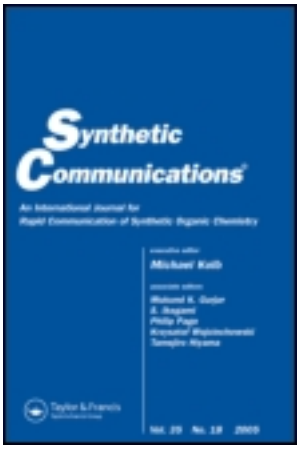

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Abstract: The Wittig reactions of three semistabilized phosphorus ylides generated in situ from the corresponding phosphonium salts with aldehydes in water without any organic cosolvent were investigated. Most of the olefination reactions completed within between 5 min and 4.5 h in refluxing water containing 1.5 equiv of LiOH and 1.4 M LiCl to afford the products in 65–100% yields. The $E:Z$ selectivity depended not only on the substituent attached to the benzene ring of the ylides but also on the substituent bound to the aromatic aldehydes. LiCl promotes the aqueous Wittig reactions and suppresses decomposition of the ylide or the corresponding phosphonium salt.

Keywords: Aldehydes, aqueous reaction, phosphorus ylide, Wittig

Aqueous organic reactions have attracted increasing attention in recent years in the search of environmentally benign chemical processes.[1] Some reactions involving organometallic species, which had previously been thought unlikely to proceed in aqueous media, have been now successfully performed in water. The Wittig reaction is one of the most versatile synthetic methods for preparation of olefins from carbonyl compounds, and it is classically carried out using a hydride or organometallic base in

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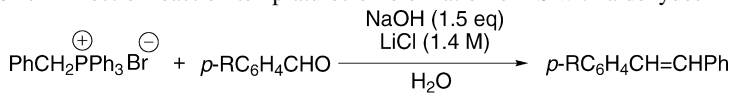
anhydrous aprotic solvents under an inert atmosphere.[2] The reactions of semistabilized phosphorus ylides with water-soluble formaldehyde have been investigated in water in the absence of organic solvents.[3] However, it was found that other aldehydes did not successfully react with semistabilized phosphorus ylides to give the products because of hydrolysis of the ylides. Industrial synthesis of vitamin A acetate is a successful example of an aqueous Wittig reaction involving a semistabilized phosphorus ylide.[4] The Hornerr–Wadsworth–Emmons (HWE) reactions of triethyl phosphonoacetate and diethyl 2-oxoalkanephosphonates with aldehydes were reported to take place in highly concentrated (6–10 M) aqueous solutions of potassium carbonate or potassium hydrogen carbonate.[5] However, decomposition of phosphonium salts and phosphorus ylides caused by aqueous bases was reported.[3b,6] For this reason, the Wittig reactions have been carried out under heterogeneous conditions with inorganic bases, including liquid–liquid,[7] solid–liquid,[8] and solid–solid phases.[9]

Recently, Russel and Warren[10a,b] took a different approach and reported the Wittig reactions of water-soluble semistabilized phosphorous ylides with aldehydes. In this approach the presence of an oxido or $-COO^-$ in the phosphonium salts may inhibit hydrolysis in basic solution, but the scope of the aldehde substrates was quite limited. Sieber et al.[10c] reported a water-soluble PEG-supported phosphonium salt used for aqueous Wittig reactions via the in situ formed semistabilized phosphorous ylide in the presence of 1 M NaOH. Various 4-substituted benzaldehydes were reacted to form the diaryl alkenes in 38–95% yields and in ca. 1 : 1–3 : 1 E : Z ratios, providing that the rate of reaction of the ylide with the aldehydes is much faster than its decomposition. In these two cases, preparation of the water-soluble or PEG-supported phosphonium salts was required. In connection with our efforts in developing the Wittig reactions under unconventional conditions by using microwave irradiation[11] and the asymmetric variations,[12] we have developed aqueous Wittig reactions of unmodified stabilized phosphorus ylides with aldehydes in the presence of LiCl.[13,14] We report here a simple procedure for carrying out heterogeneous aqueous Wittig reactions by using substituted benzyltriphenylphosphonium halides with aldehydes without using any organic cosolvent. The acceleration effect of LiCl is also examined.

Reactions of some stabilized phosphorus ylides (for example, triphenylphosphoranylideneacetonitrile) with aldehydes take place at room temperature within several minutes in water in the presence of LiCl.[13] Because semistabilized phosphorus ylides have higher reactivity than stabilized ylides, it is expected that semistabilized ylides can react with benzaldehyde (**2c**) under the similar reaction conditions. However, the reaction was found to be not as fast as expected when benzyltriphenylphosphorane, formed in situ from benzyltriphenylphosphonium bromide (**1b**) and NaOH, reacted with 4-nitrobenzaldehyde (**2a**) in water in the presence of LiCl at room temperature (Table 1, entry 1). 4-Nitrostilbene **3** ($R = NO_2$) was obtained in 65% yield with an E : Z ratio of 78 : 22. A similar yield was obtained for the reaction

Table 1. Effect of reaction tempratures on olefination of **1b** with aldehydes **2**[a]



1b **2** **3**

Entry	**2**:[b] R	Temperature (°C)	Time (h)	**3**: Yield[c] (%); $E:Z$[d]
1	**2a**: NO_2	rt	2.5	65; 78 : 22
2	**2a**	Reflux	1.5	75; 61 : 39
3	**2c**: H	rt	2	65; 46 : 54
4	**2c**	Reflux	0.25	84; 45 : 55
5	**2d**: OMe	rt	19	34; 37 : 63
6	**2d**	Reflux	3	58; 48 : 52

[a]Carried out in H_2O with 1.2 : 1 ratio of **1** and **2** in the presences of 1.5 equiv. of NaOH and 1.4 M LiCl.

[b]Mp: 105–108°C for **2a**. Bp: 178–179°C for **2c**, 248°C for **2d**.

[c]Isolated yield of both isomers.

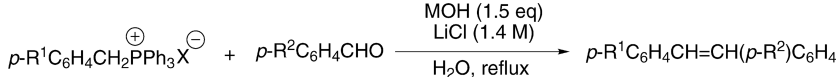
[d]Determined by ^{1}H NMR.

of **1b** with benzaldehyde (**2c**), but a nearly 1 : 1 ratio was observed for the olefin product (Table 1, entry 3). Moreover, a much slower reaction was found for a less reactive aldehyde, 4-methoxybenzaldehyde (**2d**); after reacting for 19 h at room temperature, only 34% yield of the product **3** (R = OMe) was obtained with a reversed $E:Z$ ratio of 37 : 63 (Table 1, entry 5). To enhance the reactivity of the semistabilized ylide, the olefination was performed in refluxing water and a significant temperature effect was observed (Table 1, entries 2, 4, and 6). All three aldehydes afforded synthetically useful chemical yields of 58–84% within 3 h with a slightly diminished diastereoselectivity as compared to that of the room temperature reactions. In particular, the reaction time of 4-methoxybenzaldehyde (**2d**) shortened from 19 h to 3 h in refluxing water (Table 1, entry 5 vs. entry 6). Conversely, the reactive aldehyde, 4-nitrobenzaldehyde (**2a**), showed a little temperature effect, presumably because of the phase difference in the heterogeneous reactions. The preliminary results given in Table 1 clearly demonstrate that it is feasible to use conventional reagents such as the phosphonium salt **1b** and aldehydes **2** for aqueous Wittig reactions in the presence of LiCl.[13,14] It is a remarkable extension of the early work that failed with aqueous reactions of semistabilized phosphorus ylides with non-water-soluble aldehydes.[3] The increased hydrophobic effect of LiCl[14] may significantly promote the olefination while suppressing the decomposition of the phosphonium salt or the corresponding ylide in water.

Next, we investigated the scope of the aqueous Wittig reactions by using three semistabilized phosphorus ylides formed in situ from the corresponding

phosphonium salts **1a–c** with a collection of four representative aromatic aldehydes **2a–d** (Table 2). The selected ylides and aromatic aldehydes cover the substrates with electronic-withdrawing or electronic-donating groups. All reactions were performed in refluxing water in the presence of LiCl (1.4 M) and NaOH (1.5 equiv.) (method A) or LiOH (1.5 equiv.)

Table 2. Aqueous Wittig reactions of phosphonium salts **1** with aldehydes **2** in the presence of LiCl and NaOH or LiOH[a]



1 **2** **3**

Entry	**1**:[b] R^1, X	**2**:[c] R^2	Base	Time (h)	**3**: Yield[d] (%); $E:Z$[e]
1	**1a**: NO_2, Br	**2a**: NO_2	NaOH	5	60; 20 : 80
2	**1a**	**2a**	LiOH	4.5	74; 7 : 93
3	**1a**	**2b**: Cl	NaOH	5.5	70; 89 : 11
4	**1a**	**2b**	LiOH	1.5	65; 89 : 11
5	**1a**	**2c**: H	NaOH	6	86; 100 : 0
6	**1a**	**2c**	LiOH	3.5	79; 95 : 5
7	**1a**	**2d**: OMe	NaOH	9	54; 100 : 0
8	**1a**	**2d**	LiOH	2.5	70; 75 : 25
9	**1b**: H, Br	**2a**	NaOH	1.5	75; 61 : 39
10	**1b**	**2a**	LiOH	0.92	79; 77 : 23
11	**1b**	**2b**	NaOH	0.58	79; 50 : 50
12	**1b**	**2b**	LiOH	0.33	98; 47 : 53
13	**1b**	**2c**	NaOH	0.25	84; 45 : 55
14	**1b**	**2c**	LiOH	0.22	85; 47 : 53
15	**1b**	**2d**	NaOH	3	58; 48 : 52
16	**1b**	**2d**	LiOH	0.5	84; 46 : 54
17	**1c**: OMe, Cl	**2a**	NaOH	0.5	100; 58 : 42
18	**1c**	**2a**	LiOH	0.5	87; 62 : 38
19	**1c**	**2b**	NaOH	1	63; 17 : 83
20	**1c**	**2b**	LiOH	0.08	98; 11 : 89
21	**1c**	**2c**	NaOH	1.5	81; 46 : 54
22	**1c**	**2c**	LiOH	0.08	93; 40 : 60
23	**1c**	**2d**	NaOH	2[f]	46; 21 : 79
24	**1c**	**2d**	LiOH	2	100; 16 : 84

[a]Carried out in refluxing H_2O with a 1.2 : 1 ratio of **1** and **2** in the presence of LiCl (1.4 M) and 1.5 equiv. of NaOH (method A) or LiOH (method B).

[b]Mp: 275°C (dec.) for **1a**, 295–298°C for **1b**, and 245–247°C for **1c**.

[c]Mp: 105–108°C for **2a** and 47–50°C for **2b**. Bp: 178–179°C for **2c** and 248°C for **2d**.

[d]Isolated yield of both isomers.

[e]Determined by ^{1}H NMR.

[f]Reaction was not completed.

(method B) as the base. We were delighted to find that all reactions in Table 2 proceeded smoothly to afford the desired olefin products in good to excellent yields. In general, the reactions with LiOH as the base were faster than those with NaOH; the difference in reaction time was especially much more profound for the less reactive aldehyde **2d** (Table 2, entries 7, 15, and 23 vs. entries 8, 16, and 24). The influence of counterion on the reaction time might be accounted for by the different hydrophobic effect of cations on aqueous reactions.[14] Therefore, the chemical yields were generally higher when LiOH was used as the base. Moreover, LiOH did not significantly alter diastereoselectivity of the aqueous Wittig reactions except for one case where a decreased $E:Z$ ratio was noted (Table 2, entry 7 vs. entry 8). We also examined the aqueous reaction of 4-nitrobenzyltriphenylphosphonium bromide (**1a**) with unprotected 4-hydroxybenzaldehyde in the presence of LiCl and NaOH under refluxing conditions. The desired product, (*E*)-4-hydroxy-4′-nitrostilbene, was detected but was isolated in only l4% yield along with 4-nitrotoluene (90%), arising from decomposition of the phosphonium salt. It is reasonable to assume that under the basic conditions 4-hydroxybenzaldehyde was converted into the corresponding phenoxide, which should have much lower reactivity toward the ylide, resulting in substantial decomposition of the ylide or its phosphonium salt. These results confirm that the olefination and decomposition are the two competing pathways in water for semistabilized phosphorus ylides.

It is interesting to examine the *E* and *Z* diastereoselectivity in relation with the reactivity of both ylides and aldehydes. In the case of the ylide generated from **1a**, which possesses a strong electron-withdrawing NO_2 group, its reaction with the reactive 4-nitrobenzaldehyde (**2a**) afforded a greater proportion of the *Z* alkene,[15] whereas nearly complete *E* selectivity was observed for the reactions of aldehydes **2b**–**d** (Table 2, entries 1–8). The counterion of the base LiOH enhanced the *Z* selectivity for 4-nitrobenzaldehyde (**2a**) but reduced the *E* preference for benzaldehyde (**2c**) and 4-methoxybenzaldehyde (**2d**). A reversed selectivity was found for the reactions of **2a** with the ylides formed from **1b** and **1c**; in these cases, *E*-olefins were formed as the major isomer although to a much smaller extent (Table 2, entries 9, 10, 17, and 18). For the reactions of **1b** with aldehydes **2b**–**d**, about 50 : 50 mixtures of the products were recorded. However, for the reactions of **lc** with aldehydes **2b**–**d**, the *Z*-olefins were generally formed as the dominant isomers although the selectivity was not great for the reaction of benzaldehyde (**2c**) with **1c** (Table 2, entries 19–24). Therefore, it can be concluded that aromatic aldehydes, except for the very reactive 4-nitrobenzaldehyde (**2a**), prefer to form *E*-olefins with the semistabilized phosphorus ylide possessing a strong electron-withdrawing NO_2 group and *Z*-olefins with the semistabilized phosphorus ylide possessing a strong electron-donating OMe group.

In summary, we have established a general protocol for aqueous Wittig reactions of semistabilized phosphorus ylides generated in situ from the corresponding phosphonium salts with aromatic aldehydes in the presence of

LiOH (1.5 equiv) and LiCl (1.4 M) at refluxing temperature. The heterogeneous olefination reactions of representative aromatic aldehydes complete within between 5 min and 4.5 h to furnish the products in 65–100% isolated yields. The $E:Z$ selectivity depends not only on the substituent attached to the phenyl ring of the semistabilized phosphorus ylides but also on the substituent bound to the aromatic aldehydes. As the consequence of the hydrophobic effect of LiCl, the semistabilized phosphorus ylides or the phosphonium salts do not suffer from decomposition in water. Therefore, conventional reagents can be used without extra structural modification in simple and high-yielding olefination reactions.

EXPERIMENTAL

All reagents were obtained from commercial sources and used as received. All reactions were carried out in open air in a round-bottom flask charged with a water-cooling condenser and were monitored by TLC. The olefin products are known compounds and were characterized by ^{1}H NMR on a 500 MHz instrument with comparison to the reported data.

Representative, Procedure for Aqueous Wittig Reaction

A mixture of the phosphonium salt **1** (0.4 mmol) and the aldehyde **2** (0.35 mmol) in H_2O (10 mL) containing 1.5 equiv of NaOH or LiOH and $LiCl \cdot H_2O$ (846 mg, 14.0 mmol) was refluxed in air for the indicated time. After cooling to room temperature, the reaction mixture was extracted with EtOAc (10 mL × 3) and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and condensed under reduced pressure. The residue was then purified by column chromatography (silica gel, eluting with 10–15% EtOAc in hexane) to give the olefin product **3**. The results are found in Table 2.

(*E*)- and (*Z*)-4,4′-Dinitrostilbene (3, $R^1 = R^2 = NO_2$): As a 20 : 80 mixture $E:Z$ isomers. (*E*)-4,4′-Dinitrostilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[16,17] δ 8.27 (d, $J = 8.7$ Hz, 4H), 7.69 (d, $J = 8.7$ Hz, 4H), 7.30 (s, 2H). (*Z*)-4,4′-Dinitrostilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[16,17] δ 8.12 (d, $J = 8.7$ Hz, 4H), 7.35 (d, $J = 8.7$ Hz, 4H), 6.84 (s, 2H).

(*E*)-4-Chloro-4′-nitrostilbene (3, $R^1 = NO_2$, $R^2 = Cl$): As an 89 : 11 mixture of $E:Z$ isomers. ^{1}H NMR (500 MHz, $CDCl_3$)[17] δ 8.23 (d, $J = 8.7$ Hz, 2H), 7.63 (d, $J = 8.7$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 16.0$ Hz, 1H), 7.12 (d, $J = 16.0$ Hz, 1H).

(*E*)- and (*Z*)-4-Nitrostilbene (3, $R^1 = H$, $R^2 = NO_2$ or $R^1 = NO_2$, $R^2 = H$): As a 61 : 39 mixture of $E:Z$ isomers. (*E*)-4-Nitrostilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[5a–c] δ 8.24 (d, $J = 8.7$ Hz, 2H), 7.65 (d, $J = 8.7$ Hz, 2H), 7.57

(d, $J = 7.5$ Hz, 2H), 7.38–7.41 (m, 2H), 7.32–7.35 (m, 1H), 7.28 (d, $J = 16.3$ Hz, 1H), 7.15 (d, $J = 16.3$ Hz, 1H). (*Z*)-4-Nitrostilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[5a–c] δ 8.07 (d, $J = 7.5$ Hz, 2H), 7.37 (d, $J = 7.5$ Hz, 2 H), 7.25–7.26 (m, 3H), 7.19–7.21 (m, 2H), 6.82 (d, $J = 12.0$ Hz, 1H), 6.61 (d, $J = 12.0$ Hz, 1H).

(*E*)- and (*Z*)-4-Methoxy-4′-nitrostilbene (3, $R^1 = NO_2$, $R^2 = OMe$ or $R^1 = OMe$, $R^2 = NO_2$): (*E*)-4-Methoxy-4′-nitrostiblene: ^{1}H NMR (500 MHz, $CDCl_3$)[15] δ 8.20 (d, $J = 8.6$ Hz, 2H), 7.60 (d, $J = 8.6$ Hz, 2H), 7.50 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 14.8$ Hz, 1H), 7.02 (d, $J = 14.8$ Hz, 1H), 6.94 (d, $J = 8.8$ Hz, 2H), 3.86 (s, 3H). (*Z*)-4-Methoxy-4′-nitrostilbene: As a 58 : 42 mixture of *E* : *Z* isomers. ^{1}H NMR (500 MHz, $CDCl_3$)[15] δ 8.08 (d, $J = 8.7$ Hz, 2H), 7.40 (d, $J = 8.7$ Hz, 2H), 7.14 (d, $J = 8.7$ Hz, 2H), 6.78 (d, $J = 8.7$ Hz, 2H), 6.74 (d, $J = 12.2$ Hz, 1H), 6.51 (d, $J = 12.2$ Hz, 1H), 3.80 (s, 3H).

(*E*)- and (*Z*)-4-Chlorostilbene (3, $R^1 = H$, $R^2 = Cl$): As a 47 : 53 mixture of *E* : *Z* isomers. (*E*)-4-Chlorostilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[5a–c,18,19] δ 7.51 (d, $J = 7.9$ Hz, 2H), 7.45 (d, $J = 8.5$ Hz, 2H), 7.37–7.40 (m, 2H), 7.34 (d, $J = 8.5$ Hz, 2H), 7.28–7.31 (m, 1H), 7.10 (d, $J = 16.5$ Hz, 1H), 7.06 (d, $J = 16.5$ Hz, 1H). (*Z*)-4-Chlorostilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[5a–c,18,19] δ 7.18–7.28 (m, 9H), 6.63 (d, $J = 12.2$ Hz, 1H), 6.53 (d, $J = 12.2$ Hz, 1H).

(*E*)- and (*Z*)-Stilbene(3, $R^1 = R^2 = H$): As a 45 : 55 mixture of *E* : *Z* isomers. (*E*)-Stilbene: ^{1}H NMR (500 MHz, $CDCl_2$)[5a–c,20] δ 7.52 (d, $J = 7.8$ Hz, 4H), 7.36 (t, $J = 7.8$ Hz, 4H), 7.19–7.26 (m, 2H), 7.11 (s, 2H). (*Z*)-Stilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[5a–c,20] δ 7.19–7.26 (m, 10H), 6.60 (s, 2H).

(*E*)- and (*Z*)-4-Methoxystilbene (3, $R^1 = H$, $R^2 = OMe$ or $R^1 = OMe$, $R^2 = H$): As a 48 : 52 mixture of *E* : *Z* isomers. (*E*)-4-Methoxystilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[5a–c,18–20] δ 7.49 (d, $J = 7.4$ Hz, 2H), 7.45 (d, $J = 8.6$ Hz, 2H), 7.34 (t, $J = 7.4$ Hz, 2H), 7.21–7.25 (m, 1H), 7.07 (d, $J = 16.6$ Hz, 1H), 6.97 (d, $J = 16.6$ Hz, 1H), 6.90 (d, $J = 8.6$ Hz, 2H), 3.83 (s, 3H). (*Z*)-4-Methoxystilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[5a–c,18–20] δ 7.17–7.27 (m, 5H), 7.18 (d, $J = 8.6$ Hz, 2H), 6.75 (d, $J = 8.6$ Hz, 2H), 6.53 (d, $J = 13.2$ Hz, 1H), 6.50 (d, $J = 13.2$ Hz, 1H), 3.78 (s, 3H).

(*E*)- and (*Z*)-4-Chloro-4′-methoxystilbene (3, $R^1 = OMe$, $R^2 = Cl$): As a 17 : 83 mixture of *E* : *Z* isomers. (*E*)-4-Chloro-4′-methoxystilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[20] δ 7.44 (d, $J = 7.4$ Hz, 2H), 7.41 (d, $J = 7.6$ Hz, 2H), 7.30 (d, $J = 7.6$ Hz, 2H), 7.03 (d, $J = 16.0$ Hz, 1H), 6.91 (d, $J = 16.0$ Hz, 1H, 6.90 (d, $J = 7.4$ Hz, 2H), 3.83 (s, 3H. (*Z*)-4-Chloro-4′-methoxystilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[20] δ 7.19 (br, s, 4H), 7.16 (d, $J = 7.4$ Hz, 2H), 6.77 (d, $J = 7.4$ Hz, 2H), 6.55 (d, $J = 12.4$ Hz, 1H), 6.43 (d, $J = 12.4$ Hz, 1H), 3.79 (s, 3H).

(*E*)- and (*Z*)-4,4′-Dimethoxystilbene (3, $R^1 = R^2 =$ OMe): As a 21 : 79 mixture of *E* : *Z* isomers. (*E*)-4,4′-Dimethoxystilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[9,21] δ 7.43 (d, $J = 8.5$ Hz, 4H), 6.93 (s, 2H), 6.89 (d, $J = 8.5$ Hz, 4H), 3.83 (s, 3H). (*Z*)-4,4′-Dimethoxystilbene: ^{1}H NMR (500 MHz, $CDCl_3$)[9,21] δ 7.2 (d, $J = 8.5$ Hz, 4H), 6.77 (d, $J = 8.5$ Hz, 4H), 6.44 (s, 2H), 3.79 (s, 3H).

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