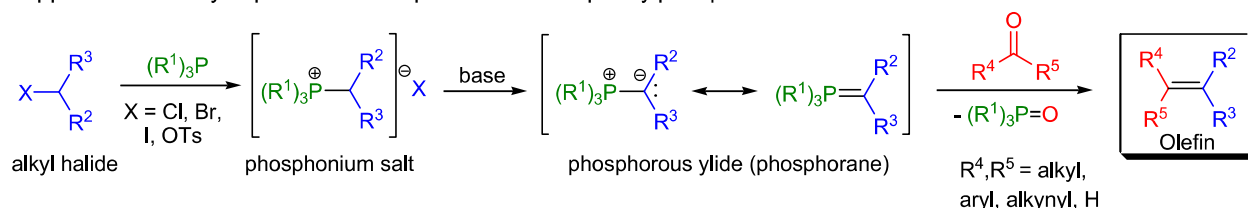


WITTIG REACTION

(References are on page 707)

Importance:[Seminal Publications¹⁻⁵; Reviews⁶⁻⁴⁰; Modifications & Improvements⁴¹⁻⁵⁴; Theoretical Studies⁵⁵⁻⁷⁰]

In the early 1950s, G. Wittig and G. Geissler investigated the chemistry of pentavalent phosphorous and described the reaction between methylenetriphenylphosphorane ($\text{Ph}_3\text{P}=\text{CH}_2$) and benzophenone, which gave 1,1-diphenylethene and triphenylphosphine oxide ($\text{Ph}_3\text{P}=\text{O}$) in quantitative yield.³ Wittig recognized the importance of this observation and conducted a systematic study in which several phosphoranes were reacted with various aldehydes and ketones to obtain the corresponding olefins.^{4,5} The formation of carbon-carbon double bonds (olefins) from carbonyl compounds and phosphoranes (phosphorous ylides) is known as the *Wittig reaction*. From a historical point of view it is important to note that Wittig was not the first to prepare a phosphorane, since Staudinger and Marvel had reported the synthesis of such compounds three decades before.^{1,2} Since its discovery, the *Wittig reaction* has become one of the most important and most effective methods for the synthesis of alkenes. The active reagent in this transformation is the phosphorous ylide, which is usually prepared from a triaryl- or trialkylphosphine and an alkyl halide (1° or 2°) followed by deprotonation with a suitable base (e.g., RLi , NaH , NaOR , etc.). There are three different types of ylides depending on the nature of the R^2 and R^3 substituents: 1) in the "stabilized" ylides the alkyl halide component has at least one strong electron-withdrawing group ($-\text{CO}_2\text{R}$, $-\text{SO}_2\text{R}$, etc.), which stabilizes the formal negative charge on the carbon; 2) "semi-stabilized" ylides have at least one aryl or alkenyl substituents as the R^2 or R^3 groups, which are less stabilizing; and 3) "nonstabilized" ylides usually have only alkyl substituents, which do not stabilize the formal negative charge on the carbon. The general features of the *Wittig reaction* are: 1) the phosphonium salts are usually prepared using triphenylphosphine, and the phosphorous ylides are generated before the reaction or *in situ*; 2) the ylides are water as well as oxygen-sensitive; 3) the phosphorous ylides chemoselectively react with aldehydes (fast) and ketones (slow), other carbonyl groups (e.g., esters, amides) remain intact during the reaction; 4) the stereoselectivity, *E*- or *Z*-selectivity, is influenced by many factors: type of ylide, type of carbonyl compound, nature of solvent, and the counterion for the ylide formation; 5) "nonstabilized" ylides under salt-free conditions in a dipolar aprotic solvent with aldehydes afford olefins with high (*Z*)-selectivity; 6) "stabilized" ylides give predominantly (*E*)-olefins with aldehydes under the same salt-free conditions; 7) "semi-stabilized" ylides usually give alkenes with poorer stereoselectivity; and 8) ether solvents such as THF, Et_2O , DME, MTBE, or toluene are used. The *Wittig reaction* has several important variants: 1) the *Horner-Wittig reaction* takes place when the phosphorous ylides contain phosphine oxides in place of triarylphosphines;⁷¹ 2) the use of stabilized alkyl phosphonate carbanions is known as the *Horner-Wadsworth-Emmons reaction* in which (*E*)- α,β -unsaturated esters are formed;⁷² 3) in the *Schlosser modification*, "nonstabilized" ylides can give pure (*E*)-alkenes when two equivalents of Li-halide salt is present in the reaction mixture;⁷³ 4) *asymmetric Wittig reaction* were also developed;⁵³ and 5) *Wittig reaction* on solid support allows easy separation of the products from triphenylphosphine oxide.⁴²

if $\text{R}^1 = \text{aryl}$ and $\text{R}^2, \text{R}^3 = \text{alkyl, H}$ \Rightarrow "nonstabilized" ylideif $\text{R}^1 = \text{aryl}$ and $\text{R}^2, \text{R}^3 = \text{aryl, alkenyl, benzyl, allyl, H}$ \Rightarrow "semi-stabilized" ylideif $\text{R}^1 = \text{aryl}$ and $\text{R}^2, \text{R}^3 = -\text{CO}_2\text{R}, -\text{SO}_2\text{R}, -\text{CN}, -\text{COR}$ \Rightarrow "stabilized" ylide**Mechanism:** 9,23,74-77,28,78-82,37