**Direct Asymmetric Synthesis of β -Amino Ketones from Sulfinimines (*N*-Sulfinyl Imines).
Synthesis of (-)-Indolizidine-209B.**

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Experimental

General Procedures. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless otherwise noted. ^1H NMR and ^{13}C NMR spectra were recorded on a GE Omega 500, operating at 500 and 125 MHz, respectively. Dichloromethane was distilled over calcium hydride under an inert atmosphere. THF and ether were freshly distilled under argon from a purple solution of sodium and benzophenone. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. (*S*)-(+)-*N*-benzylidene-*p*-toluenesulfinamide (**3**) and (*S*)-(+)-*N*-acetylidene-*p*-toluenesulfinamide (**7**) were prepared as previously described.¹ (*E*)-4-(benzyloxy)-but-2-enal (**13**) was prepared by a literature method.²

(*S*,*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1,3-diphenylpropan-1-one (4a). General Procedure. In a 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 0.4 mL (0.2 mmol) of KHMDS (0.5 M solution in toluene) in THF (10 mL). The solution was cooled to -78 °C and 0.021 mL (0.18 mmol) of acetophenone was added dropwise via syringe. The reaction was stirred for 1 h at this temperature and 0.021 g (0.1 mmol) of (*S*)-(+)-**3** in THF (1 mL) was added dropwise via cannula. After 0.5 h the reaction mixture was quenched at -78 °C by addition of sat. NH_4Cl solution (0.5 mL) and H_2O (4 mL) was added. The solution was extracted with EtOAc (2 X 10 mL), the combined organic phases were dried (Na_2SO_4), and concentrated. Column chromatography (20% EtOAc/hexane) afforded 0.034 g (95%), >96% de of a white solid, mp 94-96 °C [lit.² mp 94-96 °C]; $[\alpha]_{\text{D}}^{20} +79.5$ (*c* 0.8, CHCl_3) (lit.³ $[\alpha]_{\text{D}}^{20} +80.1$ (*c* 1.25, CHCl_3)). Spectral properties were consistent with literature values.³

(*S*,*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-one (4b) - ether solvent. Purification (20% EtOAc/hexane) afforded 0.031 g (72%, 70% de) of a colorless oil; $[\alpha]_{\text{D}}^{20} +95.3$ (*c* 0.85, CHCl_3) [lit.³ $[\alpha]_{\text{D}}^{20} +94.2$ (*c* 1.0, CHCl_3)]. Spectral properties were consistent with literature values.³

(*S*,*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-ethyl-3-phenylpropan-1-one (4c). Chromatography (20% EtOAc/hexane) afforded 0.04 g (90%) of a colorless oil, $[\alpha]_{\text{D}}^{20} +77.6$ (*c* 0.75, CHCl_3); IR (neat) 3192, 2976, 1714; ^1H NMR δ 0.96 (t, *J* = 7.5 Hz, 3 H), 2.33 (q, *J* = 7.5 Hz, 2 H), 2.41 (s, 3 H), 2.98 (d, *J* = 6.4 Hz, 2 H), 4.92 (dd, *J* = 6.4, 5.5 Hz, 1 H), 5.02 (d, *J* = 5.5 Hz, 1 H), 7.3 (m, 3 H), 7.37 (t, *J* = 7.6 Hz, 2 H), 7.41 (d, *J* = 7.6 Hz, 2 H), 7.59 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR δ 7.8, 21.8, 37.1, 50.0, 55.1, 125.7, 127.8, 128.4, 129.2, 130.0, 141.2, 141.8, 142.8, 209.8. HRMS calcd. for $\text{C}_{18}\text{H}_{21}\text{NO}_2\text{S}$ (*M* + *Na*) 338.1191; found 338.1198.

(*S*,*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-(*n*-butyl)-3-phenylpropan-1-one (4d). Chromatography (20% EtOAc/hexane) 0.032 g (83%) of a colorless oil; $[\alpha]_{\text{D}}^{20} +73.5$ (*c* 0.72, CHCl_3); IR (neat) 3192, 2930, 1710; ^1H NMR δ 0.76 (t, *J* = 7.2 Hz, 3 H), 1.13 (m, 2 H), 1.37 (m, 2 H), 2.22 (t, *J* = 7.4 Hz, 2 H), 2.33 (s, 3 H), 2.89 (d, *J* = 6.2 Hz, 2 H), 4.84 (dd, *J* = 6.2, 5.5 Hz, 1

H), 4.95 (d, $J = 5.5$ Hz, 1 H), 7.20-7.37 (m, 7 H), 7.51 (d, $J = 7.9$ Hz, 2 H); ^{13}C NMR δ 14.2, 21.8, 22.6, 25.9, 43.7, 50.2, 55.1, 125.8, 127.8, 128.4, 129.1, 130.0, 141.2, 141.8, 142.8, 209.6. HRMS calcd. for $\text{C}_{20}\text{H}_{25}\text{NO}_2\text{S}$ ($M + \text{Na}$) 366.1504; found 366.1511.

(*S,S*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-aminopentane-2-one (8). In a 100-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 10 mL of KHMDS (0.5 M solution in toluene) in ether (40 mL). The solution was cooled to -78°C , 0.216 g (3.7 mmol) of anhydrous acetone was added dropwise, and the solution was stirred for 1 h. At this time 0.45 g (2.5 mmol) of (*S*)-(+)-7 in ether (5 mL) was added via cannula; the reaction mixture was stirred for 0.5 h and quenched by addition of sat. NH_4Cl (5 mL). The solution was warmed to rt, extracted with EtOAc (2 x 15 mL), and the combined organic phases were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. Chromatography (40% EtOAc/hexane) afforded 0.412 g (70%) of a white solid, mp $75-76^\circ\text{C}$; $[\alpha]_D^{20} +151$ (c 0.7, CHCl_3); IR (neat) 3207, 2970, 1713; ^1H NMR δ 1.34 (d, $J = 6.5$ Hz, 3 H), 2.08 (s, 3 H), 2.40 (s, 3 H), 2.66 (m, 2 H), 3.79 (m, 1 H), 4.59 (d, $J = 7.8$ Hz, 1 H), 7.29 (d, $J = 8.0$ Hz, 2 H), 7.56 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR δ 21.7, 22.7, 31.1, 47.5, 51.3, 126.0, 129.9, 141.7, 142.5, 207.6. HRMS calcd. for $\text{C}_{12}\text{H}_{17}\text{NO}_2\text{S}$ ($M + \text{H}$) 240.1058; found 240.1052.

(*S*)-(+)-1-(2-Methyl-1,3-dioxan-2-yl)-4-aminopropane (5). In a 100-mL, one-necked, round-bottomed flask equipped with magnetic stirring bar and Dean-Stark condenser was placed 0.185 g (0.77 mmol) of (*S,S*)-(+)-8, 0.221 g (1.16 mmol) of TsOH, and 0.293 g (3.85 mmol) of 1,3-propandiol (freshly distilled) in dry benzene (70 mL). After refluxing for 12 h, the solution was concentrated and the residue was dissolved in DCM (20 mL) and 15 mL of a 2.6 N of KOH solution was added. The solution was stirred for 0.5 h, the aqueous phase was extracted with DCM (2 X 10 mL), the combined organic phases were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. Chromatography (CHCl_3 saturated with NH_3) gave 0.78 g (72%) of a colorless oil; $[\alpha]_D^{20} +17.8$ (c 0.8, CHCl_3); [lit.⁴ $[\alpha]_D^{20} +17.5$ (c 2.45, CHCl_3)]. Spectral properties were consistent with literature values.⁴

(*R*)-(-)-*N*-(Hexanylidene)-*p*-toluenesulfinamide (10). In a 250-mL, one-necked, round-bottomed flask equipped with magnetic stirring bar and argon balloon was placed 2.0 g (13.0 mmol) of (*R*)-(-)-9 and 1.6 mL (13.0 mmol) of *n*-hexanal in DCM (80 mL). The solution was cooled to 0°C and 13.4 mL (63.6 mmol) of titanium(IV) ethoxide was added. The reaction was stirred for 3 h at rt at which time the solution was poured into H_2O (20 mL) in a 250-mL beaker with rapid stirring. DCM (40 mL) was added to the solution, which was filtered through a Buchner funnel using filter paper of medium porosity. The filter cake was rinsed with DCM (3 X 20 mL) and the organic phase was washed with H_2O (3 X 30 mL), brine (40 mL), dried (Na_2SO_4), and concentrated. Chromatograph (10% EtOAc/hexane) gave 2.4 g (79%) of a colorless oil; $[\alpha]_D^{20} -314.9$ (c 0.63, CHCl_3); IR (neat) 2961, 1620; ^1H NMR δ 0.87 (t, $J = 7.5$ Hz, 3 H), 1.30 (m, 4 H), 1.61 (m, 2 H), 2.40 (s, 3 H), 2.47 (td, $J = 7.5, 5.0$ Hz, 2 H), 7.31 (d, $J = 7.5$ Hz, 2 H), 7.56 (d, $J = 7.5$ Hz, 2 H), 8.22 (t, $J = 5.0$ Hz, 1 H); ^{13}C NMR δ 14.3, 21.8, 22.7, 25.5, 31.7, 36.3, 125.0, 130.2, 142.1, 142.3, 167.8. HRMS calcd. for $\text{C}_{13}\text{H}_{19}\text{NOS}$ ($M + \text{H}$) 238.1266; found 238.1274.

(*R,S*)-(-)-*N*-(*p*-Toluenesulfinyl)-5-amino-3-decanone (11). To a 250-mL, one-necked, round-bottomed flask equipped with magnetic stirring bar and argon balloon was placed diethyl ether (100 mL) and the solution was cooled to -78°C . At this time 33.4 mL (16.7 mmol, 0.5 M solution in toluene) of KHMDS was added via syringe, followed by dropwise addition of 1.12 mL (12.5 mmol) of 2-butanone. The reaction mixture stirred at this temperature for 1 h at which

time 2.0 g (8.4 mmol) of (*R*)-(-)-**10** was added in ether (5 mL) via cannula. After 1.0 h, the reaction mixture was quenched by addition of sat. NH_4Cl (20 mL) solution at $-78\text{ }^\circ\text{C}$ and the solution was warmed to rt. Water (20 mL) was added, the solution was extracted with ether (2 X 30 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (15% EtOAc/hexane) gave 2.2 g (85%) of a colorless oil; $[\alpha]_{\text{D}}^{20}$ -89.0 (*c* 1.05, CHCl_3); IR (neat) 3200, 2954, 1712; ^1H NMR δ 0.80 (t, $J = 7.5$ Hz, 3 H), 0.93 (t, $J = 7.5$ Hz, 3 H), 1.22 (m, 5 H), 1.34 (m, 1 H), 1.50 (m, 2 H), 2.29 (q, $J = 9.0$ Hz, 2 H), 2.32 (s, 3 H), 2.65 (d, $J = 6.5$ Hz, 2 H), 3.58 (m, 1 H), 4.39 (d, $J = 11.5$ Hz, 1 H), 7.20 (d, $J = 10.0$ Hz, 2 H), 7.47 (d, $J = 10.0$ Hz, 2 H); ^{13}C NMR δ 6.8, 13.4, 20.7, 21.9, 25.2, 30.8, 35.2, 36.1, 47.2, 52.1, 124.8, 128.8, 140.6, 141.9, 209.7. HRMS calcd. for $\text{C}_{17}\text{H}_{27}\text{NO}_2\text{S}$ (*M* + *H*) 310.1841; found 310.1834.

(*R*)-(-)-1-(2-Ethyl-1,3-dioxan-2-yl)-2-aminoheptane (12). In a 100-mL, one-necked, round-bottomed flask equipped with magnetic stirring bar and Dean-Stark condenser was placed 1.05 g (3.37 mmol) of (*R_S*,5*R*)-(-)-**11**, 0.96 g (5.06 mmol) of TsOH monohydrate, and 1.28 (16.9 mmol) of 1,3-propanediol in benzene (65 mL). Over a period of 1 h the solution was warmed to $78\text{ }^\circ\text{C}$ and refluxed for 12 h. At this time the reaction mixture was concentrated, the residue dissolved in DCM (40 mL), and 35 mL of a 2.6 N of KOH was added. The solution was stirred for 0.5 h, extracted with DCM (2 X 20 mL), the combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Chromatography (CHCl_3 saturated with NH_3) gave 0.68 g (87%) of a pale yellow oil; $[\alpha]_{\text{D}}^{20}$ -6.6 (*c* 0.9, CHCl_3); IR (neat) 3388, 3379, 2954; ^1H NMR δ 0.69 (m, 6 H), 1.03-1.19 (m, 8 H), 1.31-1.56 (m, 6 H), 1.63 (m, 1 H), 1.76 (m, 1 H), 2.91 (m, 1 H), 3.64-3.78 (m, 4 H); ^{13}C NMR δ 8.2, 14.5, 23.1, 25.8, 25.9, 26.2, 32.4, 39.4, 43.1, 47.3, 59.6, 59.9, 101.6. HRMS calcd. for $\text{C}_{13}\text{H}_{27}\text{NO}_2$ (*M* + *H*) 230.2120; found 230.2113.

(2*S*,3*S*,6*R*)-(-)-Piperidine 15. In a 100-mL, one-necked, round-bottomed flask equipped a magnetic stirring bar and argon balloon were placed DCM (30 mL) and 2 g of anhydrous MgSO_4 followed by 0.44 g (1.92 mmol) of (*R*)-(-)-**12** and 0.36 g (1.92 mmol) of (*E*)-4-benzyloxy-but-2-enal (**13**) in DCM (3 mL). The solution was heated at reflux and monitored by TCL for the disappearance of amine (2 h). At this time the reaction mixture containing the imine **14** was filtered, concentrated, and the residue was dissolved in benzene (3 mL). In a separate 100-mL, one-necked, round-bottomed flask equipped a magnetic stirring bar and Dean-Stark condenser was placed 0.59 g (3.45 mmol) of *p*-toluenesulfonic acid monohydrate in benzene (70 mL). The solution was refluxed for 4 h, cooled to rt, and the imine solution was added. After heating the solution at $75\text{ }^\circ\text{C}$ for 3 h the reaction mixture was concentrated. To the residue was added sat. NaHCO_3 (15 mL), the solution was extracted with EtOAc (2 X 15 mL), dried (Na_2SO_4), and concentrated. Chromatography (15% EtOAc/0.5% Et_3N /hexane) gave 0.45 g (61%) of a colorless oil; $[\alpha]_{\text{D}}^{20}$ -6.3 (*c* 0.4, CHCl_3); IR (neat) 2954, 2927, 2857; 2855, 2827 cm^{-1} ; ^1H NMR δ 0.71 (t, $J = 7.5$ Hz, 3 H), 0.72 (d, $J = 7.5$ Hz, 3 H), 0.77 (dd, $J = 11.7, 13.4$ Hz, 1 H), 1.05-1.28 (m, 10 H), 1.42 (b, 1 H), 1.82 (m, 1 H), 2.51 (m, 1 H), 2.71 (dd, $J = 13.3, 2.4$ Hz, 1 H), 2.91 (dd, $J = 8.4, 10.4$ Hz, 1 H), 3.61 (m, 2 H), 3.75 (dt, $J = 2.2, 12.0$ Hz, 1 H), 3.82 (dd, $J = 5.8, 1.1$ Hz, 2 H), 3.88 (dt, $J = 2.5, 12.3$ Hz, 1 H), 4.32 (m, 2 H), 5.43 (dd, $J = 8.3, 15.5$ Hz, 1 H), 5.57 (dt, $J = 5.9, 15.5$ Hz, 1 H), 7.06-7.20 (m, 5 H); ^{13}C NMR δ 11.9, 16.3, 24.9, 27.9, 28.0, 34.3, 36.5, 39.0, 47.4, 54.4, 61.2, 61.5, 63.5, 72.7, 74.4, 100.0, 129.9, 130.1, 130.6, 131.5, 138.0, 140.5. HRMS calcd for $\text{C}_{24}\text{H}_{37}\text{NO}_3$ (*M* + *H*) 388.2852; found 388.2852.

(2*S*,3*S*,6*R*)-(-)-Indolizidine (16). In a 100-mL one-necked, round-bottomed flask equipped with magnetic stirring bar was placed 0.25 g (0.65 mmol) of (-)-(**15**) in anhydrous methanol (20 mL). After filling the flask with argon, 0.05 g of 10% Pd/C was slowly added and

the reaction flask was evacuated and filled with H₂ via a balloon. After stirring for 3 h, the solution was filtered through a pad of Celite, and methanol (2 X 10 mL) was used to wash the filter cake. The filtrate was reduced to ca. 20 mL and placed in a 100-mL, one-necked round-bottom flask equipped with magnetic stirring bar. The flask was filled with argon, 0.05 g of 20% Pd(OH)₂/C was added, and the flask evacuated and attached to an H₂ balloon. After stirring for 12 h the solution was filtered through a pad of Celite, washed with EtOAc (2 X 10 mL), and concentrated to afford 0.18 g of the crude alcohol. The crude alcohol was dissolved in DCM (20 mL), transferred into a 100-mL, one-necked, round-bottom flask equipped with a magnetic stirring bar, and the solution was cooled to 0 °C. To the reaction mixture was added 0.34 g (1.03 mmol) of CBr₄ and 0.41 g (1.37 mmol) of triphenyl phosphine. The reaction mixture was warmed to rt and stirred for 2 h. To the solution was added 0.36 mL (1.95 mmol) of triethyl amine, the reaction mixture was stirred for 0.5 h, at which time it was washed with aqueous saturated NaHCO₃ (10 mL) and extracted with DCM (2 X 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated. Chromatography (10% EtOAc/0.5% Et₃N/hexane) gave 0.13 g (74%) of a colorless oil; [α]_D²⁰ -57.5 (c 0.53, CHCl₃); IR (neat) 2956; ¹H NMR δ 0.90 (t, *J* = 7.3 Hz, 3 H), 0.94 (d, *J* = 6.3 Hz, 3 H), 1.09 (b, 1 H), 1.19-1.45 (m, 9 H), 1.49 (b, 1 H), 1.66 (m, 2 H), 1.81 (m, 2 H), 2.02 (m, 4 H), 2.88 (d, *J* = 12.1 Hz, 1 H), 3.21 (b, 1 H), 3.65 (m, 2 H), 3.94 (dt, *J* = 2.4, 12.5 Hz, 1 H), 4.06 (t, *J* = 12.4 Hz, 1 H); ¹³C NMR δ 9.9, 14.5, 21.3, 23.0, 25.8, 26.1, 29.4, 32.6, 33.1, 34.4, 46.2, 51.4, 59.0, 59.3, 60.1, 66.6, 98.7. HRMS calcd. for C₁₇H₃₁NO₂ (M + H) 282.2433; found 282.2423.

(2S,3S,6R)-(-)-Thioketal 17. In a 50-mL, round-bottomed flask equipped with magnetic stirring bar was placed 0.085 g (0.30 mmol) of (-)-**16** in DCM (10 mL) and the solution was cooled to 0 °C. To the solution was added 0.127 mL (1.51 mmol) of ethanedithiol and 0.190 mL (1.51 mmol) of boron trifluoride via syringe. The reaction was warmed to rt, stirred for 2.5 h, and quenched by addition of 2 N NaOH (10 mL). The solution was extracted with DCM (2 X 5 mL), the combined organic phases were dried (Na₂SO₄) and concentrated. Chromatography gave 0.083 g (92%) of a colorless oil; [α]_D²⁰ -64.6 (c 0.45, CHCl₃); IR (neat) 2957, 2928, 2867, 2782; ¹H NMR δ 0.88 (t, *J* = 7.0 Hz, 3 H), 1.11 (d, *J* = 6.2 Hz, 3 H), 1.20-1.41 (m, 7 H), 1.45 (b, 1 H), 1.65 (m, 2 H), 1.79 (m, 3 H), 1.86-2.08 (m, 3 H), 2.17 (b, 1 H), 2.30 (dd, *J* = 13.2, 2.1 Hz, 1 H), 3.25 (m, 5 H); ¹³C NMR δ 14.3, 14.5, 21.1, 23.0, 25.6, 29.9, 32.6, 34.3, 39.1, 40.4, 47.6, 51.3, 51.7, 62.4, 70.1, 73.5. HRMS calcd. for C₁₆H₂₉NS₂ (M + H) 300.1820; found 300.1813.

(-)-Indolizidine 209B (18). Approximately 0.4 g of Raney-nickel (2800) in H₂O, was placed in a 100 mL, two-necked, round-bottomed flask. The slurry was washed with absolute EtOH (3 X 10 mL) to remove the H₂O and 0.055 g (0.18 mmol) of thioketal (-)-**17** in absolute ethanol (10 mL) was added. After stirring for 2 h at 80 °C the reaction mixture was filtered through Celite, the filter cake was washed with EtOAc (3 X 10 mL), and concentrated. Chromatography (5% EtOAc/0.5% Et₃N/hexane) gave 0.029 g (75%) of a colorless oil; [α]_D²⁰ -93.2 (c 0.51, MeOH) [lit.⁵ [α]_D -94.3 (c 1.38, MeOH)]; IR (neat) 2922, 2851; ¹H NMR δ 0.86 (d, *J* = 6.4 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H), 0.96 (m, 1 H), 1.18-1.39 (m, 9 H), 1.39-1.53 (m, 2 H), 1.64 (m, 2 H), 1.74 (m, 3 H), 1.85 (b, 1 H), 1.88-2.01 (m, 2 H), 3.27 (dt, *J* = 8.6, 1.5 Hz, 1 H); ¹³C NMR δ 14.5, 19.3, 20.7, 23.0, 25.9, 29.4, 31.6, 32.7, 34.1, 35.0, 36.9, 52.2, 64.0, 71.7. HRMS calcd for C₁₄H₂₇N (M + H) 208.2065. Found 208.2069. These spectral properties were in agreement with literature values.⁵

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