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Supporting Information

69451 Weinheim, Germany

Practical Synthesis of Enantiopure γ-Amino Alcohols via Rh-Catalyzed Asymmetric Hydrogenation of β-Secondary Amino Ketones

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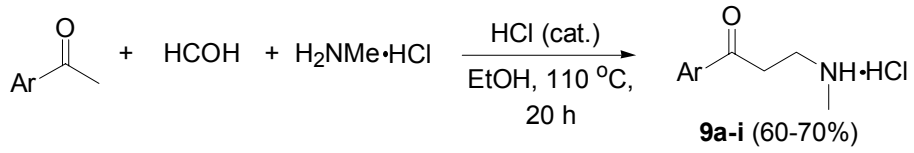
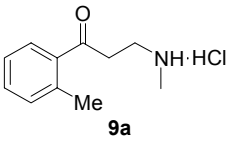
Experimental Section:

Part 1: Synthesis of β-Amino Ketone Hydrochlorides 9a-i.

Scheme 1.

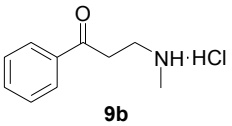


General procedure: A mixture of ketone (25.0 mmol), methylamine hydrochloride (1.86 g, 27.5 mmol), paraformaldehyde (1.05 g, 35 mmol), and conc. HCl (0.125 mL) in ethanol (12.5 mL) was heated in a sealed flask at 110 °C for 9-20 h. After being cooled to rt, the solvent was removed and 25 mL of EtOAc was added. The resulting suspension was vigorously stirred at rt for 4 h and then filtered and washed with EtOAc to afford product **9** (60-70% yield). The analytical samples were obtained by recrystallization from ^{i}PrOH**.**



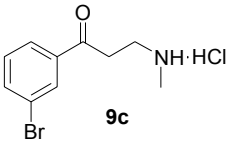
9a

3-Methylamino-1-*o*-tolylpropan-1-one hydrochloride (9a). White solid. ^{1}H MNR (300 MHz, CD_3OD) δ 7.87(d, *J* = 7.7 Hz, 1H), 7.45 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.36-7.29 (m, 2H), 3.50-3.46 (m, 2H), 3.40-3.36 (m, 2H), 2.77 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 201.7, 140.1, 137.2, 133.4, 133.2, 130.6, 127.1, 45.7, 37.7, 34.1, 21.8; HRMS (cation) *m/z* calcd. for $C_{11}H_{16}NO$ 178.12264, found 178.12406.



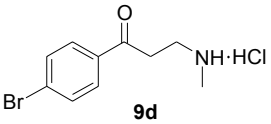
9b

3-Methylamino-1-phenylpropan-1-one hydrochloride (9b). White solid. ^{1}H MNR (300 MHz, CD_3OD) δ 8.09-8.05 (m, 2H), 7.67-7.65 (m, 1H), 7.58-7.53 (m, 2H), 3.64-3.59 (m, 2H), 3.48-3.44 (m, 2H), 2.81 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 198.6, 137.2, 134.9, 129.9, 129.2, 45.5, 35.5, 34.0; HRMS (cation) *m/z* calcd. for $C_{10}H_{14}NO$ 164.10699, found 164.10749.



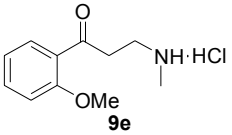
9c

1-(3-Bromophenyl)-3-methylaminopropan-1-one hydrochloride (9c). White solid. ^{1}H MNR (300 MHz, CD_3OD) δ 8.15 (t, *J* = 7.9 Hz, 1H), 8.01 (ddd, *J* = 1.0, 1.5, 7.8 Hz, 1H), 7.80 (ddd, *J* = 1.0, 1.5, 8.0 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 3.56-3.52 (m, 2H), 3.43-3.38 (m, 2H), 2.77 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 197.3, 139.1, 137.7, 132.0, 131.8, 128.1, 123.9, 45.3, 35.6, 34.0; HRMS (cation) *m/z* calcd. for $C_{10}H_{13}NOBr$ 242.01750, found 242.01734.



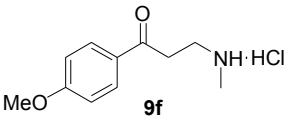
9d

1-(4-Bromophenyl)-3-methylaminopropan-1-one hydrochloride (9d). White crystalline. ^{1}H MNR (300 MHz, CD_3OD) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 3.46-3.42 (m, 2H), 3.34-3.26 (m, 2H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 196.6, 135.0, 132.1, 129.9, 128.8, 44.3, 34.3, 33.0; HRMS (cation) *m/z* calcd. for $C_{10}H_{13}NOBr$ 242.01750, found 242.01584.



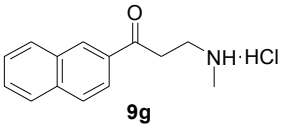
9e

1-(2-Methoxyphenyl)-3-methylaminopropan-1-one hydrochloride (9e). White solid. ^{1}H MNR (300 MHz, CD_3OD) δ 7.79 (dd, *J* = 1.8, 7.8 Hz, 2H), 7.58-7.53 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.02 (dt, *J* = 0.8, 8.0 Hz, 1H), 3.95 (s, 3H), 3.52-3.48 (m, 2H), 3.38-3.33 (m, 2H), 2.75 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 199.5, 160.9, 136.1, 131.4, 127.2, 121.7, 113.3, 56.3, 45.9, 40.8, 34.0; HRMS (cation) *m/z* calcd. for $C_{11}H_{16}NO_2$ 194.11756, found 194.11594.



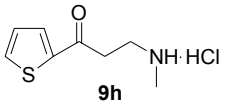
9f

1-(4-Methoxyphenyl)-3-methylaminopropan-1-one hydrochloride (9f). White solid. ^{1}H MNR (300 MHz, CD_3OD) δ 7.97 (d, *J* = 6.4 Hz, 2H), 6.97 (d, *J* = 6.4 Hz, 2H), 3.84 (s, 3H), 3.53 (br s, 2H), 3.41 (br s, 2H), 2.79 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 197.0, 165.4, 131.5, 129.9, 114.9, 56.3, 45.6, 35.1, 34.1; HRMS (cation) *m/z* calcd. for $C_{11}H_{16}NO_2$ 194.11756, found 194.11845.



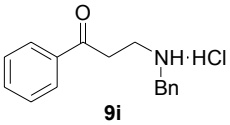
9g

3-Methylamino-1-naphthalen-2-ylpropan-1-one hydrochloride (9g). White solid. ^{1}H MNR (300 MHz, CD_3OD) δ 8.58 (s, 1H), 8.00-7.95 (m, 2H), 7.88-7.84 (m, 2H), 7.61-7.50 (m, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.44 (t, *J* = 6.3 Hz, 2H), 2.79 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 198.4, 137.2, 134.4, 133.8, 131.5, 130.7, 129.9, 129.5, 128.8, 128.0, 124.3, 45.6, 35.5, 34.1; HRMS (cation) *m/z* calcd. for $C_{14}H_{16}NO$ 214.12264, found 214.12398.



9h

3-Methylamino-1-thiophen-2-ylpropan-1-one hydrochloride (9h). White solid. ^{1}H MNR (300 MHz, CD_3OD) δ 7.89 (dd, *J* = 1.1, 3.9 Hz, 1H), 7.82 (dd, *J* = 1.1, 4.9 Hz, 1H), 7.15 (dd, *J* = 3.8, 4.9 Hz, 1H), 3.45-3.41 (m, 2H), 3.34-3.29 (m, 2H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 191.4, 143.9, 136.2, 134.9, 129.7, 45.4, 35.7, 34.0; HRMS (cation) *m/z* calcd. for $C_8H_{12}NOS$ 170.06396, found 170.06465.

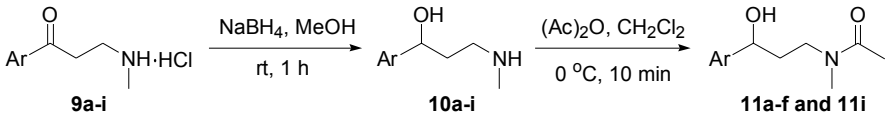


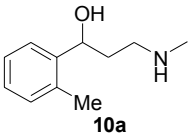
9i

3-Benzylamino-1-phenylpropan-1-one hydrochloride (9i). White solid. ^{1}H MNR (300 MHz, CD_3OD) δ 8.03-8.01 (m, 2H), 7.63-7.41 (m, 8H), 4.31 (s, 2H), 3.60 (t, *J* = 6.5 Hz, 2H), 3.46 (t, *J* = 6.1 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 198.3, 134.9, 131.1, 130.6, 130.2, 130.1, 130.0, 129.8, 129.2, 52.5, 43.5, 35.7; HRMS (cation) *m/z* calcd. for $C_{16}H_{18}NO$ 240.13829, found 240.13996.

Part 2: Preparation of Racemic γ-Amino Alcohols 10a-i and Further Transformation of 10a-f and 10i into Their *N*-acyl Derivatives 11a-f and 11i.

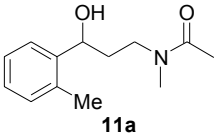
Scheme 2.





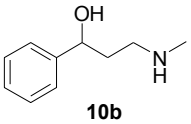
10a

General procedure for preparation of (±)-3-methylamino-1-*o*-tolylpropan-1-ol (10a) (analogously, 10b-10i). To a solution of **9a** (107 mg, 0.5 mmol) in MeOH (5 mL) was slowly added $NaBH_4$ (72 mg, 2.0 mmol) at room temperature. The resulting reaction mixture was stirred at rt for 1 h before being quenched with 2 mL of saturated NH_4Cl solution. The solvent was partially removed under reduced pressure. The residue was basicified with 5 mL of NaOH (1 N) and extracted with CH_2Cl_2 (5 mL × 4). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was passed through a short silica gel plug (EtOAc:MeOH:triethylamine = 10:10:1) to afford **10a** as a white solid (81 mg, 90% yield). ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.4 Hz, 1H), 7.24-7.07(m, 3H), 5.07 (dd, *J* = 2.5, 8.3 Hz, 1H), 3.91 (br s, 2H), 2.84-2.76 (m, 2H), 2.43 (s, 3H), 2.27 (s, 3H), 1.83-1.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 133.7, 130.0, 126.5, 125.9, 125.3, 71.6, 50.2, 35.8, 35.2, 18.8; HRMS (M^+ + 1) *m/z* calcd. for $C_{11}H_{18}NO$ 180.13829, found 180.13985.



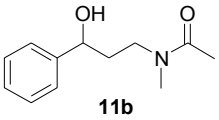
11a

General procedure for preparation of (±)-*N*-(3-hydroxy-3-*o*-tolylpropyl)-*N*-methylacetamide (11a) (analogously, 10b-10f and 10i). To a solution of **10a** (45 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added acetic anhydride (24 μL, 0.25 mmol). The resulting reaction mixture was stirred at this temperature for 10 min. After removal of the solvent, the residue was purified by flash column chromatography (eluting with EtOAc) to afford the desired *N*-acyl derivative **11a** as a mixture of rotamers. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.51-7.44 (m, 1H), 7.22-7.06 (m, 3H), 4.89 (dd, *J* = 4.0, 8.6 Hz, 0.25H), 4.70 (dd, *J* = 2.6, 10.5 Hz, 0.75H), 4.24-4.14 (m, 0.75H), 3.58-3.48 (m, 0.25H), 3.44-3.35 (m, 0.25H), 3.05-2.97 (m, 0.75H), 3.02 (s, 2.25H), 2.90 (s, 0.75H), 2.28 (s, 0.75H), 2.26 (s, 2.25H), 2.13 (s, 2.25H), 2.08 (s, 0.75H), 1.93-1.82 (m, 1.25H), 1.74-1.63 (m, 0.75H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 170.8, 142.1, 142.0, 134.0, 133.7, 130.6, 130.1, 127.5, 126.9, 126.4, 125.1, 124.9, 67.6, 66.4, 47.5, 44.7, 36.3, 36.0, 35.4, 33.1, 25.3, 21.6, 21.1, 18.9; HRMS (M^+ + 1) *m/z* calcd. for $C_{13}H_{20}NO_2$ 222.14886, found 222.15000. The two enantiomers of **11a** can be separated by chiral HPLC using an OD-H column (hexanes:isopropanol = 90:10).



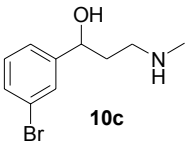
10b

(±)-3-Methylamino-1-phenylpropan-1-ol (10b). This compound was prepared from **9b** by the same method as described for preparation of **10a** in a similar yield. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.42-7.36 (m, 4H), 7.29-7.25 (m, 1H), 4.96 (dd, *J* = 3.3, 8.5 Hz, 1H), 3.94 (br s, 2H), 2.97-2.83 (m, 2H), 2.47 (s, 3H), 1.95-1.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 128.2, 126.9, 125.5, 75.4, 50.3, 36.7, 35.9; HRMS (M^+ + 1) *m/z* calcd. for $C_{10}H_{16}NO$ 166.12264, found 166.12420.



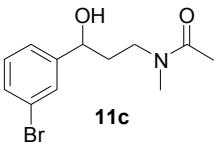
11b

(±)-*N*-(3-Hydroxy-3-phenylpropyl)-*N*-methylacetamide (11b). This compound was prepared from **10b** by the same method as described for preparation of **11a**. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 4.53-4.48 (m, 1H), 4.48-3.99 (m, 0.8H), 3.47-3.29(m, 0.4H), 3.11-3.03 (m, 0.8H), 2.96 (s, 2.4H), 2.86 (s, 0.6H), 2.13 (s, 2.4H), 2.05 (s, 2.4H), 2.03 (s, 0.6H), 2.01 (s, 0.6H), 1.96-1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 170.8, 144.1, 143.9, 128.6, 128.2, 127.8, 127.0, 126.4, 125.5, 71.2, 69.8, 47.3, 44.5, 37.2, 36.6, 36.2, 33.0, 21.5, 21.1; HRMS (M^+ + 1) *m/z* calcd. for $C_{12}H_{18}NO_2$ 208.13321, found 208.13442. The two enantiomers of **11b** can be separated by chiral HPLC using an OD-H column (hexanes:isopropanol = 90:10).



10c

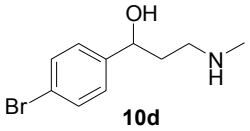
(±)-1-(3-Bromophenyl)-3-methylamino-propan-1-ol (10c). This compound was prepared from **9c** by the same method as described for preparation of **10a** in a similar yield. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.35-7.32 (m, 1H), 7.27-7.13 (m, 2H), 4.83 (dd, *J* = 2.8, 8.4 Hz, 1H), 4.67 (br s, 2H), 2.84-2.79 (m, 2H), 2.39 (s, 3H), 1.87-1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 129.8, 129.7, 128.6, 124.1, 122.3, 74.0, 49.6, 36.4, 35.5; HRMS (M^+ + 1) *m/z* calcd. for $C_{10}H_{15}NOBr$ 244.03315, found 244.03241.



11c

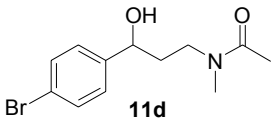
(±)-*N*-[3-(3-Bromophenyl)-3-hydroxypropyl]-*N*-methylacetamide (11c). This compound was prepared from **10c** by the same method as described for preparation of **11a**. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.45-7.42 (m, 1H), 7.33-7.27 (m, 1H), 7.22-7.07 (m, 2H), 4.54 (dd, *J* = 5.3, 7.4 Hz, 0.2H), 4.42 (dd, *J* = 3.2, 10.0 Hz, 0.8H), 4.03-3.93 (m, 1H), 3.46-3.25 (m, 0.2H), 3.01 (dt, *J* = 4.8, 14.2 Hz, 0.8H), 2.93 (s, 2.4H), 2.81 (s, 0.6H), 2.01 (s, 2.4H), 1.99 (s, 0.6H), 1.95-1.79 (m, 1.2H),

1.72-1.62 (m, 0.8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 170.8, 146.8, 146.4, 130.6, 130.1, 130.0, 129.8, 128.7, 124.2, 122.6, 122.3, 70.3, 69.0, 47.2, 44.4, 37.2, 36.6, 36.3, 33.0, 21.5, 21.0; HRMS (M^+ + 1) *m/z* calcd. for $C_{12}H_{17}NO_2Br$ 286.04372, found 286.04414. The two enantiomers of **11c** can be separated by chiral HPLC using an OD-H column (hexanes:isopropanol = 97:3).



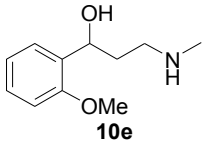
10d

(±)-1-(4-Bromophenyl)-3-methylaminopropan-1-ol (10d). This compound was prepared from **9d** by the same method as described for preparation of **10a** in a similar yield. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.43-7.39 (m, 2H), 7.24-7.18 (m, 2H), 4.84 (dd, *J* = 3.0, 8.6 Hz, 1H), 4.16 (br s, 2H), 2.84-2.79 (m, 2H), 2.39 (s, 3H), 1.84-1.76 (m, 1H), 1.72-1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 131.1, 127.3, 120.4, 74.8, 50.2, 36.6, 35.9; HRMS (M^+ + 1) *m/z* calcd. for $C_{10}H_{15}NOBr$ 244.03315, found 244.03192.



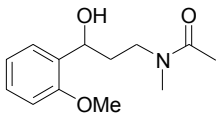
11d

(±)-*N*-[3-(4-Bromophenyl)-3-hydroxypropyl]-*N*-methylacetamide (11d). This compound was prepared from **10d** by the same method as described for preparation of **11a**. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.49-7.44 (m, 2H), 7.29-7.21 (m, 2H), 4.64 (t, *J* = 6.3 Hz, 0.2H), 4.50 (dd, *J* = 3.1, 10.1 Hz, 0.8H), 4.14-4.04 (m, 0.8H), 3.55-3.33 (m, 0.4H), 3.11-3.02 (m, 0.8H), 3.02 (s, 2.4H), 2.90 (s, 0.6H), 2.11 (s, 2.4H), 2.09 (s, 0.6H), 1.96-1.88 (m, 1.2H), 1.78-1.70 (m, 0.8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 170.5, 143.3, 143.0, 131.6, 131.2, 127.3, 127.3, 121.3, 120.6, 70.4, 69.0, 47.2, 44.4, 37.2, 36.6, 36.3, 33.0, 21.5, 21.1; HRMS (M^+ + 1) *m/z* calcd. for $C_{12}H_{17}NO_2Br$ 286.04372, found 286.04491. The two enantiomers of **11d** can be separated by chiral HPLC using an OD-H column (hexanes:isopropanol = 95:5).



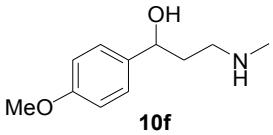
10e

(±)-1-(2-Methoxyphenyl)-3-methylaminopropan-1-ol (10e). This compound was prepared from **9e** by the same method as described for preparation of **10a** in a similar yield. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.19 (dt, *J* = 1.7, 7.8 Hz, 1H), 6.95 (dt, *J* = 0.8, 7.5 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 5.18 (dd, *J* = 3.2, 8.0 Hz, 1H), 3.78 (s, 3H), 3.74 (br s, 2H), 2.79 (t, *J* = 5.4 Hz, 2H), 2.40 (s, 3H), 1.98-1.89 (m, 1H), 1.76-1.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 133.1, 127.6, 126.4, 120.4, 109.9, 70.0, 55.1, 50.2, 36.0, 34.9; HRMS (M^+ + 1) *m/z* calcd. for $C_{11}H_{18}NO_2$ 196.13321, found 196.13345.



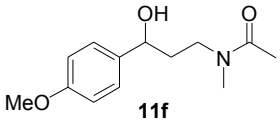
11e

(±)-*N*-[3-Hydroxy-3-(2-methoxyphenyl)propyl]-*N*-methylacetamide (11e). This compound was prepared from **10e** by the same method as described for preparation of **11a**. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 1.6, 7.6 Hz, 0.6H), 7.31 (dd, *J* = 1.6, 7.5 Hz, 0.4H), 7.26-7.16 (m, 1H), 6.94 (dt, *J* = 0.4, 7.5 Hz, 1H), 6.86-6.79 (m, 1H), 4.87 (dd, *J* = 3.9, 8.9 Hz, 0.4H), 4.79 (dd, *J* = 2.9, 9.9 Hz, 0.6H), 4.11-4.00 (m, 0.6H), 3.81 (s, 1.2H), 3.78 (s, 1.8H), 3.55-3.45 (m, 0.4H), 3.42-3.32 (m, 0.4H), 3.09-3.02 (m, 0.6H), 2.99 (s, 1.8H), 2.88 (s, 1.2H), 2.09 (s, 1.8H), 2.06 (s, 1.2H), 2.05-1.84 (m, 1.4H), 1.71-1.59 (m, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.8, 156.1, 155.6, 132.2, 131.8, 128.5, 127.8, 126.2, 126.2, 120.8, 120.7, 110.4, 110.0, 67.2, 65.2, 55.2, 47.6, 44.6, 36.0, 35.2, 34.6, 32.9, 21.6, 21.1; HRMS (M^+ + 1) *m/z* calcd. for $C_{13}H_{20}NO_3$ 238.14377, found 238.14258. The two enantiomers of **11e** can be separated by chiral HPLC using an OD-H column (hexanes:isopropanol = 90:10).



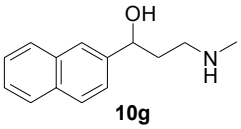
10f

(±)-1-(4-Methoxyphenyl)-3-methylaminopropan-1-ol (10f). This compound was prepared from **9f** by the same method as described for preparation of **10a** in a similar yield. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.20-7.17 (m, 2H), 6.80-6.75 (m, 2H), 4.74 (dd, *J* = 4.0, 7.9 Hz, 1H), 3.76 (br s, 2H), 3.69 (s, 3H), 2.74-2.68 (m, 2H), 2.31 (s, 3H), 1.72-1.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 137.3, 126.6, 113.4, 74.6, 55.1, 50.1, 37.0, 35.9; HRMS (M^+ + 1) *m/z* calcd. for $C_{11}H_{18}NO_2$ 196.13321, found 196.13407.



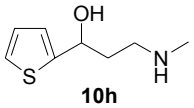
11f

(±)-*N*-[3-Hydroxy-3-(4-methoxyphenyl)-propyl]-*N*-methylacetamide (11f). This compound was prepared from **10f** by the same method as described for preparation of **11a**. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.22-7.16 (m, 2H), 6.81-6.76 (m, 2H), 4.52 (dd, *J* = 5.0, 8.0 Hz, 0.3H), 4.41 (dd, *J* = 3.5, 9.7 Hz, 0.7H), 4.00-3.90 (m, 0.7H), 3.72 (s, 0.9H), 3.71 (s, 2.1H), 3.36-3.27 (m, 0.6H), 3.05-2.97 (m, 0.7H), 2.91 (s, 2.1H), 2.81 (s, 0.9H), 2.00 (s, 2.1H), 1.97 (s, 0.9H), 1.89-1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 170.7, 159.0, 158.6, 136.3, 136.1, 126.8, 126.8, 113.8, 113.5, 70.7, 69.4, 55.2, 55.1, 47.4, 44.5, 37.1, 36.5, 36.2, 33.0, 21.5, 21.0; HRMS (M^+ + 1) *m/z* calcd. for $C_{13}H_{20}NO_3$ 238.14377, found 238.14421. The two enantiomers of **11f** can be separated by chiral HPLC using an OD-H column (hexanes:isopropanol = 95:5).



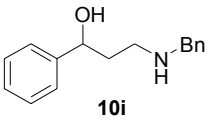
10g

(±)-3-Methylamino-1-naphthalen-2-yl-propan-1-ol (10g). This compound was prepared from **9g** by the same method as described for preparation of **10a** in a similar yield. ^{1}H MNR (360 MHz, $CDCl_3$) δ 7.92-7.82 (m, 4H), 7.50-7.43 (m, 3H), 5.12 (dd, *J* = 3.0, 8.5 Hz, 1H), 3.82 (br s, 2H), 2.96-2.86 (m, 2H), 2.48 (s, 3H), 2.01-1.96 (m, 1H), 1.88-1.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 133.3, 132.7, 127.9, 127.8, 127.6, 125.9, 125.4, 124.1, 124.0, 75.2, 50.1, 36.4, 35.7; HRMS (M^+ + 1) *m/z* calcd. for $C_{14}H_{18}NO$ 216.13829, found 216.13947. The two enantiomers of **10g** can be directly separated by chiral HPLC using an OD-H column (hexanes:isopropanol:diethylamine = 97:2:1).



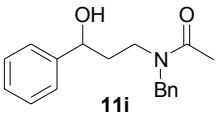
10h

(±)-3-Methylamino-1-thiophen-2-ylpropan-1-ol (10h). This compound was prepared from **9h** by the same method as described for preparation of **10a** in a similar yield. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 1.2, 5.0 Hz, 1H), 6.93-6.87 (m, 2H), 5.12 (dd, *J* = 3.5, 7.7 Hz, 1H), 4.06 (br s, 2H), 2.88-2.79 (m, 2H), 2.37 (s, 3H), 1.94-1.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 126.4, 123.6, 122.2, 71.4, 49.9, 36.9, 35.8; HRMS (M^+ + 1) *m/z* calcd. for $C_8H_{14}NOS$ 172.07961, found 172.08066. The two enantiomers of **10h** can be directly separated by chiral HPLC using an OD-H column (hexanes:isopropanol:diethylamine = 97:2:1).



10i

(±)-3-Benzylamino-1-phenylpropan-1-ol (10i). This compound was prepared from **9i** by the same method as described for preparation of **10a** in a similar yield. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.43-7.27 (m, 10H), 5.00 (dd, *J* = 3.2, 8.5 Hz, 1H), 3.95 (br s, 2H), 3.84 (ABq, *J* = 13.0, 16.2 Hz, 2H), 3.04-2.92 (m, 2H), 2.01-1.92 (m, 1H), 1.89-1.77 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 139.1, 128.4, 128.2, 128.1, 127.2, 126.8, 125.5, 75.4, 53.7, 47.6, 37.2; HRMS (M^+ + 1) *m/z* calcd. for $C_{16}H_{20}NO$ 242.15394, found 242.15288.

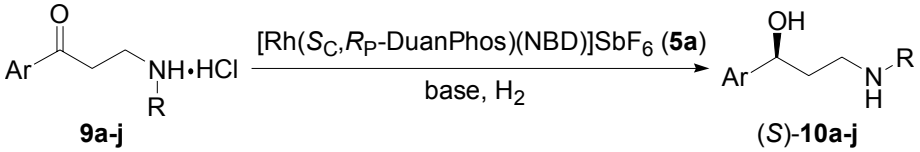


11i

(±)-*N*-Benzyl-*N*-(3-hydroxy-3-phenylpropyl)-acetamide (11i). This compound was prepared from **10i** by the same method as described for preparation of **11a**. ^{1}H MNR (300 MHz, $CDCl_3$) δ 7.39-7.15 (m, 10H), 4.62-4.41 (m, 3H), 4.10-4.00 (m, 0.75H), 3.36-3.30 (m, 0.5H), 3.17-3.09 (m, 0.75H), 2.13 (s, 2.25H), 2.11 (s, 0.75H), 1.94-1.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 170.9, 144.0, 137.6, 136.1, 129.0, 128.6, 128.5, 128.2, 128.1, 127.8, 127.2, 127.0, 126.3, 125.5,

71.4, 70.0, 52.2, 48.0, 44.5, 42.8, 37.3, 37.2, 21.5, 21.3; HRMS (M^+ + 1) *m/z* calcd. for $C_{18}H_{22}NO_2$ 284.16451, found 284.16598. The two enantiomers of **11i** can be separated by chiral HPLC using an OD-H column (hexanes:isopropanol = 90:10).

Part 3: Asymmetric Hydrogenation of β-Amino Ketone hydrochlorides 9.



9a-j (*S*)-**10a-j**

General Procedure for Asymmetric Hydrogenation:

(*S*)-3-Methylamino-1-*o*-tolylpropan-1-ol [(*S*)-10a]. To a mixture of **9a** (43 mg, 0.2 mmol) and K_2CO_3 (14 mg, 0.1 mmol) in 0.5 mL of degassed MeOH in glove-box was added [Rh(S_C,R_P-**4**)(NBD)]SbF_6 (**5a**) (0.8 mg, 0.001 mmol). The resulting solution was then transferred into an autoclave and charged with 10 bar of hydrogen. The hydrogenation was performed at room temperature for 12 h. After carefully releasing the hydrogen, the solvent was removed under reduced pressure. The resulting residue was dissolved in 3 mL of NaOH solution (1.0 N) and extracted with CH_2Cl_2 (5 mL × 4). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was passed through a short silica gel plug (eluting with a mixture of EtOAc:MeOH:triethylamine = 10:10:1) to afford (*S*)-**10a** as a white solid (33 mg, 92% yield). The enantiomeric excess of (*S*)-**10a** (99%) was determined by chiral HPLC using an OD-H column after being converted to (*S*)-**11a**. For chiral HPLC separation conditions, refer to Part 2.

(*S*)-**10b-i** were generated by asymmetric hydrogenation of **9b-i**, respectively, with Rh complex **5a** as a catalyst precursor following the general procedure (90-93% yields). The enantiomeric excesses of (*S*)-**10b-f** and (*S*)-**10i** were determined by chiral HPLC using an OD-H column after being converted to (*S*)-**11b-f and** (*S*)-**11i**, respectively. While the enantiomeric excesses of (*S*)-**10g** and (*S*)-**10h** were directly determined by chiral HPLC using an OD-H column, respectively. For chiral HPLC separation conditions, refer to Part 2.

(*R*)-**10h** was generated by asymmetric hydrogenation of **9h** with [Rh(R_C,S_P-**4**)(NBD)]SbF_6 (**5b**) as a catalyst precursor following the general procedure (93% yields). The enantiomeric excess of (*R*)-**10h** (>99%) were directly determined by chiral HPLC using an OD-H column. For chiral HPLC separation conditions, refer to Part 2.

Asymmetric hydrogenation of 3-methylamino-1-phenylpropan-1-one hydrochloride (9b) with low catalyst loading (S/C = 6000). Rh-complex **5a** (3 mg) was dissolved in 3 mL of degassed MeOH. To a suspension of **9b** (1.48 g, 7.39 mmol) in 10 mL of degassed MeOH in glove-box was added 1 mL of the above complex solution (1 mg, 0.00123 mmol of **5a**), followed by addition of K_2CO_3 (0.511 g, 3.70 mmol). The resulting mixture was transferred into an autoclave and the hydrogenation was performed under 50 bar of initial hydrogen pressure at 50 ^oC for 12 h (not optimal). After carefully releasing the hydrogen, the solvent was removed under reduced pressure. The resulting residue was dissolved in 10 mL of NaOH solution (1.0 N) and

extracted with CH_2Cl_2 (10 mL × 4). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was passed through a short silica gel plug (eluting with 30 mL of EtOAc first, and then a mixture of EtOAc:MeOH:triethylamine = 10:10:1) to afford (*S*)-**10b** as a pale yellow oil (0.91 g, 75% yield). The enantiomeric excess of (*S*)-**10b** (98%) was determined by chiral HPLC using an OD-H column after being converted to (*S*)-**11b**.

Asymmetric hydrogenation of 3-methylamino-1-thiophen-2-ylpropan-1-one hydrochloride (9h) with low catalyst loading (S/C = 6000). Rh-complex **5a** (3 mg) was dissolved in 3 mL of degassed MeOH. To a suspension of **9h** (1.52 g, 7.39 mmol) in 10 mL of degassed MeOH in glove-box was added 1 mL of the above complex solution (1 mg, 0.00123 mmol of **5a**), followed by addition of 0.5 equivalent of K_2CO_3 (0.511 g, 3.70 mmol). The resulting mixture was transferred into an autoclave and the hydrogenation was performed under 50 bar of initial hydrogen pressure at 50 ^oC for 12 h (not optimal). After carefully releasing the hydrogen, the solvent was removed under reduced pressure. The resulting residue was dissolved in 10 mL of NaOH solution (1.0 N) and extracted with CH_2Cl_2 (10 mL × 4). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was passed through a short silica gel plug (eluting with 30 mL of EtOAc first, and then a mixture of EtOAc:MeOH:triethylamine = 10:10:1) to afford (*S*)-**10h** as a pale yellow solid (0.95 g, 75% yield). The enantiomeric excess of (*S*)-**10h** (>99%) was directly determined by chiral HPLC using an OD-H column.