Highly Enantioselective Direct Alkylation of Arylacetic Acids with Chiral Lithium Amides as Traceless Auxiliaries

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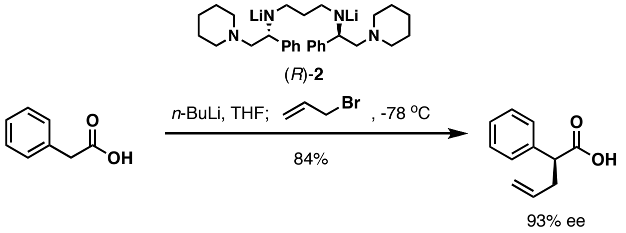
SUPPORTING INFORMATION 1

EXPERIMENTAL PROCEDURES

General Information. All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and ether (Et_2O) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, diisopropylamine, pyridine, triethylamine, and chlorotrimethylsilane were distilled from calcium hydride in a continuous still under and atmosphere of argon. Chlorotriethylsilane (TESCl), and diisopropylethylamine (Hunig's Base) were distilled from calcium hydride under an inert atmosphere of dry argon and stored over calcium hydride. Reaction temperatures were controlled by IKA ETS-D4 fuzzy thermo couples. Room temperature reactions were carried out between 22-24 °C. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F_{254} (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, and iodine staining. Flash column chromatography was preformed using 40-63 μm silica gel (Merck, Geduran, no. 11567-1) as the stationary phase. Proton magnetic resonance spectra were recorded at 400 MHz, 500 MHz, and 600 MHz on a Varian Unity Inova, Varian Unity Inova, and Varian Unity Inova AS600 600 MHz spectrometers, respectively. Carbon magnetic resonance spectra were recorded at 100 MHz, 125 MHz, and 150 MHz on a Varian Unity Inova, Varian Unity Inova, and Varian Unity Inova AS600 600MHz spectrometers, respectively. All Chemical shifts were reported in δ units relative to tetramethylsilane. Optical Rotations were measured on a Roudolph Research Analytical AUTOPOL III polarimeter. High Resolution mass spectral data were obtained by the Mass Spectrometry laboratory at the University of California, Santa Barbara.

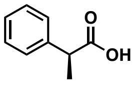
NOTE: *n*-Butyllithium was purchased from Sigma-Aldrich (2.5M solution in hexanes, catalog # 230707-100ml) and used directly as receive. The reagent was titrated before use.



General procedure 1 for enantioselective alkylation of aryl- and heteroarylacetic acids using base 2. Table 1 entry 3 (*S*)-2-phenylpent-4-enoic acid. *n*-BuLi (1.20 ml, 2.54 M in hexanes, 3.05 mmol, 4.0 equiv) is added dropwise to a solution of phenylacetic acid (0.104 g, 0.762 mmol) and (*R*)-**2** (0.350 g, 0.781 mmol, 1.03 equiv) in THF (5.1 ml, 0.15 M) at 0 °C and the reaction mixture is allowed to stir at this temperature for 15 min. The reaction mixture is cooled to -78 °C and stirred for an additional 5 min. Allyl bromide (0.26 ml, 3.05 mmol, 4.0 equiv, neat) is added to the reaction mixture dropwise over 10 min. After addition of the electrophile is complete, the reaction is immediately quenched with a 3:1 mixture of THF-MeOH (8 equiv MeOH) at -78 °C. After 4 min, 1M aqueous HCl is added. The reaction mixture was diluted with ethyl acetate and water. The aqueous layer is extracted with ethyl acetate (x3). The combined organic layers were washed with 1M aqueous HCl, brine, dried with sodium sulfate, concentrated, and residue was purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=10.1 min; t_2=13.5 min (starting material)). Yield: 84% (0.113 g, 0.641 mmol). Starting material: 11% (11 mg, 81 μmol). Ee: 93% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=18.1 min (*R*); t_2=21.6 min (*S*)). $[\alpha]_D^{23}$ +77.2° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, C_6D_6); δ(ppm): 7.17-7.14 (m, 2H); 7.06-7.03 (m, 2H); 7.02-6.98 (m, 1H); 5.61-5.53 (m, 1H); 4.98-4.93 (m, 1H); 4.87 (dd, J1=10.5 Hz, J2=1.0 Hz, 1H); 3.51 (dd, J1=J2=8.0 Hz, 1H); 2.75-2.68 (m, 1H); 2.39-2.33 (m, 1H). ^{13}C NMR (125 MHz, C_6D_6); δ(ppm): 180.4, 138.7, 135.6, 129.3, 128.7, 128.0, 117.6, 52.0, 37.7. LRMS: (FI) calcd for $C_{11}H_{12}O_2$ $[M]^+$ 176.1, found 176.1.

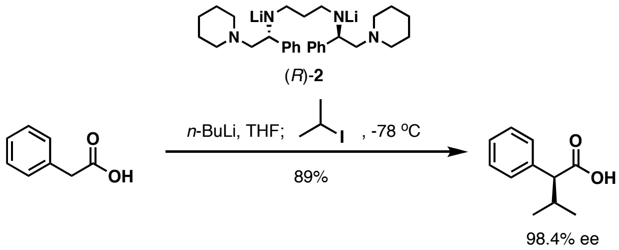
Recovery of (*R*)-2:

The combined aqueous layers were basified with sodium hydroxide and extracted with ether (x3). The combined organic layers were washed with brine, dried with sodium sulfate and concentrated to recover crude (*R*)-**2**.



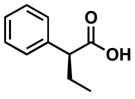
88% ee

General procedure 2 for enantioselective alkylation of aryl- and heteroarylacetic acids using base 2. Table 2, entry 1 (*S*)-2-phenylpropanoic acid. *n*-BuLi (1.20 ml, 2.34 M in hexanes, 2.81 mmol, 4.0 equiv) is added dropwise to a solution of phenylacetic acid (96 mg, 0.702 mmol) and (*R*)-**2** (0.323 g, 0.720 mmol, 1.03 equiv) in THF (4.7 ml, 0.15 M) at 0 °C and the reaction mixture is allowed to stir at this temperature for 15 min. The reaction mixture is cooled to -90 °C and stirred for an additional 5 min. Iodomethane (0.17 ml 2.81 mmol, 4.0 equiv, neat) is added dropwise to the reaction mixture over 1 min [alternatively, the reaction can be carried out at -78 °C, if iodomethane is pre-cooled to -78 °C prior to addition]. After addition of the electrophile is complete, the reaction mixture stirred for an additional 1 min and then is immediately quenched with a 3:1 mixture of THF-MeOH (8 equiv MeOH) at -90 °C. After 4 min, 1M aqueous HCl is added. The reaction mixture was diluted with ethyl acetate and water. The aqueous layer is extracted with ethyl acetate (x3). The combined organic layers were washed with 1M aqueous HCl, brine, dried with sodium sulfate, concentrated, and residue was purified by preparative HPLC (YMC Pack-Sil 250x10 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 5 ml/min; detection at 215 nm; t_1=9.9 min; t_2=11.7 min (starting material)). Yield: 84% (87 mg, 0.579 mmol). Starting material: 12% (11 mg, 81 μmol). Ee: 88% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=21.1 min (*R*); t_2=25.3 min (*S*). $[\alpha]_D^{24}$ +61.9° (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6); δ(ppm): 7.20-7.17 (m, 2H); 7.11-7.01 (m, 3H); 3.47 (ddd, J1=J2=J3=7.2 Hz, 1H); 1.29 (d, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6); δ(ppm): 181.9, 140.6, 129.2, 128.2, 127.8, 46.1, 18.6. LRMS: (GC/MS (EI)) calcd for $C_9H_{10}O_2$ $[M]^+$ 150, found 150.



10-gram scale procedure for the preparation of (S)-3-methyl-2-phenylbutanoic acid: *n*-Butyllithium (115 ml, 2.57 M in hexanes, 0.296 mol, 4.0 equiv) was added to a solution of phenylacetic acid (10.0 g, 73.5 mmol) and (*R*)-**2** (33.8 g, 75.3 mmol, 1.03 equiv) in THF (490 ml, 0.15 M) at 0 °C and the reaction mixture was allowed to stir at this temperature for 15 min. The reaction mixture was cooled to -78 °C and stirred for an additional 30 min. 2-Iodopropane (29.4 ml, 0.296 mol, 4.0 equiv, neat) is added to the reaction mixture dropwise over 15 min. After addition of the electrophile is complete, the reaction was allowed to stir for an additional 20 h and then quenched with a 3:1 mixture of THF-MeOH (8 equiv MeOH) at -78 °C. After 4 min, 1M aqueous HCl is added. The reaction mixture was diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with 1M aqueous HCl, brine, dried with sodium sulfate, concentrated, and residue was purified by column chromatography (silica gel (pretreated with 10% ethyl acetate – hexane with 0.5% acetic acid) 10% ethyl acetate – hexane with 0.4% acetic acid). Mixed fractions were collected separately and columned once again (silica gel (pretreated with 7% ethyl acetate – hexane with 0.5% acetic acid) 7% ethyl acetate – hexane with 0.4% acetic acid). Yield: 89% (11.62 g, 65.2 mmol). Ee: 98.4% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=14.9 min (*R*); t_2=21.5 min (*S*)).

Recovery of (*R*)-2: The combined aqueous layers were basified with sodium hydroxide to pH >12 and extracted with ether (x3). The combined organic layers were washed with brine, dried with sodium sulfate and concentrated to recover pure (*R*)-**2**. Yield of recovered base: 99% (33.4 g, 74.5 mmol).[1]



96% ee

Table 2, entry 2 (*S*)-4-methyl-2-phenylpent-4-enoic acid. Prepared according to general procedure 1 using 96 mg (0.702 mmol) of phenylacetic acid, 0.323 g (0.720 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.34 M in hexanes, 2.81 mmol, 4.0 equiv), 0.22 ml of iodoethane (2.81 mmol, 4.0 equiv) in THF (4.7 ml, 0.15 M). The reaction mixture was quenched immediately after addition of the electrophile. Purified by column chromatography (silica gel (pretreated with 1% trifluroracetic acid in benzene), benzene with 1% trifluoroacetic acid (100 ml)→ 3% ether-benzene

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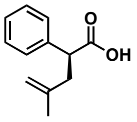
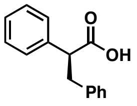
[1] If needed, the base can be recrystallized from 1.1:1 isopropanol/water.

with 1% trifluoroacetic acid) Yield: 81% (93 mg, 0.566 mmol). Starting material: 17% (16 mg, 0.118 mmol). Ee: 96% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=17.8 min (*R*); t_2=24.0 min (*S*)). $[\alpha]_D^{23}$ +70.7° (c 1.0, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6); δ(ppm): 7.20-7.16 (m, 2H); 7.09-6.98 (m, 3H); 3.30 (dd, J1=J2=7.6 Hz, 1H); 2.04-1.92 (m, 1H); 1.70-1.58 (m, 1H); 0.70 (dd, J1=J2=7.6 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6); δ(ppm): 181.2, 139.2, 129.2, 128.7, 128.0, 54.0, 27.0, 12.4. LRMS: (GC/MS (EI)) calcd for $C_{10}H_{12}O_2$ $[M]^+$ 164, found 164.



91% ee

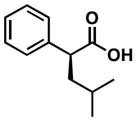
Table 2, entry 3 (*S*)-2-phenylbutanoic acid. Prepared according to general procedure 1 using 0.104 g (0.762 mmol) of phenylacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.31 ml of 3-bromo-2-methylpropene (3.05 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 20 min after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.1:0.8:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=7.0 min; t_2=9.4 min (starting material)). Yield: 80% (0.116 g, 0.610 mmol). Starting Material: 15% (16 mg, 0.118 mmol). Ee: 91% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=16.9 min (*R*); t_2=19.4 min (*S*)). $[\alpha]_D^{23}$ +72.0° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6); δ(ppm): 7.21-7.18 (m, 2H); 7.07-7.03 (m, 2H); 7.02-6.98 (m, 1H); 4.75 (s, 1H); 4.70 (s, 1H); 3.76 (dd, J1=8.5 Hz, J2=6.5 Hz, 1H); 2.77 (dd, J1=14.5 Hz, J2=8.5 Hz, 1H); 2.31 (dd, J1=14.5 Hz, J2=7.0 Hz, 1H); 1.50 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6); δ(ppm): 180.6, 142.7, 138.9, 129.2, 128.7, 128.0, 113.0, 50.8, 41.6, 23.0. LRMS: (GC/MS (EI)) calcd for $C_{12}H_{14}O_2$ $[M]^+$ 190, found 190.



92% ee

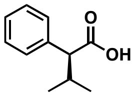
Table 2, entry 4 (*S*)-2,3-diphenylpropanoic acid. Prepared according to general procedure 1 using 0.104 g (0.762 mmol) of phenylacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.36 ml of benzyl bromide (3.05 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched immediately after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=8.6 min; t_2=10.7 min (starting material)). Yield: 85% (0.146 g, 0.645 mmol). Starting Material: 8% (8 mg, 59 μmol). Ee: 92% (Chiralcel® OJ-H; hexane/isopropanol/trifluoroacetic acid 89.9:10:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=9.8 min (*R*); t_2 14.2

(*S*)). $[\alpha]_D^{23}$ +107.0° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6); δ(ppm): 7.20-7.10 (m, 2H); 7.05-6.95 (m, 8H); 3.77 (dd, J1=J2=7.0 Hz, 1H); 3.35-3.29 (m, 1H); 0.89 (dd, J1=13.5 Hz, J2=7.0 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6); δ(ppm): 180.4, 139.4, 138.7, 129.6, 129.2, 129.0, 128.8, 128.0, 127.0, 54.3, 40.0. LRMS: (GC/MS (EI)) calcd for $C_{12}H_{14}O_2$ $[M]^+$ 226, found 226.



98% ee

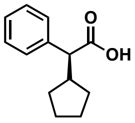
Table 2, entry 5 (*S*)-4-methyl-2-phenylpentanoic acid. Prepared according to general procedure 1 using 0.104 g (0.762 mmol) of phenylacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.38 ml of 1-iodo-2-methylpropane (3.05 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 5 h after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=7.6 min; t_2=12.8 min (starting material)). Yield: 82% (0.120 g, 0.624 mmol). Starting Material: 13% (13 mg, 95 μmol). Ee: 98% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=13.2 min (*R*); t_2=15.4 min (*S*)). $[\alpha]_D^{23}$ +59.0° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6); δ(ppm): 7.25-7.23 (m, 2H); 7.09-7.06 (m, 2H); 7.04-7.00 (m, 1H); 3.64 (dd, J1=J2=7.5 Hz, 1H); 1.93 (ddd, J1=15.5 Hz, J2=J3=7.5 Hz, 1H); 1.65-1.59 (m, 1H); 1.47-1.39 (m, 1H); 0.75 (d, J=7.0 Hz, 3H); 0.74 (d, J=7.0 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6); δ(ppm): 180.5, 139.5, 129.3, 128.8, 127.9, 50.3, 42.9, 26.5, 23.0, 22.6. LRMS: (GC/MS (EI)) calcd for $C_{12}H_{16}O_2$ $[M]^+$ 192, found 192.



97% ee

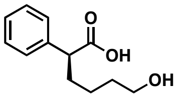
Table 2, entry 6 (*S*)-3-methyl-2-phenylbutanoic acid. Prepared according to general procedure 1 using 0.104 g (0.762 mmol) of phenylacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.30 ml of 2-iodopropane (3.05 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 20 h after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=8.2 min; t_2=11.9 min (starting material)). Yield: 85% (0.115 g, 0.645 mmol). Starting Material: 13% (13 mg, 95 μmol). Ee: 97% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=14.5 min (*R*); t_2=20.3 min (*S*)). $[\alpha]_D^{23}$ +58.3° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6); δ(ppm): 7.27-7.23 (m, 2H); 7.09-7.05 (m, 2H); 7.03-6.99 (m, 1H); 3.09 (d, J=11.0 Hz, 1H); 2.33-2.25 (m, 1H); 0.96 (d, J=6.5 Hz, 3H); 0.55 (d, J=7.0 Hz, 3H). ^{13}C NMR (125 MHz,

C_6D_6); δ(ppm): 180.9, 138.5, 129.3, 129.2, 128.0, 60.7, 32.3, 21.9, 20.5. LRMS: (GC/MS (EI)) calcd for $C_{11}H_{14}O_2$ $[M]^+$ 178, found 178.



96% ee

Table 2, entry 7 (*S*)-2-cyclopentyl-2-phenylacetic acid. Prepared according to general procedure 1 using 0.104 g (0.762 mmol) of phenylacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.35 ml of iodocyclopentane (3.05 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 20 h after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=11.4 min; t_2=15.2 min (starting material)). Yield: 76% (0.118 g, 0.578 mmol). Starting Material: 20% (21 mg, 0.154 mmol). Ee: 96% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=16.0 min (*R*); t_2=21.4 min (*S*)). $[\alpha]_D^{23}$ +56.7° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, C_6D_6); δ(ppm): 7.29-7.27 (m, 2H); 7.10-7.07 (m, 2H); 7.04-7.01 (m, 1H); 3.23 (d, J=10.5 Hz, 1H); 2.55-2.48 (m, 1H); 11.91-1.85 (m, 1H); 1.52-1.15 (m, 6H); 0.86-0.78 (m, 1H). ^{13}C NMR (125 MHz, C_6D_6); δ(ppm): 181.0, 139.2, 129.2, 129.0, 127.9, 58.5, 44.0, 32.2, 31.2, 25.8, 25.4. LRMS: (GC/MS (EI)) calcd for $C_{13}H_{16}O_2$ $[M]^+$ 204, found 204.

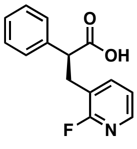


93% ee

Table 2, entry 8 (*S*)-6-hydroxy-2-phenylhexanoic acid. Prepared according to general procedure 1 using 0.105 g (0.771 mmol) of phenylacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.291 g of *tert*-butyl(4-iodobutoxy)dimethylsilane (0.925 mmol, 1.2 equiv, dissolved in 1 ml of THF) in THF (5.1 ml, 0.13 M). The reaction mixture was quenched 10 h after addition of the electrophile.

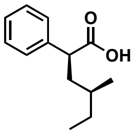
Tetrabutylammonium fluoride (1 M in THF, 3.90 ml, 3.90 mmol) was added to a solution of the crude product in THF (3.0 ml) at rt. After 12 h, saturated aqueous ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica gel, 5 % methanol-dichloromethane with 0.1 % acetic acid). Yield: 87% over 2 steps (0.140 g, 0.672 mmol). Starting Material: 11% (12 mg, 88 μmol). Ee: 93% - Determined before desilylation (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=11.0 min (*R*); t_2=13.8 min (*S*)). $[\alpha]_D^{22}$ +54.6° (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$); δ(ppm): 7.34-7.28 (m, 4H); 7.27-7.26 (m, 1H); 3.62 (ddd, J1=J2=6.6 Hz, J3=1.2 Hz, 2H); 3.57 (dd, J1=J2=7.8 Hz, 1H); 2.17-2.08 (m, 1H); 1.85-1.78 (m, 1H); 1.63-1.53 (m, 2H); 1.43-1.27 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$);

δ(ppm): 179.4, 138.7, 128.9, 128.2, 127.6, 62.7, 51.7, 33.1, 32.4, 23.9. LRMS: (ESI) calcd for $C_{12}H_{15}O_3Na_2$ $[M-H+2Na]^+$ 253.1, found 253.1.



91% ee

Table 2, entry 9 (*S*)-3-(2-fluoropyridin-3-yl)-2-phenylpropanoic acid. Prepared according to general procedure 1 using 53 mg (0.389 mmol) of phenylacetic acid, 0.179 g (0.398 mmol, 1.03 equiv) of *R*-**2**, 0.60 ml *n*-BuLi (2.59 M in hexanes, 1.55 mmol, 4.0 equiv), 88 mg of 3-(bromomethyl)-2-fluoropyridine[2] (0.463 mmol, 1.2 equiv, dissolved in 0.4 ml of THF pre-cooled to -90 °C) in THF (2.2 ml, 0.13 M). The electrophile was transferred via cannula to the reaction mixture in 10 seconds. After addition, the reaction mixture stirred for an additional 50 seconds before being quenched. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 96.9:3.0:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=13.9 min (starting material); t_2=20.5 min). Yield: 93% (89 mg, 0.363 mmol). Starting Material: 6% (3 mg, 22 μmol). Ee: 91% (Chiralcel® OD-H; hexane/isopropanol/acetic acid 94.9:5.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=11.8 min (*R*); t_2 13.8 (*S*)). $[\alpha]_D^{22}$ +117.5° (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$); δ(ppm): 8.06-8.04 (m, 1H); 7.47-7.43 (m, 1H); 7.34-7.26 (m, 5H); 7.03-6.99 (m, 1H); 3.96 (dd, J1=J2=7.8 Hz, 1H); 3.40 (dd, J1=13.8 Hz, J2=7.8 Hz, 1H); 3.07 (dd, J1=13.8 Hz, J2=7.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$); δ(ppm): 178.1, 162.2 (d, J=194 Hz), 146.0 (d, J=9.3 Hz), 145.9 (d, J=14.4 Hz), 142.3 (d, J=5.5 Hz), 137.5, 129.1, 128.1, 121.6 (d, J=4.4 Hz), 120.8 (d, J=29.7 Hz), 51.1, 32.8. LRMS: (ESI) calcd for $C_{14}H_{13}FNO_2$ $[M+H]^+$ 246.1, found 246.1.



99% d.r.

Table 2, entry 10 (2*S*,4*S*)-4-methyl-2-phenylhexanoic acid. Prepared according to general procedure 1 using 0.104 g (0.762 mmol) of phenylacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.151 g of (*S*)-1-iodo-2-methylbutane (0.762 mmol, 1.0 equiv, dissolved in 1 ml of THF) in THF (4.1 ml, 0.15 M). The reaction mixture was quenched 10 h after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=15.4 min; t_2=25.9 min (starting material)). Yield: 67% (0.106 g, 0.514 mmol). Starting Material: 31% (32 mg, 0.235 mmol). D.r.: 99%. $[\alpha]_D^{24}$ +71.3° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, C_6D_6); δ(ppm): 7.26-7.24 (m, 2H); 7.10-7.07 (m, 2H); 7.03-7.00 (m, 1H); 3.66 (dd, J1=J2=7.0 Hz, 1H); 1.90-1.79 (m, 2H); 1.24-1.15 (m, 2H); 1.04-0.97 (m, 1H); 0.74 (d, J=6.5 Hz, 3H); 0.69 (dd, J1=J2=7.0 Hz, 3H). ^{13}C NMR

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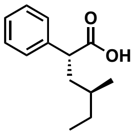
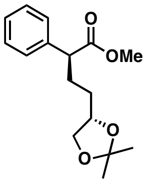
[2] Grorgio, A.; Sasmita, T. Patent: WO2010/132999 A1, **2010**.

(125 MHz, C_6D_6); δ(ppm): 181.4, 139.3, 129.3, 128.8, 127.9, 50.2, 40.5, 32.5, 30.2, 19.2, 11.6. LRMS: (GC/MS (EI)) calcd for $C_{13}H_{18}O_2$ $[M]^+$ 206, found 206.



99% d.r.

Table 2, entry 11 (2*R*,4*S*)-4-methyl-2-phenylhexanoic acid. Prepared according to general procedure 1 using 0.104 g (0.762 mmol) of phenylacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *S*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.151 g of (*S*)-1-iodo-2-methylbutane (0.762 mmol, 1.0 equiv, dissolved in 1 ml of THF) in THF (4.1 ml, 0.15 M). The reaction mixture was quenched 10 h after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=14.6 min; t_2=25.8 min (starting material)). Yield: 79% (0.124 g, 0.602 mmol). Starting Material: 20% (21 mg, 0.154 mmol). D.r.: 99%. $[\alpha]_D^{23}$ −33.2° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6); δ(ppm): 7.27-7.25 (m, 2H); 7.10-7.06 (m, 2H); 7.03-7.00 (m, 1H); 3.69 (dd, J1=9.5 Hz, J2=7.0 Hz, 1H); 2.16 (ddd, J1=13.5 Hz, J2=9.0 Hz, J3=6.0 Hz, 1H); 1.49-1.43 (m, 1H); 1.36-1.30 (m, 1H); 1.28-1.20 (m, 1H); 1.06-0.97 (m, 1H); 0.76 (d, J=6.0 Hz, 3H); 0.75 (dd, J1=J2=7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6); δ(ppm): 181.0, 139.8, 129.3, 128.7, 127.9, 50.2, 41.1, 32.9, 29.9, 19.5, 11.5. LRMS: (GC/MS (EI)) calcd for $C_{13}H_{18}O_2$ $[M]^+$ 206, found 206.



91% d.r.

Table 2, entry 12 (*S*)-methyl 4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-phenylbutanoate. Prepared according to general procedure 1 using 65 mg (0.476 mmol) of phenylacetic acid, 0.219 g (0.488 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 1.90 mmol, 4.0 equiv), 0.122 g of (*S*)-4-(2-iodoethyl)-2,2-dimethyl-1,3-dioxolane[3] (0.476 mmol, 1.0 equiv, dissolved in 1 ml of THF) in THF (2.1 ml, 0.15 M). The reaction mixture was quenched 2 h after addition of the electrophile. (Trimethylsilyl)diazomethane (0.89 M in ether, 1.10 ml, 0.952 mmol) was added to a solution of the crude product and acetic acid (30 μl, 0.476 mmol) in dichloromethane (4.0 ml) at 0 °C. After 10 min, (trimethylsilyl)diazomethane (0.89 M in ether, 1.10 ml, 0.952 mmol) was added, and the reaction mixture was warmed to rt. After 30 min of stirring at rt, additional (trimethylsilyl)diazomethane (0.89 M in ether, 1.10 ml, 0.952 mmol) was added. After another 30 min, the reaction mixture was concentrated under reduced pressure, and purified by column chromatography (silica gel, hexane (50 ml) → 5%

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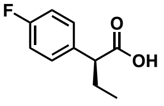
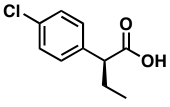
[3] Mori, K.; Watanabe, H. *Tetrahedron*, **1986**, *42*, 295.

ethyl acetate-hexane (200 ml) → 10% ethyl acetate-hexane). Yield: 74% over 2 steps (98 mg, 0.352 mmol). Methyl 2-phenylacetate: 15% (11 mg, 73 μmol). D.r.: 91%. $[\alpha]_D^{23}$ +63.5° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6); δ(ppm): 7.30-7.26 (m, 2H); 7.13-7.08 (m, 2H); 7.05-7.01 (m, 1H); 3.82-3.76 (m, 1H); 3.64 (dd, J1=8.0 Hz, J2=6.5 Hz, 1H); 3.51 (dd, J1=J2=8.0 Hz, 1H); 3.23 (s, 3H); 3.21 (dd, J1=J2=8.0 Hz, 1H); 2.36-2.28 (m, 1H); 1.82-1.74 (m, 1H); 1.50-1.43 (m, 1H); 1.39 (s, 3H); 1.31 (s, 3H); 1.24-1.17 (m, 1H). ^{13}C NMR (125 MHz, C_6D_6); δ(ppm): 174.2, 140.0, 129.3, 128.7, 127.9, 109.3, 76.4, 69.9, 52.2, 51.8, 32.2, 30.9, 27.9, 26.4. LRMS: (ESI) calcd for $C_{16}H_{22}O_4Na$ $[M+Na]^+$ 301.1, found 301.1.



96% ee

Table 3, entry 1 (*S*)-2-(4-fluorophenyl)butanoic acid. Prepared according to general procedure 1 using 0.119 g (0.771 mmol) of 4-fluorophenylacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.25 ml iodoethane (3.08 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched immediately after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=20.7 min; t_2=30.6 min (starting material)). Yield: 84% (0.118 g, 0.648 mmol). Ee: 96% (Chiralcel® OJ-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=39.4 min (*R*); t_2=45.2 min (*S*)). $[\alpha]_D^{23}$ +58.6° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6); δ(ppm): 6.96-6.91 (m, 2H); 6.73-6.68 (m, 2H); 3.19 (dd, J1=J2=7.5 Hz, 1H); 1.94-1.85 (m, 1H); 1.57-1.48 (m, 1H); 0.66 (dd, J1=J2=7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6); δ(ppm): 181.0, 162.9 (d, J=244 Hz), 134.7 (d, J=3.3 Hz), 130.3 (d, J=7.6 Hz), 116.0 (d, J=20.8 Hz), 53.1, 27.0, 12.4. LRMS: (GC/MS (EI)) calcd for $C_{10}H_{11}FO_2$ $[M]^+$ 182, found 182.



96% ee

Table 3, entry 2 (*S*)-2-(4-chlorophenyl)butanoic acid. Prepared according to general procedure 1 using 0.132 g (0.771 mmol) of 4-chlorophenylacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.25 ml iodoethane (3.08 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched immediately after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=20.3 min; t_2=30.1 min (starting material)). Yield: 81% (0.124 g, 0.624 mmol). Ee: 96% (Chiralcel® OJ-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 0.7 ml/min; detection at 215 nm; t_1=51.7 min (*R*); t_2=53.4 min (*S*)). $[\alpha]_D^{24}$ +57.9° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6); δ(ppm): 7.02-6.99 (m, 2H); 6.88-6.84 (m, 2H); 3.14 (dd, J1=J2=7.5 Hz, 1H); 1.92-1.83 (m, 1H); 1.54-1.45 (m, 1H); 0.64 (dd, J1=J2=7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6); δ(ppm): 180.9, 137.4, 134.0, 130.1,

129.4, 53.1, 26.7, 12.1. LRMS: (GC/MS (EI)) calcd for $C_{10}H_{11}ClO_2$ $[M]^+$ 198, found 198.

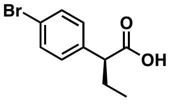


Table 3, entry 3 (*S*)-2-(4-bromophenyl)butanoic acid. Prepared according to general procedure 1 using 0.166 g (0.771 mmol) of 4-bromophenylacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.25 ml iodoethane (3.08 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched immediately after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=21.1 min; t_2=31.9 min (starting material)). Yield: 65% (0.121 g, 0.498 mmol). Ee: 93% (Chiralcel® AD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=26.5 min (*S*); t_2=28.3 min (*R*)). $[\alpha]_D^{25}$ +49.5° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, C_6D_6); δ(ppm): 7.17-7.14 (m, 2H); 6.81-6.77 (m, 2H); 3.12 (dd, J1=J2=7.5 Hz, 1H); 1.91-1.81 (m, 1H); 1.54-1.44 (m, 1H); 0.63 (dd, J1=J2=7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6); δ(ppm): 180.5, 137.9, 132.4, 130.4, 122.1, 53.3, 26.8, 12.3. LRMS: (GC/MS (EI)) calcd for $C_{10}H_{11}BrO_2$ $[M]^+$ 242, found 242.

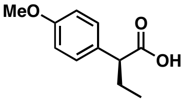
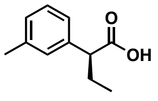
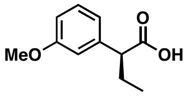


Table 3, entry 4 (*S*)-2-(4-methoxyphenyl)butanoic acid. Prepared according to general procedure 1 using 0.128 g (0.771 mmol) of 4-methoxyphenylacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.25 ml iodoethane (3.08 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 1 h 30 min after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 275 nm; t_1=22.6 min; t_2=31.8 min (starting material)). Yield: 71% (0.107 g, 0.551 mmol). Ee: 89% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 275 nm; t_1=35.7 min (*R*); t_2=49.0 min (*S*)). $[\alpha]_D^{20}$ +58.0° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.25-7.21 (m, 2H); 6.88-6.84 (m, 2H); 3.80 (s, 3H); 3.41 (dd, J1=J2=7.5 Hz, 1H); 2.12-2.03 (m, 1H); 1.82-1.73 (m, 1H); 0.90 (dd, J1=J2=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 179.9, 159.1, 130.6, 129.2, 114.2, 55.5, 52.6, 26.6, 12.3. LRMS: (ESI) calcd for $C_{11}H_{13}O_3Na_2$ $[M-H+2Na]^+$ 239.1, found 239.1.



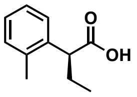
96% ee

Table 3, entry 5 (*S*)-2-*m*-tolylbutanoic acid. Prepared according to general procedure 1 using 0.116 g (0.771 mmol) of *m*-tolylacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.25 ml iodoethane (3.08 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched immediately after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=17.7 min; t_2=23.8 min (starting material)). Yield: 83% (0.114 g, 0.640 mmol). Ee: 96% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=15.7 min (*R*); t_2=24.5 min (*S*)). $[\alpha]_D^{25}$ +69.2° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.24-7.19 (m, 1H); 7.14-7.07 (m, 3H); 3.42 (dd, J1=J2=7.5 Hz, 1H); 2.34 (s, 3H); 2.14-2.05 (m, 1H); 1.85-1.75 (m, 1H); 0.91 (dd, J1=J2=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 180.4, 138.5, 138.4, 128.9, 128.7, 128.4, 125.3, 53.5, 26.5, 21.7, 12.4. LRMS: (GC/MS (EI)) calcd for $C_{11}H_{14}O_2$ $[M]^+$ 178, found 178.



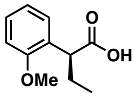
93% ee

Table 3, entry 6 (*S*)-2-(3-methoxyphenyl)butanoic acid. Prepared according to general procedure 1 using 0.128 g (0.771 mmol) of 3-methoxyphenylacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.25 ml iodoethane (3.08 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 30 min after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 275 nm; t_1=23.9 min; t_2=33.1 min (starting material)). Yield: 82% (0.123 g, 0.633 mmol). Ee: 93% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 275 nm; t_1=34.1 min (*R*); t_2=60.7 min (*S*)). $[\alpha]_D^{20}$ +57.0° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.25-7.22 (m, 1H); 6.92-6.86 (m, 2H); 6.83-6.80 (m, 1H); 3.80 (s, 3H); 3.43 (dd, J1=J2=8.0 Hz, 1H); 2.14-2.04 (m, 1H); 1.85-1.76 (m, 1H); 0.91 (dd, J1=J2=8.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 179.8, 159.9, 140.0, 129.8, 120.7, 114.0, 112.9, 55.4, 53.5, 26.5, 12.4. LRMS: (ESI) calcd for $C_{11}H_{13}O_3Na_2$ $[M-H+2Na]^+$ 239.1, found 239.1.



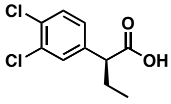
94% ee

Table 3, entry 7 (*S*)-2-*o*-tolylbutanoic acid. Prepared according to general procedure 1 using 0.115 g (0.762 mmol) of *o*-tolylacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.24 ml iodoethane (3.05 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 50 min after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=21.3 min; t_2=29.2 min (starting material)). Yield: 82% (0.112 g, 0.628 mmol). Ee: 94% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=17.1 min (*R*); t_2=20.3 min (*S*)). $[\alpha]_D^{23}$ +96.6° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.34-7.31 (m, 1H); 7.21-7.14 (m, 3H); 3.77 (dd, J1=J2=7.5 Hz, 1H); 2.39 (s, 3H); 2.18-2.08 (m, 1H); 1.84-1.75 (m, 1H); 0.93 (dd, J1=J2=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 180.3, 137.1, 136.6, 130.7, 127.3, 127.0, 126.6, 48.6, 26.1, 20.1, 12.4. LRMS: (GC/MS (EI)) calcd for $C_{11}H_{14}O_2$ $[M]^+$ 178, found 178.



93% ee

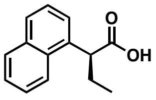
Table 3, entry 8 (*S*)-2-(2-methoxyphenyl)butanoic acid. Prepared according to general procedure 1 using 0.127 g (0.762 mmol) of 2-methoxyphenylacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.24 ml iodoethane (3.05 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 30 min after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 275 nm; t_1=25.5 min; t_2=37.7 min (starting material)). Yield: 87% (0.129 g, 0.664 mmol). Ee: 93% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 275 nm; t_1=30.8 min (*R*); t_2=40.3 min (*S*)). $[\alpha]_D^{26}$ +92.5° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.29-7.23 (m, 2H); 6.97-6.93 (m, 1H); 6.91-6.88 (m, 1H); 3.94 (dd, J1=J2=8.0 Hz, 1H); 3.84 (s, 3H); 2.14-2.05 (m, 1H); 1.85-1.75 (m, 1H); 0.92 (dd, J1=J2=8.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 180.4, 157.1, 128.6, 128.5, 127.4, 120.9, 111.0, 55.8, 46.0, 25.3, 12.4. LRMS: (ESI) calcd for $C_{11}H_{13}O_3Na_2$ $[M-H+2Na]^+$ 239.1, found 239.1.



92% ee

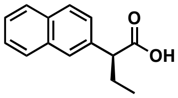
Table 3, entry 9 (*S*)-2-(3,4-dichlorophenyl)butanoic acid. Prepared according to general procedure 1 using 0.158 g (0.771 mmol) of 3,4-dichlorophenylacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.25 ml iodoethane (3.08 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched immediately after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=19.9 min; t_2=32.7 min (starting material)). Yield: 82% (0.148 g, 0.635 mmol). Ee: 92% (Chiralcel® OJ-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 0.7 ml/min; detection at 215 nm; t_1=18.9 min (*R*); t_2=20.0 min (*S*)). $[\alpha]_D^{24}$ +44.5° (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$); δ(ppm): 7.43-7.39

(m, 2H); 7.17-7.14 (m, 1H); 3.43 (dd, J1=J2=7.8 Hz, 1H); 2.13-2.05 (m, 1H); 1.83-1.75 (m, 1H); 0.91 (dd, J1=J2=7.8 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$); δ(ppm): 179.2, 138.5, 132.9, 131.9, 130.8, 130.3, 127.8, 52.6, 26.5, 12.2. LRMS: (GC/MS (EI)) calcd for $C_{10}H_{10}Cl_2O_2$ $[M]^+$ 232, found 232.



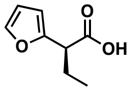
92% ee

Table 3, entry 10 (*S*)-2-(naphthalen-1-yl)butanoic acid. Prepared according to general procedure 1 using 0.142 g (0.762 mmol) of 1-naphthaleneacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.24 ml iodoethane (3.05 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 30 min after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=20.7 min; t_2=30.1 min (starting material)). Yield: 89% (0.145 g, 0.677 mmol). Ee: 92% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=52.0 min (*S*); t_2=62.9 min (*R*)). $[\alpha]_D^{23}$ +146.2° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 8.14-8.12 (m, 1H); 7.88-7.86 (m, 1H); 7.79-7.77 (m, 1H); 7.56-7.43 (m, 4H); 4.32 (dd, J1=J2=7.5 Hz, 1H); 2.34-2.25 (m, 1H); 2.03-1.94 (m, 1H); 0.99 (dd, J1=J2=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 180.3, 134.8, 134.1, 131.9, 129.1, 128.1, 126.6, 125.8, 125.7, 125.2, 123.3, 48.5, 26.2, 12.7. LRMS: (GC/MS (EI)) calcd for $C_{14}H_{14}O_2$ $[M]^+$ 214, found 214.



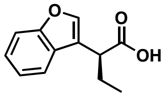
96% ee

Table 3, entry 11 (*S*)-2-(naphthalen-2-yl)butanoic acid. Prepared according to general procedure 1 using 0.144 g (0.771 mmol) of 2-naphthaleneacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.25 ml iodoethane (3.08 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched immediately after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=17.9 min; t_2=25.7 min (starting material)). Yield: 88% (0.145 g, 0.677 mmol). Ee: 96% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=34.2 min (*R*); t_2=44.6 min (*S*)). $[\alpha]_D^{23}$ +93.3° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.82-7.78 (m, 3H); 7.76 (bs, 1H); 7.48-7.43 (m, 3H); 3.64 (dd, J1=J2=7.5 Hz, 1H); 2.24-2.16 (m, 1H); 1.97-1.87 (m, 1H); 0.94 (dd, J1=J2=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 179.7, 135.9, 133.5, 132.9, 128.5, 128.0, 127.8, 127.3, 126.3, 126.1, 126.1, 53.6, 26.5, 12.4. LRMS: (GC/MS (EI)) calcd for $C_{14}H_{14}O_2$ $[M]^+$ 214, found 214.



97% ee

Table 3, entry 12 (*S*)-2-(furan-2-yl)butanoic acid. Prepared according to general procedure 1 using 0.146 g (1.16 mmol) of 2-furanacetic acid, 0.532 g (1.18 mmol, 1.03 equiv) of *R*-**2**, 1.80 ml *n*-BuLi (2.57 M in hexanes, 4.63 mmol, 4.0 equiv), 0.37 ml iodoethane (4.63 mmol, 4.0 equiv) in THF (7.7 ml, 0.15 M). The reaction mixture was quenched 1 h after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=21.0 min; t_2=29.7 min (starting material)). Yield: 60% (0.107 g, 0.694 mmol). Ee: 97% (Chiralcel® OD-H; Hexane/Isopropanol/Trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=22.9 min (*R*); t_2=30.6 min (*S*)). $[\alpha]_D^{20}$ +8.8° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.37-7.35 (m, 1H); 6.35-6.33 (m, 1H); 6.24-6.22 (m, 1H); 3.65 (dd, J1=J2=7.0 Hz, 1H); 2.10-2.01 (m, 1H); 2.00-1.91 (m, 1H); 0.96 (dd, J1=J2=7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 178.1, 151.4, 142.2, 110.5, 107.4, 47.0, 24.3, 12.1. LRMS: (ESI) calcd for $C_8H_9O_3Na_2$ $[M-H+2Na]^+$ 199.0, found 199.0.



92% ee

Table 3, entry 13 (*S*)-2-(benzofuran-3-yl)butanoic acid. Prepared according to general procedure 1 using 68 mg (0.386 mmol) of 2-(benzofuran-3-yl)acetic acid,[4] 0.177 g (0.395 mmol, 1.03 equiv) of *R*-**2**, 0.60 ml *n*-BuLi (2.57 M in hexanes, 1.54 mmol, 4.0 equiv), 0.12 ml iodoethane (1.54 mmol, 4.0 equiv) in THF (2.6 ml, 0.15 M). The reaction mixture was quenched immediately after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=18.1 min; t_2=27.2 min (starting material)). Yield: 62% (49 mg, 0.240 mmol). Ee: 92% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=28.3 min (*R*); t_2=38.6 min (*S*)). $[\alpha]_D^{22}$ +33.1° (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$); δ(ppm): 7.66-7.64 (m, 1H); 7.60 (bs, 1H); 7.49-7.47 (m, 1H) 7.32-7.29 (m, 1H); 7.26-7.23 (m, 1H); 3.72 (dd, J1=J2=7.2 Hz, 1H); 2.22-2.14 (m, 1H); 2.03-1.96 (m, 1H); 1.00 (dd, J1=J2=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$); δ(ppm): 179.8, 155.6, 142.7, 127.0, 124.7, 122.8, 120.4, 117.7, 111.8, 43.7, 25.2, 12.3. LRMS: (ESI) calcd for $C_{12}H_{11}O_3Na_2$ $[M-H+2Na]^+$ 249.1, found 249.1

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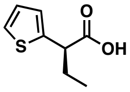
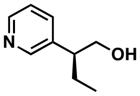
[4] Kaila, N.; Janz, K.; Huang, A.; Moretto, A.; DeBernardo, S.; Bedard, P. W.; Tam, S.; Clerin, V.; Keith J. C.; Tsao, D. H. H.; Sushkova, N.; Shaw, G. D.; Camphausen, R. T.; Schaub, R. G.; Wang, Q. *J. Med Chem.* **2007**, *50*, 40-64.



90% ee

Table 3, entry 14 (*R*)-2-(thiophen-2-yl)butanoic acid. Prepared according to general procedure 1 using 0.110 g (0.777 mmol) of 2-thiopheneacetic acid, 0.357 g (0.796 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.59 M in hexanes, 3.11 mmol, 4.0 equiv), 0.25 ml iodoethane (3.11 mmol, 4.0 equiv) in THF (5.2 ml, 0.15 M The reaction mixture was quenched 30 min after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=15.0 min; t_2=21.3 min (starting material)). Yield: 85% (0.112 g, 0.658 mmol). Ee: 90% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=23.2 min (*S*); t_2=36.1 min (*R*)). $[\alpha]_D^{20}$ +23.8° (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$); δ(ppm): 7.23-7.21 (m, 1H); 6.98-6.95 (m, 2H); 3.78 (dd, J1=J2=7.2 Hz, 1H); 2.18-2.09 (m, 1H); 1.94-1.86 (m, 1H); 0.97 (dd, J1=J2=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$); δ(ppm): 179.3, 140.7, 126.9, 126.0, 125.0, 48.6, 27.9, 12.2. LRMS: (ESI) calcd for $C_8H_9O_2SNa_2$ $[M-H+2Na]^+$ 215.0, found 215.0.

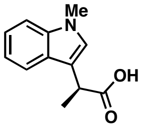


95% ee

Table 3, entry 16 (*S*)-2-(pyridin-3-yl)butan-1-ol. Prepared according to general procedure 1 using 0.106 g (0.771 mmol) of 3-pyridylacetic acid (3-pyridylacetic acid hydrochloride was neutralized with 1 equiv sodium hydroxide, and extracted with 20% methanol-chloroform (x10), filtered through sodium sulfate, evaporated and dried to obtain 3-pyridylacetic acid), 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.25 ml iodoethane (3.08 mmol, 4.0 equiv) in THF (10.2 ml, 0.08 M). The reaction mixture was quenched 1 h after addition of the electrophile. After the quench, the reaction mixture was acidified with 1M HCl to pH 1. The aqueous layer was extracted with ethyl acetate (x2). The aqueous layer was collected, evaporated, and crude residue was submitted to the next reaction without further purification.

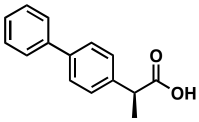
Lithium aluminum hydride (0.60 g, 15.8 mmol) was added to a solution of the crude product in THF (30 ml) at 0° C. After addition, the reaction was warmed to rt and stirred for 2 h, and then heated at reflux for 3 h. The reaction mixture was cooled to 0 °C and water (0.60 ml) was added dropwise. After 5 min, 3M aqueous sodium hydroxide (0.60 ml) was added dropwise. After and additional 5 min, water (1.80 ml) was added and the reaction mixture was allowed to stir at rt for 12 h. The white precipitate was filtered off and was washed with dichloromethane. The crude residue was purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/diethylamine 79.9:20.0:0.1; flow rate 20 ml/min; detection at 248 nm; t_1=22.4 min; t_2=42.9 min (2-(pyridin-3-yl)ethanol)). Yield: 61% over 2 steps (72 mg, 0.476 mmol). Ee: 95% (determined on the primary alcohol)(Chiralcel® OD-H; hexane/isopropanol/diethylamine 94.9:1.0:0.1; flow rate = 1.0 ml/min;

detection at 248 nm; t_1=26.8 min (*R*); t_2=28.8 min (*S*)). $[\alpha]_D^{22}$ +13.9° (c 1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$); δ(ppm): 8.43-8.36 (m, 2H); 7.54-7.52 (m, 1H); 7.25-7.21 (m, 1H); 3.82-3.73 (m, 2H); 2.72-2.66 (m, 1H); 1.85-1.78 (m, 1H); 1.62-1.54 (m, 1H); 0.83 (dd, J1=J2=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$); δ(ppm): 150.1, 147.9, 138.5, 135.7, 123.7, 66.8, 48.2, 24.9, 12.1. LRMS: (ESI) calcd for $C_9H_{14}NO$ $[M+H]^+$ 152.1, found 152.1.



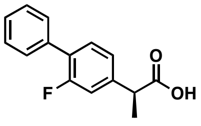
84% ee

Table 3, entry 17 (*S*)-2-(1-methyl-1*H*-indol-3-yl)propanoic acid. Prepared according to general procedure 2 using 0.146 g (0.771 mmol) of 1-methyl-3-indoleacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.19 ml iodomethane (3.08 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 92.9:7.0:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=9.6 min; t_2=10.8 min (starting material)). Yield: 71% (0.111 g, 0.546 mmol). Ee: 84% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 94.9:5.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=13.9 min (*R*); t_2=16.1 min (*S*)). $[\alpha]_D^{24}$ +61.5° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.69-7.66 (m, 1H); 7.31-7.28 (m, 1H); 7.26-7.21 (m, 1H); 7.14-7.10 (m, 1H); 7.02 (bs, 1H); 4.03 (ddd, J1=J2=J3=7.5 Hz, 1H); 3.75 (s, 3H); 1.61 (d, J=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 180.7, 137.2, 126.9, 126.6, 122.0, 119.5, 119.4, 113.4, 109.5, 37.0, 33.0, 17.9. LRMS: (ESI) calcd for $C_{12}H_{13}NO_2Na$ $[M+H]^+$ 226.1, found 226.1.



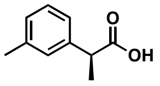
91% ee

Table 3, entry 18-1 (*S*)-2-(biphenyl-4-yl)propanoic acid. Prepared according to general procedure 2 using 83 mg (0.389 mmol) of 4-biphenylacetic acid, 0.179 g (0.398 mmol, 1.03 equiv) of *R*-**2**, 0.60 ml *n*-BuLi (2.59 M in hexanes, 1.55 mmol, 4.0 equiv), 0.10 ml iodomethane (1.55 mmol, 4.0 equiv) in THF (5.2 ml, 0.08 M). Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=21.6 min; t_2=25.8 min (starting material)). Yield: 87% (77 mg, 0.340 mmol). Ee: 91% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=34.0 min (*R*); t_2=39.9 min (*S*)). $[\alpha]_D^{22}$ +46.7° (c 1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$); δ(ppm): 7.59-7.55 (m, 4H); 7.45-7.39 (m, 4H); 7.36-7.32 (m, 1H); 3.80 (ddd, J1=J2=J3=7.2 Hz, 1H); 1.57 (d, J=6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$); δ(ppm): 180.3, 140.9, 140.6, 139.0, 129.0, 128.2, 127.7, 127.5, 127.3, 45.2, 18.3. LRMS: (GC/MS (EI)) calcd for $C_{15}H_{14}O_2$ $[M]^+$ 226, found 226.



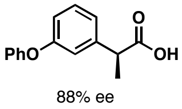
85% ee

Table 3, entry 18-2 (*S*)-2-(2-fluorobiphenyl-4-yl)propanoic acid. Prepared according to general procedure 2 using 90 mg (0.389 mmol) 2-(2-fluorobiphenyl-4-yl)acetic acid[5], 0.179 g (0.398 mmol, 1.03 equiv) of *R*-**2**, 0.60 ml *n*-BuLi (2.59 M in hexanes, 1.55 mmol, 4.0 equiv), 0.10 ml iodomethane (1.55 mmol, 4.0 equiv) in THF (2.6 ml, 0.15 M). Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=22.2 min; t_2=28.0 min (starting material)). Yield: 73% (69 mg, 0.282 mmol). Ee: 85% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=28.3 min (*R*); t_2=31.3 min (*S*)). $[\alpha]_D^{22}$ +33.5° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.55-7.52 (m, 2H); 7.47-7.33 (m, 4H); 7.19-7.12 (m, 2H); 3.80 (ddd, J1=J2=J3=6.5 Hz, 1H); 1.57 (d, J=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 180.5, 159.8 (d, J=247 Hz), 141.1 (d, J=7.6 Hz), 135.5, 131.0 (d, J=3.8 Hz), 129.1 (d, J=3.3 Hz), 128.6, 128.3 (d, J=13.6 Hz), 127.9, 123.8 (d, J=3.4 Hz), 115.5 (d, J=24 Hz), 45.1, 18.2. LRMS: (GC/MS (EI)) calcd for $C_{15}H_{13}FO_2$ $[M]^+$ 244, found 244.



92% ee

Table 3, entry 19 (*S*)-2-*m*-tolylpropanoic acid. Prepared according to general procedure 2 using 0.116 g (0.771 mmol) *m*-tolylacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.19 ml iodomethane (3.08 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=20.0 min; t_2=23.3 min (starting material)). Yield: 87% (0.110 g, 0.670 mmol). Ee: 92% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=19.0 min (*R*); t_2=25.2 min (*S*)). $[\alpha]_D^{24}$ +64.0° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.24-7.20 (m, 1H); 7.14-7.07 (m, 3H); 3.70 (ddd, J1=J2-J3=7.5 Hz, 1H); 2.35 (s, 3H); 1.50 (d, J=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 180.7, 139.9, 138.5, 128.7, 128.4, 128.3, 124.8, 45.5, 21.7, 18.4. LRMS: (GC/MS (EI)) calcd for $C_{10}H_{12}O_2$ $[M]^+$ 164, found 164.



88% ee

Table 3, entry 20 (*S*)-2-(3-phenoxyphenyl)propanoic acid. Prepared according to general procedure 2 using 0.174 g (0.762 mmol) 3-phenoxyphenylacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.19 ml iodomethane (3.05 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M).

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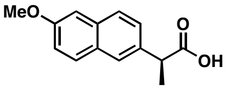
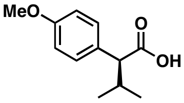
[5] Schlosser, M.; Geneste, H. *Chem.-Eur. J.* **1998**, *4*, 1969.

Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 275 nm; t_1=39.4 min; t_2=49.6 min (starting material)). Yield: 87% (0.161 g, 0.665 mmol). Ee: 88% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 275 nm; t_1=45.7 min (*R*); t_2=48.1 min (*S*)). $[\alpha]_D^{26}$ +41.2° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.36-7.31 (m, 2H); 7.30-7.26 (m, 1H); 7.13-7.09 (m, 1H); 7.07-7.04 (m, 1H); 7.03-6.99 (m, 3H); 6.90-6.87 (m, 1H); 3.72 (ddd, J1=J2-J3=7.0 Hz, 1H); 1.51 (d, J=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 180.4, 157.6, 157.1, 141.8, 130.0, 129.9, 123.5, 122.5, 119.2, 118.4, 117.7, 45.4, 18.3. LRMS: (ESI) calcd for $C_{15}H_{13}O_3Na_2$ $[M-H+2Na]^+$ 287.1, found 287.1.



96% ee

Table 3, entry 21 (*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid. Prepared according to general procedure 2 using 82 mg (0.379 mmol) 2-(6-methoxynaphthalen-2-yl)acetic acid[6], 0.175 g (0.393 mmol, 1.03 equiv) of *R*-**2**, 0.60 ml *n*-BuLi (2.54 M in hexanes, 1.52 mmol, 4.0 equiv), 0.10 ml iodomethane (1.52 mmol, 4.0 equiv) in THF (2.6 ml, 0.15 M). Purified by column chromatography (silica gel, 40% ethyl acetate-hexanes (100 ml) → 10% methanol-dichloromethane (200 ml) → 20% methanol-dichloromethane). Yield: 96% (84 mg, 0.365 mmol). Ee: 94% (Chiralcel® AD-H; hexane/isopropanol/trifluoroacetic acid 89.9:10.0:0.1; flow rate = 0.7 ml/min; detection at 254 nm; t_1=16.8 min (*R*); t_2=18.5 min (*S*)). $[\alpha]_D^{23}$ +57.8° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.71-7.67 (m, 3H); 7.42-7.39 (m, 1H); 7.15-7.09 (m, 2H); 3.91 (s, 3H); 3.87 (ddd, J1=J2-J3=7.5 Hz, 1H); 1.58 (d, J=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 179.7, 157.9, 135.1, 134.0, 129.5, 129.1, 127.4, 126.4, 126.3, 119.2, 105.8, 55.5, 45.4, 18.5. LRMS: (ESI) calcd for $C_{14}H_{14}O_3Na$ $[M+Na]^+$ 253.1, found 253.1.



97% ee

Table 3, entry 22 (*S*)-2-(4-methoxyphenyl)-3-methylbutanoic acid. Prepared according to general procedure 1 using 0.127 g (0.762 mmol) of 4-methoxyphenylacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.30 ml 2-iodopropane (3.05 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 20 h after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 275 nm; t_1=19.5 min; t_2=33.9 min (starting material)). Yield: 78% (0.124 g, 0.595 mmol). Ee: 97% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 275 nm; t_1=24.8 min (*R*); t_2=35.5 min (*S*)). $[\alpha]_D^{23}$ +50.6° (c 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.26-7.22 (m,

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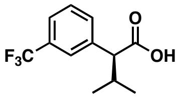
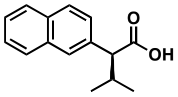
[6] Andrus, M. B.; Harper, K. C.; Christiansen, M. A.; Binkley, M. A. *Tetrahedron Lett.* **2009**, *50*, 4541.

2H); 6.86-6.83 (m, 2H); 3.79 (s, 3H); 3.10 (d, J=11.0 Hz, 1H); 2.32-2.24 (m, 1H); 1.07 (d, J=7.0 Hz, 3H); 0.71 (d, J=7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 179.7, 159.1, 130.0, 129.7, 114.1, 59.2, 55.5, 31.8, 21.7, 20.3. LRMS: (ESI) calcd for $C_{12}H_{15}O_3Na_2$ $[M-H+2Na]^+$ 253.1, found 253.1.



91% ee

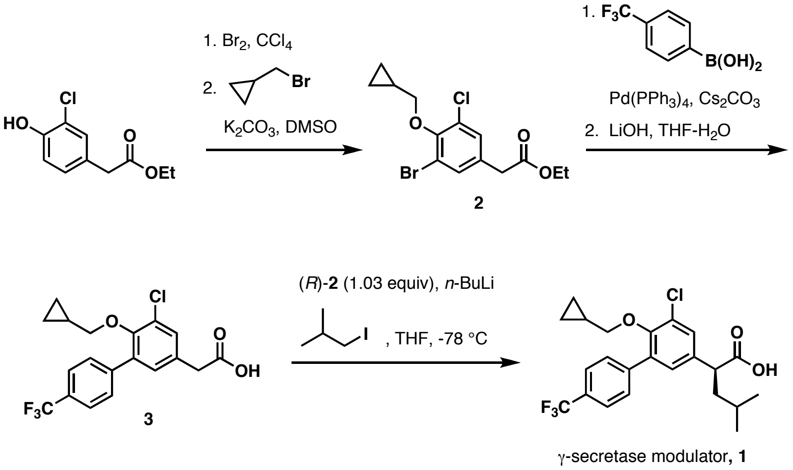
Table 3, entry 23 (*S*)-3-methyl-2-(3-(trifluoromethyl)phenyl)butanoic acid. Prepared according to general procedure 1 using 0.157 g (0.771 mmol) of 3-(trifluoromethyl)phenylacetic acid, 0.355 g (0.790 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.57 M in hexanes, 3.08 mmol, 4.0 equiv), 0.31 ml 2-iodopropane (3.08 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 20 h after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=17.5 min; t_2=32.7 min (starting material)). Yield: 70% (0.133 g, 0.540 mmol). Ee: 91% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=9.8 min (*R*); t_2=11.6 min (*S*)). $[\alpha]_D^{26}$ +32.9° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.59 (bs, 1H); 7.56-7.52 (m, 2H); 7.47-7.42 (m, 1H); 3.23 (d, J=11.0 Hz, 1H); 2.39-2.31 (m, 1H); 1.10 (d, J=6.5 Hz, 3H); 0.72 (d, J=7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 179.1, 138.8, 132.1, 131.1 (ddd, J1=J2=J3=31.8 Hz), 129.2, 125.6 (ddd, J1=J2-J3=3.8 Hz), 124.6 (ddd, J1=J2=J3=3.9 Hz), 124.2 (d, J=271 Hz), 59.9, 32.1, 21.6, 20.3. LRMS: (GC/MS (EI)) calcd for $C_{12}H_{13}F_3O_2$ $[M]^+$ 246, found 246.

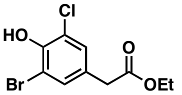


96 % ee

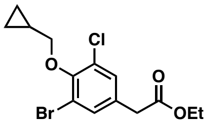
Table 3, entry 24 (*S*)-3-methyl-2-(naphthalen-2-yl)butanoic acid. Prepared according to general procedure 1 using 0.142 g (0.762 mmol) of 2-naphthaleneacetic acid, 0.350 g (0.781 mmol, 1.03 equiv) of *R*-**2**, 1.20 ml *n*-BuLi (2.54 M in hexanes, 3.05 mmol, 4.0 equiv), 0.30 ml 2-iodopropane (3.05 mmol, 4.0 equiv) in THF (5.1 ml, 0.15 M). The reaction mixture was quenched 20 h after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=15.7 min; t_2=28.1 min (starting material)). Yield: 89% (0.155 g, 0.679 mmol). Ee: 96% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 1.0 ml/min; detection at 215 nm; t_1=24.2 min (*R*); t_2=34.6 min (*S*)). $[\alpha]_D^{26}$ +85.8° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.82-7.74 (m, 4H); 7.50-7.43 (m, 3H); 3.33 (d, J=10.0 Hz, 1H); 2.50-2.40 (m, 1H); 1.13 (d, J=7.0 Hz, 3H); 0.73 (d, J=6.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 179.6, 135.4, 133.5, 133.0, 128.4, 128.0, 127.9, 127.8, 126.4, 126.3, 126.1, 60.3, 31.8, 21.8, 20.5. LRMS: (GC/MS (EI)) calcd for $C_{15}H_{16}O_2$ $[M]^+$ 228, found 228.

Synthesis of γ-secretase modulator 1:[7]





Ethyl 2-(3-bromo-5-chloro-4-hydroxyphenyl)acetate.[6] A solution of bromine (1.26 ml, 24.6 mmol) in carbon tetrachloride (47 ml) was added to a solution of ethyl 2-(3-chloro-4-hydroxyphenyl)acetate[8] in carbon tetrachloride (95 ml) at 0 °C dropwise over 30 min. After addition the reaction mixture was allowed to stir at the same temperature for 1 h. The reaction mixture was poured into a sepratory funnel containing crushed ice. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a 10% sodium bisulfite solution, dried with sodium sulfate, concentrated and the residue was purified by column chromatography (silica gel, 10 % ethyl acetate – hexanes) to obtain the title compound (3.09 g, 10.52 mmol) and recovered starting material (3.0 g, 13.97 mmol). The starting material was recycled and submitted to the reaction described above. After 1 recycle a total of 4.83 g (16.54 mmol, 67%) was isolated. Spectral data matched with those previously reported (ref 5).



Ethyl 2-(3-bromo-5-chloro-4-(cyclopropylmethoxy)phenyl)acetate.[6] Cyclopropylmethyl bromide (2.30 ml, 23.55 mmol) was added to a solution of ethyl 2-(3-bromo-5-chloro-4-hydroxyphenyl)acetate (5.76 g, 19.62 mmol) and potassium carbonate (4.07 g, 29.43 mmol) in dimethylsulfoxide (130 ml). The reaction was heated at 60 °C for 4 h. After cooling the rt, the reaction mixture was diluted with water. The aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica gel, 10% ethyl acetate-hexane) to

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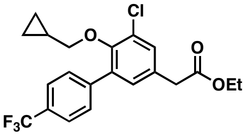
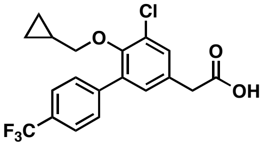
[7] Shapiro, G.; Chesworth, R. Patent: WO2009/86277 A1, **2009**

[8] Sauerberg, P.; Olsen, G. S.; Jeppesen, L; Mogensen, J. P.; Pettersson, I.; Jeppesen, C. B.; Daugaard, J. R.; Galsgaard, E. D.; Ynddal, L.; Fleckner, J.; Panajotova, V.; Polivka, Z.; Pihera, P.; Havranek, M.; Wulff, E. M. *J. Med. Chem.* **2007,** *50*, 1495.

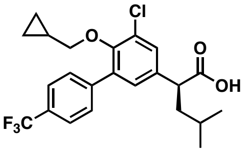
give the title compound (6.75 g, 19.42 mmol, 99%). Spectral data matched with those previously reported (ref 5).



Ethyl 2-(5-chloro-6-(cyclopropylmethoxy)-4'-(trifluoromethyl)biphenyl-3-yl)acetate.[6] Argon was bubbled through a solution containing ethyl 2-(3-bromo-5-chloro-4-(cyclopropylmethoxy)phenyl)acetate (1.02 g, 2.93 mmol), 4-(trifluoromethyl)phenylboronic acid (0.72 g, 3.79 mmol), and cesium carbonate (3.84 g, 11.72 mmol) in *N,N*-dimethylformamide (27 ml) and water (1.35 ml). After 20 min tetrakis(triphenylphosphine)palladium (0.27 g, 0.233 mmol) was added and the reaction mixture was heated at 90 °C for 1 h. The reaction mixture was cooled to rt and diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica gel, 3% ethyl acetate-hexane) to give the title compound (0.785 g, 1.90 mmol, 65%). Spectral data matched with those previously reported (ref. 5).



2-(5-chloro-6-(cyclopropylmethoxy)-4'-(trifluoromethyl)biphenyl-3-yl)acetic acid. Lithium hydroxide (0.45 g, 18.53 mmol) was added to a solution of the ethyl 2-(5-chloro-6-(cyclopropylmethoxy)-4'-(trifluoromethyl)biphenyl-3-yl)acetate (2.25 g, 5.45 mol) in methanol (30.6 ml), THF (30.6 ml) and water (6.1 ml) at rt. After 1 h 30 min, the reaction mixture was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography (silica gel, 3% methanol-dichloromethane with 0.1% acetic acid) to give the title compound (2.05 g, 5.32 mmol, 98%). ^{1}H NMR (600 MHz, $CDCl_3$); δ(ppm): 7.71-7.66 (m, 4H); 7.37-7.36 (m, 1H); 7.16-7.15 (m, 1H); 3.64 (s, 2H); 3.41 (d, J=7.2 Hz, 2H); 0.99-0.92 (m, 1H); 0.42-0.38 (m, 2H); 0.00--0.02 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$); δ(ppm): 176.5, 151.9, 141.3, 136.1, 131.2, 130.4, 130.2, 130.1, 129.9, 129.5, 125.3 (ddd, J1=J2=J3=3.9 Hz), 123.5, 78.7, 40.1, 10.9, 3.3. LRMS: (ESI) calcd for $C_{19}H_{16}ClF_3O_3Na$ $[M+Na]^+$ 407.1, found 407.1.



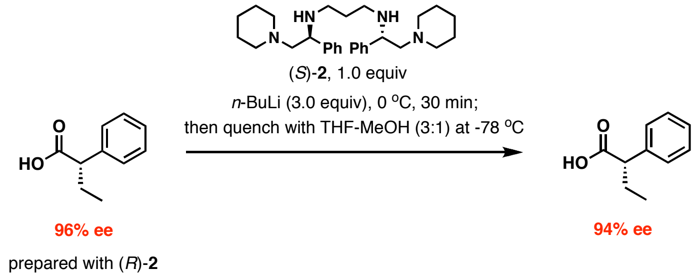
97% ee

Scheme 3, γ-secretase modulator 1 (*S*)-2-(5-chloro-6-(cyclopropylmethoxy)-4'-(trifluoromethyl)biphenyl-3-yl)-4-methylpentanoic acid.[6] Prepared according to general procedure 1 using 0.148 g (0.386 mmol) of 2-(5-chloro-6-

(cyclopropylmethoxy)-4'-(trifluoromethyl)biphenyl-3-yl)acetic acid, 0.177 g (0.395 mmol, 1.03 equiv) of *R*-**2**, 0.60 ml *n*-BuLi (2.57 M in hexanes, 1.54 mmol, 4.0 equiv), 0.19 ml 1-iodo-2-methylpropane (1.54 mmol, 4.0 equiv) in THF (2.6 ml, 0.15 M). The reaction mixture was quenched 12 h after addition of the electrophile. Purified by preparative HPLC (YMC-Pack-SIL 250x30 mm; hexane/isopropanol/acetic acid 99.2:0.7:0.1; flow rate 20 ml/min; detection at 215 nm; t_1=13.1 min; t_2=25.0 min (starting material)). Yield: 72% (0.122 g, 0.277 mmol). Starting material: 24% (36 mg, 94 µmol) Ee: 97% (Chiralcel® OD-H; hexane/isopropanol/trifluoroacetic acid 98.9:1.0:0.1; flow rate = 0.7 ml/min; detection at 215 nm; t_1=14.0 min (*R*); t_2=15.3 min (*S*)). $[\alpha]_D^{22}$ +24.7° (c 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$); δ(ppm): 7.71-7.66 (m, 4H); 7.40-7.39 (m, 1H); 7.20-7.19 (m, 1H); 3.65 (dd, J1=J2=7.8 Hz, 1H); 3.43-3.38 (m, 2H); 2.00-19.5 (m, 1H); 1.69-1.64 (m, 1H); 1.57-1.50 (m, 1H); 0.98-0.87 (m, 7H); 0.41-0.38 (m, 2H); 0.00- -0.03 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$); δ(ppm): 179.8, 151.9, 141.4, 136.1, 135.7, 130.1, 129.9, 129.8, 129.5, 129.1, 125.4 (ddd, J1=J2=J3=3.9 Hz), 123.5, 78.7, 48.9, 42.4, 26.1, 22.7, 22.5, 10.9, 3.4, 3.3. LRMS: (ESI) calcd for $C_{23}H_{24}ClF_3O_3Na$ $[M+Na]^+$ 463.1, found 463.1.

Preparation of racemic standards for HPLC analysis. Racemic aryl acetic acids were prepared in the following manner: *n*-BuLi (3 eq) was added to the aryl acetic acid (0.100 g) in THF (0.15 M) at 0 °C and stirred for 10 min. The electrophile (4 eq) was added dropwise to the reaction mixture. After 10 - 60 min (depending on electrophile), the reaction mixture was quenched with 1M aqueous HCl. The aqueous layer was extracted with ethyl acetate (x2). The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated. Racemic HPLC traces were performed on crude aryl acetic acids.

A test for the enantioselective protonation hypothesis



n-Butyllithium (2.57 M in hexanes, 0.50 ml, 3 equiv) was added dropwise to a solution of the substrate (96% ee, 70 mg, 0.43 mmol, 1 equiv) and tetraamine (*S*)-**2** (0.20 g, 0.441 mmol, 1.03 equiv) in THF (2.85 ml, 0.15 M) at 0 °C. After 30 min, the solution was cooled to -78 °C. The reaction was allowed to stir for 15 min and then quenched with a 3:1 mixture of THF:MeOH at -78 °C (dropwise, ~ 2 min) and stirred for an additional 3 min. After 1 M HCl was added, the aqueous layer was eparated and extracted with ethyl acetate (x3). The combined organic layers were washed with 1M HCl, brine, dried over sodium sulfate, and concentrated. HPLC analysis as described previously (p. S5) showed that the product has the same *S* configuration with 94% ee.