Supporting Information

Asymmetric Synthesis of Functionalized Diarylmethanols Catalyzed by a New γ -Amino Thiol

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General

All chemicals and solvents were used as received unless otherwise stated. Tetrahydrofuran (Na, benzophenone), toluene (Na, benzophenone), CH₃CN (CaH₂), hexane (CaH₂), methanol (Mg) were distilled under argon using the indicated drying reagents. ¹H and ¹³C NMR spectra were recorded with 400 MHz NMR instrument. The abbreviations for ¹H NMR were s = singlet, d = doublet, t = triplet, and m = multiplet. Carbon atoms were determined by DEPT experiments. Column chromatography was performed on silica gel with the eluent indicated.

Ligand Synthesis

(1) NaOMe, MeOH ; then BnBr, 81%; (2) NaOAc, NH₂OH·HCl, EtOH/H₂O, reflux, 98%;
(3) NaOAc, TiCl₃, tBuNH₂·BH₃, EtOH, 0 °C, 74%; (4) Br(CH₂)₂O(CH₂)₂Br, K₂CO₃, CH₃CN, reflux, 77%; (5) Na, NH₃(l), -78 °C, 64%.

(1*S*, 4*R*)-1-[(Benzylsulfanyl)methyl]-7,7-dimethyl-bicyclo[2.2.1]heptan-2-one (7)

To a 10 mL flask containing NaOCH₃ (0.040 g, 0.74 mmol) in MeOH (1 mL) was added thiol **6**¹ (0.10 g, 0.54 mmol) in MeOH (1 mL). After stirring at room temperature for 30 min, benzyl bromide (0.10 mL, 1.3 mmol in 1 mL MeOH) was added to the mixture. After 6 h at room temperature, MeOH was removed *in vacuo*,

and water was added. The mixture was extracted with EtOAc (3 × 5 mL), and the organic layer was washed with water (2 mL) and brine (2 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified using column chromatography (EtOAc : hexanes = 1:15) to give colorless oil (0.12 g, 81%). $[\alpha]_D^{24} +107.4$ (*c* 0.4, CHCl₃); ¹H NMR (CDCl₃): δ = 7.38-7.16 (m, 5H), 3.74 (s, 2H), 2.73 (d, *J* = 13.2 Hz, 1H), 2.42 (d, *J* = 13.2 Hz, 1H), 2.33 (ddd, *J* = 18.3 Hz, 5.2 Hz, 2.0 Hz, 1H), 2.04-1.98 (m, 1H), 1.93 (m, 2H), 1.83 (d, *J* = 18.3 Hz, 1H), 1.44 (t, *J* = 9.6 Hz, 1H), 1.33 (t, *J* = 8.8 Hz, 1H), 0.96 (s, 3H), 0.83 (s, 3H); ¹³C NMR (CDCl₃): δ = 217.5 (C=O), 138.4 (C), 128.9 (CH), 128.4 (CH), 126.9 (CH), 60.9 (C), 47.7 (C), 43.4 (CH), 43.1 (CH₂), 38.5 (CH₂), 28.3 (CH₂), 26.8 (CH₂), 26.7 (CH₂), 20.1 (CH₃); IR (neat) 3083, 3061, 3027, 2959, 2886, 1714, 1601, 1493, 1468, 1453 cm⁻¹; HRMS Calculated for C₁₇H₂₂OS: 274.1391. Found: 274.1385.

(1*S*,4*R*)-1-[(Benzylsulfanyl)methyl]-7,7-dimethyl-bicyclo[2.2.1]heptan-2-one oxime (8)

To a 10 mL flask was added **7** (0.89 g, 3.2 mmol), hydroxyl amine hydrochloride (0.33 g, 4.7 mmol), NaOAc (0.40 g, 4.9 mmol), ethanol (8 mL) and water (2 mL). The mixture was heated to reflux for 18 h, then was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc : hexanes = 1:6) to furnish the corresponding oxime **8** as colorless oil (0.92 g, 98%). $[\alpha]_D^{23.7} -24.3$ (*c* 1.1, CHCl₃); ¹H NMR (CDCl₃): δ = 8.13 (br, 1H), 7.42-7.16 (m, 5H), 3.73 (d, *J* = 13.6 Hz, 1H), 3.69 (d, *J* = 13.6 Hz, 1H), 2.80 (d, *J* = 12.6 Hz, 1H), 2.55 (ddd, *J* = 17.6 Hz, 4.4 Hz, 2.4 Hz, 1H), 2.47 (d, *J* = 12.6 Hz, 1H), 2.04 (d, *J* = 18.4 Hz, 1H), 1.90-1.78 (m, 3H), 1.66-1.52 (m, 1H), 1.30-1.16(m, 1H), 0.88 (s, 3H), 0.80 (s,

3H); ^{13}C NMR (CDCl_3): δ = 168.0 (C=N), 138.4 (C), 129.8 (CH), 128.3 (CH), 126.8 (CH), 54.8 (C), 49.5 (C), 44.1 (CH), 38.5 (CH_2), 32.9 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 27.0 (CH_2), 19.7 (CH_3), 19.3 (CH_3); IR (neat) 3317, 3061, 3021, 2949, 2914, 1683, 1602, 1493, 1468 cm^{-1} ; HRMS Calculated for $\text{C}_{17}\text{H}_{23}\text{NOS}$: 289.1500. Found: 289.1505.

(1*S*,4*R*)-1-[(Benzylsulfanyl)methyl]-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl amine (9)²

To a 10 mL flask was added TiCl_3 (30% in 2N HCl, 0.50 mL, 1.3 mmol) and NaOAc (0.10 g, 1.2 mmol). The mixture was cooled to 0 °C, and oxime **8** (0.10 g, 0.35 mmol) in EtOH (1 mL) was added. After 1 h, borane-*tert*-butyl amine complex (0.060 g, 0.69 mmol) was added in portions. After stirring at 0 °C for 10 h, the whole mixture was diluted with EtOAc (10 mL) and the organic layer was separated. The organic layer was washed with saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$, basified with saturated $\text{Na}_2\text{CO}_{3(\text{aq})}$ to pH = 8, and finally washed with water (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The volatile was removed *in vacuo* and the residue was purified by column chromatography (MeOH : CHCl_3 = 1:15) to furnish the corresponding amine **9** as colorless oil (0.070 g, 74%). $[\alpha]_{\text{D}}^{23.4}$ -65.2 (*c* 1.1, CHCl_3); ^1H NMR (CDCl_3): δ = 7.35-7.18 (m, 5H), 3.74 (d, *J* = 13.6 Hz, 1H), 3.67 (d, *J* = 13.6 Hz, 1H), 2.91 (dd, *J* = 9.2 Hz, 5.6 Hz, 1H), 2.63 (d, *J* = 11.0 Hz, 1H), 2.45 (d, *J* = 11.0 Hz, 1H), 1.74-1.60 (m, 3H), 1.58-1.40(m, 4H), 1.26-1.16 (m, 1H), 1.12-0.98 (m, 1H), 0.93 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (CDCl_3): δ = 138.6 (C), 128.8 (CH), 128.4 (CH), 126.9 (CH), 57.6 (CH), 51.2 (C), 47.9 (C), 45.2 (CH), 39.6 (CH_2), 37.7 (CH_2), 33.3 (CH_2), 31.5 (CH_2), 27.1 (CH_2), 21.1 (CH_3), 20.1 (CH_3); IR (neat) 3367, 3083, 3061, 3027, 2984, 2877, 1600, 1490, 1450 cm^{-1} ; HRMS Calculated for $\text{C}_{17}\text{H}_{25}\text{NS}$: 275.1708.

Found: 275.1716.

**(1*S*,4*R*)-4-{1-[(Benzylsulfanyl)methyl]-7,7-dimethyl-bicyclo[2.2.1]hept-2-yl}
morpholine (10)**

To a stirred mixture of **9** (0.50 g, 1.8 mmol) and K₂CO₃ (0.55 g, 4.0 mmol) in CH₃CN (9 mL) was added 2-bromoethyl ether (0.28 mL, 2.2 mmol) and heated to reflux. After 12 h, the reaction mixture was cooled to room temperature and was added water to dissolve the solid. The water layer was extracted with CH₂Cl₂, and the organic layer was washed with brine, dried over anhydrous Na₂SO₄ and filtered. The volatile was removed *in vacuo* and the residue was purified by column chromatography (silica gel, EtOAc : hexanes = 1:20) to furnish the cyclic amine **10** as pale yellow oil (0.48 g, 77%). [α]_D^{24.7} -93.1 (*c* 1.1, CHCl₃); ¹H NMR (CDCl₃): δ = 7.36-7.16 (m, 5H), 3.68 (d, *J* = 13.2 Hz, 1H), 3.56 (d, *J* = 13.2 Hz, 1H), 3.52-3.38 (m, 4H), 2.75 (d, *J* = 11.4 Hz, 1H), 2.64-2.50 (m, 2H), 2.47 (d, *J* = 11.4 Hz, 1H), 2.45-2.38 (m, 2H), 2.25 (dd, *J* = 8.8 Hz, 6.0 Hz, 1H), 1.91-1.78 (m, 1H), 1.72-1.52 (m, 3H), 1.30 (dd, *J* = 12.8 Hz, 9.2 Hz, 1H), 1.22-1.11 (m, 1H), 1.08-0.98 (m, 1H), 0.82 (s, 3H), 0.80 (s, 3H); ¹³C NMR (CDCl₃): δ = 138.4 (C), 128.8 (CH), 128.4 (CH), 126.8 (CH), 70.7 (CH), 67.5 (CH₂), 53.2 (CH₂), 52.5 (C), 48.3 (C), 45.0 (CH), 38.2 (CH₂), 33.4 (CH₂), 31.9 (CH₂), 31.3 (CH₂), 27.2 (CH₂), 21.2 (CH₃), 19.4 (CH₃); IR (neat) 3064, 3024, 2949, 2885, 2849, 2806, 1602, 1493, 1454 cm⁻¹; HRMS Calculated for C₂₁H₃₁NOS: 345.2126. Found: 345.2144.

(1*S*,4*R*)-(7,7-Dimethyl-2-morpholin-4-yl-bicyclo[2.2.1]hept-1-yl)methanethiol (5)

To a mixture of Na in liquid NH₃ maintained at -78 °C was added benzyl sulfide **10**

(0.85 g, 2.5 mmol) in THF (10 mL). After stirring at -78 °C for 1 h, the reaction was stopped by adding solid NH₄Cl. After NH₃ was evaporated at room temperature, CHCl₃ was added to the reaction mixture. The organic phase was filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography (silica gel, EtOAc : hexanes = 1:20) to furnish the corresponding amino thiol **5** (0.40 g, 64%) as colorless oil. $[\alpha]_D^{24}$ -79.8 (*c* 0.9, CHCl₃); ¹H NMR (CDCl₃): δ = 3.76-3.54 (m, 4H), 2.84 (dd, *J* = 13.2 Hz, 8.0 Hz, 1H), 2.70-2.50 (m, 4H), 2.42 (dd, *J* = 9.2 Hz, 6.0 Hz, 1H), 1.94-1.84 (m, 1H), 1.74-1.62 (m, 2H), 1.57-1.49 (m, 3H), 1.42-1.26 (m, 2H), 1.12-1.05 (m, 1H), 0.88 (s, 3H), 0.83 (s, 3H); ¹³C NMR (CDCl₃): δ = 70.7 (CH), 67.6 (CH₂), 53.4 (C), 53.2 (CH₂), 48.0 (C), 45.7 (CH), 34.3, (CH₂), 31.8 (CH₂), 26.8 (CH₂), 23.7 (CH₂), 21.3 (CH₃), 19.8 (CH₃); IR (neat) 2949, 2881, 2853, 2559, 1450, 1386, 1307 cm⁻¹; HRMS Calculated for C₁₄H₂₅NOS: 255.1657. Found: 255.1651.

Arylation Experiment

A flask containing toluene (2 mL), phenylboronic acid (122 mg, 1 mmol) and diethylzinc (3.0 mmol, 1.0 M solution in hexanes) was heated at 60 °C for 12 h. After the flask was cooled to room temperature, the mixture was added into another flask containing **5** (12.8 mg), and was stirred for 10 min. It was cooled to -35 °C, and a solution of 4-tolualdehyde (60 mg, 0.5 mmol) in hexanes (3 mL) was added with stirring. After 48 h at -35 °C, the reaction was quenched with saturated aqueous ammonium chloride and then extracted with CH₂Cl₂ (3 × 70 mL). The organic extracts were combined, dried and concentrated *in vacuo* to give crude product. The crude product was purified on silica gel (EtOAc : hexanes = 1:6) to afford colorless crystals (83 mg, 84%, mp: 58.5-59.5 °C).

HPLC Analysis Data

General

The enantioselectivities of the addition products were determined by High Performance Liquid Chromatography.

Phenyl-*p*-tolyl-methanol

Chiracel OD-H, uv 254 nm, 2% isopropanol / hexanes, 1 mL / min. t_R = 24.0 min (*S*, 1.4%), 26.7 min (*R*, 98.6%); 97% e.e.

Phenyl-*m*-tolyl-methanol

Chiracel OB, uv 254 nm, 10% isopropanol / hexanes, 1 mL / min. t_R = 12.3 min (*R*, 98.4%), 23.2 min (*S*, 1.6%); 97% e.e.

Phenyl-*o*-tolyl-methanol

Chiracel OB, uv 254 nm, 10% isopropanol / hexanes, 1 mL / min. t_R = 18.2 min (*R*, 100%), 21.2 min (*S*, not detected); >99.5% e.e.

(4-Chloro-phenyl)-phenyl-methanol

Chiracel OB, uv 254 nm, 10% isopropanol / hexanes, 1 mL / min. t_R = 12.7 min (*R*, 98.1%), 20.6 min (*S*, 1.9%); 96% e.e.

(3-Chloro-phenyl)-phenyl-methanol

Chiracel OD-H, uv 254 nm, 2% isopropanol / hexanes, 1 mL / min. t_R = 32.9 min (*S*, 2.3%), 36.6 min (*R*, 97.7%); 95% e.e.

(2-Chloro-phenyl)-phenyl-methanol

Chiracel OD-H, uv 254 nm, 10% isopropanol / hexanes, 0.7 mL / min. t_R = 10.9 min (*R*, 98.8%), 12.6 min (*S*, 1.2%); 98% e.e.

(4-Methoxy-phenyl)-phenyl-methanol

Chiracel OJ, uv 254 nm, 10% isopropanol / hexanes, 0.8 mL / min. t_R = 26.8 min (*R*, 98.7%), 30.5 min (*S*, 1.3%); 97% e.e.

Phenyl-(4-trifluoromethyl-phenyl)-methanol

Chiracel OB, uv 254 nm, 10% isopropanol / hexanes, 1 mL / min. t_R = 8.43 min (*R*, 98.4%), 11.7 min (*S*, 1.6%); 97% e.e.

4-(Hydroxy-phenyl-methyl)-benzoic acid methyl ester

Chiracel OD-H, uv 254 nm, 10% isopropanol / hexanes, 0.5 mL / min. t_R = 31.8 min (*R*, 98.1%), 34.3 min (*S*, 1.9%); 96% e.e.

Naphthalen-2-yl-phenyl-methanol

Chiracel OD-H, uv 254 nm, 10% isopropanol / hexanes, 0.5 mL / min. t_R = 26.9 min (*S*, 2.7%), 31.8 min (*R*, 97.3%); 95% e.e.

References

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