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Development of a Novel Horner–Wadsworth–Emmons Reagent for the Facile Preparation of Mixed Phosphonoacetates

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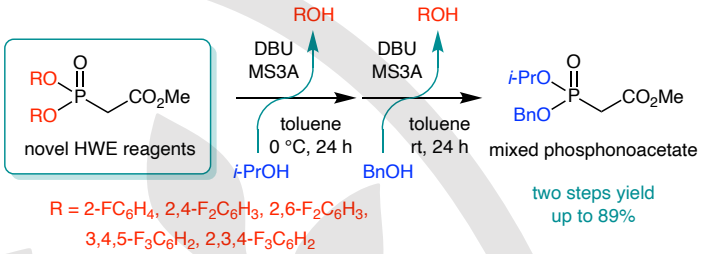

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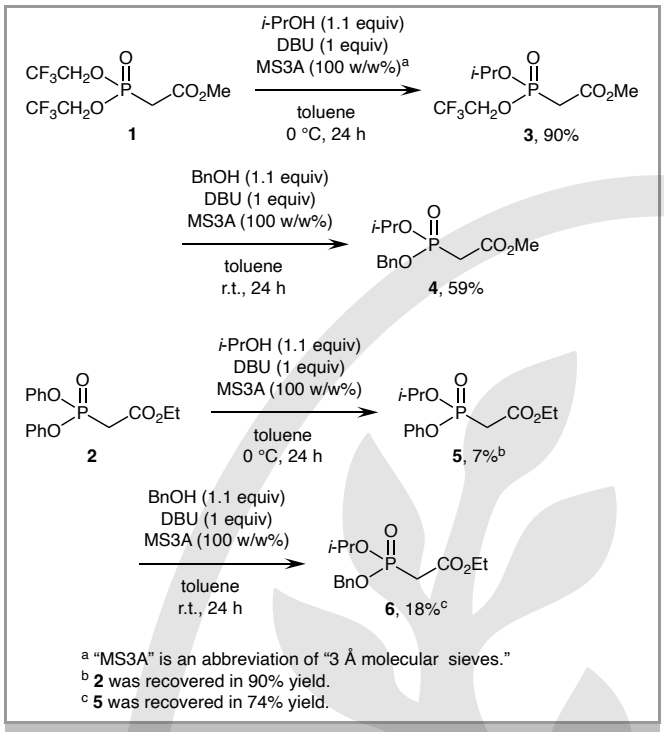
Abstract A novel Horner–Wadsworth–Emmons (HWE) reagent, methyl 2-[bis(3,4,5-trifluorophenoxy)phosphoryl]acetate, was synthesized by the reaction of methyl 2-(dichlorophosphoryl)acetate and 3,4,5-trifluorophenol. Sequential alcoholysis of this HWE reagent with isopropyl alcohol and benzyl alcohol on the phosphorus atom afforded the mixed phosphonoacetate, methyl 2-[(benzyloxy)(isopropoxy)phosphoryl]acetate, in 89% yield for the two steps.

Key words Horner–Wadsworth–Emmons reagents, methyl 2-[bis(3,4,5-trifluorophenoxy)phosphoryl]acetate, alcoholysis, fluorophenols, mixed phosphonoacetates, phosphorus–sulfur bond, phosphonothioate

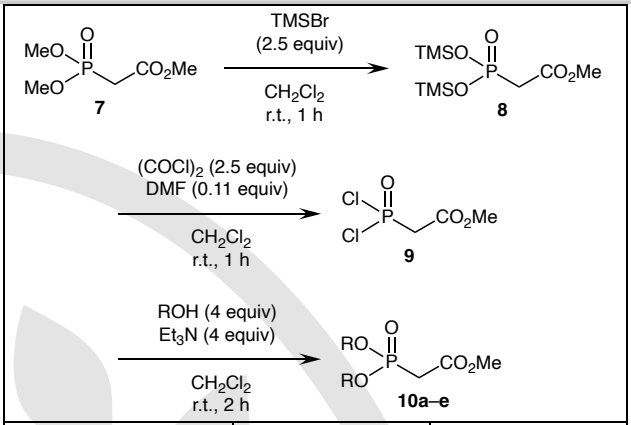
2-[Bis(alkoxy)phosphoryl]acetate ester is well known as a Horner–Wadsworth–Emmons (HWE) reagent that is extremely useful for the stereoselective synthesis of α,β-unsaturated esters.[1] Because HWE reactions are now known as a site-specific and bio-orthogonal method for the functionalization of proteins through aldehydes, their importance has further increased.[2] On the other hand, we have developed a mild and convenient synthetic method for the preparation of mixed phosphonoacetates by alcoholysis reaction on the phosphorus atoms of existing *Z*-selective HWE reagents such as methyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (Still–Gennari reagent, **1**) and ethyl diphenylphosphonoacetate (Ando reagent, **2**). Mixed phosphonoacetate is the common name for 2-[bis(alkoxy)phosphoryl]acetate ester with different alkoxy groups on the phosphorus atom.[3] The alcoholysis reactions of **1** and **2** were applied to the enzymatic synthesis of chiral *P*-stereogenic phosphonoacetates,[4] and the sequential alcoholysis was further applied to the synthesis of glycerophospholipids and their fluorinated analogues.[5] However, depending on the type of alcohol used for sequential alcoholysis, the preparation of mixed phosphonoacetates using the existing *Z*-selective HWE reagents **1** and **2** did not always give satisfactory results. As shown in Scheme 1, alcoholysis of **1** by isopropyl alcohol in toluene in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 0 °C afforded methyl 2-[isopropoxy(2,2,2-trifluoroethoxy)phosphoryl]acetate (**3**) in 90% yield. However, alcoholysis of the resulting mixed phosphonoacetate **3** with benzyl alcohol at room temperature in the presence of DBU gave methyl 2-[(benzyloxy)(isopropoxy)phosphoryl]acetate (**4**) in moderate 59% yield. Furthermore, only 7% yield of ethyl 2-[isopropoxy(phenoxy)phosphoryl]acetate (**5**) was obtained by alcoholysis of **2** with isopropyl alcohol under the same reaction conditions, and the yield of ethyl 2-[(benzyloxy)(isopropoxy)phosphoryl]acetate (**6**) by alcoholysis of **5** with benzyl alcohol was 18%. Therefore, to develop more reactive HWE reagents useful for the synthesis of mixed phosphonoacetate, we designed novel HWE reagents with various fluorophenoxy groups on the phosphorus atoms based on the chemical structure of *Z*-selective HWE reagent **2**. Since fluorophenols are more acidic than phenol, fluorophenoxy anions, the conjugate bases of fluorophenols, are expected to act as good leaving groups in the synthesis of mixed phosphonoacetate **4** by sequential alcoholysis of these HWE reagents by isopropyl alcohol and benzyl alcohol. Herein, we report the synthesis of HWE reagents **10a–e** and their application to the preparation of mixed phosphonates.



Scheme 1 Sequential alcoholysis of *Z*-selective HWE reagents **1** and **2** with isopropyl and benzyl alcohol

HWE reagents **10a–e** with various fluorophenoxy groups were synthesized by the reaction of methyl 2-(dichlorophosphoryl)acetate (**9**) with various fluorophenols as shown in Table 1. Dichloride **9** was prepared by the reaction of oxalyl chloride and methyl 2-{bis[(trimethylsilyl)oxy]phosphoryl}acetate (**8**) in the presence of a catalytic amount of DMF.[6] The intermediate **8** was obtained by bistrimethylsilylation of methyl 2-(dimethoxyphosphoryl)acetate (**7**) with trimethylsilyl bromide.[6] After evaporation of the solvent, the resulting dichloride **9** was used for the subsequent addition of various fluorophenols with triethylamine to the reaction mixture, which gave the desired methyl 2-[bis(fluorophenoxy)phosphoryl]acetates **10a–e** in 70–90% yield for three steps. Although Motoyoshiya *et al.* reported the highly *Z*-selective HWE reaction of methyl 2-[bis(2,4-difluorophenoxy)phosphoryl]acetate (**10b**), its application to the preparation of mixed phosphonoacetates has not been investigated.[7]

Table 1 Synthesis of Methyl 2-[Bis(fluorophenoxy)phosphoryl]acetate **10a–e**

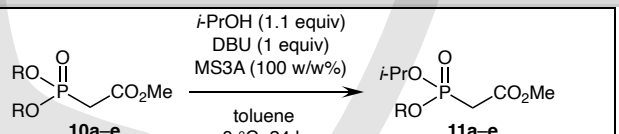


Entry	ROH	Yield of **10a–e** (%)[a]
1	2-FC_6H_4OH	70 (**10a**)
2	2,4-$F_2C_6H_3OH$	90 (**10b**)
3	2,6-$F_2C_6H_3OH$	83 (**10c**)
4	3,4,5-$F_3C_6H_2OH$	82 (**10d**)
5	2,3,4-$F_3C_6H_2OH$	89 (**10e**)

[a] Isolated yield.

To synthesize mixed phosphonoacetate **4** with both isopropoxy and benzyloxy groups on the phosphorus atom using HWE reagents **10a–e** as starting materials, the first step of alcoholysis of **10a–e** with isopropyl alcohol was investigated under reaction conditions in the presence of DBU at 0 °C as in Scheme 1. Considering the reactivity, isopropyl alcohol was used as a representative secondary alcohol in the first step of alcoholysis. As a result, mixed phosphonoacetates **11a–e** were obtained in yields of 85–97%, and the yield tended to increase as the number of fluorine atoms on the benzene ring increased (Table 2). The reaction of **10c–e** having two or three fluorine atoms in the benzene ring was completed in 2 h at 0 °C to furnish mixed phosphonoacetates **11c–e** in good yields (entries 3–5).

Table 2 First Step of Alcoholysis of Methyl 2-[Bis(fluorophenoxy)phosphoryl]acetate **10a–e** in the Presence of DBU



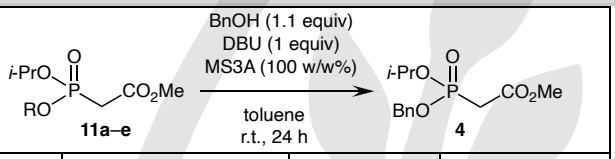
Entry	HWE reagent with fluorophenoxy groups	Yield of **11a–e** (%)[a]	Recovery of **10a–e** (%)[a]
1	**10a** (R = 2-FC_6H_4)	85 (**11a**)	ca. 11 (**10a**)[b]
2	**10b** (R = 2,4-$F_2C_6H_3$)	94 (**11b**)	ca. 6 (**10b**)[b]
3	**10c** (R = 2,6-$F_2C_6H_3$)	96 (**11c**)	0 (**10c**)
4	**10d** (R = 3,4,5-$F_3C_6H_2$)	97 (**11d**)	0 (**10d**)
5[c]	**10e** (R = 2,3,4-$F_3C_6H_2$)	97 (**11e**)	0 (**10e**)

[a] Isolated yield.
[b] Small amounts of impurities were included.
[c] Stirred for 2 h at 0 °C.

The second step of alcoholysis with benzyl alcohol was investigated on mixed phosphonoacetates **11a–e** under reaction conditions in the presence of DBU at room temperature as in

Scheme 1. Considering the reactivity, benzyl alcohol was used as a representative primary alcohol in the second step of alcoholysis. As a result, methyl 2-[(benzyloxy)(isopropoxy)phosphoryl]acetate (**4**) was obtained in yields of 75–92% as shown in Table 3, and as in the first step of alcoholysis, mixed phosphonoacetate **11d** having 3,4,5-trifluorophenoxy groups gave the highest yield among a series of mixed phosphonoacetates **11a–e** (entry 4).

Table 3 Second Step of Alcoholysis of Methyl 2-[Isopropoxy(fluorophenoxy)phosphoryl]acetate **11a–e** in the Presence of DBU

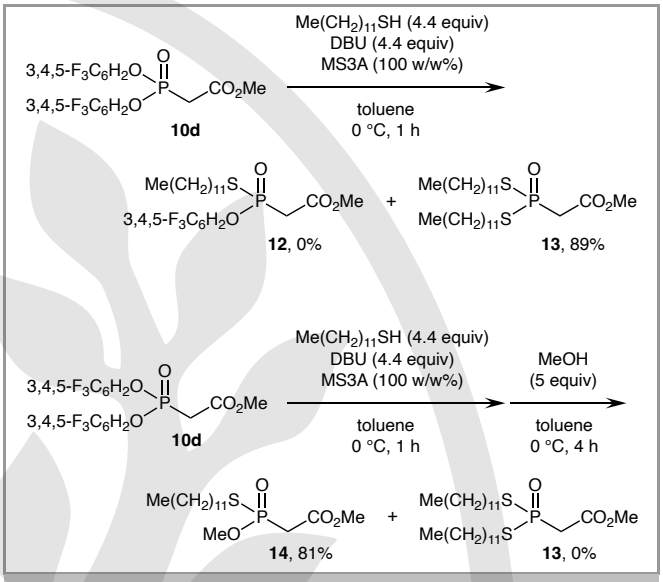


Entry	Mixed phosphonoaceate with fluorophenoxy group	Yield of **4** (%)[a]	Recovery of **11a–e** (%)[a]
1	**11a** (R = 2-FC_6H_4)	75	ca. 23 (**11a**)[b]
2	**11b** (R = 2,4-$F_2C_6H_3$)	88	ca. 11 (**11b**)[b]
3	**11c** (R = 2,6-$F_2C_6H_3$)	82	ca. 18 (**11c**)[b]
4	**11d** (R = 3,4,5-$F_3C_6H_2$)	92	ca. 4 (**11d**)[b]
5	**11e** (R = 2,3,4-$F_3C_6H_2$)	88	0 (**11e**)

[a] Isolated yield.
[b] Small amounts of impurities were included.

The results in Tables 2 and 3 indicate that, among the HWE reagents **10a–e**, the novel reagent **10d** with 3,4,5-trifluorophenoxy groups on the phosphorus atom is the most effective for the synthesis of mixed phosphonoacetate **4**. The existing *Z*-selective HWE reagent **1** sequentially reacted with isopropyl alcohol and benzyl alcohol in two steps to yield mixed phosphonoacetate **4** in 53% yield, whereas the two-step yield of mixed phosphonoacetate **4** from HWE reagent **10d** under the same reaction conditions improved the yield to 89%.

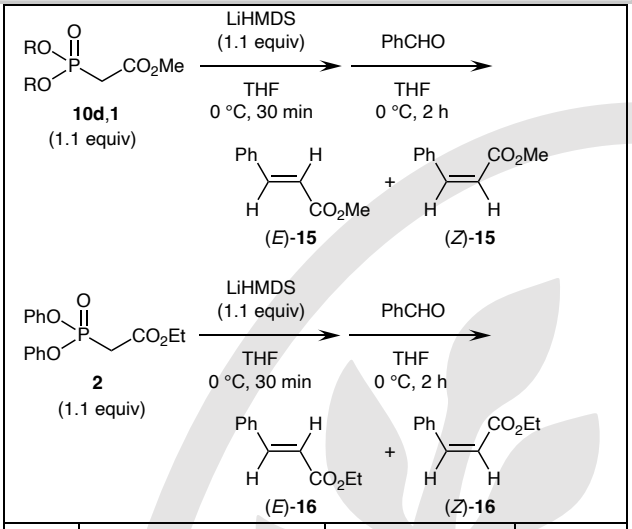
In addition to the alcoholysis reaction, the thiolysis reaction of **10d** was also investigated under the same reaction conditions. However, unlike in the alcoholysis reaction, in the presence of 1.1 equiv of dodecanthiol and 1 equiv of DBU, methyl bis(dodecylthio)phosphorylacetate **13** was obtained in ca. 53% yield based on dodecanthiol, and only trace amounts of methyl 2-[(dodecylthio)(3,4,5-trifluorophenoxy)phosphoryl]acetate **12** were detected. Increasing the amounts of dodecanthiol and DBU to 4.4 equiv improved the yield of phosphonodithioate **13** to 89%, while phosphonothioate **12** was not obtained at all, as shown in Scheme 2. In the presence of thiols, which are more nucleophilic than alcohols, the two 3,4,5-trifluorophenoxy groups of **10d** would be rapidly replaced by dodecanthiols. Phosphonothioate **12** is an unstable compound that is difficult to be isolated. Therefore, methanol was continuously added without isolation and purification of **13** after the reaction with thiol. As a result, the desired phosphonothioate **14** with both a dodecylthio group and a methoxy group on the phosphorus atom was obtained in 81% yield as the major product, and **13** could not be isolated at all. In this reaction, equilibrium is established between phosphonothioate **12** and phosphonodithioate **13** in the reaction medium, and **13** is believed to be converted to the more stable phosphonothioate **14** via the less stable **12**, which is slightly present in the reaction medium. Although the reaction mechanisms of alcoholysis and thiolysis of **10d** are different, this result suggests that **10d** is useful for the synthesis of phosphonothioate derivatives bearing both phosphorus-sulfur and phosphorus-oxygen single bonds.[8]



Scheme 2 Synthesis of methyl 2-[(dodecylthio)(methoxy)phosphoryl]acetate **14**

The reactivity and selectivity of **10d** as the HWE reagent were also preliminarily investigated as shown in Table 4. As a result, the HWE reaction of **10d** with benzaldehyde in the presence of lithium hexamethyldisilazide (LiHMDS) afforded the corresponding methyl 3-phenylacrylate **15** in 81% yield with an *E*/*Z* ratio of 22:78. Meanwhile, under the same conditions, the reaction of existing *Z*-selective HWE reagent **1** with benzaldehyde proceeded to afford methyl 3-phenylacrylate **15** in 85% yield with an *E*/*Z* ratio of 26:74. The HWE reaction of another versatile *Z*-selective HWE reagent **2** with benzaldehyde furnished ethyl 3-phenylacrylate **16** in 93% yield under these conditions, but the stereoselectivity of **16** resulted in an unexpected *E*/*Z* ratio of 46:54. It should be noted that HWE reagent **10b** has been reported to give high *Z*-selectivity (*E*/*Z* = 2:98) by kinetic reaction conditions using potassium hexamethyldisilazide (KHMDS) in the presence of 18-crown-6 at –78 °C.[7b]

Table 4 HWE Reaction of **10d**, **1**, and **2** with Benzaldehyde in the Presence of LiHMDS



Entry	HWE reagent	Yield of **15**,**16** (%)[a]	*E*/*Z*[b]
1	**10d** (R = 3,4,5-$F_3C_6H_2$)	81 (**15**)	22:78
2	**1** (R = CF_3CH_2)	85 (**15**)	26:74
3	**2**	93 (**16**)	46:54

[a] Isolated yield.
[a] Determined by ^{1}H NMR (400 MHz, $CDCl_3$) analysis.

In summary, we have synthesized a novel HWE reagent **10d** bearing two 3,4,5-trifluorophenoxy groups on the phosphorus atom by the reaction of methyl 2-(dichlorophosphoryl)acetate (**9**) with 3,4,5-trifluorophenol, and demonstrated that **10d** is useful for the synthesis of mixed phosphonoacetate **4**. HWE reagent **10d** showed better reactivity for sequential alcoholysis by isopropyl alcohol and benzyl alcohol than ordinary *Z*-selective HWE reagents **1** and **2**. Preliminary findings showed that **10d** exhibited *Z*-selectivity (*E*/*Z* = 22:78) in the HWE reaction with benzaldehyde under LiHMDS conditions. In addition, this HWE reagent was also applicable to the synthesis of phosphonothioate **14** with both phosphorus-sulfur and phosphorus-oxygen single bonds. Further investigations of the synthesis of mixed phosphonoacetates and phosphonothioates using methyl 2-[bis(3,4,5-trifluorophenoxy)phosphoryl]acetate (**10d**) are ongoing in our laboratories.

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All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained with a JASCO FT/IR-6200 IR Fourier transform spectrometer. ^{1}H NMR (400 MHz) spectra were recorded with a Bruker AV400N and Bruker AV400NEO spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded with a Bruker AV500 and JEOL JNM-ECZL500R spectrometer. Chemical shifts are given in δ values (ppm) using TMS as an internal standard. HRMS (ESI) were recorded with a Waters LCT Premier spectrometer. Elemental combustion analyses were performed with a J-SCIENCE LAB JM10. All reactions were monitored by TLC employing 0.25 mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Silica Gel PSQ 60B (Fuji Silysia Chemical) or Silica Gel 60N (Kanto Chemical)]. Anhydrous toluene, CH_2Cl_2, and THF were used as purchased from Kanto Chemical. All other reagents were used as purchased.

Methyl 2-[Bis(2-fluorophenoxy)phosphoryl]acetate (10a)

To a solution of methyl 2-(dimethoxyphosphoryl)acetate (**7**) (387 mg, 2.13 mmol) in anhydrous CH_2Cl_2 (4 mL), trimethylsilyl bromide (0.70 mL, 5.40 mmol) was added at room temperature under argon. After stirring for 1 h at room temperature, the reaction mixture was concentrated *in vacuo*. The oily residue of **8** was dissolved in CH_2Cl_2 (4 mL), then oxalyl chloride (0.45 mL, 5.25 mmol) and a catalytic amount of DMF (15 μL, 0.194 mmol) were added to the mixture. After stirring for 1 h at room temperature, the reaction mixture was concentrated *in vacuo*. The resulting dichloride **9** was dissolved in CH_2Cl_2 (7.5 mL), and then 2-fluorophenol (0.75 mL, 8.52 mmol) and triethylamine (1.15 mL, 8.52 mmol) were added to the reaction mixture. After stirring for 2 h at room temperature, the reaction mixture was quenched with 1N HCl (20 mL) and then extracted with $CHCl_3$ (20 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by flash column chromatography [Silica Gel PSQ 60B (Fuji Silysia Chemical): *n*-hexane–EtOAc (2:1)] to afford **10a** (509 mg, 70%) as a colorless oil.

IR (neat): 2955, 1744, 1609, 1598, 1502, 1458, 1438, 1396, 1261 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.31 (m, 2H), 7.19–7.13 (m, 4H), 7.12–7.06 (m, 2H), 3.79 (s, 3H), 3.44 (d, $^2J_{H,P}$ = 21.8 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.9 (d, $^2J_{C,P}$ = 6.0 Hz), 153.5 (dd, $^1J_{C,F}$ = 249.2 Hz, $^3J_{C,P}$ = 5.1 Hz), 137.4 (dd, $^2J_{C,F}$ = 12.5 Hz, $^2J_{C,P}$ = 8.7 Hz), 126.7 (dd, $^3J_{C,F}$ = 7.1 Hz, $^3J_{C,P}$ = 1.2 Hz), 124.7 (d, $^4J_{C,F}$ = 2.9 Hz), 123.0 (d, $^3J_{C,F}$ = 3.2 Hz), 117.0 (d, $^2J_{C,F}$ = 18.3 Hz), 52.9, 34.1 (d, $^1J_{C,P}$ = 139.3 Hz).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{13}F_2O_5PNa$: 365.0366; found: 365.0372.

Anal. Calcd for $C_{15}H_{13}F_2O_5P$: C, 52.64; H, 3.83. Found: C, 52.35; H, 3.81.

Methyl 2-[Bis(2,4-difluorophenoxy)phosphoryl]acetate (10b)[7,9]

Yield: 709 mg (90%); white solid; mp 30.0–31.0 °C.

IR (neat): 2957, 1745, 1619, 1508, 1438, 1396, 1294 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 2H), 6.96–6.90 (m, 2H), 6.87–6.81 (m, 2H), 3.80 (s, 3H), 3.42 (d, $^2J_{H,P}$ = 21.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.8 (d, $^2J_{C,P}$ = 5.9 Hz), 159.7 (ddd, $^1J_{C,F}$ = 247.7 Hz, $^3J_{C,F}$ = 10.4 Hz, $^6J_{C,P}$ = 1.7 Hz), 153.5 (ddd, $^1J_{C,F}$ = 252.0 Hz, $^3J_{C,F}$ = 12.5 Hz, $^3J_{C,P}$ = 4.9 Hz), 133.8 (ddd, $^2J_{C,F}$ = 12.6 Hz, $^2J_{C,P}$ = 8.8 Hz, $^4J_{C,F}$ = 4.0 Hz), 123.5 (dd, $^3J_{C,F}$ = 9.7 Hz, $^3J_{C,P}$ = 2.8 Hz), 111.5 (dd, $^2J_{C,F}$ = 23.1 Hz, $^4J_{C,F}$ = 2.4 Hz), 105.5 (dd, $^2J_{C,F}$ = 27.1 Hz, $^2J_{C,F}$ = 22.2 Hz), 53.1, 34.0 (d, $^1J_{C,P}$ = 139.7 Hz).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{11}F_4O_5PNa$: 401.0178; found: 401.0203.

Anal. Calcd for $C_{15}H_{11}F_4O_5P$: C, 47.64; H, 2.93. Found: C, 47.42; H, 2.96.

Methyl 2-[Bis(2,6-difluorophenoxy)phosphoryl]acetate (10c)[7b]

Yield: 673 mg (83%); colorless plates (CH_2Cl_2–*n*-hexane); mp 89.0–90.0 °C.

IR (KBr): 2917, 1742, 1613, 1562, 1500, 1478, 1297 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17–7.09 (m, 2H), 7.00–6.92 (m, 4H), 3.83 (s, 3H), 3.57 (d, $^2J_{H,P}$ = 22.1 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.6 (d, $^2J_{C,P}$ = 6.5 Hz), 154.9 (d, $^1J_{C,F}$ = 251.2 Hz), 126.7 (td, $^2J_{C,F}$ = 15.8 Hz, $^2J_{C,P}$ = 9.7 Hz), 126.0 (td, $^3J_{C,F}$ = 8.8 Hz, $^5J_{C,P}$ = 1.6 Hz), 112.40, 112.37, 112.2, 53.0, 34.4 (d, $^1J_{C,P}$ = 140.2 Hz).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{11}F_4O_5PNa$: 401.0178; found: 401.0149.

Anal. Calcd for $C_{15}H_{11}F_4O_5P$: C, 47.64; H, 2.93. Found: C, 47.34; H, 3.00.

Methyl 2-[Bis(3,4,5-trifluorophenoxy)phosphoryl]acetate (10d)

Yield: 700 mg (82%); colorless needles (Et_2O–*n*-hexane); mp 59.0–60.0 °C.

IR (KBr): 2907, 1737, 1628, 1523, 1451, 1330 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.00–6.92 (m, 4H), 3.81 (s, 3H), 3.30 (d, $^2J_{H,P}$ = 21.5 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.5 (d, $^2J_{C,P}$ = 5.8 Hz), 151.3 (ddd, $^1J_{C,F}$ = 252.0 Hz, $^2J_{C,F}$ = 10.8 Hz, $^3J_{C,F}$ = 5.4 Hz), 144.37, 144.34, 144.30, 144.27, 144.24, 144.21, 144.18, 144.14, 144.11, 144.08, 138.4 (dtd, $^1J_{C,F}$ = 251.0 Hz, $^2J_{C,F}$ = 15.2 Hz, $^5J_{C,P}$ = 1.3 Hz), 106.4, 106.33, 106.28, 106.22, 106.17, 106.13, 53.3, 33.5 (d, $^1J_{C,P}$ = 139.1 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_9F_6O_5PNa$: 436.9989; found: 436.9997.

Anal. Calcd for $C_{15}H_9F_6O_5P$: C, 43.50; H, 2.19. Found: C, 43.40; H, 2.38.

Methyl 2-[Bis(2,3,4-trifluorophenoxy)phosphoryl]acetate (10e)

Yield: 793 mg (89%); white solid; mp 36.0–37.0 °C.

IR (KBr): 2915, 1742, 1504, 1438, 1391, 1291 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.17–7.10 (m, 2H), 7.00–6.92 (m, 2H), 3.81 (s, 3H), 3.45 (d, $^2J_{H,P}$ = 21.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.5 (d, $^2J_{C,P}$ = 5.5 Hz), 148.9 (ddt, $^1J_{C,F}$ = 249.5 Hz, $^2J_{C,F}$ = 10.1 Hz, $^3J_{C,F}$ = $^5J_{C,P}$ = 1.8 Hz), 143.8 (dddd, $^1J_{C,F}$ = 253.9 Hz, $^2J_{C,F}$ = 11.9 Hz, $^3J_{C,F}$ = 5.3 Hz, $^3J_{C,P}$ = 3.7 Hz), 140.7 (dddd, $^1J_{C,F}$ = 253.8 Hz, $^2J_{C,F}$ = 16.5 Hz, $^2J_{C,F}$ = 13.2 Hz, $^4J_{C,F}$ = 1.1 Hz), 134.55, 134.52, 134.47, 134.44, 134.39, 134.36, 116.64, 116.61, 116.58, 116.55, 116.52, 111.4 (ddd, $^2J_{C,F}$ = 19.0 Hz, $^3J_{C,F}$ = 4.0 Hz, $^4J_{C,F}$ = 1.4 Hz), 53.2, 34.0 (d, $^1J_{C,P}$ = 140.4 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_9F_6O_5PNa$: 436.9989; found: 436.9987.

Anal. Calcd for $C_{15}H_9F_6O_5P$: C, 43.50; H, 2.19. Found: C, 43.45; H, 2.28.

Methyl 2-[(2-Fluorophenoxy)(isopropoxy)phosphoryl]acetate (11a)

Anhydrous isopropyl alcohol (28.0 µL, 0.366 mmol) and DBU (50.0 µL, 0.333 mmol) were added to a solution of methyl 2-[bis(2-fluorophenoxy)phosphoryl]acetate (**10a**) (114 mg, 0.333 mmol) and molecular sieves 3A (114 mg) in anhydrous toluene (2 mL) at 0 °C under argon. After being stirred at 0 °C for 24 h, the reaction mixture was quenched with 1N HCl (5 mL) and then extracted with $CHCl_3$ (10 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by flash column chromatography [Silica Gel PSQ 60B (Fuji Silysia Chemical): *n*-hexane–EtOAc (3:2)] to afford **11a** (82.2 mg, 85%) as a colorless oil and **10a** was recovered in ca. 11% yield.

IR (neat): 2984, 2954, 1743, 1608, 1597, 1504, 1458, 1437, 1389, 1263, 1003 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.37 (m, 1H), 7.18–7.07 (m, 3H), 4.93 (dsept, $^3J_{H,P}$ = 7.9 Hz, $^3J_{H,H}$ = 6.2 Hz, 1H), 3.76 (s, 3H), 3.17 (d, $^2J_{H,P}$ = 21.8 Hz, 2H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.30 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7 (d, $^2J_{C,P}$ = 6.0 Hz), 153.7 (dd, $^1J_{C,F}$ = 248.5 Hz, $^3J_{C,P}$ = 4.9 Hz), 137.9 (dd, $^2J_{C,F}$ = 12.2 Hz, $^2J_{C,P}$ = 8.1 Hz), 126.1 (dd, $^3J_{C,F}$ = 7.0 Hz, $^3J_{C,P}$ = 1.4 Hz), 124.6 (dd, $^4J_{C,F}$ = 4.1 Hz, $^4J_{C,P}$ = 1.6 Hz), 123.1 (d, $^3J_{C,F}$ = 3.1 Hz), 116.9 (dd, $^2J_{C,F}$ = 18.6 Hz, $^4J_{C,P}$ = 1.1 Hz), 73.4 (d, $^2J_{C,P}$ = 7.1 Hz), 52.7, 34.6 (d, $^1J_{C,P}$ = 137.9 Hz), 23.8 (d, $^3J_{C,P}$ = 5.2 Hz), 23.7 (d, $^3J_{C,P}$ = 4.1 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{16}FO_5PNa$: 313.0617; found: 313.0612.

Methyl 2-[(2,4-Difluorophenoxy)(isopropoxy)phosphoryl]acetate (11b)

Yield: 82.6 mg (94%); colorless oil.

IR (neat): 2985, 1744, 1617, 1509, 1438, 1389, 1279, 1004 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 1H), 6.95–6.89 (m, 1H), 6.87–6.81 (m, 1H), 4.92 (dsept, $^3J_{H,P}$ = 7.9 Hz, $^3J_{H,H}$ = 6.2 Hz, 1H), 3.76 (s, 3H), 3.16 (d, $^2J_{H,P}$ = 21.8 Hz, 2H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.30 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6 (d, $^2J_{C,P}$ = 6.0 Hz), 159.4 (ddd, $^1J_{C,F}$ = 247.0 Hz, $^3J_{C,F}$ = 10.4 Hz, $^6J_{C,P}$ = 1.7 Hz), 153.7 (ddd, $^1J_{C,F}$ = 251.6 Hz, $^3J_{C,F}$ = 12.4 Hz, $^3J_{C,P}$ = 4.9 Hz), 134.3 (ddd, $^2J_{C,F}$ = 12.3 Hz, $^2J_{C,P}$ = 8.3 Hz, $^4J_{C,F}$ = 4.0 Hz), 123.6 (ddd, $^3J_{C,F}$ = 9.9 Hz, $^3J_{C,F}$ = 3.1 Hz, $^3J_{C,P}$ = 1.2 Hz), 111.3 (ddd, $^2J_{C,F}$ = 23.0 Hz, $^4J_{C,F}$ = 3.9 Hz, $^4J_{C,P}$ = 1.5 Hz), 105.3 (ddd, $^2J_{C,F}$ = 27.0 Hz, $^2J_{C,F}$ = 22.2 Hz, $^4J_{C,P}$ = 1.1 Hz), 73.5 (d, $^2J_{C,P}$ = 7.0 Hz), 52.7, 34.6 (d, $^1J_{C,P}$ = 138.2 Hz), 23.8 (d, $^3J_{C,P}$ = 5.0 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{15}F_2O_5PNa$: 331.0523; found: 331.0505.

Methyl 2-[(2,6-Difluorophenoxy)(isopropoxy)phosphoryl]acetate (11c)

Yield: 117 mg (96%); colorless oil.

IR (neat): 2985, 2955, 1745, 1602, 1503, 1479, 1438, 1389, 1281, 1011 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.14–7.06 (m, 1H), 7.01–6.93 (m, 2H), 5.03 (dsept, $^3J_{H,P}$ = 8.2 Hz, $^3J_{H,H}$ = 6.2 Hz, 1H), 3.77 (s, 3H), 3.26 (d, $^2J_{H,P}$ = 22.3 Hz, 2H), 1.41 (d, *J* = 6.2 Hz, 3H), 1.38 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6 (d, $^2J_{C,P}$ = 6.1 Hz), 155.2 (dt, $^1J_{C,F}$ = 249.5 Hz, $^3J_{C,F}$ = $^3J_{C,P}$ = 3.6 Hz), 127.5 (td, $^2J_{C,F}$ = 15.8 Hz, $^2J_{C,P}$ = 8.8 Hz), 125.3 (td, $^3J_{C,F}$ = 9.1 Hz, $^5J_{C,P}$ = 1.7 Hz), 112.3 (ddd, $^2J_{C,F}$ = 17.8 Hz, $^4J_{C,F}$ = 4.7 Hz, $^4J_{C,P}$ = 1.4 Hz), 73.5 (d, $^2J_{C,P}$ = 7.3 Hz), 52.7, 34.8 (d, $^1J_{C,P}$ = 140.1 Hz), 23.9 (d, $^3J_{C,P}$ = 4.7 Hz), 23.6 (d, $^3J_{C,P}$ = 4.6 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{15}F_2O_5PNa$: 331.0523; found: 331.0524.

Methyl 2-[Isopropoxy(3,4,5-trifluorophenoxy)phosphoryl]acetate (11d)

Yield: 83.1 mg (97%); colorless oil.

IR (neat): 2986, 2957, 2939, 1746, 1628, 1590, 1524, 1452, 1439, 1389, 1278, 1051, 997 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.02–6.94 (m, 2H), 4.89 (dsept, $^3J_{H,P}$ = 7.5 Hz, $^3J_{H,H}$ = 6.3 Hz, 1H), 3.77 (s, 3H), 3.11 (dd, $^2J_{H,P}$ = 21.5 Hz, $^2J_{H,H}$ = 14.8 Hz, 1H), 3.09 (dd, $^2J_{H,P}$ = 21.8 Hz, $^2J_{H,H}$ = 14.8 Hz, 1H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4 (d, $^2J_{C,P}$ = 6.2 Hz), 151.1 (ddd, $^1J_{C,F}$ = 250.9 Hz, $^2J_{C,F}$ = 10.8 Hz, $^3J_{C,F}$ = 5.8 Hz), 145.03, 145.00, 144.97, 144.94, 144.90, 144.87, 144.84, 144.80, 144.78, 144.74, 137.8 (dtd, $^1J_{C,F}$ = 249.5 Hz, $^2J_{C,F}$ = 15.1 Hz, $^5J_{C,P}$ = 1.1 Hz), 106.30, 106.26, 106.22, 106.15, 106.11, 106.07, 73.9 (d, $^2J_{C,P}$ = 6.8 Hz), 52.8, 34.3 (d, $^1J_{C,P}$ = 137.6 Hz), 23.9 (d, $^3J_{C,P}$ = 3.7 Hz), 23.7 (d, $^3J_{C,P}$ = 5.3 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{14}F_3O_5PNa$: 349.0429; found: 349.0443.

Anal. Calcd for $C_{12}H_{14}F_3O_5P$: C, 44.18; H, 4.33. Found: C, 43.88; H, 4.45.

Methyl 2-[Isopropoxy(2,3,4-trifluorophenoxy)phosphoryl]acetate (11e)

Yield: 62.4 mg (97%); colorless oil.

IR (neat): 2986, 2956, 1745, 1623, 1507, 1439, 1389, 1378, 1281, 992 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.15 (m, 1H), 6.99–6.91 (m, 1H), 4.93 (dsept, $^3J_{H,P}$ = 7.8 Hz, $^3J_{H,H}$ = 6.2 Hz, 1H), 3.77 (s, 3H), 3.17 (d, $^2J_{H,P}$ = 21.8 Hz, 2H), 1.40 (d, *J* = 6.2 Hz, 3H), 1.31 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4 (d, $^2J_{C,P}$ = 6.0 Hz), 148.5 (ddt, $^1J_{C,F}$ = 248.2 Hz, $^2J_{C,F}$ = 10.1 Hz, $^3J_{C,F}$ = $^5J_{C,P}$ = 1.8 Hz), 143.9 (dddd, $^1J_{C,F}$ = 253.1 Hz, $^2J_{C,F}$ = 11.5 Hz, $^3J_{C,F}$ = 5.2 Hz, $^3J_{C,P}$ = 3.8 Hz), 140.7 (dddd, $^1J_{C,F}$ = 253.1 Hz, $^2J_{C,F}$ = 16.4 Hz, $^2J_{C,F}$ = 13.2 Hz, $^4J_{C,F}$ = 1.1 Hz), 135.26, 135.23, 135.22, 135.20, 135.19, 135.17, 135.16, 135.15, 135.11, 135.09, 135.08, 116.70, 116.68, 116.65, 116.61, 116.59, 111.1 (ddd, $^2J_{C,F}$ = 18.8 Hz, $^3J_{C,F}$ = 4.1 Hz, $^4J_{C,F}$ = 1.5 Hz), 73.9 (d, $^2J_{C,P}$ = 7.1 Hz), 52.8, 34.6 (d, $^1J_{C,P}$ = 138.6 Hz), 23.80 (d, $^3J_{C,P}$ = 4.1 Hz), 23.78 (d, $^3J_{C,P}$ = 5.3 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{14}F_3O_5PNa$: 349.0429; found: 349.0424.

Methyl 2-[Isopropoxy(2,2,2-trifluoroethoxy)phosphoryl]acetate (3)[4a]

Yield: 177 mg (90%); colorless oil.

IR (neat): 2986, 1744, 1263, 1173, 1089, 1007 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.83 (dsept, $^3J_{H,P}$ = 7.9 Hz, $^3J_{H,H}$ = 6.2 Hz, 1H), 4.53–4.36 (m, 2H), 3.76 (s, 3H), 3.04 (d, $^2J_{H,P}$ = 21.3 Hz, 2H), 1.37 (d, *J* = 6.2 Hz, 3H), 1.35 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9 (d, $^2J_{C,P}$ = 5.3 Hz), 122.9 (qd, $^1J_{C,F}$ = 277.5 Hz, $^3J_{C,P}$ = 8.5 Hz), 72.9 (d, $^2J_{C,P}$ = 6.8 Hz), 62.8 (qd, $^2J_{C,F}$ = 37.6 Hz, $^2J_{C,P}$ = 5.1 Hz), 52.7, 34.5 (d, $^1J_{C,P}$ = 140.7 Hz), 23.84 (d, $^3J_{C,P}$ = 5.2 Hz), 23.76 (d, $^3J_{C,P}$ = 4.1 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_8H_{14}F_3O_5PNa$: 301.0429; found: 301.0444.

Ethyl 2-[Isopropoxy(phenoxy)phosphoryl]acetate (5)[4a]

Yield: 9.7 mg (7%); colorless oil.

IR (neat): 2983, 1738, 1593, 1491, 1276, 1204, 1118, 1000 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 2H), 7.27–7.23 (m, 2H), 7.21–7.16 (m, 1H), 4.89 (dsept, $^3J_{H,P}$ = 7.7 Hz, $^3J_{H,H}$ = 6.2 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.08 (d, $^2J_{H,P}$ = 21.7 Hz, 2H), 1.38 (d, *J* = 6.2 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.27 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4 (d, $^2J_{C,P}$ = 6.4 Hz), 150.2 (d, $^2J_{C,P}$ = 8.1 Hz), 129.7, 125.2, 120.7 (d, $^3J_{C,P}$ = 4.3 Hz), 73.0 (d, $^2J_{C,P}$ = 6.8 Hz), 61.7, 34.7 (d, $^1J_{C,P}$ = 136.6 Hz), 23.84 (d, $^3J_{C,P}$ = 3.9 Hz), 23.79 (d, $^3J_{C,P}$ = 5.5 Hz), 14.1.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{19}O_5PNa$: 309.0868; found: 309.0847.

Methyl 2-[(Benzyloxy)(isopropoxy)phosphoryl]acetate (4)[4a]

Anhydrous benzyl alcohol (32.0 μL, 0.309 mmol) and DBU (42.0 μL, 0.284 mmol) were added to a solution of methyl 2-[isopropoxy(3,4,5-trifluorophenoxy)phosphoryl]acetate (**11d**) (92.6 mg, 0.284 mmol) and molecular sieves 3A (92.6 mg) in anhydrous toluene (2 mL) at room temperature under argon. After being stirred at room temperature for 24 h, the reaction mixture was quenched with 1N HCl (5 mL) and then extracted with $CHCl_3$ (10 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by flash column chromatography [Silica Gel PSQ 60B (Fuji Silysia Chemical): *n*-hexane–EtOAc (2:1 to 1:2)] to afford **4** (74.8 mg, 92%) as a colorless oil and **11a** was recovered in ca. 4% yield.

IR (neat): 2981, 2953, 1741, 1456, 1437, 1387, 1275 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.31 (m, 5H), 5.13 (d, $^3J_{H,P}$ = 8.3 Hz, 2H), 4.76 (dsept, $^3J_{H,P}$ = 7.7 Hz, $^3J_{H,H}$ = 6.2 Hz, 1H), 3.71 (s, 3H), 2.97 (d, $^2J_{H,P}$ = 21.6 Hz, 2H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.29 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2 (d, $^2J_{C,P}$ = 6.4 Hz), 136.1 (d, $^3J_{C,P}$ = 6.3 Hz), 128.6, 128.4, 127.8, 72.0 (d, $^2J_{C,P}$ = 6.4 Hz), 67.8 (d, $^2J_{C,P}$ = 6.1 Hz), 52.5, 34.8 (d, $^1J_{C,P}$ = 135.4 Hz), 23.9 (d, $^3J_{C,P}$ = 3.7 Hz), 23.8 (d, $^3J_{C,P}$ = 5.4 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{19}O_5PNa$: 309.0868; found: 309.0895.

Ethyl 2-[(Benzyloxy)(isopropoxy)phosphoryl]acetate (6)

Yield: 23.8 mg (18%); colorless oil.

IR (neat): 2981, 2937, 1738, 1456, 1387, 1271 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.31 (m, 5H), 5.13 (d, $^3J_{H,P}$ = 8.2 Hz, 2H), 4.76 (dsept, $^3J_{H,P}$ = 7.8 Hz, $^3J_{H,H}$ = 6.2 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.96 (d, $^2J_{H,P}$ = 21.6 Hz, 2H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.29 (d, *J* = 6.2 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8 (d, $^2J_{C,P}$ = 6.1 Hz), 136.1 (d, $^3J_{C,P}$ = 6.6 Hz), 128.6, 128.4, 127.8, 71.9 (d, $^2J_{C,P}$ = 6.6 Hz), 67.8 (d, $^2J_{C,P}$ = 6.0 Hz), 61.6, 35.1 (d, $^1J_{C,P}$ = 135.1 Hz), 24.0 (d, $^3J_{C,P}$ = 3.9 Hz), 23.8 (d, $^3J_{C,P}$ = 5.1 Hz), 14.1.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{14}H_{21}O_5PNa$: 323.1024; found: 323.1015.

Methyl 2-[Bis(dodecylthio)phosphoryl]acetate (13)[11]

1-Dodecanethiol (278 μL, 1.17 mmol) and DBU (175 μL, 1.17 mmol) were added to a solution of methyl 2-[bis(3,4,5-trifluorophenoxy)phosphoryl]acetate (**10d**) (110 mg, 0.266 mmol) and molecular sieves 3A (110 mg) in anhydrous toluene (2 mL) at 0 °C under argon. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with 1N HCl (5 mL) and then extracted with $CHCl_3$ (10 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was dissolved in $CHCl_3$ and washed with 1N NaOH (5 mL) and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by flash column chromatography [Silica Gel PSQ 60B (Fuji Silysia Chemical): *n*-hexane–EtOAc (2:1)] to afford **13** (124 mg, 89%) as a white solid.

IR (KBr): 2914, 2848, 1737, 1470, 1437, 1263, 1206, 1117, 1003 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.77 (s, 3H), 3.40 (d, $^2J_{H,P}$ = 16.2 Hz, 2H), 3.04–2.92 (m, 4H), 1.76–1.69 (m, 4H), 1.45–1.35 (m, 4H), 1.34–1.22 (m, 32H), 0.88 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.5 (d, $^2J_{C,P}$ = 5.4 Hz), 52.8, 45.7 (d, $^1J_{C,P}$ = 63.7 Hz), 31.9, 31.1 (d, $^2J_{C,P}$ or $^3J_{C,P}$ = 3.4 Hz), 30.7 (d, $^2J_{C,P}$ or $^3J_{C,P}$ = 5.2 Hz), 29.65, 29.64, 29.58, 29.5, 29.4, 29.0, 28.7, 22.7, 14.1.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{27}H_{55}O_3PS_2Na$: 545.3228; found: 545.3241.

Anal. Calcd for $C_{27}H_{55}O_3PS_2$: C, 62.03; H, 10.60. Found: C, 62.08; H, 10.51.

Methyl 2-[(Dodecylthio)(methoxy)phosphoryl]acetate (14)

1-Dodecanethiol (286 μL, 1.20 mmol) and DBU (180 μL, 1.20 mmol) were added to a solution of methyl 2-[bis(3,4,5-trifluorophenoxy)phosphoryl]acetate (**10d**) (113 mg, 0.273 mmol) and molecular sieves 3A (113 mg) in anhydrous toluene (2 mL) at 0 °C under argon. After being stirred at 0 °C for 1 h, MeOH (55.4 μL, 1.36 mmol) was added to the reaction mixture. After being stirred at 0 °C for 4 h, the reaction mixture was quenched with 1N HCl (5 mL) and then extracted with $CHCl_3$ (10 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by flash column chromatography [Silica Gel PSQ 60B (Fuji Silysia Chemical): $CHCl_3$–EtOAc (20:1) to $CHCl_3$–MeOH (9:1)] to afford **14** (78.3 mg, 81%) as a colorless oil.

IR (neat): 2925, 2853, 1743, 1458, 1436, 1273, 1031 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.81 (d, $^3J_{H,P}$ = 12.9 Hz, 3H), 3.77 (s, 3H), 3.21 (d, $^2J_{H,P}$ = 19.0 Hz, 2H), 2.96–2.88 (m, 2H), 1.75–1.65 (m, 2H), 1.44–1.34 (m, 2H), 1.33–1.21 (m, 16H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7 (d, $^2J_{C,P}$ = 5.5 Hz), 52.8, 52.1 (d, $^2J_{C,P}$ = 7.1 Hz), 41.2 (d, $^1J_{C,P}$ = 100.2 Hz), 31.9, 31.2 (d, $^2J_{C,P}$ or $^3J_{C,P}$ = 4.9 Hz), 30.9 (d, $^2J_{C,P}$ or $^3J_{C,P}$ = 3.4 Hz), 29.63, 29.57, 29.5, 29.4, 29.0, 28.6, 22.7, 14.1.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{33}O_4PSNa$: 375.1735; found: 375.1754.

***Z*-Selective HWE-Type Reaction of Methyl 2-[Bis(3,4,5-trifluorophenoxy)phosphoryl]acetate (10d) with Benzaldehyde**

To a solution of methyl 2-[bis(3,4,5-trifluorophenoxy)phosphoryl]acetate (**10d**) (150 mg, 0.362 mmol) in anhydrous THF (2 mL) was added LiHMDS (ca. 1.3 mol/L in THF, 280 μL, 0.362 mmol), and the solution was stirred at 0 °C for 30 min under argon. After adding benzaldehyde (33.0 μL, 0.329 mmol), the mixture was stirred at 0 °C for 2 h under argon. The reaction mixture was quenched with 1N HCl (2 mL) and extracted with $CHCl_3$ (10 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel PSQ 60B (Fuji Silysia Chemical): *n*-hexane–

EtOAc (5:1)] twice to afford α,β-unsaturated ester **15** (42.7 mg, 81%, *E*/*Z* = 22:78).

Methyl (*E*)-3-Phenylacrylate [(*E*)-15][10–12]

IR (KBr) 2947, 2846, 1718, 1638, 1495, 1452, 1315, 1172 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 16.0 Hz, 1H), 7.55–7.51 (m, 2H), 7.41–7.37 (m, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.5, 144.9, 134.3, 130.3, 128.9, 128.1, 117.8, 51.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{10}O_2Na$: 185.0578; found: 185.0588.

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.22. Found: C, 74.04; H, 6.30.

Methyl (*Z*)-3-Phenylacrylate [(*Z*)-15][11,13]

IR (neat) 2950, 1725, 1632, 1495, 1436, 1200, 1169 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ = 7.60–7.57 (m, 2H), 7.39–7.31 (m, 3H), 6.96 (d, *J* = 12.6 Hz, 1H), 5.96 (d, *J* = 12.6 Hz, 1H), 3.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.6, 143.5, 134.7, 129.7, 129.1, 128.0, 119.2, 51.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{10}O_2Na$: 185.0578; found: 185.0577.

Ethyl (*E*)-3-Phenylacrylate [(*E*)-16][12]

IR (neat) 2981, 1714, 1638, 1449, 1311, 1202, 1176 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 16.0 Hz, 1H), 7.55–7.50 (m, 2H), 7.42–7.36 (m, 3H), 6.44 (d, *J* = 16.0 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.0, 144.6, 134.5, 130.2, 128.9, 128.1, 118.3, 60.5, 14.3.

Ethyl (*Z*)-3-Phenylacrylate [(*Z*)-16][13]

IR (neat) 2981, 1718, 1631, 1495, 1449, 1180 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ = 7.59–7.55 (m, 2H), 7.37–7.30 (m, 3H), 6.95 (d, *J* = 12.6 Hz, 1H), 5.95 (d, *J* = 12.6 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.2, 143.0, 134.9, 129.7, 129.0, 128.0, 119.9, 60.3, 14.1.

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Supporting Information

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Primary Data

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Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

for

Development of a Novel Horner–Wadsworth–Emmons Reagent for the Facile Preparation of Mixed Phosphonoacetates

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^{1}H and ^{13}C NMR Spectra

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