Regiocontrolled Palladium-catalyzed and copper-mediated C-H bond functionalization of protected L-histidine

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1. General Information

All arylation reactions were carried out under an argon atmosphere, unless otherwise stated. All starting materials were commercially purchased and used further without any additional purification. Analytical thin-layer chromatography (TLC) was performed using aluminum plates precoated with silica gel (0.25 mm, 60 Å pore-size) impregnated with a fluorescent indicator (254 nm). Visualization on TLC was achieved by the use of UV light (254 nm), treatment with 10% ninhydrin in ethanol or strained with iodine vapors. Flash column chromatography was undertaken on silica gel (230-400 mesh). Proton nuclear magnetic resonance spectra (1H NMR) were recorded on 400 MHz NMR instrument. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent (CDCl3, δ 7.26 and CD3OD, δ 3.31). The following abbreviations were used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet. Coupling constants, J, were reported in Hertz unit (Hz). Carbon 13 nuclear magnetic resonance spectroscopy (13C NMR) was recorded on 100 MHz NMR instrument and was fully decoupled by broad band decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 and 49.0 ppm of chloroform-d and Methanol-d. High resolution mass spectra were taken using ESI-TOF method. Infrared (IR) spectra were reported in frequency of the absorption (cm⁻¹).

2. Experimental Procedure

2.1. Synthesis of N-α-acetyl-1-benzyl-L-histidine methyl ester (1a)

A mixture of N-α-acetyl-L-histidine methyl ester (1, 1 equiv, 2.37 mmol), benzyl bromide (1.5 equiv, 3.55 mmol) and silver carbonate (1.5 equiv, 3.55 mmol) in DMF (2 mL) was stirred at ambient temperature for 4 h. The solvent was removed under reduced pressure and residue was purified on an automated flash column chromatography system to afford 1a. Yield 90%; 1H NMR (CD3OD): δ 8.37 (s, 1H), 7.38-7.43 (m, 3H), 7.31-7.37 (m, 2H), 7.15 (s, 1H), 5.29 (s, 2H), 4.69-4.72 (m, 1H), 3.69 (s, 3H), 3.12-3.18 (m, 1H), 2.96-3.02 (m, 1H), 1.88 (s, 3H); 13C NMR (CD3OD): δ 172.0, 171.0, 147.3, 141.6, 133.7, 129.5, 127.8, 117.4, 52.0, 51.6, 26.4, 21.5; IR (neat): 2937, 1784, 1326, 1235, 1180, 1150, 1126 cm⁻¹; HRMS (ESI-TOF) m/z: [M+ H+] calculated for m/z 302.1504 found 302.1504.

2.2. General method for the synthesis and characterization of N-α-acetyl-2-aryl-1-benzyl-L-histidine methyl esters (3a, and 3d-m)

All microwave irradiation experiments were performed using a CEM Discover® microwave reactor. Reaction times refer to the hold time at the desired set temperature and not to the total irradiation time. Reaction cooling is performed by compressed air automatically after the
heating period has elapsed. All the solid reagents were weighed in air and placed in a 10 mL microwave vial equipped with a magnetic stir bar.

To a 10 ml capacity microwave vial, t-BuOK (3.0 equiv, 4.98 mmol), Pd(OAc)$_2$ (20 mol%, 0.34 mmol), P(n-Bu)(1-adamantyl)$_2$ (40 mol%, 0.66 mmol), Cul (2 equiv, 3.32 mmol) and PivOH (40 mol%, 0.66 mmol) and 1a (1 equiv, 1.66 mmol) were added and reaction mixture was purged with argon. The appropriate aryl iodide if solid (2, 2 equiv, 3.32 mmol) was added at this point. The reaction mixture was purged with argon and NMP (2 mL) was added. The aryl iodide, if liquid (2, 2 equiv, 3.32 mmol) were added at this point. Addition of solvent was done under positive argon pressure with stirring. The sealed reaction vial was then placed in the microwave reactor and stirred at 140 °C for the indicated time. The solution was then cooled to ambient temperature and diluted with EtOAc, washed with H$_2$O (3 times), dried over MgSO$_4$, filtered, and evaporated under reduced pressure. The reaction mixture was purified on a Biotage® automated flash column chromatography system to give the desired product.

$N$-$\alpha$-Acetyl-2-(4-trifluoromethylphenyl)-1-benzyl-L-histidine methyl ester (3a): Yield: 78%; $^1$H NMR (CDCl$_3$): $\delta$ 7.67-7.74 (m, 2H), 7.51-7.60 (m, 3H), 7.25-7.34 (m, 2H), 6.97-7.06 (m, 2H), 6.83 (s, 1H), 5.33 (s, 2H), 4.82-4.86 (m, 1H), 3.70 (s, 3H), 3.25 (d, $J$ = 24 Hz, 1H), 3.10 (d, $J$ = 32 Hz, 1H), 1.26 (s, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 170.8, 169.1, 126.6, 125.5, 125.1, 123.9, 122.2, 121.1, 119.8, 117.4, 116.5, 115.9, 53.0, 52.0, 48.7, 29.5, 28.2; IR (neat): 1426, 1265, 1180, 784, 750 cm$^{-1}$; HRMS (ESI-TOF): calculated for m/z 446.1691 [M+H$^+$], found 446.1690.

$N$-$\alpha$-Acetyl-2-(3-trifluoromethylphenyl)-1-benzyl-L-histidine methyl ester (3d): Yield: 74%; $^1$H NMR (CDCl$_3$): $\delta$ 7.76 (d, $J$ = 12.0 Hz, 2H), 7.52-7.59 (m, 5H), 7.42-7.46 (m, 2H), 7.37 (d, $J$ = 7.60 Hz, 1H), 6.78 (s, 1H), 4.89 (s, 2H), 4.10-4.12 (m, 1H), 3.70 (s, 3H), 3.18-3.26 (m, 1H), 3.08-3.15 (m, 1H), 1.26 (s, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 171.2, 168.2, 140.1, 139.3, 129.9, 129.4, 128.1, 127.5, 127.0, 124.7, 117.7, 114.6, 53.3, 51.1, 46.8, 28.5, 20.9; IR (neat): 2964, 1841, 1426, 1279, 1210, 1166, 1126, 764, 750 cm$^{-1}$; HRMS (ESI-TOF): calculated for m/z 446.1691 [M+H$^+$], found 446.1682.

$N$-$\alpha$-Acetyl-2-(2-trifluoromethylphenyl)-1-benzyl-L-histidine methyl ester (3e): Yield: 72%; $^1$H NMR (CDCl$_3$): $\delta$ 8.54 (s, 1H), 7.88 (d, $J$ = 16.0 Hz, 2H), 7.42-7.57 (m, 6H), 7.29-7.35 (m, 1H), 6.87 (s, 1H), 5.65 (s, 2H), 4.83 (s, 1H), 3.66 (s, 3H), 3.21 (d, $J$ = 20.0 Hz, 1H), 3.10 (d, $J$ = 28.0 Hz, 1H), 1.25 (s, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 170.2, 167.9, 134.0, 130.8, 129.7, 128.9, 127.9, 127.2, 126.4, 125.6, 124.8, 53.4, 51.4, 46.5, 30.4, 27.8; IR (neat): 2924, 1275, 1260, 1166, 1126, 764, 750 cm$^{-1}$; HRMS (ESI-TOF): calculated for m/z 446.1691 [M+H$^+$], found 446.1684.
**N-α-Acetyl-2-(4-cyanophenyl)-1-benzyl-L-histidine methyl ester (3f):** Yield: 76%; $^1$H NMR (CDCl$_3$): $\delta$ 7.78 (d, $J = 8.28$ Hz, 2H), 7.35 (d, $J = 8.28$ Hz, 2H), 7.15-7.16 (m, 3H), 6.86 (s, 1H), 6.73-6.75 (m, 2H), 5.13 (s, 2H), 4.44 (t, $J = 6.90$ Hz, 1H), 3.66 (s, 3H), 3.13 (d, $J = 7.03$ Hz, 1H), 3.10 (d, $J = 7.03$ Hz, 1H), 1.27 (s, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 172.9, 169.5, 135.3, 133.2, 132.9, 131.5, 130.8, 129.0, 128.3, 128.0, 126.8, 119.1, 110.9, 52.6, 52.2, 48.6, 29.0, 22.4; IR (neat): 3584, 2965, 1640, 1275, 1260, 1025, 764, 750 cm$^{-1}$; HRMS (ESI-TOF): calculated for m/z 403.1770 [M+H$^+$], found 403.1770.

**N-α-Acetyl-2-(4-chlorophenyl)-1-benzyl-L-histidine methyl ester (3g):** Yield: 77%; $^1$H NMR (CDCl$_3$): $\delta$ 7.40 (d, $J = 8.4$ Hz, 2H), 7.18-7.20 (m, 3H), 7.14-7.17 (m, 2H), 7.04 (d, $J = 7.6$ Hz, 2H), 6.75 (s, 1H), 5.07 (s, 2H), 4.41 (t, $J = 6.90$ Hz, 1H), 3.70 (s, 3H), 3.16-3.20 (m, 1H), 3.09-3.11 (m, 1H), 1.25 (s, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 170.4, 167.6, 133.1, 132.5, 132.0, 131.5, 130.1, 129.1, 128.9, 128.7, 128.2, 128.0, 126.8, 55.0, 52.7, 52.2, 48.4, 29.0; IR (neat): 3695, 1602, 1375, 1260, 764, 749 cm$^{-1}$; HRMS (ESI-TOF): calculated for m/z 412.1428 [M+H$^+$], found 412.1429.

**N-α-Acetyl-2-phenyl-1-benzyl-L-histidine methyl ester (3h):** Yield: 70%; $^1$H NMR (CDCl$_3$): $\delta$ 7.75 (d, $J = 12.8$ Hz, 2H), 7.53-7.60 (m, 3H), 7.44 (d, $J = 11.2$ Hz, 3H), 7.29-7.37 (m, 2H), 6.79 (s, 1H), 5.25 (s, 2H), 4.78 (t, $J = 14.1$ Hz, 1H), 3.64 (s, 3H), 3.14-3.22 (m, 1H), 3.03-3.11 (m, 1H), 1.26 (s, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 171.2, 167.9, 135.7, 133.2, 129.1, 128.0, 127.0, 124.7, 117.3, 115.7, 114.6, 54.3, 52.7, 49.6, 47.1, 27.8; IR (neat): 2998, 1635, 1559, 1426, 1250, 1210, 1025, 764, 749 cm$^{-1}$; HRMS (ESI-TOF): calculated for m/z 378.1817 [M+H$^+$], found 378.1821.

**N-α-Acetyl-2-(4-tert-butylphenyl)-1-benzyl-L-histidine methyl ester (3i):** Yield: 65%; $^1$H NMR (CDCl$_3$): $\delta$ 7.43 (d, $J = 8.03$ Hz, 2H), 7.10-7.18 (m, 3H), 7.03 (d, $J = 8.28$ Hz, 2H), 6.92 (d, $J = 4.02$ Hz, 2H), 6.76 (s, 1H), 5.04 (s, 2H), 4.41-4.42 (m, 1H), 3.67 (s, 3H), 3.18-3.21 (m, 2H), 1.26 (s, 3H), 1.20 (s, 9H); $^{13}$C NMR (CDCl$_3$): $\delta$ 172.4, 167.6, 150.3, 135.9, 134.8, 134.1, 133.0, 129.0, 128.3, 128.1, 127.1, 126.9, 126.3, 125.8, 52.8, 52.1, 48.3, 34.7, 31.4, 31.3, 29.1; IR (neat): 2917, 1475, 1260, 764, 749 cm$^{-1}$; HRMS (ESI-TOF): calculated for m/z 434.2443 [M+H$^+$], found 434.2449.

**N-α-Acetyl-2-(4-methylphenyl)-1-benzyl-L-histidine methyl ester (3j):** Yield: 65%; $^1$H NMR (CDCl$_3$): $\delta$ 7.10-7.21 (m, 5H), 7.01 (d, $J = 4.76$ Hz, 2H), 6.94 (s, 1H), 6.77 (d, $J = 7.64$ Hz, 2H), 5.04 (s, 2H), 4.39 (t, $J = 7.03$ Hz, 1H), 3.61 (s, 3H), 3.19 (d, $J = 5.52$ Hz, 1H), 3.06 (d, $J = 5.52$ Hz, 1H), 2.26 (s, 3H), 1.26 (s, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 172.5, 167.1, 135.3, 131.8, 132.1, 130.0, 129.0, 128.5, 128.0, 126.7, 126.1, 54.9, 52.9, 52.2, 48.2, 29.0, 22.4; IR (neat): 2924, 1731, 1659, 1436, 1275, 1260, 1026, 764, 749 cm$^{-1}$; HRMS (ESI-TOF): calculated for m/z 392.1974 [M+H$^+$], found 392.1974.
**N-α-Acetyl-2-(4-methoxyphenyl)-1-benzyl-L-histidine methyl ester (3k):** Yield: 64%; ¹H NMR (CDCl₃): δ 7.66 (d, J = 9.84 Hz, 2H), 7.45-7.49 (m, 3H), 7.15-7.23 (m, 2H), 6.91 (d, J = 8.44 Hz, 2H), 6.77 (s, 1H), 5.30 (s, 2H), 4.82 (s, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.20 (t, J = 12.64 Hz, 1H), 3.08 (t, J = 7.04 Hz, 1H), 1.26 (s, 3H); ¹³C NMR (CDCl₃): δ 170.2, 169.2, 138.7, 129.9, 129.3, 128.6, 125.4, 123.4, 122.1, 117.8, 114.6, 56.3, 52.7, 51.1, 46.2, 28.8, 21.3; IR (neat): 3392, 1719, 1475, 1260, 1024, 994, 764, 750 cm⁻¹; HRMS (ESI-TOF): calculated for m/z 408.1923 [M+H⁺], found 408.1923.

**N-α-Acetyl-2-biphenyl-1-benzyl-L-histidine methyl ester (3l):** Yield: 69%; ¹H NMR (CDCl₃): δ 7.71 (dd, J = 6.52, 7.51 Hz, 4H), 7.45 (d, J = 7.61 Hz, 2H), 7.33-7.37 (m, 1H), 7.25 (d, J = 8.28 Hz, 2H), 7.18-7.23 (m, 3H), 6.99 (s, 1H), 6.80-6.82 (m, 2H), 5.11 (s, 2H), 4.46 (t, J = 7.03 Hz, 1H), 3.61 (s, 3H), 3.14-3.16 (m, 1H), 3.12-3.14 (m, 1H), 1.27 (s, 3H); ¹³C NMR (CDCl₃): δ 172.4, 167.5, 140.9, 135.6, 134.3, 133.8, 132.7, 130.9, 129.6, 128.5, 128.3, 128.0, 127.1, 127.0, 126.8, 52.8, 52.2, 48.4, 31.9, 29.2; IR (neat): 3684, 2917, 2754, 1752, 1612, 1402, 1275, 1260, 1038, 764, 750 cm⁻¹; HRMS (ESI-TOF): calculated for m/z 454.2130 [M+H⁺], found 454.2134.

**N-α-Acetyl-2-(2-napthyl)-1-benzyl-L-histidine methyl ester (3m):** Yield: 69%; ¹H NMR (CDCl₃): δ 7.87-7.95 (m, 2H), 7.80-7.85 (m, 2H), 7.50-7.57 (m, 2H), 7.27 (d, J = 8.41 Hz, 1H), 7.10-7.15 (m, 3H), 6.98 (d, J = 8.01 Hz, 2H), 6.76 (s, 1H), 5.10 (s, 2H), 4.46 (d, J = 7.18 Hz, 1H), 3.67 (s, 3H), 3.16 (d, J = 6.6 Hz, 1H), 3.14 (d, J = 6.8 Hz, 1H), 1.33 (s, 3H); ¹³C NMR (CDCl₃): δ 172.5, 167.9, 136.9, 135.0, 133.1, 132.7, 129.8, 129.5, 129.0, 128.5, 128.3, 128.0, 127.9, 127.8, 127.2, 127.1, 126.9, 126.8, 55.1, 52.7, 52.2, 48.5, 29.3; IR (neat): 3685, 3416, 2863, 1746, 1378, 1375, 1219, 750 cm⁻¹; HRMS (ESI-TOF): calculated for m/z 428.1974 [M+H⁺], found 428.1973.

**2.3. Synthesis of N-α-acetyl-2-(4-trifluoromethylphenyl)-L-histidine methyl ester (4)**

A suspension of 3a (1 equiv, 1.09 mmol) in 10% Pd-C (10 equiv, 10.9 mmol) in methanol (5 mL) was treated with ammonium formate (5 equiv, 5.48 mmol), and the mixture was refluxed for 18 h. The reaction mixture was filtered through a celite pad, and solvent was removed under reduced pressure. The resulting residue upon purification on a fully automated flash column chromatography Biotage® system yielded 4. Yield: 85%; ¹H NMR (CDCl₃): δ 7.70 (d, J = 12.6 Hz, 2H), 7.43 (d, J = 15.4 Hz, 2H), 6.81 (s, 1H), 4.84-4.88 (m, 1H), 3.68 (s, 3H), 3.24 (d, J = 7.04 Hz, 1H), 3.11 (d, J = 8.44 Hz, 1H), 1.33 (s, 3H); ¹³C NMR (CDCl₃): δ 173.6, 170.8, 135.9, 131.4, 127.5, 126.3, 123.8, 54.3, 52.7, 49.1, 27.7; IR (neat): 2937, 2167, 1638, 1524, 1319, 1163, 1048, 941, 727 cm⁻¹; HRMS (ESI-TOF): calculated for m/z 356.1222 [M+H⁺], found 356.1231.
2.4. Synthesis of 2-(4-trifluoromethylphenyl)-L-histidine·2HCl (5)

2-(4-Trifluoromethylphenyl)-L-histidine·2HCl (5) was synthesized by refluxing 4 in 6N HCl for 24 h by using a procedure reported earlier.

Yield: 90%; ¹H NMR (CD$_3$OD): δ 7.84 (d, $J = 8.44$ Hz, 2H), 7.62 (d, $J = 14.08$ Hz, 2H), 7.45 (s, 1H), 4.36-4.41 (m, 1H), 3.42-3.49 (m, 1H), 3.31-3.37 (m, 1H); ¹³C NMR (CD$_3$OD): δ 167.9, 140.2, 133.6, 128.3, 126.7, 120.1, 117.6, 51.9, 24.8; IR (neat): 2981, 2454, 1690, 1490, 1170, 939, 871 cm$^{-1}$; HRMS (ESI-TOF): calculated for $m/z$ 300.0960 [M+H$^+$], found 300.0960.

3. Spectra Files (¹H and ¹³C NMR)

Figure 1. ¹H NMR of 3a
Figure 2. $^{13}$C NMR of 3a
Figure 3. $^1$H NMR of 3d
Figure 4. $^{13}$C NMR of 3d
Figure 5. $^1$H NMR of 3e
Figure 6. $^{13}$C NMR of 3e
Figure 7. $^1$H NMR of 3h
Figure 8. $^{13}$C NMR of 3h
Figure 9. $^1$H NMR of 3k
Figure 10. $^{13}$C NMR of 3k
Figure 11. $^1$H NMR of 4
Figure 12. $^{13}$C NMR of 4
Figure 13. $^1$H NMR of 5
4. Chiral HPLC method

To analyze the optical integrity of the established protocol, a representative example of 2-(4-trifluoromethylphenyl)-L-histidine·2HCl and 2-(4-trifluoromethylphenyl)-D-histidine·2HCl was analyzed using ChiralPak-WH column on HPLC. The mobile phase used in this study was 5 mM copper(II) sulfate in water and 2-propanol 95-5 % using a gradient run for 60 min. The flow rate of the mobile phase used was 1.5mL/min, column temperature 50 °C and detection at 254 nm.
Figure 15. HPLC Chromatogram of 2-(4-trifluoromethylphenyl)-L-histidine·2HCl (5, From Scheme 3)

Figure 16. HPLC Chromatogram of 2-(4-trifluoromethylphenyl)-D-histidine·2HCl (enantiomer of 5)