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Wittig Reactions of Stabilized Phosphorus Ylides with Aldehydes in Water

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Abstract: The Wittig reactions of three stabilized phosphorus ylides with aldehydes in water were investigated. Most of the olefination reactions completed within 5-60 min in refluxing water in the presence of 1.2 M LiCl to afford the olefin products in 65-98% yields. It was found that the Wittig reactions of stabilized phosphorus ylides with aldehydes in water were faster than those carried out in organic solvents.

Keywords: Aqueous reaction, aldehydes, phosphorus ylide, Wittig

INTRODUCTION

Organic reactions in water have attracted increasing attention in recent years in developing 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 anhydrous aprotic solvents under an inert atmosphere.^[2] The reactions of semistabilized phosphorus ylides (**I**) 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

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ylides (I) to give the products. Industrial synthesis of vitamin A acetate is a successful example of aqueous Wittig reaction involving a semistabilized phosphorus ylide (II).^[4]



Recently, Russell and Warren ^[5a,5b] took a different approach and reported the Wittig reactions of water-soluble semistabilized phosphorous ylides (**III**) with aldehydes, but the scope of the aldehyde substrates was quite limited. Sieber et al.^[5c] reported a water-soluble PEG-supported phosphonium salt in aqueous Wittig reactions via the in situ formed semistablized phosphorous ylide (**IV**) in the presence of 1 N 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.

The Horner-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.^[6] However, decomposition of phosphonium salts and phosphorus ylides caused by aqueous bases was reported.^[3b,7] For this reason, the Wittig reactions have been carried out under heterogeneous conditions with inorganic bases, including liquidliquid,^[8] solid-liquid,^[9] and solid-solid phases.^[10] To the best of our knowledge, aqueous Wittig reactions of stabilized phosphorus ylides have not been reported. In connection with our efforts in developing the Wittig reactions under unconventional conditions using microwave irradiation^[11] and the asymmetric variations,^[12] we systematically investigated the heterogeneous Wittig reactions in water without adding organic cosolvents. We report here on the results of Wittig reactions of three stabilized phosphorus ylides with aldehydes other than formaldehyde in water in the presence of LiCl.

First, we investigated the effect of $\text{LiCl}^{[13]}$ on the Wittig reactions of (carbethoxymethylene)triphenylphosphorane (1a) in water under the refluxing conditions (Table 1). With a reactive aldehyde, 4-nitrobenzaldehyde (2a), the reactions completed in 5 min to give the olefin 3 in excellent yields and

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	RCHO + Ph3P=CHE	H ₂ O, LiCl reflux or rt		H=CHE
	R = aryl, alkyl E = CN, CO ₂ Et, COMe	5~00 mm	yield = 65-98% <i>E:Z</i> = 98:2-49:51	
Entry	2: R	LiCl	t (min)	Yield $(\%)$, ^c $E:Z^d$
1	2a: 4-NO ₂ C ₆ H ₄	_	5	98, 89:11
2	2a	1.2	5	98, 89:11
3	2a	6.0	5	97, 94:6
4	2b : 4-MeOC ₆ H ₄	_	90	35, 91:9
5	$2\mathbf{b}^{b}$	_	60	77, 91:9
6	2b	1.2	30	94, 91:9

Table 1. Effect of LiCl on the	e Wittig reactions	of 1a with aldehydes 2^a
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^aCarried out in refluxing H₂O with a 1.2:1 ratio of **1a** and **2**.

^bCarried out in refluxing H_2O with a 1.5:1 ratio of **1a** and **2**.

^cIsolated yield of both isomers.

^dDetermined by ¹H NMR.

in \geq 89:11 isomeric ratios with or without the added LiCl (entries 1–3, Table 1). However, a significant salt effect was observed for the reactions of 4-anisaldehyde (**2b**). In the absence of LiCl, the reaction of **1a** with **2b** for 90 min afforded the product in 35% yield whereas the yield of the product increased to 77% by increasing the equivalents of **1a** from 1.2 to 1.5 (entries 4 and 5, Table 1). By adding 1.2 equivalents of LiCl, the reaction of 1a with 2b, after refluxing for 30 min, furnished the olefin in 94% yield (entry 6, Table 1). These results clearly demonstrate that LiCl accelerated the aqueous Wittig reactions because of increased hydrophobic effect^[13] and remarkably improved the chemical yields. In addition, the isomeric ratios of the olefin products are almost not influenced by addition of LiCl and a slight increase in *E*:*Z* ratio was observed at high concentration of LiCl (entry 3, Table 1).

Next, we carried out aqueous Wittig reactions of three stabilized phosphorus ylides 1a-c with a collection of representative aromatic and aliphatic aldehydes 2a-f. It is worth mentioning that all ylides and aldehydes used in this study have a melting point or boiling point higher than 100°C. All reactions, except for entries 12 and 14 in Table 2, were performed in refluxing H₂O in the presence of 1.2 MLiCl, and the results are summarized in Table 2. In general, the reactions of the ylide **1a** with aromatic aldehydes **2a–e** gave both good to excellent yields and isomer ratios (entries 1–5, Table 2).

The reaction time was found to be parallel to the intrinsic reactivity of the aldehydes and follows the order of 4-nitrobenzaldehyde (2a) (5 min) < benzaldehyde (2c) \approx 4-hydroxybenzaldehyde (2d) \approx 2-furaldehyde (2e)

		RCHO (2)			
	Ph ₃ P-CH 1	1.2 M LiCl H ₂ O, rt or reflux	► KUH-UH 3		
Entry	1: ^{<i>b</i>} E	2 : ^{<i>c</i>} R	<i>t</i> (min)	Yield (%), ^{d} E:Z ^{e}	
1	1a : CO ₂ Et	2a : 4-NO ₂ C ₆ H ₄	5	98, 89:11	
2	1 a	2b : 4-MeOC ₆ H ₄	30	94, 91:9	
3	1 a	2c : Ph	10	78, 95:5	
4	1a	2d : 4-HOC ₆ H ₄	10	96, 85:15	
5	1 a	2e: 2-furanyl	8	83, 93:7	
6	1a	2f: CH ₃ (CH ₂) ₆ -	30	72, 66:34	
7	1b: COMe	2a : 4-NO ₂ C ₆ H ₄	10	92, 91:9	
8	1b	2b : 4-MeOC ₆ H ₄	60	98, 95:5	
9	1b	2c : Ph	30	89, 98:2	
10	1b	2e: 2-furanyl	45	78, 96:4	
11	1b	2f: CH ₃ (CH ₂) ₆ -	45	81, 53:47	
12	1c: CN	2a : 4-NO ₂ C ₆ H ₄	5^f	99, 57:43	
13	1c	2b : 4-MeOC ₆ H ₄	60	65, 72:28	
14	1c	2c : Ph	15^{f}	93, 79:21	
15	1c	2e : 2-furanyl	5	96, 49:51	

Table 2. Aqueous Wittig reactions of ylides 1 with aldehydes 2^a

^{*a*}Carried out in refluxing H_2O with a 1.2:1 ratio of **1** and **2**.

^bMp: 128–130°C for **1a**, 203–205°C for **1b**, and 189–195°C for **1c**.

^cMp: 105–108[°]C for **2a**, Bp: 248[°]C for **2b**, 178–179[°]C for **2c**, MP: 117–119[°]C for **2d**, Bp: 162[°]C for **2e**, and 171[°]C for **2f**.

^dIsolated yield of both isomers.

^eDetermined by ¹H NMR.

^{*f*}Carried out in H_2O at room temperature with a 1.2:1 ratio of 1 and 2.

(8-10 min) < 4-anisaldehyde (2b) (30 min). It is interesting to find that the phenolic hydroxy group in 2d does not require protection (entry 4, Table 2). The aliphatic aldehyde, octyl aldehyde (2f) reacted with 1a for 30 min to form 3 in 72% yield and in a decreased *E*:*Z* isomer ratio of 66:34 (entry 6, Table 2). These results indicate that the Wittig reactions of 1a are much more stereoselective with aromatic aldehydes than aliphatic aldehydes. For the Wittig reactions of 1b with aromatic aldehydes, the same results were obtained (78–98% yields, >91:9 *E*:*Z* ratios) as given in entries 7–10 in Table 2. However, the reaction of 2f with 1b became nearly nonstereoselective (entry 11, Table 2). Because of the higher reactivity of the ylide 1a than 1b, slightly longer reaction times were required for the olefination of 1b.

With less sterically demanding ylides 1c, the ratios of the product isomers decreased significantly even for the aromatic aldehydes (entries 12-15,

Table 2). For example, **1c** reacted with **2a** and **2e** to afford the olefin **3** as the 57:43 and 49:51 mixture of *E*:*Z* isomers, respectively (entries 12 and 15, Table 2). It is interesting to emphasize that the heterogeneous Wittig reactions of **1c** with **2a** and **2c** took place in H₂O even at room temperature (entries 12 and 14, Table 2), respectively, to give high yields of the olefin **3**. It represents a fast reaction (5 min) between two solid reagents **1c** (mp 189–195°C) and **2a** (mp 105–108°C), both suspended on a water surface at room temperature, to form the olefin **3** in a quantitative yield. Our results listed in Table 2 are superior to the previous reports on aqueous Wittig reactions of semistabilized phosphorus ylides using water-soluble reagents^[3,5] and demonstrate that H₂O can be used to directly substitute the organic solvents used in the Wittig olefination without extra structural modifications on the substrates.

Finally, we examined the solvent effect on the Wittig reactions of the ylide **1b** with both aromatic and aliphatic aldehydes and the results are given in Table 3. Reactions in three organic solvents, PhMe, DMF, and

	Ph ₃ P=CHCOMe 1b	RCHO (2)	RCH=CHCOMe 3	
		H ₂ O or organic solvent		
Entry	2 : R	Solvent	<i>t</i> (min)	Yield (%), ^{d} E:Z ^{e}
1	2a : <i>p</i> -NO ₂ C ₆ H ₄	H_2O^b	10	92, 91:9
2	2a	PhMe	20	90, 97:3
3	2a	DMF^{c}	10	90, > 99:1
4	2a	THF	35	95, >99:1
5	2b : <i>p</i> -MeOC ₆ H ₄	H_2O^b	60	98, 95:5
6	2b	PhMe	1440	85, >99:1
7	2b	DMF^{c}	1800	91, >99:1
8	2b	THF	4320	92, >99:1
9	2c : Ph	H_2O^b	30	89, 98:2
10	2c	PhMe	120	88, >99:1
11	2c	DMF^{c}	120	87, >99:1
12	2c	THF	1200	92, >99:1
13	2f: CH ₃ (CH ₂) ₆ -	H_2O^b	45	81, 53:47
14	2f	PhMe	90	80, 78:22

Table 3. Effect of solvent on the Wittig reactions of 1b with aldehydes 2^a

^aCarried out at refluxing temperature, except for DMF, with a 1.2:1 ratio of **lb** and **2**. ^bIn the presence of 1.2 M LiCl.

In the presence of 1.2 M LIC

^cCarried out at 110°C.

^dIsolated yield of both isomers.

^eDetermined by ¹H NMR.

THF, were compared with that done in H_2O . The reaction temperatures were set closely for PhMe (110°C), DMF (110°C), and H₂O (100°C) but it was quite lower for THF (67°C). The data for aqueous Wittig reactions of 1b (entries 1, 5, 9, and 13, Table 3) are taken from Table 2. In general, the yields of the olefin 3 formed from the reactive aldehyde 2a in all four media are nearly the same (entries 1-4, Table 3), whereas extremely slow reactions of 1b with 2b were observed in PhMe and DMF even at higher temperature (entries 6 and 7 vs. entry 8, Table 3). Also, the Wittig reactions of 2c and 2f in organic solvents took longer time to complete. Therefore, it is clearly demonstrated that the heterogeneous Wittig reactions of stabilized ylides in refluxing H₂O are faster than the same reactions carried out in homogeneous organic solvents at similar reaction temperatures. This is an interesting finding that may shed light on developing "greener" chemical processes by using H₂O as the reaction medium. A weak point is that the stereoselectivity of the Wittig reactions in H₂O decreases notably for aliphatic aldehydes, but the difference is minimal for the reactions of aromatic aldehydes.

In summary, we have established a general protocol for aqueous Wittig reactions of stabilized phosphorus ylides with both aromatic and aliphatic aldehydes in the presence of 1.2 M LiCl at refluxing temperature for 5–60 min to afford the olefin products in 65–98% isolated yields. Moreover, we have demonstrated that the aqueous Wittig reactions are faster than the same reactions carried out in homogeneous organic solvents at similar reaction temperatures. Our study suggests that H_2O may be used to directly substitute for organic solvents in other types of organic reactions without structural modification on the substrates.

EXPERIMENTAL

Representative Procedure

A suspension of the ylide 1 (1.2 mmol) and the aldehyde 2 (1.0 mmol) in H₂O (5 mL) containing LiCl \cdot H₂O (362.5 mg, 6.0 mmol) was refluxing in air for the indicated time. After cooling to room temperature, the reaction mixture was extracted with EtOAc (10 mL \times 3) and the combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and condensed under reduced pressure. The residue was then purified by column chromatography over silica gel (10–30% EtOAc in hexane) to give the olefin product 3. The results are found in Table 2.

(*E*)-Ethyl 3-(4-Nitrophenyl)-2-propenoate:^[14] (R = 4-NO₂C₆H₄, E = CO₂Et, as a 89:11 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 8.25 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 16.0 Hz, 1H), 7.67 (d, *J* = 8.7 Hz, 2H), 6.56 (d, *J* = 16.0 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

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(*E*)-Ethyl 3-(4-Methoxyphenyl)-2-propenoate:^[15] (R = 4-MeOC₆H₄, E = CO₂Et, as a 91:9 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 7.64 (d, *J* = 16.0 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

(*E*)-Ethyl 3-Phenyl-2-propenoate: $^{[14,15]}$ (R = C₆H₅, E = CO₂Et, as a 95:5 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 7.68 (d, *J* = 16.0 Hz, 1H), 7.51–7.52 (m, 2H), 7.36–7.38 (m, 3H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

(E)-Ethyl 3-(4-Hydroxyphenyl)-2-propenoate:^[15] (R = 4-HOC₆H₄, E = CO₂Et, as a 85:15 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 7.64 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.30 (d, *J* = 16.0 Hz, 1H), 6.10 (bs, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H.

(*E*)-Ethyl 3-(2-Furanyl)-2-propenoate:^[16] (R = 2-furanyl, E = C0₂Et, as a 93:7 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 7.47 (d, *J* = 0.9 Hz, 1H), 7.43 (d, *J* = 15.7 Hz, 1H), 6.60 (d, *J* = 3.3 Hz, 1H), 6.46 (dd, *J* = 3.3 Hz, 0.9 Hz, 1H), 6.31 (d, *J* = 15.7 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

(*E*)-Ethyl 2-Decenoate:^[17] (R = n-CH₃(CH₂)₆, $E = CO_2Et$, as a 66:34 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 6.96 (dt, J = 15.7, 7.1 Hz, 1H), 5.80 (d, J = 15.7 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.17–2.21 (m, 2H), 1.42–1.46 (m, 2H), 1.27–1.30 (bm, 8H), 0.87–0.89 (m, 6H); (*Z*)-Ethyl 2-Decenoate:^[17] (R = n-CH₃(CH₂)₆, $E = CO_2Et$, as a 66:34 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃.) δ 6.76 (dd, J = 15.7, 6.0 Hz, 1H), 5.85 (d, J = 15.7 Hz, 1H), 4.18 (q, J = 7.2 Hz, 3H), 1.62–1.73 (m, 2H), 1.44 (bs, 2H), 1.27–1.32 (bm, 10H), 0.87–0.88 (m, 3H).

(*E*)-4-(4-Nitrophenyl)-3-buten-2-one:^[18] (R = 4-NO₂C₆H₄, E = COMe, as a 91:9 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 8.26 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 16.2 Hz, 1H), 6.82 (d, *J* = 16.2 Hz, 1H), 2.43 (s, 3H).

(*E*)-4-(4-Methoxyphenyl)-3-buten-2-one:^[15] (R = 4-MeOC₆H₄, E = COMe, as a 95:5 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 16.2 Hz, 1H), 91 (d, *J* = 8.7 Hz, 2H), 6.60 (d, *J* = 16.2 Hz, 1H), 3.84 (s, 3H), 2.37 (s, 3H).

(*E*)-4-Phenyl-3-buten-2-one:^[19,20] (R = C₆H₅, E = COMe, as a 98:2 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 7.49–7.54 (m, 3H), 7.39–7.40 (m, 3H), 6.71 (d, *J* = 16.2 Hz, 1H), 2.38 (s, 3H).

(*E*)-4-(2-Furanyl)-3-buten-2-one:^[21,22] (R = 2-furanyl, E = COMe, as a 96:4 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 7.51 (s, 1H), 7.28 (d, *J* = 16.0 Hz, 1H), 6.67 (d, *J* = 3.3 Hz, 1H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.49 (dd, *J* = 3.3 Hz, 1.7 Hz, 1H), 2.33 (s, 3H).

(*E*)-3-Undecen-2-one:^[17] (R = CH₃(CH₂)₆, E = COMe, as a 53:47 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 6.80 (dt, *J* = 16.0, 7.0 Hz,

1H), 6.07 (d, 1H, J = 16.0 Hz), 2.24 (s, 3H), 2.20–2.27 (m, 2H), 1.44–1.48 (m, 2H), 1.27–1.30 (bm, 8H), 0.89 (*t*, J = 7.0 Hz, 3H); (*Z*) -3-Undecen-2-one:^[17] (R = CH₃(CH₂)₆, E = COMe, as a 53:47 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 6.65 (dd, J = 16.0, 6.5 Hz, 1H), 6.10 (d, J = 16.0 Hz, 1H), 2.27 (s, 3H), 1.62–1.72 (m, 2H), 1.47–1.49 (m, 24H), 1.27 (bm, 8H), 0.86–0.89 (m, 3H).

(*E*)-3-(4-Nitrophenyl)-2-propenentrile:^[19,23] (R = 4-NO₂C₆H₄, E = CN, as a 57:43 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 8.28 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 16.6 Hz, 1H), 6.05 (d, *J* = 16.6 Hz, 1H); (*Z*)-3-(4-Nitrophenyl)-2-propenentrile:^[19,23] (*R* = 4-NO₂C₆H₄, E = CN, as a 57:43 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 8.31 (d, *J* = 8.7 Hz, 2H), 7.96 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 12.1 Hz, 1H), 5.71 (d, *J* = 12.1 Hz, 1H).

(*E*)-3-(4-Methoxyphenyl)-2-propenentrile:^[19] (R = 4-MeOC₆H₄, E = CN, as a 72:28 mixture of *E*:Z isomers) (500 MHz, CDCl₃) δ 7.39 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 16.6 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.71 (d, *J* = 16.6 Hz, 1H), 3.84 (s, 3H); (*Z*)-3-(4-Methoxyphenyl)-2-propenentrile:^[19] (R = 4-MeOC₆H₄, E = CN, as a 72:28 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 7.79 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 12.1 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 5.29 (d, *J* = 12.1 Hz, 1H), 3.85 (s, 3H).

(*E*)-3-Phenyl-2-propenentrile:^[19,23] (R = C₆H₅, E = CN, as a 79:21 mixture of E:Z isomers) (500 MHz, CDCl.) δ 7.37–7.45 (m, 6H), 5.87 (d, *J* = 16.6 Hz, 1H); (*Z*)-3-Phenyl-2-propenentrile:^[19,23] (R = C₆H₅, E = CN, as a 79:21 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 7.38–7.45 (m, 5H) 7.12 (d, *J* = 12.1 Hz, 1H), 5.44 (d, *J* = 12.1 Hz, 1H).

(*E*)-3-(2-Furanyl)-2-propenentrile:^[16,23] (*R* = 2-furanyl, E = CN, as a 49:51 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 7.49 (s, 1H), 7.11 (d, *J* = 16.2 Hz, 1H), 6.62 (d, *J* = 3.3 Hz, 1H), 6.50 (dd, *J* = 3.3, 1.7 Hz, 1H), 5.76 (d, *J* = 16.2 Hz, 1H); (*Z*)-3-(2-Furanyl)-2-propenentrile:^[16,23] (*R* = 2-furanyl, E = CN, as a 49:51 mixture of *E*:*Z* isomers) (500 MHz, CDCl₃) δ 7.57 (s, 1H, 7.03 (d, *J* = 3.3 Hz, 1H), 6.95 (d, *J* = 12.5 Hz, 1H), 6.53 (dd, *J* = 3.3, 1.7 Hz, 1H), 5. 23 (d, *J* = 12.5 Hz, 1H).

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