

Site-Selective Modification Of Peptides Using Rhodium And Palladium Catalysis:
Complementary Electrophilic And Nucleophilic Arylation

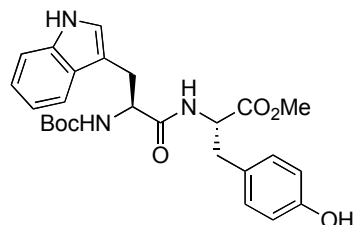
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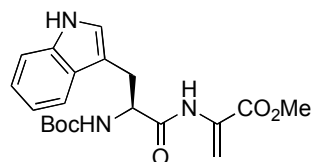
1. Substrate preparation

Boc-Trp-Tyr-OMe (6)



To a mixture of Boc-Trp-OH (2.00 g, 6.6 mmol, 1.0 equiv.) and H-Tyr-OMe·HCl (1.50 g, 6.6 mmol, 1.0 equiv.) in CH₂Cl₂ (20 mL), DCC (1.62 g, 7.8 mmol, 1.2 equiv.), HOBT (1.60 g, 7.8 mmol, 1.2 equiv.) and NMM (2.3 mL, 19.6 mmol, 3.0 equiv.) were added slowly at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 18 h. The cloudy white mixture was filtered through a short pad of celite, and the residue was washed with CH₂Cl₂ (30 mL). The combined organics were washed with 1N HCl (20 mL), saturated aqueous solution of NaHCO₃ (20 mL) and brine (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was chromatographed (ethyl acetate : petroleum ether = 1 : 2) to give the title compound (2.06 g, 65 %) as a white solid. m.p. 88-90 °C; $[\alpha]_D^{20} +19$ (c = 0.01, CH₂Cl₂); IR (KBr) 3349 (br), 3057, 2977, 1743, 1720, 1690, 1662, 1614, 1510, 1457, 1392, 1367, 1230, 1165 cm⁻¹; ¹H NMR (CDCl₃; 300 MHz) δ 8.47 (1H, br s, NH), 7.50 (1H, d, *J* = 9.0 Hz), 7.44 (1H, br s, OH), 7.22 (1H, d, *J* = 8.1 Hz), 7.07 (1H, t, *J* = 6.9 Hz), 6.99 (1H, t, *J* = 6.9 Hz), 6.74 (1H, br s, NH), 6.60-6.52 (4H, m), 6.36 (1H, d, *J* = 7.8 Hz), 5.17 (1H, m), 4.62 (1H, brs), 4.45-4.30 (1H, m), 3.50 (3H, s), 3.14 (1H, m), 3.00 (1H, dd, *J* = 14.1, 6.6 Hz), 2.75 (2H, t, *J* = 3.9 Hz), 1.37 (9H, s); ¹³C NMR (CDCl₃; 75.5 MHz) δ 172.2, 172.0, 157.8, 155.9, 136.7, 130.6, 127.8, 127.1, 123.9, 122.6, 120.0, 119.1, 116.0, 111.8, 110.2, 80.9, 55.8, 53.9, 52.7, 49.7, 37.4, 28.7; MS (ES⁺) *m/z* 504.2 (M + Na)⁺; HRMS (ES⁺) calcd for C₂₆H₃₁N₃NaO₆: 504.2111 (M + Na)⁺; found: 504.2113 (M + Na)⁺.

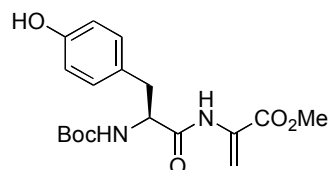
Boc-Trp-ΔAla-OMe (7)



To a stirring suspension of Boc-Trp-Ser-OMe (500 mg, 1.23 mmol) in degassed CH₂Cl₂ (15 mL) were added CuCl (37 mg, 0.3 mmol) and EDCI·HCl (260 mg, 1.35 mmol, 1.1 equiv.) at 0 °C. The mixture was stirred at room temperature for 18 h. The resulting pale yellow solution was diluted with CH₂Cl₂ (40 mL), washed with H₂O (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure and chromatographed (ethyl acetate : petroleum ether = 1 : 5) to give a title compound (260 mg, 55 %) as a white solid. m.p. 78-80 °C; $[\alpha]_D^{20} -35.8$ (c = 0.024, CH₂Cl₂); IR (KBr) 3371 (br), 3067, 2977, 2931, 2852, 1710, 1682, 1636, 1517, 1439, 1328, 1250,

1166, 1098, 1054, 1010, 961, 906, 742 cm^{-1} ; ^1H NMR (CDCl_3 ; 400 MHz) δ 8.23 (1H, br s), 8.06 (1H, br s), 7.53 (1H, d, $J = 9.0$ Hz), 7.26 (1H, d, $J = 9.0$ Hz), 7.11 (1H, t, $J = 6.9$ Hz), 7.05 (1H, t, $J = 6.9$ Hz), 6.95 (1H, br s), 6.52 (1H, br s), 5.78 (1H, br s), 5.07 (1H, br s), 4.45 (1H, br s), 3.64 (3H, s), 3.24-3.13 (2H, m), 1.32 (9H, s); ^{13}C NMR (CDCl_3 ; 75.5 MHz) δ 171.2, 164.3, 155.9, 136.7, 131.1, 127.8, 123.6, 122.7, 120.2, 119.1, 111.6, 110.6, 109.7, 80.9, 56.4, 53.2, 49.6, 28.6; MS (ES^+) m/z 388.2 ($\text{M}+\text{H}$) $^+$; HRMS (ES^+) calcd for $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}_5$: 388.1867 ($\text{M} + \text{H}$) $^+$; found: 388.1870 ($\text{M} + \text{H}$) $^+$.

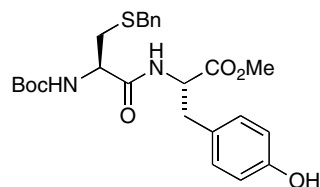
Boc-Tyr- Δ Ala-OMe (8)



To a stirring suspension of Boc-Tyr-Ser-OMe (280 mg, 0.73 mmol) in degassed CH_2Cl_2 (10 mL) were added CuCl (22 mg, 0.22 mmol, 0.3 equiv.) and EDCI-HCl (154 mg, 0.80 mmol, 1.1 equiv.) at 0 $^\circ\text{C}$. The mixture was stirred at room temperature for 18 h. The resulting pale yellow solution was diluted with CH_2Cl_2 (30 mL), washed with H_2O (15 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure and chromatographed (ethyl acetate : petroleum ether = 1 : 5) to give the title compound (119 mg, 45 %) as a white solid. m.p. 128-130 $^\circ\text{C}$; $[\alpha]_D^{20}$ -10.6 ($c = 0.0047$, CH_2Cl_2); IR (KBr) 3415, (br), 3218 (br), 3015, 2929, 1736, 1687, 1665, 1634, 1593, 1544, 1515, 1479, 1440, 1400, 1368, 1269, 1199, 1163 cm^{-1} ; ^1H NMR (CDCl_3 ; 400 MHz) δ 8.04 (1H, br s), 6.98 (2H, d, $J = 8.1$ Hz), 6.69 (2H, d, $J = 8.1$ Hz), 5.82 (1H, br s), 4.92 (1H, br s), 4.15-4.02 (1H, m), 3.73 (3H, s), 2.99-2.94 (2H, m), 1.35 (9H, s); ^{13}C NMR (CDCl_3 ; 75.5 MHz) δ 170.8, 164.4, 155.9, 130.9, 130.7, 128.1, 116.1, 116.0, 109.9, 81.1, 57.1, 53.4, 49.7, 28.6; MS (ES^+) m/z 265.2 ($\text{M}+\text{H}$) $^+$; HRMS (ES^+) calcd for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_6$: 365.1707 ($\text{M} + \text{H}$) $^+$; found: 365.1706 ($\text{M} + \text{H}$) $^+$.

1.1. Boc-Trp- Δ Ala-Tyr-OMe (15) preparation

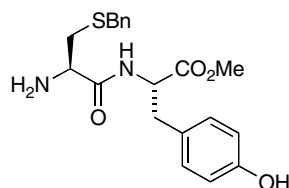
Boc-Cys(Bzl)-Tyr-OMe



To a mixture of Boc-Cys(Bzl)-OH (6.23g, 20 mmol) and H-Tyr-OMe-HCl (4.63 g, 20 mmol) in DMF (20 mL) and dichloromethane (100 mL) at 0 $^\circ\text{C}$; was added HOBt-H $_2\text{O}$ (4.22 g, 26 mmol) and NMM (2.42 mL, 22 mmol) followed by DCC (5.36 g, 26 mmol). The mixture was allowed to warm to room temperature and stirred for 18 hours. The resultant suspension was cooled to -15 $^\circ\text{C}$ and filtered through celite and the residue washed with cold DCM (20 mL). The combined organics were washed with 10% citric acid (aq.) (20 mL), saturated NaHCO_3 (aq.) (20 mL) and brine (20 mL), dried over MgSO_4 , filtered and evaporated to dryness under reduced pressure. The crude product was taken on to the next step without purification. ^1H

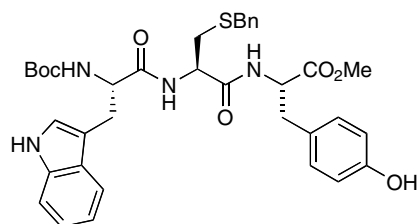
NMR (CDCl₃; 300 MHz) δ 7.33-7.23 (5H, m), 6.94 (2H, AB d, $J = 8.4$), 6.79 (1H, d, $J = 7.6$), 6.72 (2H, AB d, $J = 8.4$), 6.3-6.0 (1H, br s), 5.21 (1H, br s), 4.78 (1H, dt, $J = 5.7, 7.6$), 4.20 (1H, br d, $J = 6.3$), 3.71 (2H, s), 3.70 (3H, s), 3.06 (1H, dd, $J = 5.7, 13.9$), 3.00 (1H, dd, $J = 5.7, 13.9$), 2.79 (1H, dd, $J = 6.3, 13.9$), 2.71 (1H, dd, $J = 6.3, 13.9$), 1.45 (9H, s); ¹³C NMR (CDCl₃; 75.5 MHz) δ 171.9, 170.6, 155.6, 138.1, 130.7, 129.4, 129.0, 127.6, 127.5, 115.9, 80.8, 53.9, 52.7, 49.6, 37.4, 34.3, 33.9, 28.6; HRMS (ESI⁺) Theo. for C₂₅H₃₂N₂NaO₆S: 511.1879 [M+Na]⁺; meas. 511.1842 [M+Na]⁺.

H-Cys(Bzl)-Tyr-OMe



Boc-Cys(Bzl)-Tyr-OMe (8.1g, 16.5 mmol) was treated with TFA (20 mL) at room temperature, and followed by TLC. After 2 hours the resultant mixture was concentrated under reduced pressure, re-evaporated to from toluene (2 × 20 mL) and DCM (20 mL) to afford the trifluoroacetic acid salt as a gummy foam. The product was progressed through without purification.

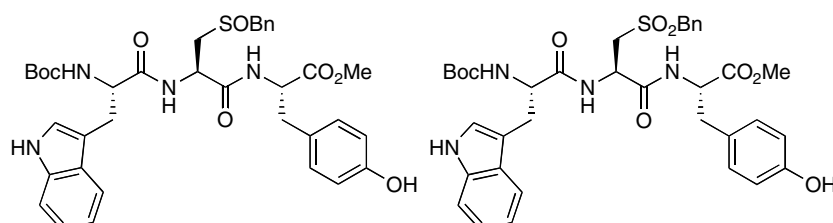
Boc-Trp-Cys(Bzl)-Tyr-OMe



To a mixture of Boc-Trp-OH (5.02g, 16.5 mmol) and H-Cys(Bzl)-Tyr-OMe·TFA-H salt (8.29 g, 16.5 mmol) in DMF (20 mL) and dichloromethane (100 mL) at 0 °C; was added HOBT·H₂O (3.49 g, 21.5 mmol) and NMM (1.99 mL, 18.2 mmol) followed by DCC (4.43 g, 21.5 mmol). The mixture was allowed to warm to room temperature and stirred for 18 hours. The resultant suspension was cooled to -15 °C and filtered through celite and the residue washed with cold DCM (20 mL). The combined organics were washed with 10% citric acid (aq.) (20 mL), saturated NaHCO₃ (aq.) (20 mL) and brine (20 mL), dried over MgSO₄, filtered and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (ethyl acetate : petroleum ether = 1:1) to afford the title compound at a white solid (6.1g, 55 % over three steps). m.p. 75-76 °C; [α]_D²⁰ -8.33 (c = 0.0048, CH₂Cl₂); IR (film, cm⁻¹) ν 3321 (br), 3061, 3012, 2979, 2930, 2853, 2369, 2341, 1888, 1738, 1651, 1616, 1596, 1515, 1456, 1392, 1368, 1219, 1170, 1123, 1104, 1071, 1051, 1013, 927, 844, 755, 703, 668; ¹H NMR (CDCl₃; 300 MHz) δ 8.24 (1H, d, $J = 1.9$), 7.61 (1H, d, $J = 7.8$), 7.33-7.04, (8H, m), 6.9 (1H, br s), 6.90, (1H, d, $J = 1.9$), 6.86 (2H, d, $J = 8.4$), 6.76 (1H, d, $J = 8.1$), 6.71 (2H, d, $J = 8.4$), 6.61 (1H, d, $J = 7.5$), 5.11 (1H, d, $J = 7.8$), 4.69 (1H, q, $J = 6.9$), 4.50-4.33 (2H, m), 3.69 (3H, s), 3.55 (2H, s), 3.34-3.21 (1H, m), 3.15 (1H, dd, $J = 6.6, 14.7$), 3.04 (1H, dd, $J = 5.4, 14.1$), 2.85 (1H, dd, $J = 6.9, 14.1$), 2.64

(1H, dd, $J=5.7, 14.1$), 2.47 (1H, dd, $J=6.9, 14.1$), 1.40 (9H, s); ^{13}C NMR (CDCl_3 ; 75.5 MHz) δ 172.1, 171.7, 169.7, 155.9, 155.5, 1238.0, 136.4, 130.5, 129.1, 128.7, 127.6, 127.3, 123.5, 122.4, 119.9, 118.9, 115.9, 111.5, 110.1, 80.8, 55.5, 53.9, 52.6, 52.4, 36.9, 36.5, 33.9, 33.1, 28.4; HRMS (ESI^+) Theo. for $\text{C}_{36}\text{H}_{43}\text{N}_4\text{O}_7\text{S}$: 675.2852 $[\text{M}+\text{H}]^+$; meas. 675.2842 $[\text{M}+\text{H}]^+$.

mixture of Boc-Trp-Cys(SOBzl)-Tyr-OMe and Boc-Trp-Cys(SO₂Bzl)-Tyr-OMe

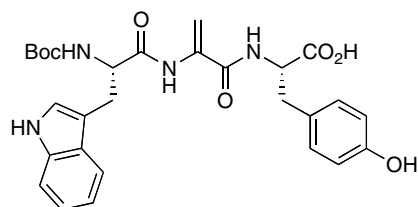


The sulphur was oxidised as described in the literature.¹

Sodium metaperiodate (1.47 g, 6.88 mmol, 2.2 equiv.) was dissolved in water (50 mL) and cooled on a ice bath. Boc-Trp-Cys(Bzl)-Tyr-OMe (2.11 g, 3.13 mmol) was dissolved in dioxane (100 mL) and added dropwise to the oxidant. The reaction was stirred on ice for 2 hours and at 40 °C for 6 hours. The reaction mixture was concentrated to ~ 50 mL, water (50 mL) was added and the product extracted into DCM (3 × 50 mL). The combined organics were washed with water (50 mL), brine (50 mL), dried (MgSO_4) and concentrated *in vacuo* to give a colourless glass which was assumed to be pure and progressed to the next step.

MS (ESI^-) m/z 705.3 and 689.3 $[\text{M}-\text{H}]^-$ sulfone and sulfoxide respectively.

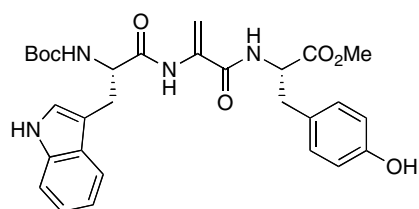
Boc-Trp- Δ Ala-Tyr-OH



Boc-Trp-Cys(SOBzl)-Tyr-OMe (2 g, 2.83 mmol), was dissolved in methanol (120 mL) and cooled on an ice-salt bath. 1M aqueous NaOH (14 mL, 5 equiv.) was added dropwise and the reaction mixture allowed to warm to room temperature over 2 hours. The reaction mixture was concentrated *in vacuo* to approx 3 mL, acidified to pH 4 with 2M KHSO_4 and the product extracted into DCM (3 × 50 mL) washed with water (100 mL), brine (50 mL), dried (MgSO_4) and concentrated to dryness to afford the title compound as a gummy foam.¹ ^1H NMR ($\text{dmsO}-d_6$; 250 MHz) δ 12.81 (1H, br s), 10.84 (1H, d, $J=1.8$ Hz), 9.23 (1H, s), 9.11 (1H, s), 8.68 (1H, d, $J=8.3$ Hz), 7.58 (1H, d, $J=7.8$ Hz), 7.34 (1H, d, $J=8.0$ Hz), 7.28 (1H, d, $J=8.0$ Hz), 7.15 (1H, d, $J=1.8$ Hz), 7.12-6.94 (4H, m), 6.67 (2H, d, $J=8.5$ Hz), 6.29 (1H, s), 5.59 (1H, s), 4.49-4.36 (1H, m), 4.32-4.19 (1H, m), 3.24-2.84 (4H, m), 1.30 (9H, s); HRMS (ESI^-) theo. for $\text{C}_{28}\text{H}_{31}\text{N}_4\text{O}_7$: 535.2198 $[\text{M}-\text{H}]^-$; meas. 535.2207 $[\text{M}-\text{H}]^-$.

¹ Burrage, S. A.; Raynham, T.; Bradley, M. *Tetrahedron Lett.* **1998**, 39, 2831-2834

Boc-Trp- Δ Ala-Tyr-OMe (15)

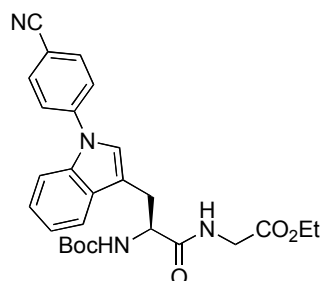


To a suspension of NaCO_3 (250 mg, 2.97 mmol, 1.1 eq), in anhydrous DMF (10 mL) was added Boc-Trp- Δ Ala-Tyr-OH (1.45 g, 2.7 mmol) and methyl iodide (186 μL , 2.97 mmol). This mixture was stirred at 25 °C for 20 hours. Distilled water was added and the product extracted with ethyl acetate (3 \times 20 mL). The combined organic phases were washed with distilled water and dried over MgSO_4 concentrated *in vacuo* to the crude product which was purified by flash chromatography (ethyl acetate : petroleum ether = 1:1) to afford the titled compound as an off white solid (930 mg, 67% over three steps).² m.p. 205 °C; $[\alpha]_D^{20}$ +9.38 (c = 0.0021, CH_2Cl_2); IR (film, cm^{-1}) ν 4214, 3362 (br), 3019, 2980, 2933, 2856, 2401, 1887, 1738, 1694, 1633, 1616, 1515, 1455, 1369, 1216, 1171, 1109, 1060, 1022, 988, 963, 892, 843, 755, 699, 668; ^1H (CDCl_3 ; 300 MHz) δ 8.31 (1H, s), 8.30 (1H, s), 7.57 (1H, d, J = 7.8 Hz), 7.32 (1H, d, J = 8.1 Hz), 7.16 (1H, dt, J = 0.9, 7.8 Hz), 7.08 (1H, dt, J = 0.9, 8.1 Hz), 6.96 (1H, d, J = 1.8 Hz), 6.88 (2H, AB d, J = 8.4 Hz), 6.74 (2H, AB d, J = 8.4 Hz), 6.54 (1H, d, J = 7.8 Hz), 6.40 (1H, br s), 6.35 (1H, s), 5.19 (1H, s), 5.16 (1H, s), 4.76 (1H, dt, J = 5.7, 7.4 Hz), 4.51 (1H, br s), 3.73 (3H, s), 3.33-3.19 (2H, m), 3.06 (1H, dd, J = 5.7, 14.1 Hz), 2.98 (1H, dd, J = 6, 14.1 Hz), 1.40 (9H, s); ^{13}C (CDCl_3 ; 75.5 MHz) δ 172.1, 171.4, 163.4, 155.9, 155.8, 136.6, 133.8, 130.7, 127.8, 127.2, 123.5, 122.6, 120.0, 119.0, 116.1, 111.6, 110.3, 103.8, 80.9, 56.5, 54.1, 52.9, 37.2, 37.1, 28.6; HRMS (ESI⁺) theo. for $\text{C}_{29}\text{H}_{35}\text{N}_4\text{O}_7$: 551.2506 $[\text{M}+\text{H}]^+$; meas. 551.2465 $[\text{M}+\text{H}]^+$.

2. Palladium-catalysed *N*-Arylations of Tryptophan containing peptides

2.1. *N*-Arylation of Boc-Trp-Gly-OEt

Boc-Trp(4-cyanophenyl)-Gly-OEt (2)

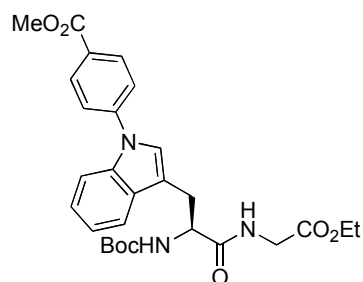


To a mixture of Boc-Trp-Gly-OEt **1** (155 mg, 0.40 mmol), $\text{Pd}(\text{OAc})_2$ (5.0 mg, 0.02 mmol, 5 mol%), Xantphos (17.5 mg, 0.03 mmol, 7.5 mol%), Cs_2CO_3 (182 mg, 0.56

² Jung, M.; Starkey, L. S. *Tetrahedron* **1997**, 53, 26, 8815-8824

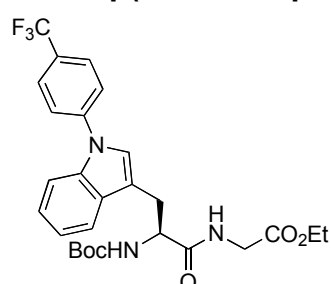
mmol, 1.4 equiv.) in dioxane (2 mL), 4-bromobenzonitrile (87 mg, 0.48 mmol, 1.2 equiv.) was added at room temperature. The mixture was stirred at 55 °C for 40 h and filtered through a short pad of celite and the residue was washed with ethyl acetate (30 mL). The combined organics were concentrated under reduced pressure. The crude mixture was chromatographed (ethyl acetate : petroleum ether = 1 : 4) to give the title compound (183 mg, 94 %) as a pale yellow solid. m.p. 81-83 °C; $[\alpha]_D^{20}$ +11.6 (c = 0.062, CH₂Cl₂); IR (KBr) 3319 (br), 3053, 2980, 2933, 2227, 1747, 1665, 1603, 1513, 1457, 1368, 1205 cm⁻¹; ¹H NMR (CDCl₃; 300 MHz) δ 7.71 (2H, d, *J* = 9.0 Hz), 7.61 (1H, d, *J* = 7.2 Hz), 7.54 (2H, d, *J* = 9.0 Hz), 7.53-7.50 (1H, m), 7.22-7.12 (3H, m), 6.47 (1H, t, *J* = 5.1 Hz), 5.13 (1H, br s), 4.52 (1H, br s), 4.06 (2H, q, *J* = 7.5 Hz), 3.87 (2H, d, *J* = 5.1 Hz), 3.23 (2H, m), 1.32 (9H, s), 1.16 (3H, t, *J* = 7.2 Hz); ¹³C NMR (CDCl₃; 75.5 MHz) δ 170.7, 168.4, 154.5, 142.4, 134.4, 132.7, 128.8, 125.0, 122.6, 122.5, 120.3, 118.6, 117.5, 112.8, 109.5, 108.1, 79.3, 60.5, 53.7, 40.3, 27.2, 26.9, 13.1; MS (ES⁺) *m/z* 491.2 (M+H)⁺; HRMS (ES⁺) calcd for C₂₇H₃₁N₄O₅: 491.2289 (M + H)⁺; found: 491.2288 (M + H)⁺.

Boc-Trp(4-methylbenzoate)-Gly-OEt



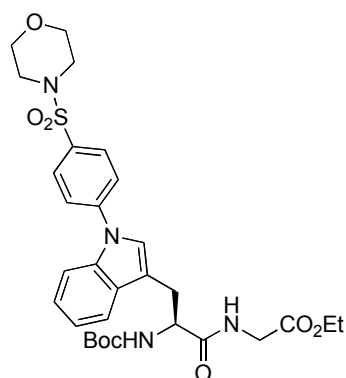
Following the procedure for Boc-Trp(4-cyanophenyl)-Gly-OEt but using methyl 4-bromobenzoate (103 mg, 0.48 mmol, 2.4 equiv.) at 60 °C for 40 h, the title compound was obtained (56 mg, 54 %) as a white solid. m.p. 73-74 °C; $[\alpha]_D^{20}$ +42.1 (c = 0.075, CH₂Cl₂); IR (KBr) 3316 (br), 2995, 2978, 2955, 1717 (br), 1663, 1603, 1515, 1457, 1367, 1280, 1202 cm⁻¹; ¹H NMR (CDCl₃; 300 MHz) δ 8.05 (2H, d, *J* = 9.0 Hz), 7.66-7.55 (1H, m), 7.48 (2H, d, *J* = 9.0 Hz), 7.28-7.06 (4H, m), 6.51 (1H, t, *J* = 5.0 Hz), 5.18 (1H, br s), 4.53 (1H, br s), 4.06 (2H, q, *J* = 7.2 Hz), 3.85 (3H, s), 3.87 (2H, d, *J* = 5.0 Hz), 3.24-3.22 (2H, m), 1.33 (9H, s), 1.18 (3H, t, *J* = 7.2 Hz); ¹³C NMR (CDCl₃; 75.5 MHz) δ 172.2, 169.8, 166.8, 155.9, 143.9, 136.0, 131.6, 129.9, 127.8, 126.8, 123.6, 123.4, 121.3, 119.8, 113.4, 111.1, 80.7, 61.9, 55.2, 52.6, 41.7, 28.6, 28.5, 14.5; MS (ES⁺) *m/z* 524.2 (M+H)⁺; HRMS (ES⁺) calcd for C₂₈H₃₄N₃O₇: 524.2391 (M + H)⁺; found: 524.2399 (M + H)⁺.

Boc-Trp(4-trifluorophenyl)-Gly-OEt



Following the procedure for Boc-Trp(4-cyanophenyl)-Gly-OEt but using 4-bromobenzotrifluoride (108 mg, 0.48 mmol, 2.4 equiv.) at 80 °C for 18 h, the title compound was obtained (75 mg, 70 %) as a white solid. m.p. 87 °C; $[\alpha]_D^{20} +11.7$ (c = 0.02, CH₂Cl₂); IR (KBr) 3310 (br), 3083, 2981, 2933, 1748 (br), 1662 (br), 1609, 1525, 1398, 1202 cm⁻¹; ¹H NMR (CDCl₃; 300 MHz) δ 6.69-7.61 (3H, m), 7.56-7.49 (3H, m), 7.24-7.11 (3H, m), 6.41 (1H, t, *J* = 5.1 Hz), 5.11 (1H, br s), 4.51-4.49 (1H, m), 4.06 (2H, q, *J* = 7.2 Hz), 3.87 (2H, d, *J* = 5.1 Hz), 3.24-3.22 (2H, m), 1.33 (9H, s), 1.15 (3H, t, *J* = 7.2 Hz); ¹³C NMR (CDCl₃; 75.5 MHz) δ 172.2, 169.8, 155.9, 142.9, 136.0, 129.9, 128.6, 128.1, 126.8, 126.2, 124.1, 122.6, 119.8, 118.9, 113.4, 110.9, 80.7, 61.9, 55.3, 41.7, 28.6, 28.4, 14.5; MS (ES⁺) *m/z* 534.2 (M+H)⁺; HRMS (ES⁺) calcd for C₂₇H₃₁F₃N₃O₅: 534.2210 (M + H)⁺; found: 534.2210 (M + H)⁺.

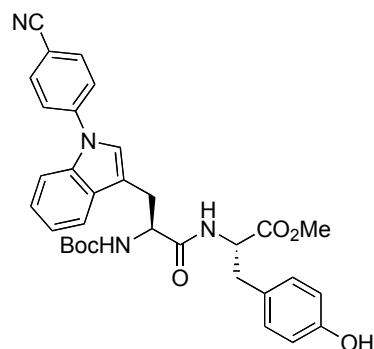
Boc-Trp(4-(morpholinosulfonyl)phenyl)-Gly-OEt



Following the procedure for Boc-Trp(4-cyanophenyl)-Gly-OEt but using 4-(4-bromophenylsulfonyl) morpholine (116.2 mg, 0.48 mmol, 2.4 equiv.) at 60 °C for 40 h, the title compound was obtained (95 mg, 86 %) as a white solid. m.p. 87-90 °C; $[\alpha]_D^{20} +16.7$ (c = 0.016, CH₂Cl₂); IR (KBr) 3318 (br), 3011, 2977, 2953, 1746 (br), 1667, 1592, 1502, 1455, 1350, 1261 cm⁻¹; ¹H NMR (CDCl₃; 300 MHz) δ 7.80 (2H, d, *J* = 9.0 Hz), 7.63 (2H, d, *J* = 9.0 Hz), 7.65-7.61 (1H, m), 7.54 (1H, d, *J* = 7.5 Hz), 7.25-7.14 (3H, m), 6.42 (1H, t, *J* = 5.4 Hz), 5.11 (1H, br s), 4.51 (1H, m), 4.08 (2H, q, *J* = 7.2 Hz), 3.88 (2H, d, *J* = 5.1 Hz), 3.70 (4H, t, *J* = 4.5 Hz), 3.25-3.23 (2H, m), 3.00 (4H, t, *J* = 4.5 Hz), 1.33 (9H, s), 1.17 (3H, t, *J* = 7.2 Hz); ¹³C NMR (CDCl₃; 75.5 MHz) δ 172.1, 169.8, 155.9, 144.1, 135.9, 132.4, 130.2, 129.9, 126.6, 123.9, 123.8, 121.7, 119.9, 114.1, 110.9, 80.7, 66.5, 61.9, 55.2, 46.4, 41.7, 28.7, 28.4, 14.5; MS (ES⁺) *m/z* 615.2 (M+H)⁺; HRMS (ES⁺) calcd for C₃₀H₃₉N₄O₈S: 615.2483 (M + H)⁺; found: 615.2484 (M + H)⁺.

2.2. N-Arylation of Boc-Trp-Tyr-OMe

Boc-Trp(4-cyanophenyl)-Tyr-OMe (9)

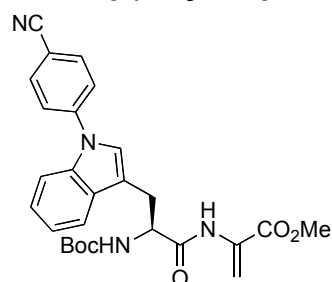


General procedure for *N*-arylation

To a mixture of Boc-Trp-Tyr-OMe (96 mg, 0.20 mmol), Pd(OAc)₂ (2.5 mg, 0.01 mmol, 5 mol%), Xantphos (9.0 mg, 0.015 mmol, 7.5 mol%), Cs₂CO₃ (91 mg, 0.28 mmol, 1.4 equiv.) in dioxane (1 mL), 4-bromobenzonitrile (91 mg, 0.50 mmol, 2.5 equiv.) was added at room temperature. The mixture was stirred at 60 °C for 40 h and filtered through a short pad of celite and the residue was washed with ethyl acetate (30 mL). The combined organics were concentrated under reduced pressure. The crude mixture was chromatographed (ethyl acetate : petroleum ether = 1 : 3) to give the title compound (108 mg, 93 %) as a white solid. m.p. 95-96 °C; $[\alpha]_D^{20} +12$ (c = 0.01, CH₂Cl₂); IR (KBr) 3346 (br), 2976, 2918, 2848, 2227, 1743 (br), 1662 cm⁻¹; Presence of rotomers was proven by ROESY experiment (CDCl₃; 500 MHz); ¹H NMR (DMSO-*d*₆; 400 MHz) δ 9.22 (0.7H, br s, OH), 9.20 (0.3 H, br s, OH), 8.31-8.27 (1H, m, NH), 8.04 (2H, d, *J* = 7.2 Hz), 7.75 (2H, d, *J* = 7.2 Hz), 7.76-7.71 (2H, m), 7.49 (1H, s), 7.28 (1H, t, *J* = 7.2 Hz), 7.20 (1H, t, *J* = 7.2 Hz), 7.00 (1.4H, d, *J* = 8.0 Hz), 6.86 (0.6 H, d, *J* = 8.0 Hz), 6.63 (1.4H, d, *J* = 8.0 Hz), 6.61 (0.6 H, *J* = 8.0 Hz), 4.48-4.41 (1H, m), 4.38-4.32 (1H, m), 3.62 (0.9 H, s, OCH₃), 3.53 (2.1 H, s, OCH₃), 3.14-3.06 (1H, m), 2.96-2.75 (4H, m), 1.29 (9H, s); ¹³C NMR (CDCl₃; 125.8 MHz) δ 172.3, 172.0, 171.7, 171.4, 156.4, 155.4, 143.3, 135.4, 133.9, 133.7, 130.2, 130.1, 129.8, 127.0, 126.9, 126.1, 125.9, 123.8, 123.6, 121.4, 119.7, 118.4, 115.6, 115.4, 113.8, 110.5, 109.1, 80.4, 54.8, 53.3, 53.1, 52.3, 37.1, 36.8, 29.7, 28.4, 28.2, 27.9; MS (ES⁺) *m/z* 605.2 (M+Na)⁺; HRMS (ES⁺) calcd for C₃₃H₃₄N₄NaO₆: 605.2371 (M + Na)⁺; found: 605.2372 (M + Na)⁺.

2.3. *N*-Arylation of Boc-Trp-ΔAla-OMe

Boc-Trp(4-cyanophenyl)-ΔAla-OMe (11)

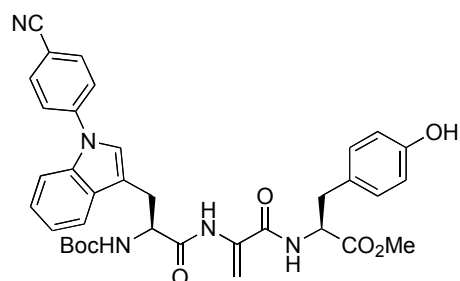


Following the general procedure for *N*-arylation but proceeded at 60 °C for 40 h using Boc-Trp-ΔAla-OMe (155 mg, 0.40 mmol) and 4-bromobenzonitrile (87 mg, 0.48 mmol, 1.2 equiv.), the title compound was obtained (141 mg, 72 %) as a white solid.

m.p. 124-125 °C; $[\alpha]_D^{20}$ -11.3 (c = 0.0115, CH₂Cl₂); IR (KBr) 3390, 3345, 2955, 2227, 1720, 1696, 1633, 1601, 1511, 1455, 1372, 1337, 1268, 1206, 1169, 1110, 1059, 999, 900, 844, 738 cm⁻¹; ¹H NMR (CDCl₃; 400 MHz) δ 8.10 (1H, br s), 7.71 (2H, d, *J* = 8.9 Hz), 7.63 (1H, d, *J* = 7.2 Hz), 7.53 (1H, d, *J* = 8.9 Hz), 7.24-7.13 (4H, m), 6.53 (1H, br s), 5.80 (1H, br s), 5.14 (1H, br s), 4.54 (1H, br s), 3.65 (3H, s), 3.25-3.22 (2H, m), 1.34 (9H, s); ¹³C NMR (CDCl₃; 75.5 MHz) δ 170.8, 164.4, 155.9, 143.7, 135.9, 134.2, 130.9, 129.9, 126.2, 124.1, 121.9, 120.0, 118.9, 115.9, 114.1, 110.9, 109.8, 109.6, 80.9, 61.9, 55.9, 53.3, 28.6; MS (ES⁺) *m/z* 489.1 (M+H)⁺; HRMS (ES⁺) calcd for C₂₇H₂₉N₄O₅: 489.2132 (M + H)⁺; found: 489.2133 (M + H)⁺.

2.4. N-Arylation of Boc-Trp-ΔAla-Tyr-OMe

Boc-Trp(4-cyanophenyl)-ΔAla-Tyr-OMe (16)

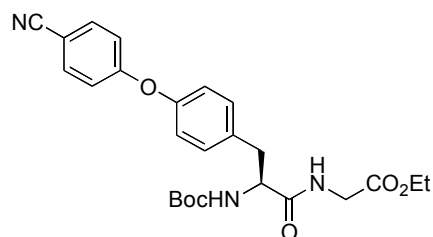


To a mixture of Boc-Trp-ΔAla-Tyr-OMe (110 mg, 0.20 mmol), Pd(OAc)₂ (2.3 mg, 0.01 mmol, 5 mol%), Xantphos (8.5 mg, 0.015 mmol, 7.5 mol%), K₃PO₄ (60 mg, 0.28 mmol, 1.4 equiv.) in dioxane (1 mL), 4-bromobenzonitrile (91 mg, 0.50 mmol, 2.5 equiv.) was added at room temperature. The mixture was stirred at 80 °C for 18 h and filtered through a short pad of celite and the residue was washed with ethyl acetate (30 mL). The combined organics were concentrated under reduced pressure. The crude mixture was chromatographed (ethyl acetate : petroleum ether = 1 : 3) to give the title compound (93 mg, 71 %) as a white solid. m.p. 72-73 °C; $[\alpha]_D^{20}$ +4.9 (c = 0.035, CH₂Cl₂); IR (KBr) 3341 (br), 3056, 2978, 2929, 2854, 2227, 1737, 1690, 1659, 1631, 1602, 1513, 1456, 1406, 1318, 1227 cm⁻¹; ¹H NMR (CDCl₃; 500 MHz) δ 8.47 (1H, br s), 7.77 (2H, d, *J* = 8.8 Hz), 7.67 (1H, d, *J* = 7.8 Hz), 7.60 (2H, d, *J* = 8.8 Hz), 7.60-7.57 (1H, m), 7.29-7.20 (2H, m), 7.03-7.00 (1H, m), 6.88 (2H, d, *J* = 8.3 Hz), 6.74 (2H, d, *J* = 8.3 Hz), 6.55 (1H, d, *J* = 7.5 Hz), 6.43 (1H, s), 6.22 (1H, br s), 5.29-5.21 (2H, m), 4.76-4.72 (1H, m), 4.63 (1H, br s), 3.73 (3H, s), 3.33 (2H, br s), 3.02 (2H, d, *J* = 10.0 Hz), 1.35 (9H, s); ¹³C NMR (CDCl₃; 125.8 MHz) δ 171.6, 170.6, 163.0, 155.4, 143.3, 135.5, 133.7, 133.4, 130.3, 128.3, 127.2, 128.0, 127.9, 125.8, 123.7, 123.6, 121.4, 120.1, 119.6, 118.5, 115.7, 110.5, 109.1, 80.6, 55.8, 53.8, 52.6, 36.8, 29.7, 28.2; MS (ES⁺) *m/z* 674.4 (M+Na)⁺; HRMS (ES⁺) calcd for C₃₆H₃₇N₅NaO₇: 674.2585 (M + Na)⁺; found: 674.2585 (M + Na)⁺.

3. Palladium-catalysed O-Arylations of Tyrosine containing peptides

3.1. O-Arylation of Boc-Tyr-Gly-OEt

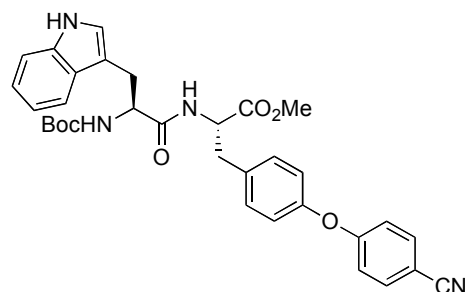
Boc-Tyr(4-cyanophenyl)-Gly-OEt (5)



To a mixture of Boc-Tyr-Gly-OEt **3** (146 mg, 0.40 mmol), Pd₂dba₃ (18 mg, 0.02 mmol, 5 mol%), ^tBu-X-Phos (26 mg, 0.05 mmol, 12.5 mol%), K₃PO₄ (170 mg, 0.80 mmol, 2.0 equiv.) in toluene (2 mL), 4-bromobenzonitrile (87 mg, 0.48 mmol, 1.2 equiv.) was added. The resulting mixture was stirred at 60 °C for 40 h and filtered through a short pad of celite and the residue was washed with ethyl acetate (30 mL). The combined organics were concentrated under reduced pressure. The crude mixture was chromatographed (ethyl acetate : petroleum ether = 1 : 3) to give the title compound (177 mg, 95 %) as a pale yellow solid. m.p. 79-103 °C; [α]_D²⁰ +7.46 (c = 0.028, CH₂Cl₂); IR (KBr) 3324 (br), 2980, 2934, 2227, 1886, 1741 (br), 1664, 1615, 1596, 1517, 1447, 1368, 1249 cm⁻¹; ¹H NMR (CDCl₃; 400 MHz) δ 7.63 (2H, d, *J* = 6.8 Hz), 7.30 (2H, d, *J* = 6.8 Hz), 7.04 (4H, d, *J* = 8.4 Hz), 6.55 (1H, m), 5.08 (1H, br s), 4.45-4.30 (1H, m), 4.25 (1H, q, *J* = 7.2 Hz), 4.11-3.98 (2H, m), 3.20 (1H, dd, *J* = 14.0, 6.8 Hz), 3.08 (1H, dd, *J* = 14.0, 6.8 Hz), 1.46 (9H, s), 1.33 (3H, t, *J* = 7.2 Hz); ¹³C NMR (CDCl₃; 75.5 MHz) δ 171.6, 169.8, 162.0, 155.7, 154.1, 134.5, 134.0, 131.5, 121.0, 119.2, 118.2, 106.1, 80.1, 62.0, 56.0, 41.7, 38.2, 28.6, 14.5; MS (ES⁺) *m/z* 468.2 (M+H)⁺; HRMS (ES⁺) calcd for C₂₅H₃₀N₃O₆: 468.2056 (M + H)⁺; found: 468.2052 (M + H)⁺.

3.2. O-Arylation of Boc-Trp-Tyr-OMe

Boc-Trp-Tyr(4-cyanophenyl)-OMe (10)



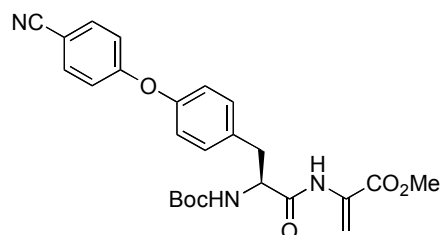
General procedure of O-arylation

To a mixture of Boc-Trp-Tyr-OMe (96 mg, 0.20 mmol), Pd₂dba₃ (9.2 mg, 0.01 mmol, 5 mol%), ^tBu-X-Phos (10.6 mg, 0.025 mmol, 12.5 mol%), K₃PO₄ (85 mg, 0.40 mmol, 2.0 equiv.) in toluene (1 mL), 4-bromobenzonitrile (91 mg, 0.5 mmol, 2.5 equiv.) was

added. The resulting mixture was stirred at 100 °C for 18 h and filtered through a short pad of celite and the residue was washed with ethyl acetate (30 mL). The combined organics were concentrated under reduced pressure. The crude mixture was chromatographed (ethyl acetate : petroleum ether = 1 : 2) to give the title compound (73 mg, 63 %) as a pale yellow solid. m.p. 75-76 °C; $[\alpha]_D^{20}$ +17.1 (c = 0.007, CH₂Cl₂); IR (KBr) 3346 (br), 3059, 2976, 2928, 2226, 1743, 1669 (br), 1597 cm⁻¹; ¹H NMR (CDCl₃; 400 MHz) δ 8.26 (1H, br s), 7.70 (1H, d, *J* = 7.6 Hz), 7.63 (2H, d, *J* = 4.8 Hz), 7.39 (1H, d, *J* = 8.0 Hz), 7.20 (1H, t, *J* = 8.0 Hz), 7.14 (1H, t, *J* = 8.0 Hz), 7.00 (1H, br s), 6.98 (2H, d, *J* = 4.8 Hz), 6.89-6.83 (4H, m), 6.34 (1H, br s), 5.19 (1H, br s), 4.76 (1H, br s), 4.48 (1H, br s), 3.69 (3H, s), 3.37 (1H, dd, *J* = 14.4, 5.2 Hz), 3.18 (1H, dd, *J* = 14.4, 7.7 Hz), 3.05-3.00 (1H, m), 2.99-2.94 (1H, dd, *J* = 14.0, 6.0 Hz), 1.47 (9H, s); ¹³C NMR (CDCl₃; 75.5 MHz) δ 171.7, 171.5, 155.8, 136.6, 134.6, 134.1, 132.9, 130.6, 127.8, 126.5, 124.0, 123.7, 122.7, 120.6, 120.4, 119.2, 118.3, 115.9, 111.6, 106.2, 80.6, 55.6, 53.6, 52.7, 37.6, 30.11, 28.7; MS (ES⁺) *m/z* 605.2 (M+Na)⁺; HRMS (ES⁺) calcd for C₃₃H₃₄N₄NaO₆: 605.2371 (M + Na)⁺; found: 605.2352 (M + Na)⁺.

3.3. O-Arylation of Boc-Tyr-ΔAla-OMe

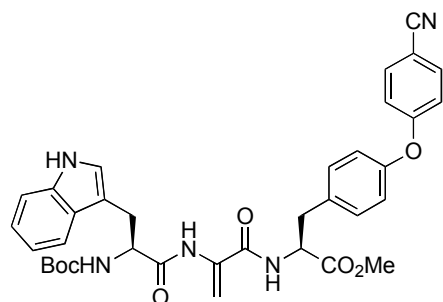
Boc-Tyr(4-cyanophenyl)-ΔAla-OMe (13)



Following the general procedure for *O*-arylation but proceeded at 80 °C for 18 h using Boc-Tyr-ΔAla-OMe (72.8 mg, 0.2 mmol) and 4-bromobenzonitrile (91 mg, 1.0 mmol, 2.5 equiv.), the title compound was obtained (38 mg, 45 %) as a white solid. m.p. 134-136 °C; $[\alpha]_D^{20}$ -43 (c = 0.01, CH₂Cl₂); IR (KBr) 3339 (br), 2977, 2932, 2227, 1693 (br), 1598, 1498, 1441, 1392, 1324, 1249, 1201, 1167, 1106, 1053 cm⁻¹; ¹H NMR (CDCl₃; 400 MHz) δ 8.01 (1H, br s), 7.50 (2H, d, *J* = 7.3 Hz), 7.20-7.11 (2H, m), 6.96-6.55 (4H, m), 6.55 (1H, s), 5.80 (1H, s), 5.00 (1H, br s), 4.36 (1H, br s), 3.75 (3H, s), 3.06-3.03 (2H, m), 1.23 (9H, s); ¹³C NMR (CDCl₃; 75.5 MHz) δ 170.39, 164.50, 162.0, 155.7, 154.2, 134.5, 133.7, 131.4, 130.9, 121.1, 119.3, 118.3, 109.9, 106.2, 81.0, 60.8, 53.4, 38.2, 28.5; MS (ES⁺) *m/z* 466.3 (M + H)⁺; HRMS (ES⁺) calcd for C₂₅H₃₁N₄O₆: 483.2238 (M + NH₄)⁺; found: 483.2234 (M + NH₄)⁺.

3.4. O-Arylation of Boc-Trp-ΔAla-Tyr-OMe

Boc-Trp- Δ Ala-Tyr(4-cyanophenyl)-OMe (17)



To a mixture of Boc-Trp- Δ Ala-Tyr-OMe (110 mg, 0.20 mmol), Pd₂dba₃ (9.2 mg, 0.01 mmol, 5 mol%), ^tBu-X-Phos (10.6 mg, 0.025 mmol, 12.5 mol%), K₃PO₄ (85 mg, 0.40 mmol, 2.0 equiv.) in dioxane (1 mL), 4-bromobenzonitrile (91 mg, 0.5 mmol, 2.5 equiv.) was added. The resulting mixture was stirred at 80 °C for 18 h and filtered through a short pad of celite and the residue was washed with ethyl acetate (30 mL). The combined organics were concentrated under reduced pressure. The crude mixture was chromatographed (ethyl acetate : petroleum ether = 1 : 2) to give the title compound (62 mg, 48 %) as sticky foam. $[\alpha]_D^{20}$ -5.37 (c = 0.0067, CH₂Cl₂); IR (KBr) 3346 (br), 3057, 2978, 2929, 2855, 2227, 1693, 1632, 1598, 1497, 1456, 1367, 1248, 1168 cm⁻¹; ¹H NMR (CDCl₃; 500 MHz) δ 8.40 (1H, br s), 8.12 (1H, br s), 7.62-7.59 (3H, m), 7.37-7.30 (1H, m), 7.19 (1H, t, *J* = 5.0 Hz), 7.13-7.00 (4H, m), 7.01-6.90 (4H, m), 6.51 (1H, d, *J* = 7.5 Hz), 6.46 (1H, s), 5.20 (1H, s), 5.02 (1H, br s), 4.83 (1H, q, *J* = 7.5 Hz), 4.53 (1H, br s), 3.77 (3H, s), 3.35-3.26 (2H, m), 3.19-3.10 (2H, m), 1.42 (9H, s); ¹³C NMR (CDCl₃; 125.8 MHz) δ 171.3, 163.0, 161.3, 154.2, 136.2, 135.2, 134.2, 134.1, 133.6, 132.4, 132.2, 131.2, 131.0, 123.7, 123.0, 122.3, 120.4, 119.8, 118.8, 118.1, 117.9, 111.2, 106.1, 80.4, 56.0, 53.5, 52.6, 52.5, 31.7, 28.2; MS (ES⁺) *m/z* 673.4 (M+Na)⁺; HRMS (ES⁺) calcd for C₃₆H₃₇N₅NaO₇: 674.2585 (M + Na)⁺; found: 674.2588 (M + Na)⁺.

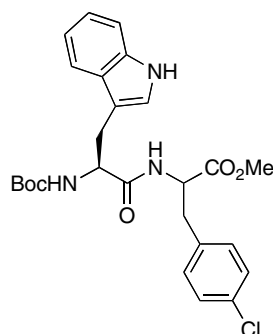
4. Rhodium-catalysed 1,4-addition to Δ Alanine containing peptides

General procedure for the rhodium catalysed 1,4-addition of aryl boronic acids to Δ Ala containing peptides.

An oven dried flask was charged with peptide (0.2 mmol), Rh(acac)(C₂H₄)₂ (6 mol%, 1.2 × 10⁻⁵ mol), rac-BINAP (6.6 mol%, 1.3 × 10⁻⁵ mol), ArB(OH)₂ (4 equiv. 0.8 mmol) and dioxane (2 mL), evacuated and backfilled with argon and stirred at room temperature for 10 minutes. Water (0.2 mL) was added and the mixture heated at 100 °C for 20 hours. After cooling to room temperature the resulting mixture was diluted with ethyl acetate (5 mL) and extracted with water (10 mL). The aqueous wash was back extracted with ethyl acetate (2 × 5 mL) and the combined organics washed with saturated NaHCO₃ solution (10 mL), brine (10 mL), dried over MgSO₄ and evaporated *in vacuo*. The residue was purified by column chromatography to afford the desired compound.

4.1. Rhodium-catalysed 1,4-additions to Boc-Trp- Δ Ala-OMe

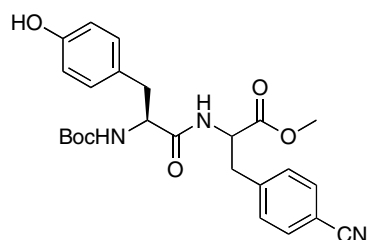
Boc-Trp-Phe(4-Cl)-OMe (12)



Following the general procedure for 1,4-addition Boc-Trp- Δ Ala-OMe (58 mg, 0.15 mmol) was reacted with 4-chlorobenzene boronic acid (70 mg, 0.45 mmol, 3 equiv.). The title compound was obtained as a mixture of diastereomers in 68 % yield (51 mg) as an off white solid. IR (film, cm^{-1}) ν 3416 (br), 3019, 1742, 1671, 1492, 1458, 1438, 1368, 1216, 1167, 1093, 1016, 842, 757, 669; ^1H NMR (CDCl_3 ; 300 MHz) mixture of diastereoisomers δ 1.40 and 1.43 (9H, s), 2.78 and 2.89 (1H, dd, $J = 5.7, 13.8$ Hz and m), 2.83-2.95 (1H, m), 3.12 and 3.23 (1H, dd, $J = 7.2, 14.4$ Hz), 3.21-3.33 (1H, m), 3.60 (3H, s), 4.38-4.52 (1H, m), 4.66-4.81 (1H, m), 5.00-5.20 (1H, m), 6.26 and 6.33 (1H, d, $J = 7.5$ Hz), 6.71 (2H, app dd, $J = 5.4, 8.4$), 6.97 and 7.00 (1H, d, $J = 2.4$ Hz), 7.05-7.12 (2H, m), 7.14 (1H, dm, $J = 7.2$ Hz), 7.21 (1H, tm, $J = 7.2$ Hz), 7.36 (1H, dm, $J = 7.8$ Hz), 7.64 (1H, app t, $J = 8.4$ Hz), 8.24 (1H, br s); ^{13}C NMR (CDCl_3 ; 75.5 MHz) 171.6, 171.5, 171.3, 171.2, 136.4, 136.3, 134.3, 134.1, 133.1, 133.0, 130.6, 130.6, 128.8, 128.7, 127.6, 123.4, 123.2, 122.5, 120.0, 119.9, 119.0, 119.0, 111.4, 111.4, 80.4, 55.3, 53.2, 53.0, 52.4, 37.3, 37.2, 28.4; HRMS (ESI $^+$) Theo. for $\text{C}_{26}\text{H}_{31}\text{O}_5\text{N}_3\text{Cl}$: 500.1947 $[\text{M}+\text{H}]^+$; meas 500.1946 $[\text{M}+\text{H}]^+$.

4.2. Rhodium-catalysed 1,4-additions to Boc-Tyr- Δ Ala-OMe

Boc-Tyr-Phe(4-cyano)-OMe (14)

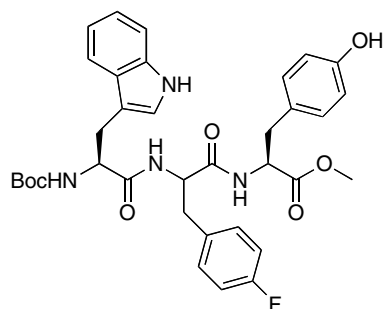


Following the general procedure for 1,4-addition Boc-Tyr- Δ Ala-OMe (55 mg, 0.15 mmol) was reacted with 4-cyanobenzene boronic acid (87 mg, 0.6 mmol, 4 equiv.) in the presence of sodium fluoride (19 mg, 0.45 mmol). The title compound was obtained as a mixture of diastereoisomers in 86 % yield (60 mg) as an off white solid. IR (film, cm^{-1}) ν 3408 (br), 3020, 2983, 2231, 1742, 1666, 1614, 1516, 1443, 1368, 1217, 1171, 1119, 1052, 1022, 850, 826, 756, 669; ^1H NMR (CDCl_3 ; 300 MHz) δ 7.53 (1H, d, $J = 8.3$ Hz), 7.51 (1H, d, $J = 8.1$ Hz), 7.13 (1H, d, $J = 8.3$ Hz), 7.05 (1H, d, $J = 8.1$ Hz), 7.02 (2H, app d, $J = 8.4$ Hz), 6.74 (1H, d, $J = 8.4$ Hz), 6.72 (1H, d, $J =$

8.4 Hz), 6.55 and 6.37 (1H, d, $J = 6.3$ and 7.8 Hz), 5.6-5.3 (1H, br s, OH), 4.99-4.73 (2H, m), 4.33-4.21 (1H, m), 3.69 and 3.68 (3H, s), 3.20-2.86 (4H, m), 1.42 and 1.40 (9H, s); ^{13}C NMR (CDCl_3 ; 75.5 MHz) mixture of diastereoisomers δ 171.71 and 171.67, 171.4 and 171.2, 155.9, 155.5, 141.9 and 141.8, 132.72 and 132.67, 130.86 and 130.83, 130.54 and 130.45, 129.1, 128.3, 127.8, 119.2, 116.0, 111.4, 81.1, 53.4, 53.2, 53.0, 38.4 and 38.3, 37.7, 28.6; HRMS (ESI $^-$) theo. for $\text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_6$: 466.1978 $[\text{M}-\text{H}]^-$; meas. 466.1977 $[\text{M}-\text{H}]^-$.

4.3. Rhodium-catalysed 1,4-additions to Boc-Trp- Δ Ala-Tyr-OMe

Boc-Trp-Phe(4-Fluoro)-Tyr-OMe (18)



Following the general procedure for 1,4-addition Boc-Trp- Δ Ala-Tyr-OMe (110 mg, 0.2 mmol) was reacted with 4-fluorobenzene boronic acid (122 mg, 0.8 mmol, 4 equiv.) in the presence of sodium fluoride (25 mg, 0.6 mmol, 3 equiv.). The title compound was obtained in 54 % yield (70 mg) as an off white solid. m.p. 92-94 $^{\circ}\text{C}$; IR (film, cm^{-1}) ν 4214, 3390 (br), 3020, 2982, 2932, 2854, 2401, 1893, 1737, 1664, 1615, 1512, 1439, 1369, 1216, 1172, 1114, 1054, 1015, 929, 844, 757, 669, 621, 575, 538; ^1H NMR (CDCl_3 ; 300 MHz) 8.28 (1H, s), 7.62 (1H, d, $J = 7.8$ Hz), 7.35 (1H, d, $J = 7.8$ Hz), 7.22-7.06 (2H, m), 6.85 (1H, d, $J = 2.1$ Hz), 6.9-6.66 (8H, m), 6.29 (1H, d, $J = 8.1$ Hz), 6.20 (1H, d, $J = 8.1$ Hz), 5.06 (1H, d, $J = 7.8$ Hz), 4.66 (1H, dt, $J = 6.9$, 6.0 Hz), 4.53-4.34 (2H, m), 3.70 (3H, s), 3.14-2.96 (3H, m), 2.83-2.73 (3H, m), 1.40 (9H, s); ^{13}C NMR (CDCl_3 ; 75.5 MHz) 172.1, 172.0, 170.3, 155.7, 152.0, 136.6, 132.2 and 132.1, 131.2 (d, $J = 8.0$ Hz), 130.7, 127.7 and 127.6, 124.1, 123.7 and 123.6, 122.9, 120.3, 119.2, 116.2, 115.7 (d, $J = 21.9$ Hz), 111.7, 110.6, 81.1, 54.1, 53.8, 52.9, 52.8, 37.3, 37.2, 30.1, 28.7; ^{19}F NMR (CDCl_3 ; 376.5 MHz) δ -115.80; HRMS (ESI $^+$) theo. for $\text{C}_{35}\text{H}_{39}\text{FN}_4\text{NaO}_7$: 669.2700 $[\text{M}+\text{Na}]^+$; meas. 669.2699 $[\text{M}+\text{Na}]^+$.