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CONTENTS

1. Learning Outcomes

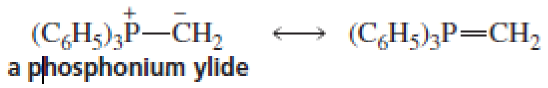
After studying this

- Know the best way to form alkene using the Wittig reaction
- Learn about phosphonium ylides, their formation and their stability
- Learn about the mechanism of the Wittig reaction and analyse the steric hindrance factors involved in the same.
- Evaluate the reaction conditions and stereochemical factors which control product formation.
- Analyse improved version of the Wittig reaction: Horner Wittig reaction.

2. Introduction

Compounds having adjacently placed covalently bonded atoms bearing opposite charges and complete octets are termed as ylides (pronounced *"ILL-id"*).

Phosphonium ylides have Phosphorus bearing positive charge covalently attached to carbon having negative charge. They can be represented by the structure where there is a double bond between phosphorus and carbon.



$$(C_6H_5)_3\overset{+}{P}-\overset{-}{C}H_2 \longleftrightarrow (C_6H_5)_3P{=}CH_2$$

a phosphonium ylide

When a phosphonium ylide is reacted with aldehyde (or ketone) , alkenes are formed and this reaction is known as Wittig reaction. The reaction is named after George Wittig, a German chemist whose studies in organic phosphorous compounds won him shared Nobel prrize in chemistry in 1979 along with H. C. Brown.

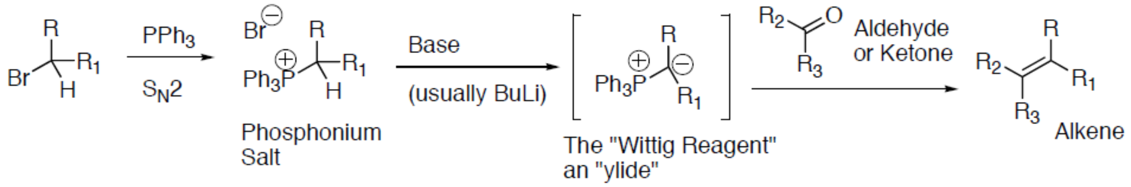
Let us study the Wittig reaction in detail.

3. Wittig Reaction

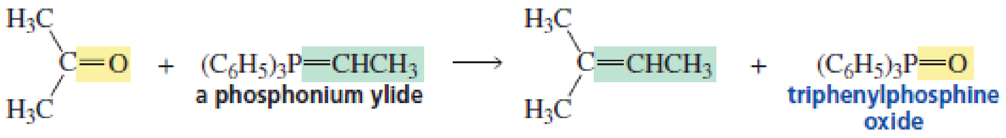
In Wittig reaction, when an aldehyde or ketone is reacted with phosphonium ylide, alkenes are formed.

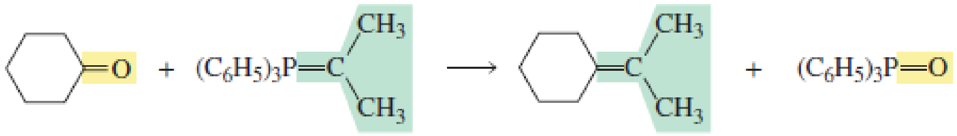
The general reaction can be represented as follows:

General Wittig Reaction: Synthesis of Alkenes



Examples:





Notice there is interchange of the doubly bonded carbon part of ylide with carbonyl oxygen and the trialkyl or triaryl phosphine oxide is the byproduct.

In order to understand the mechanism of this reaction, let us first know more about the phosphnium ylide which is also known as Wittig reagent.

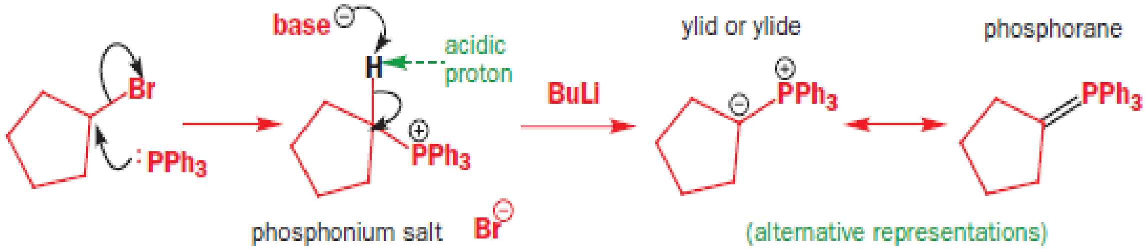
3.1 Phosphonium Ylide (Wittig Reagent)

Phosphorus atoms, especially those that are positively charged or are attached to electronegative substituents, can increase the acidity of protons adjacent to them at the carbon skeleton. Deprotonation by a moderately strong base gives rise to a species called phosphorus ylide that carry a doubly bonded species, called phosphoranes.

The phosphonium ylide required for a specific synthesis is produced by an S$_N$2 reaction of triphenylphosphine and an alkyl halide with the suitable number of carbon atoms.

$$R_3P \quad + \quad R^1CH_2X \longrightarrow \left[R_3\overset{\oplus}{P}\text{—}CH_2R^1 \right] X^{\ominus} \underset{}{\overset{\text{base}}{\rightleftharpoons}} R_3P{=}CHR^1$$

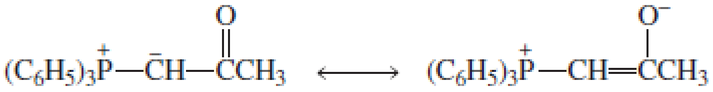
X = Cl, Br, I
R = aryl or alkyl
R^1 = alkyl



The ylides are intensed coloured resonance stabilized structures. It bears positive and negitive charge on adjacent atoms. They are generally not surrounded by the solution in which they are prepared. Therefore, they are generated insitu during the Wittig reaction.

3.2 Types of Ylides

The ylides are of two types: those with conjugating or anion-stabilizing substituents adjacent to the negative charge (such as carbonyl groups) and those without. The former are called stabilized ylides, because the negative charge is stabilized not only by the atom of phosphorous but also by the adjacent functional group via the enolate-type structure. The later ones are known as unstabilized ylides.



$$(C_6H_5)_3\overset{+}{P}\text{—}\overset{-}{C}H\text{—}\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \longleftrightarrow (C_6H_5)_3\overset{+}{P}\text{—}CH{=}\overset{\overset{\displaystyle O^-}{|}}{C}CH_3$$

a stabilized ylide

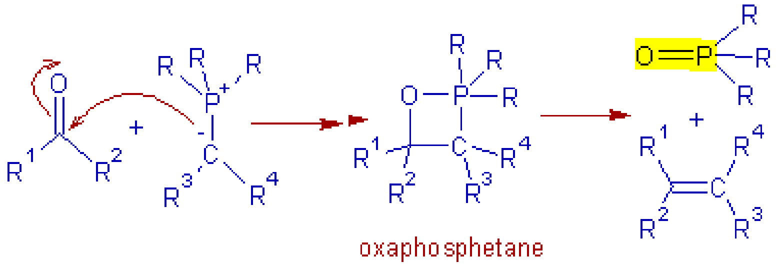
$$(C_6H_5)_3\overset{+}{P}\text{—}\overset{-}{C}HCH_2CH_3$$

an unstabilized ylide

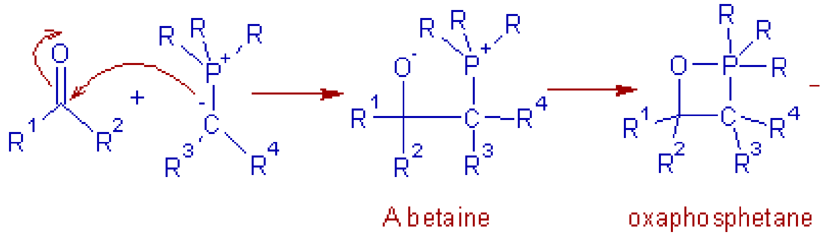
3.3 Mechanism of Wittig Reaction

The Wittig reaction converts the C=O bond of an aldehyde or ketone to a C=C double bond using phosphonium ylide.

Ylides are nucleophilic species which attack the carbonyl group of aldehydes or ketones, generating the four-membered ring oxaphosphetane intermediates. Oxaphosphetanes are unstable: they undergo elimination to form an alkene with phosphine oxide as a byproduct. The phosphorus–oxygen double bond is extremely strong and it is this that drives the whole reaction forward.



For the formation of oxaphosphetane, the following can be a reasoning. The carbon bearing negative charge in the ylide attacks on the electron deficient carbonyl carbon resulting in the formation of a betaine which further form the oxaphosphetane.



But the fact is that, the occurrence of the betaine has not been established. On the other hand, ^{31}P-NMR experiments confirm the occurrence of the four-membered oxaphosphetane intermediate.

Therefore, the initial step is believed to give the oxaphosphetane directly without the betaine formation. But the mode of attack is same, i.e., the negatively charged carbon of ylide attaching to the electron deficient carbon of the carbonyl and the positively charged phosphorus of ylide attaching to the oxygen of the carbonyl group.

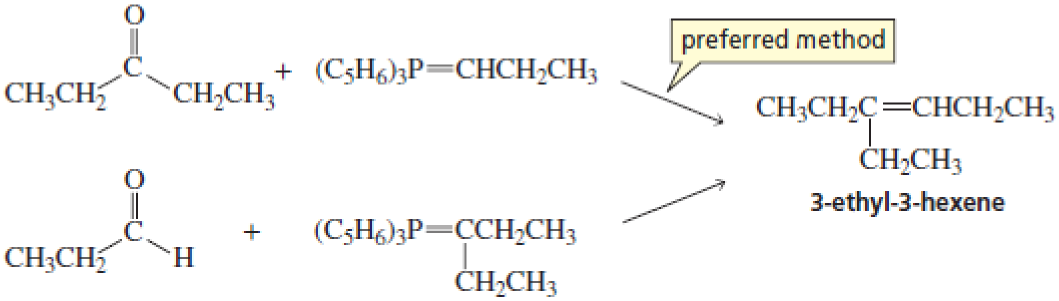
Note that the double bond of alkene is formed just where the carbonyl double bond was there in the carbonyl compound without any rearrangement. Hence Wittig Reaction provides an excellent way to prepare the alkenes, which by other methods are difficult to prepare like terminal double bonds, exocyclic double bonds, etc.

3.4 Steric Hindrance Factor in Wittig reaction

For alkene synthesis, if there are two alternative routes possible, then that route is preferred where the phosphorus ylide reagent has less steric hinderance (i.e less bulky group or less number of substituents). This is because, the preparation of less sterically hindered ylide is convenient as the preparation is an S_N2 reaction which is favoured on less hundered alkyl halide.

For example, for the synthesis of 3-ethyl-3-hexene, it is better to use a three-carbon alkyl halide (for ylide formation) and a five-carbon carbonyl compound (Route 1) than a five-carbon alkyl halide (for ylide formation) and a three-carbon carbonyl compound (Route 2)

This is because, it would be easier to form a ylide from 1-bromopropane than from 3-bromopentane.

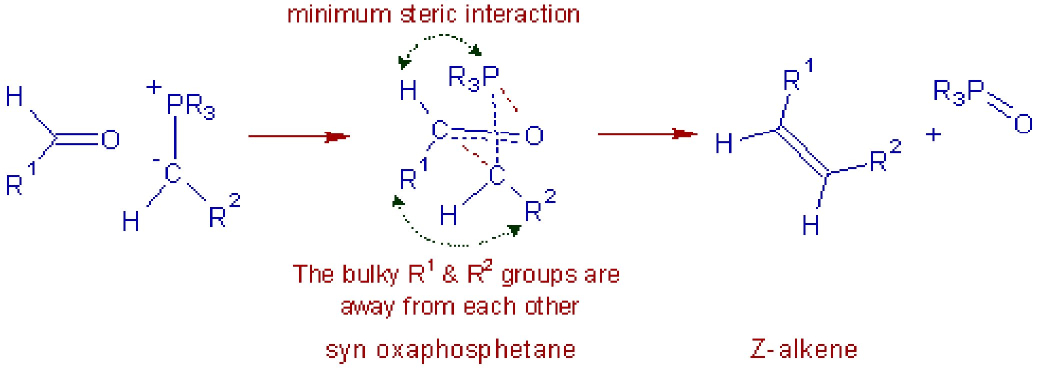


4. Stereochemical Perspective of Wittig Reaction

In the Wittig reaction, the intermediate oxaphosphetene is diastereomeric and can be syn or anti. Formation of oxaphosphetane depends on several conditions.

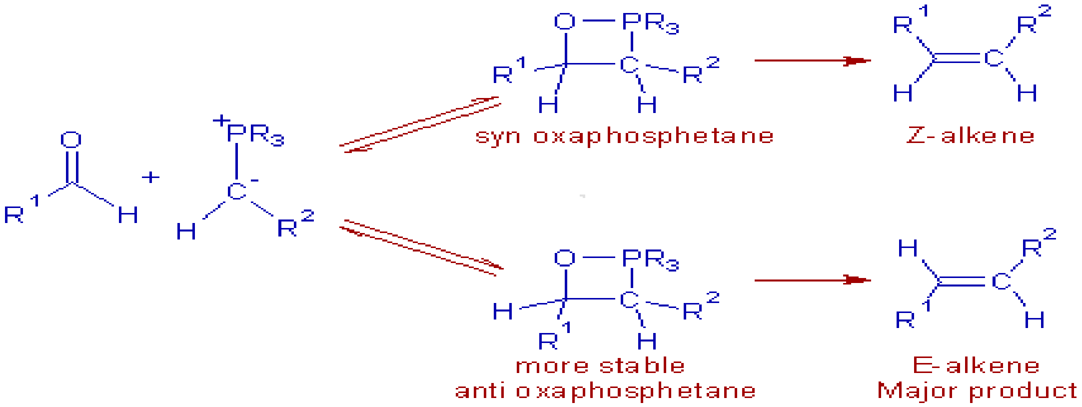
4.1.1 With unstabilized ylides:

In the Wittig reaction of unstabilized ylides, Z-alkenes are formed. The ylide approaches to carbonyl compound to form a four membered oxaphosphetane puckered ring in the intermediate state. The formation of transition state takes place in a way that the substituent larger in size kept away from each other and a syn-oxaphosphetane is formed. This is unstable but form at a faster rate that the anti oxaphosphetane. This finally produces a kinetically controlled Z-alkene.



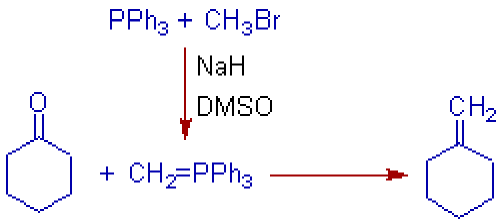
4.1.2 With stabilized ylides:

In the Wittig reaction of stabilized ylides, E-alkenes are formed. Since the oxaphosphetane formation from starting material is reversible and ylide is stable, an equilibrium is established between less stable *syn*-form and more stable *anti*- form of oxaphosphetane. Therefore, before decomposition, syn-oxaphosphetane and more stable anti form interconverts slowly. Hence E-alkene is formed. Thus the selection of the E product is thermodynamically controlled.

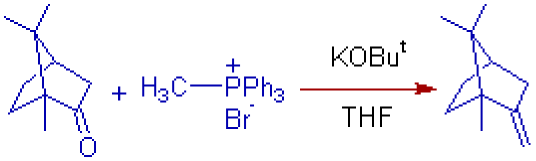


5. Examples of Wittig Reaction

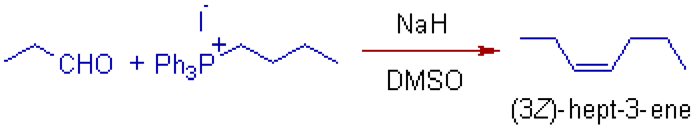
1) Methylidenecyclohexane is obtained by cyclohexanone by treatment with (methylene) triphenylphosphorane, generated in situ by the treatment of triphenylphosphine with methylbromide in the suitable base.



2) An exocyclic double bond is formed on camphor by reaction of methyl triphenyl phosphonium bromide in potassium tert-butoxide.

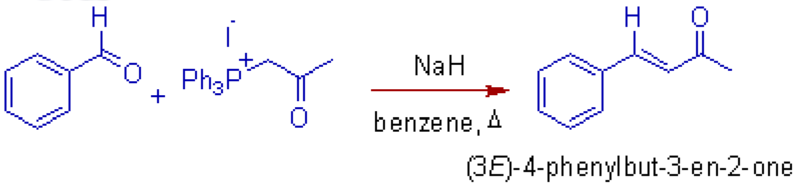


3) In the Wittig reaction of propanal with butyl triphenyl phosphonium iodide, a least stabilized ylide selectively forms (3Z)-hept-3-ene



Wittig reagent shown here is non-stabilized due to electron donating butyl group.

4) E-alkene formation when benzaldehyde reacts with a stabilized ylides.



Advantages of Wittig Reaction

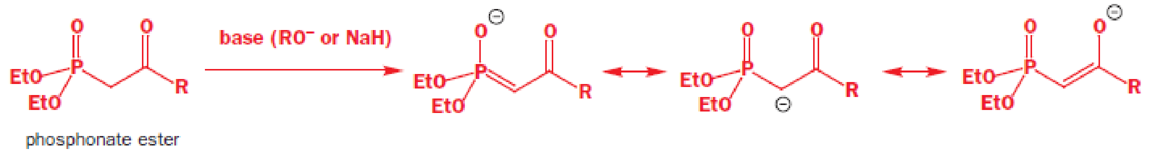
This reaction boasts higher functional groups selectivity in which carbonyl units are selectively transformed into alkenes. Another important advantage is that it involves mild reaction conditions, such as its ability to proceed at low temperature. Using an alternative olefination techniques such as these E2 elimination requires strongly acidic or basic media along with high temperatures, and yet these harsh reaction conditions are accompanied with regioselectivity issues. In contrast, the Wittig reaction is easy to control and often proceeds in high yields, and this is a strong favorite in organic synthesis.

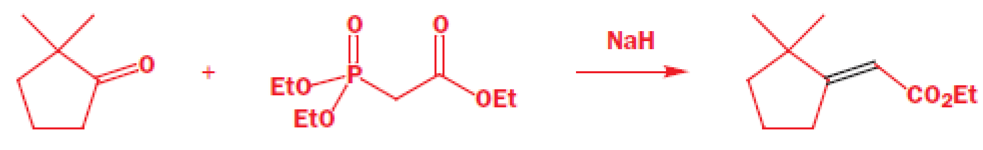
6. Horner Wittig reaction: An improved Witting Reaction

The primary disadvantage of the Wittig reaction includes the occasional difficulty of eliminating the phosphine oxide side product. An improved reaction, the Wittig-Horner reaction (also called the Horner-Wadsworth-Emmons reaction), employs phosphites in lieu of phosphines, and produces a highly polar/water-soluble phosphorus side product that can be easily removed.

Often it is better not to use the phosphonium salts, but a phosphonate instead. Sodium hydride or alkoxide anions may be used to deprotonate phosphonate esters to form enolate type anions. These anions react with aldehydes or ketones to form E-alkenes. Alkene-forming reactions of aldehydes or ketones with phosphonates are called Horner–Wadsworth–Emmons (or Horner–Emmons, Wadsworth–Emmons, or even Horner–Wittig) reactions.

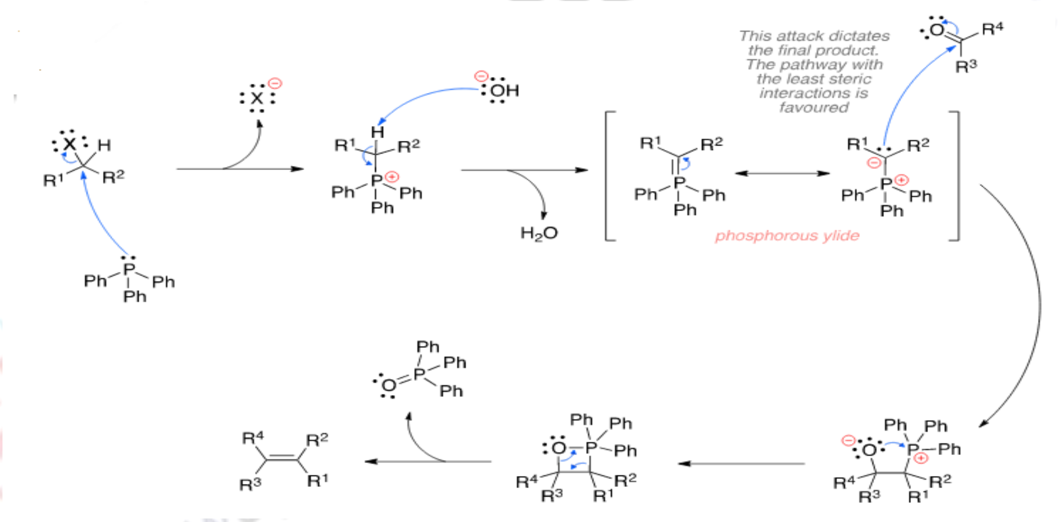
Examples:





7. Summary

- This reaction transforms C=O bonds of aldehydes and ketones to C=C bonds, and is the method most often employed for synthesizing alkenes with defined substituent geometries.
- It involves the use of phosphorus ylide which is a chemical species having phosphorus bearing positive charge and adjacent carbon bearing a negative charge.
- The primary disadvantage of the Wittig reaction includes the occasional difficulty of eliminating the phosphine oxide side product.
- An improved reaction, the Wittig-Horner reaction (also called the Horner-Wadsworth-Emmons reaction), employs phosphites in lieu of phosphines, and produces a highly polar/water-soluble phosphorus side product that can be easily removed.



- The Wittig reaction stereoselectivity depends on the structure of the ylide. Stabilized ylides produce primary *E* isomers, and unstabilized ylides form primarily *Z* isomers.