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Supporting Information

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First Asymmetric Direct Amide Synthesis *via* Kinetic Amine Resolution: A Chiral Bifunctional Amino-Boronic Acid Catalyzed Reaction Between a Racemic Amine and Achiral Carboxylic Acid.

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General Experimental Section

All glassware was oven dried (130 °C) before use and cooled under a positive pressure of argon stirred. Dry solvents were prepared using the Innovative Technology Inc. solvent purification system and analysed with Metrohm 831 KF coulometer. All other materials were purchased directly from standard chemical suppliers and used without further purification, unless stated otherwise. 2-(N-*n*-butylamine)aniline was prepared as reported.[1] TLC was performed on plastic backed silica gel plates with visualization achieved using a UV lamp. Drying was carried out over anhydrous $MgSO_4$, followed by filtration. Purification by medium pressure column chromatography was performed using silica gel 35-70 μm. Evaporations were carried out at 20 mmHg using a rotary evaporator and water bath, followed by evaporation to dryness under vacuum (<2 mmHg). Melting points are uncorrected. All ^{1}H and ^{13}C NMR were recorded with either a Varian Mercury-400, Bruker Avance-400 or Varian Inova-500 spectrometers. ^{11}B NMR were recorded with the Bruker Avance-400 at a frequency of 128 MHz. Chemical shifts are expressed as parts per million (ppm) downfield from the internal standard TMS for proton and carbon, and $BF_3.Et_2O$ for boron. Chiral HPLC analyses were performed on a Gilson HPLC system equipped with a Gilson 321 pump, a Gilson 234 autoinjector, two Gilson valvemates, a Metachem Technologies Degassit degasser, a Gilson UV/VIS detector 118 using appropriated chiral column. Elemental analysis was performed using an Exeter Analytical E-440 Elemental Analyser. EI mass spectrometry was performed on a Micromass Autospec, Finnigan MAT

900XLT or Finnigan MAT 95XP with electrspray methods.. IR spectra were recorded with a Perkin–Elmer 298 FTIR spectrometer. Molecular sieves were activated by heating to 450ºC *in vacuo* (< 2 mmHg). $[\alpha]_D$ values are given in $deg.cm^{-2}.g^{-1}$ and recorded at the D line of Sodium (589 nm). Reactions were stirred using a magnetic stirrer bar. All parallel reactions were performed on a Gilson 215 Synthesis Workstation equipped with ReactArray racks and heating block, carried out using ReactArrray Control Software (version 3,0,0,3048) and HPLC data analysed either directly using Gilson Unipoint (version 5.11) or using ReactArray DataManager (version 1,1,33,0). HPLC conditions were under Gilson Unipoint (version 5.11) control and injections carried out in conjunction with ReactArray DataManager. The HPLC system consisted of Gilson 322 Pump, Gilson 402 Syringe Pump, Agilent 1100 Series UV Diode Array Detector and Phenomenex Gemini C18 5 μm, 150 mm x 4.60 mm column.

(*pS*)-2-(2-Bromoferrocenyl)-N-*n*-butyl-benzimidazole 6

To a solution of 2-(N-*n*-butylamine)aniline **5** (1.47 g, 5.01 mmol) in DMF/water (12.5 mL/0.43 mL) were added (*pS*)-bromoferrocene carboxaldehyde **4** [2] (0.822 g, 5.01 mmol) and the Oxone® (2.0 g, 3.25 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with a saturated solution of K_2CO_3 (3 mL), extracted with ethylacetate (5x8 mL). The combined organic layer washed with water (3x8 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel with ethylacetate/hexane: 1/9 as eluent. 2.12 g (89%) of brown oil was obtained. Ee= 99%, Chiralcel OJ, hexane/ethanol/methanol: 99/0.66/0.33, 1 mL/min, λ=254 nm, 11.2 min, 13.5 min; $[\alpha]_D^{25}$= -71.7 (c=0.0046 in $CHCl_3$,); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.71 (t, *J* = 7.2 Hz, 3H), 1.07 (hextet, *J* = 7.6, 14.4, 2H), 1.49-1.58 (m, 2H), 3.90-3.98 (m, 1H), 4.00-4.09 (m, 1H), 4.26 (s br, 1H), 4.41 (s br, 1H), 4.43 (s, 5H), 4.59 (s br, 1H), 7.15-7.32 (m, 3H), 7.81-7.85 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 13.5, 19.8, 31.5, 44.1, 67.3, 69.4, 70.1, 71.2, 72.9 , 79.4, 109.7, 120.2, 121.9, 122.4, 135.5, 143.1, 149.8.

(*pS*)-2-(2-Boronoferrocenyl)-N-*n*-butylbenzimidazole 3

To a solution of **6** (3.78 g, 8.65 mmol) in dry THF (30 mL) under argon at -78°C was added *n*-butyllithium (4.46 mL, 11.25 mmol, 2.5 M in hexanes). The resulting solution was stirred for 30 min. Then the trimethylborate (10.8 mL, 86.5 mmol) was added and the mixture was stirred at -

78°C. The mixture was warmed to room temperature for 4 hours. The reaction was then quenched by 8 mL of saturated NH_4Cl solution and extracted with diethyl ether (3x8 mL). The combined organic extract was washed with brine (3x8 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The red residue was purified by flash chromatography on silica gel using a graduated elution (hexane, hexane/ethyl acetate, ethyl acetate, ethyl acetate/methanol, methanol). The fractions containing the boron compounds were concentrated to obtain a red brown oil. The dissolution of this oil in ethyl acetate, followed by the addition of hexane, allowed the precipitation of a black solid which was removed by filtration. The filtrate was washed with water (2x5 mL), dried over $MgSO_4$, filtered and concentrated to give the corresponding product as a red solid (3.25 g, 60 %). m.p. 95-100°C; $[\alpha]_D^{25}$= +100 (c=0.0022 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, 3H, J = 6.8 Hz), 1.41 (hextet, 2H, J = 6.8, 14.8), 1.75-1.90 (m, 2H), 4.09 (s, 5H), 4.14-4.21 (m, 1H), 4.32-4.40 (m, 1H), 4.59 (s br, 1H), 4.79 (s br, 1H), 4.88 (s br, 1H), 7.12-7.28 (m, 3H), 7.60-7.70 (m, 1H), 9.80 (s br, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 13.8, 20.3, 32.2, 44.8, 70.7, 71.6, 73.1, 76.4, 78.0, 109.5, 118.5, 122.6, 122.7, 135.4, 140.8, 154.6. ^{11}B NMR ($CDCl_3$, 128 MHz) δ = 29.6; Anal. Calc. for $C_{21}H_{23}BFeN_2O_2$: C, 62.73; H, 5.77; N, 6.97; found C, 62.67; H, 5.88; N, 6.56

General direct amide formation procedure (fluorobenzene).

The appropriate catalyst (0.233 mmol, 10 mol %) was manually weighed into each reaction vessel, followed by assembly of a micro-Soxhlet apparatus loaded with activated 3Å molecular sieves under argon. Solid reagents were added using the ReactArray as standard solutions (0.5 M in fluorobenzene). Naphthalene (0.35 mmol, 15 mol %) and amine (2.33 mmol) were added to the reaction vessels at ambient temperature. The appropriate amount of fluorobenzene was then added to each reaction vessel in order to give a final reaction volume of 10 mL. After heating to reflux, carboxylic acid (2.33 mmol) was added to the stirred solution. Reactions were sampled (50 μL) at 4 h intervals (48 h reaction time respectively). Samples were quenched with MeCN (950 μL), diluted once (50 μL in 950 μL MeCN) mixed and analysed by HPLC. Naphthalene was used as an internal standard, with response factors calculated automatically by ReactArray DataManager.

Recovery of catalyst.

After each reaction, the catalyst was partially recovered. The reaction mixture was concentrated, dissolved in dichloromethane (20 mL), washed with 5% (w/v) HCl (3 x 5 mL), brine (2 x 5 mL), 5% (w/v) NaOH (3 x 5 mL), brine (2 x 5 mL) and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel using a graduated elution (DCM, DCM/Ethylacetate: 8/2, ethylacetate, ethylacetate/methanol: 8/2). This allowed the collection of the amide, the protodeboronated catalyst **10** and the catalyst **3**. 35-40% of catalyst was recovered when using the 4-phenylbutyric acid, 70-80 % when using the benzoic acid.

(1-Phenylethyl)benzamide 9a [3]

To a stirred solution of benzoyl chloride (0.12 mL, 1 mmol) in dry Et_2O (6 mL) under Ar at 0°C, was added α-methylbenzylamine (0.26 mL, 2 mmol) and triethylamine (0.21 mL, 1.5 mmol). The reaction was allowed to warm to room temperature, stirred for 2 hours and then quenched with 5% (w/v) HCl (5 mL). The organic layer was separated and washed again with 5% (w/v) HCl (5 mL), then brine (5 mL), 5% (w/v) NaOH (2 x 5 mL), brine (5 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford N-(1-phenyl)ethylbenzamide (0.24 g, 100%) as a white solid. HPLC: (MeCN (0.05% TFA) / water (0.05% TFA) 65:35 for 8 minutes; 1 mL min^{-1}; 8 min; t_r = 2.94 min); chiral HPLC: Daicel Chiralcel OD. Hexane-EtOH, 90:10, 0.75 mL min^{-1}, 210 nm: t_r (*R*) = 11.9 min; t_r (*S*) = 14.2 min.

(1-Phenylethyl)-4-phenylbutyramide 9b [4]

A 2-necked round-bottomed flask was equipped with stirrer bar, pressure equalising dropping funnel (in vertical neck) with a soxhlet thimble containing CaH_2 (~1g) inside, followed by a condenser. 4-Phenylbutyric acid (0.821 g, 5 mmol), followed by fluorobenzene (50 mL), and α-methylbenzylamine (0.65 mL, 5 mmol) were added, followed by catalyst **1** (117.6 mg, 0.5 mmol, 10 mol %). The mixture was allowed to stir at reflux for 24 h, before being concentrated *in vacuo*. The residue was then redissolved in DCM (25 mL), washed with brine (25 mL), 5% (w/v) HCl (25 mL), brine (25 mL), 5% (w/v) NaOH (25 mL), brine (25 mL), dried over $MgSO_4$, and the solvent evaporated *in vacuo* to afford (1-phenylethyl)-4-phenylbutyramide (0.71 g, 53%) as a white solid. HPLC: (gradient MeCN (0.05% TFA) / water (0.05% TFA) 0:100 to 100:0 over 15 minutes; 1 mL min^{-1}; t_r = 13.10 min); chiral HPLC: Daicel Chiralcel OD. Hexane-EtOH, 97.5:2.5, 1 mL min^{-1}, 210 nm: t_r (*R*) = 34.3 min; t_r (*S*) = 41.5 min.

(1-Naphthylethyl)-4-phenylbutyramide 9c

Catalyst **1** (23.5 mg, 0.1 mmol, 10 mol %) and 4-phenylbutyric acid (164.2 mg, 1 mmol) were weighed into a ReactArray reaction vessel, followed by assembly of a micro-Soxhlet apparatus loaded with activated 3Å molecular sieves under argon. Fluorobenzene (10 mL), and 1-(1-naphthyl)ethylamine (161 μL, 1 mmol) were added and the mixture stirred at reflux for 48 h, allowed to cool and the fluorobenzene removed *in vacuo*. The residue was then redissolved in DCM (25 mL), washed with brine (10 mL), 5% (w/v) HCl (10 mL), brine (10 mL), 5% (w/v) NaOH (10 mL), brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford (1-naphthylethyl)-4-phenylbutyramide **9c** (0.273 g, 86%) as a white solid. Mp 107-108ºC; (Found: C, 82.93; H, 7.31; N, 4.33. $C_{22}H_{23}NO$ requires C, 83.24; H, 7.30; N, 4.41%); ν_{max} (film)/cm^{-1} 3297, 2931, 1633s, 1532s and 777vs; δ_H (500 MHz; $CDCl_3$) 1.67 (3H, d, *J* 6.5, C*H*$_3$), 1.93-2.01 (2H, m, C*H*$_2$), 2.09-2.20 (2H, m, C*H*$_2$CO), 2.56-2.67 (2H, m, ArC*H*$_2$), 5.62 (1H, br d, *J 8.5*, CONH), 5.96 (1H, quintet, *J* 7.0, NC*H*CH$_3$), 7.10 (2H, d, *J* 7.5, Ar*H*), 7.16 (1H, t, *J* 7.5, Ar*H*), 7.23 (2H, t, *J* 7.5, Ar*H*), 7.45 (1H, t, *J* 7.5, Ar*H*), 7.50 (2H, t, *J* 7.0, Ar*H*), 7.54 (1H, t, *J* 7.5, Ar*H*), 7.81 (1H, d, *J* 8.0, Ar*H*), 7.87 (1H, d, *J* 8.5, Ar*H*) and 8.11 (1H, d, *J* 8.5, Ar*H*); δ_C (125.7 MHz; $CDCl_3$) 20.7 (CH_2), 27.2 (CH_2), 35.2 (CH_3), 36.1 (CH_2), 44.5 (CH_2N), 122.7 (ArC), 123.6 (ArC), 125.3 (ArC), 126.1 (ArC), 126.7 (ArC), 128.48 (ArC), 128.56 (ArC), 128.61 (ArC), 128.9 (ArC), 131.3 (ArC), 134.1 (ArC), 138.3 (ArC), 141.6 (ArC) and 171.6 (CONH); *m/z* (ES) 340.2 (100%, $[M+Na]^+$). Chiral HPLC: Daicel Chiralcel OD. Hexane-EtOH, 85:15, 1 mL min^{-1}, 210 nm: t_r (*R*) = 7.60 min; t_r (*S*) = 13.9 min. The determination of enantiomers has been realized by running each enantiomer of the amide separately.

(1-Phenylpropyl)-4-phenylbutyramide 9d

In a micro-Soxhlet apparatus loaded with activated 3Å molecular sieves under argon, the solution of 1-(1-phenyl)propylamine (2.33 mmol, 4.66 mL, C=0.5 M in fluorobenzene) was added. Fluorobenzene (0.7 mL) was added to complete the total volume to 10 mL. After heating the reaction mixture to reflux, the solution of 4-(phenyl)butyric acid (2.33 mmol, 4.66 mL, C=0.5 M in fluorobenzene) was added. The mixture stirred at reflux for 48 h, allowed to cool and the fluorobenzene removed *in vacuo*. The residue was then redissolved in DCM (25 mL), washed with 5% (w/v) HCl (3 x 5 mL), brine (2 x 5 mL), 5% (w/v) NaOH (3 x 5 mL), brine (2 x 5 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford (1-phenylpropyl)-4-phenylbutyramide **9d** (0.077 g, 12%) as a white solid. Mp 96-97ºC; (Found: C, 81.11; H, 8.18; N, 4.83. $C_{19}H_{23}NO$

requires C, 81.10; H, 8.24; N, 4.98%); ν_{max} (film)/cm^{-1} 3299, 2939, 1639s, 1539s; δ_H (400 MHz; $CDCl_3$) 0.81 (3H, t, *J* 7.2, C*H*$_3$), 1.68-1.80 (2H, m, C*H*$_2$), 1.85-1.93 (2H, m, C*H*$_2$), 2.08-2.12 (2H, m, C*H*$_2$CH$_3$) 2.53-2.58 (2H, m, ArC*H*$_2$), 4.82 (1H, quartet, *J* 7.6, NC*H*CH$_2$), 5.53 (1H, br d, *J* 7.6, CONH), 7.04-7.29 (10H, m); δ_C (100.7 MHz; $CDCl_3$) 10.9 (CH_3), 27.2 (CH_2), 29.2 (CH_2), 35.3 (CH_2), 36.1 (CH_2), 54.9 (CHN), 126.1 (ArC), 126.8 (ArC), 127.5 (ArC), 128.5 (ArC), 128.7 (ArC), 128.8 (ArC), 141.6 (ArC) 142.3 (ArC) and 171.9 (CONH); *m/z* (ES) 304.2 (100%, $[M+Na]^+$). Chiral HPLC: Daicel Chiralcel OD. Hexane-EtOH, 90:10, 1 mL min^{-1}, 210 nm: t_r (*R*) = 8.2 min; t_r (*S*) = 10.9 min. The determination of enantiomers has been realized by running each enantiomer of the amide separately.

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