Supporting Information

for

^{18}F-Labelling of (Hetero)aryl Halides via Sequential Miyaura Borylation/Copper-Mediated Radiofluorination

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1. General Information

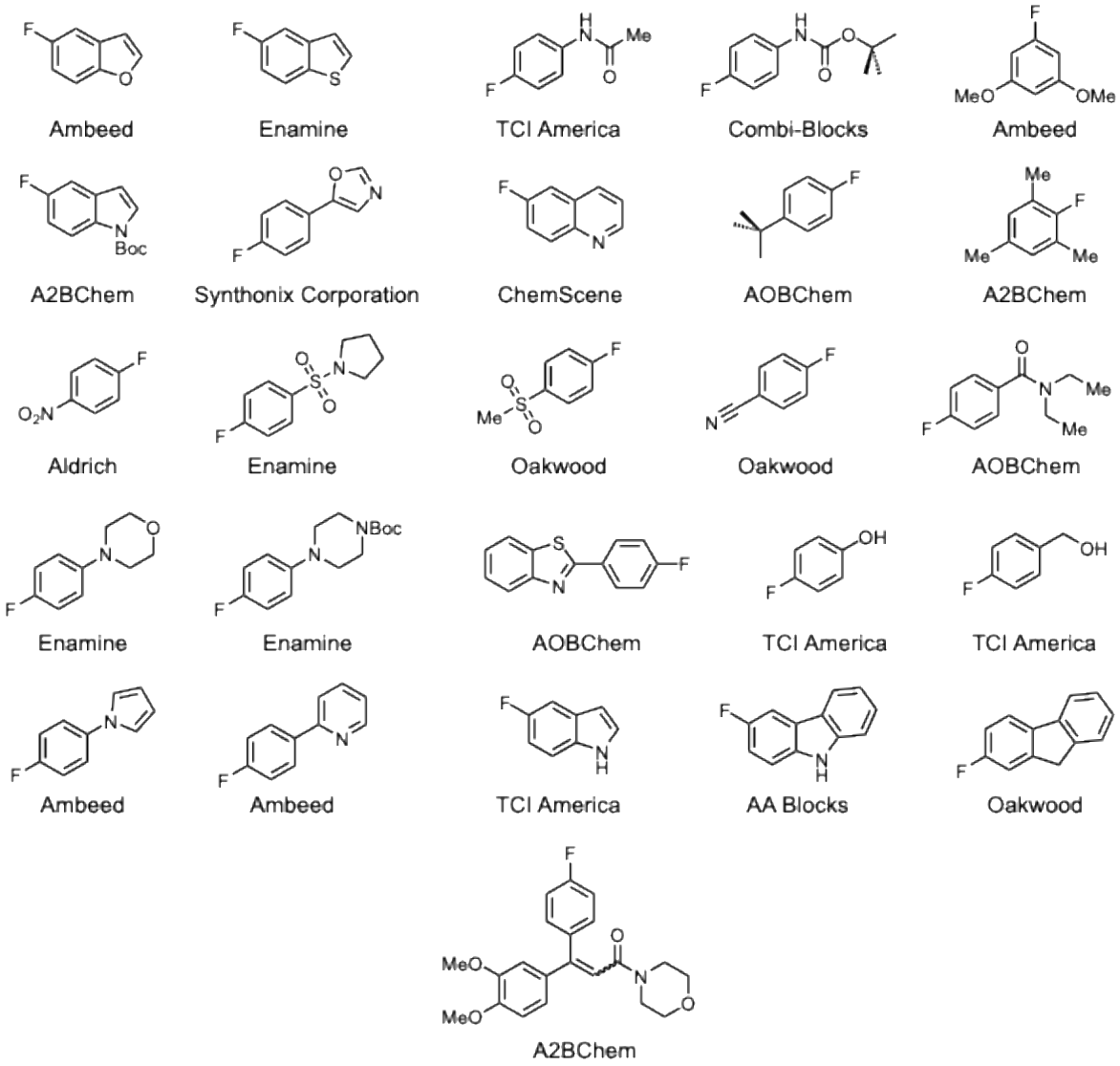
1.1 Instrument Details

NMR spectra were recorded at room temperature on a Varian Vnmrs 600 (600 MHz for ^{1}H, 151 MHz for ^{13}C and 564 for ^{19}F), Bruker Avance Neo 500 (500 MHz for ^{1}H and 126 MHz for ^{13}C), or Varian VNMRS 400 (401 MHz for 1H NMR; 375 MHz for 19F; 123 MHz for 13C). ^{19}F NMR yields were measured on a Varian Vnmrs 500 (500 MHz for ^{1}H and 471 MHz for ^{19}F) Varian. ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference.[1] ^{19}F NMR chemical shifts are reported in parts per million (ppm) relative to $CFCl_3$ as external standard. Abbreviations used in the NMR data are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dtd (doublet of triplets of doublet), m (multiplet), br. s (broad singlet), br. d (broad doublet), app. s (apparent singlet), app. d (apparent doublet), app. t (apparent triplet), app. q (apparent quartet).

1.2 Reagents and Solvents

All other reagents and solvents were purchased from commercial suppliers unless otherwise noted. Unless otherwise stated, purchased reagents and synthesized materials were stored under air. (Hetero)aryl iodide substrates were kept in the dark and wrapped in aluminum foil. $Cu(OTf)_2$ was stored under an atmosphere of dry N_2. The abbreviations EtOAc, DMSO, DMF, DMA, DCM, DCE, MeOH, TfOH, NBS, MeCN, HBTU, BTEAC, Ac_2O, Boc_2O, Et_3N, MeI, DIPEA and IPAC stand for ethyl acetate, dimethyl sulfoxide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dichloromethane, dichloroethane, methanol, trifilic acid, n-bromosuccinimide, acetonitrile, o-benzotriazole-*N,N,N',N'*-tetramethyluronium-hexafluoro-phosphate, benzyltriethylammonium chloride, acetic anhydride, di-tert-butyl decarbonate, methyl iodide, *N,N*-diisopropylethylamine and isopropyl acetate, respectively.

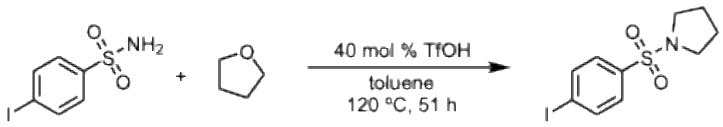
Commercial sources (authentic standards)



2. Synthesis

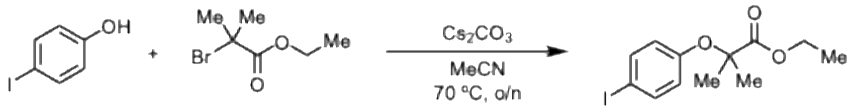
2.1 Preparation of Substrates and Authentic Standards

Synthesis of 1-(4-iodophenyl)sulfonyl pyrrolidine



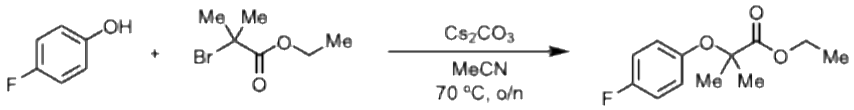
A published procedure was followed, and **^{1}H NMR** and **^{13}C NMR** spectroscopic data matched those reported in the literature.[2]

Synthesis of ethyl 2-(4-iodophenoxy)-2-methylpropanoate



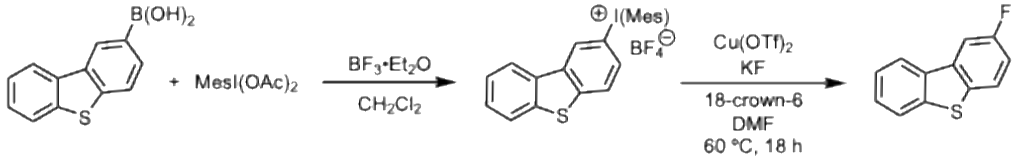
A published procedure was followed, and **^{1}H NMR** and **^{13}C NMR** spectroscopic data matched those reported in the literature.[3]

Synthesis of ethyl 2-(4-fluorophenoxy)-2-methylpropanoate



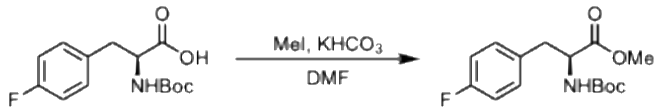
A published procedure was followed, and **^{1}H NMR** and **^{13}C NMR** spectroscopic data matched those reported in the literature.[4]

Synthesis of 2-fluoro-dibenzothiophene



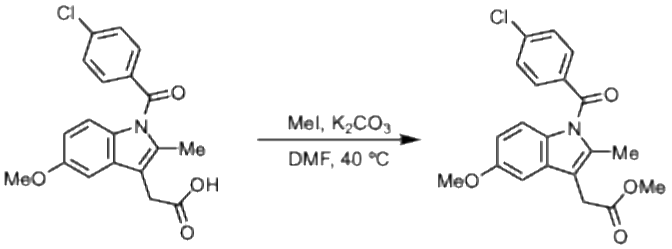
A published procedure was followed, and **^{1}H NMR** and **^{13}C NMR** spectroscopic data matched those reported in the literature.[5]

Synthesis of fluoro-phenylalanine



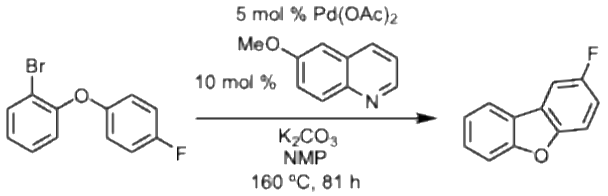
A published procedure was followed, and **^{1}H NMR** and **^{13}C NMR** spectroscopic data matched those reported in the literature.[6]

Synthesis of methyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate



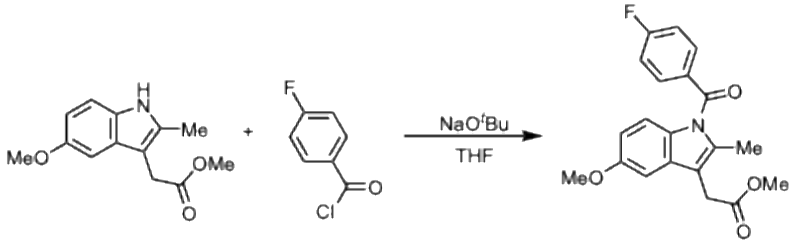
A published procedure was followed, and **^{1}H NMR** and **^{13}C NMR** spectroscopic data matched those reported in the literature.[7]

Synthesis of 2-fluoro-dibenzofuran



A reported method[8] was adapted as follows. To an oven-dried 10 mL flask was added $Pd(OAc)_2$ (23 mg, 50 µmol, 5 mol %), 1-bromo-2-(4-fluorophenoxy)benzene (539 mg, 2.02 mmol, 1 equiv), potassium carbonate (558 mg, 4.04 mmol, 2 equiv), 6-methoxyquinoline (28 mg, 0.20 mmol, 10 mol %). The reagents were dissolved in N-methyl-2-pyrrolidone (NMP, 3 mL). The reaction was heated to 160 ºC and stirred for 81 h. The reaction was allowed to cool to room temperature, diluted with dichloromethane (~ 6 mL), and filtered through a plug of celite (~2 g). The resulting solution was concentrated under vacuum, solids were dissolved in hexanes, and this solution was passed through a plug of silica gel (~2 g). The solvent was removed under vacuum, and the product was purified by column chromatography (hexanes/EtOAc, 10-20% EtOAc gradient). The title compound was obtained as a white solid (168 mg, 45% yield). **^{1}H NMR** and **^{13}C NMR** spectroscopic data matched those reported in the literature.[8]

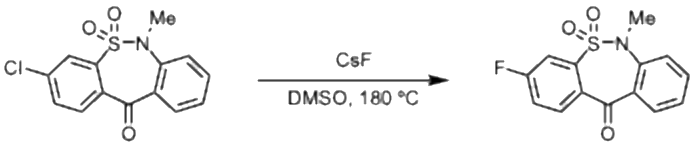
Synthesis of methyl 2-(1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate



A reported method[9] was adapted as follows. In a N_2-filled glovebox, an oven-dried flask was charged with methyl 2-(5-methoxy-2-methyl-1H-indol-3-yl)acetate (317 mg, 1.36 mmol, 1 equiv), and then anhydrous THF (8 mL) was added. The flask was sealed with a septum, removed from the glovebox, and cooled to 0 ºC. Sodium tert-butoxide (157 mg, 1.63 mmol, 1.2 equiv) was dissolved in anhydrous tetrahydrofuran (0.82 mL), and this solution was added dropwise to the indole solution. The reaction was stirred for 25 min at 0 ºC. A solution of 4-fluorobenzoyl chloride (0.19 mL, 1.2 mmol, 1.2 equiv) was then added dropwise. The resulting mixture was allowed to warm to room temperature and then stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were washed with saturated aqueous NaCl (1 x 10 mL) and water (1 x 10 mL), dried over Na_2SO_4 and then concentrated under vacuum. The residue was

purified by column chromatography (hexanes/EtOAc, 5-10% EtOAc gradient). The product was then recrystallized from pentane (~10 mL). The title compound was obtained as a white solid (109 mg, 24% yield) and stored at –20 ºC. **^{1}H NMR** and **^{13}C NMR** spectroscopic data matched those reported in the literature.[9]

Synthesis of 3-fluoro-6-methyldibenzo[c,f][1,2]thiazepin-11(6H)-one 5,5-dioxide



A reported method[10] was adapted as follows. 3-Chloro-6-methyldibenzo[c,f][1,2]thiazepin-11(6H)-one 5,5-dioxide (216 mg, 0.7 mmol, 1 equiv) and cesium fluoride (319 mg, 2.10 mmol, 3 equiv) were combined in a tall 40 mL vial. DMSO (0.72 mL) was added, the vial was sealed, and the reaction was stirred for 30 min at 180 ºC. The reaction was allowed to cool to room temperature. Water (1 x 2 mL) was added, and the reaction was extracted with EtOAc (4 x 4 mL). The organic extracts were washed with saturated aqueous NaCl (1 x 8 mL), collected, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 5-10% EtOAc gradient). The title compound was obtained as a white solid (127 mg, 62% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.03 (dd, *J* = 8.6, 5.1 Hz, 1H), 7.70-7.64 (multiple peaks, 2H), 7.43-7.34 (multiple peaks, 3H), 3.36 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 189.4, 164.2 (d, *J* = 258.9 Hz), 141.3, 139.5 (d, *J* = 7.5 Hz), 135.1, 134.8 (d, *J* = 8.6 Hz), 132.5 (d, *J* = 3.9 Hz), 132.3, 131.2, 126.5, 124.9, 120.4 (d, *J* = 21.4 Hz), 113.3 (d, *J* = 25.3 Hz), 39.2.

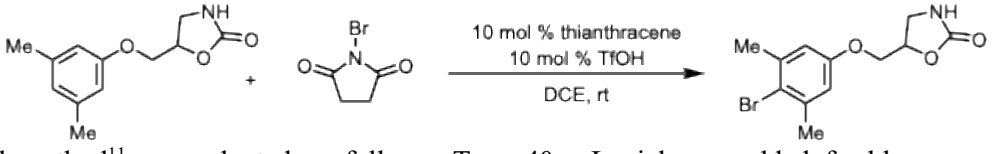
^{19}F NMR (564 MHz, $CDCl_3$): δ −103.72 (app. q, 1F).

HRMS (ESI) (m/z): [M+H] ($C_{14}H_{11}FNO_3S^+$) calc. 292.0438; observed 292.0440.

R_f = 0.3 in 20% EtOAc in hexanes.

Mp = 136-137 °C.

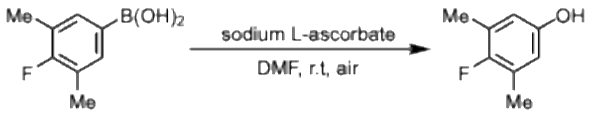
Synthesis of 5-((4-bromo-3,5-dimethylphenoxy)methyl)oxazolidin-2-one



A reported method[11] was adapted as follows. To a 40 mL vial was added freshly recrystallized *N*-bromosuccinimide (534 mg, 3.00 mmol, 1.2 equiv), thianthracene (54 mg, 250 µmol, 0.10 equiv), and dichloroethane (9 mL). This mixture was stirred for 5 min, and then 0.5 mL of a stock solution of triflic acid in dichloroethane (22 µL, 250 µmol, 0.10 equiv) was added. The mixture was allowed to stir for another 5 min, and then metaxalone (553 mg, 2.50 mmol, 1 equiv) was added. The reaction was sealed and allowed to stir for 6 h at room temperature. A saturated aqueous solution of $NaHCO_3$ (1 x 15 mL) was added, and the organic layer was separated. The aqueous extracts were back-extracted with EtOAc (2 x 12 mL)

followed by washing with saturated aqueous NaCl (1 x 10 mL). The organic extracts were combined, dried over Na_2SO_4, and concentrated under vacuum. The product was then purified by column chromatography (dichloromethane/MeOH, 0-5% MeOH gradient). The title compound (431 mg, 57% yield) was obtained as a white solid. **^{1}H NMR** and **^{13}C NMR** spectroscopic data matched those reported in the literature.[11]

Synthesis of 4-fluoro-3,5-dimethylphenol



A reported procedure[12] was adapted as follows. A 50 mL round bottom flask was charged with (4-fluoro-3,5-dimethylphenyl) boronic acid (1.33 g, 7.90 mmol, 1 equiv), sodium ascorbate (3.13 g, 15.8 mmol, 2 equiv), and *N,N*-dimethylformamide (16 mL). The reaction was stirred at room temperature overnight. EtOAc (50 mL) and 5% aqueous LiCl (15 mL) were added. Following extraction, the organic layers were collected and washed with 5% aqueous LiCl (2 x 15 mL). The aqueous layers were combined and back-extracted with EtOAc (1 x 20 mL). The organic extracts were combined, washed with water (1 x 50 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 0-20% EtOAc gradient). The title compound was obtained as a pale-yellow solid (415 mg, 37% yield).

^{1}H NMR (500 MHz, DMSO-d_6): δ 9.06 (s, 1H), 6.43 (d, J = 6.0 Hz, 2H), 2.11 (s, 6H).

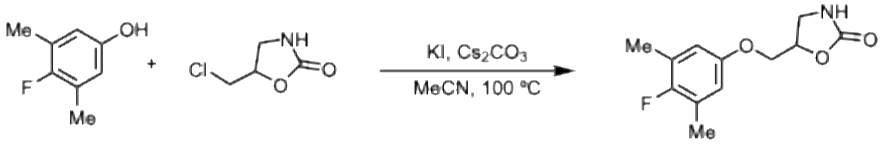
^{13}C NMR (126 MHz, DMSO-d_6) δ 153.2 (d, J = 231.6 Hz), 153.1 (d, J = 2.3 Hz), 124.6 (d, J = 19.2 Hz), 115.3 (d, J = 4.3 Hz), 14.9 (d, J = 3.8 Hz).

^{19}F NMR (377 MHz, DMSO-d_6): δ −135.25 (m, 1F).

HRMS (ESI) (m/z): [M-H] ($C_8H_8FO^-$) calc. 139.0565; observed 139.0562.

R_f = 0.18 in 10% EtOAc in hexanes.

Synthesis of 5-((4-fluoro-3,5-dimethylphenoxy)methyl)oxazolidin-2-one



To a 10 mL vial, 5-(chloromethyl)oxazolidin-2-one (102 mg, 0.750 mmol, 1 equiv), phenol (210 mg, 1.50 mmol, 2 equiv), Cs_2CO_3 (488 mg, 1.13 mmol, 1.5 equiv), and KI (150 mg, 0.90 mmol, 1.2 equiv) were combined and then dissolved in acetonitrile (1.5 mL). The reaction was stirred at 100 ºC overnight and then was allowed to cool to room temperature. Water (1 x 2 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 4 mL). The organic extracts were collected, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (dichloromethane/MeOH, 0-2% MeOH gradient). The title compound was obtained as a pale-yellow solid (26 mg, 14% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.54 (d, J = 5.8 Hz, 2H), 6.17 (s, 1H), 4.92 (m, 1H), 4.07 (d, J = 4.9 Hz, 2H), 3.75 (app. t, 1H), 3.59 (m, 1H), 2.22 (s, 6H).

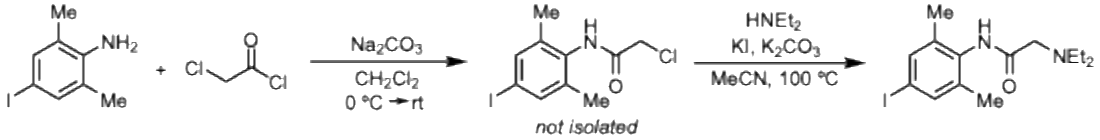
^{13}C NMR (126 MHz, $CDCl_3$): δ 159.8, 155.0 (d, *J* = 236.9 Hz), 153.5 (d, *J* = 2.6 Hz), 125.4 (d, *J* = 19.7 Hz), 114.7 (d, *J* = 4.6 Hz), 74.4, 68.7, 42.8, 15.0 (d, *J* = 4.0 Hz).

^{19}F NMR (377 MHz, $CDCl_3$): δ –130.95 (m, 1F).

HRMS (ESI) (m/z): [M+H] ($C_{12}H_{15}FNO_3^+$) calc. 240.1030; observed 240.1021.

R_f = 0.3 in 5% MeOH in dichloromethane.

Synthesis of 2-(diethylamino)-N-(4-iodo-2,6-dimethylphenyl)acetamide



4-Iodo-2,6-dimethylaniline (1.00 g, 4.05 mmol, 1 equiv) was dissolved in dichloromethane (8.1 mL). This solution was cooled to 0 ºC, and Na_2CO_3 (429 mg, 4.05 mmol, 1 equiv) was added. 2-Chloroacetyl chloride (0.35 mL, 4.5 mmol, 1.1 equiv) was then added dropwise. The reaction was allowed to warm to room temperature and then stirred overnight. Water (10 mL) was added, and the resulting mixture was extracted with EtOAc (1 x 12 mL). The organic extracts were washed with water (2 x 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4, and then concentrated over vaccum. The residue was taken forward the next step without isolation.

A reported procedure[13] was adapted as follows. Crude 2-chloro-N-(4-iodo-2,6-dimethylphenyl)acetamide (1.31 g, 4.05 mmol, 1 equiv), diethylamine (461 µL, 4.46 mmol, 1.1 equiv), KI (67.0 mg, 405 µmol, 0.60 equiv), and K_2CO_3 (616 mg, 4.46 mmol, 1.1 equiv) were combined in a 40 mL vial followed by the addition of MeCN (8.1 mL, 0.50 M). The resulting mixture was then heated to 100 ºC for 1 h. The reaction was allowed to cool to room temperature. Aqueous 1 M NaOH (1 x 10 mL) was added, and the mixture was extracted with EtOAc (3 x 10 mL). The organic extracts were collected, dried over Na_2SO_4, and concentrated under vacuum. The resulting residue was purified by column chromatography (hexanes/EtOAc, 0-30% EtOAc gradient). The title compound was obtained as a pale-orange solid (1.05 g, 72% yield over two steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (s, 1H), 7.43 (s, 2H), 3.20 (s, 2H), 2.68 (q, *J* = 7.3 Hz, 4H), 2.17 (s, 6H), 1.13 (t, *J* = 7.1 Hz, 6H).

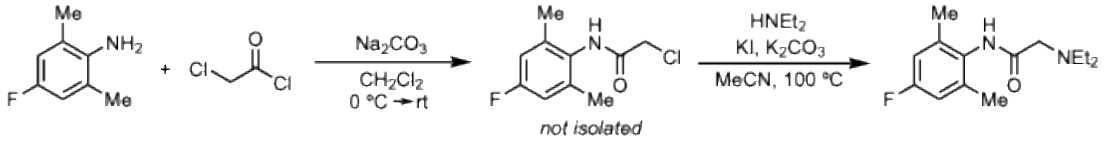
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4, 137.5, 137.1, 134.1, 92.4, 57.6, 49.1, 18.3, 12.7.

HRMS (ESI) (m/z): [M+H] ($C_{14}H_{22}IN_2O^+$) calc. 361.0771; observed 361.0755.

R_f = 0.15 in 30% EtOAc in hexanes.

Mp = 55-56 °C

Synthesis of 2-(diethylamino)-N-(4-fluoro-2,6-dimethylphenyl)acetamide

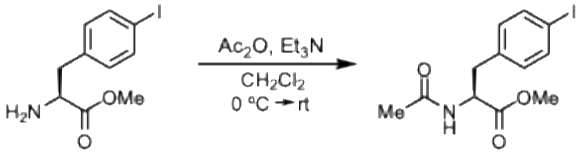


4-Fluoro-2,6-dimethylaniline (139 mg, 1.00 mmol, 1 equiv) was dissolved in dichloromethane (0.50 M, 2.0 mL). The resulting solution was then cooled to 0 °C, and Na_2CO_3 (106 mg, 1.00 mmol, 1 equiv) was added. 2-Chloroacetyl chloride (88 µL, 1.1 mmol, 1.1 equiv) was then added dropwise. The resulting mixture was allowed to slowly warm to room temperature and stir overnight. The reaction was quenched with water followed by the addition of EtOAc (1 x 4 mL). The organic layer was washed with water (2 x 2 mL) followed by saturated aqueous NaCl (1 x 4 mL). The organic extracts were collected, dried over Na_2SO_4, and concentrated over vaacuum. The residue was then taken forward to the next step without isolation.

A reported method[13] was adapted as follows. Crude 2-chloro-N-(4-fluoro-2,6-dimethylphenyl)acetamide (216 mg, 1.00 mmol, 1 equiv), diethylamine (114 µL, 1.10 mmol, 1.1 equiv), KI (99.6 mg, 600 µmol, 0.60 equiv), and K_2CO_3 (152 mg, 1.10 mmol, 1.10 equiv) were combined in a 10 mL vial, and MeCN (2 mL was added. The resulting solution was heated to 100 ºC and stirred for 1 h. The mixture was allowed to cool to room temperature. A 1 M aqueous solution of NaOH (1 x 4 mL) was added, and the aqueous layer was extracted with EtOAc (3 x 6 mL). The organic extracts were collected, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 0-30% EtOAc gradient). The title compound was obtained as a pale-orange solid (48 mg, 19% yield over two steps). **^{1}H NMR** and **^{13}C NMR** data matched those reported in the literature.[14]

2.2 General Procedures for Amino Acid Synthesis

Synthesis of Ac-Phe(4-I)-OMe



A reported method[15] was adapted as follows. Phe(4-I)-OMe (610 mg, 2.00 mmol, 1 equiv), triethylamine (0.40 mL, 3.0 mmol, 1.5 equiv), and dichloromethane (10 mL) were combined in an oven-dried 10 mL flask. The resulting solution was then cooled to 0 °C for 10 min and then acetic anhydride (245 mg, 2.40 mmol, 1.2 equiv) was added. The reaction was allowed to warm to room temperature and then stirred for 1 h. The crude mixture was extracted with 1 M aqueous HCl (1 x 10 mL), saturated aqueous Na_2CO_3 (3 x 10 mL), and saturated aqueous NaCl (1 x 10 ml). The organic extracts were combined, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 15-50% EtOAc gradient). The title compound was obtained as a white solid (347 mg, 72% yield).

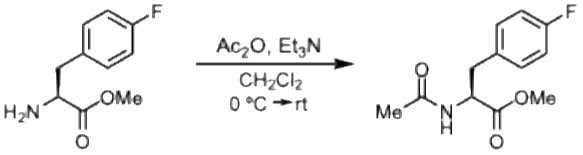
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 5.96 (d, *J* = 7.7 Hz, 1H), 4.86 (ddd, *J* = 7.7, 5.7, 5.5 Hz, 1H), 3.72 (s, 3H), 3.10 (dd, *J* = 13.9, 5.9 Hz, 2H), 3.06 (dd, *J* = 13.9, 5.5 Hz, 2H), 1.98 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.0, 169.7, 137.8, 135.7, 131.4, 92.8, 53.1, 52.6, 37.5, 23.3.

HRMS (ESI) (m/z): [M+H] ($C_{12}H_{15}INO_3^+$) calc. 348.0097; observed 348.0089.

R_f = 0.3 in 5% MeOH in dichloromethane.

Synthesis of Ac-Phe(4-F)-OMe



A reported method[15] was adapted as follows. Phe(4-F)-OMe (99 mg, 0.50 mmol, 1 equiv), triethylamine (0.10 mL, 0.75 mmol, 1.5 equiv), and dichloromethane (2.5 mL) were combined in an oven-dried 10 mL flask. The resulting solution was cooled to 0 °C for 10 min and then acetic anhydride (61 mg, 0.60 mmol, 1.2 equiv) was added. The reaction was allowed to warm to room temperature and then stirred for 1 h. The crude mixture was extracted with 1 M aqueous HCl (1 x 5 mL), saturated aqueous Na_2CO_3 (3 x 5 mL), and saturated aqueous NaCl (1 x 5 ml). The organic extracts were combined, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 15-50% EtOAc gradient). The title compound was obtained as a white solid (55 mg, 45% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.95 (app. t, 2H), 6.11 (m, 1H), 4.83 (ddd, *J* = 7.8, 5.9, 5.8 Hz, 1H), 3.70 (s, 3H), 3.10 (dd, *J* = 14.0, 5.9 Hz, 1H), 3.03 (dd, *J* = 14.0, 5.8 Hz, 1H), 1.96 (s, 3H).

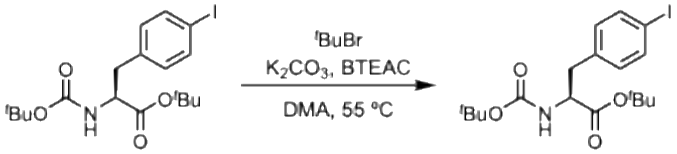
^{13}C NMR (126 MHz, CD_3CN): δ 172.9, 170.6, 162.7 (d, *J* = 242.5 Hz), 134.1 (d, *J* = 3.2 Hz), 132.0 (d, *J* = 8.1 Hz), 115.9 (d, *J* = 21.4 Hz), 54.6, 52.6, 37.3, 22.6.

^{19}F NMR (564 MHz, $CDCl_3$): δ –115.64 (tt, *J* = 9.3, 5.4 Hz, 1F).

HRMS (ESI) (m/z): [M+H] ($C_{12}H_{15}FNO_3^+$) calc. 240.1036; observed 240.1048.

R_f = 0.3 in 5% MeOH in dichloromethane.

Synthesis of Boc-Phe(4-I)-O^{t}Bu



A literature procedure[16] was followed. The product was purified by column chromatography (hexanes/EtOAc, 15-50% EtOAc gradient). The title compound was obtained as a tan solid (889 mg, 64% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.9 Hz, 2H), 6.90 (d, *J* = 7.9 Hz, 2H), 5.01 (d, *J* = 8.1 Hz, 1H), 4.40 (app. q, 1H), 3.01 (dd, *J* = 13.1, 5.6 Hz, 1H), 2.95 (dd, *J* = 13.1, 5.9 Hz, 1H), 1.40 (s, 9H), 1.39 (s, 9H).

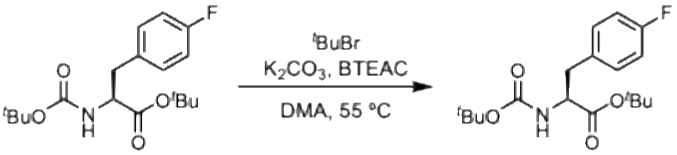
^{13}C NMR (126 MHz, DMSO-d_6): δ 171.1, 155.5, 137.7, 136.9, 131.7, 92.2, 80.6, 78.3, 55.8, 36.1, 28.2, 27.6.

HRMS (ESI) (m/z): [M+Na] ($C_{18}H_{26}INNaO_4^+$) calc. 470.0799; observed 470.0797.

R_f = 0.3 in 5% MeOH in dichloromethane.

Mp = 69-71°C.

Synthesis of Boc-Phe(4-F)-O^{t}Bu



A literature procedure was followed. The product was purified by column chromatography (hexanes/EtOAc, 15-50% EtOAc gradient). The title compound was obtained as a clear oil (616 mg, 87% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (app. t, 2H), 6.95 (app. t, 2H), 5.02 (br. s, 1H), 4.40 (app. d, 1H), 3.03 (m, 1H), 2.98 (dd, *J* = 14.4, 5.7 Hz, 1H), 1.40 (s, 9H), 1.38 (s, 9H).

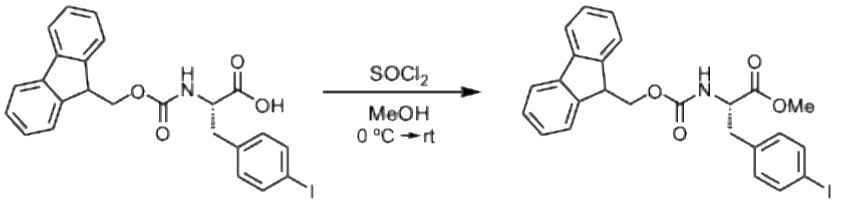
^{13}C NMR (126 MHz, $CDCl_3$): δ 171.0, 162.1 (d, *J* = 245.0 Hz), 155.2, 132.3, 131.1 (d, *J* = 8.0 Hz), 115.3 (d, *J* = 21.1 Hz), 82.3, 79.9, 55.0, 38.0, 28.5, 28.1.

^{19}F NMR (564 MHz, $CDCl_3$): δ –116.28 (app. t, 1F).

HRMS (ESI) (m/z): [M+Na] ($C_{18}H_{26}FNNaO_4^+$) calc. 362.1738; observed 362.1739.

R_f = 0.3 in 5% MeOH in dichloromethane.

Synthesis of Fmoc-Phe(4-I)-OMe



A reported method[17] was adapted as follows. In an oven-dried 10 mL flask, Fmoc-Phe(4-I) (1.03 g, 2.00 mmol, 1.00 equiv) was dissolved in MeOH (6 mL). The reaction was cooled to 0 °C, and thionyl chloride (0.90 mL, 13 mmol, 6.3 equiv) was added dropwise. The reaction was allowed to warm to room temperature and then stirred for 16 h. Volatiles were removed under a stream of N_2, which formed a white solid. The solid was then washed with diethyl ether (3 x 5 mL) and then dried under a stream of N_2. The title compound was obtained as a white solid (560 mg, 53% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 2H), 7.41 (app. t, 2H), 7.32 (tt, *J* = 7.2, 1.4 Hz, 2H), 6.82 (d, *J* = 7.8 Hz, 2H), 5.23 (d, *J* = 8.2 Hz, 1H), 4.65 (ddd, *J* = 8.2, 5.8, 5.7 Hz, 1H), 4.47 (dd, *J* = 10.7, 7.1 Hz, 1H), 4.37 (dd, *J* = 10.7, 6.8 Hz, 1H), 4.21 (app. t, 1H), 3.73 (s, 3H), 3.09 (dd, *J* = 13.9, 5.7 Hz, 1H), 3.02 (dd, *J* = 13.9, 5.8 Hz, 1H).

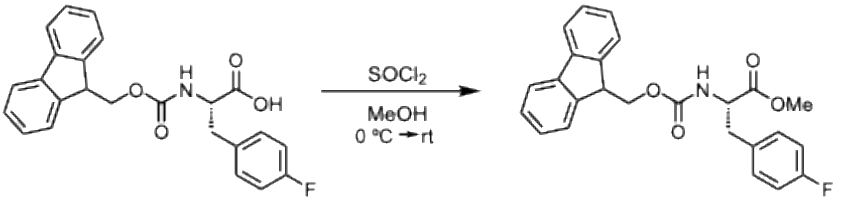
^{13}C NMR (126 MHz, CD_2Cl_2): δ 172.0, 155.8, 144.4, 144.2, 141.7, 141.7, 141.7, 138.0, 137.96, 136.3, 131.8, 128.1, 127.4, 125.4, 125.4, 120.4, 120.3, 120.3, 92.8, 92.6, 67.1, 67.07, 55.0, 52.7, 52.7, 47.6, 38.0.

HRMS (ESI) (m/z): [M+H] ($C_{25}H_{23}INO_4^+$) calc. 528.0672; observed 528.0662.

R_f = 0.3 in 30% EtOAc in hexanes.

Mp = 144-145 °C.

Synthesis of Fmoc-Phe(4-F)-OMe



A reported method was adapted as follows. In an oven-dried 10 mL flask, Fmoc-Phe(4-F) (251 mg, 0.620 mmol, 1 equiv) was dissolved in MeOH (2 mL). This solution was cooled to 0 °C, and thionyl chloride (0.30 mL, 3.9 mmol, 6.3 equiv) was added dropwise. The reaction was allowed to warm to room temperature and then stirred for 16 h. Volatiles were removed under a stream of N_2, which formed a white solid. The solid was then washed with diethyl ether (3 x 5 mL) and then dried under a stream of N_2. The title compound was obtained as a white solid (142 mg, 53% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.6 Hz, 2H), 7.57 (app. t, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.03 (app. t, 2H), 6.97 (app. t, 2H), 5.23 (d, *J* = 8.1 Hz, 1H), 4.65 (m, 1H), 4.48 (dd, *J* = 10.7, 6.9 Hz, 1H), 4.38 (dd, *J* = 10.7, 6.9 Hz, 1H), 4.21 (app. t, 1H), 3.73 (s, 3H), 3.12 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.06 (dd, *J* = 13.9, 5.7 Hz, 1H).

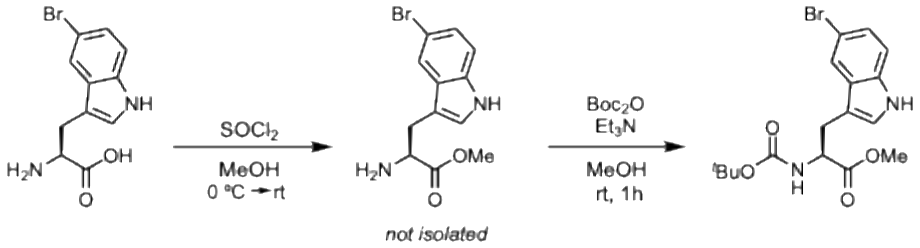
^{13}C NMR (126 MHz, CD_2Cl_2): δ 172.1, 162.4 (d, *J* = 244.5 Hz), 155.8, 144.4, 144.3, 141.7, 132.3, 131.3 (d, *J* = 8.1 Hz), 128.1, 127.4, 125.4, 125.4, 120.3 (d, *J* = 2.5 Hz), 115.7 (d, *J* = 21.3 Hz), 67.1, 55.3, 52.7, 47.6, 37.7.

^{19}F NMR (564 MHz, $CDCl_3$): δ −111.81 (m, 1F).

HRMS (ESI) (m/z): [M+H] ($C_{25}H_{23}FNO_4^+$) calc. 420.1611; observed 420.1610.

R_f = 0.3 in 30% EtOAc in hexanes.

Synthesis of Boc-Trp(5-Br)-OMe



A literature procedure was followed.[18] The title compound (311 mg, 40% yield) was obtained as a brown solid.

^{1}H NMR (600 MHz, DMSO-d_6): δ 11.16 (s, 1H), 7.76 (s, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.35–7.17 (multiple peaks, 3H), 4.26 (app. q, 1H), 3.69 (s, 3H), 3.17 (dd, *J* = 14.5, 5.3 Hz, 1H), 3.07 (dd, *J* = 14.5, 9.2 Hz, 1H), 1.40 (s, 9H).

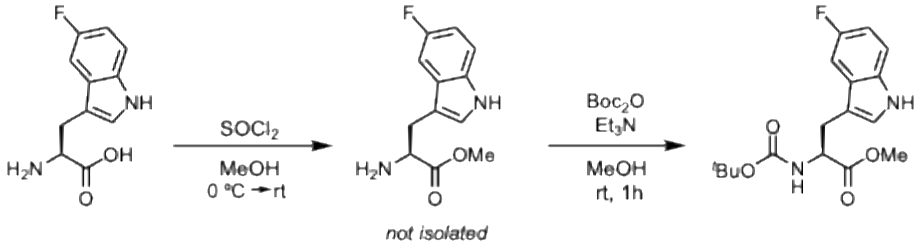
^{13}C NMR (126 MHz, DMSO-d_6): δ 173.2, 155.8, 135.2, 129.5, 126.0, 123.8, 121.0, 113.9, 111.6, 110.3, 78.8, 55.3, 52.3, 28.6, 27.1.

HRMS (ESI) (m/z): [M+Na] ($C_{17}H_{21}BrN_2NaO_4^+$) calc. 419.0577; observed 419.0575.

R_f = 0.2 in 30% EtOAc in hexanes.

Mp = 107-108 °C.

Synthesis of Boc-Trp(5-F)-OMe



A literature procedure was followed.18 The title compound (387 mg, 51% yield) was obtained as a brown solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.93 (s, 1H), 7.30 (dd, J = 8.9, 4.6 Hz, 1H), 7.24–7.14 (multiple peaks, 3H), 6.88 (m, 1H), 4.16 (m, 1H), 3.57 (s, 3H), 3.05 (dd, J = 14.8, 5.2 Hz, 1H), 2.95 (dd, J = 14.8, 9.2 Hz, 1H),1.29 (s, 9H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 172.9, 156.9 (d, J = 231.0 Hz), 155.5, 132.8, 127.5 (d, J = 9.7 Hz), 126.0, 112.4 (d, J = 9.6 Hz), 110.4 (d, J = 4.9 Hz), 109.1 (d, J = 26.2 Hz), 103.0 (d, J = 23.1 Hz), 78.4, 54.8, 51.9, 28.2, 26.8.

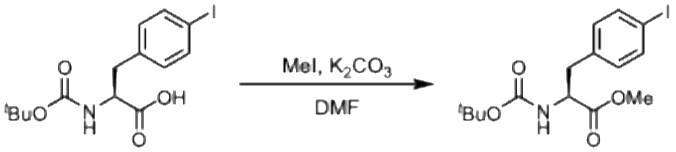
^{19}F NMR (564 MHz, $CDCl_3$): δ –124.62 (app. q, 1F).

HRMS (ESI) (m/z): [M+Na] ($C_{17}H_{21}FN_2NaO_4^+$) calc. 359.1377; observed 359.1385.

R_f = 0.2 in 30% EtOAc in hexanes.

Mp = 124-126 °C.

Synthesis of Boc-Phe(4-I)-OMe



A reported method[19] was adapted as follows. In an oven-dried 100 mL flask, Boc-Phe(4-I) (2.5 mg, 6.4 mmol, 1 equiv) and K_2CO_3 (1.06 mg, 7.68 mmol, 1.2 equiv) were dissolved in *N,N*-dimethylformamide (24 mL). Methyl iodide (0.50 mL, 7.7 mmol, 1.2 equiv) was added dropwise, and the resulting mixture was stirred for 35 min. The reaction was diluted with water (1 x 150 mL) and EtOAc (1 x 150 mL) before separating the two layers. The aqueous layer was back extracted with EtOAc (1 x 150 mL). The combined organic extracts were then washed with water (5 x 100 mL) and saturated aqueous NaCl (1 x 100 mL). The organic extracts were then dried over $MgSO_4$ and concentrated under vacuum. The title compound was obtained as a white solid (2.52 g, 97% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H), 4.95 (br. d, J = 8.3 Hz, 1H), 4.56 (app. q, 1H), 3.70 (s, 3H), 3.07 (dd, J = 13.9, 5.8 Hz, 1H), 2.98 (dd, J = 13.9, 5.2 Hz, 1H).

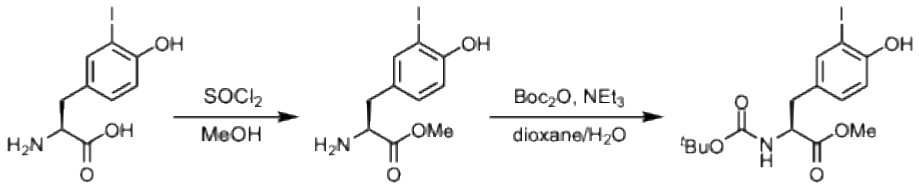
^{13}C NMR (126 MHz, $CDCl_3$): δ 172.1, 155.0, 137.6, 135.7, 131.3, 92.5, 80.1, 54.2, 52.3, 37.9, 28.3.

HRMS (ESI) (m/z): [M+Na] ($C_{15}H_{20}INNaO_4^+$) calc. 428.0335; observed 428.0328.

R_f = 0.5 in 10% EtOAc in hexanes.

Mp = 78-79 °C.

Synthesis of Boc-Tyr(3-I)-OMe



Tyr(3-I) (737 mg, 2.4 mmol, 1 equiv) was dissolved in MeOH (3 mL) in an oven-dried 10 mL flask. The resulting solution was then cooled to 0 °C for 10 min and then thionyl chloride (0.3 mL, 4.8 mmol, 2 equiv) was added dropwise. The reaction was allowed to warm to room temperature and then stirred for 16 h. The reaction mixture was dried under a stream of nitrogen until a white solid formed. The solid was then washed with diethyl ether (3 x 5 mL) before drying under a stream of N_2. The residue was then taken to the next step without isolation.

Crude Tyr(3-I)-OMe was dissolved in 4:1 dioxane: H_2O (5 mL), and triethylamine (0.3 mL, 2.4 mmol, 1 equiv) was added. Boc anhydride (498 mg, 2.28 mmol, 0.95 equiv) was added, and the resulting mixture was allowed to stir for 4 h at room temperature. The reaction was then concentrated under vacuum before redissolving in EtOAc (1 x 15 mL). This solution was extracted with 1 M HCl (1 x 5 mL), saturated aqueous Na_2CO_3 (3 x 5 mL), and saturated aqueous NaCl (1 x 5 mL). The organic extracts were collected, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 15-50% EtOAc gradient). The title compound was obtained as a white solid (369 mg, 36% yield).

^{1}H NMR (600 MHz, DMSO-d_6): δ 10.12 (s, 1H), 7.52 (s, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.05 (dd, J = 8.2, 2.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 4.07 (ddd, J = 10.2, 8.2, 5.0 Hz, 1H), 3.61 (s, 3H), 2.86 (dd, J = 13.9, 5.0 Hz, 1H), 2.71 (dd, J = 13.9, 10.2 Hz, 1H), 1.33 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 155.2, 154.3, 139.1, 131.1, 130.1, 115.2, 85.5, 80.3, 54.6, 52.5, 37.1, 28.5.

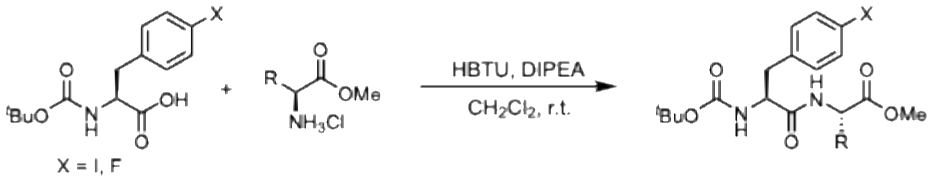
HRMS (ESI) (m/z): [M+Na] ($C_{15}H_{20}INNaO_5^+$) calc. 444.0278; observed 444.0274.

R_f = 0.5 in 20% EtOAc in hexanes.

Mp = 97-98 °C.

2.3 General Procedures for Peptide Synthesis

2.3.1 General Procedure A

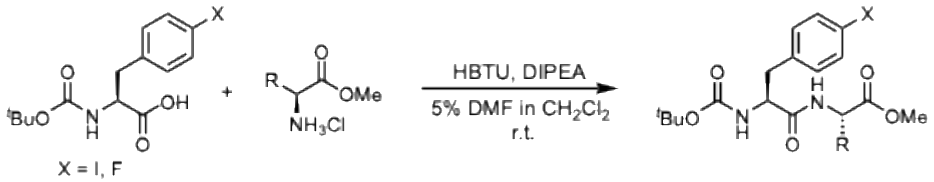


A reported method[20] was adapted as follows. The free acid (5 mmol for aryl iodides/1 mmol for aryl fluorides, 1 equiv) and HBTU (1 equiv) were combined in a dried 250 mL round bottom flask. The solids were dissolved in dichloromethane (0.04 M), and the mixture was stirred for 5 min at room temperature. The HCl salt (2 equiv) was added, the reaction was allowed to stir for an additional 5 min, and then DIPEA (2 equiv) was added. The reaction was then stirred for 90 min.

If aryl iodide: The reaction was extracted with 1 M aqueous HCl (1 x 100 mL), saturated aqueous $NaHCO_3$ (3 x 100 mL), and saturated aqueous NaCl (1 x 100 mL). The organic extracts were then dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 15-50% EtOAc gradient). The products were generally white solids.

If aryl fluoride: The reaction was extracted with 1 M aqueous HCl (1 x 20 mL), saturated aqueous $NaHCO_3$ (3 x 20 mL), and saturated aqueous NaCl (1 x 20 mL). The organic extracts were then dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 15-50% EtOAc gradient). The products were generally white solids.

2.3.2 General Procedure B

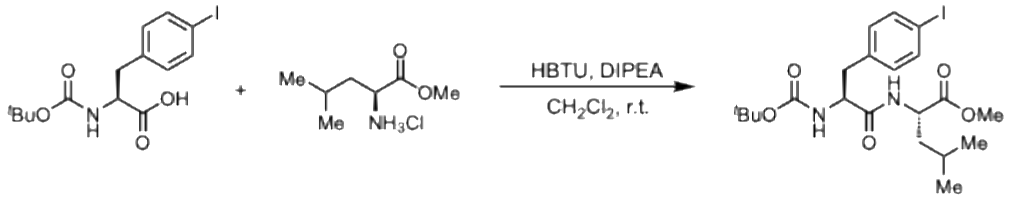


The free acid (5.00 mmol for aryl iodides/1.00 mmol for aryl fluorides, 1 equiv) and HBTU (1 equiv) were combined in a dried 250 mL round bottom flask. The solids were dissolved in 5% *N,N*-dimethylformamide in dichloromethane with (0.05 M overall concentration), and the reaction was stirred for 5 min at room temperature. The HCl salt (2 equiv) was added, the mixture was allowed to stir for an additional 5 min, and then DIPEA (2 equiv) was added. The reaction was then stirred for 90 min.

If aryl iodide: The reaction was extracted with 1 M aqueous HCl (1 x 100 mL), saturated aqueous $NaHCO_3$ (3 x 100 mL), and saturated aqueous NaCl (1 x 100 mL). The organic extracts were then dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 15-50% EtOAc gradient). The products were generally white solids.

If aryl fluoride: The reaction was extracted with 1 M aqueous HCl (1 x 20 mL), saturated aqueous $NaHCO_3$ (3 x 20 mL), and saturated aqueous NaCl (1 x 20 mL). The organic extracts were then dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (dichloromethane/MeOH, 1-5% MeOH gradient). The products were generally white solids.

Synthesis of Boc-Phe(4-I)-Leu-OMe



Following General Procedure A, the title compound was obtained as a white solid (1.95 g, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 6.5 Hz, 2H), 6.94 (d, *J* = 6.5 Hz, 2H), 6.42 (br. s, 1H), 5.09 (m, 1H), 4.53 (app. q, 1H), 4.33 (br. s, 1H), 3.69 (s, 3H), 3.01 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.94 (m, 1H), 1.64-1.43 (multiple peaks, 3H), 1.39 (s, 9H), 0.88 (t, *J* = 5.6 Hz, 6H).

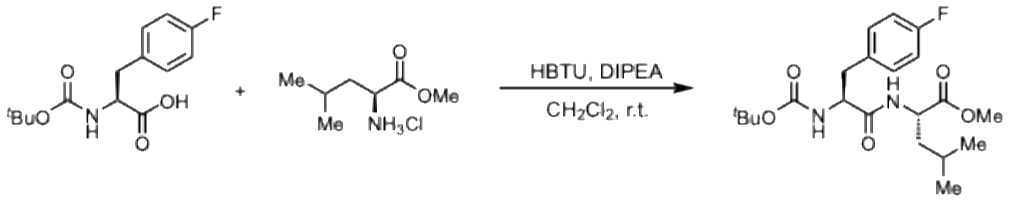
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.2, 170.9, 155.7, 137.9, 137.0, 131.9, 92.5, 55.7, 52.6, 51.1, 41.8, 37.73, 28.4, 25.1, 22.9, 21.9.

HRMS (ESI) (m/z): [M+H] ($C_{21}H_{32}IN_2O_5^+$) calc. 519.1356; observed 519.1349.

R_f = 0.5 in 10% EtOAc in hexanes.

Mp = 135-136 °C.

Synthesis of Boc-Phe(4-F)-Leu-OMe



Following General Procedure A, the title compound was obtained as a white solid (308 g, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (dd, *J* = 7.61, 5.65 Hz, 2H), 6.97 (app. t, 2H), 6.24 (br. s, 1H), 5.00 (br. s, 1H), 4.56 (ddd, *J* = 8.6, 4.8, 4.7 Hz, 1H), 4.30 (app. d, 1H), 3.69 (s, 3H), 3.11-2.95 (multiple peaks, 2H), 1.62-1.45 (multiple peaks, 3H), 1.41 (s, 9H), 0.90 (t, *J* = 6.2 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9, 170.8, 162.01 (d, *J* = 245.2 Hz), 132.4, 131.1 (d, *J* = 7.9 Hz), 115.6 (d, *J* = 21.3 Hz), 80.5, 55.9, 52.4, 50.9, 41.8, 37.4, 28.4, 24.8, 22.9, 22.0.

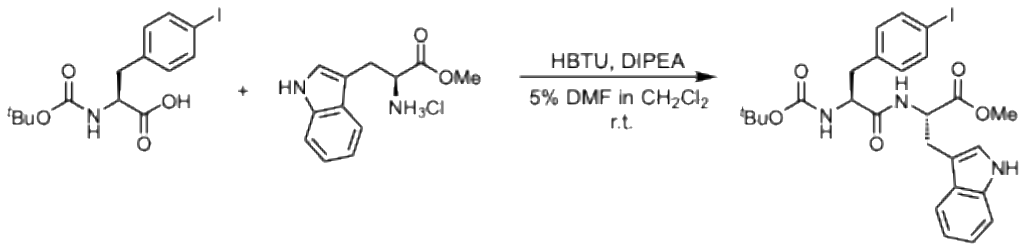
^{19}F NMR (564 MHz, CD_2Cl_2): δ –117.04 (app. s, 1F).

HRMS (ESI) (m/z): [M+H] ($C_{21}H_{32}FN_2O_5^+$) calc. 411.2295; observed 411.2288.

R_f = 0.5 in 10% EtOAc in hexanes.

Mp = 97-103 °C.

Synthesis of Boc-Phe(4-I)-Trp-Ome



Following General Procedure B, the title compound was obtained as a white solid (2.25 g, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (br. s, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.19 (app. t, 1H), 7.09 (app. t, 1H), 6.96-6.80 (multiple peaks, 3H), 6.21 (br. s, 1H), 4.91 (br. s, 1H), 4.84 (app. q, 1H), 4.27 (br s, 1H), 3.67 (s, 3H), 3.26 (app. t, 2H), 2.92 (d, *J* = 6.8 Hz, 2H), 1.38 (s, 9H).

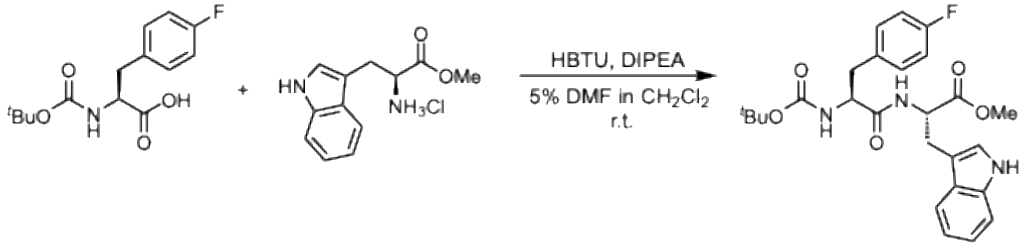
^{13}C NMR (126 MHz, $CDCl_3$): δ 171.7, 170.4, 155.2, 137.6, 136.3, 136.1, 131.5, 127.5, 122.8, 122.4, 119.8, 118.4, 111.4, 109.7, 92.4, 80.2, 55.4, 53.0, 52.5, 38.0, 28.2, 27.6.

HRMS (ESI) (m/z): [M+H] ($C_{26}H_{31}IN_3O_5^+$) calc. 592.1308; observed 592.1294.

R_f = 0.5 in 50% EtOAc in hexanes.

Mp = 177-178 °C.

Synthesis of Boc-Phe(4-F)-Trp-OMe



Following General Procedure B, the title compound was obtained as a white solid (377 mg, 78% yield).

^{1}H NMR (600 MHz, CD_2Cl_2): δ 8.29 (br. s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.29–7.04 (multiple peaks, 4H), 7.03–6.87 (multiple peaks, 3H), 6.38 (app. d, 1H), 4.94 (br. s, 1H), 4.83 (app. q,1H), 4.27 (br. s, 1H), 3.67 (s, 3H), 3.27 (d, *J* = 5.5 Hz, 2H), 3.01 (dd, *J* = 14.1, 6.4 Hz, 1H), 2.88 (m, 1H), 1.37 (s, 9H).

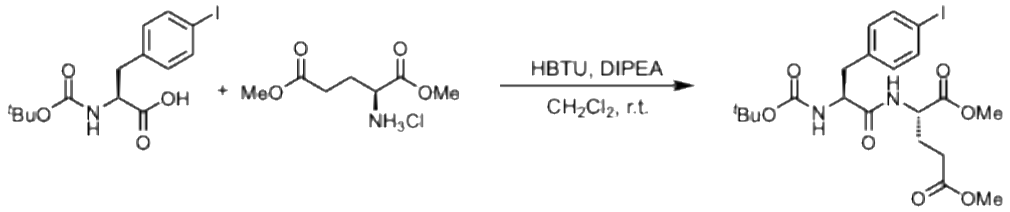
^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2, 171.7, 171.0 161.0 (d, *J* = 241.4 Hz), 155.2, 136.1, 134.2, 131.0 (d, *J* = 8.1 Hz), 127.1, 123.8, 121.0, 118.5, 114.6 (d, *J* = 20.8 Hz), 111.5, 109.2, 78.1, 55.6, 53.1, 51.9, 36.7, 28.1, 27.1.

^{19}F NMR (564 MHz, $CDCl_3$: δ –116.95 (app. s, 1F).

HRMS (ESI) (m/z): [M+H] ($C_{26}H_{31}FN_3O_5^+$) calc. 484.2248; observed 484.2243.

R_f = 0.5 in 50% EtOAc in hexanes.

Synthesis of Boc-Phe(4-I)-Glu(OMe)-OMe



Following general procedure, A, the title compound was obtained as a white solid (2.33 g, 85% yield).

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.64 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 6.63 (d, *J* = 7.8 Hz, 1H), 5.01 (br. s, 1H), 4.53 (ddd, *J* = 7.9, 7.8, 5.1 Hz, 1H), 4.30 (m, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 3.03 (dd, J = 13.9, 6.4 Hz, 1H), 2.95 (dd, J = 13.9, 7.0 Hz, 1H), 2.44-2.25 (multiple peaks, 2H), 2.16 (dtd, *J* = 14.2, 7.5, 5.1 Hz, 1H), 1.93 (dtd, *J* = 14.2, 8.0, 6.3 Hz, 1H), 1.41 (s, 9H).

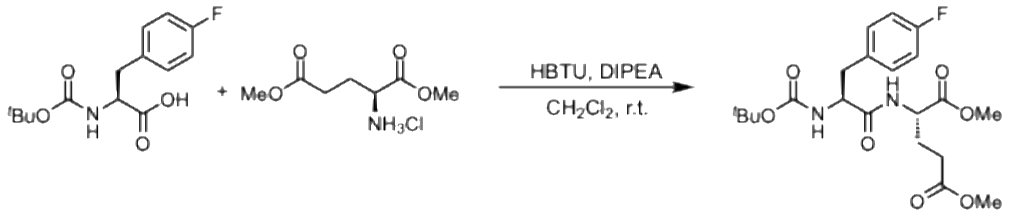
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.3, 171.7, 171.0, 155.4, 137.8, 136.2, 131.5, 92.6, 80.6, 55.6, 52.8, 52.0, 51.8, 37.8, 29.9, 28.4, 27.4.

HRMS (ESI) (m/z): [M+H] ($C_{21}H_{30}IN_2O_7^+$) calc. 549.1098; observed 549.1098.

R_f = 0.4 in 50% EtOAc in hexanes.

Mp = 141-142 °C.

Synthesis of Boc-Phe(4-F)-Glu(OMe)-OMe



Following General Procedure A, the title compound was obtained as a white solid (393 mg, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (dd, *J* = 8.4, 5.5 Hz, 2H), 6.95 (app. t, 2H), 6.65 (d, *J* = 7.7 Hz, 1H), 5.05 (d, *J* = 8.3 Hz, 1H), 4.54 (m, 1H), 4.31 (m, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.02 (app. d, 2H), 2.44-=2.21 (multiple peaks, 2H), 2.15 (m, 1H), 1.93 (dtd, *J* = 14.3, 8.1, 6.3 Hz, 1H), 1.39 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.3, 171.8, 171.1, 162.1 (d, *J* = 245.3 Hz), 155.4, 132.3, 131.0 (d, *J* = 7.9 Hz), 115.6 (d, *J* = 21.1 Hz), 80.5, 55.9, 52.7, 52.0, 51.8, 37.5, 29.9, 28.4, 27.4.

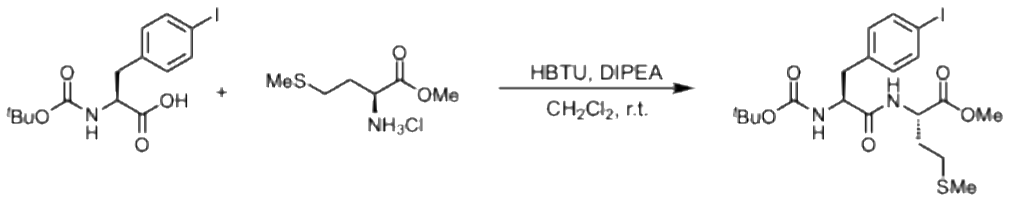
^{19}F NMR (564 MHz, CD_2Cl_2): δ –116.95 (app. s, 1F).

HRMS (ESI) (m/z): [M+H] ($C_{21}H_{30}IN_2O_7^+$) calc. 441.2037; observed 441.2029.

R_f = 0.4 in 50% EtOAc in hexanes.

Mp = 123-125 °C.

Synthesis of Boc-Phe(4-I)-Met-OMe



Following General Procedure A, the title compound was obtained as a white solid (2.31 g, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.1 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 6.53 (d, *J* = 7.7 Hz, 1H), 4.96 (br. s, 1H), 4.63 (app. q, 1H), 4.32 (m, 1H), 3.73 (s, 3H), 3.01 (d, *J* = 6.2 Hz, 2H), 2.42 (app. t, 2H), 2.23–2.02 (multiple peaks, 4H), 1.94 (m, 1H), 1.42 (s, 9H).

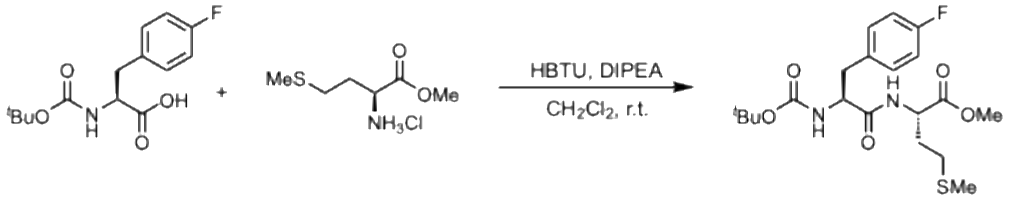
^{13}C NMR (126 MHz, $CDCl_3$): δ 171.8, 170.9, 155.4, 137.8, 136.3, 131.5, 92.6, 80.6, 55.6, 52.8, 51.7, 37.7, 31.6, 29.9, 28.4, 15.6.

HRMS (ESI) (m/z): [M+H] ($C_{20}H_{30}IN_2O_5S^+$) calc. 537.0920; observed 537.0909.

R_f = 0.55 in 50% EtOAc in hexanes.

Mp = 156-157 °C.

Synthesis of Boc-Phe(4-F)-Met-OMe



Following General Procedure A, the title compound was obtained as a white solid (382 mg, 89% yield).

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.18 (dd, *J* = 8.5, 5.6 Hz, 2H), 6.99 (m, 2H), 6.60 (br. s, 1H), 5.03 (br. s, 1H), 4.61 (ddd, *J* = 7.1, 6.4, 5.0 Hz, 1H), 4.31 (m, 1H), 3.71 (s, 3H), 3.07 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.98 (dd, *J* = 14.0, 7.1 Hz, 1H), 2.43 (app. t, 2H), 2.19–2.00 (multiple peaks, 4H), 1.92 (m, 1H), 1.39 (s, 9H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ 172.2, 171.2, 162.3 (d, *J* = 244.2 Hz), 155.7, 133.0 (d, *J* = 3.2 Hz), 131.4 (d, *J* = 7.9 Hz), 115.6 (d, *J* = 21.3 Hz), 80.5, 56.0, 52.8, 51.9, 37.5, 31.9, 30.1, 28.4, 15.5.

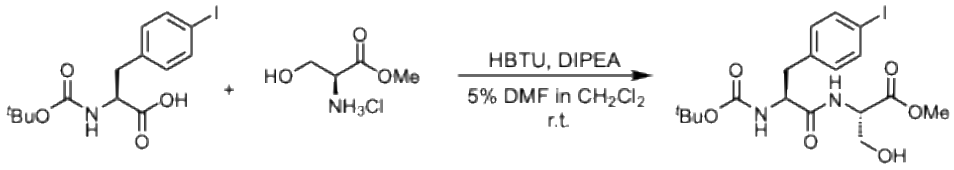
^{19}F NMR (564 MHz, $CDCl_3$): δ –116.91 (app. s, 1F).

HRMS (ESI) (m/z): [M+H] ($C_{20}H_{30}FN_2O_5S^+$) calc. 429.1859; observed 429.1855.

R_f = 0.55 in 50% EtOAc in hexanes.

Mp = 96-97 °C.

Synthesis of Boc-Phe(4-I)-Ser-OMe



Following General Procedure B, the title compound was obtained as a white solid (1.78 g, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (app. t, 2H), 7.08 (br. s, 1H), 6.96 (d, *J* = 6.6 Hz, 2H), 5.20 (m, 1H), 4.60 (m, 1H), 4.36 (m, 1H), 3.90 (s, 3H), 3.81-3.72 (multiple peaks, 3H), 3.07 (dd, *J* = 14.0, 6.2 Hz, 1H), 2.94 (m, 1H), 1.38 (app. d, 9H).

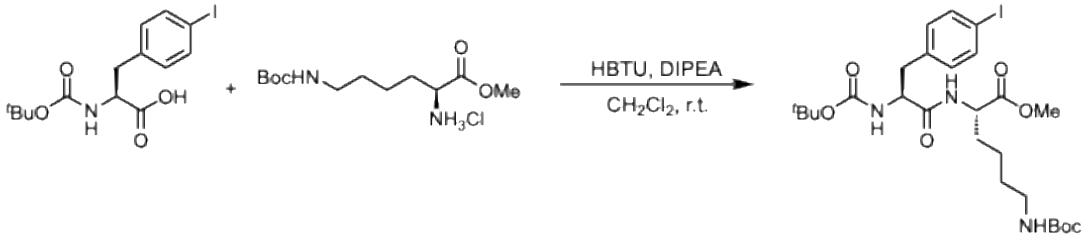
^{13}C NMR (126 MHz, $CDCl_3$): δ 171.6, 170.7, 155.9, 137.8, 136.3, 131.5, 92.5, 80.8, 62.9, 55.8, 54.9, 52.95, 37.8, 28.4.

HRMS (ESI) (m/z): [M+H] ($C_{18}H_{26}IN_2O_6^+$) calc. 493.0836; observed 493.0828.

R_f = 0.5 in 5% MeOH in dichloromethane.

Mp = 131-133 °C.

Synthesis of Boc-Phe(4-I)-Lys(Boc)-OMe



Following General Procedure A, the title compound was obtained as a white solid (2.83 g, 88% yield).

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.62 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.1 Hz, 2H), 6.52 (br. s, 1H), 5.11 (br. s, 1H), 4.71 (br. s, 1H), 4.49 (app. q, 1H), 4.32 (m, 1H), 3.70 (s, 3H), 3.10–3.01 (multiple peaks, 3H), 2.93 (dd, *J* = 14.0, 7.3 Hz, 1H), 1.80 (m, 1H), 1.65 (m, 1H), 1.51-1.36 (multiple peaks, 20H), 1.34-1.20 (multiple peaks, 2H).

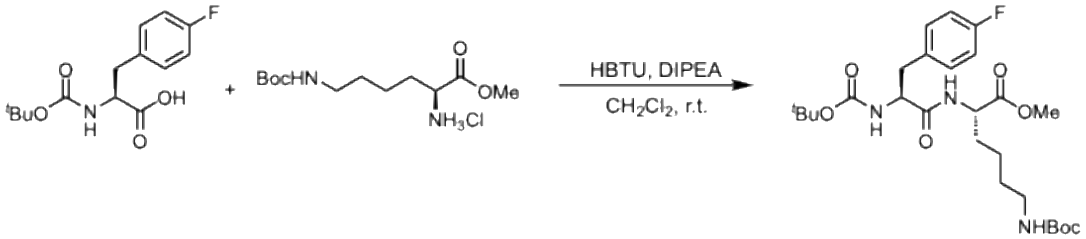
^{13}C NMR (126 MHz, CD_2Cl_2): δ 172.7, 171.2, 156.3, 155.8, 137.9, 137.1, 131.9, 92.4, 80.5, 79.1, 55.7, 52.7, 52.4, 40.5, 37.9, 32.2, 29.8, 28.6, 28.4, 22.7.

HRMS (ESI) (m/z): [M+H] ($C_{26}H_{41}IN_3O_4^+$) calc. 634.1989; observed 634.1983.

R_f = 0.4 in 50% EtOAc in hexanes.

Mp = 145-146 ºC.

Synthesis of Boc-Phe(4-F)-Lys(Boc)-OMe



Following General Procedure A, the title compound was obtained as a white solid (458 mg, 87% yield).

^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.20 (dd, *J* = 8.5, 5.6 Hz, 2H), 6.99 (dd, *J* = 9.9, 7.5 Hz, 2H), 6.76 (br. s, 1H), 5.29 (br. s, 1H), 4.90 (br. s, 1H), 4.51 (app. q, 1H), 4.39 (m, 1H), 3.70 (s, 3H), 3.09 (m, 1H), 2.95(dd, *J* = 14.0, 7.6 Hz, 1H) 1.81 (m, 1H), 1.66 (m, 1H), 1.54-1.35 (multiple peaks, 20H), 1.33-1.19 (multiple peaks, 2H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ 172.7, 171.5, 162.3 (d, *J* = 244.1 Hz), 156.3, 155.9, 133.2 (d, *J* = 3.2 Hz), 131.4 (d, *J* = 7.9 Hz), 115.5 (d, *J* = 21.2 Hz), 80.4, 79.1, 56.0, 52.6, 52.5, 40.5, 37.7, 32.3, 29.8, 28.6, 28.4.

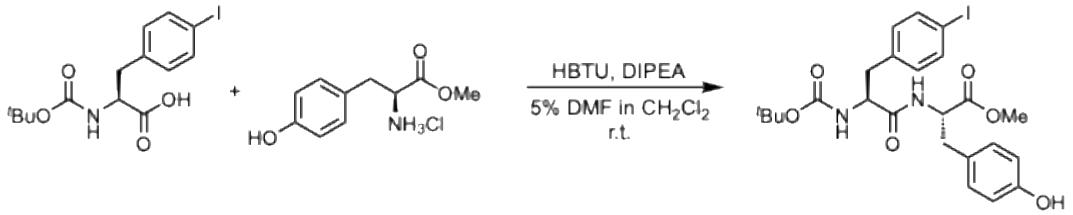
^{19}F NMR (564 MHz, $CDCl_3$): δ –117.05 (app. s, 1F).

HRMS (ESI) (m/z): [M+H] ($C_{26}H_{41}FN_3O_4^+$) calc. 526.2929; observed 526.2930.

R_f = 0.4 in 50% EtOAc in hexanes.

Mp = 122-124 ºC.

Synthesis of Boc-Phe(4-I)-Tyr-OMe



Following General Procedure B, the title compound was obtained as a white solid (2.39 g, 84% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 7.9 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 6.36 (d, *J* = 7.8 Hz, 1H), 5.87 (br. s, 1H), 5.01 (br. s, 1H), 4.74 (app. q, 1H), 4.30 (m, 1H), 3.70 (s, 3H), 3.17-2.81 (multiple peaks, 4H), 1.41 (s, 9H).

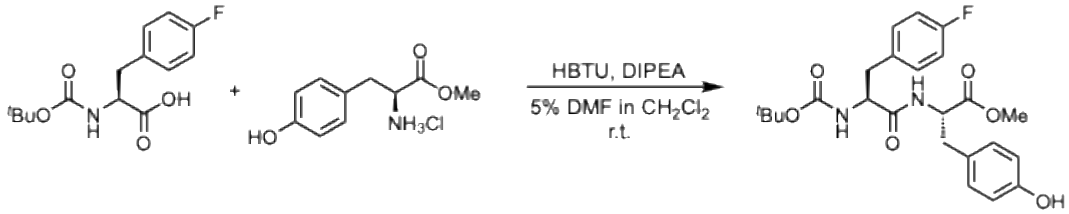
^{13}C NMR (126 MHz, DMSO-d_6): δ 171.9, 171.6, 156.1, 155.2, 137.9, 136.8, 131.8, 130.1, 126.9, 115.1, 92.1, 78.2, 55.4, 53.9, 51.9, 36.0, 28.1, 22.2, 14.0.

HRMS (ESI) (m/z): [M+H] ($C_{24}H_{30}IN_2O_6^+$) calc. 569.1149; observed 569.1138.

R_f = 0.4 in 50% EtOAc in hexanes.

Mp = 174-175 ºC.

Synthesis of Boc-Phe(4-F)-Tyr-OMe



Following General Procedure B, the title compound was obtained as a white solid (378 mg, 82% yield).

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.23 (s, 1H), 8.23 (d, J = 7.5 Hz, 1H), 7.24 (app. t, 2H), 7.07 (app. t, 2H), 7.00 (d, J = 7.9 Hz, 2H), 6.87 (d, J = 8.9 Hz, 1H), 6.67 (d, J = 8.3 Hz, 2H), 4.40 (m, 1H), 4.14 (m, 1H), 3.57 (s, 3H), 2.95-2.80 (multiple peaks, 3H), 2.66 (dd, J = 13.7, 10.7 Hz, 1H), 1.28 (s, 9H).

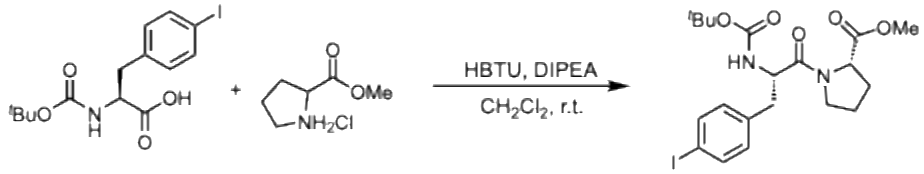
^{13}C NMR (126 MHz, $CDCl_3$): δ 171.6, 171.0, 162.1 (d, J = 245.1 Hz), 155.7, 155.4, 132.2 (d, J = 3.3 Hz), 131.0 (d, J = 8.0 Hz), 130.5, 127.1, 115.7, 115.5 (d, J = 21.2 Hz), 80.7, 55.8, 53.5, 52.5, 37.7, 37.3, 28.4.

^{19}F NMR (564 MHz, CD_2Cl_2): δ –116.84 (app. s, 1F).

HRMS (ESI) (m/z): [M+H] ($C_{24}H_{30}FN_2O_6^+$) calc. 461.2088; observed 461.2083.

R_f = 0.4 in 50% EtOAc in hexanes.

Synthesis of Boc-Phe(4-I)-Pro-OMe



Following General Procedure A, the title compound was obtained as a white solid (2.26 g, 90% yield).

^{1}H NMR(500 MHz, DMSO-d_6): Major rotamer (~83%): δ 7.61 (d, J = 7.9 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 5.22 (d, J = 8.8 Hz, 1H), 4.62 (app. q, 1H), 4.50 (dd, J = 8.4, 3.9 Hz, 1H), 3.74 (s, 3H), 3.26 (m, 1H), 3.04 (dd, J = 13.9, 6.9 Hz, 1H), 2.85 (dd, J = 13.9, 6.0 Hz, 1H), 2.19 (m, 1H), 2.02–1.73 (multiple peaks, 3H), 1.38 (s, 9H).

^{1}H NMR (500 MHz, DMSO-d_6): Minor rotamer (~17%): δ 6.97 (d, J = 7.9 Hz, 2H), 5.32 (d, J = 8.9 Hz, 1H), 4.39 (m, 1H), 3.70 (s, 3H), 3.33 (m, 1H), 2.95 (dd, J = 12.9, 5.4 Hz, 1H), 1.66 (m, 1H), 1.41 (s, 9H). Remaining minor peaks overlap with the major rotamer.

^{13}C NMR (126 MHz, $CDCl_3$): Major rotamer: δ 172.4, 170.4, 155.2, 137.5, 136.0, 132.0, 92.4, 79.9, 59.0, 53.0, 52.4, 47.0, 38.6, 29.1, 28.4, 25.0.

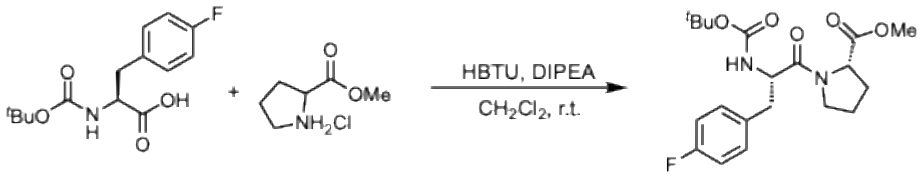
^{13}C NMR (126 MHz, $CDCl_3$): Minor rotamer: 171.9, 170.5, 154.8, 137.7, 136.3, 131.6, 92.35, 79.8, 59.2, 53.6, 46.2, 40.5, 30.9, 22.3. Remaining minor peaks overlap with the major rotamer.

HRMS (ESI) (m/z): [M+H] ($C_{20}H_{28}IN_2O_5^+$) calc. 503.1043; observed 503.1036.

R_f = 0.37 in 50% EtOAc in hexanes.

Mp = 66-69 ºC.

Synthesis of Boc-Phe(4-F)-Pro-OMe



Following General Procedure A, the title compound was obtained as a clear oil (356 mg, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$): Major rotamer: δ 7.24 (dd, *J* = 8.4, 5.6 Hz, 2H), 6.98 (app. t, 2H), 5.25 (d, *J* = 8.8 Hz, 1H), 4.62 (ddd, *J* = 8.8, 6.6, 6.6 Hz, 1H), 4.49 (dd, *J* = 8.4, 3.9 Hz, 1H), 3.74 (s, 3H), 3.60 (m, 1H), 3.21 (m, 1H), 3.07 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.89 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.01–1.86 (multiple peaks, 2H), 1.65 (m, 1H), 1.38 (s, 9H).

^{1}H NMR (500 MHz, $CDCl_3$): Minor rotamer: δ 7.18 (dd, *J* = 8.3, 5.4 Hz, 2H), 5.34 (d, *J* = 8.8 Hz, 1H), 4.40 (m, 1H), 3.70 (s, 3H), 3.66 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.33 (m, 1H), 2.99 (dd, *J* = 13.0, 5.3 Hz, 1H), 2.23 – 2.12 (multiple peaks, 2H), 1.72 (m, 1H), 1.41 (s, 9H). Remaining minor peaks overlap with the major rotamer.

^{13}C NMR (126 MHz, $CDCl_3$): Major rotamer: δ 172.4, 170.6, 162.1 (d, *J* = 244.6 Hz), 155.3, 132.1, 131.5 (d, *J* = 7.9 Hz), 115.3 (d, *J* = 21.3 Hz), 79.9, 59.0, 53.3, 52.4, 47.0, 38.4, 29.2, 28.4, 25.0.

^{13}C NMR (126 MHz, $CDCl_3$): Minor rotamer: δ 131.1 (d, *J* = 8.0 Hz), 115.5, 59.2, 52.9, 46.2, 40.2, 30.9, 29.8, 22.4. Remaining minor peaks overlap with the major rotamer.

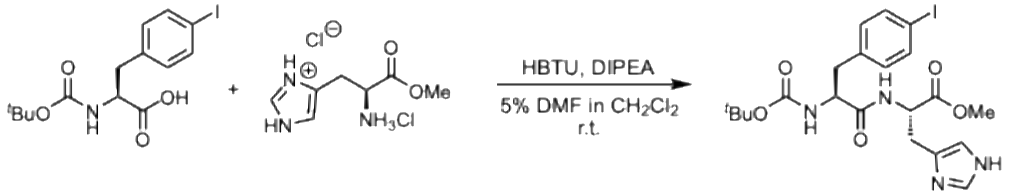
^{19}F NMR (564 MHz, $CDCl_3$): Major rotamer: δ –117.32 (tt, *J* = 9.1, 5.3 Hz).

^{19}F NMR (564 MHz, $CDCl_3$): Minor rotamer: δ –116.71 (tt, *J* = 9.0, 5.5 Hz).

HRMS (ESI) (m/z): [M+H] ($C_{20}H_{28}FN_2O_5^+$) calc. 395.1982; observed 395.1977.

R_f = 0.4 in 50% EtOAc in hexanes.

Synthesis of Boc-Phe(4-I)-His-OMe



Following General Procedure B, the title compound was obtained as a white solid (1.55 g, 57% yield).

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.79 (broad singlet, 1H), 8.33 (d, J = 7.4 Hz, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.51 (s, 1H), 7.03 (d, J = 7.9 Hz, 2H), 6.90 (d, J = 8.7 Hz, 1H), 6.80 (s, 1H), 4.46 (m, 1H), 4.11 (ddd, J = 10.2, 10.2, 4.2 Hz, 1H), 3.55 (s, 3H), 2.95-2.83 (multiple peaks, 3H), 2.61 (dd, J = 13.8, 10.5 Hz, 1H), 1.26 (s, 9H).

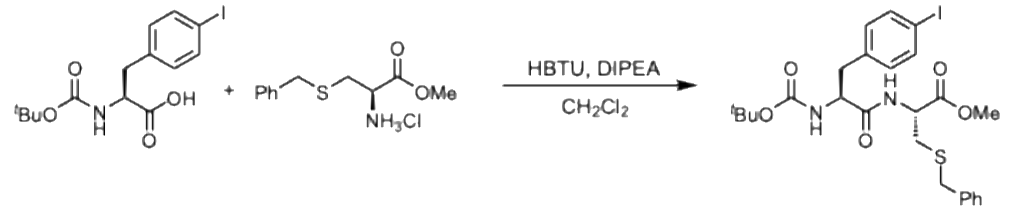
^{13}C NMR (126 MHz, DMSO-d_6): δ 186.18, 185.94, 169.56, 152.32, 151.06, 149.24, 146.06, 106.40, 92.47, 69.70, 66.77, 66.19, 51.15, 42.45.

HRMS (ESI) (m/z): [M+H] ($C_{21}H_{28}IN_4O_5^+$) calc. 543.1104; observed 543.1100.

R_f = 0.3 in 5% MeOH in dichloromethane.

Mp = 94-96 °C.

Synthesis of Boc-Phe(4-I)-Cys(Bzl)-OMe



Following General Procedure A, the title compound was obtained as a white solid (2.42 g, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 8.2 Hz, 2H), 7.32-7.20 (multiple peaks, 5H), 6.89 (d, J = 7.9 Hz, 2H), 6.46 (d, J = 7.8 Hz, 1H), 4.86 (broad singlet, 1H), 4.64 (apparent quartet, 1H), 4.27 (broad singlet, 1H), 3.66 (s, 3H), 3.60 (s, 2H), 3.01 (m, 2H), 2.83 (ddd, J = 32.85, 13.86, 5.12 Hz, 2H), 1.34 (s, 9H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 170.74, 170.66, 155.23, 137.71, 137.60, 136.10, 131.44, 128.95, 128.65, 127.33, 92.48, 80.45, 55.36, 52.75, 51.66, 37.79, 36.56, 33.30, 28.27.

HRMS (ESI) (m/z): [M+H] ($C_{25}H_{32}IN_2O_5S^+$) calc. 599.1077; observed 599.1071.

R_f = 0.5 in 20% EtOAc in hexanes.

Mp = 148-150 °C.

3. Borylation General Procedures

Note: Air-free storage of XPhos was crucial to achieving excellent borylation yields with aryl chlorides. XPhos must be stored in a glovebox to prevent long-term atmosphere exposure as it was observed that this exposure shuts down successful borylation-CMRF of aryl chlorides. This was not observed with aryl iodides or bromides. With these latter substrates, XPhos could be stored on the benchtop.

3.1 General Procedure C: Palladium-Catalyzed Method @ 1% $Pd(OAc)_2$

A 10 mL vial equipped with a stir bar was charged with aryl iodide or bromide (125 μmol, 1 equiv), potassium phosphate tribasic (275 μmol, 2.2 equiv), B_2pin_2 (150 μmol, 1.2 equiv), palladium acetate (1.25 μmol, 1 mol %), XPhos (3.75 μmol, 3 mol %), and isopropyl acetate (IPAC, 5.2 L/mol). The vial was sealed with a Teflon-lined screw cap and wrapped with electrical tape, and the reaction was stirred on a hot plate preset at 85 ºC for 16 h. The reaction was then allowed to cool to room temperature. IPAC (0.25 mL) was added, and the reaction was filtered using a syringe filter into a new vial. The original 10 mL vial was rinsed once with IPAC (0.15 mL), and this mixture was filtered. The combined IPAC filtrate was carried on to the radiofluorination procedure without further purification.

3.2 General Procedure D: Palladium-Catalyzed Method @ 2% $Pd(OAc)_2$

A 10 mL vial equipped with a stir bar was charged with aryl iodide (125 μmol, 1 equiv), potassium phosphate tribasic (275 μmol, 2.2 equiv), B_2pin_2 (150 μmol, 1.2 equiv), palladium acetate (2.5 μmol, 2 mol %), XPhos (7.5 μmol, 15 mol %), and isopropyl acetate (IPAC, 5.2 L/mol). The vial was sealed with a Teflon-lined screw cap and wrapped with electrical tape, and the reaction was stirred on a hot plate preset at 85 ºC for 16 h. The reaction was then allowed to cool to room temperature. IPAC (0.25 mL) was added, and the reaction was filtered using a syringe filter into a new vial. The original 10 mL vial was rinsed once with IPAC (0.15 mL), and this mixture was filtered. The combined IPAC filtrate was carried on to the radiofluorination procedure without further purification.

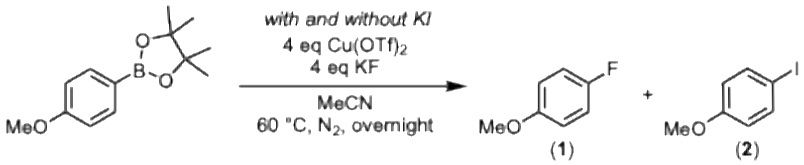
3.3 General Procedure E: Palladium-Catalyzed Method @ 5% $Pd(OAc)_2$

A 10 mL vial equipped with a stir bar was charged with aryl iodide or bromide (125 μmol, 1 equiv), potassium phosphate tribasic (275 μmol, 2.2 equiv), B_2pin_2 (150 μmol, 1.2 equiv), palladium acetate (6.25 μmol, 5 mol %), XPhos (18.75 μmol, 15 mol % or 12.5 μmol, 10.0 mol %), and isopropyl acetate (IPAC, 5.2 L/mol). The vial was sealed with a Teflon-lined screw cap and wrapped with electrical tape, and the reaction was stirred on a hot plate preset at 85 ºC for 16 h. The reaction was then allowed to cool to room temperature. IPAC (0.25 mL) was added, and the reaction was filtered using a syringe filter into a new vial. The original 10 mL vial was rinsed once with IPAC (0.15 mL), and this mixture was filtered. The combined IPAC filtrate was carried on to the radiofluorination procedure without further purification.

3.4 General Procedure F: Palladium-Catalyzed Method @ 2% $Pd_2(dba)_3$ for Aryl Chlorides

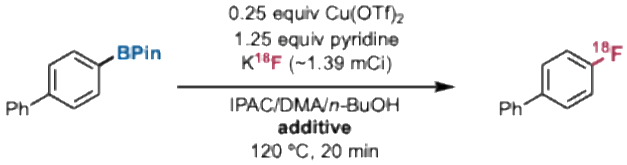
A 10 mL vial equipped with a stir bar was charged with aryl chloride (125 μmol, 1 equiv), potassium phosphate tribasic (375 μmol, 3 equiv), B_2pin_2 (375 μmol, 3 equiv), Pd_2dba_3 (5 μmol, 2 mol %), XPhos (10 μmol, 8 mol %), and isopropyl acetate (IPAC, 5.2 L/mol). The vial was sealed with a Teflon-lined screw cap and wrapped with electrical tape, and the reaction was stirred on a hot plate preset at 110 ºC for 16 h. The reaction was then allowed to cool to room temperature. IPAC (0.25 mL) was added, and the reaction was filtered using a syringe filter into a new vial. The original 10 mL vial was rinsed once with IPAC (0.15 mL), and this mixture was filtered. The combined IPAC filtrate was carried on to the radiofluorination procedure without further purification.

4. Screening



Entry	Deviation from Conditions	Yield 1 (%)
1	none	33
2	1 equiv KI	92
3	1 equiv of KI + 1 equiv AgOTf	23

Table S1. Screens to determine impact of KI on CMRF



Additive	Run 1 (RCC)	Run 2 (RCC)	Run 3 (RCC)	Run 4 (RCC)	Avg ± Std. Dev
none	97	98	96	97	97 ± 1
$Pd(OAc)_2$	54	55	95	87	73 ± 21
$Cu(OAc)_2$ instead of $Cu(OTf)_2$	0	0	---	---	0
XPhos	64	56	86	95	75 ± 18
B_2Pin_2	68	72	87	85	78 ± 9
K_3PO_4 (no overnight stir)	51	40	87	83	65 ± 23
K_3PO_4 (overnight stir @ 85°C)	0	0	0	0	0
KOAC	0	0	0	0	0
KI	0	0	0	0	0
KEH	0	0	0	0	0

Table S2. Screen to assess impact of each component of Pd-catalyzed borylation on the yield and reproducibility of CMRF

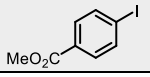
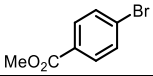
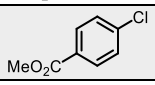
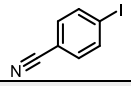
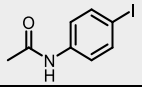
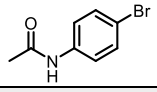
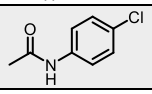
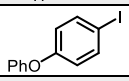
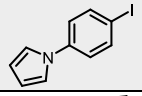
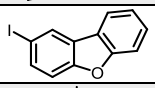
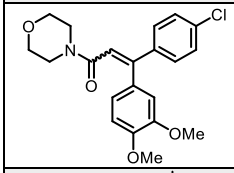
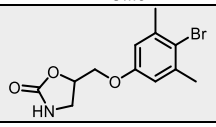
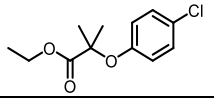
Substrates	Borylation Yield (%)	Radiochemical Yield (%)
	53 ± 4	83 ± 2
	46 ± 1	94 ± 6
	51 ± 5	79 ± 4
	55 ± 3	65 ± 6
	54 ± 1	88 ± 3
	61 ± 9	85 ± 1
	58 ± 11	86 ± 5
	58 ± 4	76 ± 2
	59 ± 0.4	75 ± 2
	63 ± 2	74 ± 1
	22 ± 3	33 ± 8
	35 ± 7	94 ± 2
	38 ± 5	86 ± 2
	65 ± 4	72 ± 7

Table S3. Examples of substrates with modest borylation yield but high RCC in subsequent CMRF

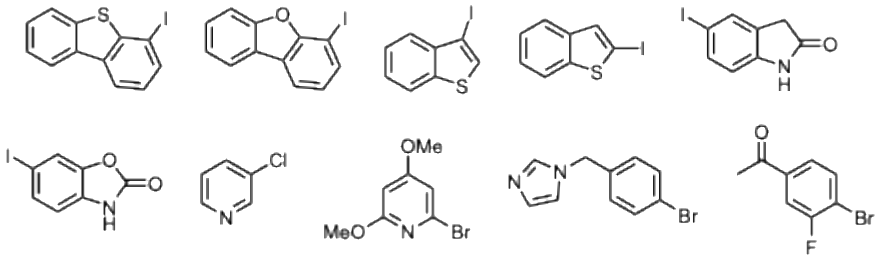


Figure S1. Substrates that afforded <1% RCC in sequential borylation-radiofluorination

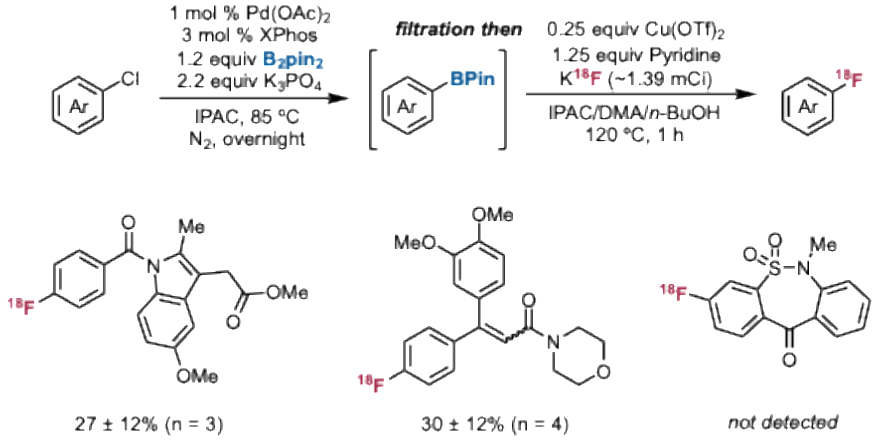


Figure S2. Bioactive aryl chlorides @ 1% $Pd(OAc)_2$ loading

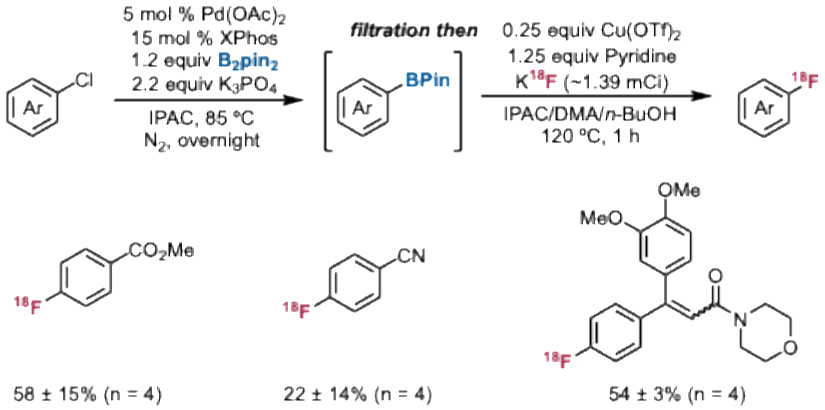


Figure S3. Bioactive aryl chlorides @ 5% $Pd(OAc)_2$ loading (XPhos stored on benchtop)

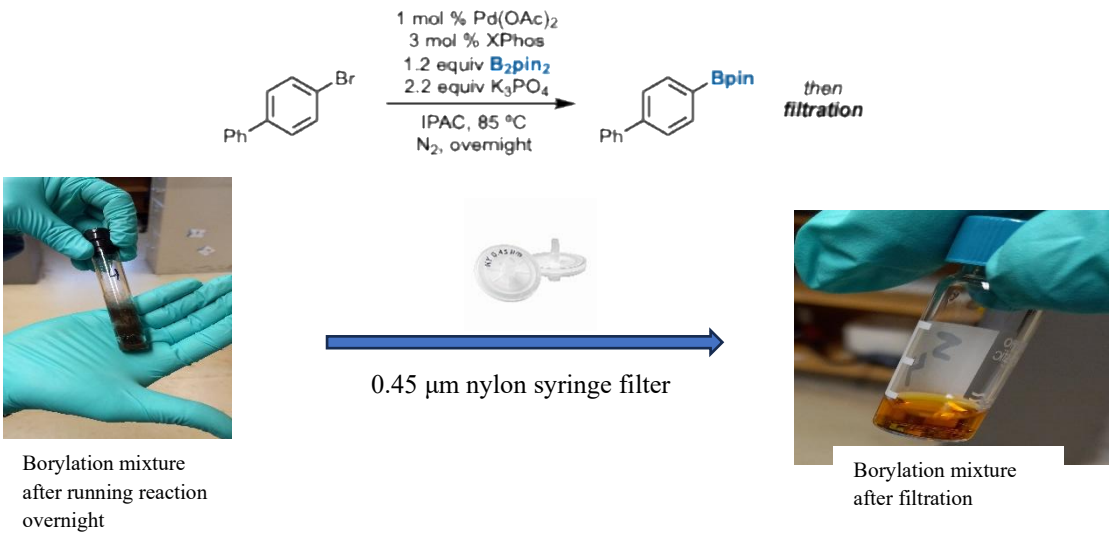


Figure S4. Photograph of telescopic borylation-CMRF of aryl halides (*Note: color of reaction varied with substrate)*

5. Radiochemistry General Details

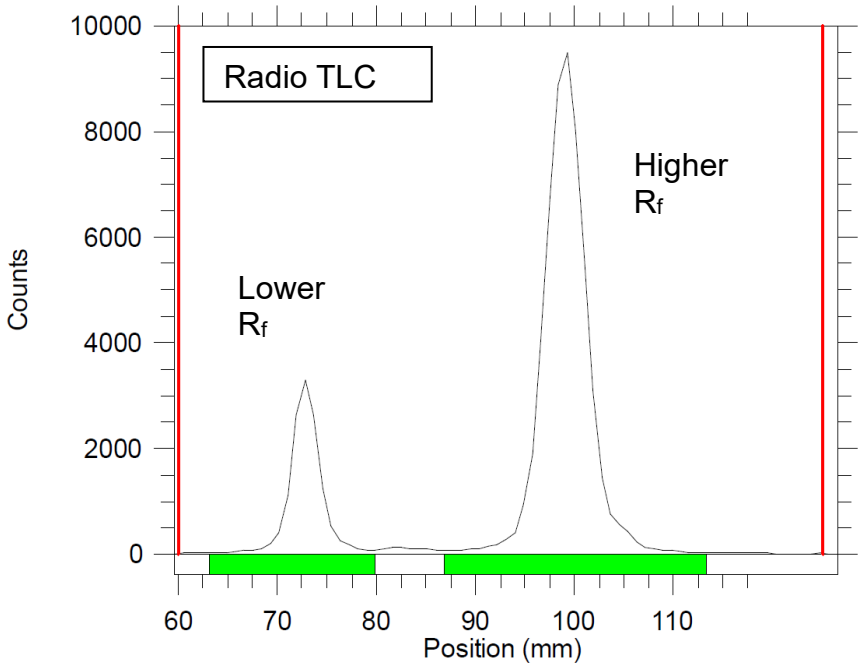
5.1 Radiochemistry Terms

Activity = the amount of radioactivity. In our research article and Supporting Information, Bq are used as the SI units, while the corresponding values in Ci and mCi are given in parentheses.

Radiochemical conversion (RCC) = % conversion of [^{18}F]KF to [^{18}F]F-labeled organic product as determined generally by radio-TLC or radio-HPLC (as specified).

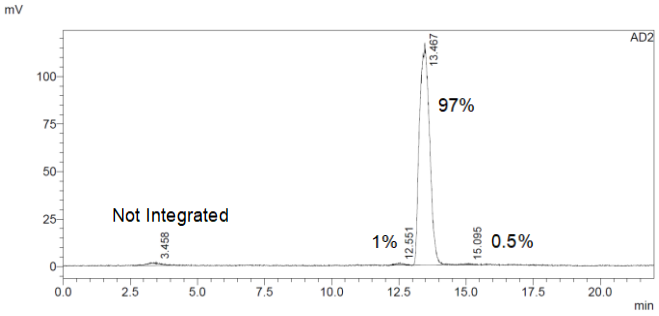
RCC (by rTLC) = RCC measured by radio-TLC (rTLC). It is defined as the amount of radioactivity in the higher R_f spot (organic product) relative to the radioactivity of the crude reaction.

An example with an RCC of 80% is shown below.



RCP (by rHPLC) = RCC determined by radio-HPLC (rHPLC). It is defined as the amount of radioactivity in the target product relative to the total radioactivity in the reaction. However, in this study, for the reactions for which rTLC analysis was used, we did not integrate HPLC peaks estimated to be ionic (^{18}F) (gamma peaks eluting before the solvent front with a high % organic mobile phase).

When rTLC is performed, RCC (by rHPLC) =



Radiochemical yield (RCY) = the yield of [^{18}F]F-labeled organic product. There are two types of RCY (non-isolated and isolated)

Non-isolated RCY = Radiochemical yield for manual reactions. If rTLC is used, non-isolated RCY is defined as RCC (by rTLC) multiplied by RCP (by rHPLC). If rTLC is not used, non-isolated RCY is equal to RCC (by rHPLC).

Isolated RCY is calculated after the final product is isolated by preparatory HPLC in a synthesis module. Decay corrected.

$$RCY = \frac{Isolated\ activity\ (mCi)}{Starting\ activity\ (mCi)} \times 100$$

Starting activity = the maximum activity [^{18}F]KF used in a radiosynthesis. The maximum activity reading was taken from the radiation detector in the hot cell.

Isolated activity = the activity of purified radiolabeled product.

Decay correction = the calculation used to compare activities of multiple compounds/aliquots that are measured at different time points.

$$A_T = A_0 \times \left(\frac{1}{2}\right)^{T/20.38} \leftrightarrow A_0 = \frac{A_T}{(\frac{1}{2})^{T/20.38}}$$

A_T = The radioactivity before decay correction (mCi)

A_0 = The radioactivity after decay correction (mCi)

T = difference (minutes) between two time points

Molar activity (A_m) = the Activity (Ci) of the radiolabeled product (μmol) of compound.

Beam length = Duration of cyclotron irradiation to generate [^{18}F]KF

6. Manual Radiofluorination Reactions

6.1 Generation of [^{18}F]KF

[^{18}F]KF was produced by cyclotron as described in the literature[21] and then trapped on a QMA Sep-Pak filter and eluted into the reaction vessel using KOTf (10 mg) and minimal K_2CO_3 (50 µg) in H_2O (0.5 mL). The solution was dried azeotropically with MeCN (1 mL). After drying, dimethyl acetamide (3 mL) was added, and the resulting solution was used in radiochemical reactions.

6.2 General Manual Radiofluorination Setup

Prepared stock solution A: *The stock solution was prepared to contain enough for 75 radiofluorinaton reactions for radiofluorination. 20 µL of this stock solution contains 5 µmol $Cu(OTf)_2$ and 25 µmol pyridine.*

$Cu(OTf)_2$ (135.75 mg) was weighed into 4 mL vial, and the vial was removed from the glovebox. Pyridine (151.2 µL), and dimethyl acetamide (DMA) (1.5 mL) were added, and the mixture was sonicated to ensure complete dissolution.

A. 20 µmol scale radiofluorination. A 4 mL vial equipped with a stir bar was charged with 80 µL (20 µmol) of the borylation reaction taken directly from the filtrate of the respective aryl iodide substrate. 20 µL of **stock solution A** was added. Within 10 min, 100 µL of [^{18}F]KF was added (1.39 mCi = 51.4 MBq). The reaction was then heated at 120 ºC in a pre-heated hotplate for 20 min. The vial was allowed to cool (over 5 min) before proceeding with radiochemical analysis.

6.3 Analysis of Manual Radiofluorination Reactions

6.3.1 Radio TLC

AR-2000 TLC Scanner (Eckert & Ziegler) was used to scan TLC plates for RCC analyses

6.3.2 Analytical HPLC

Column A : Ultremex 5µ C18 250 x 4.6 mm 5 micron
P/N = 00G-0048-E0
Coulmn B: Luna C18(2), 150x4.6 mm, 5 micron
P/N = 00F-4252-E0
Column C: Kinetex evo C18 250x4.6' 5 micron
P/N = 00G-4633-E0
Column D: Kinetex PFP column; 250x4.6' 5 micron
P/N = 00G-4602-E0

HPLC Method 1
Flow rate: 1.0 mL/min
UV Detection: 254 nm
Solvent A = H_2O + 0.5% TFA; Solvent B = MeCN + 0.5% TFA
0-2 minutes: 5% B (hold)
2-15 minutes: 5 → 95% B
15-16 minutes: 95% B (hold)
16-16.5 minutes: 95 → 5% B
16.5-22 minutes: 5% B (hold)

HPLC Method 2 (Fastramp)
Flow rate: 1.0 mL/min
UV Detection: 254 nm
Solvent A = H_2O + 0.5% TFA; Solvent B = MeCN + 0.5% TFA
0-3 minutes: 5% B (hold)
3-10 minutes: 5 → 95% B
10-15 minutes: 95% B (hold)
15-16 minutes: 95 → 5% B

16-22 minutes: 5% B (hold)

HPLC Method 3
Flow rate: 2 mL/min
UV Detection: 254 nm
Solvent A = H_2O + 0.5% TFA; Solvent B = MeCN + 0.5% TFA
0-3 minutes: 5% MeCN
3-17 minutes: 5-95% MeCN
17-20 minutes: 95% MeCN
20-30 minutes: 5% MeCN

HPLC Method 4
Flow rate: 2 mL/min
UV Detection: 254 nm
Buffer = 30% MeCN, 10 mM NH_4HCO_3, pH 10
Isocratic Gradient

HPLC Method 5
Flow rate: 2 mL/min
UV Detection: 254 nm
Solvent A = H_2O + 10 mM NaOAc; Solvent B = MeCN
0-3 minutes: 5% MeCN
3-17 minutes: 5-95% MeCN
17-20 minutes: 95% MeCN
20-30 minutes: 5% MeCN

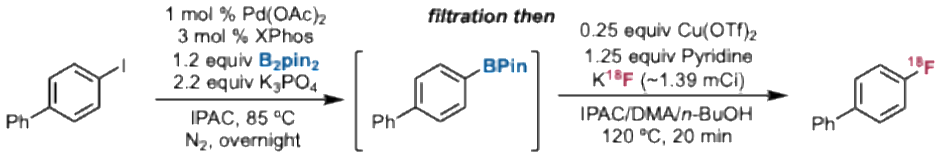
HPLC Method 6
Flow rate: 2 mL/min
UV Detection: 254 nm
Buffer = 40% MeCN, 40 mM NH_4HCO_3, pH 6.9
Isocratic Gradient

6.4 Manual Radiofluorination Yields and Analysis Spectra

The presence of the desired compound was confirmed by co-injection (the authentic standard and the crude solution were injected onto the radio-HPLC and parallel UV and RAD detectors were used). Co-injection overlap was based on the known offset due to distance in volume and flow rate between the UV and RAD detectors. Notably, the sample is detected by the UV detector first and then by the RAD detector, which impacts the retention times (difference ≤ 0.5 mins).

6.4.1 Palladium-Catalyzed Borylation Telescope of Aryl Iodides

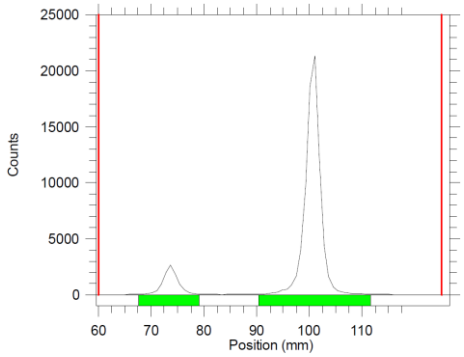
4-Iodobiphenyl (2a)



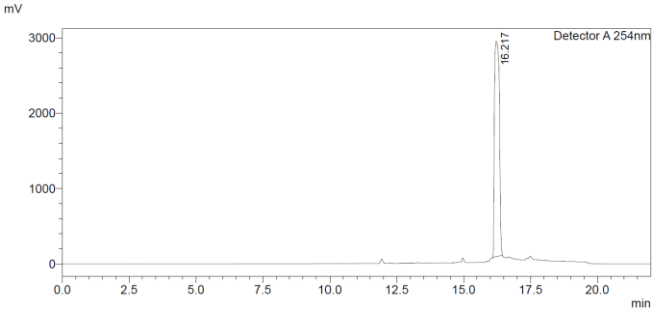
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 86 ± 7%

n	RCC [%]	RCP [%]	RCY [%]
1	74	99	74
2	92	99	92
3	89	99	89
4	89	99	89

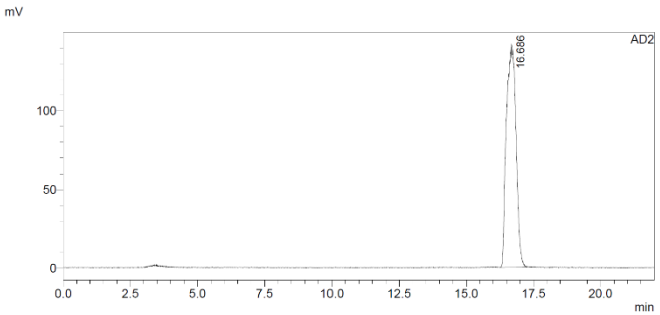
Radio TLC (Hex:EtOAc = 1:1)



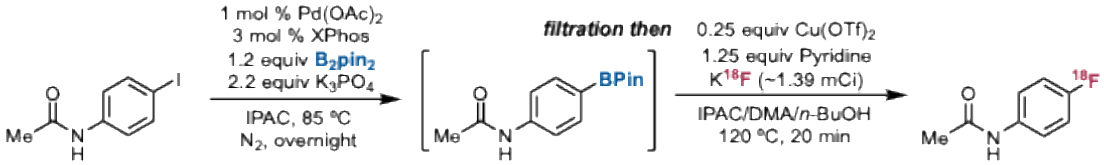
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



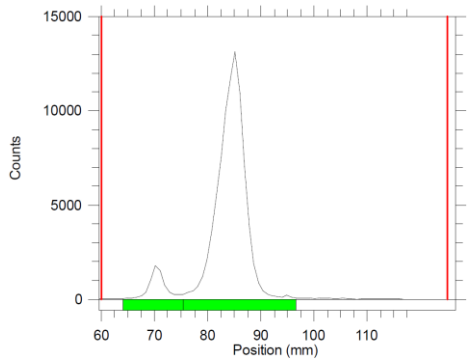
N-(4-Iodophenyl)acetamide (2b)



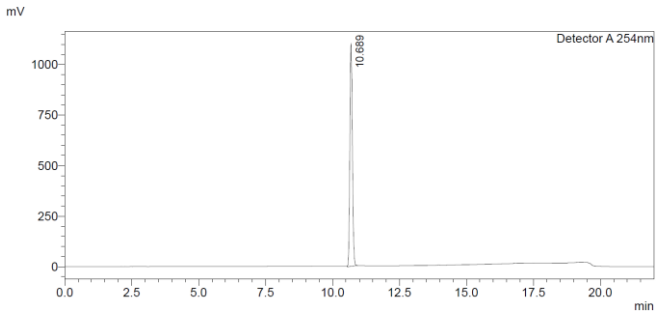
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 85 ± 6%

n	RCC [%]	RCP [%]	RCY [%]
1	92	99	92
2	86	99	86
3	86	99	86
4	77	98	76

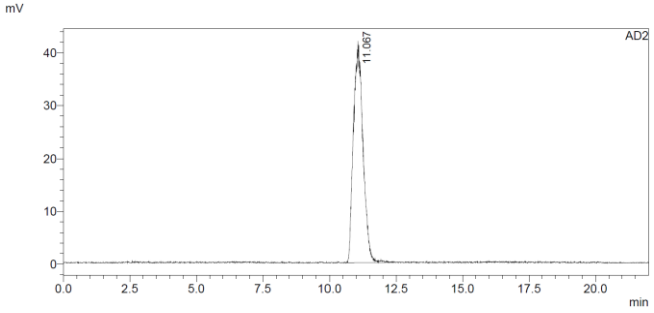
Radio TLC (Hex:EtOAc = 1:1)



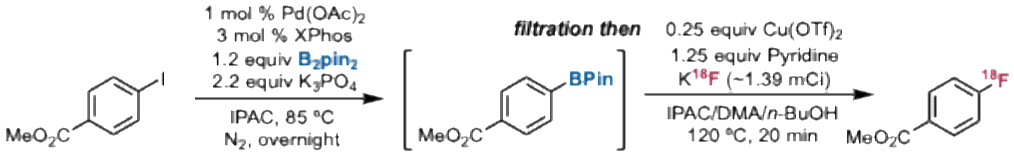
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



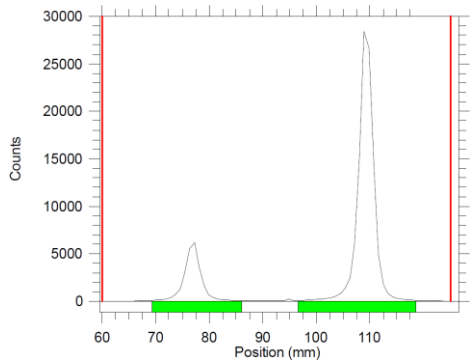
Methyl 4-iodobenzoate (2c)



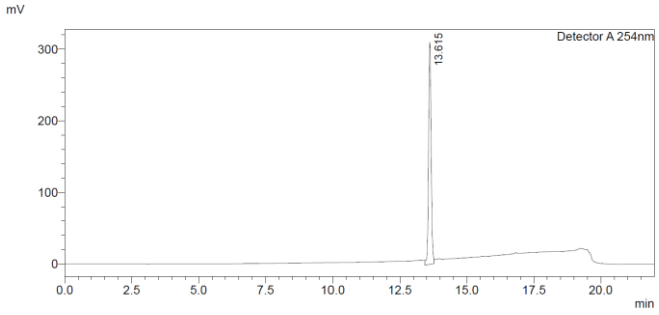
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 83 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	81	99	81
2	86	99	86
3	84	99	84
4	81	99	81

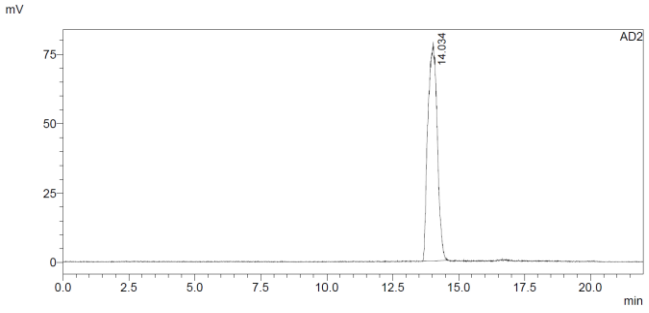
Radio TLC (Hex:EtOAc = 1:1)



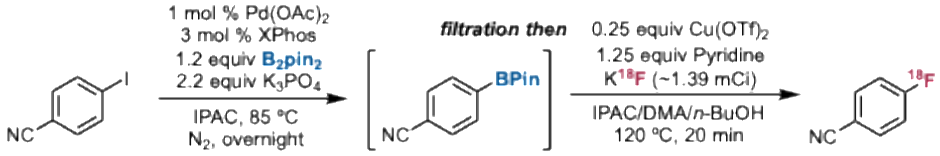
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



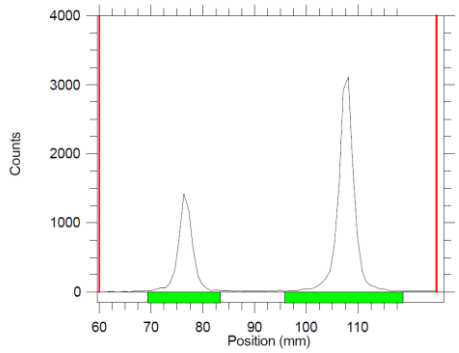
4-Iodobenzonitrile (2d)



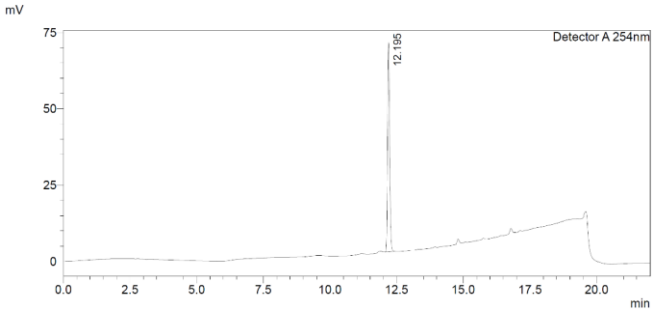
Borylation procedures: **Procedure 3.1.** Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Condition: **Method 1.** Non-isolated RCY = 66 ± 6%

n	RCC [%]	RCP [%]	RCY [%]
1	56	99	56
2	68	99	68
3	71	99	71
4	70	99	70

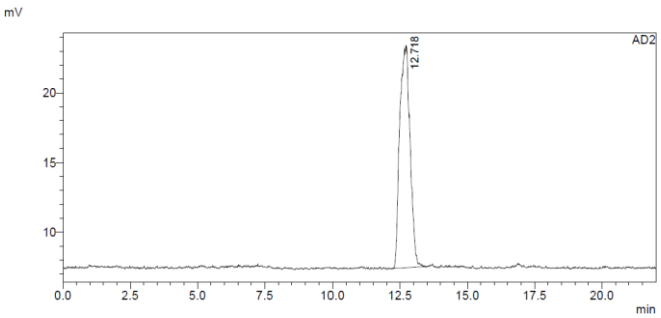
Radio TLC (Hex:EtOAc = 1:1)



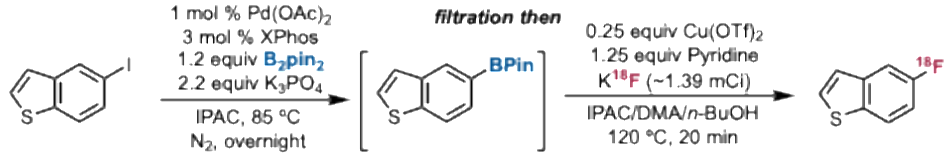
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



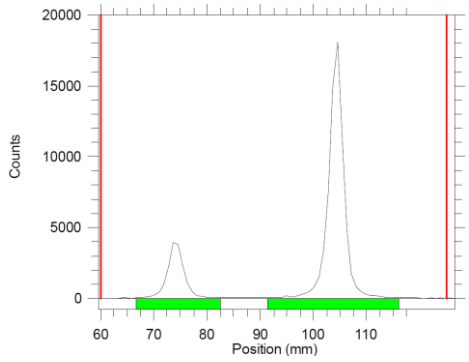
5-Iodobenzo[b]thiophene (2e)



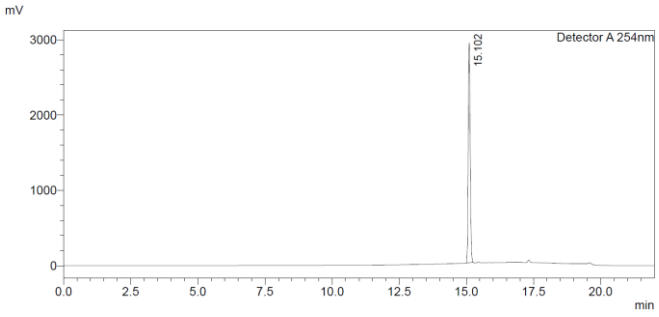
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 79 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	80	99	80
2	81	99	81
3	77	99	77
4	76	99	76

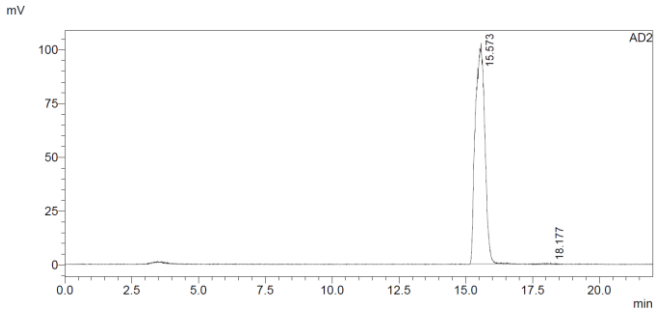
Radio TLC (Hex:EtOAc = 1:1)



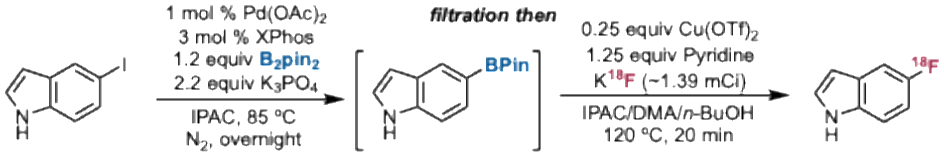
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



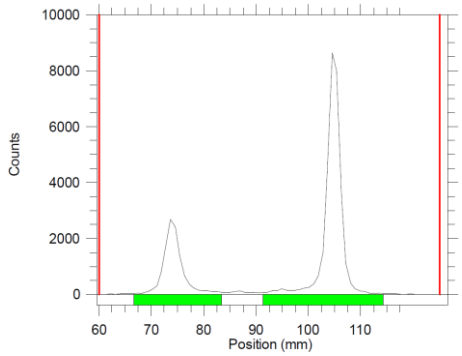
5-Iodo-1H-indole (2f)



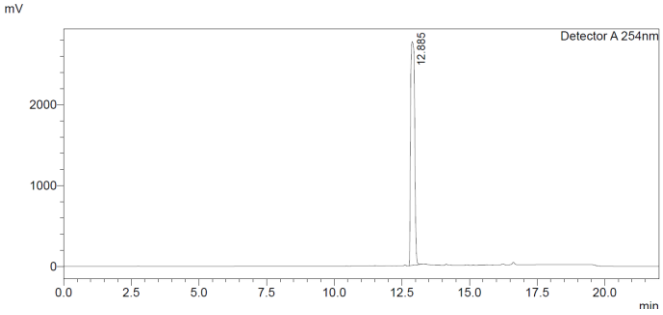
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 70 ± 3%

n	RCC [%]	RCP [%]	RCY [%]
1	73	92	67
2	72	98	70
3	78	97	76
4	75	90	68

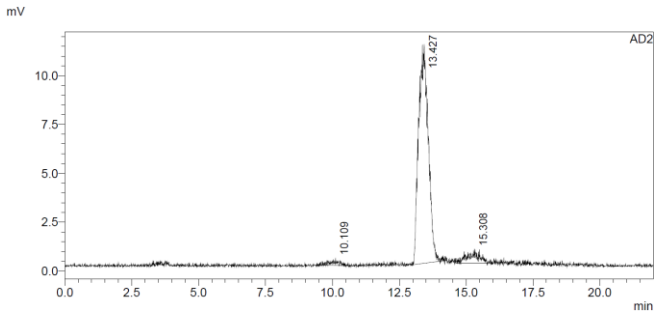
Radio TLC (Hex:EtOAc = 1:1)



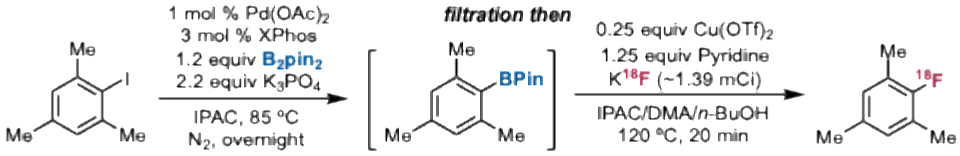
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



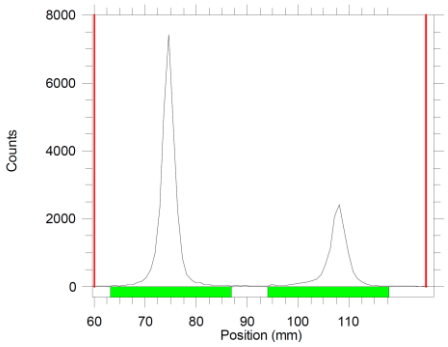
2-Iodo-1,3,5-trimethylbenzene (2g)



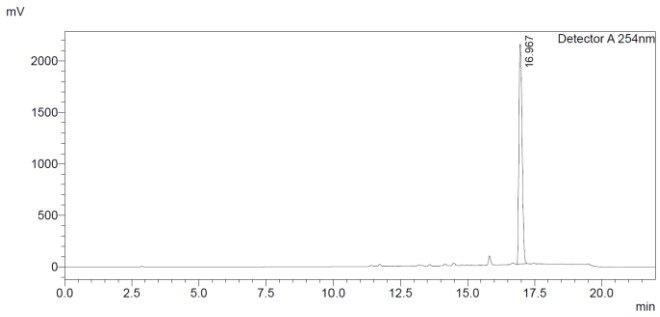
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 33 ± 7%

n	RCC [%]	RCP [%]	RCY [%]
1	45	99	45
2	31	99	31
3	29	98	28
4	28	97	27

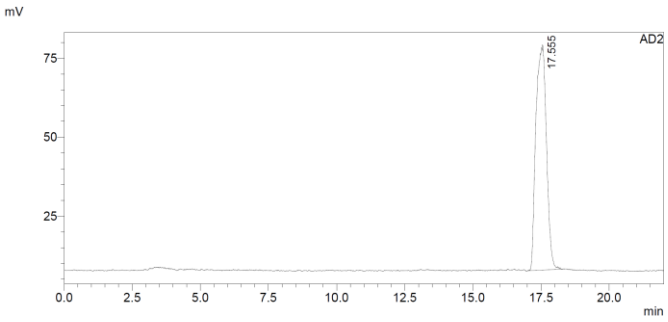
Radio TLC (Hex:EtOAc = 1:1)



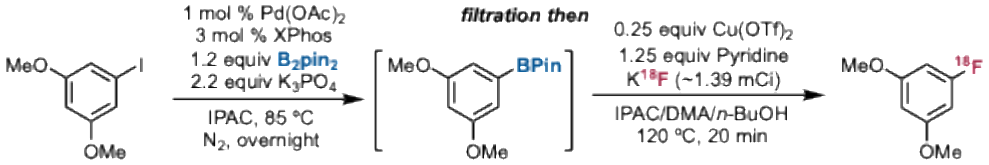
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



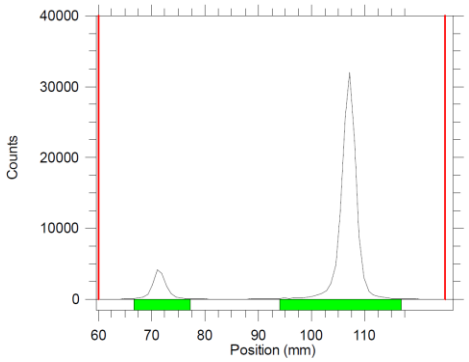
1-Iodo-3,5-dimethoxybenzene (2h)



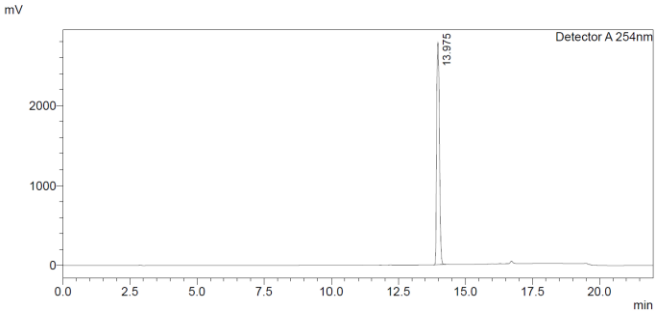
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**: HPLC Conditions: **Method 1**. Non-isolated RCY = 84 ± 4%

n	RCC [%]	RCP [%]	RCY [%]
1	89	99	89
2	83	99	83
3	85	99	85
4	78	99	77

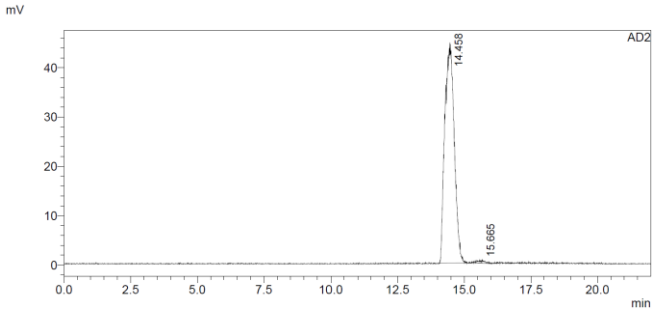
Radio TLC (Hex:EtOAc = 1:1)



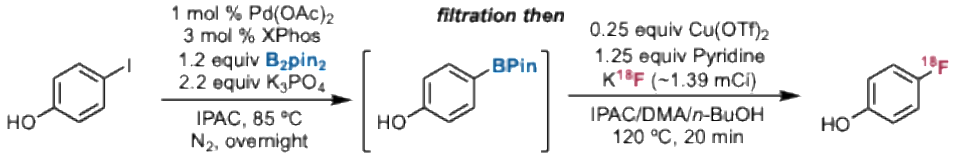
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



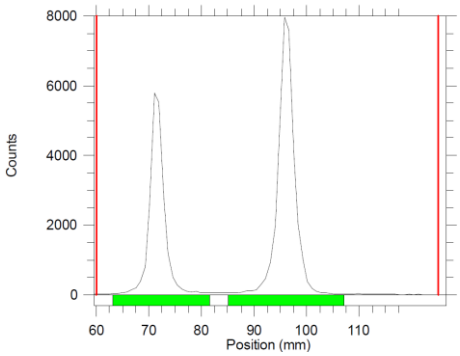
4-Iodophenol (2j)



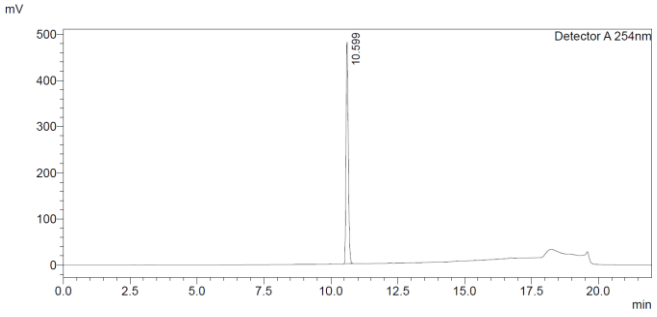
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Condition: **Method 1**. Non-isolated RCY = 59 ± 5%

n	RCC [%]	RCP [%]	RCY [%]
1	61	93	57
2	70	94	66
3	59	89	53
4	64	90	58

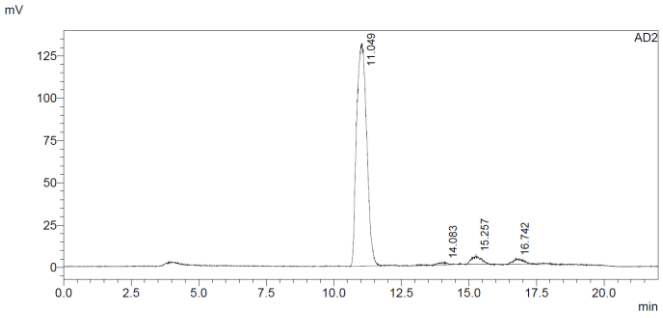
Radio TLC (Hex:EtOAc = 1:1)



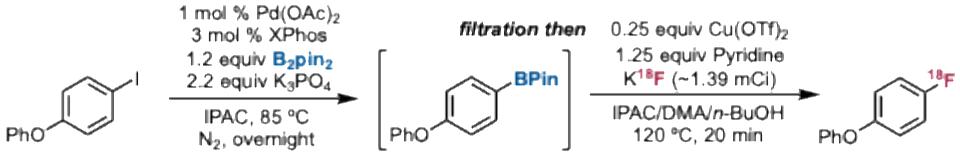
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



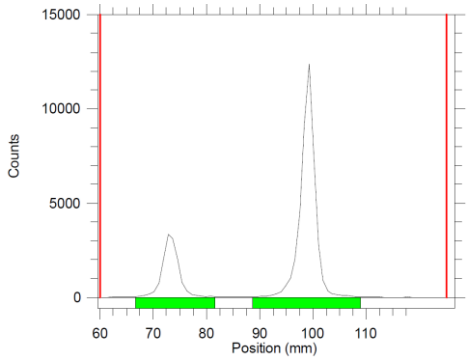
1-Iodo-4-phenoxybenzene (2k)



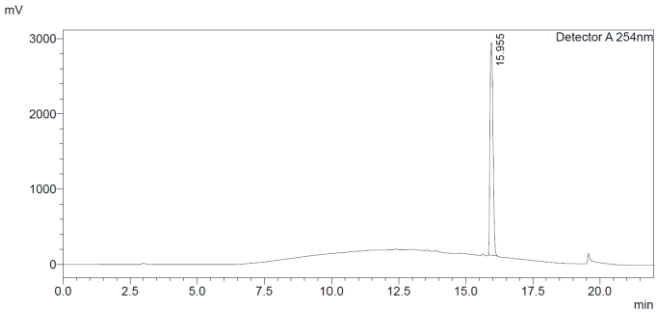
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 76 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	76	99	76
2	77	99	77
3	75	98	74

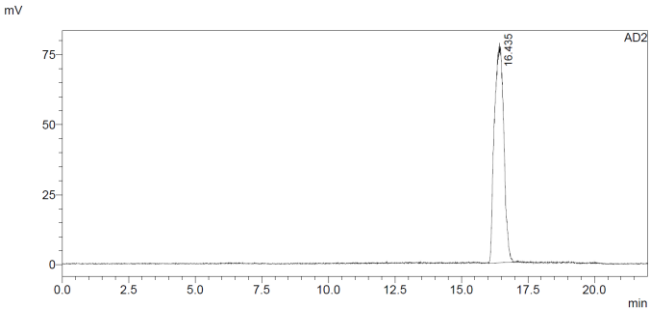
Radio TLC (Hex:EtOAc = 1:1)



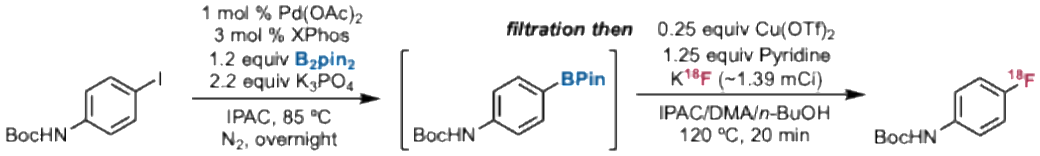
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



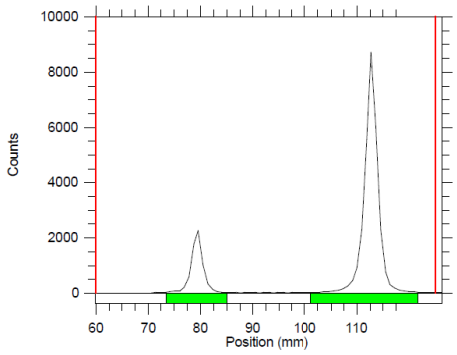
tert-Butyl (4-iodophenyl)carbamate (2l)



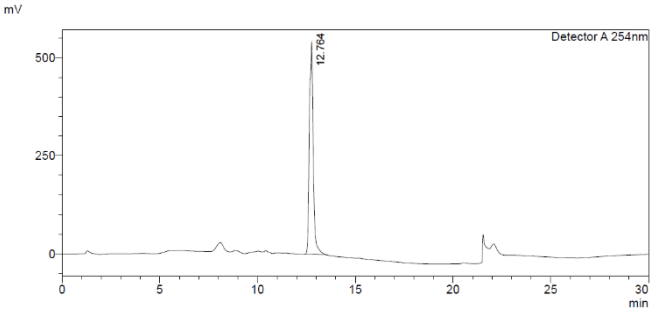
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 83 ± 9%

n	RCC [%]	RCP [%]	RCY [%]
1	70	99	70
2	90	99	90
3	81	98	80
4	94	98	92

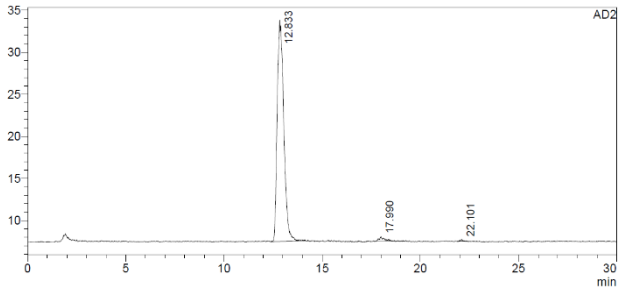
Radio TLC (Hex:EtOAc = 1:1)



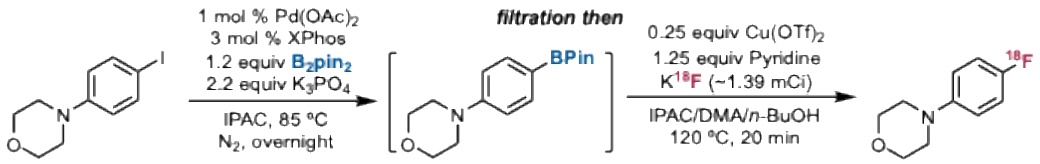
HPLC (UV trace): authentic standard



HPLC (radio trace): radio



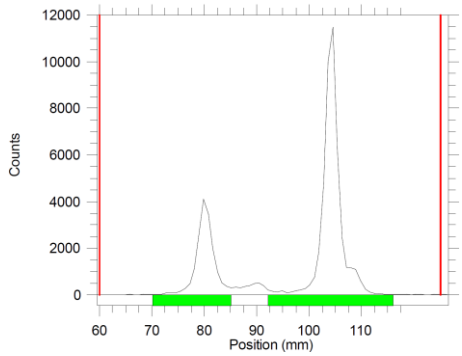
4-(4-Iodophenyl)morpholine (2m)



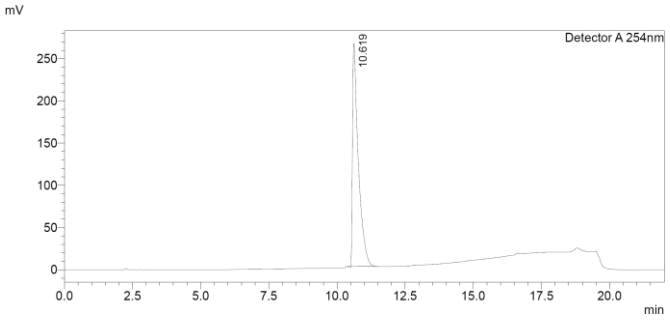
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 64 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	69	91	62
2	73	93	68
3	63	99	63
4	66	95	62

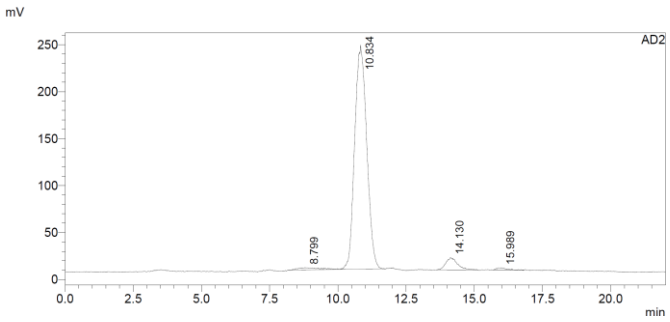
Radio TLC (Hex:EtOAc = 1:1)



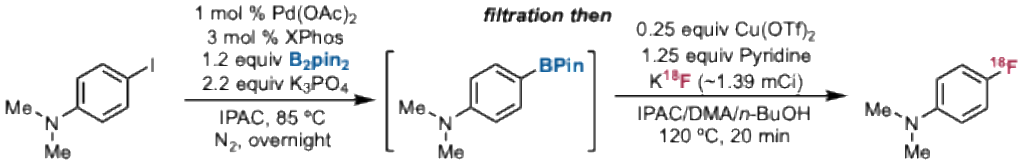
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



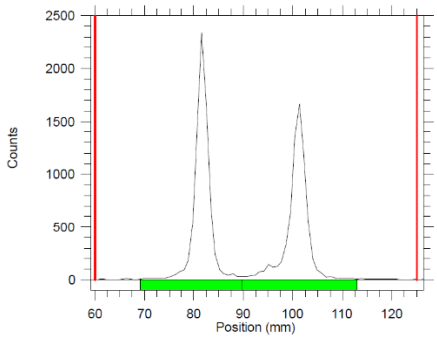
4-Iodo-*N, N*, -dimethyl aniline (2o)



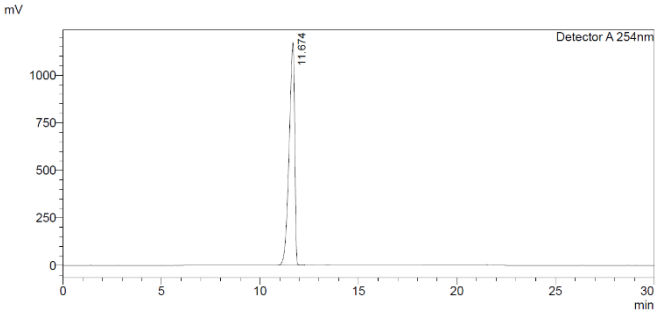
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 5**. Non-isolated RCY = 29 ± 6%

n	RCC [%]	RCP [%]	RCY [%]
1,2	37,41	58,63	21,26
3,4	55,47	71,69	34,38
5,6	47,42	69,71	33,29
7,8	40,37	68,58	27,21

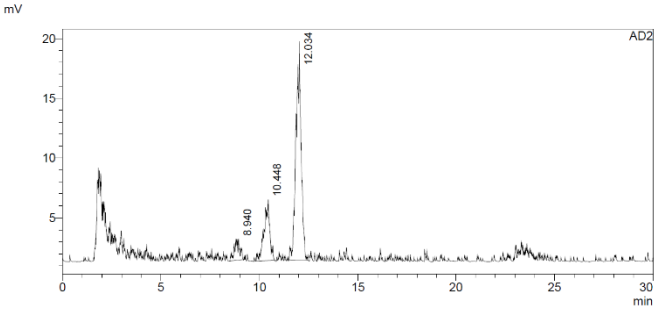
Radio TLC (Hex:EtOAc = 1:1)



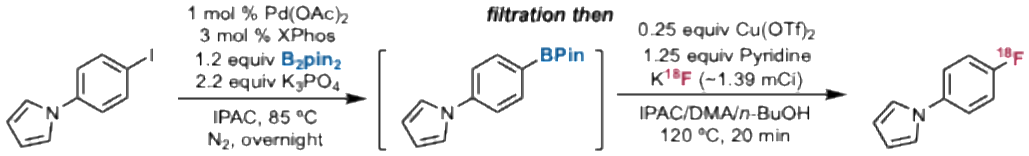
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



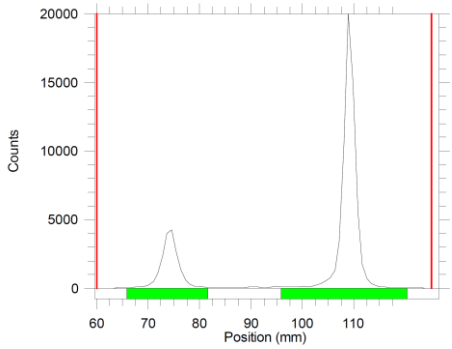
1-(4-Iodophenyl)-1H-pyrrole (2p)



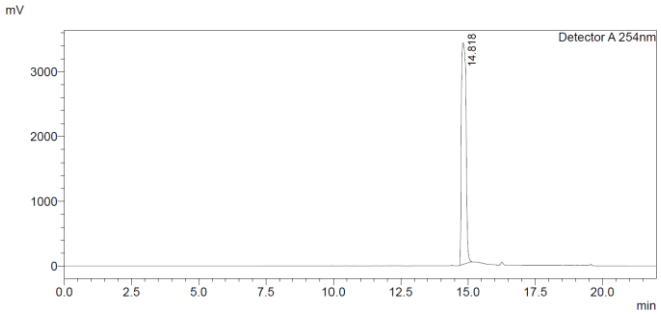
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 75 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	77	99	77
2	76	99	76
3	75	99	75
4	72	99	72

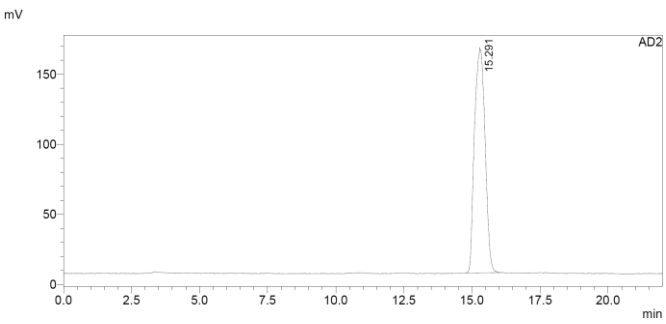
Radio TLC (Hex:EtOAc = 1:1)



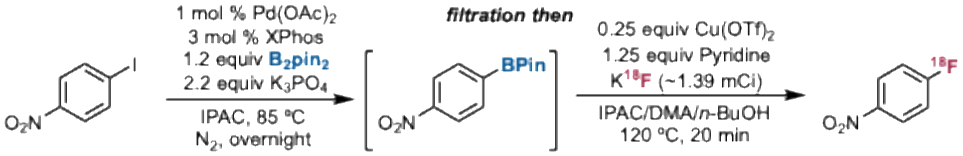
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



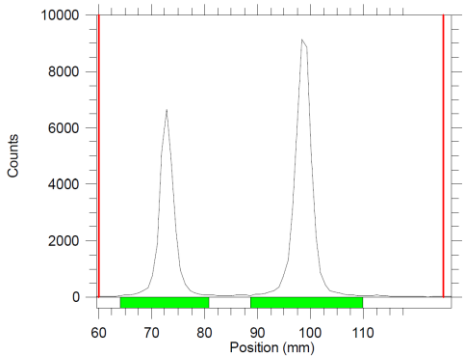
1-Iodo-4-nitrobenzene (2q)



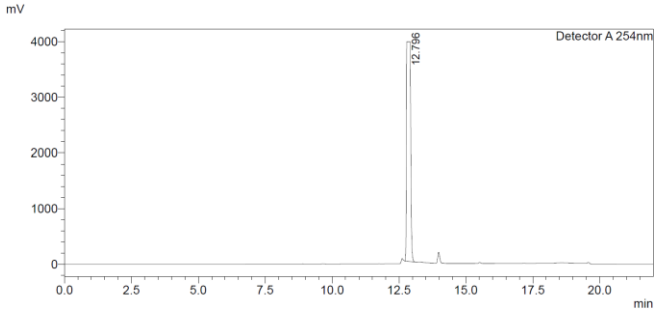
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 64 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	62	99	62
2	65	99	65
3	64	99	64

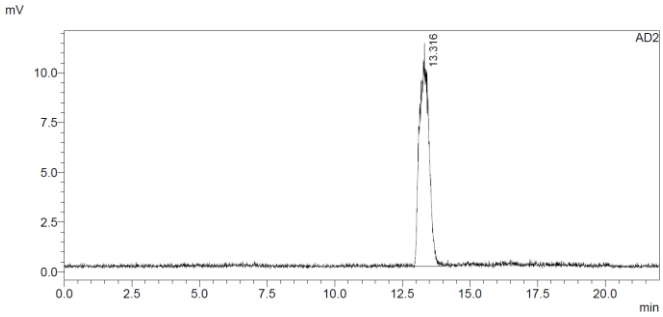
Radio TLC (Hex:EtOAc = 1:1)



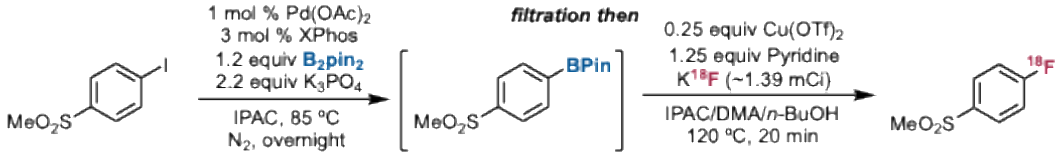
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



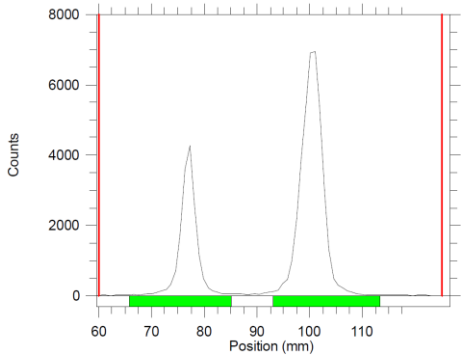
1-Iodo-4-(methylsulfonyl)benzene (2r)



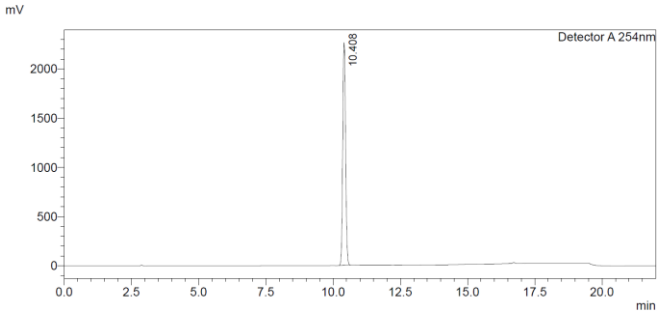
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 72 ± 5%

n	RCC [%]	RCP [%]	RCY [%]
1	70	99	70
2	65	99	65
3	79	99	79
4	75	99	75

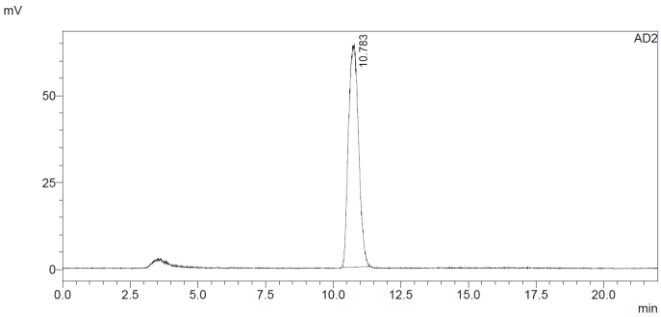
Radio TLC (Hex:EtOAc = 1:1)



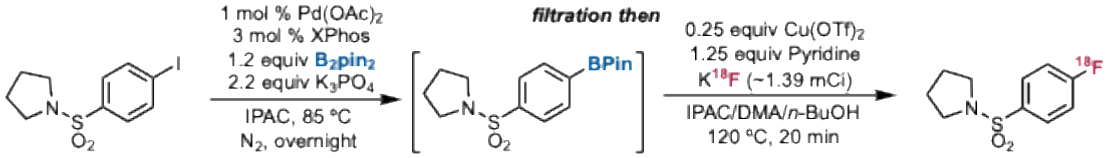
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



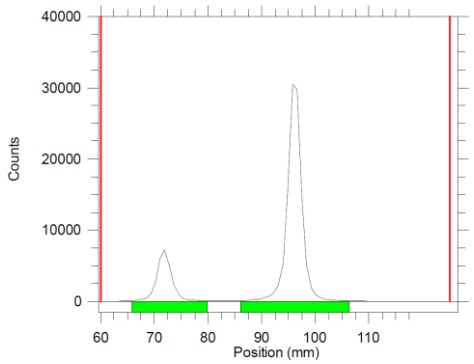
1-((4-Iodophenyl)sulfonyl)pyrrolidine (2s)



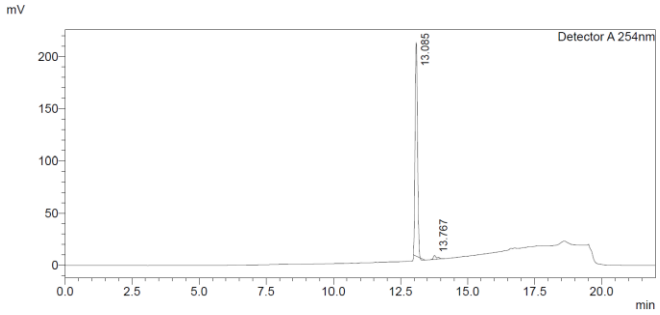
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 75 ± 4%

n	RCC [%]	RCP [%]	RCY [%]
1	80	98	79
2	72	98	71
3	77	99	77
4	71	99	71

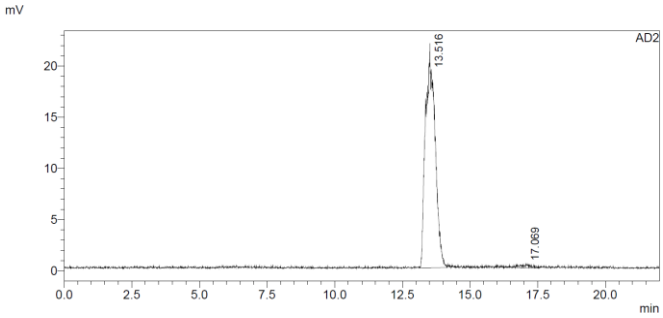
Radio TLC (Hex:EtOAc = 1:1)



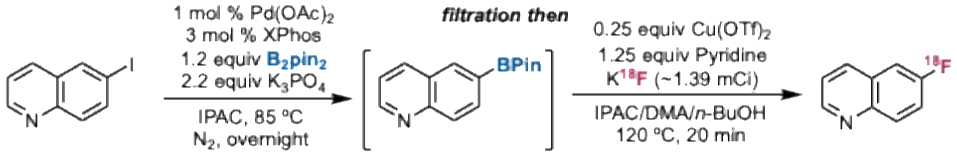
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



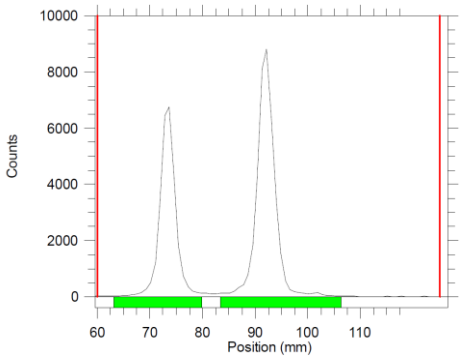
6-Iodoquinoline (2t)



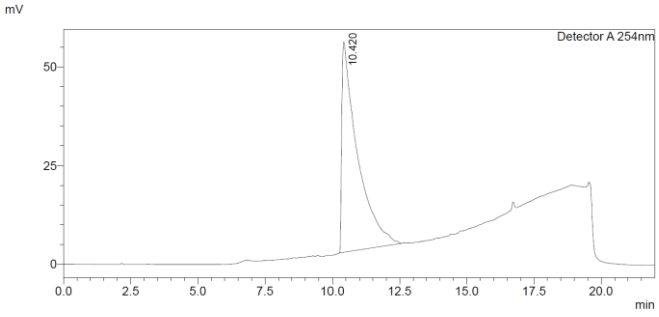
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 65 ± 4%

n	RCC [%]	RCP [%]	RCY [%]
1	59	99	59
2	64	99	64
3	68	99	68
4	69	99	69

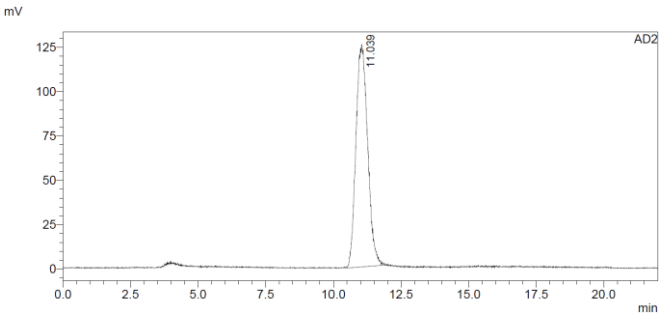
Radio TLC (Hex:EtOAc = 1:1)



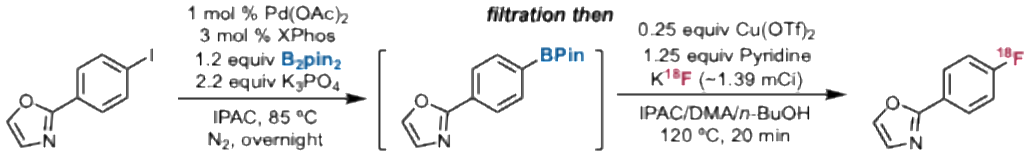
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



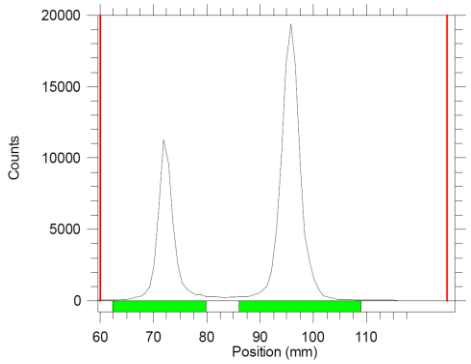
2-(4-Iodophenyl)oxazole (2v)



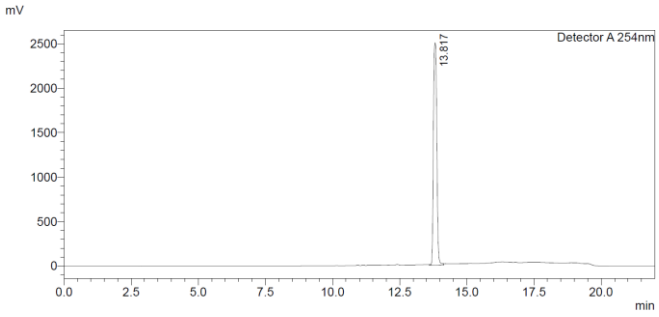
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 60 ± 3%

n	RCC [%]	RCP [%]	RCY [%]
1	68	89	60
2	73	83	61
3	65	87	57
4	70	90	63

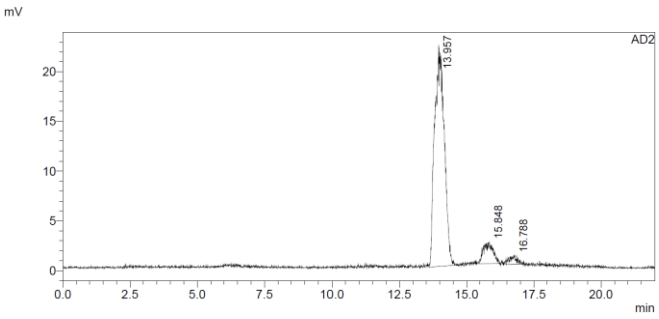
Radio TLC (Hex:EtOAc = 1:1)



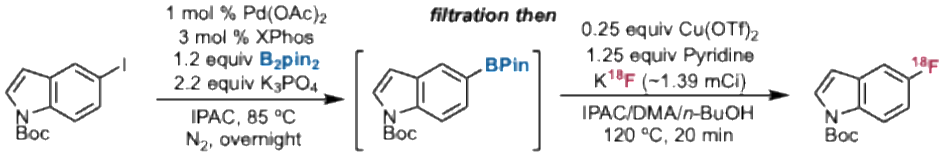
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



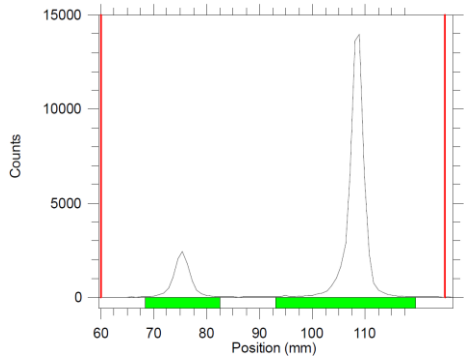
tert-Butyl 5-iodo-1H-indole-1-carboxylate (2y)



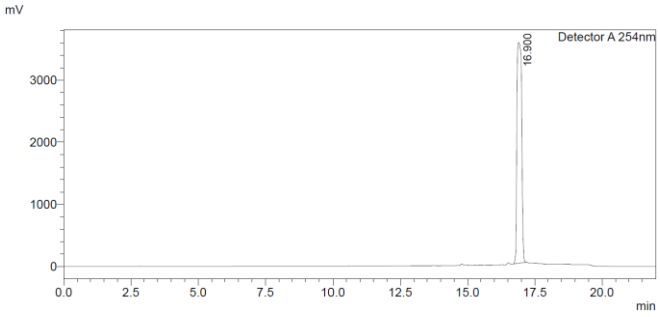
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 78 ± 3%

n	RCC [%]	RCP [%]	RCY [%]
1	84	95	80
2	83	97	81
3	77	98	75
4	76	97	74

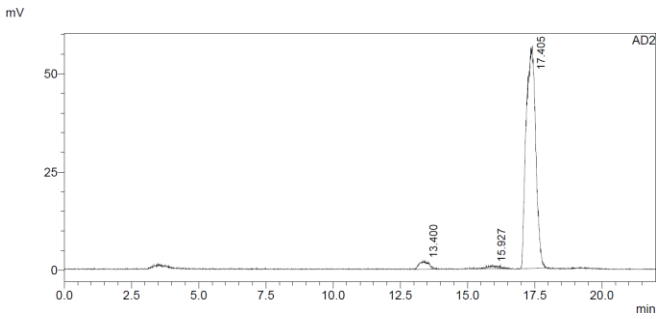
Radio TLC (Hex:EtOAc = 1:1)



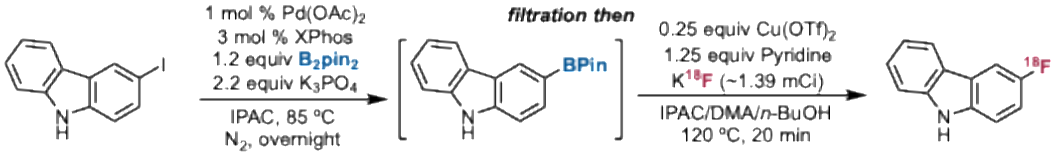
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



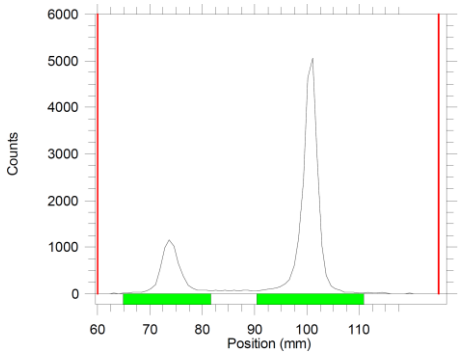
3-Iodo-9H-carbazole (2z)



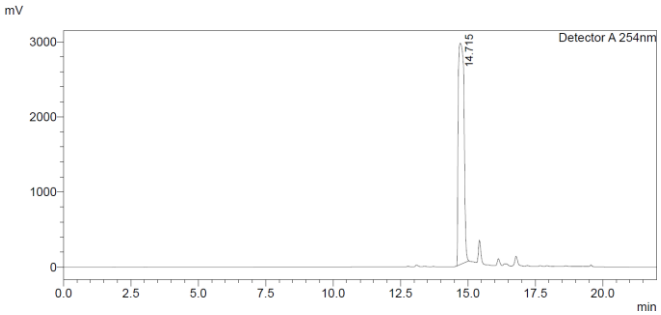
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 75 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	82	95	78
2	82	94	76
3	78	93	72
4	78	94	73

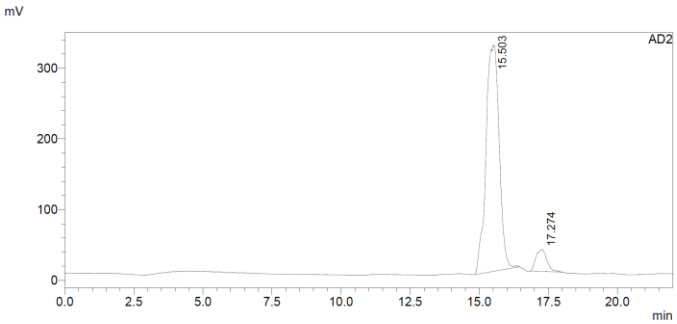
Radio TLC (Hex:EtOAc = 1:1)



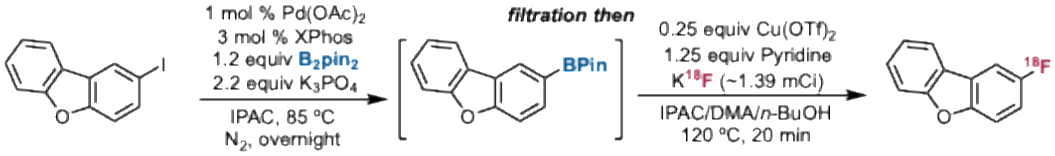
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



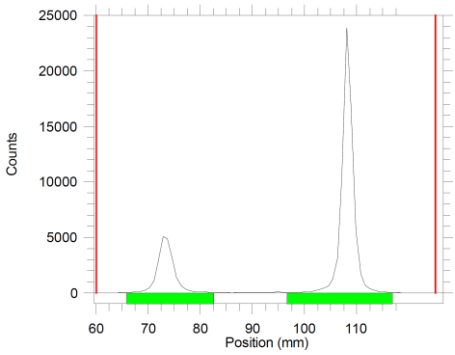
2-Iododibenzo[b,d]furan (2aa)



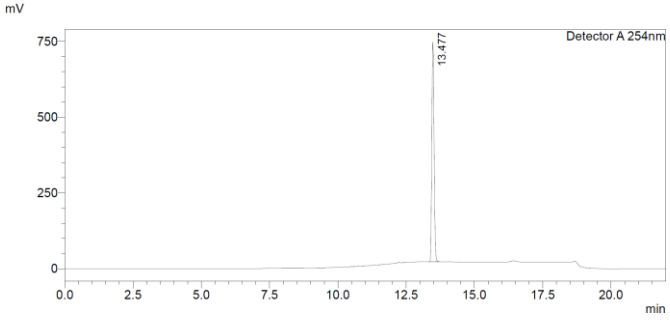
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 2**. Non-isolated RCY = 74 ± 1%

n	RCC [%]	RCP [%]	RCY [%]
1	76	99	75
2	76	98	74
3	72	99	72
4	73	99	73

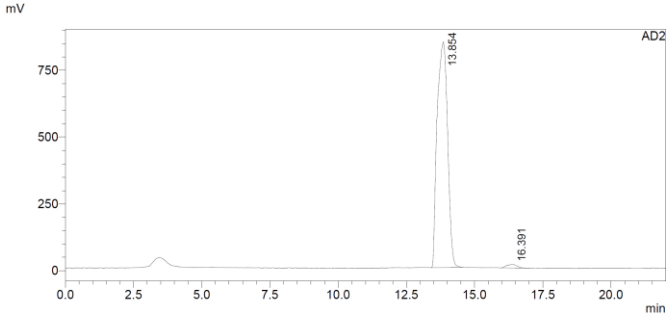
Radio TLC (Hex:EtOAc = 1:1)



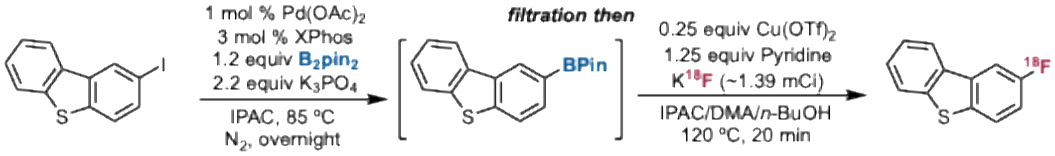
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



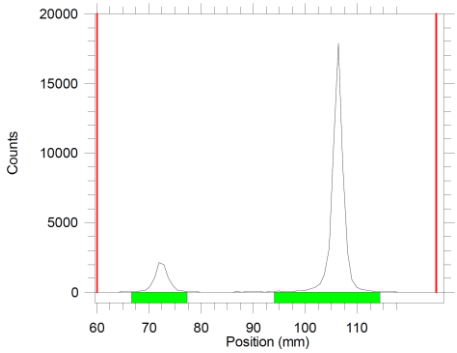
2-Iodo dibenzo[b,d]thiophene (2bb)



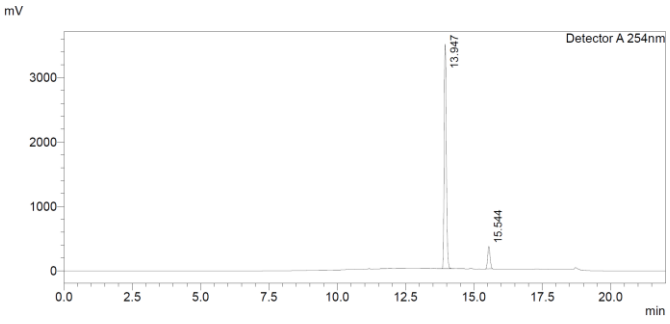
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 2**. Non-isolated RCY = 85 ± 1%

n	RCC [%]	RCP [%]	RCY [%]
1	86	98	85
2	88	98	86
3	85	99	85
4	83	99	83

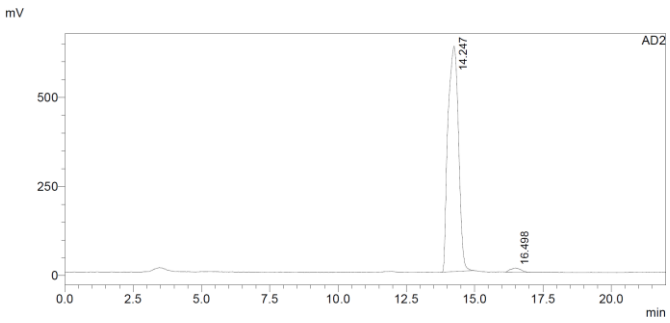
Radio TLC (Hex:EtOAc = 1:1)



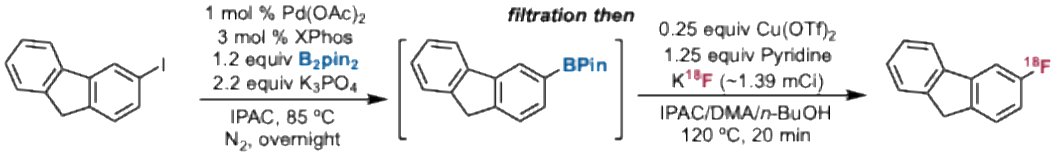
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



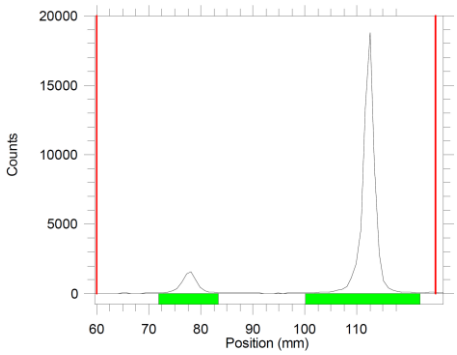
3-Iodo-9H-fluorene (2cc)



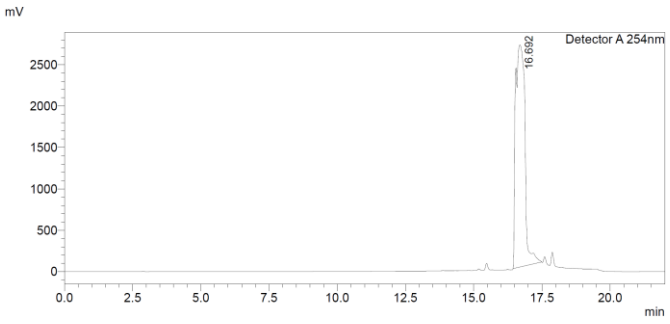
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 79 ± 3%

n	RCC [%]	RCP [%]	RCY [%]
1	90	92	83
2	90	91	82
3	84	91	76
4	84	90	76

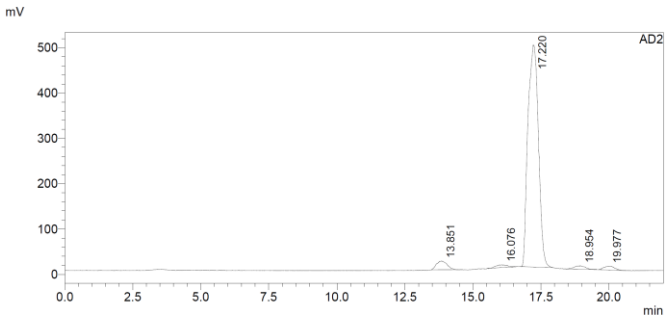
Radio TLC (Hex:EtOAc = 1:1)



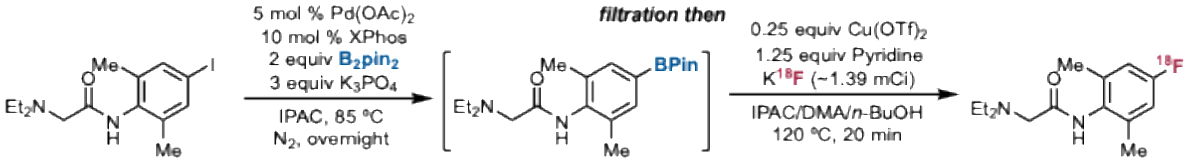
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



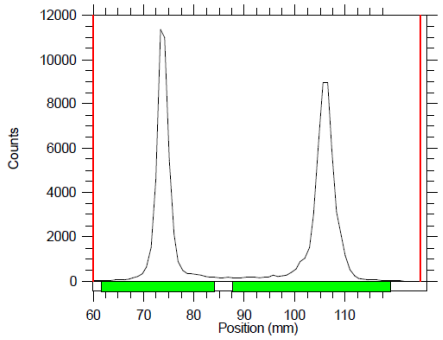
2-(Diethylamino)-N-(4-iodo-2,6-dimethylphenyl)acetamide (2hh)



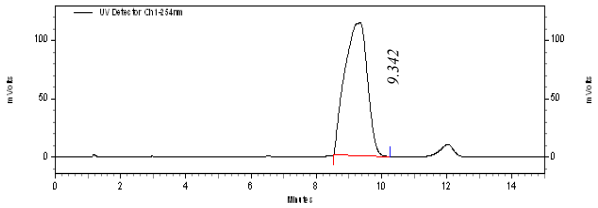
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column C**. HPLC Conditions: **Method 4**. Non-isolated RCY = 43 ± 5%

n	RCC [%]	RCP [%]	RCY [%]
1	54	89	48
2	42	85	36
3	67	64	43
4	75	62	46

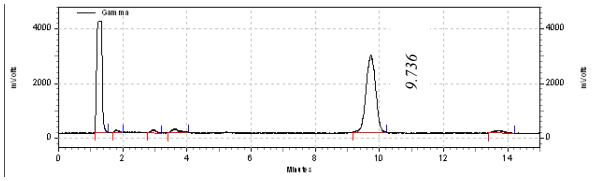
Radio TLC (dichloromethane:MeOH = 4:1)



HPLC (UV trace): authentic standard

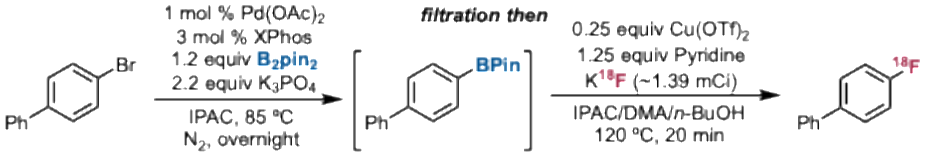


HPLC (radio trace): radiofluorination reaction (crude)



6.4.2 Palladium-Catalyzed Borylation Telescope of Aryl Bromides

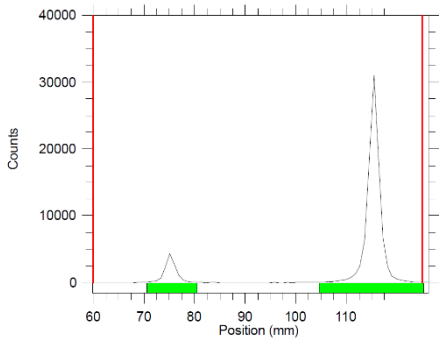
4-Bromobiphenyl (2a)



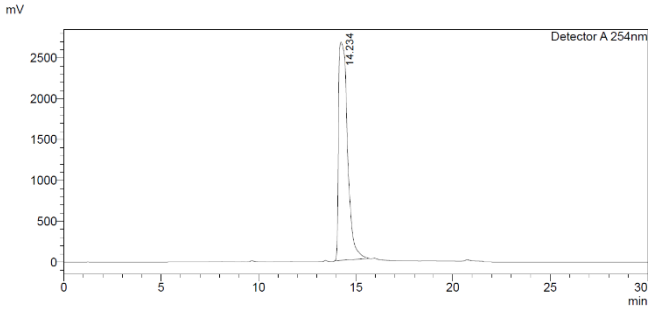
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 85 ± 4%

n	RCC [%]	RCP [%]	RCY [%]
1	83	99	83
2	89	99	89
3	79	99	79
4	88	99	88

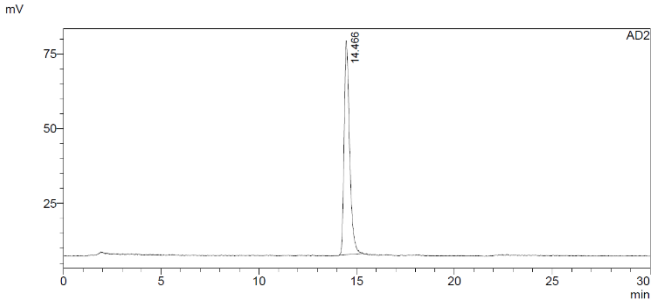
Radio TLC (Hex:EtOAc = 1:1)



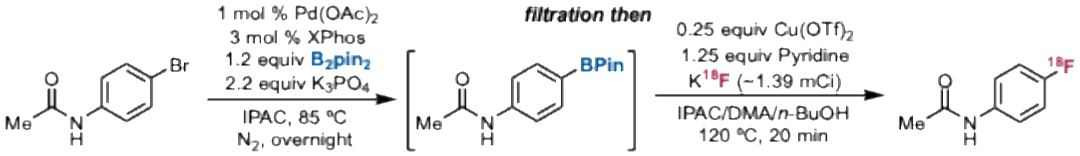
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



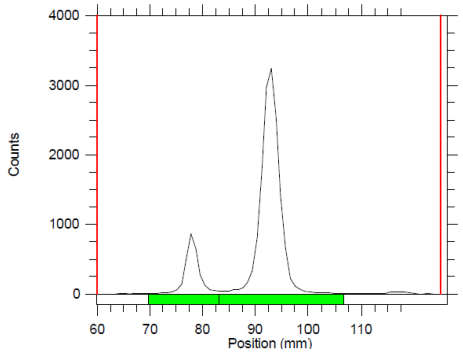
N-(4-Bromophenyl)acetamide (2b)



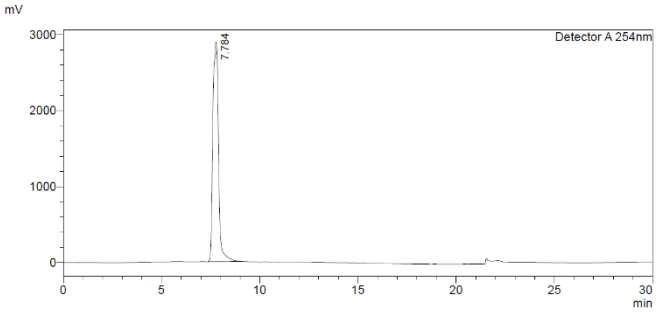
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 87 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	84	99	84
2	85	99	85
3	90	99	99
4	89	98	88

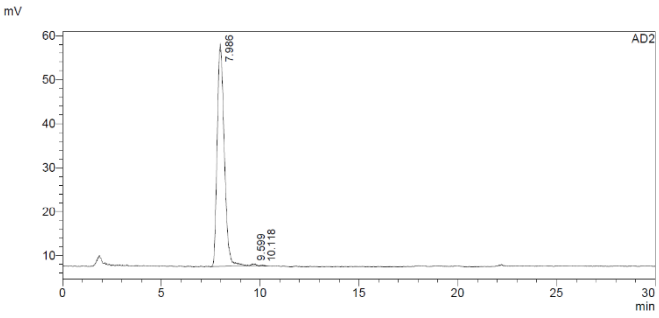
Radio TLC (Hex:EtOAc = 1:1)



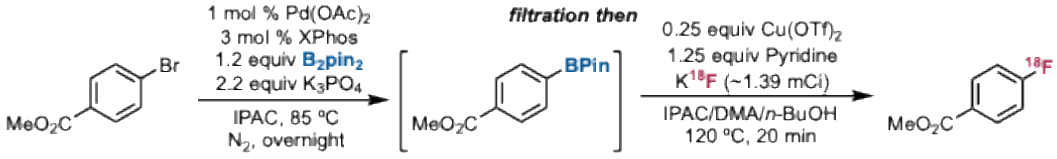
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



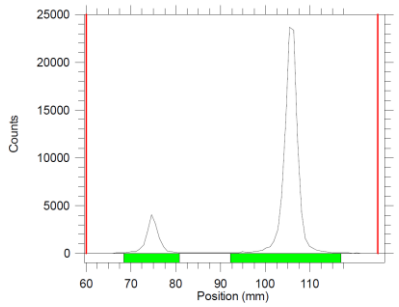
Methyl 4-bromobenzoate (2c)



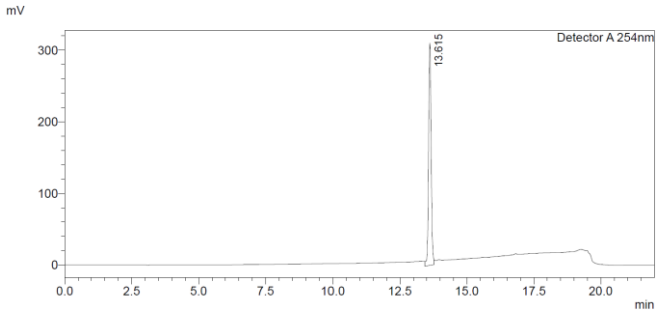
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 94 ± 6%

n	RCC [%]	RCP [%]	RCY [%]
1	87	99	86
2	95	99	94
3	96	99	96
4	99	99	99

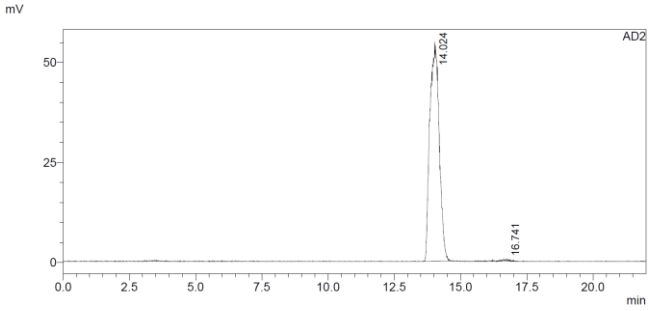
Radio TLC (Hex:EtOAc = 1:1)



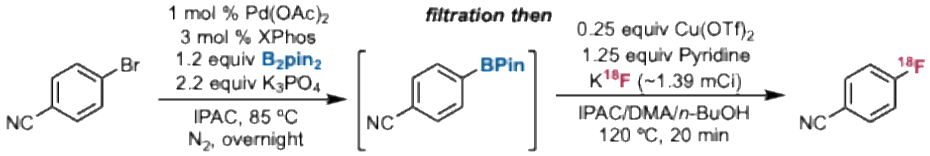
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



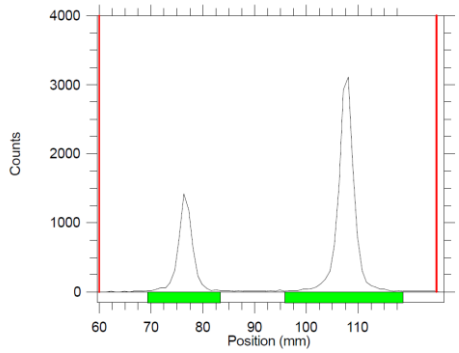
4-Bromobenzonitrile (2d)



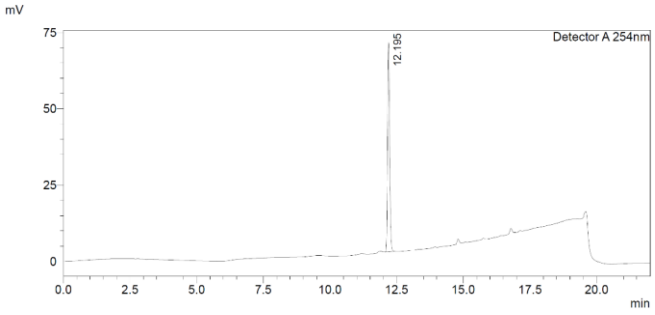
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 55 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	58	99	58
2	55	99	55
3	55	99	55
4	53	99	53

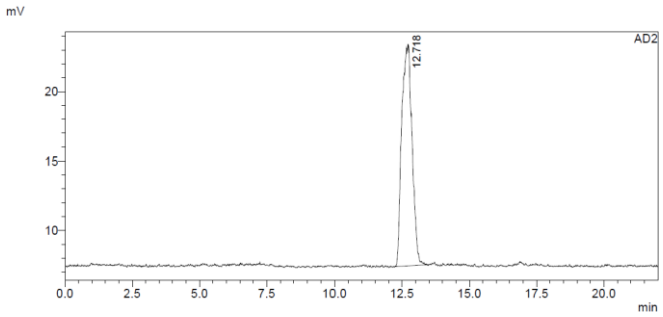
Radio TLC (Hex:EtOAc = 1:1)



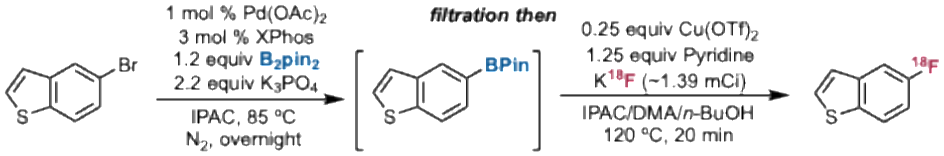
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



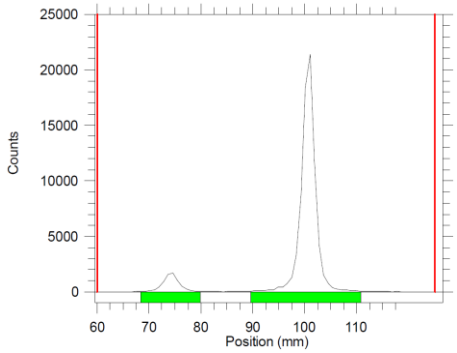
5-Bromo-benzothiophene (2e)



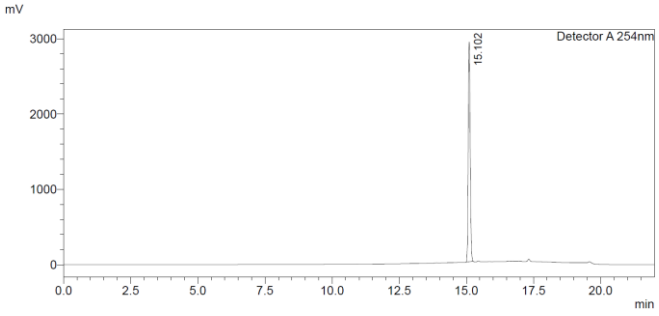
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 90 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	91	99	91
2	92	99	92
3	90	99	90
4	88	99	88

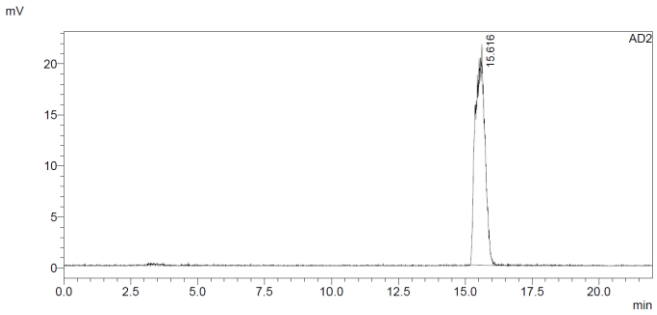
Radio TLC (Hex:EtOAc = 1:1)



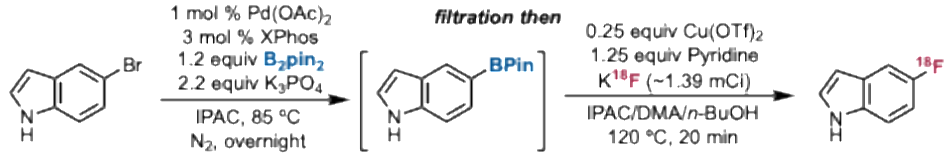
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



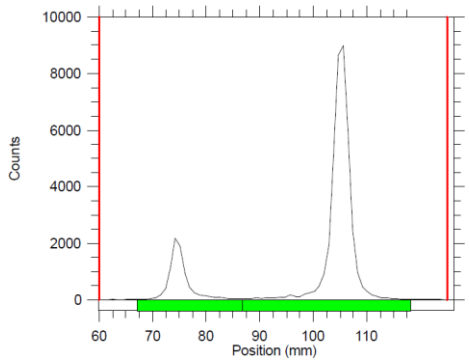
5-Bromo-1H-indole (2f)



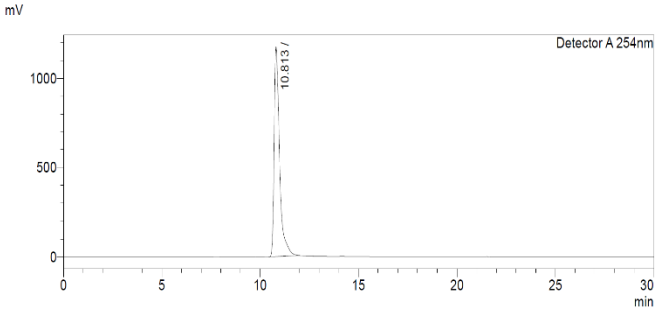
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 82 ± 5%

n	RCC [%]	RCP [%]	RCY [%]
1	87	91	80
2	90	95	86
3	82	93	76
4	77	91	70

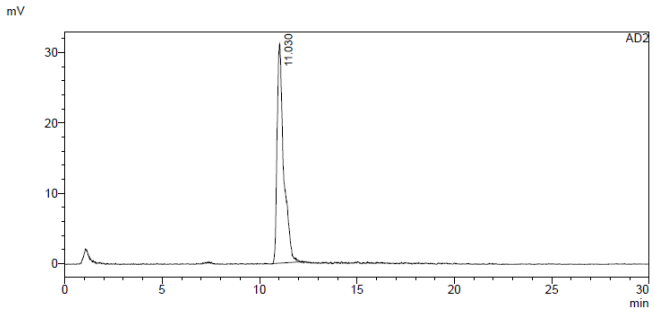
Radio TLC (Hex:EtOAc = 1:1)



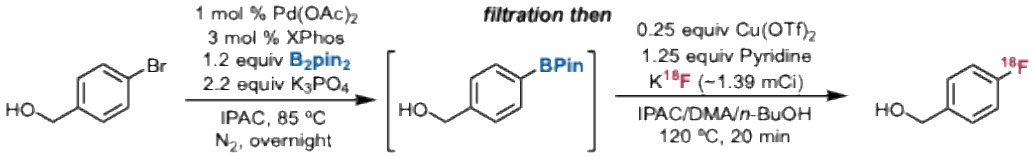
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



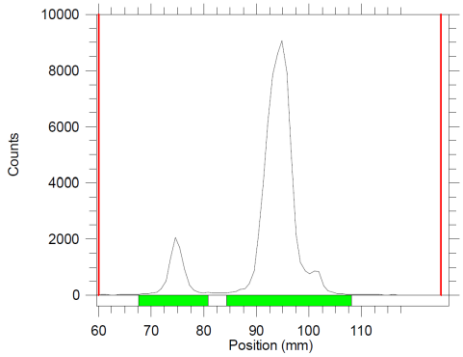
4-Bromobenzyl alcohol (2i)



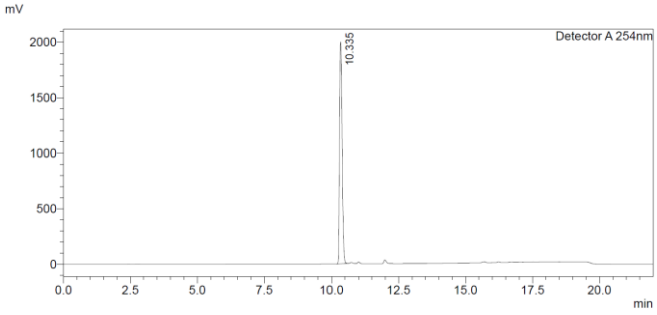
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 85 ± 3%

n	RCC [%]	RCP [%]	RCY [%]
1	89	95	84
2	86	94	81
3	91	96	87
4	92	96	89

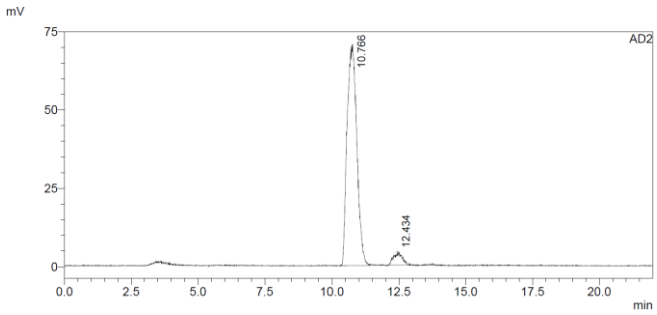
Radio TLC (Hex:EtOAc = 1:1)



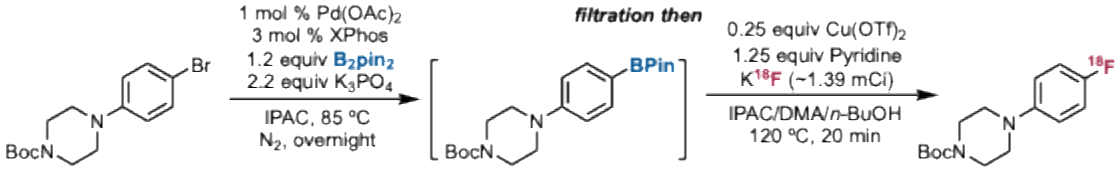
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



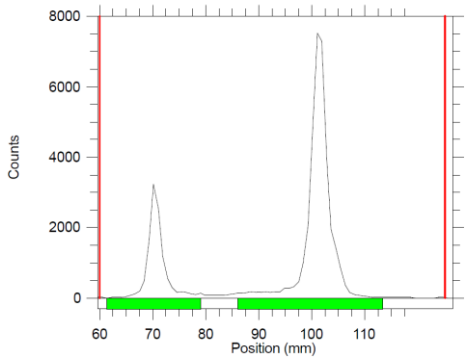
tert-Butyl 4-(4-bromophenyl)piperazine-1-carboxylate (2n)



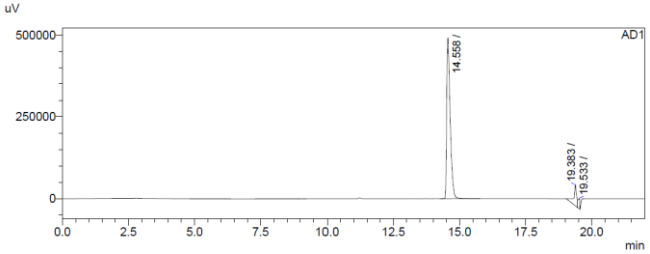
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 62 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	74	84	62
2	76	86	65
3	73	80	59
4	79	79	62

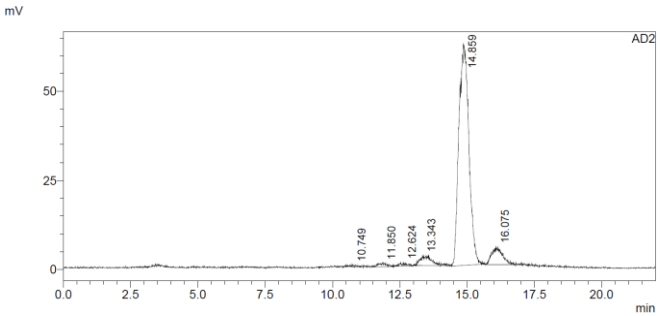
Radio TLC (Hex:EtOAc = 1:1)



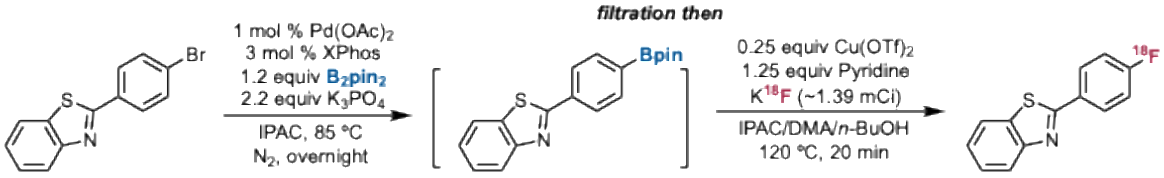
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



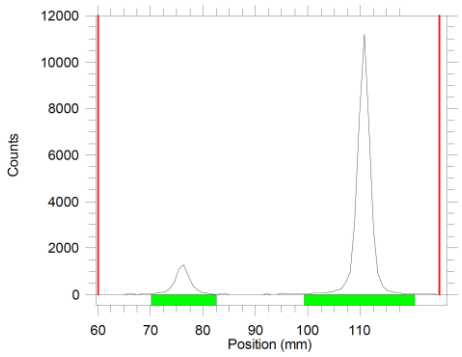
2-(4-Bromophenyl)benzo[d]thiazole (2u)



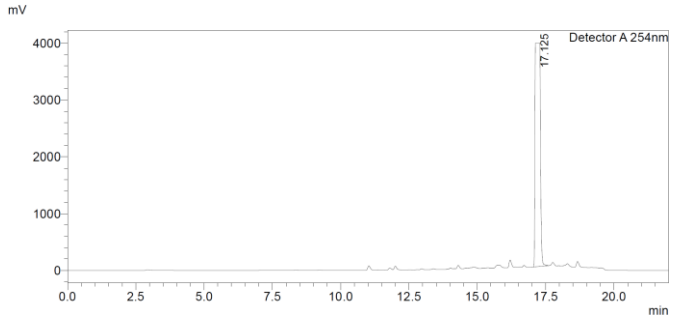
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 87 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	89	99	89
2	88	99	88
3	83	99	83
4	88	99	88

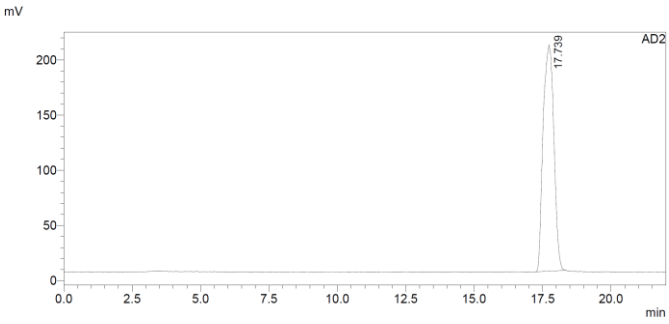
Radio TLC (Hex:EtOAc = 1:1)



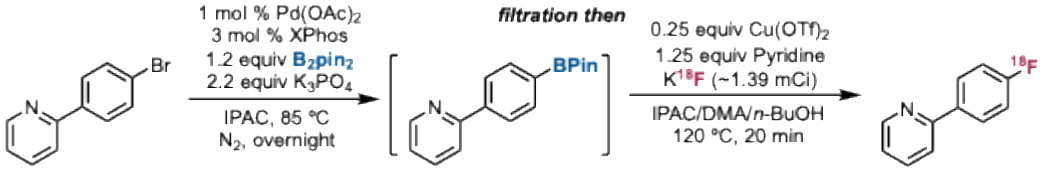
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



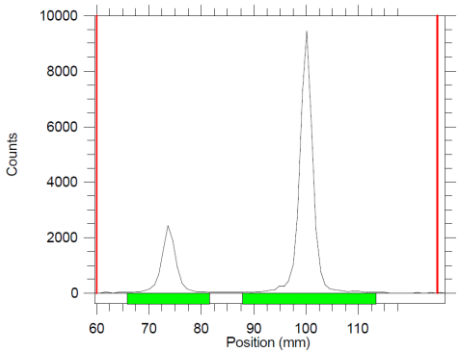
2-(4-Bromophenyl)pyridine (2w)



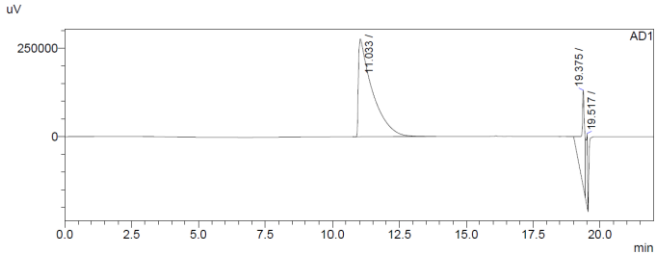
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 79 ± 1%

n	RCC [%]	RCP [%]	RCY [%]
1	79	99	79
2	78	99	78
3	80	99	80

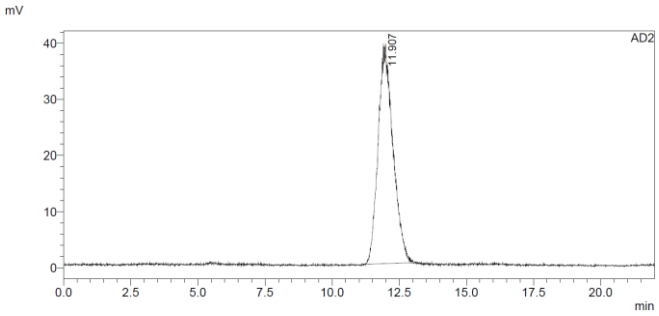
Radio TLC (Hex:EtOAc = 1:1)



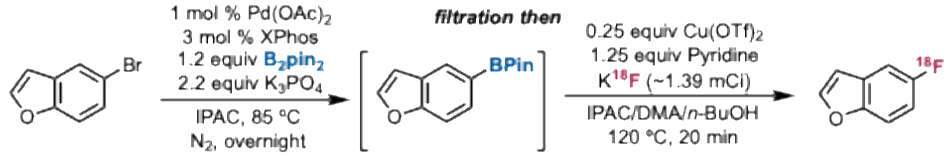
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



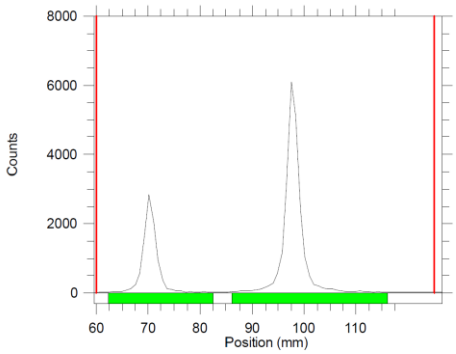
5-Bromo-benzofuran (2x)



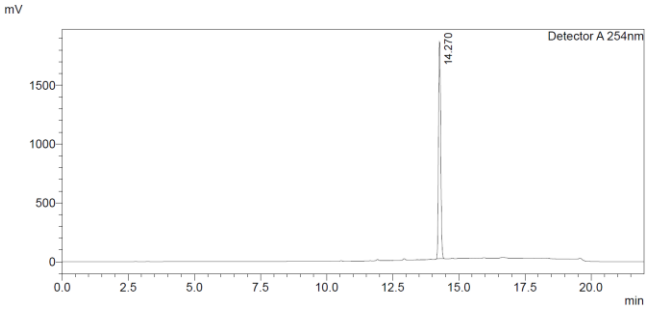
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 74 ± 4%

n	RCC [%]	RCP [%]	RCY [%]
1	70	97	68
2	79	99	78
3	78	98	76

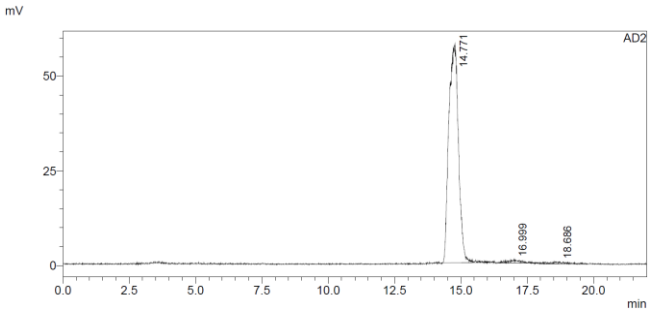
Radio TLC (Hex:EtOAc = 1:1)



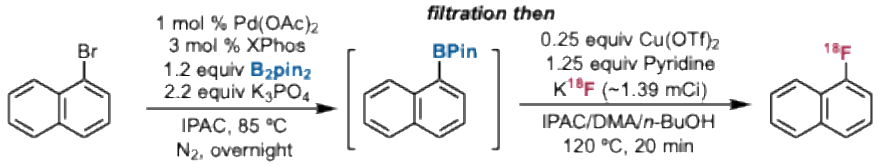
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



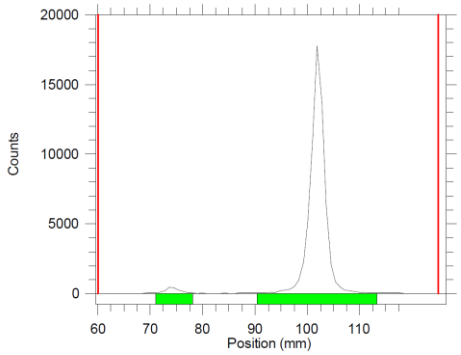
1-Bromo-napthalene (2dd)



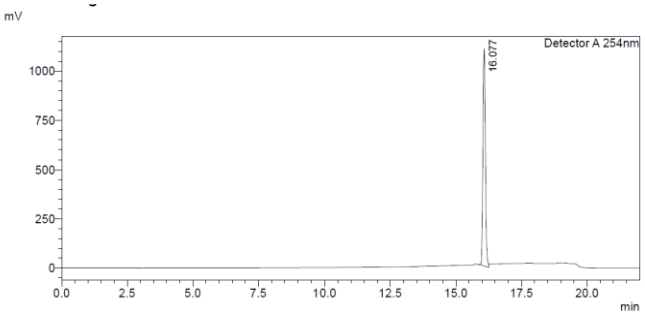
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 95 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	97	99	97
2	97	99	97
3	94	99	94
4	93	99	93

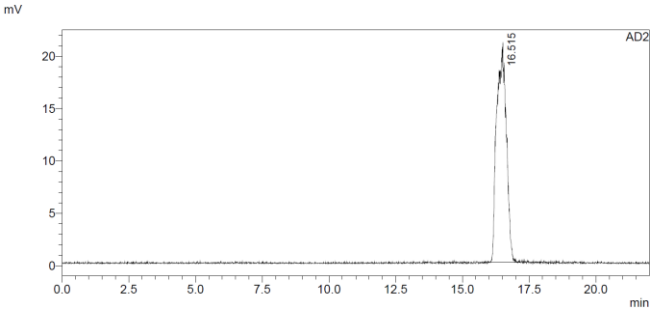
Radio TLC (Hex:EtOAc = 1:1)



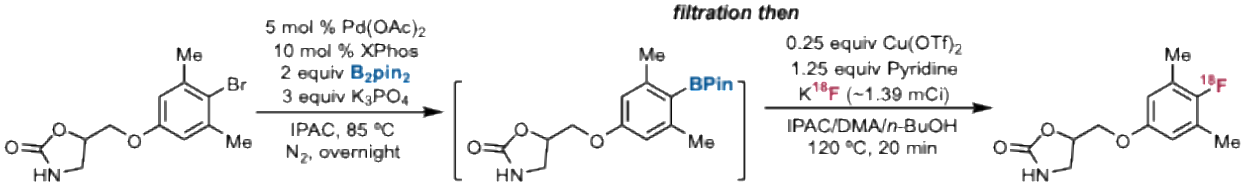
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



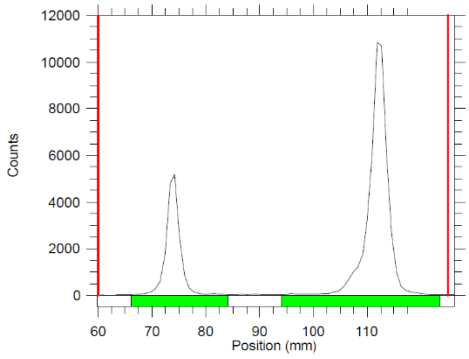
5-((4-Bromo-3,5-dimethylphenoxy)methyl)oxazolidin-2-one (2ii)



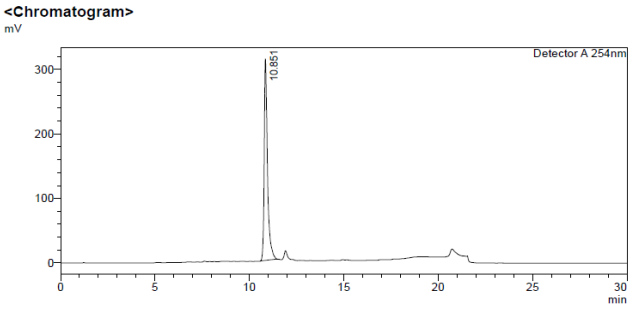
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 86 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	97	90	88
2	90	92	83
3	88	99	88
4	91	95	86

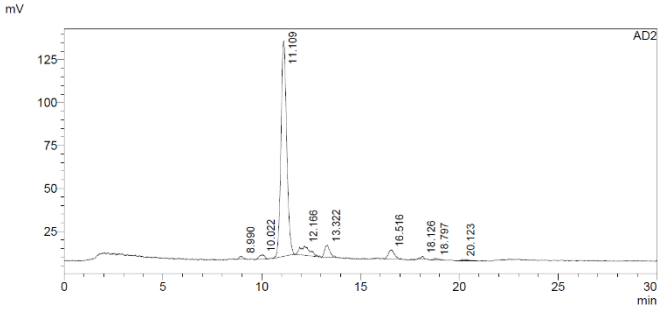
Radio TLC (Hex:EtOAc = 1:1)



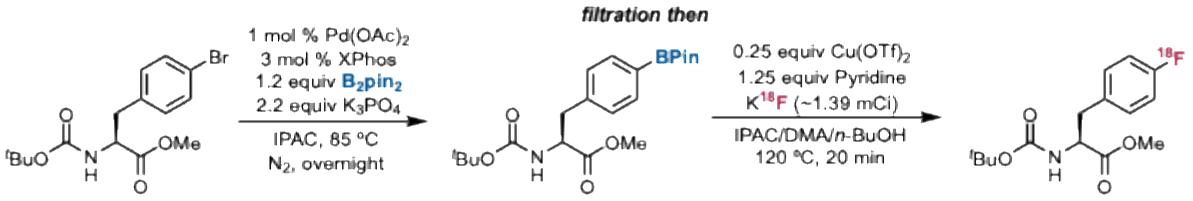
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



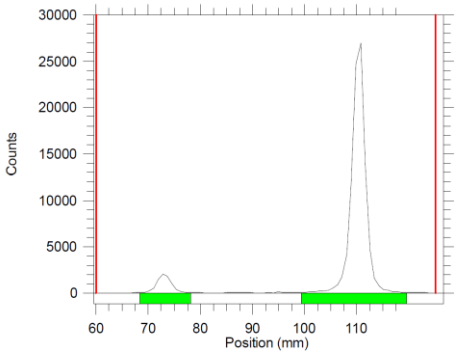
Boc-Phe(4-Br)-OMe



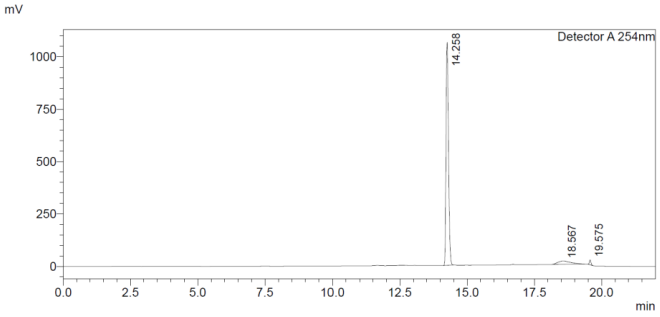
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 89 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	92	96	89
2	91	97	88
3	90	97	87
4	94	97	91

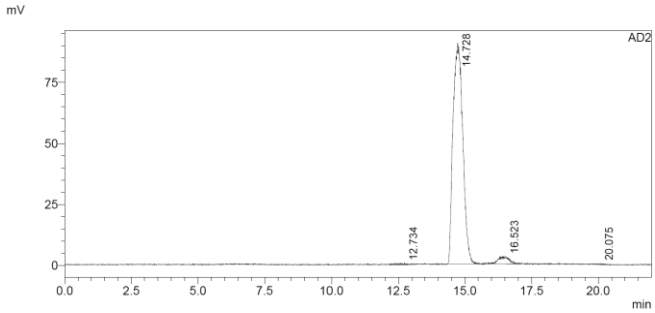
Radio TLC (Hex:EtOAc = 1:1)



HPLC (UV trace): authentic standard

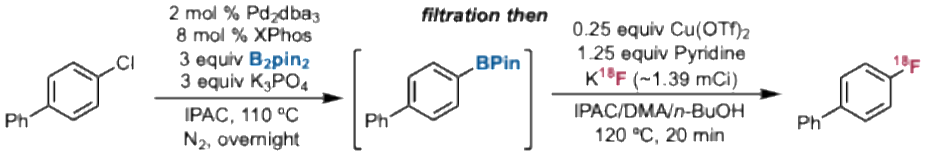


HPLC (radio trace): radiofluorination reaction (crude)



6.4.3 Palladium-Catalyzed Borylation Telescope of Aryl Chlorides

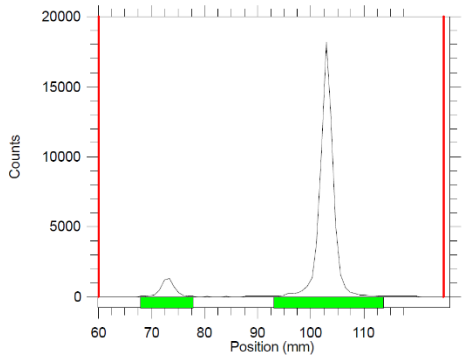
4-Chlorobiphenyl (2a)



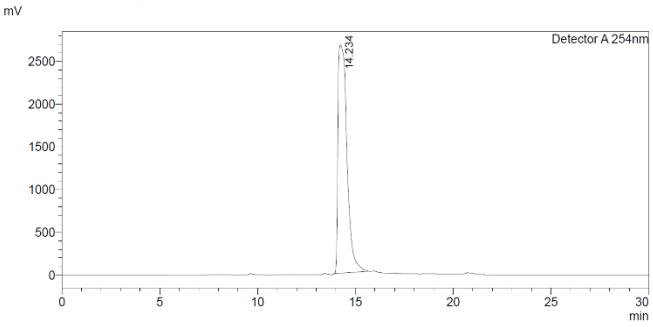
Borylation Procedure: **Procedure 3.4**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 90 ± 3%

n	RCC [%]	RCP [%]	RCY [%]
1	93	99	92
2	94	99	94
3	87	99	86
4	89	99	89

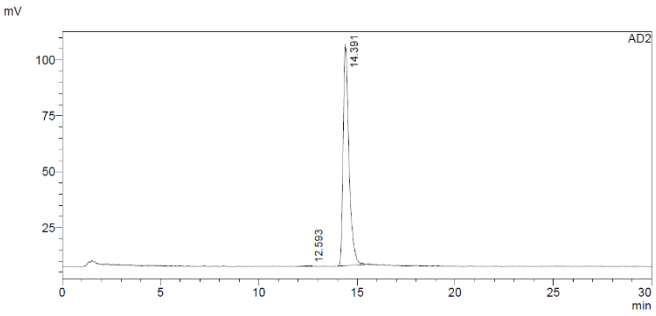
Radio TLC (Hex:EtOAc = 1:1)



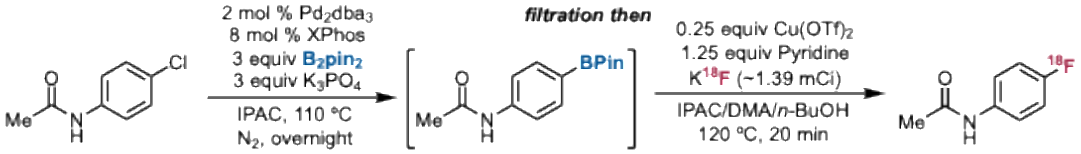
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



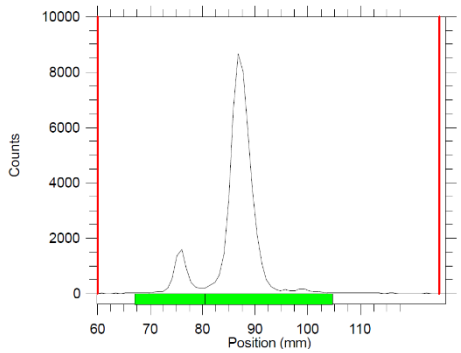
N-(4-Chlorophenyl)acetamide (2b)



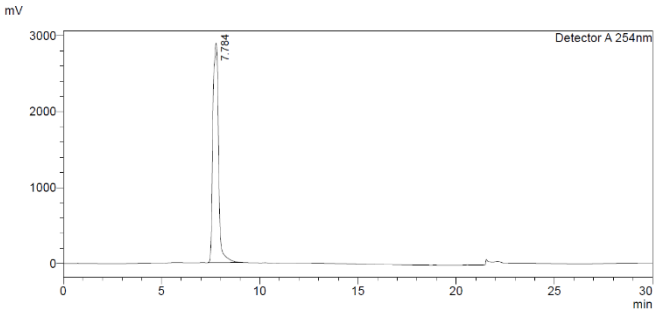
Borylation Procedure: **Procedure 3.4**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 86 ± 5%

n	RCC [%]	RCP [%]	RCY [%]
1	89	99	88
2	92	99	91
3	86	99	86
4	78	99	78

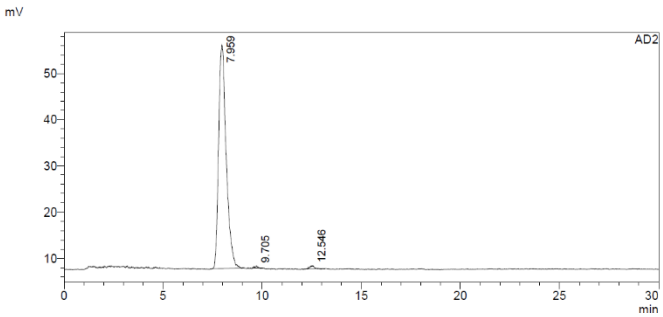
Radio TLC (Hex:EtOAc = 1:1)



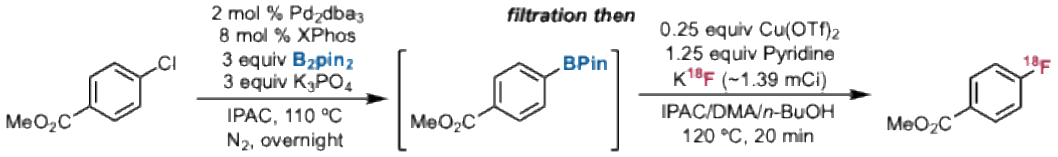
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



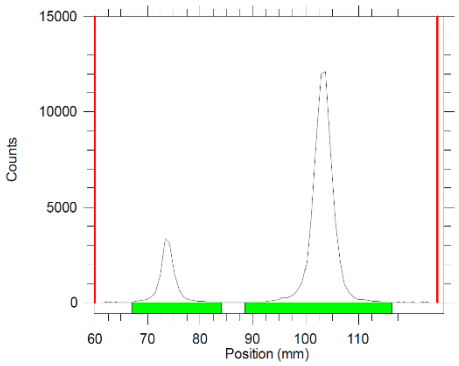
Methyl 4-chlorobenzoate (2c)



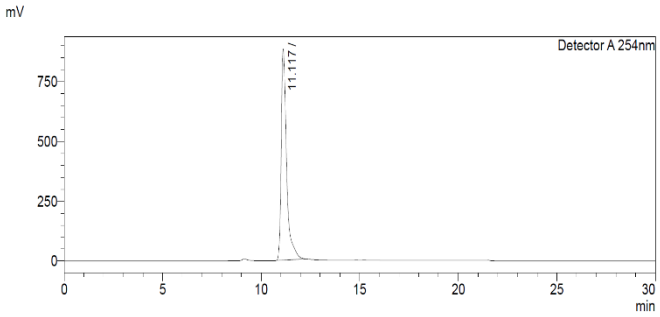
Borylation Procedure: **Procedure 3.4**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 79 ± 4%

n	RCC [%]	RCP [%]	RCY [%]
1	75	99	75
2	83	99	83
3	79	96	75
4	84	99	84

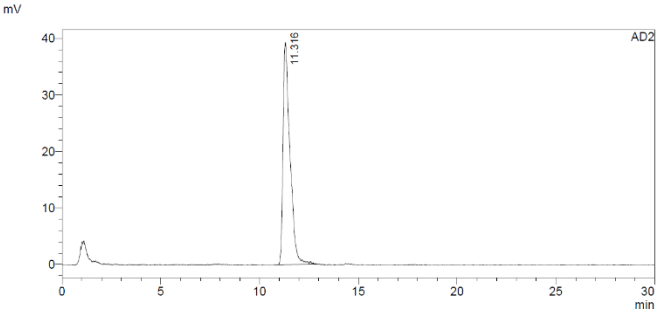
Radio TLC (Hex:EtOAc = 1:1)



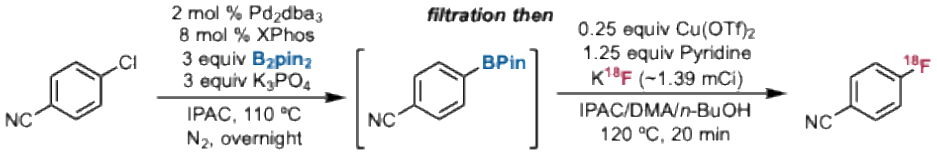
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



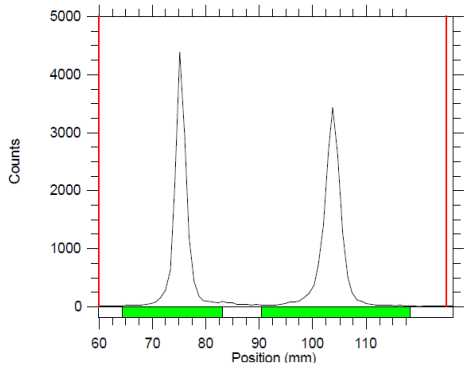
4-Chlorobenzonitrile (2d)



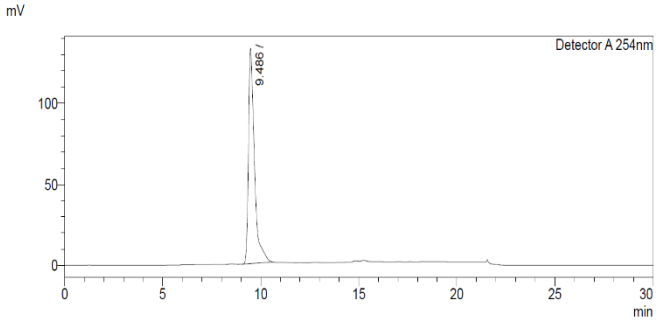
Borylation Procedure: **Procedure 3.4**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 47 ± 5%

n	RCC [%]	RCP [%]	RCY [%]
1	44	99	43
2	53	99	53
3	52	99	51
4	45	95	42

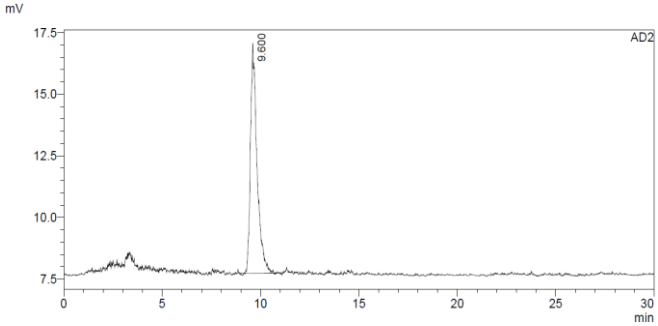
Radio TLC (Hex:EtOAc = 1:1)



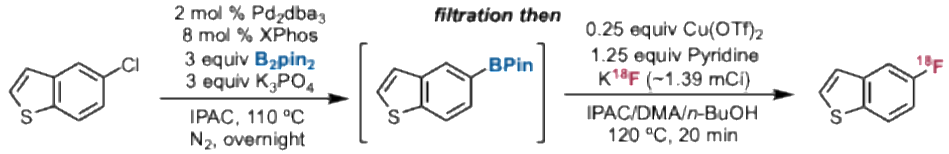
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



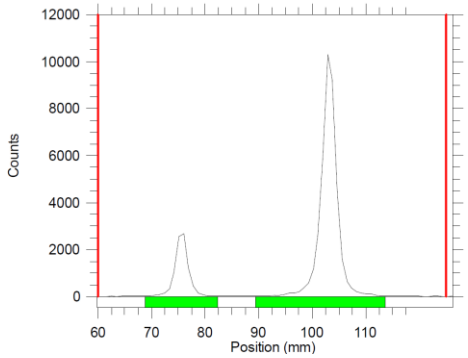
5-Chloro-benzothiophene (2e)



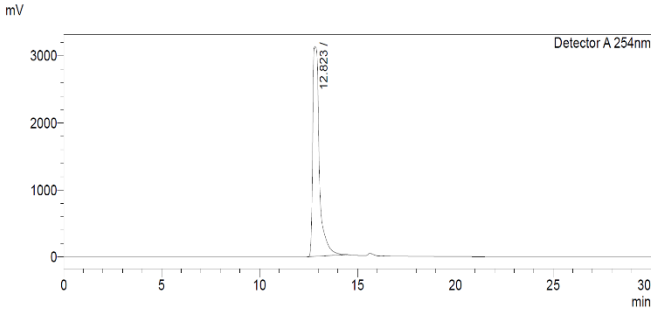
Borylation Procedure: **Procedure 3.4**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 75 ± 6%

n	RCC [%]	RCP [%]	RCY [%]
1	81	99	81
2	77	99	77
3	76	99	76
4	64	99	64

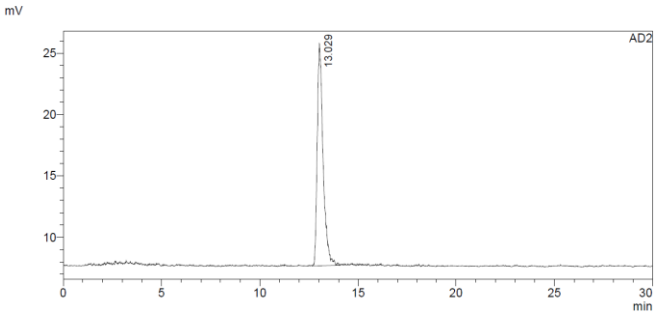
Radio TLC (Hex:EtOAc = 1:1)



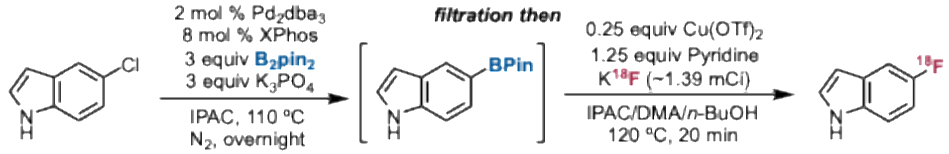
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



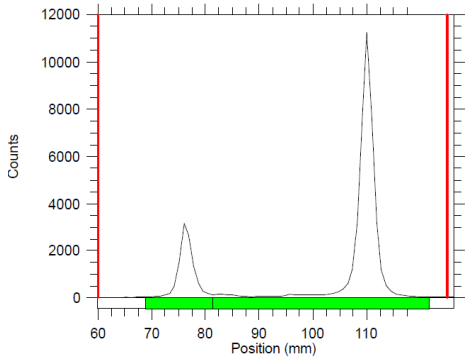
5-Chloro-1H-indole (2f)



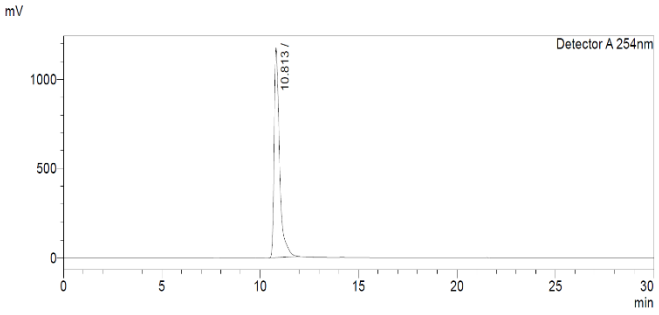
Borylation Procedure: **Procedure 3.4**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**: Non-isolated RCY = 72 ± 6%

n	RCC [%]	RCP [%]	RCY [%]
1	64	99	64
2	69	99	69
3	79	99	79
4	76	99	76

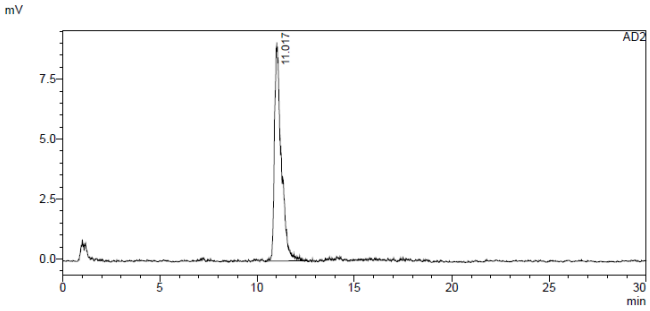
Radio TLC (Hex:EtOAc = 1:1)



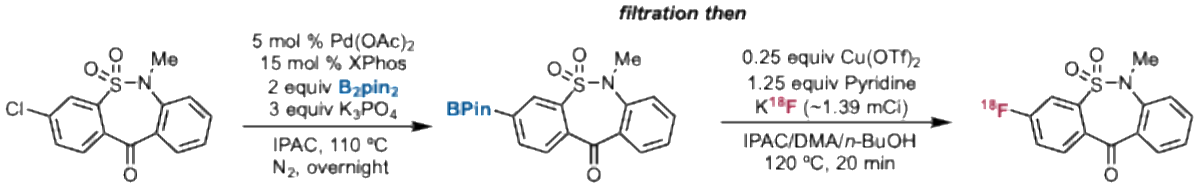
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



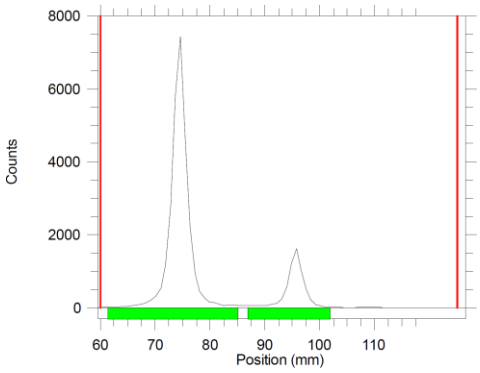
3-Chlorodibenzo[c,f][1,2]thiazepin-11(6H)-one 5,5-dioxide (2ee)



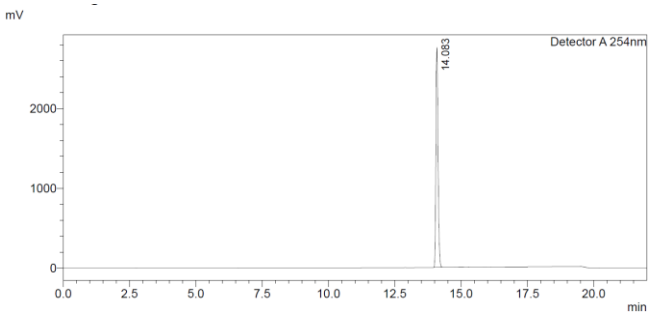
Borylation Procedure: **Procedure 3.3**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 12 ± 3%

n	RCC [%]	RCP [%]	RCY [%]
1	16	48	7
2	19	70	13
3	18	83	15
4	16	85	13

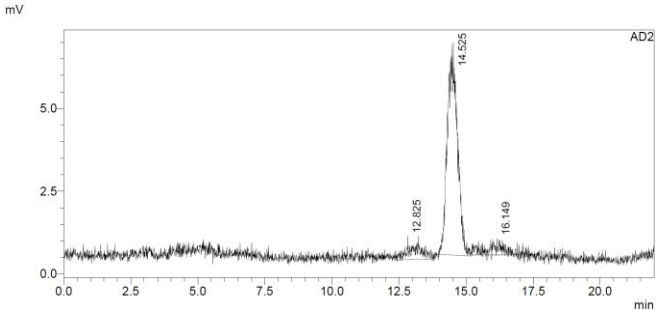
Radio TLC (Hex:EtOAc = 1:1)



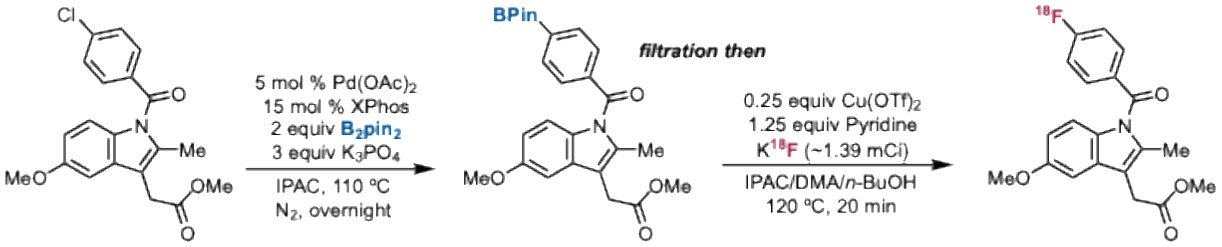
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



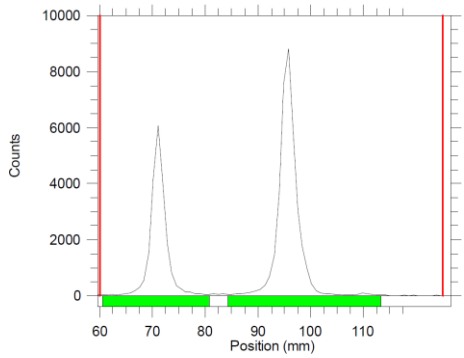
Indomethacin (2ff)



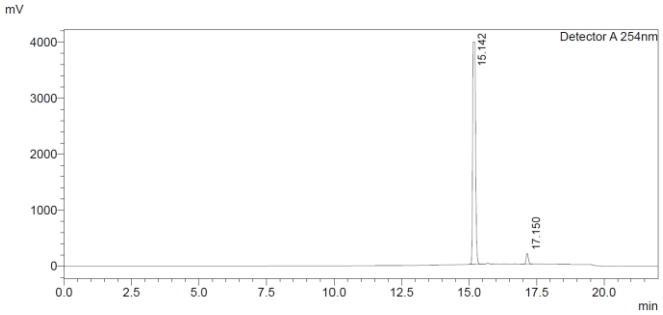
Borylation Procedure: **Procedure 3.3**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column A**. HPLC Conditions: **Method 1**. Non-isolated RCY = 53 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	64	88	56
2	59	85	50
3	61	85	52
4	62	86	53

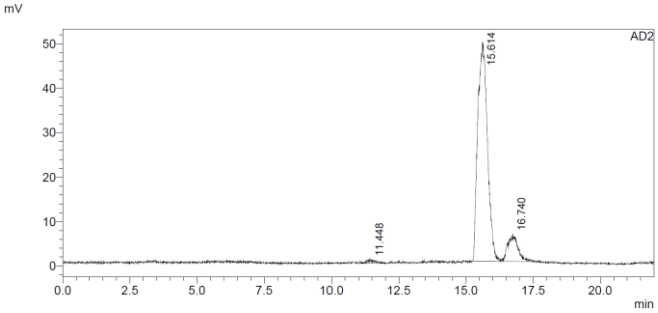
Radio TLC (Hex:EtOAc = 1:1)



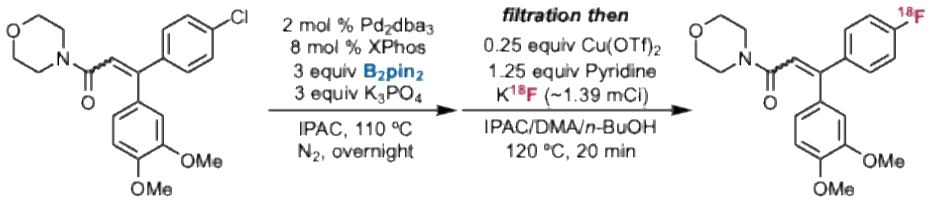
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



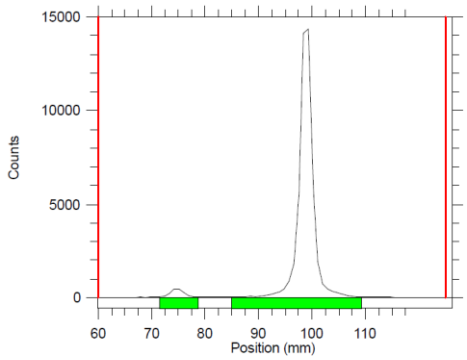
Dimethomorph (2gg)



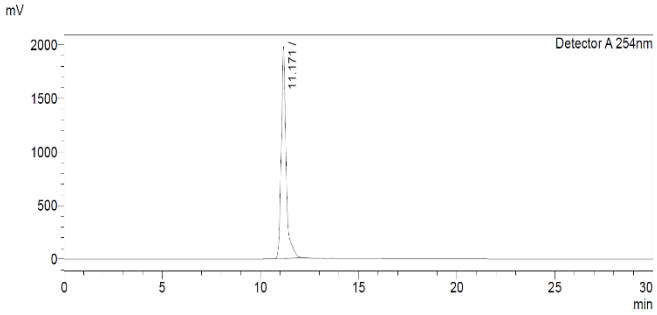
Borylation Procedure: **Procedure 3.4**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 94 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	97	99	97
2	94	99	94
3	94	99	94
4	91	99	91

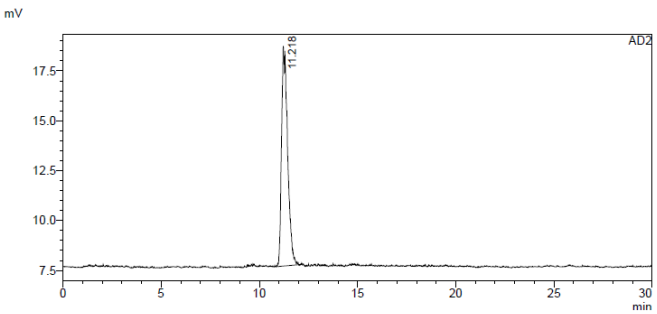
Radio TLC (Hex:EtOAc = 1:1)



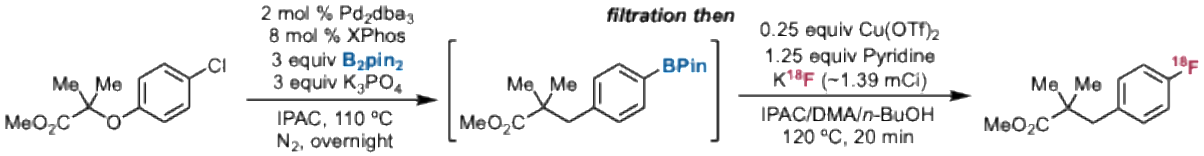
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



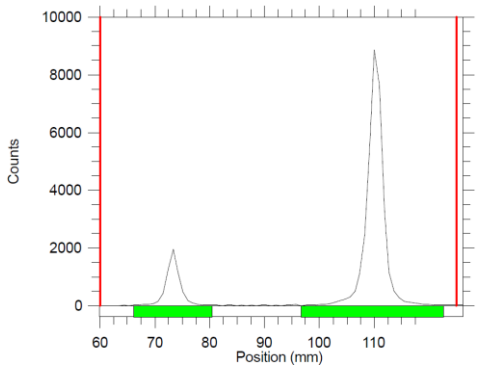
Clofibrate (2jj)



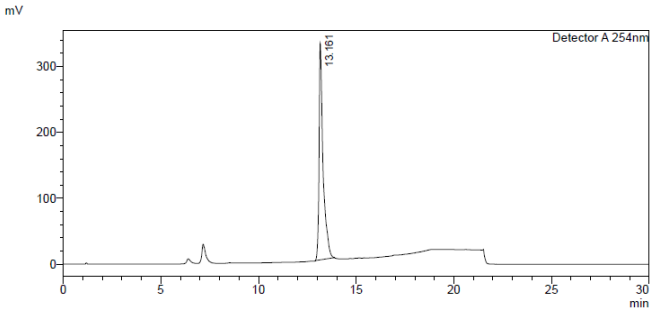
Borylation Procedure: **Procedure 3.4**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 72 ± 7%

n	RCC [%]	RCP [%]	RCY [%]
1	71	99	71
2	84	99	84
3	74	94	70
4	67	96	64

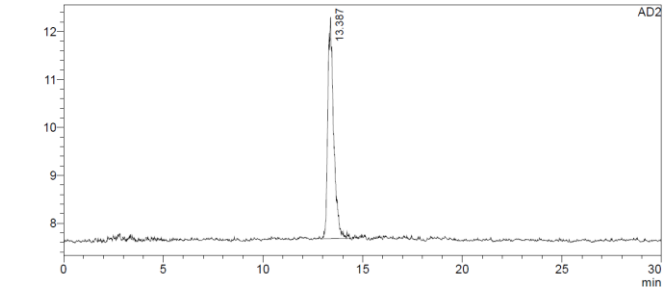
Radio TLC (Hex:EtOAc = 1:1)



HPLC (UV trace): authentic standard

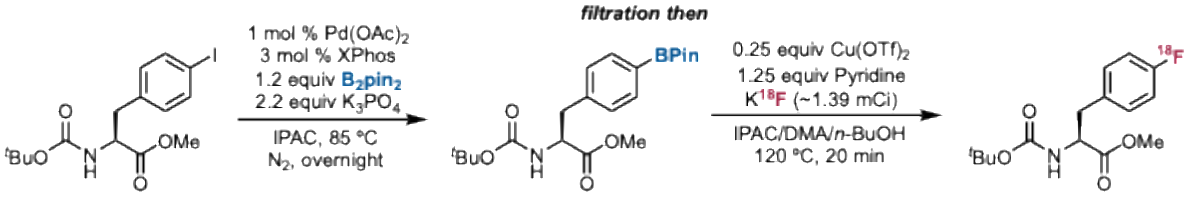


HPLC (radio trace): radiofluorination reaction (crude)



6.4.4 Amino Acids and Peptides

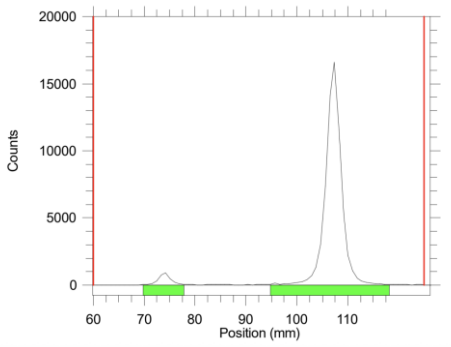
Boc-Phe(4-I)-OMe (3d)



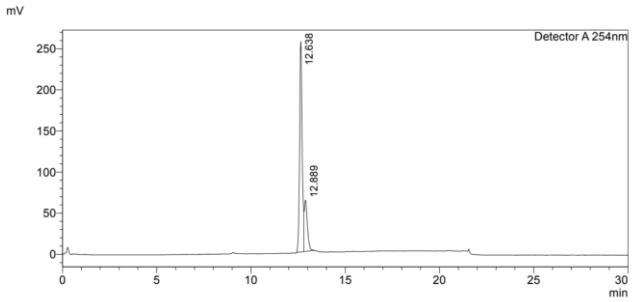
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 88 ± 4%

n	RCC [%]	RCP [%]	RCY [%]
1	90	97	87
2	85	97	82
3	96	97	93
4	95	96	91

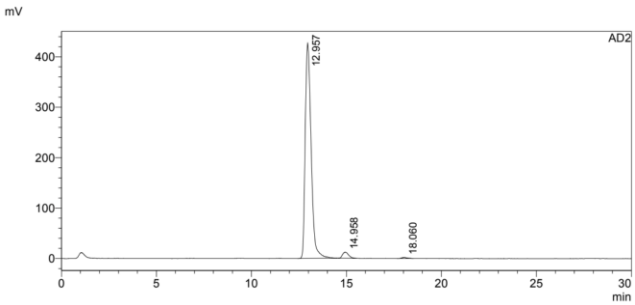
Radio TLC (Hex:EtOAc = 1:1)



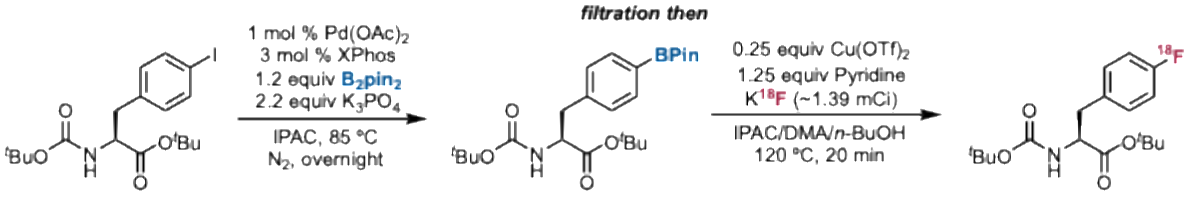
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



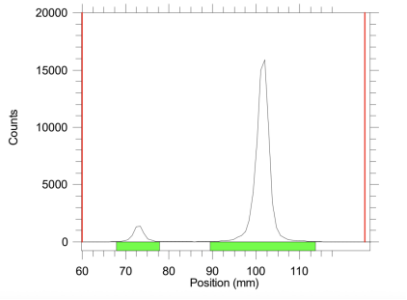
Boc-Phe(4-I)-O^{t}Bu (3e)



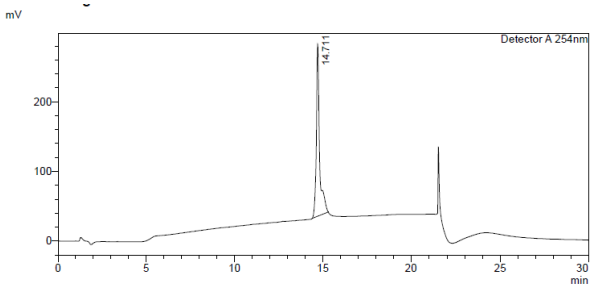
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B** HPLC Condition: **Method 3** Non-isolated RCY = 91 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	91	99	90
2	91	97	88
3	93	99	93
4	91	99	91

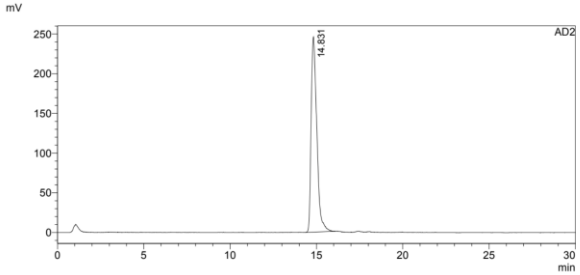
Radio TLC (Hex:EtOAc = 1:1)



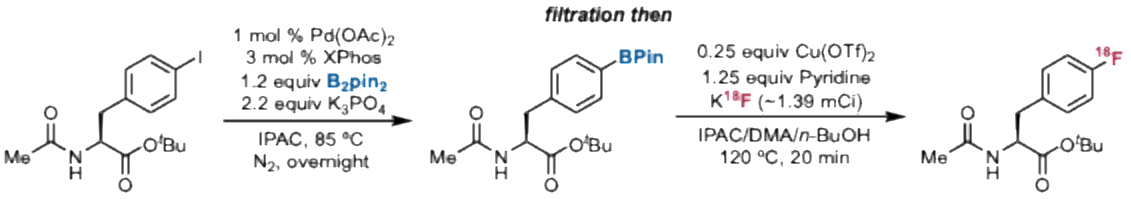
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



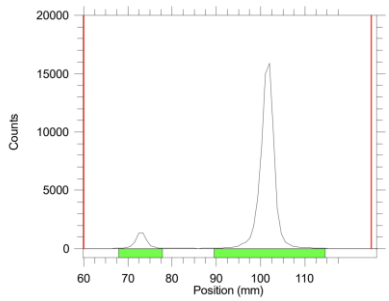
Ac-Phe(4-I)-OMe (3f)



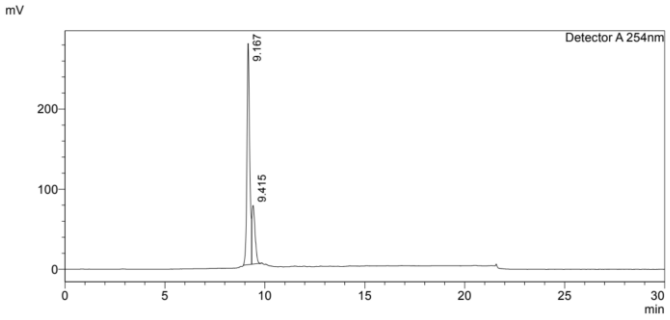
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 87 ± 3%

n	RCC [%]	RCP [%]	RCY [%]
1	93	96	89
2	91	96	87
3	93	88	82
4	94	95	89

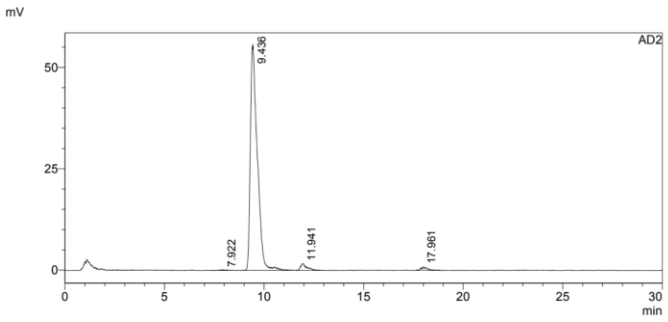
Radio TLC (Hex:EtOAc = 1:1)



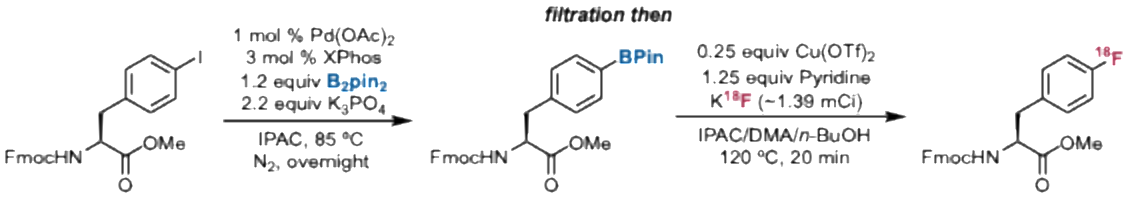
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



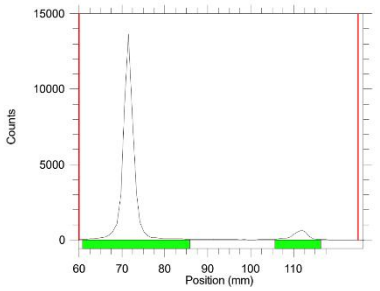
Fmoc-Phe(4-I)-OMe (3g)



Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 14 ± 10%

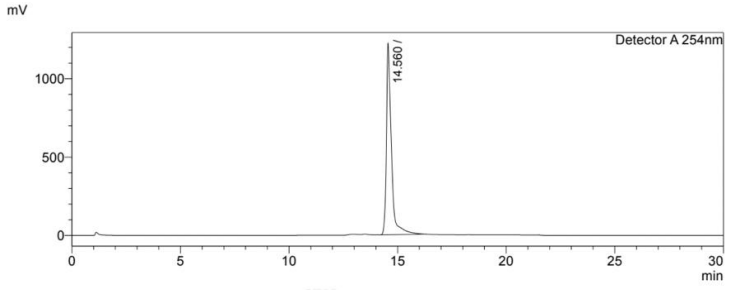
n	RCC [%]	RCP [%]	RCY [%]
1	9	99	9
2	29	99	29
3	8	99	8
4	9	99	9

Radio TLC (Hex:EtOAc = 1:1)

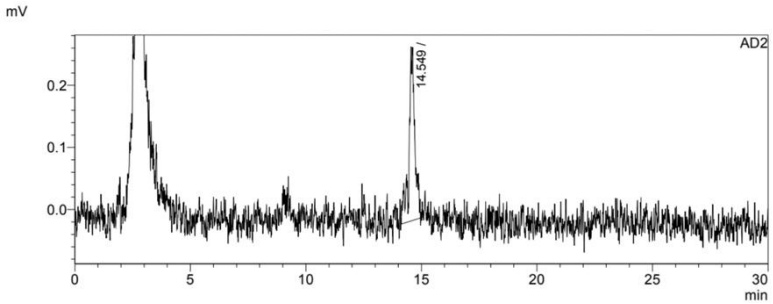


2

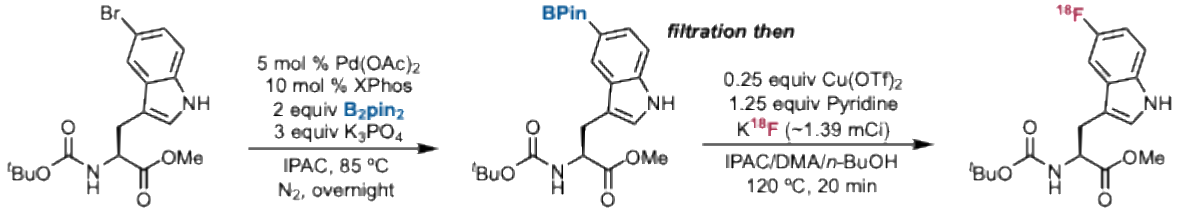
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



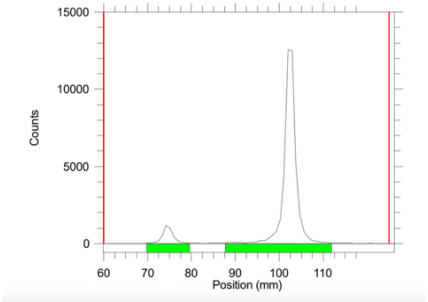
Boc-Trp(5-Br)-OMe (3h)



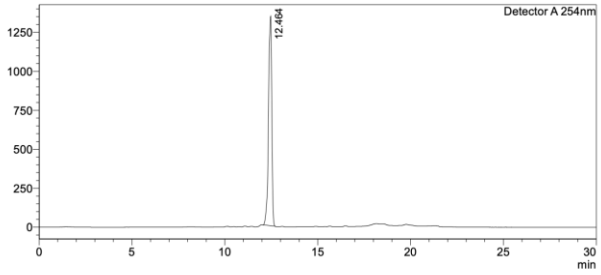
Borylation Procedure: **Procedure 3.1**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 92 ± 0%

n	RCC [%]	RCP [%]	RCY [%]
1	92	99	92
2	92	99	92
3	92	99	92
4	92	99	92

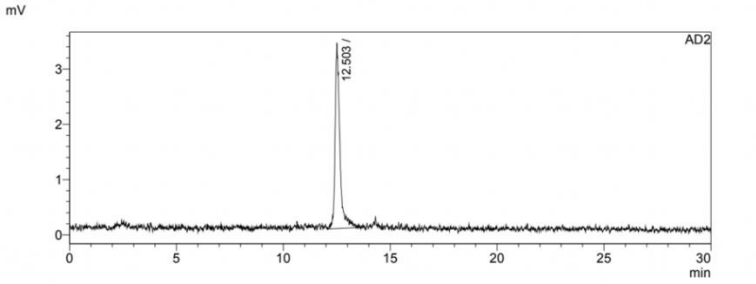
Radio TLC (Hex:EtOAc = 1:1)



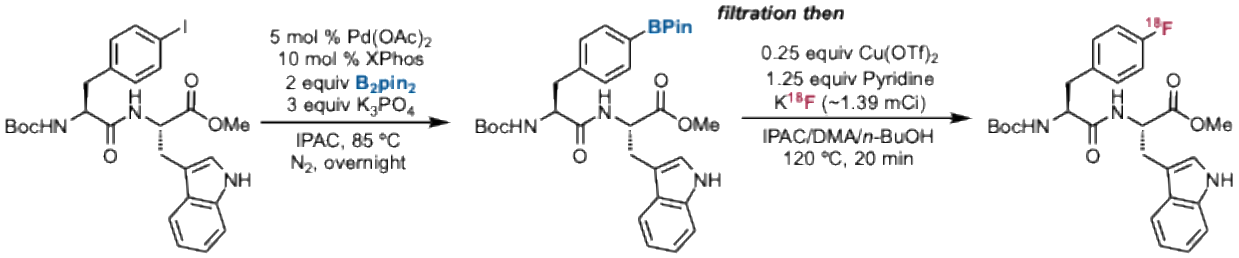
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



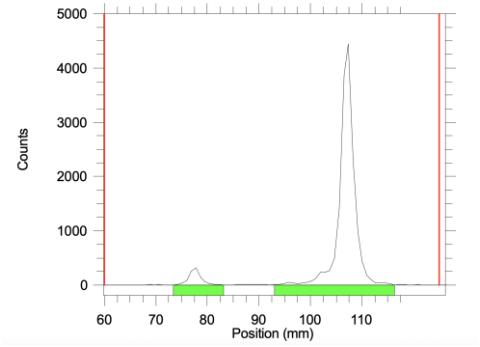
Boc-Phe(4-I)-Trp-OMe (4a)



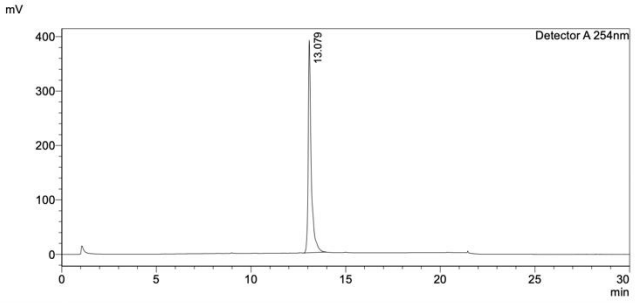
Borylation Procedure: **Procedure 3.3**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 83 ± 3%

n	RCC [%]	RCP [%]	RCY [%]
1	88	92	81
2	91	92	84
3	94	85	80
4	94	90	85

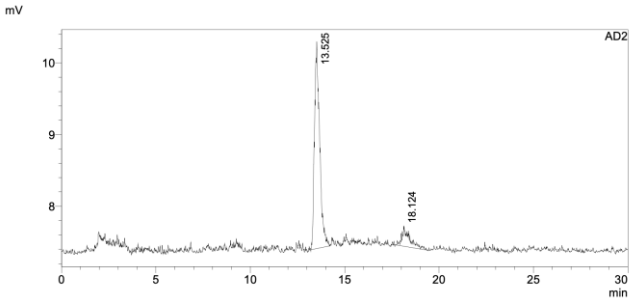
Radio TLC (Hex:EtOAc = 1:1)



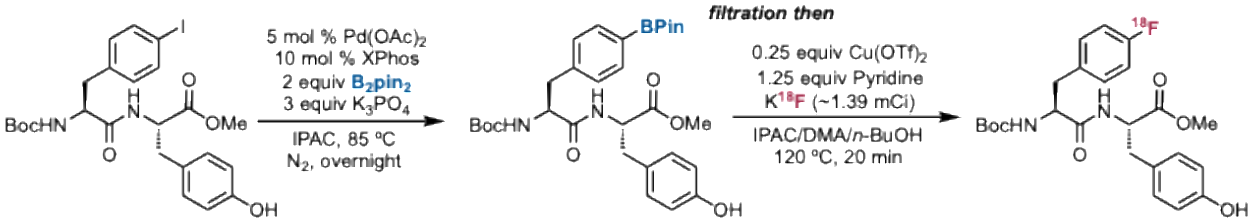
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



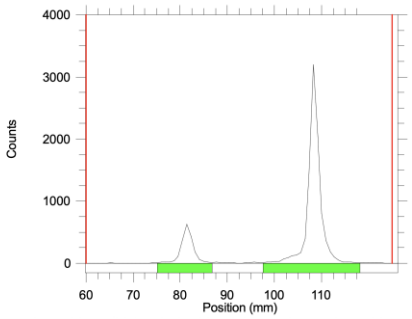
Boc-Phe(4-I)-Tyr-OMe (4b)



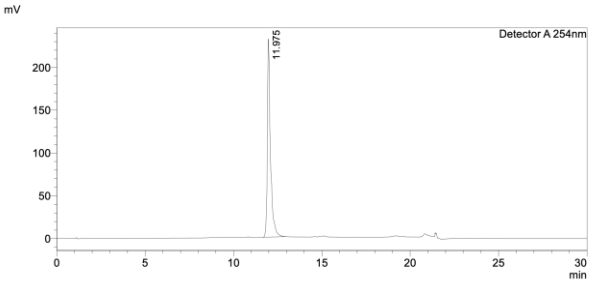
Borylation Procedure: **Procedure 3.3**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 69 ± 7%

n	RCC [%]	RCP [%]	RCY [%]
1	70	91	64
2	83	90	75
3	82	91	75
4	62	100	62

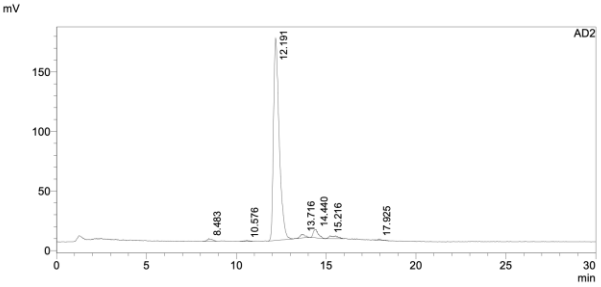
Radio TLC (Hex:EtOAc = 1:1)



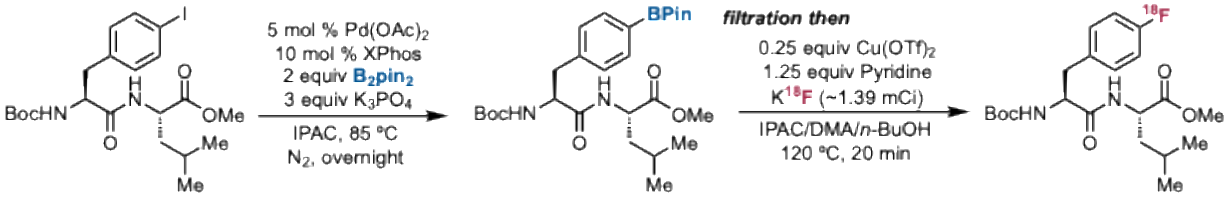
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



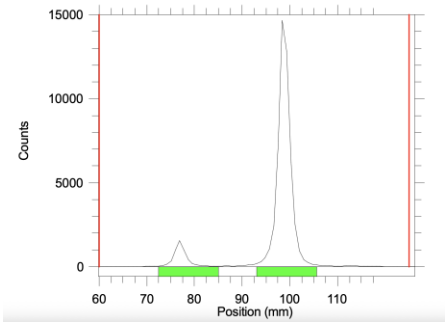
Boc-Phe(4-I)-Leu-OMe (4c)



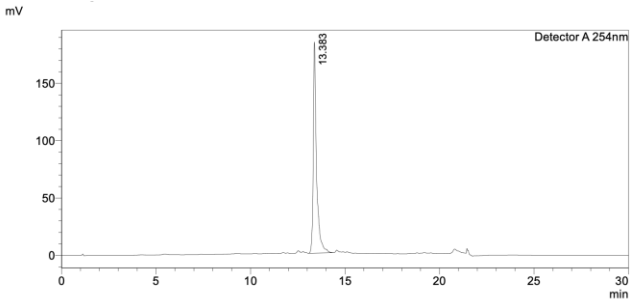
Borylation Procedure: **Procedure 3.3**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 85 ± 4%

n	RCC [%]	RCP [%]	RCY [%]
1	91	93	85
2	93	94	88
3	92	95	87
4	94	85	80

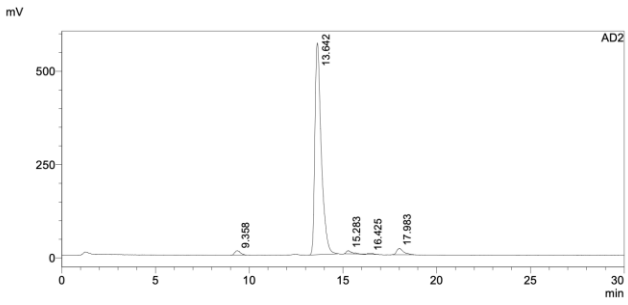
Radio TLC (Hex:EtOAc = 1:1)



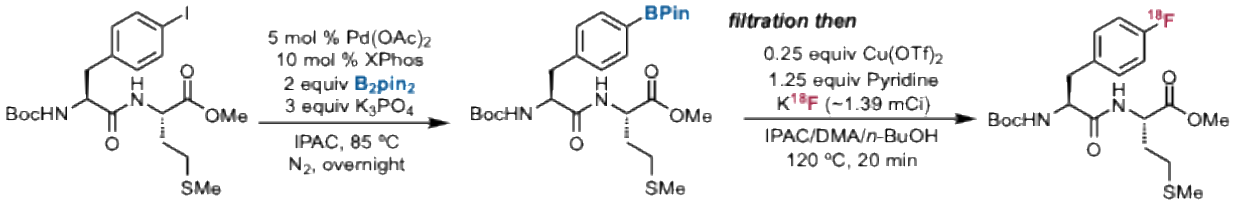
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



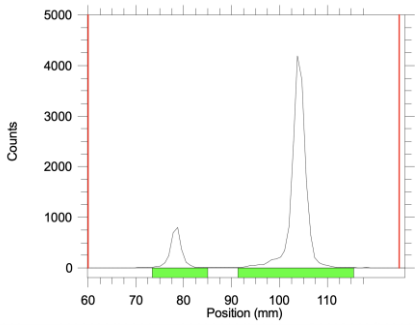
Boc-Phe(4-I)-Met-OMe (4d)



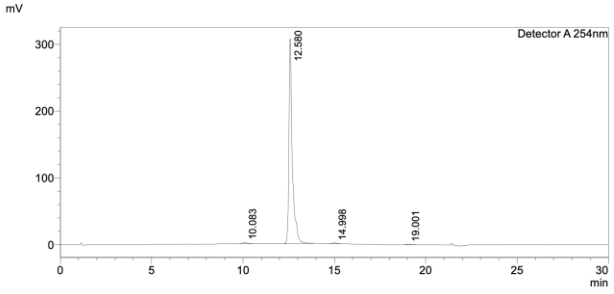
Borylation Procedure: **Procedure 3.3**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 75 ± 1%

n	RCC [%]	RCP [%]	RCY [%]
1	88	84	74
2	88	86	76
3	85	88	75
4	86	87	75

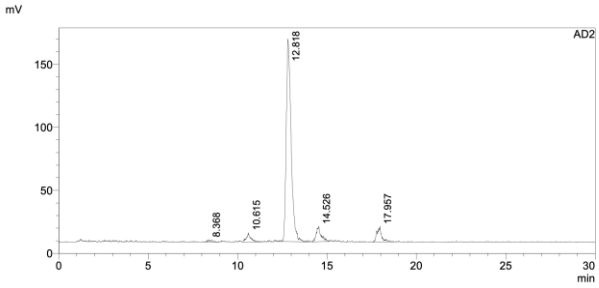
Radio TLC (Hex:EtOAc = 1:1)



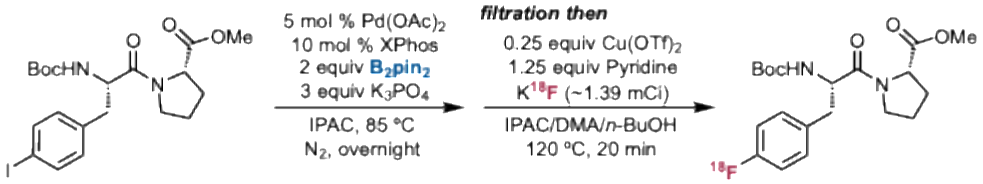
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



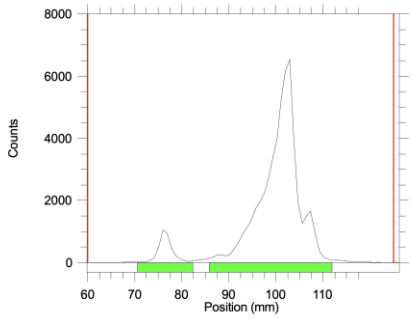
Boc-Phe(4-I)-Pro-OMe (4e)



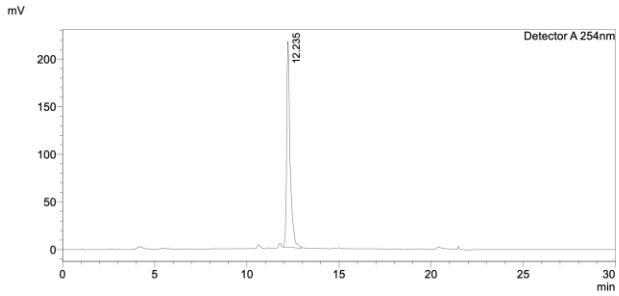
Borylation Procedure: **Procedure 3.3**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 79 ± 2%

n	RCC [%]	RCP [%]	RCY [%]
1	93	87	81
2	86	89	77
3	86	92	79
4	86	90	77

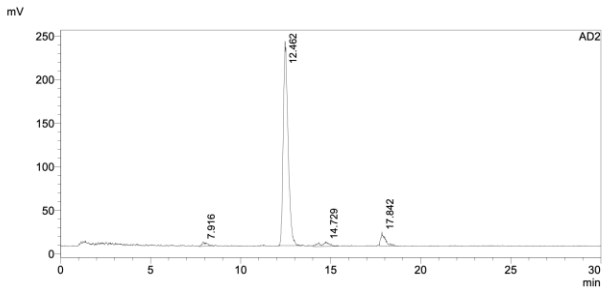
Radio TLC (Hex:EtOAc = 1:1)



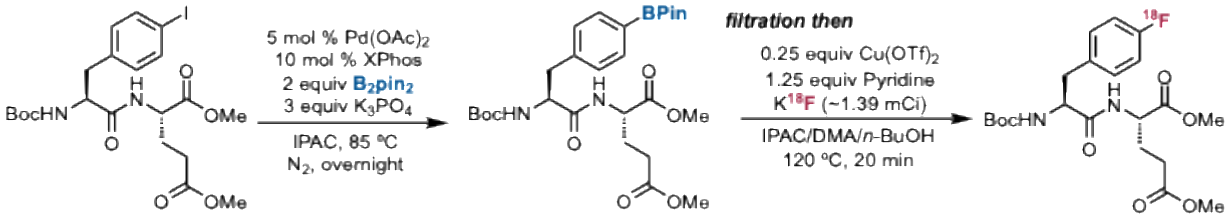
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



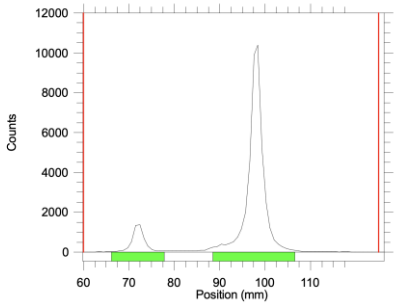
Boc-Phe(4-I)-Glu(OMe)-OMe (4f)



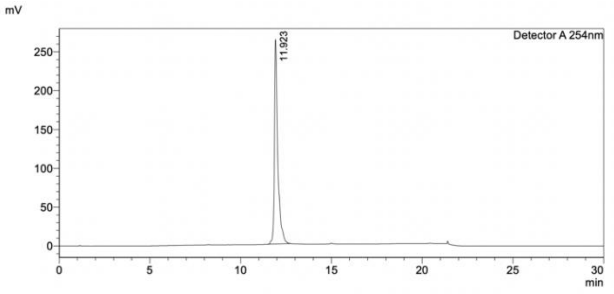
Borylation Procedure: **Procedure 3.3**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Conditions: **Method 3**. Non-isolated RCY = 76 ± 5%

n	RCC [%]	RCP [%]	RCY [%]
1	89	79	70
2	89	81	72
3	88	91	80
4	90	89	80

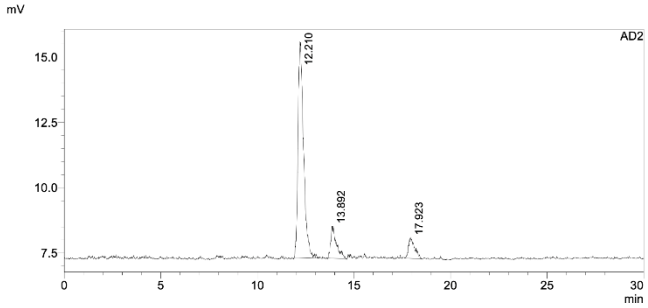
Radio TLC (Hex:EtOAc = 1:1)



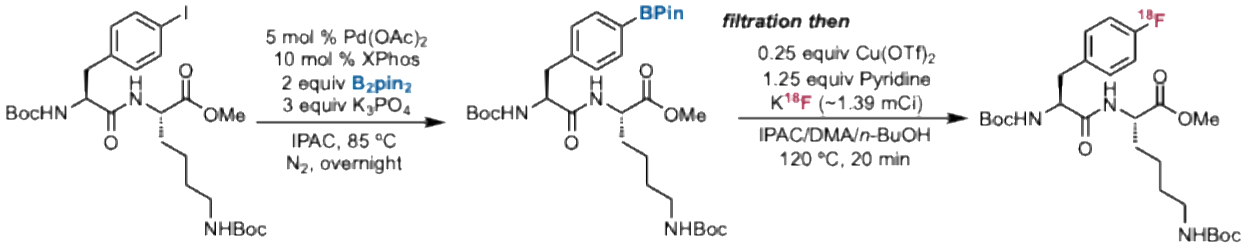
HPLC (UV trace): authentic standard



HPLC (radio trace): radiofluorination reaction (crude)



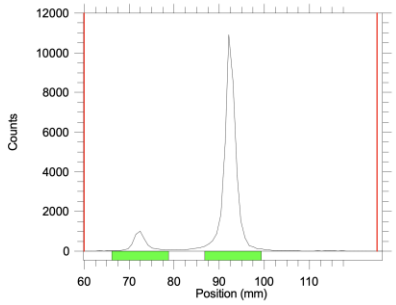
Boc-Phe(4-I)-Lys(Boc)-OMe (4g)



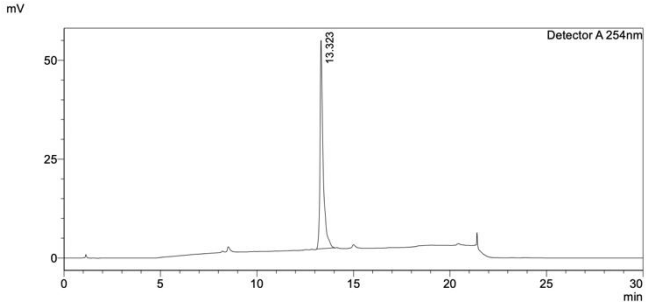
Borylation Procedure: **Procedure 3.3**. Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column B**. HPLC Condition: **Method 3**. Non-isolated RCY = 77 ± 6%

n	RCC [%]	RCP [%]	RCY [%]
1	90	84	76
2	83	83	69
3	91	90	82
4	89	90	80

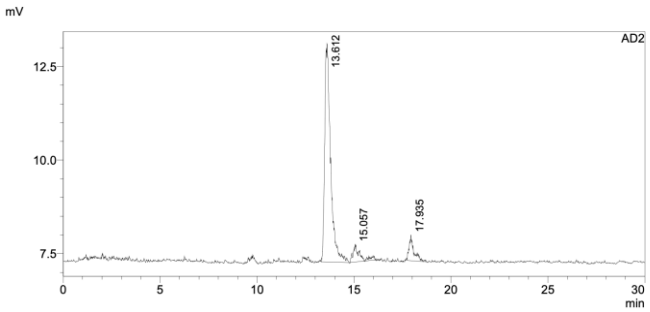
Radio TLC (Hex:EtOAc = 1:1)



HPLC (UV trace): authentic standard



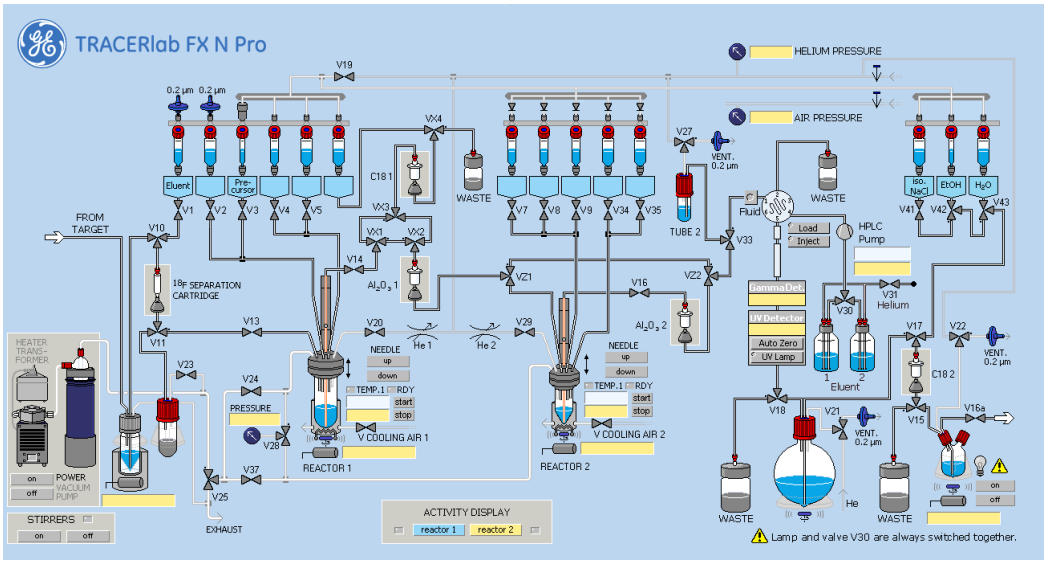
HPLC (radio trace): radiofluorination reaction (crude)



7. Automated Radiofluorination

7.1 Reaction Setup

7.1.1 Synthesis Module Configuration



Note: Line from V14 was connected to the dilution flask at V18 for reformulation after the reaction.

7.1.2 General Reaction Setup

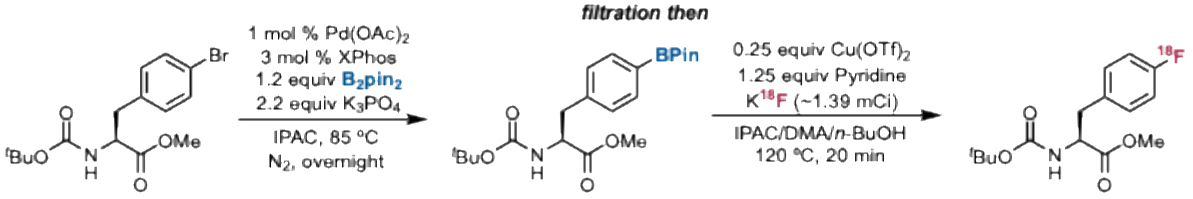
See section 3 (Borylation General Procedure) for the first step of the aryl halide radiofluorination step (Procedure 3B). Aryl halide borylation was carried out on a 125 µmol scale for 16 h. After filtration, 80 µL of the reaction was transferred to the synthesis module reactor Vial 4. DMA (40 µL) was then added.

$Cu(OTf)_2$ (18.77 equiv, 135.75 mg) was weighed into a vial under N_2. Pyridine (75 equiv, 151.2 µL) and dimethyl acetamide (DMA) (1.5 mL) were then added and the mixture was sonicated to ensure complete dissolution. An aliquot of this solution (40 µL) was added to Vial 3, followed by additional DMA (160 µL).

n-BuOH (600 µL) was added to Vial 5.

[^{18}F]KF was produced in a cyclotron (30 min beam) as described in the literature[21] and then trapped on a QMA Sep-Pak filter and eluted into the reaction vessel using KOTf (10 mg) and K_2CO_3 (50 µg) in H_2O (0.5 mL). The solution was azeotropically dried with MeCN (1 mL) at 100 °C. After drying, the reaction was allowed to cool to 50 °C before dispensing of Vials 3, 4, and 5 in the stated order. The temperature was then increased to 120 °C, and the mixture was stirred for 20 min. The reaction was allowed to cool to room temperature, water (2 mL; vial 6) was added, and the resulting solution was diluted with an additional 50 mL of H_2O in the dilution flask (modification connecting V14 to V18 is used) before transferring and trapping onto a C18 Sep-pak. The C18-Sep-pak was then washed with 10 mL of H_2O to remove inorganic impurities. Elution with 2 mL of EtOH was used to transfer the product into a 10 mL sterile vial, and then the yield and molar activity were measured.

7.2 Reaction



Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column D**. HPLC Conditions: **Method 6**.

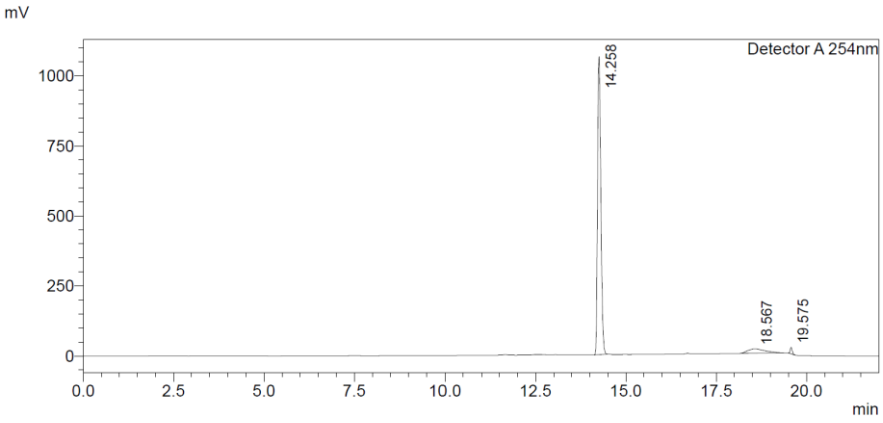
The radiofluorination was automated in a synthesis module in a hot cell

n	RCY [%]	Molar Activity (Ci/mmol)	Molar Activity (TBq/mmol)
1	2.5	20625	763
2	16.0	10586	392

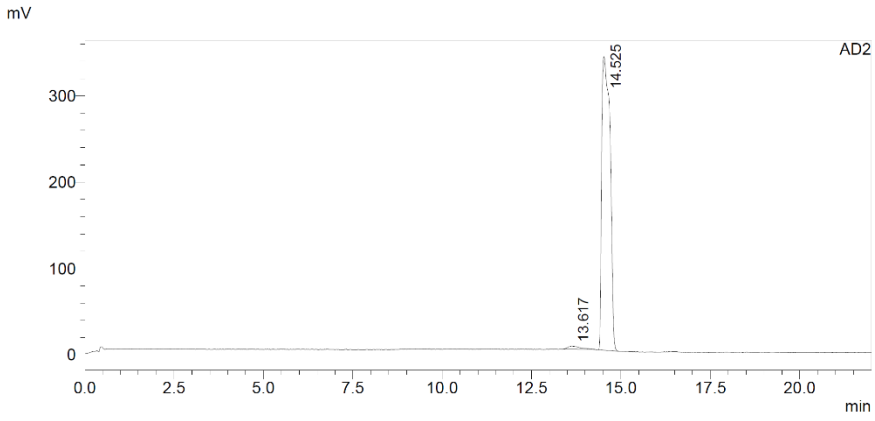
Table 4

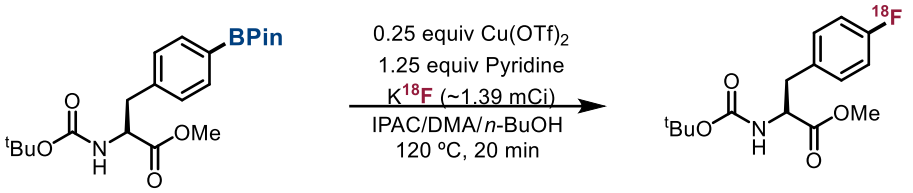
RCY = Decay-Corrected calculated via **Section 5.1**

Analytical HPLC (UV trace): authentic standard



Analytical HPLC (radio trace): authentic standard





*From commercially available pure Boc-Phe(4-BPin)-OMe via Ambeed

Radiofluorination conditions: **Procedure 6.2A**. HPLC Column: **Column D**. HPLC Conditions: **Method 6**.

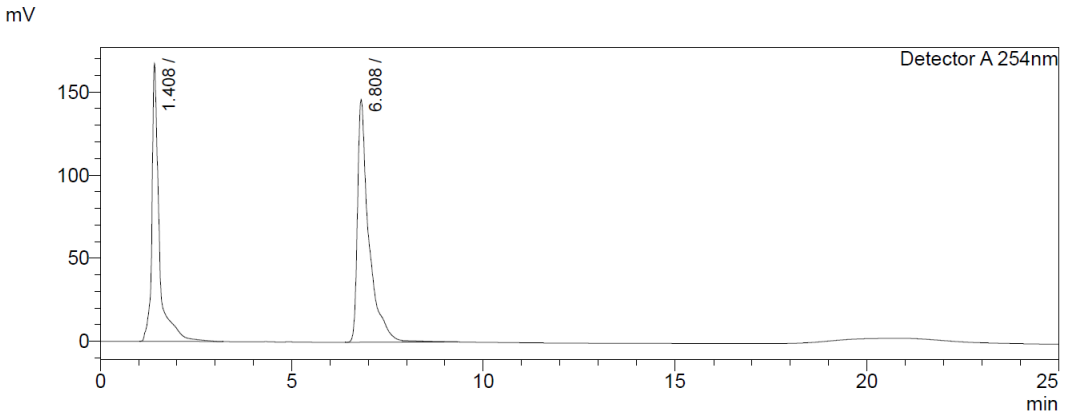
The radiofluorination was automated in a synthesis module in a hot cell

RCY = Decay-Corrected calculated via **Section 5.1**

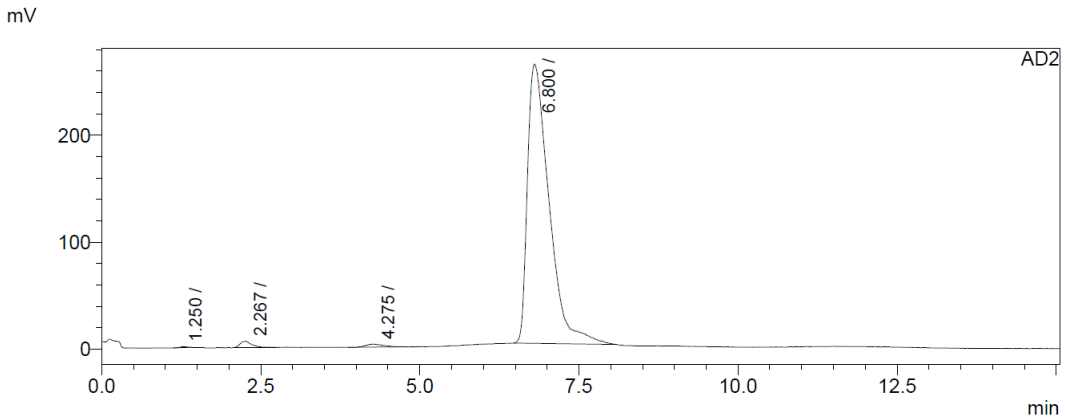
RCY [%]	Molar Activity (Ci/mmol)	Molar Activity (TBq/mmol)
13.29	1599	59

Table 5

Analytical HPLC (UV trace): authentic standard



Analytical HPLC (radio trace): authentic standard

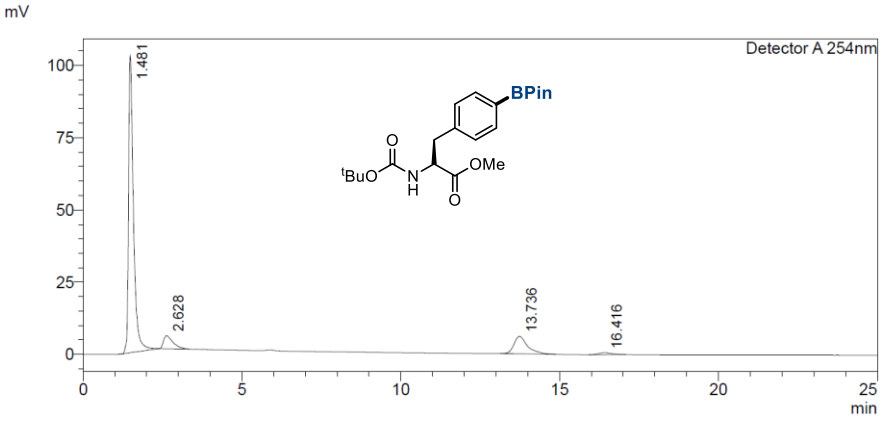


All Derivatives for Phenylalanine

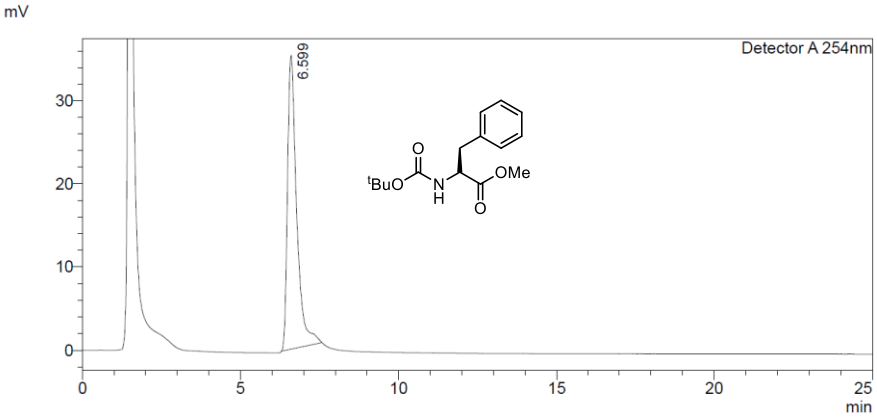
Note that the peak at 1.48 min represents the DMF that these compounds were dissolved in.

The difference in retention time compared to previous automation is due to the use of the hplc column over time. CoInjects confirmed that this was indeed still the same product as seen in the previous page.

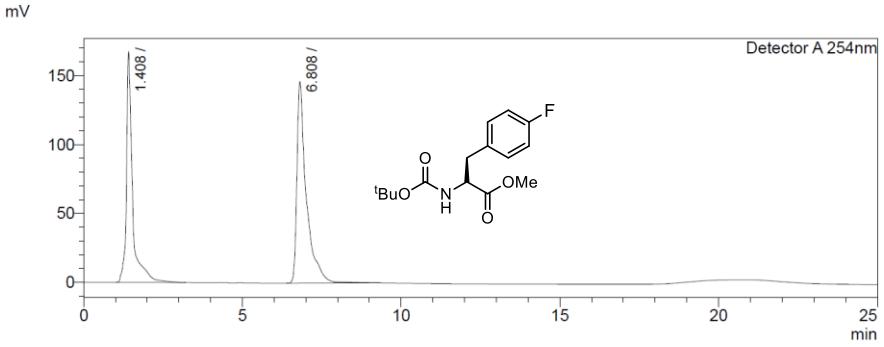
Analytical HPLC (UV trace): authentic standard for BPin



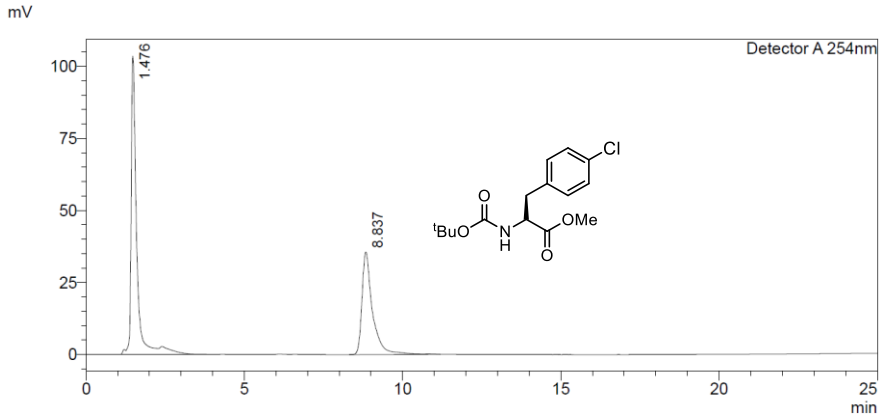
Analytical HPLC (UV trace): authentic standard for Proto



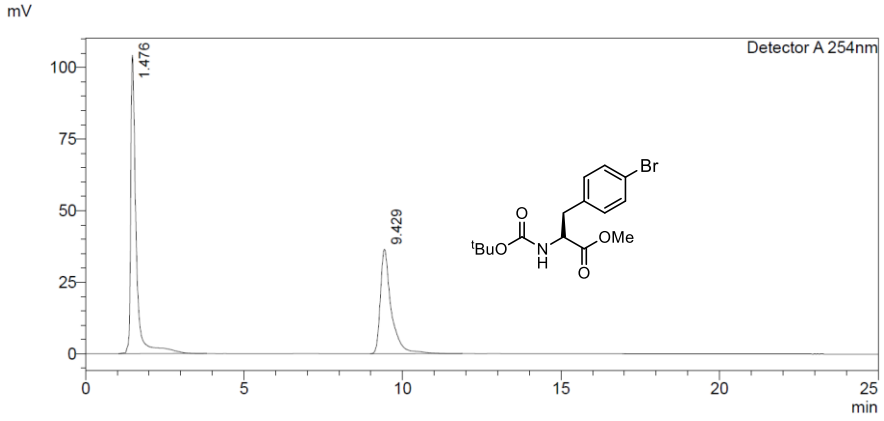
Analytical HPLC (UV trace): authentic standard for Fluoro



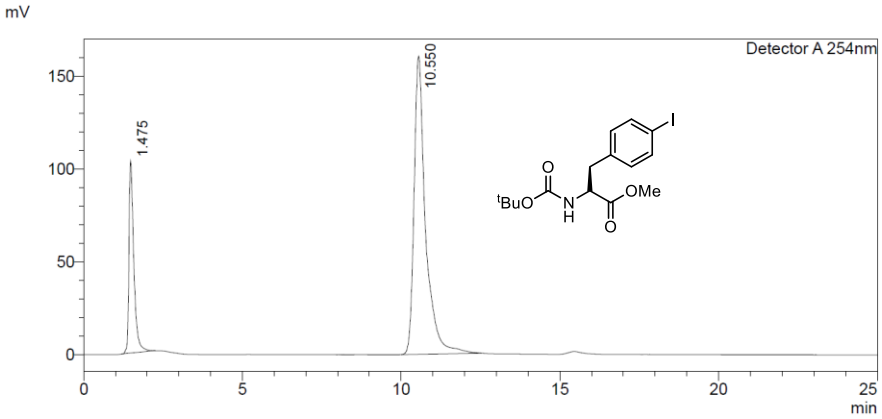
Analytical HPLC (UV trace): authentic standard for Chloro



Analytical HPLC (UV trace): authentic standard for Bromo

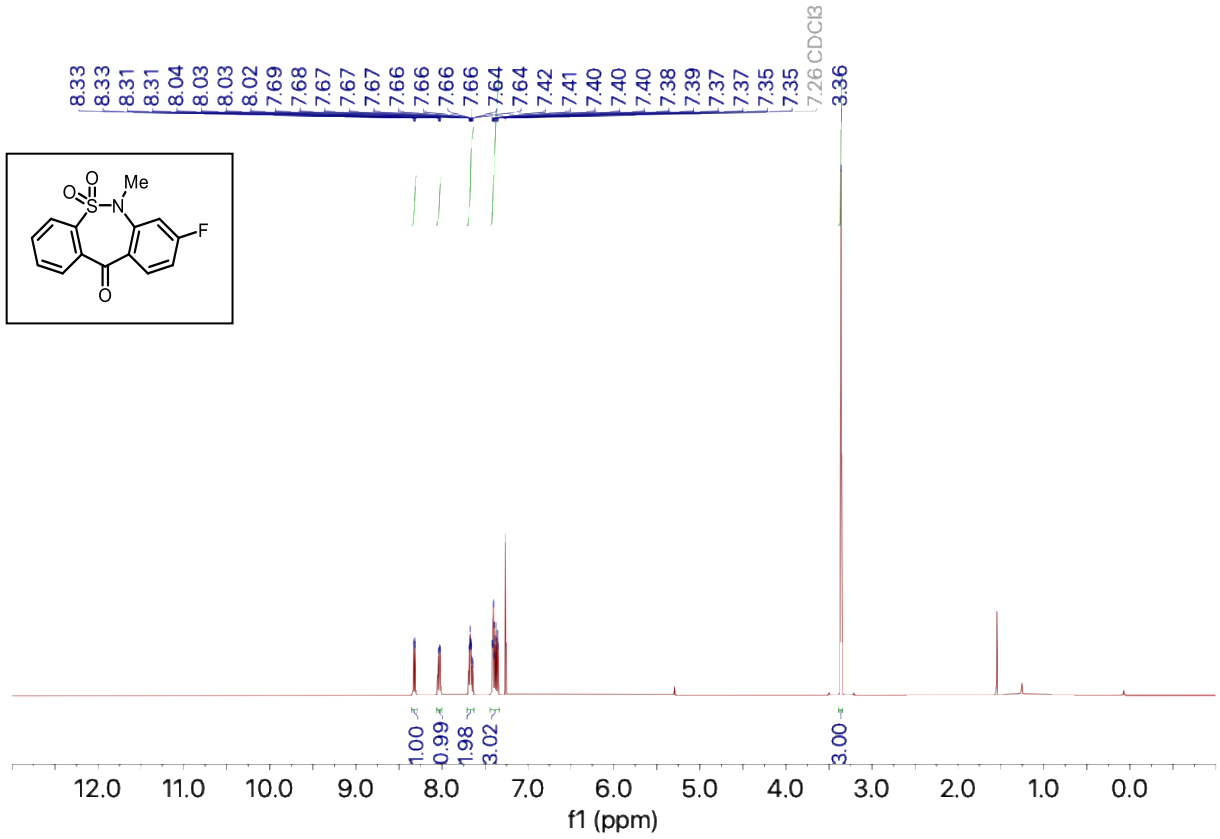


Analytical HPLC (UV trace): authentic standard for Iodo

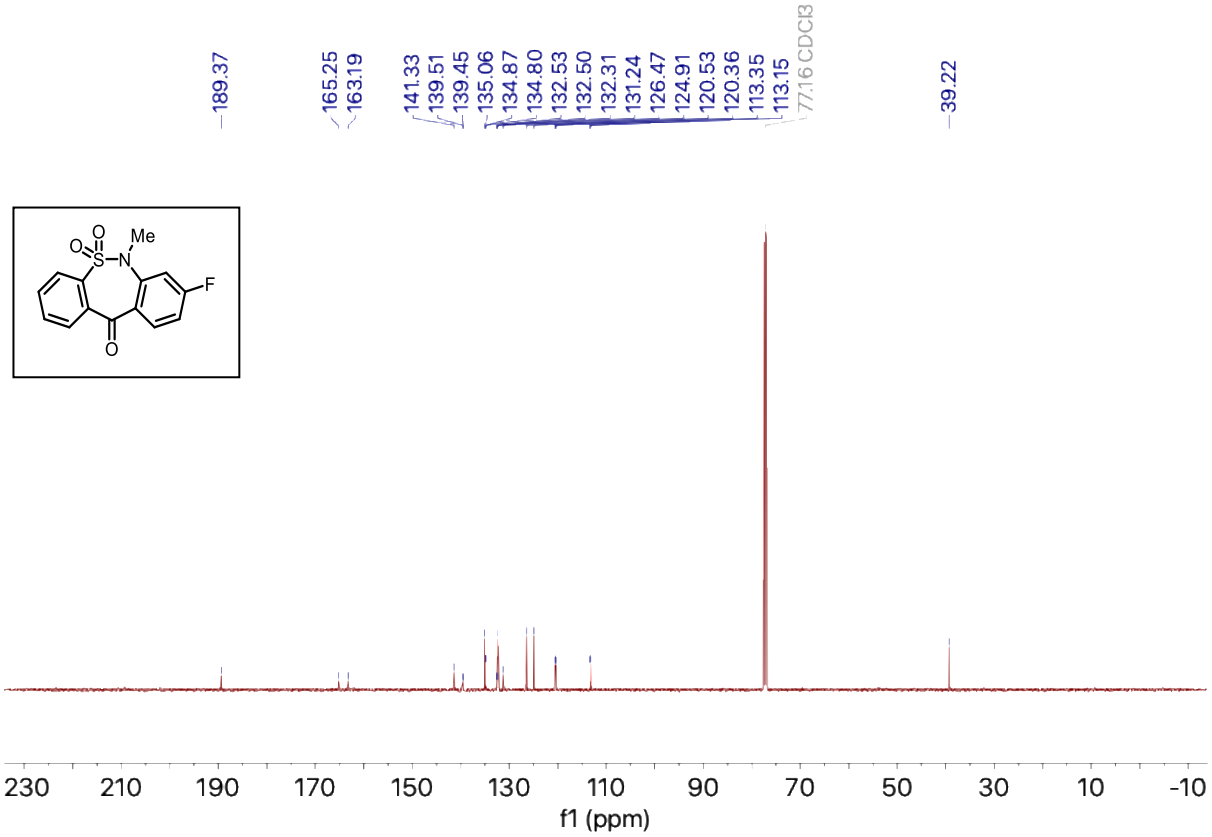


8. NMR Analysis

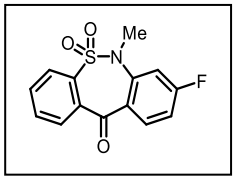
^{1}H NMR ($CDCl_3$, 500 MHz) of 8-fluoro-6-methyldibenzo[c,f][1,2]thiazepin-11(6H)-one 5,5-dioxide



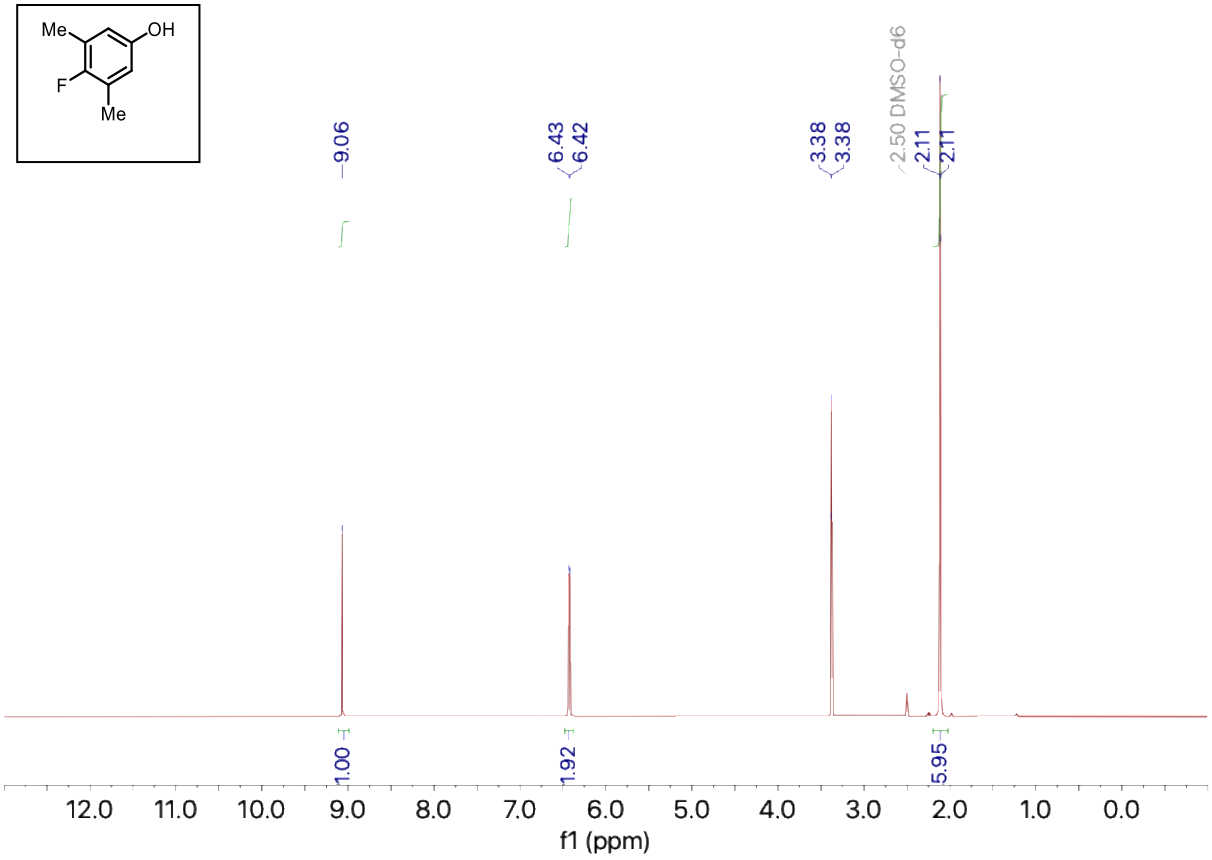
^{13}C NMR ($CDCl_3$, 126 MHz) of 8-fluoro-6-methyldibenzo[c,f][1,2]thiazepin-11(6H)-one 5,5-dioxide



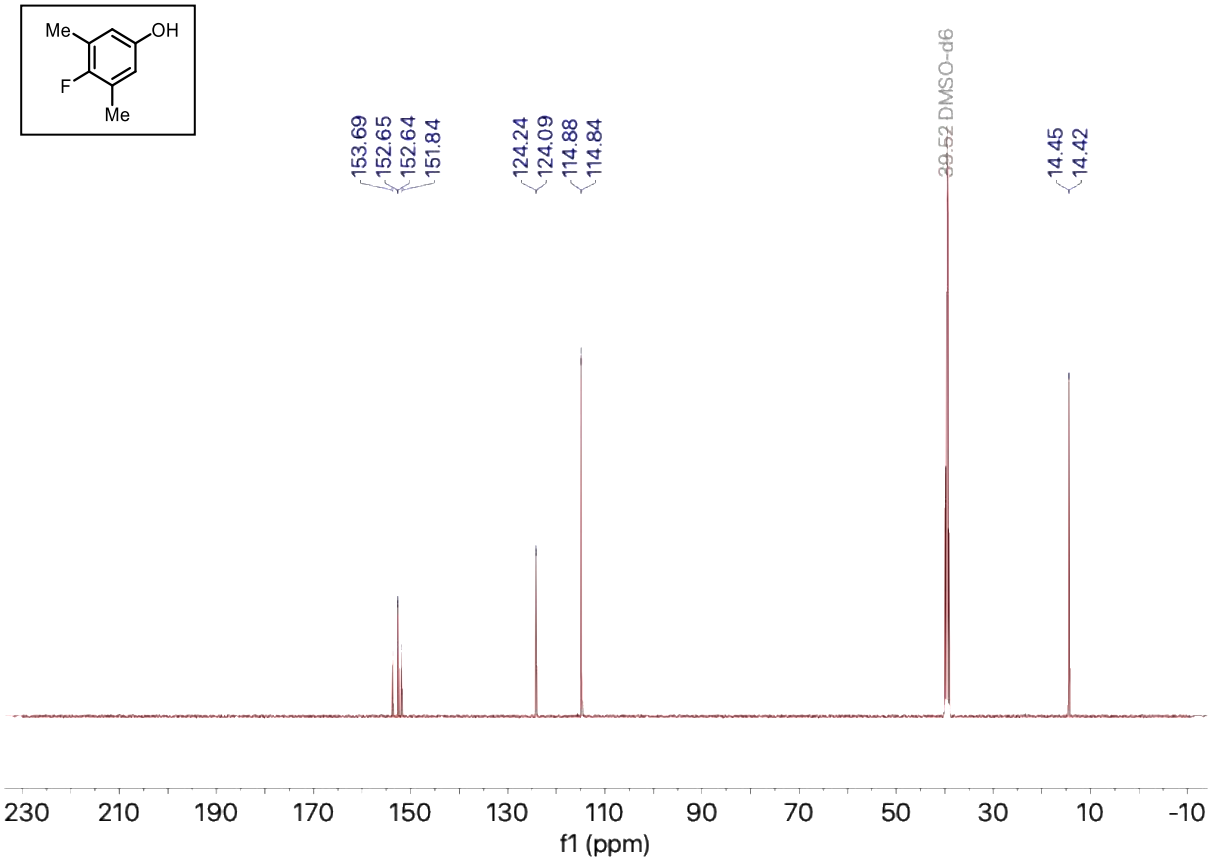
^{19}F NMR ($CDCl_3$, 377 MHz) of 8-fluoro-6-methyldibenzo[c,f][1,2]thiazepin-11(6H)-one 5,5-dioxide



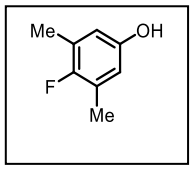
^{1}H NMR (DMSO-d_6, 500 MHz) of 4-fluoro-3,5-dimethylphenol



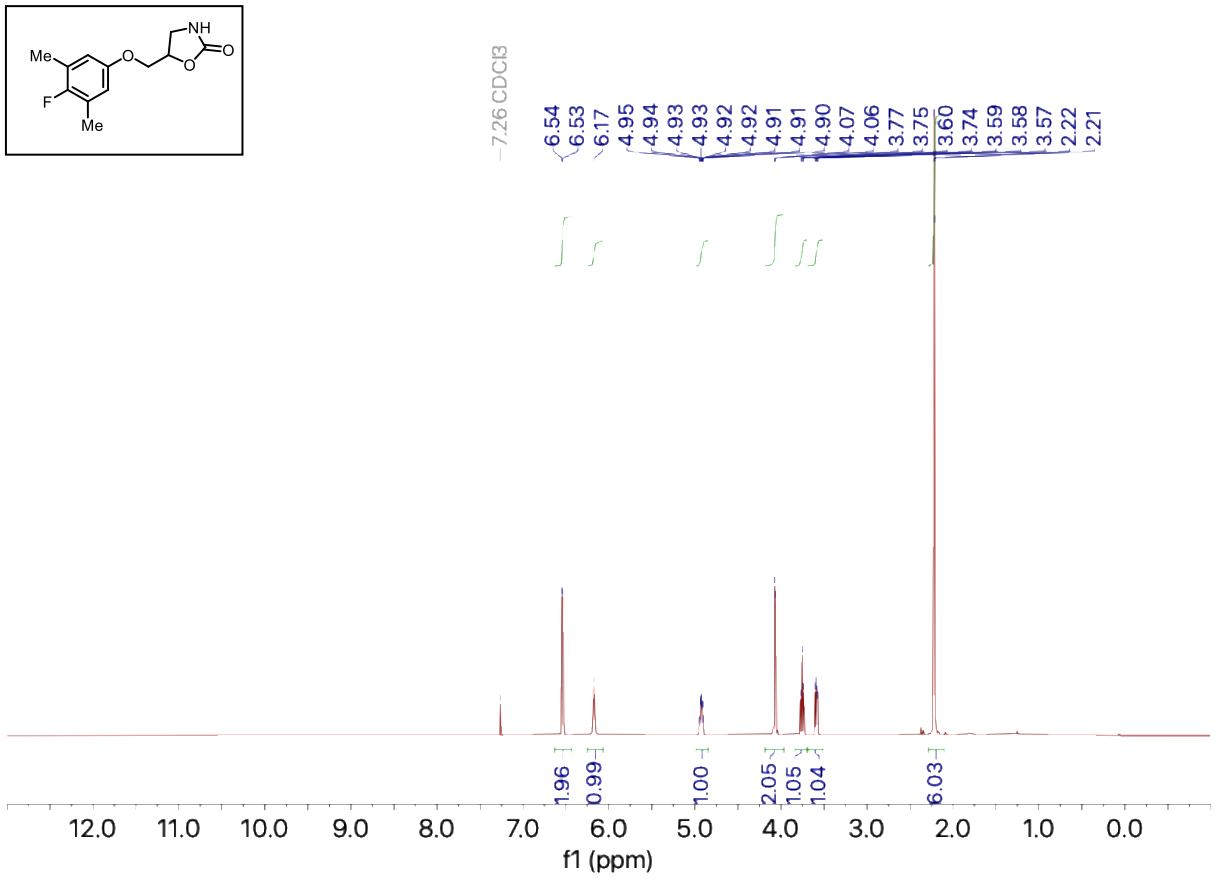
^{13}C NMR (DMSO-d_6, 126 MHz) of 4-fluoro-3,5-dimethylphenol



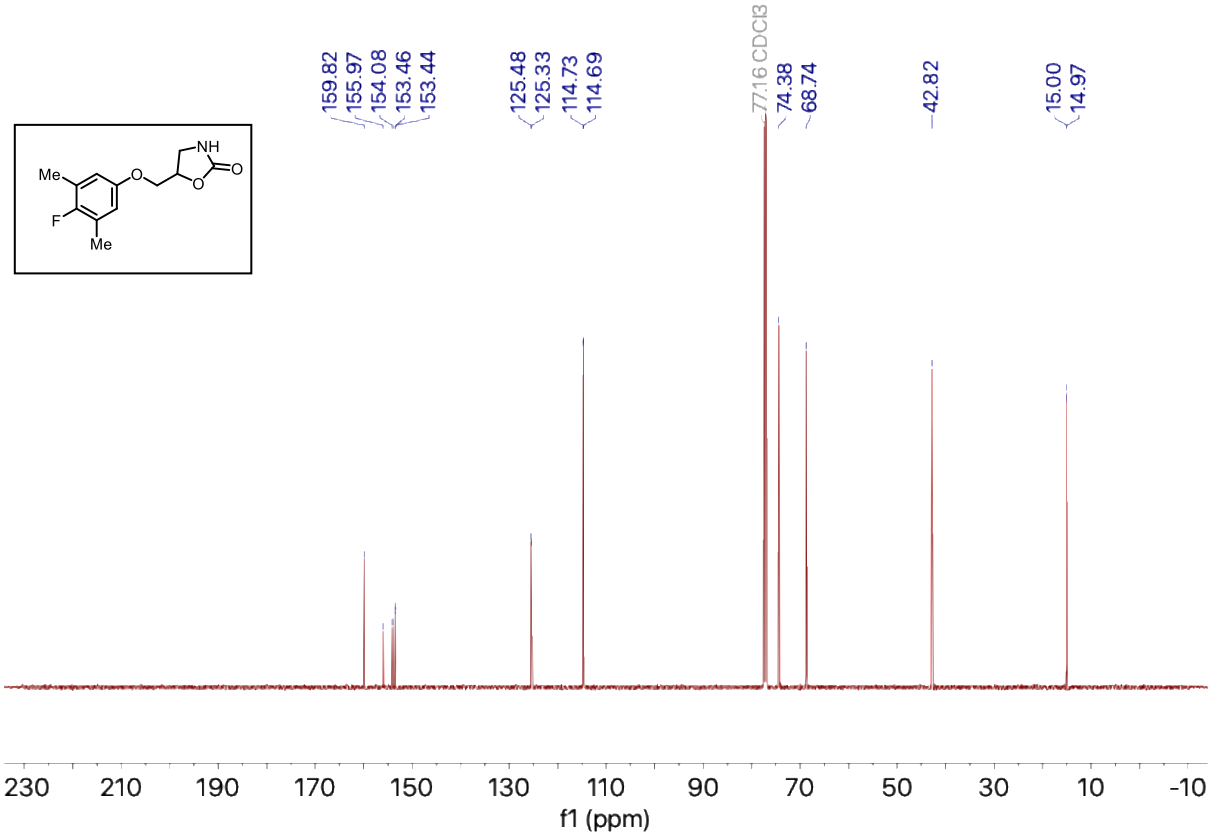
^{19}F NMR (DMSO-d_6, 377 MHz) of 4-fluoro-3,5-dimethylphenol



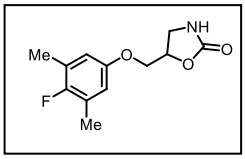
^{1}H NMR ($CDCl_3$, 500 MHz) of 5-((4-fluoro-3,5-dimethylphenoxy)methyl)oxazolidin-2-one



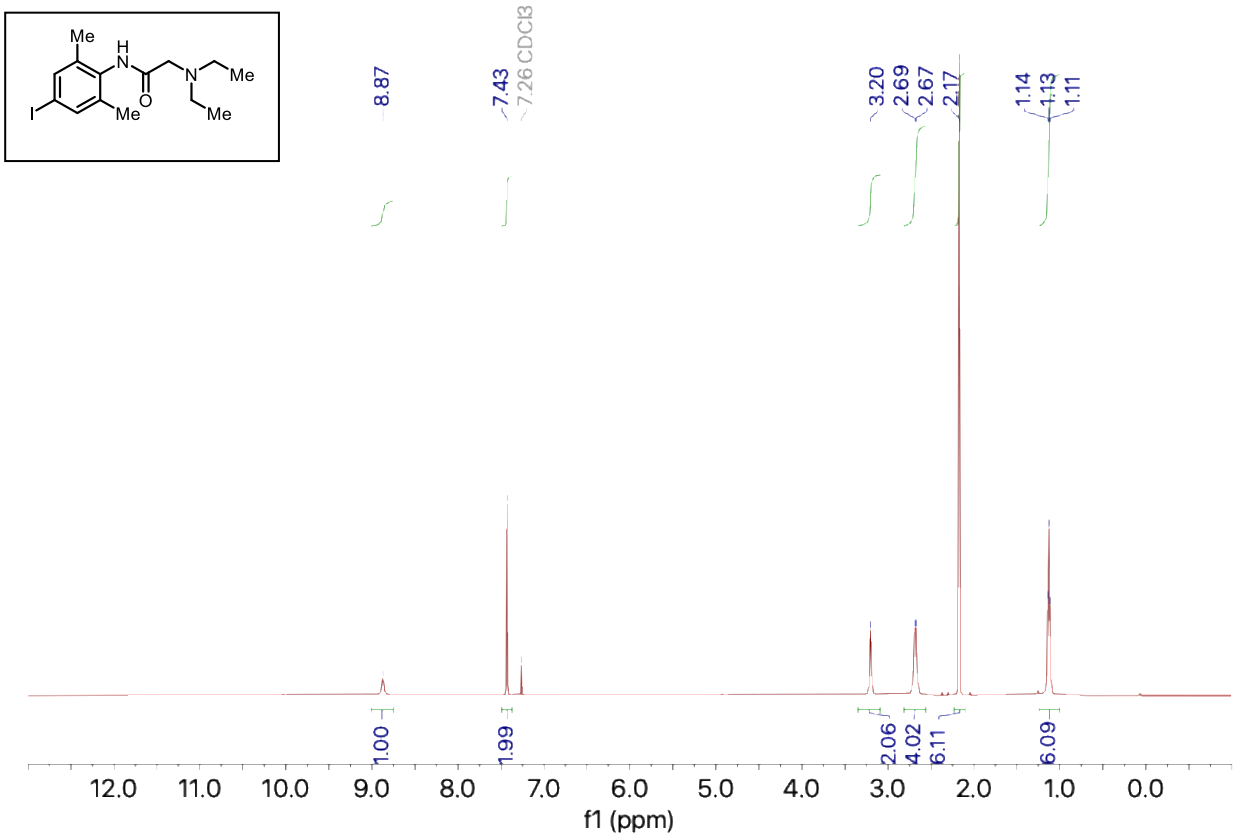
^{13}C NMR ($CDCl_3$, 126 MHz) of 5-((4-fluoro-3,5-dimethylphenoxy)methyl)oxazolidin-2-one



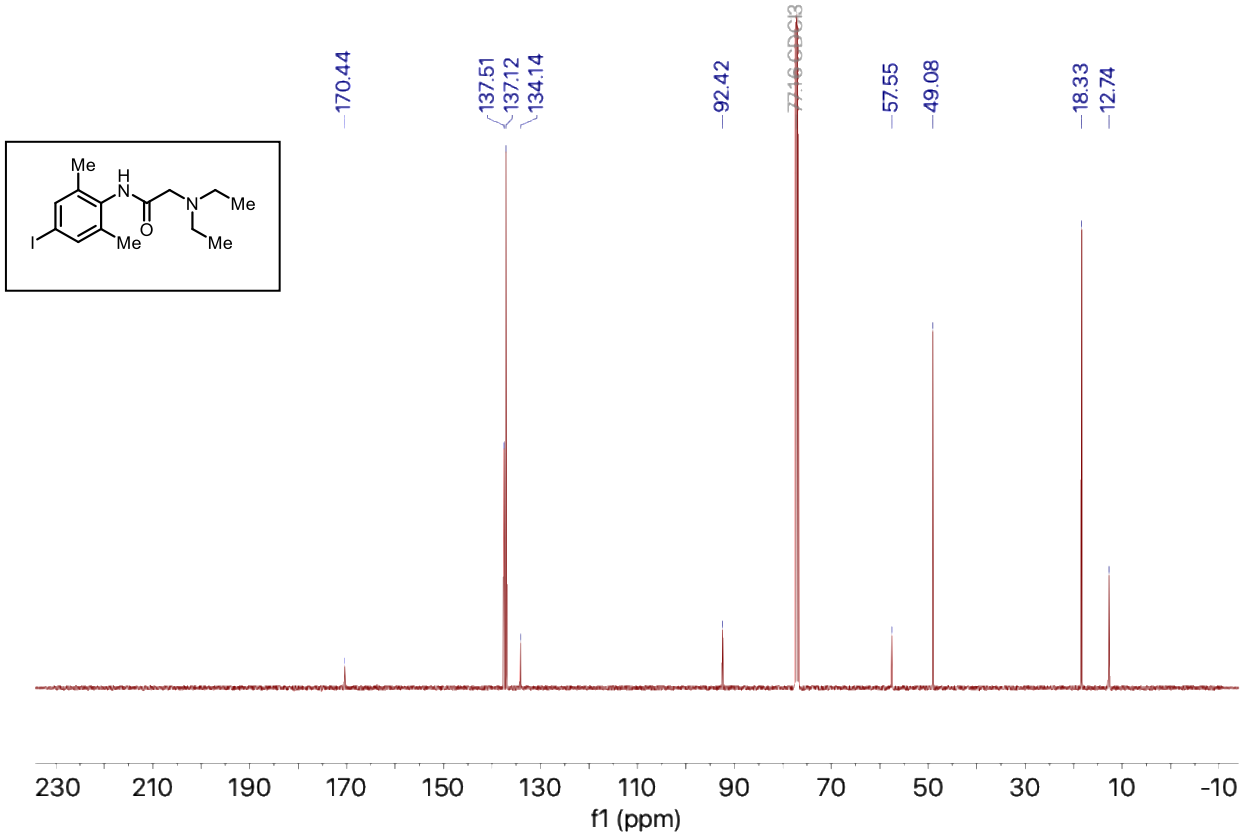
^{19}F NMR ($CDCl_3$, 377 MHz) of 5-((4-fluoro-3,5-dimethylphenoxy)methyl)oxazolidin-2-one



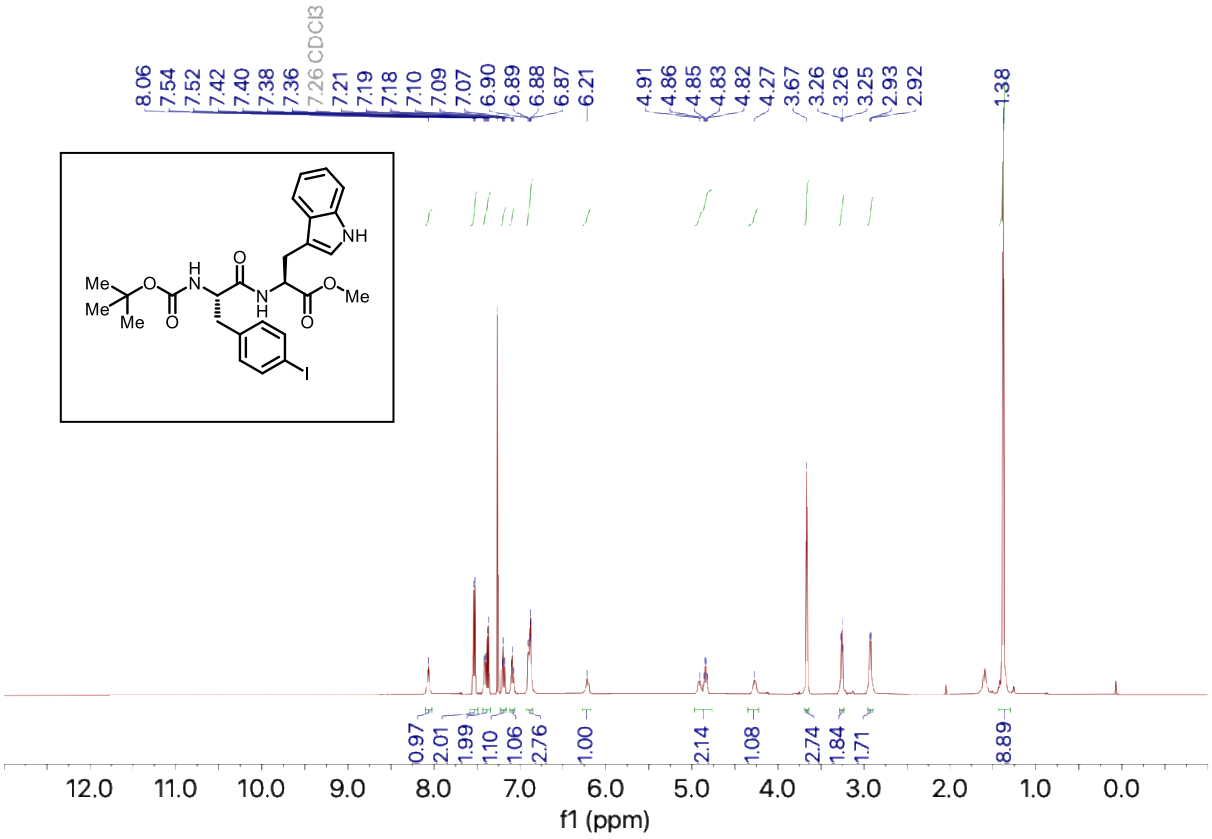
^{1}H NMR ($CDCl_3$, 500 MHz) of 2-(diethylamino)-N-(4-iodo-2,6-dimethylphenyl)acetamide



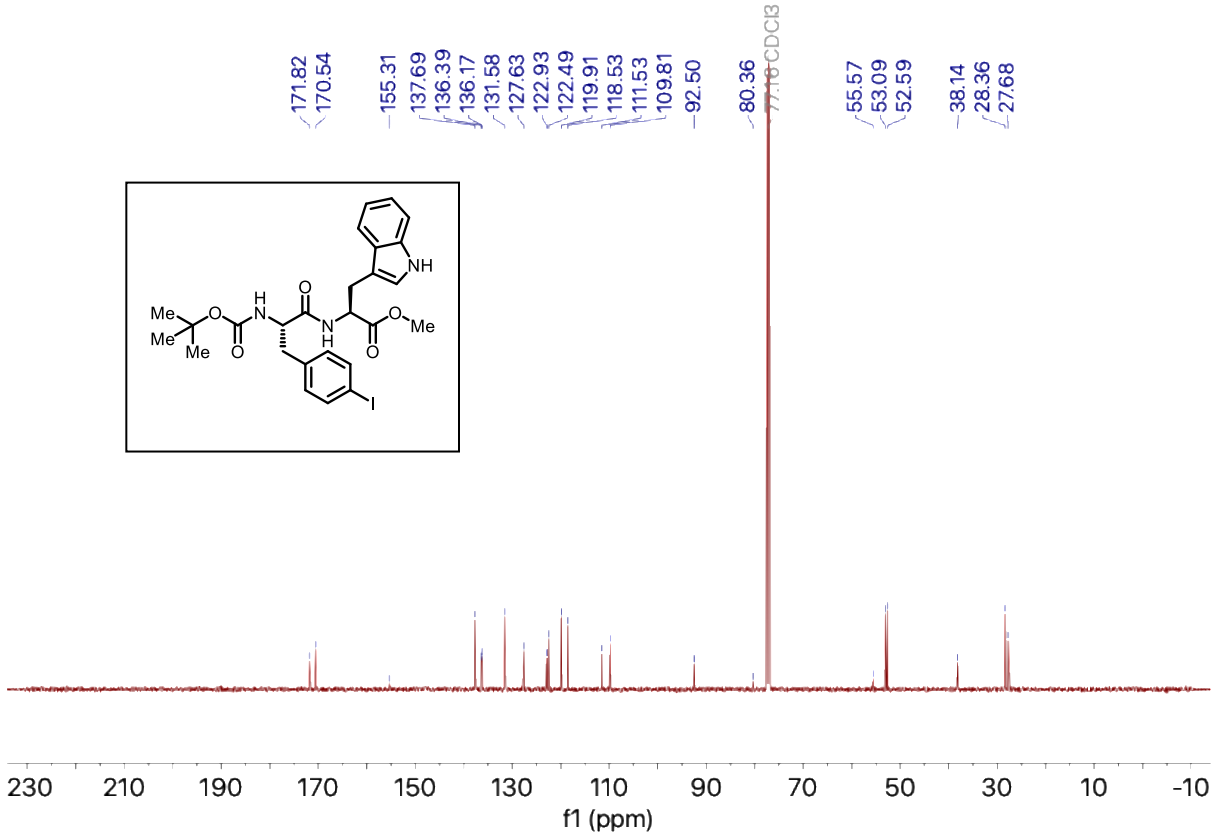
^{13}C NMR ($CDCl_3$, 126 MHz) of 2-(diethylamino)-N-(4-iodo-2,6-dimethylphenyl)acetamide



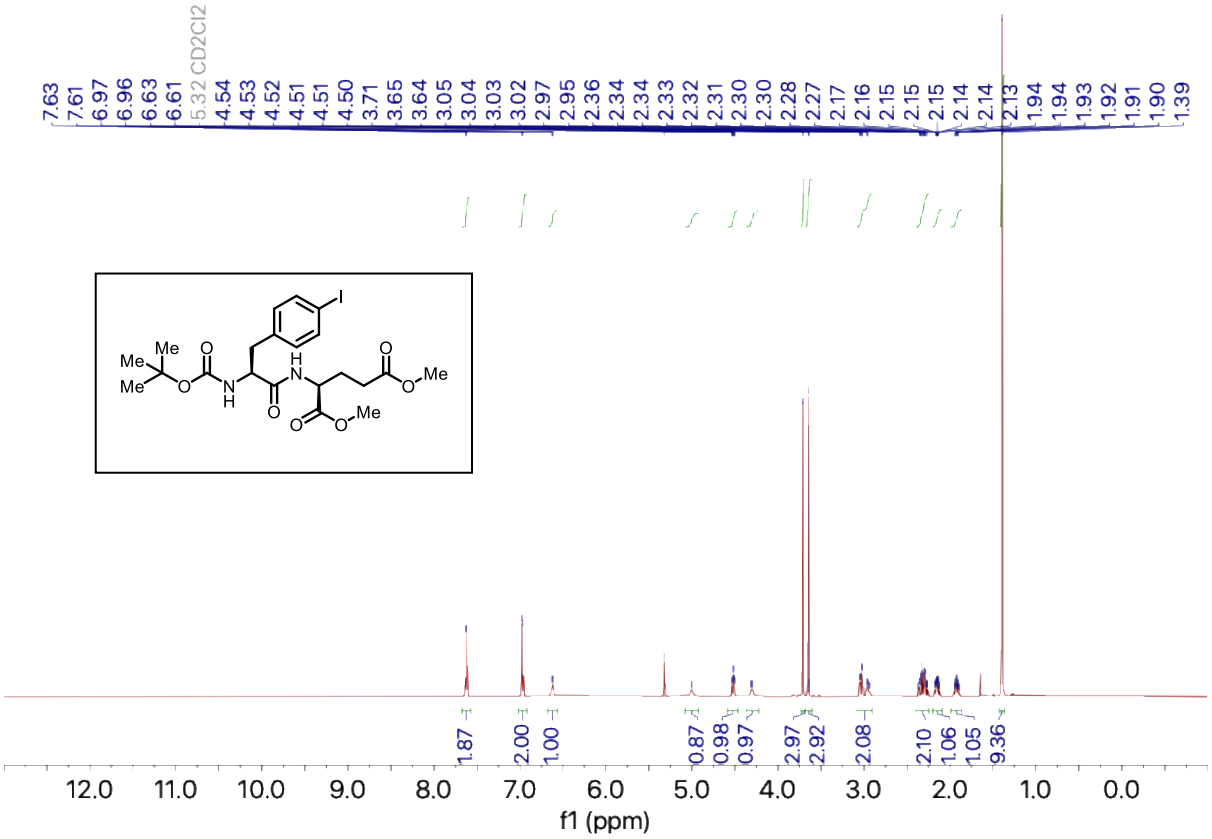
^{1}H NMR ($CDCl_3$) ($CDCl_3$, 500 MHz) of Boc-Phe(4-I)-Trp-OMe



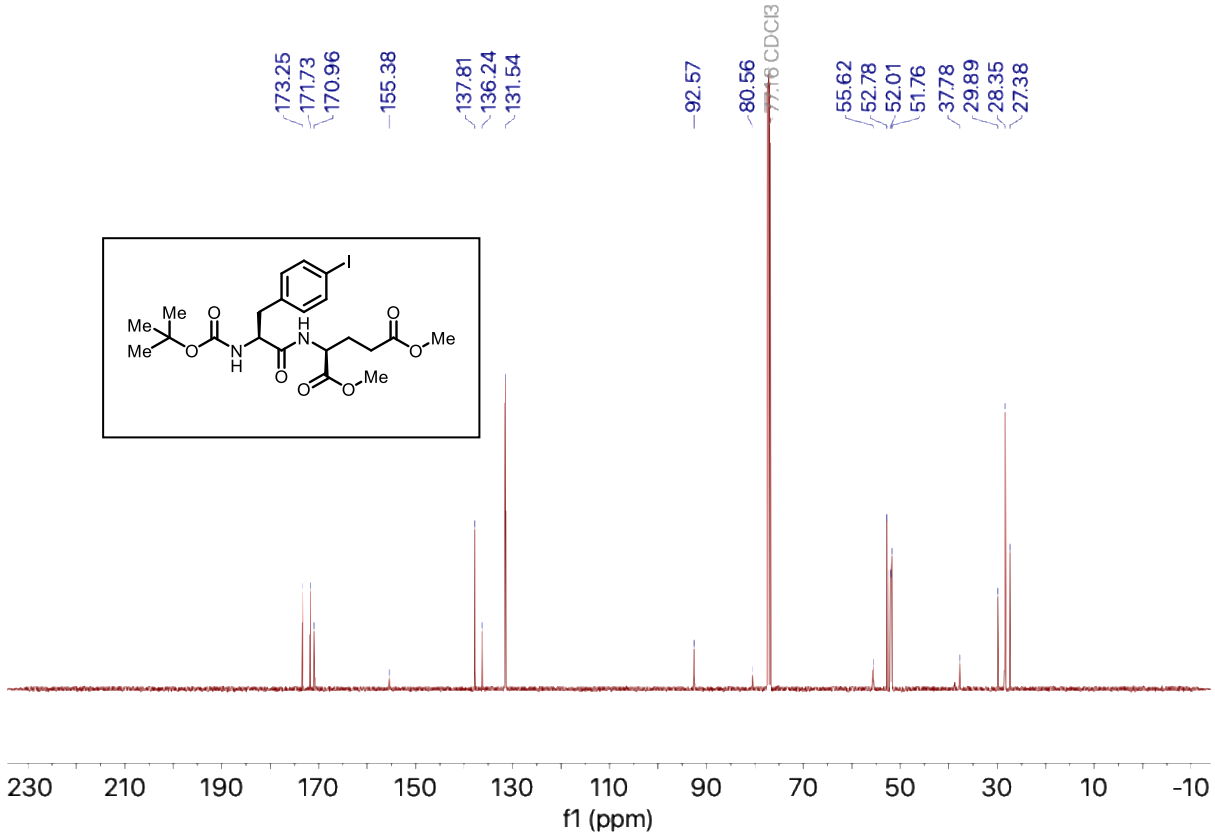
^{13}C NMR ($CDCl_3$, 126 MHz) of Boc-Phe(4-I)-Trp-OMe



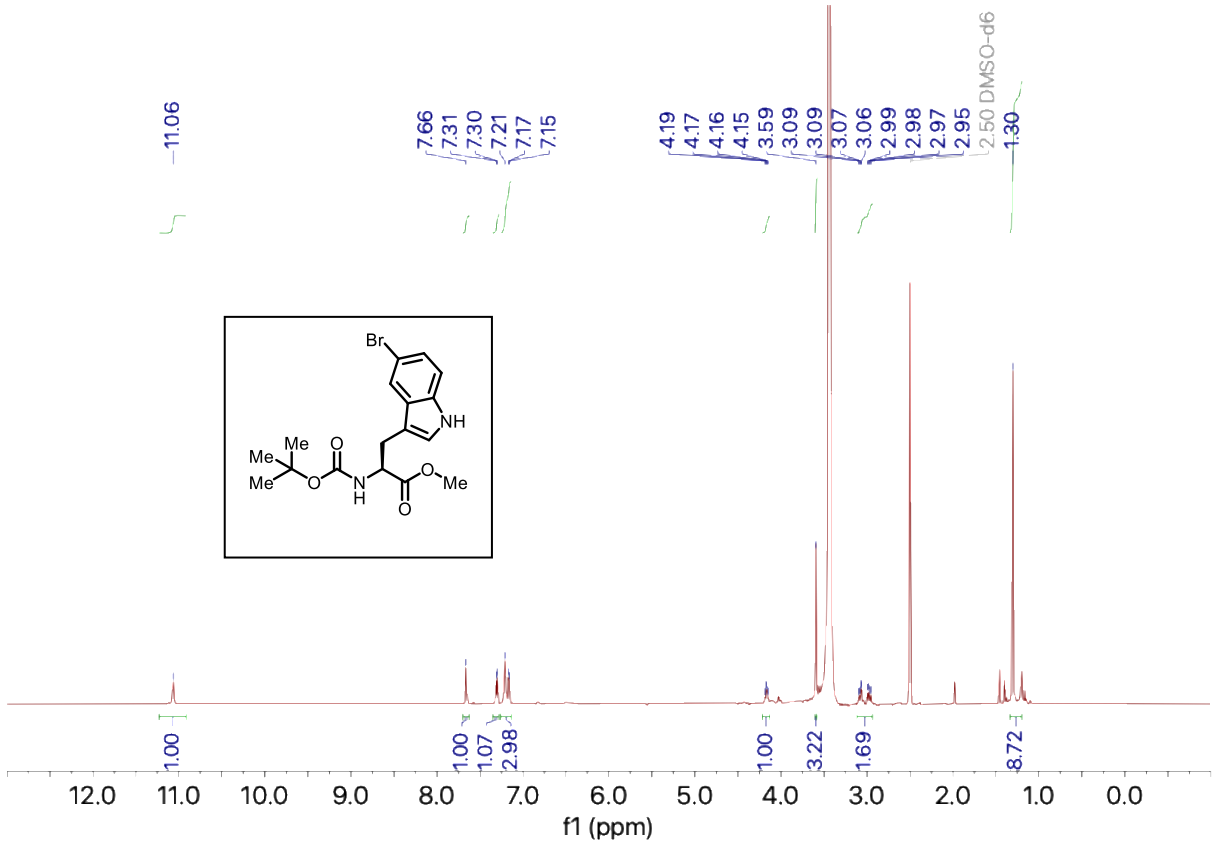
^{1}H NMR (CD_2Cl_2, 600 MHz) of Boc-Phe(4-I)-Glu(OMe)-OMe



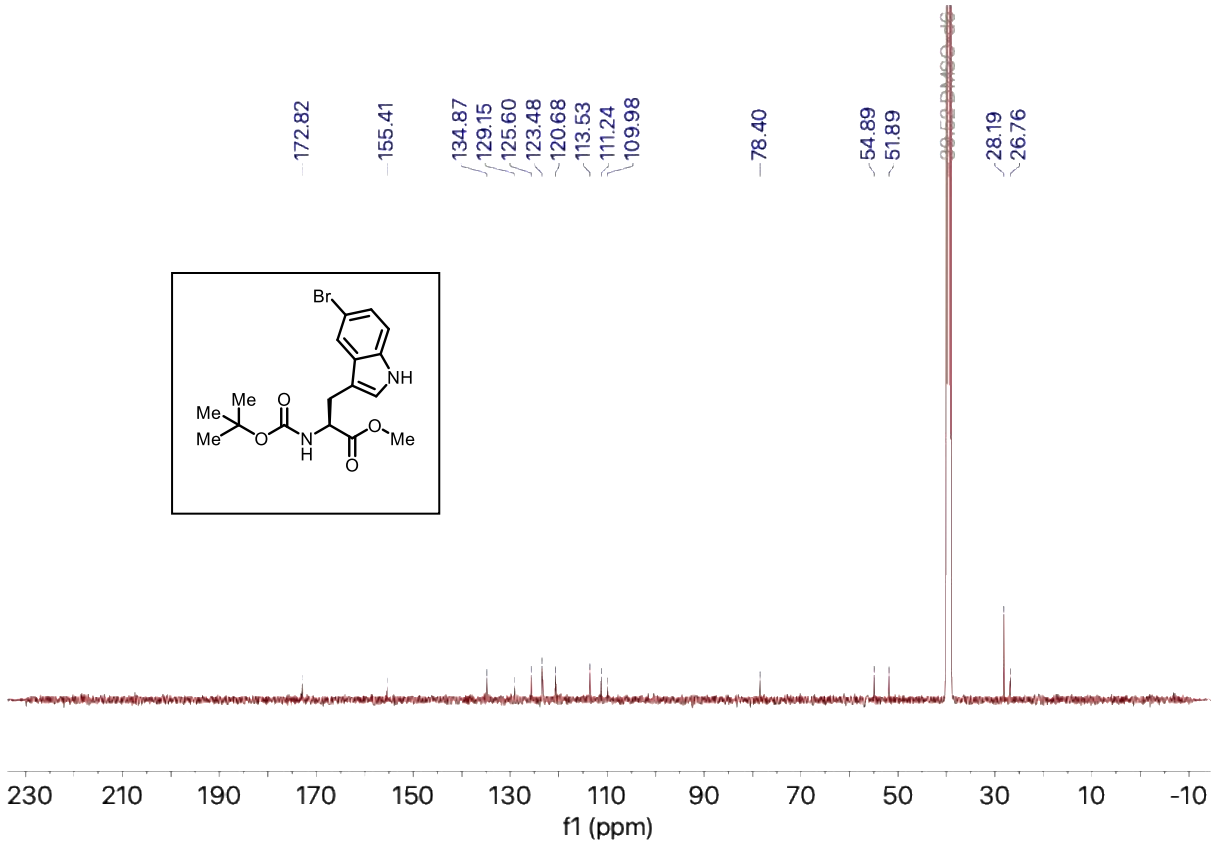
^{13}C NMR (CD_2Cl_2, 126 MHz) of Boc-Phe(4-I)-Glu(OMe)-OMe



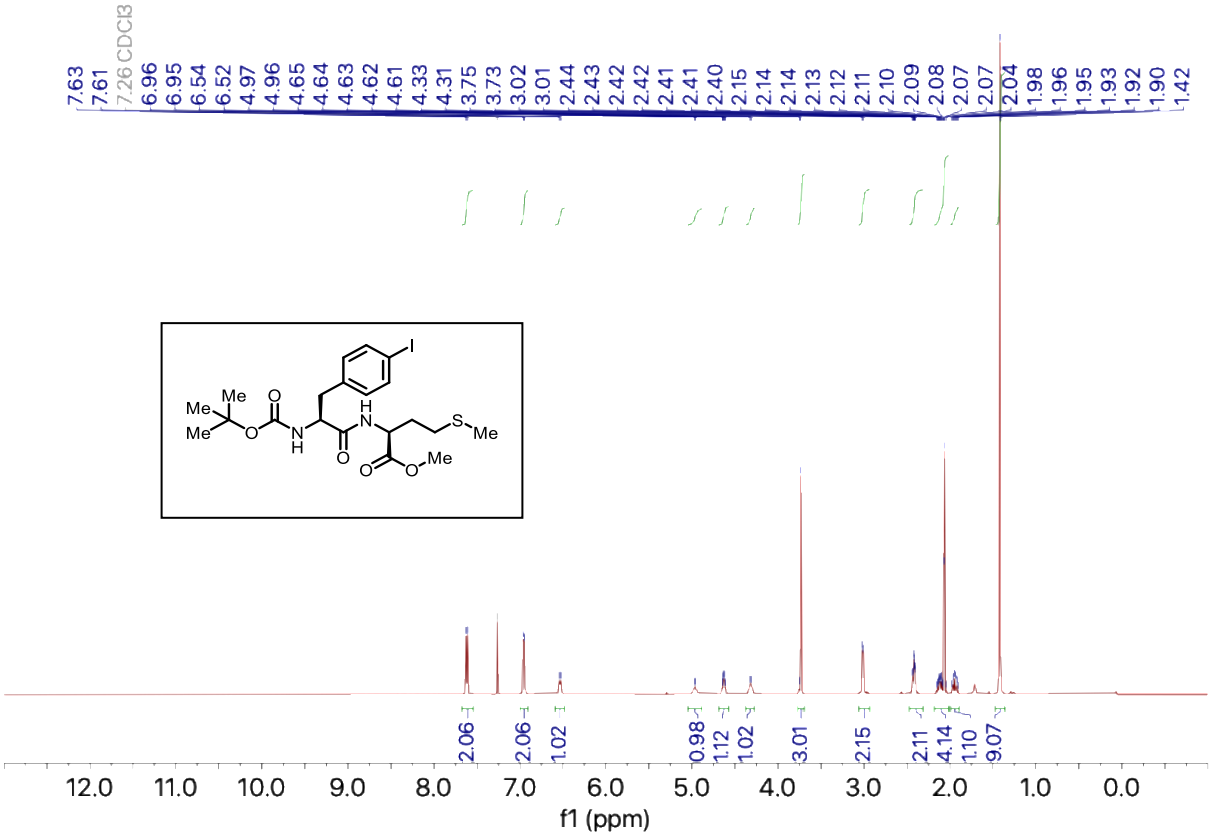
^{1}H NMR (DMSO-d_6, 600 MHz) of Boc-Trp(5-Br)-OMe



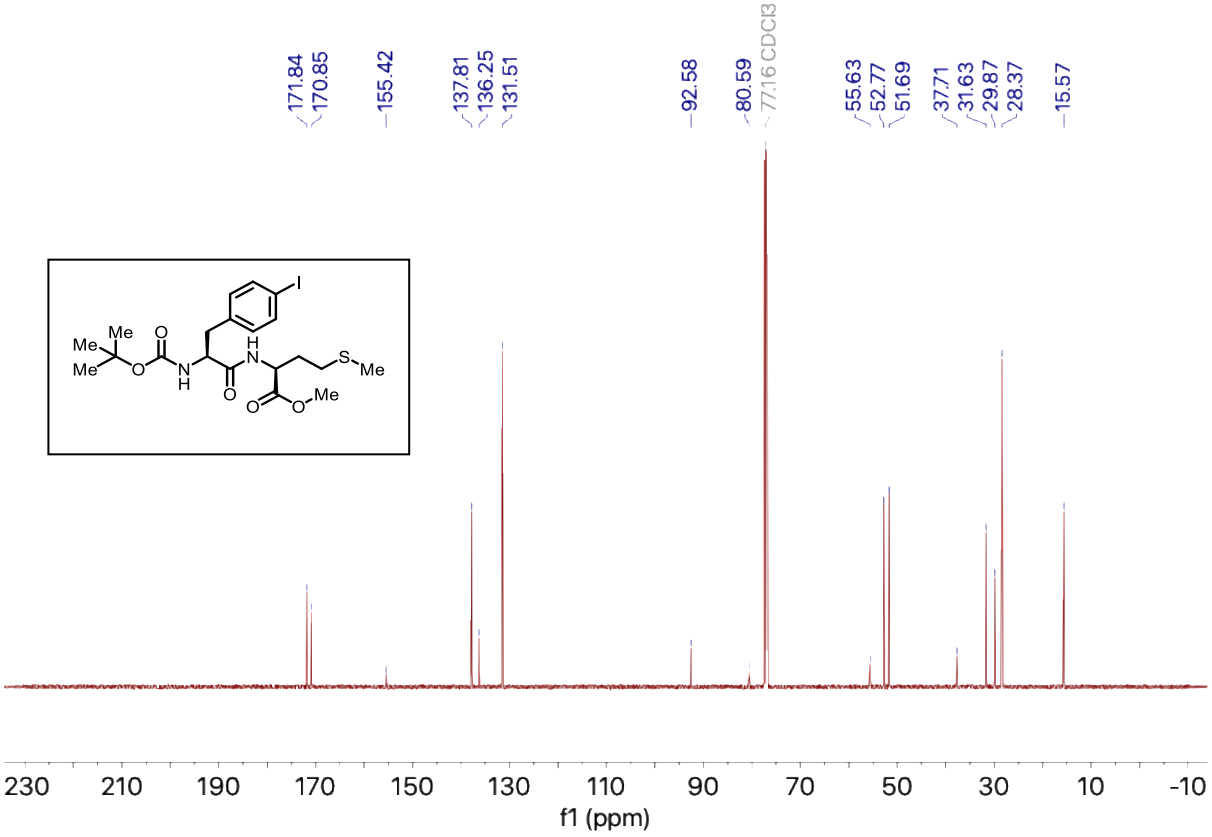
^{13}C NMR (DMSO-d_6, 126 MHz) of Boc-Trp(5-Br)-OMe



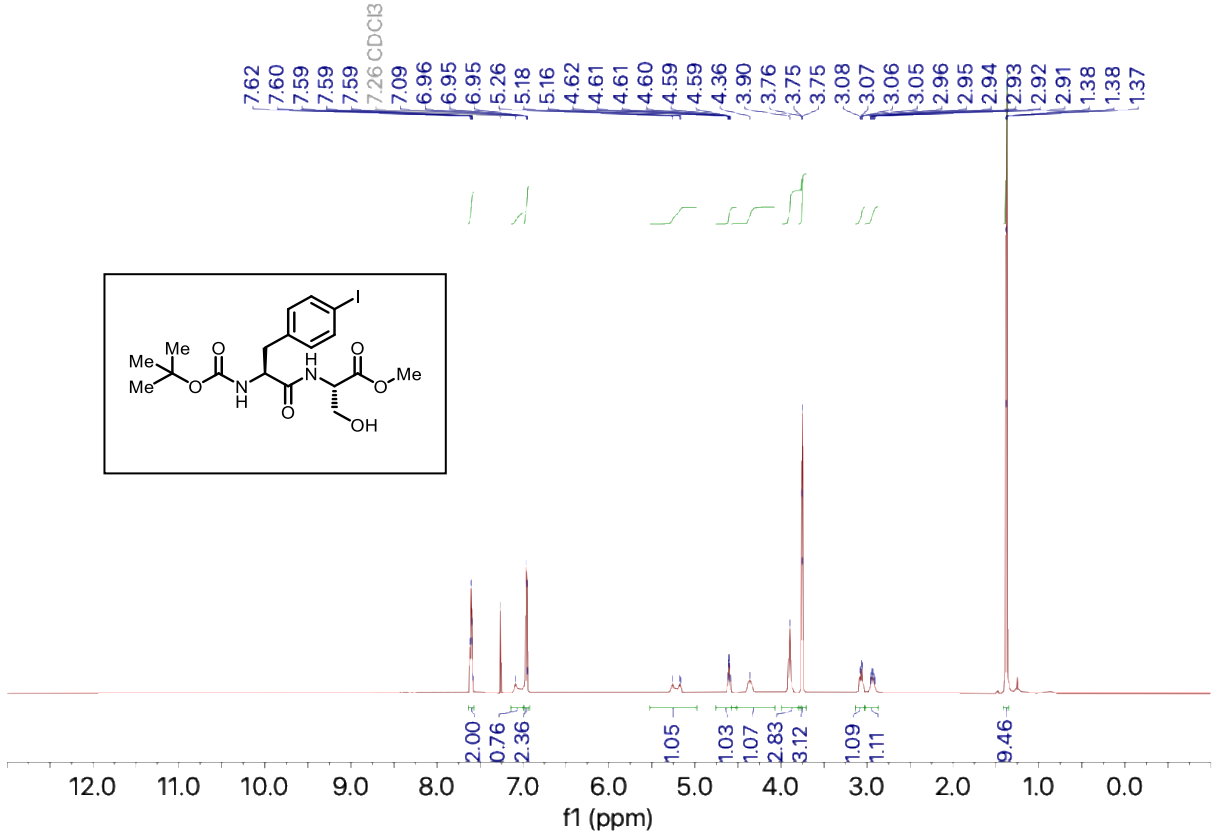
^{1}H NMR ($CDCl_3$, 500 MHz) of Boc-Phe(4-I)-Met-OMe



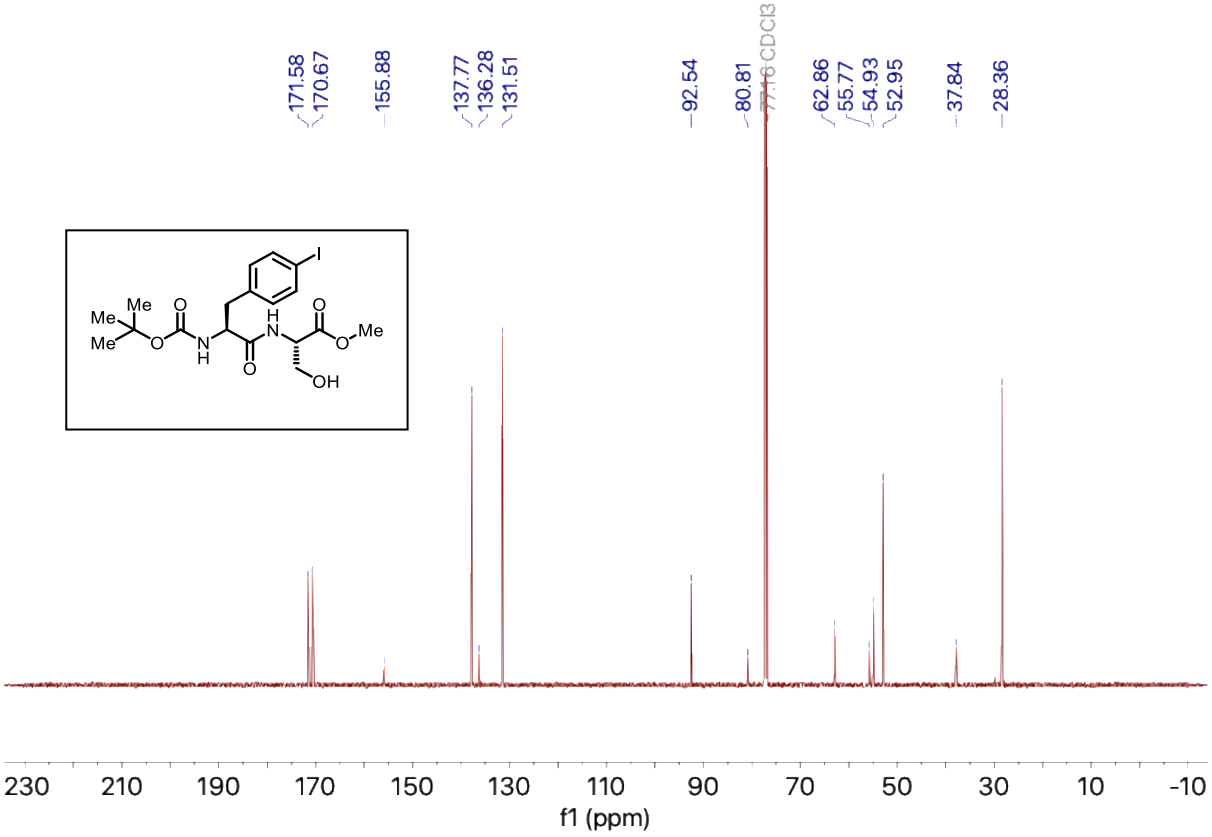
^{13}C NMR ($CDCl_3$, 126 MHz) of Boc-Phe(4-I)-Met-OMe



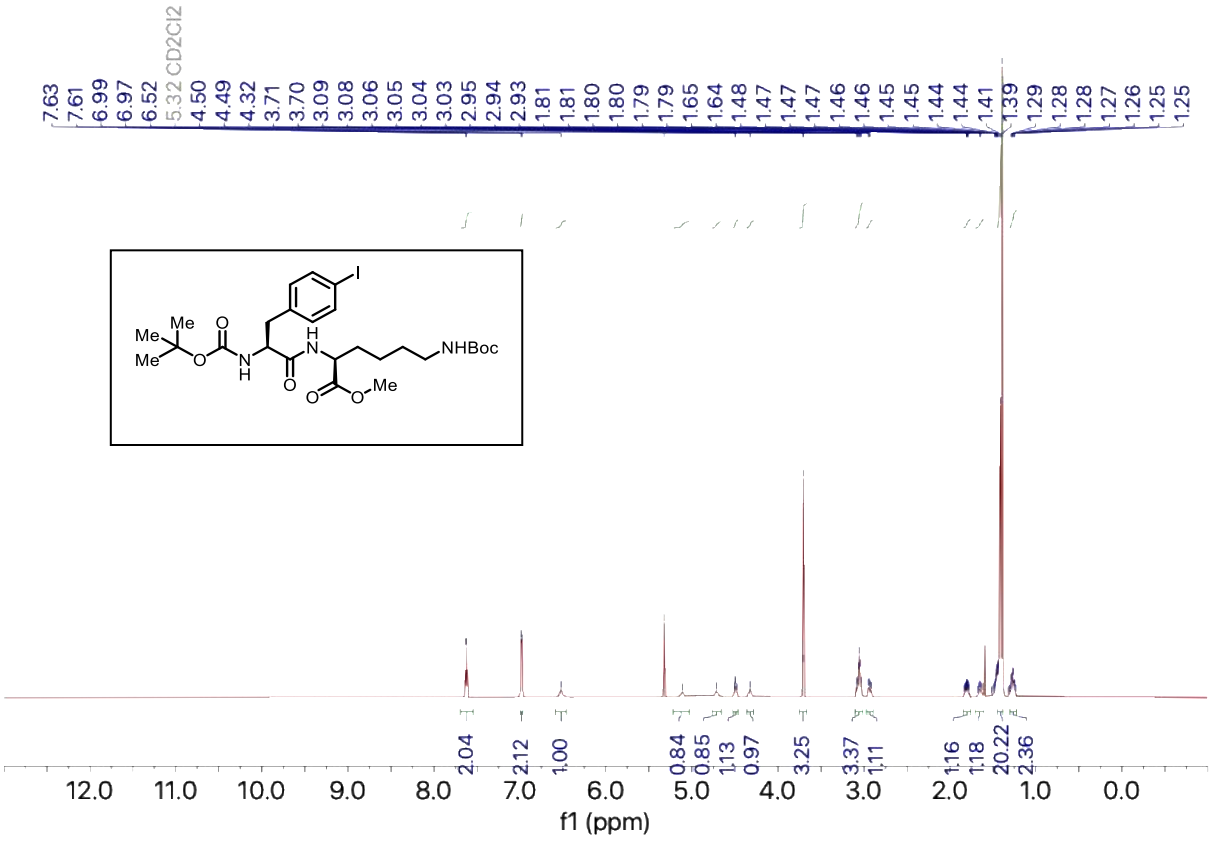
^{1}H NMR ($CDCl_3$, 600 MHz) of Boc-Phe(4-I)-Ser-OMe



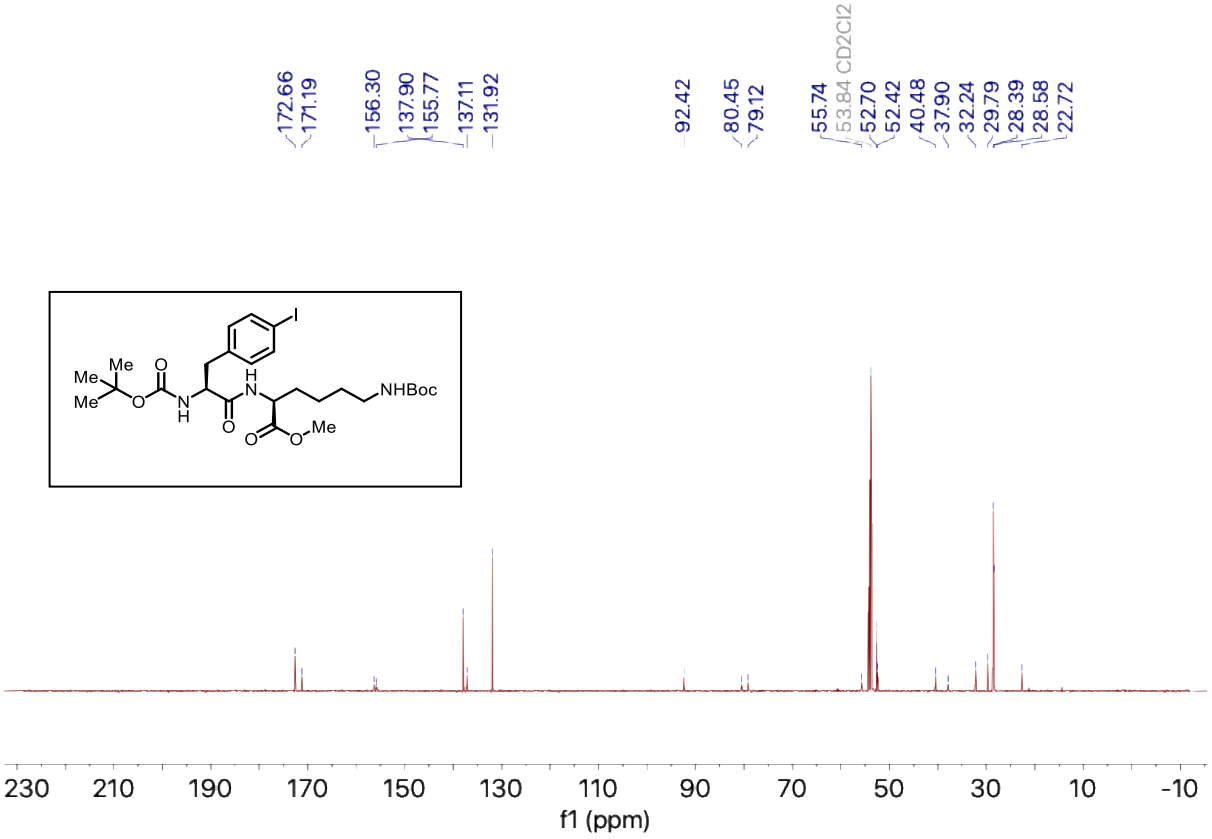
^{13}C NMR ($CDCl_3$, 126 MHz) of Boc-Phe(4-I)-Ser-OMe



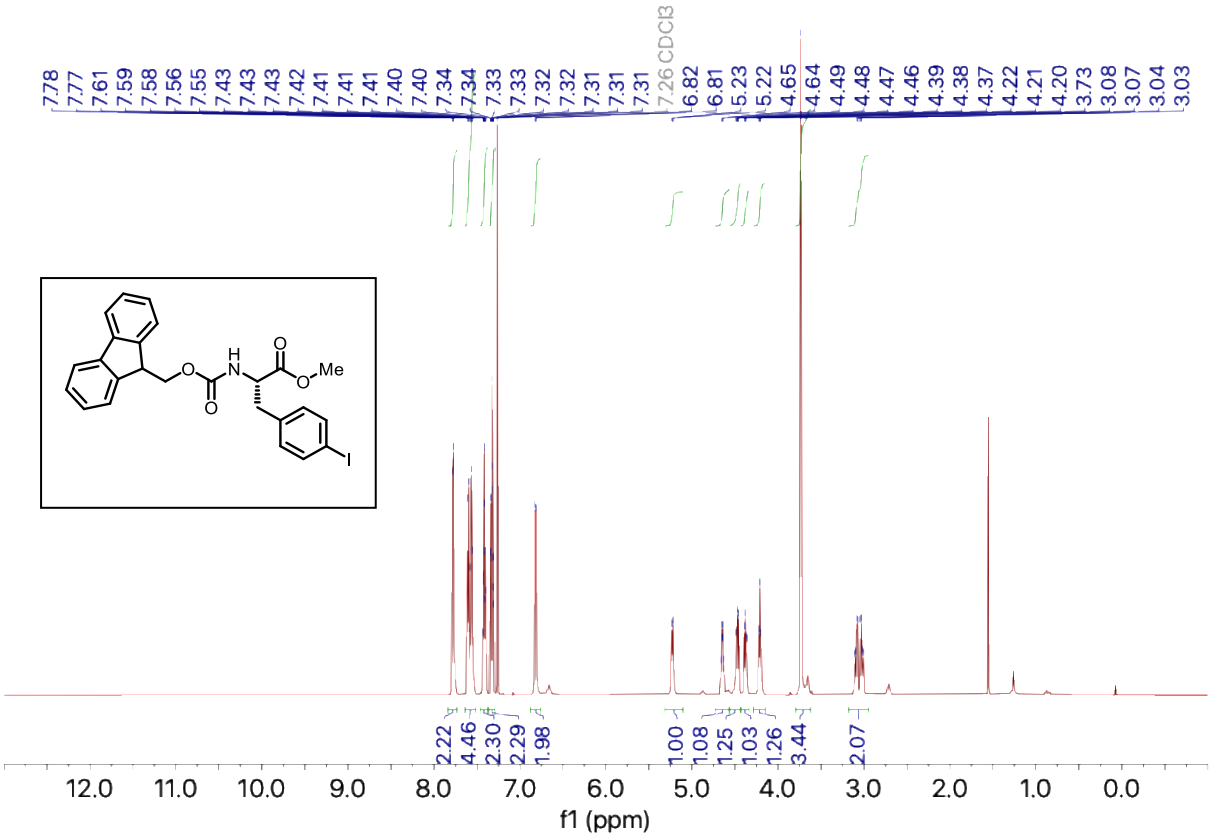
^{1}H NMR (CD_2Cl_2, 600 MHz) of Boc-Phe(4-I)-Lys(Boc)-OMe



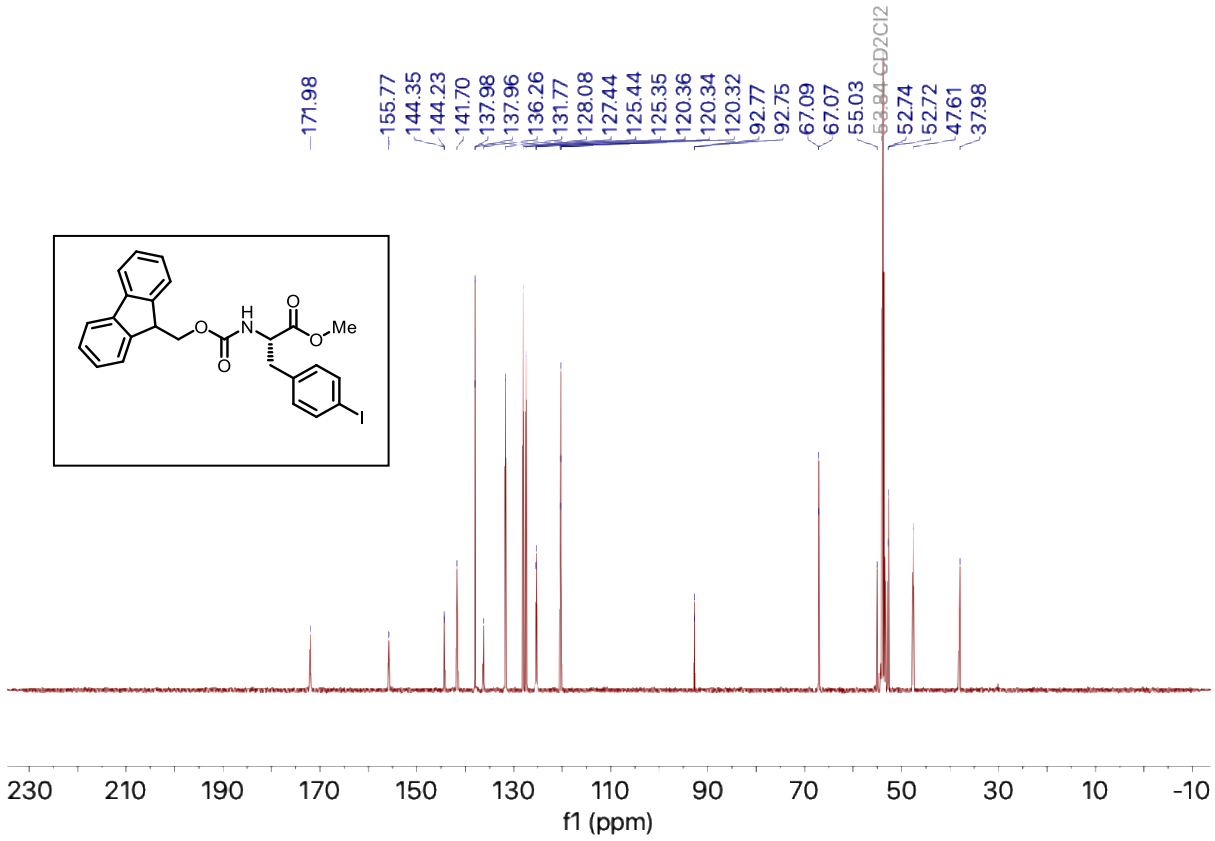
^{13}C NMR (CD_2Cl_2, 126 MHz) of Boc-Phe(4-I)-Lys(Boc)-OMe



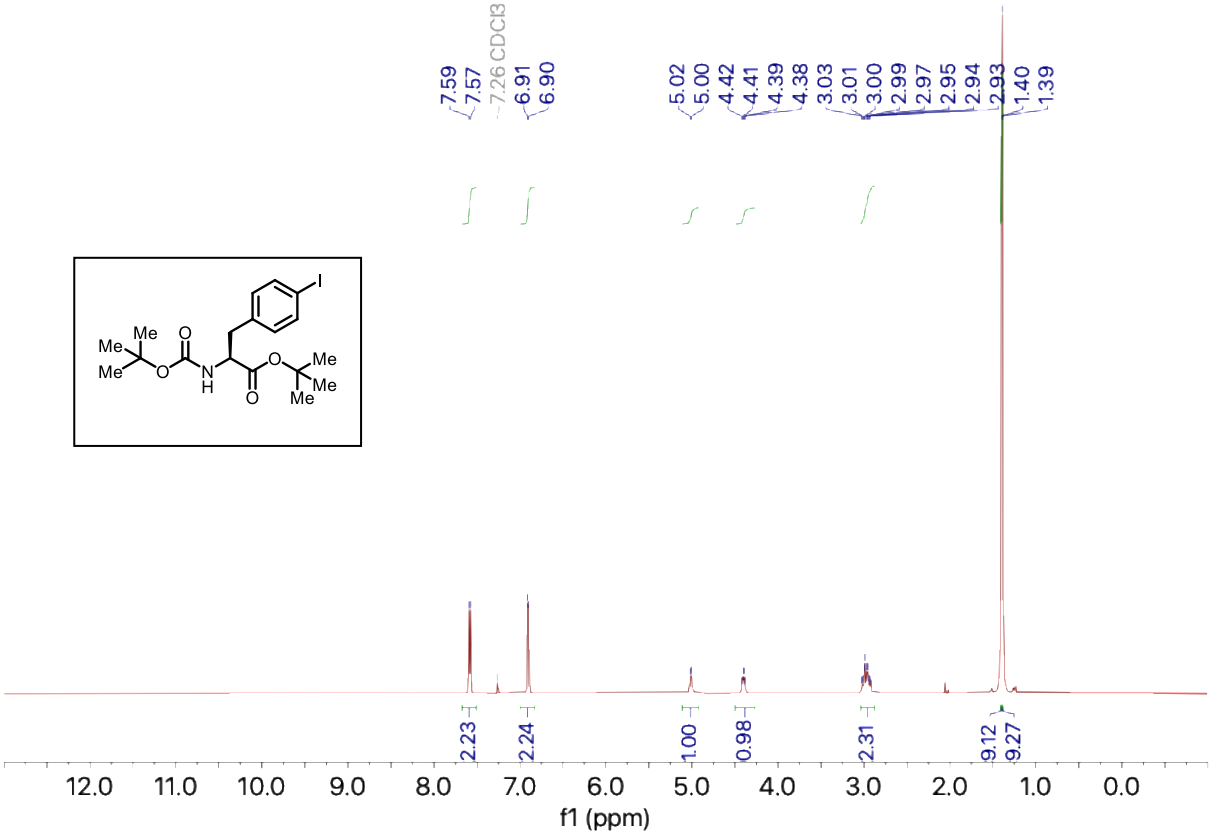
^{1}H NMR ($CDCl_3$, 600 MHz) of Fmoc-Phe(4-I)-OMe



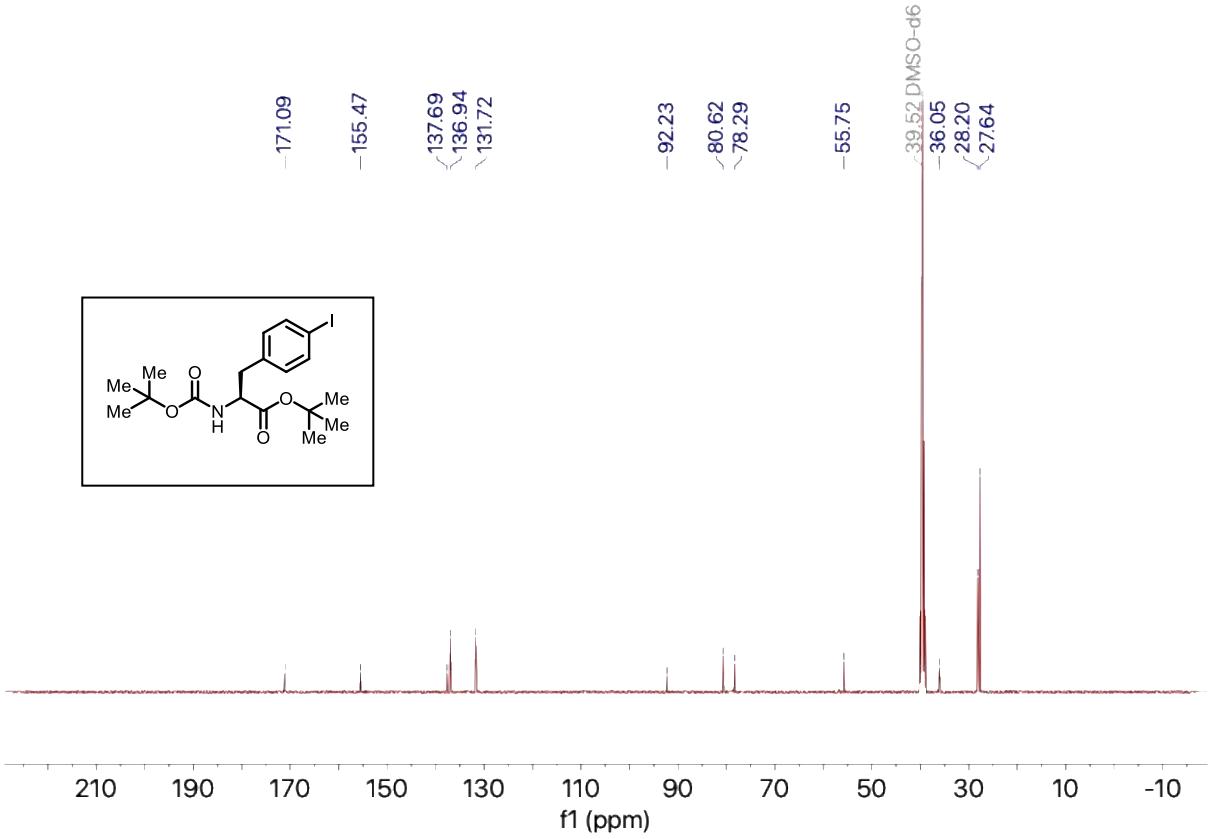
^{13}C NMR ($CDCl_3$, 126 MHz) of Fmoc-Phe(4-I)-OMe



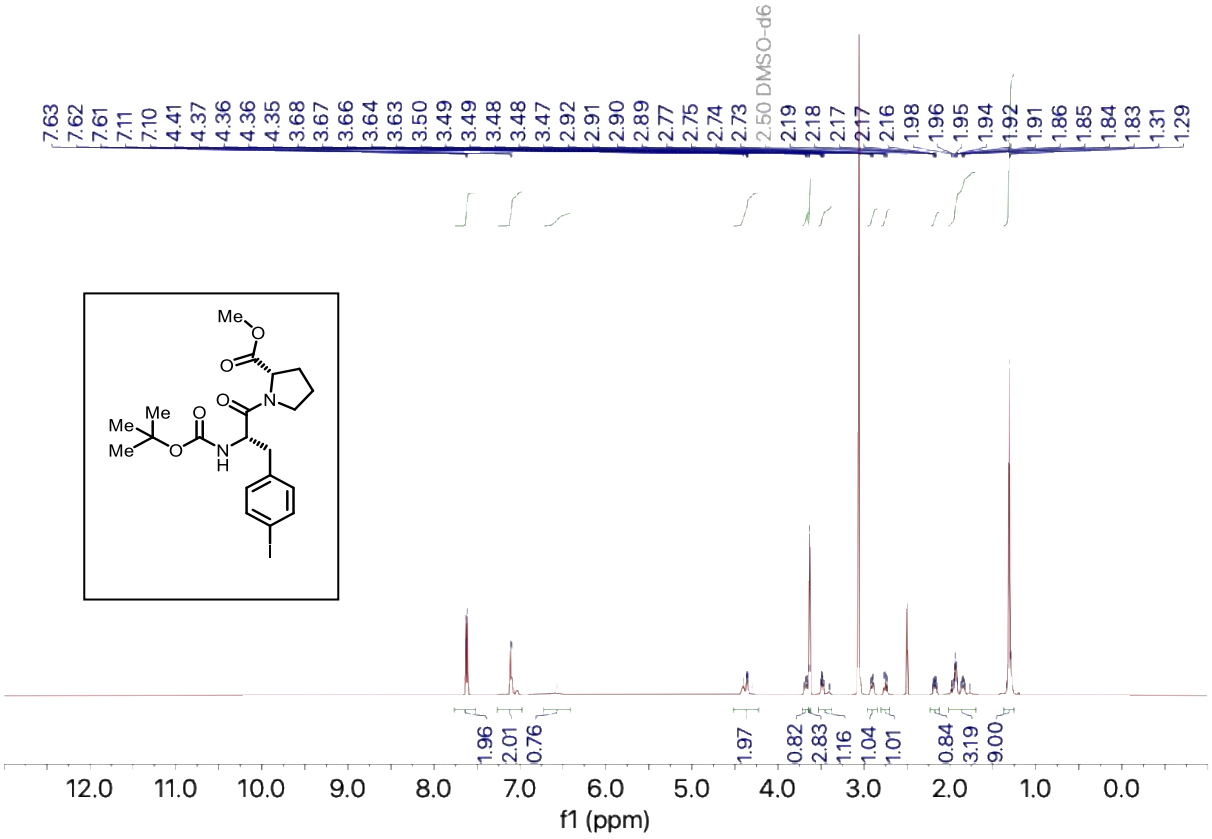
^{1}H NMR ($CDCl_3$, 500 MHz) of Boc-Phe(4-I)-O^{t}Bu



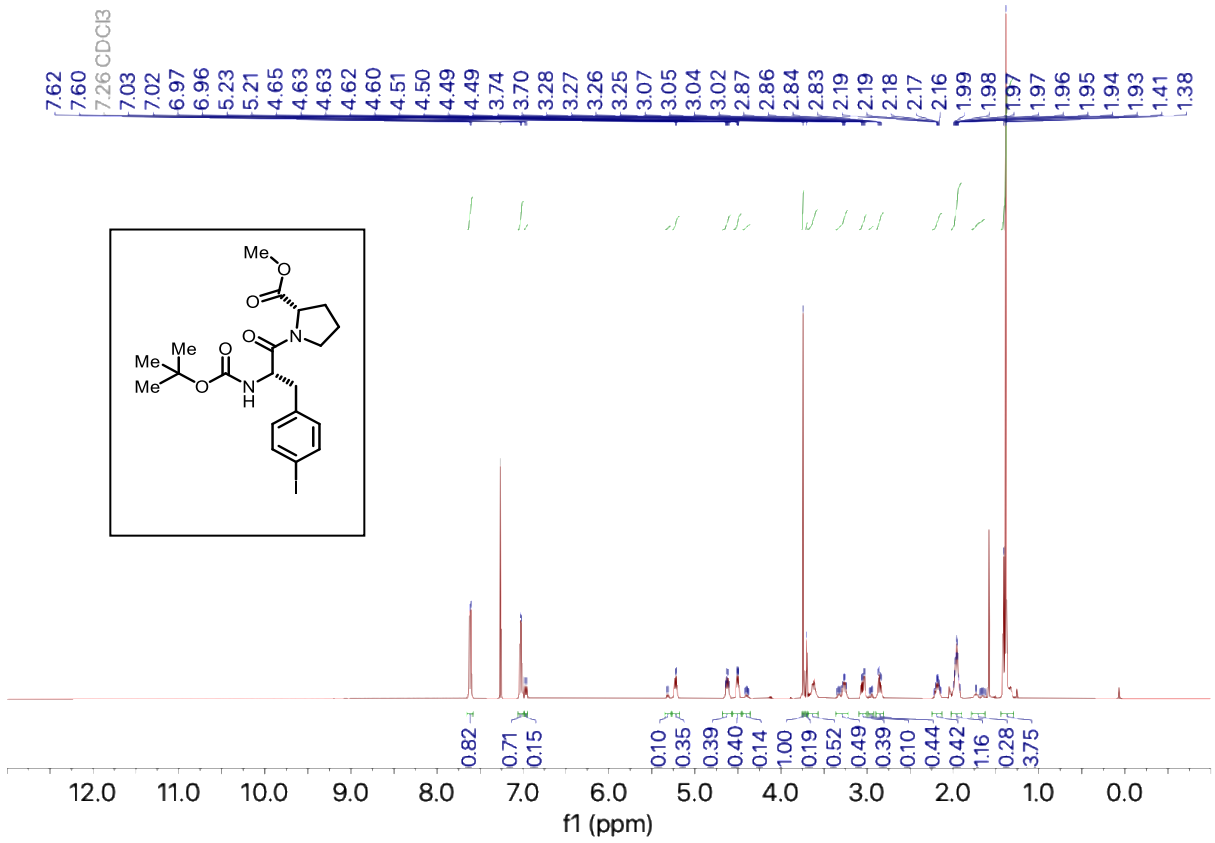
^{13}C NMR (DMSO-d_6, 126 MHz) of Boc-Phe(4-I)-O^{t}Bu



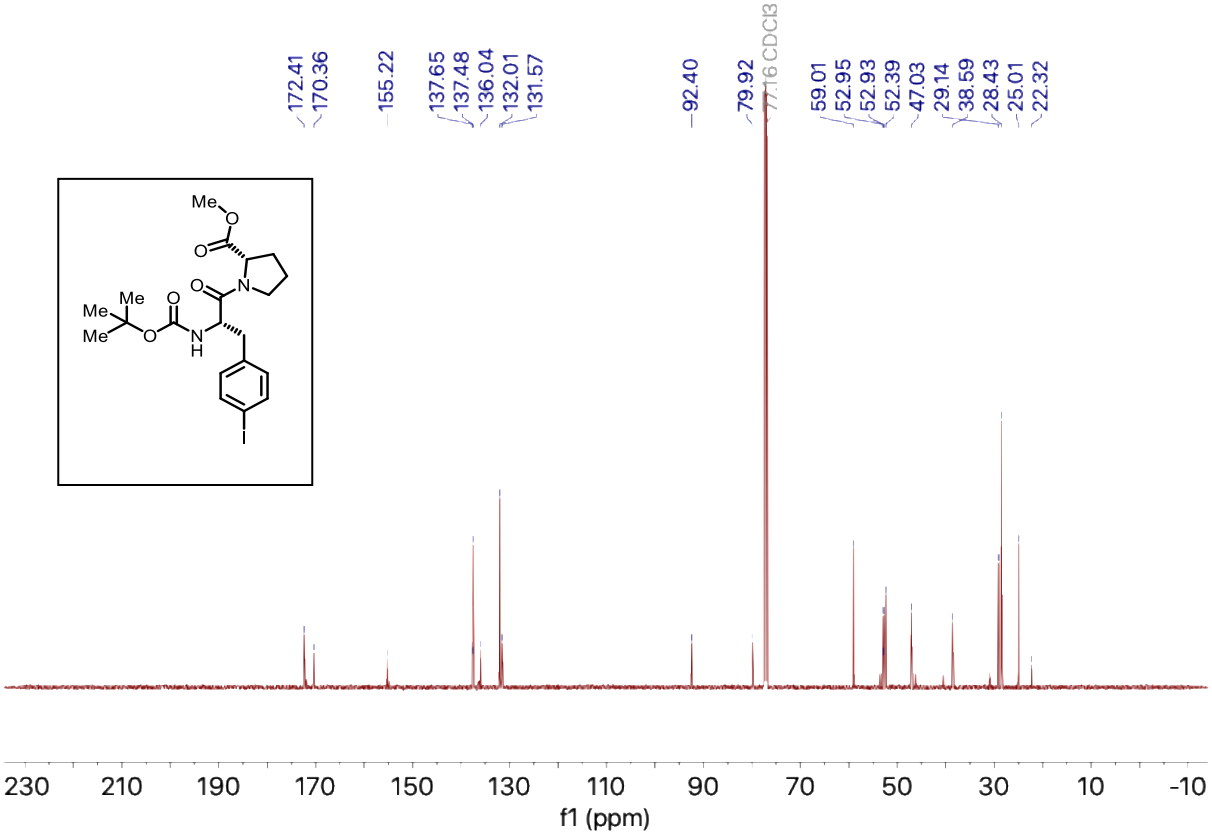
^{1}H NMR (DMSO-d_6, 600 MHz) of Boc-Phe(4-I)-Pro-OMe 80 °C



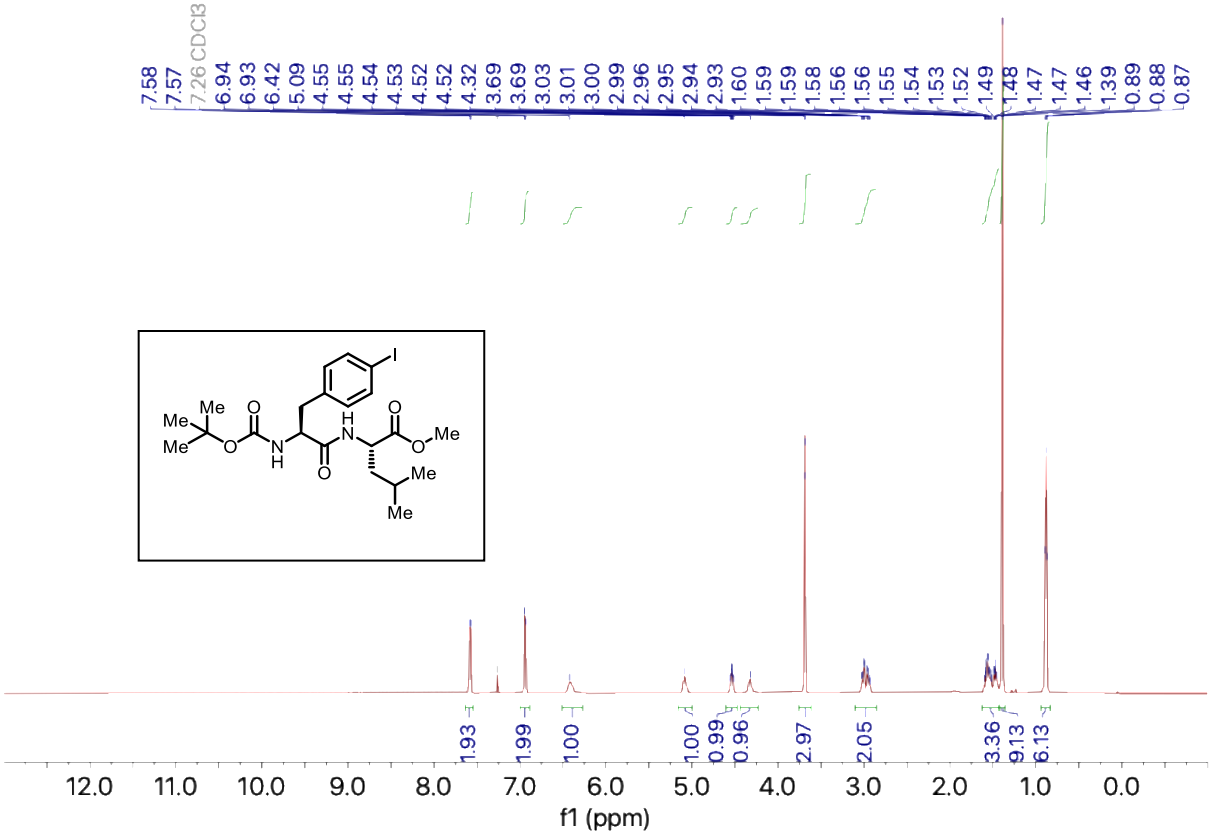
^{1}H NMR ($CDCl_3$, 500 MHz) of Boc-Phe(4-I)-Pro-OMe



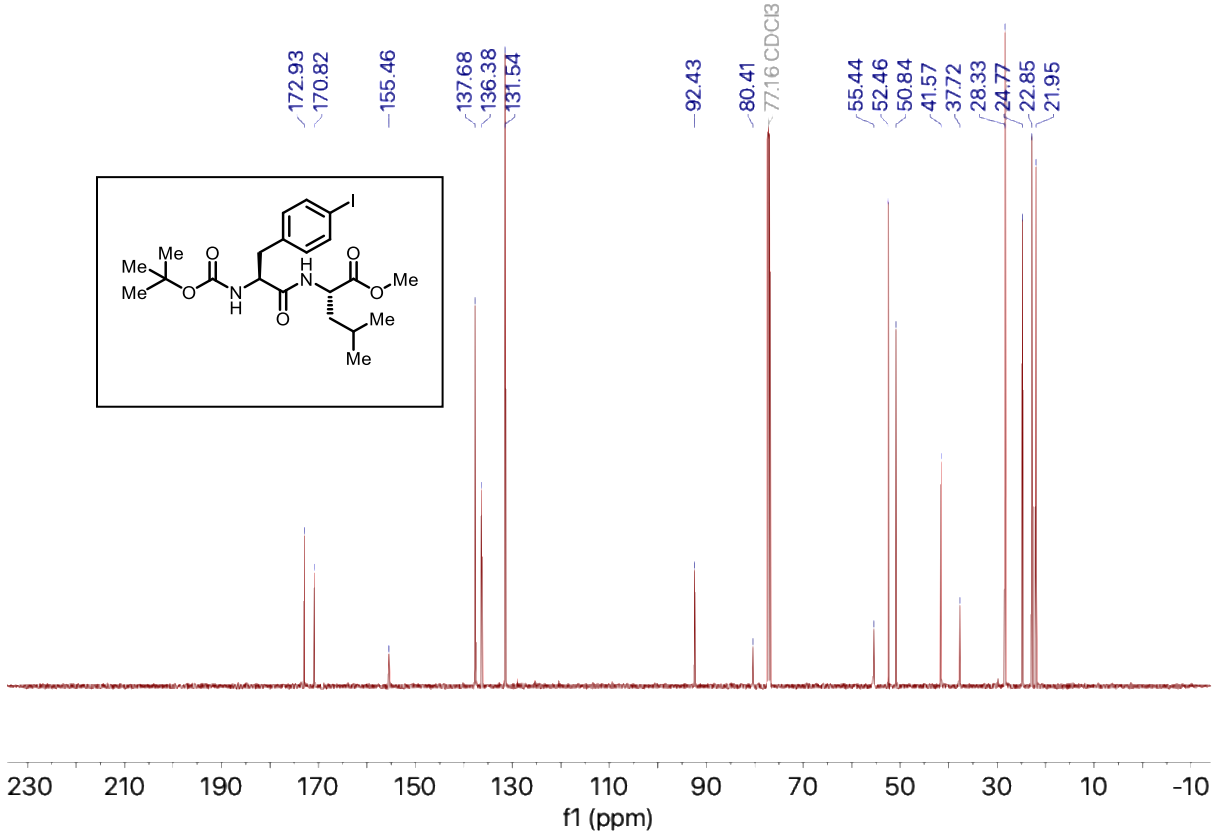
^{13}C NMR ($CDCl_3$, 126 MHz) of Boc-Phe(4-I)-Pro-OMe



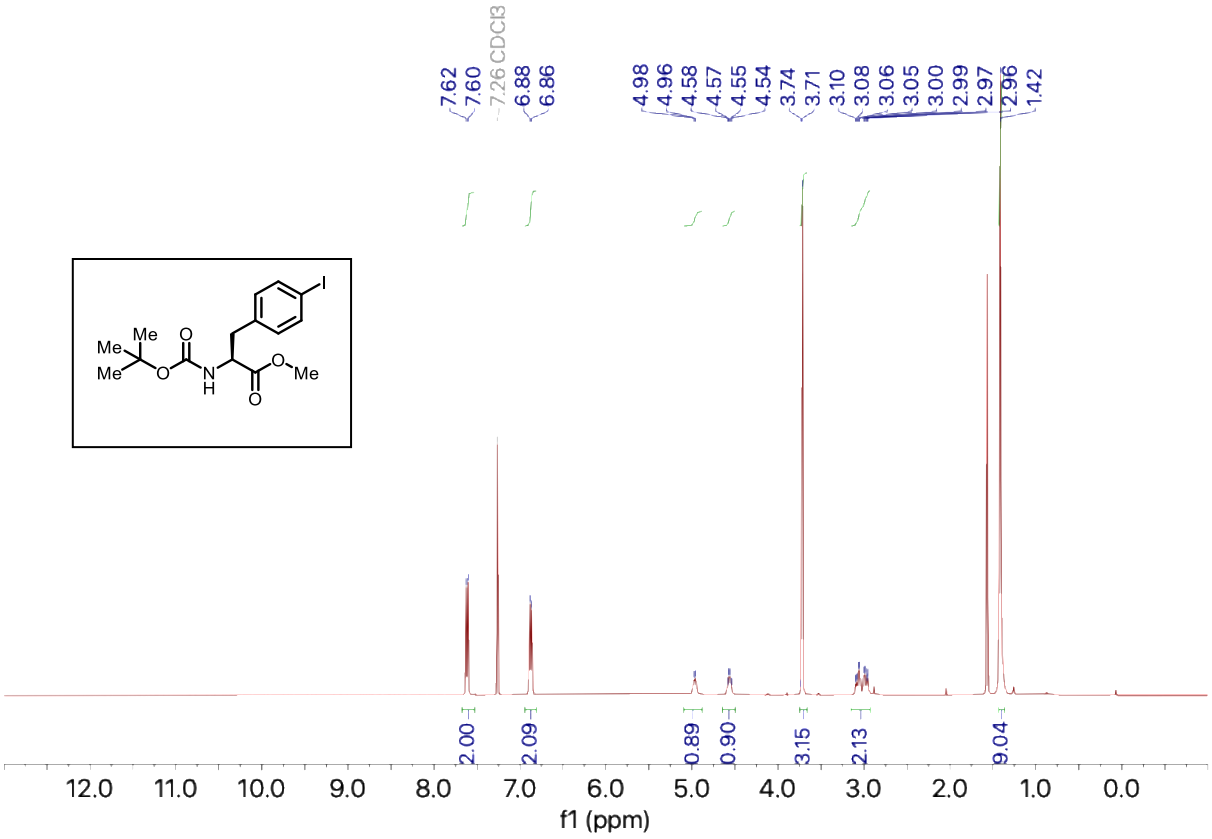
^{1}H NMR ($CDCl_3$, 600 MHz) of Boc-Phe(4-I)-Leu-OMe



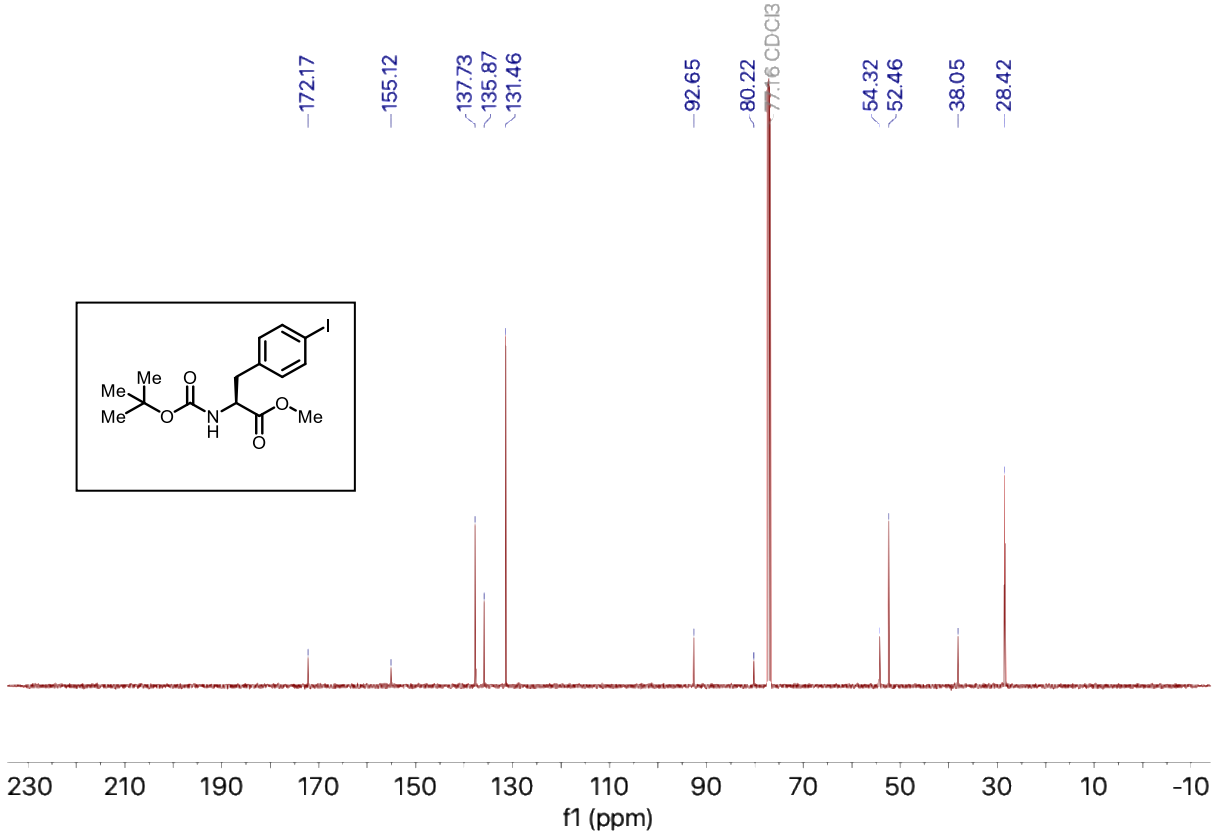
^{13}C NMR ($CDCl_3$, 126 MHz) of Boc-Phe(4-I)-Leu-OMe



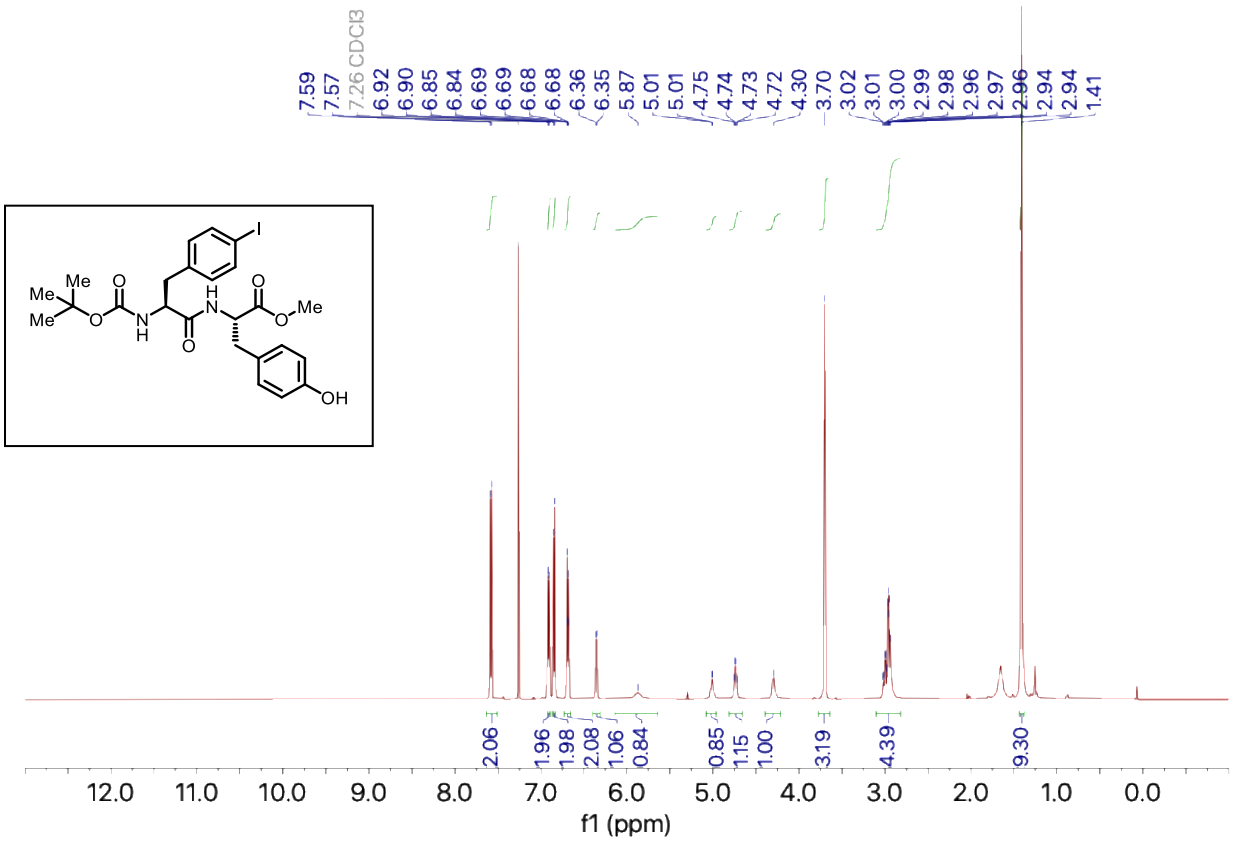
^{1}H NMR ($CDCl_3$, 401 MHz) of Boc-Phe(4-I)-OMe



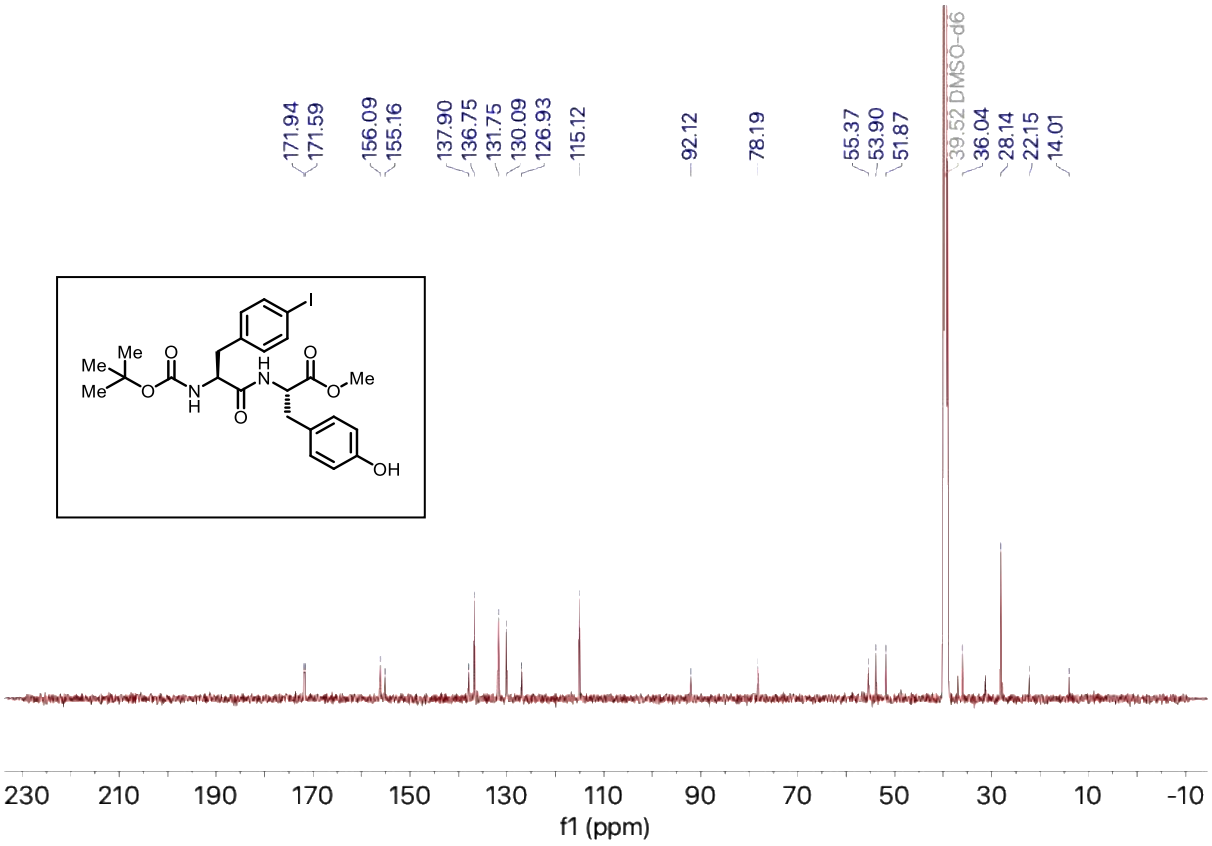
^{13}C NMR ($CDCl_3$, 126 MHz) of Boc-Phe(4-I)-OMe



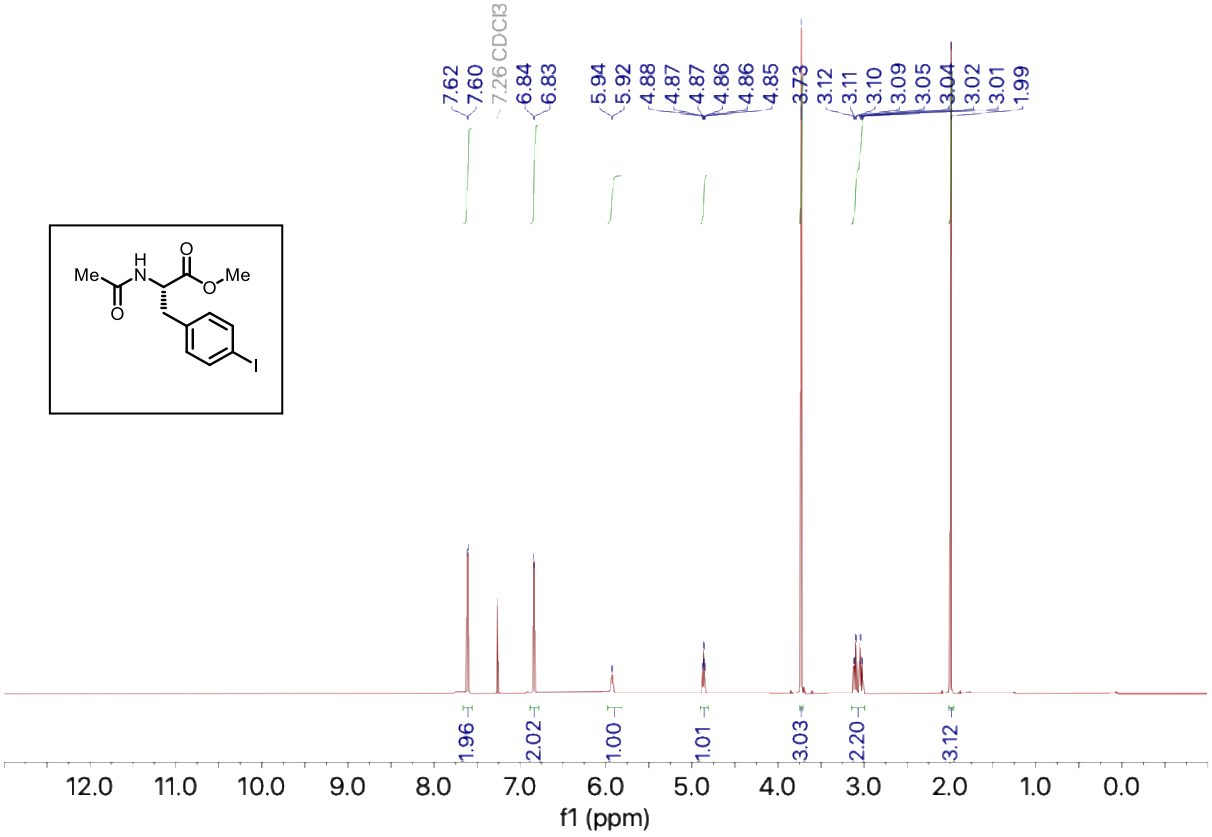
^{1}H NMR ($CDCl_3$, 600 MHz) of Boc-Phe(4-I)-Tyr-OMe



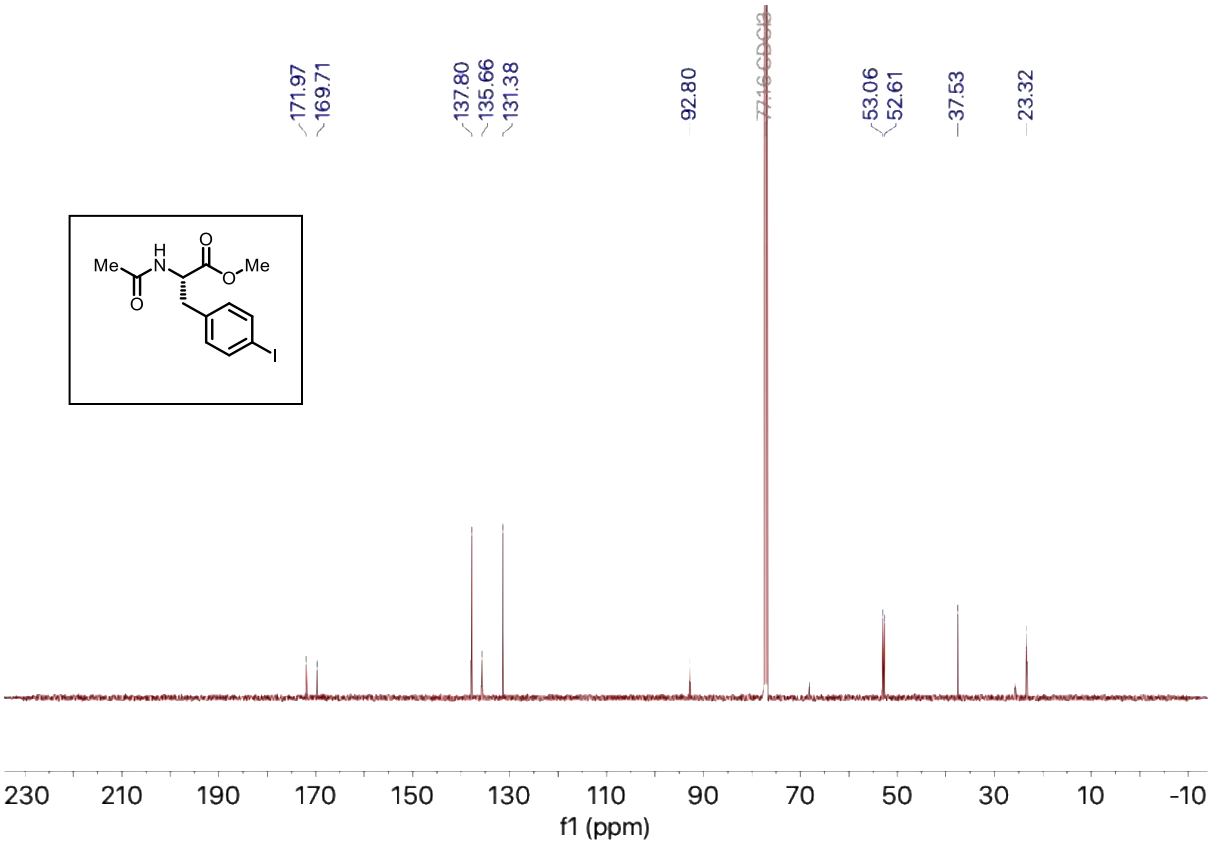
^{13}C NMR (DMSO-d_6, 126 MHz) of Boc-Phe(4-I)-Tyr-OMe



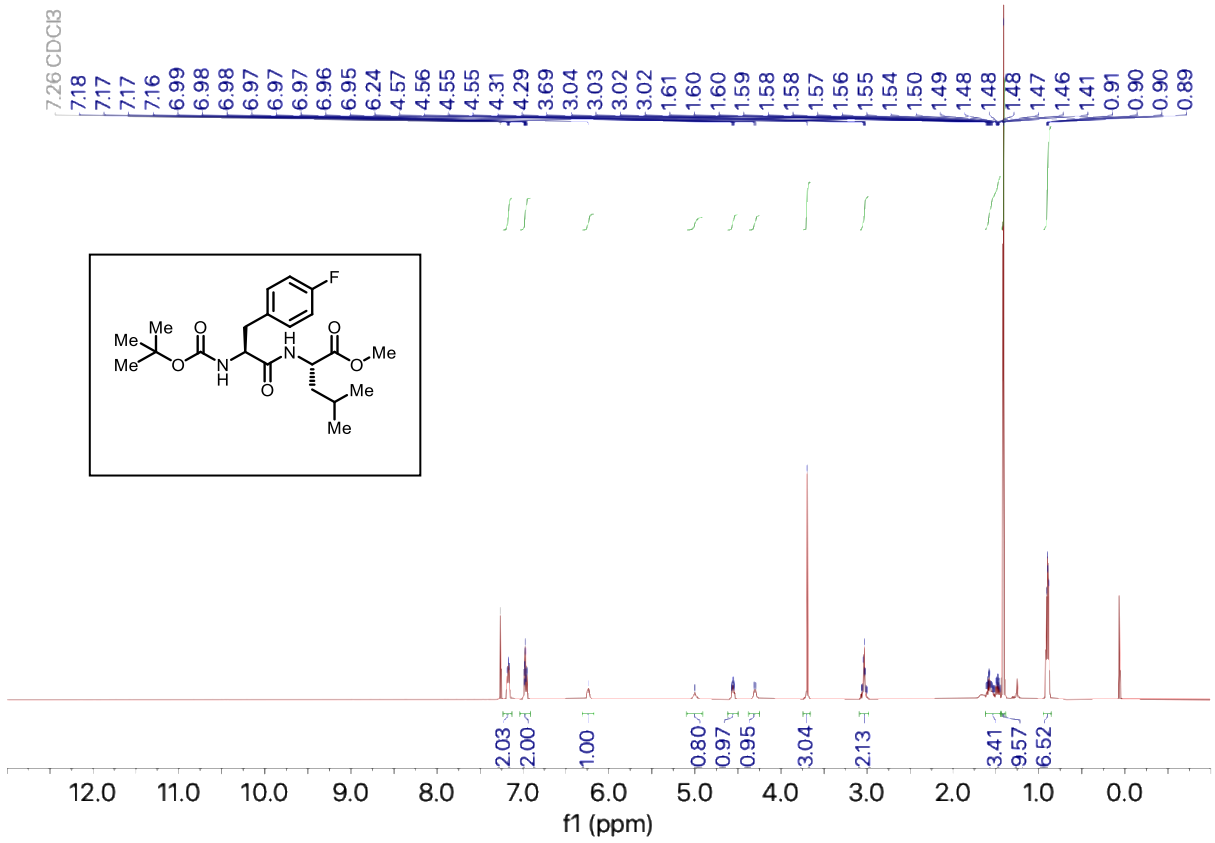
^{1}H NMR ($CDCl_3$, 600 MHz) of Ac-Phe(4-I)-OMe



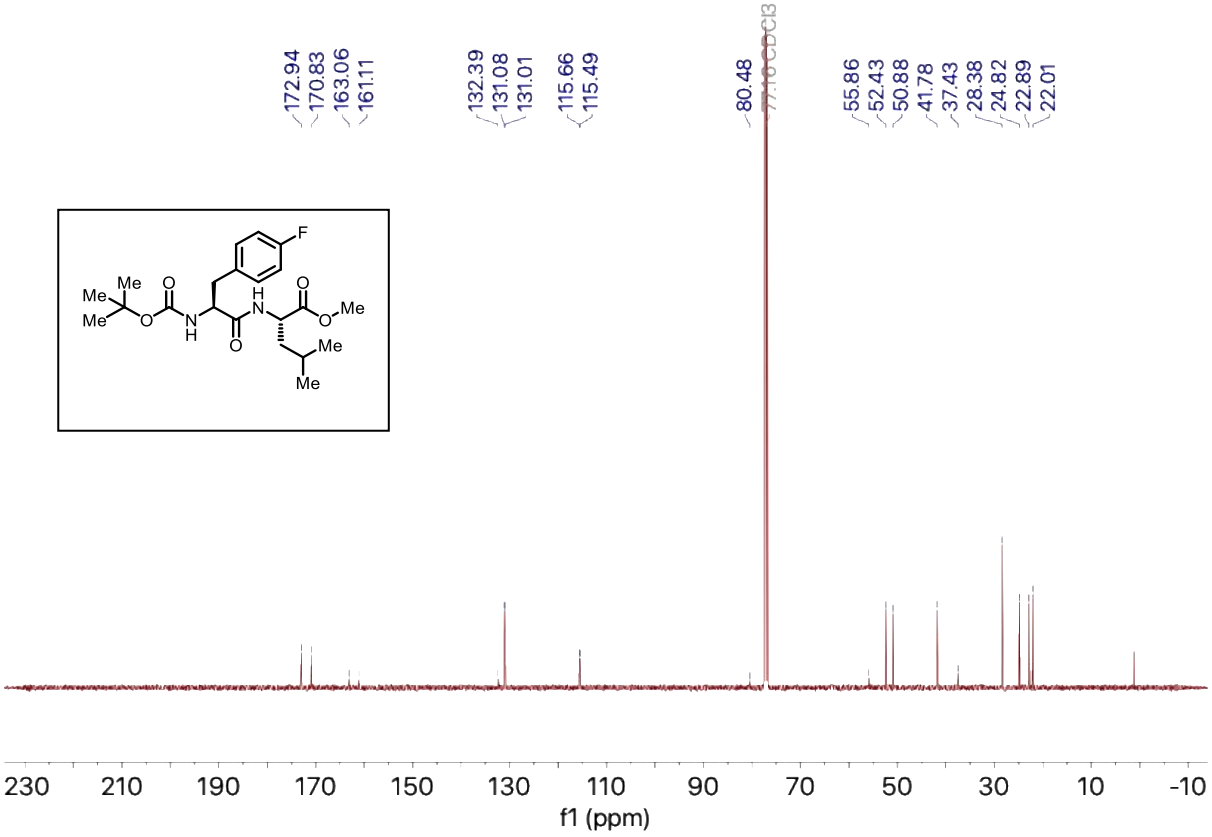
^{13}C NMR ($CDCl_3$, 126 MHz) of Ac-Phe(4-I)-OMe



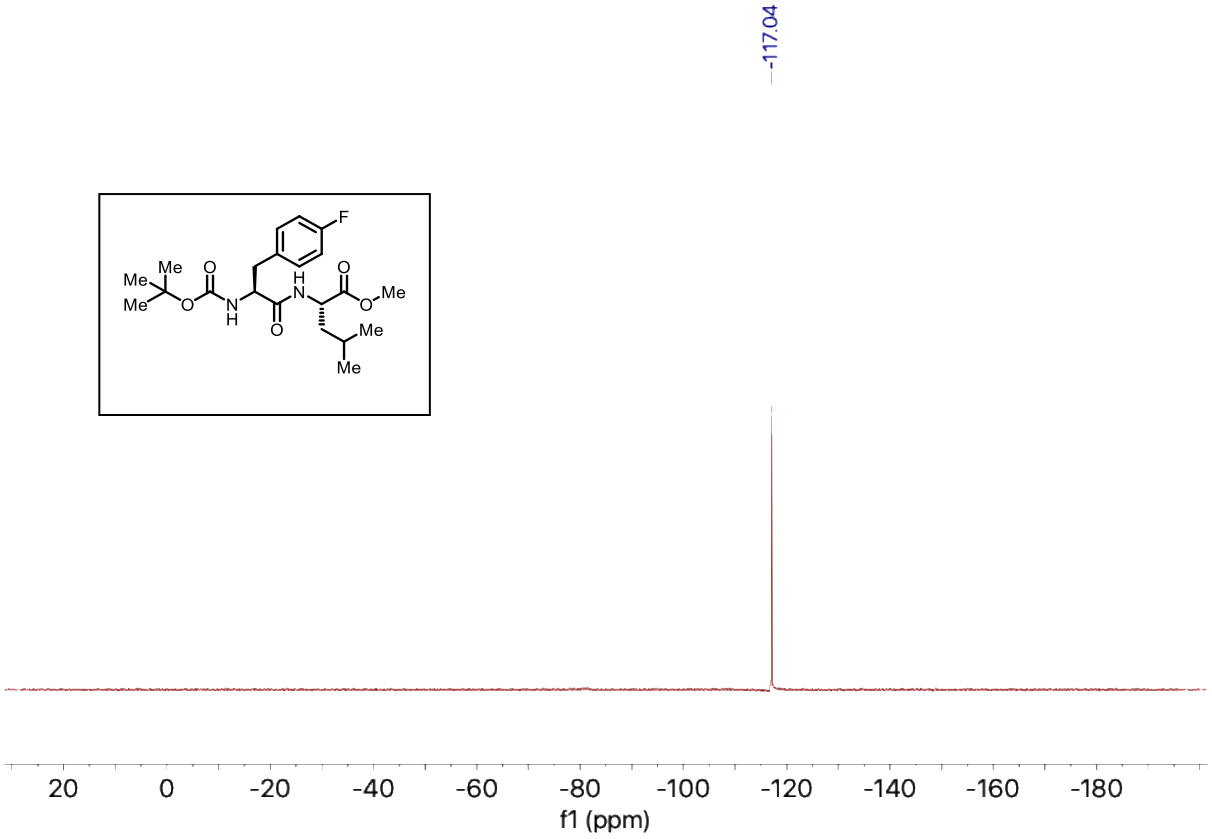
^{1}H NMR ($CDCl_3$, 600 MHz) of Boc-Phe(4-F)-Leu-OMe



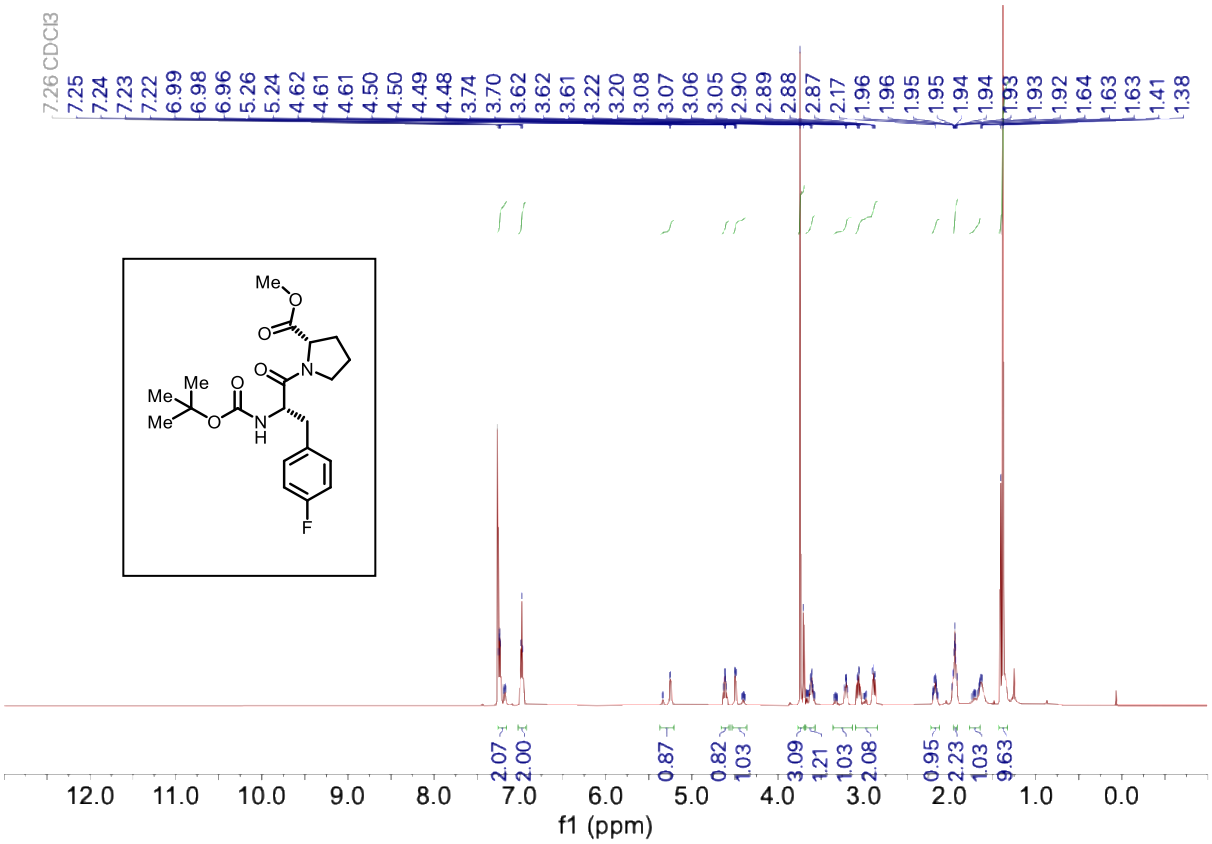
^{13}C NMR ($CDCl_3$, 126 MHz) of Boc-Phe(4-F)-Leu-OMe



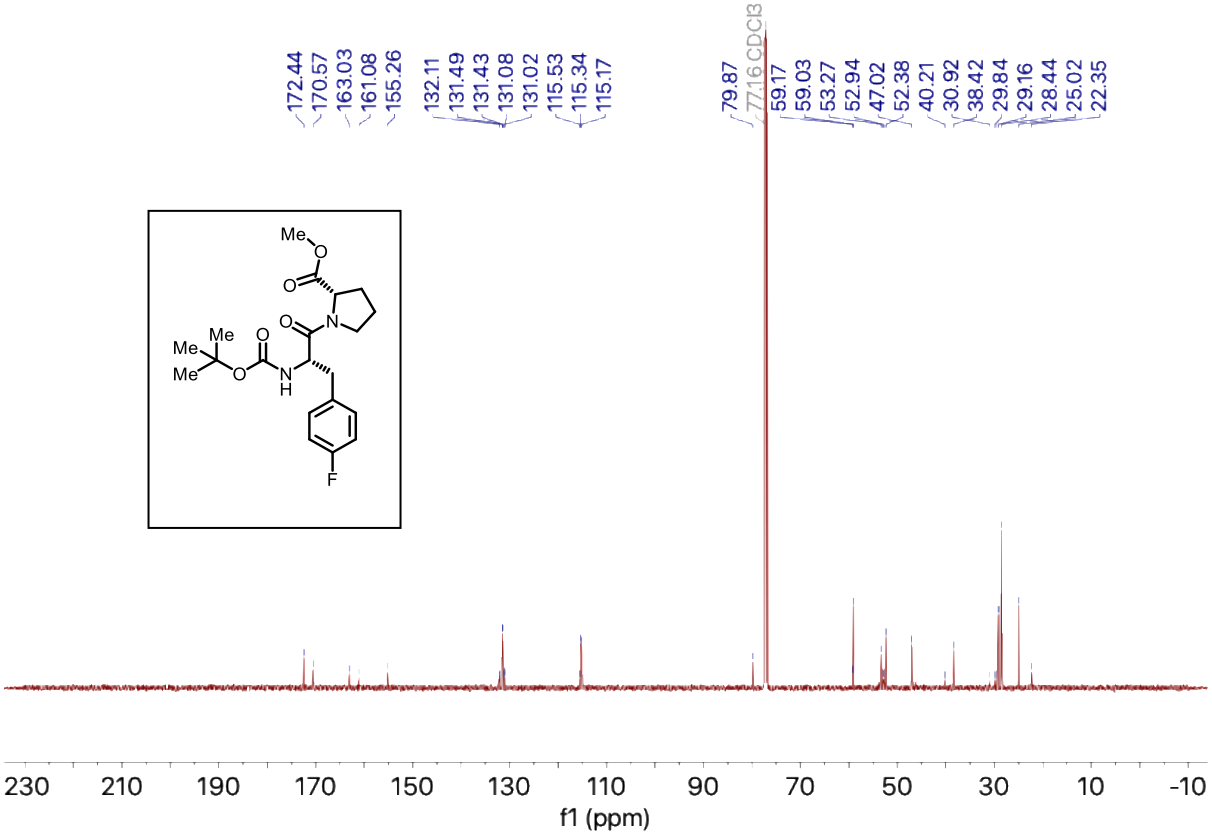
^{19}F NMR ($CDCl_3$, 564 MHz) of Boc-Phe(4-F)- Leu-OMe



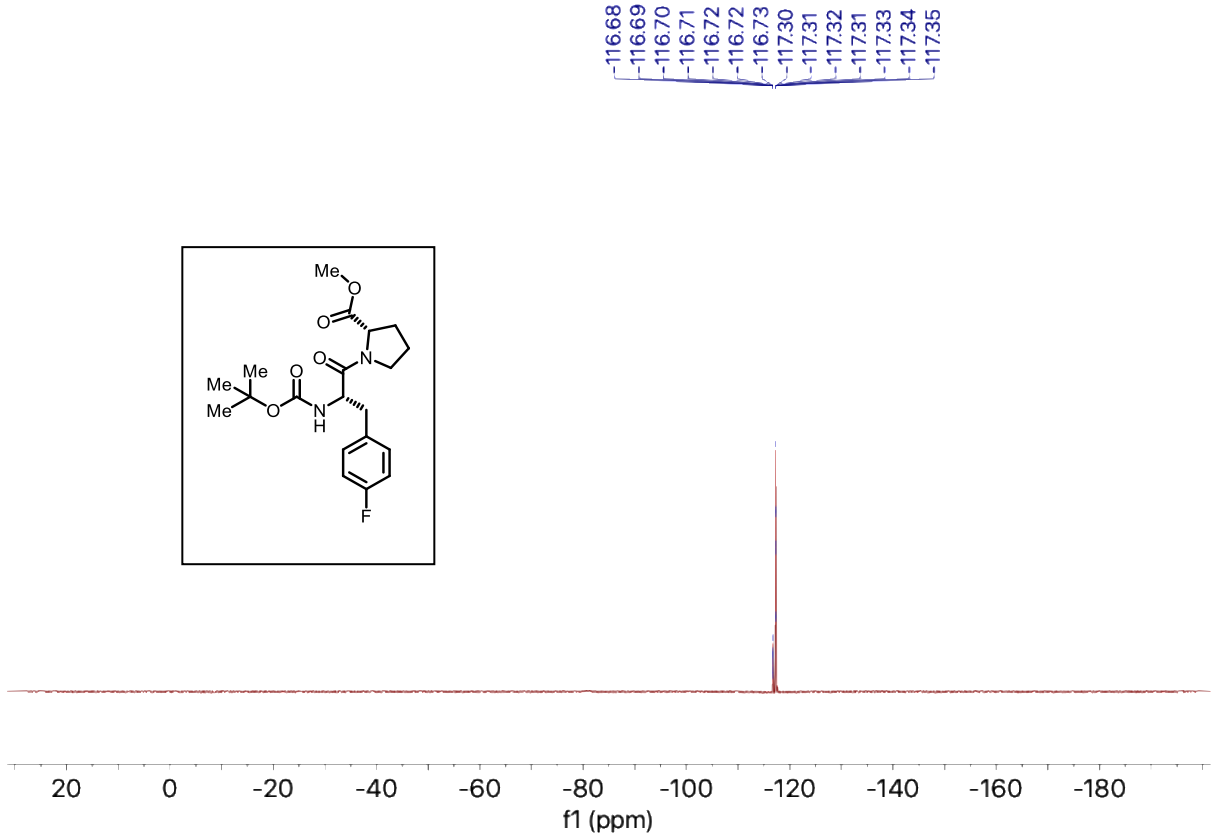
^{1}H NMR ($CDCl_3$, 600 MHz) of Boc-Phe(4-F)-Pro-OMe



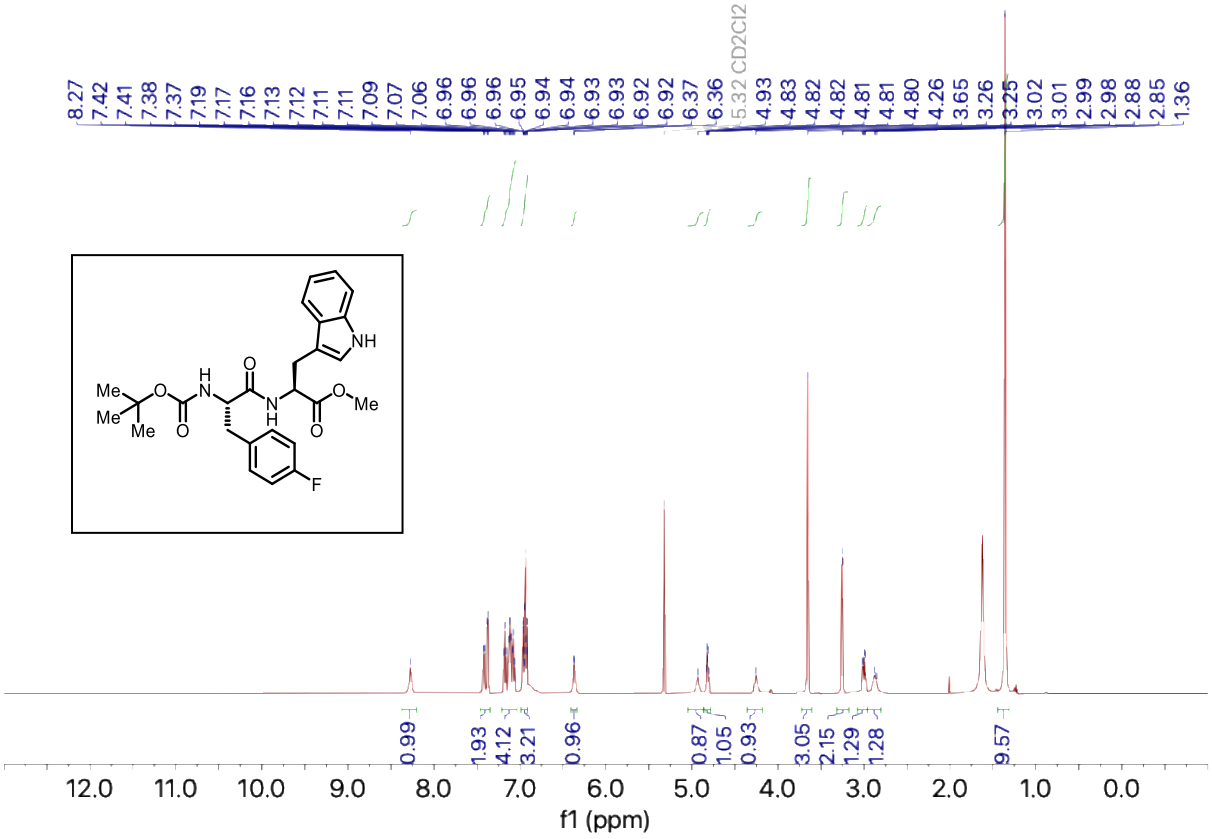
^{13}C NMR ($CDCl_3$, 126 MHz) of Boc-Phe(4-F)-Pro-OMe



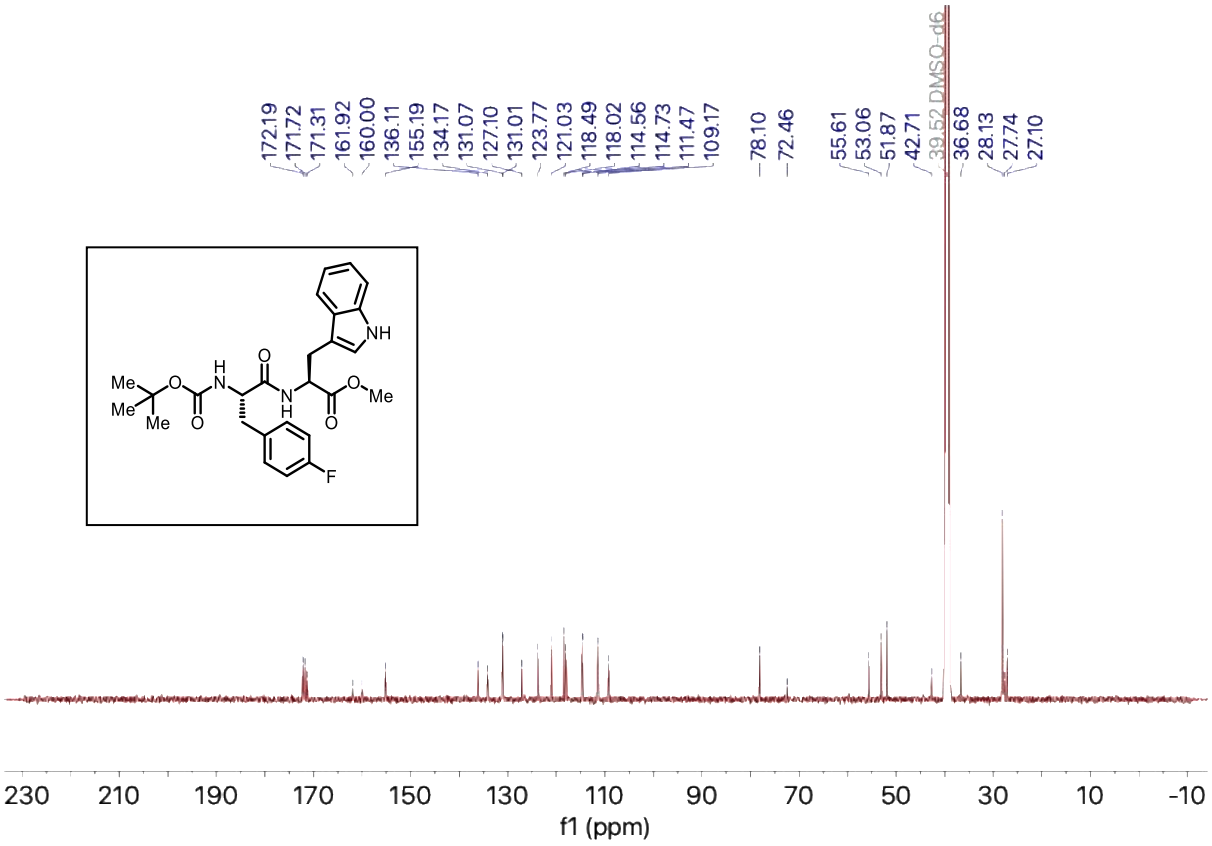
^{19}F NMR ($CDCl_3$, 564 MHz) of Boc-Phe(4-F)-Pro-OMe



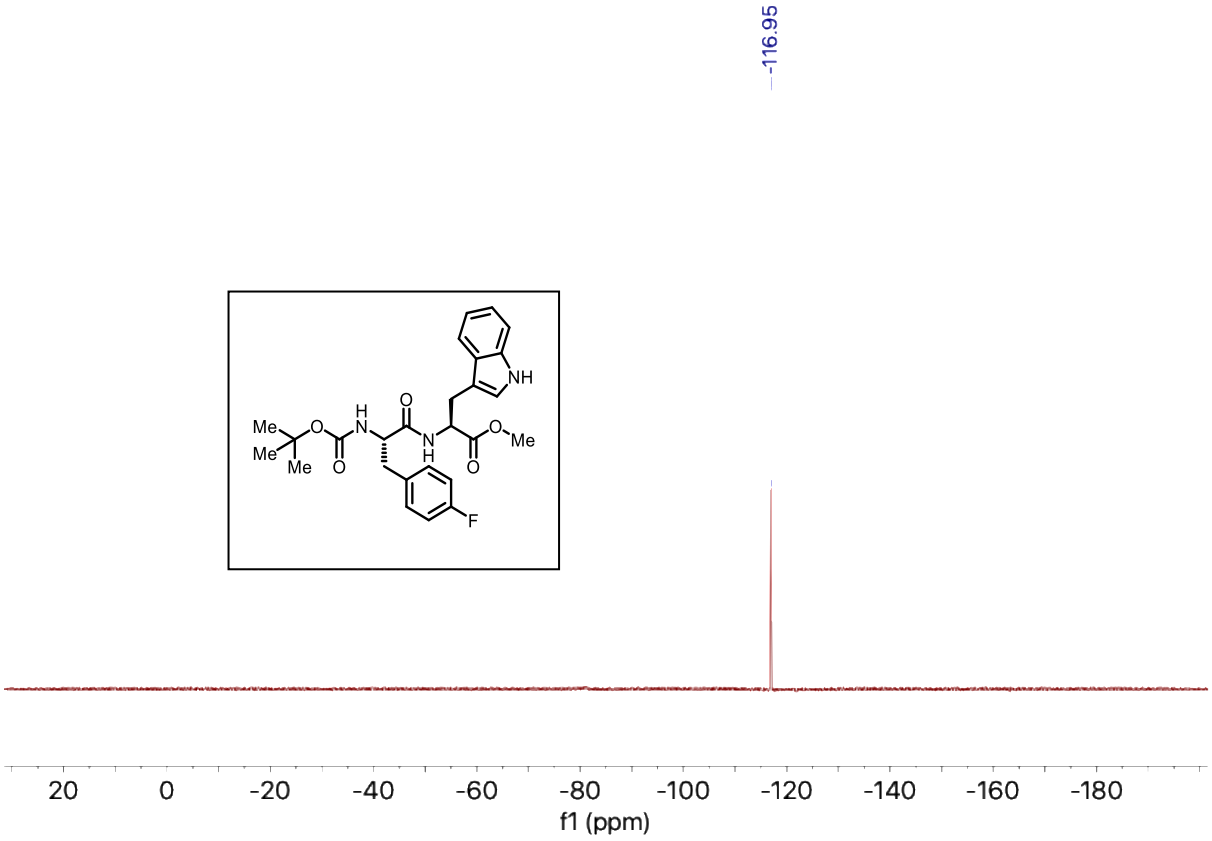
^{1}H NMR (CD_2Cl_2, 500 MHz) of Boc-Phe(4-F)-Trp-OMe



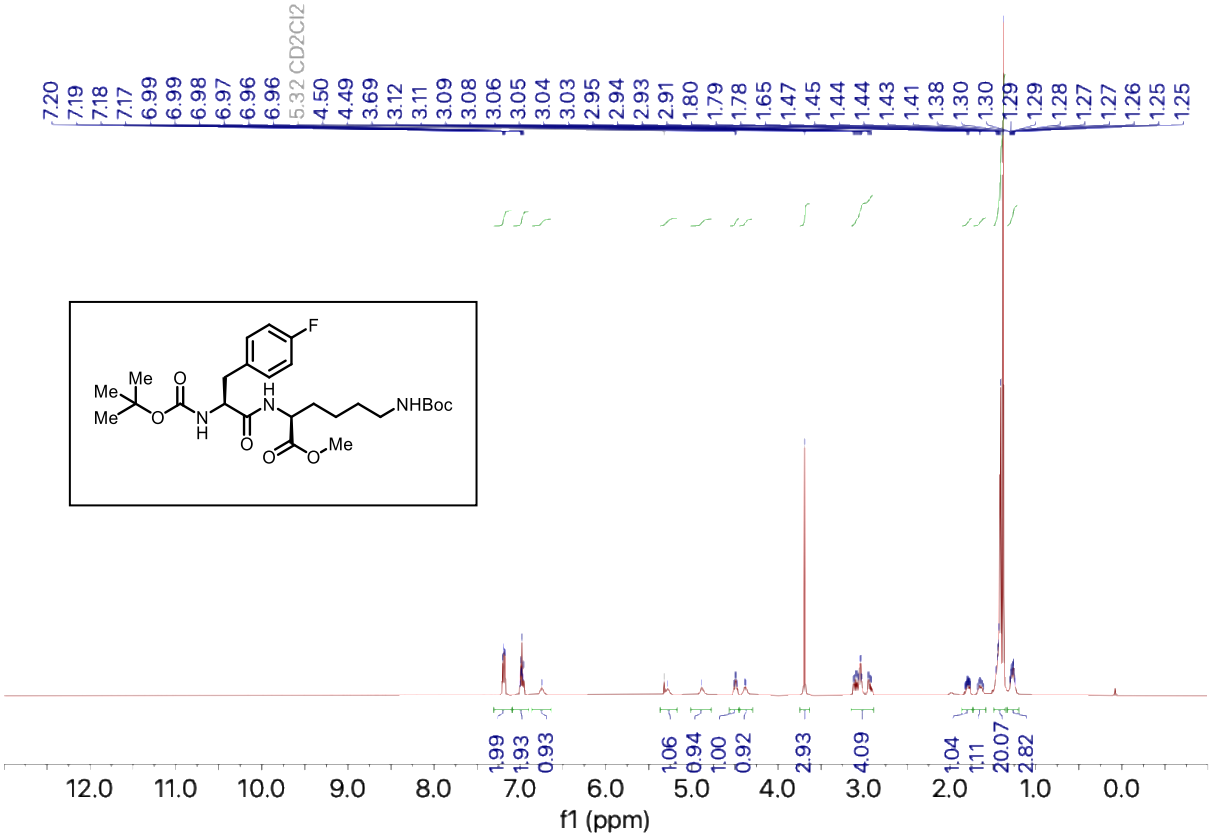
^{13}C NMR (DMSO-d_6, 126 MHz) of Boc-Phe(4-F)-Trp-OMe



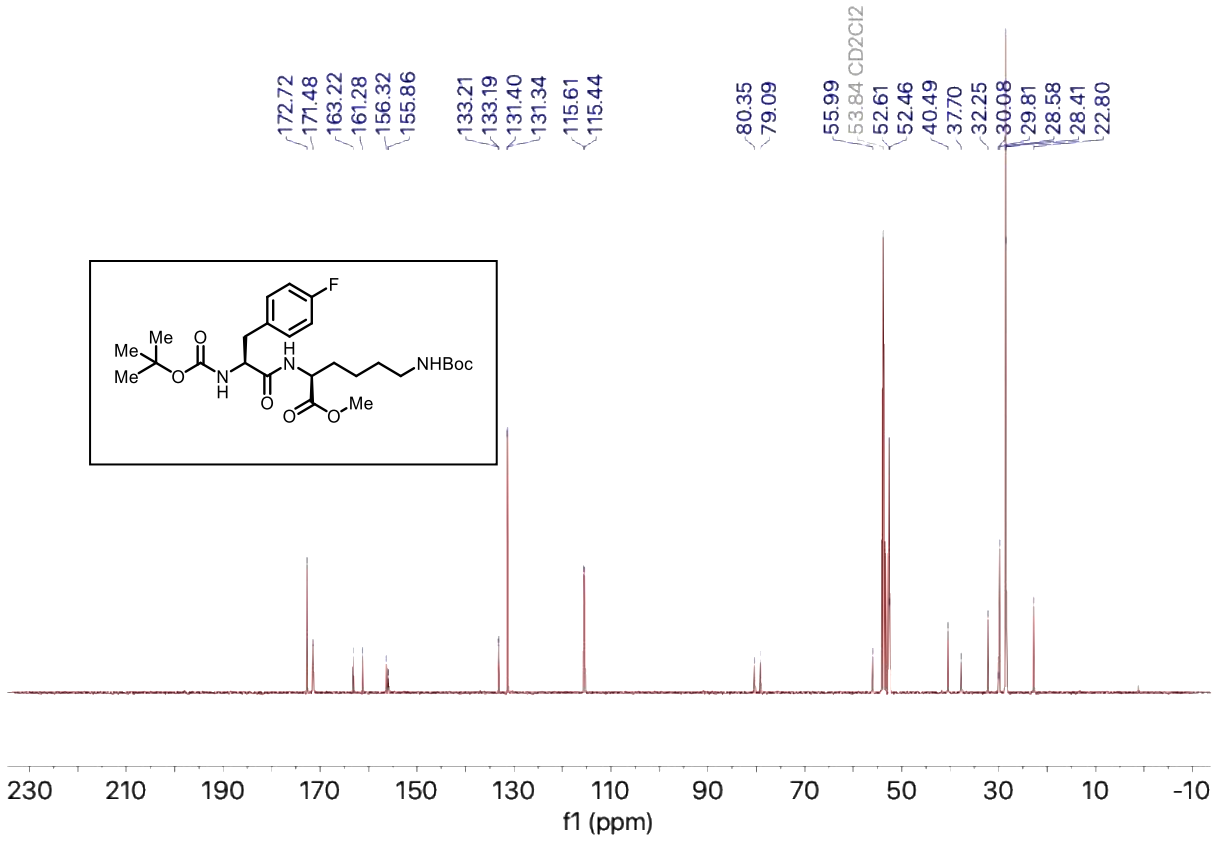
^{19}F NMR ($CDCl_3$, 564 MHz) of Boc-Phe(4-F)-Trp-OMe



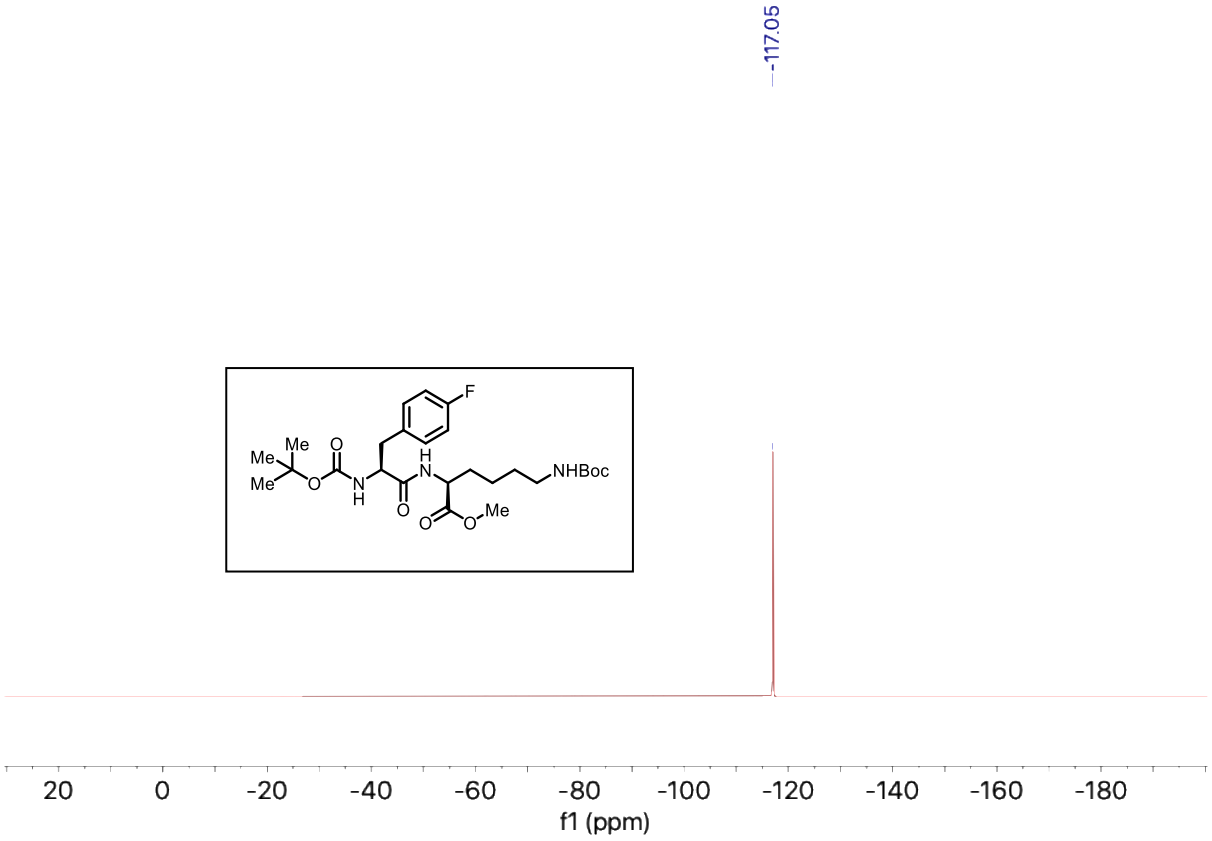
^{1}H NMR (CD_2Cl_2, 500 MHz) of Boc-Phe(4-F)-Lys(Boc)-OMe



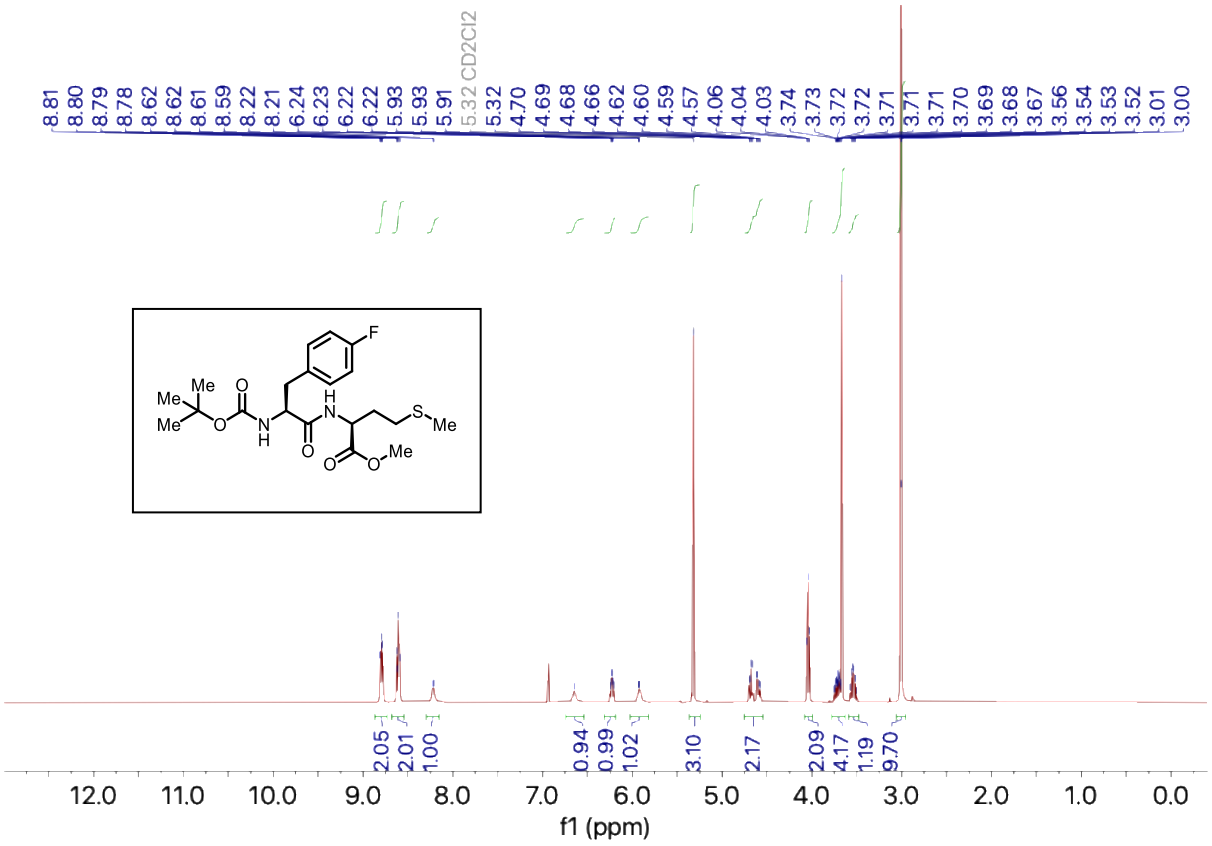
^{13}C NMR (CD_2Cl_2, 126 MHz) of Boc-Phe(4-F)-Lys(Boc)-OMe



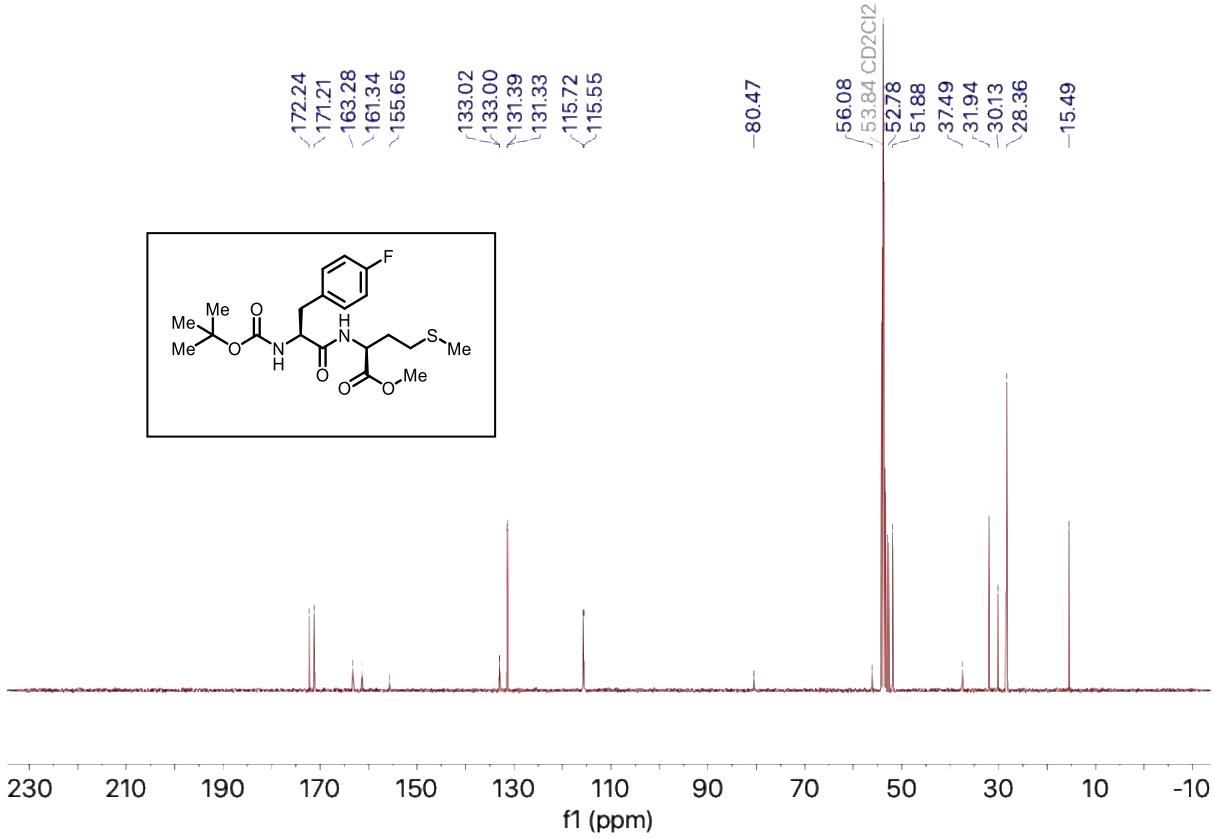
^{19}F NMR (CD_2Cl_2, 471 MHz) of Boc-Phe(4-F)-Lys(Boc)-OMe



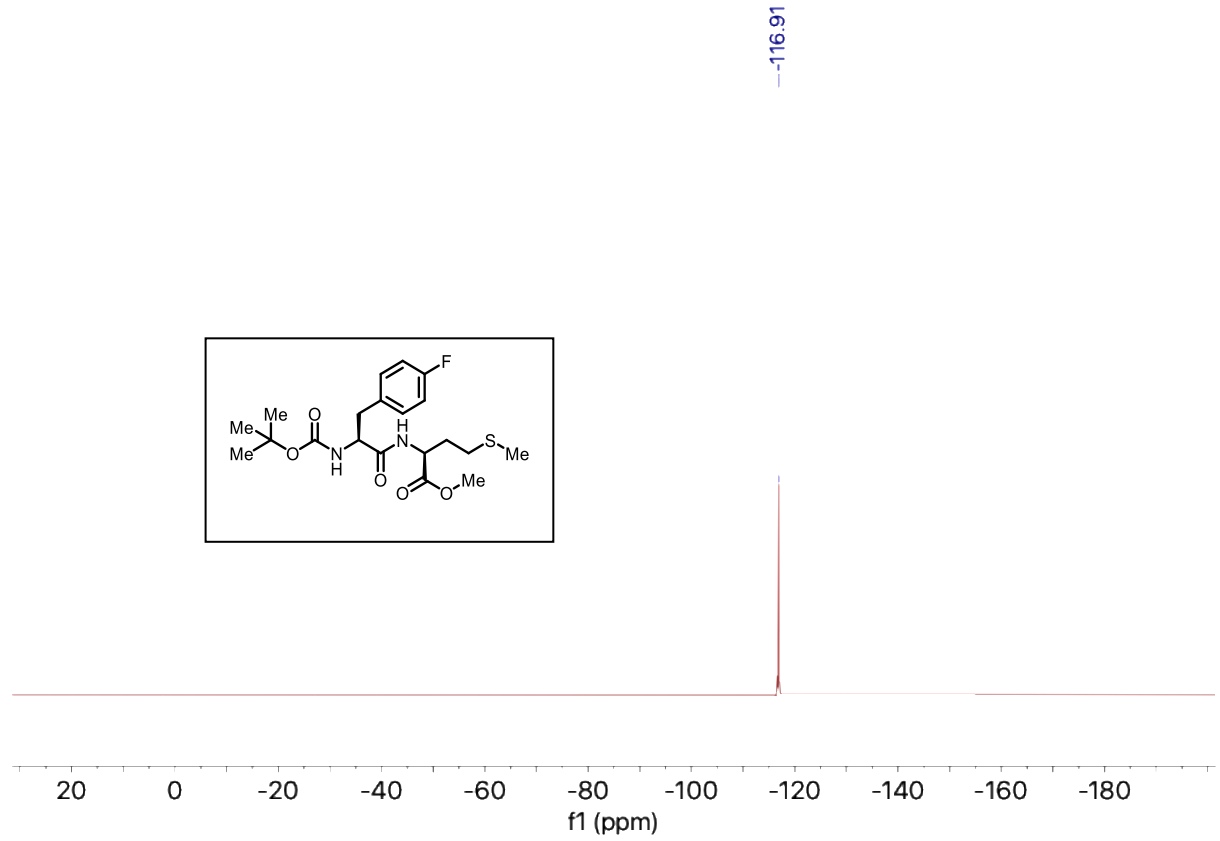
^{1}H NMR (CD_2Cl_2, 500 MHz) of Boc-Phe(4-F)-Met-OMe



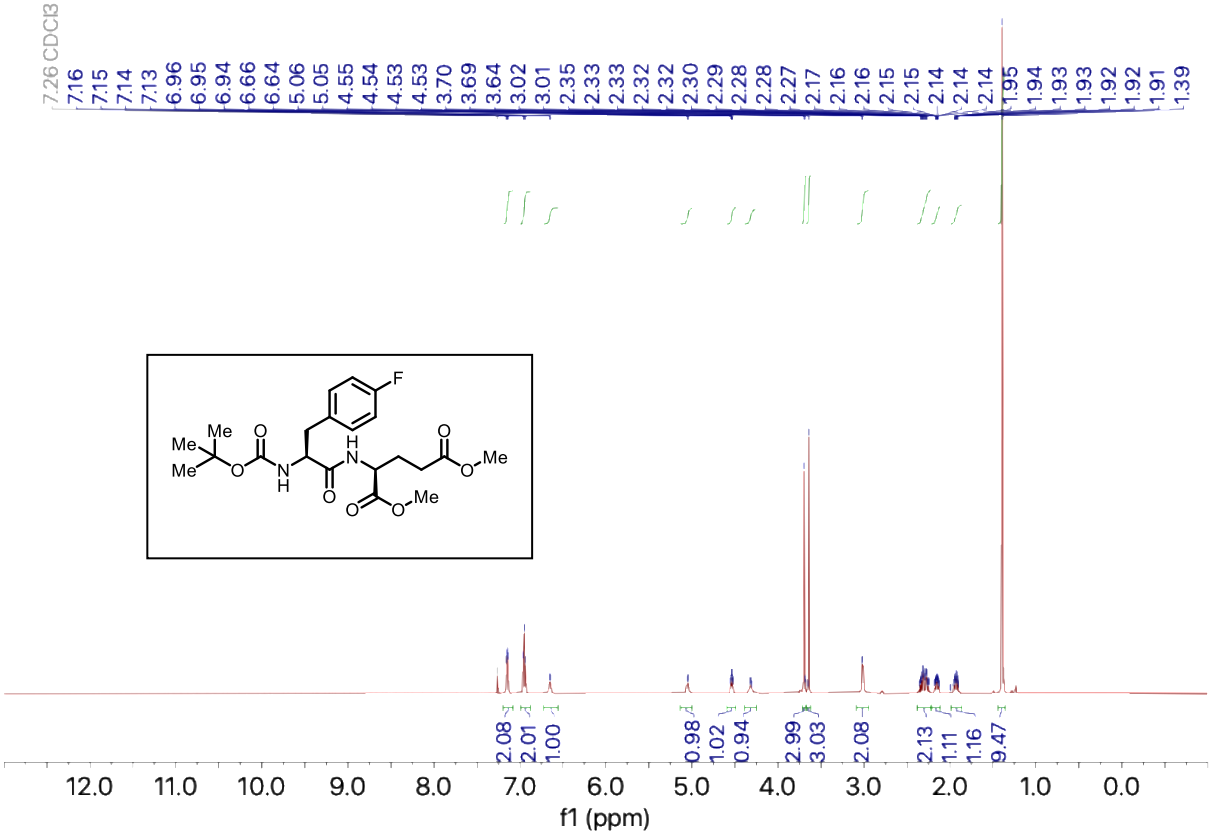
^{13}C NMR (CD_2Cl_2, 126 MHz) of Boc-Phe(4-F)-Met-OMe



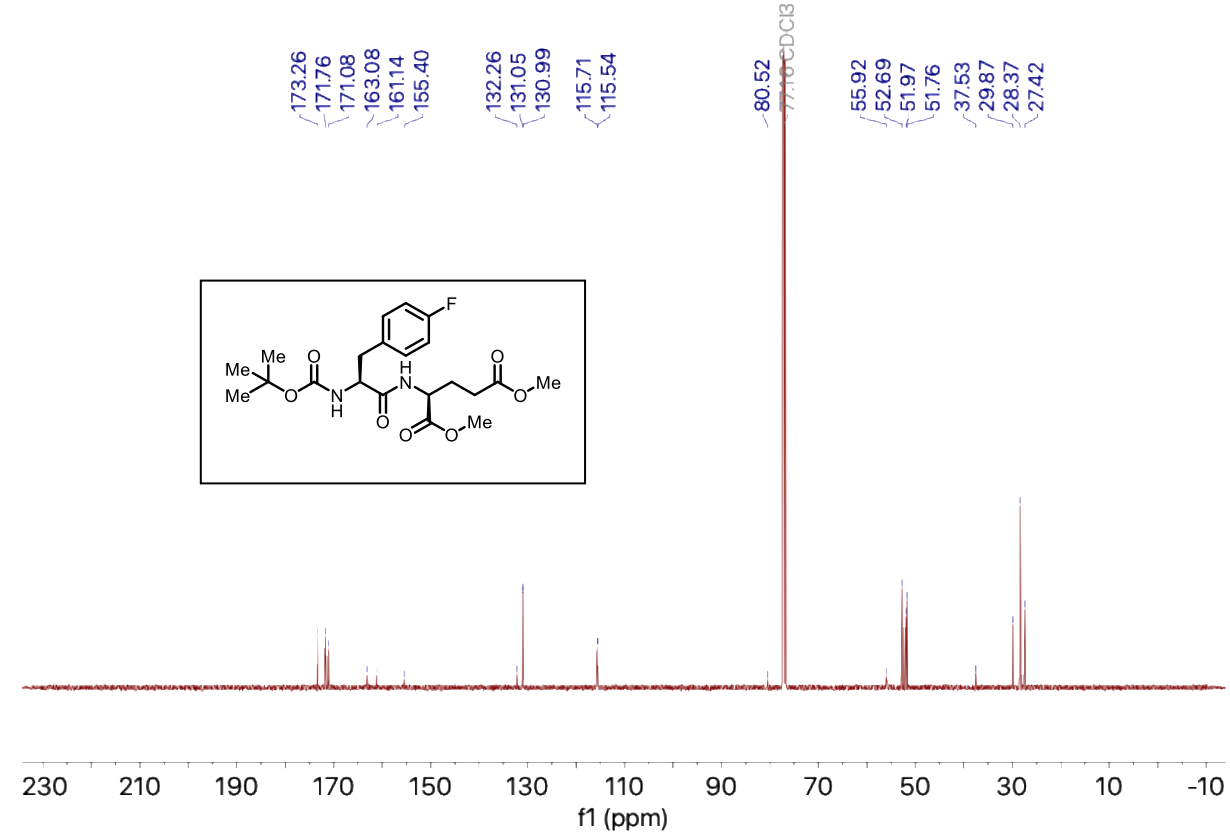
^{19}F NMR (CD_2Cl_2, 564 MHz) of Boc-Phe(4-F)-Met-OMe



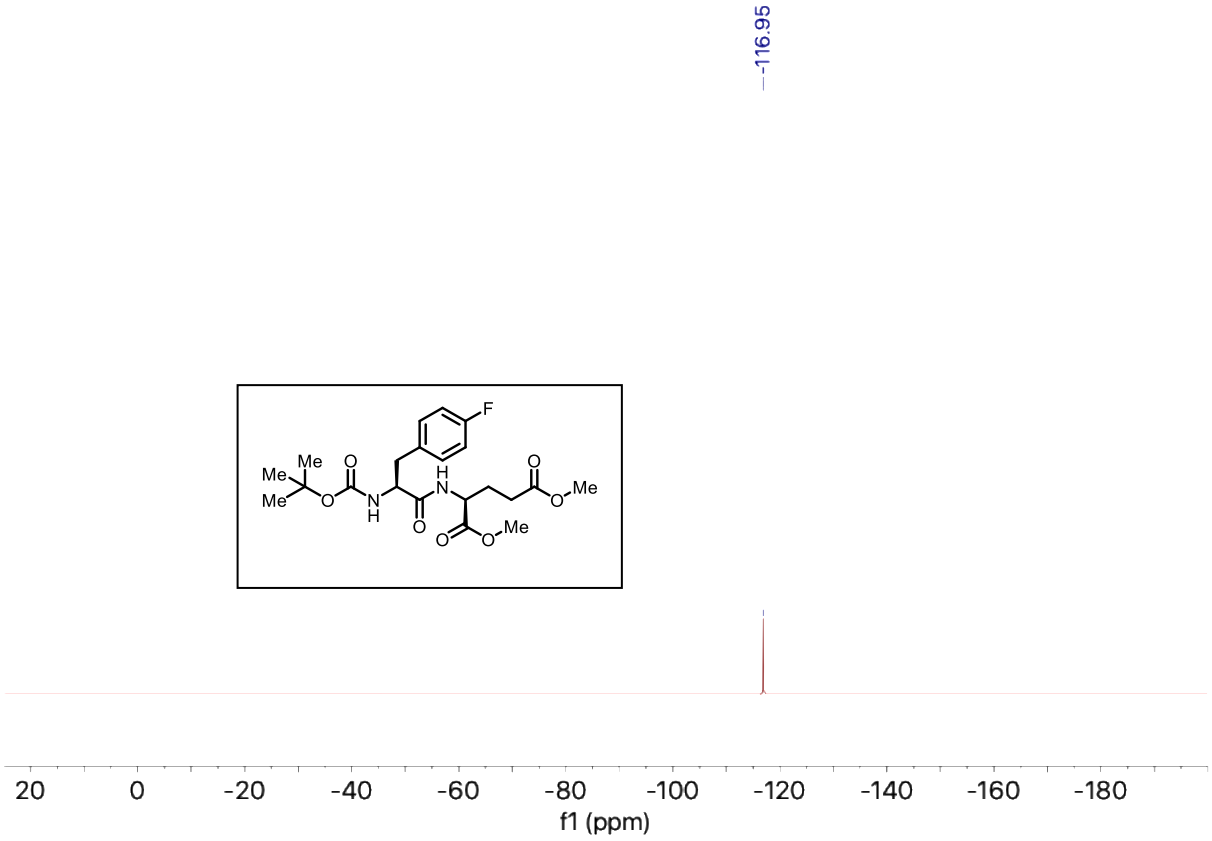
^{1}H NMR ($CDCl_3$, 600 MHz) of Boc-Phe(4-F)-Glu(OMe)-OMe



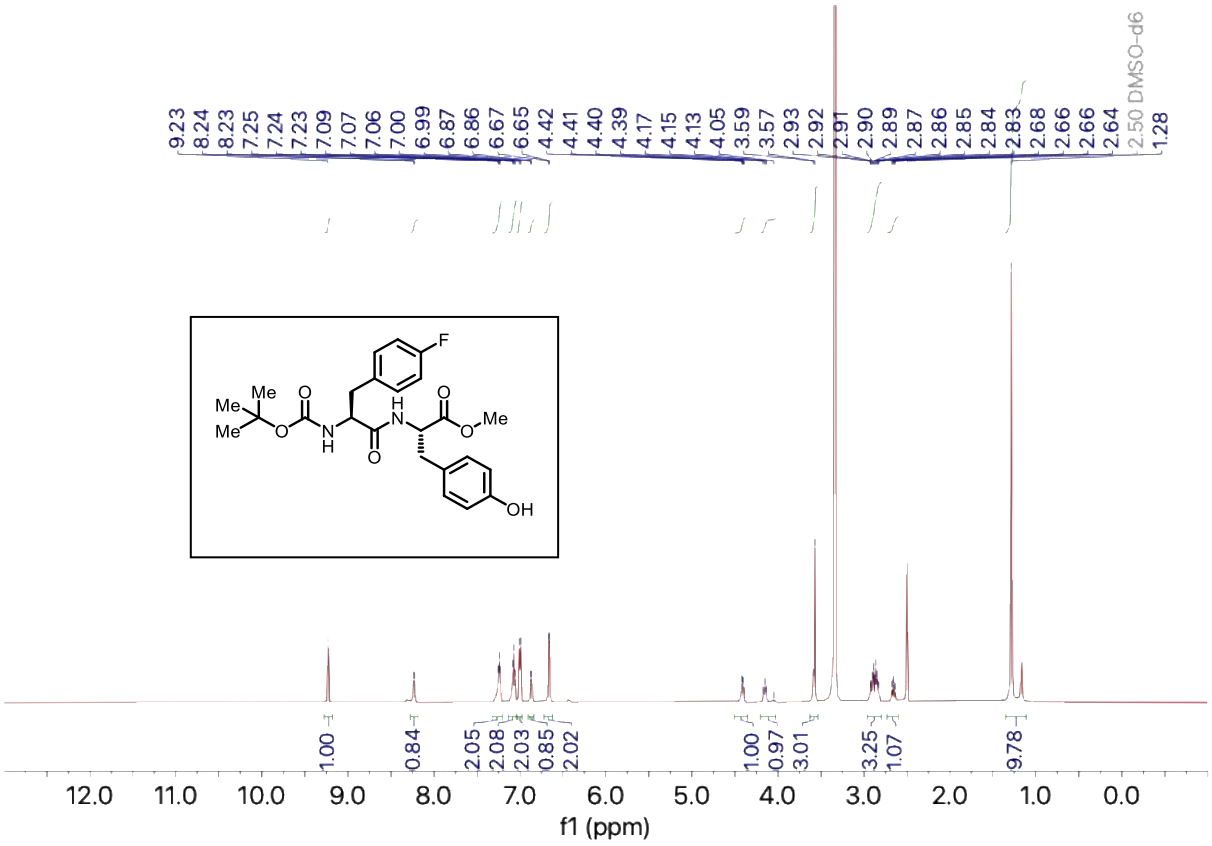
^{13}C NMR ($CDCl_3$, 126 MHz) of Boc-Phe(4-F)-Glu(OMe)-OMe



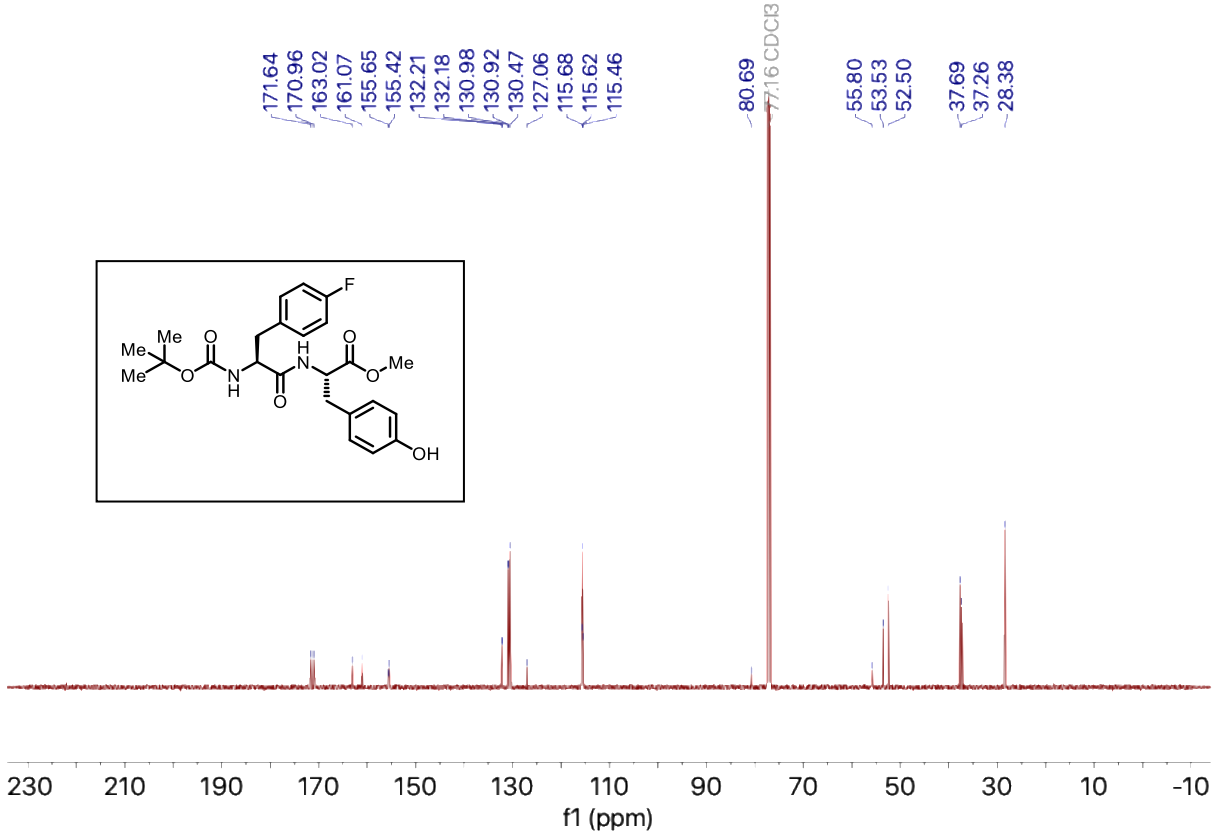
^{19}F NMR ($CDCl_3$, 564 MHz) of Boc-Phe(4-F)-Glu(OMe)-OMe



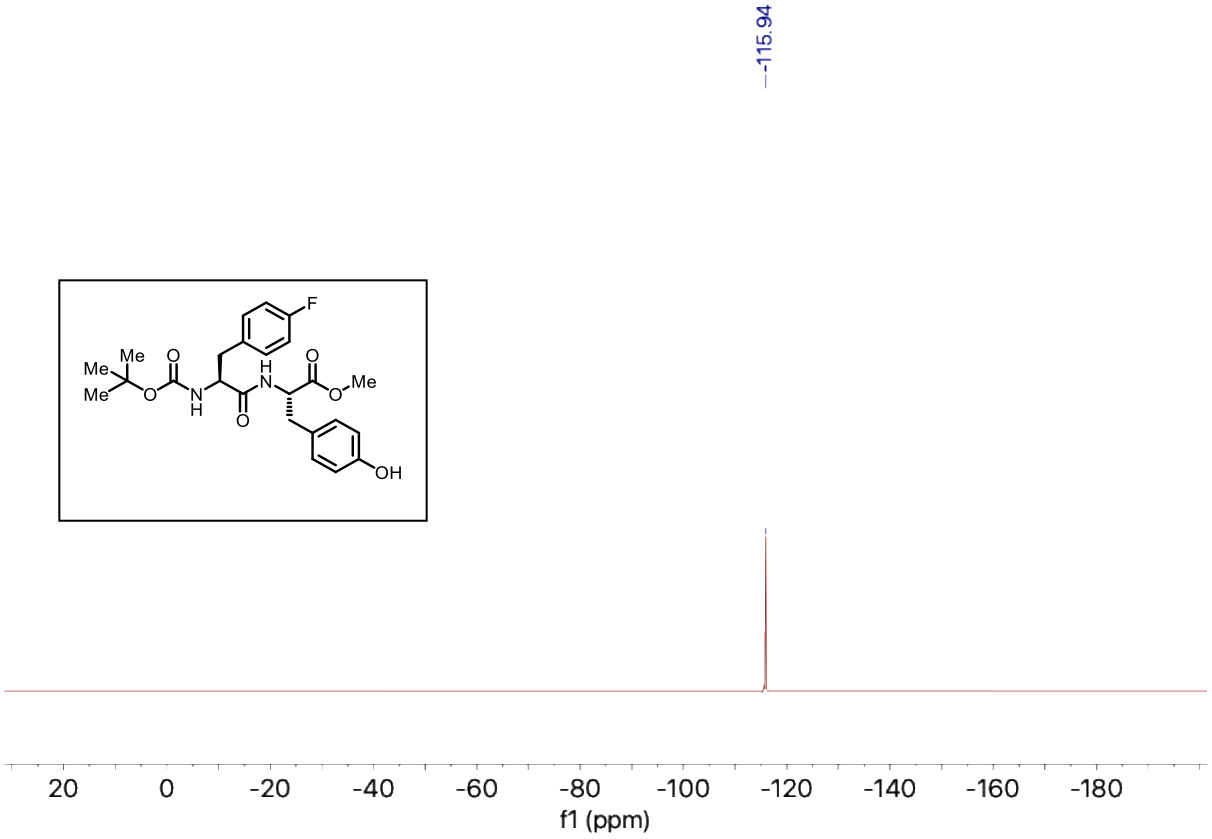
^{1}H NMR (DMSO-d_6, 600 MHz) of Boc-Phe(4-F)-Tyr-OMe



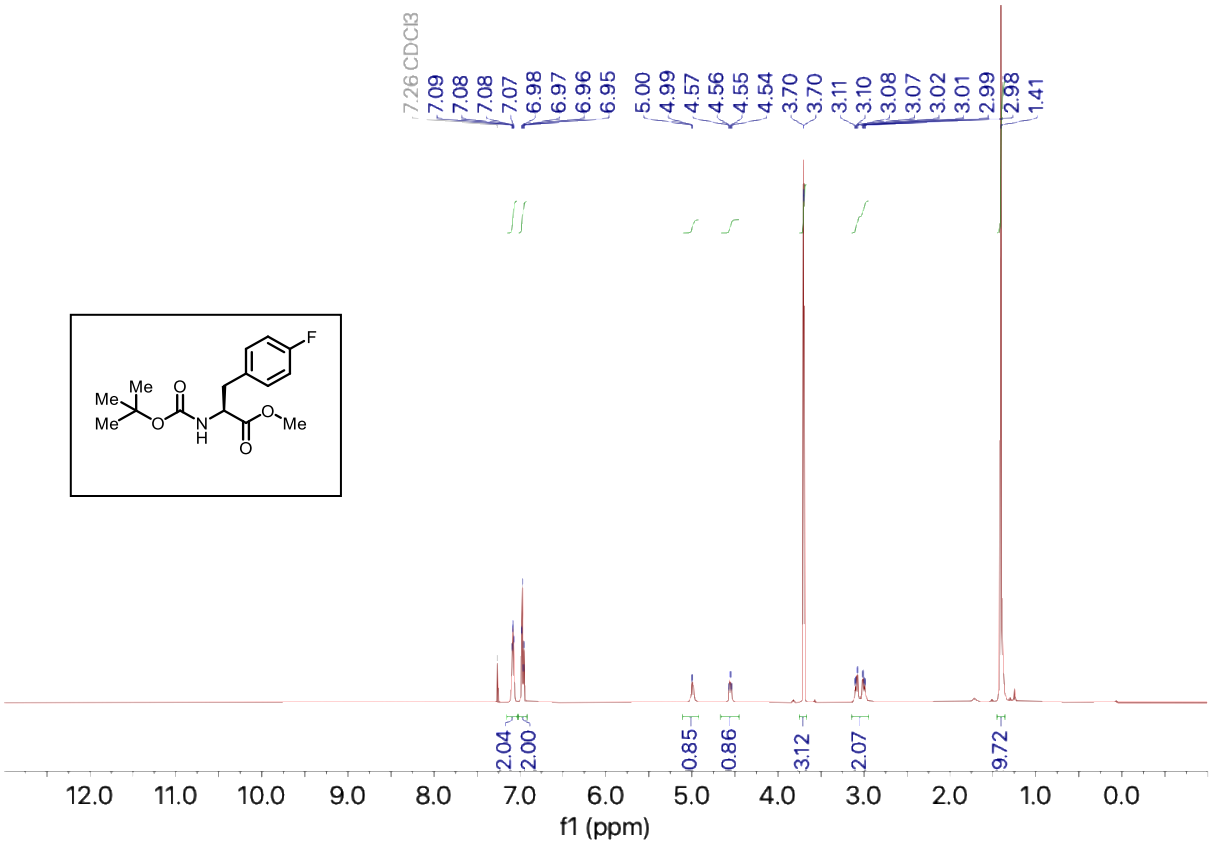
^{13}C NMR ($CDCl_3$, 126 MHz) of Boc-Phe(4-F)-Tyr-OMe



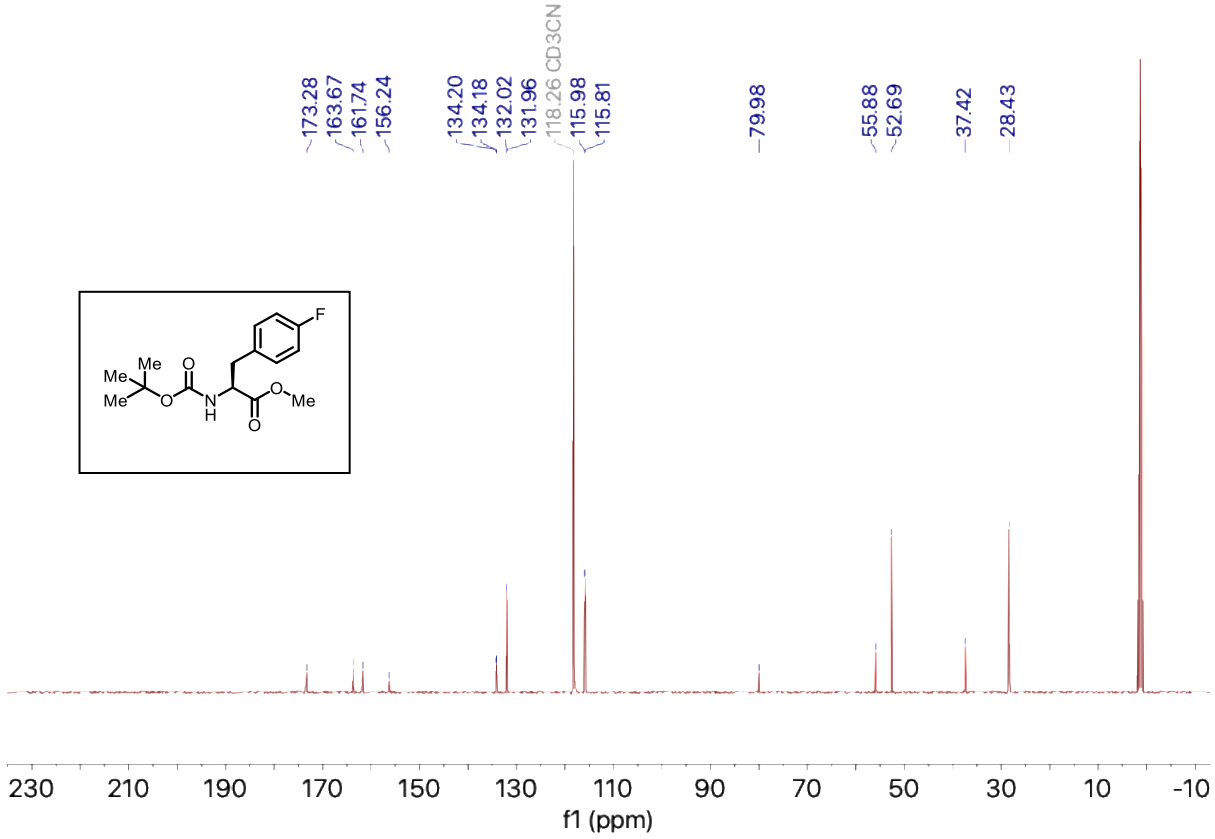
^{19}F NMR ($CDCl_3$, 564 MHz) of Boc-Phe(4-F)-Tyr-OMe



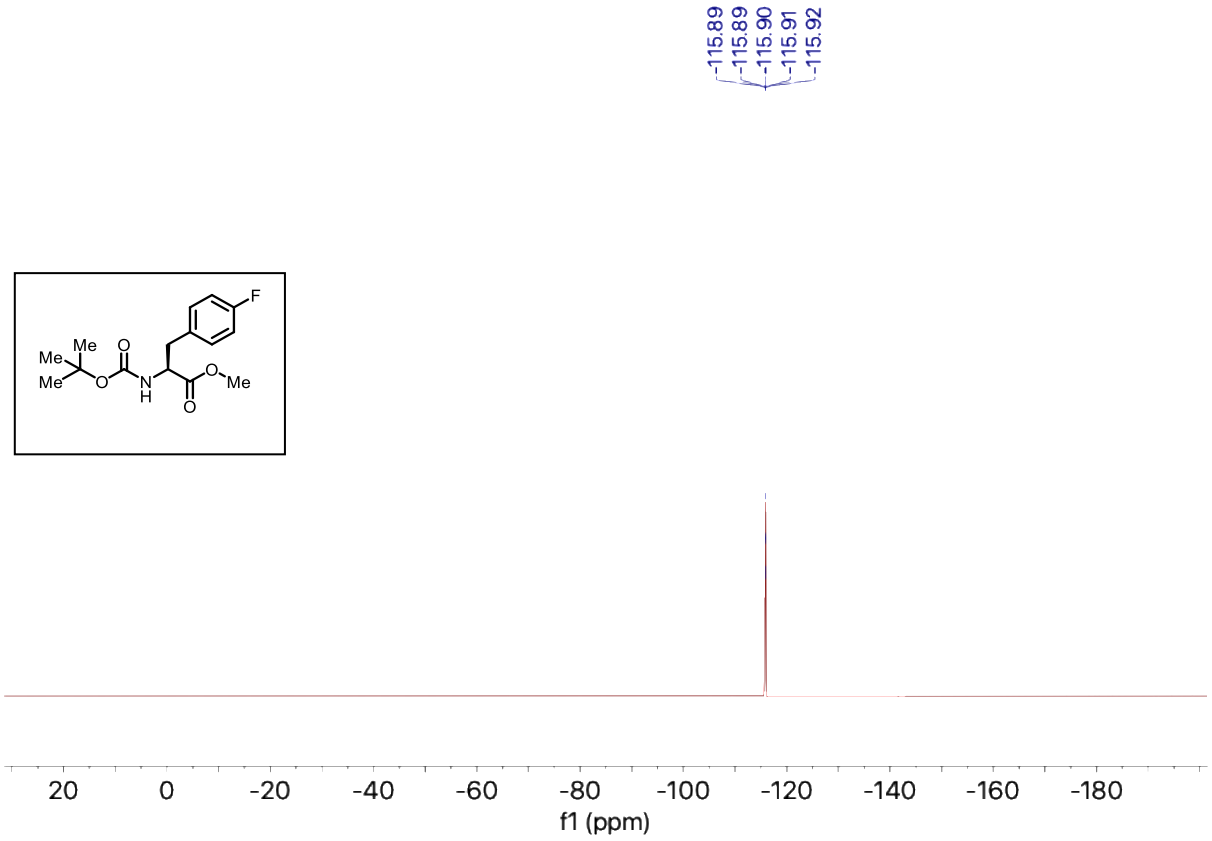
^{1}H NMR ($CDCl_3$, 600 MHz) of Boc-Phe(4-F)-OMe



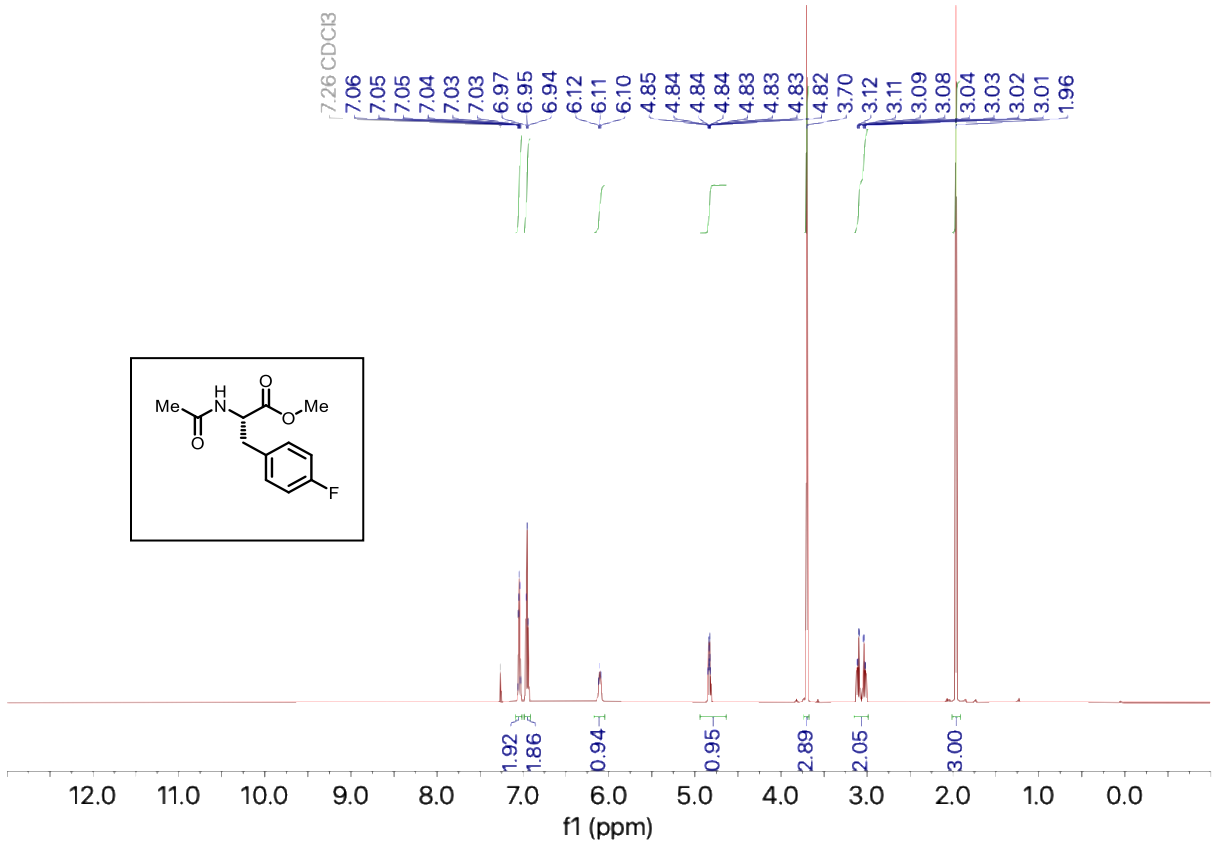
^{13}C NMR (CD_3CN, 126 MHz) of Boc-Phe(4-F)-OMe



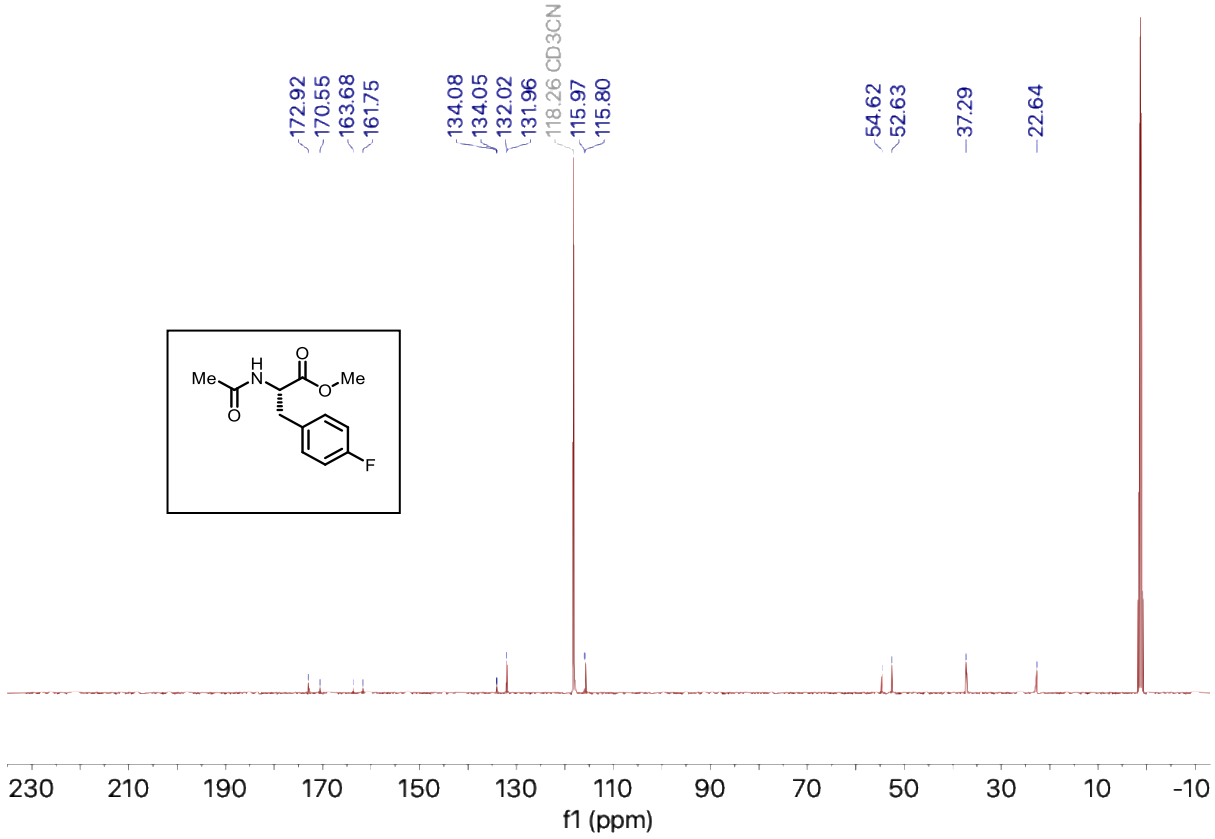
^{19}F NMR (CD_3CN, 564 MHz) of Boc-Phe(4-F)-OMe



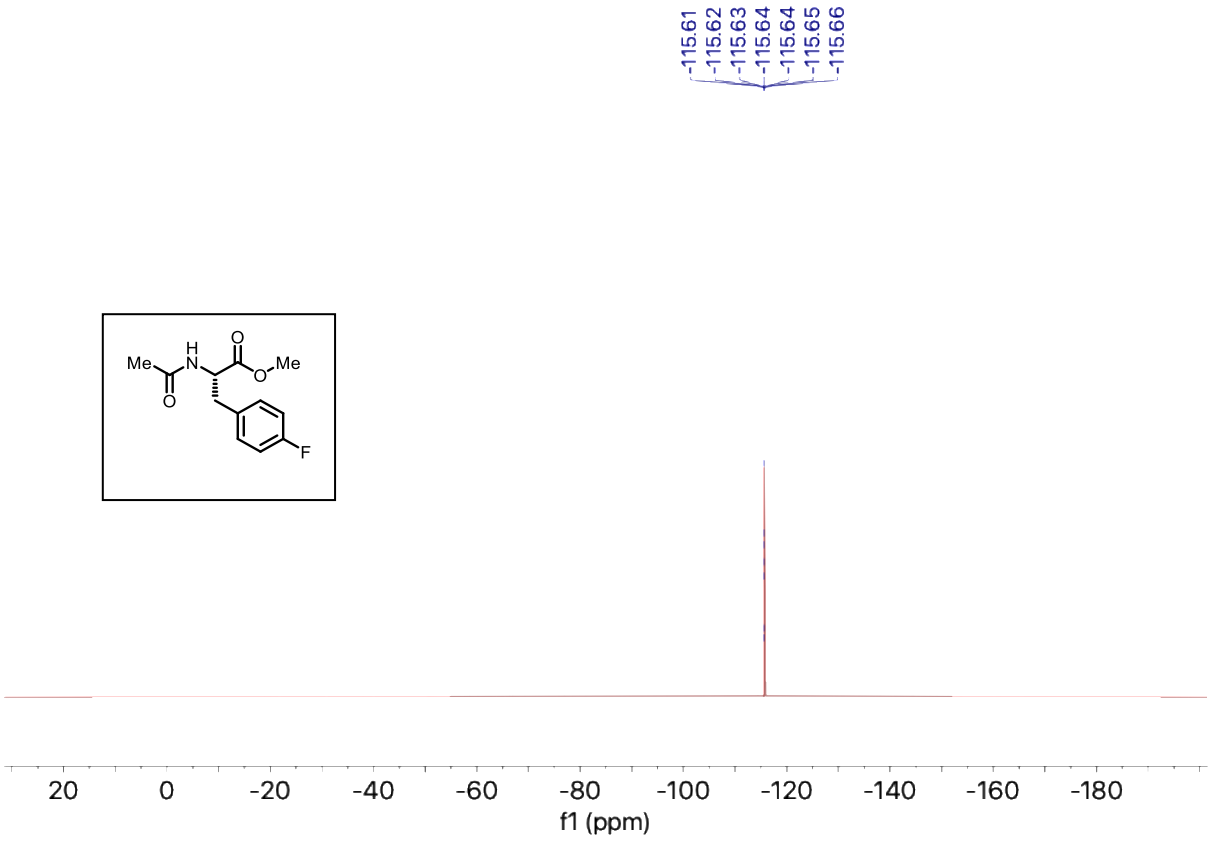
^{1}H NMR ($CDCl_3$, 600 MHz) of Ac-Phe(4-F)-OMe



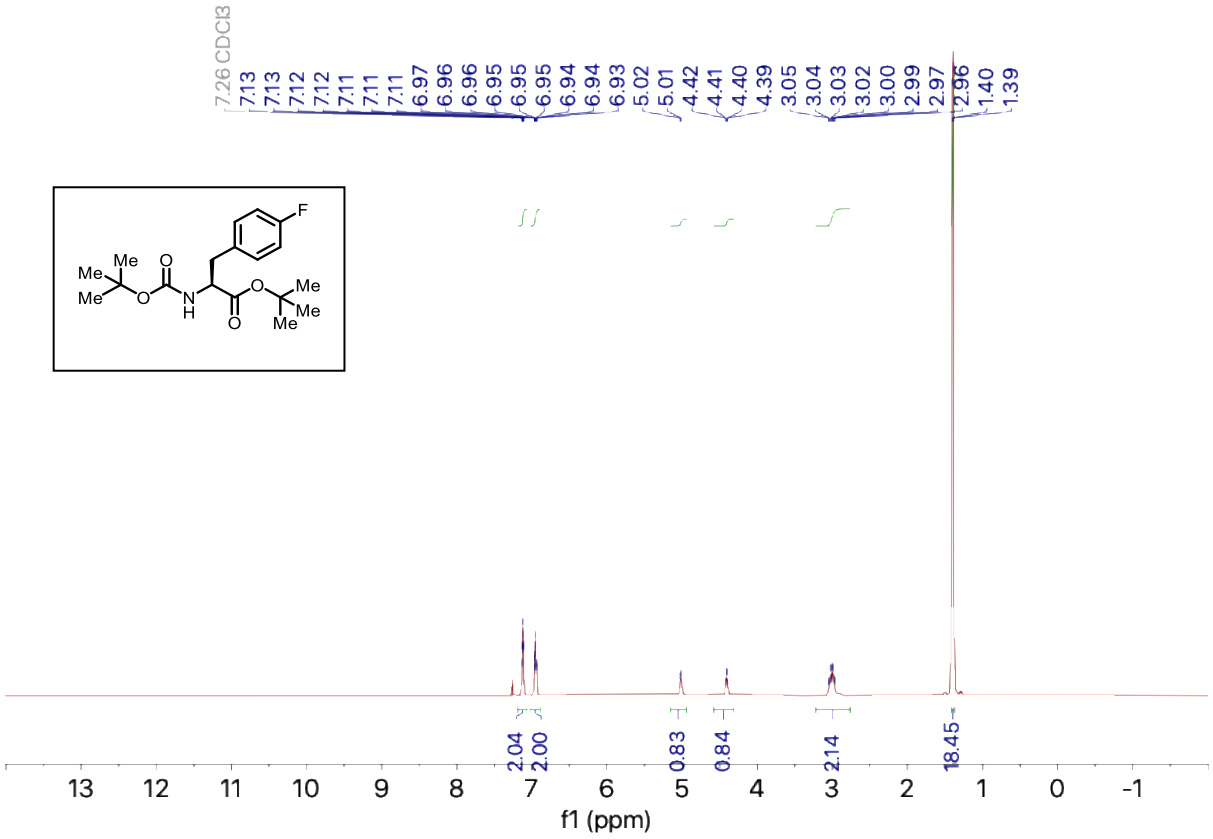
^{13}C NMR (CD_3CN, 126 MHz) of Ac-Phe(4-F)-OMe



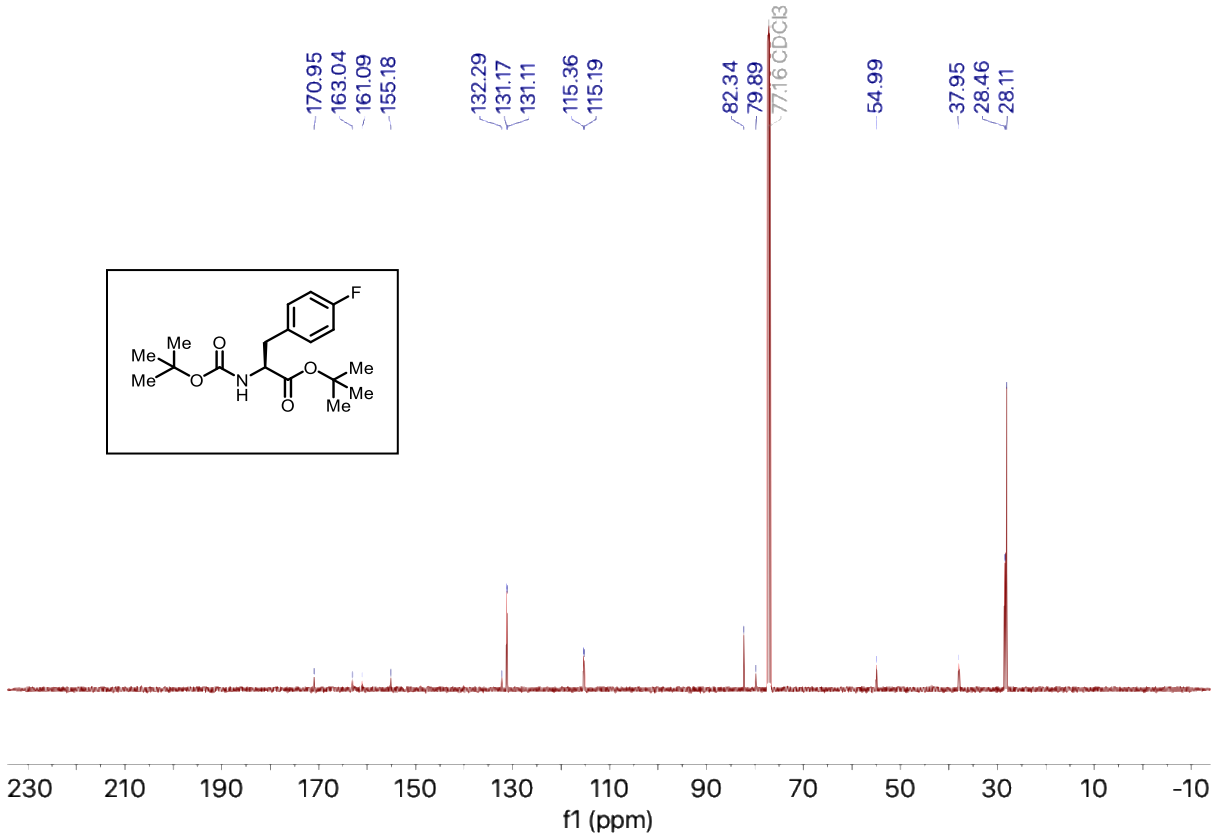
^{19}F NMR (CD_3CN, 564 MHz) of Ac-Phe(4-F)-OMe



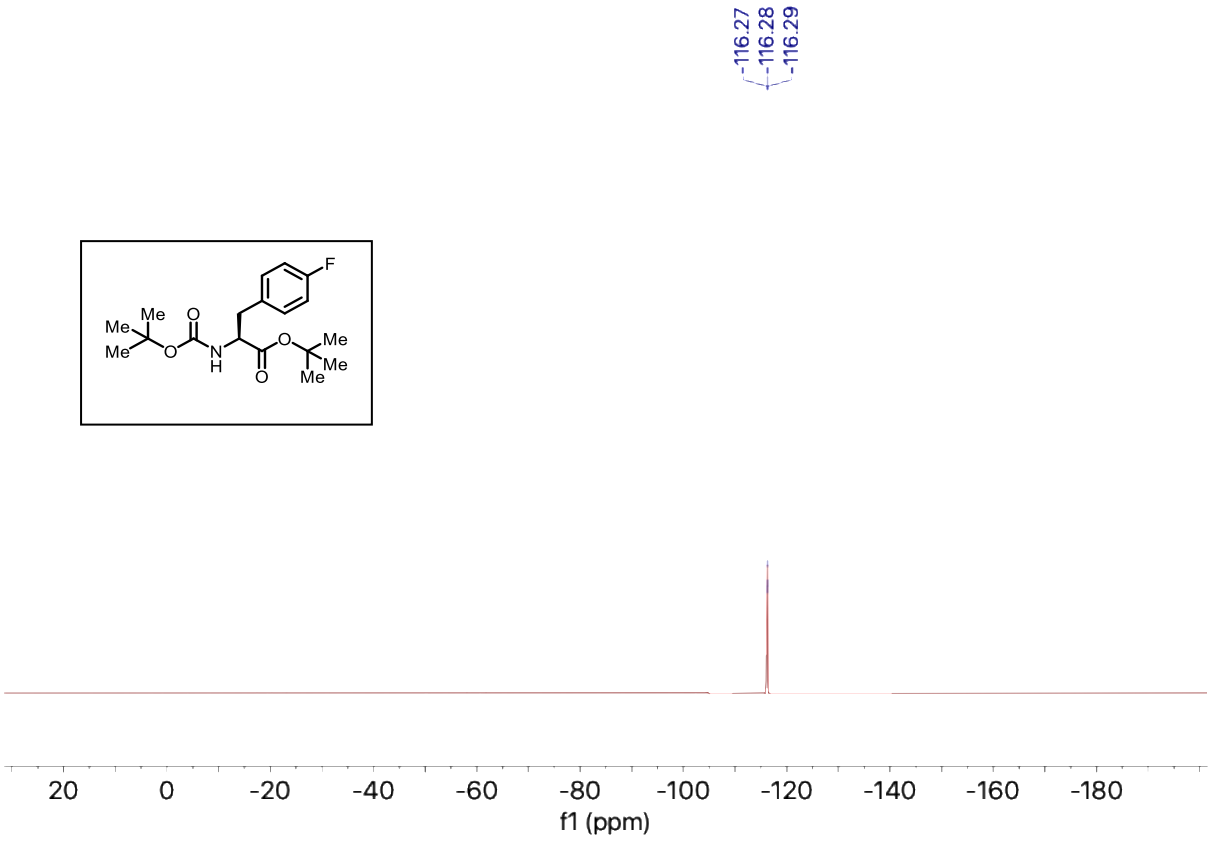
^{1}H NMR ($CDCl_3$, 600 MHz) of Boc-Phe(4-F)-O^{t}Bu



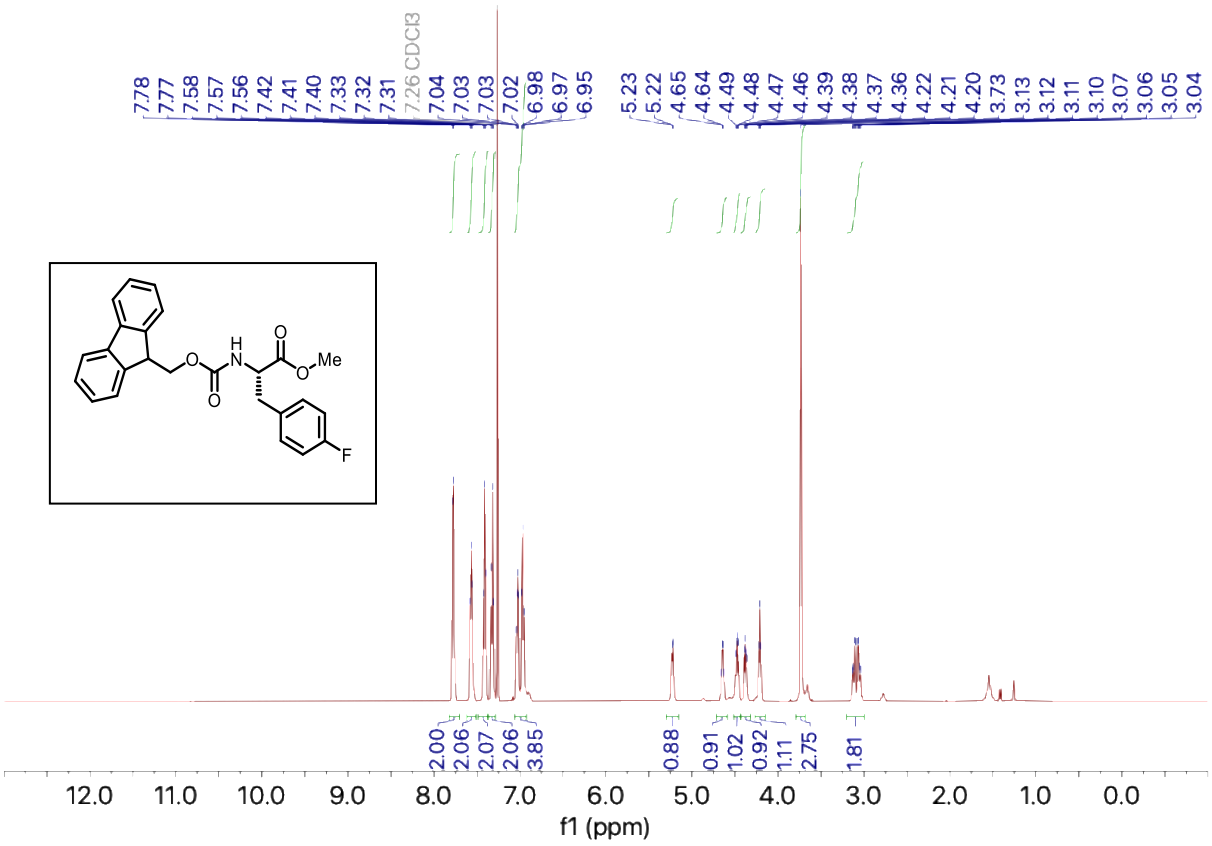
^{13}C NMR ($CDCl_3$, 126 MHz) of Boc-Phe(4-F)-O^{t}Bu



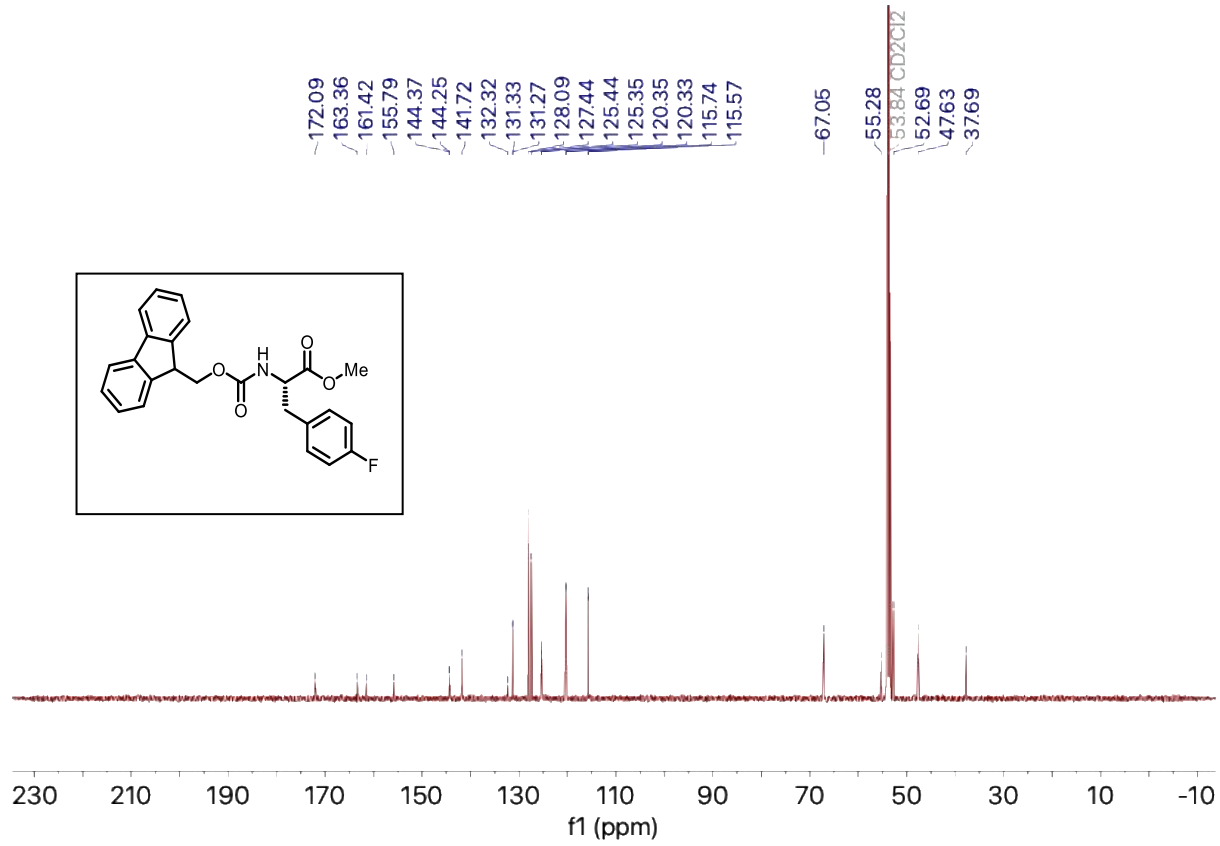
^{19}F NMR ($CDCl_3$, 564 MHz) of Boc-Phe(4-F)-O^{t}Bu



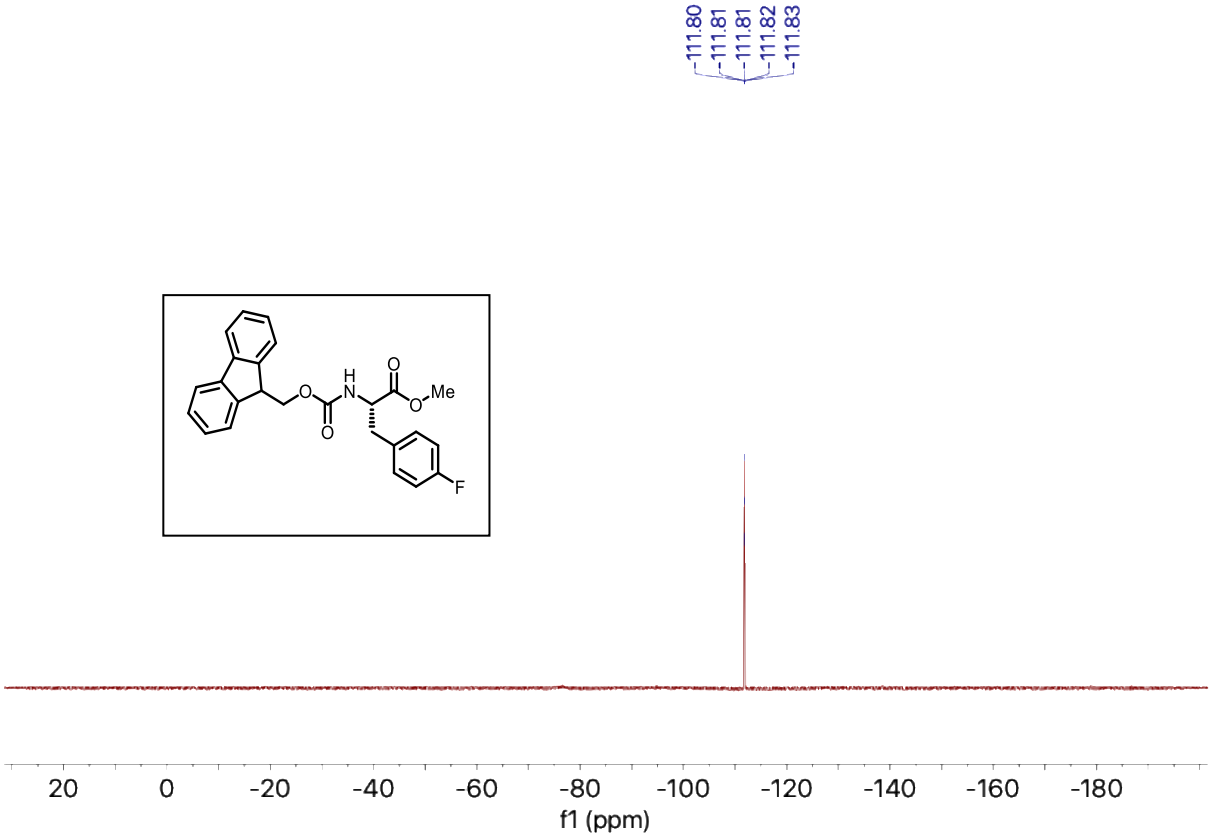
^{1}H NMR ($CDCl_3$, 600 MHz) of Fmoc-Phe(4-F)-OMe



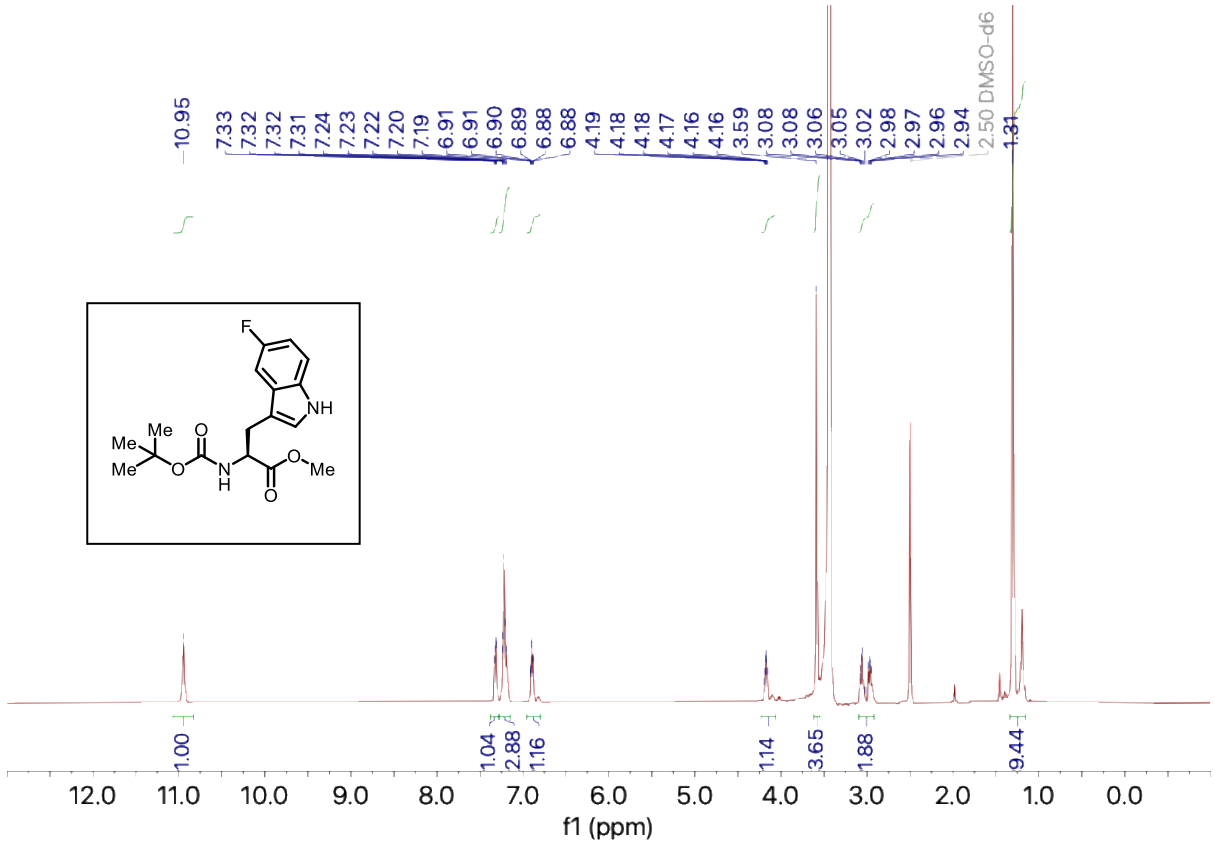
^{13}C NMR ($CDCl_3$, 126 MHz) of Fmoc-Phe(4-F)-OMe



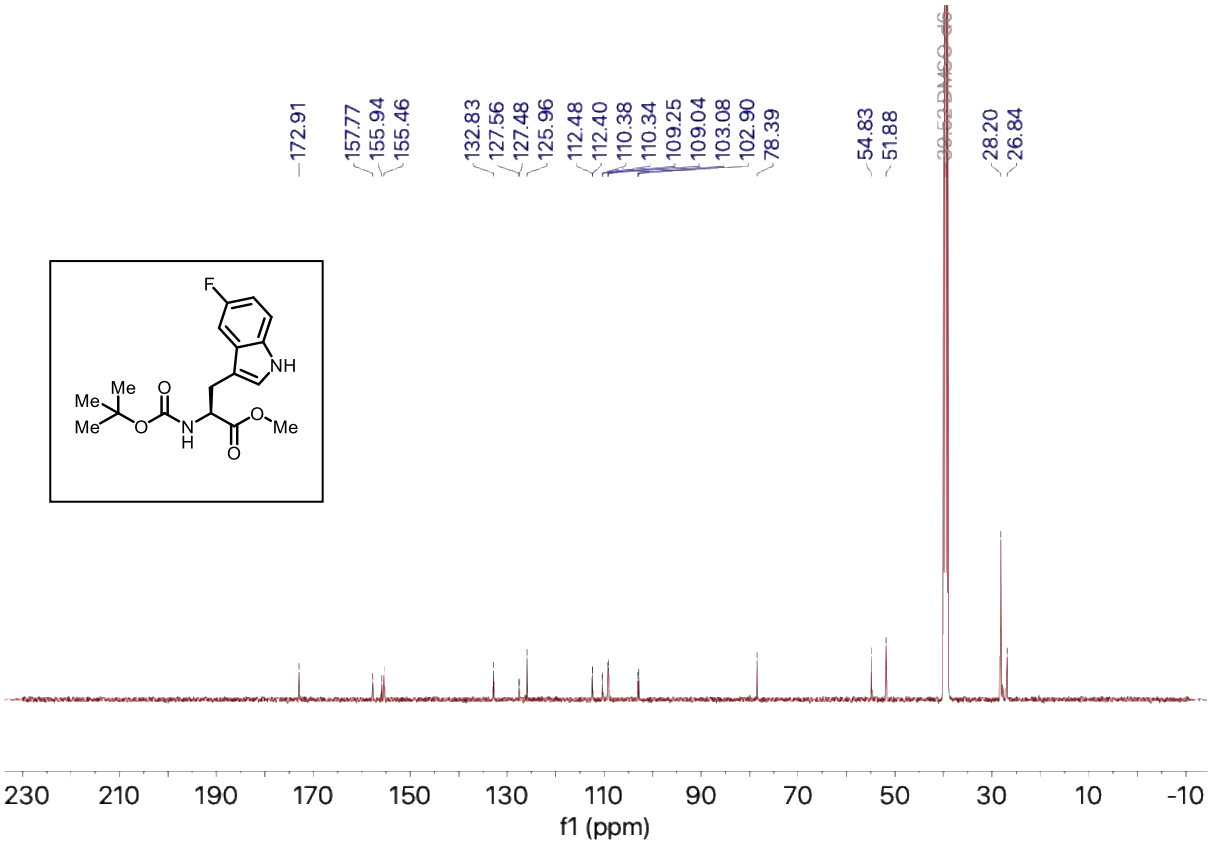
^{19}F NMR ($CDCl_3$, 564 MHz) of Fmoc-Phe(4-F)-OMe



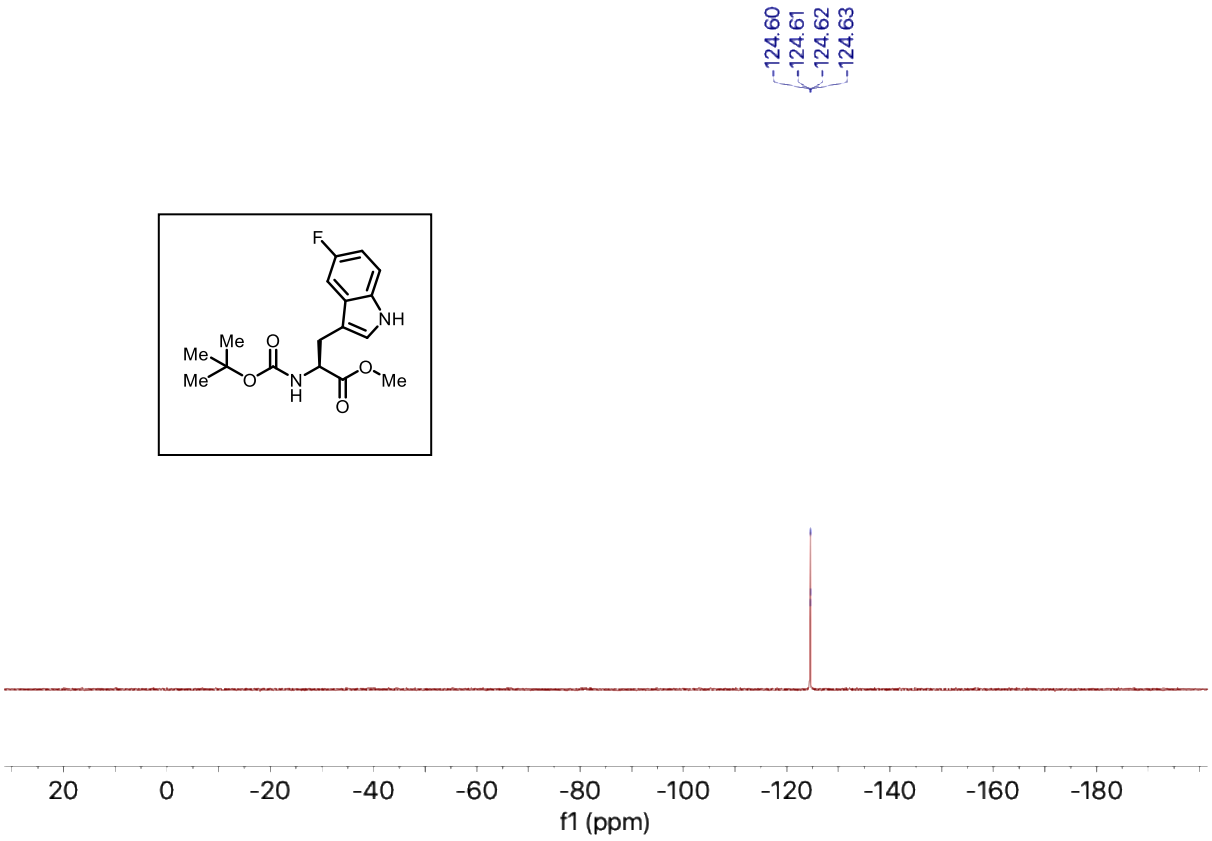
^{1}H NMR (DMSO-d_6, 500 MHz) of Boc-Trp(5-F)-OMe



^{13}C NMR (DMSO-d_6, 126 MHz) of Boc-Trp(5-F)-OMe



^{19}F NMR (DMSO-d_6, 564 MHz) of Boc-Trp(5-F)-OMe



9. References

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[2] W. Shi, C-M. Bai, K. Zhu, D-M. Cui, C. Zhang. *Tetrahedron.* 2014, **70**, 434–438.

[3] Y. Liu, S. Xing, J. Zhang, W. Liu, Y. Xu, Y. Zhang, K. Yang, L. Yang, K. Jiang, X. Shao. *Org. Chem. Front.* 2022, **9**, 1375–1382.

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