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Supporting Information

Asymmetric Hydrogenation of a-Primary and Secondary Amino Ketones: Efficient Asymmetric Syntheses of (-)-Arbutamine and (-)-Denopamine

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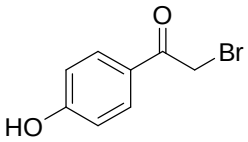
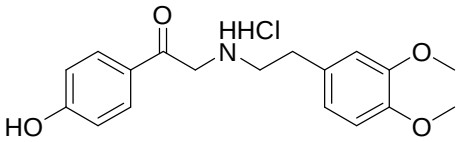
Supporting Information

Asymmetric Syntheses of (-)-Denopamine and (-)-Arbutamine.

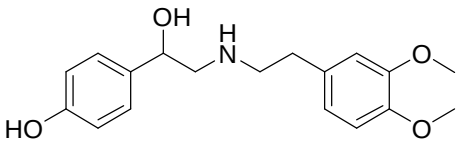
The synthesis of (-)-Denapomine:



2-Bromo-1-(4-hydroxy-phenyl)-ethanone.[1] Similar method for the synthesis of 2-Bromo-1-(3,4-dimethoxy-phenyl)-ethanone was used to prepare this compound. White solid, 75% yield, m.p. 125-126[2] °C. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.91 (d, 2H, *J* = 5.9 Hz), 6.84 (d, 2H, *J* = 5.9 Hz), 4.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): d 192.3, 164.4, 132.8, 127.1, 116.5, 31.9.

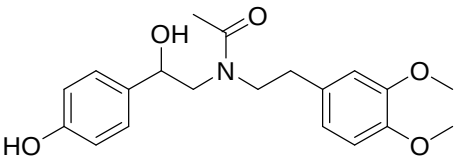


2-[2-(3,4-Dimethoxy-phenyl)-ethylamino]-1-(4-hydroxy-phenyl)-ethanone hydrochloride (1).[3] This compound was prepared in a similar manner to the general procedure for the preparation of a-secondary amino ketones. After the reaction was completed, the solvent was not evaporated and HCl was added directly. White crystalline solid, 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.91 (d, 2H, *J* = 6.9 Hz), 6.96-6.82 (m, 5H), 4.67 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.37-3.31 (m, 2H), 3.08-2.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): d 190.7, 165.3, 150.8, 149.8, 132.0, 130.3, 126.6, 122.2, 116.7, 113.7, 113.4, 56.5, 53.4, 50.0, 32.9, one peak around 56.5 was obscured. The two enantiomers could be separated by chiral HPLC (Chiralpak AD column, hexanes:iso-propanol = 90:10); $[\alpha]^{24}_{D} = 16.697^{\circ}$ (c = 0.20, $CHCl_3$).



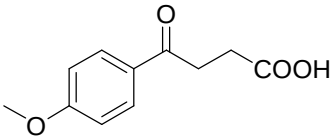
4-{2-[2-(3,4-Dimethoxy-phenyl)-ethylamino]-1-hydroxy-ethyl}-phenol (Denopamine).[4] This compound was prepared in a similar

manner to the general procedure for the preparation of 1,2-amino alcohols. White solid, m.p. 160-161[5]°C. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.16-7.09 (m, 2H), 6.83-6.54 (m, 5H), 4.69-4.60 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.87-2.65 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): d 158.1, 150.4, 148.9, 134.9, 133.5, 128.3, 121.9, 116.2, 113.5, 113.1, 72.9, 57.6, 56.5, 56.4, 51.6, 36.0.

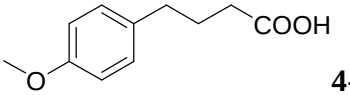


***N*-[2-(3,4-Dimethoxy-phenyl)-ethyl]-*N*-[2-hydroxy-2-(4-hydroxy-phenyl)-ethyl]-acetamide**. This compound was prepared in a similar manner to the general procedure for the derivatization of 1,2-amino alcohols. White solid. Mixture of rotamers. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.15-7.00 (m, 2H), 6,79-6.54 (m, 5H), 4.88-4.80 (m, 0.7H), 4.78-4.70 (m, 0.3H), 3.82-3.72 (m, 6H), 3.58-3.30 (m, 4H), 2.75-2.62 (m, 2H), 1.85 (s, 0.9H), 1.82 (s, 2.1H); ^{13}C NMR (75 MHz, $CDCl_3$): d 173.5, 172.2, 156.6, 156.3, 148.9, 148.6, 147.7, 147.3, 133.0, 132.5, 131.5, 130.2, 127.0, 126.9, 120.7, 120.6, 115.5, 115.3, 111.9, 111.8, 111.4, 111.2, 73.0, 71.9, 56.4, 55.8, 55.73, 55.69, 54.7, 52.2, 48.0, 34.1, 33.0, 20.9, 19.0. APCI-HRMS Calcd. for $C_{20}H_{26}NO_5$ [M+H$^+$]: 360.1811, found 360.1817.

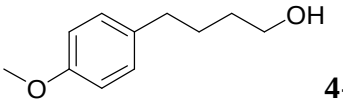
The synthesis of (-)-Arbutamine:



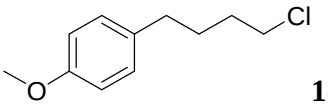
4-(4-Methoxy-phenyl)-4-oxo-butyric acid.[6] $AlCl_3$ (26 g, 0.19 mol) was added in small portions into the 1-nitropropane solution of anisole (10 g, 0.092 mol) and succinic anhydride (9.7 g, 0.097 mol) at 0 °C. The solution was stirred at r.t. for 12 h then hydrolyzed with ice water and 1 N HCl. The white solid was filtered and directly used for the next step. White solid, m.p. 144.5-146.5[7] °C, >95% yield. ^{1}H NMR (400 MHz, CD_3OD): d 7.99 (d, 2H, *J* = 4.8 Hz), 7.01 (d, 2H, *J* = 4.8 Hz), 3.87 (s, 3H), 3.26 (t, 3H, *J* = 6.5 Hz), 2.68 (t, 2H, *J* = 6.2 Hz).



4-(4-Methoxy-phenyl)-butyric acid.[8] To a 500 mL round bottom flask was added 40 g amalgated zinc followed by 30 mL water, 70 mL conc. HCl, 80 mL toluene and 4-(4-Methoxy-phenyl)-4-oxo-butyric acid (20 g, 0.96 mol). A condenser and a gas absorption tube was attached. The mixture was heated to reflux for 24 h with the addition of 20 mL conc. HCl every 6 h. The solution was cooled to r.t. and the solid was filtered. The aqueous layer was separated and extracted with ether (3 × 50 mL). The organic phase was combined and washed with water followed by brine. The solution was dried over $NaSO_4$ and the solvent was evaporated to yield a light yellow solid. Light yellow solid, m.p. 47-48[9] °C, 83% yield. ^{1}H NMR (300 MHz, CD_3OD): d 7.10 (d, 2H, *J* = 8.6 Hz), 6.84 (d, 2H, *J* = 8.6 Hz), 3.79 (s, 3H), 2.62 (t, 2H, *J* = 7.7 Hz), 2.36 (t, 2H, *J* = 7.4 Hz), 1.98-1.89 (m, 2H).

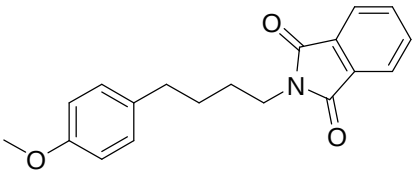


4-(4-Methoxy-phenyl)-butan-1-ol.[10] 4-(4-Methoxy-phenyl)-butyric acid (7.5 g, 0.039 mol) was dissolved in dry ether and borane-dimethyl sulphide complex (4.22 mL, 0.044 mol) was added under N_2. The mixture was gently refluxed for 1 h. After cooled to r.t. 20 mL MeOH was added dropwise to quench the reaction. The solvent was evaporated to yield a thick oil. Colorless oil, 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.11 (d, 2H, *J* = 5.8 Hz), 6.84 (d, 2H, *J* = 5.8 Hz), 3.80 (s, 3H), 3.66 (t, 2H, *J* = 6.2 Hz), 2.60 (t, 2H, *J* = 7.4 Hz), 1.70-1.58 (m, 4H), 1.41 (br 1H).

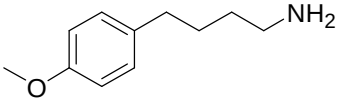


1-(4-Chloro-butyl)-4-methoxy-benzene.[11] The carbon tetrachloride solution of triphenylphosphine (7.4 g, 28.2 mmol), 4-(4-Methoxy-phenyl)-butan-1-ol (3.9 g, 21.7 mmol) was heated to reflux and monitored by TLC. After completion (4-6 h) the solution was cooled to r.t. and hexanes was added to precipitate the phosphine oxide. The solid was filtered and the organic phase was washed with water then dried over $NaSO_4$. The solvent was removed under vacuum to yield the crude product. Little remaining phosphine oxide could be removed by passing a short silica gel plug (hexanes:ethylacetate = 4:1). Clear oil, 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$): d

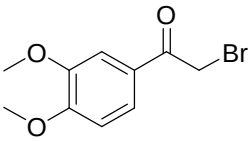
7.11 (d, 2H, *J* = 6.7 Hz), 6.85 (d, 2H, *J* = 6.7 Hz), 3.80 (s, 3H), 3.55 (t, 2H, *J* = 6.5 Hz), 2.60 (d, 2H, *J* = 7.0 Hz), 1.84-1.73 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): d 157.8, 133.9, 129.2, 113.7, 55.2, 44.9, 34.1, 32.0, 28.8.



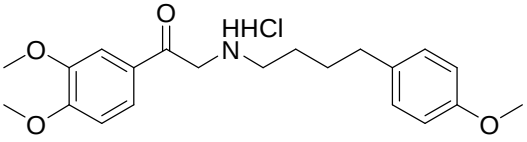
2-[4-(4-Methoxy-phenyl)-butyl]-isoindole-1,3-dione.[12] The DMF solution of 1-(4-Chloro-butyl)-4-methoxy-benzene (4.4 g, 22.2 mmol), potassium phathalimide (8.2 g, 44.4 mmol) and KI (cat) was heated to reflux for 12 h. The solvent was evaporated under vacuum and ethyl acetate was added to dissolve the residue. The organic phase was washed with 0.1 N K_2CO_3 and dried over $NaSO_4$. the solvent was then removed to yield the product. Light yellow solid, >95% yield, m.p. 102-103[13] °C. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.90-7.66 (m, 4H), 7.07 (d, 2H, *J* = 9.0 Hz), 6.80 (d, 2H, *J* = 9.0 Hz), 3.77 (s, 3H), 3.70 (t, 2H, *J* = 7.1 Hz), 2.59 (t, 2H, *J* = 7.1 Hz), 1.77-1.57 (m, 4H).



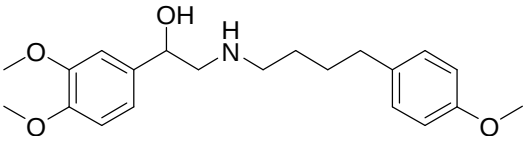
4-(4-Methoxy-phenyl)-butylamine.[14] Hydrazine monohydrate (7.9 mL, 0.16 mol) was added to the ethanol solution of 2-[4-(4-Methoxy-phenyl)-butyl]-isoindole-1,3-dione (5 g, 16 mmol) at r.t. The solution was heated to reflux for 12 h. After cooled to r.t. the solid was filtered and the solution was acidified to pH = 1 by conc. HCl. Solid precipitate was filtered and 2N NaOH was added to the solution until pH = 12. The mixture was extracted with CH_2Cl_2 (3 × 40 mL) and the combined the organic phase was washed with brine and then dried over $NaSO_4$. The solvent was then evaporated to yield the product as light yellow oil. Light yellow oil, >95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.09 (d, 2H, *J* = 4.5 Hz), 6.82 (d, 2H, *J* = 4.5 Hz), 3.78 (s, 3H), 2.70 (t, 2H, *J* = 6.8 Hz), 2.57 (t, 2H, *J* = 7.7 Hz), 1.67-1.55 (m, 2H), 1.55-1.42 (m, 2H), 1.35 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): d 157.7, 134.6, 129.2, 113.7, 55.2, 42.1, 34.8, 33.4, 28.9.



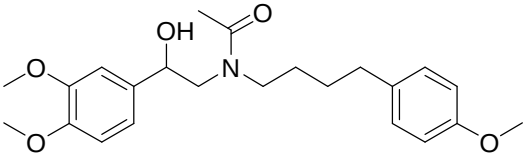
2-Bromo-1-(3,4-dimethoxy-phenyl)-ethanone.[15] To a acetic acid solution (30 mL) of 1-(3,4-Dimethoxy-phenyl)-ethanone (5 g, 27.8 mmol) was added Br_2 (1.5 mL, 29.2 mmol, 1.05 equiv.) dropwise. The reaction mixture was gently heated to initiate when the first few drops of Br_2 was added. The mixture was stirred at r.t. for 6 h and N_2 gas was blown into the solution to remove the HBr gas. The mixture was poured into 50 mL ice water and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvent under vacuum gave the crude product which was purified by flash column chromatography. White solid, m.p. 80-81[16] °C, 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.63-7.58 (m, 1H), 7.54-7.49 (m, 1H), 6.92-6.85 (m, 1H), 4.39 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): d 190.0, 153.9, 194.2, 126.9, 123.8, 110.7, 110.0, 56.1, 56.0, 30.4.



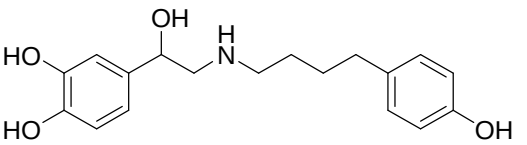
1-(3,4-Dimethoxy-phenyl)-2-[4-(4-methoxy-phenyl)-butylamino]-ethanone hydrochloride (2). This compound was prepared in a similar manner to the general procedure for the preparation of a-secondary amino ketones. After the reaction was completed, the solvent was not evaporated and was added HCl directly. White crystalline solid, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$): d 7.71-7.64 (m, 1H), 7.58-7.51 (m, 1H), 7.15-7.05 (m, 3H), 6.85-6.79 (m, 2H), 4.69 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.74 (s, 3H), 3.12 (t, 2H, J = 8.0 Hz), 2.63 (t, 2H, J = 7.0 Hz), 1.83-1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): d 191.1, 159.5, 156.4, 150.8, 134.8, 130.4, 127.9, 124.7, 114.9, 112.0, 111.4, 56.7, 56.6, 55.7, 53.4, 35.2, 29.6, 26.6. APCI-HRMS Calcd. for $C_{21}H_{28}NO_4$ [M+H$^+$]: 358.2018, found 358.2025.



1-(3,4-Dimethoxy-phenyl)-2-[4-(4-methoxy-phenyl)-butylamino]-ethanol. This compound was prepared in a similar manner to the general procedure for the preparation of 1,2-amino alcohols. White solid. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.06-6.98 (m, 2H), 6.92-6.88 (m, 1H), 6.86-6.73 (m, 4H), 4.70-4.64 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.71 (m, 3H), 3.68-3.40 (br, 2H), 2.70-2.64 (m, 2H), 2.59-2.43 (m, 4H), 1.57-1.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): d 157.3, 148.6, 147.9, 135.7, 134.0, 128.9, 117.6, 113.3, 110.6, 108.6, 71.2, 57.0, 55.52, 55.45, 54.8, 49.1, 34.4, 29.0, 28.9. APCI-HRMS Calcd. for $C_{21}H_{30}NO_4$ [M+H$^+$]: 360.2175, found 360.2173.



***N*-[2-(3,4-Dimethoxy-phenyl)-2-hydroxy-ethyl]-*N*-[4-(4-methoxy-phenyl)-butyl]-acetamide**. This compound was prepared in a similar manner to the general procedure for the derivatization of 1,2-amino alcohols. White solid. Mixture of rotamers. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.04-6.96 (m, 2H), 6.89 (s, 0.7H), 6.85 (s, 0.3H), 6.79-6.70 (m, 4H), 4.82-4.76 (m, 0.7H), 4.75-4.68 (m, 0.4H), 3.80 (s, 3H), 3.78 (s, 3H), 3.69 (s, 3H), 3.60-3.04 (m, 4H), 2.52-2.44 (m, 3H), 2.01 (s, 2.3H), 1.92 (s, 0.8H), 1.51-1.63 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): d 172.6, 171.0, 157.5, 157.3, 148.7, 148.6, 148.2, 147.9, 135.0, 134.5, 133.9, 133.2, 128.9, 128.8, 117.8, 117.6, 113.5, 113.3, 110.7, 110.6, 108.6, 73.2, 71.4, 55.8, 55.52, 55.50, 55.3, 54.8, 50.4, 45.6, 34.3, 34.1, 28.6, 28.2, 27.6, 26.5, 21.4, 21.3, some minor rotamer peaks are obscured by the major rotamer. APCI-HRMS Calcd. for $C_{23}H_{32}NO_5$ [M+H$^+$]: 402.2280, found 402.2272. The two enantiomers could be separated by chiral HPLC (Chiralpak AD column, hexanes:iso-propanol = 90:10); $[\alpha]^{24}_{D}$ = 15.876° (c = 0.25, $CHCl_3$).



4-{1-Hydroxy-2-[4-(4-hydroxy-phenyl)-butylamino]-ethyl}-benzene-1,2-diol (Abutamine).[4] ^{1}H NMR (300 MHz, $CDCl_3$): d

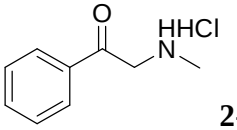
6.95-6.87 (m, 2H), 6.64-6.56 (m, 2H), 6.53-6.51 (m, 1H), 6.49-6.42 (m, 2H), 4.69-4.60 (m, 1H), 2.99-2.82 (m, 4H), 2.53-2.42 (m, 2H), 1.62-1.45 (m, 4H).

Table 1. Catalyst Screening of the Hydrogenation of Amino ketone 1 and 2.

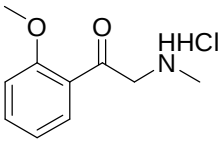
entry[a]	catalyst	*ee* (%)[b]	
		ketone **1**	ketone **2**
1	[Rh(*S*-Binapine)(cod)]BF_4 (**5**)	20	74
2	[Rh(*S*,*S*-Me-DuPhos)(cod)]BF_4 (**9**)	86	90
3	[Rh(*S*,*S*-Et-DuPhos)(cod)]BF_4 (**10**)	0	93
4	[Rh(*R*,*R*,*S*,*S*-DuanPhos)(nbd)]SbF_6 (**11**)	20	88
5	[Rh(*S*,*S*,*R*,*R*-TangPhos)(cod)]BF_4	14	68
6	[Rh(*S*-f-Binaphane)(cod)]BF_4	0	16

[a] The hydrogenation was carried out under optimized conditions for each entry with 1 mol% of Rh-precatalyst and 0.5 equiv. K_2CO_3 at 50 ^oC following the general procedure for 12 h. >95% yield was achieved with all the catalsyts screened. Estimated yields based on ^1H NMR of crude product. [b] The enantiomeric excess of the products was determined by chiral HPLC after conversion to the correspondig *N*-acyl derivatives (Cf. Experimental Section).

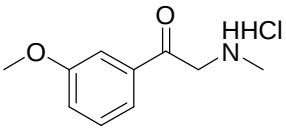
Asymmetric Hydrogenation of α-Secondary Amino Ketones.



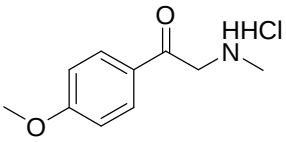
2-Methylamino-1-phenyl-ethanone hydrochloride (3a).[7] ^1H NMR (360 MHz, CD_3OD): d 8.05-8.00 (m, 2H), 7.75-7.68 (m, 1H), 7.62-7.54 (m, 1H), 4.75 (s, 1H), 2.83 (s, 1H); ^{13}C NMR (90 MHz, CD_3OD): d 192.9, 135.94, 134.92, 130.2, 129.3, 55.3, 33.6.



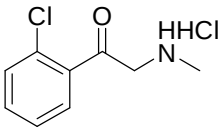
1-(2-Methoxy-phenyl)-2-methylamino-ethanone hydrochloride (3b). ^{1}H NMR (300 MHz, CD_3OD): d 7.98 (dd, 1H, *J* = 1.8, 1.9 Hz), 7.69-7.62 (m, 1H), 7.26-7.20 (m, 1H), 7.14-7.07 (m, 1H), 4.56 (s, 2H), 4.02 (s, 3H), 2.79 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): d 192.5, 161.9, 137.7, 131.7, 124.2, 122.1, 113.5, 59.6, 56.5, 33.3. APCI-HRMS Calcd. for $C_{10}H_{14}NO_2$ [M+H$^+$]: 180.1025, found 180.1022.



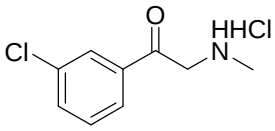
1-(3-Methoxy-phenyl)-2-methylamino-ethanone hydrochloride (3c). ^{1}H NMR (300 MHz, CD_3OD): d 7.63-7.57 (m, 1H), 7.59-7.45 (m, 2H), 7.30-7.24 (m, 2H), 4.73 (s, 1H), 3.86 (s, 1H), 2.81 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD): d 192.8, 161.7, 136.2, 131.4, 122.0, 121.7, 113.7, 56.1, 55.4, 33.6. APCI-HRMS Calcd. for $C_{10}H_{14}NO_2$ [M+H$^+$]: 180.1025, found 180.1029.



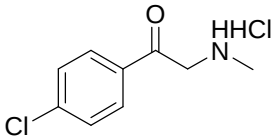
1-(4-Methoxy-phenyl)-2-methylamino-ethanone hydrochloride (3d).[9] ^{1}H NMR (300 MHz, CD_3OD): d 8.00 (d, 2H, *J* = 9.0 Hz), 7.07 (d, 2H, *J* = 9.0 Hz), 4.69 (s, 2H), 3.89 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): d 191.1, 166.4, 131.8, 127.7, 115.4, 56.3, 55.0, 33.6.



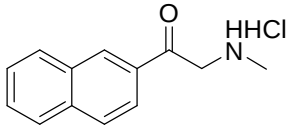
1-(2-Chloro-phenyl)-2-methylamino-ethanone hydrochloride (3e). ^{1}H NMR (400 MHz, CD_3OD): d 7.92-7.86 (m, 1H), 7.63-7.54 (m, 2H), 7.54-7.46 (m, 1H), 4.72 (s, 2H), 2.83 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): d 193.9, 135.4, 135.0, 133.5, 132.5, 131.8, 128.6, 57.7, 33.5. APCI-HRMS Calcd. for $C_9H_{10}NONaCl$ [M+Na$^+$]: 206.0349, found 206.0345.



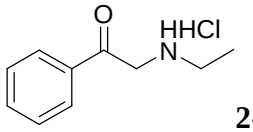
1-(3-Chloro-phenyl)-2-methylamino-ethanone hydrochloride (3f). ^{1}H NMR (400 MHz, CD_3OD): d 8.05-7.93 (m, 2H), 7.76-7.70 (m, 1H), 7.62-7.54 (m, 1H), 4.75 (s, 2H), 2.83 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): d 192.1, 136.6, 136.4, 135.7, 131.9, 129.0, 127.8, 55.4, 33.6. APCI-HRMS Calcd. for $C_9H_{10}NONaCl$ [M+Na^+]: 206.0349, found 206.0341.



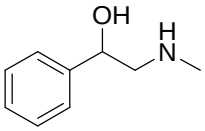
1-(4-Chloro-phenyl)-2-methylamino-ethanone hydrochloride (3g).[9] ^{1}H NMR (300 MHz, CD_3OD): d 8.02 (d, 2H, *J* = 8.8 Hz), 7.60 (d, 2H, *J* = 8.8 Hz), 4.74 (s, 2H), 2.82 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): d 192.0, 142.2, 133.5, 131.0, 130.5, 55.3, 33.6.



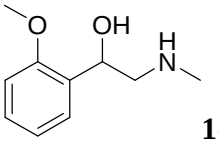
2-Methylamino-1-naphthalen-2-yl-ethanone hydrochloride (3h). ^{1}H NMR (300 MHz, CD_3OD): d 8.65 (s, 1H), 8.12-7.92 (m, 4H), 7.73-7.60 (m, 2H), 4.86 (s, 2H), 2.87 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): d 192.8, 137.7, 133.9, 132.2, 131.9, 130.9, 130.6, 130.1, 129.0, 128.4, 123.9, 55.4, 33.7. APCI-HRMS Calcd. for $C_{13}H_{14}NO$ [M+H^+]: 200.1075, found 200.1076.



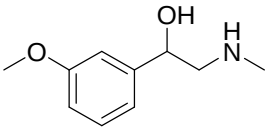
2-Ethylamino-1-phenyl-ethanone hydrochloride (3i).[17] ^{1}H NMR (300 MHz, CD_3OD): d 8.08-8.00 (m, 2H), 7.77-7.68 (m, 1H), 7.63-7.57 (m, 2H), 4.76 (s, 2H), 3.20 (q, 2H, *J* = 7.3 Hz), 1.39 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, CD_3OD): d 190.1, 133.9, 132.9, 128.2, 127.3, 51.4, 42.0, 9.4.



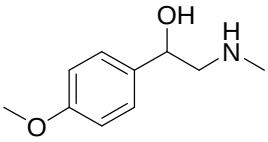
2-Methylamino-1-phenyl-ethanol (4a).[18] ^{1}H NMR (300 MHz, $CDCl_3$): d 7.38-7.23 (m, 5H), 4.76 (dd, 1H, *J* = 4.5, 8.2 Hz), 3.18 (br, 2H), 2.81-2.65 (m, 2H), 2.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): d 142.9, 128.3, 127.4, 125.8, 71.5, 59.2, 35.9.



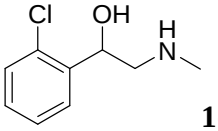
1-(2-Methoxy-phenyl)-2-methylamino-ethanol (4b).[19] ^{1}H NMR (300 MHz, $CDCl_3$): d 7.45 (dd, 1H, *J* = 1.5, 7.5Hz), 7.23-7.13 (m, 1H), 6.96-6.79 (m, 1H), 6.83-6.76 (m, 1H), 5.10 (dd, 1H, *J* = 3.0, 8.7Hz), 3.74 (s, 3H), 3.66 (br, 2H), 2.81-2.72 (m, 1H), 2.67-2.57 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): d 155.8, 131.2, 127.8, 126.4, 120.4, 109.8, 66.4, 57.3, 54.9, 35.5.



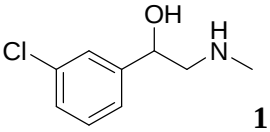
1-(3-Methoxy-phenyl)-2-methylamino-ethanol (4c).[19] ^{1}H NMR (360 MHz, $CDCl_3$): d 7.23-7.17 (m, 1H), 6.93-6.84 (m, 2H), 6.79-6.72 (m, 1H), 4.75-4.67 (m, 1H), 3.80 (br, 2H), 3.75 (s, 1H), 2.67-2.61 (m, 2H), 2.31 (s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): d 159.5, 145.0, 129.2, 118.0, 112.7, 111.1, 71.3, 59.0, 55.00, 54.95, 35.6.



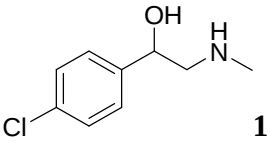
1-(4-Methoxy-phenyl)-2-methylamino-ethanol (4d).[18] ^{1}H NMR (300 MHz, $CDCl_3$): d 7.27 (d, 2H, *J* = 8.0 Hz), 6.87 (d, 2H, *J* = 8.0 Hz), 4.72-4.64 (m, 1H), 3.78 (s, 3H), 2.93 (br, 2H), 2.71-2.66 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): d 159.0, 135.0, 127.0, 113.7, 71.2, 59.2, 55.2, 35.9.



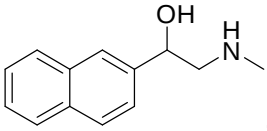
1-(2-Chloro-phenyl)-2-methylamino-ethanol (4e). ^{1}H NMR (400 MHz, $CDCl_3$): d 7.64-7.58 (m, 1H), 7.30-7.20 (m, 2H), 7.19-7.11 (m, 1H), 5.19 (dd, 1H, *J* = 2.7, 9.2 Hz), 4.03 (br, 2H), 2.81-2.74 (m, 1H), 2.58-2.49 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d 140.8, 131.4, 129.0, 128.1, 127.3, 126.8, 67.9, 57.1, 35.5.



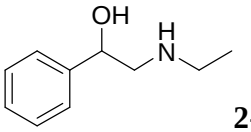
1-(3-Chloro-phenyl)-2-methylamino-ethanol (4f).[20] ^{1}H NMR (300 MHz, $CDCl_3$): d 7.33 (s, 1H), 7.28-7.14 (m, 3H), 4.68 (dd, 1H, *J* = 4.3, 8.4 Hz), 3.41 (br, 2H), 2.72-2.55 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): d 145.3, 134.2, 129.6, 127.5, 125.9, 123.9, 70.9, 59.0, 35.8.



1-(4-Chloro-phenyl)-2-methylamino-ethanol (4g).[21] ^{1}H NMR (300 MHz, $CDCl_3$): d 7.33-7.22 (m, 4H), 4.69 (dd, 1H, *J* = 4.0, 8.6 Hz), 2.95 (br, 2H), 2.79-2.60 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): d 141.5, 133.1, 128.4, 127.1, 70.9, 59.1, 35.9.



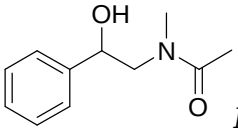
2-Methylamino-1-naphthalen-2-yl-ethanol (4h).[2] ^{1}H NMR (360 MHz, $CDCl_3$): d 7.82-7.76 (m, 4H), 7.50-7.43 (m, 4H), 4.99-4.91 (m, 1H), 3.74 (br, 2H), 2.80-2.75 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): d 140.6, 133.2, 132.8, 128.0, 127.8, 127.6, 126.0, 125.6, 124.4, 123.9, 71.6, 59.0, 35.8.



2-Ethylamino-1-phenyl-ethanol (4i).[22] ^{1}H NMR (300 MHz, $CDCl_3$): d 7.36-7.18 (m, 5H), 4.70 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.12 (br, 2H), 2.81-2.54 (m, 4H),

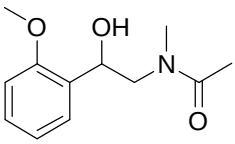
1.03 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): d 143.1, 128.3, 127.3, 125.7, 71.7, 57.0, 43.6, 15.1.

Derivatization of 1,2-Amino Alcohols.



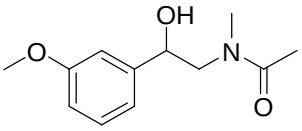
***N*-(2-Hydroxy-2-phenyl-ethyl)-*N*-methyl-acetamide**.[23]

Mixture of rotamers. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.42-7.25 (m, 5H), 4.98-4.93 (m, 0.75H), 4.93-4.87 (m, 0.25H), 4.52-4.48 (m, 1H), 3.68-3.49 (m, 1.5H), 3.38-3.25 (m, 0.5H), 2.96 (s, 0.75H), 2.87 (s, 2.25H), 2.09 (s, 2.25H), 2.00 (s, 0.75H); ^{13}C NMR (75 MHz, $CDCl_3$): d 173.4, 171.6, 142.3, 141.7, 128.7, 128.4, 128.1, 127.5, 125.8, 125.7, 73.6, 71.9, 58.5, 57.4, 38.4, 34.2, 21.7, 21.4; $[\alpha]^{24}_D$ = 66.7° (c = 0.26, $CHCl_3$, 95% *ee*). The two enantiomers could be separated by chiral HPLC (Chiralpak AS column, hexanes:iso-propanol = 90:10).

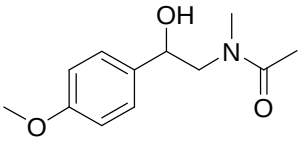


***N*-[2-Hydroxy-2-(2-methoxy-phenyl)-ethyl]-*N*-methyl-acetamide**.

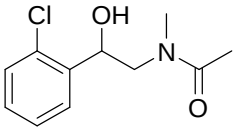
Mixture of rotamers. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.48-7.41 (m, 1H), 7.22-7.13 (m, 1H), 6.95-6.86 (m, 1H), 6.81-6.74 (m, 1H), 5.18-5.08 (m, 1H), 4.47 (br, 1H), 3.77 (s, 1.7H), 3.75 (s, 1.3H), 3.74-3.63 (m, 0.7H), 3.48-3.33 (m, 1.3H), 2.91 (s, 1.4H), 2.79 (s, 1.6H), 2.02-1.95 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): d 173.2, 171.4, 155.5, 155.4, 129.9, 128.2, 128.0, 126.5, 126.3, 120.5, 120.4, 109.7, 109.6, 68.9, 67.0, 56.9, 55.04, 54.96, 54.90, 37.8, 34.2, 21.3, 21.0; APCI-HRMS Calcd. for $C_{12}H_{18}NO_3$ [M+H$^+$]: 224.1287, found 224.1295; $[\alpha]^{24}_D$ = 151.1° (c = 0.13, $CHCl_3$, 84% *ee*). The two enantiomers could be separated by chiral HPLC (Chiralpak AS column, hexanes:iso-propanol:CH_3CN = 90:10:1);.



***N*-[2-Hydroxy-2-(3-methoxy-phenyl)-ethyl]-*N*-methyl-acetamide**.[24] Mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): d 7.18-7.10 (m, 1H), 6.88-6.77 (m, 2H), 6.73-6.67 (m, 1H), 4.82-4.76 (m, 0.6H), 4.73-4.68 (m, 0.4H), 3.68 (s, 3H), 3.48-3.39 (m, 1.6H), 3.23-3.15 (m, 0.4H), 2.81 (s, 1.2H), 2.78 (s, 1.8H), 1.93 (s, 1.8H), 1.85 (s, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$): d 172.5, 171.5, 159.35, 159.28, 143.9, 143.5, 129.1, 129.0, 117.8, 112.74, 112.70, 111.0, 110.8, 72.4, 70.9, 58.3, 56.6, 54.81, 54.79, 38.1, 33.9, 21.3, 21.0; $[\alpha]^{24}_{D}$ = 53.6° (c = 0.11, $CHCl_3$, 92% *ee*). The two enantiomers could be separated by chiral HPLC (Chiralpak AS column, hexanes:iso-propanol = 80:20).

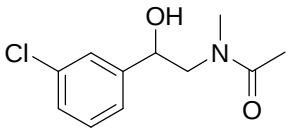


***N*-[2-Hydroxy-2-(4-methoxy-phenyl)-ethyl]-*N*-methyl-acetamide**. Mixture of rotamers. ^{1}H NMR (360 MHz, $CDCl_3$): d 7.22-7.15 (m, 2H), 6.82-6.75 (m, 2H), 4.82-4.75 (m, 0.6H), 4.75-4.67 (m, 0.4H), 4.55 (br, 1H), 3.70 (s, 3H), 3.54-3.35 (m, 1.6H), 3.23-3.14 (m, 0.4H), 3.82 (s, 1.2H), 2.79 (s, 1.8H), 1.95 (s, 1.8H), 1.86 (s, 1.2H); ^{13}C NMR (90 MHz, $CDCl_3$): d 172.5, 117.4, 158.9, 158.7, 134.3, 134.0, 126.8, 126.7, 113.4, 72.3, 70.8, 58.4, 56.8, 55.0, 54.9, 38.1, 34.0, 21.4, 21.1; $[\alpha]^{24}_{D}$ = 89.2° (c = 0.11, $CHCl_3$, 91% *ee*). The two enantiomers could be separated by chiral HPLC (Chiralpak AS column, hexanes:iso-propanol = 80:20).

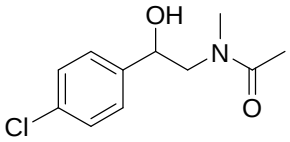


***N*-[2-(2-Chloro-phenyl)-2-hydroxy-ethyl]-*N*-methyl-acetamide**. Mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): d 7.68-7.60 (m, 1H), 7.30-7.22 (m, 2H), 7.21-7.13 (m, 1H), 5.30-5.21 (m, 1H), 3.81-3.71 (m, 0.6H), 3.49-3.34 (m, 1.4H), 2.97 (s, 1.2H), 2.85 (s, 1.8H), 2.07 (s, 1.4H), 2.03 (s, 1.6H); ^{13}C NMR (100 MHz, $CDCl_3$): d 173.7, 171.8, 139.3, 139.2, 131.04, 131.02, 128.88, 128.85, 128.5, 128.4, 127.5, 127.3,

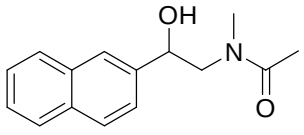
127.0, 126.9, 70.3, 67.9, 56.7, 55.0, 37.8, 33.9, 21.33, 21.27; $[\alpha]^{24}_{D}$ = 47.6° (c = 0.33, $CHCl_3$, 41% *ee*). The two enantiomers could be separated by chiral HPLC (Chiralpak AS column, hexanes:iso-propanol = 95:5).



***N*-[2-(3-Chloro-phenyl)-2-hydroxy-ethyl]-*N*-methyl-acetamide**. Mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): d 7.34 (s, 1H), 7.26-7.14 (m, 3H), 4.89-4.81 (m, 0.7H), 4.81-4.76 (m, 0.3H), 3.52-3.45 (m, 1.7H), 3.27-3.22 (m, 0.3H), 2.89 (s, 1H), 2.86 (s, 2H), 2.01 (s, 2H), 1.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): d 173.0, 171.7, 144.5, 144.1, 134.3, 134.1, 129.7, 129.5, 127.7, 127.4, 125.8, 123.90, 123.85, 72.45, 72.42, 70.5, 58.5, 56.9, 38.4, 34.0, 21.5, 21.3; $[\alpha]^{24}_{D}$ = 64.2° (c = 0.15, $CHCl_3$, 84% *ee*). The two enantiomers could be separated by chiral HPLC (Chiralpak AS column, hexanes:iso-propanol = 95:5).

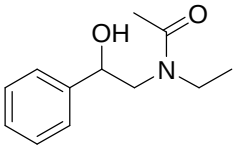


***N*-[2-(4-Chloro-phenyl)-2-hydroxy-ethyl]-*N*-methyl-acetamide**. Mixture of rotamers. ^{1}H NMR (360 MHz, $CDCl_3$): d 7.32-7.24 (m, 4H), 4.95-4.88 (m, 0.8H), 4.89-4.81 (m, 0.2H), 3.62-3.47 (m, 1.8H), 3.31-3.21 (m, 0.2H), 2.93 (s, 0.7H), 2.84 (s, 2.3H), 2.07 (s, 2.2H), 2.01 (s, 0.8); ^{13}C NMR (90 MHz, $CDCl_3$): d 173.4, 171.7, 140.8, 140.3, 133.6, 133.1, 128.7, 128.5, 127.1, 72.8, 70.8, 59.5, 57.3, 38.5, 34.2, 21.7, 21.4; $[\alpha]^{24}_{D}$ = 86.1° (c = 0.20, $CHCl_3$, 90% *ee*). The two enantiomers could be separated by chiral HPLC (Chiralpak AS column, hexanes:iso-propanol = 80:20).



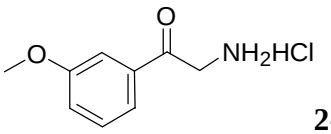
***N*-(2-Hydroxy-2-naphthalen-2-yl-ethyl)-*N*-methyl-acetamide**. Mixture of rotamers. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.84-7.75 (m, 4H), 7.48-7.38 (m, 4H), 5.12-5.04 (m, 0.7H), 5.02-4.94 (m, 0.3H), 3.66-3.54 (m, 1.7H), 3.38-3.37 (m, 0.3H), 2.94 (s, 1.0H), 2.78 (s, 2.0H), 2.03 (s, 2.0H), 2.00 (s, 1.0H); ^{13}C NMR (75 MHz, $CDCl_3$):

d 173.1, 171.7, 139.7, 139.3, 133.14, 133.08, 132.9, 132.8, 128.2, 128.0, 127.8, 127.6, 127.5, 126.1, 126.0, 125.9, 125.7, 124.6, 124.4, 123.8, 123.6, 73.3, 71.5, 58.5, 57.0, 38.3, 34.2, 21.6, 21.4; $[\alpha]^{24}_{D}$ = 110.9° (c = 0.12, $CHCl_3$, 89% *ee*). The two enantiomers could be separated by chiral HPLC (Chiralpak AS column, hexanes:iso-propanol = 80:20);

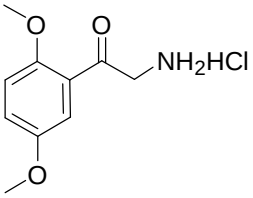


***N*-Ethyl-*N*-(2-hydroxy-2-phenyl-ethyl)-acetamide**. Mixture of rotamers. ^{1}H NMR (300 MHz, $CDCl_3$): d 7.35-7.15 (m, 5H), 4.86 (dd, 0.8H, *J* = 8.1, 2.5 Hz), 4.82-4.75 (m, 0.2H), 3.69-3.58 (m, 0.8H) 3.51-3.42 (m, 0.2H), 3.37-2.98 (m, 3H), 2.05 (s, 2.4H), 1.93 (s, 0.6H), 1.03 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): d 173.4, 142.5, 128.4, 127.5, 125.8, 74.5, 55.3, 45.4, 21.2, 13.6; APCI-HRMS Calcd. for $C_{12}H_{18}NO_2$ [M+H$^+$]: 208.1338, found 208.1340. $[\alpha]^{24}_{D}$ = -72.273° (c = 0.32, $CHCl_3$, 84% *ee*). The two enantiomers could be separated by chiral HPLC (Chiralpak AS column, hexanes:iso-propanol = 90:10).

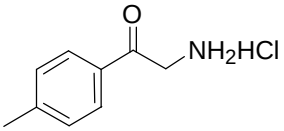
Asymmetric Hydrogenation of α-Primary Amino Ketones.



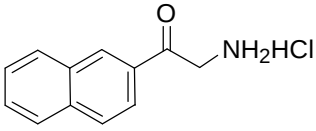
2-Amino-1-(3-methoxyphenyl)ethanone Hydrochloride (12c). ^{1}H NMR (CD_3OD, 360 MHz) δ 7.61 (dddd, *J* = 1.0, 1.6, 2.6, 7.7 Hz, 1H), 7.54 (dd, *J* = 1.6, 2.6 Hz, 1H), 7.48 (dd, *J* = 0.3, 8.2 Hz, 1H), 7.27 (dddd, *J* = 1.0, 2.6, 3.6, 8.3 Hz, 1H), 4.60 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (CD_3OD, 90 MHz) δ 193.1, 161.6, 136.3, 131.3, 121.8, 121.7, 113.6, 56.1, 46.3.



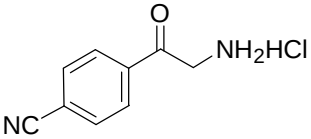
2-Amino-1-(2,5-dimethoxyphenyl)ethanone Hydrochloride (12d). This compound was prepared following the general procedure as an off-white solid (80%). ^{1}H NMR (CD_3OD, 360 MHz) δ 7.48 (d, *J* = 3.2Hz, 1H), 7.24 (dd, *J* = 3.2, 9.1 Hz, 1H), 7.17 (d, *J* = 9.1 Hz, 1H), 4.42 (s, 2H), 3.96 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (CD_3OD, 90 MHz) δ 192.6, 156.3, 155.2, 124.4, 124.0, 115.0, 114.7, 56.8, 56.3, 50.4.



2-Amino-1-*p*-tolylethanone Hydrochloride (12e). This compound was prepared following the general procedure as an off-white solid (74%). ^{1}H NMR (CD_3OD, 300 MHz) δ 7.94 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 4.57 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 193.1, 147.6, 133.0, 131.2, 129.8, 46.5, 22.2.

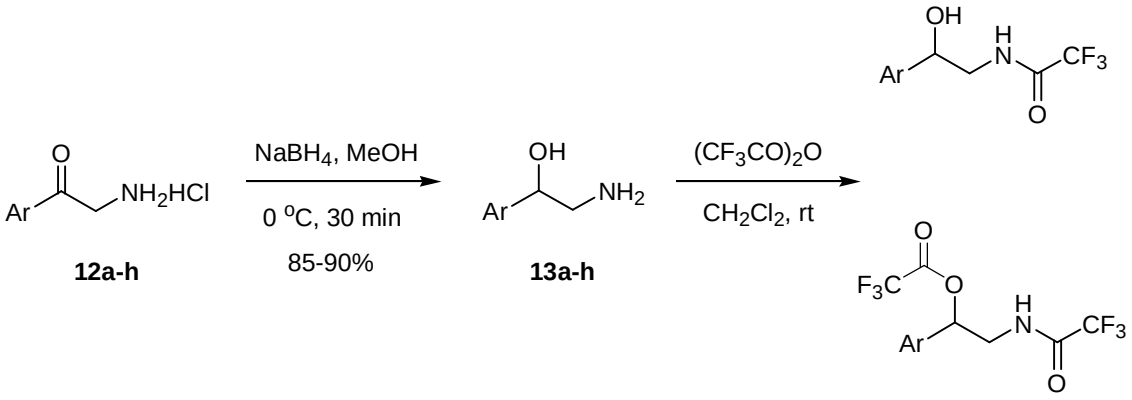


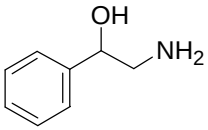
2-Amino-1-naphthalen-2-ylethanone Hydrochloride (12f). This compound was prepared following the general procedure as an off-white solid (70%). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.66 (s, 1H), 8.10-7.96 (m, 4H), 7.70-7.62 (m, 2H), 4.75 (s, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 193.1, 137.7, 133.9, 132.2, 131.8, 130.9, 130.5, 130.0, 129.0, 128.4, 124.0, 46.2.



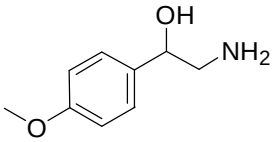
4-(2-Aminoacetyl)benzonitrile Hydrochloride (12g). This compound was prepared following the general procedure as an off-white solid (75%). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.19 (dd, *J* = 1.6, 8.3 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 2H), 4.68 (s, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 192.7, 138.1, 134.0, 129.9, 118.7, 118.6, 46.6.

Scheme 1. Preparation of Racemic Samples

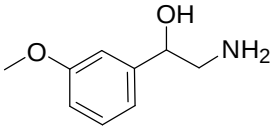




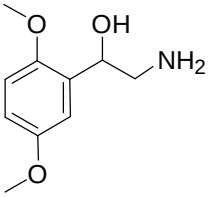
(±)-2-Amino-1-phenylethanol (13a). ^{1}H NMR (CD_3OD, 360 MHz) δ 7.35-7.25 (m, 5H), 4.62 (dd, *J* = 3.9, 7.7 Hz, 1H), 2.93 (dd, *J* = 3.7, 12.8 Hz, 1H), 2.80 (dd, *J* = 7.8, 12.8 Hz, 1H), 2.47 (s br, 3H); ^{13}C NMR (CD_3OD, 90 MHz) δ 143.3, 129.0, 128.1, 126.5, 74.9, 49.9.



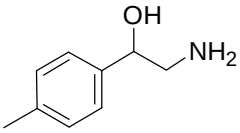
(±)-2-Amino-1-(4-methoxyphenyl)ethanol (13b). This compound was prepared from **12b** by the same method as described for preparation of **13a** in a similar yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.59 (dd, *J* = 3.9, 7.8 Hz, 1H), 3.81 (s, 3H), 2.99 (dd, *J* = 3.8, 12.7 Hz, 1H), 2.80 (dd, *J* = 7.9, 12.7 Hz, 1H), 2.06 (s br, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.0, 134.7, 127.1, 113.8, 74.0, 55.2, 49.3.



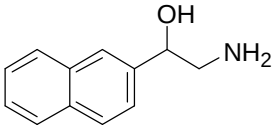
(±)-2-Amino-1-(3-methoxyphenyl)ethanol (13c). This compound was prepared from **12c** by the same method as described for preparation of **13a** in a similar yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.12 (s, 1H), 6.77-6.69 (m, 3H), 4.41(m, 1H), 3.66 (s, 3H), 3.66-1.50 (m, 5H); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.3, 144.6 (m), 128.9, 117.9, 112.3, 111.1, 73.5 (m), 54.7, 48.5 (m).



(±)-2-Amino-1-(2,5-dimethoxyphenyl)ethanol (13d). This compound was prepared from **12d** by the same method as described for preparation of **13a** in a similar yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 6.98 (s, 1H), 6.74-6.67 (m, 2H), 4.83(m, 1H), 3.71 (s, 6H), 3.30-1.50 (m, 5H); ^{13}C NMR (CD_3OD, 75 MHz) δ 153.6, 150.2, 131.9 (m), 112.7, 112.4, 111.1, 69.9 (m), 55.6 (d, *J* = 2.6 Hz), 47.5 (m).

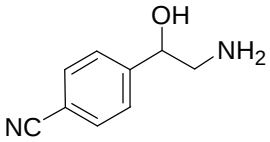


(±)-2-Amino-1-*p*-tolylethanol (13e). This compound was prepared from **12e** by the same method as described for preparation of **13a** in a similar yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.21 (d, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 2H), 4.57 (m, 1H), 2.91 (m, 1H), 2.79 (m, 1H), 2.32 (s, 3H), 2.11 (s br, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 140.0, 137.1, 129.1, 125.9, 74.2, 49.4, 21.2.

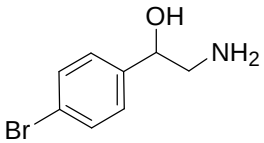


(±)-2-Amino-1-naphthalen-2-ylethanol (13f). This compound was prepared from **12f** by the same method as described for preparation of **13a** in a similar yield. ^{1}H NMR (CD_3OD, 360 MHz) δ 7.79-7.76 (m, 4H), 7.46-7.38 (m, 3H), 4.74

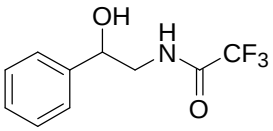
(m, 1H), 2.97-2.85 (m, 2H), 2.35 (s br, 3H); ^{13}C NMR (CD_3OD, 90 MHz) δ 141.1, 133.2, 132.9, 128.1, 127.8, 127.6, 126.1, 125.7, 124.6, 124.0, 74.3, 49.1.



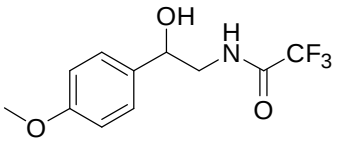
(±)-4-(2-Amino-1-hydroxyethyl)benzonitrile (13g). This compound was prepared from **12g** by the same method as described for preparation of **13a** in a similar yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.53 (d, *J* = 6.3 Hz, 2H), 7.38 (d, *J* = 6.3 Hz, 2H), 4.60 (m, 1H), 3.70-1.70 (m, 5H); ^{13}C NMR (CD_3OD, 75 MHz) δ 148.3, 131.9, 126.3, 118.6, 110.6, 73.1, 48.8.



(±)-2-Amino-1-(4-bromophenyl)ethanol (13h). This compound was prepared from **12h** by the same method as described for preparation of **13a** in a similar yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 2H), 4.55 (m, 1H), 3.50-2.20 (m, 5H); ^{13}C NMR (CD_3OD, 100 MHz) δ 141.5, 131.4, 127.5, 121.2, 73.2, 48.9.

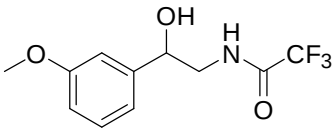


2,2,2-Trifluoro-*N*-(2-hydroxy-2-phenylethyl)acetamide. The two enantiomers were separated using a Chiral Select 1000 column (170 ^{o}C). ^{1}H NMR (CD_3OD, 400 MHz) δ 9.19 (s br, 1H), 7.39-7.32 (m, 4H), 7.29-7.25 (m, 1H), 4.80 (dd, *J* = 5.4, 7.5 Hz, 1H), 3.51-1.41 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 159.3 (q, *J* = 34.0 Hz), 143.8, 129.8, 129.2, 127.6, 117.9 (q, *J* = 284.2 Hz), 73.2, 48.6.

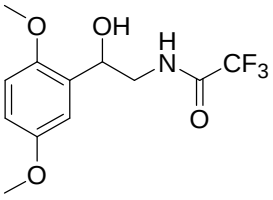


(±)-2,2,2-Trifluoro-*N*-[2-hydroxy-2-(4-methoxyphenyl)ethyl]acetamide. This compound was prepared from **13b** following the

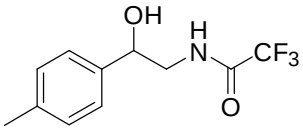
general procedure. The two enantiomers were separated using a Chiral Select 1000 column (170 ^{o}C). ^{1}H NMR (CD_3OD, 300 MHz) δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.93 (s br, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 4.70 (dd, *J* = 3.3, 8.4 Hz, 1H), 3.71 (s, 3H), 3.67-3.60 (m, 1H), 3.30-3.25 (m, 1H), 2.73 (s br, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.8, 157.7 (q, *J* = 37.3 Hz), 132.8, 127.2, 116.0 (q, *J* = 287.7 Hz), 114.3, 72.1, 55.5, 46.8.



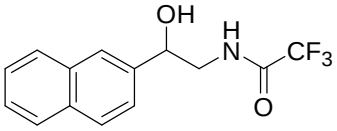
(±)-2,2,2-Trifluoro-*N*-[2-hydroxy-2-(3-methoxyphenyl)ethyl]acetamide. This compound was prepared from **13c** following the general procedure. The two enantiomers were separated using a Chiral Select 1000 column (170 ^{o}C). ^{1}H NMR (CD_3OD, 360 MHz) δ 7.26-7.22 (m, 1H), 7.06 (s br, 1H), 6.88-6.85 (m, 2H), 6.83-6.80 (m, 1H), 4.77 (dd, *J* = 3.3, 8.3 Hz, 1H), 3.75 (s, 3H), 3.69 (ddd, *J* = 3.6, 7.1, 10.8 Hz, 1H), 3.30 (ddd, *J* = 4.7, 8.4, 13.4 Hz, 1H), 3.16 (s br, 1H); ^{13}C NMR (CD_3OD, 90 MHz) δ 159.8, 157.6 (q, *J* = 37.2 Hz), 142.2, 129.8, 117.9, 115.8 (q, *J* = 287.6 Hz), 113.8, 111.2, 72.1, 55.2, 46.6.



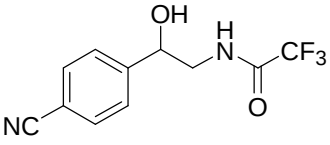
(±)-*N*-[2-(2,5-Dimethoxyphenyl)-2-hydroxyethyl]-2,2,2-trifluoroacetamide. This compound was prepared from **13d** following the general procedure. The two enantiomers were separated using a Chiral Select 1000 column (170 ^{o}C). ^{1}H NMR (CD_3OD, 300 MHz) δ 6.93-6.82 (m, 4H), 5.05-4.99 (m, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.80-3.76 (m, 1H), 3.50 (ddd, *J* = 4.5, 7.9, 12.9 Hz, 1H), 3.10 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 157.9 (q, *J* = 36.8 Hz), 154.3, 150.8, 129.6, 116.3 (q, *J* = 287.8 Hz), 114.1, 113.4, 112.0, 69.5, 56.2, 45.6.



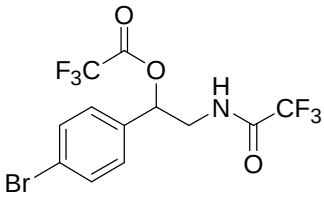
(±)-2,2,2-Trifluoro-*N*-(2-hydroxy-2-*p*-tolylethyl). This compound was prepared from **13e** following the general procedure. The two enantiomers were separated using a Chiral Select 1000 column (170 ^{o}C). ^{1}H NMR (CD_3OD, 360 MHz) δ 7.22 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.82 (s, br, 1H), 4.82 (dd, *J* = 3.4, 8.5 Hz, 1H), 3.79-3.73 (m, 1H), 3.34 (ddd, *J* = 4.3, 8.5, 13.3 Hz, 1H), 2.40 (s br, 1H), 2.33 (s, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 157.7 (q, *J* = 34.1 Hz), 138.6, 137.7, 129.7, 125.9, 116.0 (q, *J* = 285.9 Hz), 72.4, 46.7, 21.4.



(±)-2,2,2-Trifluoro-*N*-(2-hydroxy-2-naphthalen-2-ylethyl)acetamide. This compound was prepared from **13f** following the general procedure. The two enantiomers were separated using a Chiral Select 1000 column (185 ^{o}C). ^{1}H NMR (CD_3OD, 300 MHz) δ 7.86-7.81 (m, 4H), 7.52-7.42 (m, 3H), 6.81 (s br, 1H), 5.03 (dd, *J* = 3.5, 8.5 Hz, 1H), 3.89 (ddd, *J* = 3.6, 7.5, 11.1 Hz, 1H), 3.43 (ddd, *J* = 4.3, 8.5, 13.3 Hz, 1H), 2.44 (s br, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 157.7, 137.8, 133.3, 133.1, 128.8, 128.0, 127.8, 126.6, 126.4, 124.8, 123.3, 117.7, 72.6, 46.5.

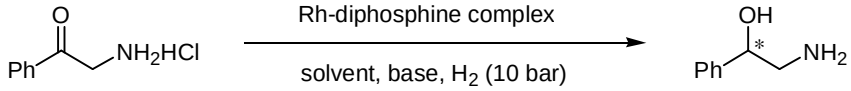


(±)-*N*-[2-(4-Cyanophenyl)-2-hydroxyethyl]-2,2,2-trifluoroacetamide. This compound was prepared from **13g** following the general procedure. The two enantiomers were separated using a Chiral Select 1000 column (170 ^{o}C). ^{1}H NMR (CD_3OD, 300 MHz) δ 7.71 (dd, *J* = 1.7, 6.6 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 4.90-4.86 (m, 1H), 3.54-3.40 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 159.2 (q, *J* = 37.1 Hz), 149.3, 133.3, 128.2, 119.7, 117.5 (q, *J* = 285.2 Hz), 112.5, 72.1, 47.8.



(±)-Trifluoroacetic Acid 1-(4-Bromophenyl)-2-(2,2,2-trifluoroacetylamino) ethyl Ester. The two enantiomers were separated using a Chiral Select 1000 column (170 ^{o}C). ^{1}H NMR (CD_3OD, 300 MHz) δ 7.61-7.57 (m, 2H), 7.29-7.25 (m, 2H), 6.82 (s br, 1H), 6.02 (dd, *J* = 4.3, 8.2 Hz, 1H), 3.93-3.74 (m, 2H), 3.50 (ddd, *J* = 4.5, 7.9, 12.9 Hz, 1H), 3.10 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 157.7 (q, *J* = 37.8 Hz), 156.4 (q, *J* = 43.4 Hz), 133.3, 132.5, 127.9, 124.1, 115.5 (q, *J* = 287.7 Hz), 114.2 (q, *J* = 285.8 Hz), 77.0, 43.7.

Table 2. Reaction Condition Screening for the Hydrogenation of a-Primary Amino Ketone **12a**.



12a **13a**

entry[a]	catalyst	solvent	base (equiv.)	temp.	yield (%)[b]	*ee* (%) (config.)[c]
1	[Rh(*R*,*R*,*S*,*S*-DuanPhos)(nbd)]SbF_6 (**11**)	MeOH	K_2CO_3 (0.5)	50 °C	90	72(*S*)
2	**11**	EtOH	K_2CO_3 (0.5)	50 °C	90	62(*S*)
3	**11**	*i*-PrOH	K_2CO_3 (0.5)	50 °C	90	42(*S*)
4	**11**	CH_2Cl_2	K_2CO_3 (0.5)	50 °C	<50	63(*S*)
5	**11**	$CF_2HCF_2CH_2OH$	K_2CO_3 (0.5)	50 °C	>95	78(*S*)
6	**11**	TFE	K_2CO_3 (0.5)	50 °C	>95	88(*S*)
7	**11**	**TFE**	**K_2CO_3 (0.5)**	**rt**	**>95**	**88(*S*)**
8	**11**	TFE	TEA (1.0)	50 °C	>95	88(*S*)
9	[Rh(*R*,*R*,*S*,*S*-DuanPhos)(cod)]BF_4	TFE	K_2CO_3 (0.5)	50 °C	>95	87(*S*)
10	[Rh(*R*,*R*,*S*,*S*-DuanPhos)Cl]$_2$	TFE	K_2CO_3 (0.5)	50 °C	>95	87(*S*)
11	[Rh(*S*,*S*,*R*,*R*-TangPhos)(ocd)]BF_4	TFE	K_2CO_3 (0.5)	50 °C	>95	87(*S*)
12	[Rh(*S*-Binapine)(cod)]BF_4	TFE	K_2CO_3 (0.5)	50 °C	>95	82(*S*)
13	[Rh(*S*,*S*-Me-DuPhos)(cod)]BF_4 (**9**)	TFE	K_2CO_3 (0.5)	50 °C	>95	80(*S*)
14	[Rh(*S*,*S*-Et-DuPhos)(cod)]BF_4 (**10**)	TFE	K_2CO_3 (0.5)	50 °C	>95	85(*S*)
15[d]	**11**	TFE	K_2CO_3 (0.5)	50 °C	80[e]	84(*S*)
16[d]	**9**	TFE	K_2CO_3 (0.5)	50 °C	40[e]	79(*S*)
17[d]	**10**	TFE	K_2CO_3 (0.5)	50 °C	<20	72(*S*)

[a] The hydrogenation was carried out under described conditions for each entry with 0.5 mol % of Rh-precatalyst following the general procedure. [b] Estimated yield based on ^{1}H NMR of crude product. [c] The enantiomeric excess of **13a** was determined by chiral GC (Chiral Select 1000 column) after conversion to the correspondig *N*-acyl derivative (Cf. Experimental Section). [d] 0.02 mol% of Rh-precatalyst was used (S/C = 5000). [e] Isolated yield.

[1] D. N. Ridge, J. W. Hanifin, L. A. Harten, B. D. Johnson, J. Menschik, G. Nicolau, A. E. Sloboda, D. E. Watts, *J. Phar. Sci.* **1979**, *22*, 1385-1389.
[2] E. D. Bergmann, Z. Goldschmidt, *J. Med. Chem*. **1968**, *11*, 1121-1125.

[3] D. Chen, H. Sun, Z. Zeng, Y. Jiang, Faming Zhuanli Shenqing Gongkai Shuomingshu, 1999, pp25.
[4] B. M. Trost, V. S. C. Yeh, H. Ito, N. Bremeyer, *Org. Lett.* **2002**, *4*, 2621-2623.
[5] A. Kamal, *Tetrahedron: Asymmetry* **2004**, *15*, 3939-3944.
[6] D. G. Thomas, A. H. Nathan, *J. Am. Chem. Soc.* **1948**, *70*, 331-334.
[7] A. Alberola, L. Calvo, A. Gonzalez-Ortega, A. P. Encabo, M. C. Sanudo, *Synthesis*, **2001**, *43*, 1941-1948.
[8] E. L. Martin, C. R. Noller, F. M. McMillan, *Org. Synth.* **1943**, *2*, 499-500; **1935**, *15*, 64-65.
[9] O. S. Radchenko, V. L. Novikov, R. H. Willis, P. T. Murphy, G. B. Elyakov, *Tetrahedron Lett.* **1997**, *38*, 3581-3584.
[10] A. Pelter, R. S. Ward, R. R. Rao, *Tetrahedron*, **1985**, *41*, 2933-2938.
[11] F. Giovanni, F. Claudio, S. Stefano, C. Marco, K. Joseph, *J. Agric. Food. Chem.* **2002**, *50*, 2748-2754.
[12] J. Apelt, X. Ligneau, H. H. Pertz, J. –M. Arrang, C. R. Ganellin, J. –C. Schwartz, W. Schunack, H. Stark, *J. Med. Chem.* **2002**, *45*, 1128-1141.
[13] C. J. Cavallito, A. E. Soria, J. O. Hoppe, *J. Am. Chem. Soc.* **1950**, *72*, 2661-2665.
[14] C.-J. Wang, X. Sun, X. Zhang, *Angew. Chem. Int. Ed.* **2005**, *44*, 4933-4935.
[15] C. Fabbri, M. Bietti, O. Lanzalunga, *J. Org. Chem.* **2005**, *70*, 2720-2728.
[16] M. H. Holshouser, *J. Pharm. Sci.* **1986**, *75*, 619-621.
[17] E. D. Sych, Z. N. Belaya, O. V. Moreiko, *Khim. Geterotsikl. Soedin.* **1970**, 282-285.
[18] J. Ortiz, A. Guijarro, M. Yus, *Tetrahedron*, **1999**, *55*, 4831-4832.
[19] B. L. Goodwin, C. R. J. Ruthven, M. Sandler, *Gen. Pharmacol.* **1997**, *28*, 535-543.
[20] A. Bai, Z. Guo, W. Hu, F. Shen, G. Cheng, *Chin. Chem. Lett.* **2001**, *12*, 775-778.
[21] U. Amschler, O. E. Schultz, *Arzneim.-Forsch*. **1972**, *22*, 2095-2096.
[22] M. Masui, Y. Kamada, S. Ozaki, *Chem. Pharm. Bull.* **1983**, *31*, 122-127.
[23] M. K. Chmielewski, V. Marchan, J. Cieslak, A. Grajkowski, V. Livengood, U. Muench, A. Wilk, S. L. Beaucage, *J. Org. Chem.* **2003**, *68*, 10003-10012.
[24] H. Bretschneider, *Monatsh. Chem.* **1949**, *80*, 517-529.