Rhodium-Catalysed Conjugate Addition-Enantioselective Protonation: The Synthesis of α,α' -Dibenzyl Esters

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Supporting Information

General information: IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrophotometer, using NaCl discs. ¹H NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 300 MHz, unless otherwise noted, with tetramethylsilane as an internal standard. *J* values are given in Hz. ¹³C NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 75 MHz, unless otherwise noted. Microwave reactions were performed in a CEM Discover model 045704 system. All dry solvents were freshly distilled under nitrogen prior to use. Tetrahydrofuran was distilled over alumina column. 1,4-Dioxane was distilled under reduced pressure over 4Å molecular sieves. MeOH was distilled over 4Å molecular sieves. Petroleum ether refers to that fraction obtained between 40-60°C. All other reagents were obtained from commercial suppliers and used as received. All glassware used under anhydrous conditions was dried in an oven and allowed to cool under nitrogen prior to use. All reactions were carried out under argon unless otherwise stated. Flash chromatography was conducted under medium pressure, using matrix 60 silica.

CCDC 639247 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Arylidine and alkylidene compounds were prepared by literature procedures.^{1,2}

General preparation of alkylidene compounds as exemplified by 2,2-dimethyl-5-(thiophen-2-ylmethyl)-1,3-dioxane-4,6-dione

2,2-Dimethyl-[1,3]dioxane-4,6-dione (6.43 g, 46.0 mmol) was added portionwise to a stirred suspension of 2-thiophene carboxaldehyde (5.00 g, 44.6 mmol) in water (65 mL) at 23 °C. A reflux condenser was attached and the mixture stirred at 75 °C for 2 hours. After cooling to room temperature, the yellow solid was collected by Buckner filtration, and washed successively with ice-cold water (2x 100 mL) and pentane (100 mL) and dried thoroughly. The crude arylidene (1.50 g, 6.30 mmol) was subsequently dissolved in CH₂Cl₂ (100 ml) and cooled to 0 °C (Ice/NaCl). Acetic acid (5 mL) was added the reaction stirred for 5 minutes under N₂. Sodium borohydride (0.710 g, 26.84 mmol) was then added portionwise over 1 hour or until the solution turned colourless. The reaction was quenched with water (50 ml) and extracted with CH₂Cl₂ (50 ml). The combined organic extracts were washed with brine (2 x 75 ml) and water (2 x 75 ml) and dried (MgSO₄), yielding the title compound as an off white solid (1.47 g, 91% yield over 2 steps); mp 100 °C (EtOH); ν_{max} (KBr)/cm⁻¹ 3100, 3014, 2936 (C-H); 1778, 1744 (C=O); 1298 (C-S) ; δ_{H} (300 MHz; CDCl₃), 8.0 (1H, dd, J 1.3, 5.0 Hz, Ar), 7.1-6.97 (1H, m, Ar); 6.94-6.90 (1H, m, Ar); 3.76 (1H, t, J 4.60 Hz, CH); 3.72 (2H, d, J 4.52 Hz, CH₂); 1.76 (3H, s, CH₃); 1.59 (3H, s, CH₃); δ_{C} (75.5 MHz; CDCl₃) 164.9, 138.1, 127.9, 126.8, 125.0, 105.3, 48.2, 28.3, 27.1, 26.4 MS (EI/CI) m/z ; 258 (M+NH₄⁺); 240 (5%, MH⁺); 173 (50% C₈H₁₀OS+NH₄⁺); HRMS(FAB⁺) *calcd* for C₁₁H₁₆O₄N₁S₁ [M+NH₄⁺]: m/z 258.0795 found: m/z 258.0791

General preparation of α - substituted *tert*-butyl acrylate esters as exemplified by *tert*-butyl 2-(thiophen-2-ylmethyl) acrylate (1):

2,2-dimethyl-5-(thiophen-2-ylmethyl)-1,3-dioxane-4,6-dione (0.50 g, 2.08 mmol) and dimethyl methylene ammonium iodide (1.00 g, 5.41 mmol) were charged to a 50 mL round bottomed flask under N_2 . The solids were dissolved in tetrahydrofuran (12 mL) and anhydrous *tert*-butanol (12 mL). The reaction mixture was then heated to 65 °C and stirred for 16 hours. Upon cooling to room temperature the solvent was removed *in vacuo*, and the yellow residue taken up in diethyl ether (25 mL), an subsequently extracted with saturated sodium bicarbonate (20 mL), 10% $KHSO_4$ solution (20 mL) and saturated sodium chloride solution (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting oils were purified via flash column chromatography (petrol: dichloromethane 2:1) to give the title product as orange oils (0.41 g, 88% yield); ν_{max} (neat)/ cm^{-1} ; 2979, 2931 ($C=H_2$); 1711 ($C=O$); 1368 ($C-S$); δ_H (300 MHz; $CDCl_3$), 8.0 (1H, dd, J 1.6, 5.3 Hz, Ar), 7.1-6.97 (1H, dd, J 3.4, 5.3 Hz, Ar); 6.84-6.81 (1H, m, Ar); 6.16 (1H, s, CH alkene); 5.50 (1H, s, CH alkene); 3.79 (2H, s, CH_2); 1.47 (9H, s, CH_3); δ_C (75.5 MHz; $CDCl_3$) 165.8, 141.6, 141.1, 126.8, 125.5, 126.8, 123.8, 80.9, 32.3, 28.8, 28.0; MS (EI/CI) m/z ; 242 ($M+NH_4^+$); 225 (25%, MH^+); 186 (50% $C_8H_7O_2S+NH_4^+$); HRMS (FAB $^+$) *calcd* for $C_{12}H_{17}O_2S_1$ [MH^+]: m/z 225.0944 found: m/z 225.0943.

Ligands used in Table 1

General preparation of α - substituted *tert*-butyl acrylate esters via heating as exemplified by 2-Benzyl-3-thiophen-2-yl-propionic acid *tert*-butyl ester (3a):

A 24 mL screw-capped vial equipped with a rubber septum was charged with *tert*-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol), phenyl boronic acid (0.098 g, 0.80 mmol) and rhodium-complex (0.004 g, 0.008 mmol). Dioxane (2 mL) and water (0.2 mL) were added by syringe and the vessel was purged with argon. The mixture was transferred with stirring to a preheated hotplate at 100 °C for 20 h. The crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: dichloromethane 2:1) to give the title product.

General preparation of α - substituted *tert*-butyl acrylate esters via microwave irradiation exemplified by (S)-2-benzyl-3-thiophen-2-yl-propionic acid *tert*-butyl ester (3a):

A 10 mL microwave tube equipped with a rubber septum was charged *tert*-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol), phenyl boronic acid (0.098 g, 0.80 mmol), acetylacetonatobis(ethylene)rhodium (I) (0.003 g, 0.008 mmol), (S)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.007 g, 0.012 mmol) and boric acid (0.040 g, 0.80 mmol). Dioxane (2 mL) was added by syringe and the vessel was purged with argon. The tube was capped and transferred to the microwave reactor (conditions; 110 W, 100 °C) for 1 h. The crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (petrol: dichloromethane 2:1) to yield the title compound as colourless oils (0.052 g, 91% yield, er = 90:10); . $[\alpha]_D^{20} = +4.6^\circ$ ($c=0.95$, CHCl_3); R_f (petrol:dichloromethane, 2:1; 0.4); ν_{max} (neat)/ cm^{-1} ; 3008, 2980 (C-H); 1723 (C=O); 1147 (C-S); δ_H (300 MHz; CDCl_3), 7.38-7.22 (5H, m, Ph), 7.18 (1H, dd, J 5.3, 1.1 Hz, CH thiophene); 7.18 (1H, dd, J 5.3, 3.4 Hz, CH thiophene); 6.86 (1H, d, J 3.4 Hz, CH thiophene); 3.28- 3.15 (1H, m, CH); 3.09- 81 (4H, m, CH_2 , CH_2); 1.32 (9H, s, CH_3); δ_C (75.5 MHz; CDCl_3); 173.7, 141.7, 139.0, 129.1, 128.3, 126.6, 126.3, 125.6, 123.7, 80.5, 50.3, 38.2, 32.2, 27.8, MS (EI/CI) m/z ; 320 (45% $\text{M}+\text{NH}_4^+$); 303.2 (5%, MH^+); 264 (50% $\text{C}_{14}\text{H}_{14}\text{O}_2\text{S}+\text{NH}_4^+$); HRMS (FAB $^+$) *calcd* for $\text{C}_{18}\text{H}_{26}\text{O}_2\text{N}_1\text{S}_1$ [$\text{M}+\text{NH}_4^+$] m/z 320.1675 found: m/z 320.1679; Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1} , t_R = 8.71 (*R*) and 9.30 (*S*).

(S)-2-Naphthalen-2-ylmethyl-3-thiophen-2-yl-propionic acid *tert*-butyl ester (3b):

Tert-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol), 2-naphthyl boronic acid (0.138 g, 0.80 mmol) were reacted under the standard reaction conditions to generate the desired compound as colourless oils (0.066 g, 94% yield); R_f (petrol:dichloromethane, 2:1; 0.35); $\nu_{\max}$ (neat)/ cm^{-1} ; 2976, 2929 (C-H); 1723 (C=O); 1356 (C-CH₃); 1148 (C-S); δ_H (400 MHz; CDCl₃), 7.98-7.91 (1H, m, Ar); 7.89-7.82 (1H, m, Ar); 7.74 (1H, dd, J 7.5, 1.8 Hz, Ar); 7.54- 7.44 (2H, m, Ar); 7.54- 7.42- 7.32 (2H, m, Ar); 7.15 (1H, dd, J 5.3, 1.1 Hz, CH thiophene); 6.92 (1H, dd, J 5.3, 3.4 Hz, CH thiophene); 6.84 (1H, dd, J 3.4, 0.75 Hz, CH thiophene); 3.46- 3.34 (1H, m, CH); 3.33- 3.21 (2H, m, CH₂); 3.13- 2.98 (2H, m, CH₂); 1.22 (9H, s, CH₃); δ_C (75.5 MHz; CDCl₃); 173.8, 141.7, 136.6, 133.5, 132.3, 128.0, 127.9, 127.7, 127.6, 126.7, 126.0, 125.9, 125.7, 125.41, 123.8, 80.67, 50.31, 38.4, 32.34, 27.9, 23.8 MS (EI/CI) m/z ; 352 (10% MH⁺); HRMS (FAB⁺) calcd for C₂₂H₂₄O₂S₁ [M+H⁺] m/z 353.1570 found: m/z 353.1569

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, t_R = 10.35 (S) and 11.04 (R).

(S)-2-(4-thiomethyl-benzyl)-3-thiophen-2-yl-propionic acid *tert*-butyl ester (3c):

Tert-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol), 4-(methylthio)phenylboronic acid (0.120 g, 0.80 mmol) were reacted under the standard reaction conditions to generate the desired compound as colourless oils (0.056 g, 81% yield); R_f (petrol:dichloromethane, 2:1; 0.2); $\nu_{\max}$ (neat)/ cm^{-1} ; 2976, 2929 (C-H); 1723 (C=O); 1356 (C-CH₃); 1148 (C-S); δ_H (300 MHz; CDCl₃), 7.11 (2H, d, J 8.29 Hz, Ar); 7.06 (1H, dd, J 5.3, 1.1 Hz, CH thiophene); 7.03 (2H, d, J 8.29 Hz, Ar); 6.83 (1H, dd, J 5.3, 3.4 Hz, CH thiophene); 6.76 (1H, dd, J 3.4, 0.75 Hz, CH thiophene); 3.14-2.99

(1H, m, CH); 2.94-2.59 (4H, m, CH₂); 2.39 (3H, s, OSH₃); 1.20 (9H, s, CH₃); δ_C (75.5 MHz; CDCl₃); 173.8, 141.7, 136.6, 133.5, 132.3, 128.0, 127.9, 127.7, 127.6, 126.7, 126.0, 125.9, 125.7, 125.41, 123.8, 80.67, 50.31, 38.4, 32.34, 27.9, 23.8 MS (EI/CI) *m/z*; 348 (30% MH⁺); HRMS (FAB⁺) *calcd* for C₁₉H₂₆N₁O₂S₂ [M+NH₄⁺] *m/z* 366.5611 found: *m/z* 366.5614

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, *t_R* = 10.35 (S) and 11.04 (R).

(S)-2-(4-Methoxy-benzyl)-3-thiophen-2-yl-propionic acid tert-butyl ester (3d):

Tert-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol) and 4-methoxy phenylboronic acid (0.121 g, 0.80 mmol) were reacted under the standard conditions to generate the desired compound as colourless oils (0.055 g, 82% yield); *R_f* (petrol:dichloromethane, 2:1; 0.18); $\nu_{\max}$ (neat)/cm⁻¹; 2977, 2932 (C-H); 1724 (C=O); 1513 (CO-CH₃) 1367 (C-CH₃); 1150 (C-S); δ_H (400 MHz; CDCl₃), 7.2-7.13 (3H, m, Ar); 6.96 (1H, t, *J* 3.8 Hz, CH thiophene); 6.9-6.80 (3H, m, Ar); 3.84 (3H, s, OCH₃); 3.23-3.14 (1H, m, CH); 3.05- 2.76 (4H, m, CH₂); 1.33 (9H, s, CH₃); δ_C (75.5 MHz; CDCl₃); 191.9, 173.1, 146.4, 141.0, 134.7, 129.7, 129.6, 129.6, 126.6, 125.8, 123.9, 80.8, 53.3, 49.8, 38.1, 32.3, 27.7; MS (EI/CI) *m/z*; 350 (65% M-NH₄⁺); HRMS (FAB⁺) *calcd* for C₁₉H₂₈N₁O₃S₁ [M+NH₄⁺] *m/z* 350.1784 found: *m/z* 350.1781

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, *t_R* = 9.57 (R) and 10.77 (S).

(S)-2-(4-tert-Butyl-benzyl)-3-thiophen-2-yl-propionic acid tert-butyl ester (3e):

Tert-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol) and 4-*tert*-butylphenylboronic acid (0.142 g, 0.80 mmol) were reacted under standard reaction conditions to generate the desired compound as colourless oils (0.067 g, 93% yield); R_f (petrol:dichloromethane, 2:1; 0.38); $\nu_{\max}$ (neat)/ cm^{-1} ; 2996, 2869 (C-H); 1718 (C=O); 1391, 1265 (C-CH₃); 1153 (C-S); δ_H (300 MHz; CDCl₃), 7.30 (2H, d, J 8.28 Hz Ar); 7.15 (1H, dd, J 5.3, 1.1 Hz, CH thiophene); 7.13 (2H, d, J 8.28, Ar); 6.92 (1H, dd, J 5.3, 3.4 Hz, CH thiophene); 6.84 (1H, dd, J 3.4, 0.75 Hz, CH thiophene); 3.22-3.08 (1H, m, CH); 3.04- 2.94 (1H, m, CH₂); 2.93- 2.72 (3H, m, CH₂); 1.31 (9H, s, CH₃); 1.26 (9H, s, CH₃); δ_C (75.5 MHz; CDCl₃); 173.8, 149.1, 141.8, 135.8, 128.7, 126.5, 125.5, 125.1, 123.5, 80.4, 50.2, 37.7, 34.3, 32.1, 31.3, 27.8; MS (EI/CI) m/z ; 359 (80% M-NH₄⁺); HRMS (FAB⁺) calcd for C₂₂H₃₄N₁O₂S₁ [M+NH₄⁺] m/z 359.2039 found: m/z 359.2043

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, t_R = 6.47 (R) and 6.65 (S).

(S)-2-Biphenyl-4-ylmethyl-3-thiophen-2-yl-propionic acid tert-butyl ester (3f):

Tert-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol) and 4-biphenyl boronic acid (0.158 g, 0.80 mmol) and rhodium-complex (0.004 g, 0.008 mmol) were reacted under the standard reaction conditions to generate the desired compound as colourless semi-solid (0.058 g, 76% yield); R_f (petrol:dichloromethane, 2:1; 0.3); $\nu_{\max}$ (neat)/ cm^{-1} ; 2976, 2930, 3029 (C-H); 1724 (C=O); 1391, 1367 (C-CH₃); 1150 (C-S); δ_H (400 MHz; CDCl₃), 7.58 (2H, d, J 8.08 Hz Ar); 7.52 (2H, dt, J 8.34, 2.02 Hz, Ar); 7.47 (2H, tt, J 8.08, 2.02 Hz, Ar); 7.33 (1H, tt, J 7.33, 1.26 Hz, Ar); 7.26 (2H, dt, J 8.34, 2.02 Hz, Ar); 7.54- 7.42- 7.32 (2H, m, Ar); 7.15 (1H, dd, J 5.3, 1.1 Hz, CH

thiophene); 6.92 (1H, dd, J 5.3, 3.4 Hz, *CH* thiophene); 6.84 (1H, dd, J 3.4, 0.75 Hz, *CH* thiophene); 3.23-3.14 (1H, m, *CH*); 3.05- 2.81 (4H, m, *CH*₂); 1.22 (9H, s, *CH*₃); δ_c (75.5 MHz; CDCl₃); 173.7, 144.6, 141.6, 140.9, 139.2, 129.4, 128.7, 127.1, 127.0, 126.9, 126.6, 125.6, 123.7, 80.6, 50.2, 37.8, 32.2, 27.8; MS (EI/CI) *m/z*; 378 (50% *M*-H⁺); HRMS (FAB⁺) *calcd* for C₂₄H₃₀N₁O₂S₁ [*M*+NH₄⁺] *m/z* 396.1992 found: *m/z* 396.1994

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, *t_R* = 11.44 (R) and 16.81 (S).

(S)-2-(4-Bromo-benzyl)-3-thiophen-2-yl-propionic acid *tert*-butyl ester (3g):

Tert-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol) and 4-bromophenylboronic acid (0.161 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as colourless oils (0.058 g, 76% yield); *R_f* (petrol:dichloromethane, 2:1; 0.36); $\nu_{\max}$ (neat)/cm⁻¹; 2978, 2930 (C-H); 1724 (C=O); 1488 (CO-CH₃) 1367 (C-CH₃); 1151 (C-S); 550 (C-Br); δ_H (400 MHz; CDCl₃), 7.39 (2H, d, J 8.59 Hz, Ar); 7.14 (1H, dd, J 5.05, 1.26 Hz, *CH* thiophene); 7.06 (2H, d, J 8.59 Hz, Ar); 6.91 (1H, dd, J 5.05, 3.54 Hz, *CH* thiophene); 6.91 (1H, dd, J 3.54, 1.26 Hz, *CH* thiophene); 3.22-3.10 (1H, m, *CH*); 3.05- 2.70 (4H, m, *CH*₂); 1.28 (9H, s, *CH*₃); δ_c (75.5 MHz; CDCl₃); 173.3, 141.3, 138.0, 131.3, 130.7, 130.7, 130.7, 126.6, 125.6, 123.7, 120.1, 80.7, 50.1, 37.4, 32.2, 27.8; MS (EI/CI) *m/z*; 381 (80% *M*H⁺); HRMS (FAB⁺) *calcd* for C₁₈H₂₅N₁BrO₂S [*M*+NH₄⁺] *m/z* 381.3271 found: *m/z* 381.3274

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, *t_R* = 8.31 (R) and 8.72 (S).

(S)-tert-butyl 3-(4-formylphenyl)-2-(thiophen-2-ylmethyl)propanoate (3h)

Tert-butyl 2-(thiophen-2-ylmethyl) acrylate (0.045 g, 0.20 mmol) and 4-formylphenylboronic acid (0.119 g, 0.80 mmol) were reacted under the standard protocol to generate the desired compound as colourless oils (0.052 g, 79% yield); R_f (petrol:dichloromethane, 2:1; 0.1); $\nu_{\max}$ (neat)/ cm^{-1} ; 2977, 2930 (C-H); 1698, 1720 (C=O); 1391, 1251 (C-CH₃); 1151 (C-S); δ_H (300 MHz; CDCl₃), 10.0 (1H, s, CHO); 7.79 (2H, d, J 7.91 Hz Ar); 7.34 (2H, d, J 7.91, Ar); 7.15 (1H, dd, J 5.3, 1.1 Hz, CH thiophene); 6.92 (1H, dd, J 5.3, 3.4 Hz, CH thiophene); 6.84 (1H, dd, J 3.4, 0.75 Hz, CH thiophene); 3.22-3.08 (1H, m, CH); 3.04- 2.81 (4H, m, CH₂); 1.24 (9H, s, CH₃); δ_C (75.5 MHz; CDCl₃); 191.9, 173.1, 146.4, 141.0, 134.7, 129.7, 129.6, 129.6, 126.6, 125.8, 123.9, 80.8, 53.3, 49.8, 38.1, 32.3, 27.7, 27.7, 27.7; MS (EI/CI) m/z ; 330 (45% M-H⁺); HRMS (FAB⁺) *calcd* for C₁₉H₂₆N₁O₃S₁ [M+NH₄⁺] m/z 348.1628 found: m/z 348.1628.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, t_R = 22.0 (R) and 24.3 (S).

(S)-2-(3,5-Bis-trifluoromethyl-benzyl)-3-thiophen-2-yl-propionic acid tert-butyl ester (3i):

Tert-butyl 2-(thiophen-2-ylmethyl)acrylate (0.045 g, 0.20 mmol) and 3,5-bis(trifluoromethyl) phenylboronic acid (0.13 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as colourless oils (0.076 g, 87% yield); R_f (petrol:dichloromethane, 2:1; 0.45); $\nu_{\max}$ (neat)/ cm^{-1} ; 2981, 2934 (C-H); 1726 (C=O); 1153 (C-S); 1108, 1130 (C-F) δ_H (300 MHz; CDCl₃), 7.73 (1H, br s, p-PhH), 7.48 (2H, br s, o-PhH); 7.18 (1H, dd, J 1.1, 4.9 Hz, CH thiophene); 6.94 (1H,

dd, J 3.4, 4.9 Hz, *CH* thiophene); 6.84 (1H, dd, J 1.1, 3.4 Hz, *CH* thiophene); 3.28-3.15 (1H, m, *CH*); 3.09- 2.85 (4H, m, *CH*₂); 1.24 (9H, s, *CH*₃); δ_{C} (75.5 MHz; CDCl₃); 172.8, 141.6, 140.5, 131.7, 131.2, 129.2, 129.1, 126.8, 126.0, 125.0, 124.1, 121.4, 120.4, 120.4, 120.3, 81.3, 49.8, 37.4, 32.5, 27.6; MS (EI/CI) *m/z*; (% *M*+NH₄⁺); (% *M*H⁺); 264 (C₂₀H₂₀F₆O₂S₁+NH₄⁺); HRMS (FAB⁺) *calcd* for C₂₀H₂₁F₆O₂S₁ [*M*+H⁺] *m/z* 437.100995 found: *m/z* 437.1005.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, *t*_R = 7.10 (R) and 7.60 (S).

(S)-2-Biphenyl-4-ylmethyl-3-thiophen-2-yl-propionic acid (4f):

(S)-2-Biphenyl-4-ylmethyl-3-thiophen-2-yl-propionic acid *tert*-butyl ester (0.150 g, 0.40 mmol) in CH₂Cl₂ (5 mL), was added trifluoroacetic acid (0.2 mL) generates the desired compound as a white solid (0.125 g, 97% yield); mp (EtOH) 158-160 °C; ν_{max} (neat)/cm⁻¹; 2976, 2930, 3029 (C-H); 1724 (C=O); 1391, 1367 (C-CH₃); 1150 (C-S); δ_{H} (250 MHz; CDCl₃), 7.57-7.40 (4H, m, Ar); 7.40 (2H, tt, J 8.08, 2.02 Hz, Ar); 7.23 (1H, tt, J 7.33, 1.26 Hz, Ar); 7.21-7.00 (2H, m, Ar); 7.12 (1H, dd, J 5.3, 1.1 Hz, *CH* thiophene); 6.08 (1H, dd, J 5.3, 3.4 Hz, *CH* thiophene); 6.79 (1H, dd, J 3.4, 0.75 Hz, *CH* thiophene); 3.23-3.14 (1H, m, *CH*); 3.05- 2.81 (4H, m, *CH*₂); δ_{C} (75.5 MHz; CDCl₃); 166.8, 141.0, 140.7, 139.4, 137.5, 129.3, 128.7, 127.2, 127.1, 126.9, 126.8, 125.8, 123.9, 64.3, 49.4, 37.0, 31.5; MS (EI) *m/z*; (15%, *M*⁺); 322 (C₂₀H₁₈O₂S₁); HRMS (FAB⁺) *calcd* for C₂₀H₁₈O₂S₁ [*M*⁺] *m/z* 322.1022 found: *m/z* 322.1025.

(S)-tert-butyl 3-(2-methoxyphenyl)-2-(naphthalen-2-ylmethyl)propanoate (5):

Tert-butyl 2-(2-methoxybenzyl)acrylate (0.050 g, 0.20 mmol) and 2-naphthyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as colourless oils (0.054 g, 71% yield); $\nu_{\max}$ (neat)/ cm^{-1} ; 2973, 2933 (C-H); 1721 (C=O); 1510 (CO-CH₃) 1362 (C-CH₃); δ_{H} (300 MHz; CDCl₃), 7.84-7.72 (3H, m, Ar), 7.65 (1, br s, naphthyl *H*); 7.48-7.38 (2H, m, Ar); 7.34 (1H, dd, *J* 8.29, 1.88 Hz, Ar); 7.23-7.11 (2H, m, Ar); 6.91-6.80 (2H, m, Ar); 3.80 (3H, s, OCH₃); 3.17-3.05 (2H, m, CH, CH₂); 2.99-2.83 (3H, m, CH₂); 1.16 (9H, s, CCH₃); δ_{C} (75.5 MHz; CDCl₃); 174.5, 157.6, 137.2, 130.8, 127.5, 127.5, 127.5, 127.4, 127.2, 125.7, 125.1, 120.1, 110.0, 79.9, 55.1, 47.7, 38.7, 33.6, 28.0, 27.7; MS (EI/CI) *m/z*; C₂₅H₃₂NO₃ (5% M+NH₄⁺); C₂₅H₃₂NO₃ (5%, MH⁺); HRMS (FAB⁺) *calcd* for C₂₅H₃₂NO₃ [M+NH₄⁺] *m/z* 394.2377 found: *m/z* 394.2374.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, *t_R* = 20.4 (R) and 24.1 (S).

(S)-tert-butyl 3-(4-methoxyphenyl)-2-(naphthalen-2-ylmethyl)propanoate (6):

Tert-butyl 2-(4-methoxybenzyl)acrylate (0.050 g, 0.20 mmol) and 2-naphthyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as colourless oils (0.056 g, 74% yield); $\nu_{\max}$ (neat)/ cm^{-1} ; 2970, 2932 (C-H); 1722 (C=O); 1512 (CO-CH₃) 1360 (C-CH₃); δ_{H} (300 MHz; CDCl₃), 7.84-7.72 (3H, m, Ar), 7.63 (1, br s, Ar*H*); 7.49-7.39 (2H, m, Ar); 7.32 (1H, dd, *J* 8.29, 1.88 Hz, Ar); 7.12 (2H, d, *J* 8.85 Hz, Ar); 6.82 ((2H, d, *J* 8.85 Hz, Ar); 3.79 (3H, s, OCH₃); 3.16-3.05 (1H, m, CH, CH₂); 2.99-2.86 (2H, m, CH₂); 2.84-2.70 (1H, m, CH₂); 1.19 (9H, s, CCH₃); δ_{C} (75.5 MHz; CDCl₃); 174.3, 158.1, 137.0, 133.5,

132.2, 131.3, 130.0, 127.8, 127.6, 127.5, 127.5, 127.4, 125.9, 125.3, 113.7, 55.2, 50.3, 38.5, 37.7, 27.8; HRMS (FAB⁺) *calcd* for C₂₅H₃₂NO₃ [M+NH₄⁺] *m/z* 394.2377 found: *m/z* 394.2373.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, *t_R* = 13.53 (R) and 14.78 (S).

(S)-tert-butyl 3-(naphthalen-1-yl)-2-(naphthalen-2-ylmethyl)propanoate (7):

Tert-butyl 2-(naphthalen-1-ylmethyl)acrylate (0.050 g, 0.20 mmol) and), 2-naphthyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as colourless oils (0.068 g, 86% yield); *v*_{max} (neat)/cm⁻¹; 2977 (C-H); 1723 (C=O); 1149 (OC-CH₃); *δ*_H (400 MHz; CDCl₃), 7.91-7.70 (6H, m, Ar), 7.67 (1, br s, naphthyl *H*); 7.50-7.40 (4H, m, Ar); 7.38 (2H, d, *J* 4.55 Hz, Ar); 7.34 (1H, dd, *J* 8.46, 1.64 Hz, Ar); 3.49-3.40 (1H, m, *m*, CH, CH₂); 3.34-3.13 (3H, m, CH, CH₂); 3.05-2.97 (1H, m, CH₂); 1.15 (9H, s, CCH₃); *δ*_C (75.5 MHz; CDCl₃); 174.2, 136.8, 135.3, 133.8, 132.2, 131.8, 128.7, 127.8, 127.5, 127.5, 127.4, 127.2, 127.1, 125.9, 125.8, 125.4, 125.3, 125.2, 123.6, 80.3, 49.2, 38.9, 35.4, 27.7; MS (EI/CI) *m/z*; C₂₈H₃₂NO₂ (80% M+NH₄⁺); C₂₈H₂₈O₂ (15%, MH⁺); HRMS (FAB⁺) *calcd* for C₂₅H₃₂NO₃ [M+NH₄⁺] *m/z* 414.2428 found: *m/z* 414.2429. Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, *t_R* = 13.90 (R) and 15.62 (S).

(S)-tert-butyl 3-(4-fluorophenyl)-2-(naphthalen-2-ylmethyl)propanoate (8):

Tert-butyl 2-(4-fluorobenzyl)acrylate (0.047 g, 0.20 mmol) and 2-naphthyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as colourless oils (0.061 g, 83% yield); $\nu_{\max}$ (neat)/ cm^{-1} ; 2977, 2930 (C-H); 1723 (C=O); 1148 (C-F); δ_{H} (300 MHz; CDCl_3), 7.84-7.72 (3H, m, Ar), 7.65 (1, br s, naphthyl *H*); 7.50-7.38 (2H, m, Ar); 7.33 (1H, dd, *J* 8.29, 1.84 Hz, Ar); 7.20-7.11 (2H, m, Ar); 6.95 (2H, tt, *J* = 8.67, 2.26 Hz, Ar); 3.18-3.03 (1H, m, *CH*, *CH*₂); 3.11-2.72 (4H, m, *CH*₂); 1.17 (9H, s, *CCH*₃); δ_{C} (75.5 MHz; CDCl_3); 174.0, 136.6, 134.9, 134.9, 133.4, 132.1, 130.4, 130.3, 127.8, 127.5, 127.4, 127.4, 127.3, 125.9, 125.3, 115.1, 114.8, 80.4, 50.1, 50.1, 38.6, 37.6, 27.7; MS (EI/CI) *m/z*; $\text{C}_{24}\text{H}_{29}\text{NF}_1\text{O}_2$ (60% $\text{M}+\text{NH}_4^+$); $\text{C}_{24}\text{H}_{29}\text{NF}_1\text{O}_2$ (25%, MH^+); HRMS (FAB^+) *calcd* for $\text{C}_{24}\text{H}_{29}\text{NF}_1\text{O}_2$ [$\text{M}+\text{NH}_4^+$] *m/z* 382.2177 found: *m/z* 382.2179.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min^{-1} , t_{R} = 10.98 (R) and 11.69 (S).

(S)-tert-butyl 2-(4-(methylthio)benzyl)-3-(4-methoxyphenyl)propanoate (9):

Tert-butyl 2-(4-methoxybenzyl)acrylate (0.050 g, 0.20 mmol) and 4-thiomethylphenyl boronic acid (0.138 g, 0.80 mmol), were reacted under the standard protocol to generate the desired compound as colourless oils (0.052 g, 70% yield); $\nu_{\max}$ (neat)/ cm^{-1} ; 2976, 2922 (C-H); 1724 (C=O); 1512 (CO-*CH*₃); 1148 (C-S); δ_{H} (300 MHz; CDCl_3), 7.17 (2H, d, *J* 8.29 Hz, Ar); 7.10 (2H, d, *J* 1.88 Hz, Ar); 7.07 (2H, d, *J* 1.88 Hz, Ar); 6.80 (2H, d, *J* 8.29 Hz, Ar); 3.78 (3H, s, *OCH*₃); 2.91-2.78 (3H, m, *CH*, *CH*₂); 2.75-2.66 (2H, m, *CH*, *CH*₂); 2.46 (3H, s, *OSH*₃); 1.22 (9H, s, *CCH*₃); δ_{C} (75.5

MHz; CDCl₃); 174.1, 158.1, 136.5, 135.8, 131.2, 129.9, 129.5, 126.9, 113.6, 55.2, 50.2, 27.8, 16.2; MS (EI/CI) *m/z*; C₂₂H₃₂NO₃S₁ (45% M+NH₄⁺); C₂₂H₂₈O₃S₁ (50%, MH⁺); HRMS (FAB⁺) *calcd* for C₂₂H₃₂NO₃S₁ [M+NH₄⁺] *m/z* 373.1832 found: *m/z* 373.1828.

Diacel Chiralcel OD-H, hexane/propan-2-ol (99:1), 1 mL min⁻¹, *t_R* = 11.723 (R) and 13.38 (S).

(S)-3a

(S)-3a

(S)-3c

(S)-3d

(S)-3d

(S)-3e

(S)-3e

(S)-3f

(S)-3f

(S)-3h

(S)-4f

(S)-5

(S)-5

(S)-7

(S)-7

HPLC Traces from substrate optimisation of 2-Benzyl-3-thiophen-2-yl-propionic acid *tert*-butyl ester (3a):

Conditions:

Flow rate = 1 ml min

99:1 Hexane: Isopropanol

Wavelength = 254 nm

RRT = 0.516 minutes

Closing signal file M:SIGNAL .BNC
Storing processed peaks to M:Q13E50B5.PRO

RUN# 82 AUG 25, 2005 10:45:08

SAMPLE# 8

SIGNAL FILE: M:SIGNAL.BNC
PEAK FILE : M:Q13E50B5.PRO
AREA%

RT	AREA	TYPE	WIDTH	AREA%
5.976	18769	PB	.121	.63009
6.430	26350	BP	.142	.88459
8.436	1415710	UU	.191	47.52643
8.929	1517956	UB	.201	50.95890

TOTAL AREA=2978786
MUL FACTOR=1.0000E+00

* RUN # 304 SEP 15, 2005 12:01:39
START

Closing signal file M:SIGNAL .BNC
Storing processed peaks to M:Q15A1225.PRO
DIRECTORY FULL

RUN# 304 SEP 15, 2005 12:01:39

SAMPLE# 13

SIGNAL FILE: M:SIGNAL .BNC
PEAK FILE : M:Q15A1225.PRO
AREA%

RT	AREA	TYPE	WIDTH	AREA%
5.789	444183	BR	129	1.47094
6.347	318892	RU	119	1.05603
6.652	175609	UR	126	0.58154
8.193	291970	PU	161	0.96688
8.597	2949090	UU	185	9.76609
9.108	25842752	UR	219	85.57981
11.749	174760	T BR	300	0.57873

TOTAL AREA=3.0197E+07
MIN FACTOR=1.0000E+00

References:

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- 2.T. Tsukamoto, B. Hin, P. Majer, *J. Org. Chem.* **2002**, 67, 7365.