Copper-catalyzed N-(hetero)arylation of amino acids in water

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Supporting Information

Table of Contents
General information and materials .................................................................................................. 1
1. General procedure for the N-arylation ......................................................................................... 2
2. Characterization data of the synthesized compounds ................................................................. 2
3. $^1$H and $^{13}$C NMR spectrum of selected compounds .............................................................. 11
4. Chiral HPLC chromatograms of representative compounds .................................................. 47

General information and materials

All the reagents were available from commercial suppliers and used without any purification unless otherwise noted. Amino acids and aryl halides, base, copper catalyst and ligands were purchased from commercial sources such as Sigma-Aldrich, Alfa-aesar, Merck, Avra, TCI and Chem-impex. NMR were recorded on a BrukerAvance-III 400 spectrometer ($^1$H NMR (400 MHz), $^{13}$C NMR (100 MHz) respectively. Chemical shifts for $^1$H NMR were reported as δ values and coupling constants were in hertz (Hz) and chemical shifts for $^{13}$C NMR reported in ppm relative to the solvent peak. If required 5-20% v/v of CD$_3$OD was added in CDCl$_3$ while recording the spectra to enhance the solubility of N-arylated amino acids in CDCl$_3$, and DCl in D$_2$O (2-3 drops) was added in MeOD while recording spectrum of N-heteroarylated compounds. The following abbreviations were used for spin multiplicity: s = singlet, d = doublet, t = triplet, dd = double doublet, m = multiplet, q = quadruplet, td = triplet of doublet, and if splitting patterns could not be interpreted easily reported as multiplet (m). Thin layer chromatography was performed on Merck precoated silica gel plates(0.25 mm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm) and visualization was observed under UV light (254 nm) or staining with iodine in silica. Synthesized compounds were isolated by
the automated flash chromatography on silica gel (200–400 mesh). HRMS were recorded on Bruker Maxis and Chiral-HPLC measurements were performed on Shimadzu Prominence using an CHIRALPAK®-WH column (250mm L x 4.6mm i.d.) and the mobile phase used in this study was 0.25mM copper(II) sulfate in water and 2-propanol (93:7), and gradient run for 180 min at flow rate of 1 mL/min.

1. General procedure for N-arylation

All the solid materials were weighed in air, transferred to a (10 mL) pre-dried MW vial equipped with magnetic stirring bar and capped with a septum. All the solid materials were added and vacuum was applied, and then back filling with argon was done; this procedure was repeated three times after which all the liquids including solvent were charged under positive pressure of argon. In the dried MW vial (10 mL) was added aryl bromide (1 mmol, 1.0 equiv.), amino acid (1.2 equiv.), copper iodide (5 mol%), 2-isobutyrylcyclohexanone (20 mol%), PEG-400 (1.5 equiv.), K₂CO₃ (2.5 equiv.) and water (2 mL). The vial was sealed and allowed to heat at constant 90 °C temperature under microwave irradiation (CEM Discover) for 50 min. After the completion of reaction, the reaction mixture was acidified to pH 3-4 by using aqueous HCl, and N-arylated amino acid was extracted with ethyl acetate (2 x 10 mL). The ethyl acetate was dried over Mg₂SO₄; solvent removed under reduced pressure, and purified using automated flash chromatography on silica gel to afford the N-arylated amino acids.

2. Characterization data of the synthesized compounds

![N-(Phenyl)-L-valine (2a):](image)

Yield = 87%; ¹H NMR [400 MHz, CD₃OD]: δ 7.13-7.09 (m, 2H), 6.67-6.63 (m, 3H), 3.75 (d, J = 6.4 Hz, 1H), 2.16-2.08 (m, 1H), 1.10-1.05 (m, 6H); ¹³C NMR (100 MHz, CD₃OD): 176.2, 148.0, 128.6, 117.2, 113.0, 62.7, 30.9, 18.2, 17.8; HRMS (ESI-TOF): m/z [M+H⁺] calculated 194.1181; found 194.1178.
**N-(4-Methylphenyl)-L-valine (2b):** Yield = 84%; $^1$H NMR [400 MHz, CD$_3$OD]: $\delta$ 7.63 (d, $J = 7.9$ Hz, 2H), 7.25 (d, $J = 7.9$ Hz, 2H), 4.44 (d, $J = 5.4$ Hz, 1H), 2.88 (s, 3H), 2.83-2.75 (m, 1H), 1.71 (t, $J = 5.7$ Hz, 6H); $^{13}$C NMR [100 MHz, CD$_3$OD]: 173.4, 149.0, 133.5, 131.6, 117.7, 66.8, 33.5, 24.0, 22.8, 22.2; HRMS (ESI-TOF): m/z [M+H$^+$] calculated 208.1337; found 208.1334.

**N-(3-Methylphenyl)-L-valine (2c):** Yield = 85%; $^1$H NMR [400 MHz, CDCl$_3$]: $\delta$ 6.99 (t, $J = 7.5$ Hz, 1H), 6.50-6.40 (m, 3H), 3.77 (d, $J = 5.2$ Hz, 1H), 2.20 (s, 3H), 2.09 (q, $J = 12.7$ Hz, 1H), 1.01-0.98 (m, 6H); $^{13}$C NMR [100 MHz, CD$_3$OD]: 176.1, 147.4, 138.9, 129.0, 119.0, 114.3, 110.5, 62.3, 29.8, 21.4, 18.9, 18.3; HRMS (ESI-TOF): m/z [M+H$^+$] calculated 208.1337; found 208.1331.

**N-(4-tert-butylphenyl)-L-valine (2d):** Yield = 80%; $^1$H NMR [400 MHz, CD$_3$OD]: $\delta$ 7.24 (q, $J = 6.6$ Hz, 2H), 6.63 (q, $J = 6.6$ Hz, 2H), 3.85 (d, $J = 5.4$ Hz, 1H), 2.24-2.19 (m, 1H), 1.29 (s, 9H), 1.08 (d, $J = 6.8$ Hz, 6H); $^{13}$C NMR [100 MHz, CD$_3$OD]: 176.1, 144.9, 140.9, 125.9, 116.0, 112.5, 62.6, 33.7, 31.3, 19.0, 18.3; HRMS (ESI-TOF): m/z [M+H$^+$] calculated 250.1807; found 250.1802.

**N-(4-Biphenyl)-L-valine (2e):** Yield = 83%; $^1$H NMR [400 MHz, CD$_3$OD]: $\delta$ 7.69 (t, $J = 1.3$ Hz, 2H), 7.68-7.61 (m, 4H), 7.50-7.48 (m, 1H), 7.01-6.97 (m, 2H), 4.10 (d, $J = 5.9$ Hz, 1H), 2.45-2.40 (m, 1H), 1.34 (t, $J = 7.1$ Hz, 6H); $^{13}$C NMR [100 MHz, CD$_3$OD]: 179.9, 151.0, 145.0, 134.6, 132.4, 131.5, 129.8, 119.8, 117.5, 66.4, 35.0, 22.7, 22.2; HRMS (ESI-TOF): m/z [M+H$^+$] calculated 270.1494; found 270.1490.
**N-(4-Napthyl)-l-valine (2f):** Yield = 81%; \(^1\)H NMR [400 MHz, CDCl\(_3\)]: \(\delta\) 7.92 (q, \(J = 6.6\) Hz, 1H), 7.84 (q, \(J = 5.9\) Hz, 1H), 7.52-7.46 (m, 3H), 7.32 (d, \(J = 2.6\) Hz, 1H), 6.64-6.61 (m, 1H), 4.09 (d, \(J = 5.5\) Hz, 1H), 2.39-2.31 (m, 1H), 1.21 (d, \(J = 6.8\) Hz, 3H), 1.15 (d, \(J = 6.7\) Hz, 3H); \(^1\)C NMR [100 MHz]: 178.1, 142.2, 134.4, 128.7, 126.4, 125.8, 124.9, 123.7, 120.0, 118.4, 105.3, 62.3, 31.4, 19.2, 18.7; HRMS (ESI-TOF): \(m/z \ [M+H^+]\) calculated 244.1337; found 244.1330.

**N-(3-Chlorophenyl)-l-valine (2g):** Yield = 88%; \(^1\)H NMR [400 MHz, CDCl\(_3\)]: \(\delta\) 7.10 (t, \(J = 8.0\) Hz, 1H), 6.74-6.72 (m, 1H), 6.64 (t, \(J = 4.2\) Hz, 1H), 6.54-6.51 (m, 1H), 3.88 (d, \(J = 5.5\) Hz, 1H), 2.23-2.16 (m, 1H), 1.08 (d, \(J = 6.8\) Hz, 6H); \(^1\)C NMR [100 MHz, CDCl\(_3\)]: 178.8, 148.2, 135.1, 130.3, 118.4, 113.3, 111.7, 62.0, 31.3, 19.1, 18.3; HRMS (ESI-TOF): \(m/z \ [M+H^+]\) calculated 228.0791; found 228.0791.

**N-(4-Chlorophenyl)-l-valine (2h):** Yield = 90%; \(^1\)H NMR [400 MHz, CD\(_3\)OD]: \(\delta\) 7.74-7.68 (m, 2H), 7.18 (t, \(J = 4.3\) Hz, 2H), 4.37 (d, \(J = 5.6\) Hz, 1H), 2.78-2.71 (m, 1H), 1.65 (t, \(J = 6.1\) Hz, 6H); \(^1\)C NMR [100 MHz, CD\(_3\)OD]: 179.7, 150.1, 132.8, 126.3, 118.4, 66.3, 33.5, 22.8, 22.2; HRMS (ESI-TOF): \(m/z \ [M+H^+]\) calculated 228.0791; found 228.0786.

**N-(4-Trifluoromethylphenyl)-l-valine (2i):** Yield = 90%; \(^1\)H NMR [400 MHz, CD\(_3\)OD]: \(\delta\) 7.27 (br.s., 2H), 6.86 (br.s., 2H), 3.76 (s, 1H), 2.16 (s, 1H), 1.11-1.07 (m, 6H); \(^1\)C NMR [100 MHz, CD\(_3\)OD]: 177.6, 150.3, 130.5, 116.8, 114.1, 110.0, 62.0, 30.7, 19.7, 19.2; HRMS (ESI-TOF): \(m/z \ [M+H^+]\) calculated 262.1055; found 262.1048.
N-(2-Nitro-4-trifluoromethylphenyl)-L-valine (2j): Yield = 82%; ¹H NMR [400 MHz, CD₂OD]: δ 8.80 (d, J = 6.5 Hz, 1H), 8.01-7.97 (m, 1H), 7.29 (t, J = 7.6 Hz, 1H), 4.52 (d, J = 4.9 Hz, 1H), 2.76-2.69 (m, 1H), 1.50-1.42 (m, 6H); ¹³C NMR [100 MHz, CD₂OD]: 176.8, 150.2, 136.1, 135.2, 128.7, 126.1, 121.9, 118.7, 65.1, 22.6, 21.8; HRMS (ESI-TOF): m/z [M+H⁺] calculated 307.0905; found 307.0902.

N-(4-Nitrophenyl)-L-valine (2k): Yield = 91%; ¹H NMR [400 MHz, CDCl₃]: δ 8.08 (d, J = 9.0 Hz, 2H), 6.62 (q, J = 17.5 Hz, 2H), 4.02 (d, J = 5.0 Hz, 1H), 2.29-2.21 (m, 1H), 1.07 (q, J = 10.1 Hz, 6H); ¹³C NMR [100 MHz, CDCl₃]: 176.7, 152.4, 138.7, 126.4, 111.8, 61.3, 31.3, 18.9, 18.3; HRMS (ESI-TOF): m/z [M+H⁺] calculated 239.1032; found 239.1027.

N-(3-Nitrophenyl)-L-valine (2l): Yield = 88%; ¹H NMR [400 MHz, CDCl₃]: δ 7.59-7.57 (m, 1H), 7.46 (t, J = 2.2 Hz, 1H), 7.30 (t, J = 8.1 Hz, 1H), 6.94-6.91 (m, 1H), 3.98 (d, J = 5.4 Hz, 1H), 2.28-2.21 (m, 1H), 1.09 (d, J = 6.8 Hz, 6H); ¹³C NMR [100 MHz]: 178.4, 149.3, 147.9, 130.0, 119.2, 113.0, 107.3, 61.7, 31.3, 19.1, 18.2; HRMS (ESI-TOF): m/z [M+H⁺] calculated 239.1032; found 239.1027.

N-(2-Nitrophenyl)-L-valine (2m): Yield = 82%; ¹H NMR [400 MHz, CDCl₃]: δ 8.21 (q, J = 8.5 Hz, 1H), 7.47-7.43 (m, 1H), 6.78-6.71 (m, 2H), 4.11 (q, J = 7.6 Hz, 1H), 2.43-2.35 (m, 1H), 1.17-1.12 (m, 6H); ¹³C NMR [100 MHz, CD₂OD]: 177.6, 144.4, 136.4, 132.8, 127.1, 116.4, 113.6, 61.2, 31.2, 19.1, 18.2; HRMS (ESI-TOF) m/z [M+Na⁺]: calculated 261.0852; found 261.0852.
N-(4-Cyanophenyl)-L-valine (2n): Yield = 86%; \(^1^H\) NMR [400 MHz, CDCl\(_3\)]: \(\delta\) 7.35 (q, \(J = 6.9\) Hz, 2H), 6.57-6.55 (m, 2H), 3.82 (d, \(J = 5.5\) Hz, 1H), 2.17-2.08 (m, 1H), 1.01-0.96 (m, 6H); \(^1^C\) NMR [100 MHz, CDCl\(_3\)]: 174.7, 150.9, 133.6, 120.3, 112.6, 98.6, 61.1, 31.0, 18.8, 18.2; HRMS (ESI-TOF): \(m/z\) [M+H\(^+\)] calculated 219.1133; found 219.1132.

N-(4-Formylphenyl)-L-valine (2o): Yield = 87%; \(^1^H\) NMR [400 MHz, CDCl\(_3\)]: \(\delta\) 9.69 (s, 1H), 7.68 (d, \(J = 8.6\) Hz, 2H), 6.66 (d, \(J = 8.6\) Hz, 2H), 4.02 (d, \(J = 5.4\) Hz, 1H), 2.28-2.20 (m, 1H), 1.09-1.05 (m, 6H); \(^1^C\) NMR [100 MHz, CDCl\(_3\)]: 190.8, 176.7, 152.6, 132.5, 126.9, 112.5, 61.2, 31.3, 18.9, 18.4; HRMS (ESI-TOF): \(m/z\) [M+H\(^+\)] calculated 222.1130; found 22.1124.

N-(3-Fluorophenyl)-L-valine (2p): Yield = 87%; \(^1^H\) NMR [400 MHz, CDCl\(_3\)]: \(\delta\) 7.15-7.09 (m, 1H), 6.48-6.41 (m, 2H), 6.37-6.33 (m, 1H), 3.87 (d, \(J = 5.5\) Hz, 1H), 2.25-2.16 (m, 1H), 1.09-1.05 (m, 6H); \(^1^C\) NMR [100 MHz, CDCl\(_3\)]: 178.7, 164 (d, \(J = 242\) Hz, 1C), 148.83 (d, \(J = 11\) Hz, 1C), 130.53 (d, \(J = 10\) Hz, 1C), 109.2, 105.03 (d, \(J = 21\) Hz, 1C), 100.41 (d, \(J = 26\) Hz, 1C), 62.1, 31.3, 19.1, 18.3; HRMS (ESI-TOF): \(m/z\) [M+H\(^+\)] calculated 212.1087; found 212.1081.

N-(3,5-Difluorophenyl)-L-valine (2q): Yield = 83%; \(^1^H\) NMR [400 MHz, CDCl\(_3\)]: \(\delta\) 6.83 (t, \(J = 9.5\) Hz, 3H), 4.46 (d, \(J = 5.3\) Hz, 1H), 2.89-2.83 (m, 1H), 1.75 (t, \(J = 6.3\) Hz, 6H); \(^1^C\) NMR [100 MHz, CDCl\(_3\)]: 179.1, 167.9 (d, \(J = 226\) Hz, 2C), 154.0, 99.8 (d, \(J = 28\) Hz, 2C), 96.5 (t, \(J = 26\) Hz, 1C), 65.8, 34.9, 22.8, 22.2; HRMS (ESI-TOF): \(m/z\) [M+H\(^+\)] calculated 230.0992; found 230.0990.
\( N-(2,4\text{-Difluorophenyl})\text{-L-valine (2r)}: \) Yield = 81%; \( ^1\text{H NMR} \) [400 MHz, CD\(_3\)OD]: \( \delta \) 7.51-7.40 (m, 2H), 7.34-7.28 (m, 1H), 4.47 (d, \( J = 5.5 \) Hz, 1H), 2.92-2.83 (m, 1H), 1.78-1.75 (m, 6H); \( ^{13}\text{C NMR} \) [100 MHz, CD\(_3\)OD]: 179.4, 158.57 (d, \( J = 236 \) Hz, 1C), 155.12 (d, \( J = 230 \) Hz, 1C), 136.3, 116.9, 114.46 (d, \( J = 25 \) Hz, 1C), 107.46 (t, \( J = 26 \) Hz, 1C), 66.5, 35.1, 22.9, 22.1; HRMS (ESI-TOF): \( m/z \) [M+H\(^+\)] calculated 230.0992; found 230.0990.

\( N-(3\text{-Pyridyl})\text{-L-valine (2s)}: \) Yield = 82%; \( ^1\text{H NMR} \) [400 MHz, CD\(_3\)OD]: \( \delta \) 8.18 (s, 1H), 8.03 (d, \( J = 4.6 \) Hz, 1H), 7.85-7.77 (m, 2H), 4.11-4.02 (m, 1H), 2.33-2.28 (m, 1H), 1.11-1.05 (m, 6H); \( ^{13}\text{C NMR} \) [100 MHz, CD\(_3\)OD]: 172.4, 147.6, 128.3, 128.1, 127.3, 124.4, 61.3, 30.5, 18.2, 17.3; HRMS (ESI-TOF): \( m/z \) [M+H\(^+\)] calculated 195.1133; found 195.1126.

\( N-(3\text{-quinolinyl})\text{-L-valine (2t)}: \) Yield = 88%; \( ^1\text{H NMR} \) [400 MHz, CD\(_3\)OD]: \( \delta \) 8.91 (d, \( J = 2.7 \) Hz, 1H), 8.71 (d, \( J = 4.9 \) Hz, 1H), 8.02 (d, \( J = 9.2 \) Hz, 1H), 7.86 (q, \( J = 8.3 \) Hz, 1H), 7.78 (d, \( J = 9.3 \) Hz, 1H), 7.04 (d, \( J = 2.2 \) Hz, 1H), 4.09-4.00 (m, 1H), 2.32-2.25 (m, 1H), 1.15-1.08 (m, 6H); \( ^{13}\text{C NMR} \) [100 MHz, CD\(_3\)OD]: 174.3, 149.3, 147.3, 143.2, 137.5, 131.8, 127.2, 121.5, 120.5, 61.9, 30.6, 18.2, 17.7; HRMS (ESI-TOF): \( m/z \) [M+H\(^+\)] calculated 245.1290; found 245.1283.

\( N-(6\text{-quinolinyl})\text{-L-valine (2u)}: \) Yield = 78%; \( ^1\text{H NMR} \) [400 MHz, CD\(_3\)OD]: \( \delta \) 8.79 (t, \( J = 7.2 \) Hz, 1H), 8.71 (d, \( J = 4.9 \) Hz, 1H), 8.02 (d, \( J = 9.2 \) Hz, 1H), 7.86 (q, \( J = 8.3 \) Hz, 1H), 7.78 (d, \( J = 9.3 \) Hz, 1H), 7.04 (d, \( J = 2.2 \) Hz, 1H), 4.09-4.00 (m, 1H), 2.32-2.25 (m, 1H), 1.15-1.08 (m, 6H); \( ^{13}\text{C NMR} \) [100 MHz, CD\(_3\)OD]: 174.3, 149.3, 147.3, 143.2, 137.5, 131.8, 127.2, 121.5, 120.5, 61.9, 30.6, 18.2, 17.7; HRMS (ESI-TOF): \( m/z \) [M+H\(^+\)] calculated 245.1290; found 245.1283.
**N-Phenylglycine (4a):** Yield = 81%; \(^1H\) NMR [400 MHz, CD\(_3\)OD]: \(\delta\) 7.17 (t, \(J = 7.9\) Hz, 2H), 6.71 (t, \(J = 7.6\) Hz, 1H), 6.63 (d, \(J = 7.1\) Hz, 2H), 3.41 (s, 2H); \(^{13}C\) NMR (100 MHz, CD\(_3\)OD): 174.4, 147.9, 129.2, 118.1, 113.7, 45.8; HRMS (ESI-TOF): \(m/z\) [M+H\(^+\)] calculated 152.0713; found 52.0710.

**N-(Phenyl)-L-alanine (4b):** Yield = 86%; \(^1H\) NMR [400 MHz, CD\(_3\)OD]: \(\delta\) \(^1H\) NMR [400 MHz, CD\(_3\)OD] \(\delta\) 7.08 (t, \(J = 7.8\) Hz, 2H), 6.62 (q, \(J = 13.7\) Hz, 3H), 4.00 (q, \(J = 13.9\) Hz, 1H), 1.43 (d, \(J = 7.0\) Hz, 3H); \(^{13}C\) NMR [100 MHz, CDCl\(_3\)]: 181.3, 151.2, 132.6, 121.4, 117.1, 55.8, 21.3; HRMS (ESI-TOF): \(m/z\) [M+H\(^+\)] calculated 166.0869; found 166.0861.

**N-(Phenyl)-D-valine (4c):** Yield = 88%; \(^1H\) NMR [400 MHz, CD\(_3\)OD]: \(\delta\) 7.13-7.08 (m, 2H), 6.67-6.63 (m, 3H), 3.75 (d, \(J = 6.4\) Hz, 1H), 2.17-2.08 (m, 1H), 1.10-1.06 (m, 6H); \(^{13}C\) NMR [100 MHz, CD\(_3\)OD]: 176.2, 148.0, 128.6, 117.2, 113.0, 62.7, 30.9, 18.2, 17.8; HRMS (ESI-TOF): \(m/z\) [M+H\(^+\)] calculated 194.1181; found 194.1175.

**N-(Phenyl)-L-isoleucine (4d):** Yield = 80%; \(^1H\) NMR [400 MHz, CD\(_3\)OD]: \(\delta\) 7.13-7.09 (m, 2H), 6.65 (t, \(J = 8.2\) Hz, 3H), 3.83 (d, \(J = 6.4\) Hz, 1H), 1.90-1.85 (m, 1H), 1.74-1.72 (m, 1H), 1.71-1.68 (m, 1H), 1.38 (d, \(J = 7.4\) Hz, 1H); \(^{13}C\) NMR [100 MHz, CD\(_3\)OD]: 176.1, 147.9, 128.6, 117.2, 113.0, 61.3, 37.3, 25.3, 14.6, 10.3; HRMS (ESI-TOF): \(m/z\) [M+H\(^+\)] calculated 208.1337; found 208.1333.

**N-(Phenyl)-L-leucine (4e):** Yield = 89%; \(^1H\) NMR [400 MHz, CD\(_3\)OD]: \(\delta\) 7.11 (t, \(J = 6.8\) Hz, 2H), 6.65 (t, \(J = 8.2\) Hz, 3H), 3.93 (q, \(J = 6.4\) Hz, 1H), 1.91-1.82 (m, 1H), 1.74-1.64 (m, 1H), 1.02 (d, \(J = 6.6\) Hz, 3H), 0.96 (d, \(J = 6.6\) Hz, 3H); \(^{13}C\) NMR (100 MHz, CD\(_3\)OD): 177.5, 147.8, 128.6, 117.2, 112.8, 55.0,
41.7, 24.6, 21.8, 21.0; HRMS (ESI-TOF): \textit{m/z} \ [\text{M+H}^+] 
calculated 208.1337; found 208.1333.

\textit{N-(Phenyl)-L-methionine (4f):} Yield = 91%; \textit{\textsuperscript{1}H} NMR [400 MHz, CD$_3$OD]: \(\delta\) 7.00-6.96 (m, 2H), 6.56-6.48 (m, 3H), 4.05-4.01 (m, 1H), 2.50-2.47 (m, 2H), 2.02-1.83 (m, 5H); \textit{\textsuperscript{13}C} NMR [100 MHz, CD$_3$OD]: 175.8, 146.7, 128.9, 117.9, 113.2, 55.1, 31.8, 29.3, 14.7; HRMS (ESI-TOF): \textit{m/z} \ [\text{M+H}^+] 
calculated 226.0901; found 226.0895.

\textit{N-(Phenyl)-L-phenylalanine (4g):} Yield = 90%; \textit{\textsuperscript{1}H} NMR [400 MHz, CD$_3$OD]: \(\delta\) 7.28-7.18 (m, 5H), 7.12 (t, \(J = 7.2\) Hz, 2H), 6.67-6.60 (m, 3H), 4.29 (t, \(J = 6.2\) Hz, 1H), 3.19 (dd, \(J = 13.7, 5.7\) Hz, 1H), 3.08 (dd, \(J = 12.4, 6.4\) Hz, 1H); \textit{\textsuperscript{13}C} NMR [100 MHz, CD$_3$OD]: 175.6, 146.7, 136.7, 129.1, 129.0 128.2, 126.6, 117.9, 113.4, 57.7, 38.1; HRMS (ESI-TOF): \textit{m/z} \ [\text{M+H}^+] 
calculated 242.1181 found 242.1174.

\textit{N-(Phenyl)-L-tryptophan (4h):} Yield = 88%; \textit{\textsuperscript{1}H} NMR [400 MHz, CD$_3$OD]: \(\delta\) 7.57 (d, \(J = 7.8\) Hz, 1H), 7.34 (d, \(J = 8.0\) Hz, 1H), 7.10 (t, \(J = 7.7\) Hz, 4H), 7.01 (t, \(J = 7.4\) Hz, 1H), 6.65-6.61 (m, 3H), 4.34 (t, \(J = 6.2\) Hz, 1H), 3.39-3.34 (m, 1H), 3.27 (dd, \(J = 14.4\) Hz, 6.2 Hz, 1H); \textit{\textsuperscript{13}C} NMR (100 MHz, CD$_3$OD): 176.4, 147.3, 136.6, 128.6, 127.5, 123.1, 120.9, 118.3, 117.9, 117.4, 113.1, 110.8, 109.6, 57.4, 27.9; HRMS (ESI-TOF): \textit{m/z} 
[M+Na$^+$] calculated 303.1110; found 303.1108.

\textit{N-(Phenyl)-L-proline (4i):} Yield = 82%; \textit{\textsuperscript{1}H} NMR [400 MHz, CDCl$_3$]: \(\delta\) 7.29-7.25 (m, 2H), 6.79 (t, \(J = 7.2\) Hz, 1H), 6.62 (d, \(J = 8.0\) Hz, 2H), 4.24 (d, \(J = 7.0\) Hz, 1H), 3.65-3.60 (m, 1H), 3.35 (q, \(J = 15.9\) Hz, 1H), 2.36-2.27 (m, 2H), 2.18-2.10 (m, 2H); \textit{\textsuperscript{13}C} NMR [100 MHz, CDCl$_3$]: 178.3, 146.7, 129.3, 117.5, 112.4, 61.2, 48.7, 31.0, 23.9; HRMS (ESI-TOF): \textit{m/z} \ [\text{M+H}^+] 

S9
calculated 192.1024; found 192.0938.

*N-(Phenyl)-L-aminobutyric acid (2k):* Yield = 84%; $^1$H NMR [400 MHz, CD$_3$OD]: $\delta$ 7.16 (t, $J$ = 7.8 Hz, 2H), 6.73-6.63 (m, 3H), 3.98 (t, $J$ = 6.1 Hz, 1H), 1.95-1.76 (m, 2H), 1.02 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR [100 MHz, CD$_3$OD]: 180.4, 150.8, 133.1, 122.0, 117.3, 61.5, 29.7, 13.7; HRMS (ESI-TOF): $m/z$ [M+H]$^+$ calculated 180.1024; found 180.1017.

1-(Phenylamino)cyclohexanecarboxylic acid (4l): Yield = 83%; $^1$H NMR [400 MHz, CDCl$_3$]: $\delta$ 7.24-7.20 (m, 2H), 6.87 (t, $J$ = 7.3 Hz, 1H), 6.69 (d, $J$ = 7.6 Hz, 2H), 2.02-1.95 (m, 4H), 1.64 (t, $J$ = 5.7 Hz, 3H), 1.47-1.39 (m, 3H); $^{13}$C NMR [100 MHz, CDCl$_3$]: 178.7, 143.6, 129.2, 120.1, 116.7, 60.6, 41.9, 31.8, 25.0, 21.1; HRMS (ESI-TOF): $m/z$ [M+H]$^+$ calculated 220.1337 found 220.1332.

2-Methyl-2-(phenylamino)propanoic acid (4m): Yield = 85%; $^1$H NMR [400 MHz, CDCl$_3$]: $\delta$ 7.74 (t, $J$ = 7.8 Hz, 2H), 7.39 (t, $J$ = 7.2 Hz, 1H), 7.29 (d, $J$ = 8.3 Hz, 2H), 2.07 (s, 6H); $^{13}$C NMR [100 MHz, CD$_3$OD]: 182.2, 147.5, 132.9, 124.0, 121.1, 62.5, 29.2; HRMS (ESI-TOF): $m/z$ [M+H]$^+$ calculated 180.1024 found 180.1027.

*N-(Phenyl)-β-alanine (4n):* Yield = 78%; $^1$H NMR [400 MHz, CDCl$_3$]: $\delta$ 7.25-7.20 (m, 2H), 6.79 (q, $J$ = 10.5 Hz, 1H), 6.69 (q, $J$ = 8.5 Hz, 2H), 3.49 (t, $J$ = 6.3 Hz, 2H), 2.73-2.68 (m, 2H); $^{13}$C NMR [100 MHz, CDCl$_3$]: 178.1, 147.0, 129.4, 118.4, 113.6, 39.5, 33.6; HRMS (ESI-TOF): $m/z$ [M+H]$^+$ calculated 166.0868 found 166.0858.
3. $^1$H and $^{13}$C NMR spectrum of selected compounds

$N$-(Phenyl)-L-valine (2a):
$N$-(4-Biphenyl)$L$-valine (2e):
N-(3-Chlorophenyl)-L-valine (2g):
$N$-(2-Nitro-4-trifluoromethylphenyl)-l-valine (2j):
N-(3-Nitrophenyl)-L-valine (2l):
\textbf{N-(2-Nitrophenyl)-L-valine (2m):}
N-(3-Fluorophenyl)-L-valine (2p):
**N-(3,5-Difluorophenyl)-L-valine (2q):**
$N$-(2,4-Difluorophenyl)-L-valine (2r):
N-(3-Pyridyl)-L-valine (2s):
N-(3-quinolinyl)-L-valine (2t):
N-(6-quinolinyl)-L-valine (2u):
N-(Phenyl)-L-methionine (4f):
N-(Phenyl)-L-phenylalanine (4g):
N-(Phenyl)-L-tryptophan (4h):
N-(Phenyl)-L-aminobutyric acid (2k):
1-(Phenylamino)cyclohexanecarboxylic acid (4l):
2-Methyl-2-(phenylamino)propanoic acid (4m):
4. Chiral HPLC chromatograms of representative compounds
Figure 1. Chiral HPLC Chromatogram of N-phenyl-\textgreek{D}-valine (4c)

Figure 2. Chiral HPLC Chromatogram of N-phenyl-\textgreek{L}-valine (2a)

Figure 3. Chiral HPLC Chromatogram of N-phenyl-\textgreek{D,L}-valine