Rh-Catalyzed Asymmetric Hydrogenation of γ-Phthalimido Substituted α,β-Unsaturated Carboxylic Acid Esters: An Efficient Enantioselective Synthesis of β-Aryl-γ-Amino Acids

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Instruments and Materials

All solvents were dried and degassed by standard methods and stored under nitrogen. All the commercially available catalysts and ligands were brought from Strem Chemicals and without further purification. Ligand 2a-e were synthesized according to the procedures reported previously.1,2 All reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques or in a nitrogen-filled glovebox, unless otherwise noted.

NMR spectra were recorded on BRUKER DRX 400 spectrometers. Chemical shifts are reported in parts per million (ppm) down field from TMS with the solvent resonance as the internal standard. Coupling constants (J) are reported in Hz and refer to apparent peak multiplications. High resolution mass spectra (HRMS) were recorded on Q-Tof (Micromass) or Bruker APEX II spectrometer. Enantiomeric excess (ee) were determined by HPLC analysis on an Agilent HP-1100. Optical rotations were measured on a JASCO P-1020 high sensitive polarimeter.

Preparation of (SC,RFc,Rp)-3: (RFc)-2-{(SC)-1-N-methyl-N-[bis(4-trifluoromethylphenyl)phosphino]aminoethyl}-1-[(RFc)-(1-naphthyl)phenylphosphino]ferrocene:

To a solution of (SC,RFc,Rp)-PPFNHMe4 (477 mg, 1.0 mmol) and Et₃N (0.28 mL, 2.0 mmol) in toluene (2.5 mL) was added dropwise bis[4-(trifluoromethyl)phenyl]chlorophosphine (0.374 g, 1.05 mmol) at 0°C. The mixture was warmed to room temperature, and stirred at room temperature overnight. The reaction mixture was filtered through a pad of neutral aluminium oxide and eluted with hexane-EtOAc (10:1) to afford the title compound (717 mg, 90%) as orange foam. ¹H NMR (400 MHz, CDCl₃): δ = 1.58 (3H, d, J = 6.8 Hz; CH₃CH), 2.22 (3H, d, J = 3.3 Hz; CH₃N), 3.44 (5H, s; C₅H₅), 4.29 (1H, m; C₅H), 4.44 (1H, m; C₅H), 4.55 (1H, s; C₅H), 5.00-5.06 (1H, m; CHCH₃), 6.86 (1H, m; Ar-H),
7.02-7.07 (6H, m; Ar-H), 7.12-7.14 (1H, m; Ar-H), 7.34-7.36 (5H, m; Ar-H), 7.39-7.42 (3H, m; Ar-H), 7.56-7.58 (1H, m; Ar-H), 7.88-7.90 (2H, m; Ar-H), 9.42 (1H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 19.26, 19.32, 31.53, 31.64, 58.21, 58.30, 58.59, 58.68, 69.48, 69.94, 70.07, 71.96, 75.40, 75.54, 97.70, 124.64, 125.27, 125.55, 126.09, 126.40, 126.85, 126.97, 127.20, 127.79, 128.38, 128.75, 129.68, 130.19, 131.95, 132.11, 134.83, 136.34, 142.19 ppm; $^{31}$P NMR (162 MHz, CDCl$_3$): $\delta$ = 55.44, -42.40 ppm; HRMS (EI) m/z calcd for C$_{43}$H$_{35}$NF$_6$FeP$_2$+: 797.1498, found: 797.1493.

**General Procedure for the Preparation of phthalimidobut-2-enoate 1.$^5$**

![Diagram of the reaction process](image.png)

To a suspension of sodium hydride (60% dispersion in mineral oil, 4 mmol) in dry THF (200 mL) was added dropwise triethyl phosphonoacetate (4 mmol) at 0°C under argon atmosphere. After 30 min, the appropriate ketone 5 (2.7 mmol) was added to the reaction mixture, which was then allowed to warm to room temperature and stirred for 24h and then cooled with a water bath. A saturated aqueous ammonium chloride solution (20 mL) was then added dropwise to the cold mixture. The aqueous phase was extracted with diethyl ether (4 x 50mL) and the combined organic phase was washed with brine (3 x 50mL), dried over sodium sulfate, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 95:5) yielded ester 6 as a clear oil with 60-80% yields.

A solution of $\alpha,\beta$-unsaturated ester 6 (1 mmol), NBS (1.2 mmol) and benzoylperoxide (0.04 mmol) in dry CCl$_4$ (35 mL) was refluxed under nitrogen atmosphere for 10 h. The resulting reaction mixture was cooled to room temperature and then filtered through a sintered funnel to separate succinimide formed during the reaction. The filtrate was concentrated under reduced pressure to obtain bromoester 7.
It was then purified by column chromatography packed with silica gel to give pure pale yellow colored gum, bromoester 7 with above 90% yields.

To the suspension of potassium phthalimide (10.0 mmol) in dry DMF (10 mL) was added a solution of bromoester 7 in dry DMF (10 mL). The reaction was run at room temperature and monitored by TLC. After the reaction was complete, the reaction mixture was poured into water and extracted with ether and concentrated in vacuum to leave a white solid. The residue can be easily purified by the recrystallization from ethyl acetate/ hexane (1/4) or by flash chromatography (hexanes/ethyl acetate, 5:1), recrystallized with ethyl acetate/ hexane (1/4), to give the desired compounds 1.

**Ethyl (Z)-3-phenyl-4-phthalimidobut-2-enoate (1a).** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$= 1.34 (3H, t, $J$ = 7.2 Hz; CH$_3$CH$_2$), 4.25 (2H, q, $J$ = 7.2 Hz; CH$_2$CH$_3$), 5.47 (2H, s; CH$_2$N), 6.17 (1H, s; =CH), 7.23-7.27 (3H, m; Ar-H), 7.36 (2H, m; Ar-H), 7.60-7.62 (2H, m; Ar-H), 7.68-7.71 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.3, 37.0, 60.5, 121.0, 123.2, 127.0, 128.4, 129.0, 131.7, 133.9, 138.0, 153.9, 166.1, 167.8 ppm.

**Ethyl (Z)-3-(2-methoxyphenyl)-4-phthalimidobut-2-enoate (1b).** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.33 (3H, t, $J$ = 7.2 Hz; CH$_3$CH$_2$), 3.74 (3H, s; CH$_3$O), 4.25 (2H, q, $J$ = 7.2 Hz; CH$_2$CH$_3$), 5.41 (2H, d; CH$_2$N), 6.00 (1H, t; =CH), 6.68-6.70 (1H, m; Ar-H), 6.77-6.79 (1H, m; Ar-H), 7.06-7.08 (1H, m; Ar-H), 7.14 (1H, m; Ar-H), 7.59-7.61 (2H, m; Ar-H), 7.67-7.69 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.3, 38.5, 55.3, 60.4, 109.9, 120.3, 121.5, 122.9, 127.7, 129.9, 130.2, 131.8, 133.7, 154.2, 156.3, 166.0, 167.6 ppm.

**Ethyl (Z)-3-(3-methoxyphenyl)-4-phthalimidobut-2-enoate (1c).** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.34 (3H, t, $J$ = 7.2 Hz; CH$_3$CH$_2$), 3.75 (3H, s; CH$_3$O), 4.26 (2H, q, $J$ = 7.2 Hz; CH$_2$CH$_3$), 5.46 (2H, d; CH$_2$N), 6.20 (1H, s; =CH), 6.76-6.78 (1H, m; Ar-H), 6.91 (1H, m; Ar-H), 6.95-6.97 (1H, m; Ar-H), 7.13-7.17 (1H, m; Ar-H), 7.61-7.63 (2H, m; Ar-H), 7.70-7.72 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.3, 37.0, 55.3, 60.5, 111.8, 115.6, 119.5, 121.0, 123.2, 129.4, 131.8, 133.9,
139.4, 153.7, 159.4, 166.1, 167.9 ppm.

**Ethyl (Z)-3-(4-methoxyphenyl)-4-phthalimidobut-2-enoate (1d).** $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 1.33 (3H, t, $J = 7.2$ Hz; CH$_3$CH$_2$), 3.72 (3H, s; CH$_3$OH), 4.27 (2H, m, CH$_2$CH$_3$), 5.47 (2H, s; CH$_2$N), 6.15 (1H, s; =CH), 6.76-6.78 (2H, m; Ar-H), 7.33-7.36 (2H, m; Ar-H), 7.61-7.63 (2H, m; Ar-H), 7.70-7.72 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 14.3, 36.6, 55.2, 60.3, 113.8, 119.7, 123.2, 128.4, 130.2, 131.8, 133.9, 153.2, 160.3, 166.2, 167.9 ppm.

Ethyl (Z)-3-(4-fluorophenyl)-4-phthalimidobut-2-enoate (1e). $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 1.34 (3H, t, $J = 7.2$ Hz; CH$_3$CH$_2$), 4.26 (2H, q, $J = 7.2$ Hz; CH$_2$CH$_3$), 5.45 (2H, s; CH$_2$N), 6.14 (1H, s; =CH), 6.91 (2H, m; Ar-H), 7.34-7.37 (2H, m; Ar-H), 7.62-7.65 (2H, m; Ar-H), 7.71-7.73 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 14.3, 36.7, 60.5, 60.3, 115.3, 115.6, 120.6, 121.1, 123.2, 128.9, 129.0, 131.7, 134.0, 152.8, 161.9, 164.4, 165.9, 167.8 ppm.

**Ethyl (Z)-3-(4-chlorophenyl)-4-phthalimidobut-2-enoate (1f).** $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 1.34 (3H, t, $J = 7.2$ Hz; CH$_3$CH$_2$), 4.26 (2H, q, $J = 7.2$ Hz; CH$_2$CH$_3$), 5.44 (2H, s; CH$_2$N), 6.15 (1H, s; =CH), 7.21 (2H, m; Ar-H), 7.31 (2H, m; Ar-H), 7.65 (2H, m; Ar-H), 7.71-7.72 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 14.3, 36.8, 60.6, 121.4, 123.3, 128.4, 128.7, 131.7, 134.0, 135.1, 136.5, 152.6, 165.8, 167.8 ppm.

**Ethyl (Z)-3-(4-bromophenyl)-4-phthalimidobut-2-enoate (1g).** $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 1.34 (3H, t, $J = 7.2$ Hz; CH$_3$CH$_2$), 4.27 (2H, q, $J = 7.2$ Hz; CH$_2$CH$_3$), 5.44 (2H, s; CH$_2$N), 6.15 (1H, s; =CH), 7.24 (2H, d, $J = 8.4$ Hz; Ar-H), 7.37 (2H, d, $J = 8.4$ Hz; Ar-H), 7.63-7.65 (2H, m; Ar-H), 7.71-7.73 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 14.3, 36.8, 60.6, 121.5, 123.3, 123.4, 128.7, 131.6, 134.0, 137.0, 152.6, 165.8, 167.8 ppm.
Ethyl (Z)-3-(4-trifluoromethylphenyl)-4-phthalimidobut-2-enolate (1h). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.35 (3H, t, $J$ = 7.2 Hz; CH$_3$CH$_2$), 4.27 (2H, q, $J$ = 7.2 Hz; CH$_2$CH$_3$), 5.47 (2H, s; CH$_2$N), 6.19 (1H, s; =CH), 7.48-7.53 (4H, m; Ar-H), 7.63-7.66 (2H, m; Ar-H), 7.71-7.73 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.3, 36.9, 60.7, 122.5, 123.3, 123.5, 125.4, 127.5, 131.6, 134.1, 141.7, 152.3, 165.6, 167.8 ppm.

Ethyl (Z)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4-phthalimidobut-2-enolate (1i). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.34 (3H, t, $J$ = 7.2 Hz; CH$_3$CH$_2$), 1.56-1.59 (2H, m; CH$_2$CH$_2$), 1.78 (4H, m; CH$_2$CH$_2$), 1.91-1.93 (2H, m; CH$_2$CH$_2$), 3.75 (3H, s; CH$_3$O), 4.27 (2H, m; CH$_2$CH$_3$), 4.72 (1H, m; CHO), 5.45 (2H, s; CH$_2$N), 6.14 (1H, s; =CH), 6.71 (1H, d, $J$ = 8.4 Hz; Ar-H), 6.87 (1H, d, $J$ = 1.6 Hz; Ar-H), 6.94 (1H, dd, $J$ = 1.6 Hz, 8.4 Hz; Ar-H), 7.61-7.63 (2H, m; Ar-H), 7.70-7.71 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.4, 24.1, 32.8, 36.9, 55.9, 60.4, 80.4, 111.4, 113.2, 119.7, 119.8, 123.2, 130.5, 131.8, 133.9, 147.2, 150.8, 153.8, 166.3, 167.9 ppm.

Ethyl (Z)-3-(2-Naphthyl)-4-phthalimidobut-2-enolate (1j). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.36 (3H, t, $J$ = 7.2 Hz; CH$_3$CH$_2$), 4.28 (2H, q, $J$ = 7.2 Hz; CH$_2$CH$_3$), 5.59 (2H, s; CH$_2$N), 6.32 (1H, s; =CH), 6.71 (1H, d, $J$ = 8.4 Hz; Ar-H), 6.87 (1H, d, $J$ = 1.6 Hz; Ar-H), 7.41-7.45 (2H, m; Ar-H), 7.49-7.55 (3H, m; Ar-H), 7.64-7.66 (2H, m; Ar-H), 7.71-7.73 (2H, m; Ar-H), 7.79-7.82 (1H, m; Ar-H), 7.91 (1H, s; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.3, 36.9, 60.5, 121.5, 123.2, 124.5, 126.4, 126.7, 126.8, 127.5, 128.1, 128.5, 131.7, 133.0, 133.4, 133.8, 135.4, 135.7, 166.1, 167.9 ppm.

Ethyl (Z)-3-(6-methoxy-naphthalen-2-yl)-4-phthalimidobut-2-enolate (1k). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.35 (3H, t, $J$ = 7.2 Hz; CH$_3$CH$_2$), 3.85 (3H, s; CH$_3$O), 4.28 (2H, q, $J$ = 7.2 Hz; CH$_2$CH$_3$), 5.59 (2H, s; CH$_2$N), 6.30 (1H, s; =CH), 7.01 (1H, s; Ar-H), 7.07 (1H, d, $J$ = 8.4 Hz; Ar-H), 7.46 (1H, d, $J$ = 8.4 Hz; Ar-H), 7.54-7.55 (2H, m; Ar-H), 7.60-7.70 (4H, m; Ar-H), 7.84 (1H, s; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.3, 36.8, 55.3, 60.5, 105.5, 119.3, 120.8, 123.2, 125.0, 126.6, 126.9, 128.4, 130.0, 131.7, 133.1, 133.8,
134.8, 153.7, 158.4, 166.2, 167.9 ppm.

**Ethyl (Z)-3-(2-thienyl)-4-phthalimidobut-2-enoate (1l).** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.35 (3H, t, $J = 7.2$ Hz; CH$_3$CH$_2$), 4.28 (2H, q, $J = 7.2$ Hz; CH$_2$CH$_3$), 5.47 (2H, s; CH$_2$N), 6.43 (1H, d; =CH), 6.94 (1H, dd, $J = 4.8$, 4.0 Hz; Ar-H), 7.22 (1H, d, $J = 4.8$ Hz; Ar-H), 7.38 (1H, d, $J = 4.0$ Hz; Ar-H), 7.64-7.67 (2H, m; Ar-H), 7.76-7.78 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.3, 35.8, 60.5, 119.7, 123.3, 127.2, 127.6, 128.1, 131.9, 134.0, 141.3, 144.1, 166.0, 167.9 ppm.

**General procedure for asymmetric hydrogenation**

In a nitrogen-filled glovebox, to a solution of [Rh(COD)$_2$]BF$_4$ (1.0 mg, 0.0025 mmol) in anhydrous and degassed CH$_2$Cl$_2$ (1 mL) was added ligand (0.00275 mmol). After stirring the mixture for 30 min, a substrate (0.25 mmol) dissolved in CH$_2$Cl$_2$ (1 mL) was added. The reaction mixture was transferred to a Par stainless autoclave. The autoclave was purged three times with hydrogen and the pressure was set to the desired pressure. The hydrogenation was performed at room temperature for 24 h. After carefully releasing the hydrogen, the solvent was removed. The enantiomeric excess was determined by HPLC after purification on silica gel.

**Ethyl 3-phenyl-4-phthalimidobutanoate (4a).** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.06 (3H, t, $J = 7.2$ Hz; CH$_3$CH$_2$), 2.72 (2H, m, $J =8.0$ Hz; CH$_2$CH), 3.70-3.78 (1H, m; CHCH$_2$), 3.89-3.95 (4H, m; OCH$_2$CH$_3$, CH$_2$N), 7.18-7.22 (1H, m; Ar-H), 7.25-7.28 (4H, m; Ar-H), 7.67-7.70 (2H, m; Ar-H), 7.79-7.81 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.0, 38.6, 40.8, 43.2, 60.5, 123.3, 127.3, 127.7, 128.6, 131.9, 134.0, 140.4, 168.1, 171.5 ppm; HRMS (ESI) m/z calcd for C$_{20}$H$_{19}$NO$_4$Na$: 360.1212$, found: 360.1223; $[\alpha]_D^{25} = -62.8$ (c 1.00, CHCl$_3$) for 95% ee; HPLC (UV 254 nm, Chiralpak AD (0.46 cm x 25 cm), i-PrOH/Hexane = 3/97, 0.8 mL/min): $t_1 = 47.0$ min, $t_2 = 56.3$ min.

**Ethyl 3-(2-methoxyphenyl)-4-phthalimidobutanoate (4b).** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.08 (3H, t, $J = 7.2$ Hz; CH$_3$CH$_2$), 2.80-2.84 (2H, m; CH$_2$CH), 3.76 (3H, s; CH$_3$O), 3.94-3.99 (5H, m; CH$_2$O,
**Supporting Information**

**C**\(_2\)N, -CH\(_2\), 6.78-6.80 (1H, m; Ar-H), 6.83-6.86 (1H, m; Ar-H), 7.66-7.69 (2H, m; Ar-H), 7.77-7.79 (2H, m; Ar-H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 14.3, 36.7, 37.2, 41.9, 55.5, 60.6, 110.9, 120.7, 123.3, 128.5, 128.7, 129.2, 132.2, 134.0, 157.9, 168.4, 172.3 ppm; HRMS (ESI) m/z calcd for C\(_{21}\)H\(_{21}\)NO\(_5\)Na\(^+\): 390.1317, found: 390.1336; \([\alpha]_D^{25} = -81.9\) (c 0.76, CHCl\(_3\)) for 96% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 25 cm), i-PrOH/Hexane = 10/90, 1.0 mL/min): \(t_1 = 9.6\) min, \(t_2 = 21.4\) min.

**Ethyl 3-(3-methoxyphenyl)-4-phthalimidobutanoate (4c).** \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.08\) (3H, t, \(J = 7.2\) Hz; CH\(_3\)CH\(_2\)), 2.70-2.72 (2H, d, \(J = 7.6\) Hz; CH\(_2\)CH), 3.72-3.76 (4H, m; CH\(_3\)O, -CH\(_2\)-), 3.88-3.94 (4H, m; CH\(_2\)O, CH\(_2\)N), 6.76 (1H, m; Ar-H), 6.81 (1H, s; Ar-H), 6.86-6.88 (1H, m; Ar-H), 7.18-7.20 (1H, m; Ar-H), 7.69-7.71 (2H, m; Ar-H), 7.80-7.82 (2H, m; Ar-H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 14.1, 38.6, 40.8, 43.2, 55.2, 60.5, 112.9, 113.3, 120.0, 123.3, 129.6, 131.9, 134.0, 142.1, 159.7, 168.2, 171.5 ppm; HRMS (ESI) m/z calcd for C\(_{21}\)H\(_{21}\)NO\(_5\)Na\(^+\): 390.1317, found: 390.1328; \([\alpha]_D^{25} = -70.0\) (c 1.00, CHCl\(_3\)) for 94% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 25 cm), i-PrOH/Hexane = 3/97, 1.0 mL/min): \(t_1 = 22.3\) min, \(t_2 = 35.1\) min.

**Ethyl 3-(4-methoxyphenyl)-4-phthalimidobutanoate (4d).** \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.07\) (3H, t, \(J = 7.2\) Hz; CH\(_3\)CH\(_2\)), 2.67-2.70 (2H, m; CH\(_2\)CH), 3.68-3.76 (1H, m; -CH\(_2\)-), 3.82 (3H, s; CH\(_3\)O), 3.85-3.88 (2H, m; CH\(_2\)N), 3.92-3.96 (2H, m; CH\(_2\)O), 6.80 (2H, d, \(J = 8.0\) Hz; Ar-H), 7.18 (2H, d, \(J = 8.0\) Hz; Ar-H), 7.67-7.71 (2H, m; Ar-H), 7.78-7.81 (2H, m; Ar-H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 14.1, 38.9, 40.0, 43.3, 55.2, 60.5, 114.0, 123.3, 128.7, 131.9, 132.4, 134.0, 158.7, 168.2, 171.6 ppm; HRMS (ESI) m/z calcd for C\(_{21}\)H\(_{21}\)NO\(_5\)Na\(^+\): 390.1317, found: 390.1328; \([\alpha]_D^{25} = -83.9\) (c 0.94, CHCl\(_3\)) for 94% ee; HPLC (UV 254 nm, Chiralcel AD (0.46 cm x 25 cm), i-PrOH/Hexane = 5/95, 0.8 mL/min): \(t_1 = 54.4\) min, \(t_2 = 74.6\) min.

**Ethyl 3-(4-fluorophenyl)-4-phthalimidobutanoate (4e).** \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.07\) (3H, t, \(J = 7.2\) Hz; CH\(_3\)CH\(_2\)), 2.68-2.72 (2H, m; CH\(_2\)CH), 3.72-3.76 (1H, m; -CH\(_2\)-), 3.86-3.88 (2H, m; CH\(_2\)O), 6.80 (2H, d, \(J = 8.0\) Hz; Ar-H), 7.18 (2H, d, \(J = 8.0\) Hz; Ar-H), 7.67-7.71 (2H, m; Ar-H), 7.78-7.81 (2H, m; Ar-H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 14.1, 38.9, 40.0, 43.3, 55.2, 60.5, 114.0, 123.3, 128.7, 131.9, 132.4, 134.0, 158.7, 168.2, 171.6 ppm; HRMS (ESI) m/z calcd for C\(_{21}\)H\(_{21}\)NO\(_5\)Na\(^+\): 390.1317, found: 390.1328; \([\alpha]_D^{25} = -83.9\) (c 0.94, CHCl\(_3\)) for 94% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 25 cm), i-PrOH/Hexane = 5/95, 0.8 mL/min): \(t_1 = 54.4\) min, \(t_2 = 74.6\) min.
3.89-3.98 (2H, m; CH₂N), 6.94 (2H, t, J = 8.4 Hz; Ar-H), 7.22-7.28 (2H, m; Ar-H), 7.69-7.71 (2H, m; Ar-H), 7.79-7.81 (2H, m; Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 14.0, 38.4, 38.7, 40.1, 43.1, 60.5, 115.4, 115.6, 123.3, 129.2, 129.3, 131.8, 134.0, 136.1, 160.7, 163.2, 168.1, 171.3 ppm; HRMS (ESI) m/z calcd for C₂₀H₁₈N₀₄FNa⁺: 378.1118, found: 378.1126; [α]D²⁵ = -88.8 (c 1.00, CHCl₃) for 96% ee; HPLC (UV 254 nm, Chiralpak AD (0.46 cm x 25 cm), i-PrOH/Hexane = 5/95, 0.8 mL/min): t₁ = 37.3 min, t₂ = 50.4 min.

**Ethyl 3-(4-chlorophenyl)-4-phthalimidobutanoate (4f).** ¹H NMR (400 MHz, CDCl₃): δ = 1.08 (3H, t, J = 7.2 Hz; CH₃CH₂), 2.68-2.72 2H, m; CH₂CH), 3.72-3.75 (1H, m; -CH-), 3.86-3.91 (2H, m; CH₂N), 3.92 (2H, q, J = 7.2 Hz; CH₂O), 7.20-7.26 (4H, m; Ar-H), 7.69-7.71 (2H, m; Ar-H), 7.79-7.81 (2H, m; Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 14.1, 38.6, 40.2, 42.9, 60.6, 123.3, 128.8, 129.1, 131.8, 133.0, 134.1, 138.9, 168.1, 171.2 ppm; HRMS (ESI) m/z calcd for C₂₀H₁₈N₀₄ClNa⁺: 394.0822, found: 394.0836; [α]D²⁵ = -96.5 (c 0.80, CHCl₃) for 95% ee; HPLC (UV 254 nm, Chiralpak AD (0.46 cm x 25 cm), i-PrOH/Hexane = 5/95, 0.8 mL/min): t₁ = 42.8 min, t₂ = 62.1 min.

**Ethyl 3-(4-bromophenyl)-4-phthalimidobutanoate (4g).** ¹H NMR (400 MHz, CDCl₃): δ = 1.08 (3H, t, J = 7.2 Hz; CH₃CH₂), 2.63-2.74 (2H, m; CH₂CH), 3.70-3.74 (1H, m; -CH-), 3.82-3.89 (2H, m; CH₂N), 3.92 (2H, q, J = 7.2 Hz; CH₂O), 7.15 (2H, d, J = 8.0 Hz; Ar-H), 7.39 (2H, d, J = 8.0 Hz; Ar-H), 7.69-7.71 (2H, m; Ar-H), 7.79-7.82 (2H, m; Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 14.1, 38.5, 40.3, 42.9, 60.6, 121.2, 123.3, 129.5, 131.7, 134.1, 139.5, 168.1, 171.1 ppm; HRMS (ESI) m/z calcd for C₂₀H₁₈N₀₄Br Na⁺: 438.0317, found: 438.0327; [α]D²⁵ = -106.7 (c 0.96, CHCl₃) for 94% ee; HPLC (UV 254 nm, Chiralpak AD (0.46 cm x 25 cm), i-PrOH/Hexane = 5/95, 1.0 mL/min): t₁ = 38.0 min, t₂ = 56.4 min.

**Ethyl 3-(4-trifluoromethylphenyl)-4-phthalimidobutanoate (4h).** ¹H NMR (400 MHz, CDCl₃): δ = 1.06-1.11 (3H, m; CH₃CH₂), 2.72-2.76 (2H, m; CH₂CH), 3.81-3.87 (1H, m; -CH-), 3.90-3.98 (4H, m;
Supporting Information

Ethyl 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4-phthalimidobutanoate (4i). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.09 (3H, t, $J$ = 7.2 Hz; CH$_3$CH$_2$), 1.55-1.57 (2H, m; CH$_2$CH$_2$), 1.73-1.89 (6H, m; CH$_2$CH$_2$), 2.68 (2H, d, $J$ = 7.2 Hz; CH$_2$CH), 3.68 (1H, m; -CH$_2$), 3.78 (3H, s; CH$_3$O), 3.85-3.89 (2H, m; CH$_2$N), 4.70 (1H, m; -CH$_2$), 6.73-6.80 (3H, m; Ar-H), 7.42-7.47 (3H, m; Ar-H), 7.65-7.68 (2H, m; Ar-H), 7.72 (1H, s; Ar-H), 7.77-7.81 (5H, m; Ar-H), 7.73 (2H, m; Ar-H), 7.79 (1H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.0, 38.8, 40.9, 43.1, 60.5, 123.3, 125.7, 125.8, 126.1, 126.7, 127.7, 127.8, 128.4, 131.9, 132.7, 133.4, 134.0, 137.9, 168.2, 171.5 ppm; HRMS (ESI) m/z calc'd for C$_{26}$H$_{29}$NO$_6$Na$: 474.1893$, found: 474.1916; $[^{\alpha}]D^{25} = -80.4$ (c 0.9, CHCl$_3$) for 97% ee; HPLC (UV 254 nm, Chiralpak AD (0.46 cm x 25 cm), i-PrOH/Hexane = 10/90, 0.8 mL/min): $t_1 = 22.5$ min, $t_2 = 30.3$ min.

Ethyl 3-(2-Naphthyl)-4-phthalimidobutanoate (4j). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.02-1.07 (3H, m; CH$_3$CH$_2$), 2.80-2.82 (2H, m; CH$_2$CH), 3.88-3.93 (3H, m; -CH$_2$-), 3.95-4.01 (2H, m; CH$_2$O), 7.42-7.47 (3H, m; Ar-H), 7.65-7.68 (2H, m; Ar-H), 7.72 (1H, s; Ar-H), 7.77-7.81 (5H, m; Ar-H), 7.73 (2H, m; Ar-H), 7.79 (1H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.0, 38.8, 40.9, 43.1, 60.5, 123.3, 125.7, 125.8, 126.1, 126.7, 127.7, 127.8, 128.4, 131.9, 132.7, 133.4, 134.0, 137.9, 168.2, 171.5 ppm; HRMS (ESI) m/z calc'd for C$_{26}$H$_{29}$NO$_6$Na$: 474.1893$, found: 474.1916; $[^{\alpha}]D^{25} = -80.4$ (c 0.9, CHCl$_3$) for 97% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 25 cm), i-PrOH/Hexane = 3/97, 1.0 mL/min): $t_1 = 27.9$ min, $t_2 = 34.9$ min.

Ethyl 3-(6-methoxy-naphthalen-2-yl)-4-phthalimidobutanoate (4k). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$
Supporting Information

= 1.03 (3H, t, J = 7.2 Hz; CH$_3$CH$_2$), 2.78 (2H, d, J = 7.2 Hz; CH$_2$CH), 3.88-3.94 (6H, m; CH$_3$O, -CH-, CH$_2$N), 3.96 (2H, m; CH$_2$O), 7.08-7.11 (2H, m; Ar-H), 7.40-7.42 (1H, m; Ar-H), 7.64-7.70 (5H, m; Ar-H), 7.78-7.80 (2H, m; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.1, 38.8, 40.8, 43.2, 55.3, 60.5, 105.6, 118.9, 123.3, 126.2, 126.5, 127.2, 128.9, 129.3, 131.9, 133.8, 134.0, 135.6, 157.6, 168.2, 171.6 ppm; HRMS (ESI) calcd for C$_{25}$H$_{23}$NO$_5$Na$: 440.1474$, found: 440.1485; $[^{\alpha}]D^{25} = -151.2$ (c 0.80, CHCl$_3$) for 94% ee; HPLC (UV 254 nm, Chiralcel OD-H (0.46 cm x 25 cm), $i$-PrOH/Hexane = 2/98, 1.0 mL/min): $t_1$ = 53.3 min, $t_2$ = 60.7 min.

**Ethyl 3-(2-thienyl)-4-phthalimidobutanoate (4l).** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.12 (3H, t, J = 7.2 Hz; CH$_3$CH$_2$), 2.75 (2H, d, J = 7.2 Hz; CH$_2$CH), 3.88-4.07 (5H, m; CH$_2$O, -CH-, CH$_2$N), 6.90 (2H, d, J = 4.0 Hz; Ar-H), 7.14 (1H, m; Ar-H), 7.70-7.72 (2H, m; Ar-H), 7.82 (2H, s; Ar-H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.1, 36.3, 39.6, 43.7, 60.7, 123.4, 124.2, 124.9, 126.8, 131.9, 134.1, 143.5, 168.1, 171.1 ppm; HRMS (ESI) m/z calcd for C$_{18}$H$_{17}$NO$_4$SNa$: 366.0776$, found: 366.0784; $[^{\alpha}]D^{25} = -62.8$ (c 0.2, CHCl$_3$) for 97% ee; HPLC (UV 254 nm, Chiralpak AD (0.46 cm x 25 cm), $i$-PrOH/Hexane = 5/95, 1.0 mL/min): $t_1$ = 28.3 min, $t_2$ = 34.0 min.

**General Procedure for Hydrolysis of Ethyl 3-(4-chlorophenyl)-4-phthalimidobutanoate to Form Baclofen.**

A mixture of 4f (0.5 mmol, 261mg), 6 M HCl (10 mL) was heated under reflux for 24 h. The solution was cooled and the precipitated phthalic acid was filtered off. The filtrate was evaporated to dryness and the result solid was resuspended in water (10 mL). Filtered, and the filtrate was evaporated to dryness under reduced pressure. The solid dried under vacuum: 95% yield. $^1$H NMR (400 MHz, D$_2$O):
δ = 2.73-2.83 (2H, m; CH₂CH), 3.24-3.40 (3H, m; CH₂N, -CH-H), 7.34-7.43 (4H, m; Ar-H) ppm; ¹³C NMR (100 MHz, D₂O): δ = 38.4, 39.5, 43.6, 129.3, 129.4, 133.4, 137.0, 175.5 ppm.

Synthesis of (-)-Rolipram.⁹,¹⁰,¹¹

To a solution of 4i (0.17 mmol) in THF (10 mL) was added hydrazine hydrate (0.5 mL) and the solution was stirred for 24 h. After complete consumption of the starting material, the reaction mixture was extracted with dichloromethane and concentrated in vacuum, the residue was dissolved in a mixture of Et₃N (0.5 mL) and toluene (2 mL) and the resultant solution heated at 110 °C for 20 h. After cooling to RT, the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc) to yield colorless crystals 36.5 mg (78%); ¹H NMR (400 MHz, CDCl₃): δ = 1.60-1.63 (2H, m; CH₂CH₂), 1.83-1.92 (6 H, m; -C-CH₂-CH₂), 2.45 (1 H, dd, J = 8.8, 16.9 Hz; CH₂CO), 2.69 (1H, dd, J = 8.8, 16.9 Hz; CH₂CO), 3.37-3.41 (1H, m; CH₂N), 3.63-3.65 (1H, m; -CH-H), 3.74-3.79 (1H, m; CH₂N), 3.83 (3H, s; CH₃O), 4.75-4.78 (1H, m; CHO), 6.21 (1H, br; N-H), 6.76-6.84 (3H, m; Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 24.1, 32.8, 38.2, 40.0, 49.9, 56.2, 80.6, 112.2, 113.9, 118.8, 134.6, 147.9, 149.2, 177.9 ppm.

References:


Supporting Information

13C NMR DJ-1 IN CDCl3 07/04/13

CO₂Et

CF₃

4h
Supporting Information

**NMR** DU-2 IN CDCl3 07/04/12

![NMR spectrum of compound 4j with chemical shifts and spectral data]

Current NMR parameters:
- **NAME**: 0
- **EXPER**: 371
- **PROC**: 1

**F2 - ACQUISITION Parameters**
- **Date**: 20070412
- **Time**: 10:44
- **INST**: dm3600
- **MODE**: 5 mm PAG00 88-
- **FULL**: 1
- **TE**: 32768
- **SOLT**: CDCl3
- **DS**: 0
- **SNH**: 0.264536 Hz
- **TD**: 128
- **DF**: 64.400 usec
- **DE**: 5.00 usec
- **TD**: 1.00000000000000000000000000000000000000000000
- **WM**: 0.00000000000000000000000000000000000000000000
- **CH**: 0.00000000000000000000000000000000000000000000

**F2 - PROCESSING Parameters**
- **SI**: 32768
- **SP**: 1000.1335 Hz
- **WM**: 0
- **DD**: 0
- **LS**: 0.10 Hz
- **PC**: 1.40

**1D NMR plot parameters**
- **CX**: 20.00 cm
- **CY**: 10.00 cm
- **FSP**: 10000 ppm
- **FL**: 400.30 Hz
- **FP**: 400.00 Hz
- **F2**: -1.000 ppm
- **FR**: 400.13 Hz
- **H2CM**: 0.000000 ppm/cm
- **H2CM**: 200.0715 Hz/cm
Supporting Information
H$_3$N$^+$ \text{COOH}$^-$

Baclofen

13C NMR DJ-2 IN D2O 07/05/19
Supporting Information

\((-\text{Rolipram})\)

\[ \text{S.H. NMR Clu-2 in CDCl3 07/05/14} \]

\[ \text{Current Data Parameters} \]

\text{NMR} \quad 0^\circ \\
\text{EXPT0} \quad \text{A2N} \\
\text{EXPT1} \\

\text{F2 - Acquisition Parameters} \\
\text{Date:} \quad 09/07/04 \\
\text{Time:} \quad 13:39 \\
\text{INSTRUM} \quad \text{NMR} \\
\text{FOH} \quad 500 \text{MHz} \\
\text{RULPROS} \quad 25 \\
\text{TD} \quad 32K \\
\text{SOLVENT} \quad \text{CDCl3} \\
\text{NS} \quad 1 \\
\text{DS} \quad 0 \\
\text{SWH} \quad 8012.800 \text{Hz} \\
\text{FIDRES} \quad 0.248537 \text{MHz} \\
\text{AQ} \quad 2.044731 \text{sec} \\
\text{TD} \quad 128 \\
\text{Dw} \quad 524000 \text{us} \\
\text{DC} \quad 5.90 \text{vppm} \\
\text{TE} \quad 2.55 \text{ps} \\
\text{DT} \quad 1.00000000 \text{sec} \\
\text{PDPEST} \quad 0.00000000 \text{sec} \\
\text{MCOHM} \quad 0.00500000 \text{sec} \\

\text{--- CHANNEL F1 ------} \\
\text{LNC1} \quad 14 \\
\text{FF1} \quad 0.25 \text{vppm} \\
\text{FF2} \quad 0.90 \text{vppm} \\
\text{SPED} \quad 400 \text{MHz} \\

\text{F2 - Processing parameters} \\
\text{S1} \quad 32K \\
\text{SF} \quad 400 \text{MHz} \\
\text{W1} \quad 0.00000000 \text{MHz} \\
\text{GGB} \quad 3 \\
\text{LJ} \quad -0.50 \text{Hz} \\
\text{GB} \quad 0.1 \\
\text{AC} \quad 1.49 \\

\text{2D NMR plot parameters} \\
\text{CX} \quad 50.00 \text{cm} \\
\text{CV} \quad 50.00 \text{cm} \\
\text{F4D} \quad 10.000 \text{ppm} \\
\text{F1} \quad 400.00 \text{MHz} \\
\text{F3P} \quad 1.000 \text{ppm} \\
\text{F2} \quad -400.00 \text{Hz} \\
\text{CMW} \quad 0.00000000 \text{ppm} \\
\text{V2CM} \quad 200.37159 \text{Hz/cm}
(-)-Rolipram

13C NMR DJ-2 IN CDCL3 07/05/16

Current Data Parameters
NAME:
INPM:
PROC:

F2 - Acquisition Parameters
SWM: 20816511
LINE: 13.62
M30TRM: 400
PROCRED 0.5 ppm PARAP RESP 0.0096
NC: 000000
SOV: 0836
NS: 1296
DS: 16
HI 23148.148 MHz
FIDRES: 5.25213 kHz
AQ: 1.454276 sec
DF: 00000
LM: 244.4 sec
DE: 0000 sec
DE: 3.9 sec
DT: 1.000000 sec
DT1: 0.000000 sec
MODE: 0.000000 sec
DMOD: 0.000000 sec

--- CHANNEL 1 ---

NCH 15C
F1 8.25 Hz
FL: 1.50 kHz
SF1 100 MHz

--- CHANNEL 2 ---

NCH 21H
F2 0.02 Hz
DFM: 400.120000 MHz

F1 - Processing parameters
SD: 32768
SF: 100 MHz
POW: 0.000000 MHz
CKM: 128
CL: 0
CB: 0.0000 Hz
CW: 0
PC: 140

1D NMR plot parameters
Zx: 20.00 cm
ZY: 10.00 cm
SF: 2000000 ppm
T1: 25100.00 sec
T2: 35000.00 sec
FW: 10000.00 Hz
PMCH: 11.000000 ppm/deg
NCH: 1107.000000 Hz/deg
N=O\[\text{CO}_2\text{Et}\]

B=Br

Supporting Information

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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: WAV1 A, Wavelength=254 nm

Peak RetTime Type Width Area Height Area
1 37.704 Min 3.344 933.89392 45.8220 49.994
2 36.40 Min 2.39 952.4507 6.7394 80.090

Total : 1896.13479 11.3014

Results obtained with enhanced integration:

*** End of Report ***