Deprotonation

Example:

Now, we will discuss mechanism of ylide formation. SN2 reaction. So this is the first reaction happens, what we told just now, that this SN2 reaction will happen you get this salt. This is a slat formation. Then the deprotonation with strong base like n-butyl lithium because this hydrogen is acidic and you get a carbanion and along with phosphorus, so this is the ylide. And this is formed a lithium X is formed. And this has an example like bromomethane, you react with triphenyl phosphine n-butyl lithium then you generate this ylide. With this CH2 minus group.

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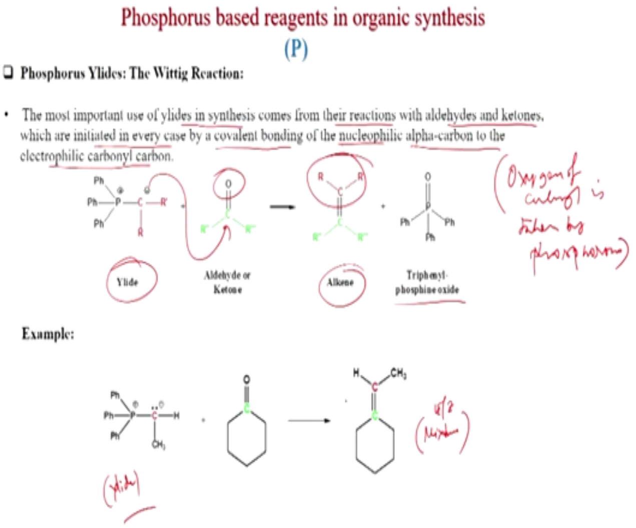

Phosphorus based reagents in organic synthesis

(P)

❑ **Phosphorus Ylides: The Wittig Reaction:**

- The most important use of ylides in synthesis comes from their reactions with aldehydes and ketones, which are initiated in every case by a covalent bonding of the nucleophilic alpha-carbon to the electrophilic carbonyl carbon.

**Example:**

The most important use of ylides is synthesis comes from their reaction with aldehydes and ketones, which are initiated in every case by a covalent bonding of the nucleophilie alpha-carbon to the electrophilic carbonyl carbon.

So this is the ylide and this is reacting here and ultimately you get an alkene. So this carbonyl oxygen is replaced by this. And triphenyl phosphine oxide is the by-product, so this oxygen of carbonyl is taken by phosphorus. So the detailed mechanism we will see and this is an example like this ylide, if you react with cyclohexanol then you get, this you will get mixture is a mixture of course, of this olefin.

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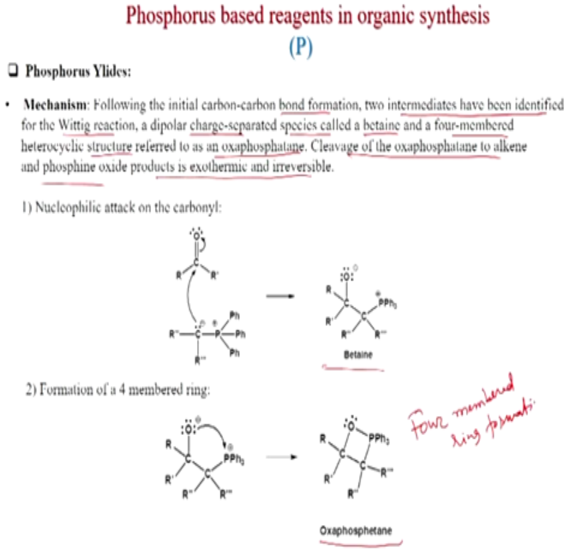

Phosphorus based reagents in organic synthesis
(P)

❑ **Phosphorus Ylides:**

- **Mechanism**: Following the initial carbon-carbon bond formation, two intermediates have been identified for the Wittig reaction, a dipolar charge-separated species called a betaine and a four-membered heterocyclic structure referred to as an oxaphosphatane. Cleavage of the oxaphosphatane to alkene and phosphine oxide products is exothermic and irreversible.

1) Nucleophilic attack on the carbonyl:

2) Formation of a 4 membered ring:

Mechanism following the initial carbon-carbon bond formation, two intermediates have been identified for the Wittig reaction, a dipolar charge-separated species called a betaine and a four-membered heterocyclic structure referred to as an oxaphosphatane. Cleavage of the oxaphosphatane to alkene and phosphine oxide products is exothermic and irreversible.

So nucleophilic attack on the carbonyl that has got betaine and formation of a four membered ring. So this O minus have reacted to this, this is called oxaphosphetane. This is the four-membered, this is important in Wittig reaction, four-membered ring formation.

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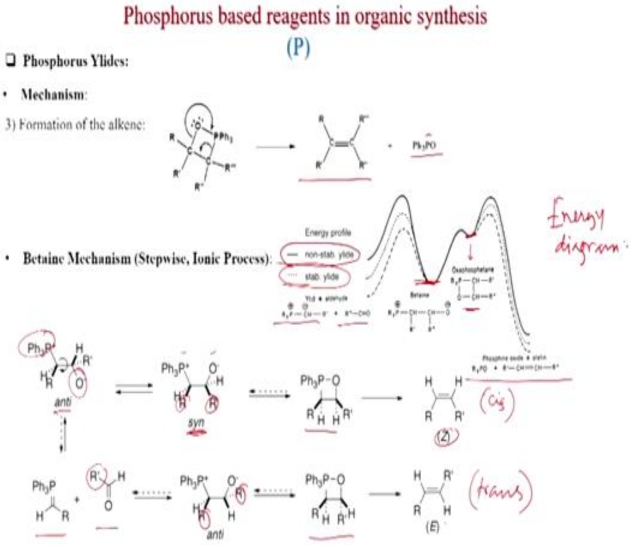

Phosphorus based reagents in organic synthesis

(P)

❑ **Phosphorus Ylides:**

- **Mechanism:**

3) Formation of the alkene:

- **Betaine Mechanism (Stepwise, Ionic Process):**

Now this oxaphosphetane this will break like this, so this bond will go to here, re-arrangement will happen to get the Olefin here. This double bond will from here and this oxygen will take by phosphorus, so you will get the triphenyl phosphine oxide.

And this is the energy graph, so if you start with an ylide and aldehyde and this one is non-stabilize, the solid one. Dotted one is stabilized ylide. Stabilized ylide has lower energy compared to the non-stabilized ylide and this is the betaine and this is oxaphosphetane. So betaine is first formed then you have to jump again to this energy barrier to get the oxaphosphetane and oxaphosphetane they will give the product olefin and phosphine oxides. So is the energy diagram.

And if you react this slide with this aldehyde then there are possibilities that there will be anti like R, R dash, R dash is with the aldehyde, it was R with this ylide. So this R, R dash they are in anti and these hydrogens are anti and now if this, they form the oxaphosphetane, it will be like this and ultimately it will give this E-alkane. So this is trans or E-alkane**.** So this anti will from and then the oxaphosphetane and then this Olefin formation will happen.

Alternatively, another anti is possible like R, R dash and these two are in the opposite side, this is also anti. And now a single one rotation will give this. After this rotation, it becomes syn now and O minus PPh3 are in the same side, so this is the syn conformer and this syn oxaphosphetane will form like this and ultimately it will give Z. So this is the cis alkene.

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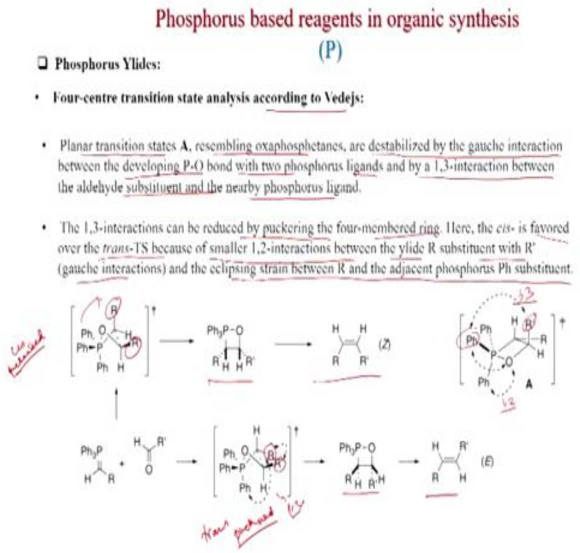

## Phosphorus based reagents in organic synthesis

(P)

❑ **Phosphorus Ylides:**

- **Four-centre transition state analysis according to Vedejs:**
  - Planar transition states **A**, resembling oxaphosphetanes, are destabilized by the gauche interaction between the developing P-O bond with two phosphorus ligands and by a 1,3-interaction between the aldehyde substituent and the nearby phosphorus ligand.
  - The 1,3-interactions can be reduced by puckering the four-membered ring. Here, the *cis*- is favored over the *trans*-TS because of smaller 1,2-interactions between the ylide R substituent with R' (gauche interactions) and the eclipsing strain between R and the adjacent phosphorus Ph substituent.

So this is the four-centre of transition state analysis according to Vedejs, this is very important. The planar transition state A, that is the oxaphosphetane resembled oxaphosphetane are destabilized by the gauche interaction between the developing P-O bond with two phosphorus ligands and by 1, 3 interaction between the aldehyde substituent and the nearby phosphorus ligand.

So this is the planar confirmer of this oxaphosphetane. So if you see there are many interaction is happening because there is a gauche interaction between developing P-O bond, this is the P-O bond developing and with these two phenyl groups, gauche interaction. Also, 1, 3 interaction is there between this group and this group. Between the aldehyde substituent and the nearby phosphorus ligand, so this is 1, 3. And these are 1, 2 interaction.

The 1, 3 interactions can be reduced by puckering the, four-membered ring. Here, the cis- is favored over the trans-transition state because of smaller 1, 2 interaction between the ylide R substituent with R dash gauche interaction and the eclipsing strain between R and the adjacent phosphorus Ph substituent. So this is the trans one, this is trans puckered. This puckered are more stable than the planar. So here, you can release some interaction.

Here, you can get still 1, 2 interaction is there between these two group and between this R and Ph also, you get some 1, 3 interaction here. So this is 1, 3 and also, 1, 2 interaction is present and this will go this oxaphosphetane and then the olefin. And this is for the cis puckered and here, you can see, the interaction is a little less because these two groups, smaller 1, 2 interaction and also this interaction also is might be less, 1, 3 interaction. So this is more preferred and this will convert to Z. So cis puckered geometry is more favoured than the trans because the smaller 1, 2 interactions.

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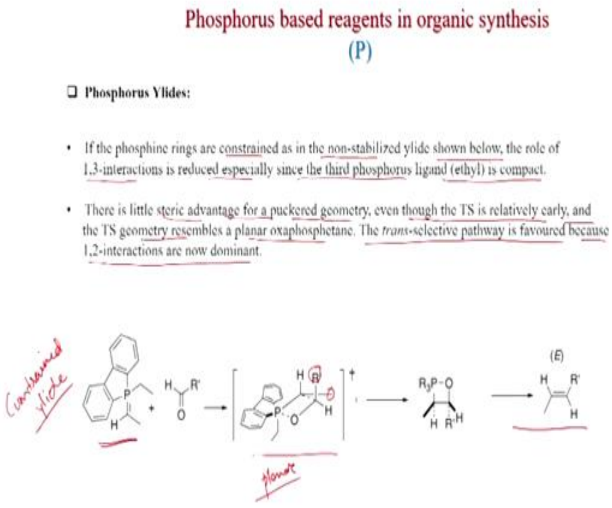

Phosphorus based reagents in organic synthesis

(P)

❑ **Phosphorus Ylides:**

- If the phosphine rings are constrained as in the non-stabilized ylide shown below, the role of 1,3-interactions is reduced especially since the third phosphorus ligand (ethyl) is compact.
- There is little steric advantage for a puckered geometry, even though the TS is relatively early, and the TS geometry resembles a planar oxaphosphetane. The *trans*-selective pathway is favoured because 1,2-interactions are now dominant.

If the phosphine rings are constrained as in the non-stabilized ylides shown below, the role of 1, 3 interactions is reduced especially since the third phosphorus ligand is compact. There is little steric advantage for a puckered geometry, so this is the ylide, you can see here is ethyl group and this is constrained ylide. And in this, this will be planar actually, if it is constant then it will planar because there is little steric advantage for a puckered geometry, even though the transition state is relatively early, and the transition state geometry resembles a planar oxaphosphetane.

The trans-selective pathway is favoured because 1, 2 interactions are now dominant. So in the cis this 1, 2 interactions will be more. But in the trans because this is planar the tarns oxaphosphetane in this case is stable. So in this case, we will get the trans olefin. So if it is constrained ylide then you get the trans Olefin. This was discussed in this paper Topic of Stereochemistry, 1994.

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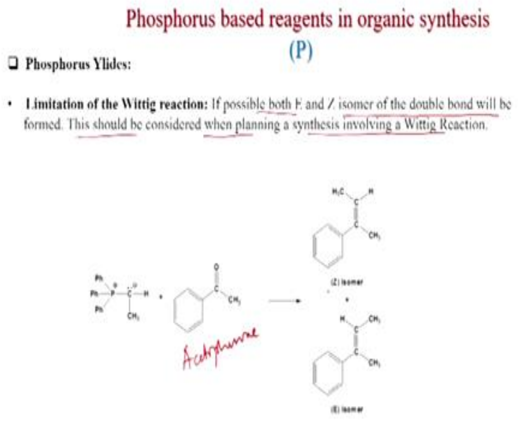

Phosphorus based reagents in organic synthesis

(P)

❑ **Phosphorus Ylides:**

- **Limitation of the Wittig reaction:** If possible both E and Z isomer of the double bond will be formed. This should be considered when planning a synthesis involving a Wittig Reaction.

Limitations of the Wittig reaction. If possible, both E and Z isomer of the double bond will be formed. This should be considered when planning a synthesis involving a Wittig reaction. So if you react with acetophenone then you get Z and E isomer.

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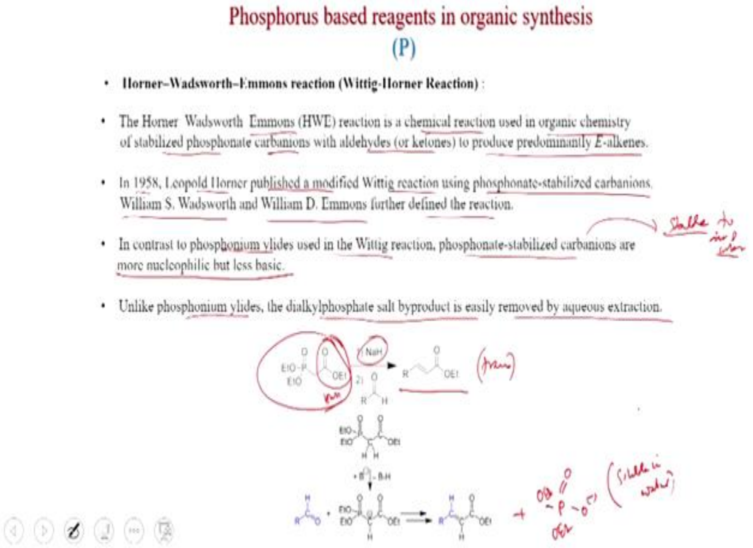

Phosphorus based reagents in organic synthesis

(P)

- **Horner–Wadsworth–Emmons reaction (Wittig-Horner Reaction)** :
- The Horner Wadsworth Emmons (HWE) reaction is a chemical reaction used in organic chemistry of stabilized phosphonate carbanions with aldehydes (or ketones) to produce predominantly *E*-alkenes.
- In 1958, Leopold Horner published a modified Wittig reaction using phosphonate-stabilized carbanions. William S. Wadsworth and William D. Emmons further defined the reaction.
- In contrast to phosphonium ylides used in the Wittig reaction, phosphonate-stabilized carbanions are more nucleophilic but less basic.
- Unlike phosphonium ylides, the dialkylphosphate salt byproduct is easily removed by aqueous extraction.

Now, we will discuss Horner-Wadsworth-Emmons reaction is a chemical reaction used in organic chemistry of stabilized phosphonate carbanions with aldehyde ketones to produce predominantly E-alkenes.

And in 1958, Leopold Horner published a modified Wittig reaction using phosphonate-stabilized carbanions William S. Wadsworth and William D. Emmons further defined the reaction.

In contrast to phosphonium ylides used in the Wittig reaction, phosphonate-stabilized carbanions are more nucleophilic but less basic. Also, these ylides are stable. So ylides are stable to air and water. So this is also very important. They are more nucleophilic but less basic.

Unlike phosphonium ylides, the dialkylphosphate salt byproduct is easily removed by aqueous extraction. This is also another advantage phosphate salt byproduct, can be easily removed. So this is the overall reaction. This is the phosphonate with a CO2Et, EWG group. And now, you can use sodium hydride and aldehyde you will get this trans product. This is the reaction base generating the carbanion that is the ylide, now react and you get this byproduct. It is soluble in water. So easily it is can extract.

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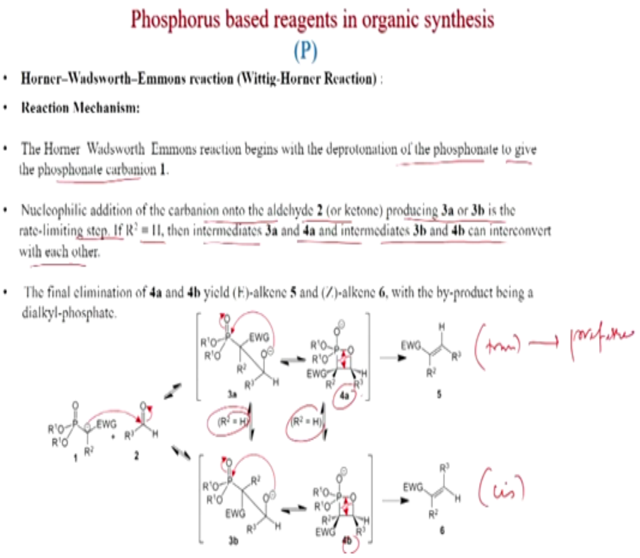

Phosphorus based reagents in organic synthesis

(P)

- **Horner–Wadsworth–Emmons reaction (Wittig-Horner Reaction) :**
- **Reaction Mechanism:**
- The Horner Wadsworth Emmons reaction begins with the deprotonation of the phosphonate to give the phosphonate carbanion **1**.
- Nucleophilic addition of the carbanion onto the aldehyde **2** (or ketone) producing **3a** or **3b** is the rate-limiting step. If $R^2 = H$, then intermediates **3a** and **4a** and intermediates **3b** and **4b** can interconvert with each other.
- The final elimination of **4a** and **4b** yield (E)-alkene **5** and (Z)-alkene **6**, with the by-product being a dialkyl-phosphate.

Now, the reaction mechanism. The reaction mechanism of the Horner-Wadsworth-Emmons reaction begins with the deprotonation of the phosphonate to give the phosphonate carbanion. Nucleophilic addition of the carbanion onto the aldehyde or ketone producing 3 A or 3 B is the rate limiting step. If R2 is equal to hydrogen, then intermediate 3 A and 4 A and intermediates 3 B and 4 B can interconvert with each other.

The final elimination of 4 A and 4 B yield E-alkene 5, and Z-alkene 6. So this is the overall reaction. So you can see this anion is reacting to the aldehyde and two oxaphosphetane will from, this one and this one. They will equilibrate if R2 = H, is equal to hydrogen and you get these two Olefin’s. So this is trans and this is cis and this is preferred, trans one is preferred.

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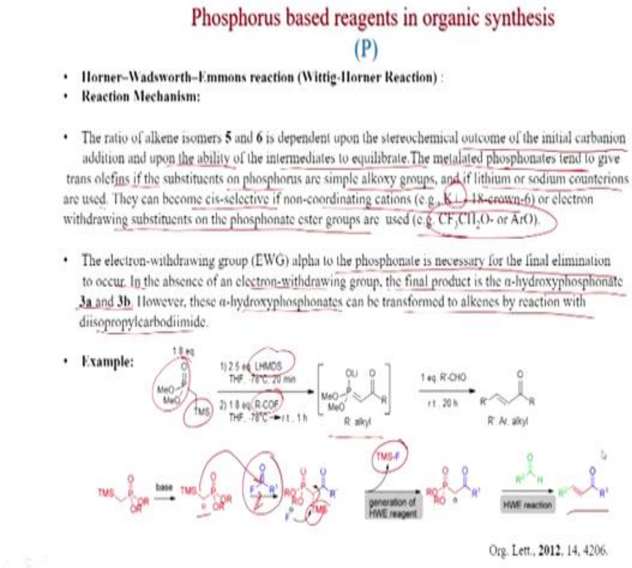

Phosphorus based reagents in organic synthesis

(P)

- **Horner–Wadsworth–Emmons reaction (Wittig-Horner Reaction)** :
- **Reaction Mechanism:**
- The ratio of alkene isomers **5** and **6** is dependent upon the stereochemical outcome of the initial carbanion addition and upon the ability of the intermediates to equilibrate. The metalated phosphonates tend to give trans olefins if the substituents on phosphorus are simple alkoxy groups, and if lithium or sodium counterions are used. They can become cis-selective if non-coordinating cations (e.g., K+, 18-crown-6) or electron withdrawing substituents on the phosphonate ester groups are used (e.g. $CF_3CH_2O$- or ArO).
- The electron-withdrawing group (EWG) alpha to the phosphonate is necessary for the final elimination to occur. In the absence of an electron-withdrawing group, the final product is the α-hydroxyphosphonate **3a** and **3b**. However, these α-hydroxyphosphonates can be transformed to alkenes by reaction with diisopropylcarbodiimide.
- **Example:**

Org. Lett., **2012**, 14, 4206.

The ratio of isomers 5 and 6 is dependent upon the stereochemical outcome of the initial carbanion addition and upon the ability of the intermediates to equilibrate the method phosphonate. The metalated phosphonates tend to give trans Olefins if the substituents on the phosphorus are simple alkoxy groups, and if lithium or sodium counterions are used. They can become cis-selective if non-coordinating cations like potassium plus, 18 crown 6 or electron withdrawing substituents on the phosphonate ester are used. This we will see later that you can get cis-olefin also.

The electron-withdrawing group alpha to the phosphonate is necessary for the final elimination to occur in the absence of an electron-withdrawing group, the final product is the alpha-hydroxyphosphonate 3 A and 3 B. However, these alpha-hydroxyphosphonates can be transformed to alkenes by reaction with diisopropylcarbodiimide. And this is an example with TM containing phosphonates. If you treat with LHMDS and with R-COF, you get ylide.

And this ylide if you react with an aldehyde then you get this double bond. So this is the mechanism base first deprotonates here. And now, this ROF if you are using, then this nucleophilic substitution reaction will happen, F minus will eliminate. And this F minus reacts with TMS, so a carbanion will from now and TMS-F will be side product. And ultimately it will react with the aldehyde, this is a Horner-Wadsworth reaction to generate the enone. This was published in Organic Letters.

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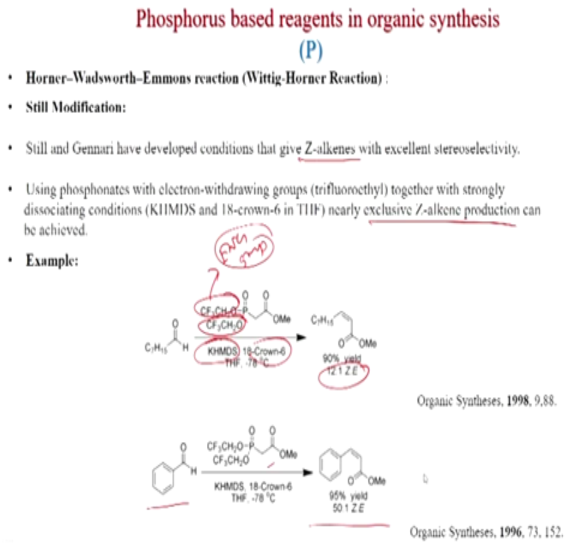

## Phosphorus based reagents in organic synthesis

(P)

- **Horner–Wadsworth–Emmons reaction (Wittig-Horner Reaction) :**
- **Still Modification:**
- Still and Gennari have developed conditions that give Z-alkenes with excellent stereoselectivity.
- Using phosphonates with electron-withdrawing groups (trifluoroethyl) together with strongly dissociating conditions (KHMDS and 18-crown-6 in THF) nearly exclusive Z-alkene production can be achieved.
- **Example:**

Organic Syntheses, **1998**, 9, 88.

Organic Syntheses, **1996**, 73, 152.

Trisubstituted alkenes. The steric bulk of the phosphonate and electron-withdrawing groups plays a critical role in the reaction of alpha-branched phosphonates with alkyl halides. Suppose if you have an alpha-branched here and then you can get E or Z and depending of R1 and R2, so this is R1 here and this is R2 on the ester motif. So if the steric increasing, steric is increasing then you get the E-isomer**.** So initially Methyl, Methyl is there, 95 percent Z, also Methyl Ethyl 90. Then Ethyl Ethyl 40, 60. Then Isopropyl Ethyl 90, 10 and both Isopropyl then you get 95:5. So with steric E prefers.

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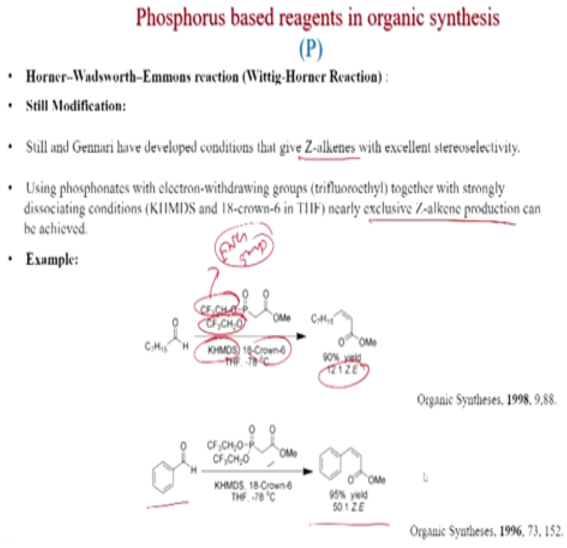

Phosphorus based reagents in organic synthesis

(P)

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- Example:

Organic Syntheses, 1998, 9, 88.

Organic Syntheses, 1996, 73, 152.

Now still modification. Still and Gennari have developed condition that give Z-alkenes with excellent stereoselectivity. Using phosphonates with electron-withdrawing groups.

Trifluoroethyl together strongly dissociating conditions potassium hexamethyldisilazane or 18 crown 6 in THF nearly exclusive Z-alkene production can be achieved.

This is the example. So this is the EWG group. EWG groups are present on this OR and with potassium we have to use and 18 crown 6 then you get 12 is to 1 Z/E. So this is very useful method published in Organic Syntheses. This is an example that benzaldehyde can be treated with this, you get this alpha,beta unsaturated ester in 50:1 Z/E. This was published in Organic Syntheses.

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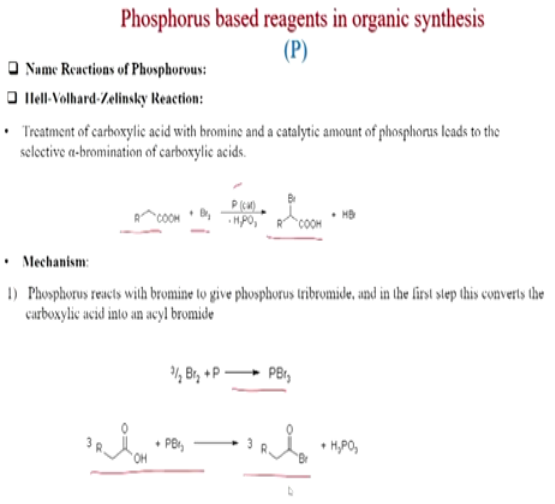

Phosphorus based reagents in organic synthesis

(P)

❑ **Name Reactions of Phosphorous:**

❑ **Hell-Volhard-Zelinsky Reaction:**

- Treatment of carboxylic acid with bromine and a catalytic amount of phosphorus leads to the selective α-bromination of carboxylic acids.

- **Mechanism**:

1) Phosphorus reacts with bromine to give phosphorus tribromide, and in the first step this converts the carboxylic acid into an acyl bromide

$$^{3}/_{2}\,Br_2 + P \longrightarrow PBr_3$$

Now, we will discuss HVZ reaction. If you react a carboxylic acid with bromine with phosphorus catalyst you get this alpha bromo carboxylic acid. And this is the mechanism, the phosphorus reacts with bromine to give phosphorus tribromide. And now, this phosphorus tribromide will react with this carboxylic acid to generate this acyl bromide.

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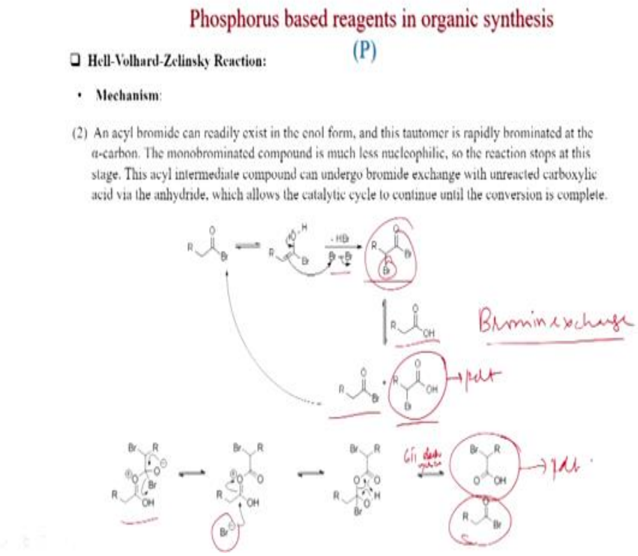

Phosphorus based reagents in organic synthesis

(P)

❑ Hell-Volhard-Zelinsky Reaction:

- Mechanism:

(2) An acyl bromide can readily exist in the enol form, and this tautomer is rapidly brominated at the α-carbon. The monobrominated compound is much less nucleophilic, so the reaction stops at this stage. This acyl intermediate compound can undergo bromide exchange with unreacted carboxylic acid via the anhydride, which allows the catalytic cycle to continue until the conversion is complete.

And now the acyl bromide, acyl bromide will take reaction with bromine to generate this alpha bromo acyl halide and now this bromine exchange will happen with this carboxylic acid, bromine exchange. The detailed mechanism we will show now. So with carboxylic acid you get this. And this acyl bromide is starting material.

So what is the mechanism first this carboxylic acid reacts with this one, this one like this form, then this bromine is eliminated here and this bromine is reacting here on the oxonium ion to generate this and now 6 pi electrocyclization will happen, electrocyclization and you get this. So this is the bromide and this is the carboxylic acid. So whatever this bromide, this is actually going to the carboxylic acid if you see, this hydrolysis is happening here means bromide is converted to the carboxylic acid, this is bromide, acyl bromide. So you get this is the product.

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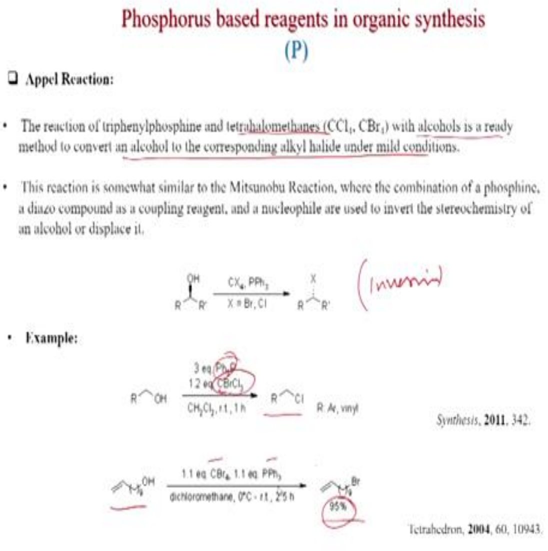

Phosphorus based reagents in organic synthesis

(P)

❑ **Appel Reaction:**

- The reaction of triphenylphosphine and tetrahalomethanes ($CCl_4$, $CBr_4$) with alcohols is a ready method to convert an alcohol to the corresponding alkyl halide under mild conditions.
- This reaction is somewhat similar to the Mitsunobu Reaction, where the combination of a phosphine, a diazo compound as a coupling reagent, and a nucleophile are used to invert the stereochemistry of an alcohol or displace it.

- **Example:**

*Synthesis*, **2011**, 342.

Tetrahedron, **2004**, 60, 10943.

Appel Reaction. This is the reaction of the triphenylphosphine and tetrahalomethanes with alcohol is a ready convert to alcohol to the corresponding alkyl halide and this is similar like Mitsunobu Reaction. So here inversion happen. And if you react with CBrCl3 triphenylphosphine then you get the alkyl chloride. This was published in Synthesis. And this is the alcohol with double bond react with 1 equivalents CBr4, 1 equivalent triphenylphosphine you get this product in 95 percent. So this method is quite efficient. It was published in Tetrahedron.

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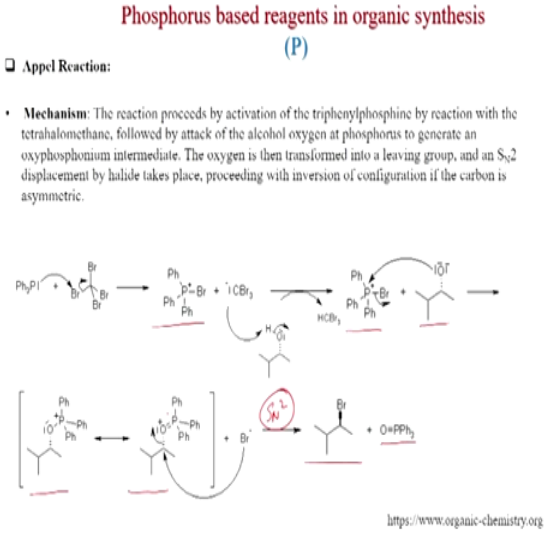

Phosphorus based reagents in organic synthesis

(P)

❑ **Appel Reaction:**

- **Mechanism**: The reaction proceeds by activation of the triphenylphosphine by reaction with the tetrahalomethane, followed by attack of the alcohol oxygen at phosphorus to generate an oxyphosphonium intermediate. The oxygen is then transformed into a leaving group, and an $S_N2$ displacement by halide takes place, proceeding with inversion of configuration if the carbon is asymmetric.

https://www.organic-chemistry.org

Appel Reaction, this is the mechanism that this substitution will take place this salt will form and this C minus then take up this acidic hydrogen and you get this and alkoxide is formed and after that you get this oxonium ion or like this is forming, this is the phosphorus oxygen double bond is forming so this is the electrophile now because this will displace with bromide and you get this SN2. So this is the main reaction SN2 is happening here and you get the inversion. And triphenylphosphine oxide is the byproduct.

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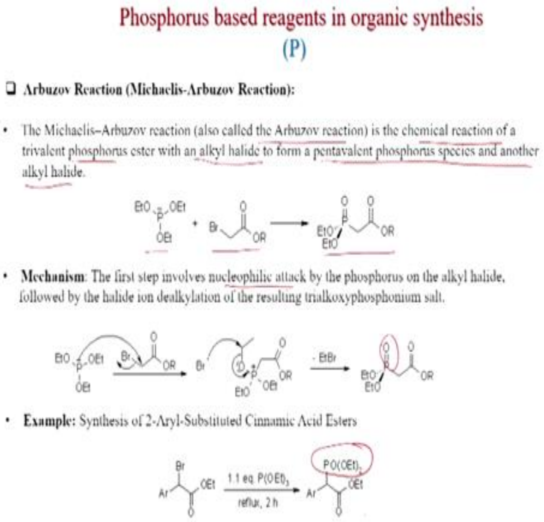

Phosphorus based reagents in organic synthesis

(P)

❑ **Arbuzov Reaction (Michaelis-Arbuzov Reaction):**

- The Michaelis–Arbuzov reaction (also called the Arbuzov reaction) is the chemical reaction of a trivalent phosphorus ester with an alkyl halide to form a pentavalent phosphorus species and another alkyl halide.
- **Mechanism**: The first step involves nucleophilic attack by the phosphorus on the alkyl halide, followed by the halide ion dealkylation of the resulting trialkoxyphosphonium salt.
- **Example:** Synthesis of 2-Aryl-Substituted Cinnamic Acid Esters

Arbuzov reaction. The Michaelis-Arbuzov reaction also called Arbuzov reaction is the chemical reaction of a trivalent phosphorus ester with an alkyl halide to form a pentavalent phosphorus species and another alkyl halide. This is the Arbuzov reaction, trialkyl phosphorus ester and with this alpha bromo ester, you will get this phosphonate.

So the first step involves nucleophilic attack like this and then this Br minus will attack here to get a carbonyl. So if this carbonyl is phosphorus oxygen double bond is formed. And examples like this Cinnamic Acid Esters can be converted to this P =O (OEt)2 to group with this triphenylphosphite.

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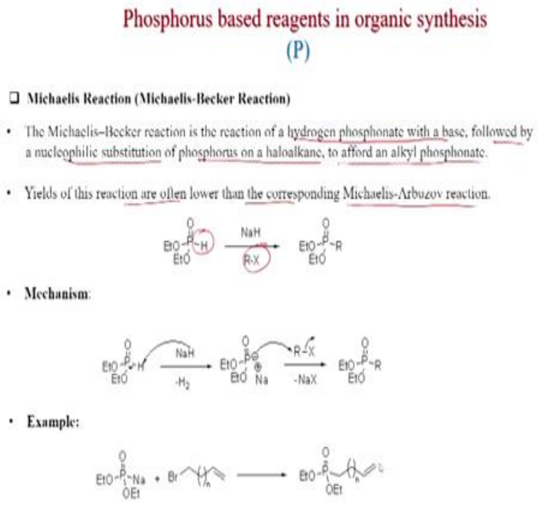

Phosphorus based reagents in organic synthesis

(P)

❑ **Michaelis Reaction (Michaelis-Becker Reaction)**

- The Michaelis–Becker reaction is the reaction of a hydrogen phosphonate with a base, followed by a nucleophilic substitution of phosphorus on a haloalkane, to afford an alkyl phosphonate.
- Yields of this reaction are often lower than the corresponding Michaelis-Arbuzov reaction.
- **Mechanism:**
- **Example:**

The Michaelis-Becker reaction is the reaction of hydrogen phosphonate with a base followed by nucleophilic substitution of phosphorus on a haloalkane to afford an alkyl phosphonate. Yields of the reaction are often lower than the corresponding Michaelis-Arbuzov reaction. So this is the acidic hydrogen can be deprotonated and then reacted with electrophile to generate this.

Mechanism, this is the mechanism first NaH will react to generate the anion then this substitution will happen. Example, if you react this with this bromine, you will get this product.

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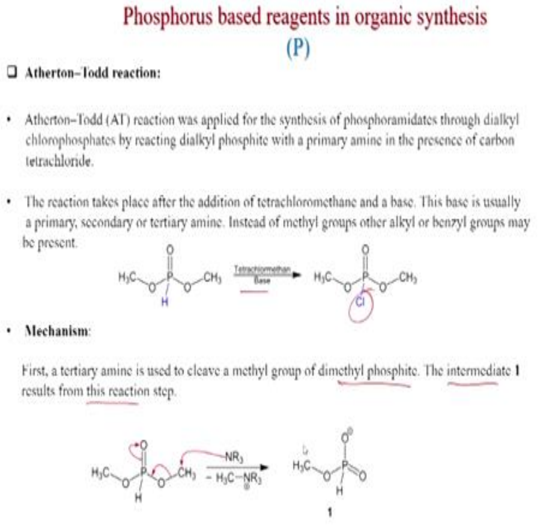

Phosphorus based reagents in organic synthesis

(P)

❑ **Atherton–Todd reaction:**

- Atherton–Todd (AT) reaction was applied for the synthesis of phosphoramidates through dialkyl chlorophosphates by reacting dialkyl phosphite with a primary amine in the presence of carbon tetrachloride.
- The reaction takes place after the addition of tetrachloromethane and a base. This base is usually a primary, secondary or tertiary amine. Instead of methyl groups other alkyl or benzyl groups may be present.
- **Mechanism:**

First, a tertiary amine is used to cleave a methyl group of dimethyl phosphite. The intermediate **1** results from this reaction step.

Now Atherton-Todd reaction was applied in the synthesis of phosphoramidates through dialkyl chlorophosphate by reacting dialkyl phosphite with a primary amine in the presence of carbon tetrachloride. And you have to use the base also carbon tetrachloride and base this is formed fast, the chloro substituent. So this is the mechanism tertiary amine is used to cleave a methyl group of dimethyl phosphite. The intermediate one result from this reaction step. So this is the first step is formed.

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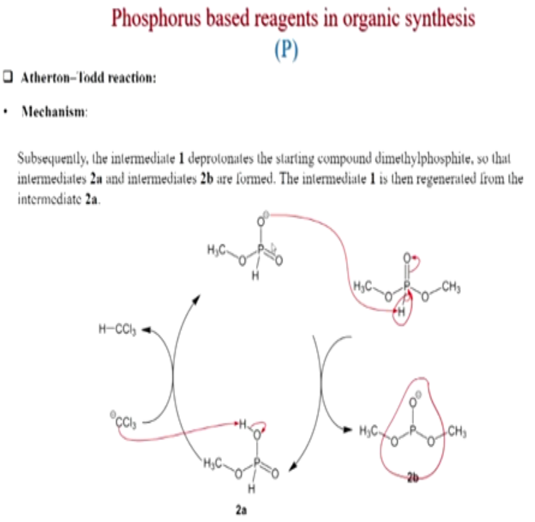

Phosphorus based reagents in organic synthesis
(P)

❑ **Atherton–Todd reaction:**

- **Mechanism**:

Subsequently, the intermediate **1** deprotonates the starting compound dimethylphosphite, so that intermediates **2a** and intermediates **2b** are formed. The intermediate **1** is then regenerated from the intermediate **2a**.

And now in the second step, this react with this so this anion will form here and this will be like this, this is the active intermediate and this 2A again goes to this compound.

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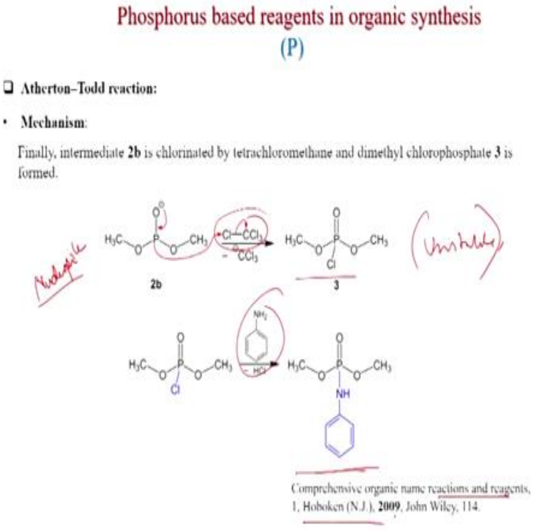

Phosphorus based reagents in organic synthesis
(P)

❑ **Atherton–Todd reaction:**

- **Mechanism**:

Finally, intermediate **2b** is chlorinated by tetrachloromethane and dimethyl chlorophosphate **3** is formed.

Comprehensive organic name reactions and reagents, 1, Hoboken (N.J.), **2009**, John Wiley, 114.

So this active 2B whatever we have seen 2B is nucleophile, nucleophile because anion is there and now this phosphorus will react with  CCl4 for to produce this intermediate and this can be reactive. So these are generally unstable, unstable. So they will react immediately with amine present to do the reaction. So you get this immediate. This was reviewed in this book Comprehensive organic name reactions.

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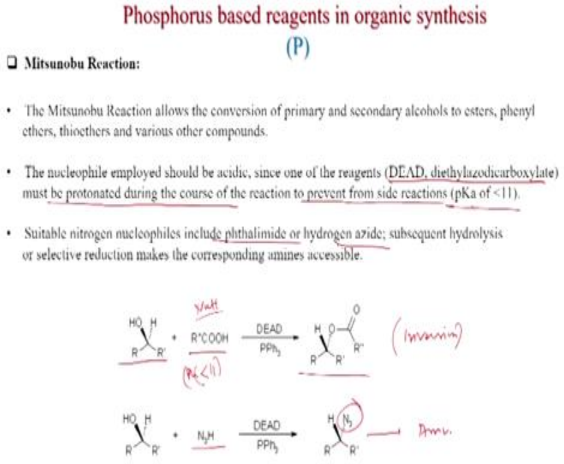

Phosphorus based reagents in organic synthesis

(P)

❑ **Mitsunobu Reaction:**

- The Mitsunobu Reaction allows the conversion of primary and secondary alcohols to esters, phenyl ethers, thioethers and various other compounds.
- The nucleophile employed should be acidic, since one of the reagents (DEAD, diethylazodicarboxylate) must be protonated during the course of the reaction to prevent from side reactions (pKa of <11).
- Suitable nitrogen nucleophiles include phthalimide or hydrogen azide; subsequent hydrolysis or selective reduction makes the corresponding amines accessible.

Now, Mitsunobu Reaction we already told this is the reaction of an alcohol with carboxylic acid or other acidic compound. So this is very important that the must be protonated during the course of the reaction to prevent from side reaction the pKa should be less than 11. So this pKa less than 11, this is anyways the pKa should be less than 11, so this will be acidic and with DEAD PPh3 you get this compound with inversion. So here also SN2 happening like Appel Reaction. Halide, hydrogen azide can be used this is like N3H you get the azide which can be converted to amine.

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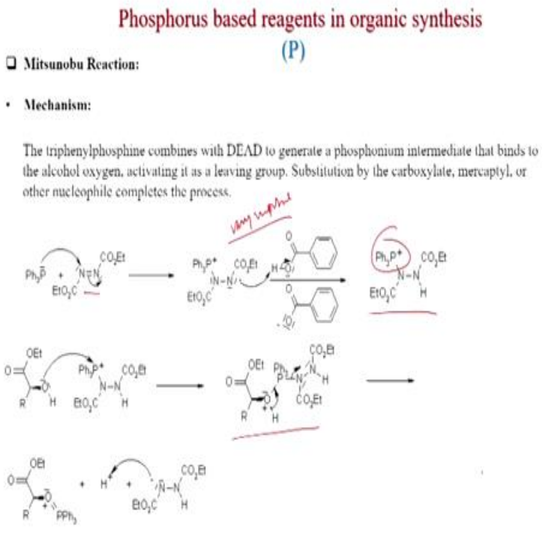

Phosphorus based reagents in organic synthesis (P)

❑ Mitsunobu Reaction:

- Mechanism:

The triphenylphosphine combines with DEAD to generate a phosphonium intermediate that binds to the alcohol oxygen, activating it as a leaving group. Substitution by the carboxylate, mercaptyl, or other nucleophile completes the process.

The procedure we will see now. So this is the mechanism. The triphenylphosphine will react with DEAD fast and this will take up this photon. So this is very important, otherwise high reaction will happen. This should be protonated immediately to generate this and now this will be taken up the alcohol to generate this intermediate. So this is now electrophile.

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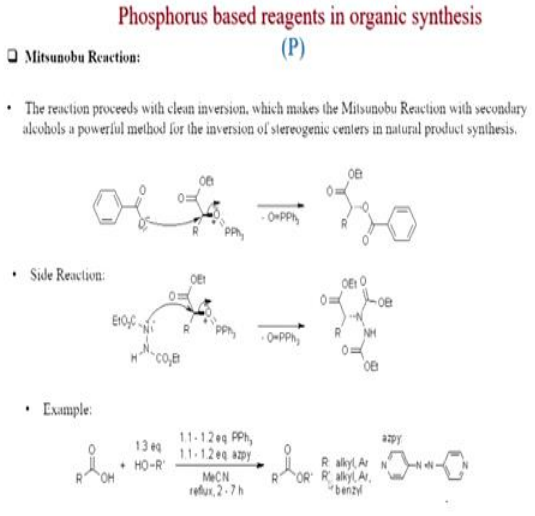

Phosphorus based reagents in organic synthesis (P)

❑ Mitsunobu Reaction:

- The reaction proceeds with clean inversion, which makes the Mitsunobu Reaction with secondary alcohols a powerful method for the inversion of stereogenic centers in natural product synthesis.
- Side Reaction:
- Example:

This is the electrophile here and you get this product. This is the side reaction will happen here also, if you do not protonate this one then the side reaction will happen. This is an example with this azpy with PPh3 you get this A start here from carboxylic acid.

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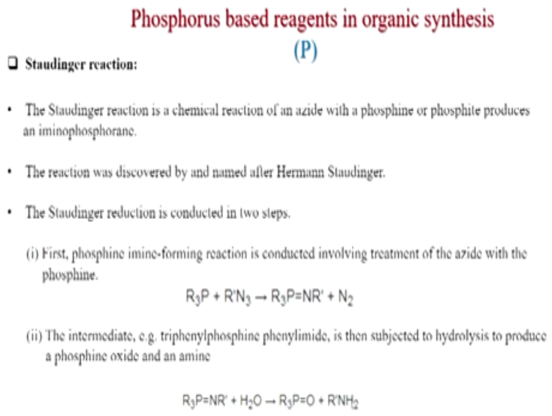

Phosphorus based reagents in organic synthesis

(P)

❑ **Staudinger reaction:**

- The Staudinger reaction is a chemical reaction of an azide with a phosphine or phosphite produces an iminophosphorane.
- The reaction was discovered by and named after Hermann Staudinger.
- The Staudinger reduction is conducted in two steps.

(i) First, phosphine imine-forming reaction is conducted involving treatment of the azide with the phosphine.

$$R_3P + R'N_3 \rightarrow R_3P{=}NR' + N_2$$

(ii) The intermediate, e.g. triphenylphosphine phenylimide, is then subjected to hydrolysis to produce a phosphine oxide and an amine

$$R_3P{=}NR' + H_2O \rightarrow R_3P{=}O + R'NH_2$$

And last reaction we will discuss Staudinger reaction is a chemical reaction of an azide with a phosphite or phosphine oxide. This is the azide to pass the imminophosphorane will from with elimination of nitrogen and this hydrolysis will give the phosphine oxide and amine. So ultimately azide is converting to amine.

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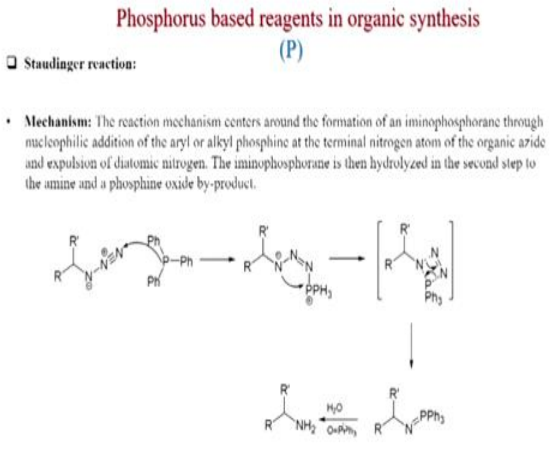

Phosphorus based reagents in organic synthesis

(P)

❑ **Staudinger reaction:**

- **Mechanism:** The reaction mechanism centers around the formation of an iminophosphorane through nucleophilic addition of the aryl or alkyl phosphine at the terminal nitrogen atom of the organic azide and expulsion of diatomic nitrogen. The iminophosphorane is then hydrolyzed in the second step to the amine and a phosphine oxide by-product.

And the mechanism is this like this triphenylphosphine will react to the azide to generate this and this four-membered ring will form after elimination of nitrogen you will get the iminophosphorane and iminophosphoranes after hydrolysis will generate the amine.

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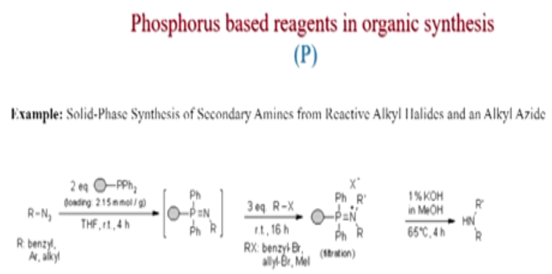

Phosphorus based reagents in organic synthesis

(P)

**Example:** Solid-Phase Synthesis of Secondary Amines from Reactive Alkyl Halides and an Alkyl Azide

And this is a Solid-Phase example. So two equivalent of this PPh2, which is connected to Solid-Phase you generate this iminophosphoranes and after 3 equivalent or RX you get an N alkylation here. N alkylation and to get this iminium salt and after hydrolysis, you get a secondary amine. So azide is converted to a secondary amine.

So in this lecture, today's lecture we have seen Phosphinates, Phosphines first, then Phosphinites, then Phosphonites, then Phosphites, then Phosphates, Phosphinous, amides, diamides, triamides, Phosphonium salt, Phosphine oxides, Phosphinates, Phosphonates, and Phosphorus Ylides.

Also name reaction we have seen Wittig reaction which is very useful reaction to generate Olefin from carbonyl compound, then Horner Wittig modification that is with alpha beta unsaturated ester preparation. Then Appel Reaction, Appel Reaction converting alcohol to halide. Arbuzov reaction, we have seen the Phosphate esters. Michaelis Reaction Phosphate esters.

Atherton-Todd reaction we have seen and Mitsunobu Reaction this is a powerful reaction to convert an alcohol with another ester, with an inversion in stereochemistry. And Staudinger reaction, in the Staudinger reaction the azide is converted to amine. So this is also powerful reaction which can be done simple by using triphenylphosphine. Thank you.