Multicomponent-Multicatalyst Reactions $(MC)^2R$: Efficient Dibenzazepine Synthesis

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Supporting information

Table of Contents:

General Considerations:

Unless otherwise stated, reactions were carried out under an argon atmosphere in oven- or flame dried flasks or vials with magnetic stirring. Organic solutions were concentrated using a Buchi rotary evaporator at 30-45°C under reduced pressure. Analytical thin later chromatography (TLC) was performed on EMD Silica Gel 60 F254 plates (0.2 mm, 60 Å pore size). Visualization was done under a 254 nm UV light source, and by immersion in potassium permanganate solution. Flash chromatography was performed employing Silicycle Ultra-Pure 230-400 mesh silica gel.

Materials:

All reagents, catalysts and ligands were purchased from Sigma Aldrich, Strem, or VWR and used without further purification. Boronic acids were purchased from CombiBlocks and used as received. Prior to use, 1,4-dioxane and THF were distilled over Na/benzophenone, 1,2-dichloroethane was distilled over CaH_2.

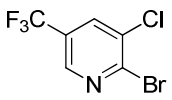
Instrumentation:

^1H, ^{13}C and ^{19}F NMR were recorded at 25°C in $CDCl_3$ on a Varian Mercury 400 MHz, 500 MHz, 600 MHz or 700 MHz, or Bruker Avance III 400 MHz spectrometer. ^1H spectra were referenced to residual protium resonances relative to Me_4Si ($CHCl_3$: δ 7.26). ^{13}C spectra were referenced to solvent carbon resonances ($CDCl_3$: δ 77.16). Chemical shifts are reported in parts per million (ppm) and coupling constants as scalar values in Hz. Data for ^1H NMR are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d

= doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, tt = triplet of triplets, qd = quartet of doublets, m = multiplet), coupling constant (*J*, Hz), and integration. High resolution mass spectra (HRMS) were obtained from an SI2 Micromass 70S-250 spectrometer operating at 70eV in EI mode, or an AB/Sciex QStar spectrometer operating in positive ESI mode. Infrared spectra were recorded using a Shimadzu FTIR 8400S spectrometer as a thin film on a NaCl disk.

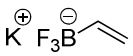
Experimental Procedures:

2-bromo-3-chloro-5-(trifluoromethyl)pyridine



2,3-dichloro-5-(trifluoromethyl)pyridine (2.20 g, 10.2 mmol, 1.0 eq.) was added to a flame dried round bottom flask/condenser setup. Proprionitrile (14 mL, freshly distilled from CaH_2) was added, followed by slow addition of trimethylsilylbromide (3.12 g, 20.4 mmol, 2.0 eq). The solution was heated to 100 °C for 15 h after which an aliquot (0.15 mL) was taken. The aliquot was filtered through a silica plug using EtOAc, the solvent was evaporated. The residue was dissolved in $CDCl_3$ and submitted for ^{1}H NMR, which showed 90 % conversion. At ambient temperature, the reaction mixture was poured into 2M NaOH (12 mL) to which ice had been added. The aqueous layer was extracted with Et_2O (3 x 10 mL), the combined organic layers were washed with H_2O (2 x 10 mL) and brine (10 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude product (2.40 g, 9.22 mmol, 90 %) as light brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.96 (s, 1H); **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.32 (s).

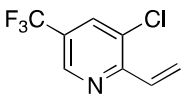
Potassium Trifluorovinylborate[1]



Trimethylborate (2.32 g, 22.3 mmol, 1.24 eq.) was dissolved in THF (15 mL) and vinylmagnesium bromide (1.0M in THF, 18.0 mL, 18.0 mmol, 1.0 eq.) was added dropwise at - 78 °C. The resulting suspension was stirred for 20 min at the same temperature and another hour at room temperature. Subsequently, the mixture was cooled to 0 °C and KHF_2 (6.97 g, 89.2 mmol, 4.95 eq.) was added in one portion. Water (12 mL) was added over 30 min and the resulting solution was stirred at room temperature for 20 min. The solvent was removed under reduced pressure, the residue was dissolved in acetone, filtered over a *Büchner* funnel and the filtrate was concentrated. The crude was dissolved in few hot acetone, reprecipitated with Et_2O, filtered off and dried under vacuum. The titled compound (1.33 g, 55 %) was obtained as a white powder. **^{1}H NMR** (400 MHz, Acetone-d_6) δ 6.04 – 5.64 (m, 1H), 5.38 – 5.00 (m, 2H), 2.91 – 2.66 (m, 1H); **^{19}F NMR** (377 MHz, Acetone-d_6) δ -142.92 (dd, J = 110.3, 54.3 Hz).

3-chloro-5-(trifluoromethyl)-2-vinylpyridine (1a)

[1] G. Molander, M. Rodriguez Rivero, *Org. Lett.* **2002**, *4*, 107

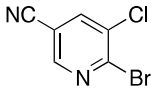


Procedure 1: Crude 2-bromo-3-chloro-5-(trifluoromethyl)pyridine (1.00 g, 3.84 mmol, 1.0 eq.), potassium trifluorovinylborate (566 mg, 4.22 mmol, 1.1 eq.), cesium carbonate (3.75 g, 11.52 mmol, 3.0 eq.), and $PdCl_2(dppf)\cdot DCM$ (282 mg, 0.346 mmol, 9.0 mol%) were added to a 100 mL round bottom flask and purged with argon. THF (40 mL) and H_2O (4 mL) were added, the flask was fitted with a condenser and the mixture was heated to 80 °C for 24 h. An aliquot (0.15 mL) was taken. The aliquot was filtered through a silica plug using EtOAc, the solvent was evaporated. The residue was dissolved in $CDCl_3$ and submitted for ^{1}H-NMR which showed full conversion. H_2O (40 mL) was added, the aqueous layer was extracted with Et_2O (3 x 40 mL) and the combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography using hexanes and Et_2O (0-2 %) yielded the titled compound (567 mg, 2.73 mmol, 71 %) as colorless oil which turned yellow overtime. The product was stored at -20 °C and was used as soon as possible.

Procedure 2: Crude 2-bromo-3-chloro-5-(trifluoromethyl)pyridine (781 mg, 3.00 mmol, 1.0 eq.), 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (485 mg, 3.15 mmol, 1.05 eq.), and potassium carbonate (1.66 g, 12.0 mmol, 4.0 eq.) were added to a 100 mL round bottom flask and purged with argon. DME (18 mL) and H_2O (9 mL) were added, followed by $Pd(PPh_3)_4$ (173 mg, 0.150 mmol, 5.0 mol%). The flask was fitted with a condenser and the mixture was heated to 100 °C for 4 h. An aliquot (0.15 mL) was taken and filtered through a silica plug using EtOAc and the solvent was evaporated. The residue was dissolved in $CDCl_3$ and submitted for ^{1}H NMR, which showed full conversion. H_2O (30 mL) was added, the aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography using hexanes and Et_2O (0-2 %) yielded the titled compound (352 mg, 1.70 mmol, 57 %) as colorless to pale yellow oil which turned yellow overtime. The product was stored at -20 °C and was used as soon as possible.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 0.8 Hz, 1H), 7.89 (d, J = 1.5 Hz, 1H), 7.27 (dd, J = 16.6, 11.0 Hz, 1H), 6.62 (dd, J = 17.0, 1.8 Hz, 1H), 5.74 (dd, J = 10.7, 1.8 Hz, 1H); **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 155.3 (q, J = 1.5 Hz), 144.3 (q, J= 4.0 Hz), 134.7 (q, J = 3.7 Hz), 130.6 130.0, 126.0 (q, J = 33.5 Hz), 124.0, 123.0 (q, J = 272.5Hz); **^{19}F NMR** (377 MHz, CD_2Cl_2) δ -63.7; **IR** (NaCl, neat): 2955, 2916, 2849, 1599, 1323, 1163, 1138, 1094, 1055 cm^{-1}; **HRMS** (ESI): calcd for $C_8H_6ClF_3N$ $(M+H)^+$: 208.0141; found. 208.0145.

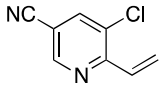
6-bromo-5-chloronicotinonitrile



A round bottom flask was charged with 2-amino-5-cyanopyridine (1.00 g, 8.40 mmol) and *N*-chlorosuccinimide (1.1 equiv, 1.24 g, 9.29 mmol) and dissolved in acetonitrile (20 mL).

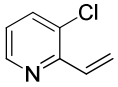
The mixture was stirred at room temperature for 39 hours, upon which TLC analysis showed incomplete consumption of starting material. The mixture was then heated to 60 ºC for 2 hours, upon which TLC showed complete consumption of starting material. After cooling to room temperature, copper (II) bromide (2 equiv. based on full conversion, 3.75 g, 16.8 mmol) and isopentyl nitrite (2 equiv. based on full conversion, 2.3 mL, d = 0.872 g/mL, 17.1 mmol) were added and the mixture was heated to 65 ºC for 2 hours. Once cooled to room temperature, the reaction was quenched with sat. NH_4Cl solution, partitioned with DCM and the aqueous layer separated and extracted three times with DCM. The combined organic layers were dried over magnesium sulphate and concentrated *in vacuo* to a brown solid. Silica flash column chromatography (11:1 Hexanes/EtOAc) gave the product (635 mg, 35 % over 2 steps) as a yellow solid. Product can be recrystallised from hexanes/DCM to give white needles. **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.55 (d, J = 2.0 Hz, 1H), 7.99 (d, J = 2.0 Hz, 1H); **^{13}C NMR** (75MHz, $CDCl_3$): δ149.7, 146.9, 140.2, 134.6, 114.6, 110.0; **IR** (NaCl, neat) 3030, 2993, 2240, 1409, 1371, 1276, 1259, 1133, 1041, 914, 765, 750 cm^{-1}; **HRMS** (DART): calcd for $C_6H_2BrClN_2^+$: 216.9168; found: 216.9165.

5-chloro-6-vinylnicotinonitrile (1b)



A 2-neck round bottom flask was charged with 2-bromo-3-chloro-5-cyanopyridine (303 mg, 1.39 mmol), K_2CO_3 (4 equiv., 763 mg, 5.53 mmol), and tetrakistriphenylphosphinepalladium(0) (5 mol %, 80 mg, 0.0692 mmol). A reflux condenser was added and the setup was purged with argon. A mixture of DME/H_2O (8 mL/4 mL) was added, plus 4,4,6-trimethyl-2-vinyl-1,2,3-dioxaborinane (1.2 equiv., 254 mg, 1.65 mmol). This mixture was heated to 80 ºC for 13 hours, at which point a small aliquot of the organic layer was removed and analysed by ^{1}H NMR, which showed complete consumption of starting material. After cooling to room temperature, the reaction was quenched with additional water, partitioned with diethyl ether, the organic layer separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulphate and concentrated *in vacuo* to a red oil. Column chromatography (40:1 → 30:1 Hexanes/EtOAc) gave the product (131 mg, 58 %) as a white solid. **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.70 (d, J = 1.9 Hz, 1H), 7.92 (d, J = 1.9 Hz, 1H), 7.24 (dd, J = 16.9, 10.7 Hz, 1H), 6.66 (dd, J = 16.9, 1.8 Hz, 1H), 5.80 (dd, J = 10.7, 1.8 Hz, 1H); **^{13}C NMR** (75MHz, $CDCl_3$): δ 155.6, 149.8, 140.2, 130.4, 130.1, 125.8, 115.7, 109.0; **IR** (NaCl, neat): 3071, 3063, 2234, 1583, 1451, 1385, 1373, 1302, 1276, 1262, 1233, 1209, 1061, 988, 944, 915, 906, 791, 748, 744 cm^{-1}; **m.p.** 87 – 89 ºC; **HRMS** (DART): calcd for $C_8H_5ClN_2^+$: 165.0220; found: 165.0219.

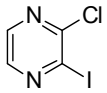
3-Chloro-2-vinylpyridine (1c)



To a round bottom flask containing a stirring bar, 2-bromo-3-chloropyridine (1.924 g, 10 mmol) and $Pd(PPh_3)_4$ (0.289 g, 0.25 mmol, 2.5 mol%) were added. The flask was fitted with

a reflux condenser and purged with nitrogen. THF (140 mL, 0.071 M) and water (40 mL, 0.25 M) were added and the reaction was stirred for 10 minutes at room temperature. The mixture became yellow. To the solution, 2,4,6-trivinyltricycloboroxane (2.12 g, 12 mmol, 1.2 equiv) and potassium carbonate (1.38 g, 10 mmol, 1 equiv) were added and the reaction was stirred at 90 °C for 16 hours. After cooling to room temperature, the solution was extracted with EtOAc, washing with H_2O. After drying over Mg_2SO_4, the solution was filtered and evaporated under reduced pressure. The resulting yellow oil was purified using flash chromatography (pentane/Et_2O, 95:5) to give the titled compound in 76% yield (1.06 g) as a colourless oil. **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ 8.48 (dd, J = 4.5, 1.3 Hz, 1H), 7.65 (dd, J = 8.1, 1.5 Hz, 1H), 7.31 – 7.20 (m, 1H), 7.13 (dd, J = 8.1, 4.6 Hz, 1H), 6.48 (dd, J = 17.0, 2.0 Hz, 1H), 5.59 (dd, J = 10.7, 2.0 Hz, 1H); **^{13}C NMR** (75 MHz, *$CDCl_3$*) δ 152.4, 147.7, 137.6, 131.7, 130.7, 123.6, 121.4; **IR** (NaCl, neat): 3047.63, 2984.94, 2925.15, 2853.78, 1445.70, 1429.30, 1418.69, 1389.79, 1046.42, 787.95 cm^{-1}; **HRMS** (EI): calcd for C_7H_6ClN $(M+1)^+$: 139.0189; found. 139.0192.

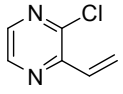
2-Chloro-3-iodopyrazine



2.55

A round bottom flask was charged with TMP (1.35 equiv., 4.6 mL, 27.3 mmol, d = 0.837 g/ML) and THF (60 mL) at room temperature, then cooled to -78 ºC. *n*-BuLi (1.25 equiv, 11.5 mL, 2.2 M, 25.3 mmol) was added dropwise at this temperature. The mixture was warmed to 0ºC and stirred for 30 minutes. This solution of LiTMP was cooled back to -78 ºC and 2-chloropyrazine (1.8 mL, 20.2 mmol, d = 1.283 g/mL) was added dropwise, such that the internal temperature did not rise above -70 ºC. The mixture was stirred for 30 mins at -78 ºC, developing a deep red colour, before iodine (2 equiv., 10.3g, 40.6 mmol) in THF (15 mL) was added dropwise, such that the internal temperature did not rise above -68 ºC. The reaction was stirred for 2 hrs at -78 ºC, quenched by the addition of MeOH (5 mL) in one portion, and allowed to come to room temperature. The solvent was concentrated *in vacuo*. The residue was taken up in DCM and sat. sodium thiosulfate solution, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over magnesium sulphate, and concentrated *in vacuo* to a red-brown oil. Silica flash column chromatography (21:1 Hex/EtOAc) gave the product (3.79g, 78%) as a yellow solid, **mp** 65-67 ºC. **^{1}H-NMR** (400MHz, $CDCl_3$): δ 8.30 (d, J = 2.4 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H); **^{13}C-NMR** (101MHz, $CDCl_3$): δ 154.6, 142.7, 142.1, 119.7; **HRMS** (DART): m/z calcd for $C_4H_3ClIN_2$ $(M+1)^+$: 240.9029, found 240.9029.

2-chloro-3-vinylpyrazine (1d)



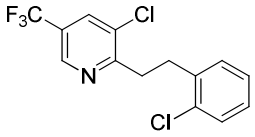
2.56

Suzuki Protocol: A 2-neck round bottom flask was charged with 2-chloro-3-iodopyrazine (1.14 g, 4.74 mmol), potassium vinyl trifluoroborate (1.2 equiv., 760 mg, 5.67 mmol), cesium carbonate (3 equiv., 4.61 g, 14.1 mmol), and 1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (10 mol%,

389 mg, 0.476 mmol). A reflux condenser was attached and the setup was purged with argon. THF (47 mL) and water (5 mL) were added, and the mixture was heated to reflux for 18 hours. At this point, an aliquot of the organic layer was withdrawn and analyzed by ^{1}H NMR, revealing full consumption of starting material. Upon cooling to room temperature, the reaction was quenched with additional water, partitioned with ether, and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted three times with ether. The combined organic layers were dried over magnesium sulphate and concentrated *in vacuo*. Silica flash column chromatography (30:1 Hexanes/EtOAc) gave the product (363 mg, 55%) as a yellow oil. **^{1}H NMR** (400MHz, $CDCl_3$): δ 8.47 (dd, J = 2.4, 0.5 Hz, 1H), 8.25 (d, J = 2.4 Hz, 1H), 7.20 (ddd, J = 16.9, 10.7, 0.5 Hz, 1H), 6.57 (ddd, J = 17.0, 1.7, 0.2 Hz, 1H), 5.72 (ddd, J = 10.8, 1.7, 0.3 Hz, 1H); **^{13}C NMR** (151MHz, $CDCl_3$): δ 149.1, 147.5, 142.5, 142.5, 130.4, 124.0.; **IR** (NaCl, neat) = 3050, 1626, 1546, 1517, 1447, 1411, 1349, 1189, 1161, 1080, 1065, 985, 945, 857, 798, 688, 657 cm^{-1}; **HRMS (DART)**: calcd for $C_6H_6ClN_2$ $(M+1)^+$ 141.0220, found 141.0221.

Note: this product is extremely volatile and several precautions were taken to ensure the best possible yield: the product was concentrated on a rotary evaporator with the heating bath set no higher than 25 ºC, at 30 – 40 mmHg; it was dried by passing a gentle stream of air over the mouth of the flask used to contain it (*not* via high vacuum); it was stored under argon in a -20 ºC freezer, but was stable only for several weeks when stored in this way, darkening upon storage; unusable samples are those which have darkened to black and/or have thickened to viscous gums.

3-Chloro-2-(2-chlorophenethyl)-5-(trifluoromethyl)pyridine (3a)



To a round-bottom flask were added 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (148.4 mg, 0.715 mmol), 2-chlorophenylboronic acid (168 mg, 1.07 mmol, 1.5 equiv), $[Rh(cod)OH]_2$ (6.52 mg, 0.014 mmol, 2 mol%), and K_2CO_3 (197 mg, 1.43 mmol, 2 equiv). The flask was fitted with a condenser and purged with argon, then 10 ml of dioxane and 1 ml of water were added and the mixture was stirred at room temperature for 5 minutes and then placed into a preheated oil bath at 60°C. The reaction was usually finished within 5h (but could be run overnight). The mixture was filtered through a silica plug with EtOAc and the solvent was removed under vacuum. The crude product was purified by silica gel chromatography (eluting with hexane: Et_2O 98:2) to give the titled compound in 81% yield (186 mg) as a colourless oil. **^{1}H NMR** (300 MHz, *$CDCl_3$*) δ 8.63 (s, 1H), 7.78 (s, 1H), 7.36 – 7.21 (m, 1H), 7.20 – 6.98 (m, 3H), 3.33 – 3.18 (m, 2H), 3.18 – 3.02 (m, 2H); **^{13}C NMR** (75 MHz, *$CDCl_3$*) δ 162.4, 144.0 (q, *J* = 4.0 Hz), 138.6, 134.3, 133.9 (q, *J* = 3.6 Hz), 131.6, 130.6, 129.7, 127.9, 127.0, 125.8 (q, *J* = 33.7 Hz), 123.0 (q, *J* = 272.7 Hz), 35.5, 31.9; **^{19}F NMR** (282 MHz, *$CDCl_3$*) δ -62.2; **IR** (NaCl, neat): 3071, 3019, 2936, 2862, 1605, 1559, 1476, 1445, 1397, 1323, 1171, 1136, 1090, 1059, 1053, 912 cm^{-1}; **HRMS** (ESI): calcd for $C_{14}H_{11}Cl_2F_3N$ $(M+H)^+$: 320.0221; found. 320.0224.

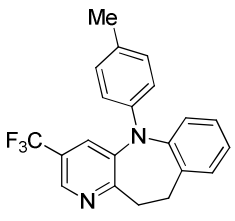
Table 1 General Procedure 1: Standard protocol for C-N coupling

To a vial were added the palladium source (5.0 mol%), ligand (0-10 mol%), and base (2.5 eq.). The vial was purged with argon, dioxane (0.3 mL) was added and the mixture was stirred for 5 minutes. To a second vial were added 3-chloro-2-(2-chlorophenethyl)-5-(trifluoromethyl)pyridine (32.0 mg, 0.10 mmol, 1.0 eq.) and *p*-toluidine (12.8 mg, 0.12 mmol, 1.2 eq.). The contents of the second vial was dissolved in dioxane (0.3 mL) and transferred to the catalyst solution *via* syringe, washing with dioxane (2 x 0.3 mL). The reaction mixture was stirred at rt for 5 min and then placed into a preheated oil bath at 110 °C. After 22 h, the reaction was cooled to room temperature, filtered through a silica plug using EtOAc and the solvent was removed under reduced pressure. ^{1}H NMR yields were determined with *p*-nitroacetophenone as internal standard. The product could be isolated by column chromatography using hexanes/EtOAc (95:5).

Table 2 General Procedure 2: Domino Process

In a 2 dram vial were combined $[Rh(cod)OH]_2$ (2.7 mg, 6 µmol, 2.0 mol%), Pd source (5.0 mol%), ligand(s) (5 mol% each) and K_2CO_3 (124.4 mg, 0.900 mmol, 3.0 eq.). The vial was fitted with a septum, purged with argon and dioxane (0.75 mL) and water (0.3 mL) were added via syringe. In a second vial were combined 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (62.3 mg, 0.300 mmol, 1.0 eq.), 2-chloroarylboronic acid (1.5 eq.) and aniline (1.65 eq.). The contents of the second vial was dissolved in dioxane (0.75 mL) and transferred to the catalyst solution via syringe, washing with dioxane (2 x 0.75 mL). The reaction mixture was stirred for 5 min at room temperature and subsequently, the septum was replaced by a *teflon* lined screw cap and the vial was placed into a preheated oil bath at 110 °C. After 22 h, the reaction was cooled to room temperature, filtered through a silica plug and the solvent was removed under reduced pressure. ^{1}H NMR yields were determined using *p*-nitroacetophenone as internal standard. The products could be isolated by column chromatography eluting with EtOAc (0-15 %) in hexanes.

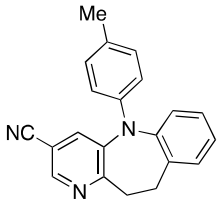
Tables 3 and 4: Representative procedure 3 for
5-(p-tolyl)-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (4a)



In a 2 dram vial were combined $[Rh(cod)OH]_2$ (1.8 mg, 4 µmol, 2.0 mol%), palladium precatalyst **6** (8.2 mg, 10 µmol, 5.0 mol%), XPhos (4.8mg, 10 µmol, 5.0 mol%) and K_2CO_3 (82.9 mg, 0.60 mmol, 3.0 eq.). The vial was fitted with a septum, purged with argon and dioxane (0.5 mL) and water (0.2 mL) were added *via* syringe. In a second vial were combined 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (41.5 mg, 0.20 mmol, 1.0 eq.), 2-chlorophenylboronic acid (46.9 mg, 0.3 mmol, 1.5 eq.) and *p*-toluidine (35.4 mg, 0.33 mmol, 1.65 eq.). The contents of the second vial was dissolved in dioxane (0.5 mL) and

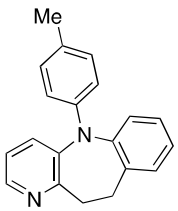
transferred to the catalyst solution via syringe, washing with dioxane (2 x 0.5 mL). The vial septum was replaced with a Teflon-lined screw cap and the reaction was placed into an oil bath at 110 °C. After 22 hours the reaction was cooled to room temperature, filtered through a silica plug, and the solvents were removed under reduced pressure. The reaction crude was purified through column chromatography (95:5 hexane: Et_2O). The cyclized product was obtained as a colourless oil in 67% yield (47.5 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.1 Hz, 1H), 7.97 (d, *J* = 1.8 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.38 – 7.29 (m, 3H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.57 – 6.51 (m, 2H), 3.33 – 3.21 (m, 2H), 3.09 – 2.99 (m, 2H), 2.26 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.7 (q, *J* = 1.3 Hz), 145.8, 143.6, 143.4 (q, *J* = 4.0 Hz), 139.7, 139.5, 134.9 (q, *J* = 3.5 Hz), 130.3, 130.0, 129.9, 128.9, 128.2, 127.7, 125.3 (q, *J* = 33.1 Hz), 123.4 (q, *J* = 272.5 Hz), 114.0 (2), 35.9, 29.0, 20.4; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.0; **IR** (NaCl, neat): 3063, 3028, 2926, 2862, 1616, 1506, 1489, 1456, 1435, 1429, 1410, 1339, 1319, 1296, 1267, 1240, 1207, 1165, 1128, 1086, 1036, 978, 947, 930, 910, 895, 808, 772, 756, 737, 721, 704, 687, 664, 646, 627 cm^{-1}; **HRMS** (ESI): calcd for $C_{21}H_{18}F_3N_2$ $(M+H)^+$: 355.1422; found. 355.1419.

5-(*p*-tolyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine-3-carbonitrile (4b)



This compound was prepared according to procedure 3: The substrates used were 5-chloro-6-vinylnicotinonitrile (16.4 mg, 0.1 mmol), 2-chlorophenylboronic acid (23.5 mg, 0.15 mmol, 1.5 equiv) and *p*-toluidine (17.7 mg, 0.165 mmol, 1.65 equiv). The reaction crude was purified through column chromatography (9:1 pentanes: Et_2O). The cyclized product was obtained as a yellow oil in 68% yield (17 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.0 Hz, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.38 - 7.28 (m, 4H), 6.99 (dt, *J* = 8.1, 0.7 Hz, 2H), 6.57 - 6.52 (m, 2H), 3.29 - 3.25 (m, 2H), 3.03 (dd, *J* = 7.4, 5.8 Hz, 2H), 2.26 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ162.12, 148.23, 145.17, 143.28, 139.97, 139.76, 139.33, 130.08, 129.91, 129.61, 129.58, 128.06, 127.66, 116.26, 114.70, 107.78, 36.41, 29.71, 28.82, 20.35; **IR** (NaCl, neat): 2953.12, 2923.22, 2852.81, 2232.68, 1615.44, 1589.40, 1507.42, 1489.10, 1449.55, 1423.51, 1400.37, 1301.03, 1274.03, 912.36, 807.24, 751.30, 648.10, 614.35 cm^{-1}; **HRMS** (DART): calcd for $C_{21}H_{17}N_3$: 311.14225; found: 312.15007 $(M+H)^+$.

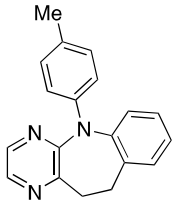
5-(*p*-tolyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine (4c)



In a 1 dram vial were combined: 3-chloro-2-vinylpyridine (28 mg, 0.2 mmol, 1 equiv), 2-chlorophenylboronic acid (46.9 mg, 0.3 mmol, 1.5 equiv), K_2CO_3 (30 mg, 0.22 mmol, 1.1 equiv) and $[Rh(cod)OH]_2$ (1.84 mg, 0.004 mmol, 2 mol%). This vial was fitted with a stirring bar and a cap with a septum and was purged with argon. Dioxane (1 ml) and water (0.1 ml) were added and the vial was placed into an oil bath at 110 °C for 0.5 hours and then was allowed to cool to room temperature. At this point into a second vial were

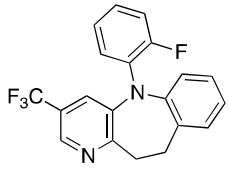
weighed precatalyst **6** (8.2 mg, 0.01 mmol, 5 mol%), XPhos (4.8 mg, 0.01 mmol, 5 mol%) and *p*-toluidine (35.4 mg, 0.33 mmol, 1.65 equiv). After purging, the Pd catalyst, ligand and amine were dissolved in dioxane (0.4 ml) and transferred into the rhodium-catalyzed reaction, along with NaO*t*Bu (48 mg, 0.5 mmol, 2.5 equiv), washing with dioxane (2x0.3 mL). The vial septum was replaced with a Teflon-lined screw cap and the reaction was placed into an oil bath at 110 ^{o}C. After 16 hours the reaction was cooled to room temperature, filtered through a silica plug, and the solvents were removed under reduced pressure. The reaction crude was purified through column chromatography (4:1 pentanes: EtOAc). The cyclized product was obtained as a colourless solid in 41% yield (17 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.72 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.48 - 7.05 (m, 4H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 8.6 Hz, 2H), 3.20 (dd, *J* = 7.7, 5.7 Hz, 2H), 3.00 (dd, *J* = 7.7, 5.7 Hz, 2H), 2.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ157.74, 147.15, 146.27, 143.85, 139.69, 138.06, 130.34, 129.90, 129.54, 127.69, 127.65, 127.34, 121.87, 113.15, 77.33, 77.01, 76.69, 35.10, 29.20, 20.26; **IR** (NaCl, thin film): 3022.55, 2924.18, 2857.64, 1615.44, 1505.49, 1489.10, 1452.45, 1438.94, 1298.14, 1273.06, 1092.71, 808.2, 800.49, 769.62, 752.26 cm^{-1}; **m. p.**: 60 – 63 ^{o}C; **HRMS** (DART): calcd for $C_{20}H_{18}N_2$: 286.14700; found: 287.15482 $(M+H)^+$.

5-(*p*-tolyl)-10,11-dihydro-5*H*-benzo[*b*]pyrazino[2,3-*f*]azepine (4d)



This compound was prepared according to procedure 3: The substrates used were 2-chloro-3-vinylpyrazine (42.0 mg, 0.3 mmol, 1 equiv), 2-chlorophenylboronic acid (70.4 mg, 0.45 mmol, 1.5 equiv), and *p*-toluidine (35.4 mg, 0.33 mmol, 1.65 equiv). The product was isolated using column chromatography (Hexanes: EtOAc 9:1) as yellow solid in 53% yield (46 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 1.2 Hz, 2H), 7.25 (d, *J* = 6.8 Hz, 2H), 7.16 – 7.10 (m, 4H), 7.10 – 7.05 (m, 3H), 3.33 (dd, *J* = 7.2, 4.7 Hz, 2H), 3.22 – 3.16 (m, 2H), 2.33 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.83, 146.55, 144.15, 143.32, 139.12, 138.18, 136.32, 133.52, 129.66, 128.96, 127.52, 127.10, 125.64, 124.11, 77.33, 77.01, 76.70, 38.66, 30.26, 20.89; **IR** (NaCl, thin film): 2925, 2855, 1510, 1505, 1492, 1455, 1397, 1395, 1316, 1299, 1276, 1132, 809, 751, 737 cm^{-1}; **m. p.**: 132 – 134 ^{o}C; **HRMS** (DART): calcd for $C_{19}H_{18}N_3$ 287.3584; found: 288.1504 $(M+H)^+$.

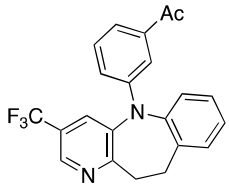
5-(2-fluorophenyl)-3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine (4e)



This compound was prepared according to procedure 3: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (62.3 mg, 0.3 mmol, 1 equiv), 2-chlorophenylboronic acid (70.4 mg, 0.45 mmol, 1.5 equiv), and 2-fluoroaniline (55.0 mg, 0.50 mmol, 1.65 equiv). The product was isolated using column chromatography (Hexanes: EtOAc 96:4) as an orange oil in 69% yield (74 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (d, J = 0.8 Hz, 1H), 7.49 (s, 1H), 7.30 – 7.23 (m, 2H), 7.21 – 7.10 (m, 6H), 3.46 – 3.38 (m,

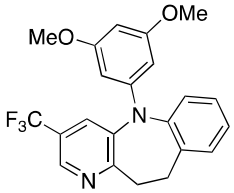
2H), 3.25 (dd, J = 7.2, 4.9 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.96 (d, J = 248.3 Hz), 156.67, 144.46, 141.66 (d, *J* = 1.1 Hz), 139.45 (q, *J* = 4.1 Hz), 137.74, 134.02 (d, *J* = 10.3 Hz), 129.57, 127.50 (p, *J* = 3.5 Hz), 127.26 (d, *J* = 1.5 Hz), 127.18, 126.63 (d, *J* = 1.6 Hz), 126.32 (d, J = 7.7 Hz), 126.04, 125.18 (d, *J* = 3.8 Hz), 124.70 (q, *J* = 32.7 Hz), 123.42 (q, *J* = 272.6 Hz), 117.56 (d, J = 20.7 Hz), 37.97, 30.51; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.16; **IR** (NaCl, neat): 3066, 3036, 2933, 2860, 2360, 2343, 1602, 1494, 1454, 1429, 1415, 1336, 1298, 1259, 1215, 1166, 1132, 1101, 974, 752; **HRMS** (ESI): calcd for $C_{20}H_{15}F_4N_2$ $(M+H)^+$: 359.11714; found: 359.11810.

1-(3-(3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepin-5-yl)phenyl)ethanone (4f)



This compound was prepared according to procedure 3: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (62.3 mg, 0.3 mmol, 1 equiv), 2-chlorophenylboronic acid (70.4 mg, 0.45 mmol, 1.5 equiv), and 1-(3-aminophenyl)ethanone (67.5 mg, 0.50 mmol, 1.65 equiv). The product was isolated using column chromatography (Hexane: Et_2O 9:1 with 5% Et_3N) as a pale yellow oil in 76% yield (41 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (d, J = 1.1 Hz, 1H), 7.99 (d, J = 1.8 Hz, 1H), 7.38 (m, 5H), 7.25 – 7.17 (m, 2H), 6.78 (dd, J = 8.2, 2.6 Hz, 1H), 3.29 (t, J = 6.7 Hz, 2H), 3.05 – 2.99 (m, 2H), 2.47 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.07, 161.87 (d, *J* = 1.2 Hz), 148.18, 144.09 (q, *J* = 4.0 Hz), 142.76, 139.28, 138.64, 138.29, 134.77 (q, J = 3.5 Hz), 130.54, 129.67, 129.52, 128.74, 128.01, 125.42 (q, *J* = 33.3 Hz), 124.47, 123.11 (q, *J* = 272.6 Hz), 117.55, 112.09, 35.44, 28.65, 26.67; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.01; **IR** (NaCl, neat): 3066, 2929, 2864, 2360, 2341, 1685, 1595, 1575, 1491, 1442, 1425, 1411, 1356, 1338, 1303, 1242, 1166, 1138, 1087, 767, 729, 688, 648, 586; **HRMS** (ESI): calcd for $C_{22}H_{17}F_3N_2O$: 382.1293; found: 383.13737 $(M+H)^+$.

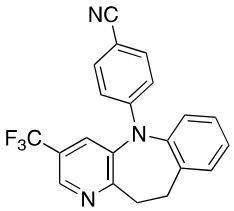
5-(3,5-dimethoxyphenyl)-3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine (4g)



This compound was prepared according to procedure 3: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (41.5 mg, 0.2 mmol, 1 equiv), 2-chlorophenylboronic acid (46.9 mg, 0.3 mmol, 1.5 equiv), and 3,5-dimethoxyaniline (50.5 mg, 0.165 mmol, 1.65 equiv). The product was isolated using column chromatography (Hexanes: EtOAc 96:4) as an off-white powder in 45% yield (36 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 1.2 Hz, 1H), 7.98 (d, *J* = 1.6 Hz, 1H), 7.42 - 7.28 (m, 4H), 5.98 (t, *J* = 2.1 Hz, 1H), 5.70 (d, *J* = 2.1 Hz, 2H), 3.66 (s, 6H), 3.27 (t, *J* = 6.7 Hz, 2H), 3.03 (dd, *J* = 7.6, 5.9 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.80, 161.49, 149.83, 143.77 (q, *J* = 4.1 Hz), 142.95, 139.33, 138.71, 134.99 (q, *J* = 3.5 Hz), 130.15, 129.67, 128.37, 127.57, 125.03 (q, *J* = 33.1 Hz), 123.04 (q, *J* = 272.6 Hz), 92.77, 90.46, 55.05, 35.34, 28.52; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.06; **IR** (NaCl, thin film): 2999.41, 2952.15, 2931.9, 2839.31, 2359.02, 2330.09, 1700.31, 1616.4, 1592.29,

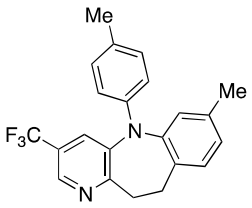
1476.56, 1457.27, 1424.48, 1410.01, 1337.68, 1233.52, 1204.59, 1153.47, 1134.18, 1085.96, 1071.49, 817.85, 766.73, 754.19, 682.82, 668.36 cm^{-1}; **m. p.**: 124 - 125 ^{o}C; **HRMS** (DART): calcd for $C_{22}H_{19}F_3N_2O_2$: 400.13986; found: 401.14769 $(M+H)^+$.

4-(3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepin-5-yl)benzonitrile (4h)



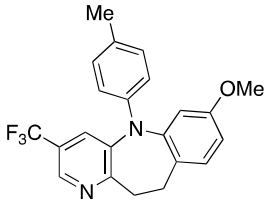
This compound was prepared according to procedure 3: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (41.5 mg, 0.2 mmol, 1 equiv), 2-chlorophenylboronic acid (46.9 mg, 0.3 mmol, 1.5 equiv), and 4-aminobenzonitrile (38.2 mg, 0.165 mmol, 1.65 equiv). The product was isolated using column chromatography (Hexanes: EtOAc 9:1) as a colourless solid in 59% yield (43 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 1.9 Hz, 1H), 7.95 (dd, J = 2.0, 0.9 Hz, 1H), 7.49 - 7.33 (m, 6H), 6.60 - 6.48 (m, 2H), 3.29 (t, J = 6.8 Hz, 2H), 3.01 (t, J = 6.8 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.77 (d, J = 1.4 Hz), 150.90, 144.86 (q, J = 4.0 Hz), 141.96, 138.75, 137.63, 134.49 (q, J = 3.4 Hz), 133.74, 130.78, 129.24, 129.09, 128.23, 125.55 (q, J = 33.5 Hz), 122.95 (q, J = 272.7 Hz), 119.59, 112.86, 101.61, 77.35, 77.04, 76.72, 35.16, 28.46; ^{19}F NMR (377 MHz, $CDCl_3$) δ -61.98; **IR** (NaCl, neat): 3060.17, 2926.11, 2854.74, 2219.18, 1599.04, 1507.42, 1437.02, 1409.05, 1339.61, 1322.25, 1166.97, 1139.00, 1086.92, 978.91, 824.60, 755.16 cm^{-1}; **m. p.**: 144 - 146 ^{o}C; **HRMS** (DART): calcd for $C_{21}H_{14}F_3N_3$: 365.11398; found: 366.12181 $(M+H)^+$.

7-methyl-5-(*p*-tolyl)-3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine (4i)



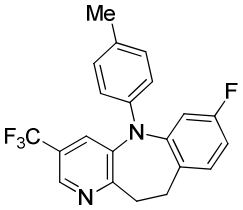
This compound was prepared according to procedure 3: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (62.3 mg, 0.3 mmol, 1 equiv), 2-chloro-4-methylphenylboronic acid (76.7 mg, 0.45 mmol, 1.5 equiv), and *p*-toluidine (53.0 mg, 0.50 mmol, 1.65 equiv). The product was isolated using column chromatography (95:5 hexanes:EtOAc) as a beige solid in 82% yield (92 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (d, J = 1.2 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.25 – 7.21 (m, 2H), 7.15 – 7.08 (m, 1H), 6.98 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 8.6 Hz, 2H), 3.30 – 3.22 (m, 2H), 3.03 – 2.95 (m, 2H), 2.37 (s, 3H), 2.26 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.90 (d, J = 1.3 Hz), 145.73, 143.29 (q, J = 4.0 Hz), 143.24, 139.46, 137.51, 136.18, 134.82 (q, J = 3.5 Hz), 130.32, 130.02, 129.75, 128.81, 128.57, 125.14 (q, J = 33.1 Hz), 123.25 (q, J = 272.5 Hz), 113.69, 35.78, 28.40, 20.98, 20.30; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.00; **IR** (NaCl, thin film): 3026, 2924, 2862, 2360, 2343, 1608, 1506, 1433, 1408, 1338, 1300, 1166, 1132, 1087, 808, 759, 572 cm^{-1}; **m. p.**: 115 ^{o}C; **HRMS** (ESI): calcd for $C_{22}H_{20}F_3N_2$ $(M+H)^+$: 369.15786; found: 369.15752.

7-methoxy-5-(*p*-tolyl)-3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine (4j)



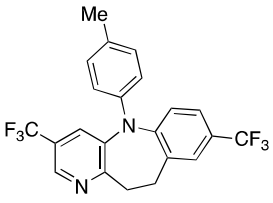
This compound was prepared according to procedure 3: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (43.2 mg, 0.2 mmol, 1 equiv), 2-chloro-4-methoxyphenylboronic acid (58.0 mg, 0.3 mmol, 1.5 equiv), and *p*-toluidine (35.4 mg, 0.33 mmol, 1.65 equiv). The product was isolated using column chromatography (95:5 hexanes:EtOAc) as an off-white solid in 74% yield (56.6 mg).[1]**H NMR** (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.2 Hz, 1H), 7.94 (d, *J* = 2.1 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.04 - 6.92 (m, 3H), 6.85 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.53 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.24 (t, *J* = 6.6 Hz, 2H), 2.95 (dd, *J* = 7.4, 5.9 Hz, 2H), 2.25 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.99, 159.00, 145.55, 144.11, 143.39 (q, *J* = 3.9 Hz), 139.32, 134.77 (q, *J* = 3.4 Hz), 131.15, 130.86, 129.80, 128.80, 125.14 (q, *J* = 33.1 Hz), 123.25 (q, *J* = 272.4 Hz). 114.92, 113.96, 113.84, 55.50, 35.86, 28.08, 20.32; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.00; **IR** (NaCl, neat): 3027.38, 20005.20, 2922.25, 2849.92, 1607.72, 1505.49, 1408.08, 1338.64, 1280.78, 1155.40, 1130.32, 1267.27, 808.20 cm^{-1}; **m. p.**: 108 – 111 °C; **HRMS** (ESI): calcd for $C_{22}H_{19}F_3N_2O$: 384.1449; found: 385.15277 $(M+1)^+$

8-fluoro-5-(p-tolyl)-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (4k)



This compound was prepared according to procedure 3: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (62.3 mg, 0.3 mmol, 1 equiv), 2-chloro-4-fluorophenylboronic acid (78.5 mg, 0.45 mmol, 1.5 equiv), and *p*-toluidine (53.0 mg, 0.50 mmol, 1.65 equiv). The product was isolated using column chromatography (95:5 hexanes:EtOAc) as a colourless solid in 82% yield (91 mg). [1]**H NMR** (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.1 Hz, 1H), 7.92 (d, *J* = 1.7 Hz, 1H), 7.29 (dd, *J* = 8.4, 6.3 Hz, 1H), 7.12 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.06 – 6.96 (m, 3H), 6.56 (d, *J* = 8.6 Hz, 2H), 3.32 – 3.21 (m, 2H), 3.08 – 2.96 (m, 2H), 2.27 (s, 3H); **^{13}C NMR** (101 MHz, *CDCl*$_3$) δ 161.7 (d, *J* = 246.8 Hz), 161.4 (q, *J* = 1.2 Hz), 145.2, 144.6 (d, *J* = 9.8 Hz), 143.4 (q, *J* = 4.0 Hz), 139.3, 134.9 (d, *J* = 3.4 Hz), 134.5 (q, *J* = 3.5 Hz), 131.4 (d, *J* = 9.1 Hz), 130.1 , 129.8, 125.4 (q, *J* = 33.3 Hz), 123.3 (q, *J* = 272.5 Hz), 116.8 (d, *J* = 21.3 Hz), 115.0 (d, *J* = 20.9 Hz), 114.8 (2), 35.8, 28.6, 20.5; **^{19}F NMR** (377 MHz, *CDCl*$_3$) δ -62.0 (s), -114.4 (dd, *J* = 15.2, 8.5 Hz); **IR** (NaCl, neat): 3063, 3030, 2926, 2861, 1607, 1506, 1499, 1424, 1343, 1302, 1273, 1260, 1242, 1221, 1165, 1128, 1086, 1015, 997, 972, 959, 922, 878, 854, 808, 762, 737, 719, 691, 664, 633, 604 cm^{-1}; **m. p.**: 62 – 65 °C; **HRMS** (ESI): calcd for $C_{21}H_{17}F_4N_2$ $(M+H)^+$: 373.1328; found. 373.1339

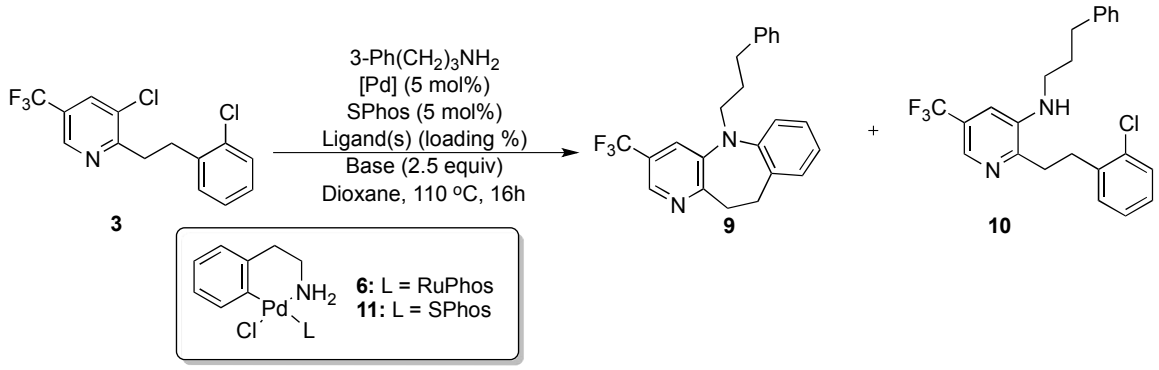
5-(*p*-tolyl)-3,8-bis(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine (4l)



This compound was prepared according to procedure 3: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (62.3 mg, 0.3 mmol, 1 equiv),

2-chloro-5-(trifluoromethyl)phenylboronic acid (101.0 mg, 0.45 mmol, 1.5 equiv), and *p*-toluidine (53.0 mg, 0.5 mmol, 1.65 equiv). The product was isolated using column chromatography (95:5 pentanes:EtOAc) as a colourless solid in 52% yield (66 mg).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.90 - 7.88 (m, 1H), 7.70 - 7.42 (m, 3H), 7.08 - 6.86 (m, 3H), 6.57 (d, *J* = 8.6 Hz, 1H), 3.50 - 3.21 (m, 2H), 3.19 - 3.03 (m, 2H), 2.28 (t, 1H); **^{13}C NMR** (151 MHz, HF-decoupled, $CDCl_3$) δ 161.16, 146.88, 145.06, 143.53, 139.58, 139.51, 134.25, 130.71, 130.46, 130.14, 129.65, 127.87, 125.70, 124.89, 124.16, 123.56, 122.84, 115.88, 35.74, 29.89, 20.74; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.07, -62.40; **IR** (NaCl, neat): 3030.27, 2927.08, 2865.35, 1609.65, 1562.39, 1510.31, 1505.49, 1435.09, 1408.08, 1336.71, 1268.24,1255.70, 1202.66, 1166.01, 1127.43, 1087.89, 972.16, 932.61, 790.84, 776.37 cm^{-1}; **m. p.**: 80 – 83 ^oC **;HRMS** (ESI): calcd $C_{22}H_{16}F_6N_2$: 422.1218; found: 423.12959 $(M+1)^+$.

Optimization for Pd-Catalyzed C-N bond formation for aliphatic amines:

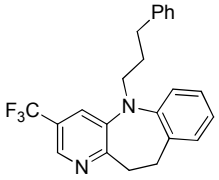


Entry	[Pd]	Base	Ligand(s)	Loading (mol %)	9 (%)[a]	10 (%)[a]
1	$Pd(OAc)_2$	NaO^tBu	RuPhos/XPhos	5+5	71	17
2	$Pd(OAc)_2$	K_2CO_3	RuPhos/XPhos	5+5	-	55
3	$Pd(OAc)_2$	NaO^tBu	RuPhos	10	79	-
4	$Pd(OAc)_2$	NaO^tBu	Josiphos	10	-	-
5	$Pd(OAc)_2$	NaO^tBu	DavePhos	10	-	61
6	**11**	NaO^tBu	-	-	38	22
7	**11**	NaO^tBu	SPhos	5	62	36
8	$Pd(OAc)_2$	NaO^tBu	Sphos/DavePhos	5+5	7	23
9	**11**	NaO^tBu	RuPhos	5	72	5

10	**6**	NaO^{t}Bu	SPhos	5	85	6
11	**6**	NaO^{t}Bu	XPhos	5	3	21
12	**6**	NaO^{t}Bu	SPhos	5	3	45

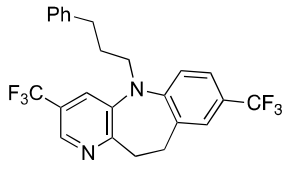
[a] Yields determined by ^{1}H NMR spectroscopy using *p*-nitroacetophenone as an internal standard

Tables 5 and 6: Representative procedure 4 for 5-(3-phenylpropyl)-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (9b)



In a 1 dram vial were combined: 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (41.5 mg, 0.2 mmol), 2-chlorophenylboronic acid (46.9 mg, 0.3 mmol, 1.5 equiv), K_2CO_3 (30 mg, 0.22 mmol, 1.1 equiv) and $[Rh(cod)OH]_2$ (1.84 mg, 0.004 mmol, 2 mol%). This vial was fitted with a stirring bar and a cap with a septum and was purged with argon. Dioxane (1 ml) and water (0.1 ml) were added and the vial was placed into an oil bath at 110 ^{o}C for 0.5 hours and then was allowed to cool to room temperature before 4Å molecular sieves (30 mg) were added. At this point into a second vial were weighed precatalyst **6** (8.2 mg, 0.01 mmol, 5 mol%) and SPhos (4.1 mg, 0.011 mmol, 5 mol%). The palladium catalyst and ligand were dissolved in dioxane (0.4 ml) and transferred into the rhodium-catalyzed reaction, along with the amine (1.65 equiv) and NaO*t*Bu (48 mg, 0.5 mmol, 2.5 equiv), washing with dioxane (2x0.3 mL). The vial septum was replaced with a Teflon-lined screw cap and the reaction was placed into an oil bath at 110 ^{o}C. After 16 hours the reaction was cooled to room temperature, filtered through a silica plug, and the solvents were removed under reduced pressure. The reaction crude was purified through column chromatography (9:1 hexane: Et_2O). The cyclized product was obtained as a colourless oil in 60% yield (46 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (d, J = 0.6 Hz, 1H), 7.44 (d, J = 1.3 Hz, 1H), 7.29 – 7.15 (m, 5H), 7.13 – 7.04 (m, 4H), 3.76 (t, J = 6.9 Hz, 2H), 3.43 – 3.34 (m, 2H), 3.33 – 3.22 (m, 2H), 2.71 – 2.61 (m, 2H), 1.96 – 1.85 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9 (q, J = 1.4 Hz), 147.5, 144.1, 141.4, 137.7 (q, J = 4.2 Hz), 137.4, 129.0, 128.6 (2), 128.4 (2), 127.1, 126.2, 124.9, 124.5 (q, J = 32.5 Hz), 123.77 (q, J = 272.5 Hz), 122.2 (q, J = 3.5 Hz), 121.8, 50.1, 37.5, 33.3, 29.8, 29.4; **^{19}F NMR** (377 MHz, *CDCl$_3$*) δ -62.1; **IR** (NaCl, neat): 3084, 3063, 3026, 2926, 2855, 1603, 1495, 1456, 1418, 1339, 1229, 1148, 1099, 1032, 972, 951, 901, 752, 743, 700, 650 cm^{-1}; **HRMS** (ESI): calcd for $C_{23}H_{22}F_3N_2$ $(M+H)^+$: 383.1735; found. 383.1735.

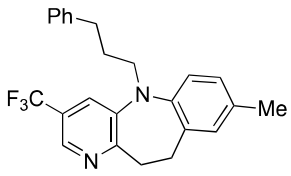
5-(3-phenylpropyl)-3,8-bis(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine (9a)



This compound was prepared according to procedure 4: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (20.8 mg, 0.1 mmol), 2-chloro-4-trifluoromethylphenylboronic acid (33.7 mg, 0.15 mmol, 1.5 equiv)

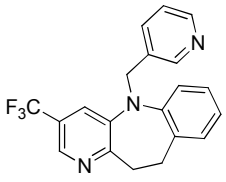
and 3-phenylpropan-1-amine (24 µl, 0.33 mmol, 1.65 equiv). The reaction crude was purified through column chromatography (9:1 pentanes: EtOAc). The cyclized product was obtained as a yellow oil in 68% yield (29 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.56 - 7.40 (m, 3H), 7.33 - 7.21 (m, 2H), 7.17 (dd, *J* = 20.2, 7.8 Hz, 2H), 7.07 (d, *J* = 6.9 Hz, 2H), 3.77 (t, *J* = 6.9 Hz, 2H), 3.39 (q, *J* = 5.7 Hz, 2H), 3.30 (q, *J* = 5.8, 5.4 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 1.89 (p, *J* = 7.2 Hz, 2H); **^{13}C NMR** (151 MHz, HF-decoupled, $CDCl_3$) δ 156.22, 150.06, 143.18, 140.82, 138.64, 136.48, 128.51, 128.19, 126.30, 126.17, 126.12, 124.61, 124.04, 123.06, 121.41, 77.19, 76.98, 76.77, 50.14, 36.27, 33.06, 29.97, 29.12; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.09, -62.12; **HRMS** (DART): calcd for $C_{24}H_{20}F_6N_2$: 450.1531; found: 451.16089 $(M+1)^+$

8-methyl-5-(3-phenylpropyl)-3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine (9c)



This compound was prepared according to procedure 4: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (20.8 mg, 0.1 mmol), 2-chloro-4-methylphenylboronic acid (25.6 mg, 0.15 mmol, 1.5 equiv) and 3-phenylpropan-1-amine (24 µl, 0.33 mmol, 1.65 equiv). The reaction crude was purified through column chromatography (92.5:7.5 pentanes: Et_2O). The cyclized product was isolated as a 1:1.5 inseparable mixture of **10c** and **9c**. Selected peaks from **^{1}H NMR** (400 MHz, $CDCl_3$) **10c:** δ 8.16 (d, *J* = 1.9 Hz, 1H), 7.34 - 6.92 (m, 8H), 6.88 (d, *J* = 2.1 Hz, 1H), 3.71 (t, *J* = 6.9 Hz, 2H), 3.10 (ddd, *J* = 12.3, 10.5, 5.9 Hz, 2H), 2.90 (dd, *J* = 10.4, 6.1 Hz, 2H), 2.76 (t, *J* = 7.5 Hz, 2H), 2.28 (s, 3H), 1.98 (p, *J* = 7.2 Hz, 2H); **9c:** δ 8.30 (d, *J* = 1.1 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.35 - 6.92 (m, 8H), 3.97 (d, *J* = 5.4 Hz, 2H), 3.34 (t, *J* = 6.4 Hz, 2H), 3.21 (dd, *J* = 7.4, 5.3 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.30 (s, 3H), 1.88 (p, *J* = 7.0 Hz, 2H).

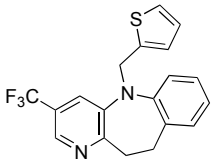
5-(pyridin-3-ylmethyl)-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (9d)



This compound was prepared according to procedure 4: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (20.8 mg, 0.2 mmol), 2-chlorophenylboronic acid (46.9 mg, 0.3 mmol, 1.5 equiv) and pyridin-3-ylmethanamine (34 µl, 0.33 mmol, 1.65 equiv). The reaction crude was purified through column chromatography (9:1 pentanes: EtOAc). The cyclized product was obtained as a colourless solid in 68% yield (48 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (br s, 1H), 8.44 (br s, 1H), 8.32 (d, *J* = 0.7 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 1.3 Hz, 1H), 7.24 – 7.10 (m, 4H), 7.10 – 7.01 (m, 1H), 4.97 (s, 2H), 3.46 – 3.34 (m, 2H), 3.34 – 3.25 (m, 2H); **^{13}C NMR** (101 MHz, *$CDCl_3$*) δ 156.2 (d, *J* = 1.4 Hz), 149.8, 149.1, 147.3, 143.2, 138.3 (q, *J* = 4.1 Hz), 136.9, 135.8, 132.4, 129.2, 127.2, 125.2, 124.4 (dd, *J* = 67.0, 34.4 Hz), 123.7, 123.6 (q, *J* = 272.5 Hz), 122.5 (q, *J* = 3.5 Hz), 121.5, 53.1, 37.4, 29.9; **^{19}F NMR** (377 MHz, *$CDCl_3$*) δ -62.3; **IR** (NaCl, thin film): 3055, 3034, 2924, 2924, 2853, 1603, 1568, 1495, 1456, 1427,

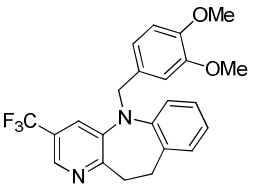
1339, 1296, 1233, 1165, 1126, 1099, 1028, 951, 937, 901, 847, 795, 762, 743, 714, 664, 633 cm^{-1}; **HRMS** (ESI): calcd for $C_{20}H_{17}F_3N_3$ $(M+H)^+$: 356.1375; found: 356.1375.

5-(thiophen-2-ylmethyl)-3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine (9e)



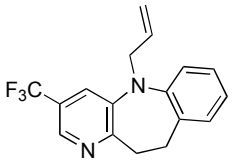
This compound was prepared according to procedure 4: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (20.8 mg, 0.2 mmol), 2-chlorophenylboronic acid (46.9 mg, 0.3 mmol, 1.5 equiv) and 2-thiophene-methylamine (33.9 µl, 0.33 mmol, 1.65 equiv). The reaction crude was purified through column chromatography (9:1 pentanes: EtOAc). The cyclized product was obtained as a colourless solid in 56% yield (40 mg). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 2.0, 1.0 Hz, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.25 - 7.11 (m, 4H), 7.07 (td, *J* = 7.3, 1.5 Hz, 1H), 7.00 (dd, *J* = 3.5, 1.1 Hz, 1H), 6.86 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.14 (s, 1H), 3.42 - 3.36 (m, 2H), 3.34 - 3.28 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.40 (q, *J* = 1.4 Hz), 147.59, 142.68, 140.55, 138.18 (q, *J* = 4.2 Hz), 136.86, 128.91, 126.97, 126.46, 126.43, 125.43, 125.14 (q, *J* = 142.0 Hz), 124.94, 124.05 (q, *J* = 32.6 Hz), 122.54 (q, *J* = 3.6 Hz), 121.17, 50.51, 37.15, 29.71; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.25; **IR** (NaCl, thin film): 2953.12, 2924.18, 2853.78, 1603.86, 1493.92, 1457.27, 1428.34, 1328.03, 1228.70, 1131.29, 1099.46, 939.36, 699.22 cm^{-1}; **m. p.:** 74-79 ^oC; **HRMS** (ESI): calcd for $C_{19}H_{15}F_3N_2$: 360.0908; found: 361.09863 $(M+H)^+$

5-(3,4-dimethoxybenzyl)-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (9f)



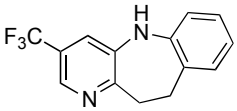
This compound was prepared according to procedure 4: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (20.8 mg, 0.1 mmol), 2-chlorophenylboronic acid (25.6 mg, 0.15 mmol, 1.5 equiv), and (3,4-dimethoxyphenyl)methanamine (24.9 µL, 0.165 mmol, 1.65 equiv). The reaction crude was purified through column chromatography (8:2 hexane: EtOAc). The cyclized product was obtained as a colourless solid in 64% yield (26 mg). **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ 8.28 (d, *J* = 0.7 Hz, 1H), 7.50 (d, *J* = 1.2 Hz, 1H), 7.24 – 7.13 (m, 3H), 7.08 – 7.02 (m, 1H), 6.92 – 6.84 (m, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 4.89 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.43 – 3.35 (m, 2H), 3.35 – 3.28 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9 (q, *J* = 1.4 Hz), 149.2, 148.4, 148.1, 143.2, 137.8 (q, *J* = 4.2 Hz), 136.6, 129.3, 129.0, 127.2, 124.8, 124.2 (q, *J* = 29.7 Hz), 123.7 (q, *J* = 272.4 Hz), 122.9 (q, *J* = 3.6 Hz), 121.7, 120.9, 111.2, 111.1, 55.9, 55.9, 55.5, 37.5, 30.1; **^{19}F NMR** (377 MHz, *$CDCl_3$*) δ -62.3; **IR** (NaCl, thin film): 3065, 3003, 2953, 2934, 2918, 2837, 1605, 1516, 1506, 1495, 1456, 1418, 1329, 1263, 1240, 1227, 1126, 1099, 1028, 943, 891, 854, 808, 764, 743, 650 cm^{-1}; **m. p.**: 107 – 109 ^oC; **HRMS** (ESI): calcd for $C_{23}H_{22}F_3N_2O_2$ $(M+H)^+$: 415.1633; found: 415.1646.

5-allyl-3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine (9g)



This compound was prepared according to procedure 4: The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (31.1 mg, 0.15 mmol), 2-chlorophenylboronic acid (35.2 mg, 0.23 mmol, 1.5 equiv), and allyl amine (31.1 μL, 0.25 mmol, 1.65 equiv). The reaction crude was purified through column chromatography (9:1 hexane: Et_2O). The cyclized product was obtained as a yellow oil in 50% yield (23 mg). **^{1}H NMR** (400 MHz, *$CDCl_3$*) δ 8.31 (dd, *J* = 2.0, 1.0 Hz, 1H), 7.44 (d, *J* = 1.9 Hz, 1H), 7.22 – 7.18 (m, 2H), 7.10 (ddd, *J* = 7.9, 1.2, 0.6 Hz, 1H), 7.07 (td, *J* = 7.4, 1.3 Hz, 1H), 5.81 – 5.70 (m, 1H), 5.36 – 5.26 (m, 1H), 5.20 (ddd, *J* = 10.3, 1.2, 0.5 Hz, 1H), 4.42 (dt, *J* = 5.7, 1.6 Hz, 2H), 3.41 – 3.34 (m, 2H), 3.28 – 3.22 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.46, 147.69, 143.08, 137.29 (q, *J* = 3.7 Hz), 136.85, 133.89, 128.70, 126.93, 124.67, 124.18 (q, *J* = 32.6 Hz), 123.6 (q, *J* = 271.82 Hz), 122.76 (q, *J* = 3.6 Hz), 121.76, 118.66, 54.39, 37.52, 29.78; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -62.33; **IR** (NaCl, thin film): 2956, 2926, 2855, 1731, 1605, 1494, 1467, 1428, 1415, 1328, 1228, 1167, 1150, 1131, 1099, 937, 803, 749 cm^{-1}; **HRMS** (DART): calcd for 304.3096; found: 305.1254 $(M+H)^{=}$.

3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine (10)



Procedure 1: A round-bottom flask was charged with 5-(3,4-dimethoxybenzyl)-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine **9f** (16.8 mg, 0.04 mmol, 1.0 equiv) and dissolved in CH_2Cl_2 (1.0 mL). The flask was fitted with a reflux condenser, and trifluoroacetic acid was then added via syringe (61.3 μL, 0.8 mmol, 20 equiv). The solution was heated to reflux and stirred for 3 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate and washed with a dilute sodium bicarbonate solution (5 mL) and brine (5 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude product. The crude product was purified by silica gel chromatography (eluting with hexane: EtOAc 9:1) to give the titled compound in 77% yield (8.2 mg) as a white solid.

Procedure 2: A round-bottom flask was charged with $Pd(PPh_3)_4$ (4.6 mg, 0.005 mmol, 20 mol%), triethylamine (8 μL, 0.06 mmol, 2.5 equiv), and formic acid (5 μL, 0.13 mmol, 6 equiv), then purged with argon. 5-allyl-3-(trifluoromethyl)-10,11-dihydro-5*H*-benzo[*b*]pyrido[2,3-*f*]azepine **9g** (6.8 mg, 0.02 mmol, 1 equiv) was dissolved in dioxane (1 mL), and added to the round-bottom flask, then the reaction was heated to 60 ^oC and stirred for 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue partitioned between DCM and sat. $NaHCO_3$. The aqueous layer was separated and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. The crude product was purified by silica gel chromatography (eluting with hexane: EtOAc 9:1) to give the titled compound in 90% yield (5.2 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 0.9 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.14 (ddd, *J* = 9.3, 7.5, 1.6 Hz, 2H), 6.91 (td, *J* = 7.4, 1.2 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.01 (s, 1H), 3.40 – 3.33 (m, 2H), 3.17 –

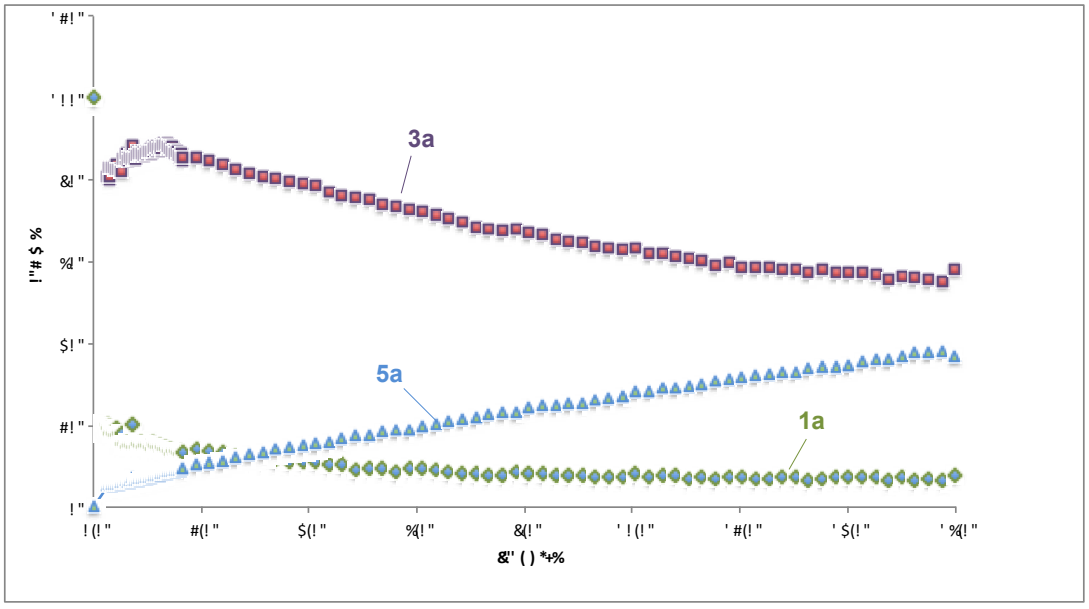
3.10 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.65, 140.89, 138.67, 135.40, 130.50, 129.78, 127.31, 125.20 (q, J = 32.4, 31.6 Hz), 125.20 (q, J = 32.4, 31.6 Hz), 123.48 (d, J = 272.2 Hz), 121.22 – 121.04 (m), 120.23, 118.53, 38.40, 32.49; **^{19}F NMR** (564 MHz, $CDCl_3$) δ -62.39; **IR** (NaCl, neat): 3300, 3232, 3206, 3139, 3121, 3043, 2962, 2925, 2854, 2359, 2346, 1544, 1438, 1495, 1468, 1442, 1418, 1343, 1238, 1126, 1095, 968, 750, 668 cm^{-1}; **m. p.**: 125 – 128 °C; **HRMS** (DART): calcd for $C_{14}H_{11}F_3N_2$: 264.2457; found. 265.0953 $(M+H)^+$.

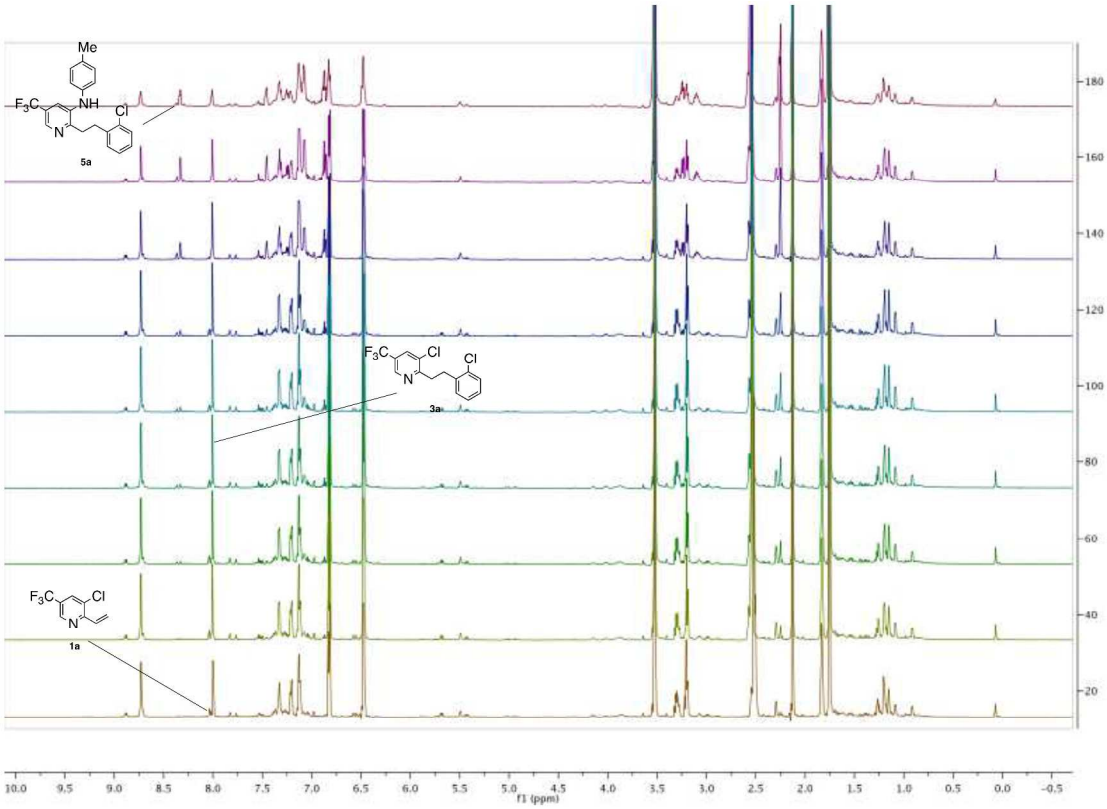
^{1}H NMR Spectroscopy Studies:

Procedure: Into a 5 mm OD Norell NMR tube were combined $[Rh(cod)OH]_2$ (1.8 mg, 4 µmol, 2.0 mol%), palladium precatalyst **6** (8.2 mg, 10 µmol, 5.0 mol%), XPhos (4.8mg, 10 µmol, 5.0 mol%) and K_2CO_3 (82.9 mg, 0.60 mmol, 3.0 eq.). The NMR tube was fitted with a septum and purged with argon. In a 2 dram vial were combined 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (41.5 mg, 0.20 mmol, 1.0 eq.), 2-chlorophenylboronic acid (46.9 mg, 0.3 mmol, 1.5 eq.) and *p*-toluidine (35.4 mg, 0.33 mmol, 1.65 eq.). The contents of the second vial was dissolved in dioxane-d_8 (0.5 mL) and transferred to the catalyst via syringe. D_2O (0.05 mL) was also added by syringe. The contents of the NMR tube were then degassed by freeze-pump-thaw method before being sealed off with a torch. The NMR tube containing the reaction mixture was then inserted into a VT spinner which allows better air flow and temperature control.

^{1}H NMR study at 95 °C over 16 hours:

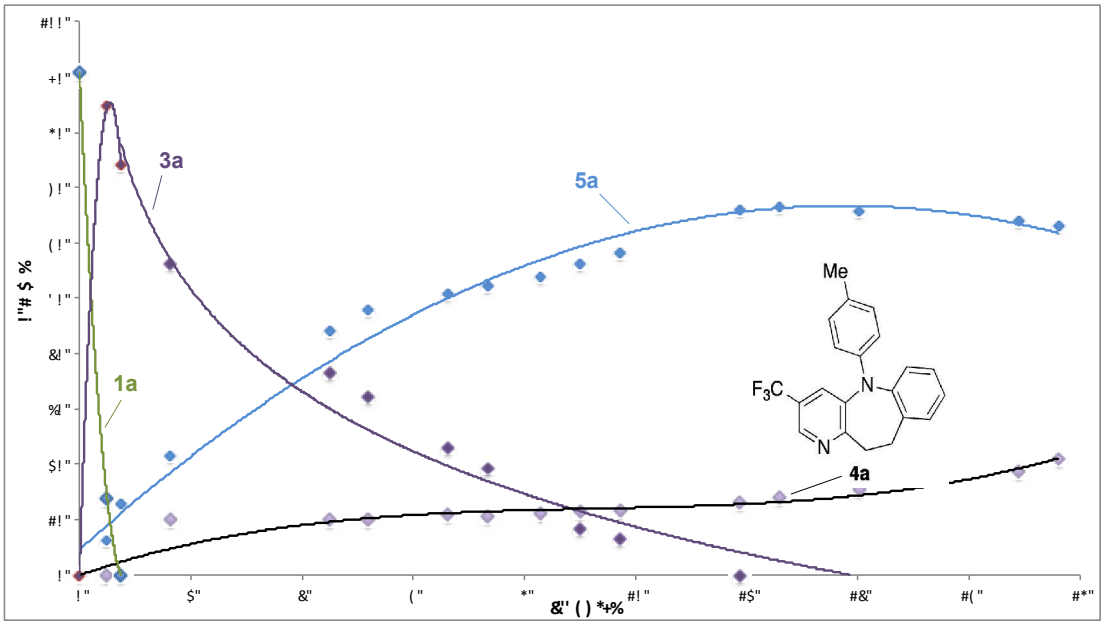
Spectral data was obtained with an Agilent DD2 600 MHz spectrometer. Probe was heated to 95 °C and stabilized for 5 minutes before spectral data was obtained. Each spectrum was obtained with a single scan at a 90 degree pulse with a 5 minute delay in the first 2 hours, and then with 30 minute delays for the following 14 hours.





^{1}H NMR study at 110 ^{o}C:

Spectral data was obtained with an Agilent DD2 600 MHz spectrometer. Probe was heated to 95 ^{o}C and stabilized for 5 minutes before the first spectrum was obtained. Each following spectrum was collected with a single scan at a 90 degree pulse at 95 ^{o}C. At the end of the acquisition period, the probe was heated to 110 ^{o}C for 40 minutes before being cooled back to 95 ^{o}C for the next scan. Each heating and cooling period lasted for approximately 10 minutes.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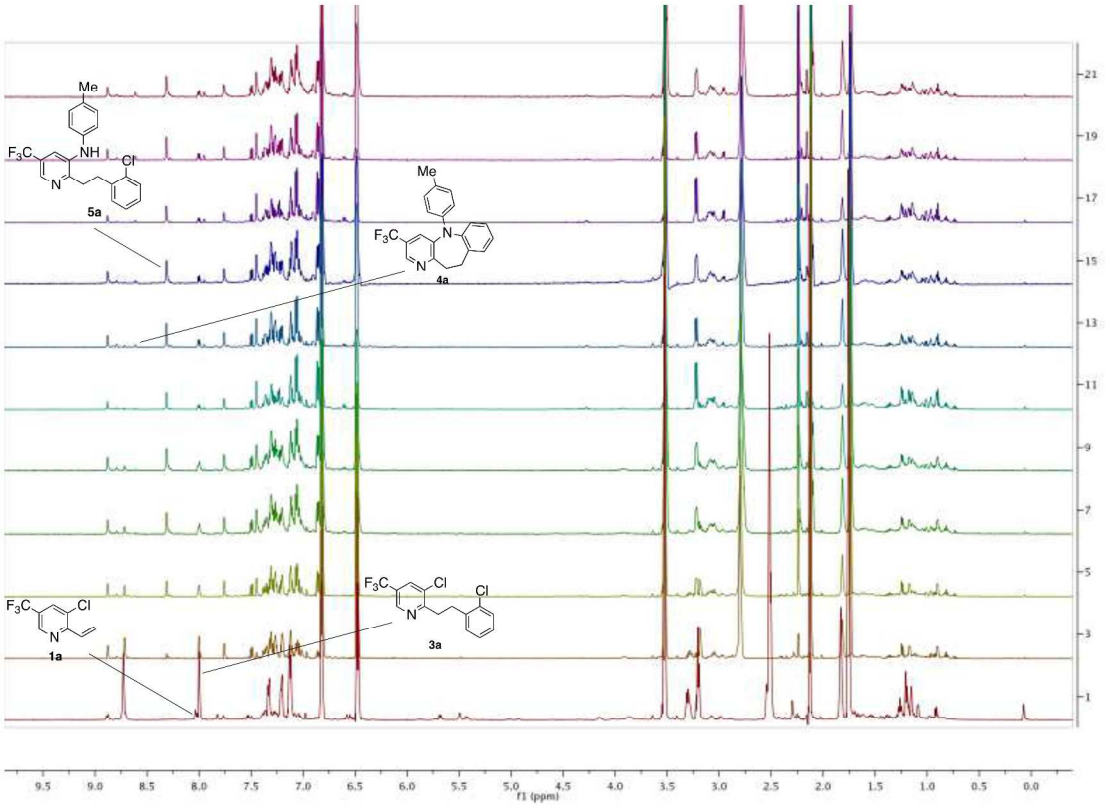
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