N-Sulfinyl Metalloenamine Conjugate Additions: Asymmetric Synthesis of Piperidines

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Supporting Information

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Experimental Section

General Methods. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Sulfinyl ketimines **1a-d** were prepared using the previously published method.¹ Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. CH₂Cl₂ and *i*-Pr₂NH were distilled from CaH₂ immediately prior to use. Toluene was distilled from Na. The concentration of commercially available solutions of *n*-butyllithium in hexanes was determined by titration with 2,6-di-*tert*-butyl-4-methylphenol and 1,10-phenanthroline. Reactions were carried out in flame- or oven- dried glassware under a N₂ atmosphere. Extracts were dried over Na₂SO₄ and concentrated using a rotary evaporator under reduced pressure. Hydrogenation reactions were carried out in a Parr apparatus. Chromatography was carried out with mesh silica gel. IR spectra were recorded on an FTIR spectrometer equipped with an attenuated total reflectance accessory and only partial data are listed. Optical rotation values were recorded on a polarimeter in CHCl₃ at 25 °C and 589 nm. ¹H and ¹³C NMR spectra were obtained in CDCl₃ at room temperature. Chemical shifts in NMR spectra are expressed in ppm relative to CDCl₃. Coupling constants are reported in Hz. For diastereomeric mixtures, only the peaks corresponding to the major diastereomer are listed. Products were isolated and used as diastereomeric mixtures unless otherwise stated. LCMS analysis was performed with an Agilent Eclipse XDB-C8 5 μm 4.6 x 150 mm reverse phase column with UV detection at 220 nm. Specific solvent conditions are described within experiments.

General Procedure for the Michael Addition of *N*-Sulfinyl Metalloenamines. To a 0.24 M solution of *i*-Pr₂NH (1.2 equiv) in THF was added *n*-butyllithium in hexanes (1.1 equiv) at 0 °C and the mixture was stirred for 20 min. The solution was then cooled to –78 °C and the

N-sulfinyl imine (1.0 equiv) was added. After stirring for 30 min, the additive (1.2 equiv) was added and the solution was stirred for 45 min. A 1.0 M solution of the Michael acceptor (1.2 equiv) cooled to $-78\text{ }^{\circ}\text{C}$ was added dropwise via cannula to the metallocenamine and stirring was continued at $-78\text{ }^{\circ}\text{C}$. To the reaction mixture was added a 4:1 (v/v) solution of THF/acetic acid until the pH of the mixture reached 6. The mixture was diluted with 30 mL of EtOAc and washed with brine (3 x 20 mL). The combined organic portions were dried, filtered, and concentrated under reduced pressure. The crude product was then dissolved in toluene and concentrated under reduced pressure (2 x 20 mL). The products were purified by silica gel chromatography (hexanes/EtOAc).

Michael product 3a. The general procedure was followed with (*R*)-(-)-*N*-(1-phenylethylidene)-2-methylpropanesulfinamide (**1a**) (100 mg, 0.448 mmol), 3-penten-2-one (**2a**) (0.0616 mL, 0.537 mmol), and ZnBr_2 (121 mg, 0.537 mmol). The reaction was quenched after 6 h. Diastereoselectivity was determined by LCMS analysis using a gradient system from 70:30 methanol/ H_2O and 0.1% TFA to 95:5 methanol/ H_2O and 0.1% TFA over 10 min and was held at this ratio for 5 min; 97:3 dr: major diastereomer, $t_{\text{R}} = 4.1$ min; minor diastereomer $t_{\text{R}} = 3.8$ min. Column chromatography (1:1 hexanes/EtOAc) afforded 115 mg (84% yield) of **3a** as a yellow oil. IR: 1571, 1591, 1604, 1717, 2871, 2923, 2961, 3062, 3407 cm^{-1} . ^1H NMR (500 MHz): δ 0.89 (d, 3H, $J = 6.3$), 1.25 (s, 9H), 2.02 (s, 3H), 2.30-2.46 (m, 3H), 3.12 (dd, 1H, $J = 13.3, 5.0$), 3.36 (dd, 1H, $J = 12.3, 9.5$), 7.35-7.40 (m, 3H), 7.86 (d, 2H, $J = 6.9$). ^{13}C NMR (125 MHz): δ 19.5, 22.6, 28.7, 30.3, 37.5, 50.2, 57.8, 127.8, 128.4, 131.4, 137.6, 178.9, 207.6. MS (FAB): m/z

308 (MH⁺). Anal. Calcd. for C₁₇H₂₅NO₂S: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.54; H, 8.51; N, 4.25.

Michael product 3b. The general procedure was followed with (*R*)-(-)-*N*-(1-phenylethylidene)-2-methylpropanesulfonamide (**1a**) (200 mg, 0.895 mmol) and 1-phenyl-2-buten-3-one (**2b**)² (0.153 mL, 1.07 mmol). The reaction was quenched after 2 h. Diastereoselectivity was determined by LCMS analysis using a gradient system from 5:95 acetonitrile/H₂O and 0.1% TFA to 95:5 acetonitrile/H₂O and 0.1% TFA over 15 min; >99:1 dr: major diastereomer, *t*_R = 20.4 min; minor diastereomer *t*_R = 20.1 min. Column chromatography (3:1 hexanes/EtOAc) afforded 273 mg (82% yield) of **3b** as a yellow oil. IR: 1447, 1569, 1602, 1685, 2964, 3067 cm⁻¹. ¹H NMR (500 MHz): δ 1.04 (d, 3H, *J* = 6.7), 1.32 (s, 9H), 2.63 (m, 1H), 2.95 (dd, 1H, *J* = 6.5, 17.0), 3.07 (dd, 1H, *J* = 7.0, 17.0), 3.30 (m, 1H), 3.52 (m, 1H), 7.41-7.66 (m, 6H), 7.91-8.01 (m, 4H). ¹³C NMR (125 MHz): δ 20.0, 22.7, 29.1, 37.8, 45.5, 57.8, 127.8, 128.0, 128.2, 128.5, 131.4, 133.0, 137.0, 137.7, 179.0, 199.1. MS (FAB): *m/z* 370 (MH⁺). Anal. Calcd. for C₂₂H₂₇NO₂S: C, 71.51; H, 7.36; N, 3.79. Found: C, 71.24; H, 7.44; N, 3.68.

Michael product 3c. The general procedure was followed with (*R*)-(-)-*N*-(1-phenylethylidene)-2-methylpropanesulfonamide (**1a**) (123 mg, 0.552 mmol), 4-phenyl-3-buten-2-one (**2c**) (96.8 mg, 0.662 mmol), and ZnBr₂ (149 mg, 0.662 mmol). The reaction was quenched

after 14.5 h at $-78\text{ }^{\circ}\text{C}$ and 7 h of warming to $-20\text{ }^{\circ}\text{C}$. Diastereoselectivity was determined by LCMS analysis using a gradient system from 70:30 methanol/ H_2O and 0.1% TFA to 95:5 methanol/ H_2O and 0.1% TFA over 10 min and was held at this ratio for 5 min; >99:1 dr: major diastereomer, $t_{\text{R}} = 5.3$ min. The minor diastereomer was not observed by LCMS or ^1H NMR. Column chromatography (1:1 hexanes/EtOAc) afforded 122 mg (60% yield) of **3c** as a yellow oil. IR: 1572, 1589, 1605, 1713, 2863, 2922, 2957, 2976, 3026, 3058 cm^{-1} . ^1H NMR (500 MHz): δ 1.18 (s, 9H), 2.04 (s, 3H), 2.85-2.94 (m, 2H), 3.49-3.51 (m, 2H), 3.83 (dd, 1H, $J = 14.7$, 11.6), 7.09 (m, 2H), 7.15-7.26 (m, 3H), 7.41-7.47 (m, 3H), 7.81 (d, 2H, $J = 7.2$). ^{13}C NMR (125 MHz): δ 22.6, 30.5, 37.8, 39.6, 49.5, 57.6, 126.4, 126.9, 127.6, 127.8, 128.5, 131.3, 137.7, 142.2, 178.0, 207.2. MS (FAB): m/z 370 (MH^+). Anal. Calcd. for $\text{C}_{22}\text{H}_{27}\text{NO}_2\text{S}$: C, 71.51; H, 7.36; N, 3.79. Found: C, 71.12; H, 7.72; N, 3.47.

Michael product 3d. The general procedure was followed with (*R*)-(-)-*N*-(3,3-dimethyl-2-butylidene)-2-methylpropanesulfonamide (**1b**) (112 mg, 0.552 mmol), 1-phenyl-2-buten-3-one (**2b**) (94.4 μL , 0.662 mmol), and ZnBr_2 (149 mg, 0.662 mmol). The reaction was quenched after 6.0 h at $-78\text{ }^{\circ}\text{C}$. Diastereoselectivity was determined by LCMS analysis using a gradient system from 70:30 methanol/ H_2O and 0.1% TFA to 95:5 methanol/ H_2O and 0.1% TFA over 10 min and was held at this ratio for 5 min; >99:1 dr: major diastereomer, $t_{\text{R}} = 7.0$ min. The minor diastereomer was not observed by LCMS or ^1H NMR. Column chromatography (3:1 hexanes/EtOAc) afforded 118 mg (61% yield) of **3d** as a white solid. IR: 1605, 1676, 1683, 2847, 2865, 2917, 2958, 3054 cm^{-1} . ^1H NMR (500 MHz): δ 1.10 (d, 3H, $J = 6.7$), 1.21 (s, 9H),

1.24 (s, 9H), 2.69 (dd, 1H, $J = 7.1, 12.6$), 2.83 (m, 1H), 2.96 (m, 2H), 3.16 (dd, 1H, $J = 8.6, 12.6$), 7.44 (m, 2H), 7.54 (m, 1H), 7.95 (m, 2H). ^{13}C NMR (125 MHz): δ 20.0, 22.5, 28.7, 28.8, 37.3, 43.5, 45.8, 57.1, 128.0, 128.5, 133.0, 137.0, 191.7, 199.4. MS (FAB): m/z 350 (MH^+). Anal. Calcd. for $\text{C}_{20}\text{H}_{31}\text{NO}_2\text{S}$: C, 68.72; H, 8.94; N, 4.01. Found: C, 68.79; H, 9.00; N, 3.91.

Michael product 3e. The general procedure was followed with (*R*)-(-)-*N*-(3-methyl-2-butyldiene)-2-methylpropanesulfonamide (**1c**) (104 mg, 0.552 mmol), 1-phenyl-2-buten-3-one (**2b**) (94.4 μL , 0.662 mmol), and ZnBr_2 (149 mg, 0.662 mmol). The reaction was quenched after 4.5 h at $-78\text{ }^\circ\text{C}$. Diastereoselectivity was determined by LCMS analysis using a gradient system from 70:30 methanol/ H_2O and 0.1% TFA to 95:5 methanol/ H_2O and 0.1% TFA over 10 min and was held at this ratio for 5 min; >99:1 dr: major diastereomer, $t_R = 6.1$ min; minor diastereomer $t_R = 5.9$ min. Column chromatography (1:1 hexanes/EtOAc) afforded 133 mg (72% yield) of **3e** as a yellow oil. IR: 1582, 1619, 1687, 2869, 2929, 2963, 3057, 3083 cm^{-1} . ^1H NMR (500 MHz): δ 1.03 (d, 3H, $J = 6.4$), 1.11 (m, 6H), 1.21 (s, 9H), 2.69-2.75 (m, 3H), 2.89-2.99 (m, 2H), 7.41-7.44 (m, 2H), 7.51-7.54 (m, 1H), 7.92-7.94 (m, 2H). ^{13}C NMR (125 MHz): δ 20.2, 21.0, 22.3, 28.2, 38.1, 41.1, 45.3, 53.4, 56.8, 128.0, 128.5, 133.0, 137.0, 191.1, 199.2. MS (FAB): m/z 336 (MH^+). Anal. Calcd. for $\text{C}_{19}\text{H}_{29}\text{NO}_2\text{S}$: C, 68.02; H, 8.71; N, 4.17. Found: C, 68.41; H, 8.97; N, 3.84.

Michael product 6a. The general procedure was followed with (*R*)-(-)-*N*-(1-phenylethylidene)-2-methylpropanesulfonamide (**1a**) (1.10 g, 4.90 mmol), *trans*- β -nitrostyrene (**5a**) (0.88 g, 5.9 mmol). The reaction was quenched after 3 h. Diastereoselectivity was determined by LCMS analysis using a gradient system from 70:30 methanol/H₂O and 0.1% TFA to 95:5 methanol/H₂O and 0.1% TFA over 10 min and was held at this ratio for 5 min; 75:25 dr: major diastereomer, t_R = 5.2 min; minor diastereomer t_R = 4.7 min. Column chromatography (3:1 hexanes/EtOAc) afforded 1.6 g (88% yield) of **6a** as a yellow oil. IR: 1555, 1593, 1604, 2864, 2924, 2957, 3029, 3059 cm⁻¹. ¹H NMR (500 MHz): δ 1.28 (s, 9H), 3.62 (m, 1H), 3.80 (quintet, 1H, J = 7.5), 3.90 (m, 1H), 4.71 (m, 2H), 7.18-7.31 (m, 5H), 7.39-7.52 (m, 4), 7.68-7.70 (m, 1H). ¹³C NMR (125 MHz): δ 23.0, 35.4, 42.9, 58.4, 79.2, 127.3, 127.6, 128.0, 128.9, 129.0, 131.8, 137.3, 137.8, 175.3. MS (FAB): m/z 373 (MH⁺). Anal. Calcd. for C₂₀H₂₄N₂O₃S: C, 64.49; H, 6.49; N, 7.52. Found: C, 64.28; H, 6.56; N, 7.44.

Michael product 6b. The general procedure was followed with (*R*)-(-)-*N*-(1-phenylethylidene)-2-methylpropanesulfonamide (**1a**) (100 mg, 0.448 mmol), *trans*-1-nitropropene (**5b**) (46.8 mg, 0.537 mmol), and ZnBr₂ (121 mg, 0.537 mmol). The reaction was quenched after 4 h. Diastereoselectivity was determined by LCMS analysis using a gradient system from 70:30 methanol/H₂O and 0.1% TFA to 95:5 methanol/H₂O and 0.1% TFA over 10 min and was held at this ratio for 5 min; 76:24 dr: major diastereomer, t_R = 8.4 min; minor diastereomer t_R = 7.7 min. Column chromatography (3:1 hexanes/EtOAc) afforded 67.1 mg (70% yield) of **6b** as a yellow oil. IR: 1552, 1590, 1605, 2872, 2928, 2965, 3063 cm⁻¹. ¹H NMR

(400 MHz): δ 1.07 (d, 3H, $J = 6.7$), 1.31 (s, 9H), 2.75 (m, 1H), 3.23 (m, 1H), 3.52 (m, 1H), 4.33 (d, 2H, $J = 7.2$), 7.43-7.49 (m, 3H), 7.76-7.82 (m, 2H). ^{13}C NMR (100 MHz): δ 17.2, 22.8, 32.0, 34.9, 58.6, 80.9, 127.4, 128.9, 131.9, 137.4, 176.0. MS (FAB): m/z 311 (MH^+). Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$: C, 58.04; H, 7.14; N, 9.02. Found: C, 58.30; H, 7.37; N, 8.63.

***trans*-1-Nitropropene (5b).** To a 1.0 M solution of 1-nitro-2-propanol³ (4.00 g, 38.1 mmol) in CH_2Cl_2 at 0 °C was added methanesulfonyl chloride (2.95 mL, 38.1 mmol). Triethylamine (10.6 mL, 76.1 mmol) was then added dropwise, and the reaction mixture was stirred for 15 min at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (30 mL), transferred to a separatory funnel and washed with H_2O (50 mL), 5% aqueous HCl (50 mL), brine (50 mL), and 2% aqueous NaOH (50 mL). The organic layer was dried and concentrated. The residual oil was purified by Kugelrohr distillation (bp 70 °C, 20 mm) to yield 1.33 g (40% yield) of **5b** as a colorless liquid. ^1H NMR (300 MHz): δ 1.95 (dd, 3H, $J = 7.3, 1.7$), 6.9 (dq, 1H, $J = 13.3, 1.6$ Hz), 7.27, (m, 1H). ^1H NMR shifts correspond with the literature data.⁴

(S)-4-Nitro-1,3-diphenyl-butan-1-one. To a 0.02 M solution of **6a** (1.58 g, 4.24 mmol, 75:25 dr) in MeOH was added 1.0 *N* aqueous AcOH (84.7 mmol) and the mixture was stirred for 24 h at 70 °C. After hydrolysis was determined to be complete by TLC, the solvent was reduced to half volume under reduced pressure. Brine (50 mL) was added to the mixture, which was then extracted with 1:4 CH_2Cl_2 /hexanes (3 x 70 mL). The combined organic portions were dried,

filtered, and concentrated. Column chromatography (70:30 hexanes/EtOAc) afforded 914 mg (80% yield) of the desired nitroketone as a white solid, mp 99-101 °C (lit. 101-103 °C). $[\alpha]_{589}^{25} = -15.7^\circ$ ($c = 1.0$, CH₃Cl, 50% ee) [lit. $[\alpha]_{589}^{25} = -9.3^\circ$ ($c = 1.0$, CH₃Cl, 35% ee)]. ¹H NMR (500 MHz): δ 3.46 (m, 2H), 4.23 (quintet, 1H, $J = 7.1$ Hz), 4.69 (dd, 1 H, $J = 12.5, 8.0$), 4.84 (dd, 1H, $J = 12.4, 6.7$ Hz), 7.25-7.59 (m, 8H), 7.91-7.93 (m, 2H). ¹³C NMR (125 MHz): δ 39.2, 41.5, 79.5, 127.4, 127.8, 128.0, 128.7, 129.0, 133.5, 136.3, 139.1, 196.8. Analytical data above correspond with the literature data.⁵

Aminoketone 7a. A 0.50 M solution of iminoketone **3a** (1.00 g, 3.25 mmol) in THF (6.50 mL) was brought to -48 °C and L-selectride (16.3 mL, 16.3 mmol, 1.0 M in THF) was added dropwise. The reaction mixture was allowed to warm to rt overnight. The mixture was then placed in an ice bath and MeOH was added dropwise. The reaction solution was washed with brine (2 x 40 mL) and the combined aqueous layers were extracted with EtOAc (1 x 40 mL). The combined organic portions were dried, filtered, and concentrated under reduced pressure. Column chromatography (90:10 CH₂Cl₂/MeOH) afforded 988 mg (98% yield) of the corresponding 1,5-amino alcohol as a pale yellow oil. Dess-Martin periodinane (919 mg, 2.02 mmol) was added to a 0.282 M solution of the 1,5-amino alcohol in H₂O saturated CH₂Cl₂ (3.41 mL). The resulting suspension was stirred at rt for 2 h. Three portions of H₂O saturated CH₂Cl₂ (0.680 mL) were added over 15 minutes. The reaction mixture was diluted with ether (3.40 mL), and a solution of sodium thiosulfate (4.12 g, 10.6 mmol, Na₂S₂O₃•5 H₂O) in 80% saturated aqueous sodium bicarbonate (3.40 mL) was added. The mixture was stirred rapidly for 10 min

until both phases were clear. The layers were separated and the aqueous layer extracted with ether (1 x 30 mL). The combined organic portions were washed with saturated aqueous sodium bicarbonate (2 x 30 mL) and brine (2 x 30 mL), dried, filtered, and concentrated to afford 302 mg (93% yield) of **7a** as a dark yellow oil. Diastereoselectivity was determined by LCMS analysis using a gradient system from 70:30 methanol/H₂O and 0.1% TFA to 95:5 methanol/H₂O and 0.1% TFA over 10 min and was held at this ratio for 5 min; 97:3 dr: major diastereomer, *t_R* = 3.4 min; minor diastereomer *t_R* = 3.9 min. IR: 1710, 2872, 2924, 2955, 3026, 3060, 3227 cm⁻¹. ¹H NMR (500 MHz): δ 0.921 (d, 3H, *J* = 6.6), 1.16 (s, 9H), 1.65 (m, 1H), 1.82 (m, 2H), 2.01 (s, 3H), 2.25 (dd, 1H, *J* = 6.5, 16.3), 2.35 (dd, 1H, *J* = 6.8, 16.3), 3.50 (d, 1H, *J* = 2.3), 4.45 (m, 1H), 7.31 (m, 5H). ¹³C NMR (125 MHz): δ 19.8, 22.5, 25.8, 30.1, 45.0, 50.9, 55.4, 57.0, 127.7, 127.8, 128.5, 141.2, 208.3. MS (FAB): *m/z* 310 (MH⁺). Anal. Calcd. for C₁₇H₂₇NO₂S: C, 65.98; H, 8.79; N, 4.53. Found: C, 65.65; H, 8.53; N, 4.32.

Aminoketone 7b. A 0.50 M solution of iminoketone **3e** (207 mg, 0.619 mmol) in THF (1.24 mL) was brought to -48 °C and L-selectride (3.09 mL, 3.09 mmol, 1.0 M in THF) was added dropwise. The reaction mixture was allowed to warm to rt overnight. The mixture was then placed in an ice bath and MeOH was added dropwise. The organics were washed with brine (2 x 20 mL) and the combined aqueous layers were extracted with EtOAc (1 x 20 mL). The combined organic portions were dried, filtered, and concentrated under reduced pressure. Column chromatography (90:10 CH₂Cl₂/MeOH) afforded 165 mg (79% yield) of the corresponding 1,5-amino alcohol as a pale yellow oil. Dess-Martin periodinane (434 mg, 1.02

mmol) was added to a 0.282 M solution of the 1,5-amino alcohol in H₂O saturated CH₂Cl₂ (1.73 mL). The resulting suspension was stirred at rt for 2 h. Three portions of H₂O saturated CH₂Cl₂ (0.350 mL) were added over 15 minutes. The reaction mixture was diluted with ether (1.73 mL), and a solution of sodium thiosulfate (2.09 g, 5.40 mmol, Na₂S₂O₃•5 H₂O) in 80% saturated aqueous sodium bicarbonate (1.73 mL) was added. The mixture was stirred rapidly for 10 min until both phases were clear. The layers were separated and the aqueous layer extracted with ether (1 x 10 mL). The combined organic portions were washed with saturated aqueous sodium bicarbonate (2 x 10 mL) and brine (2 x 10 mL), dried, filtered, and concentrated to afford 157 mg (96% yield) of **7b** as a dark yellow oil. Diastereoselectivity was determined by LCMS analysis using a gradient system from 70:30 methanol/H₂O and 0.1% TFA to 95:5 methanol/H₂O and 0.1% TFA over 10 min and was held at this ratio for 5 min; 96:4 dr: major diastereomer, *t_R* = 5.7 min; minor diastereomer *t_R* = 6.5 min. IR: 1683, 2847, 2869, 2917, 2955, 3059, 3271, 3322 cm⁻¹. ¹H NMR (500 MHz): δ 0.887 (d, 3H *J* = 3.0), 0.901 (d, 3H, *J* = 2.9), 0.962 (d, 3H, *J* = 6.7), 1.19 (s, 9H), 1.41 (m, 2H), 2.03 (m, 1H), 2.36 (m, 1H), 2.87 (m, 2H), 3.19 (m, 1H), 3.23 (d, 1H, *J* = 9.0), 7.44 (m, 2H), 7.54 (m, 1H), 7.92 (m, 2H). ¹³C NMR (125 MHz): δ 16.8, 18.7, 19.3, 22.7, 26.0, 33.2, 38.3, 46.5, 56.2, 60.0, 128.0, 128.5, 132.9, 137.1, 199.7. MS (FAB): *m/z* 338 (MH⁺). HRMS (FAB) Calcd. for C₁₉H₃₂NO₂S (MH⁺): 338.2149. Found: 338.2154.

Aminoketone 7c. A 0.04 M solution of iminoketone **3a** (800 mg, 2.60 mmol) and Ti(OEt)₄ (1.26 mL, 5.20 mmol, 85% in isopropanol) in THF and was brought to -48 °C and NaBH₄ (394 mg, 10.4 mmol) was added. The reaction mixture was allowed to warm to rt

overnight. The mixture was then placed in an ice bath and MeOH was added dropwise. The resulting mixture was poured into an equal amount of brine with rapid stirring. The suspension was filtered through a plug of Celite and the filter cake was washed with EtOAc. The filtrate was washed with brine (2 x 50 mL) and the combined aqueous layers were extracted with EtOAc (1 x 50 mL). The combined organic portions were dried, filtered, and concentrated under reduced pressure. Column chromatography (90:10 CH₂Cl₂/MeOH) afforded 770 mg (95% yield) of the corresponding 1,5-amino alcohol as a pale yellow oil. Dess-Martin periodinane (1.34 g, 3.17 mmol) was added to a 0.282 M solution of the 1,5-amino alcohol in H₂O saturated CH₂Cl₂ (5.35 mL). The resulting suspension was stirred at rt for 2 h. Three portions of H₂O saturated CH₂Cl₂ (1.08 mL) were added over 15 minutes. The reaction mixture was diluted with ether (5.35 mL), and a solution of sodium thiosulfate (6.44 g, 16.6 mmol, Na₂S₂O₃•5 H₂O) in 80% saturated aqueous sodium bicarbonate (5.35 mL) was added. The mixture was stirred rapidly for 10 min until both phases were clear. The layers were separated and the aqueous layer was extracted with ether (1 x 10 mL). The combined organic portions were washed with saturated aqueous sodium bicarbonate (2 x 40 mL) and brine (2 x 40 mL), dried, filtered, and concentrated to afford 464 mg (99% yield) of **7c** as a dark yellow oil. The diastereoselectivity was determined by ¹H NMR to be 87:13 dr. IR: 1709, 2843, 2869, 2919, 2955, 3024, 3259, 3584 cm⁻¹. ¹H NMR major diastereomer (500 MHz): δ 0.900 (d, 3H *J* = 6.7), 1.21 (s, 9H), 1.56 (m, 1H), 1.90 (m, 1H), 2.06 (s, 3H), 2.08 (m, 1H), 2.28 (dd, 1H, *J* = 7.5, 16.8), 2.44 (dd, 1H, *J* = 6.2, 16.7), 3.56 (d, 1H, *J* = 5.3), 4.37 (m, 1H), 7.31 (m, 5H). (Minor diastereomer: 2.01 (s, 3H)) ¹³C NMR major diastereomer (125 MHz): δ 20.0, 22.6, 25.7, 30.4, 44.5, 50.5, 56.0, 57.2, 126.9, 127.8, 128.7, 142.9, 208.2. MS (FAB): *m/z* 310 (MH⁺). HRMS (FAB) Calcd. for C₁₇H₂₇NO₂S (MH⁺): 310.1837. Found: 310.1841.

Piperidine 4a. To a 0.16 M solution of aminoketone **7a** in MeOH (5.00 mL) was added 2.02 mL of a 4.00 M HCl/dioxane solution. The resulting solution was stirred for 2 h at rt and concentrated. A 2.00 M aqueous solution of NaOH was used to freebase the imine salt. A 0.16 M solution of the free imine in CH₂Cl₂ (5.05 mL) was treated with DIBAL-H (4.04 mL, 4.04 mmol, 1.00 M in CH₂Cl₂) at -78 °C. After 30 min, the solution was warmed to -40 °C for 1 h, then -20 °C for 1 h, and finally 0 °C for 1 h. The reaction mixture was diluted with ether (29.0 mL) and treated with NaF (678 mg, 16.2 mmol) followed by cautious addition of H₂O (0.570 mL). After 15 min, the resulting slurry was filtered through Celite, and the filter pad was washed with ether (65 mL). The combined filtrates were dried, filtered, and concentrated. Column chromatography (90:10 CH₂Cl₂/MeOH) afforded 86.3 mg (56% yield) of **4a** as a light brown oil. Diastereoselectivity was determined by LCMS analysis using a gradient system from 25:75 methanol/H₂O and 0.1% TFA to 40:60 methanol/H₂O and 0.1% TFA over 18 min and was held at this ratio for 1 min; 97:3 dr: major diastereomer, *t_R* = 14.1 min; minor diastereomer *t_R* = 16.1 min. IR: 2805, 2832, 2868, 2912, 2956, 3026, 3060, 3082, 3266, 3301 cm⁻¹. ¹H NMR of HCl salt (500 MHz, MeOD): δ 1.27 (d, 3H, *J* = 7.4), 1.34 (d, 3H, *J* = 6.5), 1.80-1.86 (m, 3H), 2.21 (td, 1H, *J* = 14.2, 4.7), 2.34-2.39 (m, 1H), 3.61-3.68 (m, 1H), 4.46 (d, 1H, *J* = 12.0), 7.41-7.52 (m, 5H). ¹³C NMR of HCl salt (125 MHz, MeOD): δ 16.3, 17.8, 25.7, 35.1, 35.4, 49.2, 55.9, 127.0, 128.5, 128.9, 129.1. MS (FAB): *m/z* 190 (MH⁺). HRMS (FAB) Calcd. for C₁₃H₂₀N (MH⁺): 190.1601. Found: 190.1596. Absolute configuration of the stereocenters was determined by X-ray analysis of the corresponding Mosher's amide. (see page S-16)

Piperidine 4b. To a 0.16 M solution of aminoketone **7b** in MeOH (1.85 mL) was added 0.74 mL of a 4.00 M HCl/dioxane solution. The resulting solution was stirred for 2 h at rt and concentrated. A 2.00 M aqueous solution of NaOH was used to freebase the imine salt. A 0.16 M solution of the free imine in CH₂Cl₂ (1.85 mL) was treated with DIBAL-H (1.48 mL, 1.48 mmol, 1.00 M in CH₂Cl₂) at -78 °C. After 30 min, the solution was warmed to -40 °C for 1 h, then -20 °C for 1 h, and finally 0 °C for 1 h. MeOH (1.20 mL) and saturated aqueous sodium sulfate (10.15 mL) were then added to the reaction mixture and the mixture was allowed to warm to rt. Solid sodium sulfate (5.50 g) was added and the mixture was stirred for 1 h. The resulting mixture was filtered through Celite, and the filter pad was washed with CH₂Cl₂ (40 mL). The combined filtrates were dried, filtered, and concentrated. Column chromatography (90:10 CH₂Cl₂/MeOH) afforded 46.3 mg (72% yield) of **4b** as a light brown oil. The diastereoselectivity was determined by ¹H NMR to be 96:4 dr. IR: 1457, 1576, 2583, 2609, 2717, 2784, 2865, 2921, 2951, 3025, 3062, 3326 cm⁻¹. ¹H NMR of HCl salt of major diastereomer (500 MHz, MeOD): δ 1.07 (m, 9H), 1.24 (m, 1H), 1.68 (m, 1H), 2.03 (m, 4H), 3.19 (m, 1H), 4.33 (d, 1H, *J* = 13), 7.45 (m, 3H), 7.54 (m, 2H). (Minor diastereomer: 4.50 (d, 1H)). ¹³C NMR of HCl salt of major diastereomer (125 MHz, MeOD): δ 16.2, 18.5, 20.3, 29.9, 30.5, 32.1, 38.1, 62.2, 64.4, 127.3, 128.8, 129.1, 136.4. MS (FAB): *m/z* 218 (MH⁺). HRMS (FAB) Calcd. For C₁₅H₂₄N (MH⁺): 218.1907. Found: 218.1909. Relative configuration of the substituents at the 2- and 6-positions was determined by nOe. (see attached NMR spectra, p S-22)

Piperidine 4c. To a 0.16 M solution of aminoketone **7c** in MeOH (7.06 mL) was added 2.83 mL of a 4.00 M HCl/dioxane solution. The resulting solution was stirred for 2 h at rt and concentrated. A 2.00 M aqueous solution of NaOH was used to freebase the imine salt. A 0.16 M solution of the free imine in CH₂Cl₂ (7.06 mL) was treated with DIBAL-H (5.65 mL, 5.65 mmol, neat) at –78 °C. After 30 min, the solution was warmed to –40 °C for 1 h, then –20 °C for 1 h, and finally 0 °C for 1 h. The reaction mixture was quenched with MeOH (4.00 mL), then saturated aqueous Na₂SO₄ (32.0 mL) and allowed to warm to rt overnight. Solid Na₂SO₄ (17.2 g) was added and the mixture was stirred for 1 h at rt, filtered through Celite, and the filter pad was washed with CH₂Cl₂ (65 mL). The filtrate was concentrated. Column chromatography (90:10 CH₂Cl₂/MeOH) afforded 87.7 mg (41% yield) of **4c** as a light brown oil. The diastereoselectivity was determined by ¹H NMR to be 87:13 dr. IR: 2847, 2919, 2959, 3439, 3584 cm^{–1}. ¹H NMR of HCl salt of major diastereomer (500 MHz, MeOD): δ 1.08 (d, 3H, *J* = 6.3), 1.37 (d, 3H, *J* = 6.5), 1.63 (m, 2H), 2.01 (m, 5H), 3.44 (m, 1H), 4.29 (d, 1H *J* = 11.9), 7.47 (m, 5H). (Minor diastereomer: 4.46 (d, 1H, *J* = 12.0)) ¹³C NMR of HCl salt of major diastereomer (125 MHz, MeOD): δ 17.7, 20.2, 29.7, 37.7, 38.2, 54.1, 61.1, 127.0, 128.9, 129.1, 136.6. MS (FAB): *m/z* 190 (MH⁺). HRMS (FAB) Calcd. for C₁₃H₂₀N (MH⁺): 190.1595. Found: 190.1596. Relative configuration of the substituents at the 2- and 6-positions was determined by nOe as above (see attached NMR spectra, p S-23).

Mosher's amide of piperidine 4a. To a 0.10 M solution of piperidine **4a** (50.0 mg, 0.264 mmol) in CH₂Cl₂ (2.64 mL) at 0 °C was added triethylamine (0.147 mL, 1.06 mmol) followed by Mosher's acid chloride (0.199 g, 0.792 mmol). The reaction mixture was stirred at rt for 3 h, and the reaction was then quenched with H₂O. The aqueous layer was extracted with ether (3 x 20 mL), and the combined ethereal layers were dried with Na₂SO₄ and concentrated. Column chromatography (95:5 CH₂Cl₂/MeOH) afforded 24.4 mg (20% yield) of the desired amide as a white solid. X-ray quality crystals were obtained by vapor diffusion of the amide using CH₂Cl₂/pentane. IR: 1635, 2847, 2917, 2947, 3029, 3070 cm⁻¹. ¹H NMR (500 MHz): δ 0.64 (d, 3H, *J* = 7.0), 0.82 (d, 3H, *J* = 6.5), 0.83 (m, 1H), 1.29-1.36 (m, 1H), 1.57 (bs, 1H), 2.05-2.13 (m, 1H), 2.41-2.44 (m, 1H), 3.85 (s, 3H), 4.20-4.22 (m, 1H), 6.31 (d, 1H, *J* = 5.8 Hz), 7.21-7.24 (m, 1H), 7.29-7.32 (m, 2H), 7.38-7.42 (m, 5H), 7.58-7.59 (m, 2H). ¹³C NMR (125 MHz): δ 20.2, 20.3, 22.1, 34.1, 37.5, 49.2, 49.4, 56.8, 56.7, 126.61, 126.66, 126.67, 126.7, 128.1, 128.3, 129.3, 134.3, 142.3, 166.1. MS (FAB): *m/z* 406 (MH⁺). HRMS (FAB) Calcd. for C₂₃H₂₇F₃NO₂ (MH⁺): 406.1985. Found: 406.1994.

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7.547
7.534
7.481
7.467
7.452
7.441
7.428
7.413
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7.303

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4.338

4.313

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3.309

3.306

3.303

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3.224

3.198

2.068

2.035

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1.218

1.194

1.105

1.092

1.081

1.067

1.051

Current Data Parameters
NAME ~~Sample~~
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PROCNO 1

F2 - Acquisition Parameters

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PULPROG zg30
TD 65536
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DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2768500 sec
RG 406.4
DW 50.000 use
DE 7.11 use
TE 296.1 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

===== CHANNEL f1 =====

NUC1 1H
P1 12.20 use
PL1 -5.00 dB
SF01 500.1330883 MHz

F2 - Processing parameters

SI 65536
SF 500.1300127 MHz
WDW EM
SSB 0
LR 0 20 Hz

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H₂O

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1.15

4.10

1.17

0.95

2.03
3.14