Electronic Supplementary Information

Enantioselective chlorination and fluorination of β-keto phosphonates catalyzed by chiral Lewis acids

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Experimental Section

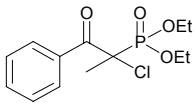
General Methods. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian AS 400 spectrometer running at 400, 100 and 376 MHz, respectively, in $CDCl_3$ as the solvent. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H NMR, to the central line of $CDCl_3$ (77.0 ppm) for ^{13}C NMR and to $CFCl_3$ (0 ppm), for ^{19}F NMR. ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES^+) ionisation techniques. Flash column chromatography (FC) was carried out using the Merck silica gel 60 (230-400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD or Daicel Chiralcel OJ columns) or by chiral stationary phase GC using a Chrompack CP-Chirasil-Dex CB column. Racemic samples were obtained using $Cu(OTf)_2$ as a catalyst.

Materials. CH_2Cl_2 was distilled from CaH_2 prior to use. All commercially available reagents were used as received. β–Keto phosphonates **1a,b,d,e,**[1] **c,**[2] **f**[3] were prepared according to literature procedures. (*R*,*R*)-4,6-Dibenzofuranidyl-2,2'-bis(4-phenyloxazoline) (Ph-DBFOX) **4a** was prepared following a literature procedure.[4]

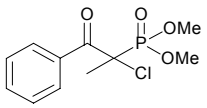
General Procedure for the Catalytic Enantioselective Chlorination of β-Keto Phosphonates 1a-f: In a flame dried Schlenk tube equipped with a magnetic stirring bar, ZnI_2 (6.4 mg, 0.02 mmol) and (*R*,*R*)-4,6-dibenzofuranidyl-2,2'-bis(4-phenyloxazoline) **4a** (10.6 mg, 0.022 mmol) were added, followed by dry CH_2Cl_2 (2 mL). The resulting clear, colourless solution was stirred under N_2 for 1 h, then $AgSbF_6$ (13.7 mg,

[1] I. Truel, A. Mohamed-Hachi, E. Aboud-Jaudet and N. Collignon, *Synth. Commun.,* 1997, **27**, 1165.
[2] R. D. Clark, L. G. Kozar and C. H. Heathcock, *Synthesis*, 1975, 635.
[3] T. Calogeropoulou, G. B. Hammond and D. F. Wiemer, *J. Org. Chem.,* 1987, **52**, 4185.
[4] U. Iserloh, D. P. Curran and S. Kanemasa, *Tetrahedron: Asymmetry,* 1999, **10**, 2417.

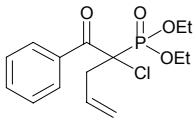
0.04 mmol) was added, and the resulting suspension was stirred in the dark for 6 h. β-Keto phosphonates **1a-f** (0.2 mmol) were then added, followed by *N*-chlorosuccinimide **2a** (29 mg, 0.22 mmol). After 20 h stirring in the dark at room temperature, the products **3a-f** were isolated by FC on silica gel (CH_2Cl_2/Et_2O mixtures).



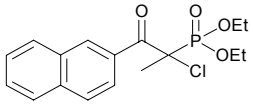
(1-Chloro-1-methyl-2-oxo-2-phenyl-ethyl)-phosphonic acid diethyl ester (3a): Following the general procedure, compound **3a** was obtained as a colourless oil in 98% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min τ_{major} = 6.1 min; τ_{minor} = 7.3 min); ^{1}H NMR δ 8.23-8.17 (m, 2H), 7.55-7.50 (m, 1H), 7.46-7.39 (m, 2H), 4.38-4.26 (m, 2H), 4.24-4.10 (m, 2H), 2.05 (d, J = 14.4 Hz, 3H), 1.38 (t, J = 6.8 Hz, 3H), 1.29 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 195.0, 135.2, 132.8, 130.3, 127.8, 67.3 (d, J = 150 Hz), 64.8 (d, J = 6.9 Hz), 64.3 (d, J = 6.8 Hz), 26.1 (d, J = 3.1 Hz), 16.5, 16.3; HRMS $C_{13}H_{18}ClO_4P$ [M + Na^+] calculated: 327.0523, found: 327.0522; $[\alpha]^{rt}_D$ = +46 (c = 0.87, $CHCl_3$), 92% ee.



(1-Chloro-1-methyl-2-oxo-2-phenyl-ethyl)-phosphonic acid dimethyl ester (3b): Following the general procedure, compound **3b** was obtained as a colourless oil in 97% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD column (*n*-hexane/*i*-PrOH = 97:3, flow rate 1.0 mL/min τ_{major} = 13.7 min; τ_{minor} = 14.9 min); ^{1}H NMR δ 8.20-8.14 (m, 2H), 7.58-7.50 (m, 1H), 7.48-7.39 (m, 2H), 3.95 (d, J = 10.8 Hz, 3H), 3.84 (d, J = 10.8 Hz, 3H), 2.07 (d, J = 14.8 Hz); ^{13}C NMR δ 194.8, 134.8, 133.0, 130.2, 127.9, 67.1 (d, J = 144.0 Hz), 55.4 (d, J = 6.9 Hz), 54.7 (d, J = 6.8 Hz), 25.9 (d, J = 2.2 Hz); HRMS $C_{11}H_{14}ClO_4P$ [M + Na^+] calculated: 299.0210, found: 299.0205; $[\alpha]^{rt}_D$ = +20 (c = 1.17, $CHCl_3$), 78% ee.

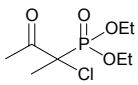


(1-Benzoyl-1-chloro-but-3-enyl)-phosphonic acid diethyl ester (3c): Following the general procedure, compound **3c** was obtained as a colourless oil in 93% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min τ_{major} = 9.4 min; τ_{minor} = 11.2 min); ^{1}H NMR δ 8.02-7.98 (m, 2H), 7.52-7.46 (m, 1H), 7.42-7.37 (ddt, J_d = 16.8, 10.0 Hz, J_t = 6.8 Hz, 2H), 5.74-5.62 (m, 1H), 5.20-5.12 (m, 2H), 4.41-4.28 (m, 2H), 4.26-4.14 (m, 2H), 3.55-3.46 (m, 1H), 2.90-2.79 (m, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 196.5, 137.2, 132.5, 131.1, 129.7, 127.9, 120.9, 72.6 (d, J = 142.6 Hz), 65.3 (d, J = 6.8 Hz), 64.9 (d, J = 7.6 Hz), 42.3 (d, J = 1.5 Hz), 16.7, 16.6; HRMS $C_{15}H_{20}ClO_4P$ [M + Na^+] calculated: 353.0680, found: 353.0680; $[\alpha]^{rt}_D$ = +36 (c = 1.17, $CHCl_3$), 92% ee.

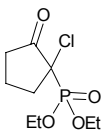


(1-Chloro-1-methyl-2-naphthalen-2-yl-2-oxo-ethyl)-phosphonic acid diethyl ester (3d): Following the general procedure, compound **3d** was obtained as a

colourless oil in 97% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min τ_{major} = 7.1 min; τ_{minor} = 16.9 min); ^{1}H NMR δ 8.90 (br s, 1H), 8.17 (dd, *J* = 9.2, 1.8 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.61-7.40 (m, 2H), 4.41-4.26 (m, 2H), 4.25-4.12 (m, 2H), 2.11 (d, *J* = 14.4 Hz, 3H), 1.39 (t, *J* = 6.8 Hz, 3H), 1.30 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 194.6, 135.2, 132.5, 132.3, 131.9, 129.9, 128.6, 127.6, 127.4, 126.6, 125.8, 67.1 (d, *J* = 146 Hz), 64.8 (d, *J* = 6.9 Hz), 64.3 (d, *J* = 7.6 Hz), 26.2 (d, *J* = 2.3 Hz), 16.5, 16.3; HRMS $C_{17}H_{20}ClO_4P$ [M + Na^+] calculated: 377.0680, found: 377.0681; $[\alpha]^{rt}_D$ = +27 (*c* = 0.88, $CHCl_3$), 93% ee.

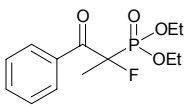


(1-Chloro-1-methyl-2-oxo-propyl)-phosphonic acid diethyl ester (3e): Following the general procedure, compound **3e** was obtained as a colourless oil in 80% yield. The ee of the product was determined by GC using a Chrompack CP-Chirasil-Dex CB column (70-110 ^{o}C (10 ^{o}C/min, 10 min) 110-140 ^{o}C (3^{o}C/min) τ_{major} = 18.4 min; τ_{minor} = 18.3 min); ^{1}H NMR δ 4.33-4.18 (m, 4H), 2.53 (s, 3H), 1.83 (d, *J* = 14.4 Hz, 3H), 1.36 (t, *J* = 6.8 Hz, 3H), 1.35 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 200.8, 68.3 (d, *J* = 144.2 Hz), 64.7 (d, *J* = 9.1 Hz), 64.5 (d, *J* = 6.8 Hz), 27.1, 23.2 (d, *J* = 2.3 Hz), 16.4, 16.3; HRMS $C_8H_{16}ClO_4P$ [M + Na^+] calculated: 265.0367, found: 265.0365; $[\alpha]^{rt}_D$ = +30 (*c* = 0.55, $CHCl_3$), 94% ee.

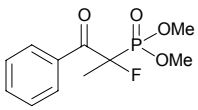


(1-Chloro-2-oxo-cyclopentyl)-phosphonic acid diethyl ester (3f): Following the general procedure, compound **3f** was obtained as a colourless oil in 40% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min τ_{major} = 13.1 min; τ_{minor} = 11.1 min); ^{1}H NMR δ 4.35-4.17 (m, 4H), 2.87-2.74 (m, 1H), 2.55-2.28 (m, 3H), 2.21-2.07 (m, 2H), 1.38 (t, *J* = 6.8 Hz, 3H), 1.36 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 207.6, 64.5 (d, *J* = 7.6 Hz), 64.3 (d, *J* = 6.9 Hz), 63.7 (d, *J* = 160 Hz), 36.8, 36.5, 19.0, 16.4, 16.3; HRMS $C_9H_{16}ClO_4P$ [M + Na^+] calculated: 277.0372, found: 277.0367; $[\alpha]^{rt}_D$ = -34 (*c* = 0.27, $CHCl_3$), 80% ee.

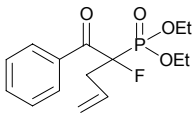
General Procedure for the Catalytic Enantioselective Fluorination of β-Keto Phosphonates 1a-d,f: In a flame dried Schlenk tube equipped with a magnetic stirring bar and containing activated 4Å molecular sieves, $Zn(ClO_4)_2 \cdot 6H_2O$ (7.4 mg, 0.02 mmol) and (*R*,*R*)-4,6-dibenzofuranidyl-2,2'-bis(4-phenyloxazoline) **4a** (10.6 mg, 0.022 mmol) were added, followed by dry CH_2Cl_2 (1 mL). The resulting solution was stirred under N_2 for 1 h, then β-keto phosphonates **1a-d,f** (0.1 mmol) were added, followed by *N*-fluorobenzenesulfonimide **2b** (95 mg, 0.3 mmol). After 60 h stirring at room temperature, the products **5a-d**,**f** were isolated by FC on silica gel (CH_2Cl_2/Et_2O mixtures).



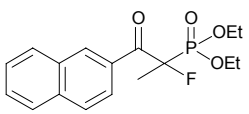
(1-Fluoro-1-methyl-2-oxo-2-phenyl-ethyl)-phosphonic acid diethyl ester (5a): Following the general procedure, compound **5a** was obtained as a colourless oil in 59% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD column (*n*-hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min τ_{major} = 11.3 min; τ_{minor} = 12.5 min); ^{1}H NMR δ 8.10-8.04 (m, 2H), 7.60-7.54 (m, 1H), 7.49-7.41 (m, 2H), 4.34-4.18 (m, 4H), 1.92 (dd, J = 24.0, 15.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 197.6 (d, J = 26.6 Hz), 134.7, 133.4, 130.0 (d, J = 7.6 Hz), 128.2, 100.5 (dd, J = 194.2, 160.8 Hz), 64.2 (d, J = 3.8 Hz), 64.1 (d, J = 3.8 Hz), 21.5 (d, J = 21.2 Hz), 16.4. 16.3; ^{19}F NMR δ –166.2 (dq, J_d = 84.2 Hz, J_q = 23.7 Hz); HRMS $C_{13}H_{18}FO_4P$ [M + Na^+] calculated: 311.0819, found: 311.0834; $[\alpha]^{rt}_D$ = +23 (c = 0.70, $CHCl_3$), 89% ee.



(1-Fluoro-1-methyl-2-oxo-2-phenyl-ethyl)-phosphonic acid dimethyl ester (5b): Following the general procedure, compound **5b** was obtained as a colourless oil in 46% yield. The ee of the product was determined by HPLC using a Daicel Chiralcel OJ column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min τ_{major} = 42.7 min; τ_{minor} = 34.9 min); ^{1}H NMR δ 8.09-8.04 (m, 2H), 7.62-7.55 (m, 1H), 7.49-7.43 (m, 2H), 3.90 (d, J = 4.8 Hz, 3H), 3.87 (d, J = 4.8 Hz, 3H), 1.93 (dd, J = 24.0, 15.2 Hz, 3H); ^{13}C NMR δ 197.4 (d, J = 22.7 Hz), 134.4 , 133.6, 129.9, 128.3, 100.5 (dd, J = 194.3, 162.4 Hz), 54.6, 54.5, 21.6 (d, J = 22.0 Hz); ^{19}F NMR δ –166.5 (dq, J_d = 85.7 Hz, J_q = 25.2 Hz); HRMS $C_{11}H_{14}FO_4P$ [M^+] calculated: 283.0506, found: 283.0510; $[\alpha]^{rt}_D$ = +19 (c = 0.45, $CHCl_3$), 70% ee.

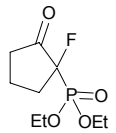


(1-Benzoyl-1-fluoro-but-3-enyl)-phosphonic acid diethyl ester (5c): Following the general procedure, compound **5c** was obtained as a colourless oil in 41% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD column (*n*-hexane/*i*-PrOH = 98:2, flow rate 1.0 mL/min τ_{major} = 19.8 min; τ_{minor} = 21.4 min); ^{1}H NMR δ 8.02-7.94 (m, 2H), 7.59-7.52 (m, 1H), 7.47-7.39 (m, 2H), 5.80-5.66 (m, 1H), 5.24-5.10 (m, 2H), 4.33-4.18 (m, 4H), 3.32-3.11 (m, 1H), 3.04-2.86 (m, 1H), 1.35 (t, J = 6.8 Hz, 3H), 1.33 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 197.8 (d, J = 26.5 Hz), 133.1, 129.7, 129.6 (dd, J = 11.4, 3.8 Hz), 128.1, 120.8, 102.4 (dd, J = 157.9, 199.6 Hz), 64.3 (dd, J = 6.8, 9.1 Hz), 39.2 (d, J = 20.5 Hz), 16.4 (d, J = 5.3, 2.2 Hz); ^{19}F NMR δ –175.9 (ddd, J = 82.7, 36.8, 11.6 Hz); HRMS $C_{15}H_{20}FO_4P$ [M + Na^+] calculated: 337.0975, found: 337.0970; $[\alpha]^{rt}_D$ = +22 (c = 0.35, $CHCl_3$), 91% ee.



(1-Fluoro-1-methyl-2-naphthalen-2-yl-2-oxo-ethyl)-phosphonic acid diethyl ester (5d): Following the general procedure, compound **5d** was obtained as a colourless oil in 71% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD column (*n*-hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min τ_{major} = 17.5 min; τ_{minor} = 28.4 min); ^{1}H NMR δ 8.73 (br s, 1H), 8.10-8.03 (m, 1H), 8.01-7.95 (m, 1H), 7.91-7.82 (m, 2H), 7.64-7.50 (m, 2H),

4.36-4.18 (m, 4H), 1.98 (dd, J = 24.0, 15.2 Hz, 3H), 1.36 (t, J = 6.8 Hz, 3H), 1.35 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 198.4 (d, J = 24 Hz), 135.5, 132.6, 132.5, 132.2 (d, J = 1.4 Hz), 103.0, 128.8, 127.9 (d, J = 1.5 Hz), 127.6, 126.6, 125,3 (d, J = 4.6 Hz), 99.2 (dd, J = 190.0, 160.9 Hz), 64.2 (dd, J = 6.8, 5.4 Hz), 21.7 (d, J = 22.0 Hz), 16.4 (dd, J = 5.3, 1.0 Hz); ^{19}F NMR δ –165.5 (dq, J = 84.3, 23.7 Hz); HRMS $C_{17}H_{20}FO_4P$ [M + Na^+] calculated: 361.0975, found: 361.0979; $[\alpha]^{rt}_D$ = -14 (c = 0.75, $CHCl_3$), 89% ee.



(1-Fluoro-2-oxo-cyclopentyl)-phosphonic acid diethyl ester (5f): Following the general procedure, compound **5f** as obtained as a colourless oil in 38% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD column (*n*-hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min τ_{major} = 11.8 min; τ_{minor} = 10.8 min); ^{1}H NMR δ 4.18-4.07 (m, 4H), 2.82-2.65 (m, 1H), 2.58-1.98 (m, 5H), 1.38 (t, J = 6.8 Hz, 3H), 1.35 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 209.0 (d, J = 9.9 Hz), 96.2 (dd, J = 199.6, 160.1 Hz), 64.2 (d, J = 7.6 Hz), 64.0 (d, J = 6.8 Hz), 35.4 (d, J = 2.3 Hz), 32.1, 31.9, 16.9, 16.3; ^{19}F NMR δ –174.5 (ddd, J = 84.2, 25.2, 10.5 Hz); HRMS $C_9H_{16}FO_4P$ [M + Na^+] calculated: 261.0662, found: 261.0658; $[\alpha]^{rt}_D$ = -125 (c = 0.3, $CHCl_3$), 91% ee.