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Amine- and Sulfonamide-Promoted Wittig Olefination Reactions in Water

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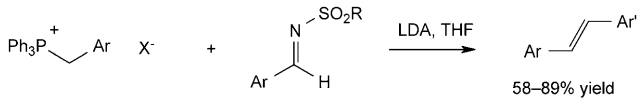
The Wittig reaction[1] has constantly evolved during the last half-century and occupies a vaulted position as one of the most strategic, reliable, widely applicable carbon–carbon olefin bond forming process available in organic synthesis. The reaction allows for olefination with complete positional selectivity, relatively high chemoselectivity and may be conducted in many cases with predictable stereocontrol.[2] For example, the Wittig reaction employing ylides derived from triphenylbenzyl phosphonium salts is the most popular route to *cis*- and *trans*-stilbenes.[3] The process is typically high yielding but suffers from poor to moderate stereocontrol requiring removal of the phosphane oxide as well as separation of the stereoisomers.

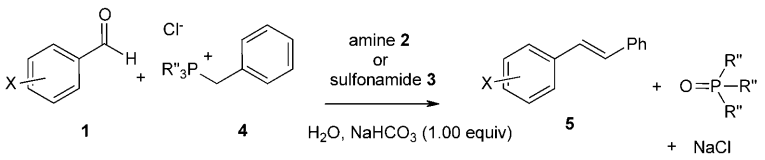
In recent work,[4] we showed that ylides derived from short-chain trialkylphosphanes could be generated in water as solvent employing bases such as LiOH and K_2CO_3 and that these conditions allowed for high *E*-selective olefination yielding a wide range of stilbenes[4a] and other alkenes.[4b,c,e] Separation of the water-soluble phosphane oxide was readily achieved through simple alkene filtration (if solid) or solvent partition in the case of liquid olefins.

Bestmann and Seng had earlier shown that replacement of the carbonyl component in the Wittig reaction with a Schiff base provided (*E*)-stilbenes in moderate yield,[5] a variation that has received little attention until recently. Tian and co-workers[6] have shown that replacement of the Schiff base (*N*-phenyl imine) with a tunable *N*-sulfonyl imine (Scheme 1, R = various groups) allows for tunable olefin stereoselectivity, providing a notable advance toward the synthesis of (*Z*)-stilbenes. In this work, the required semi-stabilized ylides were generated under standard kinetically controlled Wittig conditions by using LDA in dry THF as solvent at −78 °C. The ylide undergoes olefination with the pre-formed sulfonyl imine, which is required in stoichiometric amounts, yielding stilbenes with high stereocontrol.



Scheme 1. Stilbene synthesis from *N*-sulfonyl imines as described by Tian et al. (Ar, Ar′ = aryl; X = halide; LDA = lithium diisopropylamide).[6]

These stoichiometric imine/sulfonyl imine protocols[5,6] were appealing to us for two reasons: analysis of the steps involved revealed the possibility that distinct amine- and/or sulfonamide-catalyzed variations of these Wittig-olefination pathway might be realised directly from the reaction of a phosphonium salt and an aldehyde (Scheme 2). Iminium ion



Scheme 2. Proposed amine- or sulfonamide-catalyzed aqueous Wittig reactions (X = halide).

catalysis[7,8] has emerged as one of the keystones in organocatalytic and asymmetric organocatalytic processes that has revolutionized synthetic organic chemistry over the last decade.[7a] A recent review highlights the search for "untrodden pathways" in organocatalysis.[7b] To-date, there have been no reports of Wittig olefination reactions catalyzed by amines.[7c,8] Secondly, the development of an organocatalytic Wittig process amenable to aqueous conditions, by analogy with iminium-ion- and enamine-mediated organocatalytic processes,[7d] would allow for the increased stereochemical and processing advantages previously described.[4]

In previous work on aqueous Wittig reactions conducted in our laboratory, bases such as LiOH and K_2CO_3 were shown to be capable of ylide formation under aqueous conditions,[4d] although the olefination reactions required microwave irradiation at 75–100 °C for 30 min. Sodium bicarbonate was shown to be ineffective under these conditions and was thus chosen as the required base to minimize background reactions. Although carbonate bases have been reported previously in ylide-forming processes, for example in ball-milling,[4f] we are not aware of any prior report using

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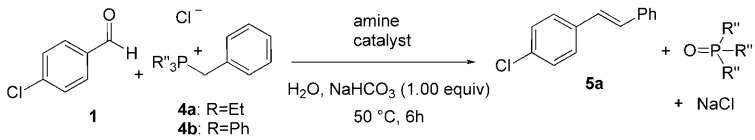
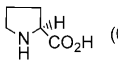
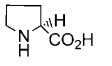
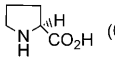
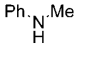
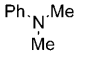
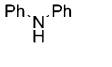
$NaHCO_3$. We postulated the net reaction (Scheme 2) to be catalytic in the presence of an amine **2**, possibly proceeding via an iminium intermediate. In a similar fashion, the reaction of a catalytic quantity of a sulfonamide **3** may be expected to produce the *N*-sulfonyl imine intermediate allowing a similar catalytic olefination process. Herein, we describe the first examples of weakly basic amine- and sulfonamide-catalyzed Wittig olefination reactions.

Model and control reactions involving the synthesis of 4-chlorostilbene (**5a**) were initially investigated with the triethyl- and triphenylbenzyl phosphonium salts **4a** and **4b**, (Table 1). A protocol involving the reaction of the aldehyde (1.00 equiv), phosphonium salt **4a** or **4b** (1.00 equiv) at a concentration of 2.0 mol L^{-1} in water with a catalytic amount of amine (2–20 mol%) and $NaHCO_3$ (1.00 equiv) at 50 °C (100 °C in the case of entries 3 and 4, Table 1) was used. Under these conditions, no reaction occurred with salt **4a** in the absence of any added amine at 50 °C (Table 1, entry 1). Addition of L-proline caused the reaction to proceed slowly (Table 1, entry 2). This olefination reaction went to completion at 100 °C over three days to give the stilbene in quantitative yield (Table 1, entry 4). A control experiment showed that only 4% olefin conversion occurred over three days at 100 °C (Table 1, entry 3) in the absence of L-proline. Reaction with the triphenyl salt **4b** proved to be much faster than **4a**. Control experiments demonstrated 13% background olefination (Table 1, entry 5) under the standard condition (50 °C, 6 h) without amine, however addition of L-proline (Table 1, entry 6) drove the reaction to completion under the same conditions. Other amines such as morpholine and ephedrine were also effective in catalyzing the olefination. We considered it necessary to focus on weakly basic amines in order to differentiate possible iminium-catalyzed process from base-mediated background processes. To this effect, the reaction was found to be effectively catalyzed by using *N*-methylaniline ($pK_a = 4.56$ (BH^+)) under the standard conditions (Table 1, entry 7), whereas the use of the tertiary amine *N,N*-dimethylaniline ($pK_a = 2.45$ (BH^+))[9] resulted in only background olefination (Table 1, entry 8). This reaction (Table 1, entry 7) was efficiently catalyzed with only 2 mol% of *N*-methylaniline.

Table 1. Various amine catalysts in the synthesis of 4-chlorostilbene (**5a**) through the aqueous Wittig reaction.



Entry	Amine (loading)	Phosphonium salt	Conversion [%]	Stilbene **5a** *E*/*Z*
1	none	**4a**	0	–
2	 (0.20)	**4a**	35	84:16
3	none	**4a**	4	–
4	 (0.20)	**4a**	>99	84:16
5	none	**4b**	13	45:55
6	 (0.20)	**4b**	>99	43:57
7	 (0.02)	**4b**	>99	50:50
8	 (0.02)	**4b**	15	44:56
9	 (0.02)	**4b**	99	50:50
10	$TosNH_2$ (0.02)	**4b**	99	46:54

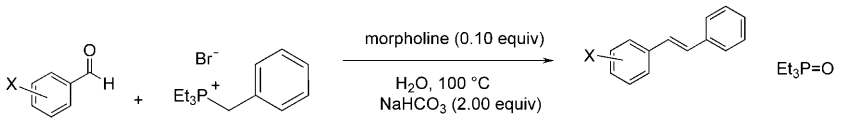
The success of *N*-methylaniline in catalyzing the olefination encouraged us to pursue even weaker bases. Diphenylamine ($pK_a = 0.78$ (BH^+)) also proved highly effective in promoting the reaction (Table 1, entry 9) at low catalyst loading, as did a catalytic amount of the very weakly basic *p*-toluenesulfonamide (Table 1, entry 10). Under the standard conditions reported in Table 1, the use of 2 mol% tosylamide promoted the reaction to full conversion within 6 h at 50 °C. This reaction completes a circle and connects the possible iminum-ion-mediated pathway as a catalytic variant of the stoichiometric *N*-sulfonyl-imine-mediated olefination described by Tian et al.[6] The *E*/*Z* olefination stereochemistry observed here is fully in accord with expected results with semi-stabilized ylides derived from triethyl-[4] and triphenylphosphane under thermodynamic aqueous conditions.[3]

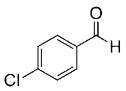
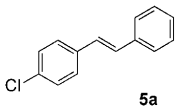
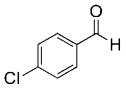
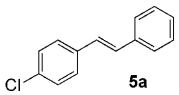
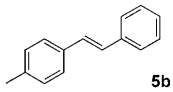
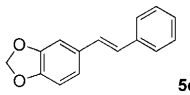
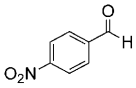
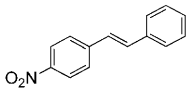
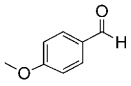
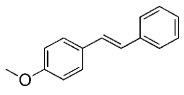
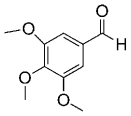
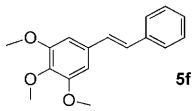
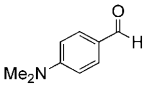
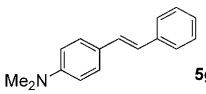
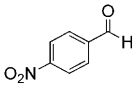
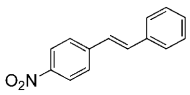
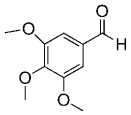
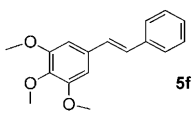
The new amine- and sulfonamide-catalyzed olefination processes were successfully extended toward the synthesis of a small panel of *trans*-stilbenes by using the triethylphosphonium salt **4a** in the presence of either a catalytic amount of morpholine, *N*-methylaniline (Table 2), or tosylamide (Table 3). Although salt **4a** reacts slower than **4b** as indicated above (Table 1), this reaction provides high *E*-selective olefins and full conversion is attained within 72 h. A range of both electron-poor and electron-rich aldehydes was shown to undergo olefination successfully. Under the conditions shown in Tables 2 and 3, a control experiment (absence of any added amine) indicated only 5% background stilbene (Table 2, entry 1). Using 10 mol% of morpholine as catalyst yields a range of *trans*-stilbenes with high *E*-selectivity (Table 2, entries 2–8). The choice of morpholine as catalyst was not critical and indeed, the present reaction was also highly successful when catalyzed by either *N*-methylaniline (Table 2, entries 9 and 10) or tosylamide (Table 3).

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 **4c**. Employing either L-proline or tosylamide as catalyst (10 mol%), the olefination occurred smoothly under our standard aminocatalysis conditions with electron-rich and electron-deficient aldehydes yielding the substituted cinnamate esters **7a**–**7c** in high yield and with exclusive *E* stereoselectivity (Table 4).

The mechanism(s) involved in the weakly basic amine- and sulfonamide-catalyzed Wittig processes described above

Table 2. Synthesis of stilbenes **5a–g** by morpholine- or *N*-methylaniline-catalyzed aqueous Wittig reactions.

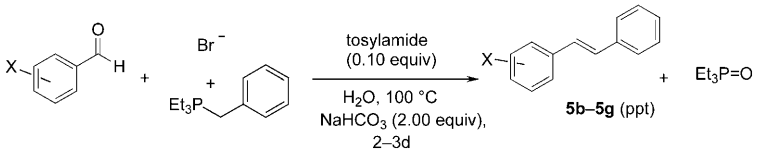


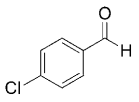
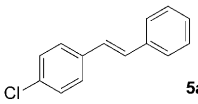
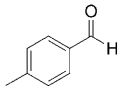
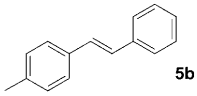
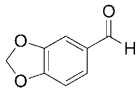
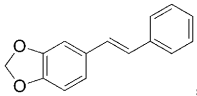
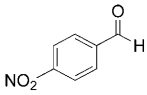
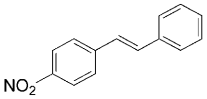
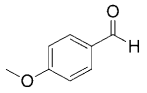
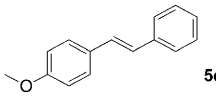
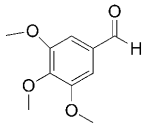
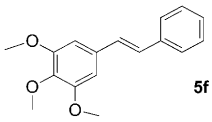
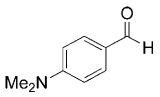
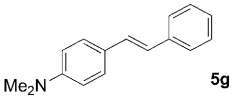
Entry	ArCHO	*trans*-Stilbene	Conversion [%][a]	*E*/*Z*
1[b]		 **5a**	< 5	
2		 **5a**	> 99 (93)	90:10
3		 **5b**	> 99 (92)	97:3
4		 **5c**	> 99 (88)	91:9
5		 **5d**	> 99 (94)	95:5
6		 **5e**	> 99 (91)	> 99 (*E*)
7		 **5f**	> 99 (85)	> 99 (*E*)
8		 **5g**	> 99 (87)	95:5
9[c]		 **5d**	> 99 (94)	95:5
10[c]		 **5f**	> 99 (85)	> 99 (*E*)

[a] Yield of isolated product is given in parentheses. [b] No amine was added [c] *N*-Methylaniline (0.10 equiv) replaced morpholine as catalyst under otherwise identical conditions.

remain speculative. At present we cannot discount the possibility of a base-catalyzed processes nor provide direct evidence in favor of iminium or sulfonyl imine intermediates. The aqueous reaction mixture is heterogeneous, which complicates kinetic investigations, although both phosphonium salt **4a** and triethylphosphane oxide are water soluble. The tosylamide-catalyzed reaction (Table 3, entry 1) was followed over 24 h (rate of triethylphosphane oxide formation) showing a clear initial rate dependence on the tosylamide concentration. This result is consistent with a pre-equilibrium involving either a base- or imine-mediated pathway. Ylide formation and olefination reactions employing amines as weakly basic as *N*-methyl aniline, diphenylamine, or tosylamide are unprecedented. If base catalysis is involved, these results demonstrate efficient Wittig olefination reactions under the mildest conditions thus far reported in the literature. Circumstantial evidence favoring either an iminium ion or sulfonyl imine can be discerned from the results. Table 1, entry 7 demonstrates the efficacy of a weakly basic secondary amine in catalyzing the olefination, whereas entries 7 and 8 in Table 1, taken together, indicate the involvement of only the secondary amine in this alternative pathway. A logical alternative reaction pathway is that proceeding through the iminium intermediate. A catalytic cycle involving an iminium intermediate is postulated in Scheme 3. Rapid and reversible condensation of an aldehyde **1** with a secondary amine **2** in water should yield a catalytic amount of the iminium salt equivalent via the aminal.[10] Based on earlier observations in aqueous media, we reasoned that this may allow conversion of a phosphonium salt **4** to catalytic amounts of the ylide. Irreversible olefination is expected to yield **5** and the aza-ylide salt **6**. In situ hydrolysis of this salt would be expected to yield the phosphane oxide and the salt of the amine from which the free base could be regenerated ($NaHCO_3$), completing a catalytic cycle. A related catalytic cycle can be postulated in the case of the sulfonamide-mediated reaction, proceeding via *N*-sulfonyl imine. The synthesis of sulfonyl imines generally requires the use of dehydrating agents and anhydrous conditions. Hence, it did not seem probable that aqueous $NaHCO_3$ solution would allow generation of these intermediates. Nonetheless, control experiments conducted in dry toluene have shown that the *N*-tosyl imine **8** derived

Table 3. Synthesis of stilbenes **5a–g** through a tosylamide-catalyzed aqueous organocatalytic Wittig protocol.

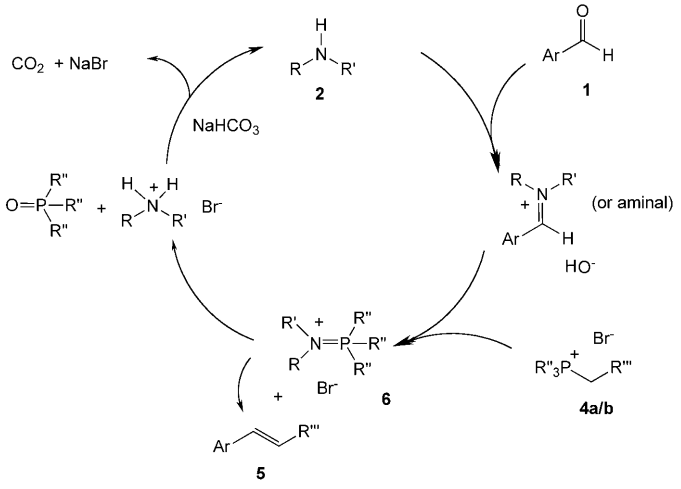


Entry	ArCHO	*trans*-Stilbene	Conversion [%][a]	*E*/*Z*
1		 **5a**	>99 (93)	96:2
2		 **5b**	>99 (92)	99:1
3		 **5c**	>99 (86)	94:6
4		 **5d**	>99 (95)	97:3
5		 **5e**	>99 (93)	97:3
6		 **5f**	>99 (84)	>99 (*E*)
7		 **5g**	>99 (88)	95:5

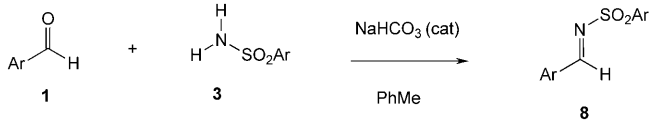
[a] Yield of isolated product is given in parentheses.

from 4-chlorobenzaldehyde and tosylamide is formed quantitatively under $NaHCO_3$ catalysis (Scheme 4). Alternatively, both the amine and sulfonamide olefination reactions may be base mediated through an initiation process that involves in situ generation of catalytic quantities of sodium carbonate, although the successful olefination processes conducted with weakly basic amines, such as diphenylamine, is difficult to rationalize through the base-mediated pathway. Irrespective of the mechanism, the mild amine- and sulfonamide-promoted olefination reactions proceed readily in water with catalyst loadings as low as 2 mol% representing a significant shift in conditions required for successful Wittig olefination processes in comparison to classical anhydrous solvent, strong-base requirements.

Lastly, from practical standpoint, product isolation and purification are often tedious processes in standard Wittig olefination reactions. One of the biggest advantages encountered using triethylphosphonium salts is the ease of purification in view of the high aqueous solubility of the phosphane oxide.[4] In all of the cases reported herein, (Tables 1–4) product isolation is relatively straightforward. Upon completion of the reaction, the mixture is simply cooled and the solid alkene isolated by suction filtration. The products are uncontaminated with phosphane oxide or amine/sulfonamide catalyst. High yields of isolated *trans*-stilbenes were achieved in all cases. *Trans*-stilbenes are highly sought as they form the core in a range of valuable materials including pharmaceuticals,[11] light emitting diodes,[12] and dye-sensitized photovoltaic solar cells.[13]

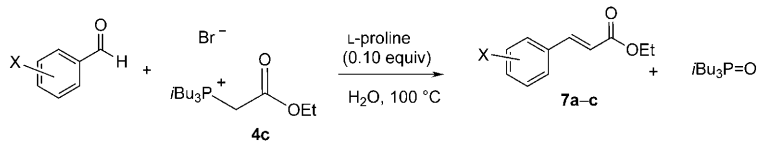


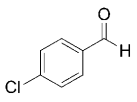
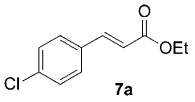
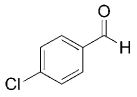
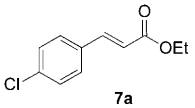
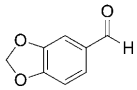
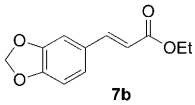
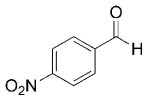
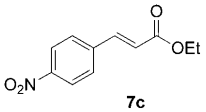
Scheme 3. Catalytic cycle involving iminium-ion-mediated Wittig olefination reactions in water.



Scheme 4. Sodium bicarbonate promoted *N*-sulfonyl imine formation in toluene.

Table 4. Synthesis of cinnamate esters **7a–7c** catalyzed by L-proline or *p*-toluenesulfonamide.



Entry	ArCHO	*trans*-Stilbene	Yield of isolated product [%]
1		 **7a**	96
2[a]		 **7a**	94
3		 **7b**	90
4		 **7c**	94

[a] Tosylamide (0.10 equiv) replaced L-proline as catalyst under otherwise identical conditions.

In conclusion, the first examples of both amine- and sulfonamide-catalyzed olefination reactions of an aldehyde reacting with a phosphonium salt are described. The reactions proceed solely in water involving the reaction of an in situ generated ylide with either the aldehyde (base-catalyzed pathway), iminium ion, or *N*-sulfonyl imine. In particular, the use of salts derived from triethylphosphane allow for high *E* stereoselectivity and straightforward product isolation. Substituted stilbenes and cinnamate esters are readily available in high yield and high *E*-olefin stereoselectivity by using this protocol. No chromatography is required at any stage and an organic solvent (Et_2O) was employed only for solvent extraction of two oily products. Further investigation into the scope of this organocatalytic aqueous olefination process and mechanistic studies are in progress.

Acknowledgements

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Keywords: alkenes · iminium ion catalysis · organocatalysis · water chemistry · Wittig reactions

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