Palladium-Catalyzed Domino Heck / Intermolecular Cross-Coupling: Efficient Synthesis of 4-Alkylated Isoquinoline Derivatives

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General Information:

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker AM 400 spectrometer (operating at 400 and 101 MHz respectively) in CDCl$_3$ (residual internal standard CHCl$_3$ = $\delta$ 7.26), DMSO-d6 (residual internal standard CD$_3$SOCD$_2$H = $\delta$ 2.50). HPLC/MS analysis was carried out with gradient elution (5% CH$_3$CN to 100% CH$_3$CN) on an Agilent 1200 RRLC with a photodiode array UV detector and an Agilent 6224 TOF mass spectrometer (also used to produce high resolution mass spectra). Melting points were determined on a Stanford Research Systems OptiMelt apparatus. The infrared (IR) spectra were acquired as thin films using a universal ATR sampling accessory on a Bruker Vertex 80 FT-IR spectrometer and the absorption frequencies are reported in cm$^{-1}$. Flash chromatography separations were carried out using silica gel columns. The new compounds were characterized by $^1$H NMR, $^{13}$C NMR, HRMS and IR. The structure of known compounds were further confirmed by comparing their $^1$H NMR and $^{13}$C NMR data with those of literature. All reagents and solvents were used as received from commercial sources without further purification. Compounds 1a,$^1$ 1o,$^2$ 1p,$^1$ 1q,$^1$ 1r,$^3$ 1s,$^1$ 1t,$^1$ 1u,$^4$ 1v,$^1$ 1w,$^5$ 1x,$^4$ 2a,$^6$ 2b,$^7$ 2c,$^6$ 2d,$^7$ 2e,$^8$ 2f,$^8$ 2g,$^6$ 2h,$^6$ 2i,$^8$ 2j,$^8$ 2k,$^7$ 2l,$^8$ 2m,$^8$ 2n$^6$ were prepared by following literature procedure.

Experimental Procedures

General Procedure for Preparation of Imine 1.$^8$

A mixture of the aldehyde (0.6 mmol) and t-BuNH$_2$ (20 equiv) was stirred at room temperature for 20 h. The progress of the reaction was monitored by NMR. The completed reaction was diluted with ethyl acetate, washed with H$_2$O, dried (MgSO$_4$) and filtered. Removal of the solvent under reduced pressure afforded desired imine, which was used without further purification.
Ethyl (E)-4-((2-((tert-butylimino)methyl)phenyl)ethynyl)benzoate (1e).
This product was obtained as yellow oil (0.1778 g, 89%). \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 8.84 (s, 1H), 8.05 – 7.96 (m, 3H), 7.75 – 7.68 (m, 2H), 7.68 – 7.63 (m, 1H), 7.55 – 7.47 (m, 2H), 4.33 (q, \(J = 7.1\) Hz, 2H), 1.33 (t, \(J = 7.1\) Hz, 3H), 1.29 (s, 9H); \(^{13}\)C NMR (101 MHz, DMSO) \(\delta\) 165.1, 152.7, 137.2, 132.5, 131.6, 130.4, 129.9, 129.5, 126.6, 125.8, 122.3, 93.9, 89.2, 61.0, 57.7, 29.5, 14.1 (one carbon missing due to overlap); IR (neat) 1647, 1524, 1369, 1319 cm\(^{-1}\); HRMS calcd for C\(_{22}\)H\(_{24}\)NO\(_2\) [M+H\(^+\)]: 334.1802, found 334.1809.

(E)-N-tert-Butyl-1-(2-((trimethylsilyl)ethynyl)phenyl)methanimine (1i). This product was obtained as a brown oil (0.1266 g, 82%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.81 (s, 1H), 8.06 – 7.98 (m, 1H), 7.45 (dd, \(J = 7.4, 1.4\) Hz, 1H), 7.36-7.25 (m, 2H), 1.29 (s, 9H), 0.25 (s, 9H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 154.5, 138.4, 132.5, 129.8, 129.0, 126.0, 123.9, 102.4, 100.3, 58.0, 29.9, 0.2; IR (neat) 1592,1387, 1351 cm\(^{-1}\); HRMS calcd for C\(_{16}\)H\(_{24}\)NSi [M+H\(^+\)]: 258.1673, found 258.1675.

(E)-N-tert-Butyl-1-(4-methyl-2-(phenylethynyl)phenyl)methanimine (1j). This product was obtained as a yellow solid (0.1454 g, 88%): mp 59-60 °C; \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 8.80 (s, 1H), 7.88 (d, \(J = 8.0\) Hz, 1H), 7.59 – 7.52
(m, 2H), 7.52 – 7.38 (m, 4H), 7.27 (d, J = 8.0 Hz, 1H), 2.34 (s, 3H), 1.26 (d, J = 1.2 Hz, 9H); ^{13}C NMR (101 MHz, DMSO) δ 152.6, 140.2, 134.5, 132.4, 131.2, 129.9, 129.1, 128.9, 125.6, 122.9, 122.1, 94.5, 86.5, 57.5, 29.5, 20.7; IR (neat) 1649, 1545, 1370, 1329 cm^{-1}; HRMS calcd for C_{20}H_{22}N [M+H]^+: 276.1747, found 276.1754.

![Structural formula](image)

**(E)-N-tert-Butyl-1-(2-(phenylethynyl)-4-(trifluoromethyl)phenyl)methanimine (1I).** This product was obtained as a yellow solid (0.1798 g, 91%): mp 65-66 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.86 (s, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.99 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.66-7.55 (m, 2H), 7.54 – 7.43 (m, 3H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, DMSO) δ 152.0, 140.3, 131.5, 130.5 (q, J = 32.3 Hz), 129.6, 129.0, 126.9, 125.5, 125.2(q, J = 4.0 Hz), 123.8, 122.3, 121.4, 96.4, 84.9, 58.2, 29.3; IR (neat) 1639, 1368, 1337, 1170, 1131 cm^{-1}; HRMS calcd for C_{20}H_{19}F_{3}N [M+H]^+: 330.1464, found 330.1469.

**General Procedure for Preparation of compound 2**

![General Procedure](image)

To a solution of 2-iodophenol (1.8 mmol) and oven-dried K_{2}CO_{3} (3.0 equiv) in acetone (18 mL), 3-chloro-2-methylprop-1-ene (2.0 equiv) were added. The resulting mixture was stirred at 60 °C overnight. The reaction was concentrated in vacuo, diluted with brine and extracted with EtOAc (3x). The combined organic layers were dried (MgSO_{4}), filtered, and concentrated. The crude product was purification by column chromatography (Silica Gel, petroleum ether / EtOAc) to afford compound 2.
1-Iodo-4-methoxy-2-((2-methylallyl)oxy)benzene (2o). This product was obtained as a colorless oil (0.3936 g, 72%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.60 (d, $J = 8.6$ Hz, 1H), 6.39 (d, $J = 2.7$ Hz, 1H), 6.30 (dd, $J = 8.6, 2.7$ Hz, 1H), 5.18 (dd, $J = 1.4, 0.8$ Hz, 1H), 5.05 – 4.97 (m, 1H), 4.43 (s, 2H), 3.76 (s, 3H), 1.85 (d, $J = 0.4$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.4, 158.0, 140.3, 139.3, 113.2, 107.4, 100.5, 75.5, 72.6, 55.7, 19.7; IR (neat) 1590, 1480, 1353, 1200, 1167 cm$^{-1}$; HRMS calcd for C$_{11}$H$_{14}$IO$_2$ [M+H]$^+$: 305.0033, found 305.0029.

4-Fluoro-2-iodo-1-((2-methylallyl)oxy)benzene (2q). This product was obtained as a yellow oil (0.2471 g, 47%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 (dd, $J = 7.6, 3.0$ Hz, 1H), 6.98 (ddd, $J = 9.0, 7.8, 3.0$ Hz, 1H), 6.71 (dd, $J = 9.0, 4.6$ Hz, 1H), 5.16 (s, 1H), 5.03 – 4.97 (m, 1H), 4.42 (s, 2H), 1.84 (d, $J = 0.5$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 157.0 (d, $J = 244.4$ Hz), 154.0 (d, $J = 3.0$ Hz), 140.3, 126.3 (d, $J = 25.3$ Hz), 115.7 (d, $J = 22.2$ Hz), 113.3, 112.6 (d, $J = 8.1$ Hz), 86.1 (d, $J = 8.1$ Hz), 73.5, 19.7; IR (neat) 1591, 1483, 1351, 1190 cm$^{-1}$; HRMS calcd for C$_{10}$H$_{11}$FIO [M+H]$^+$: 292.9833, found 292.9831.

**General procedure for the Synthesis of 4-Alkylated Isoquinoline Derivatives:**

To a solution of aryl halides (0.2 mmol), Pd(PPh$_3$)$_4$ (0.05 equiv), and oven-dried K$_2$CO$_3$ (3.0 equiv) in DMF (5mL), imine (1.2 equiv) was added. The resulting reaction mixture was heated at 100 °C under argon for 6h. The reaction were monitored by TLC to establish completion. After cooling to room temperature, the reaction was diluted with ethyl acetate (35mL), washed with water (3×15mL) and brine (15mL), dried (MgSO$_4$) and concentrated. The residue was purified by column chromatography (Silica Gel, petroleum ether / EtOAc) to afford product 3.
4-((3-Methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3a). This product was obtained as a yellow solid (0.0461 g, 71%): mp 138-139 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.21 (s, 1H), 8.01 – 7.89 (m, 1H), 7.63 (s, 1H), 7.56-7.42 (m, 6H), 7.39 (dd, $J = 8.4, 6.0$ Hz, 1H), 7.00 (t, $J = 7.7$ Hz, 1H), 6.67 (d, $J = 8.0$ Hz, 1H), 6.52 (s, 1H), 6.32 (s, 1H), 4.22 (d, $J = 8.7$ Hz, 1H), 3.82 (d, $J = 8.6$ Hz, 1H), 3.74-3.62 (m, 2H), 0.96 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.5, 153.9, 150.6, 141.8, 137.1, 134.7, 130.4, 130.1, 128.6, 128.3, 128.1, 127.9, 127.3, 126.7, 125.0, 124.3, 123.5, 120.6, 109.9, 83.2, 48.0, 36.3, 24.2; IR (neat) 1677, 1592, 1478, 1351, 973, 752, 704 cm$^{-1}$; HRMS calcd for C$_{25}$H$_{22}$NO [M+H]$^+$: 352.1696, 352.1701.

4-((3-Methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-(p-tolyl)isoquinoline (3b). This product was obtained as a white solid (0.0562 g, 77%): mp 133-135 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.20 (s, 1H), 7.97 – 7.87 (m, 1H), 7.60 (s, 1H), 7.53 – 7.37 (m, 4H), 7.26 (d, $J = 7.8$ Hz, 2H), 6.99 (td, $J = 7.9, 1.2$ Hz, 1H), 6.67 (d, $J = 8.0$ Hz, 1H), 6.51 (s, 1H), 6.33 (d, $J = 5.6$ Hz, 1H), 4.21 (d, $J = 8.7$ Hz, 1H), 3.82 (d, $J = 8.6$ Hz, 1H), 3.74-3.63 (m, 2H), 2.42 (s, 3H), 0.97 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.5, 153.7, 150.4, 138.6, 137.7, 137.3, 134.8, 130.24, 130.17, 129.4, 128.3, 128.2, 127.2, 126.7, 125.1, 124.3, 123.6, 120.6, 109.9, 83.3, 48.0, 36.3, 24.2, 21.5; IR (neat) 1592, 1385, 1350, 764 cm$^{-1}$; HRMS calcd for C$_{26}$H$_{24}$NO [M+H]$^+$: 366.1852, found 366.1862.
3-(4-Methoxyphenyl)-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)isoquinoline (3c). This product was obtained as a white solid (0.0534 g, 70%): mp 123-125 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.17 (s, 1H), 7.96 – 7.82 (m, 1H), 7.63 (s, 1H), 7.54-7.31 (m, 4H), 7.05-6.85 (m, 3H), 6.67 (d, $J = 7.9$ Hz, 1H), 6.53 (s, 1H), 6.35 (s, 1H), 4.21 (d, $J = 8.7$ Hz, 1H), 3.86 (s, 3H), 3.81 (d, $J = 8.6$ Hz, 1H), 3.71 (d, $J = 14.1$ Hz, 1H), 3.68-3.58 (m, 1H), 0.98 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 159.5, 159.3, 153.8, 150.5, 137.2, 134.8, 134.5, 131.6, 129.9, 128.3, 128.0, 127.2, 126.5, 124.8, 124.2, 123.5, 120.5, 114.0, 109.8, 83.1, 55.5, 48.0, 36.3, 24.3; IR (neat) 1650, 1613, 1513, 1476, 1371, 1327, 751 cm$^{-1}$; HRMS calcd for C$_{26}$H$_{24}$NO$_2$ [M+H]$^+$: 382.1802, found 382.1808.

3-(4-Fluorophenyl)-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)isoquinoline (3d). This product was obtained as a yellow solid (0.0456 g, 62%): mp 146-148 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.20 (s, 1H), 7.94 (d, $J = 7.3$ Hz, 1H), 7.65 (s, 1H), 7.58-7.38 (m, 4H), 7.20-7.06 (m, 2H), 6.99 (t, $J = 7.5$ Hz, 1H), 6.66 (d, $J = 7.7$ Hz, 1H), 6.52 (s, 1H), 6.27 (s, 1H), 4.22 (d, $J = 8.5$ Hz, 1H), 3.83 (d, $J = 8.3$ Hz, 1H), 3.70-3.58 (m, 2H), 1.00 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.6(d, $J = 248.5$ Hz), 159.6, 152.7, 150.5, 137.6, 137.3, 134.4, 132.1(d, $J = 8.1$ Hz), 130.4, 128.5, 128.3, 127.4, 127.0, 125.3, 124.4, 123.5, 120.7, 115.6(d, $J = 22.2$ Hz), 110.0, 83.2, 48.1, 36.5, 24.4; IR (neat) 166, 1563, 1510, 1477, 1371, 1331, 749 cm$^{-1}$; HRMS calcd for C$_{25}$H$_{21}$FNO [M+H]$^+$: 370.1602, found 370.1607.
3-Butyl-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)isoquinoline (3g). This product was obtained as a yellow oil (0.0654 g, 66%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 9.10 (s, 1H), 7.89 – 7.83 (m, 1H), 7.68 (dd, \(J = 7.0, 4.3\) Hz, 1H), 7.55-7.38 (m, 2H), 7.09 (td, \(J = 8.0, 1.2\) Hz, 1H), 6.79 (d, \(J = 7.9\) Hz, 1H), 6.65 (t, \(J = 6.6\) Hz, 1H), 6.49 (d, \(J = 7.2\) Hz, 1H), 4.51 (d, \(J = 8.7\) Hz, 1H), 4.06 (d, \(J = 8.7\) Hz, 1H), 3.45-3.35 (m, 2H), 2.63 (s, 2H), 1.55 (dt, \(J = 9.3, 7.0\) Hz, 2H), 1.38 (s, 3H), 1.27 (dt, \(J = 14.9, 7.4\) Hz, 2H), 0.86 (t, \(J = 7.3\) Hz, 3H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) δ 159.6, 155.4, 150.8, 136.9, 134.6, 129.9, 128.6, 128.2, 127.0, 125.9, 123.9, 123.80, 123.78, 120.7, 110.0, 83.3, 47.7, 36.3, 35.0, 32.4, 24.4, 23.0, 14.1; IR (neat) 1592, 1476, 1379, 1350, 974, 751 cm\(^{-1}\); HRMS calcd for C\(_{23}\)H\(_{26}\)NO [M+H]\(^+\): 332.2009, found 332.2022.

3-(Cyclohex-1-en-1-yl)-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)isoquinoline (3h). This product was obtained as a brown oil (0.0286 g, 40%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 9.08 (s, 1H), 7.85 (dd, \(J = 5.2, 4.1\) Hz, 1H), 7.58 (s, 1H), 7.50-7.36 (m, 2H), 7.12 – 6.98 (m, 1H), 6.75 (d, \(J = 8.0\) Hz, 1H), 6.70 – 6.48 (m, 2H), 5.74 (s, 1H), 4.43 (d, \(J = 8.7\) Hz, 1H), 3.98 (d, \(J = 8.6\) Hz, 1H), 3.64 (s, 2H), 2.48 (s, 1H), 2.39 (s, 1H), 2.25 – 2.15 (m, 2H), 1.81 (dt, \(J = 5.7, 5.0\) Hz, 2H), 1.72 (dt, \(J = 10.7, 4.6\) Hz, 2H), 1.31 (s, 3H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) δ 159.6, 156.7, 150.5, 138.9, 137.2, 135.4, 129.68, 129.65, 128.3, 128.0, 127.1, 126.1, 124.4, 123.7, 123.6, 120.7, 110.0, 83.3, 47.3, 36.7, 29.4, 25.7, 25.2, 23.2, 22.2; IR (neat) 2929, 1588, 1479, 1384, 1349, 974, 750 cm\(^{-1}\); HRMS calcd for C\(_{25}\)H\(_{26}\)NO [M+H]\(^+\): 356.2009, found 356.2016.
6-Methyl-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3j). This product was obtained as a yellow solid (0.0498 g, 68%): mp 128-131°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.23 (s, 1H), 7.86 (d, \(J = 8.3\) Hz, 1H), 7.62-7.52 (m, 2H), 7.52-7.45 (m, 2H), 7.43 (ddd, \(J = 7.2, 3.6, 1.3\) Hz, 1H), 7.36 (d, \(J = 8.2\) Hz, 1H), 7.30-7.10 (m, 1H), 6.96 (td, \(J = 8.0, 1.2\) Hz, 1H), 6.68 (d, \(J = 7.6\) Hz, 1H), 6.44 (s, 1H), 6.18 (s, 1H), 4.25 (d, \(J = 8.7\) Hz, 1H), 3.87 (d, \(J = 8.4\) Hz, 1H), 3.72-3.59 (m, 2H), 2.33 (s, 3H), 0.96 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 159.7, 151.1, 148.7, 142.5, 139.3, 138.1, 134.1, 130.5, 129.9, 128.9, 128.6, 128.4, 126.2, 125.3, 123.9, 123.7, 120.5, 109.8, 83.6, 47.9, 36.5, 23.8, 22.7 (one carbon missing due to overlap); IR (neat) 1662, 1569, 1478, 1454, 1371, 1331, 749, 702 cm\(^{-1}\); HRMS calcd for C\(_{26}\)H\(_{24}\)NO [M+H]\(^+\): 366.1852, found 366.1860.

6-Fluoro-4-((3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3k). This product was obtained as a yellow solid (0.0487 g, 66%): mp 146-148 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.19 (s, 1H), 7.94 (dd, \(J = 8.9, 5.8\) Hz, 1H), 7.53 (d, \(J = 7.1\) Hz, 2H), 7.47 (t, \(J = 7.3\) Hz, 2H), 7.43 - 7.37 (m, 1H), 7.26 (dt, \(J = 8.6, 2.2\) Hz, 1H), 7.09 (d, \(J = 6.3\) Hz, 1H), 6.99 (td, \(J = 8.0, 1.2\) Hz, 1H), 6.67 (d, \(J = 7.4\) Hz, 1H), 6.49 (s, 1H), 6.25 (s, 1H), 4.21 (d, \(J = 8.7\) Hz, 1H), 3.85 (d, \(J = 8.6\) Hz, 1H), 3.60 (s, 2H), 0.98 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 163.8(d, \(J = 253.5\) Hz), 159.6, 153.6, 149.7, 140.6, 139.3(d, \(J = 10.1\) Hz), 134.0, 131.2(d, \(J = 10.1\) Hz), 130.3, 128.8, 128.7, 128.4, 125.4(d, \(J = 5.1\) Hz), 124.3, 123.5, 120.5, 117.7(d, \(J = 26.3\) Hz), 110.0, 108.6(d, \(J = 23.3\) Hz), 83.3, 47.9, 36.8, 23.8; IR (neat) 1669, 1580,
4-((3-Methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenyl-6-(trifluoromethyl)isoquinoline (3l). This product was obtained as a yellow solid (0.0441 g, 53%): mp 136-138 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.28 (s, 1H), 8.01 (d, \(J = 8.5\) Hz, 1H), 7.77 – 7.53 (m, 4H), 7.49 (t, \(J = 7.4\) Hz, 2H), 7.45 – 7.38 (m, 1H), 6.93 (td, \(J = 8.0, 1.2\) Hz, 1H), 6.62 (s, 1H), 6.52-5.75 (m, 2H), 4.26 (d, \(J = 8.7\) Hz, 1H), 3.88 (d, \(J = 8.1\) Hz, 1H), 3.70 (q, \(J = 13.9\) Hz, 2H), 1.00 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 159.6, 155.6, 150.6, 141.7, 136.3, 133.4, 131.2 (q, \(J = 32.3\) Hz), 130.4, 129.0, 128.8, 128.2, 127.9, 125.8, 125.3, 123.7, 122.5, 122.3 (q, \(J = 3.0\) Hz), 122.2 (q, \(J = 4.5\) Hz), 120.4, 110.1, 48.0, 36.8, 23.8 (one carbon missing due to overlap); IR (neat) 1592, 1384, 1351, 764 cm\(^{-1}\); HRMS calcd for C\(_{26}\)H\(_{21}\)F\(_3\)NO [M+H]\(^+\): 420.1570, found 420.1579.

4-((3-Methyl-2,3-dihydrobenzofuran-3-yl)methyl)-7-nitro-3-phenylisoquinoline (3m). This product was obtained as a yellow solid (0.0413 g, 53%): mp 161-163 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.37 (s, 1H), 8.82 (d, \(J = 2.2\) Hz, 1H), 8.01 (s, 1H), 7.65 – 7.37 (m, 6H), 7.01 – 6.93 (m, 1H), 6.62 (s, 1H), 6.55-5.55 (m, 2H), 4.24 (d, \(J = 8.7\) Hz, 1H), 3.87 (d, \(J = 6.8\) Hz, 1H), 3.80-3.52 (m, 2H), 0.99 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 159.7, 157.2, 151.9, 145.5, 140.6, 139.9, 133.5, 130.3, 128.9, 128.8, 128.7, 126.4, 125.8, 124.5, 123.7, 122.6, 120.6, 110.1, 83.5, 48.0, 36.8, 23.5 (one carbon
8-((3-Methyl-2,3-dihydrobenzofuran-3-yl)methyl)-7-phenyl-[1,3]dioxolo[4,5-g]isoquinoline (3n). This product was obtained as a yellow solid (0.0540 g, 68%): mp 220-221°C; 1H NMR (400 MHz, CDCl$_3$) δ 8.94 (s, 1H), 7.48 (d, $J$ = 7.1 Hz, 2H), 7.43 (t, $J$ = 7.3 Hz, 2H), 7.40 – 7.34 (m, 1H), 7.13 (s, 1H), 7.06 – 6.97 (m, 1H), 6.86 (s, 1H), 6.68 (d, $J$ = 7.9 Hz, 1H), 6.56 (s, 1H), 6.33 (s, 1H), 6.02 (d, $J$ = 3.5 Hz, 2H), 4.18 (d, $J$ = 8.7 Hz, 1H), 3.82 (d, $J$ = 8.6 Hz, 1H), 3.66-3.40 (m, 2H), 0.95 (s, 3H); 13C NMR (101 MHz, CDCl$_3$) δ 159.5, 152.8, 151.5, 148.0, 141.4, 136.0, 134.6, 130.3, 128.6, 128.4, 127.9, 124.9, 124.8, 123.5, 120.5, 109.9, 103.3, 101.9, 101.1, 83.2, 47.9, 37.0, 24.1 (one carbon missing due to overlap); IR (neat) 1650, 1528, 1457, 1371, 1325, 1039, 793 cm$^{-1}$; HRMS calcd for C$_{25}$H$_{21}$N$_2$O$_3$ [M+H]$^+$: 397.1547, found 397.1555.

4-((6-Methoxy-3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3o). This product was obtained as a yellow oil (0.0463 g, 61%). 1H NMR (400 MHz, CDCl$_3$) δ 9.24 (s, 1H), 8.02 – 7.92 (m, 1H), 7.63 (s, 1H), 7.57 – 7.48 (m, 4H), 7.45 (t, $J$ = 7.3 Hz, 2H), 7.39 (t, $J$ = 7.2 Hz, 1H), 6.23 (s, 1H), 6.17-5.83 (m, 2H), 4.21 (d, $J$ = 8.7 Hz, 1H), 3.84 (d, $J$ = 8.4 Hz, 1H), 3.79 – 3.55 (m, 5H), 0.94 (s, 3H); 13C NMR (101 MHz, CDCl$_3$) δ 160.8, 160.7, 152.8, 150.0, 140.7, 137.5, 130.6, 130.4, 128.7, 128.3, 128.1, 127.1, 127.0, 126.5, 125.9, 124.5, 123.6, 106.2, 96.5, 55.7, 47.5, 36.5, 24.3 (one carbon missing due to overlap); IR (neat) 1655, 1621, 1562, 1527, 1480, 1342, 749, 700 cm$^{-1}$; HRMS calcd for C$_{26}$H$_{22}$NO$_3$ [M+H]$^+$: 396.1594, found 396.1601.
missing due to overlap); IR (neat) 1593, 1495, 1385, 1349, 765 cm\(^{-1}\); HRMS calcd for C\(_{26}\)H\(_{24}\)NO\(_2\) [M+H]\(^+\): 382.1802, found 382.1811.

\[
\text{IR (neat) 1597, 1470, 1359, 1086, 762, 703 cm}^{-1}\; ; \text{HRMS calcd for C}_{25}\text{H}_{22}\text{ClNO} [\text{M+H}]^+ : 386.1306, \text{found 386.1318.}
\]

4-((5-Chloro-3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3p). This product was obtained as a yellow solid (0.0403 g, 52%): mp 155-157 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.25 (s, 1H), 8.00 – 7.93 (m, 1H), 7.80-7.53 (m, 3H), 7.53-7.49 (m, 2H), 7.49 – 7.43 (m, 2H), 7.43 – 7.36 (m, 1H), 6.92 (dd, \(J = 8.5, 2.3\) Hz, 1H), 6.54 (d, \(J = 8.4\) Hz, 1H), 6.16 (s, 1H), 4.22 (d, \(J = 8.8\) Hz, 1H), 3.85 (d, \(J = 8.6\) Hz, 1H), 3.75-3.54 (m, 2H), 0.98 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 158.2, 153.1, 150.3, 140.6, 137.3, 136.3, 130.7, 130.4, 128.8, 128.5, 128.3, 127.24, 127.18, 125.5, 125.1, 124.1, 110.8, 83.6, 48.2, 36.3, 24.2 (two carbon missing due to overlap); IR (neat) 1597, 1470, 1359, 1086, 762, 703 cm\(^{-1}\); HRMS calcd for C\(_{25}\)H\(_{21}\)ClNO [M+H]\(^+\): 386.1306, found 386.1318.

\[
\text{IR (neat) 1593, 1495, 1385, 1349, 765 cm}^{-1}\; ; \text{HRMS calcd for C}_{26}\text{H}_{24}\text{NO} [\text{M+H}]^+ : 382.1802, \text{found 382.1811.}
\]

4-((5-Fluoro-3-methyl-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3q). This product was obtained as a yellow solid (0.0480 g, 65%): mp 115-117 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.21 (s, 1H), 7.95 (dd, \(J = 5.2, 4.2\) Hz, 1H), 7.63 (d, \(J = 5.5\) Hz, 1H), 7.56 – 7.47 (m, 4H), 7.47 – 7.41 (m, 2H), 7.41 – 7.35 (m, 1H), 6.66 (td, \(J = 8.8, 2.7\) Hz, 1H), 6.54 (dd, \(J = 8.6, 4.1\) Hz, 1H), 5.96 (dd, \(J = 8.6, 3.9\) Hz, 1H), 4.21 (d, \(J = 8.8\) Hz, 1H), 3.84 (d, \(J = 8.7\) Hz, 1H), 3.78-3.55 (m, 2H), 0.97 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 157.7(d, \(J = 238.4\) Hz), 155.3(d, \(J = 1.0\) Hz), 154.0, 150.8, 141.6, 137.1, 136.1, 130.3, 130.2, 128.6, 128.3, 127.9, 127.3, 126.8, 124.5,
124.0, 114.4 (d, $J = 24.2$ Hz), 110.9(d, $J = 25.3$ Hz), 110.0(d, $J = 8.0$ Hz), 83.6, 48.2 (d, $J = 2$ Hz), 36.1, 24.2; IR (neat) 1591, 1385, 1350, 767 cm$^{-1}$; HRMS calcd for C$_{25}$H$_{21}$FNO $[M+H]^+$: 370.1602, found 370.1610.

**Methyl 3-methyl-3-((3-phenylisoquinolin-4-yl)methyl)-2,3-dihydrobenzofuran-6-carboxylate (3r).** This product was obtained as a yellow oil (0.0464 g, 57%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.27 (s, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.63 (s, 1H), 7.58 – 7.34 (m, 7H), 7.28 – 7.09 (m, 1H), 6.60-5.10 (m, 2H), 4.24 (d, $J = 8.9$ Hz, 1H), 3.92 – 3.78 (m, 4H), 3.78-3.61 (m, 2H), 0.99 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.9, 159.6, 152.3, 150.0, 139.9, 139.8, 137.4, 131.1, 130.7, 130.3, 128.8, 128.7, 128.4, 127.4, 127.1, 125.5, 124.2, 123.3, 122.7, 110.8, 83.5, 52.3, 48.0, 36.1, 24.1; IR (neat) 1718, 1591, 1384, 1350, 766, 704 cm$^{-1}$; HRMS calcd for C$_{27}$H$_{24}$NO$_3$ $[M+H]^+$: 410.1751, found 410.1762.

**4-((3-(Methoxymethyl)-2,3-dihydrobenzofuran-3-yl)methyl)-3-phenylisoquinoline (3s).** This product was obtained as a yellow oil (0.0402 g, 53%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.16 (s, 1H), 8.12 – 7.83 (m, 2H), 7.64 – 7.45 (m, 3H), 7.45-7.25 (m, 5H), 6.96 (t, $J = 7.6$ Hz, 1H), 6.56 (d, $J = 7.9$ Hz, 1H), 6.42 (s, 1H), 5.97 (d, $J = 6.9$ Hz, 1H), 4.19 (d, $J = 9.1$ Hz, 1H), 4.12 (d, $J = 9.1$ Hz, 1H), 3.94 (d, $J = 15.8$ Hz, 1H), 3.75 (d, $J = 14.2$ Hz, 1H), 3.27 (d, $J = 9.0$ Hz, 1H), 3.21 – 2.99 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 160.0, 150.8, 141.7, 137.3, 130.2, 130.1, 129.9, 128.7, 128.4, 128.0, 127.5, 127.2, 126.7, 124.7, 124.2, 120.3, 109.7, 80.5, 76.7, 59.0, 52.1, 31.5(two carbon missing...
due to overlap); IR (neat) 1633, 1567, 1389, 1355, 770 cm\(^{-1}\); HRMS calcd for C\(_{26}\)H\(_{24}\)NO\(_2\) [M+H]\(^+\): 382.1802, found 382.1815.

\[
\text{IR (neat) 1594, 1353, 765 cm}^{-1}; \text{HRMS calcd for C}_{27}\text{H}_{25}\text{N}_2\text{O} [\text{M+H}]^+: 393.1961, \text{found 393.1964.}
\]

1-(3-Methyl-3-((3-phenylisoquinolin-4-yl)methyl)indolin-1-yl)ethan-1-one (3t). This product was obtained as a yellow solid (0.0550 g, 70%): mp 135-137 °C; \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.19 (s, 1H), 8.03 (d, \(J = 8.0\) Hz, 1H), 7.94 (d, \(J = 7.4\) Hz, 1H), 7.61 (d, \(J = 7.3\) Hz, 1H), 7.53 (t, \(J = 6.6\) Hz, 2H), 7.50-7.42 (m, 3H), 7.42 – 7.36 (m, 1H), 7.32 (s, 1H), 7.09 (dd, \(J = 18.6, 10.9\) Hz, 1H), 6.75 (s, 1H), 6.67-6.28 (m, 1H), 3.80 – 3.46 (m, 3H), 3.30 (d, \(J = 10.6\) Hz, 1H), 1.89 (s, 3H), 0.99 (s, 3H); \(^{13}\text{C}\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.7, 154.1, 151.0, 142.1, 142.0, 138.8, 137.1, 130.4, 130.3, 130.1, 128.7, 128.3, 128.2, 127.9, 127.3, 126.8, 124.4, 123.9, 122.8, 117.1, 61.3, 46.1, 37.4, 25.4, 24.1; IR (neat) 1594, 1353, 765 cm\(^{-1}\); HRMS calcd for C\(_{27}\)H\(_{25}\)N\(_2\)O [M+H]\(^+\): 393.1961, found 393.1964.

4-((4-Methylisochroman-4-yl)methyl)-3-phenylisoquinoline (3u). This product was obtained as a yellow solid (0.0310 g, 42%): mp 206-209 °C; \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.21 (s, 1H), 8.54 – 7.29 (m, 9H), 7.18-6.74 (m, 3H), 6.39 (dd, \(J = 19.4, 7.7\) Hz, 1H), 4.70 (broad, 2H), 3.98 (d, \(J = 14.1\) Hz, 1H), 3.67-3.61 (m, 2H), 3.23 (s, 1H), 0.76 (s, 3H); \(^{13}\text{C}\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 153.7, 150.0, 141.4, 137.6, 133.8, 130.5, 130.4, 128.5, 128.1, 127.8, 127.3, 126.9, 126.4, 126.2, 125.1, 124.1, 69.0, 39.7, 36.4, 22.6 (four carbon missing due to overlap); IR (neat) 1582, 1386, 1352, 1096, 763,701 cm\(^{-1}\); HRMS
calcd for C_{26}H_{24}NO [M+H]^+: 366.1852, found 366.1863.

4-((4-Methylchroman-4-yl)methyl)-3-phenylisoquinoline (3v). This product was obtained as a yellow solid (0.0904 g, 82%): mp 152-153 °C; ^{1}H NMR (400 MHz, CDCl_{3}) δ 9.22 (s, 1H), 8.11-7.89 (m, 2H), 7.69-7.53 (m, 2H), 7.53 – 7.25 (m, 5H), 6.98 (t, J = 8.3 Hz, 1H), 6.76 – 6.37 (m, 3H), 3.85-3.74 (m, 2H), 3.64 (s, 1H), 3.45 (td, J = 11.4, 1.8 Hz, 1H), 1.72 (d, J = 14.1 Hz, 1H), 1.67 – 1.48 (m, 1H), 0.97 (s, 3H); ^{13}C NMR (101 MHz, CDCl_{3}) δ 153.9, 150.2, 141.4, 137.6, 130.3, 129.5, 128.7, 128.4, 128.0, 127.6, 127.4, 126.9, 125.9, 124.9, 120.1, 117.2, 62.2, 38.2, 37.1, 36.0, 29.2(three carbon missing due to overlap); IR (neat) 1641, 1564, 1396, 1367, 1221, 751 cm^{-1}; HRMS calcd for C_{26}H_{24}NO [M+H]^+: 366.1852, found 366.1859.

4-Methyl-1-(methylsulfonyl)-4-((3-phenylisoquinolin-4-yl)methyl)-1,2,3,4-tetrahydroquinoline (3w). This product was obtained as a yellow oil (0.0709 g, 80%). ^{1}H NMR (400 MHz, CDCl_{3}) δ 9.17 (s, 1H), 8.03-7.87 (m, 2H), 7.64-7.48 (m, 3H), 7.46 – 7.27 (m, 5H), 7.06 (t, J = 7.7 Hz, 1H), 6.87 (d, J = 6.3 Hz, 2H), 3.75 (d, J = 14.0 Hz, 1H), 3.68 – 3.41 (m, 2H), 3.07 (t, J = 10.9 Hz, 1H), 2.54 (s, 3H), 1.78 – 1.63 (m, 1H), 1.45 – 1.31 (m, 1H), 0.99 (s, 3H); ^{13}C NMR (101 MHz, CDCl_{3}) δ 154.5, 150.6, 142.0, 137.1, 136.0, 135.8, 130.2, 130.0, 128.5, 128.4, 128.1, 127.7, 127.3, 126.9, 126.7, 124.8, 124.6, 124.4, 122.4, 42.3, 39.2, 38.91, 38.1, 35.0, 30.1; IR (neat) 1650, 1575, 1489, 1446, 1340, 1156, 963, 767 cm^{-1}; HRMS calcd for C_{27}H_{27}N_{2}O_{2}S [M+H]^+: 443.1788, found
2-Benzyl-4-methyl-4-((3-phenylisoquinolin-4-yl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (3x). This product was obtained as a yellow oil (0.0882 g, 83 %). $^1$H NMR (400 MHz, CDCl$_3$) δ 9.32 (s, 1H), 8.10 (s, 1H), 7.96 (s, 1H), 7.71 – 7.26 (m, 12H), 7.22-7.15 (m, 1H), 7.11-6.69 (m, 2H), 6.06 (s, 1H), 4.88 (d, $J$ = 13.7 Hz, 1H), 4.54 (d, $J$ = 14.2 Hz, 1H), 3.69 (s, 1H), 3.39 (d, $J$ = 12.4 Hz, 1H), 3.20 (d, $J$ = 14.3 Hz, 1H), 2.94 (d, $J$ = 12.2 Hz, 1H), 0.77 (s, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.1, 148.2, 143.0, 138.3, 137.0, 132.4, 131.7, 130.5, 129.3, 129.1, 128.9, 128.7, 128.2, 128.1, 127.5, 126.4, 125.4, 124.4, 57.9, 50.6, 39.9, 35.4, 22.5 (six carbon missing); IR (neat) 1646, 1593, 1384, 1351, 762, 701 cm$^{-1}$; HRMS calcd for C$_{33}$H$_{30}$N$_2$O [M+H]$^+$: 469.2274, found 469.2280.

**Procedure for Palladium catalyzed domino Heck / annulation of 2-alkynyl aldehyde with tert-butylamine:**

A solution of 1a (0.0822 g, 0.3 mmol), 2-(phenylethynyl)benzaldehyde (5, 0.0928 g, 0.45 mmol, 1.5 equiv) and tert-butyl amine (0.0494 g, 0.68 mmol, 2.25 equiv) in DMF (5 mL) was stirred under argon at room temperature for 30 min, before Pd(PPh$_3$)$_4$ (0.0173 g, 0.015 mmol, 0.05 equiv) and oven-dried K$_2$CO$_3$ (0.1244 g, 0.9 mmol, 3.0 equiv) were added. The resulting reaction mixture was heated at 100 °C under argon for 7h. The reaction was monitored by TLC to establish completion. After cooling to room temperature, the reaction was diluted with ethyl acetate (35mL), washed with water (3×15mL) and brine (15mL), dried (MgSO$_4$) and concentrated. The residue was purified by column chromatography (Silica Gel, petroleum ether / EtOAc) to afford product 3a (0.0295 g, 28%).

**References**


Single Crystallographic Data of 3a

Table 1. Crystal data and structure refinement for 3a.

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<th>Identification code</th>
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Absorption coefficient: 0.076 mm\(^{-1}\)
F(000): 372
Crystal size: 0.221 \(\times\) 0.207 \(\times\) 0.113 mm\(^3\)
Theta range for data collection: 3.101 to 27.604\(^\circ\).
Index ranges: -9 \(\leq h \leq\) 9, -17 \(\leq k \leq\) 17, -12 \(\leq l \leq\) 13
Reflections collected: 14464
Independent reflections: 4285 \([R(int) = 0.0657]\)
Completeness to theta = 25.242\(^\circ\): 99.8 \%
Absorption correction: Semi-empirical from equivalents
Max. and min. transmission: 0.991 and 0.983
Refinement method: Full-matrix least-squares on \(F^2\)
Data / restraints / parameters: 4285 / 1 / 245
Goodness-of-fit on \(F^2\): 1.072
Final R indices \([I>2\sigma(I)]\): R1 = 0.0618, \(wR^2 = 0.1104\)
R indices (all data): R1 = 0.1326, \(wR^2 = 0.1316\)
Absolute structure parameter: 0.9\(\pm\)10
Extinction coefficient: n/a
Largest diff. peak and hole: 0.210 and -0.172 e.\(\text{Å}^{-3}\)