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Highly *Z*-selective synthesis of α,β-unsaturated nitriles using the Horner–Wadsworth–Emmons reaction

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ABSTRACT

A new HWE reagent, (*o*-*t*BuC_6H_4O)$_2$P(O)CH_2CN (**2e**), reacts with various types of aldehydes to give *Z*-α,β-unsaturated nitriles with 86% to >99% *Z*-selectivity. Especially, the reaction of **2e** with bulkier aldehydes, both aromatic and aliphatic, gave the *Z*-olefins with extremely high selectivity. The combination of *t*-BuOK and 18-crown-6 (1 equiv) is the base of choice for aromatic aldehydes and *t*-BuOK is generally the base of choice for aliphatic aldehydes.

The stereochemistry of carbon–carbon double bonds is important in exhibiting biological activity and other functionality. Furthermore, alkenes are useful building blocks in stereo-specific reactions for the construction of chiral centers, such as the Michael reaction, chiral epoxidation, and dihydroxylation. Therefore, the stereo-defined synthesis of carbon-carbon double bonds with high selectivity is critically important. Although it is rather easy to obtain the thermodynamically favored *E*-isomers, there are only a limited number of methods for preparing the *Z*-isomers. During the course of our study on the *Z*-selective Horner–Wadsworth–Emmons (HWE) reactions, we prepared the reagent, $(ArO)_2P(O)CH_2CO_2Et$ **1**, which gave *Z*-α,β-unsaturated esters highly selectively from the reaction with aldehydes.[1–3] We also prepared the reagent $(PhO)_2P(O)CH_2CN$ **2a**. Disappointingly, **2a** reacted with aldehydes to give α,β-unsaturated nitriles with moderate *Z*-selectivity (80–83% *Z* for 3 examples) (Scheme 1).[4] Later, Zhang et al. reported the synthesis of **2a** and the reaction with bulkier aldehydes such as pivalaldehyde to give *Z*-α,β-unsaturated nitriles highly selectively.[5] However, the reaction of **2a** with benzaldehyde and less sterically hindered aliphatic aldehydes gave low selectivity (64–75% *Z*). The selective preparation of monosubstituted *Z*-α,β-unsaturated nitriles have also been reported by using the Peterson-type reaction,[6] the Wittig-type reaction,[7] and other methods.[8] Although some methods gave monosubstituted *Z*-α,β-unsaturated nitriles highly selectively, some require strong base or multi-step synthesis and some suffer from substrate limitations. Since more general and practical methods are desirable, we decided to improve the *Z*-selective HWE reagent **2a**. In our study on the *Z*-selective HWE ester reagents **1**, we found the *ortho*-substituted phenyl reagents (*o*-MeC_6H_4 and *o*-*i*PrC_6H_4) to show higher *Z*-selectivity at low temperature. After that, Touchard et al. reported improvement of the selectivity at 0 °C using the *o*-*t*BuC_6H_4 reagent.[9,10] Here, we wish to report that our new reagent (*o*-*t*BuC_6H_4O)$_2$P(O)CH_2CN **2e** reacts with a variety of aldehydes to give *Z*-α,β-unsaturated nitriles in high selectivity.

Diphenylphosphonoacetonitrile (**2a**) was readily prepared from the reaction of acetonitrile and commercially available diphenyl phosphorochloridate using 2 equiv of LDA in THF (Scheme 2). **2a** was obtained in 54% yield. This method is similar to Zhang's method.[5a] The reagents **2b**–**2e** were prepared in a similar way in 43–56% yields using $(ArO)_2P(O)Cl$, which were prepared from $P(O)Cl_3$ and 2 equiv of ArOH and 2 equiv of Et_3N in toluene in 78–88% yields except for **3e** (38% yield). Since the yield of **3e** was low, the reagent **2e** was also prepared by the Arbusov reaction of phosphite **4**[9] and bromoacetonitrile at 150 °C without solvent for 6 h in 51% yield. The attempted synthesis of the *p*-ClC_6H_4 reagent from acetonitrile and (*p*-ClC_6H_4O)$_2$P(O)Cl was unsuccessful.

The results of the HWE reaction of **2a**–**2e** with benzaldehyde are summarized in Table 1. After **2a** was treated with *t*-BuOK in THF at −78 °C for 15 min, the reaction with benzaldehyde was performed at −78 °C. **5a** was obtained in 97% yield and the *Z*/*E* ratio was 80:20[11] (entry 1). The same reaction at 0 °C gave lower 71:29 ratio (entry 2). The effect of base on the *Z*/*E* ratio was next studied using Triton B, LDA, and NaH (entries 3–5). None of the bases tested gave higher *Z*-selectivity compared with *t*-BuOK. Disappointingly, the *o*-MeC_6H_4 reagent **2b** and the *o*-*i*PrC_6H_4 reagent

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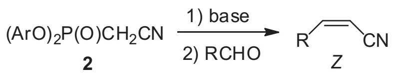
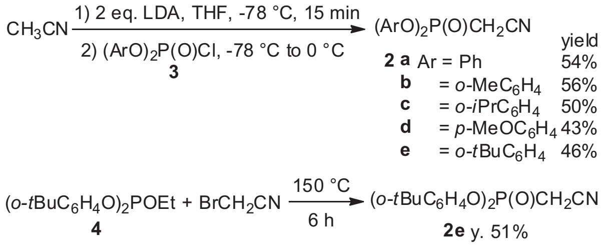
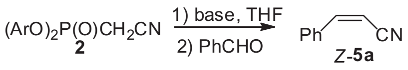


Scheme 1.



Scheme 2.

Table 1
The HWE reaction of **2** with benzaldehyde[a]



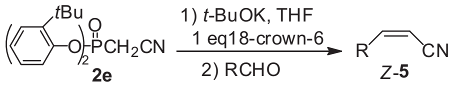
Entry	**2**	Base	Condition	Yield (%)	*Z*:*E*
1	**2a**	*t*-BuOK	−78 °C, 2 h	97	80:20
2	**2a**	*t*-BuOK	0 °C, 2 h	86	71:29
3	**2a**	Triton B	−78 °C, 2 h	87	70:30
4	**2a**	LDA	−78 °C, 2 h	84	49:51
5	**2a**	NaH[b]	−78 °C, 2 h	90	63:37
6	**2b**	*t*-BuOK	−78 °C, 2.5 h	56	65:35
7	**2c**	*t*-BuOK	−78 °C, 2.5 h	73	67:33
8	**2d**	*t*-BuOK	−78 °C, 3 h	91	64:36
9	**2e**	*t*-BuOK	−78 °C, 2 h	75	84:16
10	**2e**	*t*-BuOK[b,c]	−78 °C, 2 h	82	94:6
11	**2e**	*t*-BuOK[c]	−78 °C, 2 h	78	**95:5**
12	**2e**	NaH	−78 to 0 °C	88	64:36

[a] Compound **2** was treated with base at −78 °C except for entries 5 and 10.
[b] Compound **2** was treated with base at 0 °C.
[c] 1 equiv of 18-crown-6 was added.

2c gave lower 65:35 and 67:33 ratios, respectively (entries 6 and 7). In order to see the electronic effect, the reactions of the *p*-ClC_6H_4 reagent and the *p*-$MeOC_6H_4$ reagent **2d** were planned. Unfortunately, the *p*-ClC_6H_4 reagent was not obtained and **2d** gave low selectivity (entry 8). It seemed that the *o*-Me and *o*-*i*Pr substituents showed only an electron donating effect and their steric bulk was not enough. Therefore, we prepared the *o*-*t*BuC_6H_4 reagent **2e**. Using the same condition as entry 1, the reaction of **2e** gave a slightly higher 84:16 ratio (entry 9). In the presence of 1 equiv of 18-crown-6, the selectivity was improved to 95:5 (entry 11). The use of NaH as base resulted in low selectivity (entry 12). Thus, the highest *Z*-selectivity was obtained using the reagent **2e** and *t*-BuOK as base in the presence of 18-crown-6 in THF at −78 °C.

We examined the HWE reaction of **2e** with various aromatic aldehydes in THF (Table 2).[12] The reaction with *p*-methylbenzaldehyde at −78 °C was slow to give the olefin *Z*-**5b** in 56% yield with 95:5 ratio after 4 h (entry 2). When the reaction mixture was warmed from −78 to 0 °C over 1–2 h, the yield was increased to 79% with slightly reduced 94:6 selectivity (entry 3). The reaction with aldehydes having an electron withdrawing substituent, *p*-chlorobenzaldehyde and *p*-nitrobenzaldehyde, proceeded smoothly at −78 °C to give the *Z*-olefins **5d** and **5e** with 95:5 and 96:4 selectivity, respectively (entries 5 and 6). Bulky aromatic aldehydes were good substrates for the reaction with **2e**. Although the reaction with 1-naphthaldehyde and *o*-methoxybenzaldehyde proceeded slowly at −78 °C, *Z*-**5f** and *Z*-**5h** were obtained with 98:2 and >99:1 selectivity in good yields after warming up to 0 °C (entries 7 and 10). The reaction with *o*-methylbenzaldehyde proceeded smoothly at −78 °C to give the olefin **5g** with >99:1 *Z*-selectivity in 90% yield (entry 8). Even in the absence of 18-crown-6, *Z*-**5g** was obtained with 93:7 ratio (entry 9). These successful results obtained from bulky aromatic aldehydes are outstanding. We compared this nitrile HWE reaction with the ester HWE reaction. When our ester reagent **1a**[1] was treated with NaH in THF, the reaction with 1-naphthaldehyde gave *Z*-α,β-unsaturated ester **6** with 93:7 *Z*-selectivity after aqueous work-up (Scheme 3). However, the ratio was reduced to 79:21 after column chromatography (silica gel/hexane–AcOEt (10:1)). The ratio was further reduced to 56:44 by the treatment with silica gel in AcOEt for 30 min. On the other hand, the corresponding nitrile olefin was obtained with 98:2 *Z*-selectivity after column chromatography. No isomerization was detected in this case. Thus, a small nitrile group can be useful for the preparation of sterically hindered synthetic intermediates.

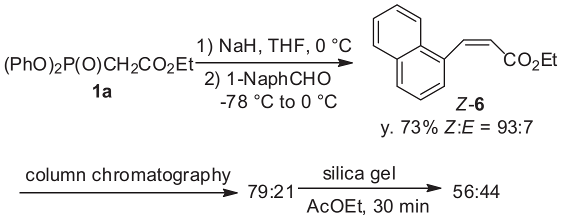
Table 2
The HWE reaction of **2e** with aromatic aldehyde



Entry	R	Condition	Yield	*Z*:*E*
1	Ph	−78 °C, 2 h	**5a** 78	**95:5**
2	*p*-MeC_6H_4	−78 °C, 4 h	**5b** 56	**95:5**
3	*p*-MeC_6H_4	−78 °C, 2 h to 0 °C[a]	**5b** 79	94:6
4	*p*-$MeOC_6H_4$	−78 to 0 °C[a]	**5c** 99	86:14
5	*p*-ClC_6H_4	−78 °C, 2 h	**5d** 84	**95:5**
6	*p*-$NO_2C_6H_4$	−78 °C, 2 h	**5e** 89	**96:4**
7	1-Naph	−78 °C, 2 h to 0 °C[a]	**5f** 79	**98:2**
8	*o*-MeC_6H_4	−78 °C, 2.5 h	**5g** 90	**>99:1**
9	*o*-MeC_6H_4	−78 °C, 5 h	**5g** 79	93:7[b]
10	*o*-$MeOC_6H_4$	−78 to 0 °C[a]	**5h** 92	**>99:1**

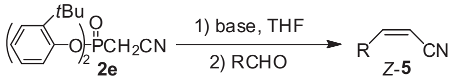
[a] The reaction temperature was warmed over 1–2 h.
[b] In the absence of 18-crown-6.

The HWE reactions of **2e** with various aliphatic aldehydes were performed and the results are summarized in Table 3. Since the reaction of **2e** with aliphatic aldehydes hardly proceeded at −78 °C, the reaction mixture was gradually warmed from −78 to 0 °C over 1–2 h after the addition of aldehydes. When **2e** was treated with *t*-BuOK, the reaction with *n*-octanal gave **5i** with 83:17 *Z*-selectivity in 82% yield (entry 1). In the presence of 18-crown-6, the selectivity was decreased (entry 2). By using NaH as base, the selectivity was increased and the ratio 89:11 was obtained (entry 3). This selectivity was further improved to 90:10 by using 3 equiv of NaH (entry 4).[14] For the reaction with sterically more congested aldehyde **7**, *t*-BuOK was the base of choice. When the reaction was performed at 0 °C using *t*-BuOK, 89:11 *Z*-selectivity was obtained in 85% yield (entry 6). The reaction with an aldehyde having a secondary alkyl group, cyclohexanecarbaldehyde, was similarly per-



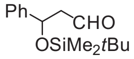
Scheme 3.

Table 3
The HWE reaction of **2e** with aliphatic aldehydes[a]



Entry	RCHO	Base	Condition	Yield	Z:E
1	*n*-Octanal	*t*-BuOK	−78 to 0 °C	**5i** 82	83:17
2	*n*-Octanal	*t*-BuOK[b]	−78 to 0 °C	**5i** 47	77:23
3	*n*-Octanal	NaH	−78 to 0 °C	**5i** 83	89:11
4	*n*-Octanal	NaH (3 equiv)	−78 to 0 °C	**5i** 95	90:10
5	**7**	NaH (3 equiv)	−78 to 0 °C	**5j** 80	76:24
6	**7**	*t*-BuOK	0 °C, 2 h	**5j** 85	89:11
7	*c*-C_6H_{11}CHO	NaH	−78 to 0 °C	**5k** 71	76:24
8	*c*-C_6H_{11}CHO	*t*-BuOK	−78 to 0 °C	**5k** 74	85:15
9	*c*-C_6H_{11}CHO	*t*-BuOK	0 °C, 2 h	**5k** 88	87:13
10	*c*-C_6H_{11}CHO	*t*-BuOK	25 °C, 2 h	**5k** 85	85:15
11	**8**	*t*-BuOK	0 °C, 2 h	**5l** 83	**97:3**
12	*t*-BuCHO	*t*-BuOK	−78 to 0 °C	**5m** 70	**98:2**
13	**9**	*t*-BuOK	−78 to 0 °C	**5n** 79	**>99:1**
14	**10**	*t*-BuOK	−78 to 0 °C	**5o** 84	**>99:1**

[a] The reaction temperature was warmed over 1–2 h except for entries 6, 9–11.
[b] 1 equiv of 18-crown-6 was added.



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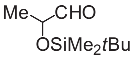

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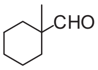

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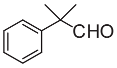

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formed by using *t*-BuOK and the reaction mixture was warmed to 0 °C to give 85:15 selectivity (entry 8). The highest selectivity was obtained from the reaction at 0 °C (87:13) (entries 9 and 10). The reaction with sterically more congested aldehyde **8** gave a much higher 97:3 selectivity (entry 11). The reactions with the aldehydes having tertiary alkyl group, pivalaldehyde, 1-methylcyclohexanecarbaldehyde **9**, and 2-methyl-2-phenylpropanal **10**, were performed by using *t*-BuOK at −78 to 0 °C. The *Z*-olefins **5m**–**5o** were obtained with 98:2, >99:1, and >99:1 selectivity in good yields, respectively (entries 12–14).

In summary, we have developed a new HWE nitrile reagent, (*o*-*t*Bu$C_6H_4O)_2P(O)CH_2CN$ (**2e**), which reacts with various types of aldehydes to give *Z*-α,β-unsaturated nitriles with 86 to >99% *Z*-selectivity. Especially, the reaction of **2e** with the bulkier aldehydes, both aromatic and aliphatic, gave the *Z*-olefines with extremely high selectivity. Since the nitrile group can be transformed to various useful functional groups such as the aldehyde, the carboxylic acid, and the amine, the present method will be of considerable utility in synthesis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.020.

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11. The *E*:*Z* ratios were determined by integration of the vinyl proton signals in 400 MHz ^{1}H NMR spectra of the crude reaction mixture. All the HWE products described in this Letter except for **5j** are known compounds. ^{1}H NMR spectra are identical to the reported values: *Z*-**5a**,[6a] *E*-**5a**,[13a] *Z*-**5b**,[8a] *E*-**5b**,[13a] *Z*-**5c**,[6a] *E*-**5c**,[13a] *Z*-**5d**,[6a] *E*-**5d**,[13a] *Z*-**5e**,[13b] *E*-**5e**,[13c] *Z*-**5f**,[7a] *E*-**5f**,[7a] *Z*-**5g**,[7a] *E*-**5g**,[13a] *Z*-**5h**,[6a] *E*-**5h**,[6a] *Z*-**5k**,[6a] *E*-**5k**,[6a] *Z*-**5l**,[13d] *E*-**5l**,[13d] *Z*-**5m**,[6a] *E*-**5m**,[6a] *Z*-**5n**,[8a] *E*-**5n**,[8a] *Z*-**5o**,[6a] *E*-**5o**,[6a] *Z*-**6**,[13e] *E*-**6**.[13f] The NMR spectrum of **5i** was not reported.[4] Both **5i** and **5j** were characterized by 400 MHz ^{1}H NMR spectra, mass spectroscopy, and HRMS.
12. *A typical procedure for the Z-selective HWE reaction (entry 8 in Table 2):* A solution of **2e** (0.30 mmol) and 18-crown-6 (0.105 g, 0.39 mmol) in THF (6 mL) was treated with *t*-BuOK (0.045 g, 0.39 mmol) at 0 °C. 15 min later, the mixture was cooled to −78 °C and *o*-methylbenzaldehyde (0.039 mL, 0.33 mmol) was added. The resulting mixture was stirred at −78 °C for 2.5 h. The reaction was quenched with aqueous NH_4Cl, and the mixture was extracted with AcOEt twice (7 and 4 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. After determining the *Z*/*E* ratio (>99:1) of the crude mixture by 400 MHz ^{1}H NMR, the olefin was isolated by flash chromatography (hexane:AcOEt = 20:1) as a colorless oil (0.039 g, 90% yield) (*Z*/*E* = >99:1).
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