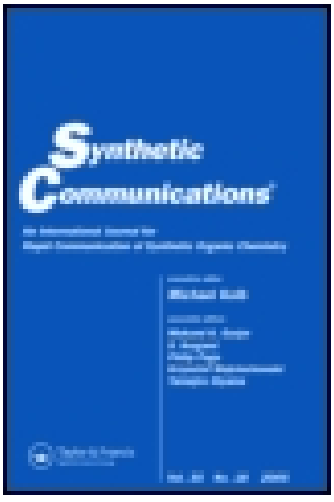

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

One-Pot Wittig Reactions in Aqueous Media: A Rapid and Environmentally Benign Synthesis of α,β-Unsaturated Carboxylic Esters and Nitriles

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Published online: 16 Feb 2007.

To cite this article: Jinlong Wu & Congyong Yue (2006) One-Pot Wittig Reactions in Aqueous Media: A Rapid and Environmentally Benign Synthesis of α,β-Unsaturated Carboxylic Esters and Nitriles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:20, 2939-2947, DOI: 10.1080/00397910600773684

To link to this article: http://dx.doi.org/10.1080/00397910600773684

Synthetic Communications®, 36: 2939–2947, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910600773684

One-Pot Wittig Reactions in Aqueous Media: A Rapid and Environmentally Benign Synthesis of α,β-Unsaturated Carboxylic Esters and Nitriles

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Abstract: One-pot Wittig reactions of ethyl bromoacetate and bromoacetonitrile with aldehydes in the presence of PPh_3 and LiOH in water were investigated. Most of the olefination reactions completed within 5–120 min in refluxing water containing 1.2 M LiCl to afford the olefin products in 71–97% yields with 100:0–55:45 ratios of *E:Z* isomers.

Keywords: Aldehydes, aqueous reaction, one-pot reaction, Wittig reaction

In recent years, organic reactions carried out in water have become increasingly popular for developing environmentally benign chemical processes. Some reactions involving organometallic species have been successfully transferred to aqueous media.[1] The Wittig reaction is one of the most versatile synthetic methods for preparation of olefins from carbonyl compounds. It classically requires use of a hydride or organometallic base and is carried out in anhydrous aprotic solvents under an inert atmosphere.[2] A number of variations on the reaction conditions have been reported for the Wittig reaction. These include (a) use of silica gel;[3] (b) under high temperatures[4] or pressures;[5] (c) use of additives;[6] (d) promoted by microwave,[7] light,[8] or sonication;[9] (e) use of ionic liquids;[10] and (f) under solvent-free

Received in R.O.C. February 16, 2006
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conditions.[11] Recently, it was reported that water is a suitable solvent for the Wittig reactions of stabilized and semistabilized phosphorus ylides with aldehydes. The reaction in water is faster than in organic solvents with higher yields and in similar *E:Z* selectivities of the olefin products.[12]

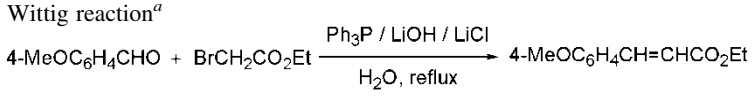
Green chemical approaches hold significant potential for establishment of a sustainable society. They cover the areas such as reduction of waste and by-products, use of safer and environmentally benign solvents, and reduction of energy costs.[13] A one-pot protocol is an efficient and economic chemical transformation coupling three or more components in a single operation. It can avoid long operational times and use of large amount of solvents or expensive purification techniques.[14]

The first one-pot Wittig reaction was reported as early as 1968,[15] but since then only limited reports on this reaction were published.[16] The one-pot reactions were carried out under either conventional conditions in organic solvents,[16a–c] microwave irradiation conditions,[16d] mechanically induced conditions,[16e] or in the presence of catalysts.[16f,g] Here we report aqueous one-pot Wittig reactions of aldehydes with ethyl bromoacetate and bromoacetonitrile, respectively, in the presence of PPh_3 for synthesis of α,β-unsaturated carboxylic esters and nitriles.

To examine the reactivity of PPh_3 with the halides in water, we first investigated the reactions of ethyl bromoacetate (**2a**) and bromoacetonitrile (**2b**) with PPh_3 in refluxing water. After the reaction of a slight excess of **2a** or **2b** with PPh_3 in refluxing water for 10 min in the presence of 1.2 M LiCl, no PPh_3 was detected in the organic extraction of the aqueous reaction mixture. The result indicated that formation of the phosphonium salt completed within only 10 min in refluxing water even for bromoacetonitrile (**2b**), which needed 336 h in refluxing benzene.[17] There are two reasons to account for this result: (a) the salt formation converts the hydrophobic substrates to the hydrophilic product and (b) the hydrophobic effect,[18] which was enhanced by addition of LiCl, in water favors aggregation of the reactants and facilitates the reaction. The unexpected rapid formation of phosphonium salts in refluxing water encouraged us to investigate the aqueous one-pot Wittig reaction starting from aldehydes, PPh_3, and the halides. We considered that deprotonation of the phosphonium salts should occur readily in aqueous media by using an inorganic base. According to our reported results of aqueous Wittig reactions of the stabilized ylide with aldehydes,[12a] the success of the one-pot protocol depends on the competitive pathways of the Wittig olefination and the decomposition of the phosphonium salt or ylide in water.

We investigated the effect of reagent ratios on the one-pot Wittig reactions of ethyl bromoacetate (**2a**) with 4-methoxybenzaldehyde (**1b**), which is a less reactive aldehyde, in refluxing water in the presece of 1.2 M LiCl (Table 1). When the ratio of **1b**–**2a**–PPh_3–LiOH was 1.0:1.2:1.2:1.5, the aldehyde **1b** did not disappear after 6 h and the isolated yield of **3b** is only 40% (Table 1, entry 1). When the ratio was increased to 1.0:1.5:1.5:1.8, the aldehyde **1b** disappeared after 70 min and the isolated yield of the product reached 90% (Table 1, entry 2). With higher ratios of **2a** and PPh_3 to the aldehyde **1b**

Table 1. Effect of ratios of ethyl bromoacetate **2a**, PPh_3, and LiOH to aldehyde **1b** on the Wittig reaction[a]



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

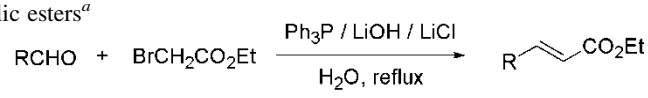
Entry	**1b**–**2a**–Ph_3P–LiOH	t (min)	Yield (%);[b] $E:Z$[c]
1	1.0:1.2:1.2:1.5	360	40; 93:7
2	1.0:1.5:1.5:1.8	70	90; 93:7
3	1.0:1.8:1.8:2.1	25	92; 91:9
4	1.0:1.8:1.8:2.1	35[d]	nd[e]

[a]Carried out in refluxing H_2O in the presence of 1.2 M LiCl.
[b]Isolated yield of both isomers.
[c]Determined by ^1H NMR.
[d]The mixture was heated for 10 min in the absence of **1b** and then for another 25 min with **1b**.

(Table 1, entry 3), the reaction completed within 25 min to afford the olefin product in 92% isolated yield. However, no olefin product was detected when the mixture of **2a**, PPh_3, and LiOH was heated for 10 min under refluxing conditions in the absence of **1b** followed by refluxing for another 25 min together with **1b**. We only recovered **1b** from this reaction mixture (Table 1, entry 4). The result implied that competition existed between the Wittig reaction of the in situ–generated phosphorus ylide with aldehyde and the decomposition of the ylide or its phosphonium precursor. It is clear that slightly excessive amounts of the reagents to the aldehyde was beneficial for high yields of the aqueous one-pot Wittig reactions. In addition, the isomeric ratios of the olefin product are almost uninfluenced by changing the reagent ratios (Table 1, entries 1–3).

With the optimized reaction conditions in hand, we investigated the aqueous one-pot Wittig reactions for synthesis of α,β-unsaturated carboxylic esters from ethyl bromoacetate (**2a**) with a collection of representative aldehydes **1a**–**h**. It should be emphasized that all substrates including ethyl bromoacetate and the aldehydes are not water soluble except for 2-hydroxybenzaldehyde (**1d**) and 4-hydroxybenzaldehyde (**1e**). All reactions were performed in refluxing H_2O in the presence of 1.2 M LiCl, and the results are summarized in Table 2. In general, the reactions of ethyl bromoacetate (**2a**) with aromatic aldehydes **1a**–**g** gave both good to excellent yields and high $E:Z$ isomer ratios (Table 2, entries 1–7). However, the $E:Z$ selectivity decreased to 74:26 for the reaction of crotonaldehyde (**1h**) (Table 2, entry 8). These results are comparable with those obtained in the reactions of the stabilized phosphorus ylide, carbethoxymethylenetriphenylphosphorane, with the corresponding aromatic aldehydes **1a**–**c**, **1e**, and **1g**.[12a]

Table 2. Aqueous one-pot Wittig reactions for synthesis of α,β-unsaturated carboxylic esters[a]



1 **2a** **3**

Entry	**1**: R	*t* (min)	Yield (%)[b]	*E*:*Z*[c]
1	**1a**: 4-$NO_2C_6H_4$	30	**3a**: 84	86:14
2	**1b**: 4-$MeOC_6H_4$	25	**3b**: 92	93:7
3	**1c**: Ph	15	**3c**: 87	98:2
4	**1d**: 2-HOC_6H_4	10	**3d**: 89	97:3
5	**1e**: 4-HOC_6H_4	120	**3e**: 72	94:6
6	**1f**: 4-ClC_6H_4	20	**3f**: 92	93:7
7	**1g**: 2-furanyl	15	**3g**: 97	99:1
8	**1h**: 2-butenyl	40	**3h**: 80	74:26

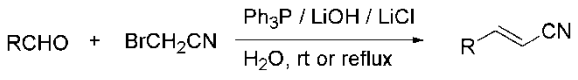
[a]Carried out in refluxing H_2O with a 1.0:1.8:1.8:2.1 ratio of **1**, **2a**, PPh_3, and LiOH in the presence of 1.2 M LiCl.
[b]Isolated yield of both isomers.
[c]Determined by ^1H NMR.

The reaction time was found to be not parallel to the intrinsic reactivity of the aldehydes in the order of 2-hydroxybenzaldehyde (**1d**) (10 min) < benzaldehyde (**1c**) ≈ 2-furaldehyde (**1g**) (15 min) < 4-chlorobenzaldehyde (**1f**) (20 min) < 4-anisaldehyde (**1b**) (25 min) < 4-nitrobenzaldehyde **1a** (30 min) < crotonaldehyde (**1h**) (40 min). For 4-hydroxybenzaldehyde (**1e**), because of its low reactivity, a much longer reaction time (120 min) was needed, and the product **3e** was obtained with a lower yield (72%) (Table 2, entry 5). It is interesting to find that the phenolic hydroxy group in **1d** and **1e** does not require protection (Table 2, entries 4 and 5). The results shown in Table 2 indicate that the reactions of **2a** with aldehydes gave high stereoselectivity (>93:7 of *E*:*Z* ratios) except for 4-nitrobenzaldehyde (**1a**) and crotonaldehyde (**1h**).

We extended the aqueous one-pot Wittig reactions to the synthesis of α,β-unsaturated nitriles. For the reactions of bromoacetonitrile (**2b**) with aldehydes, the reaction time was parallel to the reactivity of aldehydes except for 4-nitrobenzaldehyde (**1a**). This is somewhat different from the reactions of ethyl bromoacetate. For the aldehydes bearing an electron-donating group, because of the lower reactivity, a much longer reaction time (65–120 min) was needed (Table 3, entries 2, 4, and 5). For 4-hydroxybenzaldehyde, only 14% conversion was observed when it reacted with bromoacetonitrile (**2b**) (Table 3, entry 5).

Because of the less sterically demanding nitrile group, the ratios of the product isomers decreased significantly (Table 3, entries 1, 3, and 5–7). For example, **2b** reacted with **1a** and **1g** to afford the olefins **4a** and **4g** as the

Table 3. Aqueous one-pot Wittig reactions for synthesis of α,β-unsaturated nitriles[a]



1 2b 4

Entry	1:R	*t* (min)	Yield (%)[b]	*E*:*Z*[c]
1	**1a**: 4-$NO_2C_6H_4$	15	**4a**:97	55:45
2	**1b**: 4-$MeOC_6H_4$	65	**4b**:71	99:1
3	**1c**: Ph	15[d]	**4c**:95	62:38
4	**1d**: 2-HOC_6H_4	20	**4d**:92	100:0
5	**1e**: 4-HOC_6H_4	120	**4e**:14[e]	71:29
6	**1f**: 4-ClC_6H_4	5	**4f**:90	78:22
7	**1g**: 2-furanyl	5	**4g**:96	56:44

[a]Carried out in refluxing H_2O with a 1.0:1.8:1.8:2.1 ratio of **1**, **2b**, PPh_3, and LiOH in the presence of 1.2 M LiCl.
[b]Isolated yield of both isomers.
[c]Determined by ^1H NMR.
[d]Carried out in H_2O at room temperature.
[e]Conversion of the aldehyde to the olefin as determined by ^1H NMR of the crude reaction mixture.

55:45 and 56:44 mixtures of *E*:*Z* isomers, respectively (Table 3, entries 1 and 7). However, for the reaction of **2b** with **1b** and **1d**, higher *E*:*Z* selectivity (99:1 and 100:0 of *E*:*Z* ratios; Table 3, entries 2 and 4) was observed. It is interesting to emphasize that the heterogeneous one-pot Wittig reaction of **2b** with **1c** took place in H_2O even at room temperature (Table 3, entry 3) to give a high yield of the olefin **4c**.

In summary, we have established a general protocol for aqueous one-pot Wittig reactions for synthesis of α,β-unsaturated carboxylic esters and nitriles by mixing organic bromides, aldehydes, PPh_3, LiOH, and LiCl in refluxing water for 5–120 min. The reactions afford olefin products in 71–97% isolated yields with *E*:*Z* ratios ranging from 55:45 to 100:0. Our study suggests that H_2O may be used to directly substitute organic solvents in other types of organic reactions without structural modification on the substrates.

EXPERIMENTAL

Representative Procedure

A suspension of the organic bromide **2** (1.8 mmol), the aldehyde **1** (1.0 mmol), and PPh_3 (472.1 mg, 1.8 mmol) in H_2O (5 mL) containing LiOH (50.4 mg, 2.1 mmol) and $LiCl{\cdot}H_2O$ (362.5 mg, 6.0 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 over silica gel (10–30% EtOAc in hexane) to give the olefin products **3** and **4**, respectively. The results are listed in Tables 2 and 3.

Data

Ethyl (*E*)-3-(4-nitrophenyl)prop-2-enoate **3a**:[7a] (as an 86:14 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 8.25 (d, $J = 8.8$ Hz, 2H), 7.71 (d, $J = 16.0$ Hz, 1H), 7.68 (d, $J = 8.8$ Hz, 2H), 6.56 (d, $J = 16.0$ Hz, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 1.36 (t, $J = 7.1$ Hz, 3H). Ethyl (*Z*)-3-(4-nitrophenyl)prop-2-enoate **3a**:[7a] (as an 86:14 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 8.21 (d, $J = 8.8$ Hz, 2H), 7.68 (d, $J = 8.8$ Hz, 2H), 7.01 (d, $J = 12.4$ Hz, 1H), 6.13 (d, $J = 12.4$ Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 1.25 (t, $J = 7.2$ Hz, 3H).

Ethyl (*E*)-3-(4-methoxyphenyl)prop-2-enoate **3b**:[5a] (as a 93:7 mixture of *E:Z* isomers) (500 MHz, $CDCl_3$) δ 7.65 (d, $J = 16.0$ Hz, 1H), 7.48 (d, $J = 8.7$ Hz, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 6.31 (d, $J = 16.0$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.84 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H).

Ethyl (*E*)-3-phenylprop-2-enoate **3c**:[5a,7a] (as a 98:2 mixture of *E:Z* isomers) (500 MHz, $CDCl_3$) δ 7.68 (d, $J = 16.0$ Hz, 1H), 7.54–7.52 (m, 2H), 7.39–7.38 (m, 3H), 6.44 (d, $J = 16.0$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 1.34 (t, $J = 7.1$ Hz, 3H).

Ethyl (*E*)-3-(2-hydroxyphenyl)prop-2-enoate **3d**:[19] (as a 97:3 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 8.08 (d, $J = 16.0$ Hz, 1H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.32 (s, 1H), 7.25–7.21 (m, 1H), 6.92–6.88 (m, 2H), 6.67 (d, $J = 16.0$ Hz, 1H), 4.30 (q, $J = 7.2$ Hz, 2H), 1.36 (t, $J = 7.2$ Hz, 3H).

Ethyl (*E*)-3-(4-hydroxyphenyl)prop-2-enoate **3e**:[5a] (as a 94:6 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 7.64 (d, $J = 16.0$ Hz, 1H), 7.41 (d, $J = 8.5$ Hz, 2H), 7.14 (bs, 1H), 6.87 (d, $J = 8.5$ Hz, 2H), 6.29 (d, $J = 16.0$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 1.34 (t, $J = 7.1$ Hz, 3H).

Ethyl (*E*)-3-(4-chlorophenyl)prop-2-enoate **3f**:[7a] (as a 93:7 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 7.64 (d, $J = 16.0$ Hz, 1H), 7.47 (d, $J = 8.8$ Hz, 2H), 7.37 (d, $J = 8.8$ Hz, 2H), 6.42 (d, $J = 16.0$ Hz, 1H), 4.29 (q, $J = 7.2$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H). Ethyl (*Z*)-3-(4-chlorophenyl)prop-2-enoate **3f**:[7a] (as a 93:7 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 7.56 (d, $J = 8.8$ Hz, 2H), 7.34 (d, $J = 8.8$ Hz, 2H), 6.90 (d, $J = 12.8$ Hz, 1H), 5.98 (d, $J = 12.8$ Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 1.27 (t, $J = 7.2$ Hz, 3H).

Ethyl (*E*)-3-(2-furanyl)prop-2-enoate **3g**:[16f,20] (as a 99:1 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 7.47 (d, $J = 1.6$ Hz, 1H), 7.42 (d, $J = 15.6$ Hz, 1H), 6.60 (d, $J = 3.2$ Hz, 1H), 6.46 (dd, $J = 3.2$ Hz,

1.6 Hz, 1H), 6.31 (d, $J = 15.6$ Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 2H), 1.32 (t, $J = 7.2$ Hz, 3H).

Ethyl (2*E*, 4*E*)-hexa-2,4-dienoate **3h**:[21,22] (as a 74:26 mixture of 2*E*, 4*E*–2*Z*, 4*E* isomers) (400 MHz, $CDCl_3$) δ 7.25 (dd, $J = 15.4$ Hz, 9.8 Hz, 1H), 6.22–6.09 (m, 2H), 5.76 (d, $J = 15.6$ Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 1.84 (d, $J = 5.6$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H). Ethyl (2*Z*, 4*E*)-hexa-2,4-dienoate **3h**:[21] (as a 74:26 mixture of 2*E*, 4*E*–2*Z*, 4*E* isomers) (400 MHz, $CDCl_3$) δ 7.37 (dd, $J = 15.0$ Hz, 10.4 Hz, 1H), 6.53 (t, $J = 11.2$ Hz, 1H), 6.10–6.03 (m, 1H), 5.54 (d, $J = 11.6$ Hz, 1H), 4.17 (q, $J = 7.6$ Hz, 2H), 1.88 (d, $J = 7.2$ Hz, 3H), 1.29 (t, $J = 7.2$ Hz, 3H).

(*E*)-3-(4-Nitrophenyl)prop-2-enenitrile **4a**:[16b,23] (as a 55:45 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 8.28 (d, $J = 8.4$ Hz, 2H), 7.63 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 16.8$ Hz, 1H), 6.05 (d, $J = 16.8$ Hz, 1H); (*Z*)-3-(4-Nitrophenyl)prop-2-enenitrile **4a**:[16b,23] (as a 55:45 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 8.31 (d, $J = 8.4$ Hz, 2H), 7.96 (d, $J = 8.4$ Hz, 2H), 7.24 (d, $J = 12.4$ Hz, 1H), 5.71 (d, $J = 12.4$ Hz, 1H).

(*E*)-3-(4-Methoxyphenyl)prop-2-enenitrile **4b**:[23,24] (as a 99:1 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 7.39 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 16.4$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 2H), 5.71 (d, $J = 16.4$ Hz, 1H), 3.84 (s, 3H).

(*E*)-3-Phenylprop-2-enenitrile **4c**:[16b,23–25] (as a 62:38 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 7.44–7.37 (m, 6H), 5.87 (d, $J = 16.8$ Hz, 1H). (*Z*)-3-Phenyl-2-propenentrile **4c**:[16b,23–25] (as a 62:38 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 7.81–7.79 (m, 2H), 7.44–7.42 (m, 3H), 7.12 (d, $J = 12.0$ Hz, 1H), 5.44 (d, $J = 12.0$ Hz, 1H).

(*E*)-3-(2-Hydroxyphenyl)prop-2-enenitrile **4d**:[26] (as a pure (*E*) isomer) (400 MHz, $CDCl_3$) δ 7.60 (d, $J = 16.8$ Hz, 1H), 7.37 (dd, $J = 7.2$ Hz, 1.6 Hz, 1H), 7.29–7.25 (m, 1H), 6.97–6.83 (m, 1H), 6.82 (d, $J = 8.0$ Hz, 1H), 6.14 (d, $J = 16.8$ Hz, 1H), 5.81 (bs, 1H).

(*E*)-3-(4-Chlorophenyl)prop-2-enenitrile **4f**:[16b,24,25] (as a 78:22 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 5H), 5.86 (d, $J = 16.4$ Hz, 1H). (*Z*)-3-(4-Chlorophenyl)prop-2-enenitrile **4f**:[16b,24,25] (as a 78:22 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 7.75 (d, $J = 8.0$ Hz, 2H), 7.41 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 12.6$ Hz, 1H), 5.48 (d, $J = 12.6$ Hz, 1H).

(*E*)-3-(2-Furanyl)prop-2-enenitrile **4g**:[16b,20,24,25] (as a 56:44 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.11 (d, $J = 16.4$ Hz, 1H), 6.62 (d, $J = 3.2$ Hz, 1H), 6.50 (dd, $J = 3.2$, 1.6 Hz, 1H), 5.76 (d, $J = 16.4$ Hz, 1H). (*Z*)-3-(2-Furanyl)prop-2-enenitrile **4g**:[16b,20,24,25] (as a 56:44 mixture of *E:Z* isomers) (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.04 (d, $J = 3.2$ Hz, 1H), 6.95 (d, $J = 12.4$ Hz, 1H), 6.54 (dd, $J = 3.2$, 1.6 Hz, 1H), 5.23 (d, $J = 12.4$ Hz, 1H).

ACKNOWLEDGMENT

This work was supported in part by a research grand to J. Wu from Zhejiang Province Natural Science Fund (Y404302), China. The authors also thank Wei-Min Dai for his encouragement and discussion during the course of this study.

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