Supplementary Material (ESI) for Chemical Communications

Supporting Information

A versatile synthesis of diverse 3,4-fused cinnolines *via* the base-catalysed condensation of 2-amino-2'-nitrobiaryls

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Analysis

Proton and carbon NMR spectra were recorded on either a JEOL Eclipse 270 spectrometer or a Bruker Advance DPX 400 spectrometer. HRMS were recorded using an Agilent MSD-TOF (G1969A) connected to an Agilent 1100 HPLC system.

General method for Suzuki-coupling of 2-bromonitrobenzenes with 2-aminophenylboronic acid.

To a solution of the bromonitrobenzene (2 mmol), 2-aminophenylboronic acid (HCl salt) (350mg, 2 mmol) and tetrakis(triphenylphosphine)palladium(0) (116 mg) in toluene (10 ml) was added 2M aqueous sodium carbonate (4 ml), and ethanol (4 ml). The mixture was refluxed overnight, then concentrated by evaporation and extracted with ethyl acetate (3 x 25 ml) the extract was dried ($MgSO_4$), filtered then evaporated to give the crude product which was flash-chromatographed over silica to afford the product.

General method for tandem borylation-Suzuki-coupling of 2-bromoanilines with 2-bromonitrobenzenes.

A solution of the 2-bromoaniline (2 mmol), palladium(II) acetate (5 mol %), 2-(dicyclohexylphosphino)biphenyl (20 mol %) and triethylamine (4 equiv.) in dioxane was treated dropwise with pinacolborane (3 equiv.). The mixture was heated at 80º C for 1h. then water (800 µl), barium hydroxide octahydrate (3 equiv.) and the bromonitrobenzene derivative (2 mmol) dissolved in dioxane (4 ml) were added. Heating was continued at 100º C for 1h. The mixture was diluted with ethyl acetate and filtered through Celite. The organic layer was then extracted with 2M aqueous hydrochloric acid (3 x 5 ml). The aqueous phases were combined and basified with 2M aqueous sodium hydroxide then extracted with ethyl acetate (3 x 20 ml), the combined organic extracts were dried ($MgSO_4$), filtered then evaporated to give the product

General method for cyclisation of 2-amino-2'-nitrobiaryls using methanolic sodium hydroxide

A solution of the 2-amino-2'-nitrobiaryl (0.03 mmol) in 1N methanolic sodium hydroxide (10 ml) was heated at 70^0 C for 2h. The mixture was evaporated, and the residue partitioned between ethyl acetate and 2M aqueous hydrochloric acid. The extract was dried (Na_2SO_4), filtered and evaporated to afford the product.

General method for cyclisation of 2-amino-2'-nitrobiaryls using potassium *t*-butoxide in THF

To a solution of the 2-amino-2'-nitrobiaryl (0.14 mmol) in tetrahydrofuran (2 ml) was added a 1M solution of potassium *t*-butoxide in tetrahydrofuran (2.5 equiv.). The mixture was stirred at room temperature for 2 minutes and the solvent was removed by evaporation. The residue was partitioned between water (10 ml) and chloroform (3 x 10 ml). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated to give the product.

General method for deoxygenation of cinnoline-*N*-oxides using indium dust

A solution of the cinnoline *N*-oxide (0.14 mmol) in ethanol (20 ml) was treated with indium powder (1.2 equiv.) and a saturated solution of aqueous ammonium chloride (4 ml). The mixture was heated at 80º C for 1h. The residue was filtered through Celite and extracted with ethyl acetate. The organic layer was washed with water (2 x 2 ml) then dried with Na_2SO_4, filtered and evaporated to afford the product.

4'-Methoxy-2'-nitrobiphenyl-2-amine (7a)

^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 3.90 (s, 3 H) 6.71 - 6.83 (m, 2 H) 6.96 (dd, *J*=7.4, 1.5 Hz, 1 H) 7.13 - 7.22 (m, 2 H) 7.34 (d, *J*=8.7 Hz, 1 H) 7.47 (d, *J*=2.7 Hz, 1 H)
^{13}C NMR (68 MHz, DMSO-D6) δ ppm 56.52, 109.75, 115.46, 116.93, 119.91, 122.39, 126.00, 129.22, 129.72, 134.12, 146.29, 150.42, 159.28.
HRMS (ESI$^+$): Calcd for $C_{13}H_{12}N_2O_3$: 244.0848, found 244.0847.

2'-Nitro-4'-(trifluoromethyl)biphenyl-2-amine (7b)

^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 6.92 - 7.08 (m, 3 H) 7.27 - 7.35 (m, 1 H) 7.62 (d, *J*=8.2 Hz, 1 H) 7.88 (dd, *J*=7.9, 1.2 Hz, 1 H) 8.25 (s, 1 H)
HRMS (ESI$^+$): Calcd for $C_{13}H_9F_3N_2O_2$: 282.0616, found 282.0615.

4'-Methyl-2'-nitrobiphenyl-2-amine (7c)

^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 2.47 (s, 3 H) 6.74 - 6.84 (m, 2 H) 6.96 (dd, *J*=7.6, 1.6 Hz, 1 H) 7.18 (ddd, *J*=7.7, 1.7 Hz, 1 H) 7.28 - 7.36 (m, 1 H) 7.42 - 7.49 (m, 1 H) 7.76 (s, 1 H)
^{13}C NMR (68 MHz, DMSO-D6) δ ppm 20.90, 115.54, 116.94, 122.57, 124.90, 129.27, 129.51, 131.19, 132.99, 134.48, 139.21, 146.10, 149.63.
HRMS (ESI$^+$): Calcd for $C_{13}H_{12}N_2O_2$: 228.0899, found 228.0907.

2'-Nitro-4',5'-bis(trifluoromethyl)biphenyl-2-amine (7d)

^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 6.84 - 7.04 (m, 3 H) 7.26 - 7.35 (m, 1 H) 8.00 (s, 1 H) 8.40 (s, 1 H).
MS (ESI$^+$): 351 $(M+H)^+$

2'-Methyl-6'-nitrobiphenyl-2-amine (7e)

^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 2.13 (s, 3 H) 6.82 - 6.92 (m, 3 H) 7.16 - 7.24 (m, 1 H) 7.34 - 7.44 (m, 1 H) 7.46 - 7.54 (m, 1 H) 7.67 - 7.74 (m, 1 H)
^{13}C NMR (68 MHz, CHLOROFORM-D) δ ppm 20.10, 116.27, 119.60, 121.39, 122.50, 128.49, 128.83, 129.49, 132.10, 134.15, 140.81, 143.18, 151.01
HRMS (ESI$^+$): Calcd for $C_{13}H_{12}N_2O_2$: 228.0899, found 228.0896.

3'-Methyl-2'-nitrobiphenyl-2-amine (7f) AE1224005

^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 6.75 - 6.82 (m, 2 H) 7.02 (dd, *J*=7.5, 1.5 Hz, 1 H) 7.20 (td, *J*=7.8, 1.5 Hz, 1 H) 7.29 - 7.37 (m, 2 H) 7.44 - 7.49 (m, 1 H)
HRMS (ESI$^+$): Calcd for $C_{13}H_{12}N_2O_2$: 228.0899, found 228.0897.

3-Methoxybenzo[c]cinnoline 5-oxide (8a)

^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 4.03 (s, 3 H) 7.55 (dd, *J*=9.2, 2.7 Hz, 1 H) 7.65 - 7.74 (m, 2 H) 7.97 - 8.02 (m, 1 H) 8.23 (d, *J*=2.7 Hz, 1 H) 8.27 - 8.33 (m, 1 H) 8.41 (d, *J*=9.2 Hz, 1 H).
HRMS (ESI$^+$): Calcd for $C_{13}H_{10}N_2O_2$: 226.0742, found 226.0735.

3-(Trifluoromethyl)benzo[c]cinnoline 5-oxide (8b)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 7.73 – 7.88 (m, 2 H) 8.02 - 8.18 (m, 2 H) 8.41 (dd, *J*=8.0, 1.1 Hz, 1 H) 8.65 (d, *J*=8.7 Hz, 1 H) 9.17 (s, 1 H)
HRMS (ESI^{+}): Calcd for $C_{13}H_7F_3N_2O$: 264.0510, found 264.0505.

3-Methylbenzo[c]cinnoline 5-oxide (8c)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 2.63 (s, 3 H) 7.64 - 7.79 (m, 3 H) 7.97 - 8.02 (m, 1 H) 8.31 - 8.37 (m, 1 H) 8.39 (d, *J*=8.4 Hz, 1 H) 8.66 (s, 1 H)
HRMS (ESI^{+}): Calcd for $C_{13}H_{10}N_2O$: 210.0793, found 210.0799.

2,3-bis(Trifluoromethyl)benzo[c]cinnoline 5-oxide (8d)
HRMS (ESI^{+}): Calcd for $C_{14}H_6F_6N_2O$: 332.0384, found 332.0386
LCMS purity 100%, MS (ESI^{+}): 333 $(M+H)^{+}$.

1-Methylbenzo[c]cinnoline 5-oxide (8e)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 3.07 (s, 3 H) 7.61 - 7.78 (m, 4 H) 8.00 (dd, *J*=7.8, 1.1 Hz, 1 H) 8.61 (d, *J*=8.2 Hz, 1 H) 8.82 (d, *J*=7.7 Hz, 1 H)
^{13}C NMR (68 MHz, CHLOROFORM-D) δ ppm 26.07, 119.85, 120.96, 125.56, 127.13, 127.98, 128.58, 129.37, 129.75, 136.29, 136.47, 138.67, 142.81.
HRMS (ESI^{+}): Calcd for $C_{13}H_{10}N_2O$: 210.0793, found 210.0784.

4-Methylbenzo[c]cinnoline 5-oxide (8f)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 3.13 (s, 3 H) 7.50 - 7.79 (m, 4 H) 7.88 (d, *J*=8.2 Hz, 1 H) 8.28 (d, *J*=7.9 Hz, 1 H) 8.33 (d, *J*=8.2 Hz, 1 H)
^{13}C NMR (68 MHz, CHLOROFORM-D) δ ppm 25.54, 118.68, 120.69, 121.63, 125.77, 128.52, 130.50, 131.86, 133.87, 135.92, 136.08, 137.48, 142.41.
HRMS (ESI^{+}): Calcd for $C_{13}H_{10}N_2O$: 210.0793, found 210.0799.

3-Methoxybenzo[c]cinnoline (9a)
^{1}H NMR (270 MHz, DMSO-D6) δ ppm 3.94 (s, 3 H) 7.57 (dd, *J*=9.2, 2.7 Hz, 1 H) 7.78 - 7.95 (m, 2 H) 8.00 (d, *J*=2.5 Hz, 1 H) 8.53 (dd, *J*=8.0, 1.4 Hz, 1 H) 8.69 - 8.76 (m, 2 H)
^{13}C NMR (68 MHz, DMSO-D6) δ ppm 56.47, 109.86, 115.17, 121.15, 122.63, 124.13, 124.54, 129.31, 130.94, 132.72, 145.07, 147.06, 160.67.
HRMS (ESI^{+}): Calcd for $C_{13}H_{10}N_2O$: 210.0793, found 210.0785.

3-(Trifluoromethyl)benzo[c]cinnoline (9b)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 7.99 - 8.08 (m, 2 H) 8.13 (dd, *J*=8.7, 1.7 Hz, 1 H) 8.62 - 8.68 (m, 1 H) 8.74 (d, *J*=8.7 Hz, 1 H) 8.84 - 8.90 (m, 1 H) 9.08 (s, 1 H)
HRMS (ESI^{+}): Calcd for $C_{13}H_7F_3N_2$: 248.0561, found 248.0563.

3-Methylbenzo[c]cinnoline (9c)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 2.67 (s, 3 H) 7.72 (dd, *J*=8.4, 1.5 Hz, 1 H) 7.80 - 7.93 (m, 2 H) 8.45 (d, *J*=8.4 Hz, 1 H) 8.49 - 8.56 (m, 2 H) 8.67 - 8.75 (m, 1 H)
HRMS (ESI^{+}): Calcd for $C_{13}H_{10}N_2$:194.0844, found 194.0847.

2,3-bis(Trifluoromethyl)benzo[c]cinnoline (9d)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 8.03 - 8.16 (m, 2 H) 8.62 - 8.72 (m, 1 H) 8.84 - 8.93 (m, 1 H) 9.08 (s, 1 H) 9.28 (s, 1 H).
HRMS (ESI^{+}): Calcd for $C_{14}H_6F_6N_2$: 316.0435, found 316.0437.

1-Methylbenzo[c]cinnoline (9e)
^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 3.14 (s, 3 H) 7.86 - 7.91 (m, 2 H) 7.97 - 8.10 (m, 2 H) 8.77 - 8.82 (m, 1 H) 8.90 (d, *J*=8.3 Hz, 1 H) 8.94 (d, *J*=8.5 Hz, 1 H)
HRMS (ESI$^+$): Calcd for $C_{13}H_{10}N_2$: 194.0844, found 194.0849.

4-Methylbenzo[c]cinnoline 5-oxide (9f)
^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 3.11 (s, 3 H) 7.62 - 7.68 (m, 1 H) 7.70 - 7.76 (m, 1 H) 7.80 - 7.86 (m, 2 H) 8.37 (d, *J*=8.0 Hz, 1 H) 8.52 (dd, *J*=6.3, 3.3 Hz, 1 H) 8.68 (dd, *J*=6.5, 3.0 Hz, 1 H).
HRMS (ESI$^+$): Calcd for $C_{13}H_{10}N_2$: 194.0844, found 194.0841.

2-(3-Nitro-2-thienyl)aniline (13)
^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 6.80 - 6.87 (m, 2 H) 7.15 (dd, *J*=7.8, 1.5 Hz, 1 H) 7.26 - 7.32 (m, 1 H) 7.37 (d, *J*=5.5 Hz, 1 H) 7.72 (d, *J*=5.8 Hz, 1 H)
HRMS (ESI$^+$): Calcd for $C_{10}H_8N_2O_2S$: 220.0307, found 220.0312.

2-(3-Nitropyridin-2-yl)aniline (14)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 6.73 - 6.85 (m, 2 H) 7.05 (dd, *J*=7.7, 1.5 Hz, 1 H) 7.18 - 7.24 (m, 1 H) 7.43 (dd, *J*=8.2, 4.7 Hz, 1 H) 8.19 (dd, *J*=8.2, 1.7 Hz, 1 H) 8.83 (dd, *J*=4.7, 1.5 Hz, 1 H).
^{13}C NMR (68 MHz, DMSO-D6) δ ppm 116.59, 117.00, 121.28, 123.50, 129.66, 130.64, 133.57, 146.79, 146.86, 152.05, 153.06.
HRMS (ESI$^+$): Calcd for $C_{11}H_9N_3O_2$: 215.0694, found 215.0699.

2-(7-Nitroquinoxalin-6-yl)aniline (15)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 6.78 - 6.92 (m, 2 H) 7.10 (dd, *J*=7.6, 1.6 Hz, 1 H) 7.21 - 7.30 (m, 1 H) 8.23 (s, 1 H) 8.68 (s, 1 H) 8.99 (s, 2 H)
^{13}C NMR (68 MHz, CHLOROFORM-D) δ ppm 116.47, 119.49, 122.47, 125.97, 129.65, 130.19, 133.88, 134.71, 141.44, 143.51, 144.06, 147.12, 147.81, 150.57.
HRMS (ESI$^+$): Calcd for $C_{14}H_{10}N_4O_2$: 266.0804, found 266.0794.

Thieno[3,2-c]cinnoline 4-oxide (16)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 7.59 - 7.67 (m, 2 H) 7.69 - 7.76 (m, 1 H) 7.91 - 7.97 (m, 2 H) 8.02 (ddd, *J*=8.4, 1.3, 0.7 Hz, 1 H).
^{13}C NMR (68 MHz, CHLOROFORM-D) δ ppm 118.88, 120.82, 122.12, 126.41, 127.75, 128.99, 130.78, 140.10, 141.23, 143.18.
HRMS (ESI$^+$): Calcd for $C_{10}H_6N_2OS$: 202.0201, found 202.0199.

Pyrido[3,2-c]cinnoline 5-oxide (17)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 7.74 - 7.90 (m, 3 H) 8.03 (d, *J*=7.9 Hz, 1 H) 8.90 (dd, *J*=7.9, 1.5 Hz, 1 H) 9.07 (dd, *J*=8.7, 1.7 Hz, 1 H) 9.21 (dd, *J*=4.3, 1.6 Hz, 1 H).
HRMS (ESI$^+$): Calcd for $C_{11}H_7N_3O$: 197.0589, found 197.0583.

Quinoxalino[6,7-c]cinnoline 6-oxide (18)
^{1}H NMR (270 MHz, DMSO-D6) δ ppm 7.78 - 7.98 (m, 3 H) 8.96 (dd, *J*=7.7, 1.5 Hz, 1 H) 9.19 (dd, *J*=10.0, 1.4 Hz, 2 H) 9.24 (s, 1 H) 9.57 (s, 1 H).
HRMS (ESI$^+$): Calcd for $C_{14}H_8N_4O$: 248.0698, found 248.0686.

Pyrido[3,2-c]cinnoline (20)
^{1}H NMR (270 MHz, DMSO-D6) δ ppm 8.05 (dd, *J*=8.4, 4.21 Hz, 1 H) 8.09 - 8.20 (m, 2 H) 8.71 - 8.81 (m, 1 H) 8.98 - 9.13 (m, 2 H) 9.31 (dd, *J*=4.2, 1.3 Hz, 1 H).
HRMS (ESI$^+$): Calcd for $C_{11}H_7N_3$: 181.0640, found 181.0643.

Quinoxalino[6,7-c]cinnoline (21)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 7.99 - 8.06 (m, 2 H) 8.73 - 8.87 (m, 2 H) 9.09 (s, 2 H) 9.34 (s, 1 H) 9.60 (s, 1 H).
HRMS (ESI$^+$): Calcd for $C_{14}H_8N_4$: 232.0749, found 232.0747.

5-Isopropyl-2'-nitro-4'-(trifluoromethyl)biphenyl-2-amine (23)
^{1}H NMR (270 MHz, METHANOL-D3) δ ppm 1.18 (d, *J*=6.9 Hz, 6 H) 2.77 (sept, *J*=6.9, 1 H) 6.74 - 6.79 (m, 2 H) 7.05 (dd, *J*=8.3, 2.1 Hz, 1 H) 7.68 (d, *J*=8.2 Hz, 1 H) 8.00 (dd, *J*=8.2, 1.2 Hz, 1 H) 8.27 (d, *J*=1.2 Hz, 1 H).
HRMS (ESI$^+$): Calcd for $C_{16}H_{15}F_3N_2O_2$: 324.1086, found 324.1098.

2-Isopropyl-8-(trifluoromethyl)benzo[c]cinnoline 6-oxide (24)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 1.40 (d, *J*=6.9 Hz, 6 H) 3.18 (sept, *J*=6.9 Hz, 1 H) 7.73 (dd, *J*=8.4, 1.7 Hz, 1 H) 7.98 (d, *J*=8.4 Hz, 1 H) 8.11 (dd, *J*=8.7, 1.7 Hz, 1 H) 8.20 (d, *J*=1.5 Hz, 1 H) 8.66 (d, *J*=8.4 Hz, 1 H) 9.17 (s, 1 H).
HRMS (ESI$^+$): Calcd for $C_{16}H_{13}F_3N_2O$: 306.0980, found 306.0983.

2-Isopropyl-8-(trifluoromethyl)benzo[c]cinnoline (25)
^{1}H NMR (270 MHz, CHLOROFORM-D) δ ppm 1.45 (d, *J*=6.7 Hz, 6 H) 3.29 (sept, *J*=6.7 Hz, 1 H) 7.93 (dd, *J*=8.5, 1.6 Hz, 1 H) 8.11 (dd, *J*=8.7, 1.7 Hz, 1 H) 8.42 (d, *J*=1.5 Hz, 1 H) 8.72 - 8.82 (m, 2 H) 9.07 (s, 1 H).
HRMS (ESI$^+$): Calcd for $C_{16}H_{13}F_3N_2$: 290.1031, found 290.1024.