Supporting Information

Straightforward preparation of biologically active 1-aryl- and 1-heteroarylpropan-2-amines in enantioenriched form

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1. General procedures

Lipase B from Candida antarctica (CAL-B, available immobilized on polyacrylamide as Novozyme 435, 7300 PLU/g), and immobilized Lipozyme® RM (<15% in weight) were generously given by Novozymes. Pseudomonas cepacia lipase “Amano IM” (943 u/g) was a gift from Amano Enzymes Inc. Amano Lipase AK from Pseudomonas fluorescens (22100 u/g) was provided by Aldrich, and lipase from pancreas porcine (30-90 u/mg protein using triacetin) was supplied by Sigma. For the enzymatic reactions, ethyl methoxyacetate (stored with 4 Å molecular sieves) and anhydrous THF were used. Thin-layer chromatography was performed on precoated TLC plates of Merck silica gel 60F254, using a potassium permanganate solution as developing reagent. Merck silica gel 60 (particle size, 40 - 63 µm) was used for column chromatography. Optical rotations were measured at the sodium D line at 20 °C, the [α] values being given in 10−1 deg cm2 g−1. Mass spectra (m/z) were recorded in ElectronSpray Ionisation (ESI+). 1H NMR and proton-decoupled 13C NMR spectra (CDCl3 solutions) were recorded using AV-300, AC-300 or DPX-300 (1H, 300.13 MHz and 13C, 75.5 MHz) spectrometers using the δ scale (ppm) for chemical shifts. Calibration was
made on the CDCl₃ (¹³C, 76.95 ppm) or the residual CHCl₃ (¹H, 7.26 ppm), and J values are given in Hz.

2. Synthetic procedures and spectroscopical data for novel compounds

2.1. 1-(Triphenylmethyl)-1H-imidazole-4-carbaldehyde 1e
To a solution of 1H-imidazole-4-carbaldehyde (400 mg, 4.16 mmol) in anhydrous dichloromethane (21 cm³), triethylamine (0.636 cm³, 4.58 mmol) was added under nitrogen atmosphere, and the resulting solution cooled at 0 °C. Then, triphenylmethyl chloride (1.28 g, 4.58 mmol) was added. The reaction mixture was stirred at room temperature for 1.5 h until complete consumption of the starting material (analysis by TLC, methanol/dichloromethane 1:9 as eluent). The solvent was evaporated and the crude material purified by flash chromatography (ethyl acetate/hexane 1:1) to yield the trityl derivative 1e (1.38 g, 98%) as a white solid. Mp: 193-196 °C (lit.,¹ 193-196 °C).

2.2. Full characterization of racemic 1-(hetero)arylpropan-2-amines 3a-e

(±)-1-(1-Naphthyl)propan-2-amine 3a

![Chemical structure of 1-(1-Naphthyl)propan-2-amine 3a]

Yield, 74%; yellow oil; δH(300 MHz, CDCl₃) 1.21 (3 H, d, J 6.4, CH₃), 1.67 (2 H, br s, NH₂), 2.96 (1 H, dd, J 13.4 and 8.0, CHH), 3.22 (1 H, dd, J 13.4 and 5.2, CHH), 3.32-3.44 (1 H, m, CH), 3.46 (1 H, dd, J 13.4 and 5.2, CH), 3.74-3.85 (4 H, m), 7.75 (1 H, d, J 7.8), 7.86 (1 H, dd, J 7.2 and 3.0), 8.05 (1 H, d, J 8.2); δC(75.5 MHz, CDCl₃) 23.7 (CH₃), 43.5 (CH₂), 47.6 (N-CH), 123.8 (CH), 125.3 (CH), 125.4 (CH), 125.7 (CH), 127.0 (CH), 127.2 (CH), 128.7 (CH), 132.0 (C), 133.9 (C), 135.7 (C); HRMS (ESI+) calcd. for C₁₃H₁₆N ([M+H]⁺): 186.1277; found: 186.1272.

(±)-1-(2-Naphthyl)propan-2-amine 3b

Yield, 72%; pale yellow oil; $\delta_{\text{H}}$(300 MHz, CDCl$_3$) 1.17 (3 H, d, $J$ 6.0, CH$_3$), 1.61 (2 H, br s, NH$_2$), 2.68 (1 H, dd, $J$ 13.2 and 8.0, CHH), 2.88 (1 H, dd, $J$ 13.2 and 5.4, CHH), 3.27 (1 H, m, N-CH), 7.33 (1 H, d, $J$ 7.8, H-3), 7.42-7.50 (2 H, m), 7.64 (1 H, s), 7.78-7.84 (3 H, m); $\delta_{\text{C}}$(75.5 MHz, CDCl$_3$) 23.4 (CH$_3$), 46.6 (CH$_2$), 48.2 (CH), 125.2 (CH), 125.8 (CH), 127.3 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 132.0 (C), 133.4 (C), 137.1 (C); HRMS (ESI+) calcd. for C$_{13}$H$_{15}$N ([M+H]$^+$): 186.1277; found: 186.1279.

(±)-1-(1H-Indol-3-yl)propan-2-amine 3c

Yield, 68%; mp 86-90 ºC; $\delta_{\text{H}}$(300 MHz, CDCl$_3$) 1.22 (3 H, d, $J$ 6.4, CH$_3$), 1.52 (2 H, br s, NH$_2$), 2.69 (1 H, ddd, $J$ 14.3, 8.3 and 0.7, CHH), 2.93 (1 H, ddd, $J$ 14.3, 5.0 and 1.0, CHH), 3.29-3.38 (1 H, m, N-CH), 6.98 (1 H, br d, $J$ 1.0, H-2), 7.13-7.25 (2 H, m, H-5 and H-6), 7.35 (1 H, ddd, $J$ 7.9, 1.3 and 0.9, H-7), 7.66 (1 H, m, H-4), 8.91 (1 H, br s, NH); $\delta_{\text{C}}$(75.5 MHz, CDCl$_3$) 23.6 (CH$_3$), 35.8 (CH$_2$), 47.2 (N-CH), 111.1 (CH), 113.3 (C-3), 118.8 (CH), 119.0 (CH), 121.7 (CH), 122.5 (CH), 127.6 (C-3a), 136.3 (C-7a); HRMS (ESI+) calcd. for C$_{11}$H$_{15}$N$_2$ [(M+H)$^+$]: 175.1230; found: 175.1230.

(±)-1-(3-Pyridyl)propan-2-amine 3d

Yield, 33%; pale yellow oil; $\delta_{\text{H}}$(300 MHz, CDCl$_3$) 1.06 (3 H, d, $J$ 6.4, CH$_3$), 2.4 (2 H, br s, NH$_2$), 2.51 (1 H, dd, $J$ 13.5 and 7.7, CHH), 2.62 (1 H, dd, $J$ 13.5 and 5.7, CHH), 3.12 (1 H, sex, $J$ 6.2, N-CH), 7.14-7.18 (1 H, m, H-5), 7.45 (1 H, d, $J$ 7.9, H-4), 8.38-8.40 (2 H, m, H-2 and H-6); $\delta_{\text{C}}$(75.5 MHz, CDCl$_3$) 23.0 (CH$_3$), 43.1 (CH$_2$), 48.0 (N-CH), 123.1 (C-5), 134.6 (C-3), 136.5 (C-4), 147.5 (C-2 or C-6), 150.3 (C-6 or C-2); HRMS (ESI+) calcd. for C$_8$H$_{13}$N$_2$ [(M+H)$^+$]: 137.1073; found: 137.1068.
(±)-1-[1-(Triphenylmethyl)-1H-imidazol-4-yl]propan-2-amine 3e

Yield, 44%; pale yellow semi-solid; δ(300 MHz, CDCl₃) 1.07 (3 H, d, J 6.3, CH₃), 2.47 (1 H, dd, J 14.3 and 7.7, CHH), 2.61 (1 H, dd, J 14.3 and 5.5, CHH), 3.12 (2 H, br s, NH₂), 3.24 (1 H, sex, J 6.4, N-CH), 6.56 (1 H, m, H-5), 7.09-7.33 (16 H, m); δ(75.5 MHz, CDCl₃) 22.0 (CH₃), 37.5 (CH₂), 47.0 (N-CH), 75.0 [C(Ph)₃], 119.1 (C-5), 127.9 (9 x CH, Ph), 129.6 (6 x CH, Ph), 138.5 (C-2), 138.8 (C-4), 142.4 (3 x C, Ph); HRMS (ESI+) calcd. for C₂₅H₂₆N₃ [(M+H)⁺]: 368.2121; found: 368.2117; calcd. for C₂₅H₂₅N₃Na [(M+Na)⁺]: 390.1941; found: 390.1942.

2.3. Full characterization of optically active amines 3a-e

(S)-1-(1-Naphthyl)propan-2-amine 3a
Yield: 81%; [α]D²⁰ +57.9 (c 1 in CHCl₃), ee = 87%. HPLC conditions for its acetamide derivative: Chiralcel OJ-H, n-hexane/propan-2-ol 95:5, 0.8 cm³/min, 40 °C, UV 210 nm, tᵣ = 22.4 (R) and 24.3 (S) min; Rs = 1.4.

(S)-1-(2-Naphthyl)propan-2-amine 3b
Yield: 96%; [α]D²⁰ +21.6 (c 0.8 in CHCl₃), ee = 91%. HPLC conditions for its acetamide derivative: Chiralcel OJ-H, n-hexane/ propan-2-ol 90:10, 0.8 cm³/min, 20 °C, UV 210 nm, tᵣ = 18.5 (S) and 20.4 (R) min; Rs = 1.9.
(S)-1-(1H-Indol-3-y1)propan-2-amine 3c
Yield: 81%; $[\alpha]_D^{20} +20.8$ (c 1 in MeOH), $ee = 99\%$. HPLC conditions for its acetamide derivative: Chiralcel OJ-H, n-hexane/ethanol 85:15, 0.8 cm$^3$/min, 40 °C, UV 210 nm, $t_R = 13.9$ (R) and 16.2 (S) min; Rs = 2.9.

Acetamide obtained from (±)-3c

Acetamide with $ee = 99\%$

(S)-1-(3-Pyridyl)propan-2-amine 3d
Yield: 36%; $[\alpha]_D^{20} +8.0$ (c 0.25 in CHCl$_3$), $ee = 98\%$. HPLC conditions for its acetamide derivative: Chiralcel OJ-H, n-hexane/ethanol 97:3, 0.8 cm$^3$/min, 40 °C, UV 210 nm, $t_R = 22.2$ (R) and 24.2 (S) min; Rs = 2.0.

Acetamide obtained from (±)-3d

Acetamide with $ee = 98\%$

(S)-1-[1-(Triphenylmethyl)-1H-imidazol-4-yl]propan-2-amine 3e
Yield: 71%; $[\alpha]_D^{20} +6.3$ (c 1 in CHCl$_3$), $ee = 97\%$. HPLC conditions for its acetamide derivative: Chiralcel OJ-H, n-hexane/ethanol 95:5, 0.8 cm$^3$/min, 40 °C, UV 210 nm, $t_R = 6.9$ (S) and 8.8 (R) min; Rs = 3.1.

Acetamide obtained from (±)-3e

Acetamide with $ee = 97\%$
2.4. Full characterization of optically active amides 5a-e

(R)-N-[1-(1-Naphthyl)propan-2-yl]-2-methoxyacetamide 5a

Yield, 99%; mp 73-76 °C; \([\alpha]_D^{20} -30.7\) (c 1 in CHCl₃), \(ee = 99\%\); \(\delta_H(300 MHz, CDCl₃) 1.17 (3 H, d, J 6.6, CH₃), 2.99 (1 H, dd, J 8.3 and 13.6, CHH-Ar), 3.33 (3 H, s, O-CH₃), 3.54 (1 H, dd, J 5.5 and 13.6, CHH-Ar), AB system \(|\delta_A = 3.83, \delta_B = 3.89, |^2J_{AB}| = 15.1, \ O-CH₂\), 4.44 (1 H, m, CH), 6.50 (1 H, br d, J 7.0, NH-CO), 7.27-7.60 (4 H, m), 7.75 (1 H, d, J 8.1), 7.85 (1 H, d, J 7.9) and 8.31 (1 H, d, J 8.6); \(\delta_C(75.5 MHz, CDCl₃) 19.9 (CH₃), 39.9 (Ar-CH₂), 45.4 (N-CH), 58.9 (O-CH₃), 71.8 (O-CH₂), 124.1 (CH), 125.1 (CH), 125.5 (CH), 126.0 (CH), 127.2 (CH), 127.4 (CH), 128.5 (CH), 132.2 (C), 133.8 (C), 134.2 (C) and 169.0 (C=O); HRMS (ESI+) \(m/z\) calcd for \(C_{16}H_{19}NNaO₂ (\text{M+Na}^+): 280.1308 \); found: 280.1319; \(m/z\) calcd for \(C_{16}H_{20}NO₂ (\text{M+H}^+): 258.1489 \); found: 258.1478; HPLC conditions: Chiralcel OJ-H, n-hexane/propan-2-ol 95:5, 0.8 cm\(^3\)/min, 40 °C, UV 210 nm, \(t_R = 19.2\) (R) and 23.7 (S) min; \(R_s = 5.3\).

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<th>Methoxyacetamide (±)-5a</th>
<th>Methoxyacetamide with (ee = 99%)</th>
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(R)-N-[1-(2-Naphthyl)propan-2-yl]-2-methoxyacetamide 5b

Yield, 99%; pale yellow semi-solid; \([\alpha]_D^{20} +18.0\) (c 1 in CHCl₃), \(ee = 99\%\); \(\delta_H(300 MHz, CDCl₃) 1.17 (3 H, d, J 6.6, CH₃), 2.87 (1 H, dd, J 7.3 and 13.5, CHH-Ar), 3.03 (1 H, dd, J 6.1 and 13.5, CHH-Ar), 3.31 (3 H, s, O-CH₃), AB system \(|\delta_A = 3.80, \delta_B = 3.86, |^2J_{AB}| = 15.1, \ O-CH₂\), 4.40 (1 H, m, CH), 6.46 (1 H, br d, J 7.7, NH-CO), 7.34 (1 H, d, J 8.4, H-3), 7.37-7.52 (2 H, m), 7.63 (1 H, s, H-1), 7.70-7.90 (3H, m); \(\delta_C(75.5 MHz, CDCl₃) 19.9 (CH₃), 42.6 (Ar-CH₂), 45.5 (N-CH), 59.0 (O-CH₃), 71.8 (O-CH₂), 125.3 (CH), 125.9 (CH), 127.4 (CH), 127.5 (CH), 127.66 (CH), 127.70 (CH), 127.9 (CH), 132.1 (C), 133.4 (C), 135.4 (C) and 168.7 (C=O); HRMS (ESI+) \(m/z\) calcd for
C_{16}H_{19}NNaO_{2} ([M+Na]^{+}): 280.1308; found: 280.1314; m/z calcld for C_{16}H_{20}NO_{2} ([M+H]^{+}): 258.1489; found: 258.1477; HPLC conditions: Chiralcel OJ-H, n-hexane/propan-2-ol 90:10, 0.8 cm^3/min, 20 °C, UV 210 nm, t_R = 22.7 (S) and 32.5 (R) min; Rs = 7.1.

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\text{Methoxyacetamide (±)-5b}
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\text{Methoxyacetamide with ee = 98%}
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(R)-N-[1-(1H-Indol-3-y)propan-2-yl]-2-methoxyacetamide 5c
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Yield, 76%; brown oil; [\alpha]_D^{20} +17.6 (c 1 in CHCl_3), ee = 95%; \delta_H(300 MHz, CDCl_3) 1.20 (3 H, d, J 6.6, CH_3), part AB of an ABX system (\delta_A = 2.91, \delta_B = 3.00, |^{2}J_{A,B}| = 14.5, ^{3}J_{A,X} = 6.9, ^{3}J_{B,X} = 5.7, 

CHH-CH), 3.29 (3H, s, O-CH_3), MN system (\delta_M = 3.82, \delta_N = 3.87, |^{2}J_{M,N}| = 15.0, O-CH_2), 4.41 (1 H, m, CH), 6.52 (1 H, br d, J 7.7, NH-CO), 7.00 (1 H, d, J 2.4, H-2), 7.11 [1 H, dt, J 1.1 (d) and 7.9 (t), H-5 or H-6], 7.18 [1 H, dt, J 1.3 (d) and 7.9 (t), H-6 or H-5], 7.35 (1 H, br d, J 7.9, H-7), 7.65 (1 H, br d, J 7.9, H-4) and 8.49 (1 H, br s, NH of indol); \delta_C(75.5 MHz, CDCl_3) 20.3 (CH_3), 31.9 (Ar-CH_2), 45.2 (N-CH), 58.9 (O-CH_3), 71.9 (O-CH_2), 111.0 (CH), 111.7 (C-3), 118.8 (CH), 119.2 (CH), 121.8 (CH), 122.6 (CH), 127.8 (C-3a), 136.2 (C-7a) and 168.8 (C=O); HRMS (ESI+) calcld. for C_{14}H_{19}N_2O_2 ([M+H]^{+}): 247.1441; found: 247.1442; calcld. for C_{14}H_{18}N_2NaO_2 ([M+Na]^{+}): 269.1260; found: 269.1272; HPLC conditions: Chiralcel OJ-H, n-hexane/ethanol 85:15, 0.8 cm^3/min, 40 °C, UV 210 nm, t_R = 17.9 (R) and 21.2 (S) min; Rs = 3.3.

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\text{Methoxyacetamide (±)-5c}
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\text{Methoxyacetamide with ee = 95%}
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(R)-N-[1-(3-Pyridyl)propan-2-yl]-2-methoxyacetamide 5d

Yield, 96%; brown oil; $[^{19}D]_{D}^{20} +14.1$ (c 1 in CHCl$_3$), ee = 85%; $\delta_H$(300 MHz, CDCl$_3$) 1.13 (3 H, d, J 6.6, CH$_3$), part AB of an ABX system ($\delta_A = 2.73$, $\delta_B = 2.82$, $|2J_{AB}| = 13.7$, $|3J_{AX}| = 7.0$, $|3J_{BX}| = 6.3$, $CHH\text{-CH}$), 3.33 (3H, s, O-CH$_3$), MN system ($\delta_M = 3.77$, $\delta_N = 3.81$, $|2J_{MN}| = 15.1$, O-CH$_2$), 4.26 (1 H, m, CH), 6.38 (1 H, br d, J 6.8, NH-CO), 7.21 (1 H, dd, J 4.6 and 7.7, H-5), 7.52 (1 H, d, J 7.7, H-4) and 8.43 (2 H, br s, H -2 and H-6);
$\delta_C$(75.5 MHz, CDCl$_3$) 19.8 (CH$_3$), 39.6 (Ar-CH$_2$), 45.2 (N-CH), 59.0 (O-CH$_3$), 71.7 (O-CH$_2$), 123.3 (C-5), 133.4 (C-3), 136.7 (C-4), 147.7 (C-6 or C-2), 150.2 (C-2 or C-6) and 168.7 (C=O); HRMS (ESI+) m/z calcld for C$_{11}$H$_{16}$N$_2$O$_2$ ([M+Na]$^+$): 231.1104; found: 231.1103.

HPLC conditions: Chiralcel OJ-H, n-hexane/ethanol 97:3, 0.8 cm$^3$/min, 40 ºC, UV 210 nm, $t_R$ = 25.6 (R) and 28.4 (S) min; Rs = 2.2.

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<th>Methoxyacetamide (±)-5d</th>
<th>Methoxyacetamide with ee = 85%</th>
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<td><img src="image1" alt="Methoxyacetamide (±)-5d" /></td>
<td><img src="image2" alt="Methoxyacetamide with ee = 85%" /></td>
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(R)-N-[1-(1-Triphenylmethyl-1H-imidazol-4-yl)propan-2-yl]-2-methoxyacetamide 5e

Yield, 83%; mp 149-153 ºC; $[^{19}D]_{D}^{20} +15.0$ (c 1 in CHCl$_3$), ee = 96%; $\delta_H$(300 MHz, CDCl$_3$) 1.12 (3 H, d, J 6.6, CH$_3$), part AB of an ABX system ($\delta_A = 2.78$, $\delta_B = 2.66$, $|2J_{AB}| = 14.6$, $|3J_{AX}| = 5.9$, $|3J_{BX}| = 5.2$, $CHH\text{-CH}$), 3.36 (3H, s, O-CH$_3$), MN system ($\delta_M = 3.78$, $\delta_N = 3.85$, $|2J_{MN}| = 15.0$, O-CH$_2$), 4.29 (1 H, m, CH), 6.62 (1 H, s, H-5), 7.00-7.50 (17 H, m); $\delta_C$(75.5 MHz, CDCl$_3$) 20.0 (CH$_3$), 34.0 (Ar-CH$_2$), 44.4 (N-CH), 59.1 (O-CH$_3$), 72.1 (O-CH$_2$), 75.2 [C(Ph)$_3$], 119.4 (C-5), 128.0 (9 x CH, Ph), 129.6 (6 x CH, Ph), 137.5 (C-4), 138.3 (C-2), 142.3 (3 x C, Ph) and 168.6 (C=O); HRMS (ESI+) m/z calcld. for C$_{28}$H$_{30}$N$_3$O$_2$ ([M+H]$^+$): 440.2333; found: 440.2332; calcd. for C$_{28}$H$_{29}$N$_3$NaO$_2$ ([M+Na]$^+$): 462.2152; found: 462.2154; HPLC conditions: Chiralcel OJ-H, n-hexane/ethanol 95:5, 0.8 cm$^3$/min, 40 ºC, UV 210 nm, $t_R$ = 9.4 (S) and 14.0 (R) min; Rs = 3.4.

S8
Methoxyacetamide (±)-5e

Methoxyacetamide with ee = 96%

Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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