

Enantioselective Friedel-Crafts Alkylation Reaction of Indoles with α,β -Unsaturated Acyl Phosphonates Catalyzed by Chiral Phosphoric Acid

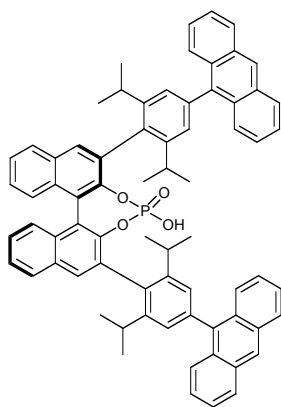
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1. General Experimental details:

All the reaction flasks were dried by flame, and all reactions were carried out under N₂ unless otherwise noted. All the solvents were distilled under nitrogen and stored over MS 4Å prior to use. The reagents were purchased from commercial sources and used directly. Thin layer chromatography was performed on Merck 60 F₂₅₄ silica gel plates and visualization was accomplished by irradiation with UV light or by treatment with a solution of phosphomolybdic acid solution followed by heating. Crude products were purified by column chromatography on silica gel of 100-200 mesh. NMR spectra were recorded on Unity Inova-400 instrument (Varian Japan Ltd., 400 MHz for ¹H, 100 MHz for ¹³C) using CDCl₃ as a solvent. Chemical shifts (δ) for ¹H were referenced to tetramethylsilane (δ = 0.0 ppm) as an internal standard. Chemical shifts (δ) for ¹³C were referenced to a solvent signal (CDCl₃, δ = 77.0 ppm). H₃PO₄ was used as an external standard (δ = 0) for ³¹P NMR. IR spectra were recorded on a Shimadzu FT-IR 8600 spectrometer using CHCl₃ as a solvent. Mass spectra were measured on JMS-AX505HA instrument (JEOL). Elemental analysis (EA) was carried out on EA1110 instrument (Amco Inc.). Specific rotation was recorded on SEPA-300 instrument (HORIBA, Ltd.).

1. Catalyst 4f:¹



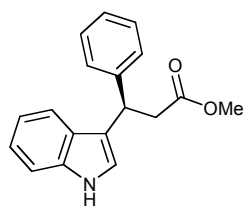
Catalyst **4f** was prepared as per reported procedure.

$[\alpha]_D^{22}$ -173 (c 1.06, EA); ¹H NMR (400 MHz, DMSO) δ = 8.69 (s, 2H), 8.28-8.14 (m, 8H), 7.83-7.72 (m, 4H), 7.60-7.40 (m, 12H), 7.30 (d, J = 28.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 3.20-2.92 (m, 2H), 2.84-2.74 (m, 2H), 1.28 (d, J = 6.4 Hz, 2H), 1.28 (d, J = 6.4 Hz, 6H), 1.19 (d, J = 6.8 Hz, 6H), 1.13 (d, J = 6.8 Hz, 6H), 1.01 (d, J = 6.8 Hz, 6H); ¹³C NMR (100 MHz, DMSO) δ = 148.2, 147.2, 137.4, 134.0, 133.9, 133.8, 132.3, 132.0, 131.8, 131.2, 130.6, 129.8, 129.7, 128.8, 128.7, 126.9, 126.5, 126.4, 126.2, 126.1, 126.0, 125.7, 125.5, 125.4, 124.8, 121.9, 30.9, 30.7, 26.4, 24.9, 23.3, 23.1; ³¹P NMR (162 MHz, CDCl₃) δ = 3.27; MS (ESI) m/z 1019(M⁺).

1.2 General Procedure for the Friedel-Crafts Alkylation Reaction:

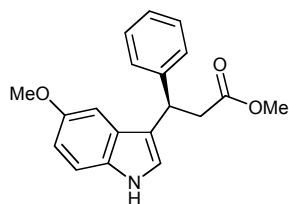
A mixture of α,β -unsaturated acyl phosphonate **2** (0.11 mmol) and phosphoric acid **4g** (0.01 mmol) in dry toluene (1.0 mL) was flushed with nitrogen for 1 min followed by the addition of indole (0.10 mmol) at room temperature. The resulting mixture was allowed to stir at room temperature. After confirming the disappearance of the starting material by TLC analysis, the reaction mixture was cooled to $-10\text{ }^{\circ}\text{C}$ and added methanol (150 μL) and DBU (30 μL). After stirring for 30 min at $-10\text{ }^{\circ}\text{C}$, the reaction mixture was allowed to warm to room temperature and stirred another 20 min. The reaction mixture was diluted with ethyl acetate (10 mL), then washed with sat. NH_4Cl solution (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4 . The organic extract was concentrated under reduced pressure and the residue purified by either flash chromatography or p-TLC using hexane-ethyl acetate as eluent to yield the corresponding ester.

(*R*)-3-(1-*H*-Indol-3-yl)-3-phenyl-propionic acid methyl ester **3a**:



Using the Friedel-Crafts alkylation procedure described above afforded the title compound as a pale pink solid in 73% yield, mp $124\text{--}125\text{ }^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{25} -39.4$ (c 1.80, CH_2Cl_2). The chromatographed material was determined to be of 92% ee by chiral HPLC analysis (Chiralpak AD-H, *n*-hexane/*i*PrOH, 10:1, 1.0 mL/min) *R* isomer (major) tr = 17.4 min and *S* isomer (minor) tr = 20.3 min. IR (CHCl_3 , cm^{-1}) 3479, 3013, 2955, 1732, 1493, 1439, 1234, 1161, 1096, 802; ^1H NMR (400 MHz, CDCl_3) δ = 8.01 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.30–7.21 (m, 5H), 7.17–7.09 (m, 2H), 7.01–6.97 (m, 1H), 6.90 (d, J = 2.4 Hz, 1H), 4.80 (t, J = 8.0 Hz, 1H), 3.54 (s, 3H), 3.14 (dd, J = 15.2, 8.0 Hz, 1H), 3.01 (dd, J = 15.2, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ = 172.7, 143.6, 136.4, 128.4, 127.6, 126.4, 126.4, 122.0, 121.1, 119.3, 119.2, 118.4, 111.1, 51.6, 41.2, 39.1; MS(EI) m/z 279(M^+ , 38), 278($\text{M}^+ - 1$, 100), 220(31), 207(81), 206(100), 178(25), 102(22); Calcd. For $\text{C}_{18}\text{H}_{17}\text{NO}_2$: C, 77.40; H, 6.13. Found: C, 77.45; H, 6.22.

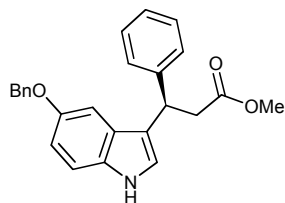
(*R*)-3-(5-Methoxy-1-*H*-indol-3-yl)-3-phenyl-propionic acid methyl ester **3b**:



Using the Friedel-Crafts alkylation procedure described above afforded the title compound as a pale reddish color solid in 70% yield, mp $64\text{--}65\text{ }^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{25} -2.1$ (c 0.7, CH_2Cl_2). The chromatographed material was determined to be of 90% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 85:15, 0.7 mL/min) *R* isomer (major) tr = 21.5 min and *S* isomer (minor) tr = 26.6 min. IR (CHCl_3 , cm^{-1}) 3479, 3017, 2955, 1732, 1585, 1485, 1439, 1292, 1030, 802; ^1H NMR (400 MHz, CDCl_3) δ = 8.02 (s, 1H), 7.31–7.10 (m, 6H), 6.91 (d, J = 2.4 Hz, 1H), 6.81–6.76 (m, 2H), 4.74 (dd, J = 7.9, 7.9 Hz, 1H), 3.70 (s, 3H), 3.56 (s, 3H), 3.13 (dd, J = 15.2, 7.9 Hz, 1H), 3.00 (dd, J = 15.2, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ = 172.6, 153.6, 143.5, 131.6, 128.4, 127.6, 126.9, 126.4, 121.9, 118.1, 112.0,

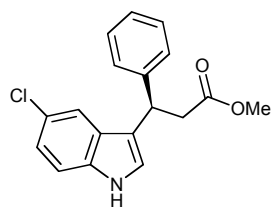
111.8, 101.2, 55.7, 51.6, 41.1, 39.1; MS(EI) m/z 310($M^+ + 1$, 7), 308($M^+ - 1$, 100), 250(7), 249(33), 237(12), 235(100), 203(42), 164(16), 118(15), 177(9); Calcd. For $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53 Found: C, 73.47; H, 6.03; N, 4.26.

(*R*)-3-(5-(Benzyloxy)-1-*H*-indol-3-yl)-3-phenyl-propionic acid methyl ester 3c:



Using the Friedel-Crafts alkylation procedure described above afforded the title compound as a pale pink solid in 75% yield, mp 141-142 °C, $[\alpha]_D^{25} +17.3$ (c 2.65, CH_2Cl_2). The chromatographed material was determined to be of 88% ee by chiral HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*PrOH, 85:15, 0.7 mL/min) *R* isomer (major) t_r = 33.9 min and *S* isomer (minor) t_r = 51.4 min. IR ($CHCl_3$, cm^{-1}) 3479, 3013, 2955, 1732, 1481, 1454, 1204, 1022, 795; 1H NMR (400 MHz, $CDCl_3$) δ = 7.92 (s, 1H), 7.41-7.22 (m, 9H), 7.19-7.15 (m, 2H), 6.95 (d, J = 2.0 Hz, 1H), 6.90-6.85 (m, 2H), 4.96 (dd, J = 14.4, 1.6 Hz, 2H), 4.72 (dd, J = 7.9, 7.9 Hz, 1H), 3.57 (s, 3H), 3.12 (dd, J = 15.2, 7.7 Hz, 1H), 2.99 (dd, J = 15.2, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.6, 152.9, 143.5, 137.5, 131.8, 128.4, 127.7, 127.6, 127.6, 126.9, 126.4, 121.9, 118.4, 112.9, 111.7, 103.0, 70.8, 51.6, 41.1, 39.1; MS(EI) m/z 386($M^+ + 2$, 6), 278($M^+ - 1$, 94), 311(43), 293(24), 220(38), 219(100), 191(20), 91(34); Calcd. For $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63 Found: C, 77.67; H, 6.03; N, 3.44.

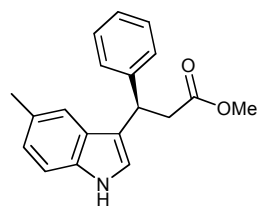
(*R*)-3-(5-Chloro-1-*H*-indol-3-yl)-3-phenyl-propionic acid methyl ester 3d:



Using the Friedel-Crafts alkylation procedure described above afforded the title compound as a cream color solid in 60% yield, mp 153-154 °C, $[\alpha]_D^{25} +4.9$ (c 1.24, CH_2Cl_2). The chromatographed material was determined to be of 72% ee by chiral HPLC analysis (Chiralpak AD-H, *n*-hexane/*i*PrOH, 10:1, 1.0 mL/min) *R* isomer (major) t_r = 13.4 min and *S* isomer (minor) t_r = 14.7 min. IR ($CHCl_3$, cm^{-1}) 3479, 3020, 2955, 1732, 1462, 1439, 1211, 1161, 1103, 795; 1H NMR (400 MHz, $CDCl_3$) δ = 8.15 (s, 1H), 7.35 (d, J = 1.6 Hz, 1H), 7.26-7.14 (m, 6H), 7.05 (dd, J = 8.8, 2.0 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 4.73 (dd, J = 7.9, 7.9 Hz, 1H), 3.57 (s, 3H), 3.11 (dd, J = 15.2, 7.7 Hz, 1H), 3.00 (dd, J = 15.2, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.5, 143.1, 134.8, 128.5, 127.5, 127.5, 126.6, 125.0, 122.5, 122.4, 118.7, 118.2, 112.1, 51.7, 41.1, 38.9; MS(EI) m/z 314($M^+ + 1$, 24), 312($M^+ - 2$, 72), 253(12), 241(75), 240(40), 239(100), 203(27); Calcd. For $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14; N, 4.46 Found: C, 68.68; H, 5.23; N, 4.35.

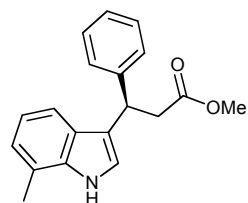
(*R*)-3-(5-Methyl-1-*H*-indol-3-yl)-3-phenyl-propionic acid methyl ester 3e:

Using the Friedel-Crafts alkylation procedure described above afforded the title compound as a off white solid in 79% yield, mp 115-116 °C, $[\alpha]_D^{25} -8.7$ (c 1.26, CH_2Cl_2). The chromatographed material was determined to be of 87% ee by chiral HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*PrOH, 85:15, 0.7 mL/min) *R* isomer (major) t_r = 19.6 min and *S* isomer (minor) t_r =



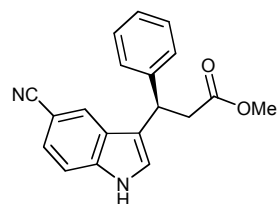
22.3 min. IR (CHCl₃, cm⁻¹) 3479, 3028, 2955, 1732, 1439, 1211, 1157, 1096, 930, 802; ¹H NMR (400 MHz, CDCl₃) δ = 7.89 (s, 1H), 7.30-7.11 (m, 7H), 6.95-6.93 (m, 1H), 6.85 (d, *J* = 2 Hz, 1H), 4.77 (dd, *J* = 7.9, 7.9 Hz, 1H), 3.55 (s, 3H), 3.13 (dd, *J* = 15.2, 7.7 Hz, 1H), 3.00 (dd, *J* = 15.2, 8.2 Hz, 1H), 2.35 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.7, 143.6, 134.8, 128.5, 128.4, 127.6, 126.7, 126.3, 123.7, 121.3, 118.8, 117.9, 110.7, 51.6, 41.2, 39.1, 21.4; MS(EI) *m/z* 293(M⁺, 17), 292(M⁺-1, 80), 272(11), 233(20), 219(49), 220(100), 217(21), 203(19); Calcd. For C₁₉H₁₉NO₂: C, 77.79; H, 6.53; N, 4.77 Found: C, 77.58; H, 6.72; N, 4.98.

(*R*)-3-(5-Methyl-1-*H*-indol-3-yl)-3-phenyl-propionic acid methyl ester 3f:



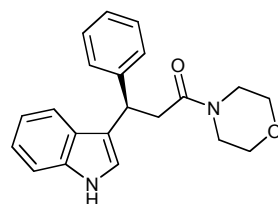
Using the Friedel-Crafts alkylation procedure described above afforded the title compound as a white solid in 75% yield, mp 120-121 °C, [α]_D²⁵ -21.33 (c 1.13, CH₂Cl₂). The chromatographed material was determined to be of 19% ee by chiral HPLC analysis (Chiralpak AD-H, *n*-hexane/*i*PrOH, 10:1, 1.0 mL/min) *R* isomer (major) tr = 11.6 min and *S* isomer (minor) tr = 13.3 min. IR (CHCl₃, cm⁻¹) 3479, 3028, 2955, 1732, 1497, 1435, 1335, 1234, 1161, 795; ¹H NMR (400 MHz, CDCl₃) δ = 7.96 (s, 1H), 7.30-7.15 (m, 6H), 6.98-6.92 (m, 3H), 4.79 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.56 (s, 3H), 3.15 (dd, *J* = 15.2, 7.7 Hz, 1H), 3.00 (dd, *J* = 15.2, 8.0 Hz, 1H), 2.40 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.6, 143.6, 136.1, 128.4, 127.6, 126.4, 126.1, 122.6, 120.8, 120.2, 119.6, 119.1, 117.1, 51.6, 41.2, 39.3, 16.5; MS(EI) *m/z* 294(M⁺+1, 10), 293(M⁺, 47), 234(10), 221(27), 220(100), 218(12), 217(7); Calcd. For C₁₉H₁₉NO₂: C, 77.79; H, 6.53; N, 4.77 Found: C, 77.62; H, 6.81; N, 5.04.

(*R*)-3-(5-Cyano-1-*H*-indol-3-yl)-3-phenyl-propionic acid methyl ester 3g:



Using the Friedel-Crafts alkylation procedure described above afforded the title compound as a white solid in 52% yield, mp 197-198 °C, [α]_D²⁵ +28.22 (c 1.32, CH₂Cl₂). The chromatographed material was determined to be of 75% ee by chiral HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*PrOH, 85:15, 0.7 mL/min) *R* isomer (major) tr = 19.7 min and *S* isomer (minor) tr = 31.5 min. IR (CHCl₃, cm⁻¹) 3472, 3028, 2222, 1732, 1620, 1439, 1269, 1157, 1096, 802; ¹H NMR (400 MHz, CDCl₃) δ = 8.57 (s, 1H), 7.71 (s, 1H), 7.36 (s, 1H), 7.31-7.19 (m, 7H), 4.78 (dd, *J* = 8.0, 7.7 Hz, 1H), 3.61 (s, 1H), 3.13 (dd, *J* = 15.2, 8.0 Hz, 1H), 3.00 (dd, *J* = 15.2, 7.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.2, 142.8, 138.2, 128.7, 127.4, 126.9, 126.4, 125.1, 125.1, 123.2, 120.7, 119.5, 112.0, 102.4, 51.8, 41.1, 38.9; MS(EI) *m/z* 305(M⁺+1, 5), 304(M⁺, 25), 232 (17), 231 (100), 229 (12); Calcd. For C₁₉H₁₆N₂O₂: C, 74.98; H, 5.30; N, 9.20 Found: C, 74.81; H, 5.08; N, 9.29.

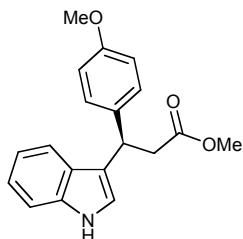
(*R*)-3-(1-*H*-Indol-3-yl)-1-morpholino-3-phenylpropan-1-one 3h:



Using the Friedel-Crafts alkylation procedure described above afforded the title compound as a white solid in 73% yield, mp 236-237 °C, [α]_D²⁵ -28.6 (c 1.80, CH₂Cl₂). The chromatographed material was determined to be of 88% ee by chiral HPLC analysis (Chiralpak IB, *n*-hexane/*i*PrOH,

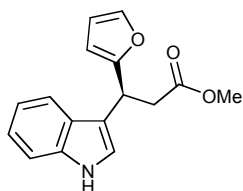
9:1, 1.0 mL/min) *R* isomer (major) *tr* = 60.4 min and *S* isomer (minor) *tr* = 80.0 min. IR (CHCl₃, cm⁻¹) 3479, 3013, 1632, 1458, 1435, 1230, 1115, 729; ¹H NMR (400 MHz, CDCl₃) δ = 8.34 (s, 1H), 7.37-7.10 (m, 8H), 7.00-6.96 (m, 2H), 4.86 (dd, *J* = 7.8, 7.8 Hz, 1H); 3.60-3.43 (m, 4H), 3.21-3.02 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.4, 143.8, 136.6, 128.4, 127.8, 126.5, 122.0, 121.5, 119.5, 119.3, 118.7, 111.2, 66.6, 66.2, 46.3, 41.9, 39.9, 38.7; MS(EI) *m/z* 335(M⁺+1, 20), 334(M⁺, 85), 247(11), 220(48), 219(46), 207(38), 206(100), 178(14), 117(4); Calcd. For C₂₁H₂₂N₂O₂: C, 75.42; H, 6.63; N, 8.38 Found: C, 75.18; H, 6.45; N, 8.16.

(*R*)-3-(1-*H*-Indol-3-yl)-3-(4-methoxyphenyl)-propionic acid methyl ester 3i:



Using the Friedel-Crafts alkylation procedure described above afforded the title compound as a pale reddish color solid in 68% yield, mp 127-128 °C, [α]_D²⁵ -33.3 (c 1.35, CH₂Cl₂). The chromatographed material was determined to be of 85% ee by chiral HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*PrOH, 95:5, 0.7 mL/min) *R* isomer (major) *tr* = 93.1 min and *S* isomer (minor) *tr* = 104.5 min. IR (CHCl₃, cm⁻¹) 3479, 2955, 1732, 1612, 1458, 1269, 1034, 833; ¹H NMR (400 MHz, CDCl₃) δ = 8.07 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.23-7.17 (m, 3H), 7.13-7.09 (m, 1H), 7.01-6.97 (m, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.81-6.74 (m, 2H), 4.75 (dd, *J* = 7.8 Hz, 1H), 3.70 (s, 3H), 3.56 (s, 3H), 3.12 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.97 (dd, *J* = 15.2, 7.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.7, 157.9, 136.5, 135.7, 128.5, 126.4, 122.0, 121.0, 119.3, 119.2, 118.7, 113.7, 111.1, 55.0, 51.6, 41.3, 38.3; MS(EI) *m/z* 309(M⁺, 35), 308(M⁺-1, 100), 249(13), 237(12), 235(100), 233(15), 207(24), 204(11), 203(16), 117(16); Calcd. For C₁₉H₁₉NO₃: C, 73.77; H, 6.19; N, 4.53 Found: C, 73.57; H, 6.35; N, 4.49.

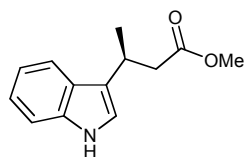
(*S*)-3-(Furan-2-yl)-3-(1-*H*-indol-3-yl)-propionic acid methyl ester 3j:



Using the Friedel-Crafts alkylation procedure described above afforded the title compound as a colorless liquid in 69% yield, [α]_D²⁵ +15.3 (c 1.30, CH₂Cl₂). The chromatographed material was determined to be of 70% ee by chiral HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*PrOH, 85:15, 0.7 mL/min) *R* isomer (minor) *tr* = 18.4 min and *S* isomer (major) *tr* = 20.3 min. IR (CHCl₃, cm⁻¹) 3479, 3013, 2955, 1732, 1620, 1458, 1439, 1357, 1272, 1161, 1011, 910; ¹H NMR (400 MHz, CDCl₃) δ = 8.06 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.30-7.27 (m, 2H), 7.21-7.05 (m, 2H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.26 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.05 (d, *J* = 3.2 Hz, 1H), 4.87 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.60 (s, 3H), 3.17 (dd, *J* = 15.2, 7.6 Hz, 1H), 3.05 (dd, *J* = 15.6, 7.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 172.3, 156.3, 141.3, 136.3, 126.1, 122.0, 121.9, 119.4, 119.2, 115.8, 111.2, 110.1, 105.5, 51.7, 39.2, 33.1; MS(EI) *m/z* 269(M⁺, 46), 268(M⁺-1, 100), 197(8), 196(94), 195(100), 154(11), 179(35), 167(33), 166(65), 117(8); Calcd. For C₁₆H₁₅NO₃: C, 71.36; H, 5.61; N, 5.20 Found: C, 71.12; H, 5.61; N, 4.90.

(*S*)-3-(1-*H*-Indol-3-yl)-butyric acid methyl ester 3k:²

Using the Friedel-Crafts alkylation procedure described above afforded the title compound as a colorless liquid in 71% yield, [α]_D²⁵ +7.2 (c 2.70, C₆H₆) {lit.² [α]_D¹⁹ +10.9 (c = 2.12, C₆H₆)}.

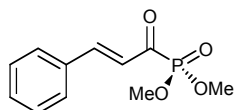


The chromatographed material was determined to be of 82% ee by chiral HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*PrOH, 85:15, 0.7 mL/min) *S* isomer (major) *tr* = 24.2 min and *R* isomer (minor) *tr* = 15.2 min. ^1H NMR (400 MHz, CDCl_3) δ = 7.99 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.34-7.32 (m, 1H), 7.20-7.10 (m, 2H), 6.96 (d, J = 2.4 Hz, 1H), 3.64 (s, 3H), 3.62-3.59 (m, 1H), 2.83 (dd, J = 14.8, 6.0 Hz, 1H), 2.58 (dd, J = 14.8, 8.4 Hz, 1H), 1.41 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ = 173.3, 136.4, 126.3, 122.0, 120.7, 120.0, 119.2, 119.1, 111.2, 51.5, 42.2, 27.9, 21.0.

1.3 General procedure for synthesis of acyl phosphonates:

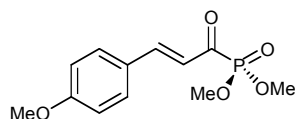
To a mixture of dimethyl phosphite (6.00 mmol) and triethylamine (3.52 mmol) in 25 mL round-bottom flask was added α,β -unsaturated aldehyde (6.24 mmol) in portion wise (1 portion/5min) at room temperature. The resulting mixture was allowed to stir at 70 °C for 1 h. After confirming the disappearance of the starting material by TLC analysis, the reaction mixture was cooled to rt, diluted with ethyl acetate (40 mL), and washed with H_2O (30 mL) and then brine (10 mL). The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give thick oil, which was subsequently used in oxidation reaction without further purification. To a solution of crude hydroxy phosphonate (4.70 mmol) and diisopropylethylamine (14.14 mmol) in 60 mL of dichloromethane at -10 °C was added SO_3 ·pyridine complex (14.14 mmol) in 13 mL of DMSO in dropwise for 30 mins. After stirring 1 h at -10 °C, the reaction mixture was diluted with 200 mL of diethyl ether and washed with H_2O (35 mL), 5% NaHCO_3 (35 mL), brine (35 mL) and dried over anhydrous Na_2SO_4 . The organic extract was concentrated under reduced pressure and the residue purified by flash chromatography to yield the corresponding α,β -unsaturated acyl phosphonate.

Dimethyl [(*E*)-3-phenyl-prop-2-enoyl]phosphonate:³



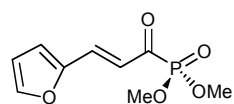
^1H NMR (400 MHz, CDCl_3) δ = 8.11 (d, J = 16.3 Hz, 1H), 7.64-7.62 (m, 2H), 7.46-7.42 (m, 3H), 7.08 (dd, J = 16.4, 12.8 Hz, 1H), 3.90 (d, J = 10.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ = 197.6 (d, J = 173.9 Hz), 148.9, 133.7, 131.7, 128.9, 125.2, 124.5, 53.9 (d, J = 7.3 Hz); ^{31}P NMR (162 MHz, CDCl_3) δ = 1.53.

Dimethyl [(*E*)-3-(4-methoxyphenyl)-prop-2-enoyl]phosphonate:⁴



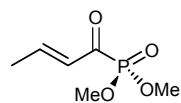
^1H NMR (400 MHz, CDCl_3) δ = 8.09 (d, J = 16.0 Hz, 1H), 7.61-7.59 (m, 2H), 7.02-6.93 (m, 3H), 3.89 (d, J = 10.8 Hz, 6H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ = 197.1 (d, J = 172.8 Hz), 162.8, 149.0, 131.2, 126.6, 123.2, 122.5, 114.6, 55.4, 54.0 (d, J = 7.2 Hz); ^{31}P NMR (162 MHz, CDCl_3) δ = 1.00.

Dimethyl [(*E*)-3-furan-2-yl-acryloyl]phosphonate:⁵



^1H NMR (400 MHz, CDCl_3) δ = 7.90 (d, J = 16.0 Hz, 1H), 7.59 (dd, J = 1.2 Hz, 1H), 6.93 (dd, J = 14.0, 16.0 Hz, 1H), 6.86 (d, J = 3.2 Hz, 1H), 6.56 (dd, J = 3.6, 1.6 Hz, 1H), 3.89 (d, J = 10.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ = 196.7 (d, J = 174.3 Hz), 150.3, 146.4, 133.8, 122.1 (d, J = 67.2 Hz), 119.2, 113.3, 53.6 (d, J = 6.8 Hz); ^{31}P NMR (162 MHz, CDCl_3) δ = 1.45.

Dimethyl [(E)-but-2-enoyl]phosphonate:²



To a freshly distilled crotonyl chloride at 0 °C was added trimethyl phosphate in dropwise over 30 min in 100 mL round-bottom flask with fitted a vent to a gas bubbler. After completion of the addition, the reaction was warmed to room temperature and stirred another 2 h. The reaction mixture was put under vacuum for 30 min and was subsequently distilled to afford the title compound as yellow liquid: bp 100 °C (1 torr). ^1H NMR (400 MHz, CDCl_3) δ = 7.58-7.49 (m, 1H), 6.46-6.37 (m, 1H), 3.86 (d, J = 10.8 Hz, 6H), 2.03-2.0 (m, 3H), 2.02 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ = 151.6, 131.7, 131.0, 53.7 (d, J = 7.2 Hz), 19.1; ^{31}P NMR (162 MHz, CDCl_3) δ = 1.31.

References:

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