Wittig reaction

The **Wittig reaction** or Wittig olefination is a chemical reaction of an aldehyde or ketone with a triphenyl phosphonium ylide (often called a **Wittig reagent**) to give an alkene and triphenylphosphine oxide.

It is widely used in organic synthesis for the preparation of alkenes.[1][2][3] It should not be confused with the Wittig rearrangement.

Wittig reactions are most commonly used to couple aldehydes and ketones to singly-substituted triphenylphosphonium ylides. For the reaction with aldehydes, the double bond geometry is readily predicted based on the nature of the ylide. With unstabilised ylides (R^3 = alkyl) this results in (*Z*)-alkene product with moderate to high selectivity. With stabilized ylides (R^3 = ester or ketone), the (*E*)-alkene is formed with high selectivity. The (*E*)/(*Z*) selectivity is often poor with semistabilized ylides (R^3 = aryl).[4]

To obtain the (*E*)-alkene for unstabilized ylides, the Schlosser modification of the Wittig reaction can be used. Alternatively, the Julia olefination and its variants also provide the (*E*)-alkene selectively. Ordinarily, the Horner–Wadsworth–Emmons reaction provides the (*E*)-enoate (α,β-unsaturated ester), just as the Wittig reaction does. To obtain the (*Z*)-enoate, the Still-Gennari modification of the Horner-Wadsworth-Emmons reaction can be used.

Wittig reaction	
Named after	Georg Wittig
Reaction type	Coupling reaction
Reaction	
aldehyde or **ketone** + **triphenyl phosphonium ylide** ↓ **alkene** + triphenylphosphine oxide	
Conditions	
Typical solvents	typically THF or diethyl ether
Identifiers	
March's Advanced Organic Chemistry	16–44 (6th ed.)
Organic Chemistry Portal	wittig-reaction
RSC ontology ID	RXNO:0000015 ✓
✗(what is this?) (verify) (https://en.wikipedia.org/w/index.php?&diff=cur&oldid=342064940)	

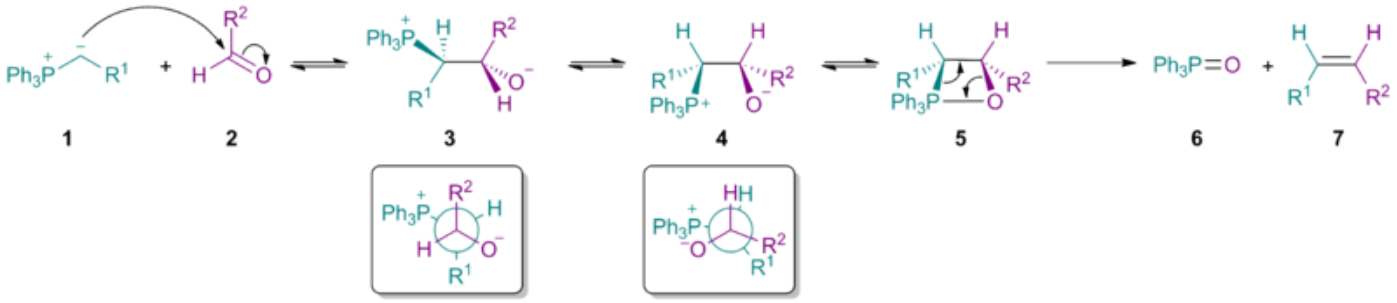
Contents

Reaction mechanism

Classical mechanism

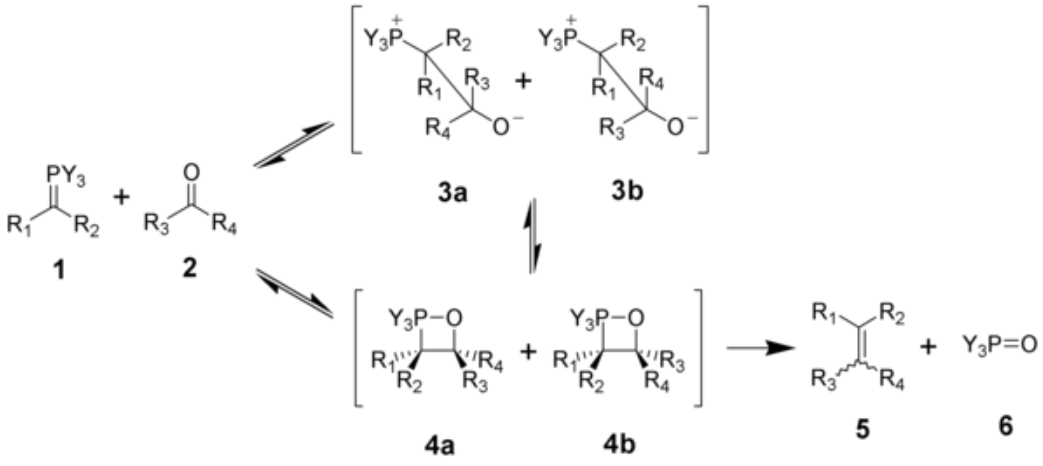
The steric bulk of the ylide **1** influences the stereochemical outcome of nucleophilic addition to give a predominance of the betaine **3** (cf. Bürgi–Dunitz angle). Note that for betaine **3** both R_1 and R_2 as well as PPh_3^+ and O^- are positioned anti to one another.

Carbon-carbon bond rotation gives the betaine **4**, which then forms the oxaphosphetane **5**. Elimination gives the desired Z-alkene **7** and triphenylphosphine oxide **6**. With simple Wittig reagents, the first step occurs easily with both aldehydes and ketones, and the decomposition of the betaine (to form **5**) is the rate-determining step. However, with stabilised ylides (where R_1 stabilises the negative charge) the first step is the slowest step, so the overall rate of alkene formation decreases and a bigger proportion of the alkene product is the E-isomer. This also explains why stabilised reagents fail to react well with sterically hindered ketones.



Mechanism

Mechanistic studies have focused on unstabilized ylides, because the intermediates can be followed by NMR spectroscopy. The existence and interconversion of the betaine (**3a** and **3b**) is subject of ongoing research.[5] For lithium-free Wittig reactions, most recent studies support a concerted formation of the oxaphosphetane without intervention of a betaine. In particular, phosphonium ylides **1** react with carbonyl compounds **2** via a [2+2] cycloaddition that is sometimes described as having $[_\pi 2_s + _\pi 2_a]$ topology to directly form the oxaphosphetanes **4a** and **4b**. Under lithium-free conditions, the stereochemistry of the product **5** is due to the kinetically controlled addition of the ylide **1** to the carbonyl **2**. When lithium is present, there may be equilibration of the intermediates, possibly via betaine species **3a** and **3b**.[6][7][8] Bruce E. Maryanoff and A. B. Reitz identified the issue about equilibration of Wittig intermediates and termed the process "stereochemical drift". For many years, the stereochemistry of the Wittig reaction, in terms of carbon-carbon bond formation, had been assumed to correspond directly with the Z/E stereochemistry of the alkene products. However, certain reactants do not follow this simple pattern. Lithium salts can also exert a profound effect on the stereochemical outcome.[9]

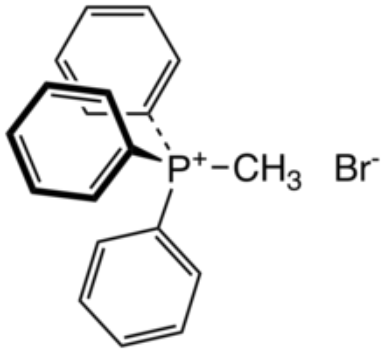


Mechanisms differ for aliphatic and aromatic aldehydes and for aromatic and aliphatic phosphonium ylides. Evidence suggests that the Wittig reaction of unbranched aldehydes under lithium-salt-free conditions do not equilibrate and are therefore under kinetic reaction control.[10][11] E. Vedejs has put forth a theory to explain the stereoselectivity of stabilized and unstabilized Wittig reactions.[12]

Strong evidence indicated that under Li-free conditions, Wittig reactions involving unstabilized (R_1= alkyl, H), semistabilized (R_1 = aryl), and stabilized (R_1 = EWG) Wittig reagents all proceed via a [2+2]/retro-[2+2] mechanism under kinetic control, with oxaphosphetane as the one and only intermediate.[13]

Wittig reagents

Preparation



$[Ph_3PCH_3]^+Br^-$, typical phosphonium salt.

Simple phosphoranes typically hydrolyze and oxidize readily. They are therefore prepared using air-free techniques. Phosphoranes are more air-stable when they contain an electron withdrawing group attached to the carbon. Some examples are $Ph_3P{=}CHCO_2R$ and $Ph_3P{=}CHPh$. These ylides are sufficiently stable to be sold commercially.[14]

Wittig reagents are usually prepared from a phosphonium salt, which is in turn prepared by the quaternization of triphenylphosphine with an alkyl halide. The alkylphosphonium salt is deprotonated with a strong base such as *n*-butyllithium:

$$[Ph_3P^+CH_2R]X^- + C_4H_9Li \rightarrow Ph_3P{=}CHR + LiX + C_4H_{10}$$

Besides *n*-butyllithium (^{n}BuLi), other strong bases like sodium and potassium *t*-butoxide (^{t}BuONa, ^{t}BuOK), lithium, sodium and potassium hexamethyldisilazide (LiHMDS, NaHMDS, KHDMS, where HDMS = $N(SiMe_3)_2$), or sodium hydride (NaH) are also commonly used. For stabilized Wittig reagents bearing conjugated electron-withdrawing groups, even relatively weak bases like aqueous sodium hydroxide or potassium carbonate can be employed.

The identification of a suitable base is often an important step when optimizing a Wittig reaction. Because phosphonium ylides are seldom isolated, the byproduct(s) generated upon deprotonation essentially plays the role of an additive in a Wittig reaction. As a result, the choice of base has a strong influence on the efficiency and, when applicable, the stereochemical outcome of the Wittig reaction.

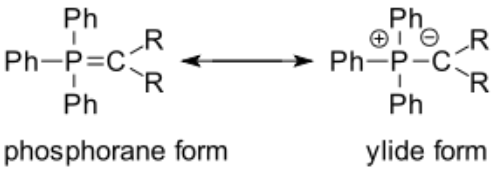
One of the simplest ylide is methylenetriphenylphosphorane ($Ph_3P{=}CH_2$).[15] It is also a precursor to more elaborate Wittig reagents. Alkylation of $Ph_3P{=}CH_2$ with a primary alkyl halide $R{-}CH_2{-}X$, produces substituted phosphonium salts:

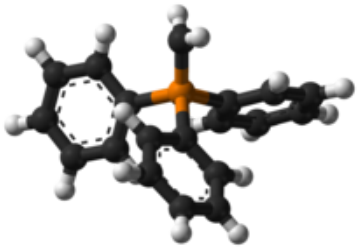
$$Ph_3P{=}CH_2 + RCH_2X \rightarrow Ph_3P^+\,CH_2CH_2R\;X^-$$

These salts can be deprotonated in the usual way to give $Ph_3P{=}CH{-}CH_2R$.

Structure of the ylide

The Wittig reagent may be described in the **phosphorane** form (the more familiar representation) or the **ylide** form:




Ball-and-stick model of $Ph_3P{=}CH_2$, as found in the crystal structure

The ylide form is a significant contributor, and the carbon atom is nucleophilic.

Scope and limitations

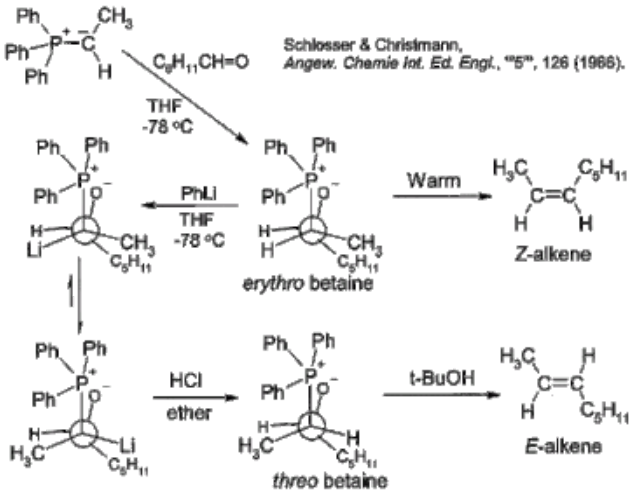
The Wittig reaction is a popular method for the synthesis of alkene from ketones and aldehydes. The Wittig reagent can generally tolerate carbonyl compounds containing several kinds of functional groups such as OH, OR, aromatic nitro and even ester groups. There can be a problem with sterically hindered ketones, where the reaction may be slow and give poor yields, particularly with stabilized ylides, and in such cases the Horner–Wadsworth–Emmons (HWE) reaction (using phosphonate esters) is preferred. Another reported limitation is the often labile nature of aldehydes which can oxidize, polymerize or decompose. In a so-called tandem oxidation-Wittig process the aldehyde is formed in situ by oxidation of the corresponding alcohol.[16]

As mentioned above, the Wittig reagent itself is usually derived from a primary alkyl halide. Quaternization of triphenylphosphine with most secondary halides is inefficient. For this reason, Wittig reagents are rarely used to prepare tetrasubstituted alkenes. However the Wittig reagent can tolerate many other variants. It may contain alkenes and aromatic rings, and it is compatible with ethers and even ester groups. Even C=O and nitrile groups can be present if conjugated with the ylide- these are the stabilised ylides mentioned above. Bis-ylides (containing two P=C bonds) have also been made and used successfully.

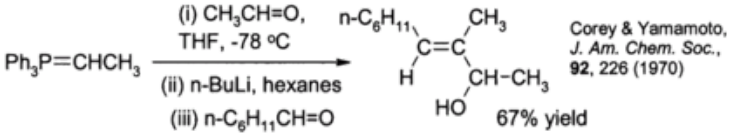
One limitation relates to the stereochemistry of the product. With simple ylides, the product is usually mainly the Z-isomer, although a lesser amount of the E-isomer is often formed also – this is particularly true when ketones are used. If the reaction is performed in dimethylformamide in the presence of lithium iodide or sodium iodide, the product is almost exclusively the Z-isomer.[17] If the E-isomer is the desired product, the Schlosser modification may be used. With stabilised ylides the product is mainly the E-isomer, and this same isomer is also usual with the HWE reaction.

Schlosser modification

The main limitation of the traditional Wittig reaction is that the reaction proceeds mainly via the erythro betaine intermediate, which leads to the Z-alkene. The erythro betaine can be converted to the threo betaine using phenyllithium at low temperature.[18] This modification affords the E-alkene.

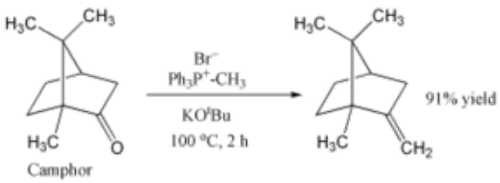


Allylic alcohols can be prepared by reaction of the betaine ylide with a second aldehyde.[19] For example:

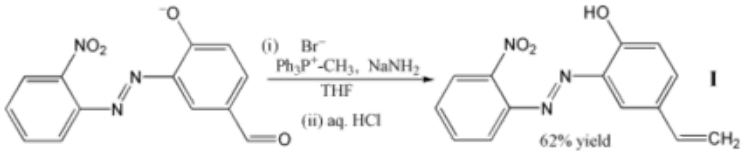


Examples

Because of its reliability and wide applicability, the Wittig reaction has become a standard tool for synthetic organic chemists.[20]

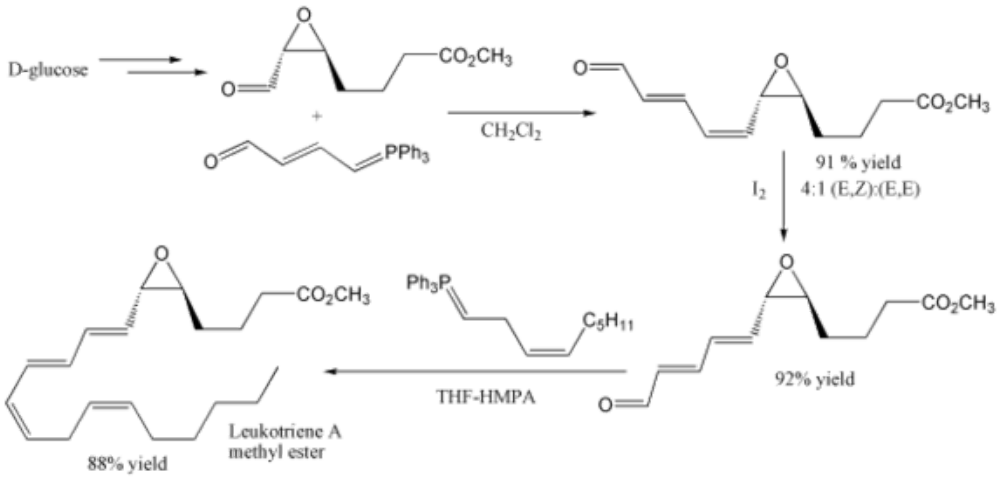


The most popular use of the Wittig reaction is for the introduction of a methylene group using methylenetriphenylphosphorane ($Ph_3P{=}CH_2$). Using this reagent, even a sterically hindered ketone such as camphor can be converted to its methylene derivative. In this case, the Wittig reagent is prepared *in situ* by deprotonation of methyltriphenylphosphonium bromide with potassium tert-butoxide.[21] In another example, the phosphorane is produced using sodium amide as a base, and this reagent converts the aldehyde shown into alkene **I** in 62% yield.[22] The reaction is performed in cold THF, and the sensitive nitro, azo and phenoxide groups are tolerated. The product can be used to incorporate a photostabiliser into a polymer, to protect the polymer from damage by ultraviolet radiation.



Another example of its use is in the synthesis of leukotriene A methyl ester.[23][24] The first step uses a stabilised ylide, where the carbonyl group is conjugated with the ylide preventing self condensation, although unexpectedly this gives mainly the *cis* product. The second Wittig reaction uses a non-stabilised Wittig reagent, and as expected this gives mainly the *cis* product.

Note that the epoxide and ester functional groups survive intact.



Methoxymethylenetriphenylphosphine is a Wittig reagent for the homologation of aldehydes and ketones. After the Wittig reaction, hydrolysis of the methoxyalkene gives an enol, which tautomerizes to an aldehyde.

History

The Wittig reaction was reported in 1954 by Georg Wittig and his coworker Ulrich Schöllkopf. In part for this contribution, Wittig was awarded the Nobel Prize in Chemistry in 1979.[25][26]

See also

- Corey–Chaykovsky reagent
- Horner–Wadsworth–Emmons reaction
- Julia olefination
- Peterson olefination
- Tebbe's reagent
- Organophosphorus chemistry
- Homologation reaction
- Kauffmann olefination
- Titanium–zinc methylenation

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- Wittig reaction in Organic Syntheses, Coll. Vol. 10, p. 703 (2004); Vol. 75, p. 153 (1998). (Article (http://www.orgsynth.org/orgsyn/prep.asp?prep=v75p0153))
- Wittig reaction in Organic Syntheses, Coll. Vol. 5, p. 361 (1973); Vol. 45, p. 33 (1965). (Article (http://www.orgsynth.org/orgsyn/prep.asp?prep=cv5p0361))