Z-Selective Horner–Wadsworth–Emmons Reaction of α-Substituted Ethyl (Diarylphosphono)acetates with Aldehydes[1]

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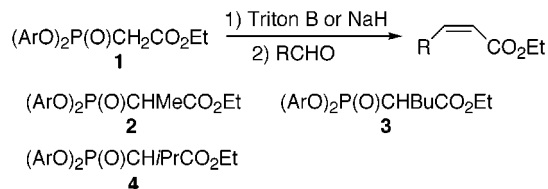
New Horner–Wadsworth–Emmons reagents, ethyl 2-(diarylphosphono)propionates (**2**), ethyl 2-(diarylphosphono)hexanoates (**3**), and ethyl 2-(diarylphosphono)-3-methylbutanoates (**4**) were prepared by alkylation of ethyl (diarylphosphono)acetates. The reaction of **2**–**4** with various types of aldehydes gave Z-α,β-dialkyl-α,β-unsaturated esters highly selectively. Remarkable temperature-dependent selectivity was observed in the reaction of $(PhO)_2P(O)CHBuCO_2Et$ with octyl aldehyde.

Stereodefined synthesis of carbon–carbon double bonds with high selectivity is critically important in organic synthesis. The Wittig reaction and related reactions have served as the most powerful method for the construction of double bonds. Especially the Horner–Wadsworth–Emmons (HWE) modification of the Wittig reaction is widely employed. Since the HWE reaction preferentially gives more stable E-α,β-unsaturated esters in general,[2] extensive effort has been devoted for the last few decades to the stereoselective construction of Z-α,β-unsaturated esters.[3–5] Recently we have reported the preparation of ethyl (diarylphosphono)acetates (**1**) and the reaction of **1** with various types of aldehydes in the presence of an inexpensive base, Triton B or NaH in THF.[6,7] This method provides simple, economical, and highly selective routes to a wide range of *cis*-α,β-unsaturated esters (disubstituted Z-olefins) in almost quantitative yields.

For the preparation of trisubstituted olefins, Kishi and others reported that HWE reaction of α-branched aldehydes (except α,β-unsaturated and aromatic aldehydes) with trimethyl or triethyl α-phosphonopropionate afforded primarily the Z-isomers.[8] Still and Gennari reported improved Z-selectivity by using methyl [bis-(trifluoroethyl)phosphono]propionate in the presence of KHMDS/18-crown-6 in THF.[4] However, the studies of Marshall and others showed that the Z-selectivity of this type of reagent having α-substituents larger than a methyl group is diminished.[9–11] Patois and Savignac

reported the use of five-membered cyclic phosphonamide reagents prepared in situ for the synthesis of Z-isomers.[5] It seems that the latter reagents have not been used extensively. To expand the scope and utility of the (diarylphosphono)acetate method, we prepared ethyl 2-(diarylphosphono)propionates (**2**), ethyl 2-(diarylphosphono)hexanoates (**3**), and ethyl 2-(diarylphosphono)-3-methylbutanoates (**4**) and examined their reactions with various aldehydes. In these HWE reactions we attained much higher selectivity in the preparation of trisubstituted Z-olefins. We now report our most recent results.

Results

Horner–Wadsworth–Emmons Reaction of Ethyl 2-(Diarylphosphono)propionates. Ethyl 2-(diarylphosphono)propionates (**2**) were prepared by alkylation of the corresponding ethyl (diarylphosphono)acetates (**1**) with methyl iodide after treatment with NaH in dimethyl sulfoxide (DMSO). The products **2** were obtained in moderate yields (60–66%) along with the dialkylation products and the starting acetates **1**.
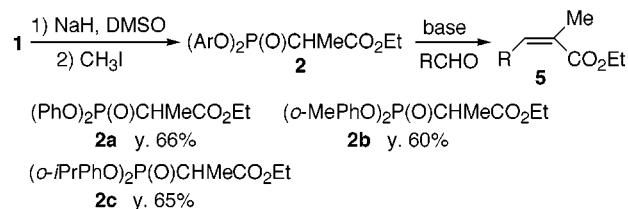
(1) This paper is dedicated with all best wishes to Professor Kenji Koga on the occasion of his 60th birthday.

(2) Reviews of Horner–Wadsworth–Emmons reaction: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99.

(3) Breuer, E.; Bannet, D. M. *Tetrahedron Lett.* **1977**, 1141–1144.

(4) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

(5) Patois, C.; Savignac, P. *Tetrahedron Lett.* **1991**, *32*, 1317–1320.

(6) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939. Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105–4108.

(7) Kokin, K.; Motoyoshiya, J.; Hayashi, S.; Aoyama, H. *Synth. Commun.* **1997**, *27*, 2387–2392.

(8) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873–3888. Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259–260. Etemad-Moghadam, G.; Seyden-Penne, J. *Tetrahedron* **1984**, *40*, 5153–5166. Kinstle, T. H.; Mandanas, B. Y. *J. Chem. Soc., Chem. Commun.* **1968**, 1699–1700.

(9) Marshall, J. A.; DeHoff, B. S.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 1735–1741. Hammond, G. B.; Cox, M. B.; Wiemer, D. F. *J. Org. Chem.* **1990**, *55*, 128–132.

(10) Medina, J. C.; Guajardo, R.; Kyler, K. S. *J. Am. Chem. Soc.* **1989**, *111*, 2310–2311.

(11) Highly Z-selective olefin formation was also reported in some cases: Rübsam, F.; Evers, A. M.; Michel, C.; Giannis, A. *Tetrahedron* **1997**, *53*, 1707–1714. Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 1411–1414. Xiao, X.; Prestwich, G. D. *Tetrahedron Lett.* **1991**, *32*, 6843–6846.

**Table 1.   HWE Reaction of α-Methyl Reagents 2 with Benzaldehyde and *trans*-2-Hexenal in THF Solvent**

entry	reagent	R (RCHO)	base[a]	conditions	yield (%)	5 (*Z:E*)
1	**2a**	Ph	Triton B	−78 °C, 1 h	100	91:9
2	**2a**	Ph	Triton B	−95 °C, 30 min; −78 °C, 1 h	100	94:6
3	**2a**	Ph	*t*-BuOK	−78 °C, 1 h	98	95:5
4	**2a**	Ph	*t*-BuOK	−95 °C, 30 min; −78 °C, 1 h	98	95:5
5	**2b**	Ph	Triton B	−78 °C, 1.5 h	100	92:8
6	**2b**	Ph	Triton B	−95 °C, 30 min; −78 °C, 1 h	98	96:4
7	**2b**	Ph	*t*-BuOK	−78 °C, 1 h	97	95:5
8	**2b**	Ph	*t*-BuOK	−95 °C, 30 min; −78 °C, 1 h	95	96:4
9	**2c**	Ph	Triton B	−78 °C, 2 h	97	91:9
10	**2c**	Ph	Triton B	−95 °C, 30 min; −78 °C, 1 h	99	97:3
11	**2c**	Ph	*t*-BuOK	−78 °C, 1 h	100	96:4
12	**2c**	Ph	*t*-BuOK	−95 °C, 30 min; −78 °C, 1 h	100	97:3
13	**2a**	PrCH=CH[t]	Triton B	−78 °C → −35 °C[b]	86	72:28
14	**2a**	PrCH=CH[t]	*t*-BuOK	0 °C, 1 h	98	78:22
15	**2b**	PrCH=CH[t]	Triton B	−78 °C → −20 °C[b]	97	89:11
16	**2b**	PrCH=CH[t]	*t*-BuOK	−78 °C → −25 °C[b]	97	82:18
17	**2c**	PrCH=CH[t]	Triton B	−78 °C → 0 °C[b]	95	89:11
18	**2c**	PrCH=CH[t]	NaH	−78 °C → 0 °C[b]	99	80:20
19	**2c**	PrCH=CH[t]	NaH	0 °C, 2 h	91	48:52
20	**2c**	PrCH=CH[t]	KHMDS[c]	−78 °C → −20 °C[b]	57(30)	91:9

[a] **2** was treated with Triton B at −78 °C for 10 min, *t*-BuOK at 0 °C for 10 min, and NaH at 0 °C for 15 min, respectively. [b] The reaction mixture was warmed over 1−2 h. [c] 18-crown-6 (5 equiv) was added.

HWE reaction was first carried out with benzaldehyde and *trans*-hexenal. The results are summarized in Table 1. When ethyl 2-(diphenylphosphono)propionate (**2a**) was treated with benzyltrimethylammonium hydroxide (40% MeOH solution) (Triton B) at −78 °C for 15 min followed by benzaldehyde in tetrahydrofuran (THF) at −78 °C, 91% *Z*-selectivity was obtained (entry 1). At a lower temperature (−95 °C), the selectivity was improved to 94:6 (entry 2). The use of *t*-BuOK as the base gave a better result (95:5) both at −78 °C and at −95 °C (entries 3, 4). The *o*-tolyl reagent **2b** and *o*-isopropylphenyl reagent **2c** gave slightly enhanced selectivities, 96:4 and 97:3, respectively (entries 5−12).

The reaction of **2a** with *trans*-2-hexenal was carried out in THF by using Triton B as the base (entry 13). Since the reaction did not proceed at −78 °C, the mixture was warmed to −35 °C over 1−2 h. The obtained *Z*-selectivity was disappointingly low (72:28). The use of either di-*o*-tolyl reagent **2b** or di-*o*-isopropylphenyl reagent **2c** improved the *Z*-selectivity to 89% (entries 15, 17). Changing the base to *t*-BuOK or NaH did not improve the selectivity, but the selectivity was raised to 91% (entry 20) by use of KHMDS and 18-crown-6 (5 equiv).

Next, the HWE reactions of **2** with saturated aliphatic aldehydes were performed (Table 2). After the reagent **2** was treated with NaH in THF at 0 °C for 15 min, the mixture was cooled to −78 °C and aldehyde was added. This mixture was warmed to 0 °C over 1−2 h. In the reaction of **2a** with *n*-octyl aldehyde, 83% selectivity was obtained (entry 1). The use of **2b** and **2c** improved the selectivity to 94% and 97%, respectively (entries 2, 3). Even when the reaction was performed at 0 °C, **2c** showed 91% selectivity (entry 4). The reaction of 2-ethylhexanal was more selective, giving 98%, 99%, and 99% selectivity with **2a**, **2b**, and **2c**, respectively (entries 5−7). A similar selectivity was obtained with cyclohexanecarboxaldehyde (98−99%, entries 8, 9). The reactions with aldehydes **6**−**8**, containing an oxygen functionality at the α- or β-position, were also highly *Z*-selective (95−98%) (entries 11, 14, 16).
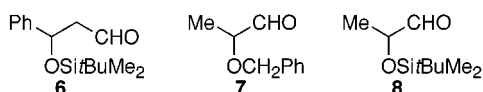
Table 2.   HWE Reaction of 2 with Aliphatic Aldehydes in THF Solvent[a]

entry	reagent	R	conditions[b]	yield (%)	5 (*Z:E*)
1	**2a**	*n*-C₇H₁₅	−78 °C → 0 °C	95	83:17
2	**2b**	*n*-C₇H₁₅	−78 °C → 0 °C	96	94:6
3	**2c**	*n*-C₇H₁₅	−78 °C → 0 °C	100	97:3
4	**2c**	*n*-C₇H₁₅	0 °C, 1 h	89 (11)[c]	91:9
5	**2a**	BuCHEt	−78 °C → 0 °C	97	98:2
6	**2b**	BuCHEt	−78 °C → 0 °C	100	99:1
7	**2c**	BuCHEt	−78 °C → 0 °C	95	99:1
8	**2a**	cyclohexyl	−78 °C → 0 °C	93	98:2
9	**2b**	cyclohexyl	−78 °C → 0 °C	99	99:1
10	**2b**	**6**	−78 °C → 0 °C	90[d]	96:4
11	**2c**	**6**	−78 °C → 0 °C	91[d]	98:2
12	**2a**	**7**	−78 °C → 0 °C	83[d]	92:8
13	**2b**	**7**	−78 °C → 0 °C	85[d]	95:5
14	**2c**	**7**	−78 °C → 0 °C	79[d]	98:2
15	**2b**	**8**	−78 °C → 0 °C	78[d]	92:8
16	**2c**	**8**	−78 °C → 0 °C	66[d]	95:5

[a] The reagent was treated with NaH as the base at 0 °C for 15 min. [b] The reaction mixture was warmed over 1−2 h except entry 4. [c] The number in parentheses is the recovered yield of **2** (%). [d] The aldehyde was prepared by DIBAL reduction of the corresponding ethyl ester. The yield was calculated from the starting ester.

Thus the HWE reaction of ethyl 2-(diarylphosphono)-propionates (**2**) with many types of aldehydes gave trisubstituted olefins **5** with high *Z*-selectivity (95−99%) in quantitative yields by simple operations except for the case of *trans*-2-hexenal. The *Z*-selectivity increased with increasing size of the ortho substituent on the aryl group (Ph → *o*-MePh → *o*-*i*-PrPh). The best results were obtained with *o*-isopropylphenyl reagent **2c**. Triton B or *t*-BuOK is the best base for both aromatic and α,β-unsaturated aldehydes, and NaH is a good one for saturated aliphatic aldehydes.

The *Z:E* ratios of all the HWE products **5**, **9**, and **10** were determined by integrating the vinyl proton signals in the 500 MHz ¹H NMR spectra. In general, the vinyl proton of a *Z*-isomer exhibits signals that are upfield compared to those of the corresponding *E*-isomer. The *E*-isomers were also separately prepared. The signal assignments were confirmed by nuclear Overhauser effect (NOE) experiments.

Horner−Wadsworth−Emmons Reaction of Ethyl 2-(Diarylphosphono)hexanoates. Ethyl 2-(diaryl-

Table 3. HWE Reaction of α-Butyl Reagents 3 with Aldehydes

entry	reagent	R (RCHO)	base	solvent	conditions	yield (%)[a]	9 (Z:E)
1	**3a**	Ph	Triton B	THF	−78 °C, 2 h	97	67:33
2	**3a**	Ph	*t*-BuOK	THF	−78 °C, 5 h	87 (11)	73:27
3	**3a**	Ph	NaH	THF	−78 °C, 5 h	95	97:3
4	**3a**	Ph	NaH	THF	0 °C, 2 h	100	93:7
5	**3b**	Ph	Triton B	THF	−78 °C, 2 h	100	61:39
6	**3b**	Ph	NaH	THF	−78 °C, 5 h	71 (29)	85:15
7	**3a**	*n*-C$_7$H$_{15}$	NaH	THF	−78 °C → 10 °C	99	65:35
8	**3a**	*n*-C$_7$H$_{15}$	NaH	THF	0 °C, 2 h	94 (6)	83:17
9	**3a**	*n*-C$_7$H$_{15}$	NaH	THF	−20 °C, 3 h	88 (12)	82:18
10	**3a**	*n*-C$_7$H$_{15}$	NaH	THF	−40 °C, 4 h	58 (42)	69:31
11	**3a**	*n*-C$_7$H$_{15}$	*t*-BuOK	THF	0 °C, 1 h	88 (12)	49:51
12	**3a**	*n*-C$_7$H$_{15}$	*t*-BuOK	THF	−78 °C → 0 °C	94 (6)	26:74
13	**3a**	*n*-C$_7$H$_{15}$	*t*-BuOK	THF	−78 °C, 2 h → −40 °C	69 (31)	12:88
14	**3a**	*n*-C$_7$H$_{15}$	EtONa	THF	−78 °C → 10 °C	100	40:60
15	**3a**	*n*-C$_7$H$_{15}$	LDA	THF	−78 °C → 10 °C	80 (20)	54:46
16	**3b**	*n*-C$_7$H$_{15}$	NaH	THF	−78 °C → 10 °C	99	64:36
17	**3b**	*n*-C$_7$H$_{15}$	NaH	THF	0 °C, 4 h	90 (10)	84:16
18	**3c**	*n*-C$_7$H$_{15}$	NaH	THF	0 °C, 2 h; rt, 15 h	32 (44)	94:6
19	**3c**	*n*-C$_7$H$_{15}$	BuLi−LiBr	toluene	0 °C, 7 h; rt, 1 h	78 (22)	94:6
20	**3a**	BuCHEt	NaH	THF	−78 °C → 10 °C	80 (19)	95:5
21	**3a**	BuCHEt	NaH	THF	0 °C, 1 h; rt, 4 h	85	95:5
22	**3b**	BuCHEt	NaH	THF	0 °C, 2 h; rt, 2 h	51 (38)	89:11
23	**3a**	cyclohexyl	NaH	THF	−78 °C → 10 °C	88 (12)	97:3
24	**3a**	cyclohexyl	NaH	THF	0 °C, 4 h	91 (9)	96:4
25	**3a**	**7**	NaH	THF	−78 °C → 10 °C	66[b]	82:18
26	**3a**	**7**	NaH	THF	0 °C, 3 h	86	86:14
27	**3c**	**7**	BuLi−LiBr	toluene	0 °C, 5 h, rt, 1h	68[b]	98:2
28	**3a**	PrCH=CH*t*	NaH	THF	−78 °C → 10 °C	85	74:26
29	**3a**	PrCH=CH*t*	NaH	THF	0 °C, 3 h	98	77:23
30	**3a**	PrCH=CH*t*	NaH	THF	−20 °C, 2.5 h	100	77:23
31	**3c**	PrCH=CH*t*	NaH	THF	0 °C, 2 h; rt, 3 h	59 (33)	91:9
32	**3c**	PrCH=CH*t*	BuLi−LiBr	toluene	−20 °C, 2 h; 0 °C, 2 h	78 (22)	86:14
33	**3c**	PrCH=CH*t*	BuLi−LiBr	toluene	0 °C, 5 h; rt, 1 h	92 (8)	88:12

[a] The number in parentheses is the recovered yield of **3** (%). [b] The aldehyde was prepared by DIBAL reduction of the corresponding ethyl ester. The yield was calculated from the starting ester.

phosphono)hexanoates (**3**) were prepared by alkylation of the corresponding ethyl (diarylphosphono)acetates (**1**) with butyl iodide. The products **3** were obtained in good yields (77−85%) along with the dialkylation products and the starting acetates **1**.
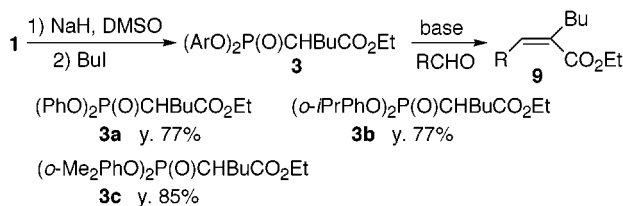
The results of the HWE reactions of **3** are summarized in Table 3, which shows a quite different tendency for favorable reaction conditions. Using the established reaction conditions discussed above, i.e., Triton B or *t*-BuOK in THF at −78 °C, the reaction of **3a** with benzaldehyde was performed. To our disappointment, the selectivity was just moderate (67% and 73%, entries 1, 2). Using NaH as the base improved the selectivity to 97% (entry 3). Even at 0 °C, 93% selectivity was obtained (entry 4). The *o*-isopropylphenyl reagent **3b** showed lesser selectivity than the reagent **3a** (entries 5, 6). This is also quite different from the results of the α-unsubstituted and α-methyl phosphonate reagents (**1** and **2**).

The standard condition for saturated aliphatic aldehydes (NaH, −78 °C to 10 °C) was applied to the reaction of **3a** with *n*-octyl aldehyde. Only 2:1 selectivity was obtained (entry 7). To our surprise, the *Z*-selectivity increased at higher temperatures. When the reaction

was performed at 0, −20, and −40 °C, 83%, 82%, and 69% selectivity was obtained, respectively (entries 8−10). In other words, the reaction gave more *E*-isomer at lower temperatures. This tendency is especially remarkable when *t*-BuOK is used as the base (entries 11−13). At lower temperatures, the main product was the *E*-isomer (*E*:*Z* = 88:12).[12,13] This 88% *E*-selectivity was the highest one in our hands among the attempts to prepare this *E*-isomer! When NaH was used as the base, the reagent **3b** showed a selectivity similar to that of the reagent **3a** (entries 16, 17) but *o*-dimethylphenyl reagent **3c** was found to be highly *Z*-selective (94%, entry 18). The yield was improved by the use of BuLi and LiBr (3 equiv) in toluene without reducing the selectivity (entry 19).

The reactions with 2-ethylhexanal and cyclohexane-carboxaldehyde were highly *Z*-selective when the standard conditions were used (95−97%, entries 20−24). The reaction with 2-benzyloxypropanal (**7**) needs the reagent **3c** in order to get high *Z*-selectivity (98%, entry 27). *trans*-2-Hexenal reacted with the anion of **3c** to give *Z*-product in 91% selectivity (entry 31).

Horner−Wadsworth−Emmons Reaction of Ethyl 2-(Diphenylphosphono)-3-methylbutanoate. Ethyl 2-(diphenylphosphono)-3-methylbutanoate (**4a**) was prepared by alkylation of ethyl (diphenylphosphono)acetate (**1a**) with isopropyl iodide after treatment with *t*-BuOK

(12) In an asymmetric HWE reaction of 8-phenylmenthyl (di-*o*-tolylphosphono)acetate, (*o*-tolyl-O)$_2$P(O)CH$_2$CO$_2$(8-Ph-menthyl), highly *E*-selective olefin formation was reported: Kreuder, R.; Rein, T.; Reiser, O. *Tetrahedron Lett.* **1997**, *38*, 9035−9038.
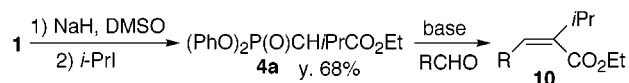
(13) In ether solvent, the reaction of (PhO)$_2$P(O)CH$_2$CO$_2$Et with PhCHO gave mainly the *E*-isomer.[6]

Table 4. HWE Reaction of α-Isopropyl Reagent 4a with Aldehydes in THF Solvent

entry	R (RCHO)	base	conditions	yield (%)	10 (Z:E)
1	Ph	Triton B	−78 °C → 0 °C	66 (10)	97:3
2	Ph	t-BuOK	0 °C, 1 h	89 (11)	95:5
3	Ph	NaH	0 °C, 2 h	96	99:1
4	PrCH=CH^t	Triton B	−78 °C → 10 °C	12	77:23
5	PrCH=CH^t	t-BuOK	0 °C, 1 h; rt, 1 h	76	80:20
6	PrCH=CH^t	NaH	0 °C, 1 h; rt, 1 h	90 (10)	92:8
7	PrCH=CH^t	NaH	−78 °C → 0 °C, 1 h	91 (8)	94:6
8	n-C$_7$H$_{15}$	NaH	−78 °C → rt, 15 h	61	93:7
9	n-C$_7$H$_{15}$	NaH	0 °C, 3 h; rt, 3 h	57 (36)	95:5
10	n-C$_7$H$_{15}$	NaH−LiBr	0 °C, 4 h	75 (11)	91:9
11	cyclohexyl	NaH	0 °C → rt, 15 h	35 (3)	98:2
12	cyclohexyl	NaH	0 °C, 4 h; rt, 1 h	21 (61)	99:1
13	cyclohexyl	NaH−LiBr	0 °C, 4 h; rt, 1 h	42 (29)	99:1
14^a	cyclohexyl	NaH−LiBr	0 °C, 6 h; rt, 1 h	58	99:1
15	7	NaH	−78 °C → rt, 15 h	69	95:5
16	7	NaH	0 °C, 4 h; rt, 1 h	65	98:2

^{a} 1.5 equiv of **4a** was used.

in DMSO. The product **4a** was obtained in 68% yield along with **1a** (21%).

1) NaH, DMSO
1 ────────────→ (PhO)₂P(O)CH*i*PrCO₂Et ──base──→
2) *i*-PrI   **4a** y. 68%   RCHO
R   *i*Pr
   \\   /
   C=C
   /   \\
        CO₂Et
        10

The results of the HWE reactions of **4a** are summarized in Table 4. When Triton B was used as the base in THF, the reaction with benzaldehyde did not proceed at −78 °C. By warming (−78 °C to 0 °C), the reaction gave Z-product (97%) in 66% yield (entry 1). Since Triton B reacts with diarylphosphono reagents **1**−**4** as a nucleophile above 0 °C, this moderate yield suggests that this reaction occurred around 0 °C. The use of NaH gave both a high yield (96%) and high Z-selectivity (99%) (entry 3). Since *trans*-hexenal is less reactive than benzaldehyde, the reaction with *trans*-hexenal in the presence of Triton B gave a miserable yield (12%) along with a large quantity of phenol. The use of NaH again improved both the yield (91%) and the Z-selectivity (94%) (entry 7).

For saturated aliphatic aldehydes, the problem was the low reactivity of **4a**. The reaction with *n*-octyl aldehyde gave 95% Z-selectivity in 56% yield (entry 9) when NaH was used as the base. An attempt to increase the yield by adding LiBr did increase the yield (75%) but decreased the selectivity (91%) (entry 10). The reaction with cyclohexanecarboxaldehyde was highly Z-selective but gave olefins in low yields (entries 11, 12). By using NaH−LiBr as the base and 1.5 equiv of **4a**, a 58% yield of Z-product was obtained in 99% selectivity (entry 14). The reaction with 2-benzyloxypropanal (**7**) showed also high Z-selectivity (98%) (entry 16).

In general, the reactions of α-isopropyl reagent **4a** with several types of aldehydes were highly Z-selective (94−99%). The only problem with **4a** is its low reactivity. Thus the reaction gave high yields with aromatic and α,β-unsaturated aldehydes, moderate yields with saturated *n*-aliphatic and α-methylaliphatic aldehydes, and low yields with more highly hindered aldehydes.

Discussion

The HWE reaction is generally believed to proceed as shown in Scheme 1. That is, the phosphoryl-stabilized carbanion attacks the carbonyl in a stepwise manner, to give the erythro and threo adducts, which then decompose via four-centered transient species **11** and **12** to

Scheme 1
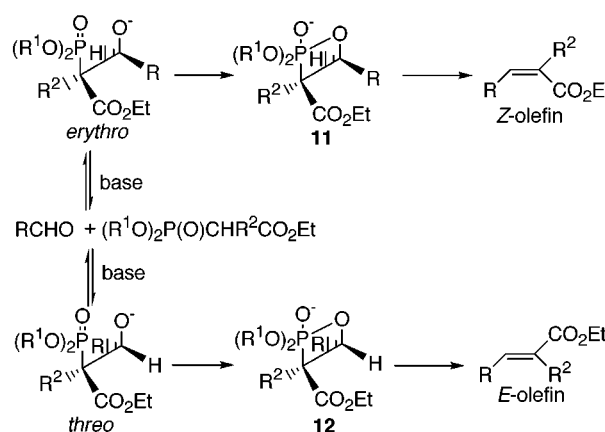
olefin products. The stereochemistry is determined by a combination of the stereoselectivity in the carbon−carbon bond-forming step and reversibility of the intermediate adducts.[2,14] The predominant formation of Z-olefins via diarylphosphono reagents **1**−**4** can be interpreted as a result of the predominant formation of erythro adducts which then irreversibly collapse to the Z-olefins. Due to the electron-withdrawing character of the aryloxy group (pK_a(PhOH) = 10.0 vs pK_a(CH₃CH₂OH) = 16), the electrophilicity of the phosphorus in the intermediate adducts to form **11** or **12** should be enhanced. Ab initio molecular orbital calculations show that the transition state leading to the erythro adduct is preferred to the transition state leading to the threo adduct in the presence of a metal ion (Li⁺ or Na⁺) (Figure 1).[15,16]

For the α-methyl reagents **2**, the rate-limiting step was the first carbanion attack on the aldehyde carbonyl. Thus the bigger the substituent of the aryl group on **2**, the higher the Z-selectivity obtained. Also lower reaction temperatures were preferred for the formation of Z-product. On the other hand, the rate-limiting step of the reaction of α-butyl reagents **3** seems to be more dependent on the reaction conditions. At lower temperatures, the second ring closure of an oxyanion to an oxaphos-

(14) Kumamoto, T.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 753−755.

(15) Ando, K. Unpublished results. A manuscript of a theoretical study of the HWE reaction is now in preparation.

(16) For a free anion system, the rate-determining step was the ring closure of an oxyanion to an oxaphosphetane: Brandt, P.; Norrby, P.-O.; Martin, I.; Rein, T. *J. Org. Chem.* **1998**, *63*, 1280−1289.
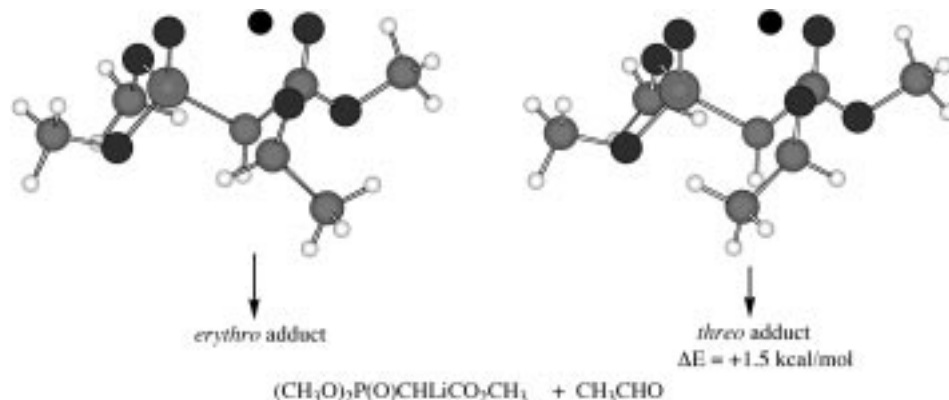
Figure 1. Ab initio transition structures for C−C bond-forming step in the reaction of Li enolate derived from trimethyl phosphonoacetate with acetaldehyde (RHF/6-31+G*). ● = Li.

phetane could be the rate-limiting step. The ring-closure step is more hindered for the reactions of **3** compared to the reactions of **2**. On the other hand, the reactivity of **2** and **3** in the first step, carbanion attack, seems to be similar. As a consequence, reversibility of the intermediate adducts allowed the formation of the thermodynamically more stable threo adducts and therefore gave more *E*-olefins. At higher temperatures, the rate-limiting step became the carbanion attack. Thus high *Z*-selectivity was obtained. For the α-isopropyl reagent **4a**, both the reactivities of the carbanion attack and the ring closure are diminished compared to those for **2**. Thus the carbanion attack determined the final product stereochemistry the same as in the case of reagents **1** and **2**, and higher temperatures (0 °C to room temperature) were required. Since the mechanistic details of the HWE reaction remain unclear, these results can only be tentatively interpreted. We believe that these results are important not only from a synthetic point of view but also for the mechanistic elucidation of the HWE reaction.

In summary, the present study indicates that α-alkyl-substituted HWE reagents **2−4** are highly *Z*-selective for the formation of a wide range of α,β-dialkyl-α,β-unsaturated esters (trisubstituted olefins). Our method did not require any expensive chemicals and generally gave both high *Z*-selectivity and high yields by simple operations. Also we would like to add the possibility of the *E*-selective reaction of the reagents **1−4** by choosing the reaction conditions as shown at entry 13 in Table 3. Since it is difficult to get *E*-isomer highly selectively when a HWE reagent has an α-substituent larger than methyl group,[2,9,17] this aspect could be synthetically important. To understand the reaction mechanism of the HWE reaction, we are now pursuing both experimental and computational study.[15]

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone just before use. All reactions were conducted under an argon atmosphere. Column chromatography was performed on silica gel (Wakogel C-300). A melting point was determined in an open capillary and is uncorrected. The ^{1}H NMR spectra were recorded in CDCl$_3$ at 500 MHz, and the

(17) Rousseau, J.-F.; Dodd, R. H. *J. Org. Chem.* **1998**, *63*, 2731−2737. Noguchi, H.; Aoyama, T.; Shioiri, T. *Tetrahedron* **1995**, *38*, 10545−10560. Hoffman, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849−3859.

chemical shifts are expressed in parts per million relative to internal tetramethylsilane.

Ethyl 2-(Diphenylphosphono)propionate (2a). To a solution of ethyl (diphenylphosphono)acetate (**1a**) (1.60 g, 5.0 mmol) in DMSO (6 mL) was added NaH (0.20 g, 5.0 mmol) at about 15 °C in a water bath. After the mixture was stirred for 20 min at room temperature, methyl iodide (0.34 mL, 5.5 mmol) was added to the above solution and the mixture was stirred for 1 h. The reaction was quenched with saturated NH$_4$Cl, and the mixture was extracted with AcOEt (20 mL × 2). The combined extracts were washed with water (20 mL × 2) followed by brine, dried (MgSO$_4$), and concentrated to a pale yellow residue. Column chromatography (silica gel/hexane−AcOEt (8:1)) provided **2a** (1.10 g, yield 66%) (along with **1a** (18%)) as a colorless oil: ^{1}H NMR δ 1.27 (3H, t, *J* = 7 Hz), 1.64 (3H, dd, *J* = 7, 19 Hz), 3.37 (1H, dq, *J* = 24, 7 Hz), 4.20−4.27 (2H, m), 7.16−7.21 (6H, m), 7.29−7.33 (4H, m); MS *m/e* 334 (M$^+$); HRMS calcd for C$_{17}$H$_{19}$O$_5$P 334.0969, found 334.0971.

The above method was applied for the other alkylation reactions of ethyl (diarylphosphono)acetate except for the preparation of **4a**.

Ethyl 2-(Diphenylphosphono)isopropylacetate (4a). To a solution of ethyl (diphenylphosphono)acetate (**1a**) (0.320 g, 1.00 mmol) in DMSO (1 mL) was added *t*-BuOK (90%) (0.137 g, 1.10 mmol) at about 15 °C in a water bath. After the mixture was stirred for 20 min at room temperature, isopropyl iodide (0.106 mL, 1.05 mmol) was added to the above solution and the mixture was stirred for 6 h. The following reaction procedure was the same as described for the preparation of **2a**. **4a** was obtained as a colorless oil (0.246 g, yield 68%) (along with **1a** (21%)): ^{1}H NMR δ 1.12 (3H, dd, *J* = 7, 1 Hz), 1.25 (3H, t, *J* = 7 Hz), 1.28 (3H, d, *J* = 7 Hz), 2.57−2.67 (1H, m), 3.09 (1H, dd, *J* = 20, 8 Hz), 4.16−4.25 (2H, m), 7.13−7.32 (10H, m); MS *m/e* 362 (M$^+$); HRMS calcd for C$_{19}$H$_{23}$O$_5$P 362.1282, found 362.1286.

Typical Procedure for HWE Reaction with Benzaldehyde (Entry 10 in Table 1). A solution of **2c** (0.30 mmol) in THF (5.5 mL) was treated with Triton B (0.178 mL, 0.39 mmol) at −78 °C for 15 min. The mixture was cooled to −95 °C, and benzaldehyde (0.33 mL, 0.31 mmol) in THF (0.5 mL) was then added. After 30 min, the mixture was warmed to −78 °C and stirred at −78 °C for 1 h. The reaction was quenched with saturated NH$_4$Cl, and the mixture was extracted with AcOEt (10 mL × 3). The combined extracts were washed with water (20 mL × 2) followed by brine, dried (MgSO$_4$), and concentrated. After the *Z*:*E* ratio of the crude mixture was determined by 500 MHz ^{1}H NMR, ethyl cinnamate was isolated by flash chromatography as a colorless oil. The *Z*:*E* ratio did not change by flash chromatography. For characterization, separation of the isomers by pTLC was attempted.

Ethyl (*Z*)-2-methylcinnamate: colorless oil as a mixture of *Z*:*E* = 30:1; ^{1}H NMR δ 1.10 (3H, t, *J* = 7 Hz), 2.10 (3H, d, *J* = 1 Hz), 4.11 (2H, q, *J* = 7 Hz), 6.71 (1H, q, *J* = 1 Hz),

7.20−7.33 (5H, m); MS *m/e* 190 (M+); HRMS calcd for $C_{12}H_{14}O_2$ 190.0993, found 190.1009.

Ethyl (*E*)-2-methylcinnamate: colorless oil as a mixture of *E:Z* = 106:1; ^{1}H NMR δ 1.35 (3H, t, *J* = 7 Hz), 2.12 (3H, d, *J* = 1 Hz), 4.28 (2H, q, *J* = 7 Hz), 7.29−7.43 (5H, m), 7.69 (1H, q, *J* = 1 Hz); MS *m/e* 190 (M+); HRMS calcd for $C_{12}H_{14}O_2$ 190.0993, found 190.1001.

Typical Procedure for HWE Reaction with 2-Ethylhexanal (Entry 6 in Table 2). A solution of **2b** (0.30 mmol) in THF (1.5 mL) was treated with NaH (60%) (0.017 g, 0.42 mmol) at 0 °C for 15 min. After the mixture was cooled to −78 °C, 2-ethylhexanal (0.53 mL, 0.33 mmol) was added. After 30 min, the resulting mixture was warmed to 0 °C over 2 h. The following reaction procedure was the same as described for entry 10 in Table 1.

Ethyl (2*Z*)-4-ethyl-2-methyloctenoate: colorless oil; ^{1}H NMR δ 0.83 (3H, t, *J* = 7 Hz), 0.87 (3H, t, *J* = 7 Hz), 1.14−1.47 (8H, m), 1.30 (3H, t, *J* = 7 Hz), 1.91 (3H, d, *J* = 1 Hz), 2.89−2.97 (1H, m), 4.19 (2H, q, *J* = 7 Hz), 5.57 (1H, dq, *J* = 10, 1 Hz); MS *m/e* 212 (M+); HRMS calcd for $C_{13}H_{24}O_2$ 212.1775, found 212.1791.

Ethyl (2*E*)-4-ethyl-2-methyloctenoate: colorless oil; ^{1}H NMR δ 0.83 (3H, t, *J* = 7 Hz), 0.87 (3H, t, *J* = 7 Hz), 1.12−1.34 (9H, m), 1.41−1.54 (2H, m), 1.83 (3H, d, *J* = 1 Hz), 2.24−2.32 (1H, m), 4.19 (2H, q, *J* = 7 Hz), 6.49 (1H, dq, *J* = 10, 1 Hz); MS *m/e* 212 (M+); HRMS calcd for $C_{13}H_{24}O_2$ 212.1775, found 212.1780.

Typical Procedure for HWE Reaction with *n*-Octyl Aldehyde (Entry 19 in Table 3). A mixture of **3c** (0.30 mmol) and LiBr (0.0906 g, 0.99 mmol) in toluene (1.5 mL) was treated with *n*-BuLi (0.264 mL, 0.42 mmol) at 0 °C for 30 min. After *n*-octyl aldehyde (0.53 mL, 0.33 mmol) was added, the resulting mixture was stirred at 0 °C for 7 h and then at room temperature for 1 h. The following reaction procedure was the same as described for entry 10 in Table 1.

Ethyl (2*Z*)-2-butyldecenoate: colorless oil; ^{1}H NMR δ 0.88 (3H, t, *J* = 7 Hz), 0.89 (3H, t, *J* = 7 Hz), 1.21−1.43 (17H, m), 2.23 (2H, t, *J* = 7 Hz), 2.38 (2H, q, *J* = 7 Hz), 4.20 (2H, q, *J* = 7 Hz), 5.82 (1H, t, *J* = 7 Hz); MS *m/e* 254 (M+); HRMS calcd for $C_{16}H_{30}O_2$ 254.2244, found 254.2243.

Ethyl (2*E*)-2-butyldecenoate: colorless oil; ^{1}H NMR δ 0.89 (3H, t, *J* = 7 Hz), 0.91 (3H, t, *J* = 7 Hz), 1.22−1.46 (17H, m), 2.16 (2H, q, *J* = 7 Hz), 2.28 (2H, t, *J* = 8 Hz), 4.18 (2H, q, *J* = 7 Hz), 6.72 (1H, t, *J* = 8 Hz); MS *m/e* 254 (M+); HRMS calcd for $C_{15}H_{20}O_2$ 254.2244, found 254.2262.

Typical Procedure for HWE Reaction with Cyclohexanecarboxaldehyde (Entry 14 in Table 4). A solution of **4a** (0.45 mmol) in THF (1.0 mL) was treated with NaH (0.0216 g, 0.54 mmol) at 0 °C for 15 min and then LiBr (0.0329 g, 0.36 mmol) for 5 min. After cyclohexanecarboxaldehyde (0.37 mL, 0.30 mmol) was added, the resulting mixture was stirred at 0 °C for 6 h and then at room temperature for 1 h. The following reaction procedure was the same as described for entry 10 in Table 1.

Ethyl (2*Z*)-3-cyclohexyl-2-isopropylpropenoate: colorless oil; ^{1}H NMR δ 1.04 (6H, d, *J* = 7 Hz), 1.00−1.34 (5H, m), 1.31 (3H, t, *J* = 7 Hz), 1.60−1.74 (5H, m), 2.49−2.57 (1H, m), 2.64 (1H, septet, *J* = 7 Hz), 4.22 (2H, q, *J* = 7 Hz), 5.47 (1H, d, *J* = 10 Hz); MS *m/e* 224 (M+); HRMS calcd for $C_{14}H_{24}O_2$ 224.1774, found 224.1772.

Ethyl (2*E*)-3-cyclohexyl-2-isopropylpropenoate: colorless oil as a mixture of *E:Z* = 96:4; ^{1}H NMR δ 1.18 (6H, d, *J* = 7 Hz), 1.10−1.34 (5H, m), 1.30 (3H, t, *J* = 7 Hz), 1.54−1.77 (5H, m), 2.34−2.42 (1H, m), 2.90 (1H, septet, *J* = 7 Hz), 4.17 (2H, q, *J* = 7 Hz), 6.39 (1H, d, *J* = 10 Hz); MS *m/e* 224 (M+); HRMS calcd for $C_{14}H_{24}O_2$ 224.1774, found 224.1770.

Supporting Information Available: Characterization data for **2b**,**c**, **3a**−**c**, and the remaining olefin products (both *Z* and *E*) (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.