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The Horner–Wadsworth–Emmons reaction of mixed phosphonoacetates and aromatic aldehydes: geometrical selectivity and computational investigation

Jiro Motoyoshiya,* Tatsuya Kusaura, Keisuke Kokin, Sei-ichi Yokoya, Yutaka Takaguchi, Susumu Narita and Hiromu Aoyama

Department of Chemistry, Faculty of Textile Science and Technology, Shinshu University, Ueda 386-8567, Japan

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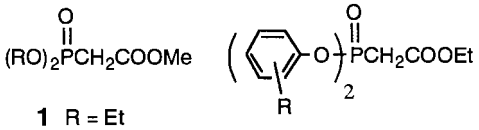
Abstract—The substituent effect on the geometrical selectivity in the Horner–Wadsworth–Emmons (HWE) reaction was studied employing several mixed phosphonoacetates. Their reactions with aromatic aldehydes showed a gradual change in *Z*-selectivity according to the electron-withdrawing ability of the phosphonate substituents, and there was a good correlation between the observed selectivities and ^{31}P chemical shifts of the phosphonoacetates. Some variables such as the metal cation and crown ether also affected the selectivity. A computational study using ab initio and semi-empirical calculations suggests that the electron-withdrawing substituents stabilize the intermediates as well as the transition states, which reduces the reversibility to increase *Z*-products. This is in agreement with the experimentally observed selectivity. © 2001 Elsevier Science Ltd. All rights reserved.

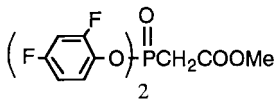
1. Introduction

The Horner–Wadsworth–Emmons (HWE) reaction[1,2] is one of much versatile tools in organic synthesis. While the general phosphonoacetates with alkyl phosphonate substituents, for example, methyl diethylphosphonoacetate (**1**) as a representative reagent, give mostly thermodynamically favored *E*-alkenes in the reactions of aldehydes or ketones, some *Z*-selective phosphonoacetates have been developed so far. For instance, methyl bis(2,2,2-trifluoroethyl)phosphonoacetates (**2**) (Still's reagents)[3] are of much value in the synthesis of *Z*-unsaturated esters.[4] On the other hand, Ando[5] has developed several ethyl diarylphosphonoacetates (**3**), which provide a high level of *Z*-selectivity enough to serve the practical use under the convenient reaction conditions. Recently, we have also reported[6] that methyl bis(2,4-difluorophenyl)phosphonoacetate (**4**) is highly *Z*-selective even when aliphatic aldehydes were employed.



1 R = Et
2 R = CF_3CH_2

3 R = H, alkyl



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Though the central device of above *Z*-selective HWE reagents is an introduction of the electron-withdrawing groups as the phosphonate substituents, the pentacoordinate spirophosphoranes have also proved to undergo a Wittig reaction with high *Z*-selectivity.[7] Several works have been dealing with the HWE reaction from mechanistic viewpoints,[8] but there remain some problems to be further elucidated, for instance, the origin of *Z*-selectivity of the above phosphonoacetates. Therefore, to explore the effect of the electron-withdrawing substituents on the selectivity, we have investigated the HWE reaction of new mixed phosphonoacetates, which are expected to expose the electronic effect of the phosphonate substituents on the selectivity. Additionally, a computational study was made to explain the experimentally observed substituent effect.

2. Results and discussion

2.1. Preparation of mixed phosphonoacetates (5a–j) and ^{31}P NMR chemical shifts

The mixed phosphonoacetates used in the present study were prepared by two reaction procedures as shown in Scheme 1. The reactions of methyl dichlorophosphinylacetate

Keywords: Horner–Wadsworth–Emmons reaction; phosphonoacetate; selectivity; substituent effect.

* Corresponding author. Fax: +81-268-21-5391; e-mail: jmotoyo@giptc.shinshu-u.ac.jp

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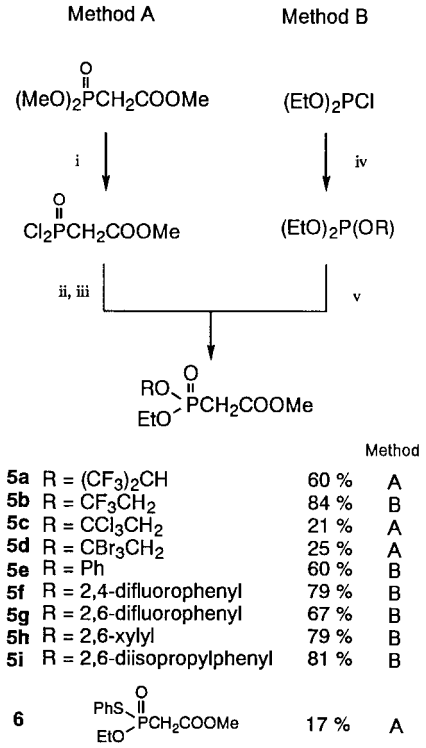


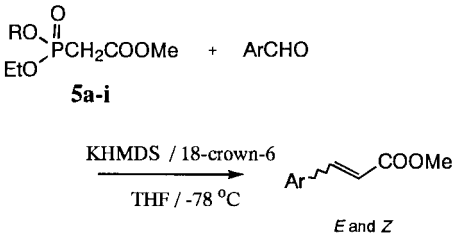
Scheme 1. *Reagents and conditions*: (i) PCl_5, heat; (ii) EtOH, Et_3N, PhH, 0°; (iii) ROH, Et_3N, PhH, 0°C; (iv) ROH, Et_3N, Et_2O, 0°C; (v) $BrCH_2COOMe$, heat.

with halogenated alcohols followed by an addition of ethanol in the presence of triethyl amine gave **5a**, **5c** and **5d** in low to medium yields (Method A). This method was also applied to the preparation of phosphonothioate **6** using thiophenol. Alternatively, the Arubzov reaction of mixed phosphites with methyl bromoacetate afforded **5b**, and **5e**–**i** in relatively good yields (Method B). The ^{31}P NMR spectra of these phosphonoacetates are shown in Table 1. The phosphorus signals tend to shift to down fields as the electronegativity of the substituent increases among **5a**–**d**. The difference in the chemical shifts might be related to the electrophilicity of the phosphorus atoms. The phosphorus signal of **5e** having a phenyl group was observed in a high field, as the phosphorus nuclei bearing phenoxy groups generally resonate at higher fields than those with alkoxy groups.[9] Also in the aromatic series (**5e**–**i**), a relationship between the chemical shifts and the electronic factor of the substituents on the aromatic rings can be observed.

Table 1. Select ^{31}P chemical shifts

R		δ (ppm)[a]
CH_3CH_2	(**1**)	20.1
$(CF_3)_2CH$	(**5a**)	23.1
CF_3CH_2	(**5b**)	21.9
CCl_3CH_2	(**5c**)	21.2
CBr_3CH_2	(**5d**)	20.2
Ph	(**5e**)	17.1
2,4-Difluorophenyl	(**5f**)	18.2
2,6-Difluorophenyl	(**5g**)	19.0
2,6-Xylyl	(**5h**)	16.5
2,6-Diisopropylphenyl	(**5i**)	16.1

Measured in $CDCl_3$.
[a] 85% H_3PO_4 as a standard.

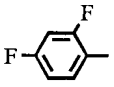
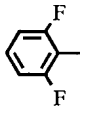
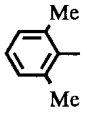
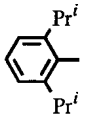


Scheme 2.

2.2. The HWE reaction

The HWE reaction of phosphonoacetates **5a**–**i** and **6** with aromatic aldehydes was carried out under the kinetically controlled condition using potassium hexamethyldisilazide (KHMD) in THF at −78°C in the presence of 18-crown-6 (Scheme 2).[3,10] The results are summarized in Table 2. In some reactions, the yields were low and unreacted aldehydes were detected by ^1H NMR spectrum, which would be ascribed to the low reactivity as well as lability of the phosphonoacetates. As expected, *Z*-selectivities of the mixed phosphonoacetates were diminished below half comparing to the parent *Z*-selective phosphonoacetates. For example, while the reactions of **2**, **3**, and **4** with benzaldehyde provided the high *Z*-selectivities (>98%), those of mixed phosphonoacetates **5b**, **5e** and **5f** gave *E*-cinnamate preferentially under the same reaction condition.[3] Only **5a** bearing a highly electron-withdrawing substituent such as a 1,1,1,3,3,3-hexafluoroisopropyl group showed the moderate *Z*-selectivity. Of particular interest is that the ratios of the *Z*-isomer gradually changed according to the electronic nature of the phosphonate substituents rather than a steric factor as observed in the reactions of **5a** (R=$(CF_3)_2CH$: Entry 1), **5b** (R=CF_3CH_2: Entry 6), **5c** (R=CCl_3CH_2: Entry 9) and **5d** (R=CBr_3CH_2: Entry 10). A choice of the mixed phosphonoacetates clarified the substituent effect on the selectivity, because bis(trichloroethyl)phosphonoacetate[11] is known to be as *Z*-selective as Still's reagent **2**. In contrast, the effect of aldehyde substituents was much less than that of the phosphonate substituents (Entries 2–5, 7 and 8), which indicated that the electrophilicity of the phosphorus atom would control the stereochemistry rather than the rate of initial addition of the phosphonate carbanions to aldehydes. The degree of the electrophilicity of the phosphorus atom can be connected with the phosphorus chemical shifts as described in Table 1. Such a tendency could also be seen in the reactions of **5e**–**g** having aromatic substituents, namely, the ratio of *Z*-isomers increased by the introduction of fluorine atoms to benzene rings (Entries 11–13). Contrary, the alkyl groups attached on both *o*-positions in **5h** and **5i** reduced the *Z*-isomer remarkably (Entries 14 and 15). This drastic decrease of *Z*-isomers would be attributed to much reduced electrophilicity of the phosphorus atoms rather than the steric effect, because more sterically hindered phosphonoacetates such as methyl bis(2,6-dimethylphenyl)- and bis(2,6-diisopropylphenyl)phosphonoacetates provided moderate *Z*-selectivity.[6b] Also in this series of aromatic phosphonoacetates, the order of *Z*-selectivity is completely consistent with the order of the chemical shifts of **5e**–**i** as described in Table 1. On the other hand, the phosphonothioate (**6**) gave only *E*-cinnamate but in low yield (Entry 16).

Table 2. Reaction of phosphonoacetates (**5a–i**, **6**) with ArCHO

Entry[a]	R		Ar	Yield (%)[b]	*Z*/*E*[c]
1	$(CF_3)_2CH$	(**5a**)	Ph	55	88:12
2			*p*-NO_2–C_6H_4–	53	72:28[d]
3			*p*-Cl—C_6H_4–	41	71:29
4			*p*-MeO–C_6H_4-	37[e]	67:33
5			*p*-Me_2N–C_6H_4–	–[f]	–
6	CF_3CH_2	(**5b**)	Ph	56	49:51
7			*p*-NO_2–C_6H_4–	77	43:57
8			*p*-MeO–C_6H_4–	52	35:65
9	CCl_3CH_2	(**5c**)	Ph	37	35:65
10	CBr_3CH_2	(**5d**)	Ph	62	29:71
11	Ph	(**5e**)	Ph	80	31:69
12		(**5f**)	Ph	68	41:59
13		(**5g**)	Ph	80	65:35
14		(**5h**)	Ph	62	15:85
15		(**5i**)	Ph	74	6:94
16	PhS	(**6**)	Ph	25	Only *E*

[a] Reaction condition: KHMDS/18-crown-6/THF/−78°C.
[b] Isolated yield by column chromatography.
[c] Determined by ^{1}H NMR otherwise noted.
[d] Determined by gas chromatography.
[e] This yield was estimated by ^{1}H NMR.
[f] No reaction.

2.3. Effect of some variables on the selectivity

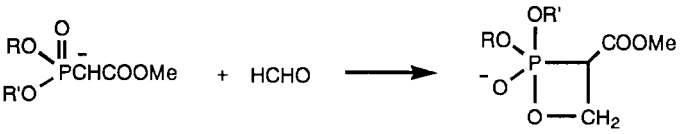
As it is known that the variables such as the base, metal cation, crown ether and solvent affect the selectivity,[12] several controlled experiments were made using **5a** and benzaldehyde. The results are summarized in Table 3. Removal of crown ether[13] markedly lowered the *Z*-selectivity as well as the yield of cinnamate (Entries 1 and 2). While the use of DBU (1,8-diazabicyclo[5.4.0]-7-undecene) as a base[14] instead of KHMDS led to much decrease of the ratio of *Z*-cinnamate (Entry 3), drastic increase of *Z*-isomer and the yield was observed when KI and crown ether were present (Entry 4). Whereas increase of *Z*-isomer in the presence of KI was also observed in DMF (Entry 5–7), the definite effect of crown ether could not be seen in this solvent because of its high polarity (Entry 7–9). Probably, chelation of the metal cation by the negatively charged oxyanion as well as ester and phosphoryl oxygens

Table 3. The HWE reaction of **5a** and PhCHO. Effect of reaction conditions on the ratio of *Z*- and *E*-cinnamates

Entry	Base/additive	Solvent/temperature (°C)	Yield (%)[a]	*Z*/*E*[b]
1	KHMDS/18-crown-6	THF/−78	55	88:12
2	KHMDS	THF/−78	12	44:56
3	DBU[c]	THF/−78	25	15:85[d]
4	DBU/KI/18-crown-6 (1/5/5)[e]	THF/−78	74	53:47
5	DBU	DMF/0	43	8:92
6	DBU/KI (1/1)	DMF/0	55	15:85
7	DBU/KI (1/5)	DMF/0	37	20:80
8	DBU/KI/18-crown-6 (1/1/5)	DMF/0	62	15:85
9	DBU/KI/18-crown-6 (1/5/5)	DMF/0	49	25:75

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectrum.
[c] 1,8-Diazabicyclo[5,4.0]-7-undecene.
[d] The fluctuating *Z*/*E* ratios from 3:97 upto 33:67 were observed under the same system at 0°C.
[e] Molar ratio of base and additives.

Table 4. Relative energies of oxaphosphetanes formed from the metal free phosphonoacetates and formaldehyde (RHF/6-31+G*)



Phosphonoacetate	R	R′	ΔG (kcal/mol)
1	Et	Et	+3.39
2	CF_3CH_2	CF_3CH_2	−3.45
5a	Et	$(CF_3)_2CH$	−2.57
5b	Et	CF_3CH_2	−1.11
5c	Et	Cl_3CH_2	−1.56

Relative energy is a difference from the sum of the energies of the reactants. All oxaphosphetanes are slightly puckered with the OR′ group at an apical position. Bond lengths for P–C: 1.86–1.89 Å, C–C: 153 Å, C–O: 1.39 Å, P–O: 1.76–1.82 Å.

would stabilize the kinetically favored *erythro*-transition states, the precursors of *erythro*-oxaphosphetanes and *Z*-products, as can be seen in *erythro*-selective aldol condensation of *Z*-enolates and aldehydes[15] or *erythro*-selective addition of the phosphorus stabilized carbanions to aldehydes.[16] The effect of the crown ether seems to conflict with the chelate effect at the transition state, but assuming that this chelation is stronger than that by the crown ether and it diminishes along with the structural transformation to the oxaphosphetane, a possible explanation of the role of the crown ether is increase of the electrophilicity of the oxyanion leading to rapid ring closure to the oxaphosphetane.

2.4. Calculations

Recent theoretical investigations of the HWE reaction suggest that the reaction proceeds via a scarcely detected oxaphosphetane[17] as an intermediate and the rate determining step is ring closure to the oxaphosphetane.[18,19] Although the predominance of *E*-olefins in the general HWE reactions has been explained,[19] a theoretical inquiry of the factors enhancing *Z*-selectivity should be made toward further understanding of this subject. According to the previously proposed mechanism for *Z*-selectivity,[2b] stabilization of the transition state for ring closure suppresses the reverse process and increases a proportion of the kinetic intermediate, *erythro*-oxaphosphetane whose rapid decomposition forms a *Z*-olefin. When the Hammond postulate is applied, the factor that stabilizes the transition states would also affect the stabilization of the oxaphosphetanes, because of a structural similarity among the transition state for ring closure and the oxaphosphetane.[17] Therefore, we compared the energies of the oxaphosphetanes formed from the selected phosphonate carbanions and formaldehyde using ab initio RHF calculations with the 6-31+G* basis set.[20] Comparison of the relative energies of oxaphosphetanes in Table 4 revealed the effect of

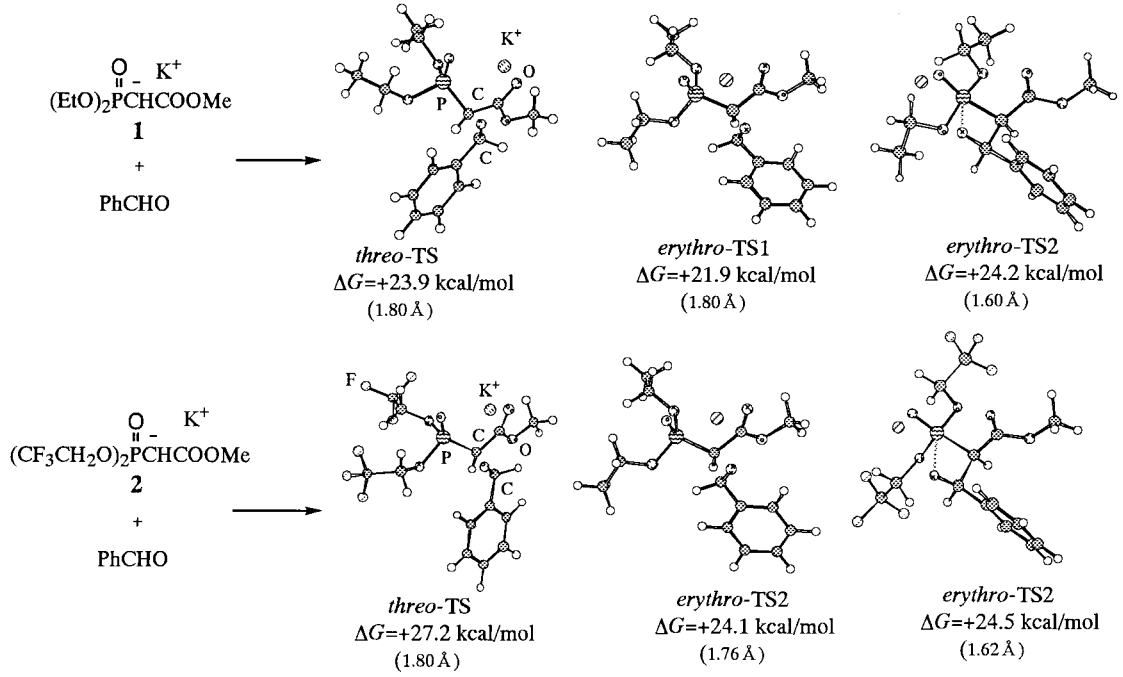


Figure 1. Structures, relative energies and atomic distances of the forming C–C bonds (parenthesis) of the transition states in the reaction of **1** and **2** with benzaldehyde in the presence of potassium ions (PM3).

electron-withdrawing substituents on the stabilization of the corresponding oxaphosphetanes, namely, the larger stabilization in **2** and **5a** than in **1**, **5b** and **5c** is in agreement with a known matter that electron-withdrawing groups at the apical positions stabilize the pentacoordinated phosphorus compounds. Next, we settled for an investigation to compare the stability of *threo*- and *erythro*-transition states, the precursors for *E*- and *Z*-olefins, respectively. The calculations were done by semi-empirical PM3 method[21] to submit the realistic model systems.[22] The reactions of potassium salts of the phosphonoacetates **1** and **2**, the former is a typical *E*-selective HWE reagent and the latter is the *Z*-selective one, with benzaldehyde were chosen as the representatives. Our calculation[23] provided two transition states, *erythro*-**TS1** and **TS2** for each initial addition and ring closure to *erythro*-oxaphosphetane, respectively, but a sole transition state, *threo*-**TS**, was located for the formation of *threo*-oxaphosphetanes as previously noted.[19] The structures and relative energies of these transition states are described in Fig. 1. The lower energies of both *erythro*-**TS1**s than *threo*-**TS**s agree with the previously reported result,[19] but we can point out that *erythro*-**TS2** having 2,2,2-trifluoroethyl groups is more stabilized than that having ethyl groups. This supports the preference of *Z*-product in the reaction of **2**.

3. Conclusions

The present study showed a close relationship between the electronic nature of the phosphonate substituents and geometrical selectivity in the HWE reaction. A gradual enhancement of *Z*-selectivity due to electron-withdrawing groups was observed in a series of the reactions of the mixed phosphonoacetates. This effect is ascribed to the changeable electrophilicity of the phosphorus atoms and the stability of the oxaphosphetane intermediates as well as the transition states, which was supported by the computational study.

4. Experimental

^{1}H NMR (400 or 60 MHz), ^{13}C NMR (100 MHz) and ^{31}P NMR (162 MHz) spectra were taken in $CDCl_3$ as a solvent, using tetramethylsilane (TMS) as the internal standard for ^{1}H and ^{13}C NMR, and 85% phosphoric acid as the external standard for ^{31}P NMR. The mass spectra were determined at an ionizing voltage of 70 eV. Analytical gas chromatography was performed using PEG-20M or DC-550 packed column. All solvents were dried by standard methods. The column chromatography was done with Wacogel C-200. Methyl (dichlorophosphoryl)acetate was prepared by Still's method.[3] Diethyl phenyl phosphite, diethyl (2,2,2-trifluoroethyl) phosphite, diethyl (2,6-xylyl) phosphite and diethyl (2,6-diisopropylphenyl) phosphite were prepared according to the procedure previously reported.[6b]

4.1. Preparation of mixed phosphonoacetates

4.1.1. Methyl ethyl(1,1,1,3,3,3-hexafluoroisopropyl)phosphonoacetate (5a). *Typical procedure A*. A solution of 1,1,1,3,3,3-hexafluoroisopropylalcohol (7.2 ml, 69 mmol) and triethyl amine (6.98 g, 69 mmol) in benzene (80 ml) was added to a solution of methyl (dichlorophosphoryl)-acetate (13.11 g, 69 mmol) in benzene (60 ml) at 0°C. After being stirred for 3 h at room temperature, a solution of ethanol (3.18 g, 69 mmol) and triethylamine (6.98 g, 69 mmol) in benzene (80 ml) was then added at 0°C, and the mixture was stirred at room temperature for 3 h. After removal of precipitated ammonium chloride and the solvent, the oily residue was distilled in vacuo to give **5a** as a colorless oil (14.17 g, yield 60%); bp 78–80°C, 3 mm Hg (Found M^+: 332.0230. $C_8H_{11}O_5F_6P$ requires 332.0246); ^{1}H NMR (400 MHz) δ=1.07 (t, 3H, CH_3CH$_2$O, J=7.2 Hz), 2.87 (d, 2H, P(O)CH_2, J_{PH}=22.4 Hz), 3.45 (s, 3H, COOCH_3), 3.91–4.02 (m, 2H, CH$_3$CH_2O), 5.23–5.29 (m, 1H, (CF$_3$)$_2$CHO); ^{13}C NMR (100 MHz) δ=16.1 (*C*H$_3$CH$_2$O), 34.4 (d, P(O)*C*H$_2$, J_{PC}=40.9 Hz), 53.0 (COO*C*H$_3$), 64.2 (CH$_3$*C*H$_2$O), 69.9–71.3 (m, (CF$_3$)$_2$*C*H$_2$O), 123.6 (m, (*C*F$_3$)$_2$CHO, J_{FC}=280.5 Hz), 165.1 (*C*=O); *m/z* 332 (M^+).

4.1.2. Methyl ethyl(2,2,2-trifluoroethyl)phosphonoacetate (5b). *Typical procedure B*. A mixture of diethyl 2,2,2-trifluoroethyl phosphite (2.61 g, 12.19 mmol) and methyl bromoacetate (1.05 ml, 11.09 mmol) was heated at 120°C for 24 h. The oily product was purified by bulb-to-bulb distillation under reduced pressure to give **5b** (1.92 g, 84%). Bp 130°C at 12 mm Hg (oven temp.) (Found M^+: 264.0355. $C_7H_{12}O_5FP$ requires 264.0373); ^{1}H NMR (400 MHz) δ=1.37 (t, 3H, CH_3CH$_2$O, J=7.2 Hz), 3.07 (d, 2H, P(O)CH_2, J_{PH}=21.2 Hz), 3.76 (s, 3H, COO*C*H$_3$), 4.19–4.25 (m, 2H, CH$_3$CH_2O) 4.41–4.50 (m, 2H, CF$_3$CH_2O); ^{13}C NMR (100 MHz) δ=16.3 (*C*H$_3$CH$_2$O), 34.2 (d, P(O)*C*H$_2$, J_{PC}=140.0 Hz), 53.0 (COO*C*H$_3$), 63.2 (CH$_3$*C*H$_2$O), 63.5 (CF$_3$*C*H$_2$O), 123.1 (m, *C*F$_3$CH$_2$O, J_{FC}=260.0 Hz), 166.1 (*C*=O); *m/z* 264 (M^+).

4.1.3. Methyl ethyl(2,2,2-trichloroethyl)phosphonoacetate (5c). Prepared in 21% yield by procedure A (Found M^+: 311.9527. $C_7H_{12}O_5Cl_3P$ requires 311.9487); ^{1}H NMR (400 MHz) δ=1.39 (t, 3H, CH_3CH$_2$O, J=6.8 Hz), 3.12 (d, 2H, P(O)CH_2, J_{PH}=21.6 Hz), 3.77 (s, 3H, COOCH_3), 4.25–4.30 (m, 2H, CH$_3$CH_2O), 4.65–4.68 (d, 2H, CCl$_3$CH_2O); ^{13}C NMR (100 MHz) δ=16.2 (s, *C*H$_3$CH$_2$O), 34.0 (d, P(O)*C*H$_2$, J_{PC}=136.1 Hz), 52.7 (COO*C*H$_3$), 63.2 (CH$_3$*C*H$_2$O), 76.2 (CCl$_3$*C*H$_2$O), 95.5 (*C*Cl$_3$CH$_2$O), 165.7 (s, *C*=O); *m/z* 312(M^+) (as Cl=35).

4.1.4. Methyl ethyl(2,2,2-tribromoethyl)phosphonoacetate (5d). Prepared in 25% yield by procedure A (Found M^+ +1: 446.8047. $C_7H_{13}O_5PBr_3$ (M^++1) requires 446.8032); ^{1}H NMR (400 MHz) δ=1.40 (dt, 3H, CH_3CH$_2$O, J=7.1 Hz), 3.15 (d, 2H, P(O)CH_2, J_{PH}=20.0 Hz), 3.78 (s, 3H, COOCH_3), 4.29–4.34 (m, 2H, CH$_3$CH_2O), 4.82–4.84 (d, 2H, CBr$_3$CH_2O); ^{13}C NMR (100 MHz) δ=16.5 (s, *C*H$_3$CH$_2$O), 34.2 (d, P(O)*C*H$_2$, J_{PC}=137.2 Hz), 37.6 (CH$_3$*C*H$_2$O), 52.9 (COO*C*H$_3$), 63.5 (CH$_3$*C*H$_2$O), 76.8 (*C*Br$_3$CH$_2$O), 165.9 (*C*=O); *m/z* 447 (M^++1).

4.1.5. Methyl ethylphenylphosphonoacetate (5e). Prepared in 60% yield by procedure B (Found M^+: 258.0642. $C_{11}H_{15}O_5P$ requires 258.0656); ^{1}H NMR (400 MHz) δ=1.33 (t, 3H, CH_3CH$_2$O, J=7.2 Hz), 3.12 (d, 2H, P(O)CH_2, J_{PH}=21.6 Hz), 3.74 (s, 3H, COOCH_3),

4.23–4.30 (m, 2H, CH_3CH_2O), 7.16–7.36 (m, 5H, Ar*H*); ^{13}C NMR (100 MHz) δ=16.6 (s, *C*H_3CH_2O), 34.3 (d, P(O)*C*H_2, J_{PC}=140.0 Hz), 53.0 (COO*C*H_3), 64.20 (CH_3*C*H_2O), 120.9, 121.0, 125.7, 130.1, 150.5 (Aromatic *C*), 166.1 (*C*=O); *m/z* 258 (M^+).

4.1.6. Methyl ethyl(2,4-difluorophenyl)phosphonoacetate (5f). Prepared in 67% yield by procedure B (Found M^+: 265.0057. $C_9H_{18}O_5F_2P$ ($M^+-{}^+C_2H_5$) requires 265.0076); ^1H NMR (400 MHz) δ=1.35 (t, 3H, C*H*$_3CH_2O$, *J*=7 Hz), 3.18 (d, 2H, P(O)C*H*$_2$, J_{PH}=22 Hz), 3.76 (s, 3H, COOC*H*$_3$), 4.28–4.35 (m, 2H, CH_3C*H*$_2$O), 6.82–6.95, 7.12–7.41 (m, 3H, Ar*H*); ^{13}C NMR (100 MHz) δ=16.5 (d, *C*H_3CH_2O, J_{PC}=6 Hz), 34.4 (d, P(O)*C*H_2, J_{PC}=137 Hz), 53.1 (COO*C*H_3), 64.3 (d, CH_3*C*H_2O, J_{PC}=7 Hz), 105.3–105.8 (m, Ar*C*3), 111.5–111.8 (m, Ar*C*5), 123.8–123.9 (m, Ar*C*6), 134.5–134.7 (m, Ar*C*1), 152.7–161.0 (m, Ar*C*2, *C*4), 165.5 (d, *C*=O, J_{PC}=5 Hz); *m/z* 294 (M^+).

4.1.7. Methyl ethyl(2,6-difluorophenyl)phosphonoacetate (5g). Prepared in 72% yield by procedure B (Found M^+: 294.0446. $C_{11}H_{13}O_5F_2P$ requires 294.0467); ^1H NMR (400 MHz) δ=1.39 (t, 3H, C*H*$_3CH_2O$, *J*=7 Hz), 3.27 (d, 2H, P(O)C*H*$_2$, J_{PH}=22 Hz), 3.77 (s, 3H, COOC*H*$_3$), 4.32–4.41 (m, 2H, CH_3C*H*$_2$O), 6.94–6.99, 7.08–7.10 (m, 3H, Ar*H*); ^{13}C NMR (100 MHz) δ=16.5 (d, *C*H_3CH_2O, J_{PC}=6 Hz), 34.7 (d, P(O)*C*H_2, J_{PC}=137 Hz), 53.1 (COO*C*H_3), 64.2 (d, CH_3*C*H_2O, J_{PC}=7 Hz), 112.5–112.7 (m, Ar*C*3, *C*5), 125.6–125.9 (m, Ar*C*4), 128.7 (Ar*C*1), 154.2–156.7 (m, Ar*C*2, *C*6), 165.7 (d, *C*=O, J_{PC}=6 Hz); *m/z*294 (M^+).

4.1.8. Methyl ethyl(2,6-xylyl)phosphonoacetate (5h). Prepared in 79% yield by procedure B (Found M^+: 286.0988. $C_{13}H_{19}O_5P$ requires 286.0968); ^1H NMR (400 MHz) δ=1.22 (t, 3H, C*H*$_3CH_2O$, *J*=7 Hz), 2.53 (s, 6H, ArC*H*$_3$), 3.20 (d, 2H, P(O)C*H*$_2$, J_{PH}=21 Hz), 3.77 (s, 3H, COOC*H*$_3$), 4.28–4.35 (m, 2H, CH_3C*H*$_2$O), 6.94–7.12 (m, 3H, Ar*H*); ^{13}C NMR (100 MHz) δ=16.2 (d, *C*H_3CH_2O, J_{PC}=5 Hz), 17.4 (Ar*C*H_3), 34.7 (d, P(O)*C*H_2, J_{PC}=139 Hz), 52.6 (COO*C*H_3), 64.1 (d, CH_3*C*H_2O, J_{PC}=7 Hz), 125.2, 129.0 (Ar*C*3, *C*4, *C*5), 130.5 (d, Ar*C*2, *C*6, J_{PC}=3 Hz), 147.5 (d, Ar*C*1, J_{PC}=11 Hz), 166.0 (d, *C*=O, J_{PC}=6 Hz); *m/z* 286 (M^+).

4.1.9. Methyl ethyl(2,6-diisopropylphenyl)phosphonoacetate (5i). Prepared in 81% yield by procedure B (Found $M^+-{}^{\cdot}CH3$: 327.1382. $C_{16}H_{24}O_5P$ ($M^+-{}^{\cdot}CH3$) requires 327.1359); ^1H NMR (400 MHz) δ=1.19 (t, 3H, C*H*$_3CH_2O$, *J*=7 Hz), 1.21, 1.22 (d, 12H, (C*H*$_3$)$_2$CH, *J*=7 Hz), 3.22 (d, 2H, P(O)C*H*$_2$, J_{PH}=22 Hz), 3.44–3.51 (m, 2H, (CH$_3$)$_2$C*H*), 3.77 (s, 3H, COOC*H*$_3$), 4.09–4.21 (m, 2H, CH_3C*H*$_2$O), 7.13 (s, 3H, Ar*H*); ^{13}C NMR (100 MHz) δ=16.5 (d, *C*H_3CH_2O, J_{PC}=6 Hz), 23.8, 23.9 ((*C*H$_3$)$_2$CH), 27.5 ((CH$_3$)$_2$*C*H), 34.9 (d, P(O)*C*H_2, J_{PC}=138 Hz), 52.9 (COO*C*H_3), 65.1 (d, CH_3*C*H_2O, J_{PC}=6 Hz), 124.6, 126.2 (Ar*C*3, *C*4, *C*5), 141.0 (d, Ar*C*2, *C*6, J_{PC}=3 Hz), 145.2 (d, Ar*C*1, J_{PC}=11 Hz), 166.4 (d, *C*=O, J_{PC}=6 Hz); *m/z*342 (M^+).

4.1.10. Methyl (ethoxyphenylthiophosphoryl)acetate (6). Prepared in 17% yield by procedure A (Found M^+: 274.0439. $C_{11}H_{15}O_4SP$ requires 274.0427); ^1H NMR (60 MHz) δ=1.32 (t, 3H, C*H*$_3CH_2O$), 2.97 (d, 2H, P(O)C*H*$_2$, J_{PH}=18.0 Hz), 3.56 (s, 3H, COOC*H*$_3$), 3.83–4.36 (m, 2H, CH_3C*H*$_2$O, J_{PH}=7.0 Hz), 7.13–7.43 (m, 5H, Ar*H*); *m/z* 274 (M^+).

4.2. The HWE reaction

4.2.1. Typical procedure (KHMDS, 18-crown-6, −78°C, THF). A solution of KHMDS (0.5 mol/l toluene solution, 2.0 ml, 1.00 mmol) was added dropwise to a solution of **5a** (0.33 g, 1.00 mmol) and 18-crown-6 (1.32 g, 5.00 mmol) in THF (20 ml) at −78°C, and the mixture was stirred at this temperature for 1 h under N_2. A solution of benzaldehyde (0.11 g, 1.00 mmol) in THF (2 ml) was then added and the mixture was stirred for 18 h at that temperature. After the reaction was quenched with saturated NH_4Cl at room temperature, the THF layer was separated, and the products were further extracted with Et_2O (20 ml×2) from an aqueous layer. The combined extract was washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel using benzene as an eluant to give methyl cinnamate (0.09 g, 55%). The ratio of *Z*/*E* cinnamate was determined by ^1H NMR comparing integrations of vinyl protons which appeared at δ 5.74 (PhCH=C*H*COOMe, *J*=12 Hz) as a doublet for *Z*-cinnamate and δ 6.24 (PhC*H*=CHCOOMe, *J*=16 Hz) as a doublet for *E*-cinnamate. On the other hand, the *Z*/*E* ratios of the substituted methyl cinnamates were estimated by gas chromatography when the signals of vinyl protons in ^1H NMR were overlapped.

4.2.2. Entry 1 (KHMDS, −78°C, THF). The same procedure described above was done without addition of 18-crown-6.

4.2.3. Entry 2 (DBU, −78°C, THF). A solution of DBU (0.15 g, 1.00 mmol) in THF (20 ml) was added dropwise to **5a** (0.33 g, 1.00 mmol) in THF (20 ml) at −78°C, and the mixture was stirred at this temperature for 1 h under N_2. A solution of benzaldehyde (0.11 g, 1.00 mmol) in THF (2 ml) was then added, and the mixture was stirred for 18 h. The similar work-up described in the typical procedure was done.

4.2.4. Entry 3 (DBU, −78°C, THF, KI, 18-crown-6). This reaction was done in a similar manner described above except addition of KI (0.85 g, 5.00 mmol) and 18-crown-6 (1.32 g, 5.00 mmol) to a solution of **5a** in THF before cooling.

4.2.5. Entry 4 (DBU, 0°C, DMF). A solution of DBU (0.15 g, 1.00 mmol) in DMF (20 ml) was added dropwise to **5a** (0.33 g, 1.00 mmol) in DMF (20 ml) at 0°C, and the mixture was stirred at this temperature for 1 h under N_2. A solution of benzaldehyde (0.11 g, 1.00 mmol) in DMF (2 ml) was then added, and the mixture was stirred for 18 h. The reaction was quenched with saturated NH_4Cl at room temperature. The products were extracted with Et_2O (20 ml×2) from the mixture, and the extract was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was

chromatographed on silica gel using benzene as an eluant to give methyl cinnamate (0.07 g, 43%).

4.2.6. Entry 5, 6, 7 and 8 (DBU, 0°C, DMF, KI). These reactions were done by the similar manner described above except addition of the corresponding amount of KI and 18-crown-6 to the solution of **5a** in DMF before cooling.

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