

Wittig and Wittig-Horner reactions under phase transfer catalysis conditions

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Abstract: Wittig and Wittig-Horner reactions are favorite tools in preparative organic chemistry. These olefination methods enjoy widespread and recognition because of their simplicity, convenience, and efficiency. Phase transfer catalysis (PTC) is a very important method in synthetic organic chemistry having many advantages over conventional, homogenous reaction procedures. In this paper, we attempt to summarize the aspects concerning Wittig and Wittig-Horner reactions that take place under phase transfer catalysis conditions.

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Keywords: Wittig reactions, Wittig-Horner reactions, phase transfer catalysis

1 Introduction

Thanks to numerous theoretical and practical implications, the modern chemistry of phosphorus draws increasing attention. Many scientists have dedicated their work investigating some of the unexplained aspects of organophosphorus compounds. They have synthesized new compounds and have used them in the new field of fine organic synthesis or in order to clarify some of the reaction mechanisms.

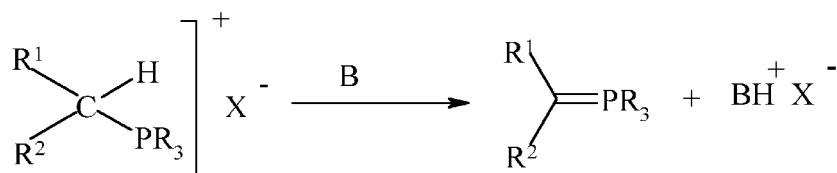
Although vast literature concerning phase transfer catalysis is available, information concerning the Wittig and Wittig-Horner reactions are treated separately, not as a whole. The aim of this review is to join together, in a more systematic manner, the information regarding the phase transfer catalysis of Wittig and Wittig-Horner reactions.

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2 The Wittig reaction mechanism

The Wittig reaction is known as one of the most versatile methods in organic chemistry for alkene synthesis. Alkylidene phosphoranes react with aldehydes or ketones to produce olefins. A carbon-carbon double bond is formed in place of carbonyl group; this rule is kept even in the case of the α,β -unsaturated compounds.

The ylide is formed as is shown in Scheme 1:



Scheme 1

The structural requirement of this reaction is the existence of a hydrogen atom at the carbon adjacent to the phosphorus atom contained in the quaternary phosphonium salt [1]. The mechanism of the homogenous reaction, discovered by Georg Wittig [2], involves two main steps:

- (1) a reversible step which consists of nucleophilic addition of the phosphorus ylide to the carbonyl compound giving betaine or oxaphosphetane intermediates;
- (2) an irreversible decomposition of the betaine or oxaphosphetane to give *Z* and *E* alkenes and trialkylphosphine oxide (Scheme 2) [3].

In order to elucidate the mechanism of the Wittig reaction, it is necessary to understand formation of the two intermediates: the betaine and the oxaphosphetane. A long time ago, an attempt to isolate and characterize the intermediates was reported with the formation in most of the cases of the oxaphosphetane, which was detected as a short-lived species. Betaines were isolated as lithium salt adducts.

G. Wittig [2] proposed oxaphosphetanes as intermediates. In an NMR study, E. Vedejs [4] observed only 1,2- λ^5 -oxaphosphetanes as intermediates. T. Kowashima and coworkers [5-8] have isolated other stable 1,2- λ^5 -oxaphosphetanes.

The stable 1,2- λ^5 -oxaphosphetanes having pyridyl groups [9] and furyl groups [10] were isolated by S. Berger and his team. In order to analyze the oxaphosphetane structures, the mass spectra of the isolated intermediates were studied by C. H. Wang [11].

M. Schlosser [12] proposed betaines as Wittig reaction intermediates.

Clarification of the different factors influencing the Wittig reaction, led naturally to attempts to control the stereochemistry. Thus, extensive investigations of the effect of the ylides, of the carbonyl compounds, and the reaction conditions on the *Z/E* ratio have been carried out. According to their general reactivity, which is dictated by the substituents on the ylide carbon, phosphonium ylides have been classified into three categories [3]:

- stabilized ylides - bearing substitutes with a large conjugate capacity, such as -COOMe, -CN, -SO₂R, preferentially form *E* alkenes;
- semistabilized ylides - bearing substitutes with a small conjugation capacity, such as -phenyl, propargyl, vinyl, fluorine, represent a more complex situation because a mixture of *Z* and *E* alkenes is formed. The high degree of *Z*- or *E*- stereoselectivity depends upon the reaction conditions.
- nonstabilized ylides - bearing substitutes without conjugation capacity such as -CH₃, -H, preferentially form *Z* alkenes.

However, there are exceptions to this generalized stereoselectivity. For example, B.E. Maryanoff [13] observed an anomalous *E* stereoselectivity in reaction of 4-carboxy-butyldiene-triphenylphosphorane with aromatic aldehydes. This result is believed to involve an intramolecular interaction of the terminal carboxyl group.

The mechanism of Wittig-type transformations are discussed in detail by W.A. Johnson [14], E. Vedejs [15] and O.I. Kolodiazhny [16], and will not be expanded on here.

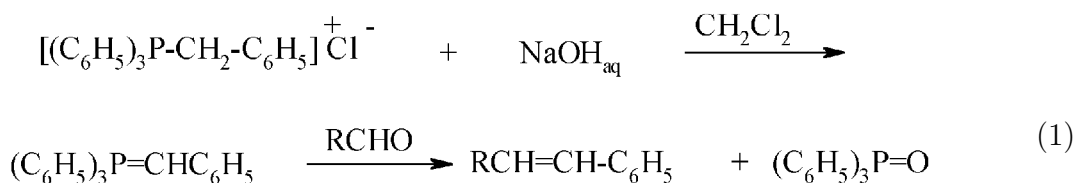
3 Alkene Synthesis using phase transfer catalysis (PTC) Wittig reactions

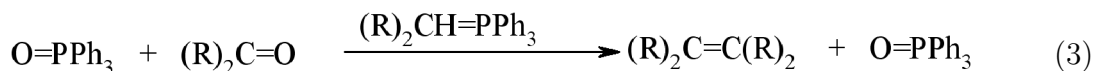
In 1973, it was discovered that Wittig reactions can be carried out under phase transfer catalysis conditions. The main advantage of this method is the ease with which the synthesis is performed [17]. NaOH or KOH, either in concentrated aqueous solutions or in the solid form, are the bases most often used under PTC conditions, as opposed to classical conditions, where more reactive bases such as *n*-BuLi or NaH are used. The temperatures (room temperature or 60-70°C) are also easier to achieve, compared to those under the classical conditions (-100°C to -70°C).

An interesting observation is that the catalyst can be present or absent in PTC reactions. Sometimes the phosphonium salts are at the same time the reagent and the catalyst.

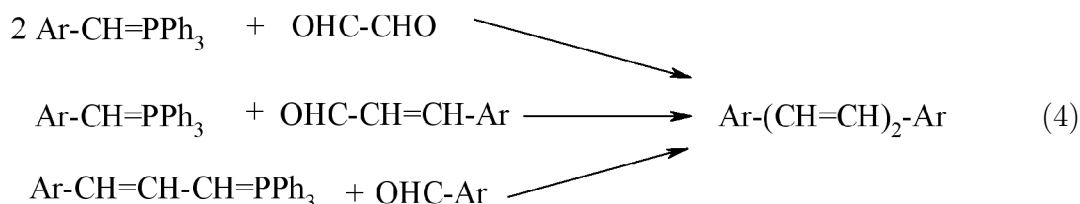
3.1 Witting reactions in liquid-liquid systems

E. Märkl [18] showed that alkyltriphenylphosphonium salts generate ylides in the presence of an NaOH_{aq} solution. The isolation of the ylides is not very important because the ylides decompose quickly in the presence of the aldehydes (Reactions 1, 2 and 3) [19, 20].

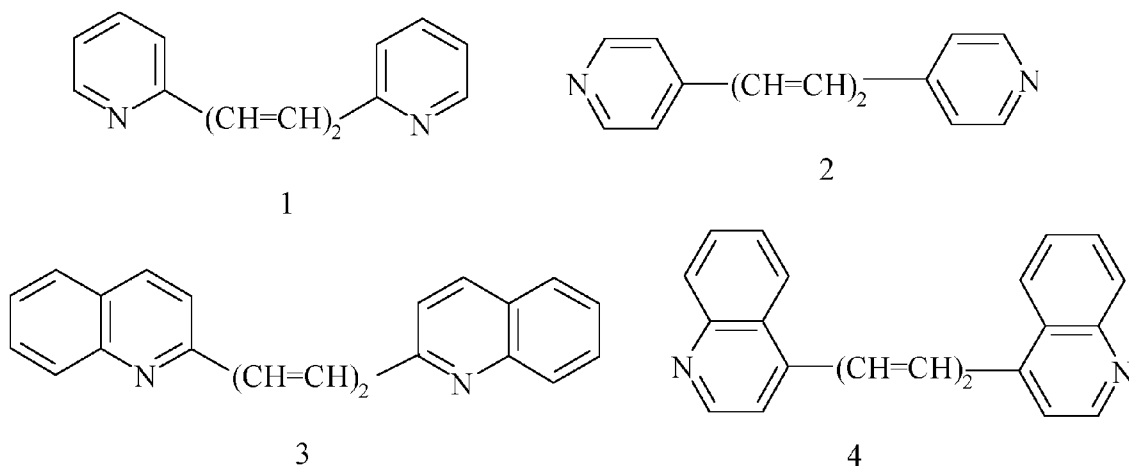




S. Hünig [21] obtained 1,4-diaryl-1,3-butadiene under the PTC conditions (Reaction 4).



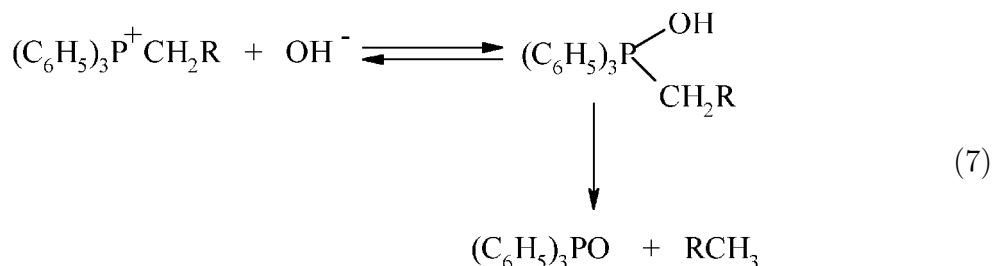
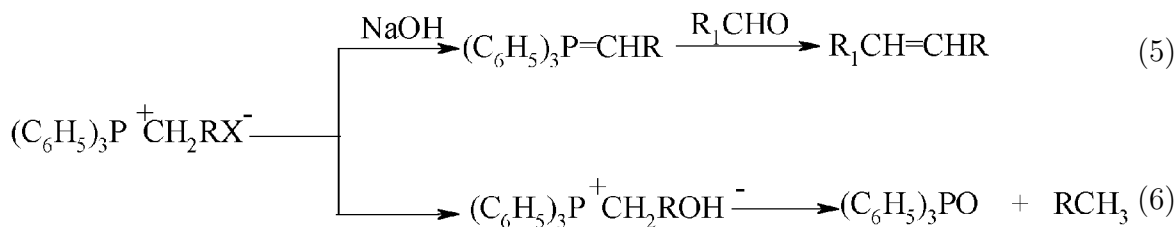
The products were dipiridyl butadiene (1 and 2) and dicinconyl butadiene (3 and 4) (Scheme 3).



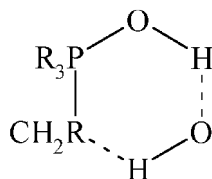
Scheme 3

W. Togaki and coworkers [22] examined the PTC Wittig reaction conditions in detail for obtaining of the maximum yield of olefin. In a series of experiments, increasing the NaOH concentration increases the yield of olefins (Reaction 5). The maximum yield depends on the alkyl group bonded at the triphenylphosphonium salt in the initial anions. The phosphonium salts are consumed in the concurrent reaction (Reaction 6).

The main forces that drive the formation of hydrocarbons in alkaline solution are the formation of a pentacoordinate intermediate and a strong P=O bond (Reaction 7).



The decomposition of the phosphonium salt in a concentrated hydroxide medium may be caused by the implication of a hydroxyl anion in the decomposition of the above intermediate.



E. Dehmlow [23] shows that a variety of solvents (e.g. tetrahydrofurane, benzene, methylene chloride) can be used in this PTC system. Depending upon the phosphonium salt $[\text{Ph}_3\text{P}-\text{CH}_2-\text{R}_3]^+\text{X}^-$, the yield of the reaction is about 60-80%, when $\text{R}_3=\text{aryl}$ and only about 20-30%, when $\text{R}_3=\text{CH}_3$.

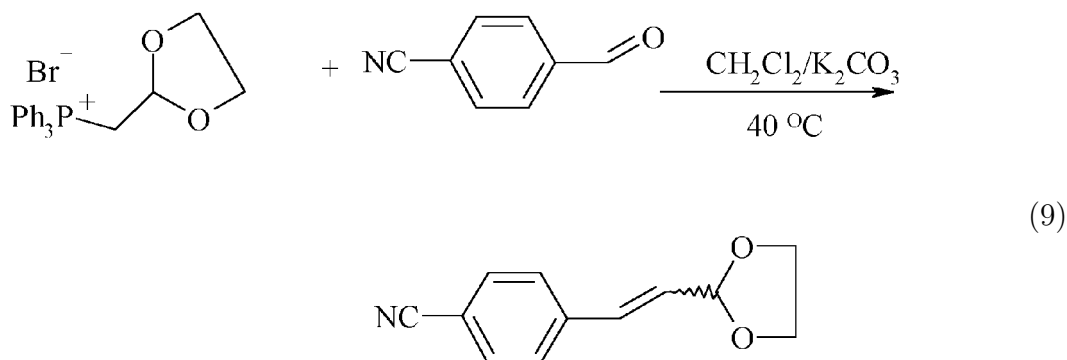
The *Z/E* ratio in the PTC Wittig reactions is similar to that observed for classical reactions of $[\text{Ph}_3\text{P}-\text{CH}_2-\text{R}_3]^+\text{X}^-$ with R_1CHO (*Z/E*=1/1), when $\text{R}_3=\text{phenyl}$ or a *m*-, *p*-substituted phenyl. If $\text{R}_3=\text{C}_6\text{H}_5-\text{CH}=\text{CH}$ or 9-antraceny, the percentage of the *Z* product decreases from 36% to 0%, respectively [18].

Other Wittig reactions using formaldehyde [24], substituted benzaldehyde [25, 26], and glyoxal [21] in aqueous solution were also performed.

Using PTC liquid-liquid systems, the reactions of phosphonium salts ($[\text{Ph}_3\text{P}-\text{CH}_2-\text{R}]^+\text{X}^-$), where $\text{R}=\text{C}_6\text{H}_5, \text{CH}=\text{CH}-\text{CH}_2, \text{C}_6\text{H}_5-\text{CH}_2, \text{CH}_3$, with various aldehydes were carried out in different solvents (tetrahydrofurane, CHCl_3 , C_6H_6 , $\text{C}_6\text{H}_5\text{CH}_3$) [27-33].

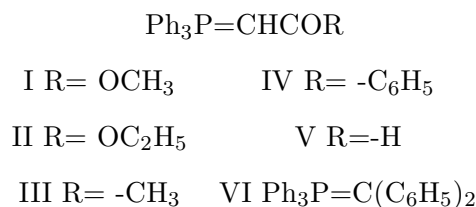
The PTC Wittig reaction of *o*-quinones with 2,5-dimethylthiophene-3,4-diylbis-(methylene)-triphenylphosphonium chloride [34] is very interesting. The reaction is carried out in an aqueous lithium hydroxide/ CH_2Cl_2 liquid-liquid system (Reaction 8).

N. Daubresse and coworkers [35] performed the PTC Wittig reaction of 1,3-dioxolan-2-yl-methyltriphenylphosphonium salts with aromatic and aliphatic aldehydes in liquid-liquid systems. The reaction is *Z*- stereoselective (Reaction 9). Table 1 shows that yields are high and the *Z*-isomer is formed preferentially.



Detailed studies were made by E. Vedejs [36] on semistabilized ylides with ester, vinyl and benzyl substituents.

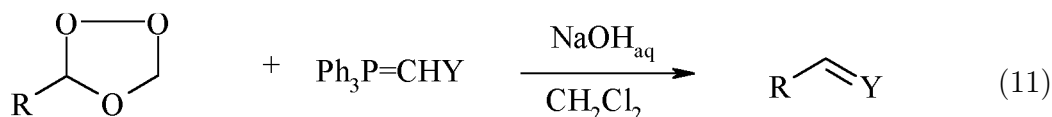
W. Abdou [37] studied the reaction of the α,β -unsaturated nitriles with three types of stabilized ylides as Wittig reagents: alcoxycarbonyl (I-II), β -ceto-methylenetriphenylphosphorane (III-V), and arylidenephosphorane (VI).



T. Tsunoda and coworkers [38] studied the PTC Wittig reaction of cyanomethylene-trimethylphosphorane with various aldehydes and ketones (Reaction 10).

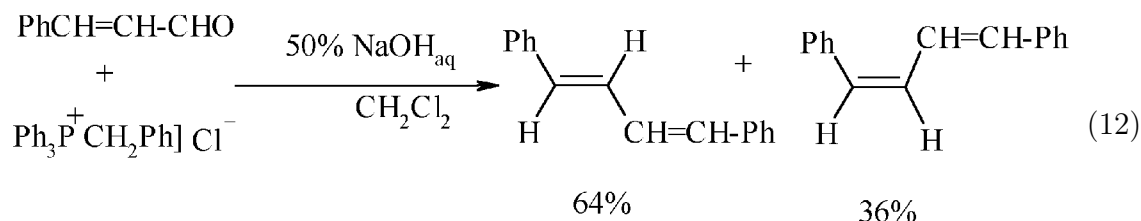


The α,β -unsaturated carbonyl compounds were synthesized starting from monosubstituted ozonides and stabilized phosphorus ylide (Reaction 11) [39].

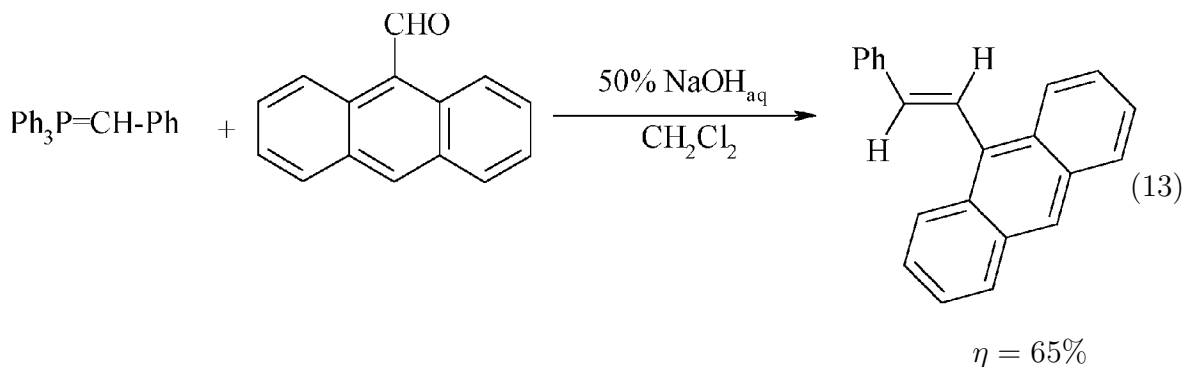


In all of these cases, the reaction is *E* stereoselective, as shown in Table 2. In the case of carboxymethyl stabilized ylides, the yield is 93%. The reaction of stabilized ylides with 2-acetyl-5-bromothiophene and 5-methylfuran were studied under phase transfer catalysis conditions [40].

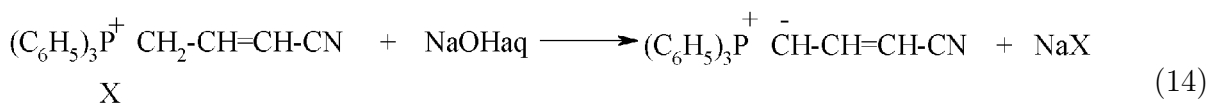
An alkene mixture is frequently obtained when the ylides are semistabilized (Reaction 12) [41].



Benzyltriphenylphosphonium ylide reacts with 9-anthraldehyde to give *E*-alkenes. This result is compared to the reaction of benzaldehyde in which the final mixture contains a *Z* : *E* = 59:41 isomer ratio (Reaction 13).



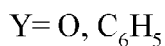
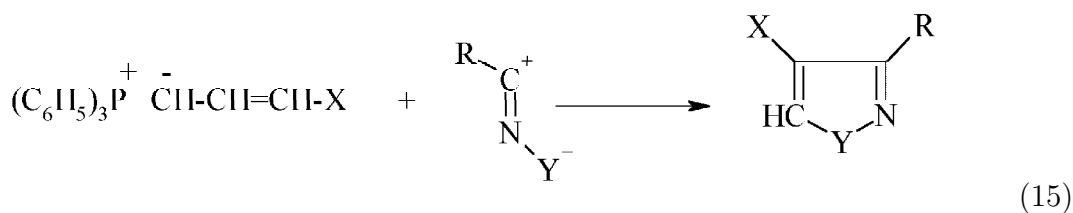
The vinyl-semistabilized ylides can be prepared and isolated by the reaction of the phosphonium salts with a NaOH solution (Reaction 14) [42].



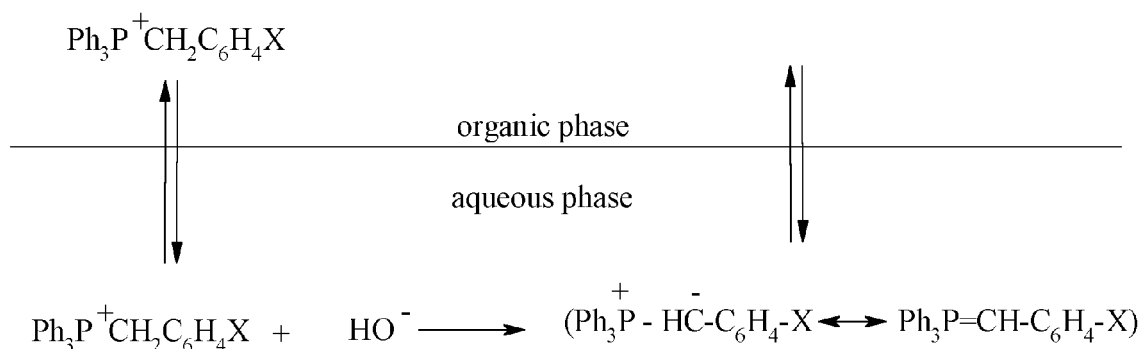
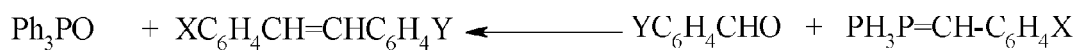
This type of ylide is synthesized with the phosphonium salts containing COOCH_3 [43] or CHO [44] replacing CN group (Reaction 15). This is advantageous for obtaining heterocyclic compounds [42].

J.-J. Hwang and coworkers [45] have investigated the PTC Wittig reaction of benzyltriphenylphosphonium salts with benzaldehyde in a biphasic organic solvent/ NaOH_{aq} system (Scheme 4).

Stilbenes (Reaction 16) are obtained using 0,1 N NaOH aqueous solution and CH_2Cl_2 . Regarding the organic solvent used for the synthesis of the *Z*-alkenes, CHCl_3 produces

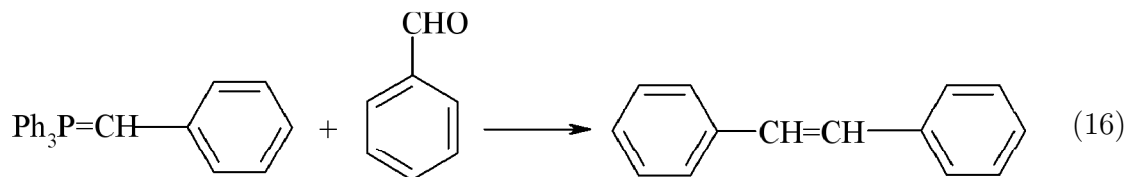


$$\eta = 65 - 80\%$$

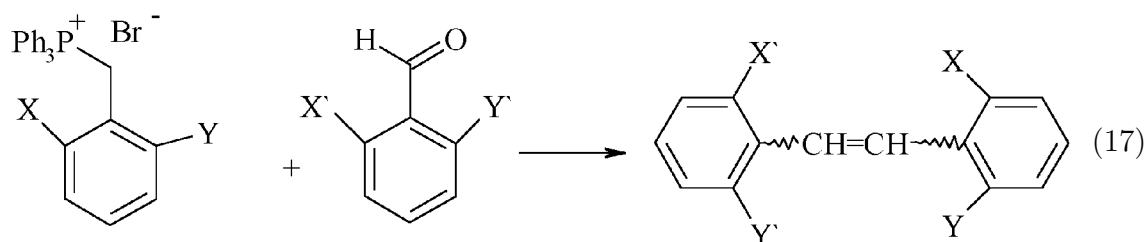


Scheme 4

more of the Z isomer than CH_2Cl_2 , as presented in Table 3.



E.C. Dunne and coworkers [46] studied the reaction of benzyltriphenylphosphorane with substituted benzaldehydes (Reaction 17). The resulting alkenes are stilbene derivatives. NaOH_{aq} (50%) and CHCl_3 are used in the liquid – liquid system.



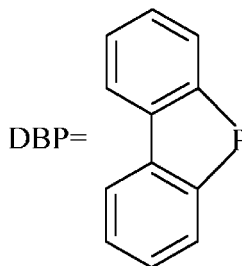
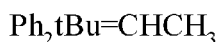
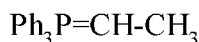
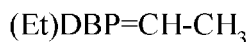
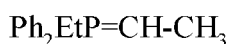
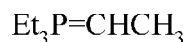
Generally, semistabilized ylides gives both *Z* and *E* olefins.

Nonstabilized ylides attack ketones and aldehydes in an equimolar ratio to form oxaphosphetane adducts. These decompose into triphenylphosphine oxide and olefins [47]. J. Gillois and coworkers [48] performed Wittig reactions under phase transfer catalyst conditions. The formation of nonstabilized ylides takes place in anhydrous solvents with strong bases.

This type of ylide forms preferentially contra thermodynamic *Z*-alkenes. The stereoselectivity depends upon the nature of the substituents on the ylide carbon and on the P atom. *Z*-Alkenes are formed in the case of ylides $R_3P=CHR'$, where R' = alkyl and R=phenyl.

This stereochemistry results when the reagents approach in the “*anti*” position. The “*anti*” transition state will most likely be formed in a solvent with increased polarity (Scheme 5) [49].

E. Vedejs [50] used the following nonstabilized ylides.



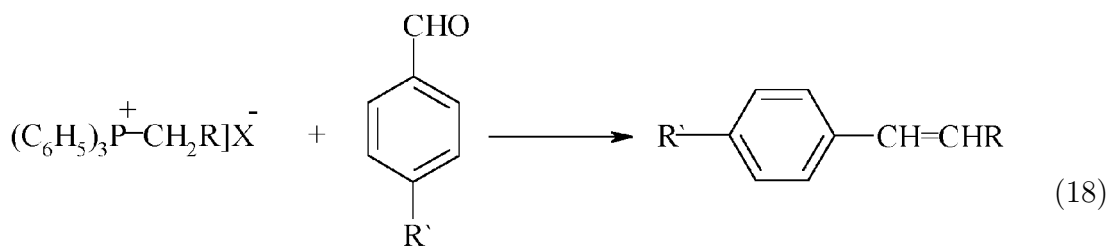
When using $Ph_3P=CH-CH_3$, the *Z/E* ratio was 16:1 ($\eta=92\%$) when reacted with $Ph-CH_2-CH_2CHO$ and 32:1 ($\eta=85\%$) when reacted with $Ph-CH_2-CH(CH_3)CHO$. The reaction of $(Et)DBP=CH-CH_3$ is an exception to the general rule because *Z/E* ratio is 1:18 ($\eta=83\%$) for $Ph-CH_2-CH_2CHO$.

3.2 Wittig reactions in liquid-solid systems

Solid base is used in other Wittig reaction path, where triphenyl-alkylphosphonium salts react with aldehydes [35]. Triphenylalkylphosphonium chlorides or bromides may be used with addition of NaF ($\eta=7-20\%$ in alkenes) or tetramethyl ammonium fluoride as catalysts ($\eta=63-69\%$). Good yields were the result in the last case because of the high solubility of the phosphonium salts in the organic phase (Reaction 18).

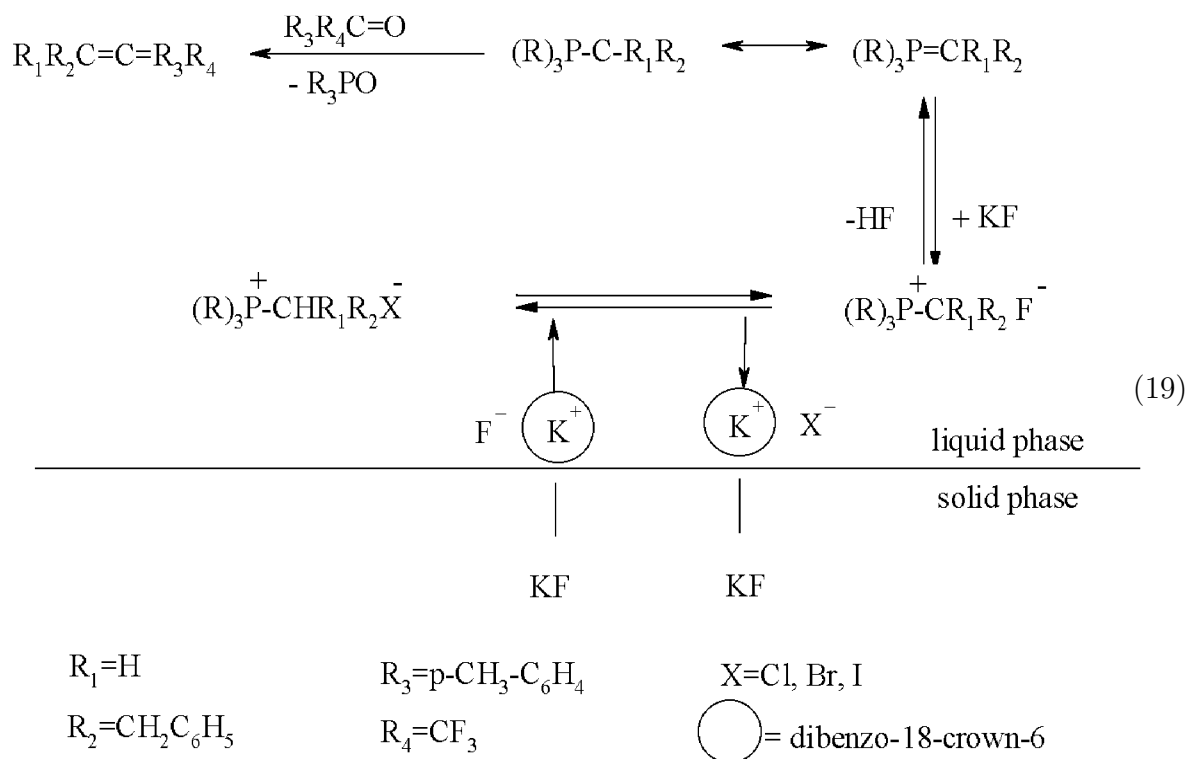
G. Koßmehl [51] found a new method to transform phosphonium chlorides, bromides and iodides into fluorides using dibenzo-18-crown-6 as the catalyst in organic solvents using an excess of solid KF. The phosphonium fluorides react quickly with carbonyl compounds (Reaction 19).

The mechanism of the ylide formation presumes that the fluoride anion is transported with a potassium counteranion (K^+) from the solid phase into the organic phase by the crown ether. At the same time, the phosphonium halide is transformed into phosphonium fluoride.



$\text{R} = \text{CN}, \text{OAc}, \text{COCH}_3$

$\text{R}' = \text{NO}_2, \text{N}(\text{CH}_3)_2$

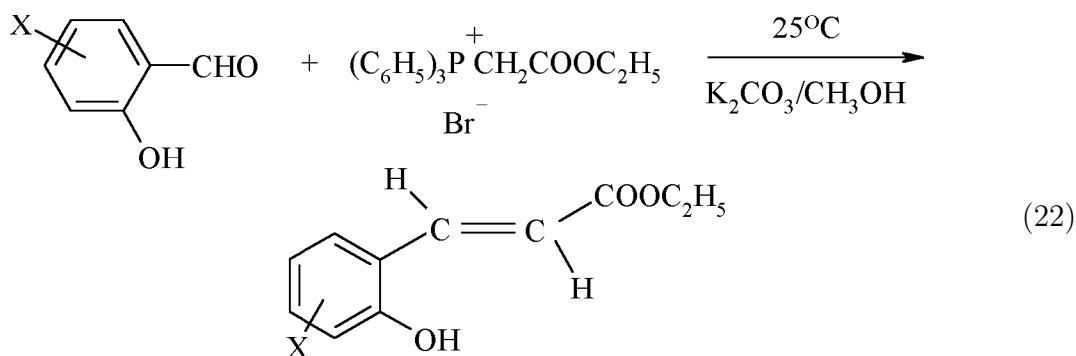
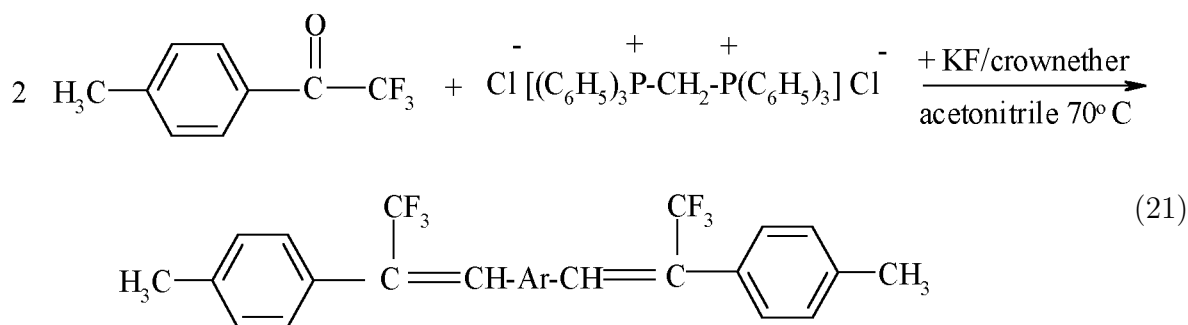
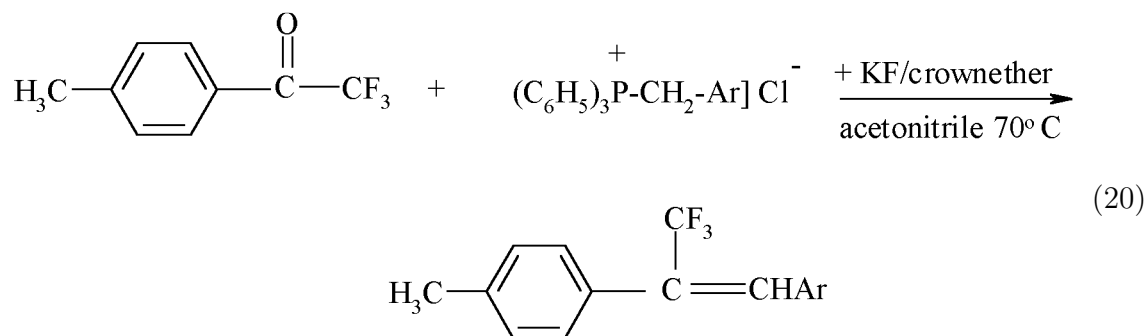


The reaction of ω,ω,ω -trifluoro-*p*-methylacetophenone with phosphonium salts was studied (Reaction 20, 21).

R.M. Boden [52] obtained *trans*-stilbene in a liquid-solid system using THF and CH_2Cl_2 as solvents and *t*- $\text{C}_4\text{H}_9\text{OK}$ or K_2CO_3 as solid bases; the reaction yield was higher.

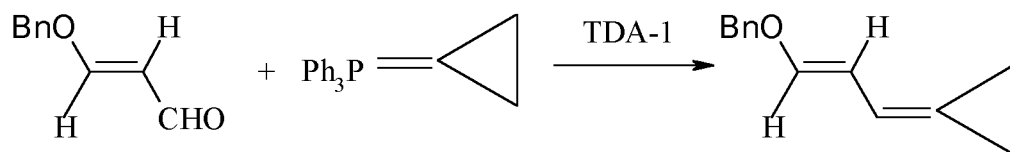
For the synthesis of hydroxycinnamic esters, J.F. Dupin [53] reports the results of the reaction of (carbethoxymethyl)triphenylphosphonium bromide with aromatic *o*-hydroxyaldehydes in a liquid-solid binary system (Reaction 22). The reaction was carried out in potassium carbonate/methanol system and good yields of alkene were reported.

The PTC Wittig reaction between cyclopropylenetriphenylphosphorane was studied by J.A. Stafford and coworkers [54]. They used TDA-1 as a catalyst in order to increase the reaction yield ($\eta = 59\text{--}95\%$) (Reaction 23).

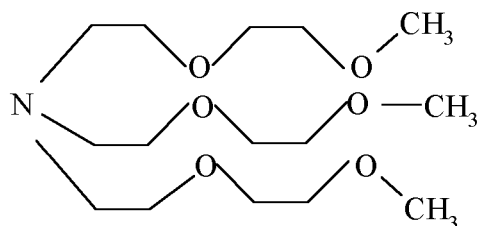


The reaction of various azadicyclo-ketones with diverse phosphonium salts (e.g. triphenylmethylphosphonium iodide, triphenylethylphosphonium iodide) in the following systems: solid potassium carbonate/benzene, solid potassium *t*-butoxide/benzene and 60% aqueous sodium hydroxide/dichloromethane were also investigated [55]. The best system was the combination of *t*-BuOK/benzene.

J.G. Cui and coworkers [56] synthesized steroids using Wittig reaction in solid-liquid phase transfer conditions.

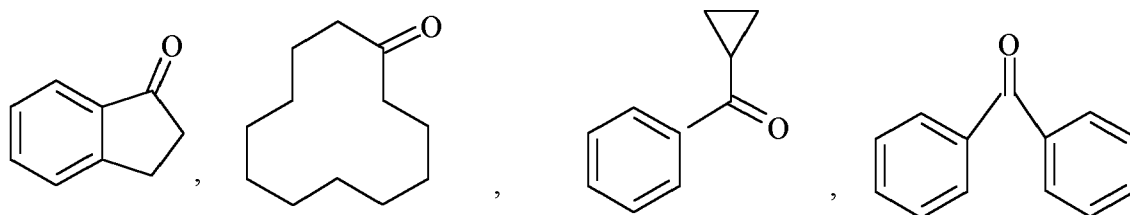


TDA-1



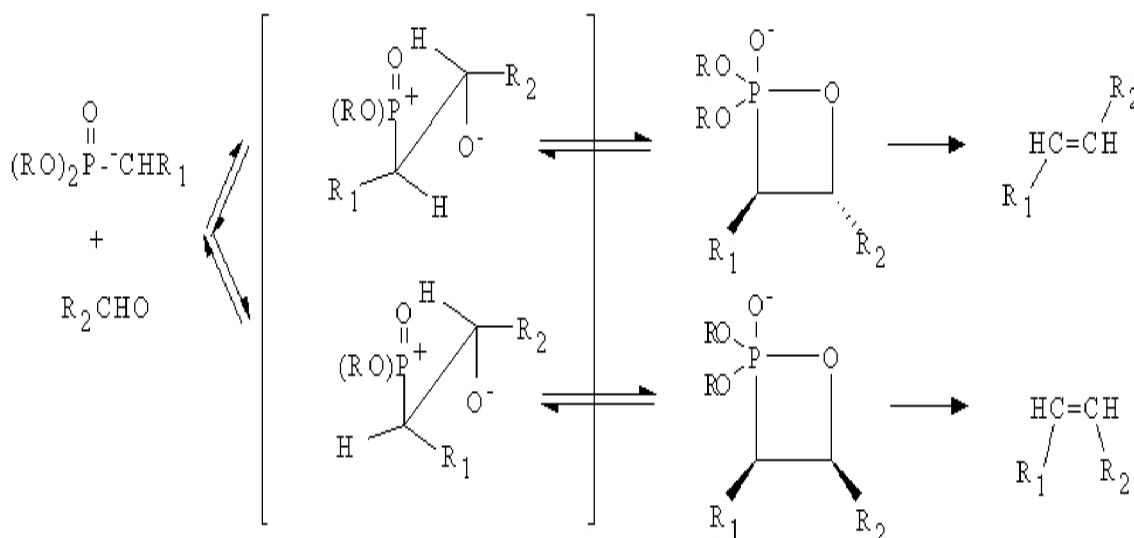
(23)

The following carbonyl compounds were used.



4 The Wittig-Horner reaction mechanism

The mechanism of the homogenous Wittig-Horner reaction closely resembles that of the Wittig reaction (Scheme 6) [57].

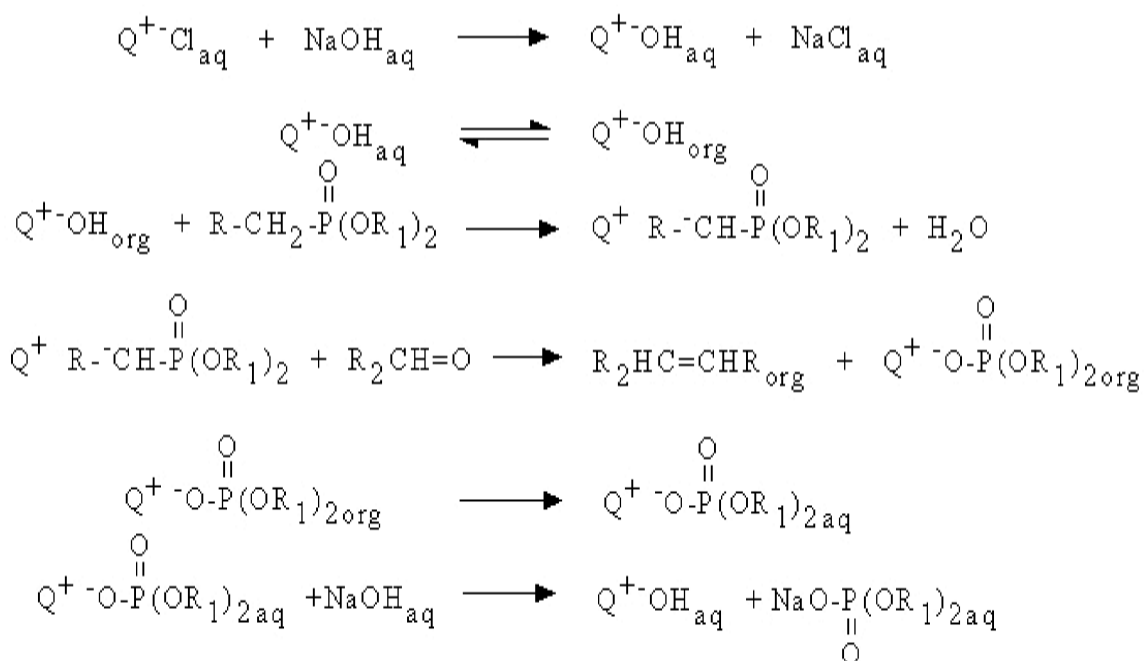


Scheme 6 The Wittig-Horner reaction mechanism.

In the presence of a strong bases (metallic Na, NaH) phosphonates produce the carbanions for the Wittig-Horner reaction. The carbanion reacts with carbonyl compounds passing through a betaine intermediate and then through a cyclic oxaphosphetane intermediate. Depending on the carbanion stability, the final products of the reaction are *cis* or *trans* alkenes. In the case of phosphonates, the major product is a *trans*-olefin [58].

Under phase transfer catalysis conditions, the base moves from the aqueous phase to the organic phase aided by the phase transfer catalyst. There the carbanion is formed, and it reacts with the carbonyl compound. Olefins are formed in the organic phase (Scheme 7). The phosphonate moves back from organic phase into the aqueous phase as an ion pair with the catalyst.

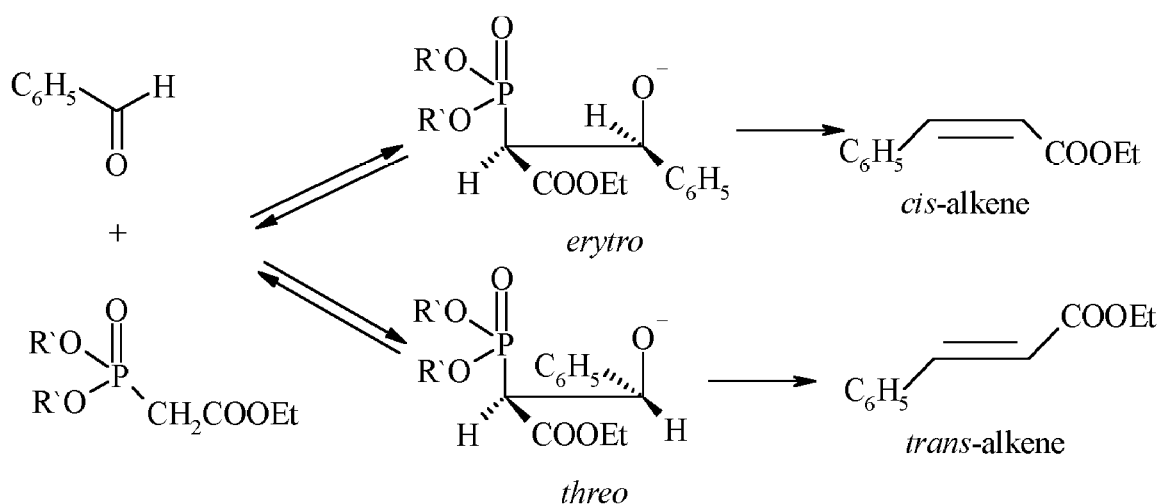
In a liquid – solid system, the process takes place on the surface of the solid base, via a complex intermediate. In order to elucidate the Wittig-Horner reaction mechanism quantum chemical and molecular mechanics methods were employed. The stereoselectivity is normally influenced by the two different transition states: the addition and closeness of the oxaphosphetane ring need to develop two molecular mechanics models [59].



Scheme 7

A theoretical study of the Wittig-Horner reaction of the dialkylphosphonoacetate with acetaldehyde is reported by K. Ando (Scheme 8) [58].

RHF/6-31 + G* *ab initio* calculations show that the selectivity of the Wittig-Horner reaction is the result of both kinetic and thermodynamic control of the reversible formation of the *erythro* and *threo* intermediate states followed by the decomposition of the intermediate into the corresponding alkene. The typical formation of *trans* alkenes in Wittig-Horner reactions can be explained by the formation of the *threo* adduct that is

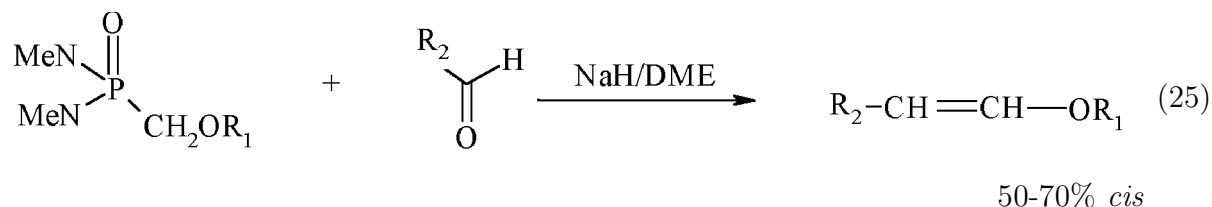
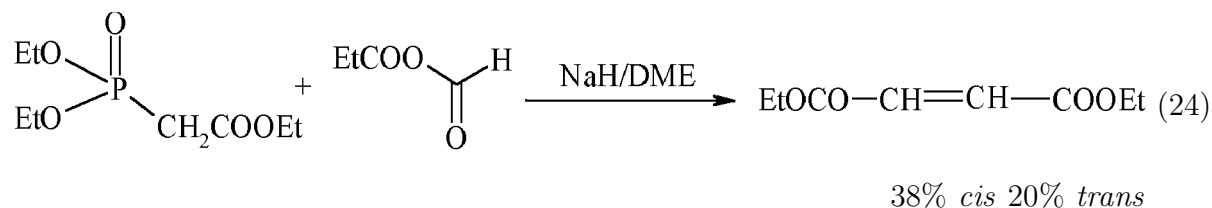


Scheme 8

thermodynamically more stable.

5 Stereochemical control

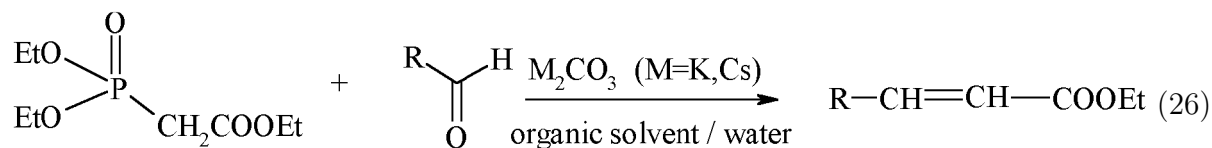
The literature data show that the majority of olefins obtained from homogenous Wittig-Horner reactions are *trans*-selective. This is surprising, since the investigated systems generally contain groups capable of forming conjugate systems with the incipient double bond that diminish the steric factors and favor *trans*-olefin formation. However, in the literature *cis*-olefins formation was reported, especially in the case of *tri* or *tetra*-substituted olefins, and some experiments show the formation of *cis*-alkenes with significant yields (Reaction 24, 25) [60]. This unusual stereoselectivity is based upon unexpected stereochemistry.



In the case of PTC Wittig-Horner reaction the stereochemistry is influenced by many factors such as the solvent, temperature, catalyst, carbanions and carbonyl compounds.

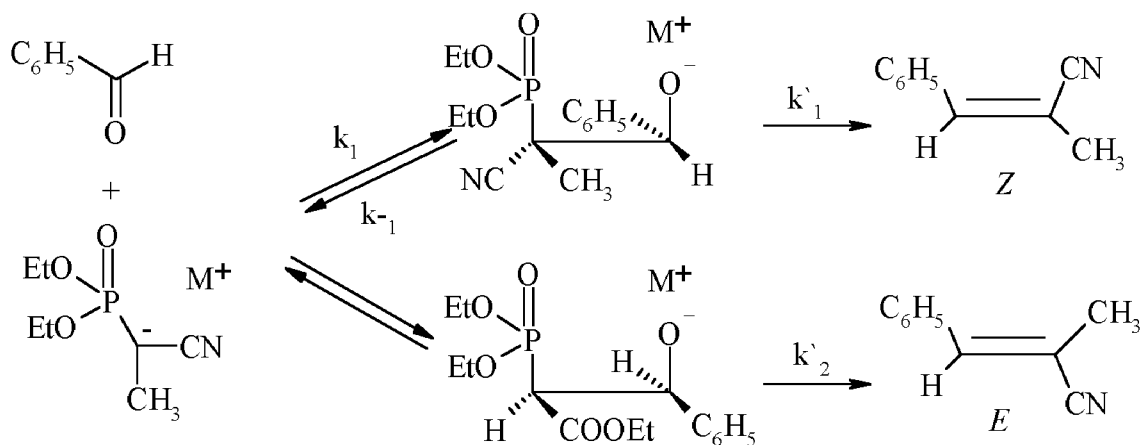
The influence of the catalyst on the *Z/E* ratio.

Z. Mouloungui and coworkers studied the influence of the catalyst of the reaction of diethylphosphonoacetate with 2-carbonyl-pirole, 3-carbonyl-indole, salicylic aldehyde and *p*-hydroxybenzaldehyde. The research was carried out in a solid-liquid system using phase transfer catalysis (Reaction 26) [61].



Cs_2CO_3 is an efficient phase transfer catalyst for Wittig-Horner reactions, giving the higher yields and *trans*-stereoselectivity (Table 5).

According to E. D'Incan [64] the catalyst and its quantity are important in PTC Wittig-Horner reaction. The stereoselectivity of the reaction depends on the stereoselectivity factors: k_{-1}/k_1' and k_{-2}/k_2' and by the k_1/k_2 ratio (Scheme 9).



Scheme 9

As is shown in Table 6, all catalysts facilitate *E*-isomer formation, but the stereospecificity is not very good [64].

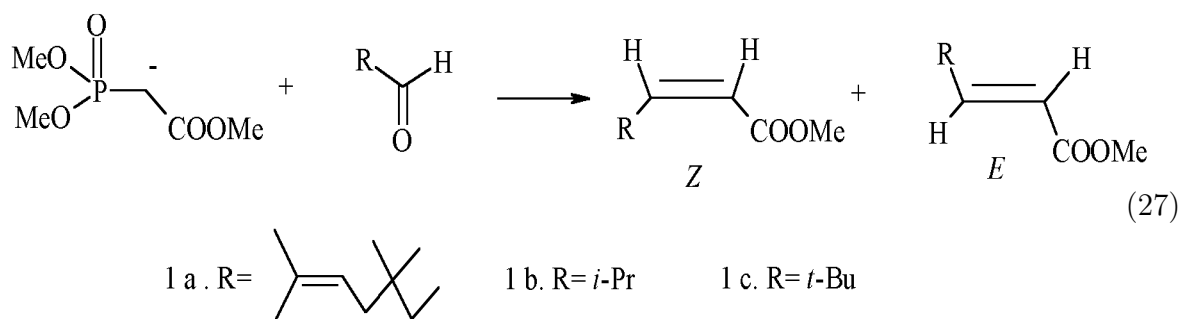
The data from Table 7 confirm that the influence of the catalyst has only a small influence, while the solvent has a major influence on the reaction stereochemistry.

The influence of the solvent on the *Z/E* ratio.

According to the data in Table 7, CH_2Cl_2 facilitates the *E* isomer formation, and C_6H_6 facilitates the *Z* isomer formation.

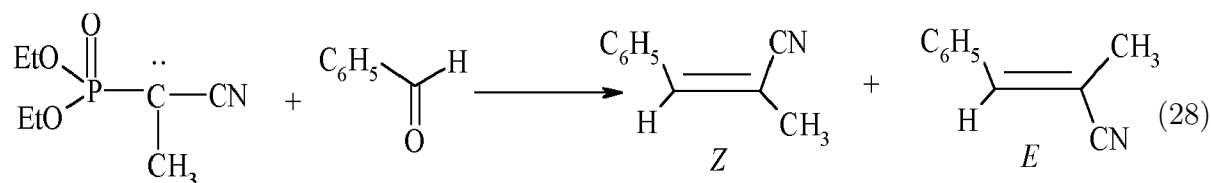
S.K. Thompson [64] confirms that the solvent plays a very important role on *Z/E* ratio (Reaction 27 and Table 8).

The Li^+ cations in DME and at room temperature confer the highest *E*-stereoselectivity. The nature of solvent influences the reaction (Table 9) [63].



Nonpolar solvents facilitate the formation of *Z*-isomers, while the presence of polar solvents (CH_2Cl_2 , CHCl_3) facilitates the formation of *E* isomers.

Solvents have a major influence under classical homogeneous conditions [65]; thus, the reaction between benzaldehyde and diethoxyacrylonitrilphosphonate (Reaction 28) using NaH or *t*-BuONa/THF/20°C gives a ratio $Z/E = 40/60$, while the same reaction with NaH or *t*-BuONa/HMPT/20°C gives a ratio $Z/E = 20/80$. (HMPT=hexamethylphosphorous triamide).



J.H. Babler [67] studied the reaction between cyanomethyl-diethyl phosphonate with 3,3-dimethylbenzophenone under various conditions such as MeLi/Benzene or NaH/DMF or DMSO. In MeLi/ Benzene, the percentage of the *Z* isomer is 28% and the *E* isomer is 72% and in the NaH/DMF or DMSO systems, the percentages are 60% (*Z*) and 40% (*E*).

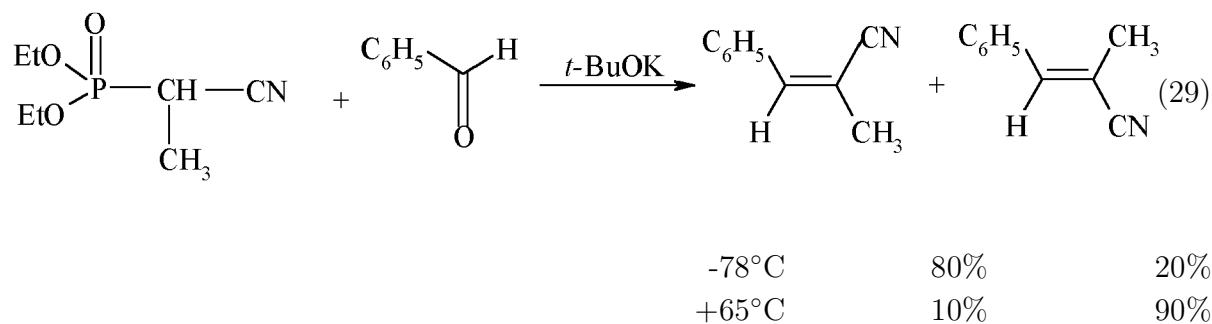
In both phase transfer catalysis and under classical conditions, nonpolar solvents facilitate the formation of *Z*-isomers.

The influence of temperature on the Z/E ratio.

According to S.K. Thompson [64], the effect of the temperature on the reaction 27 depends upon the cation and the solvent used in the reaction. In this case, as the temperature is increased from -78 to 23°C, it was observed that the use of Li^+ cation at room temperature increases the *E*-stereoselectivity. (Table 8)

S. Kojima and coworkers [67] used β -hydroxy- α,β -diphenylspiroposphonates in order to obtain *cis* and *trans* stilbene at temperatures between -60 and -5°C. In the reaction of benzaldehyde with diethyl-2-cyanoethylphosphonate, the reaction temperature markedly influences the Z/E alkene ratio (Reaction 29) [62].

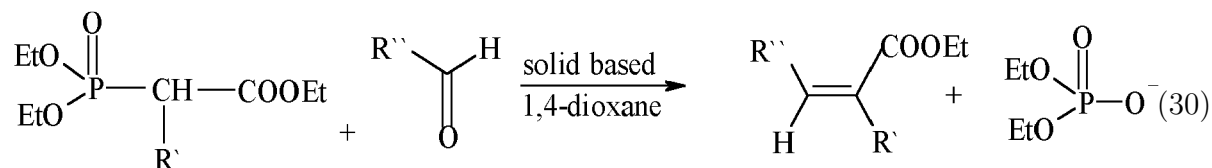
J. Petrova [68] noticed that at -33°C the *cis* isomer is regularly formed, and at 10°C the *trans* isomers predominate for the reaction of benzylidene with phosphonate in NaNH_2 ,



or liquid ammonia and ether.

This aspect was emphasized in the case of classical Wittig-Horner reactions. In the case of PTC Wittig-Horner reactions, the temperature has a reduced effect on the *Z/E* ratio and a slight influence is observed on the yield.

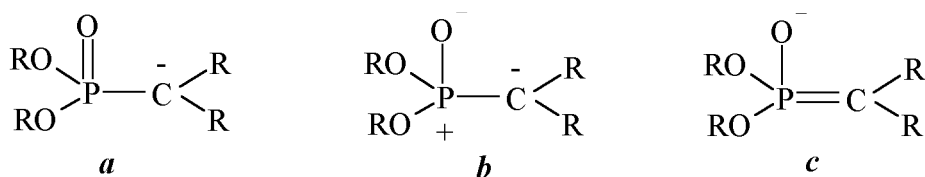
In a biphasic solid-liquid system synthesis, J.V. Sinisterra and coworkers [69] have studied the effect of cesium carbonate (Cs_2CO_3) as catalyst and the effect of temperature, concluding that the temperature does not influence the reaction yields (Table 10) (Reaction 30).



The influence of carbanions.

A very easy way to prepare carbanions is to add phosphonates at room temperature to a NaOH solution in 1,2-dimethoxyethane. The alkyl phosphonate carbanions that do not bear activating groups, cannot be prepared because the anion formed is not stable at the reaction temperature.

In order to synthesize cyclopropane, only carbanions that contain activating groups, such as carboethoxy or cyan, are used. The resonance structures of carbanions are shown (Scheme 10).

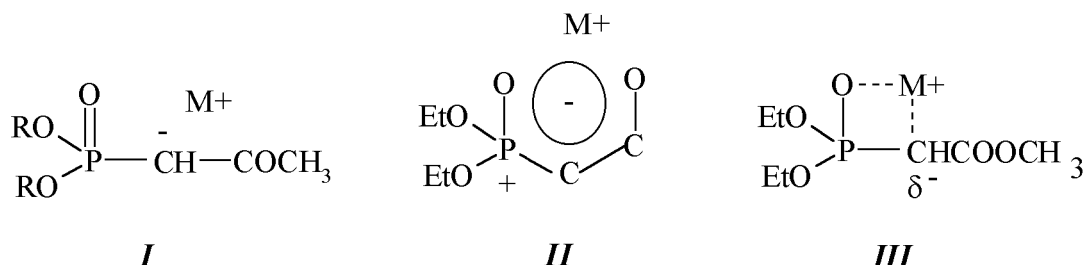


Scheme 10

Structures *a* and *b* use a phosphorus *d* orbital, as in phosphorane. It is well known that P=O bond in phosphate and phosphonates, exhibit some characteristics of a single

bond, which can be explained by structures *b* and *c* [70].

Although phosphonates were studied using a variety of physical methods, similar studies were done on carbanions. The ^{31}P -NMR chemical shift for a β -keto-carbanion (*I*) is about -38 ppm, and it is independent of the carbanion. However the situation is more complex for stabilized carbanions esters. They seem to exist as a dependent mixture of cations in one of two forms, *II* and *III* (Scheme 11) in *t*-butanol/THF [71].



Scheme 11

The results of the different spectroscopic studies suggest that the phosphonate group is just as efficient as a carbonyl group for stabilizing an adjacent carbanion but is less efficient than a phosphonium group; this is confirmed by their relative reactivities.

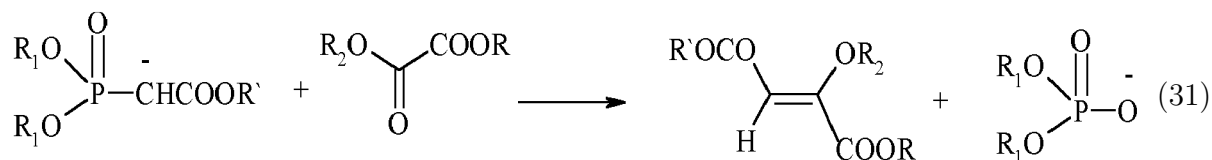
The influence of the carbonyl compound.

The carbonyl compounds used in Wittig-Horner reactions are various aldehydes or ketones. Ketones are generally less reactive than aldehydes, and they frequently require special conditions, , because of steric effects [72]. Compared to steric effects, electronic effects have a minor importance, although trifluoromethylketones have an increased reactivity.

Aldehydes with long hydrocarbon chains are less reactive or in some cases nonreactive [73].

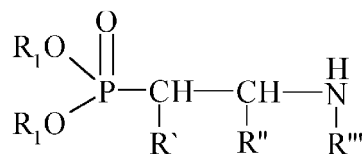
Ketones can be enolized faster and lead to olefins but the yields are poor. Cyclopentanone and acetophenone are the well-known examples. This aspect is not very important when phosphonates have a more acidic character [74].

Ketones react with phosphonate carbanions producing allenes, an aspect that is not very well studied. Similar reactions with carbonyl esters are rare, e.g. oxalic acid esters give vinyl esters (Reaction 31).



Imines react similarly with aldehydes and ketones to form olefins, but an excess of base must be used. Otherwise the β -amine phosphonate, shown in the Scheme 12, will

be formed.



Scheme 12

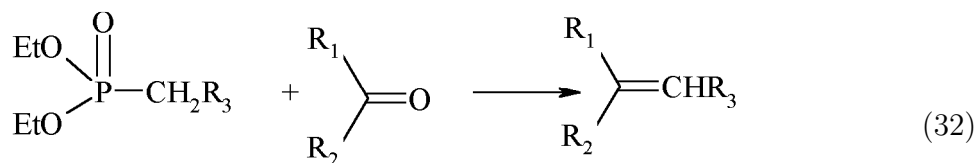
6 Alkenes synthesis under PTC conditions

The phase transfer catalysis method represents a new and efficient way to facilitate the contact between a nonpolar substrate situated in an organic phase and an ionic reagent situated in an aqueous phase that is in contact with the organic phase.

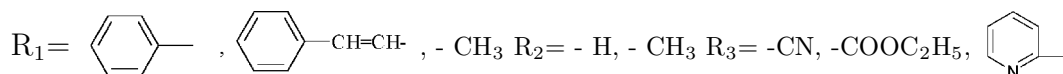
The transfer of reagent from the aqueous phase to the organic phase is achieved by a phase transfer catalyst. This type of catalysis in Wittig-Horner reactions can be achieved in both liquid-liquid and liquid-solid systems [75]. The Horner reaction is applied to different combinations than the Wittig reaction. The two methods complement each other and extend the synthetic possibilities of unsaturated compounds.

6.1 PTC Wittig-Horner reactions in liquid-liquid systems

According to J. Dockx [76], the anionic intermediate is generated in an aqueous solution by NaOH, and the reaction takes place in an organic solvent in the presence of a phosphonium salt with bulky alkyl groups. C. Piechucki [77] performed the Wittig-Horner synthesis under the following conditions: NaOH_{aq} (50%) and CH₂Cl₂, using tetrabutylammonium iodide as the catalyst (Reaction 32).

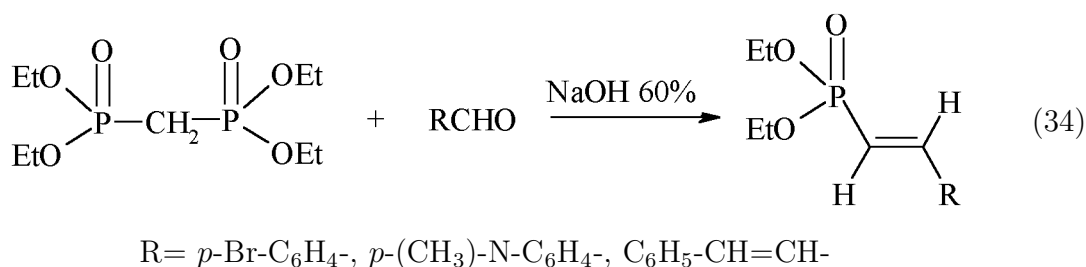
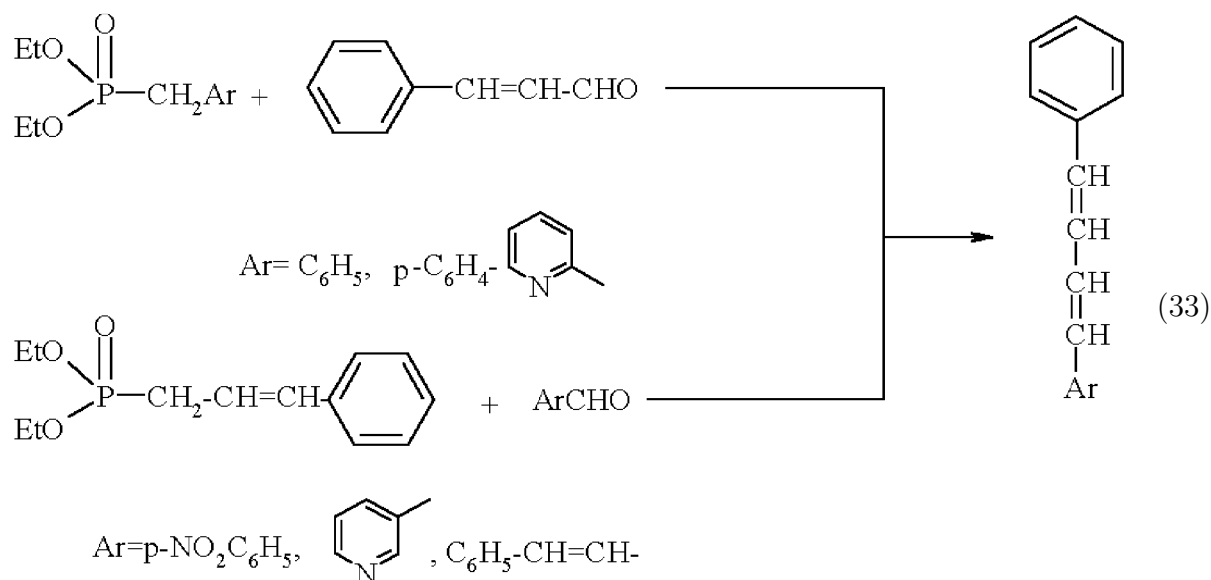


where



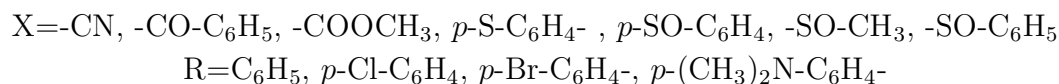
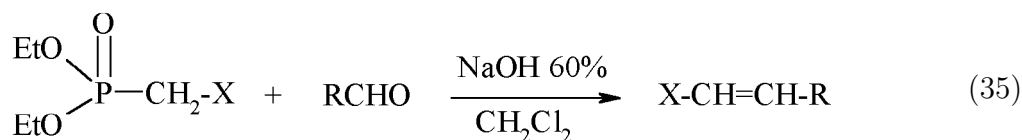
Benzene was used as the solvent for different phosphonates and aldehydes in order to obtain the same diene or triene (when the radical contains a double bond) [79] (Reaction 33 and 34).

M. Mikolajczyk [79] carried out the reaction of phosphonates with aldehydes in molar ratio 1:1. The alkene is formed at one phosphonic group (Reaction 34).



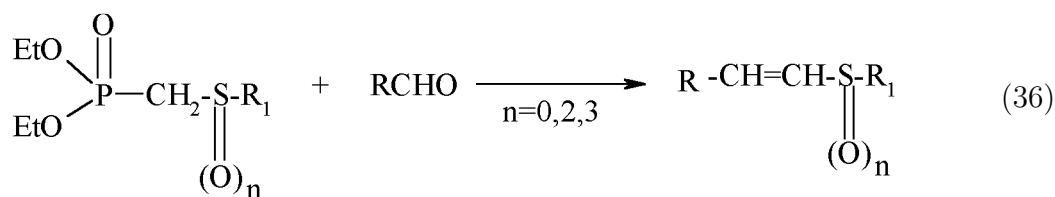
This reaction is used for the synthesis of styryl phosphonate, because of the good *E*-stereoselectivity and the good yield.

Analogous to the reaction studied by C. Piechucki [77, 78], M. Mikolajczyk [79] has worked with different aldehydes and phosphonates in liquid-liquid systems (Reaction 35).



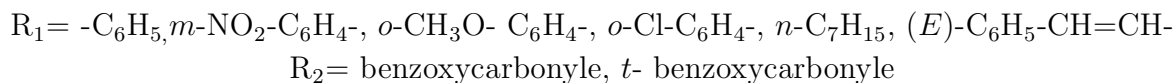
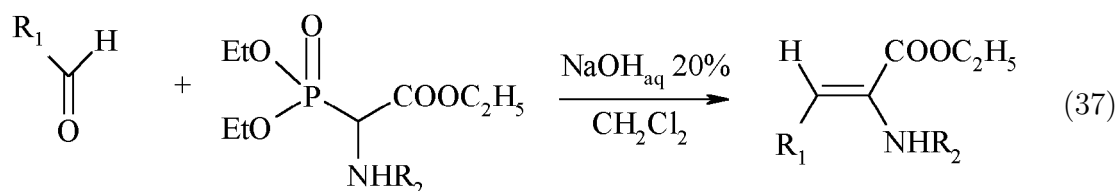
Thus M. Mikolajczyk and coworkers [80] have obtained a diverse set of olefins (Reaction 36).

The $\text{CH}_2\text{Cl}_2/\text{NaOH}$ aq system is specific for aromatic aldehydes (Reaction 36). Ketones and aliphatic aldehydes are unreactive. If $n = 1$ or 2 , *cis/trans* mixtures were obtained, and if $n = 3$ only *trans* compounds are produced. When quaternary ammonium chloride is used, *Z* and *E* olefins are obtained; on the contrary, quaternary ammonium



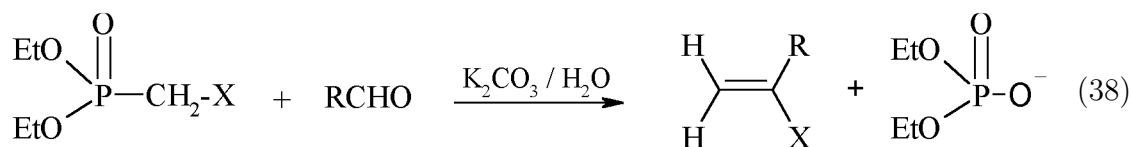
bromide or iodide give predominately *E* alkenes.

According to P.G. Ciattini [81], the reaction of N-acyl-2-(diethoxyphosphoryl)-glycylmethyl ester with different aldehydes, result in anionic derivatives (Reaction 37). The reaction conditions were a 20% NaOH solution / CH₂Cl₂ without a typical catalyst.



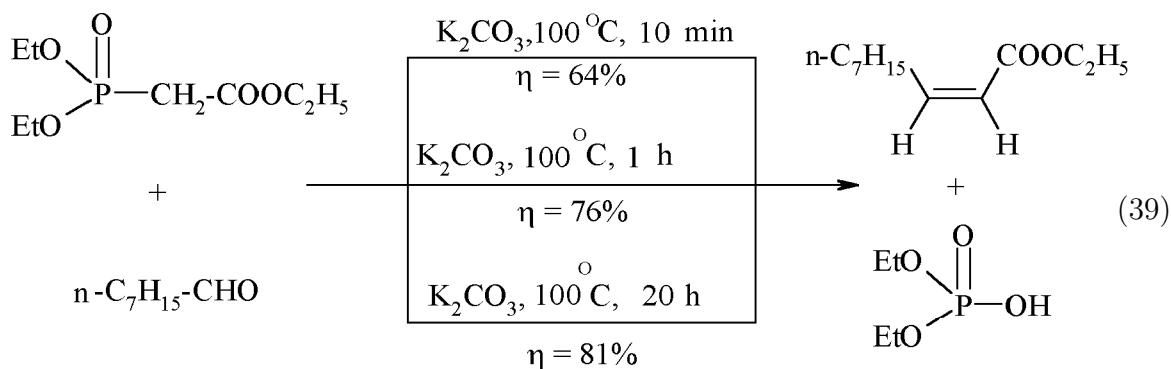
The reaction is carried out at room temperature. The reaction yield is between 45 and 95% and is *Z*-stereoselective.

Recently, J. Villieras and coworkers [82] described the synthesis of α -acrylates from triphenylphosphonoacetate and formaldehyde under PTC conditions (Reaction 38).

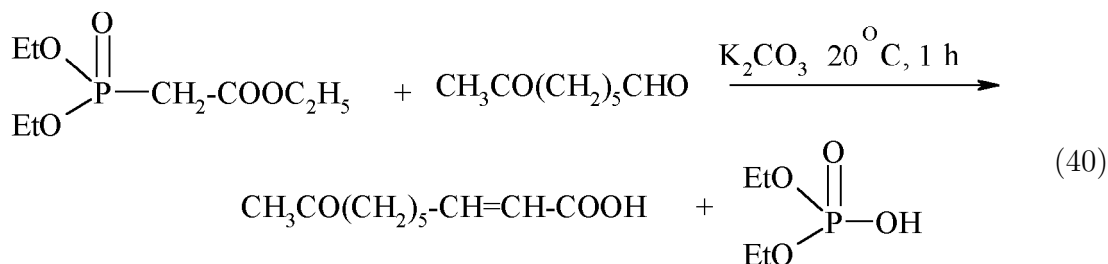


Reaction times and temperature depend upon the methylene proton acidity from α radicals, the electrophilic character of the carbonyl compound, the reagents and the reaction conditions. The reactions are carried out without solvent.

The influence of the temperature and the reaction time was studied for reactions of aldehydes with long carbon chains. Yields are higher at room temperature and when the reaction time increases (Reaction 39).

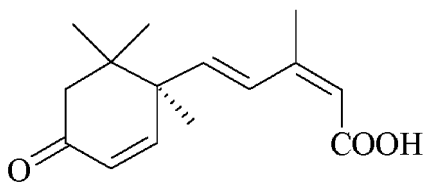


It is also possible to obtain a pheromone secreted by the mandibles glands of the royal bee under PTC conditions in good yield (Reaction 40) [83].



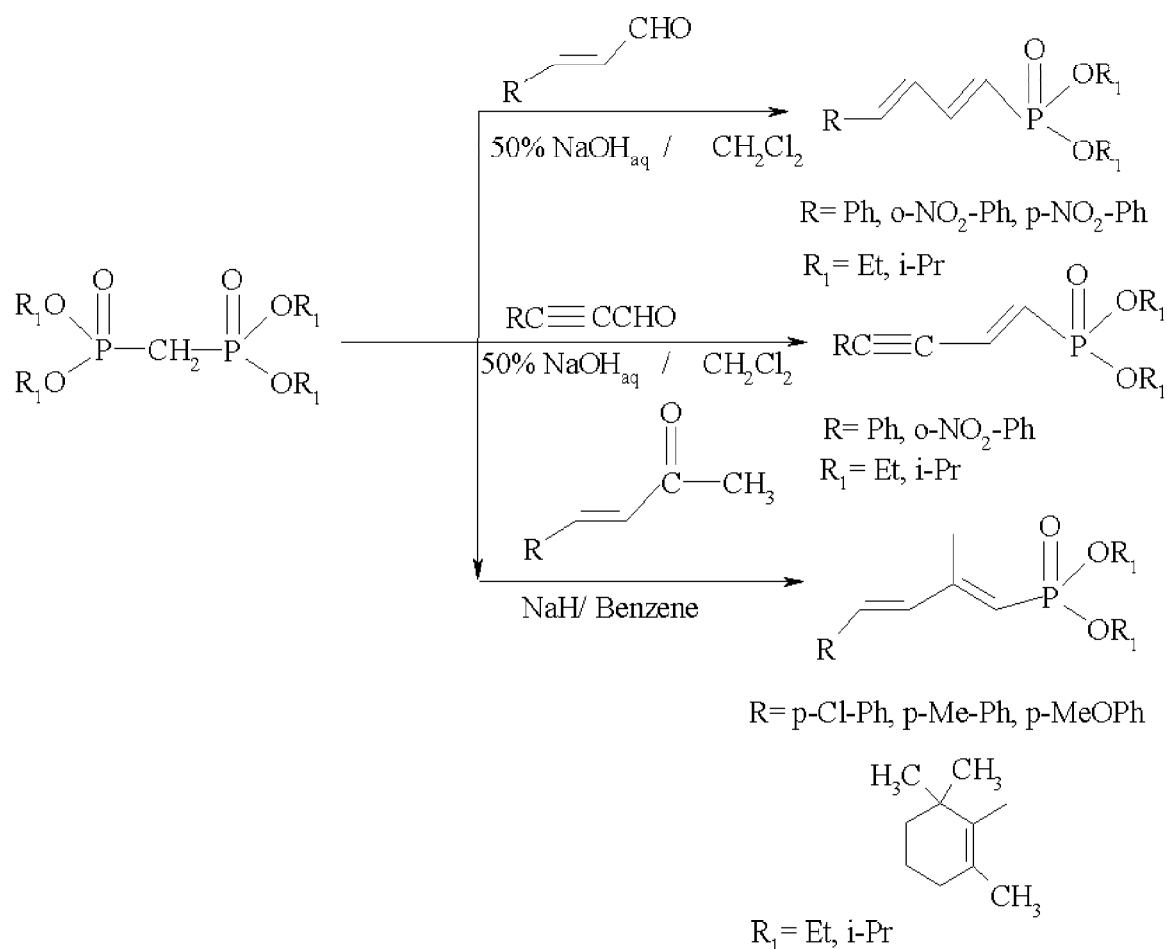
$$\eta = 81\%$$

D.-Q. Shi and coworkers [84] have synthesized a series of compounds with structures similar to abscisic acid (ABA), from bisphosphorylmethane with α -substituted propenals, α , β -substituted propargyl aldehydes and α , β -substituted methyl ketones (Scheme 13 and 14).



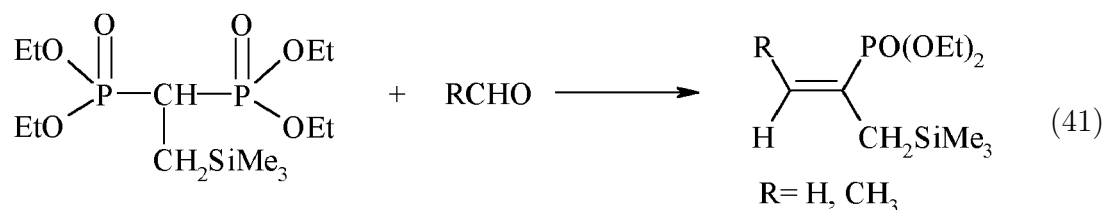
ABA

Scheme 13



Scheme 14

Unsaturated phosphonates were obtained in 53-78% yields. This type of phosphonate has been synthesized by M.A. Loreto [85] starting from trimethylsilanylmethyl-tetraethylmethylene diphosphonate and various aldehydes (Reaction 41).

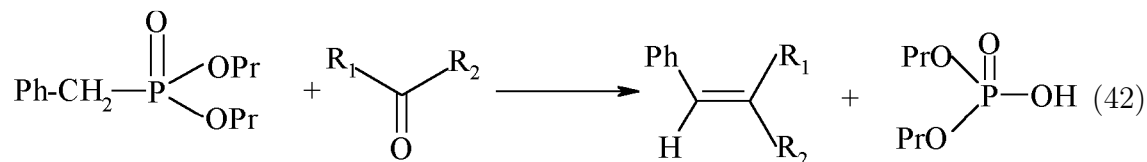


The PTC Wittig-Horner reaction was performed in a liquid-liquid system of $NaOH_{aq}$ (50%) and CH_2Cl_2 ; when $R = CH_3$, a tetrabutylammonium iodide catalyst is necessary.

6.2 PTC Wittig-Horner reactions in liquid-solid systems

Recently, a new way has been developed to perform Wittig-Horner reactions under PTC conditions using a liquid-solid system. E. V. Dehmlow [86] uses solid KOH, NaOH,

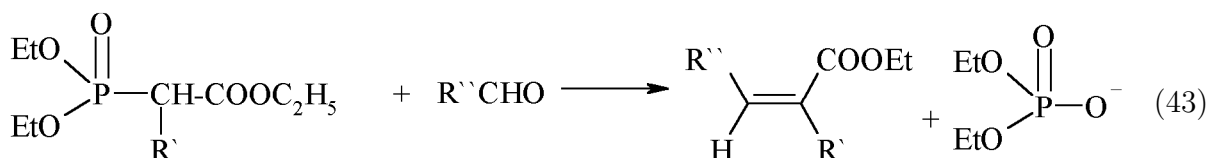
K_2CO_3 , and KF in the reaction between benzylphosphonic acid diisopropyl ester and various carbonyl compounds (Reaction 42).



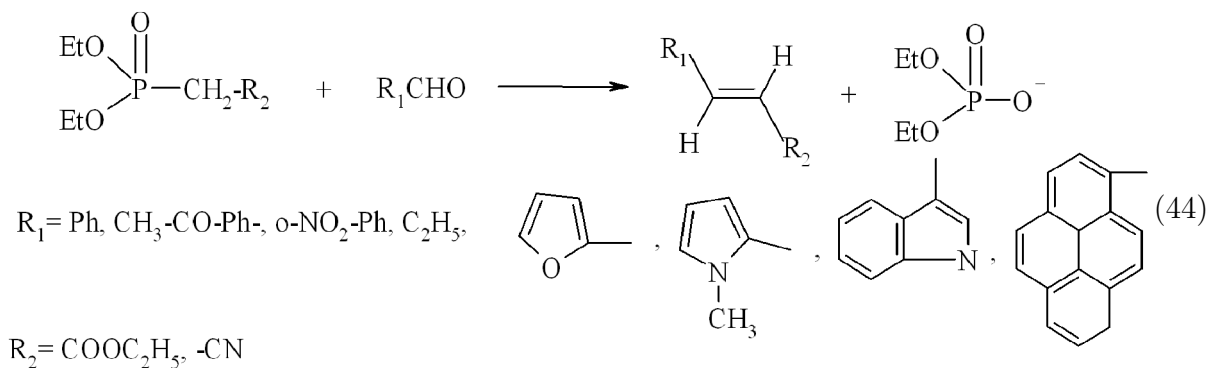
For the reaction of benzaldehyde in the $\text{NaOH}_{\text{solid}}/\text{CH}_2\text{Cl}_2$ system, the yield of olefins is 23% without a catalyst, and 66% with TEBA as the catalyst. For the $\text{KOH}_{\text{solid}}/\text{benzene}$ system, the yield is 52% without catalyst and 78% with 18-crown-6 ether as the catalyst.

Ba(OH)_2 , K_2CO_3 , and Cs_2CO_3 are the bases utilized most in liquid-solid systems. Solid bases are not as efficient when hydroxybenzaldehyde or aldehydes with acidic H are used, e.g. N-H bond, because this poisons the catalyst.

J.V. Sinisterra [69] described the efficiency of cesium carbonate as a catalyst in Wittig-Horner reactions in a solid-liquid system; this catalyst is more efficient than K_2CO_3 or Ba(OH)_2 (Reaction 43).

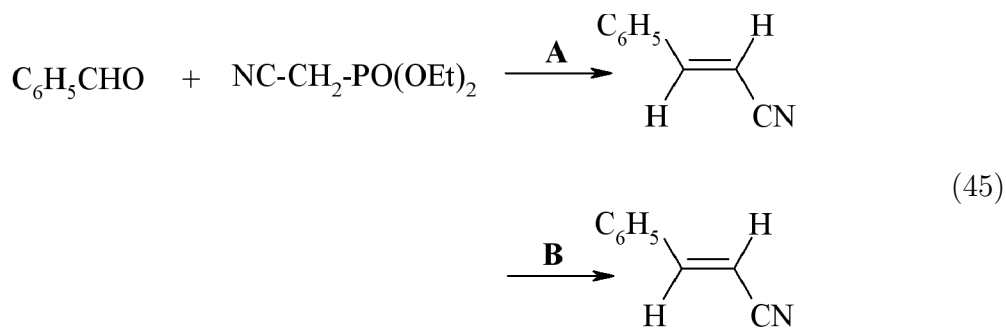


Also J.V. Sinisterra [87] proposes using barium hydroxide as a base in the synthesis of ethyl-3-(1'-pyrenyl)-acrylate and ethyl-3-(1'-pyrenyl)-acrylonitrile (Reaction 44).



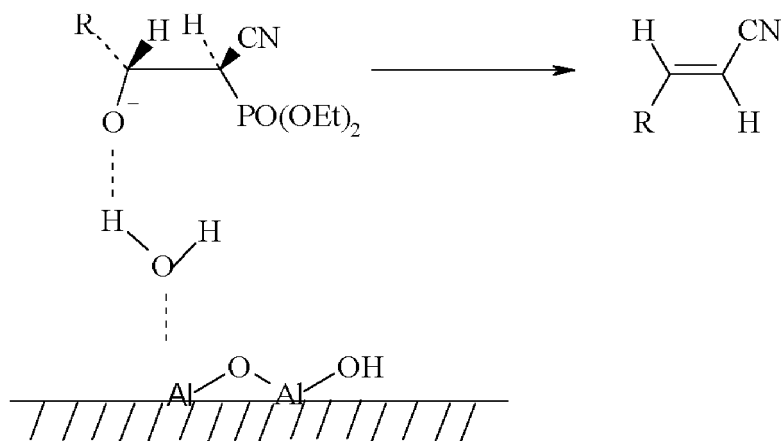
F. Textier-Boulet [88] transforms aldehydes and ketones into esters and α,β -unsaturated nitriles using the $\text{KOH}_{\text{solid}}/\text{THF}$ system. The same author improves the selectivity and control of the hydration of the reaction medium by depositing KF on Al_2O_3 (Reaction 45) [92].

Reaction B is a well known Wittig-Horner reaction, and A is the Knoevenagel reaction. The stereoselectivity for reactions using KF deposited on Al_2O_3 is given in Table 13.



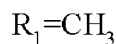
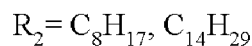
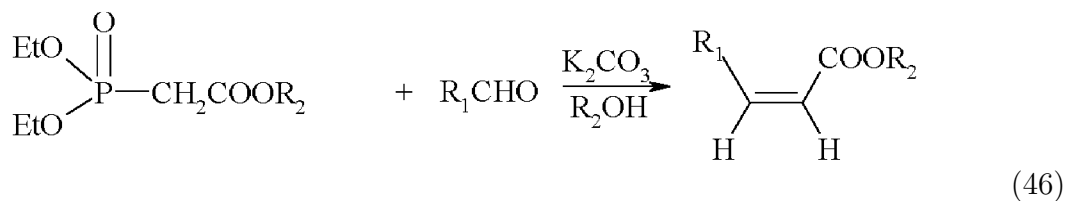
The phase transfer catalyst increases the stereoselectivity in this case.

Scheme 15 shows how the betaine intermediate is attached on the catalytic support (KF/Al₂O₃). Water molecules on the catalyst surface make the product separation possible.



Scheme 15

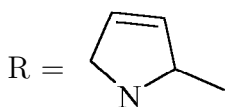
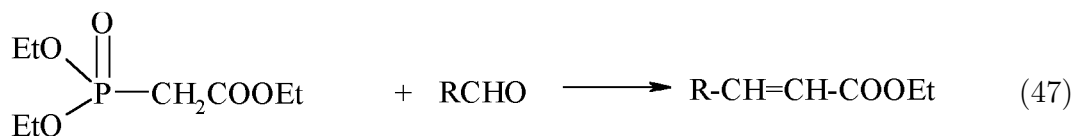
M. Delmas [90, 91] studied PTC Wittig-Horner reactions using K₂CO₃ in fat alcohols. The reaction produces ethylene compounds and is coupled with a transesterification reaction (Reaction 46).



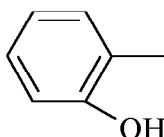
$$\eta = 54 - 90\%$$

Primary, secondary and tertiary alcohols such as methanol, ethanol, propanol, *n*-butanol, izopropanol, and *t*-butanol were used as solvents, too.

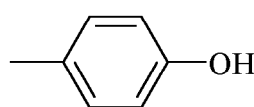
Cesiumcarbonate catalyzes the transformation of pyrol-2-carboxaldehyde, salicylic aldehyde, *p*-hydroxyl benzaldehyde to olefins (Reaction 47) [61].



$\eta = 86\%$



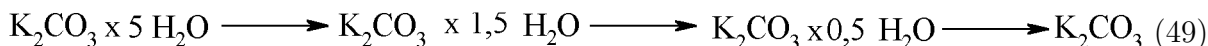
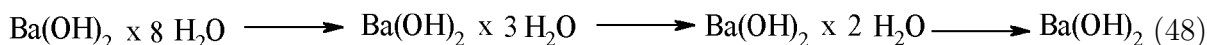
98%



66%

Cs_2CO_3 facilitates reactions in cases where the substrate contains an acidic group (*p*-hydroxyl benzaldehyde). Other bases, e.g. $\text{Ba}(\text{OH})_2$, tend to have no effect ($\eta=0\%$), but K_2CO_3 produces yields between 0 and 15 %.

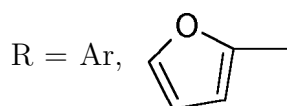
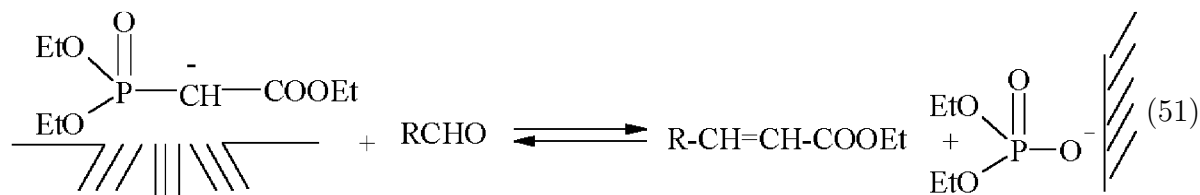
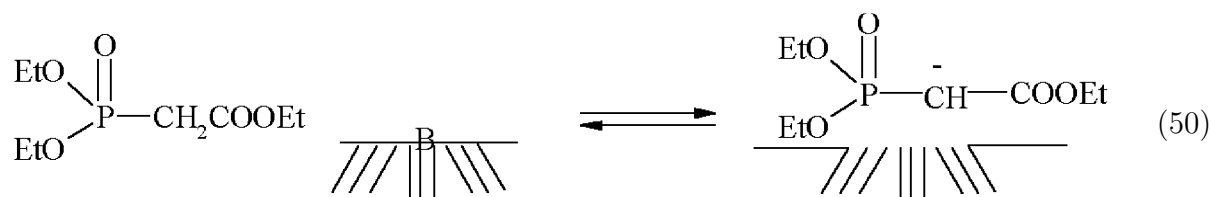
Z. Mouloungui and coworkers [92] studied the conversion of furfural and benzaldehyde into α,β -unsaturated compounds by reaction with triethyl-phosphonoacetate in the presence of $\text{Ba}(\text{OH})_2 \cdot \text{xH}_2\text{O}$, $\text{K}_2\text{CO}_3 \cdot \text{xH}_2\text{O}$, and $\text{Cs}_2\text{CO}_3 \cdot \text{xH}_2\text{O}$. They were interested in the determination of the carbanion structures and the effect of water on carbanion formation. The quantity of water needed to accelerate the reaction depends upon the nature of base cation. Apparently, water decreases the reticulation energy of the crystalline structure at the interface level. The interaction between water and the solid base corresponds to the solid/liquid equilibrium in binary system (Reaction 48 and 49).



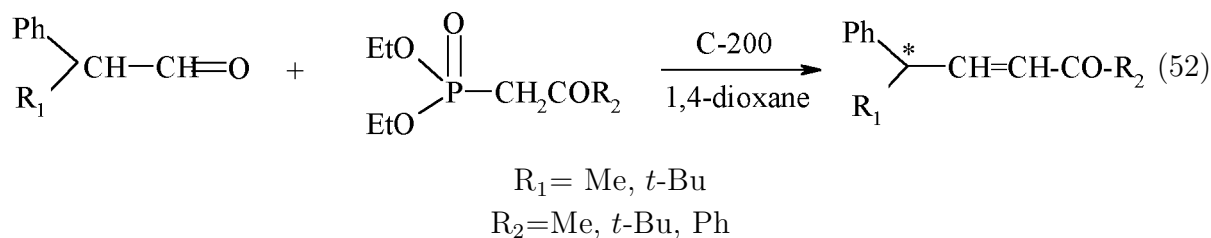
The reactions under the specified conditions proceed through three distinct steps:

- (1) Phosphonate absorption on the base active center and carbanion formation (Reaction 50)
- (2) The reaction between carbanion and carbonyl substrate with the formation of the final product (Reaction 51)
- (3) The dissociation of the reaction product.

C. Alvarez-Ibarra [93] studied the effect of $\text{Ba}(\text{OH})_2$ on Wittig-Horner reaction's stereoselectivity in the case of α,β -unsaturated ketones.

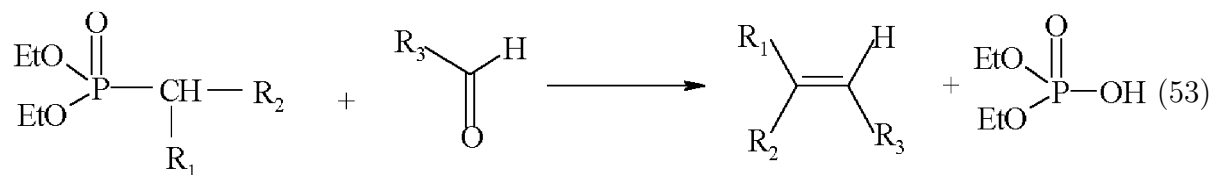


has been studied under PTC conditions using a solid-liquid system of $\text{Ba}(\text{OH})_2 \times 0.8 \text{ H}_2\text{O}$ (C-200) and 1,4-dioxan (Reaction 52).

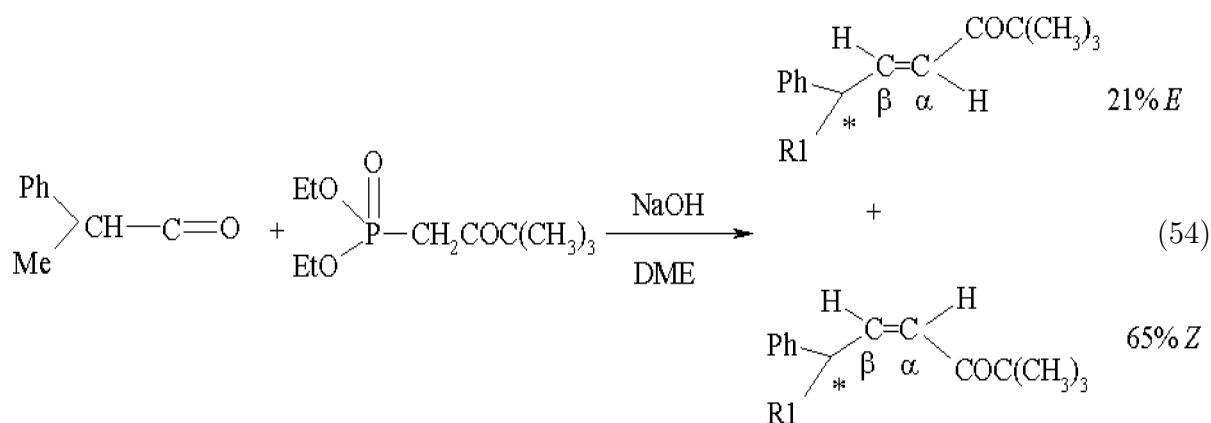


The yields are between 75-98%.

In comparison, the results of Wittig-Horner reactions in liquid-liquid and liquid-solid systems show that the yields and the stereospecificity are higher in the liquid-solid system. Table 14 presents the results in the case of Reaction 53.



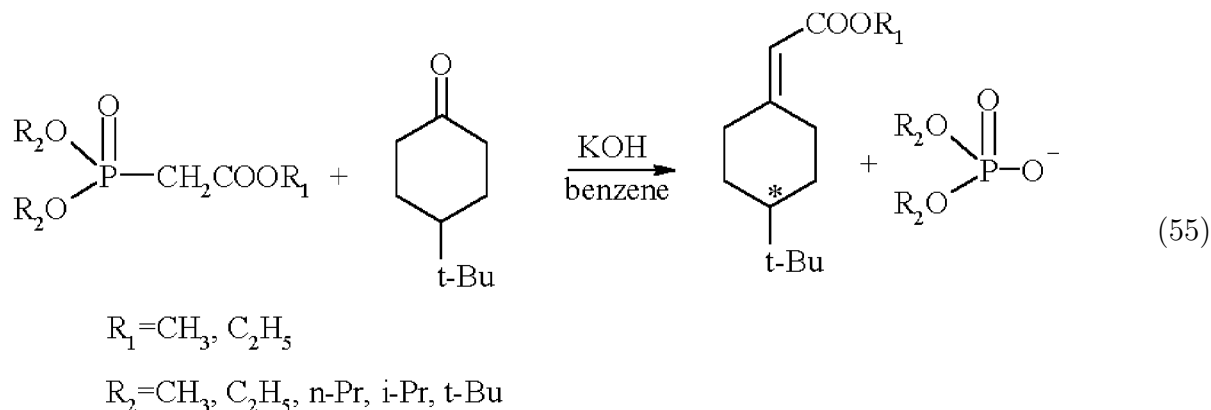
The same research group obtains α,β -unsaturated ketones with an asymmetrical carbon (Reaction 54) [94].



E-2,2-dimethyl-6-phenylhepten-4-en-3-one is partially transformed into *Z*- and *E*-2,3-dimethyl-6-phenylhepten-5-en-3-one isomer mixtures.

For $\text{R}_1 = \text{Me}$, $\text{R}_2 = \text{Me}$, C-200 as the catalyst, and 1,4-dioxane as the solvent, the yields are between 45 and 96% (Reaction 52).

S. Arai [95] studied the Wittig-Horner reaction of cinchonine derivatives using an asymmetric catalyst. The treatment of a prochiral ketone with phosphonates leads to unsaturated asymmetrical ketones. Quaternary ammonium salts are used as catalysts 55).



The asymmetrical catalyst is studied intensively because reactions lead to isomers that are very hard to separate. Recently, many reactions have been developed for asymmetrical Wittig-Horner reactions [96, 97, 98].

P. Tundo [99, 100] has demonstrated the Wittig-Horner reactions in a gas-liquid phase transfer catalysis system.

Conclusions

PTC Wittig and Wittig-Horner reactions need milder conditions (room temperature, smooth bases, and cheaper solvents) than the same reactions under classical conditions.

The carbanion obtained in such PTC reactions is extremely nucleophilic and reacts with a larger number of carbonyl compounds.

One major problem in the Wittig reaction is separation of the alkene and phosphine oxide products. Phosphoric acid derivatives obtained from the Wittig-Horner reaction are all soluble in water, so separation of the olefin is easily to achieve.

While phosphonium ylides require relatively expensive phosphines as starting materials, phosphonates are cheaply and conveniently prepared from phosphates by the Michaelis-Arbuzov reaction. This does not apply to phosphine oxides, and since these reagents are less reactive towards carbonyl compounds, but more sensitive to air than phosphonate carbanions, they have generally been used less.

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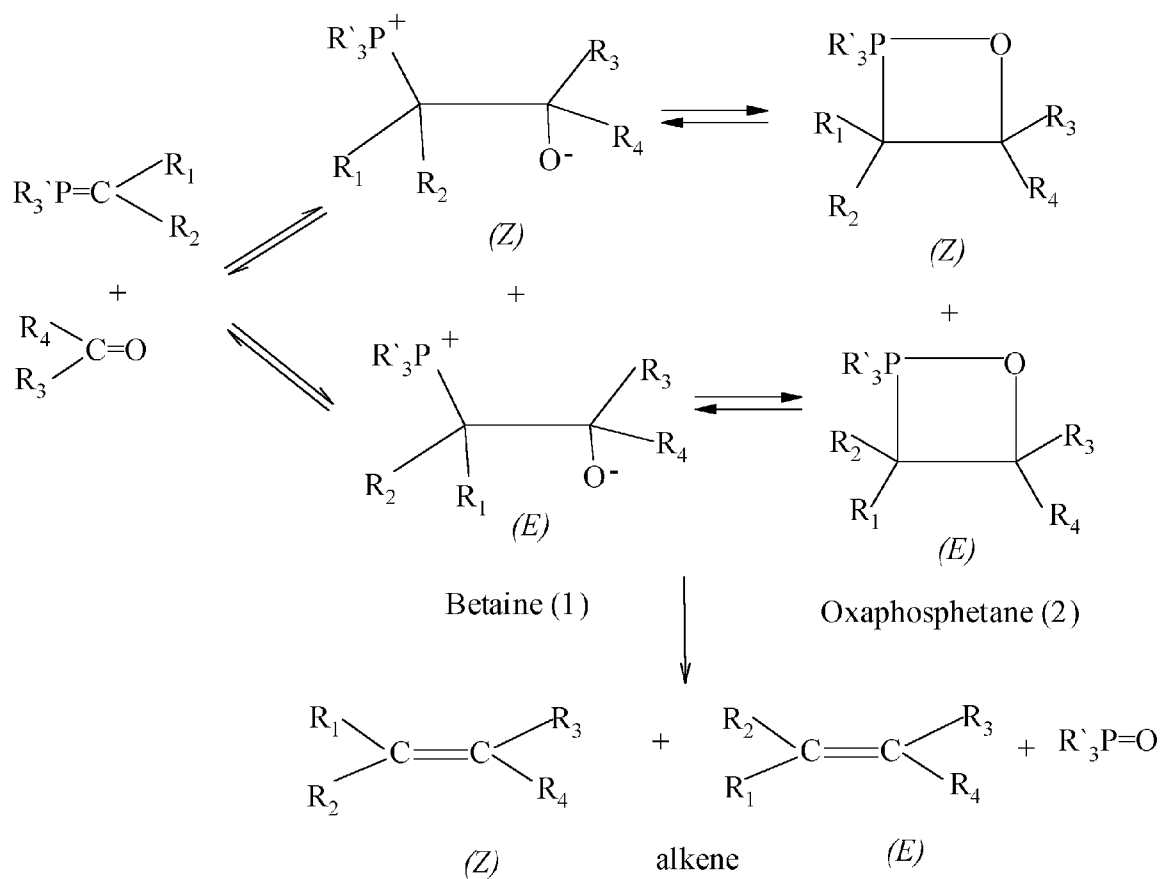
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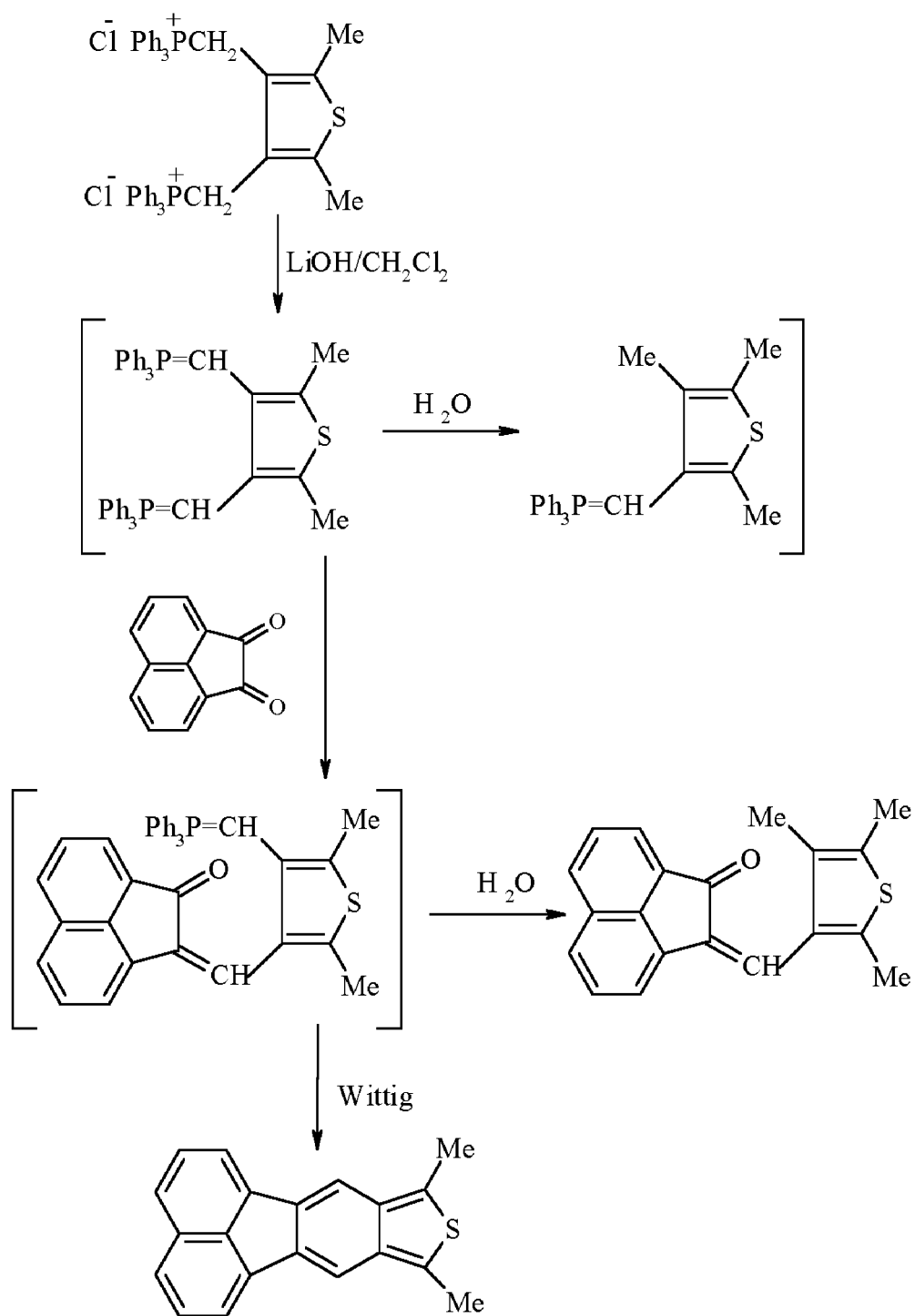
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Scheme 2 The mechanism of the Wittig reaction.



R	Yield (%)	<i>Z/E</i>
H	95	66:34
2-NO ₂	91	52:48
2-OMe	71	63:37
2-F	84	60:40
2-Cl	89	55:45
2-Br	80	52:48
3-Me	76	64:36
3-NO ₂	90	58:42
3-OMe	75	63:37
3-F	100	62:38
3-Cl	97	61:39
3-Br	98	60:40
4-Me	78	66:34
4-CN	100	72:28
4-NO ₂	88	60:40
4-F	77	60:40
4-Cl	86	63:37
4-Br	86	61:39

Table 1 Yields and *Z/E* ratios for the reaction of 1,3-dioxolan-2-yl-methyltriphenylphosphonium salts with *o*-, *m*-,*p*- substituted benzaldehyde.

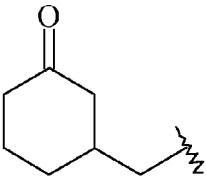
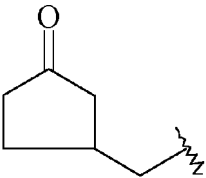
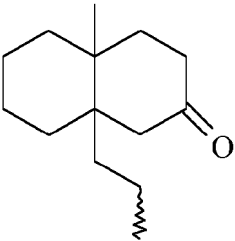
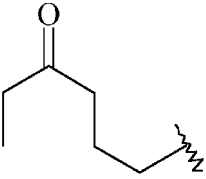
R	Y	<i>E</i> %
	COOMe	85
	COPh	55
	COOMe	93
	COPh	72
	COOMe	93
	COPh	65
	COOMe	91
PhCH ₂ CH-	COPh	67

Table 2 The stereoselectivity in the synthesis of α,β -unsaturated carbonyl compounds from the reaction of the monosubstituted ozonides and stabilized phosphorus ylides.

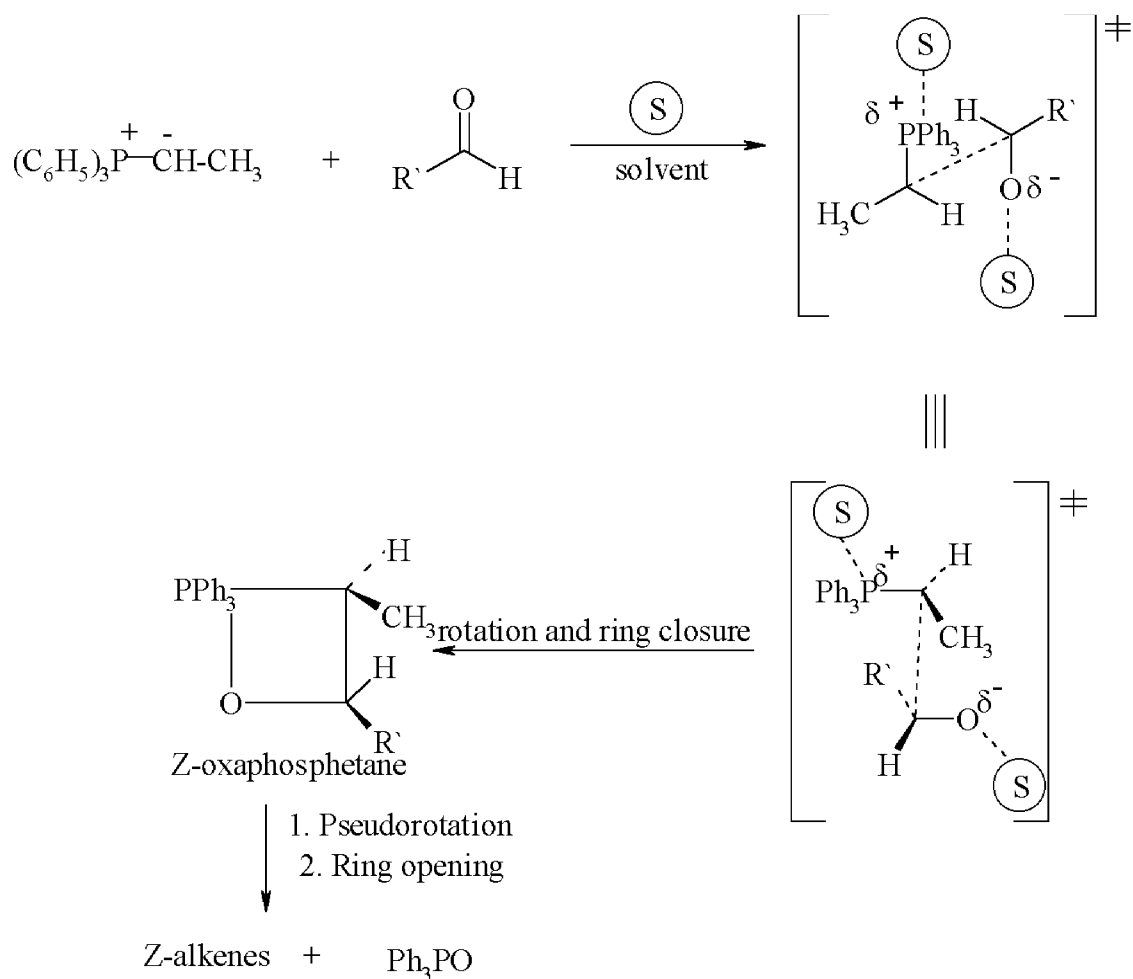
Stilbene	<i>Z/E</i> ratio (yield %)	
	CH ₂ Cl ₂	CHCl ₃
2-ClSB	0.92 (55)	0.92 (52)
3-ClSB	1.5 (82)	1.5 (79)
2,2'-Cl ₂ SB	1.8 (86)	3.5 (80)
4,4'-Cl ₂ SB	2.1 (90)	2.3 (93)
2,3'-Cl ₂ SB	1.4 (90)	1.7 (87)
2,4'-Cl ₂ SB	1.2 (90)	1.5 (83)
3,4'-Cl ₂ SB	1.2 (90)	1.2 (94)
2'-ClSB	2.1 (50)	-
4-ClSB	2.7 (98)	2.9 (97)
3,3'-Cl ₂ SB	1.7 (92)	1.9 (94)
3,2'-Cl ₂ SB	3.3 (81)	5.5 (81)
4,2'-Cl ₂ SB	2.7 (95)	5.3 (96)
4,3'-Cl ₂ SB	1.3 (90)	1.5 (92)

Table 3 The substituent effect upon the *Z/E* ratio of stilbene compounds.

SB=stilbene

Salt		Aldehyde		Z/E
Y	X	Y'	X'	
H	H	F	H	70:30
F	H	H	H	26:74
F	H	F	H	90:10
F	F	H	H	14:86
H	H	F	F	9:91
F	H	F	F	23:77
F	F	F	H	25:75
H	H	H	H	40:60
H	H	H	H	61:39
H	H	Cl	H	77:23
Cl	H	H	H	23:77
Cl	H	Cl	H	87:13
Cl	Cl	H	H	1:99
H	H	Cl	Cl	5:95
Cl	H	Cl	Cl	25:75
Cl	Cl	Cl	Cl	40:60
Cl	Cl	Cl	Cl	1:99
H	H	Cl	H	95:5
H	H	Br	H	85:15
Br	H	H	H	50:50
Br	H	Br	H	95:5
F	H	Br	H	95:5
Br	H	F	H	95:5
Me	H	Cl	H	90:10
Cl	H	Br	H	70:30
H	H	Me	H	57:43
Me	H	H	H	67:33

Table 4 The Z/E ratio of the alkenes obtained in reaction of o,o' -substituted benzyltriphenylphosphonium bromides with substituted benzaldehydes.



Scheme 5 The possible mechanism of *Z*-oxaphosphetane formation in solution.

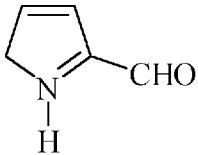
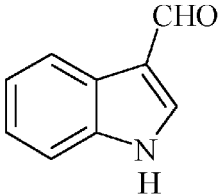
Aldehyde	Base	Solvent	Reaction time (h)	Yield (%)	<i>E/Z</i>
	K ₂ CO ₃	1,4-dioxane / water	3	0	100
	Cs ₂ CO ₃			86	
	C-200*			0	
	K ₂ CO ₃	1,4-dioxane / water	3	15	100
	Cs ₂ CO ₃			46	
	C-200*			0	

Table 5 The influence of the PT catalyst on yield.C-200 = Ba(OH)₂ * H₂O

Catalyst	<i>n</i> -Bu ₄ NCl	<i>n</i> -Bu ₄ NBr	<i>n</i> -Bu ₄ NI	Ph ₄ PCl	Ph ₄ AsCl
Reaction time (min.)	15	40	50	5	5
<i>Z/E</i>	43/57	43/57	48/52	44/56	44/56

Table 6 The influence of an equimolecular quantity of the catalyst under the specified PTC conditions: NaOH 0,2 N/CH₂Cl₂, 25°C.