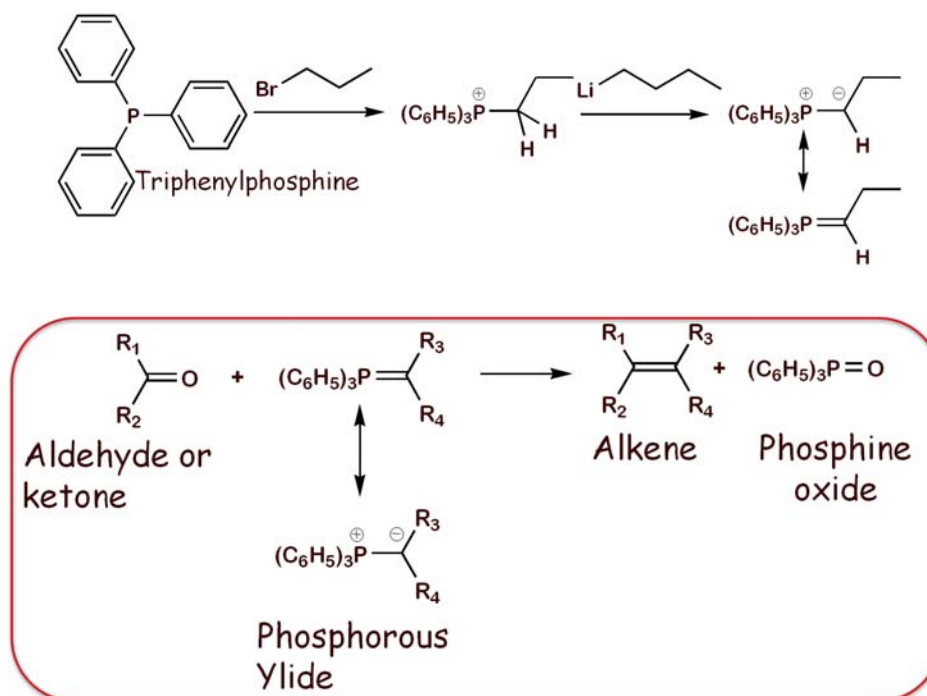


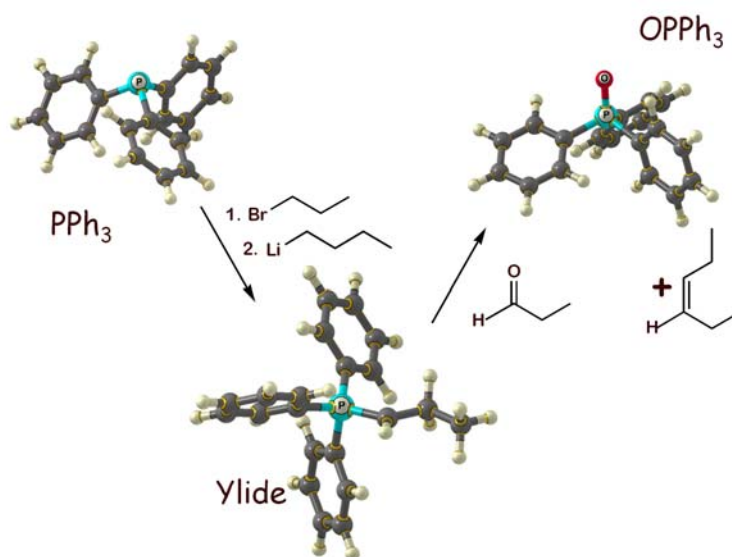
The Diels Alder reaction was our first great synthetic reaction. The Wittig reaction is the second. It allows one to selectively prepare alkenes in a manner unmatched by any other methodology. The starting materials are an alkyl halide and an aldehyde or ketone.

### Wittig Reaction

To initiate the Wittig reaction an alkyl halide is allowed to react with a phosphine to give a four coordinate phosphine cation. This cation is subsequently deprotonated with a strong base, like butyl lithium, to give a neutral compound called a phosphorous ylide. The negatively charged carbon of the ylide can act as a nucleophile and attacks the carbon of the aldehyde or keton carbonyl.



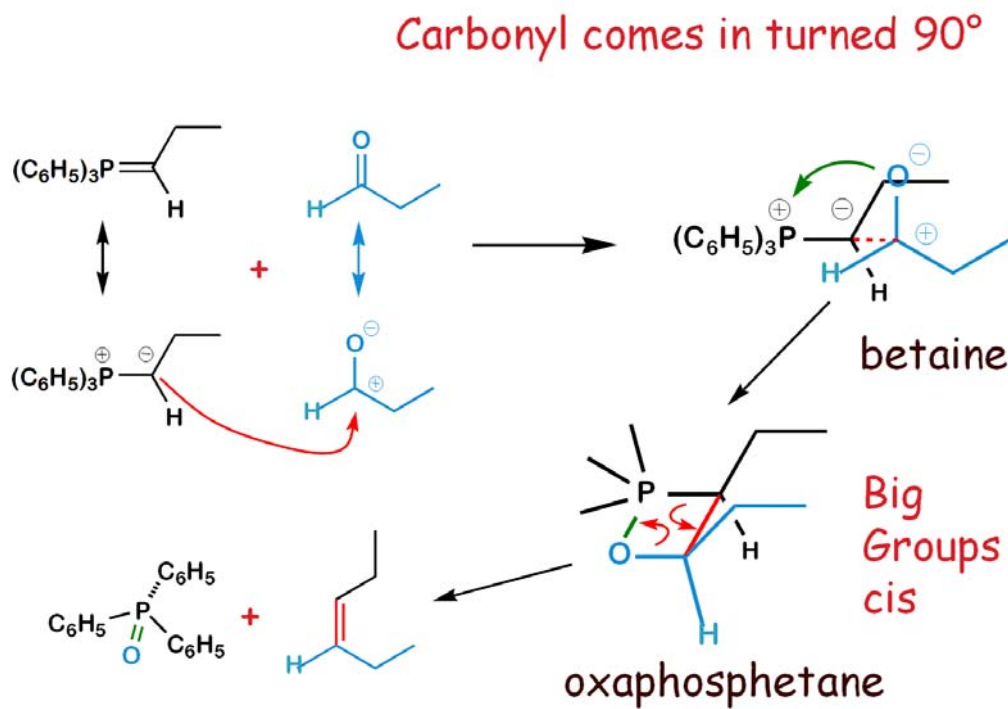
The phosphine is very big and there is a major steric factor governing the stereochemistry of the addition.



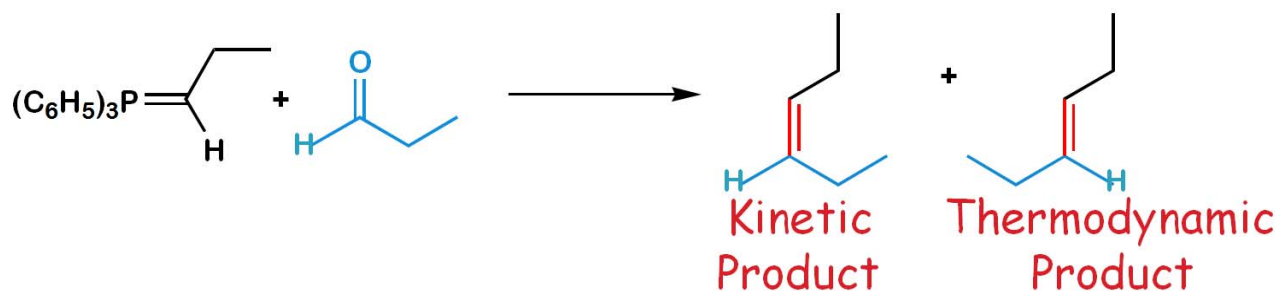
The remarkable thing is that for simple compounds, the reaction is **Z** selective. The reaction is under kinetic control.

The first step of the reaction between the ylide and the carbonyl involves the formation of an intermediate called a betaine.

The carbonyl approaches the ylide carbon turned at a 90° angle with respect to the C-P bond. This path is the best path in terms of sterics and is also consistent with a detailed molecular orbital analysis of the problem. Once the betaine is formed the oxygen atom can swing over and form a new covalent bond to the phosphorous atom. Phosphorous likes to form five bonds and forms very strong bonds to oxygen in particular. The result of this new bond is a four membered ring compound called a oxaphosphetane.

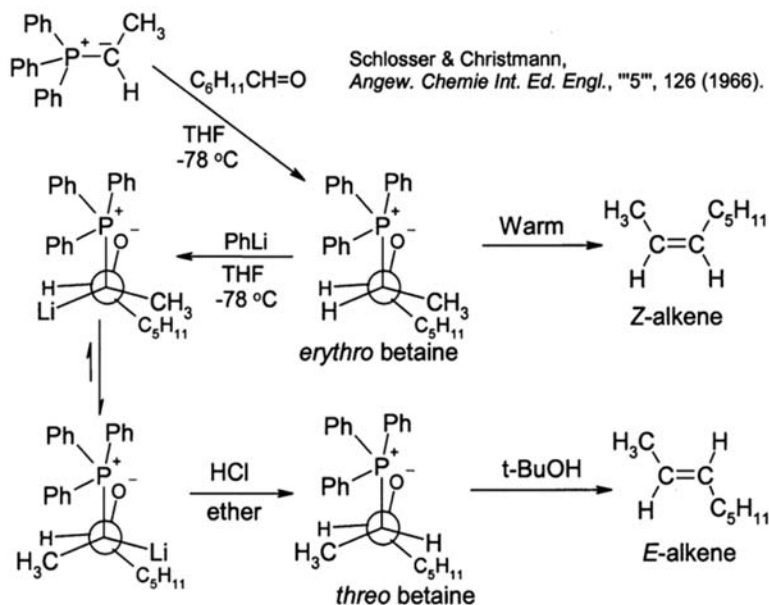


When the oxaphosphatane forms the stereochemistry of the substituents turns out to be cis. This is due to the chosen path of the carbonyl when the betaine was formed. This means that the favored final alkene product is will be the **Z** isomer.



The **Z** isomer is not the thermodynamic product, it is the kinetic product. The key to a good yield of the kinetic **Z** isomer is to minimize anything that would equilibrate the betaine and thus the subsequent oxaphosphetane ring. Doing the reaction at low temperature helps, so does minimizing extraneous salts that would help stabilize the charged intermediates.

But what if one wanted the thermodynamic product, the **E** isomer? Then one would want to intentionally isomerize the betaine to lead to the more stable product. A method for doing this has been discovered by a chemist named Schlosser. It involves the addition of a mole of strong base, usually phenyl lithium, to the betaine.



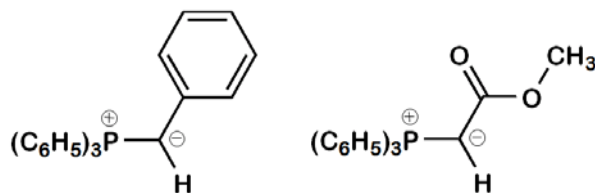
[http://en.wikipedia.org/wiki/Wittig\\_reaction](http://en.wikipedia.org/wiki/Wittig_reaction)

The terms erythro and threo are stereochemical designators for open chain compounds that we do not need to be concerned about. The added PhLi deprotonates the betaine and leads to an isomerization. The **E**-alkene is the final result.

The Wittig reaction works very well with aldehydes. It can also be used with ketones, but the stereochemistry control is not as good.

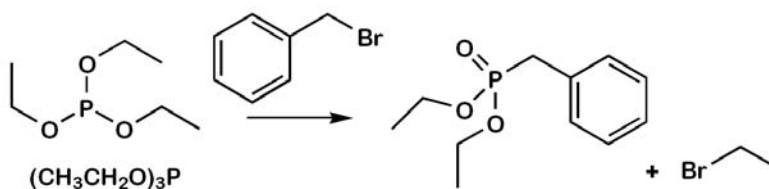
### The Horner-Wadsworth-Emmons Reaction

One limitation of the Wittig reaction is that phosphorous ylides that contain stabilizing groups next to the negatively charged carbon are not reactive enough to undergo the desired reaction with a carbonyl.

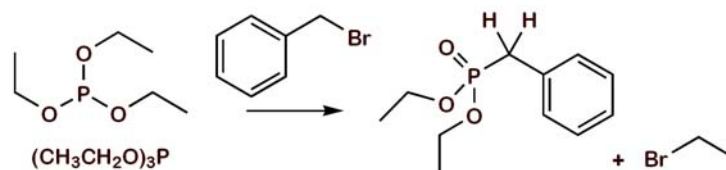
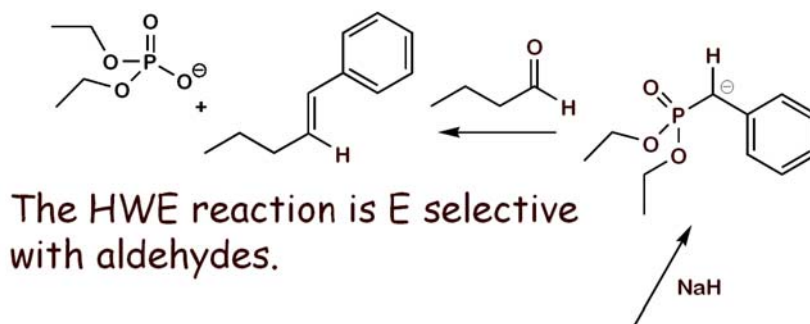


### Examples of Ylides with stabilizing groups.

The stabilizing groups can spread out the negative charge via resonance and thus reduce the nucleophilicity of the carbon atom. The way around the problem is to use a more reactive phosphorous compound to form the ylide. The most popular method is the Horner-Wadsworth-Emmons (HWE) reaction, which starts with triethyl phosphate to form a phosphonate ester.

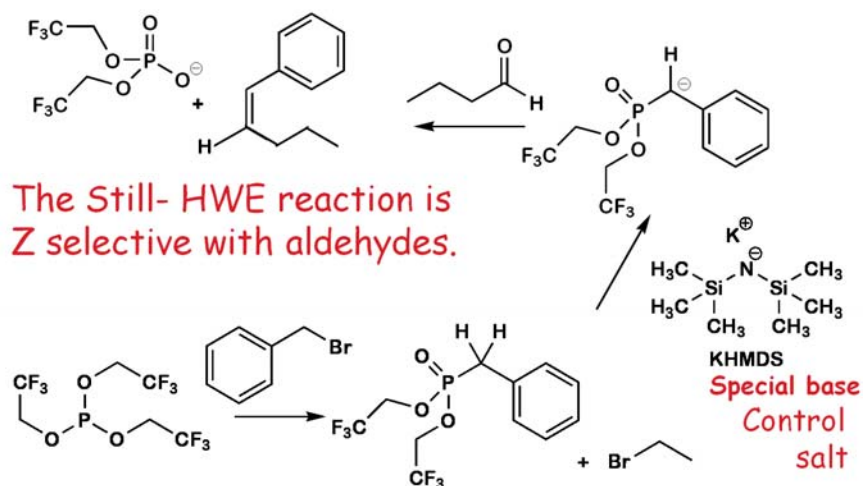


The phosphonate ester products will react with a base such as NaH to give ylides reactive enough to carry out the reaction.



## Horner-Wadsworth-Emmons (HWE) modification

The reaction is slow enough that it gives the thermodynamic *E* isomer. But what if we wanted the *Z* isomer of an alkene derived from a stabilized ylide? People have worked on that problem as well. A chemist named Still found that if you added electron withdrawing  $\text{CF}_3$  groups to the phosphite you would get a more reactive ylide. The more reactive ylide reacts faster and once again the reaction is under kinetic control. The *Z* isomer is the result. °



$\text{CF}_3$  groups withdraw electrons make compound more reactive, returning reaction kinetic control.

The Still-HWE procedure a special base is used, KHMDS, potassium hexamethyldisilamide. A crown ether 18-crown-6 is added to bind the potassium. See page 504 in your text.

Ketones are difficult to reactive with stabilized ylides and the stereochemical selectivity is poor.

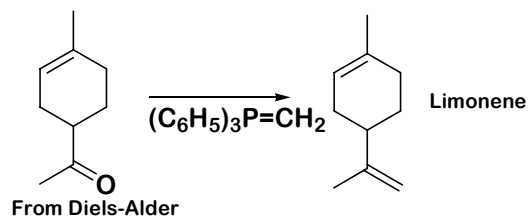
All of this sounds wonderful and it is, but one must realize that all of this is highly variable. None of the reactions listed here are perfect and mixtures of isomers are the norm. In most cases one can predict the predominate product stereochemistry, but in most cases one will have to be prepared for a surprise.

### Web references.

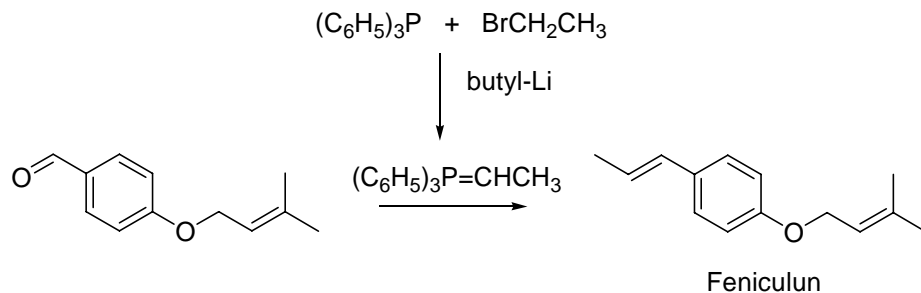
[http://en.wikipedia.org/wiki/Wittig\\_reaction](http://en.wikipedia.org/wiki/Wittig_reaction) and <http://en.wikipedia.org/wiki/Horner-Wadsworth-Emmons>

## Examples.

1. Limonene is terpene found in lemons and oranges



2. Feniculum is found in fennel.



3. The four compounds prepared below are “Sting Bug” pheromones. You don’t have to be a stink bug to enjoy the syntheses.

