An Intra/Intermolecular Suzuki Sequence to Benzopyridyloxepines Containing Geometrically Pure Exocyclic Tetra-substituted Alkenes

Supporting Information

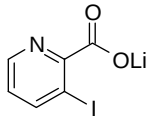
Matthew W. Carson, Matthew W. Giese, and Michael J. Coghlan

Discovery Chemistry Research and Technology
Lilly Research Laboratories
Eli Lilly and Company
Lilly Corporate Center
Indianapolis IN, 46285

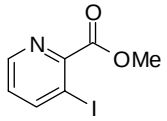
General

All reactions, unless specified, were carried out under an atmosphere in over-dried glassware. Reagents and solvents were used as purchased from Aldrich and Strem. 3-Bromo-pyridine-4-carbaldehyde **(16)**[1] and (2-Bromo-pyridin-3-yl)-methanol **(6d)**[2] were prepared according to literature procedures. LCMS analysis of the crude reaction mixtures was carried out on an Agilent® 1100 Series LC/MSD using 5-100% ACN/ 0.1% Formic Acid over 7.0min. Flash chromatography was carried out using Biotage® KP-Sil* silica cartridges. Ion exchange chromatography was carried out on Varian® Mega BondElut-SCX cartridges (10g) using 20:80 methanol:CH_2Cl_2 to wash the column and eluting with 20:80 2.0 M NH_3/methanol:CH_2Cl_2. Reverse-phase purification was carried out on a Waters X-Bridge Prep C18, OBD 19x100mm with a gradient of 5-95% acetonitrile/water(with 0.1% TFA) over 8 minutes at 20 mL/min.

Preparation of A-ring fragments (6-6d).

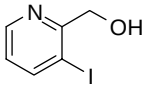


Lithium; 3-iodo-pyridine-2-carboxylate (10). A 500 mL round-bottomed flask was charged with 2,2,6,6-tetramethylpiperidine (27.81 mL, 164 mmol, 2 eq) and THF (200 mL) and cooled to – 78 ºC. Butyl lithium (2.5 M in hexanes, 98.5 mL, 246 mmol, 3 eq) was added dropwise via addition funnel to the solution and the resultant mixture was warmed to -40 ºC and stirred for 30 minutes to give a clear yellow solution. To the mixture was added 2-pyridinecarboxylic acid (10.1 g, 82 mmol, 1 eq) portion wise via solid addition funnel, maintaining the temperature below – 30 ºC. The mixture was allowed to warm to -10 ºC to give a dark red solution. The mixture was transferred via cannula to a solution of iodine (41.6 g, 164 mmol, 2 eq) in THF (275 mL) at -10 ºC. The mixture was stirred at -10 ºC for 20 min. Water (11mL) was added and the mixture was stirred an additional 10 minutes. The suspension was filtered, the solid rinsed with THF, and the residue dried in a vacuum oven overnight to give 18.9 g of lithium; 3-iodo-pyridine-2-carboxylate **(10)** as a tan powder (90%). ^{1}H NMR (500 MHz, DMSO) δ 8.37 (d, J = 4 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.00 (dd, J = 4.6, 7.9, 1H); ^{13}C NMR (500 MHz, DMSO) δ 169.8, 161.5, 147.7, 124.2, 90.6; HRMS (ESI) *m/z* calcd for $C_6H_3O_2NI$ = 247.9214, found 247.9216.

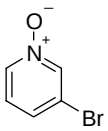


3-Iodo-pyridine-2-carboxylic acid methyl ester (11). A 500 mL round-bottomed flask was charged with methanol (185 mL) and concentrated sulfuric acid (19 mL). The mixture was cooled to 0 ºC and lithium; 3-bromo-pyridine-2-carboxylate **(10)** (18.90 g, 74.1 mmol) was added portion wise. The mixture was heated to 70 ºC for 18 h, cooled to 0 ºC, and a solution of K_2CO_3 (46.0 g) in water (225 mL) was added until a pH of 5-6 was obtained. The solids were filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate and the combined extracts were washed with water, washed with brine, dried over $MgSO_4$, and filtered over celite. Removal of the solvent under reduced pressure provided 10.80 g of 3-iodo-pyridine-2-carboxylic acid methyl ester **(11)** as a brown oil (55%) which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (dd, J = 1.5, 4.8 Hz, 1H), 8.14 (dd, J = 1.3, 7.9 Hz, 1H), 7.01 (dd, J = 4.4, 8.1, 1H), 3.87 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 165.8, 151.6, 148.4,

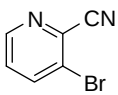
148.1, 126.4, 90.9, 53.0; HRMS (ESI) *m/z* calcd for $C_7H_7O_2NI$ $[M+H]^+$= 263.9516, found 263.9515.



(3-Iodo-pyridin-2-yl)-methanol (6). A 200 mL round-bottomed flask was charged with 3-Iodo-pyridine-2-carboxylic acid methyl ester **(11)** (10.8 g, 41.1 mmol, 1 eq) and CH_2Cl_2 (100 mL). The solution was cooled to -10 ºC and DIBALH (1.0M in CH_2Cl_2, 45.2 mL, 45.2 mmol, 1.1 eq) was added drop-wise via addition funnel over 25 minutes. The reaction was stirred at -10 ºC for 1 h and then poured into a solution of sodium potassium tartrate tetrahydrate (21.6 g) in water (180 mL). The resulting suspension was stirred overnight, the pH was adjusted to 5-6 with acetic acid, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organics were washed with water, washed with brine, dried over $MgSO_4$, and filtered over celite. Removal of the solvent provided 8.63 g of the intermediate aldehyde as a brown liquid which was dissolved in ethanol (100 mL) and cooled to -10 ºC. Sodium borohydride (588 mg, 16.4 mmol, 0.4 eq) was added portion wise and the mixture was stirred at -10 ºC for 20 minutes. The pH was adjusted to 3 by addition of 1.0N HCl and the ethanol was removed under reduced pressure. The residue was partitioned between ethyl acetate and water, the aqueous layer extracted with ethyl acetate, and the combined organics were washed with water, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. The residue was purified via flash chromatography using 20:80 ethyl acetate/hexane to give 6.05 g (3-iodo-pyridin-2-yl)-methanol **(6)** as a white solid (63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, J = 3.1 Hz, 1H), 8.07 (d, J = 7.8 Hz, 1H), 6.99 (m, 1H), 4.63 (s, 2H), 4.52 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.7, 147.0, 146.4, 123.8, 92.7, 66.5; HRMS (ESI) *m/z* calcd for $C_6H_7O_2NI$ $[M+H]^+$= 235.9567, found 235.9565.

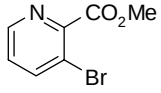


3-Bromo-pyridine 1-oxide (12). A 200 mL round-bottomed flask was charged with 3-bromopyridine (37.1 g, 235 mmol, 1 eq), CH_2Cl_2 (100 mL) and methyltrioxorhenium (234 mg, 0.9 mmol, 0.004 eq). Hydrogen peroxide (30% aqueous, 53 mL, 470 mmol, 2 eq) was added and the mixture was stirred for 18 h at room temperature. Manganese dioxide was added (90 mg) and the mixture was stirred for 1 hour. Another portion of manganese dioxide was added (60 mg) and the mixture was stirred an additional hour. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with water, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure to give 25.28 g of 3-bromo-pyridine 1-oxide **(12)** as an orange oil (62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.04 (d, J = 4 Hz, 1H), 7.29 (d, J = 8 Hz, 1H), 7.09 (t, J = 5.6 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 140.9, 138.2, 128.6, 126.0, 120.4; HRMS (ESI) *m/z* calcd for $C_5H_5ON^{79}Br$ $[M+H]^+$= 173.9549, found 173.9548.

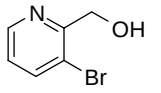


3-Bromo-pyridine-2-carbonitrile (13). A 500 mL round-bottomed flask was charged with 3-bromo-pyridine 1-oxide **(12)** (25.28 g, 145 mmol, 1 eq) and acetonitrile (160 mL). Triethylamine (40 mL) was added in a single portion followed by trimethylsilyl cyanide (58 mL, 436 mmol, 3 eq). The mixture was heated to 100 ºC for 24 h, cooled to º0, and poured into cold 5N NaOH (300 mL). The mixture was extracted with dichloromethane and the combined extracts were washed

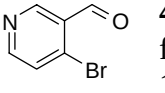
with water, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. The residue was purified via flash chromatography using 30:70 ethyl acetate/hexane to give 18.30 g 3-bromo-pyridine-2-carbonitrile **(13)** as a pale yellow solid (69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 4.2 Hz, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.42 (dd, J = 4.7, 8.1 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 149.1, 140.7, 135.2, 127.7, 124.6, 115.7; HRMS (ESI) *m/z* calcd for $C_6H_4N_2{}^{79}Br$ $[M+H]^+$= 182.9552, found 182.9552.



3-Bromo-pyridine-2-carboxylic acid methyl ester (14). A 100 mL round-bottomed flask was charged with 3-bromo-pyridine-2-carbonitrile **(13)** (18.30 g, 100 mmol, 1 eq) and concentrated HCl (60 mL). The mixture was heated to 110 ºC for 24 h, cooled to 0 ºC, and the precipitate was filtered off and dried. The precipitate was then dissolved in methanol (100 mL) and the solution was cooled to 0 ºC. Concentrated sulfuric acid (8 mL) was added drop-wise and the reaction was heated to 90 ºC for 18 h. The mixture was cooled to room temperature, the methanol removed under reduced pressure, and saturated $NaHCO_3$ was added slowly until a pH of 8-9 was obtained. The solution was extracted with ethyl acetate and the combined extracts were washed with water, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure to give 16.60 g of 3-bromo-pyridine-2-carboxylic acid methyl ester **(14)** as a pale yellow solid (77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (m, 1H), 7.99 (m, 1H), 7.28 (m, 1H), 3.99 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 165.2, 148.9, 147.7, 141.9, 126.5, 119.1, 53.0; HRMS (ESI) *m/z* calcd for $C_7H_7O_2N^{79}Br$ $[M+H]^+$= 215.9655, found 215.9653.

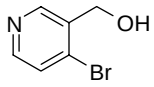


(3-Bromo-pyridin-2-yl)-methanol (6a). A 500 mL round-bottomed flask was charged with 3-Bromo-pyridine-2-carboxylic acid methyl ester **(14)** (16.60 g, 76.8 mmol, 1 eq) and methanol (190 mL) and cooled to º0 C. To the mixture was added $NaBH_4$ (14.53 g, 384 mmol, 5 eq) portionwise (3.5 g portions), warming to room temperature after each addition and cooling to 0 ºC before the subsequent addition. The mixture was stirred an additional 3 hours at room temperature after the final addition. The methanol was removed under reduced pressure and the residue was taken up in water and extracted with CH_2Cl_2. The combined extracts were washed with water, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure to give 11.93 g of (3-bromo-pyridin-2-yl)-methanol **(6a)** as a pale yellow solid (83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (br, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.13 (t, J = 6.1 Hz, 1H), 4.72 (s, 1H), 4.43 (s, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 156.5, 146.5, 140.0, 123.5, 118.8, 63.1; HRMS (ESI) *m/z* calcd for $C_6H_7ON^{79}Br$ $[M+H]^+$= 187.9706, found 187.9705.

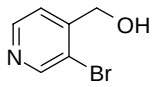


4-Bromo-pyridine-3-carbaldehyde (15). A 1 L 3-neck round-bottomed flask was charged with N,N,N'-trimethylenediamine (11.9 mL, 92 mmol, 1.15 eq) and THF (400 mL) and cooled to – 78 ºC. Butyl lithium (2.5 M in hexanes, 37 mL, 91 mmol, 1.15 eq) was added drop-wise via addition funnel and the mixture was stirred at – 78 ºC for 15 minutes. To the mixture was added 3-pyridinecarboxaldehyde (7.5 mL, 80 mmol, 1 eq) drop-wise via syringe and the reaction was stirred an additional 15 minutes at -78 ºC. To the mixture was added butyl lithium

(2.5 M in hexanes, 40 mL, 100 mmol, 1.25 eq) and the reaction was warmed to -42 ºC and stirred an additional 4 hours. The solution was cooled to –78 ºC and $C_2Br_2F_4$ was added rapidly via syringe. The reaction was warmed to room temperature and stirred for 2 hours. The mixture was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl, washed with brine, dried over $MgSO_4$, filtered over celite, and adsorbed onto SiO_2 under reduced pressure. Purification via flash chromatography using 40:60 ethyl acetate/hexane gave 5.2 g of 4-bromo-pyridine-3-carbaldehyde **(15)** as a yellow solid (35%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.97 (s, 1H), 8.54 (d, J = 5.5 Hz, 1H), 7.60 (d, J = 5.5 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 190.3, 154.3, 151.1, 136.4, 129.0, 128.8; HRMS (ESI) *m/z* calcd for $C_6H_5ON^{79}Br$ $[M+H]^+$ = 185.9549, found 185.9542.

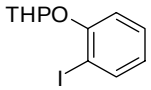


(4-Bromo-pyridin-3-yl)-methanol (6b). A 100 mL round-bottomed flask was charged with 4-bromo-pyridine-3-carbaldehyde **(15)** (1.51 g, 8 mmol, 1 eq) and methanol (20 mL). To the solution was added $NaBH_4$ (349 mg, 9.7 mmol, 1.2 eq) portion-wise and the mixture was stirred at room temperature overnight. The reaction was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. The solid was rinsed with hexane, filtered, and dried to give 1.10 g of (4-bromo-pyridin-3-yl)-methanol **(6b)** as a white solid (72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.22 (d, J = 4.5 Hz, 1H), 7.45 (d, J = 5.4 Hz, 1H), 4.74 (s, 1H), 4.32 (br, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 149.1, 148.8, 136.5, 133.3, 127.7, 62.3; HRMS (ESI) *m/z* calcd for $C_6H_7ON^{79}Br$ $[M+H]^+$ = 187.9706, found 187.9703.



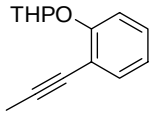
(3-Bromo-pyridin-4-yl)-methanol (6c). A 200 mL round-bottomed flask was charged with 3-bromo-pyridine-4-carbaldehyde **(16)** (10.52 g, 57 mmol, 1 eq) and methanol (80 mL) and cooled to -10 C. A solution of NaBH4 (2.57 g, 68 mmol, 1.2 eq) in methanol (60 mL) was added dropwise. The reaction was stirred at -10 C for an additional 2 hours. The mixture was diluted with ethyl acetate, quenched with saturated NH4Cl, and extracted with ethyl acetate. The combined extracts were washed with water, washed with saturated $NaHCO_3$, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure to give 7.6 g of (3-bromo-pyridin-4-yl)-methanol **(6c)** as a white solid (72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.52 (d, J = 5.2 Hz, 1H), 7.52 (t, J = 4.5 Hz, 1H), 5.67 (br, 1H), 4.50 (s, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.8, 150.7, 148.9, 122.9, 119.6, 62.2; HRMS (ESI) *m/z* calcd for $C_6H_7ON^{79}Br$ $[M+H]^+$ = 187.9706, found 187.9701.

Preparation of the C-ring phenol fragments (7, 8b, and 8c).

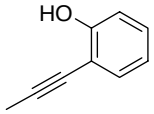


2-(2-Iodo-phenoxy)-tetrahydro-pyran (17). A 100 mL round-bottomed flask was charged with 2-iodophenol (15.00 g, 68 mmol, 1 eq) and CH_2Cl_2 (30 mL). To the solution was added 1 drop of concentrated HCl followed by the dropwise addition of dihydropyran (15.6 mL, 170 mmol, 2.5 eq). The reaction was stirred at room temperature for 18 hours. The mixture was then diluted with hexanes and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with hexanes and the combined extracts were washed with 5.0 N NaOH, washed with water,

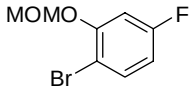
washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure to give 18.11 g of 2-(2-iodo-phenoxy)-tetrahydro-pyran **(17)** as an orange oil (87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.73 (t, J = 7.5 Hz, 1H), 5.54 (s, 1H), 3.88 (t, J = 11.2 Hz, 1H), 3.60 (d, J = 11.2 Hz, 1H), 2.23 – 1.58 (m, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 155.5, 139.3, 129.4, 123.3, 115.2, 96.4, 87.5, 61.7, 30.2, 25.3, 18.3; HRMS (CI) *m/z* calcd for $C_{11}H_{13}O_2I$ = 303.9960, found 303.9987.



2-(2-Prop-1-ynyl-phenoxy)-tetrahydro-pyran (18). A 350 mL screw-cap vial was charged with 2-(2-iodo-phenoxy)-tetrahydro-pyran **(17)** (18.10 g, 60 mmol, 1 eq) and diethylamine (150 mL). Propyne was bubbled through the solution and CuI (3.40 g, 18 mmol, 0.3 eq) was added in a single portion followed by $PdCl_2(PPh_3)_4$ (4.18 g, 6 mmol, 0.1 eq). The flask was sealed and heated to 50 ºC for 18 hours. The mixture was cooled to room temperature, diluted with diethyl ether, and quenched with saturated aqueous NH_4Cl. The ether layer was separated and washed with saturated aqueous NH_4Cl, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. The residue was purified via flash chromatography using 10:90 diethyl ether/hexane to give 10.90 g of 2-(2-prop-1-ynyl-phenoxy)-tetrahydro-pyran **(18)** as an orange oil (85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 7.4 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 5.51 (t, J = 2.8 Hz, 1H), 3.98 (dt, J = 3.1, 10.9 Hz, 1H), 3.62 – 5.56 (m, 1H), 2.09 (s, 3H), 2.15 – 1.58 (m, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.4, 133.2, 128.7, 121.6, 115.9, 114.8, 96.6, 89.5, 75.9, 61.8, 30.3, 25.3, 18.4, 4.5; HRMS (CI) *m/z* calcd for $C_{14}H_{16}O_2$ = 216.1150, found 216.1186.

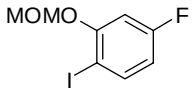


2-Prop-1-ynyl-phenol (7). A 500 mL round-bottomed flask was charged with 2-(2-prop-1-ynyl-phenoxy)-tetrahydro-pyran **(18)** (10.90 g, 50 mmol, 1 eq) and ethanol (250 mL). PPTS (3.8 g, 15 mmol, 0.3 eq) was added and the reaction was heated to 50 ºC for 3 hours. The ethanol was removed under reduced pressure and the residue was taken up in ethyl acetate, washed with water, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. The residue was purified via flash chromatography using 10:90 diethyl ether/hexane to give 5.91 g of 2-prop-1-ynyl-phenol **(7)** as an orange oil (89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 7.2 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.85 (t, J = 7.6 Hz, 1H), 5.91 (br, 1H), 3.19 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 156.6, 131.5, 129.6, 120.2, 114.4, 110.2, 93.2, 73.9; HRMS (CI) *m/z* calcd for C_9H_8O = 132.0575, found 132.0678.

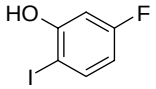


1-Bromo-4-fluoro-2-methoxymethoxy-benzene (19). A 200 mL round-bottomed flask was charged with 2-bromo-5-fluoro phenol (20.00 g, 105 mmol, 1 eq) and CH_2Cl_2 (100 mL) and cooled to 0 ºC. To the solution was added diisopropylethylamine (23.7 mL, 136 mmol, 1.3 eq) drop-wise via addition funnel followed by the dropwise addition of MOMCl (10.4 mL, 136 mmol, 1.3 eq). The reaction was warmed to room temperature and stirred for 18 h. The reactions was quenched with saturated aqueous NH4Cl, washed with water, washed with 2.0N

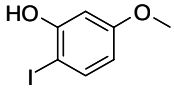
NaOH, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure to give 21.4 g of 1-bromo-4-fluoro-2-methoxymethoxy-benzene **(19)** as an orange liquid (87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, J = 5.8, 9.4 Hz, 1H), 6.93 (dt, J = 10.1, 3.6 Hz, 1H), 6.63 (dt, J = 2.9, 7.9 Hz, 1H), 5.22 (s, 2H), 3.50 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 163.6, 161.2, 154.6, 133.5, 133.4, 109.9, 109.6, 107, 106.9, 104.3, 104, 95.0, 56.3; HRMS (CI) *m/z* calcd for $C_8H_8{}^{79}BrFO_2$ = 233.9692, found 233.9716.



4-Fluoro-1-iodo-2-methoxymethoxy-benzene (20). A 1 L round-bottomed flask was charged with 1-Bromo-4-fluoro-2-methoxymethoxy-benzene **(19)** (21.40 g, 91 mmol, 1 eq) and ether (300 mL) and cooled to -78 ºC. To the solution was added ^{t}BuLi (1.7 M in hexanes, 118 mL, 200 mmol, 2.2 eq) drop-wise via addition funnel. The mixture was stirred at -78 ºC for 1 h and a solution of I_2 (27.70 g, 109 mmol, 1.2 eq) in ether (100 mL) was added via cannula. The mixture was warmed to room temperature over a period of approximately 1 h, quenched with saturated aqueous NH_4Cl, washed with saturated aqueous $Na_2S_2O_3$, washed with water, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. The residue was purified via flash chromatography using 2:98 diethyl ether/hexane to give 21.80 g of 4-fluoro-1-iodo-2-methoxymethoxy-benzene **(20)** as a pale orange oil (85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, J = 6.5, 8.0 Hz, 1H), 6.86 (dd, J = 10.9, 2.9 Hz, 1H), 6.54 (dt, J = 2.9, 8.0 Hz, 1H), 5.22 (s, 2H), 3.50 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.9, 162.4, 157.1, 139.54, 139.45, 110.7, 110.5, 103.3, 103.1. 95.0, 56.5; HRMS (CI) *m/z* calcd for $C_8H_8FIO_2$ = 281.9553, found 281.9510.



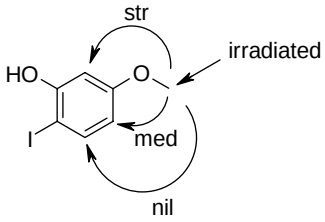
5-Fluoro-2-iodo-phenol (8b). To a solution of 4-Fluoro-1-iodo-2-methoxymethoxy-benzene **(20)** (10.00 g, 35 mmol, 1 eq) in acetone (100 mL) cooled to 0 º C was added a solution of concentrated HCl (23 mL) in acetone (130 mL). The mixture was warmed to room tempterature and stirred for 4 h, diluted with ethyl acetate, washed with water, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. The residue was purified via flash chromatography using 15:85 diethyl ether/hexane to give 6.40 g of 5-fluoro-2-iodo-phenol **(8b)** as a pale yellow liquid (76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.8, 6.3 Hz, 1H), 6.75 (dd, J = 8.8, 2.5 Hz, 1H), 6.49 (dt, J = 2.5, 8.2 Hz, 1H), 5.38 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 165.4, 162.9, 156.0, 155.9, 138.5, 138.4, 110.1, 109.8, 103.1, 102.9; HRMS (ESI) *m/z* calcd for C_6H_3OF = 236.9218, found 236.9218.



2-Iodo-5-methoxy-phenol (8c). A 500 mL round-bottomed flask was charged with 3-methoxyphenol (5.00 g, 40 mmol, 1 eq), $CHCl_3$ (40 mL), and $Ag(CO_2CF_3)_2$ (8.90 g, 40 mmol, 1 eq). A solution of I_2 (10.22 g, 40 mmol, 1 eq) in $CHCl_3$ (200 mL) was added dropwise via addition funnel over a period of approximately 1.5 h and the mixture was stirred an additional hour. The mixture was filtered over celite and the precipitate washed with $CHCl_3$. The organics were washed with 5% aqueous $Na_2S_2O_3$, washed with 5% aqueous $NaHCO_3$, washed with water, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. The residue was purified via flash chromatography using CH_2Cl_2 to give 6.23 g of 2-iodo-5-methoxy-phenol **(8c)** as a pale yellow crystalline solid (62%). ^{1}H

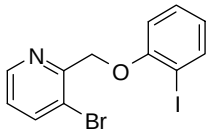
NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.7 Hz, 1H), 6.59 (d, J = 2.9 Hz, 1H), 6.33 (dd, J = 2.9, 8.7 Hz, 1H), 5.26 (s, 1H), 3.77 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 161.6, 155.6, 138.1, 109.4, 101.0, 74.4, 55.5; HRMS (ESI) *m/z* calcd for $C_7H_6O_2I$ = 248.9418, found 248.9418.

NOE:

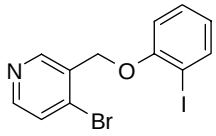


Preparation of aryl ethers (1, 1d, and 9a – 9f) via Mitsonobu reaction.

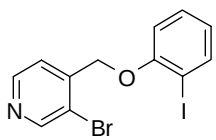
Typical Procedure: A round-bottomed flask was charged with the pyridyl alcohol (1 eq), phenol (1.05 eq) and benzene (0.3 M) and cooled to 0 ºC. P^nBu_3 (3 eq) was added via syringe followed by a single portion of ADDP (1.5 eq). The mixture was warmed to room temperature for 30 minutes and the thick slurry was then heated to 40 ºC for 3 h. The reaction was dilted with ethyl acetate, washed with 5.0 N NaOH, washed with brine, dried over $MgSO_4$, filtered over celite, and adsorbed onto SiO_2 under reduced pressure. Purification via flash chromatography provided the desired aryl ethers.



3-Bromo-2-(2-iodo-phenoxymethyl)-pyridine (9a). Prepared from (3-bromo-pyridin-2-yl)-methanol **(6a)** (3.00 g, 16 mmol) and 2-iodophenol according to the typical procedure. Purification via flash chromatography using 20:80 ethyl acetate/hexane provided 4.51 g of 3-bromo-2-(2-iodo-phenoxymethyl)-pyridine **(9a)** as a white solid (72%). ^1H NMR (500 MHz, DMSO) δ 8.57 (dd, J = 4.6, 1.4 Hz, 1H), 8.14 (dd, J = 7.8, 1.4 Hz, 1H), 7.75 (dd, J = 7.8, 1.4 Hz, 1H), 7.35 (m, 2H), 7.12 (dd, J = 7.8, 1.4 Hz, 1H), 6.74 (dt, J = 1.4, 7.4 Hz, 1H), 5.27 (s, 2H); ^{13}C NMR (500 MHz, DMSO) δ 157.3, 153.7, 148.4, 141.5, 139.5, 130.1, 126.0, 123.4, 121.9, 113.4, 86.9, 72.1; HRMS (ESI) *m/z* calcd for $C_{12}H_{10}ON^{79}BrI$ $[M+H]^+$= 389.8985, found 389.8994.

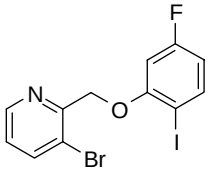


4-Bromo-3-(2-iodo-phenoxymethyl)-pyridine (9b). Prepared from (4-bromo-pyridin-3-yl)-methanol **(6b)** (700 mg, 3.7 mmol) and 2-iodophenol according to the typical procedure. Purification via flash chromatography using 20:80 ethyl acetate/hexane provided 1.07 g of 4-bromo-3-(2-iodo-phenoxymethyl)-pyridine **(9b)** as a white solid (74%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (br, 1H), 8.39 (br, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 5.1 Hz, 1H), 7.32 (t, J = 8.9 Hz, 1H), 6.91 (d, J = 8.9 Hz, 1H), 6.77 (t, J = 8.9 Hz, 1H), 5.181 (s, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 156.5, 150.0, 149.8, 139.7, 132.4, 131.9, 129.5, 127.4, 123.4, 112.5, 86.6, 68.4; HRMS (ESI) *m/z* calcd for $C_{12}H_{10}ON^{79}BrI$ $[M+H]^+$= 389.8985, found 389.8995.

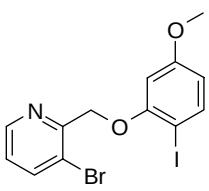


3-Bromo-4-(2-iodo-phenoxymethyl)-pyridine (9c). Prepared from (3-Bromo-pyridin-4-yl)-methanol **(6c).** (500 mg, 2.7 mmol) and 2-

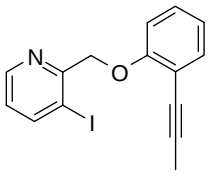
iodophenol according to the typical procedure. Purification via flash chromatography using 20:80 ethyl acetate/hexane provided 663 mg of 3-bromo-4-(2-iodo-phenoxymethyl)-pyridine **(9c)** as a white solid (64%). ^{1}H NMR (500 MHz, DMSO) δ 8.75 (s, 1H), 8.61 (d, J = 5.2 Hz, 1H), 7.80 (dd, J = 7.9, 1.5 Hz, 1H), 7.70 (d, J = 4.8 Hz, 1H), 7.37 (dt, J = 1.4, 7.9 Hz, 1H), 7.07 (dd, J = 8.3, 1.3 Hz, 1H), 6.80 (dt, J = 1.3, 7.9 Hz, 1H), 5.20 (s, 2H); ^{13}C NMR (500 MHz, DMSO) δ 156.4, 151.6, 149.2, 145.4, 139.6, 130.3, 123.9, 123.6, 120.1, 113.4, 87.0, 68.9; HRMS (ESI) *m/z* calcd for $C_{12}H_{10}ON^{79}BrI$ $[M+H]^{+}$= 389.8985, found 389.8973.



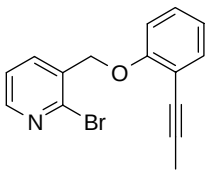
3-Bromo-2-(5-fluoro-2-iodo-phenoxymethyl)-pyridine (9d). Prepared from (3-bromo-pyridin-2-yl)-methanol **(6a)** (500 mg, 2.7 mmol) and 5-fluoro-2-iodo-phenol **(8b)** according to the typical procedure. Purification via flash chromatography using 15:85 ethyl acetate/hexane provided 668 mg of 3-bromo-2-(5-fluoro-2-iodo-phenoxymethyl)-pyridine **(9d)** as a white solid (62%). ^{1}H NMR (500 MHz, DMSO) δ 8.58 (dd, J = 4.8, 1.3 Hz, 1H), 8.15 (dd, J = 8.1, 1.3 Hz, 1H), 7.76 (dd, J = 8.7, 6.4 Hz, 1H), 7.38 (dd, J = 8.1, 4.8 Hz, 1H), 7.11 (dd, J = 11.3, 2.9 Hz, 1H), 6.66 (dt, J = 2.6, 8.7 Hz, 1H), 5.29 (s, 2H); ^{13}C NMR (500 MHz, DMSO) δ 164.8, 162.4, 158.6, 258.5, 153.3, 148.5, 141.6, 140.0, 139.9, 126.1, 121.9, 110.2, 110.0, 102.0, 101.8, 80.53, 80.51, 72.4; HRMS (ESI) *m/z* calcd for $C_{12}H_{9}ON^{79}BrFI$ $[M+H]^{+}$= 407.8891, found 407.8892.



3-Bromo-2-(2-iodo-5-methoxy-phenoxymethyl)-pyridine (9e). Prepared from (3-bromo-pyridin-2-yl)-methanol **(6a)** (500 mg, 2.7 mmol) and 2-iodo-5-methoxy-phenol **(8c)** according to the typical procedure. Purification via flash chromatography using 20:80 ethyl acetate/hexane provided 887 mg of 3-bromo-2-(2-iodo-5-methoxy-phenoxymethyl)-pyridine **(9e)** as a white solid (79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, J = 4.2 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.14 (dd, J = 7.8, 4.2 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.31 (dd, J = 3.0, 8.4 Hz, 1H), 5.30 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 161.1, 158.0, 153.8, 147.8, 140.9, 139.2, 124.7, 108.1, 101.0, 75.3, 72.0, 55.5; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}O_2N^{79}BrI$ $[M+H]^{+}$= 419.9091, found 419.9077.



3-Iodo-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine (1). Prepared from (3-iodo-pyridin-2-yl)-methanol **(6)** (2.000 g, 8.5 mmol) and 2-prop-1-ynyl-phenol **(7)** according to the typical procedure. Purification via flash chromatography using 30:70 ethyl acetate/hexane provided 2.07 g of 3-iodo-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1)** as a white solid (70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, J = 4.8 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 6.95 (m, 2H), 6.88 (t, J = 7.3 Hz, 1H), 5.33 (s, 2H), 2.05 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.9, 156.7, 148.4, 147.2, 133.6, 128.6, 124.3, 121.2, 114.2, 113.5, 94.9, 90.2, 75.9, 74.5, 4.9; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}ON$ = 350.0036, found 350.0033.

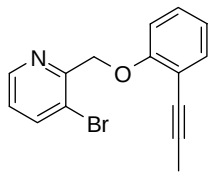


2-Bromo-3-(2-prop-1-ynyl-phenoxymethyl)-pyridine (1d). Prepared from (2-bromo-pyridin-3-yl)-methanol **(6d)** (800 mg, 4.3

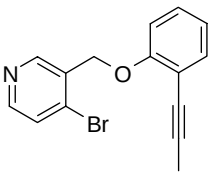
mmol) and 2-prop-1-ynyl-phenol **(7)** according to the typical procedure. Purification via flash chromatography using 15:85 ethyl acetate/hexane provided 932 mg of 2-bromo-3-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1d)** as a clear colorless oil (72%). ^{1}H NMR (500 MHz, DMSO) δ 8.35 (dd, J = 4.9, 2.0 Hz, 1H), 7.96 (dd, J = 7.5, 1.6 Hz, 1H), 7.51 (dd, J = 7.9, 4.9 Hz, 1H), 7.35 (dd, J = 7.5, 1.6 Hz, 1H), 7.28 (dt, J = 1.6, 7.9 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.93 (dt, J = 1.0, 7.5 Hz, 1H), 5.15 (s, 2H), 2.04 (s, 1H); ^{13}C NMR (500 MHz, DMSO) δ 158.5, 149.9, 141.7, 137.9, 134.0, 133.5, 129.7, 124.1, 121.7, 113.6, 113.5, 91.0, 76.3, 68.5, 4.6; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}ON^{79}Br$ $[M+H]^+$= 302.0175, found 302.0165.

Preparation of alkynes (1a-1h) via Sonogashira coupling.

Typical Procedure: A screw-cap vial was charged with the appropriate iodide (1eq), diethylamine (0.5 M), and acetonitrile (0.5 M). In some cases THF (0.5 M) was added to aid in solubility. The mixture was purged with N_2 for 15 minutes and then cooled to 0 ºC. An excess of the alkyne was bubbled through the solution (or added via syringe in the case of isopropylacetylene) and CuI (0.3 eq) was added in a single portion followed by $PdCl_2(PPh_3)_2$ (0.1 eq). The screw-cap vial was sealed and allowed to warm to room temperature. After 1 hour at room temperature the reaction was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. Purification via flash chromatography provided the desired alkynes.

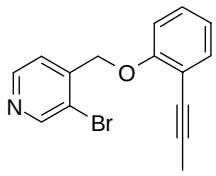


3-Bromo-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine (1a). Prepared from 3-bromo-2-(2-iodo-phenoxymethyl)-pyridine **(9a)** (4.51 g, 12 mmol) and propyne according to the typical procedure. Purification via flash chromatography using 40:60 ethyl acetate:hexane provided 3.09 g of 3-bromo-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1a)** as a pale yellow solid (88%). ^{1}H NMR (500 MHz, DMSO) δ 8.55 (dd, J = 4.8, 1.8 Hz, 1H), 8.12 (dd, J = 8.3, 1.8 Hz, 1H), 7.33 (m, 2H), 7.23 (dt, J = 7.9, 1.8 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.88 (dt, J = 7.9, 0.9 Hz, 1H), 5.28 (s, 2H), 1.97 (s, 3H); ^{13}C NMR (500 MHz, DMSO) δ 159.1, 154.0, 148.4, 141.4, 133.6, 129.5, 125.8, 121.5, 121.3, 113.45, 113.44, 90.5, 76.5, 71.2, 4.7; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}ON^{79}Br$ $[M+H]^+$= 302.0175, found 302.0172.

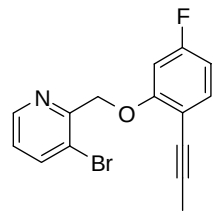


4-Bromo-3-(2-prop-1-ynyl-phenoxymethyl)-pyridine (1b). Prepared from 4-bromo-3-(2-iodo-phenoxymethyl)-pyridine **(9d)** (1.070 g, 2.7 mmol) and propyne according to the typical procedure. A significant amount of the bis-alkyne was formed, however purification via flash chromatography using 30:70 ethyl acetate:hexane provided 491 mg of 4-bromo-3-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1b)** as an orange oil (59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.35 (d, J = 6.0 Hz, 1H), 7.49 (d, J = 5.5 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.92 (t, J = 8.6 Hz, 1H), 5.18 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.4, 149.8, 149.6, 133.6, 132.44, 132.38, 128.8, 127.3, 121.6,

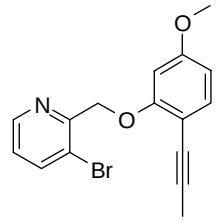
114.3, 112.8, 90.6, 75.5, 68.1, 4.64; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}ON^{79}Br$ $[M+H]^+$= 302.0175, found 302.0202.



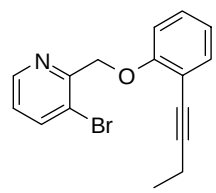
3-Bromo-4-(2-prop-1-ynyl-phenoxymethyl)-pyridine (1c). Prepared from 3-bromo-4-(2-iodo-phenoxymethyl)-pyridine **(9c)** (663 mg, 1.7 mmol) and propyne according to the typical procedure. Purification via flash chromatography using 20:80 ethyl acetate:hexane provided 404 mg of 3-bromo-4-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1c)** as a pale yellow solid (79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (br, 1H), 8.56 (br, 1H), 7.69 (br, 1H), 7.42 (dd, J = 7.7, 1.7 Hz, 1H), 7.23 (dt, J = 2.1, 7.7 Hz, 1H), 6.94 (dt, J = 0.9, 7.3 Hz, 1H), 6.84 (d, J = .7. Hz, 1H), 5.16 (s, 2H), 2.13 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.1, 151.2, 148.5, 145.6, 133.7, 128.9, 122.9, 121.6, 114.0, 112.5, 90.5, 75.6, 68.5, 4.6; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}ON^{79}Br$ $[M+H]^+$= 302.0175, found 302.0173.



3-Bromo-2-(5-fluoro-2-prop-1-ynyl-phenoxymethyl)-pyridine (1e). Prepared from 3-bromo-2-(5-fluoro-2-iodo-phenoxymethyl)-pyridine **(9d)** (608 mg, 1.5 mmol) and propyne according to the typical procedure. Purification via flash chromatography using 20:80 ethyl acetate:hexane provided 354 mg of 3-bromo-2-(5-fluoro-2-prop-1-ynyl-phenoxymethyl)-pyridine **(1e)** as a pale yellow solid (74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (dd, J = 4.8, 1.4 Hz, 1H), 7.88 (dd, J = 8.1, 1.4 Hz, 1H), 7.30 (dd, J = 6.7, 8.4 Hz, 1H), 7.14 (dd, J = 8.1, 4.8 Hz, 1H), 6.71 (dd, J = 10.9, 2.5 Hz, 1H), 6.59 (dt, J = 2.2, 8.4 Hz, 1H), 5.34 (s, 2H), 2.03 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 163.8, 161.3, 160.1, 153.7, 147.9, 140.7, 134.3, 134.2, 124.5, 121.1, 110.20, 110.17, 108.0, 107.8, 101.9, 101.7, 89.64, 89.62, 74.8, 71.6, 4.72; HRMS (ESI) *m/z* calcd for $C_{15}H_{12}ON^{79}BrF$ $[M+H]^+$= 320.0081, found 320.0072.

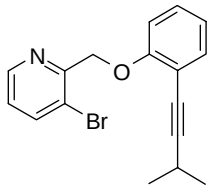


3-Bromo-2-(5-methoxy-2-prop-1-ynyl-phenoxymethyl)-pyridine (1f). Prepared from 3-bromo-2-(2-iodo-5-methoxy-phenoxymethyl)-pyridine **(9e)** (789 mg, 1.9 mmol) and propyne according to the typical procedure. Purification via flash chromatography using 30:70 ethyl acetate:hexane provided 568 mg of 3-bromo-2-(5-methoxy-2-prop-1-ynyl-phenoxymethyl)-pyridine **(1f)** as a pale yellow solid (91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (dd, J = 4.8, 1.4 Hz, 1H), 7.88 (dd, J = 8.1, 1.4 Hz, 1H), 7.30 (dd, J = 6.7, 8.4 Hz, 1H), 7.14 (dd, J = 8.1, 4.8 Hz, 1H), 6.71 (dd, J = 10.9, 2.5 Hz, 1H), 6.59 (dt, J = 2.2, 8.4 Hz, 1H), 5.34 (s, 2H), 2.03 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 163.8, 161.3, 160.1, 153.7, 147.9, 140.7, 134.3, 134.2, 124.5, 121.1, 110.20, 110.17, 108.0, 107.8, 101.9, 101.7, 89.64, 89.62, 74.8, 71.6, 4.72; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}O_2N^{79}Br$ $[M+H]^+$= 332.0281, found 332.0275.



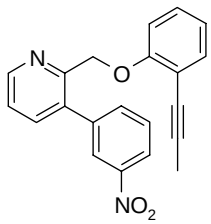
3-Bromo-2-(2-but-1-ynyl-phenoxymethyl)-pyridine (1g). Prepared from 3-bromo-2-(2-iodo-phenoxymethyl)-pyridine **(9a)** (867 mg, 2.2 mmol) and butyne according to the typical procedure. Purification via flash chromatography using 20:80 THF:hexane provided 566 mg of 3-

bromo-2-(2-but-1-ynyl-phenoxymethyl)-pyridine **(1g)** as a pale orange oil (81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (dd, J = 4.7, 1.2 Hz, 1H), 7.87 (dd, J = 8.2, 1.2 Hz, 1H), 7.37 (dd, J = 7.8, 1.2 Hz, 1H), 7.18 (dt, J = 7.8, 1.6 Hz, 1H), 7.12 (dd, J = 8.2, 4.7 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.89 (t, J = 7.4 Hz, 1H), 5.36 (s, 2H), 2.42 (q, J = 7.8 Hz, 2H), 1.19 (t, J = 7.4 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.1, 154.4, 147.8, 140.6, 133.5, 128.6, 124.3, 121.23, 121.20, 114.3, 113.7, 96.0, 75.9, 71.7, 30.3, 13.9, 13.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}ON^{79}Br$ $[M+H]^+$= 316.0332, found 316.0323.



3-Bromo-2-[2-(3-methyl-but-1-ynyl)-phenoxymethyl]-pyridine (1h). Prepared from 3-bromo-2-(2-iodo-phenoxymethyl)-pyridine **(9a)** (589 mg, 1.5 mmol) and isopropylacetylene according to the typical procedure. Purification via flash chromatography using 15:85 THF:hexane provided 408 mg of 3-bromo-2-[2-(3-methyl-but-1-ynyl)-phenoxymethyl]-pyridine **(1h)** as a yellow oil (82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (dd, J = 4.6, 1.5 Hz, 1H), 7.87 (dd, J = 8.0, 1.5 Hz, 1H), 7.35 (dd, J = 7.2, 1.5 Hz, 1H), 7.18 (dt, J = 1.9, 8.4 Hz, 1H), 7.11 (dd, J = 8.0, 4.6 Hz, 1H), 6.99 (dd, J = 8.4, 0.8 Hz, 1H), 6.88 (dt, J = 1.1, 7.2 Hz, 1H), 5.35 (s, 2H), 2.77 (q, J = 7.0 Hz, 1H), 1.21 (d, J = 6.9 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.1, 154.5, 147.7, 140.6, 133.4, 128.6, 124.3, 121.3, 121.2, 114.4, 113.8, 100.1, 75.8, 71.8, 23.0, 21.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{17}ON^{79}Br$ $[M+H]^+$= 330.0488, found 330.0479.

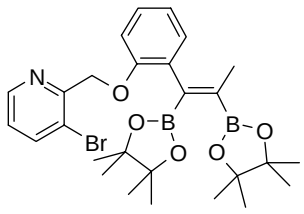
Attempted Heck-Suzuki.



3-(3-Nitro-phenyl)-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine (3). A 75 mL screw-cap vial was charged with 3-iodo-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1)** (500 mg, 1.4 mmol, 1 eq), 3 nitrophenylboronic acid (263 mg, 1.6 mmol, 1.1 eq), 1,4-dioxane (12 mL) and water (3 mL) and the mixture was purged with N_2 for 15 minutes. To the mixture was added Na_2CO_3 (455 mg, 4.3 mmol, 3 eq) and $Pd(OAc)_2$ (6.4 mg, 0.03 mmol, 0.02 eq) and the flask was sealed and heated to 80 ºC for 24 h. Crude LCMS indicated the formation of multiple products and TLC indicated extensive decomposition. The mixture was cooled to room temperature, diluted with ethyl acetate, washed with water, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. Purification via flash chromatography using 200 mL 30:70 ethyl acetate:hexane then 2000 mL 40:60 ethyl acetate:hexane provided a number of products including trace amounts of recovered starting material and the desired cyclic oxepine. The only product to be isolated in notable quantity and reasonable purity was 51 mg (10%) of 3-(3-nitro-phenyl)-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(3)**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (dd, J = 1.5, 4.6 Hz, 1H), 8.22 (t, J = 2.0 Hz, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.65 (dd, J = 1.5, 8.2 Hz, 1H), 7.54 (m, 1H), 7.40 (dd, J = 5.1, 7.7 Hz, 1H), 7.27 (m, 1H), 7.12 (dt, J = 1.5, 7.7 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.83 (t, J = 7.7 Hz, 1H), 5.20 (s, 2H), 1.97 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.2, 153.3, 149.0, 148.2, 140.1, 138.2, 136.3, 135.2, 133.6, 129.2, 128.6, 123.8, 123.5, 122.7, 120.9, 113.7, 112.8, 107.9, 89.7, 75.7, 70.9, 67.6, 29.1, 23.9, 4.6; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}O_3N_2$ $[M+H]^+$= 345.1234, found 345.1226.

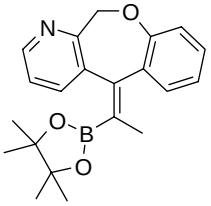
Preparation of pyridyl oxepines (2a-2m) via diboration-sequential Suzuki.

Typical Procedure: A: A round-bottomed flask was charged with the appropriate alkyne (1 eq) and DMF (0.1M) and purged with N_2 for 15 minutes. Bis(pinacolato)diboron (1.1 eq) was added in a single portion followed by $Pt(PPh_3)_4$ (0.08 eq) and the mixture was heated to 80 ºC for 24 hours. Analysis of the crude reaction mixture by LCMS verified the consumption of the alkyne and the formation of the 1,2-bis(boronate) ester. The reaction was cooled to room temperature, diluted with ethyl acetate, washed repeatedly with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, gravity filtered, and concentrated under reduced pressure to give the crude 1,2-bis(boronate) ester, which was used without further purification. **B:** This residue was dissolved in 1,4-dioxane (0.01 M) and purged with N_2 for 15 minutes. Crushed K_3PO_4 was added in a single portion followed by $PdCl_2dppf•CH_2Cl_2$ and the mixture was heated to 80 ºC for 24 h. Again, analysis of the crude reaction mixture by LCMS verified the consumption of the 1,2-bis(boronate) ester and the formation of the cyclic vinyl boronic ester. The reaction was cooled to room temperature, diluted with ethyl acetate, washed repeatedly with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, gravity filtered, and concentrated under reduced pressure to give the crude cyclic vinyl boronic ester, which was used without further purification. **C:** The residue was dissolved in 1,4-dioxane (0.15 M) 6M aqueous KOH (0.4 M) and the solution was purged with N_2 for 15 minutes. The appropriate aryl iodide (1.5 eq) was added followed by 3,5-dimethoxyphenol (5 eq) and $Pd(PPh_3)_4$ and the reaction was heated to 80 ºC for 18 h. The mixture was cooled to room temperature, diluted with ethyl acetate, washed with 5.0 N NaOH, washed with brine, dried over $MgSO_4$, filtered over celite, and concentrated under reduced pressure. Purification via flash chromatography (and in some cases ion exchange) provided the desired oxepines. For **2a** and **2g** the crude 1,2-bis(boronate)esters and cyclic vinyl boronic esters were characterized by NMR and HRMS, however in all other cases the intermediates were simply identified by LCMS analysis of the crude reaction mixtures and used without purification.

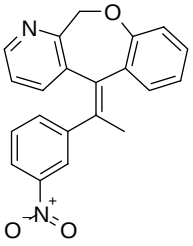


2-{2-[1,2-Bis-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-propenyl]-phenoxymethyl}-3-bromo-pyridine (4a). Prepared according to part A of the typical procedure using 3-bromo-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1a)** (2.81 g, 9 mmol) to give 5.03 g of the desired product **(4a)** as a pale orange foam (97%, crude). Proton NMR and HRMS analysis of the crude were consistent with the desired product and carbon NMR showed the closely spaced singlets at 83.5 and 83.4 ppm characteristic of the 1,2-bis(boryl) alkene moiety. ^{1}H NMR (500 MHz, DMSO) δ 8.51 (dd, J = 1.3, 4.4 Hz, 1H), 8.07 (dd, J = 1.3, 8.0 Hz, 1H), 7.31 (dd, J = 4.9, 8.4 Hz, 1H), 7.12 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.88 (m, 2H), 5.16 (s, 2H), 1.55 (s, 3H), 1.23 (s, 12H), 1.10 (s, 12H); ^{13}C NMR (500 MHz, DMSO) δ 155.9, 154.4, 148.4, 141.2, 132.0, 131.9, 131.3, 130.4,

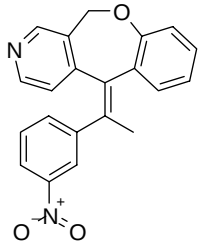
129.2, 129.1, 127.8, 125.5, 121.3, 121.0, 113.7, 83.5, 83.4, 81.8, 71.2, 25.0, 24.92, 24.85, 19.6; HRMS (ESI) *m/z* calcd for $C_{27}H_{37}O_5NB_2{}^{79}Br$ $[M+H]^+$= 556.2036, found 556.2032.



5-[1-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (5a). Prepared according to part B of the typical procedure using 2-{2-[1,2-bis-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-propenyl]-phenoxymethyl}-3-bromo-pyridine **(4a)** (5.03 g, 9 mmol) to give 3.17 g of the desired product **(5a)** as an orange foamy solid (100%, crude). HRMS of the crude was consistent with the desired product while the proton NMR clearly showed the diastereotopic doublets of the cyclic product at 5.55 and 4.89 ppm and the carbon NMR showed a single diagnostic vinyl boronic ester signal at 83.7 ppm. ^{1}H NMR (500 MHz, DMSO) δ 8.42 (d, J = 4.8 Hz, 1H), 7.28 (dd, J = 5.1, 7.5 Hz, 1H), 7.20 (dt, J = 1.6, 7.8 Hz, 1H), 7.12 (dd, J = 1.3, 7.5, 1H), 6.93 (m, 2H), 5.55 (d, J = 12.9 Hz, 1H), 4.89 (d, J = 12.9 Hz, 1H), 1.89 (s, 3H), 1.05 (s, 12H); ^{13}C NMR (500 MHz, DMSO) δ 154.6, 152.4, 148.5, 144.9, 138.9, 136.1, 132.0, 131.9, 130.7, 130.0, 129.2, 129.1, 127.7, 123.5, 121.7, 120.4. 83.7, 73.9, 72.5, 25.4, 25.0, 24.9, 24.5, 19.0; HRMS (ESI) *m/z* calcd for $C_{21}H_{25}O_3NB$ $[M+H]^+$= 350.1922, found 350.1916.

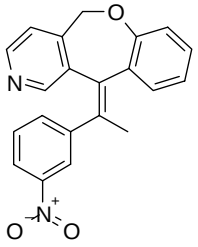


5-[1-(3-Nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (2a). Prepared according to part C of the typical procedure using 5-[1-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene **(5a)** (500mg, 1.4 mmol) and 3-iodonitrobenzne. Purification using ion-exchange chromatography followed by flash chromatography using 30:70 THF/hexane provided 223 mg of 5-[1-(3-nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene **(2a)** as a white solid (44% over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (dd, J = 1.4, 4.5 Hz, 1H), 8.06 (s, 1H), 8.00 (dt, J = 7.3, 1.8 Hz, 1H), 7.28 (m, 4H), 7.06 (s, 1H), 7.04 (s, 1H), 6.94, (dd, J = 1.4, 8.2 Hz, 1H), 6.82 (dd, 4.5, 7.7 Hz, 1H), 5.80 (d, J = 14.1 Hz, 1H), 5.09 (d, J = 14.1 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 155.2, 153.5, 148.1, 148.0, 144.3, 137.0, 136.0, 135.02, 134.99, 134.5, 130.0, 129.8, 129.0, 123.4, 122.4, 122.1, 121.7, 120.7, 73.4, 22.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{15}O_3N_2$ $[M+H]^+$= 343.1088, found 343.1092.

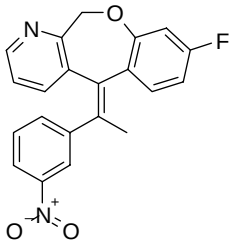


5-[1-(3-Nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-2-aza-dibenzo[a,d]cycloheptene (2b). Prepared according to the typical procedure using 4-bromo-3-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1b) (**480 mg, 1.6 mmol) and 3-iodonitrobenzne. Purification by ion – exchange chromatography followed by flash chromatography using 40:60 ethyl acetate/hexane provided 175 mg of 5-[1-(3-nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-2-aza-dibenzo[a,d]cycloheptene **(2b)** as a pale yellow solid (32% over 3 steps). ^{1}H NMR (500 MHz, DMSO) δ 8.55 (br, 1H), 8.21 (br, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.32-7.20 (m, 4H), 6.96 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.56 (br, 1H), 5.79 (d, J = 12.7 Hz, 1H), 5.03 (d, J = 12.7 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 154.7, 150.6, 150.0,

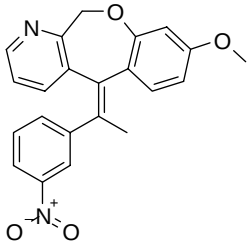
148.6, 147.9, 144.0, 135.0, 134.7, 134.1, 131.2, 130.1, 129.1, 123.6, 122.9, 122.4, 122.3, 121.9, 120.8, 120.0, 67.3, 22.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}O_3N_2$ $[M+H]^+$= 345.1234, found 345.1225.



5-[1-(3-Nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-3-aza-dibenzo[a,d]cycloheptene (2c). Prepared according to the typical procedure using 3-bromo-4-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1c) (**404 mg, 1.3 mmol) and 3-iodonitrobenzne. Purification by flash chromatography using 40:60 ethyl acetate/hexane provided 147 mg of 5-[1-(3-nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-3-aza-dibenzo[a,d]cycloheptene **(2c)** as a pale yellow solid (30% over 3 steps). ^{1}H NMR (500 MHz, DMSO) δ 8.27 (d, J = 3.4 Hz, 1H), 7.96 (s, 2H), 7.77 (s, 1H), 7.45-7.33 (m, 4H), 7.20 (t, J = 6.8 Hz, 1H), 6.98 (t, J = 7.9 Hz, 1H), 9.87 (d, J = 7.9 Hz, 1H), 5.74 (d, J = 13.6 Hz, 1H), 4.98 (d, J = 13.8 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 154.8, 149.5, 148.4, 147.9, 144.2, 142.3, 136.4, 135.3, 134.6, 133.0, 130.4, 129.8, 129.1, 128.3, 123.4, 122.0, 121.9, 121.4, 120.4, 70.1, 22.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}O_3N_2$ $[M+H]^+$= 345.1234, found 345.1227.

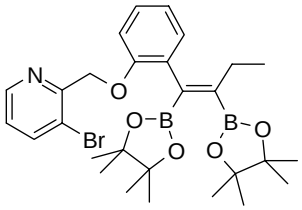


8-Fluoro-5-[1-(3-nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (2e). Prepared according to the typical procedure using 3-bromo-2-(5-fluoro-2-prop-1-ynyl-phenoxymethyl)-pyridine **(1e) (**343 mg, 1.1 mmol) and 3-iodonitrobenzne. Purification by flash chromatography using 20:80 ethyl acetate/hexane provided 155 mg of 8-fluoro-5-[1-(3-nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene **(2e)** as a pale yellow foam (40% over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 4.5 Hz, 1H), 8.01-7.99 (m, 2H), 7.32-7.20 (m, 3H), 6.94 (dd, J = 1.5, 7.8 Hz, 1H), 6.87 (dd, J = 4.8, 7.8 Hz, 1H)6.76-6.70 (m. 2H), 5.83 (d, J = 13.4 Hz, 1H), 5.11 (d, J = 14.6 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.4, 162.0, 156.3, 156.2, 152.5, 148.2, 148.0, 144.1, 136.8, 136.5, 135.3, 134.7, 133.6, 131.6, 131.5, 129.0, 123.2, 123.1, 123.03, 122.97, 121.8, 108.9, 108.7, 107.5, 107.3, 72.8, 22.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{16}O_3N_2$ $[M+H]^+$= 363.1139, found 363.1141.

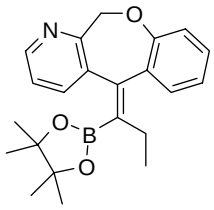


8-Methoxy-5-[1-(3-nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (2f). Prepared according to the typical procedure using 3-bromo-2-(5-methoxy-2-prop-1-ynyl-phenoxymethyl)-pyridine **(1f) (**560 mg, 1.7 mmol) and 3-iodonitrobenzne. Purification by flash chromatography using 40:60 ethyl acetate/hexane provided 241 mg of 8-methoxy-5-[1-(3-nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene **(2f)** as a pale orange solid (38% over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (dd, J = 1.3, 4.5 Hz, 1H), 7.99-7.95 (m, 2H), 7.29-7.24 (m, 1H), 7.21-7.18 (m, 2H), 6.90 (d, J = 7.6 Hz, 1H), 6.83 (dd, J = 4.2, 7.6 Hz, 1H), 6.58 (dd, J = 1.7, 8.5 Hz, 1H), 6.52 (d, J = 1.7 Hz, 1H), 5.81 (d, J = 13.6 Hz, 1H), 5.09 (d, J = 13.6 Hz, 1H), 3.75 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.8, 156.1, 152.8, 148.0, 144.4, 137.2, 136.4, 134.8, 134.2, 134.1, 131.2, 128.9, 123.3, 122.8, 121.6, 119.2, 108.3,

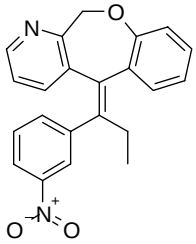
104.6, 72.6, 55.3, 22.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{19}O_4N_2$ $[M+H]^+$= 375.1339, found 375.1338.



2-{2-[1,2-Bis-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-but-1-enyl]-phenoxymethyl}-3-bromo-pyridine (4g). Prepared according to part A of the typical procedure using 3-bromo-2-(2-but-1-ynyl-phenoxymethyl)-pyridine **(1g)** (511 mg, 1.6 mmol) to give 825 mg of the desired product **(4g)** as a pale yellow solid (90%, crude). Proton NMR and HRMS analysis of the crude were consistent with the desired product and carbon NMR showed the closely spaced singlets at 83.5 and 83.4 ppm characteristic of the 1,2-bis(boryl) alkene moiety. ^{1}H NMR (500 MHz, DMSO) δ 8.50 (d, J = 4.8 Hz, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.30 (dd, J = 4.8, 7.7 Hz, 1H), 7.10 (dt, J = 1.5, 7.7 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 6.85 (m, 2H), 5.14 (br, 2H), 1.93, (q, J = 7.7 Hz, 2H), 1.23 (s, 12H), 1.07 (s, 12H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (500 MHz, DMSO) δ 155.9, 154.4, 148.3, 141.2, 131.94, 131.85, 131.6, 130.1, 129.2, 129.1, 127.7, 125.5, 121.3, 121.0, 113.5, 83.5, 83.4, 71.1, 26.7, 24.9, 24.8, 24.7, 14.0; HRMS (ESI) *m/z* calcd for $C_{28}H_{39}O_5NB_2{}^{79}Br$ $[M+H]^+$= 570.2192, found 570.2175.

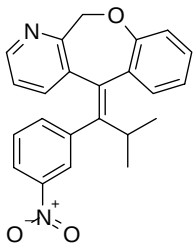


5-[1-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-propylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (5g). Prepared according to part B of the typical procedure using 2-{2-[1,2-bis-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-but-1-enyl]-phenoxymethyl}-3-bromo-pyridine **(4g).** (795 mg, 1.4 mmol) to give 455 mg of the desired product **(5g)** as a dark yellow oily foam (90%, crude). HRMS of the crude was consistent with the desired product while the proton NMR clearly showed the diastereotopic doublets of the cyclic product at 5.56 and 4.85 ppm. The carbon NMR showed a single diagnostic vinyl boronic ester signal at 83.7 ppm, however technical difficulties with the decoupler made it impossible to obtain a suitable spectrum and due to instability the sample was carried into the next step before repairs could be made. ^{1}H NMR (500 MHz, DMSO) δ 8.42 (d, J = 3.9 Hz, 1H), 7.29, (dd, J = 5.2, 7.5 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 6.93 (m, 2H), 5.57 (d, J = 13.7 Hz, 1H), 4.86 (d, J = 13.7 Hz, 1H), 2.33 (m, 2H), 1.09 (s, 6H), 1.05 (s, 6H), 0.98 (m, 3H); HRMS (ESI) *m/z* calcd for $C_{22}H_{27}O_3NB$ $[M+H]^+$= 364.2079, found 364.2068.

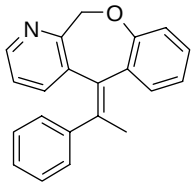


5-[1-(3-Nitro-phenyl)-propylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (2g). Prepared according to part C of the typical procedure using 5-[1-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-propylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene **(5g)** (414mg, 1.1 mmol) and 3-iodonitrobenzne. Purification by flash chromatography using 500 mL 20:80 ethyl acetate/hexane followed by 30:70 ethyl acetate/hexane provided 168 mg of 5-[1-(3-Nitro-phenyl)-propylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene **(2g)** as a pale yellow chalky solid (33% over 3 steps). ^{1}H NMR (500 MHz, DMSO) δ 8.25 (dd, J = 1.6, 4.8 Hz, 1H), 8.01 (m, 2H), 7.47 (m, 2H), 7.37 (dd, J = 1.6, 7.7 Hz, 1H), 7.24 (dt, J = 1.6, 7.7 Hz, 1H), 7.06-6.91 (m, 4H), 5.89 (d, J

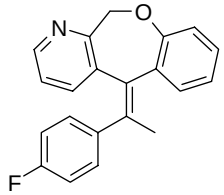
= 13.2 Hz, 1H), 4.94 (d, J = 13.2 Hz, 1H), 2.78 (m, J = 7.4 Hz, 1H), 2.67 (m, J = 7.4 Hz, 1H), 0.79, (t, J = 7.4 Hz, 3H); ^{13}C NMR (500 MHz, DMSO) δ 155.0, 152.6, 148.30, 148.27, 147.9, 142.5, 141.8, 137.3, 136.4, 133.1, 131.1, 130.2, 129.8, 126.7, 123.9, 123.5, 122.1, 121.7, 120.2, 72.4, 27.4, 12.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{19}O_3N_2$ $[M+H]^+$= 359.1390, found 359.1377.



5-[2-Methyl-1-(3-nitro-phenyl)-propylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (2h). Prepared according to the typical procedure using 3-bromo-2-[2-(3-methyl-but-1-ynyl)-phenoxymethyl]-pyridine **(1h)** (356 mg, 0.9 mmol) and 3-iodonitrobenzne. Purification by flash chromatography using 20:80 THF/hexane followed by reverse-phase purification provided 147 mg of 5-[2-methyl-1-(3-nitro-phenyl)-propylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene **(2h)** as a pale orange foamy solid (43% over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 4.3 Hz, 1H), 8.03 (dd, J = 1.9, 8.8 Hz, 1H), 7.98 (br, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.30-7.23 (m, 3H), 7.03 (m, 2H), 6.94 (dd, J = 1.4, 7.8 Hz, 1H), 6.78 (dd, J = 4.7, 7.8 Hz, 1H), 5.77 (d, J = 13.8 Hz, 1H), 5.06 (d, J = 13.8 Hz, 1H), 3.36 (m, J = 6.9 Hz, 1H), 1.28 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 7.1 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 155.0, 152.6, 147.8, 147.5, 145.6, 139.9, 136.5, 136.4, 136.3, 134.1, 129.8, 128.6, 127.8, 124.6, 122.5, 121.9, 121.8, 120.5, 72.9, 31.1, 21.9, 21.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{21}O_3N_2$ $[M+H]^+$= 373.1547, found 373.1560.

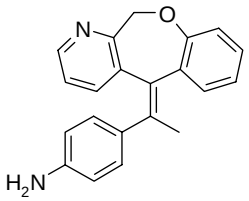


5-(1-Phenyl-ethylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (2i). Prepared according to the typical procedure using 3-bromo-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1a)** (500 mg, 1.4 mmol) and iodobenzne. Purification by flash chromatography using 20:80 THF/hexane provided 154 mg of 5-(1-phenyl-ethylidene)-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene **(2i)** as a pale yellow solid (36% over 3 steps). ^{1}H NMR (500 MHz, DMSO) δ 8.25 (dd, J = 1.9, 5.0 Hz, 1H), 7.34 (dd, J = 1.9, 7.5 Hz, 1H), 7.25-7.05 (m, 6H), 7.02-6.90 (m, 4H), 5.84 (d, J = 13.4 Hz, 1H), 4.93 (d, J = 13.4 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (500 MHz, DMSO) δ 154.9, 152.7, 148.0, 142.8, 138.1, 137.8, 136.6, 131.6, 131.4, 129.9, 128.6, 128.4, 127.6, 127.0, 123.4, 121.6, 120.2, 72.6, 22.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{18}ON$ $[M+H]^+$= 300.1383, found 300.1372.

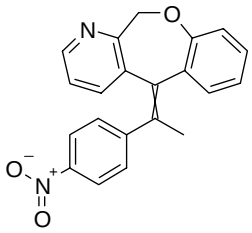


5-[1-(4-Fluoro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (2j). Prepared according to the typical procedure using 3-bromo-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1a)** (500 mg, 1.4 mmol) and 4-fluoro-iodobenzne. Purification by ion exchange chromatography followed by flash chromatography using 20:80 ethyl acetate/hexane provided 192 mg of 5-[1-(4-fluoro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene **(2j)** as a white chalky solid (42% over 3 steps). ^{1}H NMR (500 MHz, DMSO) δ 8.27 (t, J = 3.1 Hz, 1H), 7.34 (dd, J = 1.5, 7.6 Hz, 1H), 7.22 (dt, J = 1.5, 7.6 Hz, 1H), 7.14-7.08 (m, 2H), 7.04-6.96 (m, 5H), 6.92 (d, J = 7.9 Hz, 1H), 5.83 (d, J = 13.7 Hz, 1H), 4.92 (d, J = 13.2 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (500 MHz, DMSO) δ 154.9, 152.7, 148.1, 139.10, 139.08, 138.0,

136.8, 136.6, 132.0, 131.4, 130.8, 130.7, 129.9, 127.4, 123.5, 121.5, 120.1, 115.3, 115.1, 72.6, 22.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}ONF$ $[M+H]^+$= 318.1289, found 318.1277.\

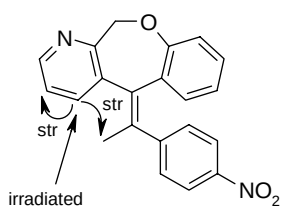


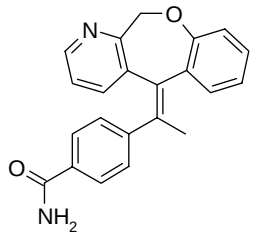
4-[1-(11H-10-Oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene)-ethyl]-phenylamine (2k). Prepared according to the typical procedure using 3-bromo-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1a)** (500 mg, 1.4 mmol) and 4-iodoaniline. Purification by ion exchange chromatography followed by flash chromatography using 700 mL 30:70 THF/hexane then 700 mL 40:60 THF/hexane provided 139 mg of 4-[1-(11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene)-ethyl]-phenylamine **(2k)** as a pale yellow chalky solid (31% over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 3.2 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.07-6.95 (m, 3H), 6.88-6.79 (m, 3H), 6.47 (d, J = 9.6 Hz, 2H), 5.81 (d, J = 13.9 Hz, 1H), 5.07 (d, J = 13.9 Hz, 1H), 3.60 (br, 2H), 2.22 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 155.2, 153.1, 147.3, 144.9, 137.9, 137.33, 137.30, 132.6, 130.75, 130.66, 129.7, 129.6, 129.1, 122.5, 121.5, 120.3, 114.5, 73.3, 22.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{19}ON_2$ $[M+H]^+$= 315.1492, found 315.1481.



5-[1-(4-Nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene (2l). Prepared according to the typical procedure using 3-bromo-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1a)** (500 mg, 1.4 mmol) and 4-iodonitrobenzene. Purification by ion exchange chromatography followed by flash chromatography using 1500 mL 30:70 ethyl acetate/hexane then 1500 mL 40:60 ethyl acetate/hexane provided 102 mg of E-5-[1-(4-nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene **(2l-E)** as an orange powdery solid (21% over 3 steps) and 81 mg of Z-5-[1-(4-nitro-phenyl)-ethylidene]-5,11-dihydro-10-oxa-1-aza-dibenzo[a,d]cycloheptene **(2l-Z)** as an orange crystalline solid (16% over 3 steps). E isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 4.4 Hz, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.30-7.23 (m, 4H), 7.07-7.03 (m, 2H), 6.93 (d, J = 7.5 Hz, 1H), 6.83 (dd, J = 4.8, 7.5 Hz, 1H), 5.79 (d, J = 14.5 Hz, 1H), 5.09 (d, J = 14.5 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 155.2, 153.5, 149.7, 148.2, 146.4, 137.0, 136.0, 135.4, 134.6, 129.9, 129.8, 129.6, 129.1, 123.4, 122.5, 122.1, 120.7, 73.4, 22.1; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}O_3N_2$ $[M+H]^+$= 345.1234, found 345.1221. Z isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 4.3 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.31-7.26 (m, 1H), 7.05 (dt, J = 1.8, 7.8 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.58-6.52 (m, 2H), 5.84 (d, J = 13.8 Hz, 1H), 5.11 (d, J = 13.8 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 155.2, 153.1, 149.8, 148.6, 146.3, 136.2, 135.8, 135.0, 134.8, 131.1, 129.7, 129.5, 128.1, 123.3, 122.7, 121.8, 120.1, 72.7, 21.6; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}O_3N_2$ $[M+H]^+$= 345.1234, found 345.1221.

NOE:





4-[1-(11H-10-Oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene)-ethyl]-benzamide (2m). Prepared according to the typical procedure using 3-bromo-2-(2-prop-1-ynyl-phenoxymethyl)-pyridine **(1a)** (500 mg, 1.4 mmol) and 4-iodobenzonitrile. It is believed the amide was obtained by hydrolysis of the nitrile under the reaction conditions. Purification by ion exchange chromatography followed by flash chromatography using 500 mL 40:60 THF/hexane then 1000 mL 80:20 THF/hexane provided 106 mg of 4-[1-(11H-10-oxa-1-aza-dibenzo[a,d]cyclohepten-5-ylidene)-ethyl]-benzamide **(2m)** as an off white powdery solid (22% over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 5.1 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 6.7 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.95 (dd, J = 1.6, 8.0 Hz, 1H), 6.80 (dd, J = 4.6, 7.7 Hz, 1H), 6.17 (br, 2H), 5.79 (d, J = 13.9 Hz, 1H), 5.09 (d, J = 13.9 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 169.1, 155.2, 153.2, 147.8, 146.6, 137.1, 136.5, 133.2, 131.5, 130.2, 129.6, 129.1, 128.9, 127.2, 122.5, 121.9, 120.5, 73.3, 22.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}O_2N_2$ $[M+H]^+$= 341.1296, found 341.1302. IR: 1666 cm^{-1}.

References:

1. Numata, A., Kondo, Y., Sakamoto, T., *Synthesis* **1999**, 2, 306
2. Srinivasan, J.M., Burks, H.E., Smith, C.R., Viswanathan, R., Johnston, J.N., *Synthesis* **2005**, 2, 330