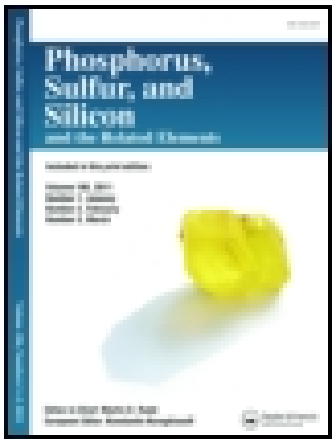

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Wittig Reactions of Trialkylphosphine-derived Ylides: New Directions and Applications in Organic Synthesis

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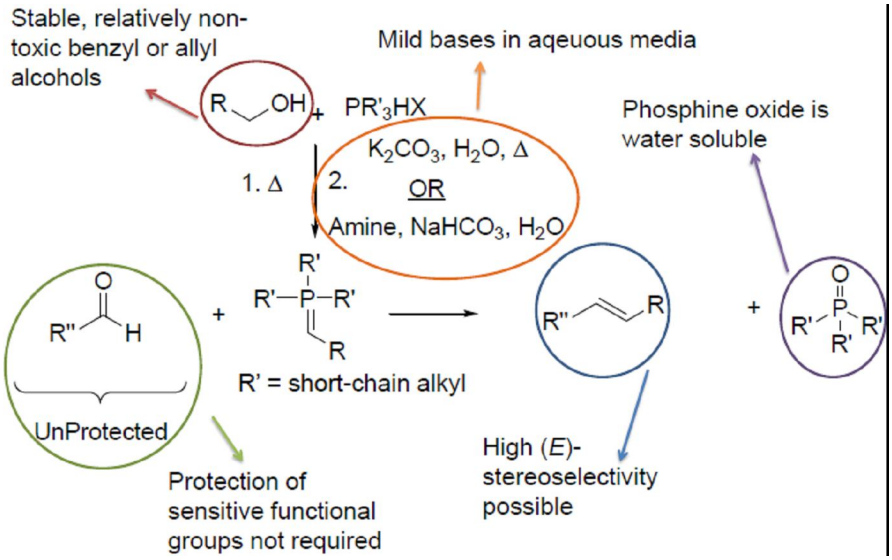
Abstract

The development of semi-stabilized, stabilized and functionalized ylides derived from short-chain trialkylphosphines in Wittig-type olefination reactions towards the synthesis alkenes, including stilbenes, styrenes and 1,3-dienes, as well as reagents for homologation reactions are described. The methods allow easy access to alkenes with high (*E*)-stereoselectivity in good yield. These reactions are conducted with weak bases in aqueous media and allow easy separation of water soluble phosphine oxides. The development of a mild organocatalytic process for the Wittig reaction and extension toward the preparation of reporter stilbenes under biological conditions is also described. Applications towards the preparation of biologically active natural products and derivatives are discussed.



Keywords

Wittig reaction, olefination, alkene, stilbene, organocatalysis, aqueous chemistry

Introduction

Wittig[1] and related olefination reactions are among the most widely employed C=C bond forming processes used in synthesis today. This may be attributed to the ready availability of reactants, functional group tolerance, complete regiocontrol and the high degree of stereocontrol that is now possible. The development of a unified, generally accepted view of the mechanisms (Li-salt and Li-salt-free) involved is also a significant achievement in the field.[2] Recent developments include successful olefination reactions under increasingly milder and highly chemoselective conditions and the development of catalytic variations.[2] The Wittig olefination reaction is regarded as a strategic C-C bond forming reaction due to its reliability and it is frequently encountered in complex organic syntheses used to couple fragments late in target construction. In addition, the reaction has found numerous applications in industrial, fine chemical and pharmaceutical syntheses.[3]

Despite these advantages, there are several known drawbacks to the "Classic" Wittig reaction that need to be addressed in order to fully evaluate and develop the true potential of this reaction. Problems include issues of atom-economy, stereocontrol in certain cases, employment of reactive alkyl halides, strong bases and the use of organic solvents in general.

The reaction is often criticized for being of low atom-economy. The classical reaction necessitates the addition of a stoichiometric quantity of ylide, derived from a phosphonium salt and at least one equivalent of a strong base, and results in the production of an equivalent of triphenylphosphine oxide side product that must be removed. While functional group tolerance is good, acidic NH as well as alcohol or phenolic hydroxyl groups often require protection, or else a second equivalent of base (or ylide) is required and consumed in the process.

While good, predictable levels of stereocontrol are achievable in many cases, there are still unresolved stereochemical issues such as the direct synthesis of (*E*)-aliphatic olefins from non-stabilized ylides and the poor level of stereocontrol that is often encountered employing semi-stabilized ylides. Phosphonium salt precursors are typically prepared through quaternization of triphenylphosphine with alkyl halides many of which are toxic lachrymators, especially allylic, benzylic and other activated halides. The required ylide is typically prepared from the phosphonium salt precursor requiring the use of a strong base in an anhydrous organic solvent (such as THF, toluene or diethyl ether), often at cryogenic temperatures that may be a limiting factor in industrial applications. The use of petroleum-based solvents accounts for most of the carbon footprint left by the global chemical industry contributing to the generation of greenhouse gases, volatile organic compounds and ozone depleting substances.[5] Solvent choice is considered critical in eventually developing a sustainable, carbon neutral economy. All of these issues come into play in the example shown in Scheme 1 involving a Wittig approach towards the asymmetric synthesis of sphingomimetics.[4] Protection of the C2-hydroxyl group was required in this work. The reaction was conducted in dry THF at -78 ºC using the strong base NaHMDS to generate the required ylide. Only the (*Z*)-alkene could be readily obtained, and the product required chromatographic purification to remove the phosphine oxide. The reaction reliably delivers the (*Z*)-olefin with complete regiocontrol and without epimerization of the α–stereogenic centre. Notwithstanding the problems and side issues described, the synthetic power of the reaction is obvious.

As a means of addressing many of the problems noted, over the last six years, our research group has investigated Wittig-type olefination reactions employing ylides derived from

short-chain trialkylphosphines,[6] notably triethylphosphine and tripropylphosphine.[7-17] Use of these materials has allowed for the elimination of organic solvents in many olefination reactions, has permitted the direct, solvent-free synthesis of phosphonium salts from alcohols, thus eliminating the need for toxic lachrymators, and provided high levels of stereocontrol. These reagents also allow for easy purification and product processing as the phosphine oxides derived from these phosphine precursors are highly water soluble in contrast to the notoriously problematic triphenylphosphine oxide. We have also progressed from the use of strong bases to develop the first examples of Wittig and Wittig Horner reactions under progressively milder conditions. We have shown that the reaction is amenable to mild organocatalytic conditions (water, pH = 8.0, 37 ºC, L-proline, etc) and recently described the first examples of Wittig olefination conducted under biological conditions, in a living plant, demonstrating the reaction to be applicable to bioorthogonal applications. A summary on the development of this work, applications, comments and future directions is provided.

Stilbenes

Principle methods for the preparation of stilbenes involve the Wittig reaction for (*Z*)-stilbenes and the Wittig-Horner olefination reaction for (*E*)-stilbenes. The Wittig reaction employing triphenyl(benzylidene) ylides remains the most common route to stilbenes, despite its notoriously low stereoselectivity with (*E*):(*Z*) ratios often approaching 50:50! Prior to our work, the use of trialkylphosphine-derived ylides in Wittig olefination reactions had been shown to give higher (*E*)-olefin content.[2e] Given the solubility of short-chain phosphine oxides in water, it was surprising that the reaction of benzyl and allylic salts derived from such phosphines had not been investigated in water. Ylide formation introduces a regiochemical issue (Scheme 2) not

encountered using triphenylphosphine analogs. We showed that deprotonation occurs exclusively at the benzylic position (H_b) over the alkyl positions (H_a) with reaction proceeding exclusively through the semi-stabilized ylide. Similar regioselectivity is known with both allylic and benzylic salts in organic media.[6]

Operationally, after addition of the aldehyde and base to the dissolved phosphonium salt in water and warming, the stilbene product precipitates from solution. Upon cooling, the (*E*)-stilbene is simply collected by suction filtration and washed with water. The stilbene is not contaminated with triethylphosphine oxide, inorganic salts or any remaining base, all of which fully partition in the aqueous phase, as shown by ^{31}P-NMR. In this manner, the reaction provided for the synthesis of a wide range of stilbenes with very high (*E*)-stereoselectivity and near quantitative isolated yield (Table 1).[7] No chromatography whatsoever is required in this process.

We were able to apply this aqueous Wittig process successfully in the synthesis of a wide range of stilbenes including the phytoalexin resveratrol, the anticancer agent DMU212,[7] pterostilbene,[9] the immunosuppressant FTY720 (fingolimod)[10] used to treat relapsing multiple sclerosis, as well as to donor-acceptor flanked stilbenes (D-A-stilbenes) that are of interest in the materials field as organic-based dyes or emitters in photovoltaic and OLED devices (Table 1).[11]

In terms of green chemistry, the use of water as solvent is a considerable improvement. However, disadvantages of the above process include the need to handle benzylic halides, many of which are toxic, and triethylphosphine, which is an odorous, pyrophoric liquid. Further consideration in terms of safety, economy of steps and avoidance of auxiliary issues prompted us to develop the route shown in Table 2 toward the required phosphonium salts. The synthesis of an allylic triphenylphosphonium salt from an allylic alcohol and acidic Ph_3P•HBr (pKa = 2.73)

was reported by chemists at BASF in the late 1950's, towards the synthesis vitamin A.[18] We reasoned that a similar process might be viable using Et_3P•HBr (pKa = 8.69)[8] but it was not obvious that this salt would be acidic enough to allow conversion of benzylic or allylic alcohols to their corresponding phosphonium salts. Triethylphosphine hydrobromide was readily prepared and is an easy to handle, odorless, hygroscopic solid. Using this salt, we were able to convert a range of benzylic and allylic alcohols to the corresponding phosphonium salts directly (solvent free) on heating. This process avoids the use of any solvent, reactive alkyl halides and direct use of triethylphosphine free base. We are not aware of any other reports on the direct conversion of benzylic alcohols to phosphonium salts using weakly acidic trialkylphosphine hydrohalide salts. With direct conversion of allylic or benzylic alcohols to their corresponding phosphonium salts under these solvent-free, thermal conditions it was also possible to perform the aqueous Wittig through a one-pot telescoped procedure, according to the procedure described in Table 1.

Encouraged by recent reports of microwave-assisted Wittig reactions, mainly employing stabilized ylides, the above aqueous Wittig reaction was subject to microwave dielectric heating with remarkable results.[19] Under microwave (MW) irradiation only a slight excess (1.1 equivalents) of base was required and the method was shown to be successful using the weaker base potassium carbonate. In addition to requiring less base, the reaction was also complete within 30 minutes compared with 3 h under conventional thermal conditions. The solid stilbenes could be isolated by direct filtration upon cooling and washing with water, as before. Surprisingly, under these mildly basic aqueous conditions unprotected 2-salicylaldehyde reacted to yield the hydroxyl-substituted stilbene directly in high yield and with (*E*)-stereocontrol (Table 2, entry 1). Similarly, the MW-version of the aqueous Wittig reaction with both unprotected

indole-3-carboxaldehyde and pyrrole-2-carboxaldehyde was clean, both aldehydes readily reacted with a range of ylides, generated under the aforementioned conditions, yielding the hetero-stilbenes without requiring NH protection.

Alkenes

While the aqueous Wittig reaction provided exceptional (*E*)-selectivity and clean conversion in the preparation of stilbenes from aromatic aldehydes, it was not clear if enolizable aldehydes would be tolerated. Typically, aliphatic aldehydes undergo the Wittig reaction with a stronger preference for (*Z*)-alkene formation. In the present case the reaction was successful but indeed provided higher (*Z*)-alkene stereoselectivity than aromatic aldehydes (Table 3). The method readily tolerates enolizable aliphatic aldehydes suppressing aldol or Cannizzaro side products demonstrating high chemoselectivity but lower stereoselectivity.

The success of the aqueous Wittig reaction using semi-stabilzied trialkyl(benzyl)phosphonium salts led us to consider using related trialkyl(allyl)phosphonium salts in order to access a variety of 1,3-dienes and homologous polyenes. The preparation of these functionalities, and specifically the 1,3-diene subunit, is of great concern in synthetic organic chemistry. Conjugated dienes are found in many bio-active materials and natural products such as terpenes, fatty acids and other lipids, pheromones and serve as central components for cycloaddition reactions. The use of allyltriphenylphosphonium-derived ylides in Wittig reactions has historically afforded poor stereocontrol. The desired allyltrialkylphosphonium salts were readily generated as discussed above from the corresponding

allylic alcohol. These were screened under aqueous Wittig conditions indicating that (*E*)-stereoselectivity increases with decreasing chain length.[12] Triethylallylphosphonium bromide was therefore used for subsequent olefination reactions (Table 4). The (*E*):(*Z*)-stereoselectivity of these aqueous Wittig reactions was generally high, and in accord with earlier results conducted in THF using t-BuOK or n-BuLi as base.[2f] The general reaction proved applicable to a range of substituted aromatic aldehydes, including *ortho*-substituted derivatives, α,β-unsaturated and aliphatic aldehydes. The unsaturated aldehydes allowed ready access to the corresponding 1,3,5-trienes from a variety of structural types (Table 4, entries 4, 5 and 6). Only trace polar impurities were observed even using reactive enolizable aldehydes. This chemoselectivity favoring olefination over potential homo-aldol or Cannizzaro-type products under conditions that are classically known to effect these reactions is surprising. We postulated that this chemoselectivity may be due to the formation of phosphonium salt-stabilized micelles that effectively partition the organic materials from the aqueous basic environment during the reaction. Ylide formation occurs at the interface, and delivery of the neutral ylide and the olefination process occurs in the organic interior of the micelle.

To highlight the utility of the aqueous Wittig to natural product synthesis we conducted a synthesis of the natural anticancer sesquiterpenoid (+)-caparratriene **3-1**.[13] The high stereoselectivity observed using triethylallylphosphonium bromide in the aqueous Wittig with aliphatic aldehydes allowed for a straightforward retrosynthetic analysis in which would begin from commercially available (+)-citronellal **3-2** and (*E*)-2-methylbutene-1-ol. The alcohol was directly converted to the allylic phosphonium salt **3-3** with triethylphosphine hydrobromide as described above. The aqueous Wittig reaction of the derived C5-allylic phosphonium salt and

citronellal (Scheme 3) occurred with complete (*E*)-stereocontrol, but with partial isomerization at the C2-C3 olefin (3:1, (*E*):*Z*)).

Styrene and functionalized styrenes are among the most versatile of olefins with an extensive range of applications in fine chemical synthesis and as precursors to fuctionalized polymers.[20] Functionalized styrenes are routinely employed in developments in a variety of processes including the Mizoroki-Heck reaction, hydrogenation, epoxidation, metathesis, hydroboration, carbonylation, hydroamination, hydrophosphination, hydroarylation, and aziridination. In addition, applications in the area of functionalized polymers have called for efficient access to styrene and functionalized styrene monomers. As before, conversion of benzylic alcohols to the corresponding trialkylphosphine-derived salts could be achieved via direct reaction with triethylphosphine-HBr at 100 °C over 8 h without the need for organic solvents. We now discovered that this reaction was also subject to a remarkable microwave-effect, and could be completed in only 10 minutes (Scheme 4) at the same temperature in a sealed microwave vial, solvent free! Addition of water, potassium carbonate and 37% aqueous formaldehyde followed by further microwave irradiation at 100 °C induced rapid Wittig olefination, completed within 5 minutes. This overall process could be conducted sequentially in a single microwave reaction vial and proved to be general allowing entry to a wide range of functionalized styrenes summarized in Table 5.

Carbonyl Homologation

We recently reported the development of a new pinacolacetal-functionalized tripropylphosphine-derived phosphonium salt and its reaction with aldehydes to give stable two-carbon homologated derivatives as well as two methods for their hydrolysis, including a one-pot

operation, leading to the desired (*E*)-2-alkenals, in water. We considered a functionalized phosphonium salt of general type **5-4** (Scheme 5) as a potentially valuable trialkylphosphonium salt that would be chemically robust and convey the advantages described above for (*E*)-stereoselectivity, allow generation and trapping of its ylide in water, provide ease of purification, etc. The conversion of an aldehyde to its C2-homologated alkenal is a common transformation in organic synthesis, given the ready availability of a wide range of aldehydes and the useful, wide reactivity profile of the alkenal products. The transformation is most typically conducted in three separate steps, HWE or Wittig-Horner reaction of the aldehyde yielding the unsaturated ester, reduction of the ester to the allylic alcohol and chemoselective reoxidation to the alkenal. The aldehyde-to-alkenal homologation has been described in two steps using reagents such as **5-1** and **5-2** several times in the literature.[21] Our initial work generating and trapping ylides derived from salt **5-3** with aldehydes in water proved to be capricious, resulting in formation of side products, which we attributed to the instability of the acetal under the reaction conditions. The design of salts such as **5-4** was based on the known greater stability of cyclic acetals,[21a,b] and inspired by some of the recent chemistry documented for stable functionalized pinacolboronates.[22] To this end, the tripropylphosphine derived pinacolacetal phosphonium salt **5-8** was synthesized (Scheme 5, bottom) from bromoacetal **5-5** and acetone-pinacol **5-6**.

We next investigated chemoselective olefination reactions using **5-8** under aqueous Wittig conditions using 4-chlorobenzaldehyde as the initial substrate. The reaction was completed within 24h using aqueous sodium hydroxide as base and reagent **5-8**, and the homologated acetal was obtained in 87% isolated yield. The reaction was successful with a range

of aromatic and unsaturated aldehydes leading to protected alkenals (Table 6). Enolizable aldehydes provided lower isolated yields under these conditions. The isolated intermediate vinylic pinacolacetals were found to be very stable under the reaction conditions.

Two methods were developed for acetal hydrolysis under mild acidic conditions, given the sensitivity of the final alkenal products. Dilute phosphoric acid (25% w/w) was initially satisfactory but the use of a solid-supported acid catalyst (IR-120H resin) proved quite efficacious. With two chemoselective methods for acetal hydrolysis on hand, we were also able to develop a one-flask, telescoped operation that allows the overall aldehyde to alkenal homologation to proceed without isolation of the intermediate pinacolacetal. Process chemistry optimization on the synthesis of the pinacol-containing phosphonium salt **5-8** has been completed to 50 g scale at present and extensive investigations on the use of this salt are under investigation.

As an illustrative example on the value of this new C2-aldehyde to alkenal homologation reaction, we recently completed a total asymmetric synthesis of the anticancer amaryllidaceae natural product (+)-*trans*-dihydrolycoricidine **6-4** (Scheme 6) in only nine steps.[23] The sequence began with conversion of piperonal **6-1** (Scheme 6) to its corresponding cinnamaldehyde derivative **6-2** using reagent **5-8** as described above (Table 6, entry 6). The (*E*):(*Z*) ratios reported in Table 6 are for the crude alkenals and the cinnamaldehyde **6-2** was isolated in 76% yield as the (*E*)-isomer. A one-pot sequential asymmetric Michael-aldol [3+3]-cycloaddition reaction with azidoacetone and **6-2**, employing a dual silylprolinol and cinchona catalyst system, yielded the functionalized cyclohexane **6-3**, containing three stereogenic centres with high enantioselectivity and complete regiocontrol, directed by the azido group. The cyclohexane C

was converted to this nanomolar active anticancer **6-4** in eight further steps.[23] Only a handful of simple alkenals such as cinnamaldehyde itself, several aliphatic examples, such as acrolein, and a few natural products are commercially available. Many unsaturated aldehydes are unstable and polymerize, photodegrade or disproportionate. The new functionalized reagent **5-8** and aqueous Wittig process that we describe therefore serves as a valuable process to convert readily available aldehydes to their useful C2-extended (*E*)-alkenal derivatives as needed, in one-pot if desired, for further elaboration.

Organocatalysis

Organocatalysis, iminium ion catalysis in particular, has emerged as one of the cornerstones in organocatalytic and asymmetric organocatalytic processes that has revolutionized synthetic organic chemistry over the last decade. Bestmann had previously shown that replacement of the carbonyl component in the Wittig reaction with a Schiff-base provide (*E*)-stilbenes in moderate yield,[24] a variation that has received little atttention until recently. Tian and co-workers[25] have shown that replacement of the Schiff-base (*N*-phenyl imine) with a tunable *N*-sulfonyl imine allows for tunable olefin stereoselectivity, providing a notable advance toward the synthesis of both (*E*)- and (*Z*)-stilbenes. With these precedents in mind and our earlier work with mild aqueous Wittig procedures we postulated whether an organocatalytic variant of the Wittig reaction might be possible.[16]

After screening a number of secondary amines, including non-basic entities such as tosyl amide, in concert with the necessary control reactions, we reported the first organocatalytic Wittig reaction.[17] The new amine and sulfonylamide catalyzed olefination process was

successfully extended toward the synthesis of a small panel of *trans*-stilbenes using the triethylbenzylphosphonium salt in the presence of either a catalytic amount of morpholine, *N*-methylaniline or tosylamide (Table 7). Upon completion of the reaction, the mixture is simply cooled and the solid stilbene was isolated by suction-filtration and aqueous wash. As before, the products are uncontaminated with phosphane oxide or amine/sulfonamide catalyst. High isolated yields of the *trans*-stilbenes were achieved in all cases and no Cannizzaro side products were detected.

We further extended the applicability of the organocatalytic Wittig reaction to include the generation and trapping of stabilized ylides derived from the (ethoxycarbonylmethyl)-triisobutylphosphonium bromide (Wittig-Horner type adducts). Employing L-proline as catalyst (10 mol%), olefination occurred smoothly under our standard conditions with both electron rich and electron deficient aldehydes yielding substituted cinnamate esters in very high yield and with exclusive (*E*)-stereoselectivity (Table 7, entries 11 and 12). In our view, the examples collected in Table 7 stand in stark contrast to those conducted under Classic Wittig or Wittig-Horner conditions, with the reaction now occurring in water with weakly basic organic catalysts, delivering clean (*E*)-stilbenes or (*E*)-cinnamates in high yield and in a process-friendly manner.

The reaction conditions are in-fact so mild that we were encouraged to attempt the Wittig reaction under physiological conditions. We prepared the acetamide-substituted aldehyde **7-1** and morpholinamido phosphonium salt **7-2** shown in Scheme 7. Separate administration of these precursors to growing seedlings of the plant *Calystegia sepium* (morning glory) led to the formation of readily detectable quantities of the "reporter" stilbene **7-3**.[17] Thus, we demonstrated

the first examples of physiological Wittig-olefination, allowing formation of non-natural reporter stilbenes, in this case connecting and amine (morpholine) to a carboxylic acid (acetic acid). The process is so simple that we introduced the term “click-stilbenes” in the hope that others may be encouraged to apply the process in the development of bioorthogonal applications. A major advantage of the click-stilbene paradigm is that the fluorescent “reporter” functionality does not enter the process as an existing tagged reagent, a process that results in background fluorescence. Formation of the reporter unit is intrinsic to the coupling process itself. The synthesis of these reporter stilbenes was also successful using our organocatalytic procedure, with L-proline (cat) in water at 37 °C, giving the product **7-3** as shown in Scheme 7 in 84% isolated yield.

Conclusion

The Wittig reaction has constantly evolved during the last half-century and occupies a vaulted position as one of the most strategic, reliable, widely-applicable olefination processes available in organic synthesis. The classical reaction suffers a few notable drawbacks including problems with stereoselectivity, the use of alkyl halide lachrymators to prepare phosphonium salts, requirement of strong bases and organic solvents and the removal of a stoichiometric amount of phosphine oxide. It is only within the past decade that a number of these problems have been attenuated through various strategies. Over the last six years we have shown that the use of short-chain trialkylphosphines, notably triethylphosphine and tripropylphosphine, can eliminate many of these issues. Use of the simple, air stable hydrobromide salts of these phosphines allows direct conversion of benign allylic and benzylic alcohols to the corresponding phosphonium salts in high yield and without solvent. The use of

toxic lachrymators can also now be avoided using this one step phosphonium salt formation from these bench stable phosphine-hydro halide salts. Functionalized salts can also be obtained from their reaction with acetals, olefination reactions of which lead to vinyl ethers and 1- or 2-alkoxysubstituted 1,3-dienes.[26] We have shown that it is now possible to achieve high (*E*)-olefin selectivity employing these phosphonium salts in water as the solvent and with weak bases, including secondary amine catalysis, and even under physiological reaction conditions! From a processing viewpoint, these reagents allow for complete removal of the corresponding phosphine oxide through filtration aqueous organic partition. Finally, a new phosphonium salt for the two carbon homologation of aldehydes in aqueous media has been prepared that allows for stereoselective synthesis of protected α,β-unsaturated aldehydes which are stable to column chromatography and do not require painstaking removal of phosphine oxides. The synthesis of a wide range of alkenes, styrenes, stilbenes and 1,3-dienes has been achieved with these reagents as has their application towards the synthesis of a number of bioactive compounds, natural products and materials-related products. These developments, along with others involving advances in stereocontrol, catalytic relay versions, and further advancement of functionalized versions ensure that the Wittig and related reactions will continue to be a cornerstone of organic synthesis in the decades ahead.

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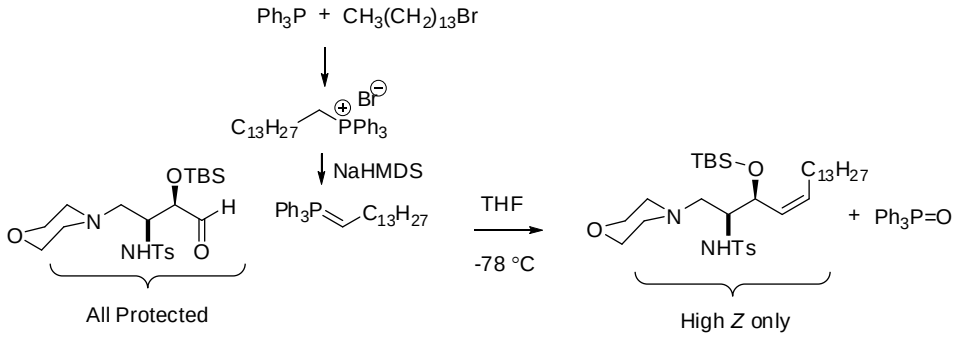
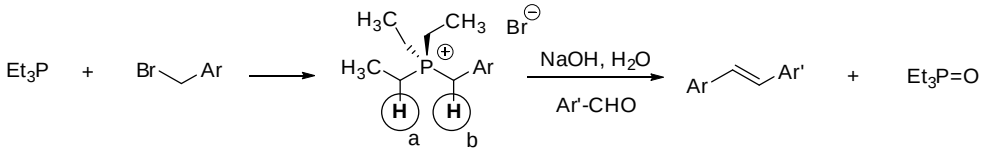
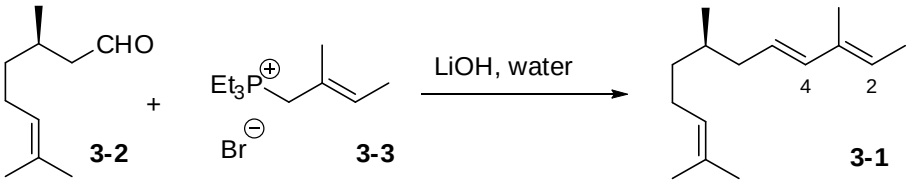


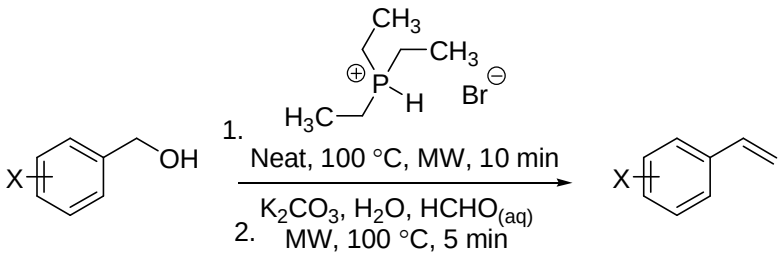
Scheme 1. Representative example of a Wittig reaction in the preparation of sphingomimetics.[4]



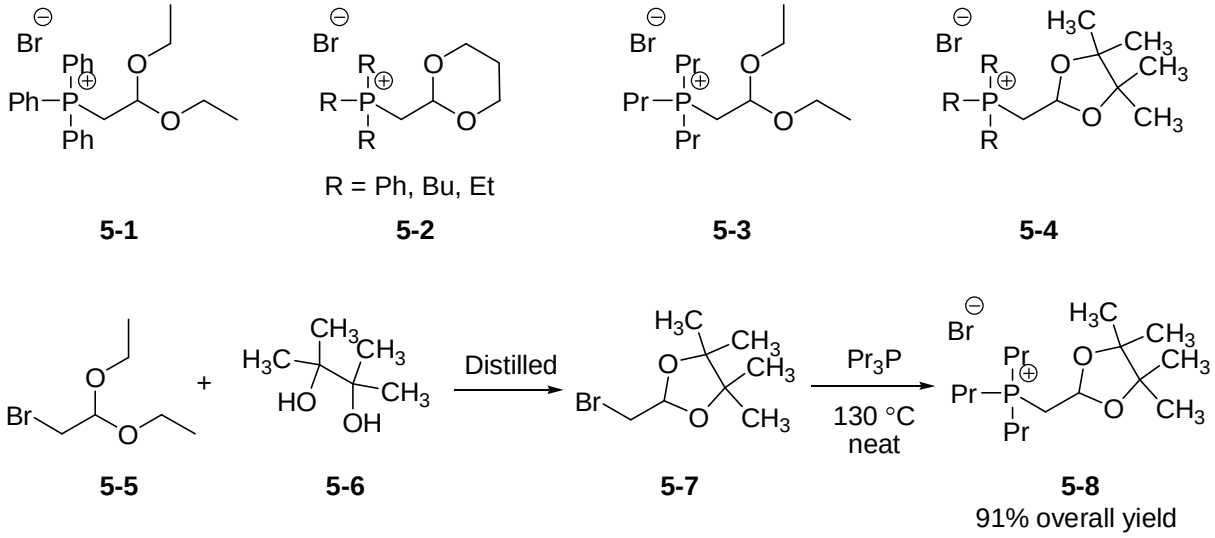
Scheme 2. Synthesis of stilbenes using the aqueous Wittig reaction



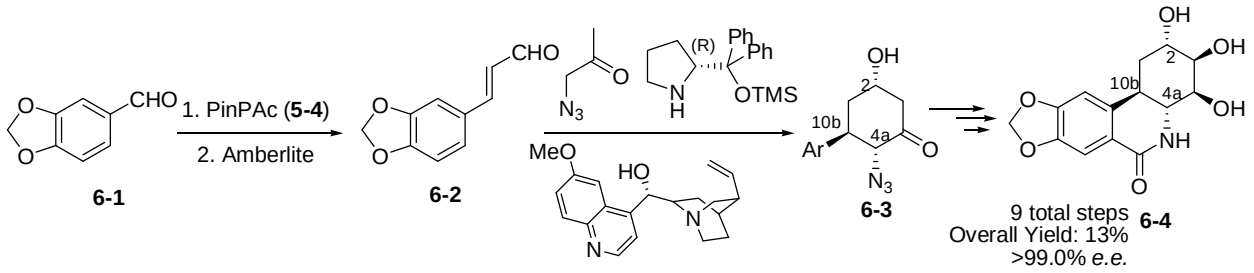
Scheme 3. Aqueous Wittig reaction to give (*R*)-(+)-Caparratriene



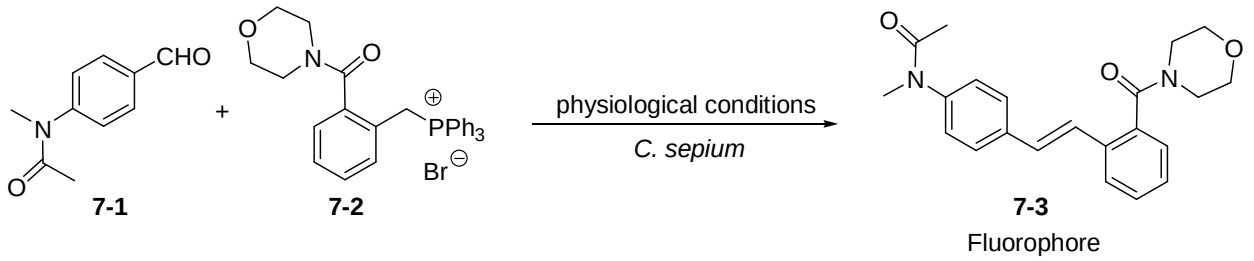
Scheme 4. Microwave-assisted synthesis of styrenes[14]



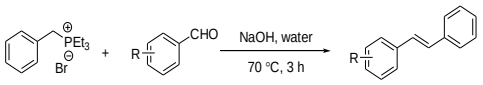
Scheme 5. Novel salt **5-8** and previously used acetaldehyde acetal based phosphonium salts[15]

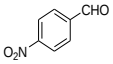
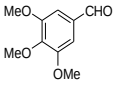
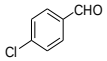
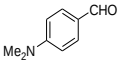


Scheme 6. Synthesis of (+)-*trans*-dihydrolycoricidine D from piperonal A[23]



Scheme 7. Synthesis of donor-acceptor flanked "reporter" stilbene in a living plant.



Entry	Aldehyde	(*E*):(*Z*)	Yield %	Entry	Aldehyde	(*E*):(*Z*)	Yield %
1		80 : 20	99	5		80 : 20	99
2		99 : 1	99[a]	6		90 : 10	99
3		95 : 5	97	7		95 : 5	98
4		90 : 10	99	8		99 : 1	99

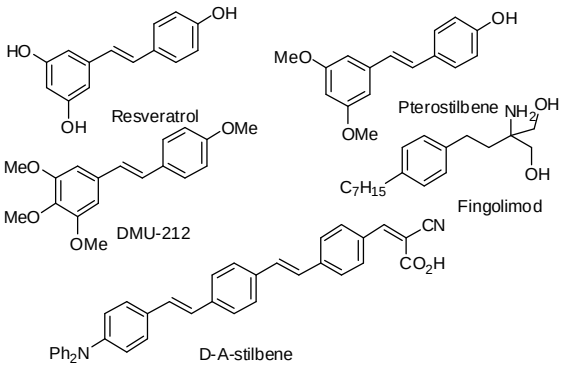
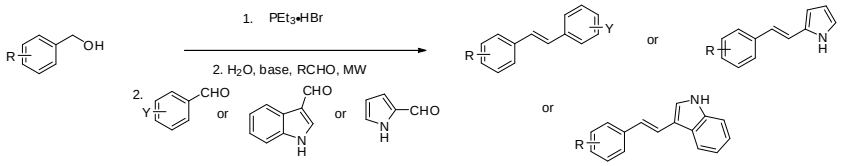
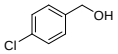
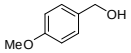
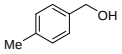
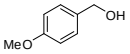


Table 1. Stilbene formation using the aqueous Wittig reaction and applications to biologically active and materials related products



Entry	Benzyl Alcohol	Aldehyde	(*E*):(*Z*)	Yield %	Entry	Benzyl Alcohol	Aldehyde	(*E*):(*Z*)	Yield %
1[a]		**1c**	>99 (*E*)	83	5[c]		**1b**	>99 (*E*)	92
2[b]		**1a**	>99 (*E*)	80	6[c]		**1b**	>99 (*E*)	95
3[b]		**1a**	>99 (*E*)	75	7[c]		**1b**	>99 (*E*)	93
4[b]		**1a**	>99 (*E*)	83	8[c]		**1b**	>99 (*E*)	93

[a] NaOH, 100 °C, 30 min. [b] K_2CO_3, 100 °C, 30 min.
[c] NaOH, 100 °C, 25 min.

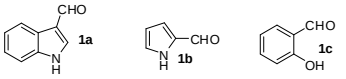
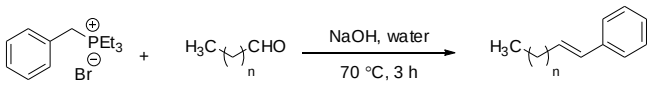
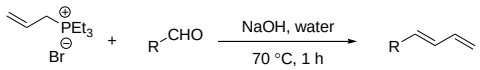
Aldehydes: 

Table 2. Preparation of stilbenes and heteroaromatic stilbenes from benzylic alcohols via MW activation



Entry	Aldehyde	(*E*):(*Z*)	Yield %	Entry	Aldehyde	(*E*):(*Z*)	Yield %
1	$H_3C(CH_2)_2CHO$	2 : 3	65	3	$H_3C(CH_2)_9CHO$	7 : 3	72
2	$H_3C(CH_2)_4CHO$	6.2 : 3.8	70	4	$H_3C(CH_2)_{10}CHO$	3 : 1	77

Table 3. Extension of the aqueous Wittig to enolizable aldehdyes



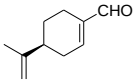
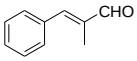
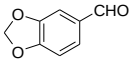
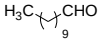
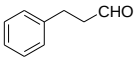
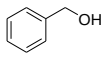
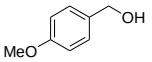
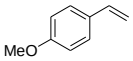
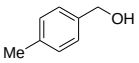
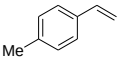
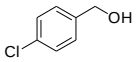
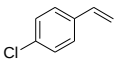
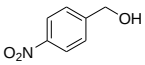
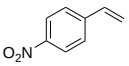
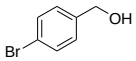
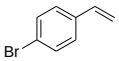
Entry	Aldehyde	(*E*):(*Z*)	Yield %	Entry	Aldehyde	(*E*):(*Z*)	Yield %
1		4 : 1	80	5		9 : 1	78
2		3.5 : 1	83	6		4 : 1	79
3		4 : 1	85	7		4 : 1	70
4		9 : 1	80	8		4 : 1	73

Table 4. Preparation of various conjugated 1,3-dienes and 1,3,5-trienes

Entry	Alcohol	Styrene	Yield %
1			98
2			96
3			95
4			97
5			98
6			96

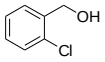
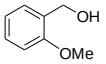
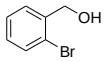
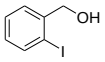
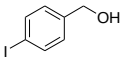
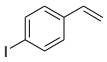
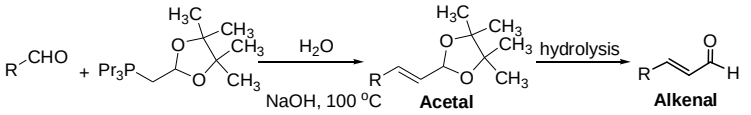
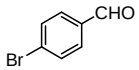
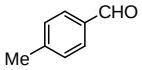
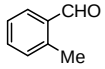
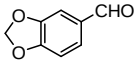
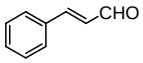
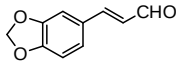
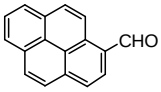
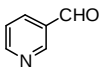
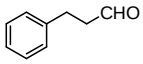
Entry	Alcohol	Styrene	Yield %
7			97
8			96
9			92
10			96
11			97

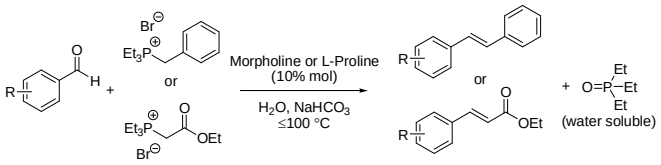
Table 5. Synthesis of functionalized styrenes in water with aqueous formalin

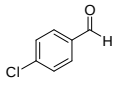
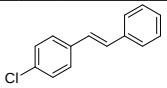
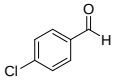
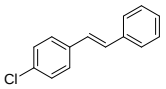
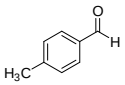
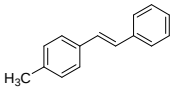
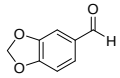
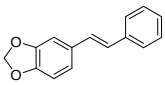
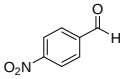
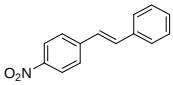
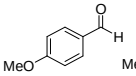
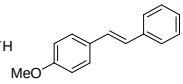
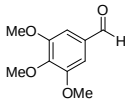
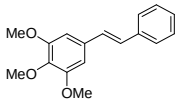
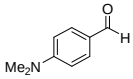
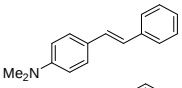
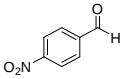
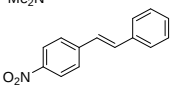
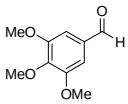
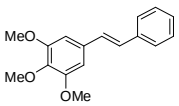
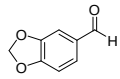
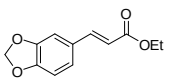
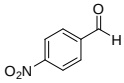
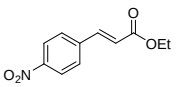


Entry	Aldehyde	Time (h)	Yield **Acetal** (%)	Yield **Alkenal** (%)	(*E*):(*Z*)
1		24	91	93[a]	>99:1
2		24	89	94[a]	>99:1
3		24	90	83[a]	>99:1
4		72	96	95[a]	>99:1
5		48	36	68[b]	95:5
6		48	53	76[b]	92:8
7		48	92	81[b]	99:1
8		48	75	nd	
9		48	48	82[b]	95:5

[a]Hydrolysis with phosphoric acid. [b]Hydrolysis with amberlite resin.

Table 6. Two-carbon homologation of aldehydes to acetals and hydrolysis to enals under aqueous Wittig conditions



Entry	ArCHO	*trans*-Stilbene	Conv. (Isolated Yield)	(E):(Z)
1[a]			< 5	
2			>99 (92)	97 : 3
3			>99 (88)	91 : 9
4			>99 (93)	90 : 10
5			>99 (94)	95 : 5
6			>99 (91)	>99 (*E*)
7			>99 (85)	>99 (*E*)
8			>99 (87)	95 : 5
9[b]			>99 (94)	95 : 5
10[b]			>99 (85)	>99 (*E*)
11			>99 (90)	>99 (*E*)
12			>99 (94)	>99 (*E*)

[a]No amine added. [b]*N*-Methylaniline (0.10 eq) replaced morpholine as catalyst under otherwise identical conditions.

Table 7. Synthesis of stilbenes and cinnamates via the morpholine or *N*-methylaniline organocatalytic aqueous Wittig protocol