Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Efficient Enantioselective Synthesis of Piperidines through Catalytic Asymmetric Ring-Opening/Cross-Metathesis Reactions

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SUPPORTING INFORMATION. PART A

General: All reactions were conducted in oven- (135 ^{o}C) or flame-dried glassware under an inert atmosphere of dry N_2, unless otherwise stated. Infrared (IR) spectra were recorded on a Nicolet 210 spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m) or weak (w). ^{1}H NMR spectra were recorded on a Varian Gemini 2000 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26, C_6D_6: δ 7.16). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet or combinations thereof), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal reference ($CDCl_3$: δ 77.16, C_6D_6: δ 128.10). Enantiomer ratios were determined by chiral HPLC (Chiral Technologies Chiralpak OD column, Chiralpak AD, Chiralcel OJ, and Chiralcel OB-H (4.6 mm x 250 mm)). High-resolution mass spectrometry was performed at the University of Illinois Mass Spectrometry Laboratories (Urbana-Champaign, IL). Optical rotation values were recorded on a Rudolph Research Analytical Autopol IV polarimeter.

Materials: Solvents were purged with Ar and then purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: CH_2Cl_2 was passed through activated alumina columns; benzene was passed successively through activated Cu and alumina columns. Tetrahydrofuran was purified by distillation from sodium benzophenone ketal immediately prior to use. All reagents were purchased from Aldrich Chemical Company, Lancaster Synthesis, or Strem Chemicals, Inc., and purified by appropriate methods prior to use. Lithium aluminum hydride was purchased in powder form and was stored in a N_2-filled glovebox. Mo complex **6** was prepared

according to published procedures.[1] Mo complexes were handled under an inert atmosphere in a N_2-filled glovebox. Substrates were dried by repeated (three times) azeotropic distillation of water with benzene under high vacuum unless otherwise stated. Ru complexes **1a-2b** were prepared according to published procedures.[2] All reactions were allowed to stir with a magnetic stir bar and performed at 22 ^oC, unless otherwise stated. All filtrations involved gravity filtration, unless otherwise stated. Filtrations under reduced pressure were conducted with coarse fritted Buchner funnels; gravity filtrations were conducted with Whatman® filter papers. Silica gel chromatography was driven with compressed air and performed with silica gel 60 (230-400 mesh; pH (10% suspension) 6.5-7.0; surface area 500 m^2/g; pore volume 0.75 mL/g) obtained from TSI Chemical Co. (Cambridge, MA). Alumina gel chromatography was driven with compressed air and performed with neutral alumina Brockman Activity Grade 1 (60-325 mesh) purchased from Fisher Scientific (Fair Lawn, NJ).

Characterization Data for Piperidine Products:

Representative procedure for Mo-catalyzed asymmetric ring-opening/cross-metathesis reactions: In a N_2-filled glovebox, Mo complex **6** (2.4 mg, 0.0030 mmol, 0.05 equiv.) was dissolved in C_6H_6 (0.250 mL) in a 4-mL vial. Styrene (68.0 μL, 0.593 mmol, 10 equiv.) was added to this solution by syringe. The resulting mixture was allowed to stir for 1 min, and added by syringe to a solution of azabicycle **7** (15.0 mg, 0.0592 mmol) in C_6H_6 (0.250 mL) in a 4-mL vial.[3] The reaction mixture was allowed to stir for 1 h. At this time, the vial was removed from the glovebox, and the volatiles were removed in vacuo. The resulting dark brown residue was purified by silica gel chromatography (9:1 CH_2Cl_2:MeOH) to afford piperidine **8** as colorless oil (20.4 mg, 0.0570 mmol, 95%).

Piperidine 8. IR (neat): 2949 (s), 2930 (s), 2772 (s), 2363 (s), 1646 (w). ^1H NMR (400 MHz, $CDCl_3$): d 7.39–7.20 (m, 5H), 6.48 (d, *J* = 15.6 Hz, 1H), 6.15 (dd, *J* = 15.6, 8.8 Hz, 1H), 5.79 (ddd, *J* = 17.2, 10.4, 8.8 Hz, 1H), 5.15 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.05 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.77–3.68 (m, 1H), 2.77–2.60 (m, 1H), 2.58–2.48 (m, 1H), 2.18 (s, 3H), 1.87–1.78 (m, 2H), 1.60–1.51 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): d 141.9, 137.1, 133.4, 130.7, 128.7, 127.6, 126.4, 115.7, 68.7, 67.6, 66.7,

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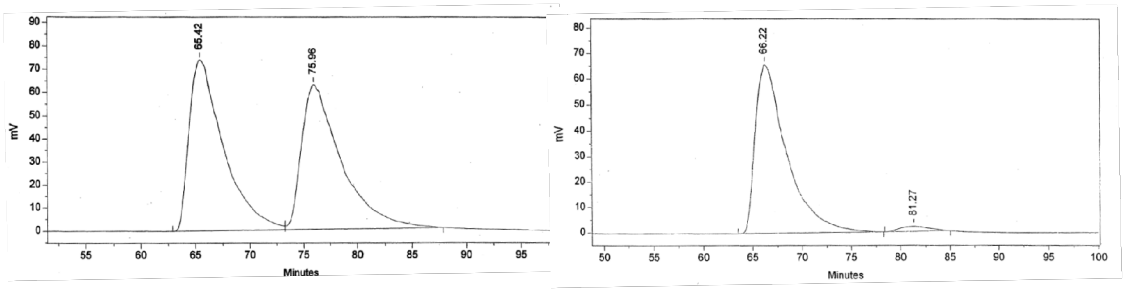
[1] W. C. P. Tsang, J. A. Jernelius, G. A. Cortez, G. S. Weatherhead, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, 2591–2596.

[2] a) J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955. b) J. J. Van Veldhuizen, J. E. Campbell, R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.

[3] Mo complex **6** is pre-treated with styrene to ensure formation of the chiral Mo benzylidene complex.

43.0, 42.9, 41.5, 25.9, 18.3, –4.39. HRMS EI (*m/z*) Calcd for $C_{22}H_{35}NOSi$ 357.2488 $(M)^+$, Found 357.2482.

Representative procedure for deprotection of secondary alcohols in piperidine products:[4] A 4-mL vial was charged with **8** (20.4 mg, 0.0570 mmol), THF (0.500 ml), and TBAF (285 μL, 0.285 mmol, a 1.00 M solution in THF, 5 equiv.). The vial was tightly sealed with a Teflon cap, placed in a heating mantle at 65 °C, and the reaction mixture was allowed to stir for 1 h. At this time, the vial was cooled to 22 °C over 15 min, and the volatiles were removed in vacuo. The resulting yellow residue was purified by silica gel chromatography (4:1 CH_2Cl_2:MeOH) to afford piperidine **8-OH** as colorless oil (13.2 mg, 0.0541 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.38–7.21 (m, 5H), 6.49 (d, *J* = 15.6 Hz, 1H), 6.16 (dd, *J* = 15.6, 8.8 Hz, 1H), 5.76 (ddd, *J* = 17.2, 10.4, 8.8 Hz, 1H), 5.17 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.07 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.82–3.70 (m, 1H), 2.77–2.60 (m, 1H), 2.58–2.48 (m, 1H), 2.20 (s, 3H), 2.00–1.92 (m, 2H), 1.55–1.43 (m, 3H). $[\alpha]_D^{20}$ –75.2 (*c* = 0.2, $CHCl_3$) for a sample of *94% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 99:1 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *94% ee*.



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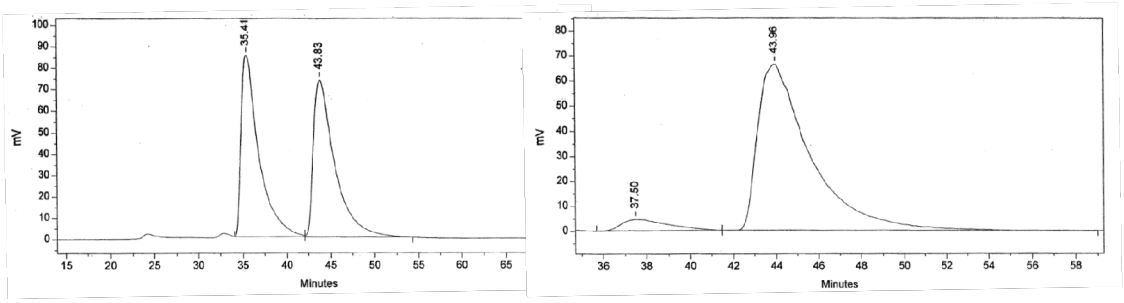
1	66.225		0.0000	0.000	1455198.0	97.304	BB	3.682	65865.27	97.070
2	81.270		0.0000	0.000	403201.3	2.696	BB	3.380	1988.16	2.930

Piperidine 9 (homodimer byproduct). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.39–7.20 (m, 5H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.13 (dd, *J* = 16.0, 8.8 Hz, 1H), 5.79 (ddd, *J* = 16.0, 10.0, 8.8 Hz, 1H), 5.52–5.47 (m, 2H), 5.13 (dd, *J* = 16.0, 1.6 Hz, 1H), 5.03 (dd, *J* = 10.0, 1.6 Hz, 1H), 3.75–3.62 (m, 2H), 2.68–2.60 (m, 1H), 2.58–2.40 (m, 3H) 2.18–2.11 (m, 6H), 1.84–1.20 (m, 8H), 0.87 (s, 18H), 0.05 (s, 12H).

Piperidine 10. IR (neat): 2955 (s), 2923 (s), 2854 (s), 2772 (m), 1508 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 6.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.00 (dd, *J* = 8.8, 7.2 Hz, 1H), 5.76 (ddd, *J* = 17.2, 10.0, 8.8 Hz, 1H), 5.18 (d, *J* = 17.2 Hz, 1H), 5.07 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.80–3.67 (m, 1H), 2.63–2.55 (m,

[4] Determination of *ee* of **8**, as in some other cases, involved the piperidine derived from TBAF deprotection of the secondary alcohol.

1H), 2.55–2.46 (m, 1H), 2.18 (s, 3H), 1.86–1.76 (m, 2H), 1.61–1.48 (m, 2H), 0.85 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 141.9, 131.1, 130.2, 129.9, 127.6, 115.6, 114.2, 68.7, 67.6, 66.8, 55.5, 43.1, 42.9, 41.4, 26.0, 18.3, –4.4. HRMS ES (*m/z*) Calcd for $C_{28}H_{40}NOSi$ 434.2879 $(M+H)^+$, Found 434.2889. $[\alpha]_D^{20}$ –31.99 (*c* = 0.5, $CHCl_3$) for a sample of *89% ee*. Determination of enantiomeric excess of **10** involved the piperidine derived from TBAF deprotection of the secondary alcohol in **10**. **Piperidine 10-OH** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.29 (m, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.43 (d, *J* = 15.6 Hz, 1H), 6.01 (dd, *J* = 15.2, 8.4 Hz, 1H), 5.78 (ddd, *J* = 17.2, 10.0, 8.8 Hz, 1H), 5.17 (d, *J* = 17.2 Hz, 1H), 5.07 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.80–3.70 (m, 1H), 2.70–2.60 (m, 1H), 2.60–2.50 (m, 1H), 2.22 (s, 3H), 2.02–1.90 (m, 2H), 1.60–1.44 (m, 3H). The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 99:1 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *89% ee*.



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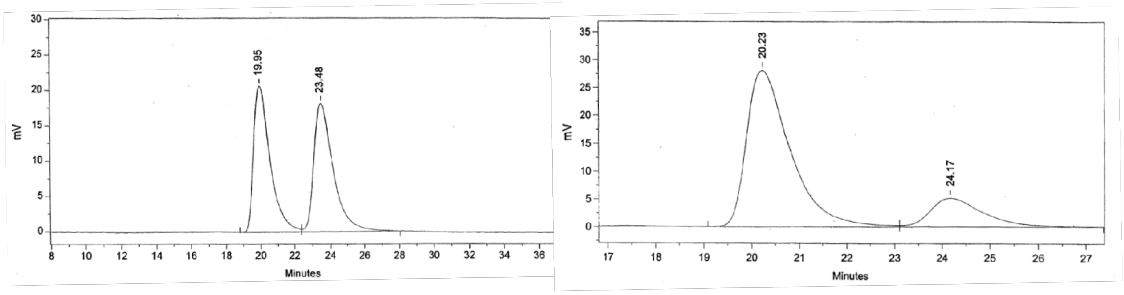
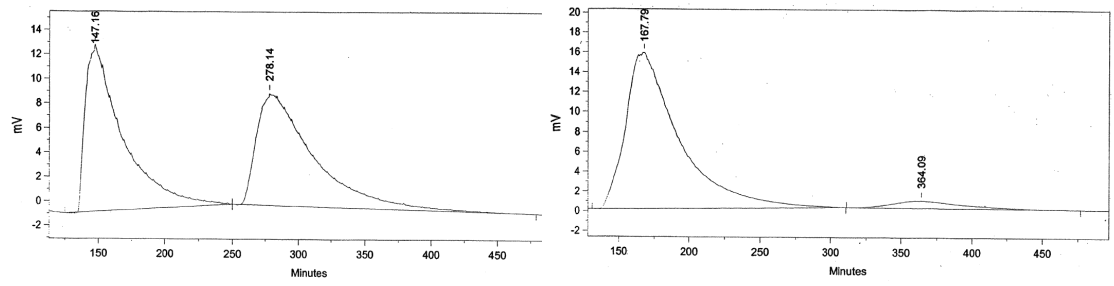
1	37.501		0.0000	0.000	691439.1	5.726	BB	2.510	4591.43	6.475
2	43.961		0.0000	0.000	11384710.0	94.274	BB	2.861	66319.44	93.525

Piperidine 11. IR (neat): 2949 (s), 2924 (s), 2779 (m), 1615 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 15.6 Hz, 1H), 6.26 (dd, *J* = 8.4, 7.2 Hz, 1H), 5.76 (ddd, *J* = 18.0, 9.6 Hz, 1H), 5.17 (d, *J* = 17.2 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 3.75–3.67 (m, 1H), 2.69–2.61 (m, 1H), 2.54–2.47 (m, 1H), 2.17 (s, 3H), 1.86–1.74 (m, 2H), 1.62–1.48 (m, 2H), 0.87 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 140.6, 136.2, 129.4, 126.5, 125.7, 125.6, 123.0, 115.9, 68.6, 67.5, 66.6, 42.9, 42.8, 41.5, 25.9, 18.3, –4.4. HRMS ES (*m/z*) Calcd for $C_{23}H_{35}NOF_3Si$ 426.2440 $(M+H)^+$, Found 426.2451. Determination of enantiomeric excess of **11** involved the piperidine derived from TBAF deprotection of the secondary alcohol in **11**. **Piperidine 11-OH** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.26 (dd, *J* = 8.8, 8.0 Hz, 1H), 5.76 (ddd, *J* = 18.0, 9.6 Hz, 1H), 5.18 (d, *J* = 16.4 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 3.81–3.75 (m, 1H), 2.76–2.66 (m, 1H), 2.60–2.50 (m, 1H), 2.19 (s, 3H), 1.99–1.94 (m, 2H), 1.57–1.46 (m, 2H), 1.29–1.20 (br s, 1H). $[\alpha]_D^{20}$ –15.40 (*c* = 0.5, $CHCl_3$) for a sample of *64% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *64% ee*.



PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	20.228		0.0000	0.000	1803209.0	81.866	BV	1.072	28035.64	84.481
2	24.166		0.0000	0.000	399424.8	18.134	VB	1.293	5150.06	15.519

Piperidine 12. IR (neat): 2949 (s), 2924 (s), 2855 (s), 2363 (m), 1463 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54–7.40 (m, 2H), 7.26–7.22 (m, 1H), 7.09–7.05 (m, 1H), 6.83 (d, *J* = 15.6 Hz, 1H), 6.09 (dd, *J* = 8.8, 6.8 Hz, 1H), 5.77 (ddd, *J* = 18.4, 9.6 Hz, 1H), 5.15 (d, *J* = 17.2 Hz, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 3.75–3.68 (m, 1H), 2.73–2.67 (m, 1H), 2.53–2.48 (m, 1H), 2.19 (s, 3H), 1.85–1.76 (m, 2H), 1.60–1.47 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 136.9, 136.3, 132.1, 129.5, 128.9, 127.7, 127.1, 123.6, 115.8, 68.6, 67.5, 66.6, 43.0, 42.9, 41.5, 25.9, 18.3, –4.4. HRMS ES (*m/z*) Calcd for $C_{22}H_{35}NOSiBr$ 436.1671 $(M+H)^+$, Found 436.1678. $[\alpha]_D^{20}$ –30.89 (*c* = 0.5, $CHCl_3$) for a sample of *88% ee*. Determination of enantiomeric excess of **12** involved the piperidine derived from TBAF deprotection of the secondary alcohol in **12**. **Piperidine 12-OH** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.50 (m, 2H), 7.30–7.24 (m, 1H), 7.11–7.07 (m, 1H), 6.85 (d, *J* = 15.6 Hz, 1H), 6.12 (dd, *J* = 8.8, 6.8 Hz, 1H), 5.77 (ddd, *J* = 18.4, 9.6 Hz, 1H), 5.18 (d, *J* = 17.2 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 3.83–3.70 (m, 1H), 2.80–2.70 (m, 1H), 2.62–2.55 (m, 1H), 2.23 (s, 3H), 2.03–1.93 (m, 2H), 1.60–1.52 (m, 2H), 1.40 (br s, 1H). The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralcel OJ (4.6 x 250 mm), 99.8:0.2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *88% ee*.



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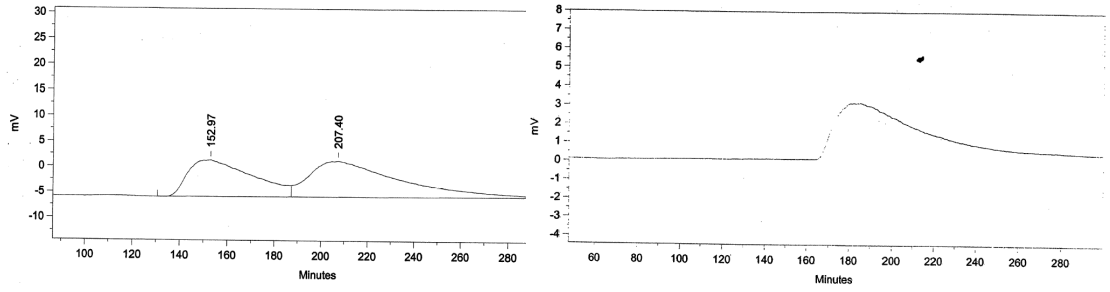
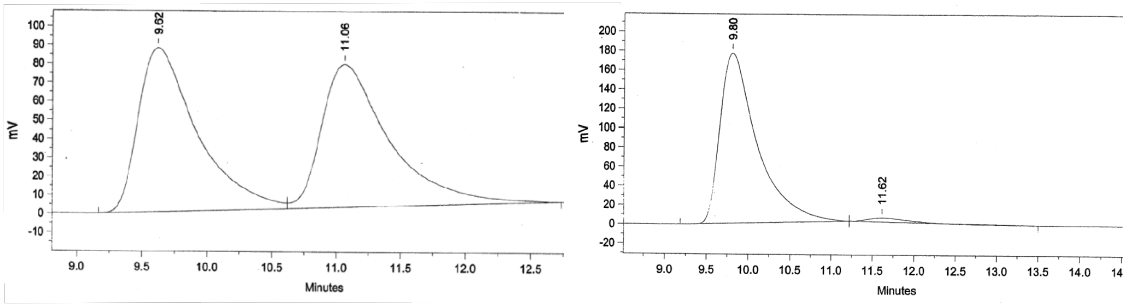
2	364.092		0.0000	0.000	2594679.0	5.887	BB	56.947	759.38	4.605

Piperidine 13. IR (neat): 2949 (s), 2930 (s), 2854 (s), 2364 (m), 2338 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.40 (m, 1H), 7.18–7.12 (m, 3H), 6.81 (d, *J* = 16.0 Hz, 1H),

6.03 (dd, *J* = 8.8, 7.2 Hz, 1H), 5.77 (ddd, *J* = 18.4, 10.0 Hz, 1H), 5.15 (d, *J* = 16.8 Hz, 1H), 5.04 (d, *J* = 10.4 Hz, 1H), 3.73 (dddd, *J* = 15.2, 10.4, 4.8 Hz, 1H), 2.68–2.62 (m, 1H), 2.53–2.48 (m, 1H), 2.35 (s, 3H), 2.19 (s, 3H), 1.86–1.76 (m, 2H), 1.63–1.49 (m, 2H), 0.88 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 136.1, 135.3, 134.7, 130.4, 128.5, 127.5, 126.3, 125.8, 115.7, 68.7, 67.6, 67.0, 43.2, 43.0, 41.5, 25.9, 20.0, 18.3, –4.4. HRMS ES (*m/z*) Calcd for $C_{23}H_{38}NOSi$ 372.2723 $(M+H)^+$, Found 372.2728. Determination of the enantiomeric excess of **13** involved the piperidine derived from TBAF deprotection of the secondary alcohol in **13**. **Piperidine 13-OH** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.40 (m, 1H), 7.18–7.13 (m, 3H), 6.73 (d, *J* = 15.6 Hz, 2H), 6.11–6.04 (m, 1H), 5.88–5.76 (m, 1H), 5.20 (d, *J* = 17.2 Hz, 1H), 5.10 (d, *J* = 9.6 Hz, 1H), 3.85–3.75 (m, 1H), 2.80–2.55 (m, 2H), 2.34 (s, 3H), 2.26 (s, 3H), 2.04–1.95 (m, 2H), 1.70–1.50 (m, 2H), 1.22 (br s, 1H). The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OJ (4.6 x 250 mm), 99.8:0.2 hexanes:*i*-PrOH, 1 mL/min, λ = 254 nm, *>98% ee*.



Piperidine 14. IR (neat): 3030 (m), 2943 (s), 2924 (s), 2773 (s), 1451 (s). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.30–7.10 (m, 10H), 6.41 (d, *J* = 16.0 Hz, 1H), 6.10 (dd, *J* = 8.8, 7.2 Hz, 1H), 5.72 (ddd, *J* = 18.8, 10.4, 8.8 1H), 5.10 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.00 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.48 (s, 2H), 3.48–3.38 (m, 1H), 2.59–2.53 (m, 1H), 2.47–2.41 (m, 1H), 2.12 (s, 3H), 2.04–1.92 (m, 2H), 1.57–1.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): d 142.9, 139.8, 137.6, 134.3, 130.6, 128.9, 128.6, 127.7, 127.6, 127.5, 126.7, 114.9, 74.5, 69.6, 67.5, 66.6, 41.6, 40.0, 39.9. HRMS EI (*m/z*) Calcd for $C_{23}H_{28}NO$ 334.2171 $(M+H)^+$, Found 334.2174. $[\alpha]_D^{20}$ –14.80 (*c* = 0.1, $CHCl_3$) for a sample of *96% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *96% ee*.



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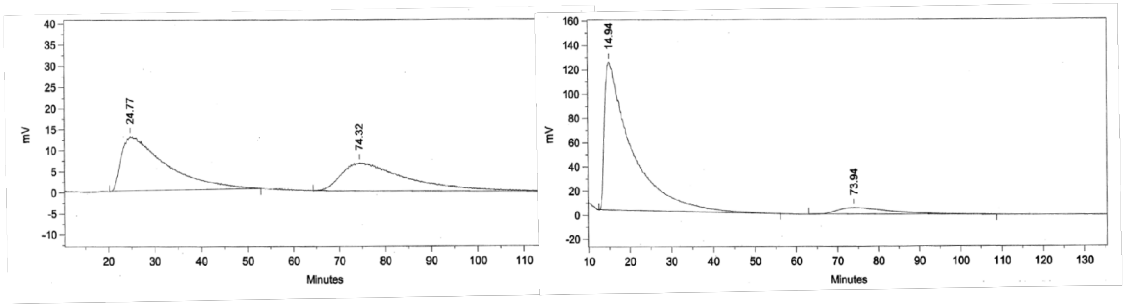
1	9.804		0.0000	0.000	5478271.0	98.076	BV	0.517	176525.90	- 0.002
3	11.615		0.0000	0.000	107475.1	1.924	BB	0.427	4191.67	0.000

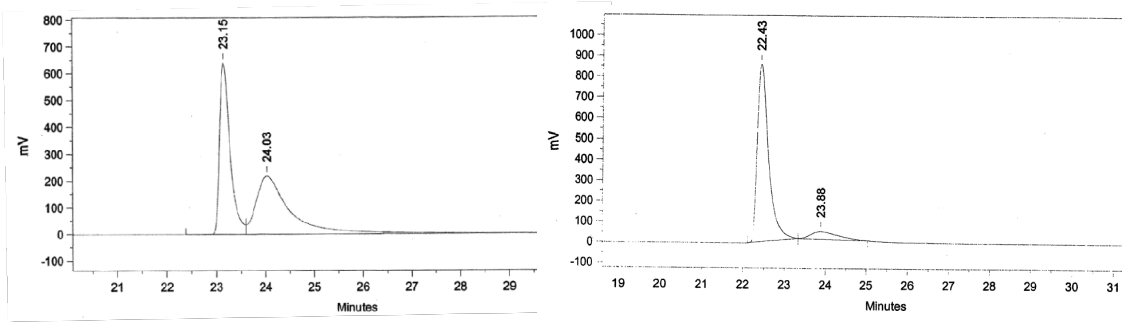
Piperidine 15. IR (neat): 2961 (s), 2930 (s), 2854 (m), 1256 (m). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.40–7.20 (m, 5H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.15 (dd, *J* = 9.7, 7.2 Hz, 1H), 5.74 (ddd, *J* = 18.4, 9.6 Hz, 1H), 5.15 (d, *J* = 16.8 Hz, 1H), 5.03 (d, *J* = 10.0 Hz, 1H), 4.07 (br s, 1H), 3.10–3.00 (m, 1H), 2.99–2.90 (m, 1H), 2.20 (s, 3H), 1.80–1.55 (m, 4H), 0.91 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): d 142.0, 137.2, 133.7, 130.8, 128.7, 127.5, 126.4, 115.9, 64.9, 63.0, 62.2, 41.8, 40.9, 26.0, 18.3, –4.60, –4.70. HRMS EI (*m/z*) Calcd for $C_{22}H_{36}NOSi$ 358.2566 $(M+H)^+$, Found 358.2571. Determination of enantiomeric excess of **15** involved the piperidine derived from TBAF deprotection of the secondary alcohol in **15**. **Piperidine 15-OH** ^{1}H NMR (400 MHz, $CDCl_3$, TMS): d 7.38–7.20 (m, 5H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.12 (dd, *J* = 16.0, 8.8 Hz, 1H), 5.72 (ddd, *J* = 18.4, 9.6 Hz, 1H), 5.20 (d, *J* = 17.2 Hz, 1H), 5.06 (d, *J* = 16 Hz, 1H), 4.17 (s, 1H), 3.10–3.00 (m, 1H), 2.98–2.90 (m, 1H), 2.25 (s, 3H), 1.80–1.70 (m, 4H). $[\alpha]_D^{20}$ –79.98 (*c* = 0.01, $CHCl_3$) for a sample of *84% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OJ (4.6 x 250 mm), 97:3 hexanes:*i*-PrOH, 1.2 mL/min, λ = 254 nm, *84% ee*.



PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	14.942		0.0000	0.000	55070540.0	92.332	BB	7.541	121712.40	95.793
2	73.940		0.0000	0.000	4573726.0	7.668	BB	14.259	5345.85	4.207

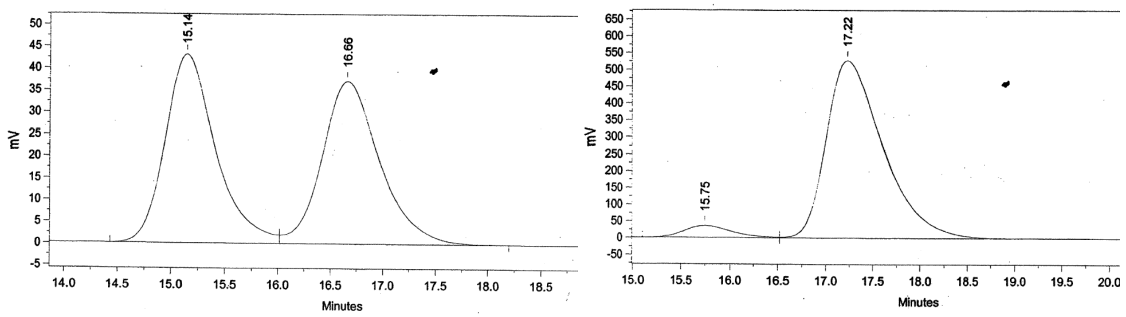
Piperidine 16. IR (neat): 2930 (s), 2848 (m) 2773 (s), 1445 (w). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.40–7.20 (m, 5H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.18 (dd, *J* = 8.8, 7.2 Hz, 1H), 5.82–5.73 (m, 1H), 5.15 (dd, *J* = 17.6, 2.0 Hz, 1H), 5.03 (dd, *J* = 10.4, 1.6 Hz, 1H),

2.60–2.54 (m, 1H), 2.47–2.42 (m, 1H), 2.21 (s, 3H), 1.80–1.42 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): d 142.7, 137.4, 134.3, 130.5, 128.8, 127.5, 126.4, 115.5, 69.4, 68.5, 42.3, 33.9, 33.8, 24.0. HRMS EI (*m/z*) Calcd for $C_{16}H_{21}N$ 227.1674 $(M)^+$, Found 227.1679. $[\alpha]_D^{20}$ –31.19 (*c* = 0.5, $CHCl_3$) for a sample of *80% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *80% ee*.



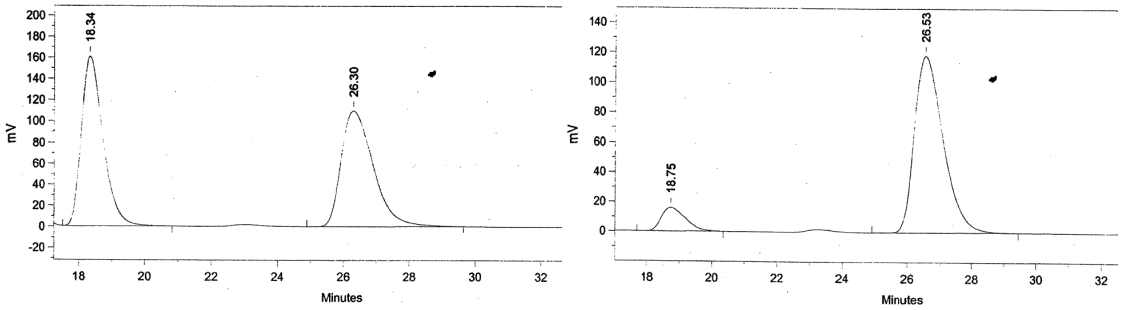
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	22.426		0.0000	0.000	16050500.0	90.266	BB	0.312	856385.20	95.775
2	23.882		0.0000	0.000	1730848.0	9.734	BB	0.764	37781.50	4.225

Piperidine 17. IR (neat): 2955 (m), 2923 (m), 2855 (w), 1697 (s), 1073 (s). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.37–7.19 (m, 10H), 6.68 (dd, *J* = 16.0, 8.4 Hz, 1H), 6.40 (d, *J* = 15.2 Hz, 1H), 6.28 (ddd, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.19–5.01 (m, 4H), 4.98–4.92 (m, 1H), 4.86–4.78 (m, 1H), 4.16 (dddd, *J* = 7.6, 4.4, Hz 1H), 2.10–1.84 (m, 4H), 0.89 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): d 156.1, 141.5, 137.4, 136.9, 132.8, 130.5, 128.6, 128.5, 128.2, 128.0, 127.3, 126.5, 114.9, 67.4, 64.9, 52.4, 52.3, 36.7, 36.5, 26.0, 18.2, –4.7. HRMS EI (*m/z*) Calcd for $C_{28}H_{36}NO_3Si$ 462.2465 $(M–H)^+$, Found 462.2464. $[\alpha]_D^{20}$ 92.8 (*c* = 0.08, $CHCl_3$) for a sample of *90% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 99.5:0.5 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *90% ee.*



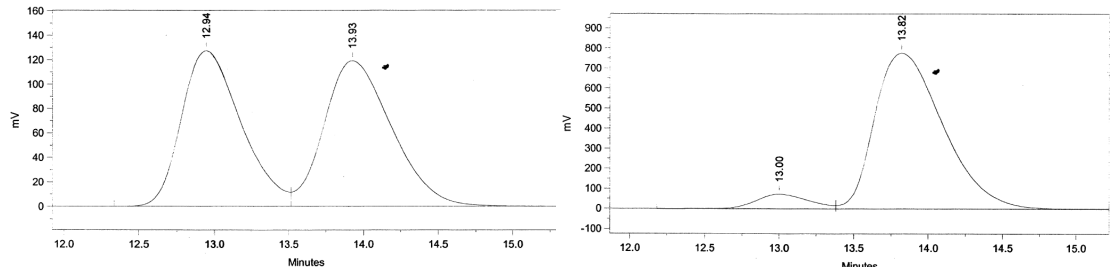
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	15.745		0.0000	0.000	1212583.0	5.205	BV	0.561	36049.54	6.398
2	17.224		0.0000	0.000	22083840.0	94.795	VB	0.698	527388.10	93.602

Piperidine 18. IR (neat): 2949 (s), 2924 (s), 2855 (m), 1697 (s), 1508 (s), 1250 (s). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.38–7.30 (m, 7H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.53 (dd, *J* = 16.0, 8.4 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.28 (ddd, *J* = 17.2, 10.4, 7.6 Hz, 1H), 5.19–5.08 (m, 2H), 5.07–5.06 (m, 1H), 5.01 (dd, *J* = 12.0, 1.2 Hz, 1H), 4.94–4.90 (m, 1H), 4.84–4.80 (m, 1H) 4.18–4.11 (m, 1H), 3.80 (s, 2H), 2.05–1.85 (m, 4H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 189.7, 158.8, 141.2, 130.4, 129.7, 128.2, 127.8, 127.7, 127.4, 114.5, 113.6, 67.0, 64.7, 55.1, 52.2, 36.5, 36.3, 25.7, 17.9, –0.2, –5.1. HRMS ES (*m/z*) Calcd for $C_{30}H_{42}NO_4Si$ 508.2883 $(M+H)^+$, Found 508.2871. $[\alpha]_D^{20}$ 23.99 (*c* = 0.1, $CHCl_3$) for a sample of *80% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD-R (4.6 x 250 mm), 99.5:0.5 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *80% ee*.



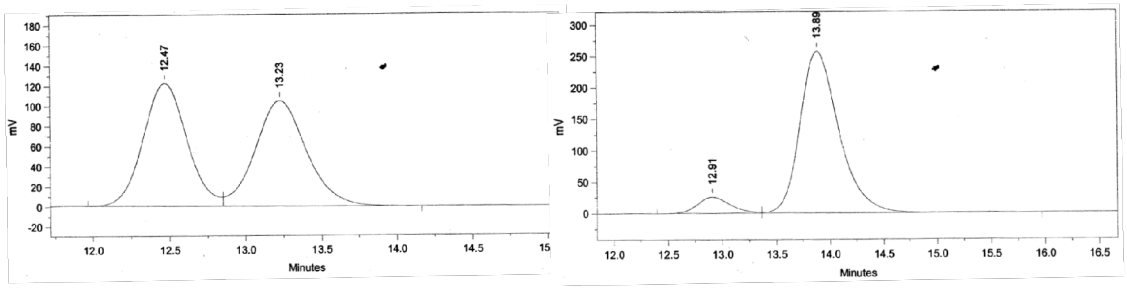
PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	18.745		0.0000	0.000	799673.6	9.855	BB	0.836	15946.00	11.885
2	26.533		0.0000	0.000	7314482.0	90.145	BB	1.031	118218.20	88.115

Piperidine 19. IR (neat): 2949 (s), 2924 (s), 2855 (m), 1697 (s), 1400 (m), 1073 (s). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.38–7.26 (m, 7H), 7.20–7.10 (m, 2H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.55 (dd, *J* = 16.0, 8.0 Hz, 1H), 6.28 (ddd, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.15 (s, 2H), 5.10 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.02 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.00–4.96 (m, 1H), 4.84–4.80 (m, 1H), 4.16 (dddd, *J* = 8.0, 4.4 Hz, 1H), 2.22 (s, 3H), 2.05–1.87, (m, 4H) 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 141.5, 137.0, 136.4, 135.5, 134.0, 130.2, 128.6, 128.2, 128.1, 128.0, 127.2, 126.0, 125.6, 114.9, 67.4, 65.0, 52.6, 52.4, 36.8, 36.6, 26.0, 19.9, 18.2, 0.2, –4.8. HRMS ES (*m/z*) Calcd for $C_{30}H_{42}NO_3Si$ 492.2934 $(M+H)^+$, Found 492.2928. $[\alpha]_D^{20}$ 47.99 (*c* = 0.3, $CHCl_3$) for a sample of *86% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD-R (4.6 x 250 mm), 99.5:0.5 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *86% ee*.



PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	13.002		0.0000	0.000	1815532.0	6.861	BV	0.413	73257.07	8.624
2	13.819		0.0000	0.000	24645590.0	93.139	VB	0.529	776164.30	91.376

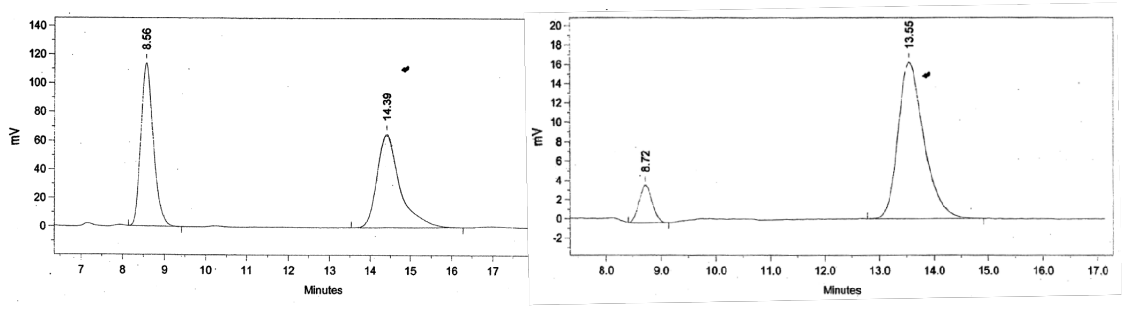
Piperidine 20. IR (neat): 2955 (s), 2924 (s), 2861 (m), 1697 (s), 1400 (s). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.37–7.22 (m, 10H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.24 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.93 (ddd, *J* = 16.4, 10.8, 6.0 Hz, 1H), 5.21–5.10 (m, 5H), 5.00–4.98 (m, 1H), 4.17 (dddd, *J* = 11.2, 7.2, 4.0 Hz, 1H), 2.10–2.05 (m, 2H), 1.83–1.67 (m, 2H), 0.90 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): d 155.8, 139.7, 137.0, 136.8, 130.8, 130.6, 128.7, 128.6, 128.1, 128.0, 127.7, 126.5, 115.5, 67.5, 62.3, 53.6, 53.5, 38.5, 38.0, 26.0, 18.3, –4.37. HRMS EI (*m/z*) Calcd for $C_{29}H_{39}NO_3Si$ 477.2693 $(M)^+$, Found 477.2699. $[\alpha]_D^{20}$ 39.9 (*c* = 0.01, $CHCl_3$) for a sample of *85% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 99.5:0.5 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *85% ee*.



PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	12.910		0.0000	0.000	530022.3	7.598	BV	0.343	25752.90	9.093
2	13.886		0.0000	0.000	6445757.0	92.402	VB	0.417	257468.20	90.907

Piperidine 21. IR (neat): 2955 (m), 2930 (m), 2855 (w), 1697 (s), 1073 (s). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.34–7.19 (m, 5H), 6.65 (dd, *J* = 15.6 8.4 Hz, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.22 (ddd, *J* = 17.6, 10.4, 7.6 Hz, 1H), 5.10 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.03 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.96–4.90 (m, 1H), 4.82–4.76 (m, 1H), 4.20–4.09 (m, 2H), 2.02–1.84 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): d 156.3, 141.6, 137.5, 133.1, 130.3, 128.5, 127.3, 126.5, 114.7, 64.9, 61.4, 52.2, 52.1, 36.7, 36.5, 26.0, 18.2, 14.8, –4.8. HRMS EI (*m/z*) Calcd for $C_{24}H_{37}NO_3Si$ 415.2543 $(M)^+$, Found 415.2551. Determination of enantiomeric excess of

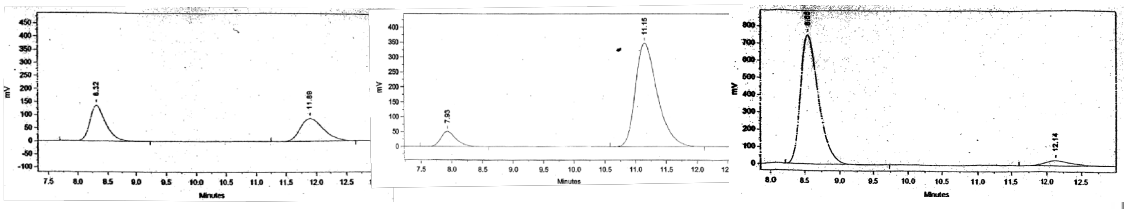
21 involved the piperidine derived from TBAF deprotection of the secondary alcohol in **21**. **Piperidine 21-OH** ^{1}H NMR (400 MHz, $CDCl_3$): d 7.36–7.21 (m, 5H), 6.54–6.48 (m, 2H), 6.20 (ddd, *J* = 16.8, 10.0, 6.4 Hz, 1H), 5.18 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.10 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.00–4.94 (m, 1H), 4.86–4.80 (m, 1H), 4.24–4.20 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.12–1.96 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 3H). $[\alpha]_D^{20}$ 27.0 (*c* = 0.1, $CHCl_3$) for a sample of *79% ee*. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 90:10 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *79% ee*.



PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	8.721		0.0000	0.000	62366.3	10.522	BB	0.266	3910.58	19.444
2	13.551		0.0000	0.000	530377.3	89.478	BB	0.546	16201.38	80.556

Representative procedure for Ru-catalyzed asymmetric ring-opening/cross-metathesis: Ru complex **1a** (6.0 mg, 0.0084 mmol, 0.10 equiv.) was dissolved in styrene (96.0 μL, 0.839 mmol, 10 equiv.) in a 4-mL vial. The resulting mixture was added by syringe to a solution of the azabicyclic precursor to **22** (22.0 mg, 0.0839 mmol) in styrene (96.0 μL, 0.839 mmol, 10 equiv.) in a 4-mL vial. The mixture was allowed to stir for 24 h, upon which time the volatiles were removed in vacuo. The resulting dark brown residue was purified by silica gel chromatography (CH_2Cl_2) to yield piperidine **22** (19.8 mg, 0.0570 mmol, 70%) as colorless oil. IR (neat): 2936 (w), 1697 (s), 1407 (m). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.39–7.21 (m, 10H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.34 (dd, *J* = 16.0, 7.1, Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.20 (d, *J* = 12.3 Hz, 1H), 5.14 (d, *J* = 12.3 Hz, 1H), 5.14–5.10 (m, 2H), 5.05–4.97 (m, 1H), 4.88–4.85 (m, 1H), 1.94–1.72 (m, 5H), 1.60–1.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): d 156.0, 139.6, 137.2, 136.9, 130.6, 128.6, 128.5, 128.1, 128.0, 127.5, 126.4, 115.4, 67.3, 53.5, 52.5, 52.4, 29.1, 28.3, 15.1. HRMS EI (*m/z*) Calcd for $C_{23}H_{25}NO_2$ 347.1892 $(M)^+$, Found 347.1885. $[\alpha]_D^{20}$ 53.58 (*c* 0.05, $CHCl_3$) for a sample of *82% ee* accessed with **6**. $[\alpha]_D^{20}$ –78.14 (*c* = 1.0, $CHCl_3$) for a sample of *-90% ee* obtained with **1a**. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *82% ee* with **6**, *-90% ee* with **1a**.

Authentic Racemic ***82% ee*** ***-90% ee***

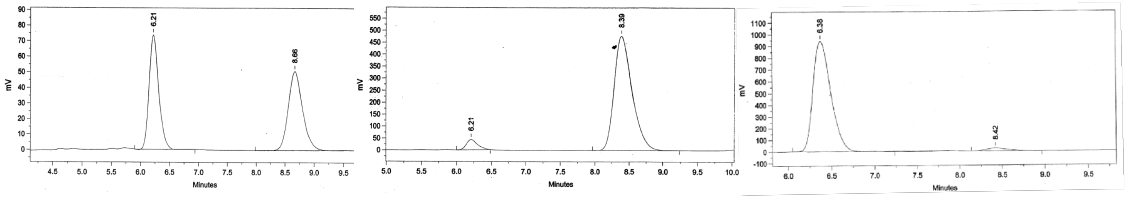


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	7.928		0.0000	0.000	870515.8	9.133	BB	0.284	51077.28	12.820
2	11.151		0.0000	0.000	8660895.0	90.867	BB	0.416	347339.50	87.180

Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
8.549		0.0000	0.000	13830810.0	94.676	BB	0.307	750064.50	96.283
12.136		0.0000	0.000	777764.2	5.324	BB	0.448	28953.87	3.717

Piperidine 23. IR (neat): 2936 (w), 2357 (m), 2332 (m), 1690 (s). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.34–7.18 (m, 5H), 6.48 (d, *J* = 16.4 Hz, 1H), 6.31 (dd, *J* = 16.4, 9.2 Hz, 1H), 5.95 (ddd, *J* = 17.6, 10.8, 6.0 Hz, 1H), 5.14 (dd, *J* = 17.6, 1.6 Hz, 1H), 5.11 (dd, *J* = 10.8, 1.6 Hz, 1H), 4.97–4.92 (m, 1H), 4.82–4.77 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 1.92–1.62 (m, 4H), 1.58 (br, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): d 156.3, 139.8, 137.4, 131.0, 130.4, 128.6, 127.5, 126.4, 115.3, 61.4, 52.4, 52.2, 29.0, 28.3, 15.2, 14.8. HRMS EI (*m/z*) mass Calcd for $C_{18}H_{23}NO_2$ 285.1720 $(M)^+$, Found 285.1728. $[\alpha]_D^{20}$ 52.87 (*c* = 1.0, $CHCl_3$) for a sample of *90% ee* obtained with **6**. $[\alpha]_D^{20}$ –129.05 (*c* = 1.0, $CHCl_3$) for a sample of *-94% ee* accessed with **1a**. The optical purity of this compound was determined by HPLC analysis in comparison with authentic racemic material, shown below: Chiralpak OD (4.6 x 250 mm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min, λ = 254 nm, *90% ee* with **6**, *-94% ee* with **1a**.

Authentic Racemic ***90% ee* with 6** ***-94% ee* with 1a**

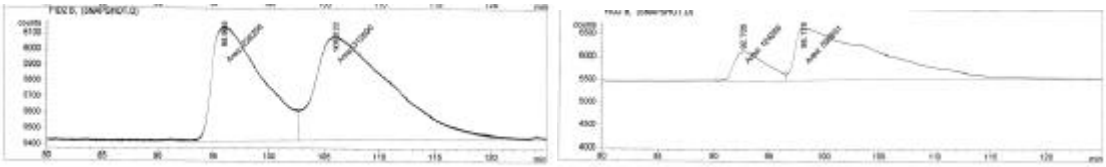


PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	6.214		0.0000	0.000	488872.4	5.401	BB	0.188	43369.62	8.327
2	8.389		0.0000	0.000	8562277.0	94.599	BB	0.299	477439.50	91.673

PK#	Ret Time	Name	Amount	Amount%	Area	Area%	Type	Width	Height	Height%
1	6.379		0.0000	0.000	13312090.0	97.190	BB	0.236	938960.90	97.663
2	8.420		0.0000	0.000	384856.5	2.810	BB	0.285	22466.99	2.337

Piperidine 24. IR (neat): 2924 (s), 2848 (s), 2766 (w), 1099 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73 (ddd, *J* = 18.8, 10.0 Hz, 1H), 5.50 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.28 (dd, *J* = 15.2, 8.8 Hz, 1H), 5.12 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.02 (dd, *J* = 10.0, 1.2 Hz, 1H), 3.65 (dddd, *J* = 15.2, 10.4, 4.4 Hz, 1H), 2.43 (dd, *J* = 8.8 Hz, 1H), 2.36 (dd, *J* = 8.8 Hz, 1H),

2.11 (s, 3H), 1.98–1.86 (m, 1H), 1.80–1.58 (m, 6H), 1.54–1.38 (m, 2H), 1.30–1.00 (m, 6H), 0.87 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2, 138.0, 130.8, 115.4, 68.8, 67.6, 66.6, 43.3, 43.1, 41.1, 40.3, 33.0, 26.4, 26.2, 26.0, 18.3, –4.4. HRMS ES (*m/z*) Calcd for $C_{22}H_{42}NOSi$ 364.3035 $(M+H)^+$, Found 364.3036. Determination of enantiomeric excess of **24** involved the piperidine derived from TBAF deprotection of the secondary alcohol in **24**. **Piperidine 24-OH.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (ddd, *J* = 18.8, 9.2 Hz, 1H), 5.51 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.31 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.15 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.05 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.75–3.67 (m, 1H), 2.52–2.40 (m, 2H), 2.14 (s, 3H), 1.98–1.86 (m, 2H), 1.72–1.60 (m, 5H), 1.51–1.36 (m, 2H), 1.25–0.83 (m, 6H). The optical purity of this compound was determined by GC analysis in comparison with authentic racemic material, shown below: Alltech Associated Chiral Betadex 120 column (30 m x 0.25 mm), 130 °C, 20 psi.



Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	95.985	MF	5.2590	2.26258e5	717.04938	41.98139
2	106.022	FM	7.8456	3.12690e5	664.26031	58.01861

Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	92.705	MF	3.2765	1.24266e5	632.10815	17.16621
2	98.178	FM	8.7504	5.99631e5	1142.10352	82.83379

1,3-Aminoalcohol 27. A 25-mL round-bottom flask was charged with Na (40.0 mg, 1.74 mmol, 48 equiv.), the flask was fitted with a cold-finger condenser, and the reaction vessel was cooled to –78 °C in a dry ice/acetone bath. Ammonia gas (*circa* 5 mL) was condensed into the flask; upon dissolution of Na in liquid ammonia the solution became deep blue in appearance. Piperidine **8** (13.0 mg, 0.0360 mmol) in *t*-BuOH (0.120 mL), and Et_2O (2.0 mL) was added to this solution by syringe. The reaction mixture was allowed to stir at –78 °C for 15 min, after which time the reaction was quenched by the addition of CH_2Cl_2 (10 mL), and the cold bath was removed. The resulting mixture was warmed to 22 °C over 15 min, and was transferred to a 60-mL separatory funnel. At this instance, H_2O (10 mL) was transferred to the separatory funnel, and the resulting biphasic layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to deliver analytically pure amino alcohol **27** as yellow oil (11.0 mg, 0.0304 mmol, 85%). IR (neat): 2949 (s), 2924 (s), 2855 (m), 2773 (w), 1105 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.16 (m, 5H), 5.77 (ddd, *J* = 17.6, 10.4, 8.4 Hz, 1H), 5.12 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.04 (dd, *J* = 10.4, 0.8 Hz), 3.65–3.59 (m, 1H), 2.78–2.70 (m, 1H), 2.61–2.50 (m, 1H), 2.18 (s, 3H), 2.05–1.42 (m, 7H), 0.89 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.5, 125.9, 115.4, 69.3, 67.3, 66.0, 61.5, 42.0, 40.2, 38.5, 35.7, 31.3, 29.8, 26.0, 18.3, 15.4, –4.40. HRMS ES (*m/z*) mass Calcd for $C_{22}H_{37}NOSi$ 359.2644 $(M-H_2)^+$, Found 359.2647.

Alcohol 28. A 25-mL round-bottom flask was charged with piperidine **23** (0.250 g, 0.876 mmol), THF (9.0 mL), 9-borabicyclo[3.3.1]nonane (0.130 g, 1.10 mmol, 1.25

equiv.), and allowed to stir for 1 h. At this time, the reaction mixture was cooled to –10 °C in a NaCl/ice bath, and the reaction was quenched by the (slowly and sequentially) addition of a 30% aqueous solution of H_2O_2 (0.880 mL, 1 mL/mmol of **23**), and a 1.0 M solution of NaOH (0.880 mL, 1 mL/mmol of **23**). The resulting mixture was warmed to 22 °C over 30 min, after which time it was transferred to a 60-mL separatory funnel. At this point, EtOAc (15 mL), and a saturated aqueous solution of NaCl (10 mL) were transferred to the separatory funnel, and the resulting biphasic layers were separated. The organic layer was washed with H_2O (2 × 10 mL), dried ($MgSO_4$), filtered, and the volatiles were removed in vacuo. The resulting colorless residue was purified by silica gel chromatography (1:1 EtOAc:hexanes) to deliver **28** as colorless oil (0.258 mg, 0.850 mmol, 97%). IR (neat): 3446 (br), 2943 (m), 2867 (m), 1659 (s), 1413 (m). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.30–7.20 (m, 5H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.19 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.00–4.92 (br, 1H), 4.52–4.44 (m, 1H), 4.28–4.14 (m, 2H), 3.62–3.42 (m, 2H), 1.98–1.55 (m, 8H), 1.25 (t, *J* = 9.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): d 171.1, 136.8, 130.8, 130.1, 128.6, 127.6, 126.2, 61.9, 60.4, 58.8, 51.1, 46.7, 37.1, 29.4, 28.3, 21.0, 14.8, 14.7, 14.2. HRMS EI (*m/z*) Calcd for $C_{18}H_{25}NO_3$ 303.1834 $(M)^+$, Found 303.1833.

Piperidine *d*$_1$-29. In a N_2-filled glovebox, a 4-mL vial was charged with piperidine **28** (15.0 mg, 0.0494 mmol), THF (0.500 mL), and lithium aluminum hydride (6.0 mg, 0.099 mmol, 2 equiv.). The vial was tightly sealed with a Teflon cap, placed in a heating mantle at 65 °C, and the reaction mixture was allowed to stir for 1 h. At this point, the reaction mixture was cooled to 22 °C over 15 min, the vial was removed from the glovebox, and the reaction was quenched by the slow addition of MeOD[5] (0.500 mL). The resulting mixture was allowed to stir for 12 h. To this mixture was (slowly and sequentially) added H_2O (15.0 μL, 1 μL/mg of **28**), a 3.8 M solution of NaOH (45.0 μL, 3 μL/mg of **28**), and H_2O (15.0 μL, 1 μL/mg of **28**). The resulting mixture was subjected to vacuum filtration (to remove Al salts), and eluted with EtOAc. The filtrate was dried (Na_2SO_4), re-filtered, and the volatiles were removed in vacuo. The resulting colorless residue was purified by neutral alumina gel chromatography (20:1 CH_2Cl_2:MeOH) to provide piperidine ***d*$_1$-29** as colorless oil (11.8 mg, 0.0475 mmol, 95%). IR (neat): 3371 (br), 2930 (s), 2855 (m), 1055 (w). ^{1}H NMR (400 MHz, C_6D_6): d 7.20–7.10 (m, 5H), 3.92 (ddd, *J* = 10.4, 5.2 Hz, 1H), 3.86–3.79 (m, 1H), 2.52–2.42 (m, 2H), 2.30–2.20 (m, 1H), 2.02 (s, 3H), 1.59–0.86 (m, 8H). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): d 7.30–7.18 (m, 5H), 3.92 (ddd, *J* = 10.8, 5.2 Hz, 1H), 3.86–3.79 (m, 1H), 2.82–2.76 (m, 1H), 2.62–2.50 (m, 2H), 2.27 (s, 3H), 1.82–1.24 (m, 8H). ^{13}C NMR (100 MHz, C_6D_6): d 143.0, 129.0, 128.9, 126.3, 64.4, 62.9, 62.5, 36.3, 33.9, 32.1, 31.9, 31.7, 30.0, 26.2, 26.0, 25.4. HRMS

[5] MeOD was removed from a freshly opened ampule of 99.95 atom % D.

EI (*m/z*) Calcd for $C_{16}H_{25}DNO$ 249.2077 $(M+H)^+$, Found 249.2015. ^2H NMR (400 MHz, $CDCl_3$): d 2.50–2.40 (br s).

Piperidine 29. The procedure to synthesize piperidine **29** was identical to that used for the synthesis of ***d*$_1$-29**, however, MeOH was used to quench the reaction mixture. IR (neat): 3390 (br), 2930 (s), 2855 (m), 1457 (w), 1055 (w). ^1H NMR (400 MHz, C_6D_6): d 7.30–7.25 (m, 3H), 7.20–7.14 (m, 2H), 3.92 (ddd, *J* = 10.4, 5.2 Hz, 1H), 3.86–3.79 (m, 1H), 2.84–2.76 (br, 1H), 2.68–2.55 (m, 3H), 2.02 (s, 3H), 1.59–0.86 (m, 8H). ^1H NMR (400 MHz, $CDCl_3$): d 7.30–7.18 (m, 5H), 3.92 (ddd, *J* = 10.8, 5.2 Hz, 1H), 3.86–3.79 (m, 1H), 2.82–2.76 (m, 1H), 2.62–2.50 (m, 3H), 2.27 (s, 3H), 1.82–1.24 (m, 8H). ^{13}C NMR (100 MHz, C_6D_6): d 142.6, 128.5, 125.8, 94.5, 64.6, 63.2, 62.6, 36.1, 32.6, 32.0, 29.8, 26.0, 25.7, 24.9. HRMS EI (*m/z*) Calcd for $C_{16}H_{26}NO$ 248.2014 $(M+H)^+$, Found 248.2015.

Piperidine 30. In a N_2-filled glovebox, a 4-mL vial was charged with piperidine **28** (40.0 mg, 0.130 mmol), THF (1.30 mL), and lithium aluminum hydride (10.0 mg, 0.260 mmol, 2 equiv.). The vial was tightly sealed with a Teflon cap, placed in a heating mantle at 65 ^oC, and the mixture was allowed to stir for 1 h. At this moment, the reaction mixture was cooled to 22 ^oC over 15 min, the vial was removed from the glovebox, and O_2 (balloon passed through drying tube filled with P_2O_5) was bubbled through the reaction mixture for 1 h. To this mixture was (slowly and sequentially) added H_2O (40.0 μL, 1 μL/mg of **28**), a 3.8 M solution of NaOH (0.120 mL, 3 μL/mg of **28**), and H_2O (40.0 μL, 1 μL/mg of **28**). The resulting mixture was subjected to vacuum filtration (to remove Al salts), and eluted with EtOAc. The filtrate was dried (Na_2SO_4), re-filtered, and the volatiles were removed in vacuo. The resulting colorless residue was purified by neutral alumina gel chromatography (10:1 CH_2Cl_2:MeOH) to provide piperidine **30** as colorless oil (18.8 mg, 0.0715 mmol, 55%). IR (neat): 3370 (br), 2930 (s), 2855 (m), 1451 (w), 1055 (w). Isolated as a 1:1 mixture of diastereomers, ^1H NMR (400 MHz, $CDCl_3$, TMS): d 7.39–7.23 (m, 5H), 5.00 (t, *J* = 6.0 Hz, 0.5H), 4.92 (dd, *J* = 10.0, 3.6 Hz, 0.5H), 3.82–3.64 (m, 2H), 3.14–3.00 (m, 1H), 2.84–2.60 (m, 1H), 2.34 (s, 1.5H), 2.28 (s, 1.5H), 2.00–1.20 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): d 191.7, 145.9, 145.4, 128.8, 127.6, 127.4, 127.3, 126.2, 126.0, 75.6, 72.2, 64.1, 63.2, 62.9, 62.6, 62.3, 61.6, 61.3, 61.0, 60.9, 40.9, 40.8, 35.8, 35.4, 32.8, 30.3, 30.2, 26.7, 25.4, 25.3, 25.0, 24.2, 24.0. HRMS EI (*m/z*) mass Calcd for $C_{16}H_{25}NO_2$ 263.1885 $(M)^+$, Found 263.1883.

Piperidine 31. A 25-mL round-bottom flask was charged with **28** (317 mg, 1.05 mmol), CH_2Cl_2 (10.5 mL), NaOAc (85.0 mg, 1.05 mmol, 1 equiv.), powdered 4Å molecular sieves (15.9 mg, 5 wt. %), PCC (339 mg 1.58 mmol, 1.5 equiv.), and the mixture was allowed to stir for 2 h. To the reaction mixture was added Et_2O (5.0 mL), and resulting

mixture was allowed to stir for 15 min. At this time, the mixture was filtered through Florisil® by vacuum filtration, eluted with EtOAc, and the filtrate was collected in a 25-mL round-bottom flask. The volatiles were removed in vacuo. The resulting slightly yellow residue was dissolved in *t*-BuOH (5.3 mL), and tetramethylethylene (936 μL, 7.88 mmol, 7.5 equiv.). To this solution was added a solution of $NaClO_2$ (712 mg, 7.88 mmol, 7.5 equiv.), and NaH_2PO_4 (942 mg, 6.83 mmol, 6.5 equiv.) dissolved in H_2O (5.3 mL). The reaction mixture was allowed to stir for 1 h, after which time the volatiles were removed in vacuo. To this mixture was added EtOAc (10 mL), H_2O (10 mL), the mixture was transferred to a 60-mL separatory funnel, and the resulting biphasic layers were separated. The organic layer was washed with a saturated aqueous solution of NaCl (10 mL), H_2O (10 mL), dried (Na_2SO_4), filtered, and concentrated to yellow oil. This oil was dissolved in minimal EtOAc, transferred to a 25-mL round-bottom flask, and re-concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (10.5 mL). To this solution was added Et_3N (295 μL, 2.10 mmol, 2 equiv.), EDC (301 mg, 1.58 mmol, 1.5 equiv.), HOBt (241 mg, 1.58 mmol, 1.5 equiv.), *N*,*O*-dimethylhydroxylamine hydrochloride (154 mg, 1.58 mmol, 1.5 equiv.), and the mixture was allowed to stir for 2 h. At this time, the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL), the mixture was transferred to a 60-mL separatory funnel, and the resulting biphasic layers were separated. The organic layer was washed with H_2O (2 x 10 mL), dried (Na_2SO_4), and the volatiles were removed in vacuo. The resulting yellow residue was purified through silica gel chromatography (1:1 EtOAc:hexanes) to furnish **31** as colorless oil (295 mg, 0.819 mmol, 87% over three steps). IR (neat): 2936 (s), 1690 (s), 1407 (m), 1312 (m), 1268 (m). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.39–7.22 (m, 5H), 6.53 (d, *J* = 16.4 Hz, 1H), 6.32 (dd, *J* = 16.4, 5.2 Hz, 1H), 5.01 (br, 1H), 4.78 (br, 1H), 4.24–4.10 (m, 2H), 3.52 (s, 3H), 3.13 (s, 3H), 2.96–2.84 (m, 1H), 2.55 (dd, *J* = 14.8, 3.6 Hz, 1H), 2.05–2.0 (m, 1H), 1.82–1.60 (m, 5H), 1.30–1.22 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): d 156.0, 137.5, 137.2, 131.4, 130.1, 128.7, 127.6, 126.3, 61.5, 61.3, 60.5, 50.8, 47.5, 36.1, 32.2, 27.8, 21.2, 14.9, 14.6, 14.3. HRMS EI (*m/z*) mass Calcd for $C_{20}H_{28}N_2O_4Na$ 383.1947 $(M+Na)^+$, Found 383.1928.

Piperidine *d*$_1$-32.[6] A 4-mL vial was charged with **31** (20.0 mg, 0.0555 mmol), and THF (555 μL). Methylmagnesium chloride (a 2.40 M solution in THF, 25.4 μL, 0.0610 mmol, 1.1 equiv.) was added to this solution by syringe, and the mixture was allowed to stir for 30 min. At this time, the vial was relocated into a N_2-filled glovebox. To this mixture was added lithium aluminum hydride (2.1 mg, 0.055 mmol, 1 equiv.), the vial was tightly sealed with a Teflon cap, placed in a heating mantle at 65 ^{o}C, and allowed to stir for 1 h. At this point, the mixture was cooled to 22 ^{o}C over 15 min, the vial was removed from

[6] It is well established that β-amino ketones of this type readily epimerize to a mixture of 2,6-cis and trans piperidines. See: R. W. Bates, K. Sa-Ei, *Tetrahedron*, **2002**, *58*, 5957–5978.

the glovebox, and the reaction was quenched by the slow addition of MeOD[5] (500 μL). The resulting mixture was allowed to stir for 12 h. To this mixture was (slowly and sequentially) added H_2O (20 μL, 1 μL/mg of **31**), a 3.8 M solution of NaOH (60 μL, 3 μL/mg of **31**), and H_2O (20 μL, 1 μL/mg of **31**). The mixture was filtered under vacuum (to remove Al salts), and eluted with EtOAc. The resulting filtrate was dried (Na_2SO_4), re-filtered, and the volatiles were removed in vacuo. The resulting yellow residue was purified by neutral alumina gel chromatography (20:1 CH_2Cl_2:MeOH) to provide piperidine ***d*$_1$-32** as colorless oil (10.8 mg, 0.0415 mmol, 75%). IR (neat): 3345 (w), 2930 (s), 2855 (s), 1709 (s), 1451 (m). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): d 7.30–7.17 (m, 5H), 2.70–2.40 (m, 4H), 2.32 (s, 3H), 2.15 (s, 3H), 1.80–1.25 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): d 142.2, 133.6, 128.6, 128.5, 128.4, 125.9, 62.8, 59.6, 56.2, 55.0, 52.5, 50.5, 38.9, 38.1, 36.0, 32.3, 32.2, 31.8, 29.8, 27.4, 26.9, 24.7, 24.6, 19.7. HRMS EI (*m/z*) mass Calcd for $C_{17}H_{26}NOD$ 261.2077 $(M+H)^+$, Found 261.2085. ^{2}H NMR (400 MHz, $CDCl_3$): d 2.16 (br s).

Piperidine 32. IR (neat): 3320 (w), 2923 (s), 2855 (s), 1709 (s), 1602 (m). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.30–7.17 (m, 5H), 2.70–2.40 (m, 4H), 2.34 (s, 3H), 2.20 (s, 3H), 2.16 (d, J = 7.2 Hz, 2H), 1.80–1.25 (m, 8H). HRMS EI (*m/z*) mass Calcd for $C_{17}H_{25}NO$ 259.1936 $(M)^+$, Found 259.1935.

Absolute Stereochemistry Determination for Piperidine Products: The absolute stereochemistry for piperidine **28** was determined by chemical correlation to a previously reported compound with established absolute stereochemistry (Scheme 1).[7] Piperidine **28** of *80% ee* was prepared from piperidine **23** of *80% ee* (obtained from the AROM/CM catalyzed by **6**).[8] Oxidation of **28** to the corresponding aldehyde with PCC, followed by alkylation with diphenylzinc furnished a mixture of alcohols **33** and **34** that were separable by silica gel chromatography. Treatment of piperidine **34** with LAH[9] afforded piperidine **35**[10] of known absolute stereochemistry. The calculated enantiomeric excess for a sample of **35** of α_D^{20} 15.6 (c = 0.1, $CHCl_3$) is *76% ee*, correlating to our observed value of *80% ee*. The absolute stereochemistry of piperidines **17-22** is assigned by inference based on the absolute stereochemistry of piperidine **23**. Piperidine **23** was converted to piperidine **16** by LAH[9] reduction of the ethyl carbamate. The absolute stereochemistry of piperidines **8,** and **10-16** is assigned by inference based on the absolute stereochemistry of piperidine **23**.

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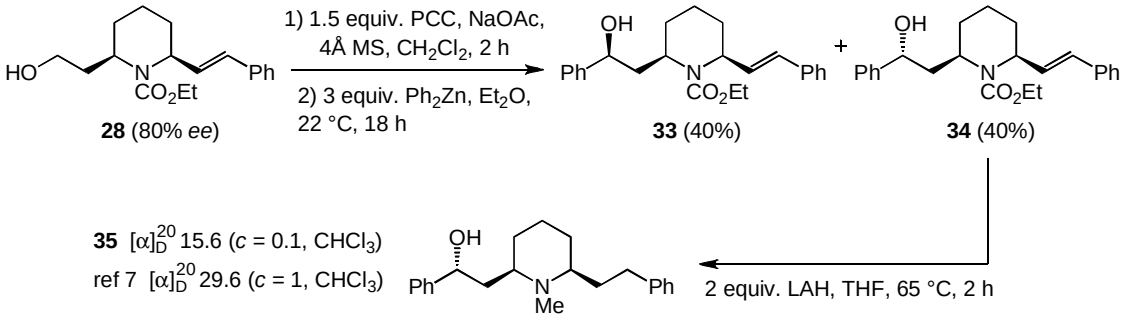
[7] D. Flammia, M. Dukat, M. I. Damaj, B. Martin, R. A. Glennon, *J. Med. Chem*. **1999**, *42*, 3726–3731.

[8] Under optimized reaction conditions established for catalytic AROM/CM, piperidine **23** is obtained in *90% ee*.

[9] The same reaction conditions used in the formation of **29** were followed.

[10] The spectral data for **35** have been reported in ref. 7.



Piperidines 33 and 34. In a N_2-filled glovebox, diphenylzinc (22.0 mg, 0.0990 mmol, 3 equiv.) was added to a solution of the aldehyde derived from **28** (10.0 mg, 0.0330 mmol, 1 equiv.) in Et_2O (0.400 mL) and the reaction mixture was allowed to stir for 18 h. At this time, the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (2 mL) and diluted with Et_2O (2 mL), the mixture was transferred to a 30-mL separatory funnel, and the resulting biphasic layers were separated. The organic layer was washed with H_2O (2 x 10 mL), dried (Na_2SO_4), and the volatiles were removed in vacuo. The resulting colorless residue was purified through silica gel chromatography (1:5 EtOAc:hexanes) to furnish **33** as colorless oil (5.0 mg, 0.013 mmol, 40%, TLC R_f = 0.35) and **34** as colorless oil (5.0 mg, 0.013 mmol, 40%, TLC R_f = 0.2). ^{1}H NMR of **33** (400 MHz, $CDCl_3$): d 7.39–7.27 (m, 5H), 7.13–7.09 (m, 5H), 6.65 (d, *J* = 15.6 Hz, 1H), 6.38 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.08–4.26 (m, 3H), 4.24–4.18 (m, 2H), 2.20 (dd, *J* = 12.8, 1.6 Hz, 1H), 2.00–1.90 (m, 1H), 1.84–1.70 (m, 2H), 1.66–1.1.50 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 0.90–0.78 (m, 2H). ^{1}H NMR of **34** (400 MHz, $CDCl_3$): d 7.36–7.21 (m, 10H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.24 (dd, *J* = 16.0, 7.2 Hz, 1H), 4.96–4.86 (m, 1H), 4.70–4.64 (m, 1H), 4.46–4.40 (m, 1H), 4.25–4.13 (m, 2H), 2.26–1.90 (m, 2H), 1.80–1.70 (m, 2H), 1.60–1.54 (m, 2H), 1.34–1.22 (m, 3H), 0.90–0.80 (m, 2H).

SUPPORTING INFORMATION. PART B

Synthesis and Characterization of Azabicyclic Substrates

Please Note: Piperidine products are numbered as they appear in the text. Azabicyclic substrates and their corresponding precursors, discussed below, are identified alphabetically.

Synthesis and spectral data for azabicyclic substrates that deliver piperidines 16, 22, and 23:

Preparation of azabicycle **D** was previously reported from azabicycle **C** (*vide infra*).[11] However, the cost of the commercially available starting material (6-*exo*-hydroxytropinone, $200/g from Aldrich) and the length of the reported synthetic route prompted us to develop an alternative route to azabicycle **C**, shown in Scheme 1 (*vide infra*).

A modified procedure for the Robinson-type annulation[12] of allylamine with 2,5-dimethoxyfuran, and acetonedicarboxylic acid afforded **A**, which was used in the subsequent step without purification. Wolff-Kischner reduction of **A** provided intermediate **B**, which was also taken forward without purification. A two-step, one-pot procedure was then performed to obtain azabicycle **C**; a single purification was required in the sequence carried out to arrive at **C**. To this end, treatment of **B** with ethylchloroformate, followed by treatment with mesyl chloride provided pure **C** after silica gel chromatography (34% overall yield). It is worth noting that an advantage of our synthesis for **C** is that intermediate **B** can be utilized to access different azabicyclic derivatives; the amino group in **B** can be selectively functionalized prior to functionalization of the carbinol.

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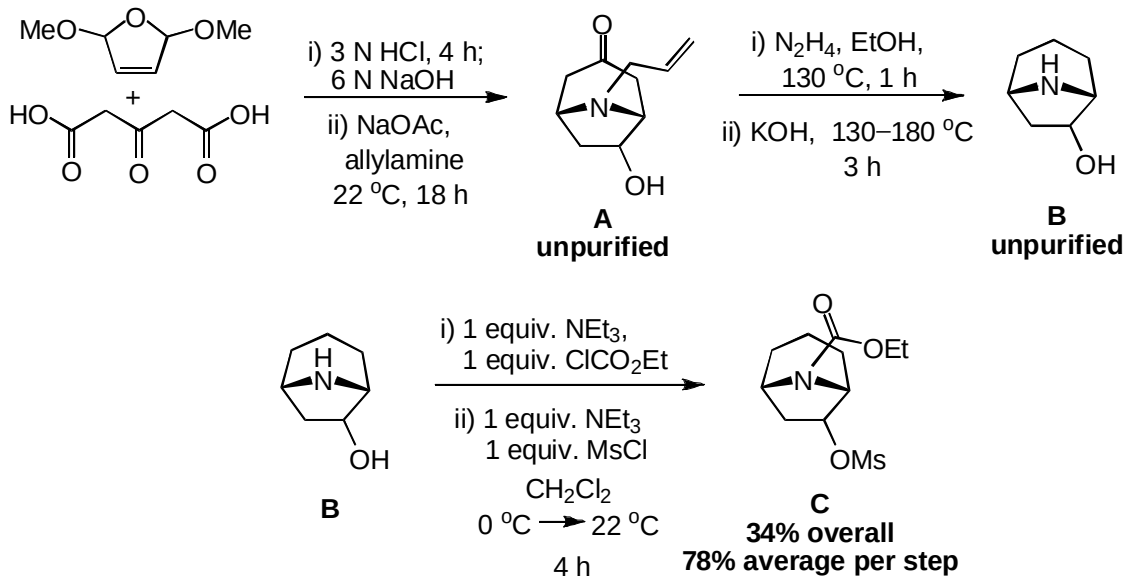
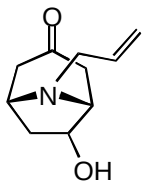
[11] S. Bai, R. Xu, G. Chu, X. Zhu, *J. Org. Chem.* **1996**, *61*, 4600–4606.
[12] L. Zhao, K. M. Johnson, M. Zhang, J. Flippen-Anderson, A. P. Kozikowski, *J. Med Chem.* **2000**, *43*, 3283–3294.

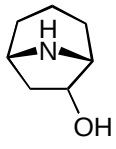
Scheme 1





A

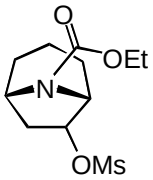
Azabicycle A. 2,5-Dimethoxyfuran (20.0 g, 0.150 mol) was dissolved in a 3.0 N solution of HCl (280 mL) in a 500-mL Erlenmeyer flask, and was allowed to stir for 4 h. At this time, a 6.0 N solution of NaOH (140 mL) was added to this solution, and the resulting solution was allowed to stir for 30 min. At this period, the mixture was added to a solution of NaOAc (98.4 g, 1.20 mol, 8 equiv.), allylamine (22.5 mL, 0.300 mol, 2 equiv.), and acetonedicarboxylic acid (43.8 g, 0.300 mol, 2 equiv.) in distilled H_2O (2.0 L) in a 4-L Erlenmeyer flask. The reaction mixture was allowed to stir for 18 h. To this mixture was added K_2CO_3 (25 g, 1.25 wt %), NaCl (25 g, 1.25 wt %), and the resulting mixture was allowed to stir for 1 h, after which time it was transferred to a 4-L separatory funnel, and washed with CH_2Cl_2 (6 × 500 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford **A** as viscous brown oil (20.0 g); **A** was used in the subsequent reaction without purification. IR (neat): 3408 (br), 2948 (m), 1709 (s), 1413 (m), 1344 (m). ^{1}H NMR (400 MHz, $CDCl_3$): d 6.5.95 (dddd, J = 16.4, 12.8, 10.4, 6.4 Hz, 1H), 5.32–5.25 (m, 2H), 4.07 (dd, J = 6.8, 2.4 Hz, 1H), 3.69 (br, 1H), 3.52–3.40 (m, 5H), 2.68–2.56 (m, 2H), 2.26–1.94 (m, 2H), 1.80 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4, 135.3, 117.3, 74.9, 66.1, 56.9, 51.2, 44.4, 42.1, 40.7. HRMS ES (*m/z*) Calcd for $C_{10}H_{15}NO_2$ 182.1181 $(M)^+$, Found 182.1175.



B

Azabicycle B. A 500-mL round-bottom flask was charged with azabicycle **A** (20.0 g, 0.110 mol), anhydrous EtOH (200 mL), hydrazine hydrate (48.0 mL, 0.990 mol, 9 equiv.), the flask was fitted with a reflux condenser, and the

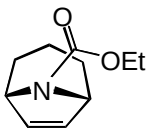
mixture was allowed to stir at 120 °C for 1.5 h. At this time, EtOH was removed in vacuo to yield viscous dark brown oil. To this oil was added powdered KOH (56.0 g, 0.990 mol, 9 equiv.),[13] and the resulting mixture was allowed to stir at 130 °C for 1 h, at 160 °C for 1 h, and at 180 °C for 2.5 h. After this period, the reaction mixture was cooled to 22 °C, and the reaction was quenched by the addition of H_2O (200 mL). The resulting mixture was transferred to a 1-L separatory funnel, and washed with CH_2Cl_2 (6 × 500 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to give **B** as viscous brown oil (14.0 g); **B** was used in the next step without purification. IR (neat): 3361 (br), 3261 (br), 2926 (s), 2864 (m), 1635 (w), 1536 (w), 1437 (m). ^{1}H NMR (400 MHz, $CDCl_3$): 5.48 (br s, 2H), 4.25–4.20 (m, 1H), 3.85–3.80 (m, 1H), 3.25 (br s, 1H), 2.20–2.15 (m, 1H), 1.90–1.82 (m, 1H), 1.80–1.65 (m, 2H), 1.62–1.42 (m, 2H), 1.40–1.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 73.7, 63.5, 55.5, 39.7, 29.5, 27.6, 16.8. HRMS ES (*m/z*) Calcd for $C_7H_{14}NO$ 128.1075 $(M+H)^+$, Found 128.1071.



C

Azabicycle C. A two-neck 250-mL round-bottom flask, fitted with an addition funnel, was charged with **B** (2.20 g, 15.9 mmol), CH_2Cl_2 (100 mL), Et_3N (2.22 mL, 15.9 mmol, 1 equiv.), and cooled to 0 °C in an ice bath. Ethyl chloroformate (1.51 mL, 15.9 mmol, 1 equiv.) was added to this solution dropwise by addition funnel; after the addition was complete the ice bath was removed, and the mixture was allowed to stir for 2 h. To this solution was added Et_3N (2.22 mL, 15.9 mmol, 1 equiv.), and the resulting solution was cooled to 0 °C in an ice bath. To this solution was added methanesulfonyl chloride (1.23 mL, 15.9 mmol, 1 equiv.) dropwise by addition funnel; after the addition was complete the ice bath was removed, and the mixture was allowed to stir for 2 h. At this time, the reaction was quenched by the addition of H_2O (75 mL), the mixture was transferred to a 250-mL separatory funnel, and the resulting biphasic layers were separated. The organic layer was washed with a saturated aqueous solution of NaCl (1 x 75 mL), and H_2O (1 x 75 mL), after which time the organic layer was dried ($MgSO_4$), filtered, and the volatiles were removed in vacuo. The resulting yellow oil was purified by silica gel chromatography (gradient elution, 1:1 Et_2O:hexanes followed by 100% Et_2O) to provide **C** as colorless oil (2.78 g, 9.00 mmol, 34% yield starting from 2,5-dimethoxyfuran). Compound **C** has been prepared previously; full characterization data for **C** were reported.[2] ^{1}H NMR (400 MHz, $CDCl_3$): d 5.13 (dd, *J* = 6.4, 3.2 Hz, 1H), 4.50–4.35 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.03 (s, 3H), 2.27–2.17 (m, 1H), 1.78–1.23 (m, 7H), 1.20 (t, *J* = 7.2 Hz, 3H).

[13] A mortar and pestle were used to crush KOH granules into a powder.



D

Azabicycle D (Substrate Precursor to Piperidine 23). A 100-mL round-bottom flask was charged with **C** (7.21 g, 23.3 mmol), collidine (30 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.20 mL, 27.9 mmol, 1.2 equiv.). The flask was fitted with a reflux condenser, and the reaction mixture was allowed to stir at 160 °C for 24 h. At this period, the reaction mixture was cooled to 22 °C, and the reaction was quenched by the addition of H_2O (100 mL). The resulting mixture was transferred to 250-mL separatory funnel, and was washed with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with a 0.5 M solution of HCl (4 x 50 mL), a solution of saturated aqueous $NaHCO_3$ (50 mL), and a solution of saturated aqueous NaCl (50 mL). The organic layer was dried (Na_2SO_4), filtered, and the volatiles were removed in vacuo. The resulting viscous brown oil was purified by silica gel chromatography (99:1 CH_2Cl_2:MeOH) to provide **D** as yellow oil (3.50 g, 19.3 mmol, 81% yield). Compound **D** has been prepared previously, and full characterization data for **D** were reported.[1] ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers: d 6.02–5.99 (m, 2H), 4.60–4.44 (m, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.80–1.30 (m, 6H), 1.25 (t, *J* = 7.2 Hz, 3H).

E

Azabicycle E (Substrate Precursor to Piperidine 16). Azabicycle **E** was prepared by lithium aluminum hydride reduction of the carbamate in **D**; for a representative procedure, see azabicycle **7** (*vide infra*). Compound **E** has been prepared previously, and full characterization data for **E** were reported.[14] ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (s, 2H), 3.40 (s, 2H), 2.20 (s, 3H), 1.80–1.20 (m, 6H).

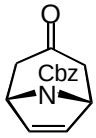
F

Azabicycle F (Substrate Precursor to Piperidine 22). The precursor to **F** (not shown) was prepared by utilizing CbzCl, in place of ethylchloroformate, in the carbamate formation of the sequence shown in Scheme 1 (*vide supra*). A 25-mL round-bottom flask was charged with the precursor to **F** (0.220 mg, 0.840 mmol), collidine (4.20 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.120 mL, 1.01 mmol, 1.2 equiv.), the flask was fitted with a reflux condenser, and the reaction mixture was allowed to stir at 160 °C for 24 h. At this time, the reaction mixture was cooled to 22 °C, and the reaction was quenched by the addition of a solution of saturated aqueous NH_4Cl (10 mL). The resulting mixture was transferred to a 50-mL separatory funnel, and washed with CH_2Cl_2 (4 x 10 mL). The combined organic layers were washed with a 0.5 M solution of HCl (3 x 15 mL), a saturated aqueous solution of $NaHCO_3$ (20 mL), and a solution of saturated aqueous NaCl (15 mL). The organic layer was dried (Na_2SO_4), filtered, and the volatiles were removed in vacuo. The resulting brown residue was purified by silica gel chromatography (gradient elution, 1:9 Et_2O:hexanes followed by 1:1 Et_2O:hexanes) to provide **F** as colorless oil (0.140 g, 0.580 mmol, 70% yield). IR (neat):

[14] N. M. Howarth, C. R. Smith, J. R. Malpass, *Tetrahedron* **1998**, *54*, 10899–10914.

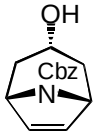
2939 (m), 2858 (w), 1704 (s), 1418 (s), 1306 (s), 1095 (s). ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers: δ 7.39–7.28 (m, 5H), 6.09–6.01 (m, 2H), 5.17 (s, 2H), 4.60–4.56 (m, 2H), 1.82–1.63 (m, 3H), 1.47–1.43 (m, 1H), 1.35–1.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 137.0, 130.5, 130.1, 128.4, 127.9, 127.8, 66.4, 58.5, 58.5, 24.4, 23.5, 16.3. HRMS ES (*m/z*) Calcd for $C_{15}H_{17}NO_2$ 243.1254 $(M)^+$, Found 243.1259.

Synthesis and spectral data for azabicyclic substrates that deliver piperidines 8, 10-15, and 17-21:



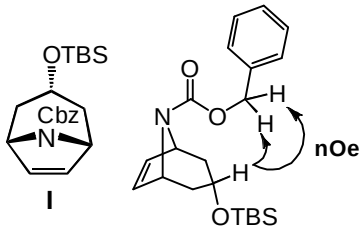
G

For the preparation of azabicyclic substrates that provide 2,4,6-substituted piperidines, we utilized intermediate azabicycle **G**, which has been previously prepared.[5]



H

Azabicycle H. A two-neck 200 mL round-bottom flask, fitted with addition funnel, was charged with **G** (1.00 g, 3.89 mmol), THF (40 mL), and cooled to –78 °C in a dry ice/acetone bath. L-Selectride® (a 1.00 M solution in THF, 4.30 mL, 4.28 mmol, 1.1 equiv.) was added to this solution over 10 min by addition funnel, after which time the mixture was warmed to 22 °C, and the resulting mixture was allowed to stir for 1 h. At this period, the reaction mixture was cooled to 0 °C in an ice bath, and the reaction was quenched by the (slow and sequential) addition of a 1.0 M solution of NaOH (20 mL), and a solution of H_2O_2 (37 wt % in H_2O, 20 mL). The resulting mixture was warmed to 22 °C, and was allowed to stir for 15 min. At this time, EtOAc (20 mL), and a 1.0 M solution of HCl (20 mL) were added to this mixture. The resulting mixture was transferred to a 250-mL separatory funnel, and the resulting biphasic layers were separated. The organic layer was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the volatiles were removed in vacuo. The resulting yellow oil was purified by silica gel chromatography (3:2 EtOAc:hexanes) to provide **H** as colorless oil (0.811 g, 3.12 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): 1:1 mixture of carbamate rotamers, δ 7.37–7.31 (m, 5H), 6.43–6.30 (m, 2H), 5.17 (s, 2H), 4.67–4.60 (m, 2H), 3.97–3.91 (m, 1H), 2.34–2.14 (m, 2H), 1.82–1.76 (d, *J* = 14.8 Hz, 2H).

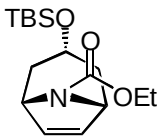


I

Azabicycle I (Substrate Precursor to Piperidines 17-19). Azabicycle **I** was prepared by TBS protection of the alcohol in azabicycle **H**.[6] The relative stereochemistry at the protected hydroxyl group carbon was determined by

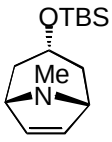
[5] C. E. Neipp, S. F. Martin, *J. Org. Chem.* **2003**, *68*, 8867–8878.
[6] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

nOe analysis. IR (neat): 2951 (m), 2920 (m), 2858 (m), 1710 (s), 1412 (m) 1300 (m), 1244 (m), 1089 (s). ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers: δ 7.37–7.26 (m, 5H), 6.04–5.99 (m, 2H), 5.18 (s, 2H), 4.68–4.65 (m, 2H), 3.99 (t, *J* = 5.2 Hz, 1H), 2.25–2.00 (m, 2H), 1.60–1.52 (m, 2H), 0.81 (s, 9H), –0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 137.1, 134.0, 133.6, 128.6, 128.0, 127.9, 66.7, 65.1, 57.4, 36.0, 35.2, 25.8, 17.9, –4.8. HRMS ES (*m/z*) Calcd for $C_{21}H_{31}NO_3Si$ 373.2073 M^+ Found 373.2071



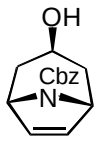
J

Azabicycle J (Substrate Precursor to Piperidine 21). Azabicycle **J** was prepared by utilizing the same sequence to form **I**, however, ethylchloroformate was used in the place of CbzCl at the beginning of the synthetic route. IR (neat): 2955 (m), 2923 (m), 2848 (w), 1702 (s). ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers: δ 6.18–6.02 (m, 2H), 4.59–4.44 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.99 (t, *J* = 5.6 Hz, 1H), 2.22–2.02 (m, 2H), 1.56 (d, *J* =14.4 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), –0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 133.6, 65.1, 60.9, 57.3, 57.2, 35.9, 35.1, 25.8, 17.9, 14.9, –4.8. HRMS ES (*m/z*) Calcd for $C_{16}H_{29}NO_3Si$ 311.1917 $(M)^+$, Found 311.1923.



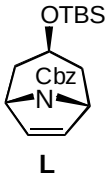
7

Azabicycle 7 (Precursor to Piperidines 8, 10-13). Representative procedure for lithium aluminum hydride reduction of carbamate protected azabicycles: In a N_2-filled glovebox, a 4-mL vial was charged with **I** (40.0 mg, 0.0800 mmol), THF (0.800 mL), and lithium aluminum hydride (6.1 mg, 0.16 mmol, 2 equiv.). The vial was tightly sealed with a Teflon cap, placed in a heating mantle at 65 °C, and the reaction mixture was allowed to stir for 1 h. At this point, the reaction mixture was cooled to 22 °C over 15 min, the vial was removed from the glovebox, and the reaction was quenched by the (slow and sequential) addition of H_2O (40.0 μL, 1 μL/mg of **I**), a 3.8 M solution of NaOH (0.120 mL, 3 μL/g of **I**) and H_2O (40.0 μL, 1 μL/mg of **I**). The resulting mixture was subjected to vacuum filtration (to remove Al salts), and eluted with EtOAc. The filtrate was dried (Na_2SO_4), re-filtered, and the volatiles were removed in vacuo. The resulting yellow residue was purified by silica gel chromatography (9:1 CH_2Cl_2:MeOH) to afford **7** as colorless oil (18.2 mg, 0.0720 mmol, 90%). IR (neat): 2930 (s), 2854 (m), 1256 (w), 1067 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (s, 2H), 3.95 (t, *J* = 5.6 Hz, 1H), 3.34 (br s, 2H), 2.27 (s, 3H), 2.13–2.07 (m, 2H), 1.57 (d, *J* = 14.0 Hz, 2H), 0.84 (s, 9H), –0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.4, 65.9, 64.2, 41.4, 37.1, 25.5, 17.6, –5.1. HRMS ES (*m/z*) Calcd for $C_{14}H_{27}NOSi$ 253.1857 $(M)^+$, Found 253.1862.

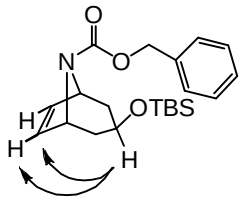


K

Azabicycle K. In a N_2-filled glovebox, a 25-mL round-bottom flask was charged with Sm (132 mg, 0.880 mmol), and 1,2-diiodoethane (248 mg, 0.880 mmol), after which the flask was capped with a rubber septa. The flask was removed from the glovebox, and purged under a steady stream of N_2 for 10 min, at which point THF (4.5 mL) was added to the mixture. After the resulting solution became deep blue (*circa* 1 h), a solution of **G** (0.100 g, 0.440 mmol) in isopropanol (33.0 μL, 0.440 mmol), and THF (4.0 mL) was added to the deep blue solution. At this moment, a reflux condenser was attached to the flask, and the reaction mixture was allowed to stir at 65 °C for 12 h. At this time, the reaction mixture was cooled to 22 °C, and the reaction was quenched by the addition of H_2O (10 mL). The resulting mixture was filtered through celite by vacuum filtration, and eluted with EtOAc. The volatiles were removed from the filtrate in vacuo, the resulting mixture was transferred to a 60-mL separatory funnel, and the mixture was washed with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield yellow oil. This oil was purified by silica gel chromatography (dry load, 1:1 to 1:2 hexanes:EtOAc to 100% EtOAc) to give **K** as colorless oil (68.0 mg, 0.260 mmol, 60%). IR (neat): 3404 (br), 2945 (w), 2926 (w), 1685 (s), 1418 (s) 1319 (m), 1288 (m), 1102 (s). ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers: δ 7.37–7.26 (m, 5H), 6.04–5.99 (m, 2H), 5.18–5.10 (m, 2H), 4.68–4.65 (m, 2H), 3.90 (dddd, *J* = 12.8, 12.8, 6.6, 6.4 Hz, 1H), 1.97 (dd, *J* = 12.8, 6.4 Hz, 2H), 1.86 (s, 1H), 1.64–1.58 (m, 1H), 1.51–1.45 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 136.7, 131.0, 130.8, 128.5, 128.1, 128.0, 66.8, 64.7, 57.2, 34.7, 33.9. HRMS ES (*m/z*) Calcd for $C_{15}H_{17}NO_3$ 259.1208 $(M)^+$, Found 259.1206.

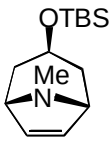


L



nOe

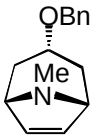
Azabicycle L (Substrate Precursor to Piperidine 20). Azabicycle **L** was prepared by TBS protection of the alcohol in azabicycle **K**.[6] The relative stereochemistry at the protected hydroxyl group carbon was determined by nOe analysis. IR (neat): 2951 (m), 2920 (m), 2858 (m), 1710 (s), 1412 (m) 1300 (m), 1244 (m), 1089 (s). ^{1}H NMR (400 MHz, $CDCl_3$), 1:1 mixture of carbamate rotamers: δ 7.37–7.26 (m, 5H), 6.04–5.99 (m, 2H), 5.18–5.10 (m, 2H), 4.68–4.65 (m, 2H), 3.94–3.90 (m, 1H), 1.85–1.77 (m, 2H), 1.72–1.50 (m, 2H), 0.86 (s, 9H), 0.00 (s, 6H) .^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 136.9, 131.1, 130.8, 128.5, 128.3, 128.0, 127.9, 66.7, 65.5, 65.4, 57.3, 57.1, 35.0, 34.9, 34.2, 25.8, 22.3, 18.1, –4.6. HRMS ES (*m/z*) mass Calcd for $C_{21}H_{31}NO_3Si$ 373.2073 $(M)^+$ Found 373.2068.



M

Azabicycle M (Substrate Precursor to Piperidine 15). Azabicycle **M** was prepared by lithium aluminum hydride reduction of the carbamate in **L**; for a

representative procedure, see azabicycle **7** (*vide supra*). IR (neat): 2930 (s), 2855 (m), 1470 (w), 1256 (m), 1099 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (s, 2H), 3.74 (dddd, *J* = 16.0, 8.8, 6.8 Hz, 1H), 3.47 (br s, 2H), 2.22 (s, 3H), 1.90–1.85 (m, 2H) 1.70–1.60 (m, 2H), 0.82 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.5, 66.5, 65.4, 40.5, 35.8, 25.9, 18.1, –4.4. HRMS ES (*m/z*) Calcd for $C_{14}H_{27}NOSi$ 253.1862 $(M)^+$, Found 253.1866.



N

Azabicycle N (Precursor to Piperidine 14). Azabicycle **N** was prepared by benzyl protection[7] of the alcohol in azabicycle **H**, followed by lithium aluminum hydride reduction of the carbamate; for a representative procedure, see azabicycle **7** (*vide supra*). IR 2930 (s), 2848 (m), 1451 (w), 1067 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.25 (m, 5H), 6.04 (s, 2H), 4.40 (s, 2H), 3.64 (t, *J* = 6.4 Hz, 1H), 3.41 (br s, 2H), 2.31 (s, 3H), 2.17–2.11 (m, 2H), 1.86 (d, *J* = 14 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.5, 132.1, 127.3, 127.2, 71.6, 70.1, 66.0, 53.6, 41.8, 33.7. HRMS ES (*m/z*) Calcd for $C_{15}H_{19}NO$ 229.1467 $(M)^+$, Found 229.1461.

[7] S. Czernecki, C. Georgoulis, C. Provelenghiou, *Tetrahedron Lett.* **1976**, *17*, 3535–3536.