Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

Prof. Santanu Panda

Department of Chemistry

Indian Institute of Technology, Kharagpur

Lecture 55: Organophosphorus Chemistry

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. In the previous class, I started talking about the phosphorus the organophosphorus chemistry. I talk about the different type of trivalent and also tetravalent and pentavalent phosphorus compound. The Wittig olefination reaction several different variation how you can see sometime you are seeing formation of the E versus the Z-olefin in case of the stabilized versus the unstabilized cases.

And then also I talk about the Schrodinger reaction and Appel reaction. In the today's class I am going to talk about some of the other important reaction using a phosphorous.

The first thing is very important reaction called the Mitsunobu reaction. We are going to talk about that, then the the Michaelis-Arbuzov reaction, then the Michaelis-Becker reaction, then the Perkow reaction, Korey-Fuchs, there are Vilsmeier-Haack reaction. So, you are going to see lot of different name reaction in this part. So, and these are very important, you will see lot of questions comes in the competitive exam.

- Mitsunobu reaction
- Michaelis-Arbuzov reaction
- Michaelis-Becker reaction
- Perkow reaction
- Corey-Fuchs alkyne synthesis
- Vilsmeier-Haack reaction
- Phosphines

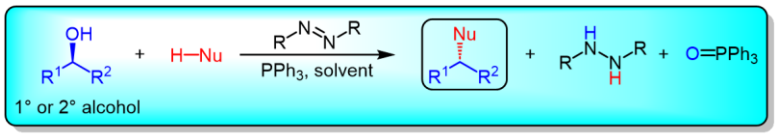
We start with the very important Mitsunobu reaction. It is a organic reaction that converts the alcohol into a variety of functional groups using triphenylphosphine and a azodicarboxylate.

So, what is the azodicarboxylate you can see we are going to talk about first this one, this is called diethyl azodicarboxylate. And if you have a R equal to ethyl or R equal to isopropyl, we call it diisopropyl azodicarboxylate.

So in this compound what is the important of this compound we are going to learn in a minute.But let us learn what is actually mitsunobu reaction is doing. It converting this 1º or 2º alcohol to the corresponding variety of product. As I mentioned that means, variety of nucleophile can participate. But this is we are talking about that the stereochemistry will be a inversion going to happen here. So, you can see the stereochemistry of the OH going to get for inversion that means, there will be some sort of a S_N2 reaction you are going to see here correct because there will be inversion going to happen. And, the important thing is here we can see clearly the OH is going to get getting out and a nucleophile is coming in. That means, what is happening here there is some sort of a activated oxygen this is going to form which the nucleophile can come and attack and remove it which we have seen also in case of Appel reaction. If you remember in Appel reaction, there was the nucleophile which is coming back and attacking here the halide which is coming back attacking here. So that means in case of Appel reaction also you have seen that if you come with a chiral alcohol you end up forming the corresponding inversion going to happen there.

So again you can see here we are using this diethyl as a dicarboxylate or the diisopropyl one carboxylic acid can be converted to the corresponding ester, alcohol or phenol can be converted to the ethers, thiol can be converted to thioethers.
Hydrozoic acid going to give alkyl azide and then imide can be going to get substituted imide and more and more. So it is a very important reaction we will learn in a minute the mechanism.

Mitsunobu Reaction



H-Nu	Product
Carboxylic acid	ester
Alcohol or phenol	ether
thiol	thioether
hydrazoic acid	alkyl azide
imide	substituted imide
sulfonamide	substituted sulfonamide

Again the triphenyl phosphine going to use in the reaction we have learned these are nucleophilic species in the phosphorous. So it is going to attack on this because you can see this is N=N with electron withdrawing group.

So the PPh_3 can attack on the nitrogen formation and formation of this anion here on the top of the nitrogen So this is getting stabilized by presence of this corresponding ester groups here.
So that is the first step once it is forming this anion what is going to happen here that you have a nucleophile in the reaction. So the nucleophile having a proton with a oxygen or with a sulfur with a acid that proton will be abstracted to generate. So now the nucleophile is ready to react. So now we have to generate the corresponding electrophile. So we learn that we are forming this species with a P with a + charge.
If you remember in case of Appel reaction we have shown you that we are forming something like this PPh_3^+Cl after attacking to the CCl_4. Here also what is going to happen and then the alcohol going to attack here very similarly in the previous case alcohol was attacking in this case. So the alcohol is attacking here. Here also the alcohol is going to attack to the PPh_3^+ the positive charge on the phosphorus is there so alcohol would attack the phosphorus forming this species.

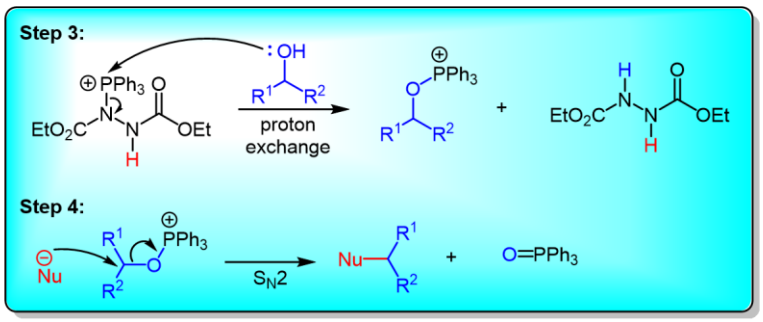
Now you can see that it is getting very similar to the intermediate where you have seen in case of Appel there so now the nucleophile going to come back and attack.
It is a S_N2 attack happen it is a backside attack going to happen to form the corresponding product. So that is why we end up a inversion happening.

Mitsunobu Reaction

❑ **Mechanism:**

❖ Then the positively charged phosphorus is now attacked by the alcohol, displacing a second nitrogen anion in an S_N2 reaction at phosphorus.

❖ Finally, the nucleophile attacks the phosphorus derivative of the alcohol in an S_N2 fashion to form the desired product.

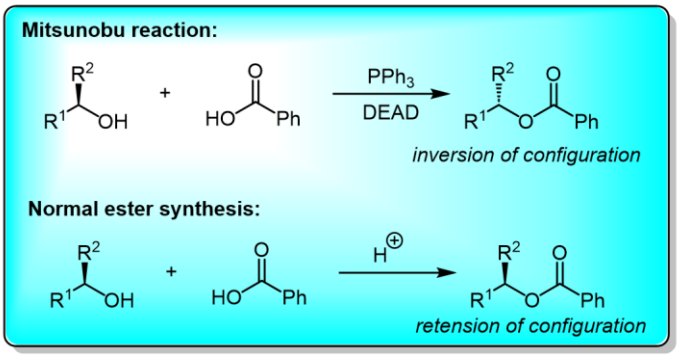


You can see in this reaction application suppose you have a chiral alcohol. You want to form this corresponding ester with a inversion then you have to use a Mitsunobu condition with the corresponding acid. If you want a retention then you can use a simple ester synthesis in place of acid that is that can give you the product. So, you can able to get both the compound using the one is using the Mitsunobu reaction if you want inversion and retention using normal ester.

Mitsunobu Reaction

❑ **Synthetic Application:**

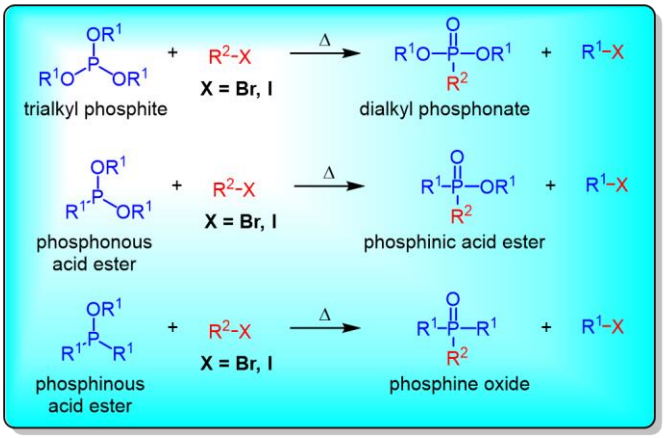
❖ It is a reliable way to replace OH with a nucleophile with a complete inversion of configuration.



So, after the mitsunobu reaction I am going to talk about another important reaction is the Michaelis- Arbuzov reaction. It was discovered in 1898 by professor A Michaelis and R. Kaehne. So this was a very important reaction which convert the trialkyl phosphite to the corresponding dialkyl phosphonate so you can see what is happening here you can clearly see a trivalent phosphorus going to convert to a pentavalent one a phosphonous acid ester going to convert to phosphinic acid ester. And then phosphinous acid ester going to convert to the corresponding phosphine oxide. So what is happening here if you see from here to here in every cases so a trivalent to a pentavalent so lets and then you are using what you are using you are using alkyl halide using alkyl halide you able to do that.

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.
- First reported by A. Michaelis and R. Kaehne in 1898; explored broadly by A. Arbuzov.




Prof. A. Michaelis

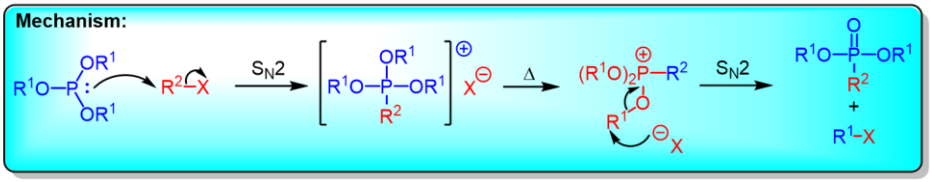

Prof. A. Arbuzov

And also you can see there is a change of oxidation number as well happening here. So, in this reaction you can see only the the tertiary alkyl halide did not react here and also the aryl and alkene of course, the aryl going to not going to work here because the first step is the S_N2 reaction. So in case of what we talk about in the Appel reaction also if you use aryl halide that reaction does not work. Because where about there will be S_N2 with alkyl halide you can think about the S_N2 will happen very nicely with primary but with also a secondary. But with tertiary the S_N2 is not favorable and you will not see much product from it so that is why this reaction is limited with the primary and secondary first thing is what is happening here the nucleophilic attack of the P.Once the S_N2 attack is happening here formation of this species here with the phosphorus with the + charge now this X^- going to come back and take this R^1 and form this phosphorous oxygen double bond. So, what we are seeing here from going from here to here the first is S_N2 and then the X^- is also a kind of this group is acting as a activated. So, this oxygen is acting as a oxygen with activated. You can think about a very similar thing like a acting as a leaving group that is why this can happen another S_N2 can happen here.

So there is two different S_N2 is happening that means if you see about your in this particular cases you start with suppose a secondary one and you have this particular stereochemistry of the X then in the product also that stereochemistry will be retain. What is going to happen here of course, you will be your this group will be changing here I think you know you can give them name R^2 or R^1'. Because what is happening here first thing is there is two different S_N2 happening first there is a S_N2 happening first this first there is a S_N2 here and then there is another S_N2 happening to form this product. So that means that is why it is a neat retention going to happen.

Michaelis-Arbuzov Reaction

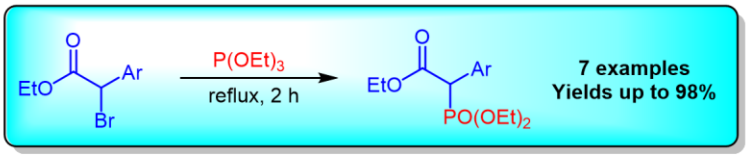
- The reaction usually proceeds well with primary alkyl halides and with some selected secondary alkyl halides.
- Aryl, alkenyl, and tertiary alkyl halides didn't react.



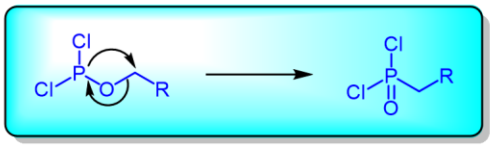
Again the α-bromo esters can also undergoes this reaction if you have α-bromo ester do the very similar condition you can end up going to the product. Also there is Arbuzov type rearrangement can also occur where the oxygen from the OR group act as a leaving group.You can see some Arbuzov type rearrangement can also happen to get to the corresponding product.

Michaelis-Arbuzov Reaction

- α-bromo esters also undergoes the reaction.



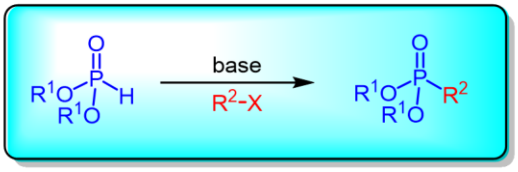
- An Arbuzov-type rearrangement can also occur where the O from an OR group acts as the leaving group in the initial S_N2 attack of the phosphorus.



Again the Michaelis-Becker reaction what is happening we talk about in the previous cases now we are talking about the hydrogen phosphonate. We talk about the phosphonate in the last slide here we are talking about if you have a hydrogen phosphonate and if you use a base and R^2-X. This is called a Michaelis-Becker reaction here the base first going for the proton abstraction first this proton is getting abstracted generate this anion which can now go for a SN2 reaction to get to the corresponding product.

Michaelis-Becker Reaction

- The reaction of a hydrogen phosphonate with a base and an alkyl halide to form an alkyl phosphonate is known as the Michaelis-Becker reaction.
- First, the base abstracts the proton from the hydrogen phosphonate followed by a substitution reaction that leads to the product formation.

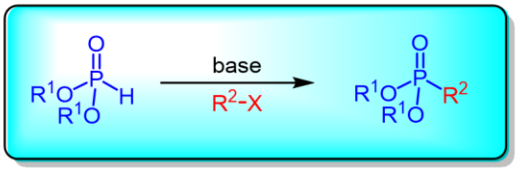


Other modification here again the Perkow reaction here we are talking about if you have a like we talk about alkyl halide in the previous case here you have a α-haloketone. If you have a α-halo ketone then what is going to happen. Then you end up forming a di-alkyl vinyl phosphate so you are forming a di-alkyl vinyl phosphate here. If you treat with $P(OR)_3$ and then of course you have to heat up the reaction so let us try to understand what is happening here.

Here what is happening the phosphorus is attacking to the corresponding carbonyl group here forming this O^-. And then that O^- & come taking the P generating. So, you can think about generating some sort of a formation of this O-P with OR and then you have generated this X and a - here. You have seen very similar things in case of the Brook rearrangement where you have seen the Si. Here the O is taking the P generating - getting rid of this x formation this double bond. Now what is going to happen the X- which is getting out from here can attack on this alkyl halide. Because again you can see this O and the P is + charge this can act as a leaving group so the X can attack for a X can attack for SN2 reaction here.So, it can go for SN2 reaction here the alkyl in halide going to form and you end up forming this corresponding vinyl phosphate.

Michaelis-Becker Reaction

- The reaction of a hydrogen phosphonate with a base and an alkyl halide to form an alkyl phosphonate is known as the Michaelis-Becker reaction.
- First, the base abstracts the proton from the hydrogen phosphonate followed by a substitution reaction that leads to the product formation.

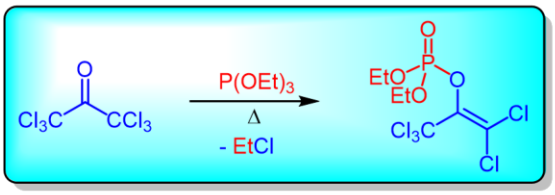


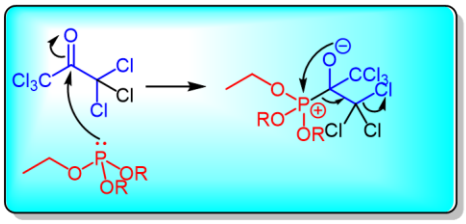
Some of the modified version here you can see if you use this compound with CCl_3 on the both side the EtCl going to come out from here and you end up forming this compound. Again very similar thing going to happen this P that means what we are talking about here we are talking about the α-halo carbonyl compound where actually you have lot of electron withdrawing group attached. In that case what is happen the carbonyl is very very reactive I think you guys have heard about this type of reactivity in the halo form reaction.

And the haloform reaction final step where we will see the hydrolysis going to happen. It is very similar reactivity happen the OH- attacks here get rid of the formation of the corresponding haloform over here. Here also what is going to happen the P going to attack here to the C that is why it is going to attack to the C. After that attack of the carbon the O- going to take the P formation of the carbanion here get rid of the Cl. And then again once then the once it is going to form the Cl- can comes back and attack here for the SN2 get rid of this that can end up formation of this compound the vinyl phosphate going to form at the end.

Perkow Reaction

❖ **Selected example:**





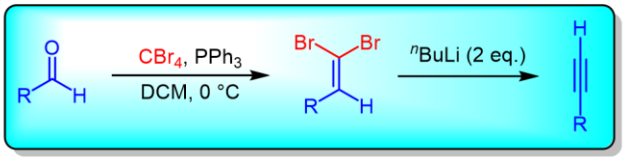
So I am going to talk about another important reaction again discover by Professor E. J. Corey Corey-Fuchs alkyne synthesis. It is a one C homologation of aldehyde to the corresponding terminal alkyne. It is very important reaction which convert the corresponding aldehyde to the corresponding alkyne and the first step is what is what you are using the CBr_4, PPh_3 a very similar reagent you have used for Appel reaction. So there it was a alcohol here you have aldehyde.

Because of alcohol you see is forming corresponding alkyl halide here you are seeing formation of the corresponding dibomide and now you treat with corresponding $^{n}BuLi$.

You have to treat 2 eq. of it that is going to convert this corresponding dibomo to corresponding terminal alkyne.

Corey-Fuchs Alkyne Synthesis

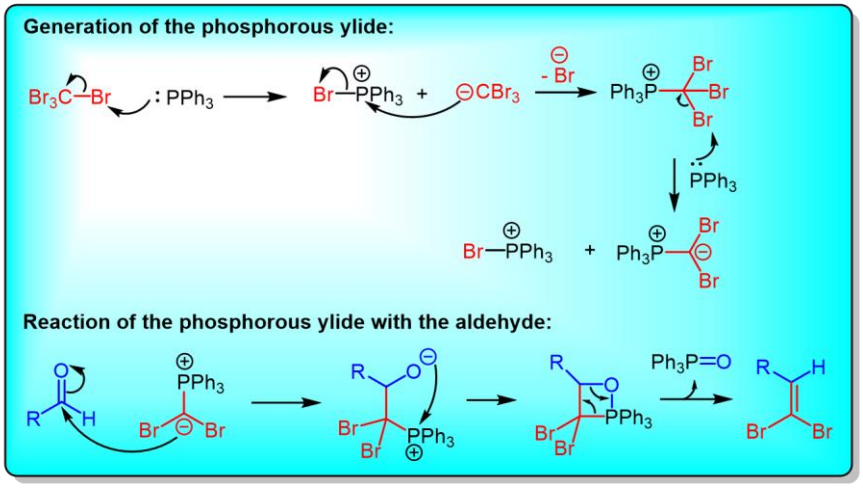
- The one-carbon homologation of aldehydes to the corresponding terminal alkynes using CBr_4 and PPh_3 is known as the **Corey-Fuchs alkyne synthesis**.
- The first step is the conversion of the aldehyde to the corresponding homologated dibromoolefin.
- In the second step the dibromoolefin is converted to terminal alkyne by treatment of two equivalents of *n*-butyl lithium, this process is known as **Fritsch-Buttenberg-Wiechell rearrangement**.



Try to understand the mechanism very similar mechanism of the Appel reaction first for PPh_3 going to attack here formation of this species where you have this CBr_3^-. So, the CBr_3^- going to now attack there to the PPh_3 and then going to form this species here and finally, it can form this corresponding ylide species here. So, the PPh_3 can take another Br here to generate a ylide species. Now, this ylide so here you are seeing a generation of a P ylide which was different compared to once you have the in case of the Appel reaction.So here this ylide going to now attack to the corresponding carbonyl compound. - going to attack here formation of this 4 member the oxaphosphate intermediate very similar to the Wittig reaction and then it can form this PPh3=O and form the corresponding dibromide.

Corey-Fuchs Alkyne Synthesis

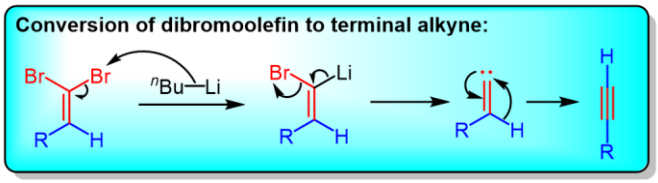
❑ **Mechanism:**



Once you have this vinyl dibromide species, this can react with the butyl lithium to so first there will be a metal halogen exchange. You guys have learned in the Li chemistry generate the corresponding Li which can generate again it can generate the corresponding carbene here which can finally form the corresponding alkyne. It could be α-elimination to generate that and then the carbene and then form the corresponding alkyne.

Corey-Fuchs Alkyne Synthesis

❑ **Mechanism:**



Other important reaction is Vilsmeier-Haack reaction. So again I think, I am not spending too much time on each of this reaction. I am going to see talk about more problem during the problem discussion classes. The Vilsmeier-Haack reaction is another important reaction where you can able to convert the aryl ring or the the heteroaryl ring and you introduce the corresponding the CHO group using DMF and $POCl_3$.

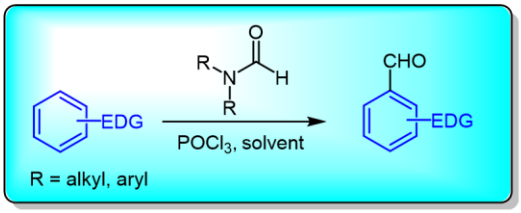
So that is another, I think a pentavalent P compound $POCl_3$.

So, with that + DMF can be used for this reaction. So, usually electron rich aromatic and hetero aromatic compounds worked well. So, this you can see this is a one type of

Friedel-Craft reaction of the aromatic compounds. So, you can see electron rich aromatic and hetero aromatic works fine.

Vilsmeier-Haack Reaction

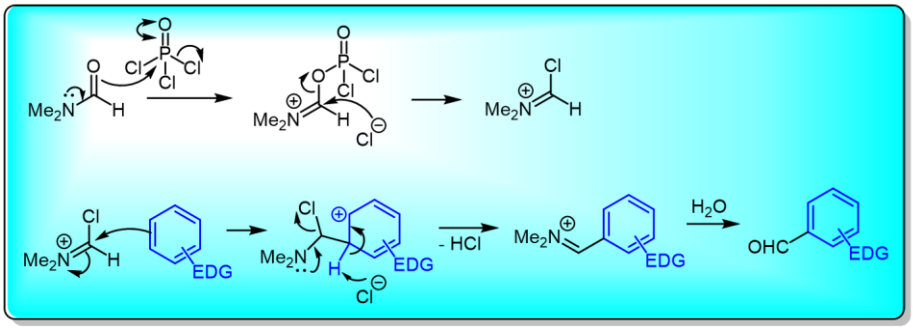
- The introduction of a formyl group into electron-rich aromatic compounds using a *N,N*-disubstituted formamide and $POCl_3$.
- Generally, DMF/$POCl_3$ combination is used.
- Usually, electron-rich aromatic and heteroaromatic compounds are worked well.
- The relative reactivity of five-membered heterocycles is pyrrole > furan > thiophene.



So, first thing is the generation of the reactive chloroiminium ion.This is the reactive intermediate which going to form by reacting DMF with $POCl_3$. So, DMF can attack through this O here first attacking happening to the $POCl_3$. The Cl- get out, the Cl- attacking to this imine and the N in a lone pair going to come back get rid of this one to form the corresponding chloroiminium. Now, the chloroiminium is very reactive. So, it can now it can take part in the Friedel-Craft reaction.So, aromatic ring in the electron density can be attacked there, formation of this intermediate. Now, the H the C-H bond going to cleaved and form the double bond here to neutralize the positive charge and once you have this imine it can hydrolyze it to corresponding aldehyde.

Vilsmeier-Haack Reaction

❑ **Mechanism:**

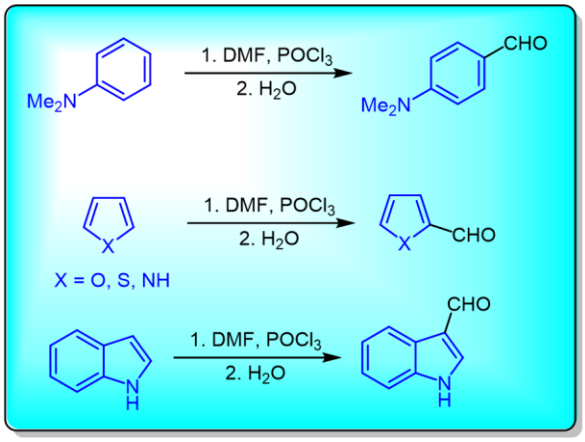


There are some other example here you can see using this particular component you can see electron rich here.

So, now this can be directing group effort like where it can able to step now you can see this because of this N electron rich it can give electron density into the p-position. So, it follows the very similar rule of the electrophilic aromatic substitution. So, it is a o,p-directing group here going to form this product as a major product. The heteroatom can also work here using the DMF, $POCl_3$ can introduce aldehyde here one of the example with indoles it can also in you can see indoles can also react with electrophile in the C-3 position to get the aldehyde in the C-3 position.

Vilsmeier-Haack Reaction

❑ **Selected examples:**



So, we talk about different type of name reaction using P and now I think I am move forward and talk about one of the important class of the P type the ligand called phosphine.So, this is again as I mentioned at the beginning the one of the important use of P based ligand or phosphine for different type of cross coupling reaction using transition metal.

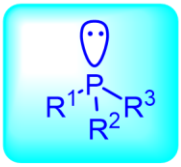
So, this is again as I mentioned at the beginning the one of the important use of phosphorous based ligand or phosphine for different type of cross coupling reaction using transition metal.So, again you can see these are the common structure of the phosphine. P having this lone pair and attached with the three different alkyl or three different aryl groups or even three or again the same groups also. Again there are a lot of different chiral P compounds I think I am not having time to discuss all of this here. But again I think if you want to learn more about the P chemistry I think you can learn some of these things from organometallic course.

I am going to briefly talk about that the phosphines can be a σ-donor or a π-acceptor.

So, we are going to talk about that generally there are different type of P the phosphine ligands we are going to talk about one is trialkyl phosphines are usually act as a σ-donor if you have a trialkyl one. Once you have a triaryl phosphines or a phosphites, these are a π-acceptor. So, this can accept π-density from the metal.

Phosphine

- Phosphines with a chemical formula of $PR^1R^2R^3$ (R^1, R^2, R^3 = alkyl, aryl, alkoxy etc.), are used as ligands in metal complexes and in catalysis reactions.
- Depending on the R group, the steric and electronic properties can vary.
- They may be σ-donors and/or π-acceptors.
- Trialkyl phosphines are usually act as a σ-donors.
- Phosphites and triaryl phosphines are π-acceptors.

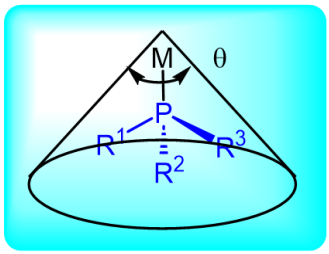


So, I am going to just finish with the phosphine discover the phosphine discussion with two important thing one is the cone angle another is the bite angle. So, you are going to heard about these things once I talk about the reactivity of different ligand in a reaction. So, again these are the steric bulk of the phosphine ligand is a very important determine some of the reactivity. So, there is a Tolman use this name cone angle to understand the space occupancy. The cone angle is defined that a solid angle which is going to form where you keep the metal at the vertex and and form a cone and the outermost edge of the Van der Waals sphere of the ligand.

So, this is the outermost sphere of the Van der Waals over walls of the ligand. So, this is forming a angle. So, this is a angle called a cone angle. Again there are this cone angle is very important you can see the phosphine with a larger cone angle leads to fast reductive elimination. Again this cone angle can depend on the size of this group you can clearly understand if you know these Van der Waals radius or the Van der Waals sphere as I mentioned here can be dictate based on the size. The size is bigger than the Van der Waals spheres will be bigger in size the cone angle will be higher. And going from PH_3 to PF_3, $POMe_3$ in this direction what you are seeing here? We are seeing the cone angle getting increased because the bulkiness of this. So, once you come to P-tBu used in lot of the reaction you can see the cone angle is 182º, where increase of PMe_3 you can see it is 118º. So, that can control the reductive elimination which is a very critical stage which is the last step of most of the cross coupling reactions.

Phosphine

- Steric bulk of a phosphine ligand can be determined by their 3-D space occupancy.
- Tolman uses the name **cone angle** (Θ) to understand the space occupancy.
- It is defined as the solid angle formed with the metal at the vertex of a cone and the outermost edge of the van der Walls spheres of the ligand atoms at the perimeter of the base of the cone.
- Phosphine with a larger **cone angle** leads to fast reductive elimination.



Cone angles for some common phosphine ligands are:

Phosphine Ligand	Cone Angle
PH_3	87°
PF_3	104°
$P(OMe)_3$	107°
PMe_3	118°
PMe_2Ph	122°
PEt_3	132°
PPh_3	145°
PCy_3	170°
$P(t\text{-}Bu)_3$	182°
$P(mesityl)_3$	212°

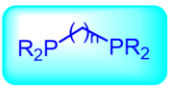
Other angle is the bite angle. So, bite angle is mostly comes to the picture when you have a bidentate phosphine ligands. Once you have a bidentate ligands means 2 phosphines with the C skeleton.

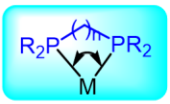
So, these are means two of the P is binding with your metal you call them a bidentate phosphine or diphosphine or bisphosphine ligand. There are also chiral and achiral version of that and they can form they can bind with the metal like that. So, once the ligand metal ligand. So, this bond is called a bite angle and this bite angle is very important a larger bite angle can leads to faster reductive elimination.Again you can see the reductive elimination is a very important step lot of the cases instead of the reductive elimination the β-hydride elimination happen in case of the Pd catalysis.

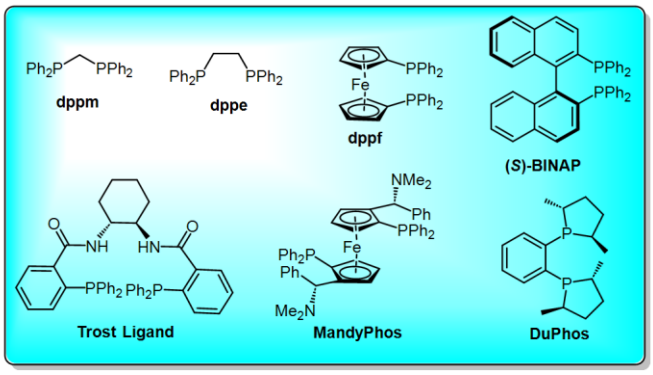
So, that time this bite angle and the cone angle play important role. So, you can see this, there are different type of the bisphosphine ligand which I listed here. So, these are the some of the achiral one, some of the chiral one here which can be Mandyfos and then the Dufos and then the Trost have develop this ligands here which are not a. So, if you see here these are the connected in the with the two C in the backbone here, here because of Trost ligand there are also N. So, now, if the metal can bind with, there are 4 coordination here.

Phosphine

- There is another types of bidentate phosphine ligands known as diphosphines or bisphosphines.
- In case of bidentate ligands, the L-M-L angle is known as **bite angle**.
- Also phosphine with larger **bite angle** leads to fast reductive elimination.







So, that is all about the phosphine ligands in this particular part of the P chemistry, we learn lot of the name reaction. Very important the Mitsunobu reaction, the Michaeliss-Arbuzov reaction and then of course, some of the other name reaction of the some of the other variation of the reaction. Then another Corey-Fuchs alkyne synthesis, we have seen how we convert the corresponding aldehyde to the corresponding terminal alkyne. Vilsmeier-Haack reaction convert the corresponding aryl species, you introduce the aldehyde group in aryl or heteroaryl and we talk about the phosphine based ligand.

- Mitsunobu reaction
- Michaelis-Arbuzov reaction
- Michaelis-Becker reaction
- Perkow reaction
- Corey-Fuchs alkyne synthesis
- Vilsmeier-Haack reaction
- Phosphines

Again these are the references and thank you so much for coming to the class I am going to see you guys in the next class. Thank you.