Asymmetric Reductive Amination: Convenient Access to Enantioenriched Alkyl-Alkyl or Aryl-Alkyl Substituted \( \alpha \)-Chiral Primary Amines


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SUPPORTING INFORMATION

General Remarks

NMR spectra were recorded on JEOL ECX 400 spectrometer, operating at 400 MHz \((^1\text{H})\) and 100 MHz \((^1\text{C})\) respectively. Chemical shifts \((\delta)\) were reported in parts per million (ppm) downfield from TMS \((= 0)\) or relative to CHCl\(_3\) \((7.26 \text{ ppm})\) for \(^1\text{H}\) NMR. For \(^1\text{C}\) NMR, chemical shifts were reported in the scale relative to CHCl\(_3\) \((77.0 \text{ ppm})\) as an internal reference. Multiplicities are abbreviated as: s, singlet; d, doublet; q, quartet; m, multiplet; br, broad. The coupling constants are measured in Hertz. FTIR spectra were obtained on Nicolet Avatar 370 spectrometer. Mass spectra were recorded on a Finnigan MAT 95 (EI) with an ionization potential of 70 eV. Elemental analyses were performed at Analytische Laboratorien, Lindlarp, Germany on an Elementar Vario EL III instrument. For amine products 2, reaction progress and d.r. measurements were obtained using Shimadzu GC-2010 instrument on a Rtx-5 amine column (Restec, 30 m x 0.25mm); \(T_{\text{inj}} = 300 \degree \text{C} \text{and } T_{\text{det}} = 300 \degree \text{C} \text{were always constant; Program A: 50 \degree \text{C} \text{(1 min); then 20 \degree \text{C/min to 280 } \degree \text{C, then hold 2 min; Program B: 50 \degree \text{C (1 min), then 5 \degree \text{C/min to 210\degree } \text{C, then hold 2 min and Program C: 50 \degree \text{C (1 min), then 14 \degree \text{C/min to 280 \degree } \text{C, then hold 5 min. For hydrogenolyzed products (primary amines, 3) the enantiomeric excess of the trifluoroacetamide derivative was determined by gas chromatography using a Shimadzu GC-2010 instrument on a Chiraldex B-DP column (Astec, 30 m x 0.25mm); \(T_{\text{inj}} = 200 \degree \text{C}, T_{\text{det}} = 200\degree \text{C and carrier gas He @ 23.6 psi were constant; Program D: 150 \degree \text{C, isothermal, split ratio 100:1; Program E: 145 \degree \text{C, isothermal, split ratio 100:1; Program F: 116 \degree \text{C, isothermal, split ratio 100:1. The enantiomeric excess of the benzoyl derivative of 3f was determined by HPLC using a Shimadzu CLASS-VP instrument on a Chiralcel OD-H column (Diacel, 0.46 cm x 25 cm); \(n\)-hexane/i-ProOH = 16/1, 0.1 mL/min, 254 nm, \(T_{\text{col}} = 15 \degree \text{C, 22 bar. Column chromatography was performed using silica gel 60 (0.040 – 0.063 mm). Thin-layer chromatography (TLC) was performed using precoated plates of silica gel 60 F\(_{254}\) and visualized under ultraviolet irradiation (254 nm). All reagents were obtained from Sigmaaldrich and used without further purification. 99.999% grade Ti(O\text{iPr})\(_4\) was used for all screening reactions (2.0-5.0 mmol) and 97.0% grade Ti(O\text{iPr})\(_4\) was used for all large scale reactions (30-69 mmol). The (R)-\(\alpha\)-methylbenzylamine was purchased from Aldrich (Catalog number, 115541, 98% pure and 95.5% ee) and (S)-\(\alpha\)-methylbenzylamine was purchased from Aldrich (Catalog number, 115568, 98% pure and 97.5% ee). The Raney-Nickel (in water) was purchased from Fluka (Catalog number, 83440). Pd(OH)\(_2\)/C \((\leq 50\% \text{ water, 20 wt \% loading (dry basis) was purchased from Aldrich (Catalog number, 212911). Pd/C \((\leq 50\% \text{ water, 5 wt \% loading (dry basis) was purchased from Aldrich (Catalog number, 276707). Pt/C (1-4\% \text{ water, 5 wt \% loading) was purchased from Aldrich (Catalog number, 205931). All reactions were performed under an argon atmosphere and under anhydrous conditions. General procedure for asymmetric reductive amination of prochiral ketones. In an anhydrous solvent (0.50–0.83 M) a prochiral ketone (2.50-5.00 mmol) \((1), \text{ titanium tetraisopropoxide (1.25 equiv), and (R)- or (S)-\(\alpha\)-methylbenzylamine (1.00-1.10 equiv) were combined and stirred at room temperature for 30 min. A heterogeneous catalyst Raney Ni (70-100 wt \%, pre-triturated with EtOH \) was used without further purification. 99.999% grade Ti(O\text{iPr})\(_4\) was used for all screening reactions (2.0-5.0 mmol) and 97.0% grade Ti(O\text{iPr})\(_4\) was used for all large scale reactions (30-69 mmol).
(x2) and then the anhydrous reaction solvent (x2), Pt/C (0.30 mol %), or Pd/C (0.23 mol %) was then added and the vessel pressurized at 120 psi (8.3 bar) of hydrogen. At complete conversion (<1 area % of ketone by GC), the reaction mixture was quenched by stirring with aqueous 1.0 M NaOH (10-15 mL) for 1 h. The heterogeneous mixture was then filtered through a bed of celite and the celite subsequently washed with CH₂Cl₂ or EtOAc. The filtrate was concentrated (rotary evaporator, T ≤ 25 °C) to remove the low boiling organics and the remaining aqueous solution was then extracted with CH₂Cl₂ (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered, concentrated (rotary evaporator, T ≤ 25 °C). Des were then determined by analysis of the crude product. The diastereomeric yield is determined after flash chromatography, using the following protocol. Due to the high volatility of most of the amine products 2, the column fractions are rotary evaporated (T ≤ 25 °C), and then ethereal HCl (1.50-2.00 equiv) is added. After very brief stirring, the ethereal solution of diastereomeric amine HCl salts is rotary evaporated and the resulting solid or viscous liquid high vacuum dried for ≥24 h. The major (R,R) or (S,S) diastereomer was isolated in pure form only after further careful flash chromatography of the free amine diastereomeric mixture.

### Asymmetric reductive amination of Raney Nickel ketone substrates.

<table>
<thead>
<tr>
<th>Ketone [R'C(O)R²] substrates requiring Raney Ni, 2.5 – 5.0 mmol scale</th>
<th>Wt % Raney Ni</th>
<th>Turnover number[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>la</td>
<td>c-hexyl</td>
<td>methyl</td>
</tr>
<tr>
<td>lb</td>
<td>i-propyl</td>
<td>methyl</td>
</tr>
<tr>
<td>lc</td>
<td>phenyl</td>
<td>methyl</td>
</tr>
<tr>
<td>ld</td>
<td>i-butyl</td>
<td>methyl</td>
</tr>
<tr>
<td>le</td>
<td>PhCH₂CH₂-</td>
<td>methyl</td>
</tr>
<tr>
<td>lf</td>
<td>ethyl</td>
<td>methyl</td>
</tr>
<tr>
<td>lg</td>
<td>n-hexyl</td>
<td>methyl</td>
</tr>
<tr>
<td>lh</td>
<td>n-butyl</td>
<td>methyl</td>
</tr>
<tr>
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<td>n-propyl</td>
</tr>
<tr>
<td>lj</td>
<td>phenyl</td>
<td>n-propyl</td>
</tr>
</tbody>
</table>

[a] Defined as: mmoles of ketone per gram of Raney Ni used. [b] These ketones have been examined at the 5.0 or 10.0 g scale, see this experimental and experimental section of reference 41.

### Bis((R)-1-phenylethyl)amine (2c)

![Chemical structure of Bis((R)-1-phenylethyl)amine (2c)](image)

Reaction details: 2.50 mmol scale, 0.50 M; solvent: EtOAc (5.0 mL); pre-stirred 30 min; hydrogen pressure 120 psi (8.3 bar); Raney Ni (300 mg, 100 wt %), room temperature. Reaction time: 8 h; 95% de. The mixture of diastereomers was isolated as a colorless viscous oil (0.48 g, 85% yield) using flash chromatography (EtOAc/heptane/NH₄OH, 25:74:1). GC (program A, see General section): retention time [min]: major (R,R)-2c isomer, 11.4; minor (S,R)-2c isomer, 11.6. Based on the previous characterization of this compound we have assigned the major diastereomer as the (R,R)-isomer.¹¹ (Rf 0.44) ¹H NMR (CDCl₃, 400 MHz): δ 7.21-7.35 (10H, m), 3.49 (1H, q, J = 6.6 Hz), 1.55 (1H, br.s), 1.27 (6H, d, J = 6.6 Hz).
Scale-up reaction of [(2R)-N-((R)-1-phenylethyl)butan-2-amine] (2f)

\[
\begin{align*}
\text{(S,S)-2f} \\
\text{HN} & \quad \text{Ph}
\end{align*}
\]

A mixture of 2-butanone (1.00 equiv, 69.30 mmol, 6.2 mL), titanium tetraisopropoxide (97% grade) (1.25 equiv, 86.7 mmol, 25.3 mL), and (S)-\(\alpha\)-methylbenzylamine (1.10 equiv, 76.2 mmol, 9.7 mL) in THF (99.0 mL) were combined. This mixture is prestirred for 15 min and then hydrogenated at 120 psi (8.3 bar) in the presence of Raney Ni (1.5 g) (prewashed with EtOH (x3) and then with THF (x3)) under vigorous overhead stirring (1100 rpm) at 30 \(\degree\)C. The reaction was monitored by GC.

At complete conversion, 12 h, the reaction mixture was treated with an aqueous solution of 4.0 M NaOH (30 mL) and stirred for 2 h using the overhead stirrer (300 rpm). The solution was then filtered through celite and the celite washed with diethylether (4 x 30 mL). The filtrate was rotary evaporated (T \(\leq\) 25 \(\degree\)C) to remove most of the THF, and the remaining aqueous solution then extracted with Et\(_2\)O (3 x 50 mL). The combined extracts were then rotary evaporated (T \(\leq\) 25 \(\degree\)C) and aqueous HCl (40.0 mL, 4.0 M) was added. This aqueous solution was washed twice with Et\(_2\)O (2 x 40 mL) to remove the neutral organic materials. The aqueous acid layer was basified with aq. NaOH (10 ml, 2.0 M) to pH 10-12 and the free amine extracted with CH\(_2\)Cl\(_2\) (4 x 50 mL). The combined organic extracts were reduced to 30 mL, treated with aqueous saturated NaCl (30 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated (rotary evaporator, T \(\leq\) 25 \(\degree\)C). The qualitatively pure secondary amine was then treated with ethereal HCl (3.0 M, 2.00 equiv) to afford the HCl salt (14.0 g, 94% yield, 74\% de) after high vacuum drying (\(\geq\) 24 h). GC (program B, see General section). GC retention time [min]: major (S,S)-2f isomer, 20.22; minor (R,S)-2f isomer, 19.94.

\[\text{R}_f = 0.56 \text{ (heptane/EtOAc/NH}_4\text{OH, 29:20:1)}.\] Major (S,S)-2f: IR (KBr): 3432, 3041, 2966, 2939, 1589, 1456 cm\(^{-1}\); \(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.21-7.34 (5H, m), 3.86 (1H, q, \(J = 6.4\) Hz), 2.41-2.49 (1H, m), 1.48-1.58 (1H, m), 1.33 (3H, d, \(J = 6.4\) Hz), 1.24-1.28 (1H, m), 0.95 (3H, d, \(J = 4.4\) Hz), 0.84 (3H, d, \(J = 7.4\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 136.6, 129.4, 129.1, 127.9, 56.2, 53.5, 24.1, 21.3, 16.9, 9.8; LRMS (EI): m/z (%): 177 (35), 162 (14), 148 (39), 105 (100), 77 (6), 58 (10), 44 (57); Anal. calcld (%) for C\(_{12}\)H\(_{20}\)ClN: C, 67.43; H, 9.43; Cl, 16.59; N, 6.55; Found: C, 67.34; H, 9.47; Cl, 16.57, N, 6.51.

(2R)-N-((R)-1-phenylethyl)hexan-2-amine (2h)

\[
\begin{align*}
\text{(R,R)-2h} \\
\text{HN} & \quad \text{Ph} \\
\text{H}_3\text{C} & \quad \text{CH}_3
\end{align*}
\]

Reaction details: 5.00 mmol scale, 0.83 M; solvent: CH\(_2\)Cl\(_2\) (6.0 mL); prestirred 15 min; Raney Ni (500 mg, 100 wt %); hydrogen pressure (60 psi); reaction time: 8 h; 66\% de. The mixture of diastereomers was isolated as a colorless viscous oil (0.81 g, 74\% yield) using flash chromatography (heptane/EtOAc/NH\(_4\)OH, 89:5:5:5). The major diastereomer was obtained by recrystallization. GC (program C, see General section): retention time [min]: major (R,R)-2h isomer, 12.44; minor (S,R)-2h isomer, 12.27. Major (R,R)-2h: \(R_f = 0.44 \text{ (heptane/EtOAc/NH}_4\text{OH, 82:13:5)}.\) IR (KBr): 3432, 2958, 2858, 1450 cm\(^{-1}\); \(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.19-7.33 (5H, m), 3.87 (1H, q, \(J = 6.5\) Hz), 2.49 (1H, m), 1.49 (1H, m), 1.31 (3H, d, \(J = 6.5\) Hz), 1.15-1.28 (6H, m), 0.94 (3H, d, \(J = 6.34\) Hz), 0.88 (3H, t, \(J = \))
6.95 Hz; $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 146.4, 128.3, 126.6, 126.5, 55.1, 50.1, 36.0, 27.9, 24.6, 22.9, 21.3, 14.1; LRMS (EI): m/z (%): 205 (M$^+$, 2), 190 (14), 148 (55), 105 (100), 44 (87); Anal calcd (%) for C$_{14}$H$_{23}$N: C, 81.89; H, 11.29; N, 6.82; Found C, 81.79; H, 11.41; N, 6.78.

(1R)-1-phenyl-N-((R)-1-phenylethyl)butan-1-amine (2j)

\[
\text{HN} \quad \text{Ph}
\]

(R,R)-2j

Reaction details: 5.01 mmol scale, 0.50 M; solvent: EtOAc (10.0 mL); prestirred for 2 h; hydrogen pressure 120 psi (8.3 bar); Raney Ni (500 mg, 100 wt %); 35 °C. Reaction time: 15 h; 94% de. The mixture of diastereomers was isolated as a colorless syrupy liquid (1.17 gm, 92% yield). An analytically pure sample of the (R,R)-2j diastereomer was obtained by repeated recrystallization of the HCl salt of the diastereomeric mixture from hexane:EtOH. GC (program C, see General section): retention time [min]: major (R,R)-2j isomer, 15.6; minor (S,R)-2j isomer, 15.8.

Major (R,R)-2j: R$_f$ = 0.6 (cyclohexane/EtOAc/NH$_4$OH, 15:83:2) [R$_f$ of (S,R)-2j diastereomer = 0.6]; IR (KBr): 3445, 2958, 1602, 1492, 1453 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.34-7.15 (10H, m), 3.47 (1H, q, $J$ = 6.4 Hz), 3.28 (1H, t, $J$ = 6.8 Hz), 1.60 (2H, m), 1.51 (1H, m), 1.24 (3H, d, $J$ = 6.8 Hz), 1.08 (1H, m), 0.77 (3H, t, $J$ = 7.2 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 145.8, 144.9, 128.3, 128.25, 127.2, 126.7, 59.8, 54.8, 41.0, 25.1, 19.6, 14.0; LRMS (EI): m/z (%): 253 (4) [M$^+$], 238 (25), 210 (100), 105 (86), 91 (33), 77 (14); Anal. calcd (%) for C$_{18}$H$_{23}$N: C, 85.32; H, 9.15; N, 5.53; Found: C, 84.75; H, 9.24; N, 5.48.

Asymmetric reductive amination of Pt/C ketone substrates.

(2R)-3,3-dimethyl-N-((R)-1-phenylethyl)butan-2-amine (2k)

\[
\text{HN} \quad \text{Ph}
\]

(R,R)-2k

Reaction details: 5.00 mmol scale, prestirred for 2 h (neat); 0.83 M; solvent: hexane (6.0 mL); hydrogen pressure 120 psi (8.3 bar); Pt/C (60.0 mg, 0.3 mol %) [the 60 mg of Pt/C was added in three equal portion, thus 20 mg at t= 0 h, t= 3 h, and finally at t= 6 h]; 50 °C. Reaction time: 20 h; 87% de. The mixture of diastereomers was isolated as a colorless viscous oil (0.78 g, 76% yield) using flash chromatography (cyclohexane/EtOAc/NH$_4$OH, 94.5:1.5:4). The major diastereomers was separately obtained by further flash chromatography (cyclohexane/EtOAc/NH$_4$OH, 95:1:4). GC (program C, see General section): retention time [min]: major (R,R)-2k isomer, 11.97; minor (S,R)-2k isomer, 11.76.

Major (R,R)-2k: R$_f$ = 0.47 (cyclohexane/EtOAc/NH$_4$OH, 91:6:3); IR (KBr): 3427, 3027, 2960, 2868, 2361, 1601 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.19-7.36 (5H, m), 3.77 (1H, q, $J$ = 6.5 Hz), 2.29 (1H, q, $J$ = 6.5 Hz), 1.27 (3H, d, $J$ = 6.5 Hz), 0.84-0.89 (12H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 147.6, 128.2, 126.7, 126.6, 59.5, 57.0, 34.7, 26.5, 23.6, 15.9; LRMS (EI), m/z (%): 205.1.
(1R)-2,2-dimethyl-N-((R)-1-phenylethyl)cyclopentanamine (2l)

Reaction details: 5.00 mmol scale, pre-stirred for 3 h (neat); 0.83 M; solvent: EtOH (6.0 mL); hydrogen pressure 120 psi (8.3 bar); Pt/C (60.0 mg, 0.3 mol %) [the 60 mg of Pt/C was added in four equal portions, thus 15 mg at t= 0 h, t= 2 h, t= 4 h, and finally at t= 8 h]; 50 °C. Reaction time: 20 h; 92% de. Purification by column chromatography (cyclohexane/EtOAc/NH4OH, 88:10:02) provided the mixture of diastereomers as a colorless viscous liquid, which was then converted to the HCl salt (1.04 g, 82% yield). The analytically pure major (R,R)-2l diastereomer was obtained by further column chromatography (cyclohexane/EtOAc/NH4OH, 90:8:2) of the diastereomeric amine mixture. GC (program C, see General section): retention time [min]: major (R,R)-2l isomer, 13.4; minor (S,R)-2l isomer, 13.3.

Major (R,R)-2l: Rf = 0.64 (cyclohexane/EtOAc/NH4OH, 75:20:5) [Rf of (S,R)-2l diastereomer = 0.5]; IR (KBr): 3441, 2955, 2864, 1465 cm⁻¹; 1H NMR (CDCl₃, 400 MHz): δ 7.34-7.20 (5H, m), 3.86 (1H, q, J = 6.4 Hz), 2.53 (1H, m), 1.78-1.33 (6H, m), 1.30 (3H, d, J = 6.4 Hz), 1.02 (3H, s), 0.86 (3H, s); 13C NMR (CDCl₃, 100 MHz): δ 147.2, 128.2, 126.7, 126.6, 65.6, 57.2, 40.9, 39.9, 32.0, 28.1, 24.6, 21.1, 19.7; LRMS (EI): m/z (%): 217 (22), 202 (54), 160 (58), 146 (10), 105 (100), 56 (26); Anal. calcd (%) for C₁₅H₂₃N: C, 82.89; H, 10.67; N, 6.44; Found: C, 83.04; H, 10.57; N, 6.50.

Asymmetric reductive amination of Pd/C ketone substrates.

(S)-1,2,3,4-tetrahydronaphthalen-1-amine (3m)

A mixture of α-tetralone (1.00 equiv, 2.50 mmol, 0.33 mL), titanium tetraisopropoxide (1.25 equiv, 3.13 mmol, 0.92 mL), and (S)-α-methylbenzylamine (1.10 equiv, 2.75 mmol, 0.35 mL) was pre-stirred (1 h) neat in the reaction vessel. tert-Butylmethylether (5.0 mL) was added along with Pd/C (0.23 mol %, 24.0 mg) and the reaction was immediately hydrogenated at 120 psi (8.3 bar) at 40 °C. At complete conversion, after 27 h, the reaction was quenched with 10 mL of 1.0 M NaOH. The inorganic precipitate along with the catalyst was filtered over a bed of celite and the celite washed with CH₂Cl₂ (4 x 20 mL). The organic layer was removed and further washed with deionized water (2 x 20 mL). The organic layer was then dried over Na₂SO₄, filtered, and concentrated (rotary evaporator, T ≤ 25 °C) providing the mixture of diastereomers as a pale yellow liquid (954.0 mg). To the crude diastereomeric mixture in methanol (7.0 mL) was added acetic acid (4.00 equiv, 15.20 mmol, 0.90 mL) and Pd/C (6.0 mol %, 970.0 mg). Hydrogenolysis was initiated with a hydrogen pressure of 60 psi (4.14 bar) at room temperature. At completion of the reaction
after 14 h the mixture was filtered through celite and celite washed with methanol (2 x 20 mL). To the filtrate was added aq. HCl (5.0 mL, 1.0 M) and the solution reduced to remove the MeOH. The salt was then washed with Et₂O (2 x 20 mL) to remove neutrals. The aqueous acid layer was basified with aq. NaOH (10 ml, 2.0 M) to pH 10-12. The basic water layer was then extracted with CH₂Cl₂ (3 x 30 mL). The combined CH₂Cl₂ extracts were then reduced in volume and washed with saturated NaCl (2 x 10 mL) and dried over Na₂SO₄. After filtration, ethereal HCl (3.0 M, 2.00 equiv) was added and the mixture was then evaporated to dryness to obtain the crude hydrochloride salt of the primary amine 3m (747.6 mg). CH₂Cl₂ was added (0.50 M) to the salt, followed by trifluoroacetic anhydride (4.00 equiv, 16.3 mmol, 2.3 mL) and triethylamine (5.00 equiv, 20.35 mmol, 2.8 mL), then gently refluxed. After 40 min the reaction mixture was quenched with saturated NaHCO₃ (2 x 10 mL), the CH₂Cl₂ layer was dried over Na₂SO₄, filtered, and evaporated to dryness to obtain the crude amide which was then purified by flash chromatography (heptane/EtOAc, 19:1) to give 462 mg (76% overall yield from starting α-tetralone) of a white solid and in 92% ee (chiral GC program D, see General section). GC retention time [min]: major (S)-3m trifluoroacetamide derivative, 32.7; minor (R)-3m trifluoroacetamide derivative, 34.7.

(S)-3m trifluoroacetamide derivative: Rf = 0.41 (heptane/EtOAc, 84:16); IR (KBr): 3295, 2935, 1697 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.13-7.24 (4H, m), 6.56 (1H, br.s), 5.16-5.20 (1H, m), 2.76-2.89 (2H, m), 2.07-2.13 (1H, m), 1.87-1.91 (3H, m); ¹³C NMR (CDCl₃, 100 MHz): δ 157.1, 156.7, 156.4, 156.0, 138.0, 134.4, 129.6, 128.6, 128.1, 126.7, 120.3, 117.4, 114.5, 111.7, 48.5, 29.5, 29.0, 19.7, LRMS (EI): m/z (%): 243 (2), 146 (3), 130 (100), 129 (16), 115 (6), 91 (4); Anal. calcld (%) for C₁₂H₁₂F₃NO: C, 59.26; H, 4.97; N, 5.76; Found: C, 59.29; H, 4.95; N, 5.64.

(S)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-amine (3n)

To benzosuberone (1.00 equiv, 2.50 mmol 0.37 mL) was added titanium tetraisopropoxide (1.25 equiv, 3.13 mmol, 0.92 mL) and (S)-α-methylbenzylamine (1.15 equiv, 2.88 mmol, 0.37 mL) and this mixture was pre-stirred (5 h) neat in the reaction vessel. EtOAc (5.0 mL) was added along with Pd/C (0.23 mol%, 24.0 mg; pre-activated for 1 h at 60 °C and 0.3 mbar pressure) and the reaction was then hydrogenated at 120 psi (8.3 bar) at room temperature. At complete conversion, after 36 h, the reaction was quenched with aq. NaOH (10 mL, 1.0 M). The heterogeneous mixture was filtered over a bed of celite and the celite washed with CH₂Cl₂ (4 x 20 mL). After thorough mixing, the organic layer was washed with deionized water (2 x 20 mL) and then dried over Na₂SO₄. After filtration, the solvent was rotary evaporated to provide the mixture of diastereomers as a pale yellow liquid (659.0 mg). To the crude mixture of amine diastereomers was added MeOH (5.0 mL), acetic acid (4.00 equiv, 10.0 mmol, 0.6 mL), and Pd/C (6.0 mol %, 638.0 mg). Hydrogenolysis was initiated with a hydrogen pressure of 60 psi (4.14 bar) under room temperature. At completion of reaction, after 14 h, the mixture was filtered through celite and the celite washed with methanol (2 x 20 mL). To the filtrate was added aq. HCl (5.0 mL, 1.0 M) and the solution reduced to remove the MeOH. The acidic aqueous solution was then washed with Et₂O (2 x 20 mL) to remove the neutrals. The water layer was then basified with 1.0 M NaOH to a pH 10-12. The water layer was then extracted with CH₂Cl₂ (3 x 30 mL). The combined CH₂Cl₂ extracts were then reduced in volume and washed with saturated NaCl (2 x 10 mL), and dried over Na₂SO₄. After filtration, ethereal HCl (3.0 M, 2.00 equiv) was added and the mixture evaporated to dryness to obtain the crude hydrochloride salt of the primary amine 3n (520.0 mg). CH₂Cl₂ was then added (0.50 M) to the salt along with trifluoroacetic anhydride (4.00 equiv, 7.00 mmol, 1.0 mL) and triethylamine

\[
\text{NH}_2
\]

(S)-3n

To benzosuberone (1.00 equiv, 2.50 mmol 0.37 mL) was added titanium tetraisopropoxide (1.25 equiv, 3.13 mmol, 0.92 mL) and (S)-α-methylbenzylamine (1.15 equiv, 2.88 mmol, 0.37 mL) and this mixture was pre-stirred (5 h) neat in the reaction vessel. EtOAc (5.0 mL) was added along with Pd/C (0.23 mol%, 24.0 mg; pre-activated for 1 h at 60 °C and 0.3 mbar pressure) and the reaction was then hydrogenated at 120 psi (8.3 bar) at room temperature. At complete conversion, after 36 h, the reaction was quenched with aq. NaOH (10 mL, 1.0 M). The heterogeneous mixture was filtered over a bed of celite and the celite washed with CH₂Cl₂ (4 x 20 mL). After thorough mixing, the organic layer was washed with deionized water (2 x 20 mL) and then dried over Na₂SO₄. After filtration, the solvent was rotary evaporated to provide the mixture of diastereomers as a pale yellow liquid (659.0 mg). To the crude mixture of amine diastereomers was added MeOH (5.0 mL), acetic acid (4.00 equiv, 10.0 mmol, 0.6 mL), and Pd/C (6.0 mol %, 638.0 mg). Hydrogenolysis was initiated with a hydrogen pressure of 60 psi (4.14 bar) under room temperature. At completion of reaction, after 14 h, the mixture was filtered through celite and the celite washed with methanol (2 x 20 mL). To the filtrate was added aq. HCl (5.0 mL, 1.0 M) and the solution reduced to remove the MeOH. The acidic aqueous solution was then washed with Et₂O (2 x 20 mL) to remove the neutrals. The water layer was then basified with 1.0 M NaOH to a pH 10-12. The water layer was then extracted with CH₂Cl₂ (3 x 30 mL). The combined CH₂Cl₂ extracts were then reduced in volume and washed with saturated NaCl (2 x 10 mL), and dried over Na₂SO₄. After filtration, ethereal HCl (3.0 M, 2.00 equiv) was added and the mixture evaporated to dryness to obtain the crude hydrochloride salt of the primary amine 3n (520.0 mg). CH₂Cl₂ was then added (0.50 M) to the salt along with trifluoroacetic anhydride (4.00 equiv, 7.00 mmol, 1.0 mL) and triethylamine
(5.00 equiv, 8.40 mmol, 1.2 mL), and then gently refluxed. After 40 min the reaction mixture was quenched with saturated NaHCO₃ (2 x 10 mL), the CH₂Cl₂ layer was dried over Na₂SO₄, filtered, and evaporated to dryness to obtain the crude amide as a white solid (443 mg, 69% yield, ≥93% purity by GC). The overall yield from starting benzosuberone is 64%. The trifluoroacetyl derivative of the sample shows 76% ee (chiral GC program E, see General section). GC retention time [min]: (S)-3n trifluoroacetyl derivative, 49.4; minor (R)-3n trifluoroacetyl derivative, 50.6.

(S)-3n trifluoroacetyl derivative: Rf = 0.39 (heptane/EtOAc, 84:16); IR (KBr): 3293, 2929, 1694, 1556 cm⁻¹; H NMR (CDCl₃, 400 MHz): δ 7.14-7.21 (4H, m), 6.62 (1H, br.s), 5.18-5.22 (1H, t, J = 8 Hz), 2.78-2.93 (2H, m), 1.56-2.03 (6H, m); C NMR (CDCl₃, 100 MHz): δ 156.6, 156.3, 155.9, 155.5, 141.2, 139.4, 130.5, 127.9, 126.6, 125.9, 120.2, 117.4, 114.5, 111.6, 54.6, 36.0, 33.2, 27.7, 27.3; LRMS (EI): m/z (%): 257 (6), 256 (10), 228 (4), 144 (100), 143 (7), 129 (34), 116 (12), 91 (7); Anal. calcd (%) for C₁₃H₁₄F₃NO: C, 60.7; H, 5.49; N, 5.44; Found: C, 60.47; H, 5.38; N, 5.56.

Asymmetric reductive amination of 4-phenyl-2-butanone (1e) in presence of NaBH₄.[²]

A mixture of 4-phenyl-2-butanone (1.00 equiv, 5.00 mmol, 0.75 mL), titanium tetraisopropoxide (1.25 equiv, 6.25 mmol, 1.83 mL) and (S)-α-methylbenzylamine (1.10 equiv, 5.5 mmol, 0.7 mL) were stirred vigorously for 3 h at room temperature. At this stage, EtOH (10.0 mL) was added followed by NaBH₄ (1.50 equiv, 7.50 mmol, 0.284 g) at 0 ºC. The reaction mixture was then vigorously stirred under nitrogen for 12 h. The reaction was then cooled in an ice-bath and the NaBH₄ (1.50 equiv, 7.50 mmol, 1.60 g) added. The reaction mixture was further stirred under an argon atmosphere vigorously for 14 h. The reaction was quenched with aq. NaOH (10 mL, 1.0 M) and stirred for 1 h and then rotary evaporated to remove the organic solvents. The aqueous layer was then extracted with CH₂Cl₂ (2 x 30 mL) and the combined organic extracts were then dried over Na₂SO₄, filtered, and rotary evaporated. The crude mixture was purified by flash chromatography (heptane/EtOAc/NH₄OH, 84:15:1) to obtain the diastereomeric mixture as colorless oil with 47% de (1.04 g, 82% yield).

₁H NMR (CDCl₃, 400 MHz): δ 7.32-7.16 (10H, m), 3.87 (1H, q, J = 6.4 Hz), 2.66 (1H, m), 2.55 (2H, m), 1.82 (1H, m), 1.60 (1H, m), 1.30 (3H, d, J = 6.8 Hz), 1.03 (3H, d, J = 6.4 Hz).

Asymmetric reductive amination of 1e in presence of NaB(OAc)₃H.

4-Phenyl-2-butancne (1.00 equiv, 5.00 mmol, 0.63 mL) and (S)-α-methylbenzylamine (1.10 equiv, 5.50 mmol, 0.71 mL) were mixed in THF (10.0 mL) followed by titanium tetraisopropoxide (1.25 equiv, 6.25 mmol, 1.83 mL) and stirred vigorously for 3 h under argon atmosphere at room temperature. The reaction was then cooled in an ice-bath and the NaB(OAc)₃H (1.50 equiv, 7.50 mmol, 1.60 g) added. The reaction mixture was further stirred under an argon atmosphere vigorously for 14 h. The reaction was quenched with aq. NaOH (10 mL, 1.0 M) and stirred for 1 h and then rotary evaporated to remove the organic solvents. The aqueous layer was then extracted with EtOAc (2 x 40 mL) and the combined organic extracts then dried over Na₂SO₄, filtered, and concentrated (rotary evaporator, T < 25 ºC). The resulting oil was dissolved in 20 mL of Et₂O, and the amine extracted with aq. HCl (10 mL, 1.0 M) to remove the neutral materials. The aqueous acid layer was basified with aq. NaOH (10 ml, 2.0 M) to pH 10-12. The product was then extracted with CH₂Cl₂ (3 x 25 mL). The CH₂Cl₂ extracts were dried over Na₂SO₄, filtered, and concentrated to...
give the crude product which was purified by column chromatography (heptane/EtOAc/NH₄OH, 84:15:1) providing the mixture of diastereomers as a colorless oil with 18% de (0.899 g, 71% yield).

**Hydrogenolysis of secondary amines.**

**(S)-Butan-2-amine hydrochloride, hydrogenolysis of (S,S)-2f**[3]

![NH₂·HCl](image)

(S)-3f

The diastereomeric amine mixture 2f (2.50 mmol, 0.443 g) was dissolved in MeOH (5.0 mL) and acetic acid (4.00 equiv, 10.0 mmol, 0.60 mL) added, followed by hydrogenation in the presence of Pd(OH)₂/C (6.0 mol %, 0.211 g) at 60 psi (4.14 bar) at room temperature. After 16 h, the catalyst was filtered through celite and the celite washed with MeOH (4 x 10 mL). To the filtrate was added aq. HCl (10.0 mL, 1.0 M), and this solution concentrated so as to remove the MeOH. The remaining acidic aqueous layer was washed with Et₂O (2 x 10 mL), and then basified with 1.0 M NaOH to a pH 10-12. The basic aqueous layer was then extracted with CH₂Cl₂ (3 x 30 mL), and the combined CH₂Cl₂ extracts were then washed with saturated NaCl, dried over Na₂SO₄, and filtered. To the filtrate was added 3.0 M ethereal HCl (2.0 mL, 6.00 equiv) and this solution concentrated to obtain a white solid. Further drying (high vacuum) for 12 h provided a free-flowing white solid (0.233 g, 85% yield, ¹H NMR ≥ 90% purity). Note, the overall isolated yield from 2-butanone is 71%. The benzoyl derivative of the sample shows 74% ee (HPLC, see General section). HPLC retention time [min]: major (R)-3f benzamide derivative, 30.3; minor (S)-3f benzamide derivative, 23.5. An analytically pure HCl salt of the (S)-3f was obtained by crystallization of the above white solid from ethanol:toluene.

(S)-3f.HCl salt: ¹H NMR (CDCl₃, 400 MHz): δ 8.31 (3H, br.s), 3.25 (1H, br.s), 1.79-1.86 (1H, m), 1.62-1.68 (1H, m), 1.38 (3H, d, J = 5.6 Hz), 1.02 (3H, t, J = 6.8 Hz); ¹³C NMR (CDCl₃, 100 MHz): δ 49.9, 28.0, 18.3, 10.1.

**(R)-1-Phenylbutan-1-amine hydrochloride, hydrogenolysis of (R,R)-2j**

![NH₂·HCl](image)

(R)-3j

The diastereomeric amine mixture 2j (2.00 mmol, 0.507 g) was dissolved in MeOH (5.0 mL) and hydrogenolysis was carried out in presence of Pd/C (6.0 mol%, 0.511 g) at 60 psi (4.14 bar) of hydrogen pressure at room temperature. After 11 h, the catalyst was filtered through celite and the celite washed with MeOH (4 x 10 mL). To the filtrate was added 4.0 M ethereal HCl (2.5 mL, 5.00 equiv) and after brief stirring the solution was concentrated. The resulting oil was repetitively (3-4 times) triturated with Et₂O and evaporated to provide a white solid. High vacuum drying provided a free-flowing white solid (0.341 g, 80% yield, retention time 10.2 min, achiral GC program A, see General Section). The trifluoroacetyl derivative of the sample shows 90% ee (chiral GC program F, see General section). GC retention time [min]: major (R)-3j trifluoroacetamide derivative, 86.5; minor (S)-3j trifluoroacetamide derivative, 84.4. An analytically pure HCl salt of the (R)-α-Phenylbutanamine was obtained by crystallization of the above white solid from acetonitrile.
(R)-3j HCl salt; IR (KBr): 3419, 2891, 1600 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.7 (3H, brs), 7.44-7.33 (5H, m), 4.13 (1H, dd, \(J = 6.0\) Hz), 2.05 (1H, m), 1.92 (1H, m), 1.21 (2H, m), 0.86 (3H, d, \(J = 7.6\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 136.4, 129.0, 128.9, 127.3, 56.2, 36.6, 19.0, 13.5; LRMS (EI): m/z (%): 149 (06) [M\(^+\) - HCl], 148 (24), 106 (100), 79 (20), 77 (12), 36 (11); Anal. calcd (%) for C\(_{10}\)H\(_{16}\)NCl: C, 64.68; H, 8.68; N, 7.54; Cl, 19.09; Found: C, 64.84; H, 8.71; N, 7.52; Cl, 19.25.


Hydrochloride salt of (S,S)-2f
(R,R)-2j
(R,R)-2k

HN
Ph

ppm (t1)
(R,R)-21
(R,R)-21
Hydrochloride salt of (S)-3f

\[ \text{NH}_2 \cdot \text{HCl} \]
Hydrochloride salt of (S)-3f
HN
O
Ph

HN
O
Ph

Benzoyl derivative of (S)-3f

Benzoyl derivative of (R)-3f
74% ee
Benzoyl derivative of (S)-3f

Benzoyl derivative of (R)-3f
Hydrochloride salt of (R)-3j
Hydrochloride salt of (R)-3j

NH₂·HCl
Racemic trifluoroacetyl derivatives
of 3j

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90% ee
Trifluoroacetyl derivative of (R)-3j

Trifluoroacetyl derivative of (S)-3j

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Trifluoroacetyl derivative of (S)-3m
Trifluoroacetyl derivative of (S)-3m
Racemic trifluoroacetyl derivatives of 3m

- Trifluoroacetyl derivative of (R)-3m
- Trifluoroacetyl derivative of (S)-3m

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Trifluoroacetyl derivative of (R)-3m

92% ee
Trifluoroacetyl derivative of (S)-3m

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Trifluoroacetyl derivative of (S)-3-n-O

- 156.615
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- 127.933
- 126.610
- 125.858
- 120.220
- 117.352
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- 111.618
- 77.355
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- 54.607
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Trifluoroacetyl derivative of (S)-3n
Racemic trifluoroacetyl derivatives of 3n

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Trifluoroacetyl derivative of (R)-3n

76% ee
Trifluoroacetyl derivative of (S)-3n

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