Cyrene as a Bio-based Solvent for HATU mediated Amide Coupling

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Contents

Abbreviations

HATU 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate

1. General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.

1.1 Purification of Solvents

Cyrene was supplied directly by Circa and used as obtained. DMF was dried by heating to reflux over previously activated 4 Å molecular sieves and distilling under vacuum before being purged with, and stored under N_2 in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves. THF was obtained from a PureSolv SPS-400-5 solvent purification system and transferred to and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves and purged with and stored under N_2. CH_2Cl_2, Et_2O, EtOAc, MeCN, and petroleum ether 40-60° for purification purposes were used as obtained from suppliers without further purification.

1.2 Experimental Details

Reactions were carried out using conventional glassware equipped with a Biotage magnetic stirrer bar (10-20 mL, product number 353930). Room temperature was generally *ca.* 20 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

1.3 Purification of Products

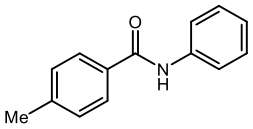
Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using vanillin solution. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel. Reverse phase flash chromatography was carried out using IST Isolute C18 cartridges.

1.4 Analysis of Products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{1}H, ^{13}C, and ^{19}F spectra were obtained on either a Bruker DRX 500 spectrometer (Avance III HD console, Ascend 500 MHz magnet, BBO smart probe) at 500 MHz, 126 MHz, and 471 MHz respectively, or Bruker AV 400 at 400 MHz, 101 MHz and 376 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 (^{1}H) and 77.1 ppm (^{13}C) and DMSO-d_6 referenced at 2.50 (^{1}H) and 39.5 (^{13}C). Samples for quantitative NMR analysis were prepared through the addition of 1 mL of a 0.0625 M 1,4-dinitrobenzene standard to the organics prior to concentration. The conversion to product **4a** was calculated from the peak ratio of 4-methyl-N-phenylbenzamide (δ 2.40 ppm), and 1,4-dinitrobenzene (δ 8.39 ppm). High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

2. General Experimental Procedures

General Procedure A: Optimized Conditions



For example, synthesis of 4-methyl-*N*-phenylbenzamide, **3a**.

To a 5 mL round-bottomed flask was added *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was stirred at room temperature for 10 mins before the addition of aniline (25 µL, 0.275 mmol, 1.1 equiv) and subsequently maintained at this temperature for 1 h with stirring. The solution was then diluted with EtOAc (20 mL), and washed with 2 M HCl (2 x 20 mL), sat. solution $NaHCO_3$ (2 x 20 mL), H_2O (20 mL), and brine (20 mL). The organics were then dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which was subsequently purified by flash chromatography (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a white solid (51 mg, 97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (br s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.8, 142.5, 138.2, 132.3, 129.6, 129.2, 127.2, 124.6, 120.3, 21.6.

Characterization data is consistent with literature reported values.[1]

3. Reaction Optimization Data

3.1. Time Study

Reactions were carried out according to General Procedure A using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (87 µL, 0.5 mmol, 2 equiv), aniline (25 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After **X** h at room temperature, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure. Note that these experiments were run before stirring rate was identified as a key factor (see **3.2**).

Entry	Time (h)	Conversion µ ± σ (%)[a]
1	1	84 ± 21
2	2	83 ± 27
3	4	81 ± 0
4	8	98 ± 2
5	16	91 ± 13
6	24	87 ± 13
7	48	86 ± 7

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

3.2. Stirring Rate Study

Reactions were carried out according to General Procedure A using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (87 µL, 0.5 mmol, **2 equiv**), aniline (25 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was stirred at **X** rpm for 1 h. After 1 h at room temperature, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Stirring Rate (rpm)	Conversion µ ± σ (%)[a]
1	100	51 ± 10
2	200	73 ± 3
3	400	71 ± 3
4	800	96 ± 7
5	1200	91 ± 11

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

3.3. Base Equivalency Study

Reactions were carried out according to General Procedure A using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (**X** equiv), aniline (25 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was stirred at 400 rpm for 1 h. After 1 h at room temperature, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Base equiv	Base Vol (µL)	Conversion µ ± σ (%)[a]
1	1	44	83 ± 4
2	2	87	96 ± 7
3	3	131	92 ± 2
4	5	220	90 ± 6
5	10	440	96 ± 4
6	20	880	76 ± 2

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

3.4. Stirring Rate Study 2

Reactions were carried out according to General Procedure A using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, **3 equiv**), aniline (25 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was stirred at **X** rpm for 1 h. After 1 h at room temperature, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Stirring Rate (rpm)	Conversion μ ± σ (%)[a]
1	200	92 ± 5
2	400	92 ± 2
3	800	100 ± 0

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

3.5. Variation of Coupling Reagent

Reactions were carried out according to General Procedure A using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), **coupling reagent** (0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 μL, 0.75 mmol, 3 equiv), aniline (25 μL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was stirred at 400 rpm for 1 h. After 1 h at room temperature, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Coupling Reagent	Conversion μ ± σ (%)[a]
1	HATU	92 ± 2
2	COMU	14 ± 2
3	DIC/HOBt	9 ± 7
4	PyBOP	29 ± 1
5	T3P	4 ± 2

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

3.6. Variation of Base

Reactions were carried out according to General Procedure A using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), **base** (0.75 mmol, 3 equiv), aniline (25 μL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). The reaction mixture was stirred at 400 rpm for 1 h. After 1 h at room temperature, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Base	Conversion μ ± σ (%)[a]
1	DIPEA	92 ± 2
2	Et_3N	67 ± 4
3	NMM	43 ± 3
4	Lutidine	35 ± 1

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

3.7. Solvent Comparison

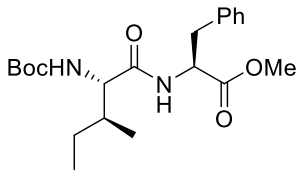
Reactions were carried out according to General Procedure A using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 μL, 0.75 mmol, 3 equiv), aniline (25 μL, 0.275 mmol, 1.1 equiv), and **Solvent** (1.25 mL, 0.2

M). The reaction mixture was stirred at 400 rpm for 1 h. After 1 h at room temperature, the reaction mixture was subjected to the purification and sampling methods outlined in the General Procedure.

Entry	Solvent	Conversion μ ± σ (%)[a]
1	DMF	94 ± 1
2	Cyrene	92 ± 2
3	CPME	18 ± 2
4	EtOAc	72 ± 6
5	IPA	29 ± 4
6	2-MeTHF	28 ± 5

[a] % conversion calculated by ^{1}H NMR using an internal standard. Presented as an average with standard deviation as a measure of consistency. n=3.

4. Procedure for the Large Scale Synthesis of Boc-Ile-Phe-OMe, 6c



To a 100 mL round-bottomed flask was added Boc-Ile-OH (1 g, 4.3 mmol, 1 equiv), HATU (2 g, 5.2 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (2.2 mL, 12.9 mmol, 3 equiv), and Cyrene (22 mL, 0.2 M). The reaction mixture was stirred at room temperature for 10 mins before the addition of Phe-OMe.HCl (1 g, 4.8 mmol, 1.1 equiv) and subsequently maintained at this temperature for 1 h with stirring. The solution was then diluted with EtOAc (40 mL), and washed with 2 M HCl (2 x 100 mL), sat. solution $NaHCO_3$ (2 x 100 mL), H_2O (100 mL), and brine (50 mL). The organics were then dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which was subsequently triturated with cold Et_2O to afford the title compound as a white solid (1.7 g, quant).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 – 7.21 (m, 3H), 7.13 – 7.10 (m, 2H), 6.27 (d, *J* = 5.1 Hz, 1H), 4.97 (d, *J* = 4.7 Hz, 1H), 4.87 (dd, *J* = 13.7, 6.0 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.71 (s, 3H), 3.17 – 3.06 (m, 2H), 1.86 – 1.79 (m, 1H), 1.58 (br s, 1H), 1.44 (s, 9H), 1.07 (br s, 1H), 0.89 - 0.86 (m, 6H).

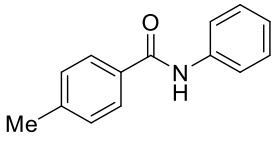
^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.8, 171.3, 155.8, 135.8, 129.4, 128.8, 127.3, 80.0, 59.4, 53.2, 52.4, 38.1, 37.4, 28.4, 24.8, 15.6, 11.6.

Characterization data is consistent with literature reported values.[2]

5. Compound Characterisation Data

5.1. Products from Schemes 1

3a: 4-Methyl-*N*-phenylbenzamide



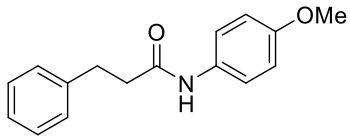
Prepared according to General Procedure A using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), aniline (25 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a white solid (51 mg, 97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (br s, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.8, 142.5, 138.2, 132.3, 129.6, 129.2, 127.2, 124.6, 120.3, 21.6.

Characterization data is consistent with literature reported values.[1]

3b: *N*-(4-Methoxyphenyl)-3-phenylpropanamide



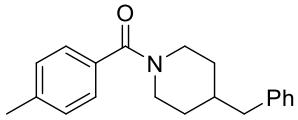
Prepared according to General Procedure A using 3-phenylpropanoic acid (37.5 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), 4-methoxyaniline (33.9 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a white solid (60.5 mg, 95%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 – 7.20 (m, 7H), 6.89 (s, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 3.78 (s, 3H), 3.06 (t, *J* = 7.6 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.3, 156.6, 140.9, 130.9, 128.8, 128.6, 126.5, 122.0, 114.3, 55.6, 39.5, 31.8.

Characterization data is consistent with literature reported values.[3]

3c: (4-Benzylpiperidin-1-yl)(*p*-tolyl)methanone



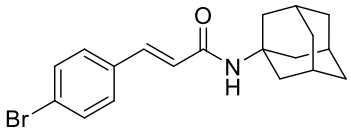
Prepared according to General Procedure A using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), 4-benzylpiperidine (48 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-25% EtOAc in petroleum ether) to afford the title compound as a colourless oil (73.7 mg, quant).

υ_{max} (liquid film): 2916, 2849, 1625, 1434 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.21 (m, 6H), 7.20 – 7.16 (m, 3H), 4.00 (s, 2H), 2.87 (t, *J* = 12.6 Hz, 2H), 2.57 (d, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 1.88 – 1.79 (m, 1H), 1.62 (d, *J* = 12.8 Hz, 2H), 1.17 (qd, *J* = 12.6, 4.2 Hz, 2H).

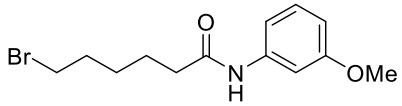
^{13}C NMR (DMSO-d_6, 126 MHz): δ 168.6, 139.5, 138.2, 133.4, 128.3, 128.2, 127.5, 126.1, 125.2, 43.9, 41.5, 36.7, 31.2, 20.2.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{24}NO$) requires *m/z* 294.1852, found *m/z* 294.1852.

3d: (*E*)-*N*-((3s,5s,7s)-Adamantan-1-yl)-3-(4-bromophenyl)acrylamide



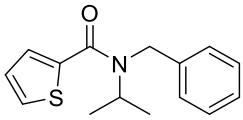
Prepared according to General Procedure A using (*E*)-3-(4-bromophenyl)acrylic acid (56.8 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), 1-adamantylamine (41.6 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a white solid (83.8 mg, 93%).
υ_{max} (solid): 3304, 2901, 2854, 1659, 1616, 1536 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50 – 7.45 (m, 3H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.32 (d, *J* = 15.5 Hz, 1H), 5.36 (br s, 1H), 2.10 (app s, 3H), 2.07 (app s, 6H), 1.70 (app s, 6H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 164.6, 139.0, 134.1, 132.1, 129.2, 123.6, 123.0, 52.4, 41.8, 36.5, 29.6.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}BrNO$) requires *m/z* 362.0937, found *m/z* 352.0940.

3e: 6-Bromo-*N*-(3-methoxyphenyl)hexanamide



Prepared according to General Procedure A using 6-bromohexanoic acid (48.8 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), 3-methoxyaniline (31 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (70.4 mg, 94%).
υ_{max} (liquid film): 3291, 2929, 2856, 1659, 1597, 1543 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42 (br s, 1H), 7.31 (s, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 3.78 (s, 3H), 3.40 (t, *J* = 6.7 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.91 – 1.84 (m, 2H), 1.74 (m, 2H), 1.51 (m, 2H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.2, 160.3, 139.3, 129.8, 112.0, 110.2, 105.7, 55.4, 37.6, 33.7, 32.6, 27.8, 24.7.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{19}BrNO_2$) requires *m/z* 302.0573, found *m/z* 302.0574.

3f: *N*-Benzyl-*N*-isopropylthiophene-2-carboxamide



Prepared according to General Procedure A using 2-thiophenecarboxylic acid (32 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), *N*-isopropylbenzylamine (46 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a colourless oil (61.3 mg, 95%).

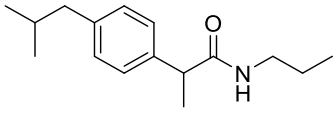
υ_{max} (liquid film): 2966, 2931, 1601 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.67 (d, *J* = 5.0 Hz, 1H), 7.35 – 7.28 (m, 5H), 7.23 (t, *J* = 6.9 Hz, 1H), 7.07 (t, *J* = 8.7 Hz, 1H), 4.68 (s, 2H), 4.48 (hept, *J* = 6.7 Hz, 1H), 1.18 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 163.6, 138.9, 138.1, 128.4, 127.8, 127.4, 126.5, 126.2, 126.2, 49.1, 45.7, 20.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}NOS$) requires *m/z* 260.1104, found *m/z* 260.1104.

3g: 2-(4-Isobutylphenyl)-*N*-propylpropanamide



Prepared according to General Procedure A using 2-(4-isobutylphenyl)propanoic acid (51.6 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), propylamine (23 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (48.4 mg, 78%).

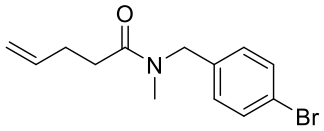
υ_{max} (liquid film): 3286, 2955, 2927, 2867, 1644, 1547 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 5.33 (br s, 1H), 3.52 (q, *J* = 7.2 Hz, 1H), 3.14 (q, *J* = 7.0 Hz, 2H), 2.45 (d, *J* = 7.2 Hz, 2H), 1.91 – 1.79 (m, 1H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.45 – 1.37 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.80 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.6, 140.8, 138.8, 129.7, 127.5, 46.9, 45.1, 41.4, 30.3, 22.9, 22.5, 18.6, 11.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{26}NO$) requires *m/z* 248.2009, found *m/z* 248.2011.

3h: *N*-(4-Bromobenzyl)-*N*-methylpent-4-enamide



Prepared according to General Procedure A using 4-pentenoic acid (25.5 μL, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 μL, 0.75 mmol, 3 equiv), (4-bromobenzyl)methylamine (55 μL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (67.1 mg, 95%).

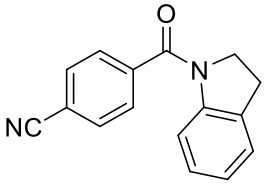
υ_{max} (liquid film): 2920, 1634, 1488, 1400 cm^{-1}.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 5.91 – 5.81 (m, 1H), 5.04 (d, *J* = 17.2 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 4.51 (s, 2H), 2.90 (s, 3H), 2.45 (t, *J* = 7.3 Hz, 2H), 2.32 (q, *J* = 7.1 Hz, 2H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 171.1, 137.4, 136.9, 130.8, 128.9, 119.5, 114.2, 49.6 (br s), 33.9 (br s), 31.3, 28.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{17}BrNO$) requires *m/z* 284.0468, found *m/z* 248.0467.

3i: 4-(Indoline-1-carbonyl)benzonitrile



Prepared according to General Procedure A using 4-cyanobenzoic acid (36.8 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 μL, 0.75 mmol, 3 equiv), indoline (28.1 μL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether) to afford the title compound as a white solid (57 mg, 92%).

υ_{max} (solid): 2921, 2226, 1640, 1597, 1398 cm^{-1}.

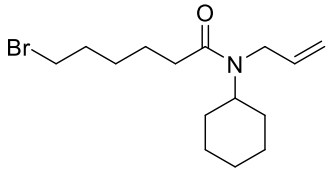
^{1}H NMR (DMSO-d_6, 500 MHz, 300 K): δ 8.10 (app s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.79 (app s, 2H), 7.29 (d, J = 7.2 Hz, 1H), 7.23 (app s, 1H), 7.08 (app s, 1H), 3.95 (app s, 2H), 3.09 (t, J = 8.1 Hz, 2H).

^{1}H NMR (DMSO-d_6, 500 MHz, 355 K): δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 3.98 (t, *J* = 8.3 Hz, 2H), 3.11 (t, *J* = 8.3 Hz, 2H). Indicated proton is not observed.

^{13}C NMR (DMSO-d_6, 126 MHz, 355 K): δ 165.9, 141.9, 140.9, 132.3, 132.1, 127.4, 126.4, 124.6, 123.6, 117.7, 115.9, 112.3, 49.6, 27.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}NO$) requires *m/z* 249.1022, found *m/z* 249.1022.

3j: *N*-Allyl-6-bromo-*N*-cyclohexylhexanamide



Prepared according to General Procedure A using 6-bromohexanoic acid (48.8 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), allylcyclohexylamine (40 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a colourless oil (70.6 mg, 90%).

υ_{max} (liquid film): 2925, 2853, 1633, 1413 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.87 – 5.70 (m, 1H), 5.19 – 5.02 (m, 2H), 4.47 – 4.37 (m, 0.58H), 3.88 (app d, *J* = 5.6 Hz, 0.74H), 3.83 – 3.79 (m, 1.23H), 3.56 (tt, *J* = 11.8, 3.6 Hz, 0.38H), 3.40 (app q, *J* = 7.0 Hz, 2H), 2.38 – 2.33 (m, 0.73H), 2.28 – 2.24 (m, 1.23H), 1.93 – 1.60 (m, 9H), 1.54 – 1.24 (m, 6H), 1.14 – 0.99 (m, 1H). Rotamers observed

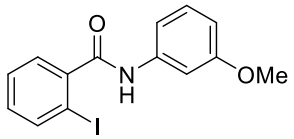
^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.1, 172.1, 135.9, 135.8, 116.2, 115.6, 57.4, 53.4, 45.6, 44.1, 33.9, 33.5, 33.4, 32.8, 32.8, 32.1, 30.9, 28.1, 28.1, 26.1, 25.9, 25.7, 25.4, 24.6. Rotamers observed

^{1}H NMR (DMSO-*d*$_6$, 500 MHz, 373 K): δ 5.86 – 5.76 (m, 1H), 5.16 – 5.04 (m, 2H), 3.86 (d, *J* = 5.0 Hz, 2H), 3.50 (t, *J* = 6.7 Hz, 2H), 2.29 (app s, 2H), 1.87 – 1.80 (m, 2H), 1.76 (d, *J* = 13.2 Hz, 2H), 1.65 – 1.55 (m, 6H), 1.50 – 1.40 (m, 4H), 1.35-1.27 (m, 2H), 1.15 – 1.05 (m, 1H).

^{13}C NMR (DMSO-*d*$_6$, 126 MHz, 373 K): δ 171.0, 136.2, 114.6, 60.3, 49.1, 34.0, 32.1, 31.7, 30.3, 26.9, 25.1, 24.5, 23.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{27}BrNO$) requires *m/z* 316.1271, found *m/z* 316.1273.

3k: 2-Iodo-*N*-(3-methoxyphenyl)benzamide



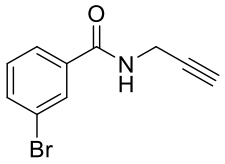
Prepared according to General Procedure A using 2-iodobenzoic acid (62 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), 3-methoxyaniline (31 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a white solid (62.9 mg, 71%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91 (d, *J* = 7.9 Hz, 1H), 7.53 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.45 – 7.40 (m, 3H), 7.27 (t, *J* = 8.1 Hz, 1H), 7.15 (td, *J* = 7.8, 1.5 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.73 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.3, 160.4, 142.3, 140.2, 138.9, 131.7, 129.9, 128.7, 128.53, 112.3, 110.9, 105.9, 92.4, 55.6.

Characterization data is consistent with literature reported values.[4]

3l: 3-Bromo-*N*-(prop-2-yn-1-yl)benzamide



Prepared according to General Procedure A using 3-bromobenzoic acid (50.3 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 μL, 0.75 mmol, 3 equiv), propargylamine (17.6 μL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a white solid (37.6 mg, 63%).

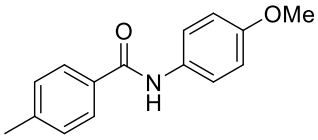
υ_{max} (solid): 3280, 3065, 2914, 2847, 1638, 1536 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.93 (t, *J* = 1.8 Hz, 1H), 7.70 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 6.23 (br s, 1H), 4.25 (dd, *J* = 5.2, 2.6 Hz, 2H), 2.30 (t, *J* = 2.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 165.8, 135.9, 134.9, 130.4, 130.4, 125.7, 123.0, 79.3, 72.4, 30.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{10}H_9BrNO$) requires *m/z* 239.9842, found *m/z* 239.9845.

3m: *N*-(4-Methoxyphenyl)-4-methylbenzamide



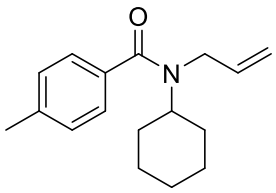
Prepared according to General Procedure A using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 μL, 0.75 mmol, 3 equiv), 4-methoxyaniline (33.9 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a white solid (61.5 mg, 95%).

^1H NMR ($CDCl_3$, 400 MHz): δ 7.78 (br s, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.9 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.7, 156.7, 142.3, 132.3, 131.3, 129.5, 127.1, 122.2, 114.4, 55.6, 21.6.

Characterization data is consistent with literature reported values.[5]

3n: *N*-Allyl-*N*-cyclohexyl-4-methylbenzamide



Prepared according to General Procedure A using *p*-toluic acid (34 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), allylcyclohexylamine (40 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a white solid (41.5 mg, 63%).

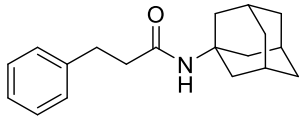
υ_{max} (solid): 2925, 2853, 1625, 1409 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ 7.22 (app s, 4H), 5.84 (m, 1H), 5.14 (d, J = 17.2 Hz, 1H), 5.07 (dd, J = 10.3, 1.5 Hz, 1H), 3.92 (d, J = 5.2 Hz, 2H), 3.71 (app s, 1H), 2.34 (s, 3H), 1.76 – 1.65 (m, 4H), 1.63 – 1.51 (m, 3H), 1.08 (m, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 170.2, 137.9, 135.8, 134.5, 128.3, 125.6, 115.1, 56.5, 44.8, 30.4, 25.1, 24.4, 20.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{24}NO$) requires *m/z* 258.1852, found *m/z* 258.1853.

3o: *N*-((3s,5s,7s)-Adamantan-1-yl)-3-phenylpropanamide



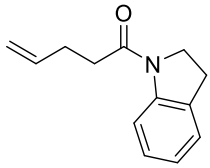
Prepared according to General Procedure A using 3-phenylpropanoic acid (37.5 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), 1-adamantylamine (41.6 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was diluted with EtOAc (20 mL), and washed with 2 M HCl (2 x 20 mL), sat. solution NaHCO3 (2 x 20 mL), H_2O (20 mL), and brine (20 mL). The organics were then dried over Na_2SO_4 and concentrated under reduced pressure to give a residue which was recrystallized from EtOAc/petroleum ether to afford the title compound as a white solid (71.6 mg, quant.).

^1H NMR ($CDCl_3$, 500 MHz): δ 7.30 – 7.25 (m, 2H), 7.21 – 7.17 (m, 3H), 4.99 (br s, 1H), 2.92 (t, J = 7.6 Hz, 2H), 2.37 (t, J = 7.6 Hz, 2H), 2.04 (app s, 3H), 1.92 (app d, J = 2.7 Hz, 6H), 1.65 (app s, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.3, 141.2, 128.6, 126.2, 51.9, 41.7, 39.7, 36.5, 31.9, 29.5.

Characterization data is consistent with literature reported values.[6]

3p: 1-(Indolin-1-yl)pent-4-en-1-one

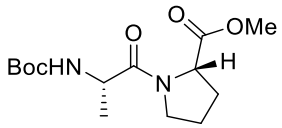


Prepared according to General Procedure A using 4-pentenoic acid (25.5 µL, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), indoline (28.1 µL, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the

General Procedure (silica gel, 0-25% EtOAc in petroleum ether) to afford the title compound as a white solid (47.8 mg, 95%).
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.24 (d, *J* = 8.0 Hz, 1H), 7.21 – 7.16 (m, 2H), 7.01 (td, *J* = 7.5, 0.7 Hz, 1H), 5.98 – 5.89 (m, 1H), 5.11 (d, *J* = 17.2 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 4.06 (t, *J* = 8.5 Hz, 2H), 3.20 (t, *J* = 8.4 Hz, 2H), 2.52 (app s, 4H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.6, 143.2, 137.6, 131.1, 127.7, 124.6, 123.7, 117.2, 115.5, 48.1, 35.4, 28.7, 28.2.
Characterization data is consistent with literature reported values.[7]

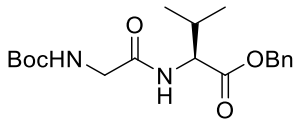
5.2. Products from Scheme 2

6a: Boc-Ala-Pro-OMe



Prepared according to General Procedure A using Boc-Ala-OH (47.3 mg, 0.25 mmol, 1 equiv), HATU (238 mg, 0.625 mmol, 2.5 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Pro-OMe.HCl (45.5 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (67.2 mg, 89%).
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.33 (d, *J* = 7.8 Hz, 1H), 4.56 – 4.41 (m, 2H), 3.71 (s, 3H), 3.74 – 3.67 (m, 1H), 3.63 – 3.56 (m, 1H), 2.27 – 2.17 (m, 1H), 2.10 – 1.95 (m, 3H), 1.42 (s, 9H), 1.35 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.6, 171.9, 155.4, 79.7, 58.8, 52.4, 47.9, 46.9, 29.1, 28.5, 25.1, 18.5.
Characterization data is consistent with literature reported values.[8]

6b: Boc-Gly-Val-OBn

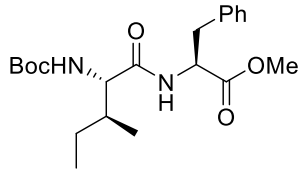


Prepared according to General Procedure A using Boc-Gly-OH (43.8 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Val-OBn.HCl (67 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-35% EtOAc in petroleum ether) to afford the title compound as a colouless oil (50 mg, 56%).

Prepared according to General Procedure A using Boc-Gly-OH (43.8 mg, 0.25 mmol, 1 equiv), HATU (238 mg, 0.625 mmol, 2.5 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Val-OBn.HCl (67 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the

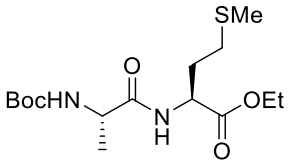
General Procedure (silica gel, 0-35% EtOAc in petroleum ether) to afford the title compound as a colouless oil (50 mg, 77%).
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42 – 7.31 (m, 5H), 6.60 (d, *J* = 7.9 Hz, 1H), 5.17 (q, *J* = 12.2 Hz, 2H), 5.15 (br s, 1H), 4.61 (dd, *J* = 8.8, 4.7 Hz, 1H), 3.82 (ddd, *J* = 44.0, 16.7, 5.8 Hz, 2H), 2.24 – 2.16 (m, 1H), 1.45 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.8, 169.6, 156.2, 135.4, 128.8, 128.6, 128.5, 80.5, 67.2, 57.1, 44.7, 31.5, 28.4, 19.1, 17.6.
Characterization data is consistent with literature reported values.[9]

6c: Boc-Ile-Phe-OMe



Prepared according to General Procedure A using Boc-Ile-OH (57.8 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Phe-OMe.HCl (59.3 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a white solid (93 mg, 95%).
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 – 7.21 (m, 3H), 7.13 – 7.10 (m, 2H), 6.27 (d, *J* = 5.1 Hz, 1H), 4.97 (d, *J* = 4.7 Hz, 1H), 4.87 (dd, *J* = 13.7, 6.0 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.71 (s, 3H), 3.17 – 3.06 (m, 2H), 1.86 – 1.79 (m, 1H), 1.58 (br s, 1H), 1.44 (s, 9H), 1.07 (br s, 1H), 0.89 - 0.86 (m, 6H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.8, 171.3, 155.8, 135.8, 129.4, 128.8, 127.3, 80.0, 59.4, 53.2, 52.4, 38.1, 37.4, 28.4, 24.8, 15.6, 11.6.
Characterization data is consistent with literature reported values.[2]

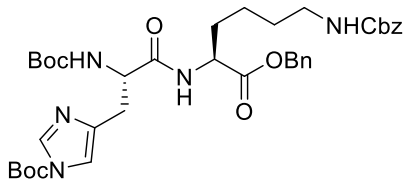
6d: Boc-Ala-Met-OEt



Prepared according to General Procedure A using Boc-Ala-OH (47.3 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Met-OEt.HCl (58.8 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a white solid (47.3 mg, 54%).
Prepared according to General Procedure A using (*tert*-butoxycarbonyl)-*L*-alanine (47.3 mg, 0.25 mmol, 1 equiv), HATU (238 mg, 0.625 mmol, 2.5 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), ethyl *L*-methioninate hydrochloride (58.8 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the

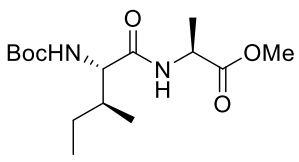
purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a white solid (87.3 mg, quant.).
$[\alpha]_D^{20} = -6.97$ (c 0.01, CH_2Cl_2).
υ_{max} (solid): 3331, 3308, 2975, 2927, 1746, 1679, 1651, 1515, 1158 cm^{-1}.
^1H NMR ($CDCl_3$, 500 MHz): δ 6.78 (d, *J* = 7.3 Hz, 1H), 5.02 (br s, 1H), 4.65 (td, *J* = 7.6, 5.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.16 (br s, 1H), 2.52 – 2.47 (m, 2H), 2.20 – 2.11 (m, 1H), 2.08 (s, 3H), 2.03 – 1.93 (m, 1H), 1.44 (s, 9H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.6, 171.8, 155.6, 80.3, 61.8, 51.7, 50.2, 31.9, 30.0, 28.4, 18.2, 15.6, 14.3.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{30}N_2O_5S$) requires *m/z* 349.1792, found *m/z* 349.1792.

6e: Boc-His(Boc)-Lys(CBz)-OBn



Prepared according to General Procedure A using Boc-His(Boc)-OH (88.8 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Lys(CBz)-OBn.HCl (111.9 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-50% EtOAc in petroleum ether) to afford the title compound as a white gum (140.8 mg, 80%).
$[\alpha]_D^{20} = +3.7$ (c 0.01, CH_2Cl_2).
υ_{max} (solid): 3331, 3282, 3308, 2977, 2927, 1748, 1681, 1651, 1517, 1158 cm^{-1}.
^1H NMR ($CDCl_3$, 500 MHz): δ 7.98 (s, 1H), 7.36 – 7.28 (m, 11H), 7.14 (s, 1H), 6.08 (s, 1H), 5.17 – 5.08 (m, 4H), 4.91 (s, 1H), 4.59 – 4.53 (m, 1H), 4.43 (s, 1H), 3.12 – 2.88 (m, 4H), 1.86 (s, 1H), 1.80 – 1.71 (m, 1H), 1.67 – 1.59 (m, 2H), 1.58 (s,9H), 1.43 (s, 9H), 1.20 - 1.14 (m, 2H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.89, 171.49, 156.6, 155.8, 147.1, 139.3, 136.9, 136.8, 135.4, 128.7, 128.6, 128.5, 128.3, 128.2, 114.9, 85.9, 80.2, 67.2, 66.7, 54.3, 52.0, 40.7, 32.1, 30.2, 29.2, 28.4, 28.0, 22.1. CBz carbonyl not observed.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{37}H_{50}N_5O_9$) requires *m/z* 708.3603, found *m/z* 708.3598.

6f: Boc-Ile-Ala-OMe



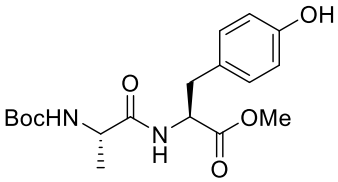
Prepared according to General Procedure A using Boc-Ile-OH (57.8 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Ala-OMe.HCl (38.4 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a white solid (55.4 mg, 72%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.46 (d, J = 5.8 Hz, 1H), 5.06 (d, J = 5.4 Hz, 1H), 4.58 (p, J = 7.2 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.74 (s, 3H), 1.86 (s, 1H), 1.50 (s, 1H), 1.44 (s, 9H), 1.40 (d, J = 7.2 Hz, 3H), 1.19 – 1.09 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.3, 171.2, 155.9, 80.1, 59.3, 52.6, 48.1, 37.5, 28.4, 24.9, 18.5, 15.6, 11.6.

Characterization data is consistent with literature reported values.[10]

6g: Boc-Ala-Tyr-OMe



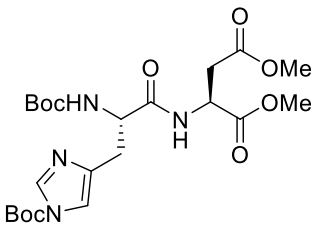
Prepared according to General Procedure A using Boc-Ala-OH (47.3 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Tyr-OMe.HCl (63.7 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (64.4 mg, 70%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.93 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.3 Hz, 2H), 6.60 (d, J = 7.1 Hz, 1H), 6.15 (s, 1H), 5.01 (s, 1H), 4.81 (dt, J = 7.9, 5.8 Hz, 1H), 4.14 (s, 1H), 3.72 (s, 3H), 3.11 – 2.96 (m, 2H), 1.44 (s, 9H), 1.30 (d, J = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.5, 172.0, 155.4, 130.6, 127.4, 115.7, 80.5, 53.5, 52.5, 50.3, 37.3, 28.5, 18.4. C=O of carbamate overlaps with OH bearing carbon.

Characterization data is consistent with literature reported values.[11]

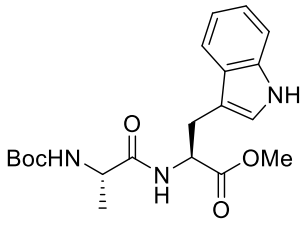
6h: Boc-His(Boc)-Asp(OMe)-OMe



Prepared according to General Procedure A using Boc-His(Boc)-OH (88.8 mg, 0.25 mmol, 1 equiv), HATU (238 mg, 0.625 mmol, 2.5 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Asp(OMe)-OMe.HCl (54.3 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined

in the General Procedure (silica gel, 0-70% EtOAc in petroleum ether) to afford the title compound as a colourless oil (78.1 mg, 63%).
$[\alpha]_D^{20} = +40.3$ (c 0.002, CH_2Cl_2).
υ_{max} (liquid film): 3338, 2977, 2953, 2927, 1752, 1391, 1255, 1160 cm^{-1}.
^1H NMR ($CDCl_3$, 500 MHz): δ 7.98 (s, 1H), 7.39 (br s, 1H), 7.15 (s, 1H), 6.06 (br s, 1H), 4.83 – 4.73 (m, 1H), 4.45 (br s, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.08 (d, *J* = 10.8 Hz, 1H), 2.93 (dd, *J* = 17.2, 4.6 Hz, 2H), 2.71 (dd, *J* = 17.1, 4.5 Hz, 1H), 1.60 (s, 9H), 1.45 (s, 9H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.4, 171.2, 170.9, 155.7, 147.1, 139.1, 136.9, 114.9, 85.8, 80.2, 54.4, 52.8, 52.1, 48.7, 36.2, 30.3, 28.4, 28.0.
HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{35}N_4O_9$) requires *m/z* 499.2399, found *m/z* 499.2391.

6i: Boc-Ala-Trp-OMe

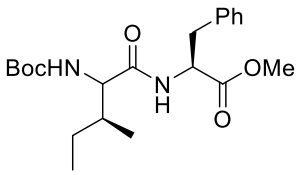


Prepared according to General Procedure A using Boc-Ala-OH (47.3 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Trp-OMe.HCl (70 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-35% EtOAc in petroleum ether) to afford the title compound as a white solid (85.6 mg, 88%).
^1H NMR ($CDCl_3$, 500 MHz): δ 8.22 (br s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.02 (s, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 4.94 (br s, 1H), 4.90 (dt, *J* = 7.7, 5.4 Hz, 1H), 4.13 (br s, 1H), 3.66 (s, 3H), 3.32 (d, *J* = 5.4 Hz, 2H), 1.41 (s, 9H), 1.29 (d, *J* = 6.3 Hz, 3H).
^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.4, 172.2, 155.5, 136.2, 127.8, 123.1, 122.4, 119.8, 118.7, 111.4, 110.0, 80.1, 60.5, 53.1, 52.5, 28.4, 27.7, 18.5.
Characterization data is consistent with literature reported values.[12]

6. Evidence of Enantiopurity

The DL-L enantiomers of the following peptides were synthesized and the 1H NMR of the diastereotopic mixture compared to those of the enantiopure analogues.

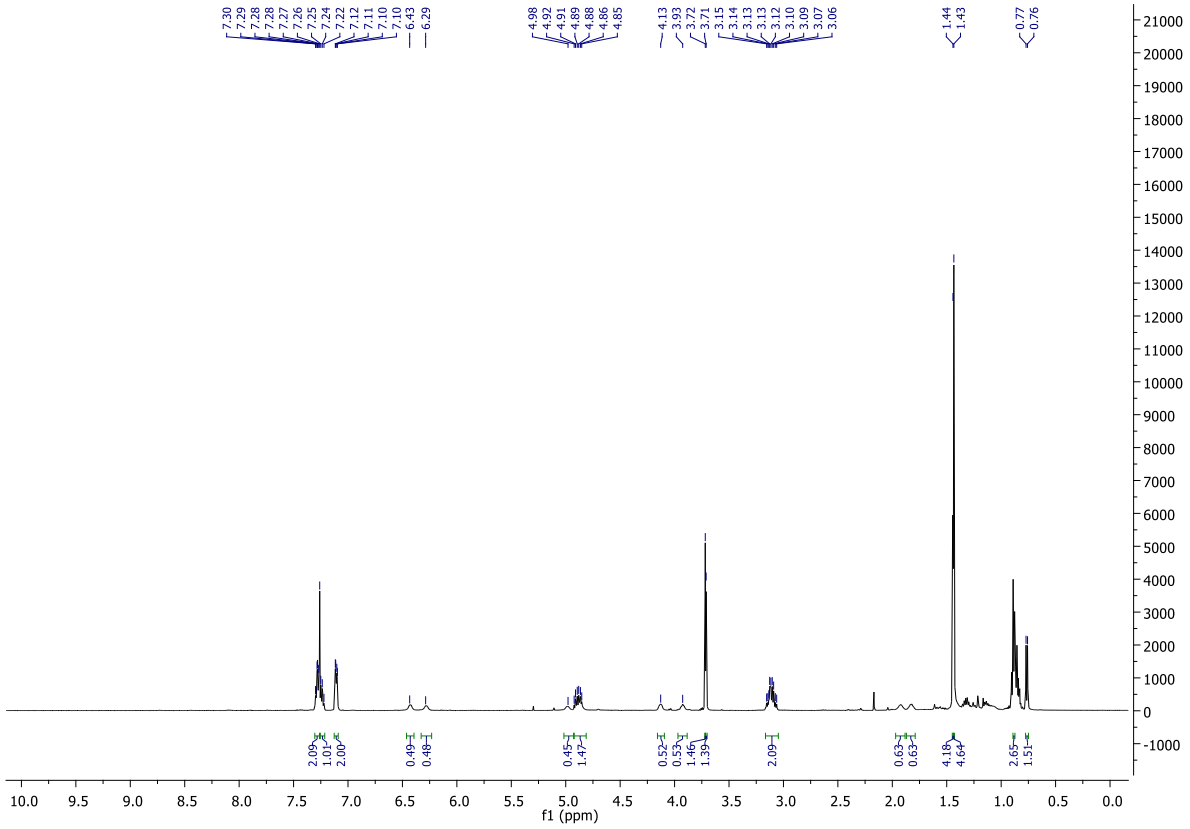
Boc-(DL)Ile-Phe-OMe



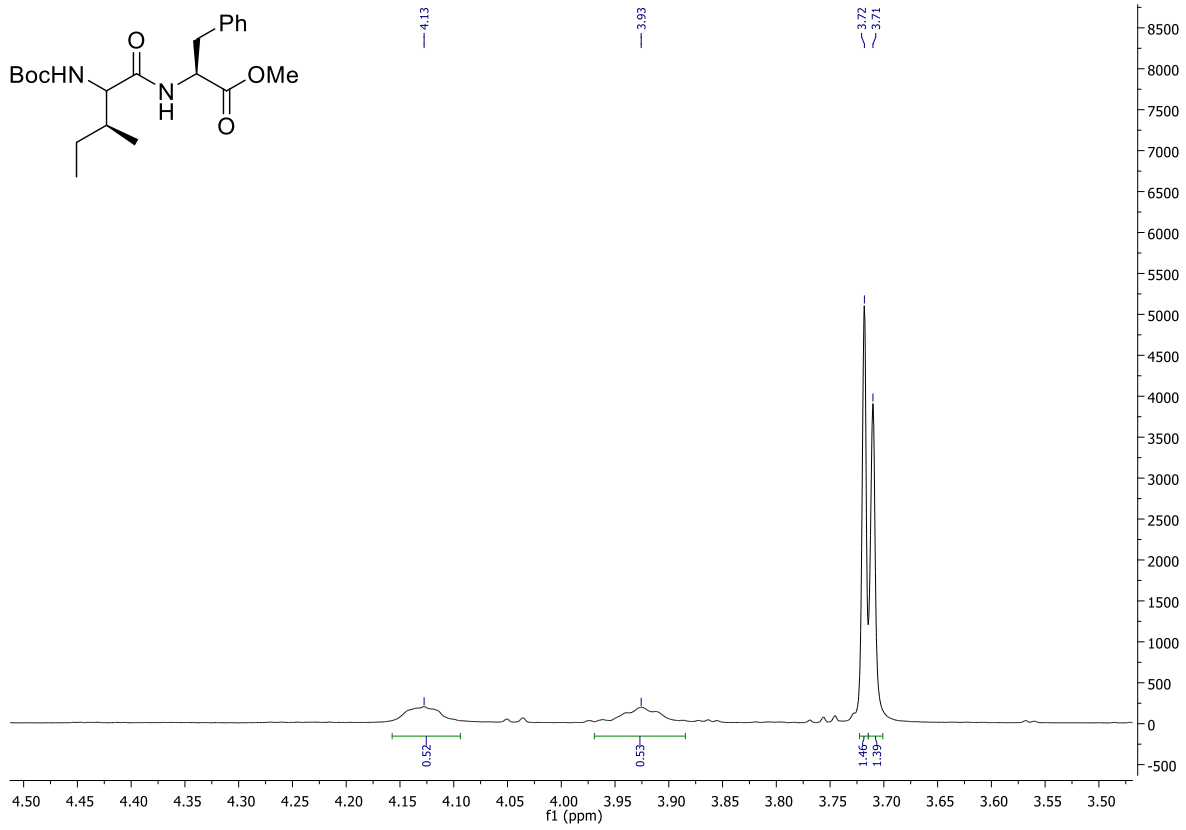
Prepared according to General Procedure A using Boc-(DL)Ile-OH (57.8 mg, 0.25 mmol, 1 equiv), HATU (114 mg, 0.3 mmol, 1.2 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Phe-OMe.HCl (59.3 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether) to afford the title compound as a white solid (102 mg, quant).

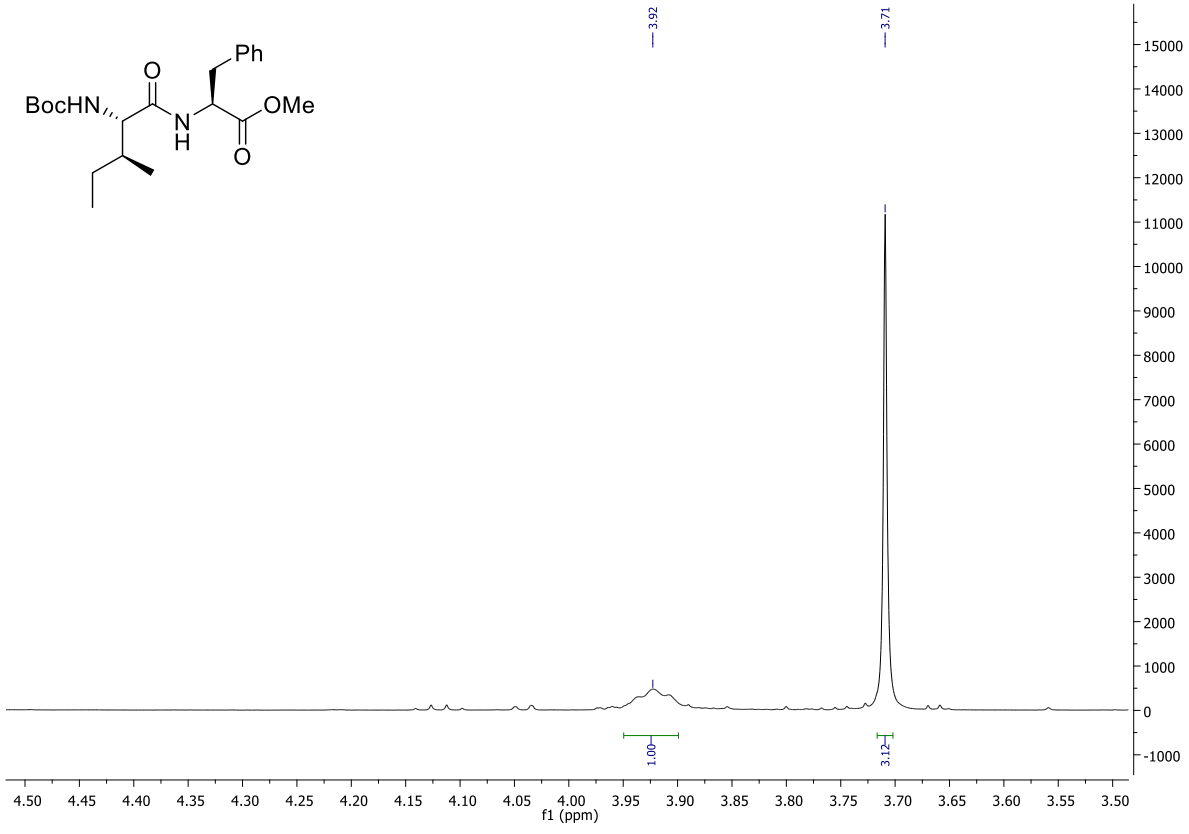
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1H NMR (500 MHz, CDCl3) δ 7.31 – 7.21 (m, 3H), 7.11 (m, 2H), 6.43 (DL br s, 0.5H), 6.29 (LL br s, 0.5H), 4.98 (LL br s, 0.5H), 4.89 (m, 1.5H), 4.13 (DL br s, 0.5H), 3.93 (LL br s, 0.5H), 3.72 (DL s, 1.5H), 3.71 (LL s, 1.5H), 3.17 – 3.05 (m, 2H), 1.92 (DL br s, 0.5H), 1.83 (LL br s, 0.5H), 1.44 (LL s, 4.5H), 1.43 (DL s, 4.5H), 0.88 (m, 6.5H), 0.76 (DL d, J = 6.9 Hz, 1.5H).

^{1}H NMR of Diastereotopic Mixture

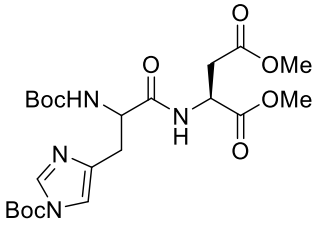


^{1}H Spectra (4.5-3.5 ppm) of diastereotopic mixture vs enantiopure compound





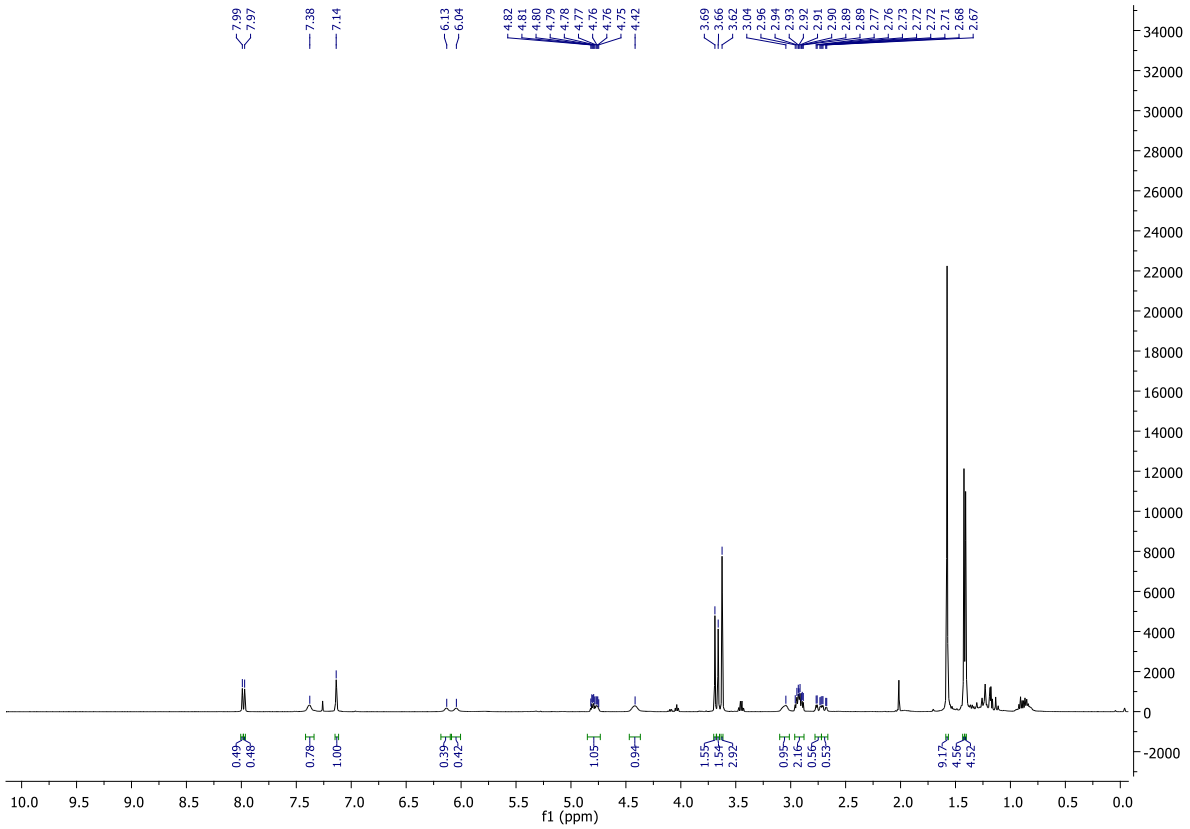
Boc-(DL)His(Boc)-Asp(OMe)-OMe



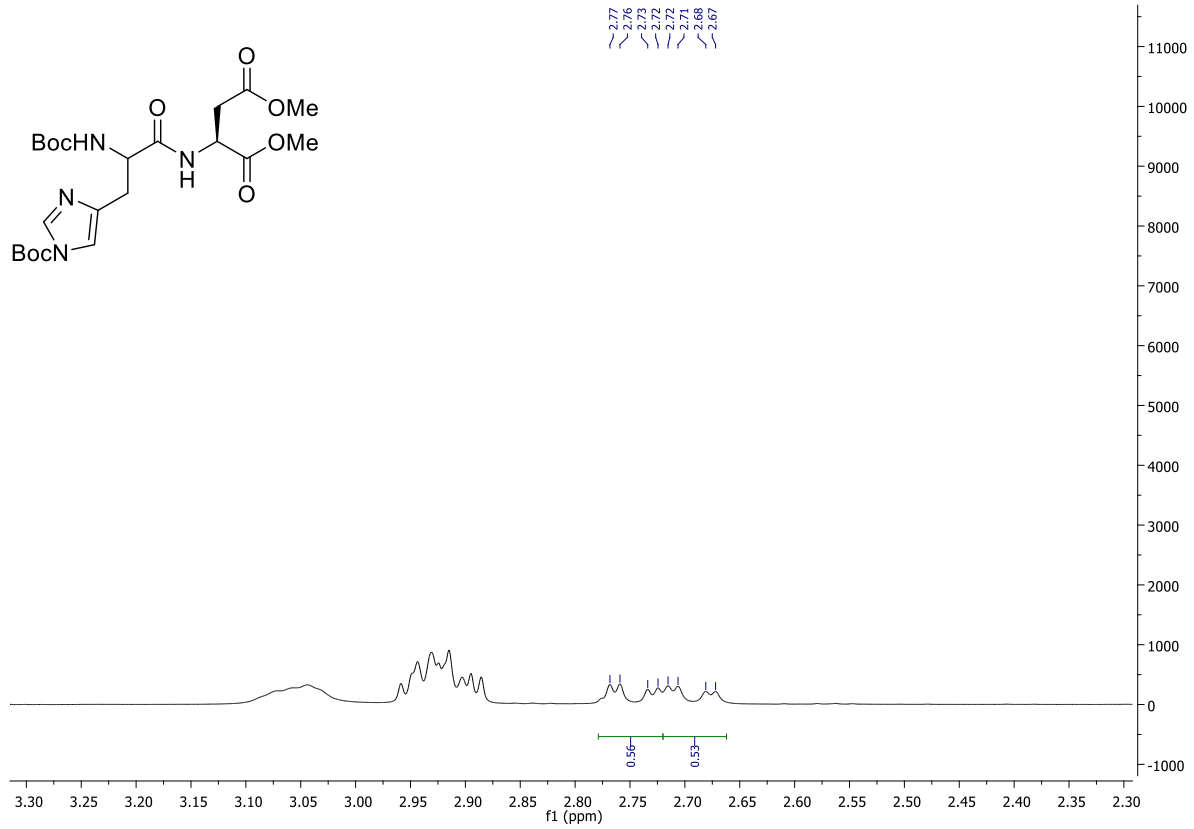
Prepared according to General Procedure A using Boc-(DL)His(Boc)-OH (88.8 mg, 0.25 mmol, 1 equiv), HATU (238 mg, 0.625 mmol, 2.5 equiv), *N*,*N*-diisopropylethylamine (131 µL, 0.75 mmol, 3 equiv), Asp(OMe)-OMe.HCl (54.3 mg, 0.275 mmol, 1.1 equiv), and Cyrene (1.25 mL, 0.2 M). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-70% EtOAc in petroleum ether) to afford the title compound as a colourless oil (74.2 mg, 59%).

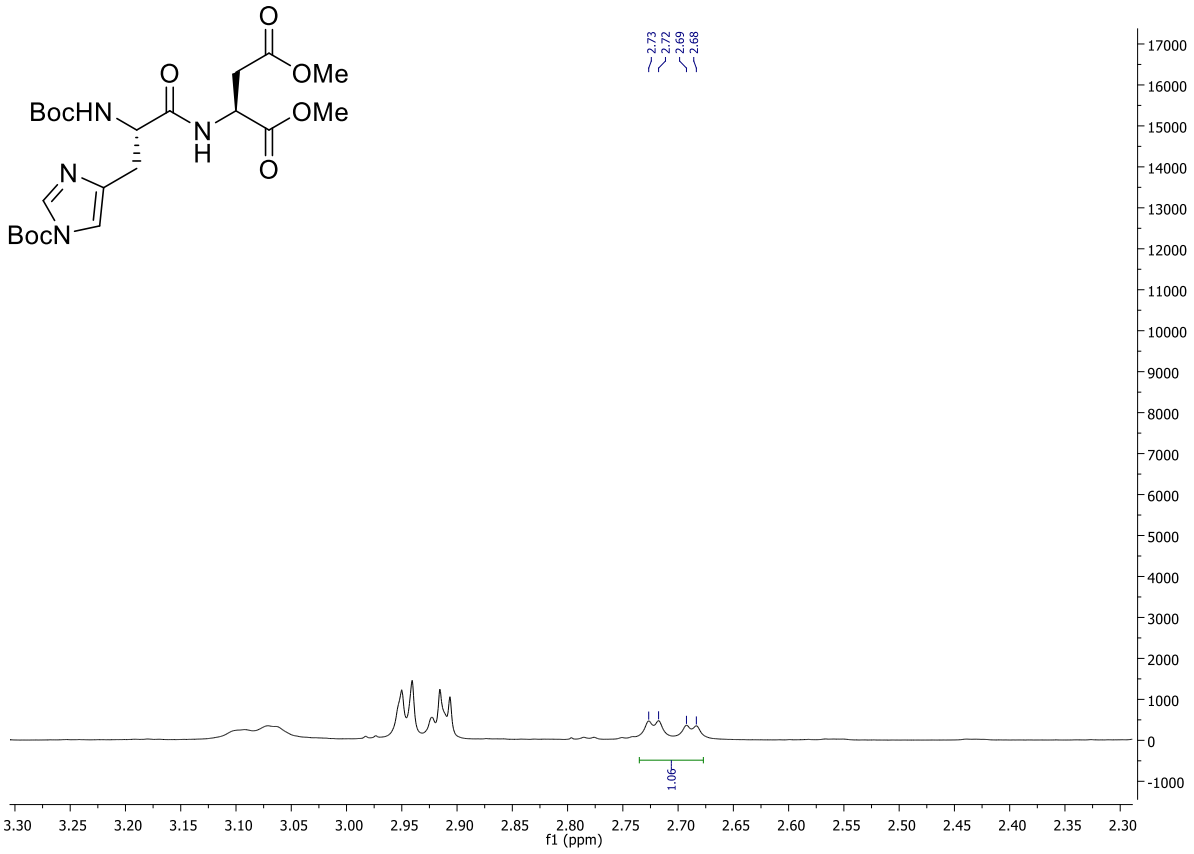
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1H NMR (500 MHz, CDCl3) δ 7.99 (DL s, 0.5H), 7.97 (LL s, 0.5H), 7.38 (br s, 1H), 7.14 (s, 1H), 6.13 (DL br s, 0.5H), 6.04 (LL br s, 0.5H), 4.84 – 4.73 (m, 1H), 4.42 (br s, 1H), 3.69 (LL s, 1.5H), 3.66 (DL s, 1.5H), 3.62 (s, 3H), 3.04 (br s, 1H), 2.92 (m, 2H), 2.75 (DL dd, J = 17.3, 4.6 Hz, 0.5H), 2.69 (LL dd, J = 17.1, 4.5 Hz, 0.5H), 1.58 (s, 9H), 1.42 (LL s, 4.5H), 1.41 (DL s, 4.5H).

^{1}H NMR of Diastereotopic Mixture



^{1}H Spectra (3.3-2.3 ppm) of diastereotopic mixture vs enantiopure compound





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