Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information for:

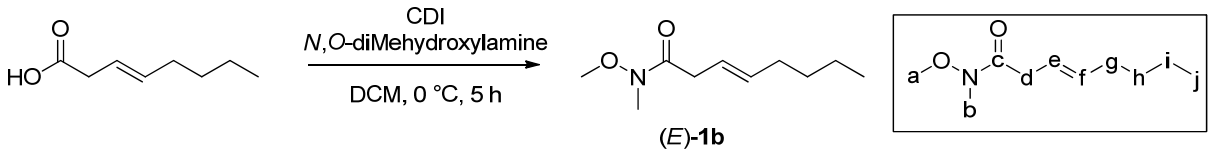
Catalytic Asymmetric Hydroboration of *β,γ*-Unsaturated Weinreb Amides: Surprising Influence of the Borane.

Sean M. Smith, Maulen Uteuliyev, and James M. Takacs*

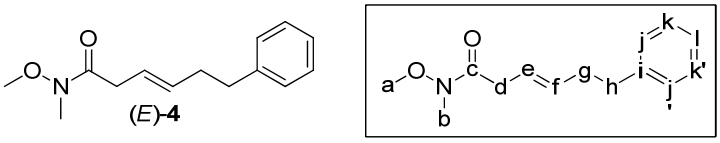
Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE 68588-0304

General procedures. Reactions were carried out in a dry nitrogen atmosphere. Dichloromethane (DCM), tetrahydrofuran (THF), and benzene were freshly distilled under the following conditions: benzene from sodium metal, THF from sodium metal and benzophenone, and DCM from calcium hydride. HPLC solvents were filtered through Millipore filter paper. When indicated in the following procedures, solvents were degassed by freezing under reduced pressure followed by a dry nitrogen atmosphere thaw (3–4 times). All boranes were distilled immediately before use. All synthesized compounds were purified with flash chromatography (hexanes:ethyl acetate) using EMD Silica Gel 60 Geduran®, or distilled via short path distillation. Thin Layer Chromatography analyses were performed on Analtech Silica Gel HLF (0.25 mm) precoated analytical plates and visualized with use of handheld short wavelength UV light, Iodine stain (I_2 and EMD Silica Gel 60 Geduran®) and Vanillin stain (Ethanol, H_2SO_4, and vanillin). HPLC analyses were performed with use of an ISCO model 2360 HPLC and Chiral Technologies, Inc. chiral HPLC column (Chiralcel OD; column: 250 x 4.6 mm). Data were recorded and analyzed with ChromPerfect chromatography software (version 5.1.0). NMR spectra were recorded on 600, 400, and 300 MHz Bruker Advance NMR spectrometers using residue $CHCl_3$ (δ 7.27 ppm) or $CDCl_3$ (δ 77.0 ppm) for reference unless otherwise specified. Peaks are expressed as m (unresolved multiplet), q (quartet), t (triplet), d (doublet) or s (singlet). IR spectra were recorded using an Avatar 360 FT-IR. Optical rotations were measured as solutions, 1.0 g/100 mL in chloroform unless indicated otherwise, and recorded using an Autopol III automatic polarimeter. HRMS analyses were performed by the Nebraska Center for Mass Spectrometry.

General procedure for the preparation of *β,γ*-unsaturated Weinreb amides.[1]



Preparation of (*E*)-3-octenoic acid *N,O*-dimethyl hydroxylamide ((*E*)-1b). To a cooled (0 °C) solution of (*E*)-3-octenoic acid (623 mg, 4.38 mmol) in dichloromethane (DCM, 25 mL) was added 1,1-carbonyl diimidazole (CDI, 850 mg, 5.24 mmol). After stirring at the same temperature for 0.5 h, *N,O*-dimethyl hydroxylamine hydrochloride (1.06 g, 10.9 mmol) was added and the reaction was allowed to rise to room temperature. After 5 h, the resultant mixture was filtered and the filtrate was washed with HCl (2 M, 25 mL), NaOH (2 M, 25 mL), and brine (25 mL). The organic layer was dried (anhyd. $MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel (85:15 hexanes:ethyl acetate) affords the title compound (690 mg, 85%) as a colorless oil: TLC analysis R_f 0.6 (50:50 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60–5.40 (2H, m, e,f), 3.65 (3H, s, a), 3.15–3.05 (2H, suspected d, d), 2.05–1.95 (2H, m, g), 1.40–1.20 (4H, m, h,i), 0.84 (3H, t, J = 7.0 Hz, j); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.08 (c), 134.36 (f), 122.22 (e), 61.24 (a), 36.08 (d), 32.19 (g), 32.08 (b), 31.34 (h), 22.15 (i), 13.87 (j); IR (neat) 2958 (CH sp^2 stretch), 2929 (CH sp^3 stretch), 2873, 1667 (C=O stretch), 1465, 1414, 1379 (C-N stretch), 1175, 1102 (C-O stretch), 999, 969, 933 cm^{-1}; HRMS (CI) calcd. for $C_{10}H_{20}NO_2$ (M+H): 186.1494, found 186.1488 *m/z*.

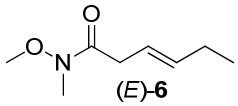


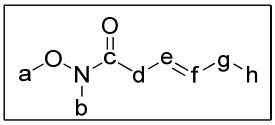
(*E*)-6-Phenyl-3-hexenoic acid *N,O*-dimethyl hydroxylamide ((*E*)-4).[2] Using the general procedure, (*E*)-6-phenyl-3-hexenoic acid (833 mg, 4.38 mmol) affords, after flash chromatography on silica gel (85:15 hexanes:ethyl acetate), the title compound (797 mg, 78%) as a colorless oil: TLC analysis R_f 0.60 (50:50 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$)

[1] S. M. Ng, S. J. Bader and M. L. Snapper, *J. Am. Chem. Soc.*, 2006, **128**, 7315–7319.

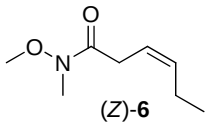
[2] *β,γ*-Unsaturated acid and synthetic precursors were prepared as previously described. See: S. M. Smith, N. C. Thacker and J. M. Takacs, *J. Am. Chem. Soc.*, 2008, **130**, 3734–3735.

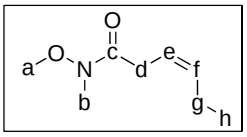
δ 7.35–7.25 (2H, m, k,k'), 7.25–7.15 (3H, m, j,j',l), 5.20–5.10 (2H, m, e,f), 3.68 (3H, s, a), 3.15–3.05 (2H, suspected d, d), 3.20 (3H, s, b), 2.72 (2H, t, J = 7.5 Hz, h), 2.45–2.35 (2H, m, g); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.95 (c), 141.88 (i), 133.37 (f), 128.45 (j,j'), 128.30 (k,k'), 125.80 (l), 123.11 (e), 61.32 (a), 36.06 (d), 35.68 (h), 34.36 (g), 32.15 (b); IR (neat) 3026 (CH sp^2 stretch), 2936 (CH sp^3 stretch), 1657 (C=O stretch), 1454, 1382 (C-N stretch), 1176, 1108 (C-O stretch), 1000, 967, 746, 699 cm^{-1}; HRMS (FAB) calcd. for $C_{14}H_{20}NO_2$ (M+H): 234.1495, found 234.1504 *m/z*.





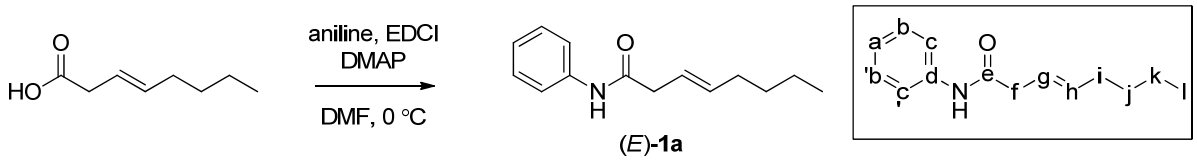
(*E*)-3-Hexenoic acid *N,O*-dimethyl hydroxylamide ((*E*)-6). Using the general procedure, (*E*)-3-hexenoic acid (500 mg, 4.38 mmol) affords, after flash chromatography on silica gel (85:15 hexanes:ethyl acetate), the title compound (572 mg, 83%) as a colorless oil: TLC analysis R_f 0.5 (50:50 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60–5.40 (2H, m, e,f), 3.66 (3H, s, a), 3.15–3.10 (2H, suspected d, d), 3.14 (3H, s, b), 2.05–1.95 (2H, m, g), 0.95 (3H, t, J = 7.4 Hz, h); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.11 (c), 135.88 (f), 121.30 (e), 61.26 (a), 36.00 (d), 32.09 (b), 25.52 (g), 13.45 (h); IR (neat) 2964 (CH sp^2 stretch), 2937 (CH sp^3 stretch), 1660 (C=O stretch), 1462, 1411, 1381 (C-N stretch), 1175, 1102, 1013 (C-O stretch), 967, 937, 820, 780 cm^{-1}; HRMS (CI) calcd. for $C_8H_{16}NO_2$ (M+H): 158.1181, found 158.1176 *m/z*.





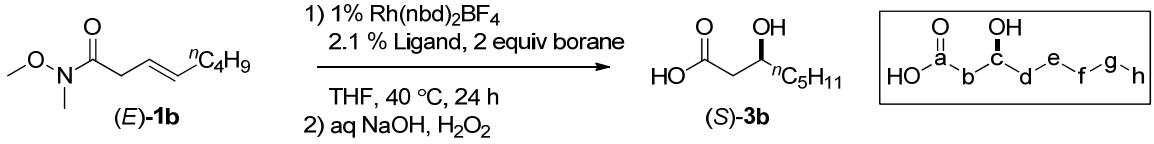
(*Z*)-3-Hexenoic acid *N,O*-dimethyl hydroxylamide ((*Z*)-6). Using the general procedure, (*Z*)-3-hexenoic acid (500 mg, 4.38 mmol) affords, after flash chromatography on silica gel (85:15 hexanes:ethyl acetate), the title compound (551 mg, 80%) as a colorless oil: TLC analysis R_f 0.5 (50:50 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60–5.50 (2H, m, e,f), 3.70 (3H, s, a), 3.21 (2H, d, J = 4.9 Hz, d), 3.18 (3H, s, b), 2.15–2.05 (2H, m, g), 0.99 (3H, t, J = 7.5 Hz, h); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.93 (c), 134.61 (f), 120.91 (e), 61.24 (a), 32.22 (b), 30.89 (d), 20.81 (g), 13.95 (h); IR (neat) 2965 (CH sp^2 stretch), 2937 (CH sp^3 stretch), 1665 (C=O stretch), 1463, 1376 (C-N stretch), 1241, 1176, 1119 (C-O stretch), 989, 924, 785, 703 cm^{-1}; HRMS (CI) calcd. for $C_8H_{16}NO_2$ (M+H): 158.1181, found 158.1176 *m/z*.

General procedure for the preparation of *β,γ*-unsaturated phenyl amides.



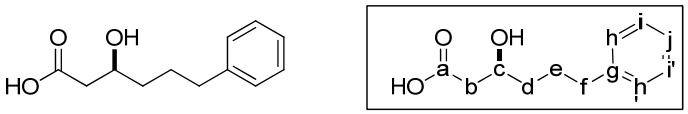
Preparation of (*E*)-3-octenoic acid phenyl amide ((*E*)-1a). To a cooled (0 °C) degassed solution of (*E*)-3-octenoic acid (2.49 g, 17.5 mmol) in *N,N*-dimethylformamide (DMF, 50 mL) was slowly added aniline (1.63 g, 17.5 mmol). The resulting solution was stirred (0.5 h, 0 °C) and then *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (3.35 g, 17.5 mmol) and 4-(dimethylamino)pyridine (DMAP, 1.07 g, 17.5 mmol) were added. The resulting mixture was allowed to slowly warm to room temperature and stirred overnight. The reaction mixture was quenched by the addition of satd. aq. sodium bicarbonate (50 mL) and extracted with diethyl ether (2 x 50 mL). The combined ether extracts were dried (anhyd. $MgSO_4$) and concentrated under vacuum via rotovap. Flash chromatography on silica gel (80:20 hexanes:ethyl acetate) followed by recrystallization (10:1 hexanes:ethyl acetate) affords the title compound (3.23 g, 85%) as a fluffy white solid: mp 47–49 °C; TLC analysis R_f 0.5 (75:25 hexanes:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, br s, NH), 7.54 (2H, d, J = 8.0 Hz, c,c'), 7.31 (2H, t, J = 7.8 Hz, b,b'), 7.11 (1H, t, J = 7.4 Hz, a), 5.76-5.59 (2H, m, g,h), 3.12 (2H, d, J = 6.7 Hz, f), 2.14–2.08 (2H, m, i), 1.44–1.33 (4H, m, j,k), 0.94 (3H, t, J = 7.01 Hz, l); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.58 (e), 137.85 (d), 137.49 (g), 128.98 (b,b'), 124.20 (a), 122.29 (h), 119.72 (c,c'), 41.63 (f), 32.27 (i), 31.31 (j), 22.25 (k), 13.91 (l); IR (neat) 3292 (N-H stretch), 2948, 2923, 2864, 6959, 1596, 1525 (N-H bend), 1498, 1440, 1357, 1250, 1187 cm^{-1}; HRMS (FAB) calcd. for $C_{14}H_{19}NO$ (M+H): 218.1545, found 218.1536 *m/z*.

Representative procedure for rhodium-catalyzed asymmetric hydroboration of *β,γ*-unsaturated Weinreb amides.



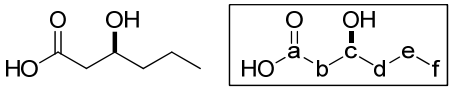
Preparation of (*S*)-3-Hydroxyoctanoic acid ((*S*)-3b).[3] A solution containing $Rh(nbd)_2BF_4$ (2.6 mM) and (BINOL)PN(Me)Ph (**L**, 5.6 mM) in THF (2 mL) was prepared. To the resulting yellow solution [$Rh(nbd)_2BF_4$ (2.0 mg, 0.0053 mmol) and **L** (4.6 mg, 0.011 mmol)] was added *β,γ*-unsaturated Weinreb amide (*E*)-**1b** (97.8 mg, 0.528 mmol) as a solution in THF (2 mL). To the resulting cooled (0 °C) solution was slowly added (i.e., dropwise over the course of 0.5 h) a solution of 4,4-dimethyl-1,3,2-dioxaborinane (**B8**, 125 mg, 1.1 mmol) in THF (1 mL). The ice bath was removed and after stirring for 0.5 h, the mixture was heated at 40 °C for 24 h. Afterwards, the reaction was cooled (0 °C) followed by the slow addition of 3 *N* aq NaOH (6 mL) and dropwise addition of 30% H_2O_2 (1 mL). The resulting mixture was stirred cold (0 °C, 0.5 h) and then at room temperature (1.5 h). Sodium metabisulfite ($Na_2S_2O_5$, 10% , 6 mL) was then added followed by a 15 min stir. The resultant mixture was washed with diethyl ether (3 x 20 mL) and then acidified (6M HCl). After extracting with dichloromethane (4 x 15 mL), the combined organic extracts were dried (anhyd. $MgSO_4$), concentrated via rotovap, and purified via flash chromatography on silica gel (60:40 hexanes:ethyl acetate) to afford the title compound (68.5 mg, 81%) as a colorless oil: TLC analysis R_f 0.4 (30:70 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = +14.2° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (2H, br s, COOH, OH), 4.10–4.00 (1H, m, c), 2.57 and 2.47 (2H, overlapping dd's, J_1 = 16.5 Hz, 3.3 Hz, J_2 = 16.5 Hz, 8.8 Hz, b), 1.60–1.40 (2H, m, d), 1.40–1.20 (6H, m, e,f,g), 0.90 (3H, t, J = 6.5 Hz, h); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.94 (a), 68.08 (c), 41.09 (b), 36.39 (d), 31.64 (e), 25.11 (f), 22.56 (g), 14.00 (h); IR (neat) 3391 (OH stretch), 2930, 2860 (CH sp^3 stretch), 1709 (C=O stretch), 1378 (C- N stretch), 1156, 1126, 1080 (C-O stretch), 1044, 950, 883, 828 cm^{-1}.

[3] K. I. Booker-Milburn, R. Gillan, M. Kimberley, T. Taguchi, K. Ichinose, G. R. Stephenson, Y. Ebizuka and D. A. Hopwood, *Angew. Chem. Int. Ed.*, 2005, **44**, 1121–1125.



(*S*)-**5**

(*S*)-3-Hydroxy-6-phenylhexanoic acid ((*S*)-5).[4] Using the general procedure with (BINOL)PN(Me)Ph (**L**, 4.6 mg, 0.011 mmol) and 4,4,6-trimethyl-1,3,2-dioxaborinane (TMDB, **B7**, 135 mg, 1.1 mmol), rhodium-catalyzed hydroboration of unsaturated Weinreb amide (*E*)-**4** (123 mg, 0.528 mmol) affords, after flash chromatography on silica gel (60:40 hexanes:ethyl acetate), the title compound (83.6 mg, 76%) as a colorless oil: TLC analysis R_f 0.5 (30:70 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = +13.8º (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (2H, m, i,i'), 7.25–7.15 (3H, m, h,h',j), 5.60 (2H, br s, COOH, OH), 4.10–4.00 (1H, m, c), 2.66 (2H, t, *J* = 7.5 Hz, f), 2.55 and 2.46 (2H, overlapping dd's, J_1 = 16.6 Hz, 2.9 Hz, J_2 = 16.6 Hz, 8.9 Hz, b), 1.90–1.75 (1H, m, d), 1.75–1.65 (1H, m, d), 1.65–1.60 (1H, m, e), 1.60–1.50 (1H, m, e); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.30 (a), 142.07 (g), 128.41 (h,h'), 128.35 (i,i'), 125.83 (j), 67.87 (c), 41.08 (b), 35.94 (d), 35.63 (f), 27.24 (e); IR (neat) 3230 (OH stretch), 2932 (CH sp^3 stretch), 2547, 1689 (C=O stretch), 1447, 1407, 1311, 1291, 1194 (C-O stretch), 1075, 938, 877, 736, 699 cm^{-1}.



(*S*)-**7**

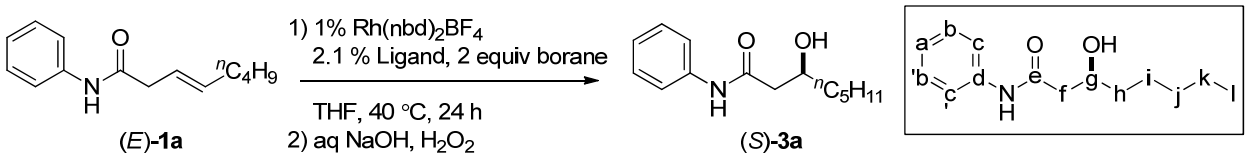
(*S*)-3-hydroxyhexanoic acid ((*S*)-7).[5] Using the general procedure with ((BINOL)PN(Me)Ph (**L,** 4.6 mg, 0.011 mmol) and 4,4,6-trimethyl-1,3,2-dioxaborinane (TMDB, **B7**, 135 mg, 1.1 mmol), rhodium-catalyzed hydroboration of unsaturated Weinreb amide (*E*)-**6** (83.0 mg, 0.528 mmol) affords, after flash chromatography on silica gel (60:40 hexanes:ethyl acetate), the title compound (50.9 mg, 73%) as a colorless oil: TLC analysis R_f 0.3 (30:70 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = +13.0º (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (2H. br s, COOH, OH), 4.10–4.00 (1H, m, c), 2.57 and 2.47 (2H, overlapping dd's, J_1 = 16.5 Hz, 3.0 Hz, J_2 = 16.5 Hz, 8.9 Hz), 1.60–1.50 (1H, m, d),1.50–1.40 (2H, m, d,e), 1.40–1.35 (1H, m, e), 0.95 (3H, t, *J* = 7.0 Hz, f); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.38 (a), 67.79 (c), 41.06 (b), 38.55 (d), 18.65 (e), 13.89 (f); IR

[4] E. R. Olivera, D. Carnicero, R. Jodra, B. Minambres, B. Garcia, G. A. Abraham, A. Gallardo, J. S. Roman, J. L. Garcia, G. Naharro and J. M. Luengo, *Environmental Microbiology*, 2001, **3**, 612–618.

[5] Y. Wang and T. Yan, *J. Org. Chem.*, 2000, **65**, 6752–6755.

(neat) 3522 (OH stretch), 2959 (CH sp^3 stretch), 2932, 2874, 1708 (C=O stretch), 1467, 1380, 1177 (C-O sretch), 1122, 1075, 1019, 952, 883, 827 cm^{-1}.

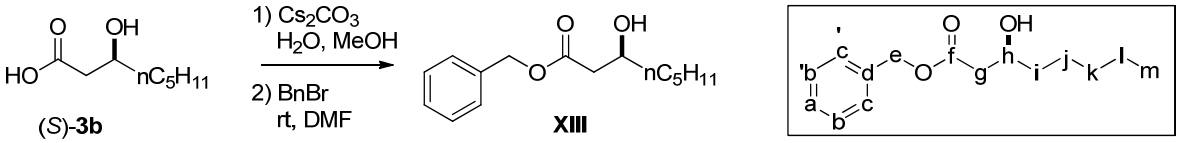
Representative procedure for rhodium-catalyzed asymmetric hydroboration of *β,γ*-unsaturated phenyl amides.



Preparation of (*S*)-3-Hydroxyoctanoic acid phenyl amide ((*S*)-3a). A solution containing $Rh(nbd)_2BF_4$ (2.6 mM) and (BINOL)PN(Me)Ph (**L**, 5.6 mM) in THF (2 mL) was prepared. To the resulting yellow solution [$Rh(nbd)_2BF_4$ (2.0 mg, 0.0053 mmol) and **L** (4.6 mg, 0.011 mmol)] was added *β,γ*-unsaturated phenyl amide (*E*)-**1a** (114.8 mg, 0.528 mmol) as a solution in THF (2 mL). To the resulting cooled (0 °C) solution was slowly added (i.e., dropwise over the course of 0.5 h) a solution of pinacolborane (PinBH, **B1**, 135 mg, 1.1 mmol) in THF (1 mL). The ice bath was removed and after stirring for 0.5 h, the mixture was heated at 40 °C for 24 h. Afterwards, the reaction mixture was re-cooled (0 °C), diluted with THF (15 mL) and quenched by the slow addition of methanol (6 mL) followed by the dropwise addition of 3 *N* aq. NaOH (8 mL) and 30% H_2O_2 (1 mL). The resulting mixture was stirred cold (0 °C, 0.5 h) and then at room temperature (1.5 h). After extracting with dichloromethane (DCM, 2 x 50 mL), the combined organic extracts were dried (anhyd. $MgSO_4$) and concentrated via rotovap. Flash chromatography on silica gel (70:30 hexanes:ethyl acetate) affords the title compound (97.0 mg, 78%) as a white solid: mp 113–114 °C; TLC analysis R_f 0.60 (50:50 hexanes:ethyl acetate); $[\alpha]_D^{20} = +7.0^o$ (*c* 0.5, ethanol); chiral HPLC analysis (Chiralpak-AD, 85:15 hexanes:isopropanol) showed peaks at 23.5 minutes (3.5% (R)) and 26.5 minutes (96.5% (S)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, br s, NH), 7.52 (2H, d, J = 8.0 Hz, c, c'), 7.33 (2H, t, J = 7.7 Hz, b, b'), 7.13 (1H, t, J = 7.3 Hz, a), 4.20-4.00 (1H, m, g), 3.14 (1H, br s, OH), 2.57 and 2.47 (2H, overlapping dd's, J_1 = 15.4 Hz, 2.5 Hz, J_2 = 15.4 Hz, 8.8 Hz, f), 1.70-1.20 (8H, m, h,i,j,k), 0.92 (3H, t, J = 6.6 Hz, l); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.50 (e), 137.65 (d), 129.00 (c,c'), 124.41 (a), 120.04 (b,b'), 68.85 (g), 43.85 (f), 36.98 (h), 31.68 (i), 25.15 (j), 22.56 (k), 13.96 (l); IR (neat) 3304 (N-H stretch), 2951, 2928, 2868, 1661 (C=O stretch), 1598, 1537 (N-H bend), 1498, 1442, 1308 (C-

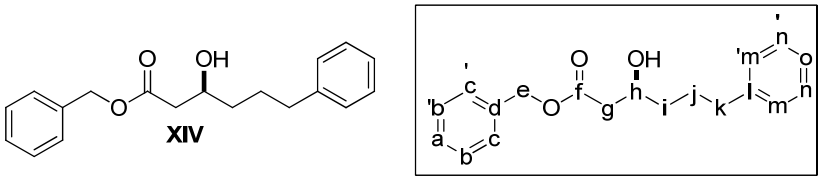
N stretch), 1253, 1123 (C-OH stretch), 1071, 756, 690 cm^{-1}; HRMS (FAB) calcd. for $C_{14}H_{22}NO_2$ (M+H): 236.1651, found 236.1661 *m/z*.

General procedure for the preparation of *β*-hydroxy benzyl esters.

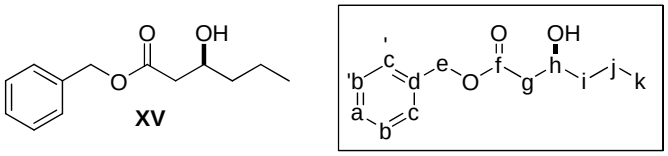


Preparation of (*S*)-3-Hydroxyoctanoic acid benzyl ester (XIII).[6] To a cooled (0 °C) solution of (*S*)-3-hydroxyoctanoic acid ((*S*)-**3b**, 16.0 mg, 0.10 mmol) in methanol (0.3 mL) was slowly added a solution of Cs_2CO_3 (16.3 mg, 0.050 mmol) in H_2O (0.3 mL). The mixture was allowed to stir for 0.5 h at the same temperature before rising to room temperature and an additional 0.5 h stir. After concentration under reduced pressure, the dry cesium carboxylate salt was taken up in dimethylformamide (DMF, 0.4 mL). To the resultant mixture was added benzyl bromide (18 μL, 0.15 mmol) dropwise at room temperature. After 6 h, H_2O (2 mL) was added and the resultant mixture was extracted with diethyl ether (3 x 1 mL). The combined organic extracts were dried (anhyd. $MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel (90:10 hexanes:ethyl acetate) affords the title compound (20.5 mg, 82%) as a light yellow oil: TLC analysis R_f 0.6 (80:20 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = +14.2º (*c* 0.5, $CHCl_3$); chiral HPLC analysis (Chiralcel-OD, 80:20 hexanes: isopropanol) showed peaks at 11 minutes (1.5% (R)) and 14 minutes (98.5% (S)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.30 (5H, m, a,b,b',c,c'), 5.18 (2H, s, e), 4.10–4.00 (1H, m, h), 2.94 (1H, br s, OH), 2.58 and 2.48 (2H, overlapping dd's, J_1 = 16.4 Hz, 3.4 Hz, J_2 = 16.4 Hz, 8.8 Hz, g), 1.60–1.40 (3H, m, i,j), 1.40–1.20 (5H, m, j,k,l), 0.91 (3H, t, *J* = 6.6 Hz, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.87 (f), 135.63 (d), 128.63 (c,c'), 128.38 (a), 128.27 (b,b'), 68.05 (h), 66.47 (e), 41.39 (g), 36.51 (i), 31.71 (j), 25.15 (k), 22.58 (l), 14.02 (m); IR (neat) 3441 (OH stretch), 2954 (CH sp^3 stretch), 2930, 2859, 1728 (C=O stretch), 1456, 1278, 1160 (C-O stretch), 969, 736, 695 cm^{-1}.

[6] T. Mukaiyama, S. Kobayashi and T. Sano, *Tetrahedron*, 1990, **46**, 4653–4662.



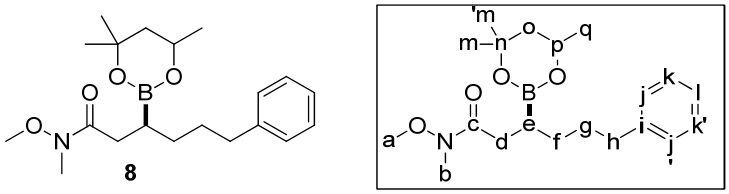
(*S*)-3-Hydroxy-6-phenylhexanoic acid benzyl ester (XIV). Using the general procedure, (*S*)-3-hydroxy-6-phenylhexanoic acid ((*S*)-**5**, 20.8 mg, 0.10 mmol) affords, after flash chromatography on silica gel (90:10 hexanes:ethyl acetate), the title compound (25.1 mg, 84%) as a light yellow oil: TLC analysis R_f 0.5 (80:20 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = +15.9º (*c* 0.5, $CHCl_3$); chiral HPLC analysis (Chiralcel-OD, 80:20 hexanes: isopropanol) showed peaks at 22 minutes (2.0% (R)) and 31 minutes (98.0% (S)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.35 (5H, m, a,b,b',c,c'), 7.35–7.25 (2H, m, n,n'), 7.25–7.15 (3H, m, m,m',o), 5.18 (2H, s, e), 4.15–4.00 (1H, m, h), 2.97 (1H, br s, OH), 2.67 (2H, t, J = 7.4 Hz, k), 2.58 and 2.49 (2H, overlapping dd's, J_1 = 16.5 Hz, 3.6 Hz, J_2 = 16.5 Hz, 8.6 Hz, g), 1.90–1.80 (1H, m, i), 1.75–1.60 (1H, m, i), 1.60–1.40 (2H, m, j); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.82 (f), 142.17 (l), 135.60 (d), 128.66 (c,c'), 128.42 (m,m',a), 128.34 (n,n'), 128.30 (b,b'), 125.81 (o), 67.89 (h), 66.53 (e), 41.39 (g), 36.02 (i), 35.69 (k), 27.27 (j); IR (neat) 3434 (OH stretch), 2938 (CH sp^3 stretch), 2859, 1728 (C=O stretch), 1496, 1454, 1168 (C-O stretch), 1087, 967, 748, 696 cm^{-1}; HRMS (CI) calcd. for $C_{19}H_{22}NaO_3$ (M+Na): 321.1467, found 321.1472 *m/z*.



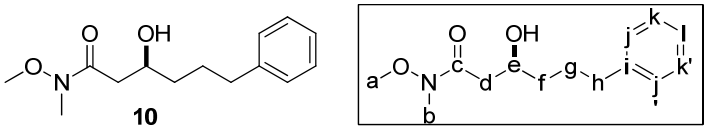
(*S*)-3-hydroxyhexanoic acid benzyl ester (XV).[7] Using the general procedure, (*S*)-3-hydroxyhexanoic acid ((*S*)-**7**, 13.2 mg, 0.10 mmol) affords, after flash chromatography on silica gel (90:10 hexanes:ethyl acetate), the title compound (17.3 mg, 78%) as a light yellow oil: TLC analysis R_f 0.5 (80:20 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = +13.8º (*c* 0.5, $CHCl_3$); chiral HPLC analysis (Chiralcel-OD, 80:20 hexanes: isopropanol) showed peaks at 9 minutes (1.5% (R)) and 12 minutes (98.5% (S)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.35 (5H, m, a,b,b',c,c'), 5.18 (2H, s, e), 4.10–4.00 (1H, m, h), 2.86 (1H, br s, OH), 2.58 and 2.48 (2H, overlapping dd's, J_1 = 16.5 Hz, 3.4 Hz, J_2 = 16.5 Hz, 8.8 Hz, g), 1.60–1.35 (4H, m, i,j), 0.95 (3H, t, J = 7.0 Hz, k); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.90 (f), 135.60 (d), 128.64 (c,c'), 128.40 (a), 128.28 (b,b'), 67.76 (h),

[7] S. G. Nelson and K. L. Spencer, *J. Org. Chem.*, 2000, **65**, 1227–1230.

66.50 (e), 41.36 (g), 38.63 (i), 18.67 (j), 13.96 (k); IR (neat) 3444 (OH stretch), 2958 (CH sp^3 stretch), 2932, 2872, 1728 (C=O stretch), 1455, 1381, 1262, 1163 (C-O stretch), 980, 906, 736, 696 cm^{-1}.

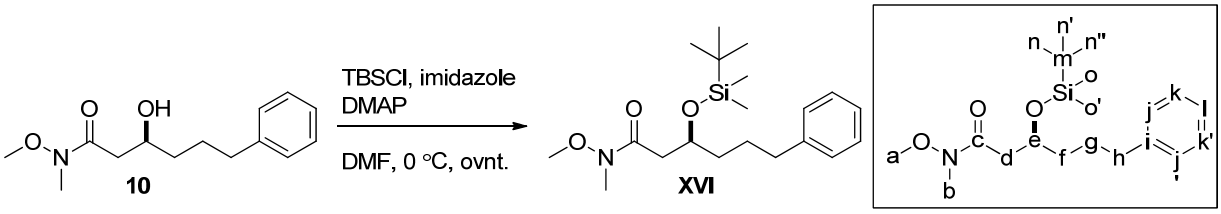


Preparation of 3-(4,4,6-trimethyl-1,3,2-dioxaborato)-6-phenylhexanoic acid *N,N*-methoxymethyl amide (8). The general procedure for the rhodium-catalyzed asymmetric hydroboration of Weinreb amide (*E*)-**4** without oxidative work-up affords, after flash chromatography on silica gel (85:15 hexanes:ethyl acetate), the title compound (134 mg, 79%) as a light yellow oil: TLC analysis R_f 0.5 (60:40 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = -8.0º (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (2H, m, k,k'), 7.25–7.15 (3H, m, j,j',l), 4.25–4.10 (1H, m, q), 3.68 (3H, s, a), 3.20 and 3.17 (3H, s's, b), 2.62 (2H, t, *J* = 6.8 Hz, h), 2.50–2.40 (2H, m, d), 1.72 (1H, dd, *J* = 13.7 Hz, 3.0 Hz, o), 1.70–1.60 (2H, m, f), 1.60–1.30 (4H, m, o,g,e), 1.29 (3H, s, m), 1.25 (3H, s, m'), 1.25–1.20 (3H, m, q); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.13 (i), 128.42 (j,j'), 128.16 (k,k'), 125.44 (l), 70.19 and 70.14 (n), 64.41 and 64.28 (p), 61.22 and 61.09 (a), 45.90 and 45.83 (o), 36.21 (h), 33.95 (d), 32.17 (b), 31.29 (m), 30.97 (g), 30.88 and 30.85 (f), 27.93 and 27.81 (m'), 27.73 (e), 23.22 (q); IR (neat) 2858 (CH sp^3 stretch), 2926, 2856, 1662 (C=O stretch), 1454, 1378, 1314, 1144 (C-O stretch), 1001, 967, 867, 670 cm^{-1}; HRMS (CI) calcd. for $C_{20}H_{33}BNO_4$ (M+H): 362.2503, found 362.2511 *m/z*.



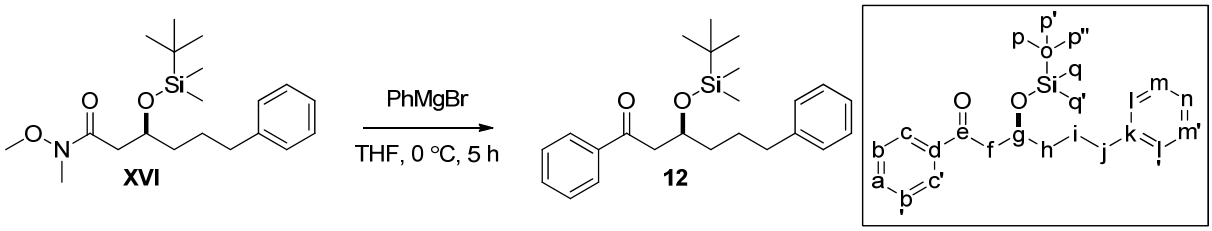
Preparation of 3-hydroxy-6-phenylhexanoic acid *N,N*-methoxymethyl amide (10). To a cooled (0 °C) solution of organoboronate **8** (108 mg, 0.30 mmol) in a 50/50 mixture of THF and H_2O (5 mL) was added sodium perborate tetrahydrate (231 mg, 1.5 mmol) in one portion. After 0.5 h, the mixture was allowed to rise to room temperature. After an additional 1.5 h stir, H_2O (5 mL) was added and the resultant mixture was extracted with diethyl ether (10 mL x 3). The combined organic extracts were dried (anhyd. $MgSO_4$) and then concentrated under reduced pressure. Flash chromatography on silica gel (60:40 hexanes:ethyl acetate) affords the title

compound (73.1 mg, 97%) as a light yellow oil: TLC analysis R_f 0.4 (25:75 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = +21.5° (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (2H, m, k,k'), 7.25–7.15 (3H, m, j,j',l), 4.10–4.00 (1H, m, e), 3.89 (1H, br s, OH), 3.68 (3H, s, a), 3.68 (3H, s, b), 2.67 (2H, t, *J* = 7.5 Hz, h), 2.70–2.60 (1H, suspected dd, d), 2.46 (1H, dd, *J* = 16.8 Hz, 9.6 Hz, d), 1.90–1.80 (1H, m, f), 1.80–1.70 (1H, m, f), 1.70–1.60 (1H, m, g), 1.60–1.45 (1H, m, g); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.86 (c), 142.36 (i), 128.45 (j,j'), 128.29 (k,k'), 125.72 (l), 67.72 (e), 61.25 (a), 38.22 (d), 36.08 (f), 35.79 (h), 31.84 (b), 27.36 (g); IR (neat) 3427 (OH stretch), 2962 (CH sp^3 stretch), 1639 (C=O stretch), 1453, 1387 (C-N stretch), 1258, 1088 (C-O stretch), 1004, 870, 789, 699 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{21}NaNO_3$ (M+Na): 274.1419, found 274.1414 *m/z*.

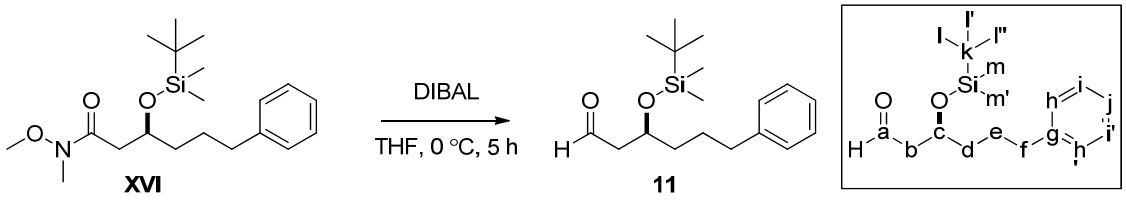


Preparation of 3-(*tert*-butyldimethylsiloxy)-6-phenylhexanoic acid *N,N*-methoxymethyl amide (XVI). To a cooled (0 °C) solution of Weinreb amide **10** (126 mg, 0.50 mmol), imidazole (51.0 mg, 0.75 mmol), and (dimethylamino)pyridine (DMAP, 12.2 mg, 0.10 mmol) in *N,N*-dimethylformamide (DMF, 0.50 mL) was added a solution of *tert*-butyl(chloro)dimethylsilane (TBSCl, 89.7 mg, 0.60 mmol) in DMF (0.50 mL). The resultant mixture was stirred for an additional 0.5 h at the same temperature and then allowed to rise to room temperature and stirred overnight. To the mixture was added satd. sodium chloride (2 mL) followed by extraction with diethylether (3 x 3 mL). The combined organic extracts were washed with H_2O (2 mL), dried (anhyd. $MgSO_4$), and concentrated under reduced pressure. Flash chromatography on silica gel (90:10 hexanes:ethyl acetate) affords the title compound (150 mg, 82%) as a light yellow oil: TLC analysis R_f 0.30 (90:10 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = +° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (2H, m, k,k'), 7.25–7.15 (3H, m, j,j',l), 4.35–4.25 (1H, m, e), 3.69 (3H, s, a), 3.19 (3H, s, b), 2.75 and 2.39 (2H, overlapping dd's, J_1 = 14.6 Hz, 7.3 Hz, J_2 = 14.6 Hz, 5.3 Hz, d), 2.64 (2H, t, *J* = 7.5 Hz, h), 1.80–1.65 (2H, m, f), 1.65–1.50 (2H, m, g), 0.88 (9H, s, n,n',n''), 0.07 (3H, s, o), 0.04 (3H, s, o'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.43 (c), 142.44 (i), 128.39 (j,j'), 128.27 (k,k'), 125.67 (l), 69.25 (e), 61.30 (a), 39.51 (d), 37.41 (f), 35.97 (h), 31.94 (b), 26.70 (g), 25.86 (n,n',n''), 18.04 (m), -4.65 (o), -4.71 (o'); IR (neat) 2929

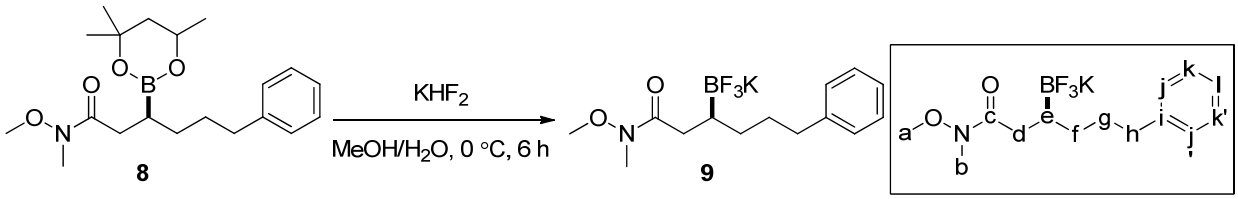
(CH sp^3 stretch), 2855, 1661 (C=O stretch), 1472, 1385, 1252, 1090 (C-O stretch), 1004, 939, 834, 775, 732, 698 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{35}NNaO_3Si$ (M+Na): 388.2284, found 388.2283 *m/z*.



Preparation of 3-(*tert*-butyldimethylsiloxy)-6-phenylhexanoic acid phenyl ketone (12). To a cooled (0 °C) solution of TBS-protected Weinreb amide **XVI** (36.6 mg, 0.10 mmol) in THF (1 mL) was added phenylmagnesium bromide (PhMgBr, 0.10 mL of a 3.0 M solution in THF, 0.30 mmol) dropwise. The resultant mixture was allowed to rise to room temperature. After 4 h, satd. sodium chloride (1 mL) was added to the reaction followed by extraction with diethylether (3 x 1 mL). The combined organic extracts were dried (anhyd. $MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel (95:5 hexanes:ethyl acetate) affords the title compound (36.0 mg, 94%) as a light yellow oil: TLC analysis R_f 0.6 (90:10 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = +21.2° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05–7.95 (2H, m, c,c'), 7.60–7.55 (1H, m, a), 7.55–7.45 (2H, m, b,b'), 7.35–7.25 (2H, m, m,m'), 7.25–7.15 (3H, m, l,l',n), 4.45–4.35 (1H, m, g), 3.26 and 2.93 (2H, overlapping dd's, J_1 = 15.4 Hz, 7.1 Hz, J_2 = 15.4 Hz, 5.3 Hz, f), 2.66 (2H, t, J = 7.3 Hz, j), 1.80–1.70 (2H, m, h), 1.70–1.55 (2H, m, i), 0.83 (9H, s, p,p',p''), 0.06 (3H, s, q), -0.06 (3H, s, q'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.43 (e), 142.36 (k), 137.63 (d), 133.00 (a), 128.51 (b,b'), 128.40 (l,l'), 128.39 (m,m'), 128.31 (c,c'), 125.74 (n), 69.38 (g), 45.96 (f), 37.58 (h), 35.96 (j), 26.72 (i), 25.82 (p,p',p''), 17.99 (o), -4.62 (q), -4.73 (q'); IR (neat) 2928 (CH sp^3 stretch), 2855, 1684 (C=O stretch), 1598, 1474, 1448, 1360, 1252, 1210, 1090 (C-O stretch), 1019, 1003, 833, 775, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{34}NaO_2Si$ (M+Na): 405.2226, found 405.2223 *m/z*.



Preparation of 3-(*tert*-butyldimethylsiloxy)-6-phenylhexanal (11).[8] To a cooled (0 °C) solution of TBS-protected Weinreb amide **XVI** (36.6 mg, 0.10 mmol) in THF (1 mL) was added Diisobutylaluminum hydride (DIBAL, 0.20 mL of a 1.0 M solution in THF, 0.20 mmol) dropwise. The resultant mixture was allowed to rise to room temperature. After 4 h, satd. sodium chloride (1 mL) was added to the reaction followed by extraction with diethylether (3 x 1 mL). The combined organic extracts were dried (anhyd. $MgSO_4$) and concentrated under reduced pressure. Flash chromatography on silica gel (95:5 hexanes:ethyl acetate) affords the title compound (27.9 mg, 91%) as a light yellow oil: TLC analysis R_f 0.4 (90:10 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = +5.5º (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (1H, t, *J* = 2.3 Hz, a), 7.35–7.25 (2H, m, i,i'), 7.25–7.15 (3H, m, h,h',j), 4.25–4.15 (1H, m, c), 2.70–2.60 (2H, m, f), 2.60–2.50 (2H, m, b), 2.75–2.65 (2H, m, d), 2.65–2.55 (2H, m, e), 0.89 (9H, s, l,l',l''), 0.07 (3H, s, m), 0.06 (3H, s, m'); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.24 (a), 142.06 (g), 128.35 (h,h',i,i'), 125.83 (j), 68.00 (c), 50.80 (b), 37.29 (d), 35.78 (f), 26.73 (e), 25.76 (l,l',l''), 17.98 (k), -4.44 (m), -4.70 (m'); IR (neat) 2929 (CH sp^3 stretch), 2857, 1725 (C=O stretch), 1471, 1361, 1253, 1095 (C-O stretch), 1027, 1005, 834, 774, 698 cm^{-1}.



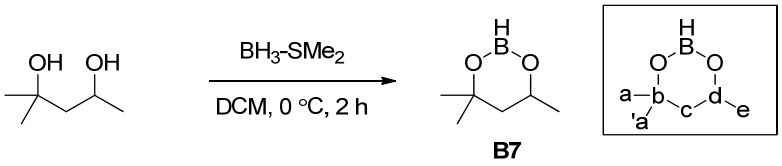
Preparation of 3-trifluoroborato-6-phenylhexanoic acid *N*,*N*-methoxymethyl amide potassium salt (9).[9] To a cooled (0 °C) solution of organoboronate **8** (90.2 mg, 0.25 mmol), in methanol (0.3 mL) was added satd. aqueous KHF_2 (0.3 mL, 4.5 M) dropwise via syringe. After allowing the mixture to slowly rise to room temperature and stir for an additional 5 h, concentration to dryness under reduced pressure afforded a crude solid which was taken up in

[8] S. Kiyooka, T. Yamaguchi, H. Maeda, H. Kira, M. A. Hena and M. Horiike, *Tetrahedron Lett.*, 1997, **38**, 3553–3556.

[9] S. D. Dreher, P. G. Dormer, D. L. Sandrock and G. A. Molander, *J. Am. Chem. Soc.*, 2008, **130**, 9257–9259.

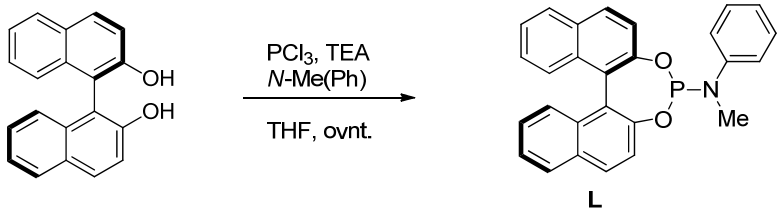
acetone (3 mL). After filtration, the filtrate was concentrated under reduced pressure and taken up in diethylether (0.5 mL). The resulting solution was cooled (0 °C) and left overnight. After decantation, the resultant mixture was dried under reduced pressure to afford the title compound (70.2 mg, 82%) as a white solid: mp 235–236 ^{o}C; $[\alpha]_D^{20}$ = -10.2º (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 7.25–7.20 (2H, m, k,k'), 7.20–7.15 (2H, m, j,j'), 7.15–7.05 (1H, m, l), 3.68 (3H, s, a), 3.17 (3H, s, b), 2.60–2.50 (2H, m, h), 2.40–2.20 (2H, m, d), 1.70–1.60 (2H, m, g), 1.55–1.45 (1H, m, f), 1.30–1.15 (1H, m, f), 0.95 (1H, br s, e); ^{13}C NMR (100 MHz, MeOD) δ 178.71 (c), 143.39 (i), 128.05 (j,j'), 127.68 (k,k'), 124.90 (l), 60.26 (a), 36.41 (h), 33.44 (d), 31.18 (e,f), 30.90 (b,g); ^{19}F NMR (376 MHz, MeOD) δ -146.53; IR (neat) 2958 (CH sp^3 stretch), 2856, 1668 (C=O stretch), 1454, 1390, 1300, 1144 (C-O stretch), 1000, 955, 854, 660 cm^{-1}. HRMS (CI) calcd. for (M-BF_3K+2H): 236.1651, found 236.1654 *m/z*.

Illustrative procedure for the preparation of 1,3,2-dioxaborinanes, -borolanes, and -borinine.



B7

Preparation of 4,4,6-Trimethyl-1,3,2-dioxaborinane (TMDB, B7). To a cooled (0 °C) solution of 2-methyl-2,4-pentanediol (1.54 g, 12 mmol) in dichloromethane (6 mL) was slowly added borane (BH_3, 1 mL of a 10 M solution in dimethylsulfide, 10 mmol) dropwise. After the resulting mixture was stirred for 1.5 h at the same temperature, the ice bath was removed and the reaction was allowed to stir for an additional 0.5 h. Volatiles were carefully removed under reduced pressure (i.e., concentration via rotovap while the mixture was submerged in a room temperature water bath). After complete removal of dichloromethane and dimethylsulfide (SMe_2), the residue was purified via bulb-to-bulb distillation (160–165 °C) to afford the title compound (960 mg, 75%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30–4.15 (1H, m, d), 3.84 (1H, q, J = 155.6 Hz, BH), 1.90–1.75 (1H, m, c), 1.60–1.45 (1H, m, c), 1.31 (3H, s, a), 1.29 (3H, s, a'), 1.26 (3H, d, J = 6.2 Hz, e); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.99 (b), 64.73 (d), 46.17 (c), 31.02 (a), 28.14 (a'), 22.93 (e); ^{11}B NMR (193 MHz, THF with residual $CDCl_3$) δ 24.96 (d, J = 169.1 Hz); IR (neat) 2976 (CH sp^3 stretch), 2879, 2400, 1495, 1427, 1384, 1291, 1156 (C-O stretch), 1094, 1024, 889, 789, 666 cm^{-1}; HRMS (CI) calcd. for $C_6H_{14}BO_2$ (M+H): 129.1087, found 129.1082 *m/z*.



L

Preparation of (BINOL)PN(Me)Ph (L). To a cooled (0 °C) solution of *N*-methylaniline (98.6 mg, 0.92 mmol) in dry THF (50 mL) was added PCl_3 (82 μL, 0.92 mmol) dropwise. The resulting clear solution was stirred at room temperature for 1 h and then cooled (-78 °C) and triethylamine (TEA, 130 μL, 0.92 mmol) was added dropwise. After stirring at -78 °C (0.5 h), a solution of (*R*)-(+)-1,1'-bi-2-naphthol (263.4 mg, 0.92 mmol) and triethylamine (300 μL, 2.12 mmol) in dry THF (2 mL) was slowly added. The resulting milky white suspension was stirred at room temperature overnight and then filtered under nitrogen through a pad of celite. The celite was further washed with dry THF and the volatile solvents were removed via rotovap. The residue was dried on a vacuum line. Flash chromatography (25:75 DCM: hexanes) affords the title compound (202.6 mg, 52%) as a white foamy solid: mp 94–95 °C; TLC analysis R_f 0.60 (75:25 hexanes: DCM); $[\alpha]_D^{20}$ = -87.2° (*c* 0.5, ethanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (1H, d, *J* = 8.8 Hz), 8.00-7.90 (3H, m), 7.60-7.55 (1H, m), 7.50-7.41 (4H, m), 7.41-7.25 (7H, m), 7.17-7.10 (1H, m), 2.67 (3H, d, *J* = 2.51 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.89, 149.18, 146.39, 146.13 132.86, 132.64, 131.53, 130.90, 130.49, 130.24, 129.17, 128.39, 128.33, 127.02, 126.93, 126.22, 124.98, 124.79, 124.07, 123.23, 122.72, 121.83, 121.28, 121.12, 33.53 (J_{CP} = 4.02 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 143.76; IR (neat) 3061, 2935 (P-O stretch), 1589, 1489, 1330, 1269, 1226, 1061, 938, 804, 769 cm^{-1}; HRMS (FAB) calcd. for $C_{27}H_{20}NO_2P$ (M+H): 422.1310, found 422.1307 *m/z*.