A Facile Method for the Stereoselective Horner–Wadsworth–Emmons Reaction of Aryl Alkyl Ketones

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Excellent *Z* or *E* selectivity was observed in the Horner–Wadsworth–Emmons (HWE) reactions of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate or ethyl 2-fluoro-2-diethylphosphonoacetate with aryl alkyl ketones bearing substituents on an aromatic moiety employing $Sn(OSO_2CF_3)_2$ in the presence of *N*-ethylpiperidine.

Key words Horner–Wadsworth–Emmons reaction; α,β-unsaturated ester; aryl alkyl ketone; methyl bis(2,2,2-trifluoroethyl)-phosphonoacetate; ethyl 2-fluoro-2-diethylphosphonoacetate; Wittig reaction

The Horner–Wadsworth–Emmons (HWE) reaction is an important method for syntheses of α,β-unsaturated esters, α,β-unsaturated ketones, and other conjugated systems.[1)] We have previously reported a new reaction mode for the stereoselective HWE reaction that can be used to prepare α-hydro- and α-fluoro-α,β-unsaturated esters, as shown in Chart 1.[2—5)] As an extension of the stereoselective HWE reaction, we describe herein highly stereoselective *E*- or *Z*-alkene formation in the HWE reaction of aryl alkyl ketones bearing substituents on the aromatic moiety.

An excellent *Z*-selectivity was observed in the HWE reactions of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**1**)[6)] with phenyl or naphthyl alkyl ketones using $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine. The mode of the reactions, however, was remarkably different from that of HWE reactions using NaH.[2)] To our knowledge, detailed information regarding the substituent effects of the aromatic moiety on HWE reactions of aryl alkyl ketones under specific conditions with $Sn(OSO_2CF_3)_2$ has not been reported. We therefore carried out HWE reactions of phosphonate **1** with aryl alkyl ketones **3a**—**g** bearing various substituents on the aromatic moiety, as shown in Chart 2. Results of the HWE reactions of these ketones employing $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine are summarized in Table 1. In the cases of aromatic compounds **3a**, **b**, **d**, all having electron-donating methyl or methoxy group(s), the *E* : *Z* stereoselectivity was excellent, with ratios of 2 : 98, 4 : 96, and 2 : 98, respectively (entries 1, 2, and 4 in Table 1). No reaction occurred in the case of ketone **3c** with a bulky mesityl group (entry 3). In contrast, the similar reactions of ketones **3e**, **f**, both having an electron-withdrawing nitro or trifluoromethyl group, resulted in a slightly lower stereoselectivity (*E* : *Z* = 17 : 83 or 9 : 91) (entries 5 and 6). The reaction of **3g** (entry 7) was carried out as an application of this HWE reaction to the *Z*-selective synthesis of **4g**, a compound related to ozagrel. Ozagrel is an inhibitor of thromboxane A_2 synthetase and has already been launched on the market as an antithrombic and antiasthmatic drug.[7—9)] The stereoselective outcome with excellent *Z*-selectivity in the $Sn(OSO_2CF_3)_2$-mediated HWE reactions can be rationalized in terms of a six-membered transition state proposed by us.[2)] The HWE reaction employing NaH afforded a mixture of geometric isomers in a lower stereoselective manner, as shown in Table 2. It is worth noting that the HWE reaction of ketone **3b** with the *o*-tolyl group has not been observed to occur under NaH conditions, whereas the reaction readily proceeds under $Sn(OSO_2CF_3)_2$ conditions (each entry 2 in Tables 1 and 2). The geometry of **4a**, **b**, **d**—**g** was confirmed by ^1H–^1H nuclear Overhauser effect (NOE) (400 MHz, $CDCl_3$) experiments. The *E* : *Z* ratios of **4a**, **b**, **d**—**g** were determined by utilizing ^1H-NMR analysis (400 MHz, $CDCl_3$).

Ethyl 2-fluoro-2-diethylphosphonoacetate (**2**),[10)] an efficient fluorinating building-block,[11,12)] also provided the excellent stereoselectivity in the HWE reaction under the $Sn(OSO_2CF_3)_2$ conditions, as shown in Chart 3 and Table 3. (*E*)-α-Fluoro-α,β-unsaturated esters **5a**, **b**, **d**—**f** were obtained as major products in each corresponding reaction (entries 1, 2, 4, 5, and 6 in Table 3). In other words, the aromatic and ester moieties are on the same side of the double bond of (*E*)-**5** as well as in the cases of (*Z*)-**4**. The HWE reaction of aryl alkyl ketone **3g** with α-fluorophosphonate **2** using $Sn(OSO_2CF_3)_2$ in the presence of *N*-ethylpiperidine produced **5g** with high *E* selectivity (entry 7 in Table 3). In contrast, similar HWE reactions of **2** with **3a**—**g** by the conventional methods using NaH gave *E*-selective products **5a**, **b**, **d**—**g** in a range of *E* : *Z* ratios, 80 : 20—88 : 12, as listed in Table 4. The geometries of **5a**, **b**, **d**, **f**, **g** were confirmed on the basis of ^1H–^1H NOE experiments (400 MHz, $CDCl_3$) of the corresponding primary alcohols derived by reduction of

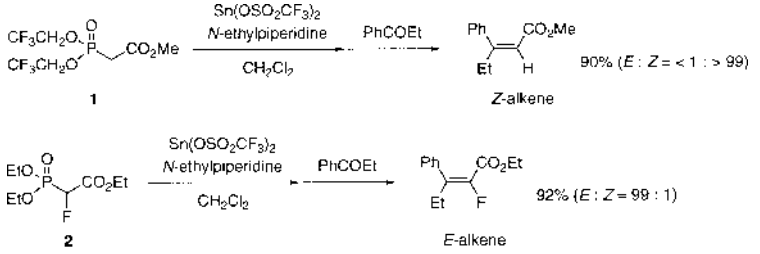

Chart 1

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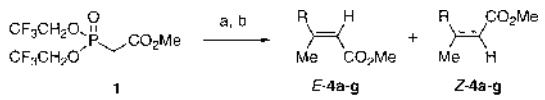


a: R = 3,5-xylyl, **b**: R = *o*-tolyl, **c**: R = mesityl, **d**: R = *p*-methoxyphenyl, **e**: R = *p*-nitrophenyl, **f**: R = *p*-(trifluoromethyl)phenyl, **g**: R = *p*-(1*H*-imidazol-1-ylmethyl)phenyl

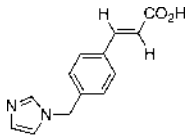
a) $Sn(OSO_2CF_3)_2$ - *N*-ethylpiperidine or NaH , b) RCOMe (**3a-g**)

Chart 2

Table 1. $Sn(OSO_2CF_3)_2$-Mediated Horner–Wadsworth–Emmons Reactions of **1** with Ketones **3a**—**g**[a]

Entry	Ketone	Time (h)	Yield (%)[b]	Alkene (*E*/*Z*)[c]
1	**3a**	19	55	**4a** (2 : 98)
2	**3b**	21	84	**4b** (4 : 96)
3	**3c**	60[d]	—[e]	—
4	**3d**	21	95	**4d** (2 : 98)
5	**3e**	14	100	**4e** (17 : 83)
6	**3f**	19	97	**4f** (9 : 91)
7	**3g**	20	65	**4g** (8 : 92)

a) Conditions: CH_2Cl_2, 0 °C, **1**/$Sn(OSO_2CF_3)_2$/*N*-ethylpiperidine/**3** (1.4 : 1.68 : 1.54 : 1). *b*) Isolated yields. *c*) ^{1}H-NMR (400 MHz, $CDCl_3$) analysis. *d*) 0 °C, 20 h→ room temperature (rt), 40 h. *e*) No reaction.

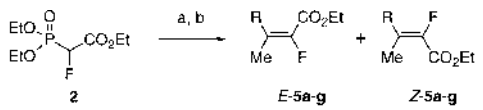


ozagrel

Table 2. NaH-Mediated Horner–Wadsworth–Emmons Reactions of **1** with Ketones **3a**—**g**[a]

Entry	Ketone	Time (h)	Yield (%)[b]	Alkene (*E*/*Z*)[c]
1	**3a**	45[d]	54	**4a** (43 : 57)
2	**3b**	24	—[f]	—
3	**3c**	23[e]	—[f]	—
4	**3d**	19	33	**4d** (51 : 49)
5	**3e**	19	99	**4e** (35 : 65)
6	**3f**	18	92	**4f** (39 : 61)
7	**3g**	16	58	**4g** (43 : 57)

a) Conditions: THF, 0 °C to rt, **1**/NaH/**3** (1.7 : 1.5 : 1). *b*) Isolated yields. *c*) ^{1}H-NMR (400 MHz, $CDCl_3$) analysis. *d*) rt. *e*) 0 °C, 16 h→reflux, 7 h. *f*) No reaction.



a: R = 3,5-xylyl, **b**: R = *o*-tolyl, **c**: R = mesityl, **d**: R = *p*-methoxyphenyl, **e**: R = *p*-nitrophenyl, **f**: R = *p*-(trifluoromethyl)phenyl, **g**: R = *p*-(1*H*-imidazol-1-ylmethyl)phenyl

a) $Sn(OSO_2CF_3)_2$ - *N*-ethylpiperidine or NaH , b) RCOMe (**3a-g**)

Chart 3

5a, **b**, **d**, **f**, **g**. In the case of **5e**, the geometry of the major product was established to be *E* by X-ray crystallographic analysis.[13] The diastereomer ratios of **5a**, **b**, **d**—**g** were determined by ^{1}H-NMR (400 MHz, $CDCl_3$) analysis.

In conclusion, we have demonstrated that the $Sn(OSO_2CF_3)_2$-mediated HWE reactions of several aryl alkyl ketones bearing various substituents on the aromatic moiety proceed in a highly stereoselective manner and involve generality.

Table 3. $Sn(OSO_2CF_3)_2$-Mediated Horner–Wadsworth–Emmons Reactions of **2** with Ketones **3a**—**g**[a]

Entry	Ketone	Time (h)	Yield (%)[b]	Alkene (*E*/*Z*)[c]
1	**3a**	18	84	**5a** (>99 : <1)
2	**3b**	18	100	**5b** (98 : 2)
3	**3c**	60[d]	—[e]	—
4	**3d**	18	69	**5d** (98 : 2)
5	**3e**	17	96	**5e** (97 : 3)
6	**3f**	18	100	**5f** (97 : 3)
7	**3g**	22	70	**5g** (96 : 4)

a) Conditions: CH_2Cl_2, 0 °C, **2**/$Sn(OSO_2CF_3)_2$/*N*-ethylpiperidine/**3** (1.4 : 1.68 : 1.54 : 1). *b*) Isolated yields. *c*) ^{1}H-NMR (400 MHz, $CDCl_3$) analysis. *d*) 0 °C, 20 h→rt, 40 h. *e*) No reaction.

Table 4. NaH-Mediated Horner–Wadsworth–Emmons Reactions of **2** with Ketones **3a**—**g**[a]

Entry	Ketone	Time (h)	Yield (%)[b]	Alkene (*E*/*Z*)[c]
1	**3a**	20	100	**5a** (87 : 13)
2	**3b**	19	100	**5b** (88 : 12)
3	**3c**	30[d]	—[e]	—
4	**3d**	14	100	**5d** (87 : 13)
5	**3e**	6	97	**5e** (81 : 19)
6	**3f**	6	97	**5f** (83 : 17)
7	**3g**	20	73	**5g** (80 : 20)

a) Conditions: THF, 0 °C to rt, **2**/NaH/**3** (1.7 : 1.5 : 1). *b*) Isolated yields. *c*) ^{1}H-NMR (400 MHz, $CDCl_3$) analysis. *d*) 0 °C, 20 h→reflux, 10 h. *e*) No reaction.

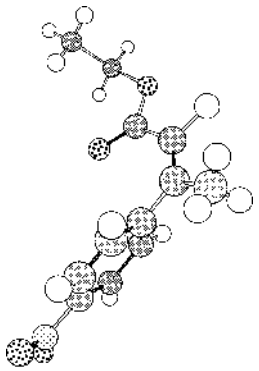


Fig. 1. Computer-Generated Drawing Derived from the X-Ray Coordinates of (*E*)-**5e**

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1720 IR Fourier transform spectrometer. ^{1}H-NMR (200 and 400 MHz) spectra were recorded on a JEOL JNM-FX 200, JEOL JNM-GSX400, or Bruker ARX-400 spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as an internal standard. Electron impact (EI)-MS were recorded on a JEOL JMS SX-102A spectrometer. Elementary combustion analyses were performed by a Yanaco CHN CORDER MT-5. All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Preparative TLC (PTLC) was performed on 0.5-mm silica gel plates (Merck 5744; 60 F_{254}). Column chromatography was carried out on silica gel (Katayama Chemical K070; 70—300 mesh, Merck 9385; 230—400 mesh). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under N_2. *N*-Ethylpiperidine and CH_2Cl_2 were distilled

from CaH_2. All other solvents were distilled prior to use. All reagents were used as purchased.

Typical Procedure for the HWE Reaction with $Sn(OSO_2CF_3)_2$ To a suspension of $Sn(OSO_2CF_3)_2$ (350 mg, 0.84 mmol) and methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**1**) (150 μl, 0.70 mmol) in anhydrous CH_2Cl_2 (5 ml) was added *N*-ethylpiperidine (106 μl, 0.77 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h under argon, and *p*-methoxyphenyl ethyl ketone (**3d**) (75 mg, 0.50 mmol) was added. After being stirred at 0 °C for 21 h under argon, the reaction mixture was poured into H_2O (15 ml) and then extracted with $CHCl_3$ (50 ml×3). To the $CHCl_3$ extract was added *n*-hexane (180 ml), and the mixture was submitted to filtration through a silica gel short column. The filtrate was evaporated *in vacuo* to afford a crude product **4d** (*E* : *Z*=2 : 98), which was purified by PTLC [*n*-hexane/AcOEt (6 : 1)] to obtain *E*-**4d** (2 mg, 2%) and *Z*-**4d** (96 mg, 93%) as a colorless oil, respectively.

Typical Procedure for the HWE Reaction with NaH To a suspension of NaH (abs. 60% in oil, 52 mg, 1.35 mmol) in anhydrous THF (5 ml) was added methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**1**) (320 μl, 1.53 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min under argon, and *p*-methoxyphenyl ethyl ketone (**3d**) (136 mg, 0.90 mmol) was added. After being stirred at 0 °C for 19 h under argon, 5% HCl (15 ml) was added and then extracted with ether (40 ml×3). The extract was washed with brine, dried over anhydrous $MgSO_4$. Evaporation *in vacuo* afforded a crude product **4d** (*E* : *Z*=51 : 49), which was purified by PTLC [*n*-hexane/AcOEt (6 : 1)] to obtain *E*-**4d** (34 mg, 18%) and *Z*-**4d** (28 mg, 15%) as a colorless oil, respectively.

Methyl (*E*)-3-(3,5-Xylyl)-2-butenoate [(*E*)-**4a**]: Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.33 (6H, s), 2.55 (3H, s), 3.75 (3H, s), 6.11 (1H, s), 7.01—7.08 (3H, m); IR (neat) 2950, 1718, 1628, 1377, 1316, 1218, 1165, 1107 cm^{-1}; EI-MS Calcd for $C_{13}H_{16}O_2$ MW 204.1150, Found *m*/*z* 204.1150 (M^+).

Methyl (*Z*)-3-(3,5-Xylyl)-2-butenoate [(*Z*)-**4a**]: Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.15 (3H, d, *J*=1.4 Hz), 2.31 (6H, s), 3.56 (3H, s), 5.88 (1H, q, *J*=1.4 Hz), 6.81 (2H, s), 6.94 (1H, s); IR (neat) 2949, 1732, 1642, 1601, 1435, 1284, 1160, 1106 cm^{-1}; EI-MS Calcd for $C_{13}H_{16}O_2$ MW 204.1150, Found *m*/*z* 204.1175 (M^+).

Methyl (*E*)-3-(*o*-Tolyl)-2-butenoate [(*E*)-**4b**]: Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.29 (3H, s), 2.45 (3H, d, *J*=0.9 Hz), 3.75 (3H, s), 5.77 (1H, q, *J*=0.9 Hz), 7.06—7.08 (1H, m), 7.15—7.21 (3H, m); IR (neat) 2950, 1719, 1642, 1375, 1265, 1170, 765 cm^{-1}; EI-MS Calcd for $C_{12}H_{14}O_2$ MW 190.0994, Found *m*/*z* 190.0991 (M^+).

Methyl (*Z*)-3-(*o*-Tolyl)-2-butenoate [(*Z*)-**4b**]: Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.12 (3H, d, *J*=0.9 Hz), 2.20 (3H, s), 3.53 (3H, s), 5.99 (1H, q, *J*=0.9 Hz), 6.94—6.96 (1H, m), 7.17—7.19 (3H, m); IR (neat) 2950, 1732, 1647, 1373, 1202, 1122, 768 cm^{-1}; EI-MS Calcd for $C_{12}H_{14}O_2$ MW 190.0994, Found *m*/*z* 190.0996 (M^+).

Methyl (*E*)-3-(*p*-Methoxyphenyl)-2-butenoate [(*E*)-**4d**]: Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.57 (3H, d, *J*=1.0 Hz), 3.74 (3H, s), 3.83 (3H, s), 6.11 (1H, q, *J*=1.0 Hz), 6.87—6.92 (2H, m), 7.43—7.47 (2H, m); IR (neat) 3015, 1709, 1605, 1514, 1438, 1253, 1213, 833 cm^{-1}; EI-MS Calcd for $C_{12}H_{14}O_3$ MW 206.0943, Found *m*/*z* 206.0939 (M^+); *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.00; H, 6.96.

Methyl (*Z*)-3-(*p*-Methoxyphenyl)-2-butenoate [(*Z*)-**4d**]: Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.17 (3H, d, *J*=1.2 Hz), 3.58 (3H, s), 3.81 (3H, s), 5.88 (1H, q, *J*=1.2 Hz), 6.86—6.90 (2H, m), 7.17—7.22 (2H, m); IR (neat) 2950, 1725, 1608, 1511, 1377, 1251, 833 cm^{-1}; EI-MS Calcd for $C_{12}H_{14}O_3$ MW 206.0943, Found *m*/*z* 206.0934 (M^+); *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.55; H, 6.91.

Methyl (*E*)-3-(*p*-Nitrophenyl)-2-butenoate [(*E*)-**4e**]: Colorless needles (EtOH): mp 206—208.5 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.60 (3H, d, *J*=1.0 Hz), 3.79 (3H, s), 6.19 (1H, q, *J*=1.0 Hz), 7.60—7.64 (2H, m), 8.22—8.26 (2H, m); IR (KBr) 3079, 2958, 1743, 1729, 1515, 1345, 1292, 1147, 1010, 853 cm^{-1}; EI-MS Calcd for $C_{11}H_{11}NO_4$ MW 221.0688, Found *m*/*z* 221.0701 (M^+); *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.65; H, 5.10; N, 6.23.

Methyl (*Z*)-3-(*p*-Nitrophenyl)-2-butenoate [(*Z*)-**4e**]: Colorless needles (EtOH): mp 117.5—120 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.20 (3H, d, *J*=1.2 Hz), 3.57 (3H, s), 6.01 (1H, q, *J*=1.2 Hz), 7.33—7.37 (2H, m), 8.21—8.25 (2H, m); IR (KBr) 2953, 1743, 1728, 1632, 1515, 1345, 1010, 852 cm^{-1}; EI-MS Calcd for $C_{11}H_{11}NO_4$ MW 221.0688, Found *m*/*z* 221.0707 (M^+); *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.77; H, 5.09; N, 6.26.

Methyl (*E*)-3-[*p*-(Trifluoromethyl)phenyl]-2-butenoate [(*E*)-**4f**]: Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.58 (3H, d, *J*=0.7 Hz), 3.77 (3H, s), 6.15 (1H, q, *J*=0.7 Hz), 7.58—7.62 (4H, m); IR (neat) 2953, 1723, 1635, 1437, 1327, 1275, 1083, 723 cm^{-1}; EI-MS Calcd for $C_{12}H_{11}O_2F_3$ MW 244.0711, Found *m*/*z* 244.0733 (M^+).

Methyl (*Z*)-3-[*p*-(Trifluoromethyl)phenyl]-2-butenoate [(*Z*)-**4f**]: Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.18 (3H, d, *J*=1.2 Hz), 3.57 (3H, s), 5.98 (1H, q, *J*=1.2 Hz), 7.29—7.33 (2H, m), 7.60—7.64 (2H, m); IR (neat) 2953, 1729, 1651, 1445, 1327, 1239, 1086, 729 cm^{-1}; EI-MS Calcd for $C_{12}H_{11}O_2F_3$ MW 244.0711, Found *m*/*z* 244.0735 (M^+); *Anal.* Calcd for $C_{12}H_{11}O_2F_3$: C, 59.02; H, 4.54. Found: C, 58.59; H, 4.62.

An Inseparable Mixture of Methyl (*E*)- and (*Z*)-3-[*p*-(1*H*-Imidazol-1-ylmethyl)phenyl]-2-butenoate [(*E*)- and (*Z*)-**4g**]: Pale yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.16 (3H, d, *J*=1.2 Hz, *Z*-isomer), 2.56 (3H, d, *J*=1.0 Hz, *E*-isomer), 3.56 (3H, s, *Z*-isomer), 3.76 (3H, s, *E*-isomer), 5.14 (2H, s, *E*- and *Z*-isomer), 5.93 (1H, d, *J*=1.2 Hz, *Z*-isomer), 6.12 (1H, d, *J*=1.0 Hz, *E*-isomer), 6.91—7.65 (7H, m, *E*- and *Z*-isomer); EI-MS Calcd for $C_{15}H_{16}N_2O_2$ MW 256.1212, Found *m*/*z* 256.1194 (M^+).

Ethyl (*E*)-2-Fluoro-3-(3,5-xylyl)-2-butenoate [(*E*)-**5a**]: Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.03 (3H, t, *J*=7.3 Hz), 2.10 (3H, d, $^4J_{H,F}$=4.6 Hz), 2.29 (6H, s), 4.04 (2H, q, *J*=7.3 Hz), 6.77 (2H, s), 6.92 (1H, s); IR (neat) 2983, 1730, 1658, 1445, 1376, 1333, 851, 722 cm^{-1}; EI-MS Calcd for $C_{14}H_{17}O_2F$ MW 236.1213, Found *m*/*z* 236.1209 (M^+); *Anal.* Calcd for $C_{14}H_{17}O_2F$: C, 71.17; H, 7.25. Found: C, 70.68; H, 7.28.

Ethyl (*Z*)-2-Fluoro-3-(3,5-xylyl)-2-butenoate [(*Z*)-**5a**]: Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, t, *J*=7.3 Hz), 2.32 (6H, s), 2.39 (3H, d, $^4J_{H,F}$=3.7 Hz), 4.32 (2H, q, *J*=7.3 Hz), 6.95—6.97 (3H, m); IR (neat) 2984, 1724, 1644, 1446, 1369, 1289, 1062 cm^{-1}; EI-MS Calcd for $C_{14}H_{17}O_2F$ MW 236.1213, Found *m*/*z* 236.1203 (M^+); *Anal.* Calcd for $C_{14}H_{17}O_2F$: C, 71.17; H, 7.25. Found: C, 70.93; H, 7.37.

Ethyl (*E*)-2-Fluoro-3-(*o*-tolyl)-2-butenoate [(*E*)-**5b**]: Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.97 (3H, t, *J*=6.8 Hz), 2.09 (3H, d, $^4J_{H,F}$= 4.1 Hz), 2.21 (3H, s), 4.00 (2H, q, *J*=6.8 Hz), 6.98—6.99 (1H, m), 7.14—7.21 (3H, m); IR (neat) 2985, 1732, 1664, 1445, 1376, 1284, 1053, 864 cm^{-1}; EI-MS Calcd for $C_{13}H_{15}O_2F$ MW 222.1056, Found *m*/*z* 222.1029 (M^+).

Ethyl (*Z*)-2-Fluoro-3-(*o*-tolyl)-2-butenoate [(*Z*)-**5b**]: Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.38 (3H, t, *J*=7.3 Hz), 2.25 (3H, s), 2.35 (3H, d, $^4J_{H,F}$=3.2 Hz), 4.34 (2H, q, *J*=7.3 Hz), 7.06—7.07 (1H, m), 7.19—7.23 (3H, m); IR (neat) 2984, 1724, 1657, 1489, 1370, 1263, 1058, 861 cm^{-1}; EI-MS Calcd for $C_{13}H_{15}O_2F$ MW 222.1056, Found *m*/*z* 222.1052 (M^+); *Anal.* Calcd for $C_{13}H_{15}O_2F$: C, 70.25; H, 6.80. Found: C, 70.06; H, 6.87.

Ethyl (*E*)-2-Fluoro-3-(*p*-methoxyphenyl)-2-butenoate [(*E*)-**5d**]: Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.10 (3H, t, *J*=7.1 Hz), 2.13 (3H, d, $^4J_{H,F}$=4.4 Hz), 3.82 (3H, s), 4.08 (2H, q, *J*=7.1 Hz), 6.86—6.90 (2H, m), 7.10—7.15 (2H, m); IR (neat) 2984, 1729, 1654, 1577, 1466, 1377, 1151, 833 cm^{-1}; EI-MS Calcd for $C_{13}H_{15}O_3F$ MW 238.1005, Found *m*/*z* 238.1012 (M^+); *Anal.* Calcd for $C_{13}H_{15}O_3F$: C, 65.54; H, 6.35. Found: C, 65.16; H, 6.35.

Ethyl (*Z*)-2-Fluoro-3-(*p*-methoxyphenyl)-2-butenoate [(*Z*)-**5d**]: Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.37 (3H, t, *J*=7.1 Hz), 2.43 (3H, d, $^4J_{H,F}$=3.7 Hz), 3.83 (3H, s), 4.33 (2H, q, *J*=7.1 Hz), 6.89—6.94 (2H, m), 7.36—7.40 (2H, m); IR (neat) 2984, 1719, 1607, 1460, 1369, 1304, 1182, 834 cm^{-1}; EI-MS Calcd for $C_{13}H_{15}O_3F$ MW 238.1005, Found *m*/*z* 238.1006 (M^+); *Anal.* Calcd for $C_{13}H_{15}O_3F$: C, 65.54; H, 6.35. Found: C, 65.65; H, 6.38.

Ethyl (*E*)-2-Fluoro-3-(*p*-nitrophenyl)-2-butenoate [(*E*)-**5e**]: Colorless plates (EtOH): mp 97—98 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.09 (3H, t, *J*=7.3 Hz), 2.17 (3H, d, $^4J_{H,F}$=4.6 Hz), 4.09 (2H, q, *J*=7.3 Hz), 7.35—7.37 (2H, m), 8.22—8.24 (2H, m); IR (KBr) 3011, 2966, 1725, 1662, 1515, 1349, 1271, 1156, 1046, 852 cm^{-1}; EI-MS Calcd for $C_{12}H_{12}NO_4F$ MW 253.0750, Found *m*/*z* 253.0748 (M^+); *Anal.* Calcd for $C_{12}H_{12}NO_4F$: C, 56.92; H, 4.78; N, 5.53. Found: C, 56.98; H, 4.86; N, 5.52.

Ethyl (*Z*)-2-Fluoro-3-(*p*-nitrophenyl)-2-butenoate [(*Z*)-**5e**]: Colorless needles (EtOH): mp 70.5—72 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.39 (3H, t, *J*=7.3 Hz), 2.46 (3H, d, $^4J_{H,F}$=3.7 Hz), 4.36 (2H, q, *J*=7.3 Hz), 7.54—7.56 (2H, m), 8.24—8.26 (2H, m); IR (KBr) 3001, 1719, 1646, 1519, 1352, 1278, 1152, 1052, 855 cm^{-1}; EI-MS Calcd for $C_{12}H_{12}NO_4F$ MW 253.0750, Found *m*/*z* 253.0737 (M^+); *Anal.* Calcd for $C_{12}H_{12}NO_4F$: C, 56.92; H, 4.78; N, 5.53. Found: C, 56.73; H, 4.77; N, 5.41.

Ethyl (*E*)-2-Fluoro-3-[*p*-(trifluoromethyl)phenyl]-2-butenoate [(*E*)-**5f**]: Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.04 (3H, t, *J*=7.3 Hz), 2.15 (3H, d, $^4J_{H,F}$=4.1 Hz), 4.06 (2H, q, *J*=7.3 Hz), 7.29—7.31 (2H, m), 7.60—7.63 (2H, m); IR (neat) 1730, 1665, 1618, 1446, 1327, 1269, 1166, 1048, 775 cm^{-1}; EI-MS Calcd for $C_{13}H_{12}O_2F_4$ MW 276.0773, Found *m*/*z* 276.0775 (M^+); *Anal.* Calcd for $C_{13}H_{12}O_2F_4$: C, 56.53; H, 4.38. Found: C, 56.36; H,

4.44.

Ethyl (*Z*)-2-Fluoro-3-[*p*-(trifluoromethyl)phenyl]-2-butenoate [(*Z*)-**5f**]: Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.38 (3H, t, J=7.3 Hz), 2.44 (3H, d, $^4J_{H,F}$=3.7 Hz), 4.35 (2H, q, J=7.3 Hz), 7.48—7.50 (2H, m), 7.64—7.66 (2H, m); IR (neat) 1727, 1619, 1326, 1307, 1269, 1128, 733 cm^{-1}; EI-MS Calcd for $C_{13}H_{12}O_2F_4$ MW 276.0773, Found *m*/*z* 276.0770 (M^+); *Anal.* Calcd for $C_{13}H_{12}O_2F_4$: C, 56.53; H, 4.38. Found: C, 56.70; H, 4.49.

An Inseparable Mixture of Ethyl (*E*)- and (*Z*)-2-Fluoro-3-[*p*-(1*H*-imidazol-1-ylmethyl)phenyl]-2-butenoate [(*E*)- and (*Z*)-**5g**]: Pale yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.06 (3H, t, J=7.1 Hz, *E*-isomer), 1.38 (3H, t, J=7.3 Hz, *Z*-isomer), 2.12 (3H, d, $^4J_{H,F}$=4.4 Hz, *E*-isomer), 2.42 (3H, d, $^4J_{H,F}$=2.2 Hz, *Z*-isomer), 4.07 (2H, q, J=7.1 Hz, *E*-isomer), 4.34 (2H, q, J=7.3 Hz, *Z*-isomer), 5.14 (2H, s, *E*- and *Z*-isomer), 6.92—7.56 (7H, m, *E*- and *Z*-isomer); EI-MS Calcd for $C_{16}H_{17}N_2O_2$ MW 288.1274, Found *m*/*z* 288.1287 (M^+).

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13) The crystallographic data of (*E*)-**5e** are as follows. (*E*)-**5e**: $C_{12}H_{12}NO_4F$, M=253.23, monoclinic, $P2_1/n$, a=12.485(4) Å, b=6.989(1) Å, c=13.984(4) Å, β=103.47(1)°, V=1186.6(5) Å^3, Z=4, D_{Calcd}=1.417 g/cm^3.