# **General Synthetic Procedure A:** Hydrazone Formation

# This procedure was adapted from the CRO method.23 Compounds 22, 25, 34 and 37 (part 1) were prepared using this procedure. To a stirred solution of 21 (crude, 1 equiv.) and acetic acid (glacial, 1 equiv.) in acetonitrile (to 0.60 M of 21) was added the appropriate aldehyde (1 equiv.). The reaction mixture was stirred at rt for 2.5–36 h until complete by TLC (30% ethyl acetate/hexanes). The reaction was concentrated under reduced pressure and dried *in vacuo* to give the crude material and used as crude in the subsequent reaction or subjected to the stated purification by flash chromatography over silica.

# 4-((2-(6-Chloropyrazin-2-yl)hydrazono)methyl)benzonitrile 22

# 21 (crude, 1.68 g, ~12.0 mmol, 1 equiv.) and 4-formylbenzonitrile (1.52 g, 11.6 mmol, 1 equiv.) were reacted according to General Synthetic Procedure A. The crude material was a pale orange powder (3.04 g, 102%) and was used in subsequent steps without purification; mp 191–193 °C; νmax (film)/cm-1 x; δH (200 MHz; DMSO-*d6*) 11.91 (s, 1 H), 8.64 (s, 1 H), 8.12 (s, 1 H), 8.11 (s, 1 H), 7.96–7.84 (m, 4 H); δC (101 MHz; DMSO-*d6*) 152.0, 145.5, 140.6, 139.0, 133.1, 132.6, 129.1, 127.1, 118.8, 111.1; *m/z* (APCI) 258 (MH+, 100%); HRMS (ESI) 258.05406 ([M+H]+), calcd. for C12H9N5Cl+ 258.05410.

# 2-Chloro-6-(2-(4-chlorobenzylidene)hydrazinyl)pyrazine 25

# 21 (crude, 2.51 g, ~17.0 mmol, 1.0 equiv.) and 4-chlorobenzaldehyde (1.95 g, 13.9 mmol, 0.8 equiv.) were reacted according to General Synthetic Procedure A to give the crude material as a pale yellow powder (3.89 mg, 105%); mp 224–226 °C; νmax (film)/cm-1 3026, 1582; δH (300 MHz; DMSO-*d6*) 11.63 (s, 1 H), 8.58 (s, 1 H), 8.06 (s, 1 H), 8.05 (s, 1 H), 7.77 (d, *J* = 8.7, 2 H), 7.48 (d, *J* = 8.4, 2 H); δC (75 MHz; DMSO-*d6*) 152.2, 145.5, 141.3, 133.8, 133.4, 132.6, 131.0, 128.8, 128.2; HRMS (ESI) 267.01999 ([M+H]+), calcd. for C11H9Cl2N4+ 267.01988.

# 2-Chloro-6-(2-(pyridin-4-ylmethylene)hydrazinyl)pyrazine 34

**21** (crude, 1.0 g, ~7.0 mmol, 1.0 equiv.) and 4-pyridinecarboxaldehyde (0.65 mL, 740 mg, 6.9 mmol, 1.0 equiv.) were reacted according to General Synthetic Procedure A. The crude material was a bright yellow powder (1.97 g, 122%) and was purified by flash chromatography (Biotage isolera, 40-90% ethyl acetate/hexanes/1% TEA) to give the title compound as a pale yellow powder (377 mg, 23%); mp 254–256 °C; νmax (film)/cm-1 3188, 3035, 2971, 1586, 1561, 1417; δH (200 MHz; DMSO-*d6*) 11.89 (b, 1 H), 8.66 (s, 1 H), 8.62–8.59 (m, 2 H), 8.13 (s, 1 H), 8.03 (s, 1 H) 7.71–7.68 (m, 2 H); δC (75 MHz; DMSO-*d6*) 153.0, 151.1, 146.5, 142.5, 140.8, 134.3, 130.1, 121.5; *m/z* (APCI) 234 (MH+, 100%); HRMS (ESI) 234.05414 ([M+H]+), calcd. for C10H9ClN5+ 234.05410.

# General Synthetic Procedure B: Oxidative Cyclisation of Hydrazones

# This procedure was adapted from the CRO method.23 Compounds 23, 26, 35 and 37 were prepared using this procedure. To a stirred solution of a hydrazone (crude or pure, 1 equiv.) in dichloromethane (to 60 mM of hydrazone) was added phenyliodine diacetate (1 equiv.). The reaction mixture was stirred at room temperature for 2–36 h until complete by TLC (30% ethyl acetate/hexanes). The reaction was stopped and the organic layer washed with a solution of saturated NaHCO3. The inorganic layer was extracted with dichloromethane (3–6 times). The organic fractions were dried (MgSO4), concentrated under reduced pressure and *in vacuo*. The crude material subjected to the stated purification by flash chromatography over silica

# 4-(5-Chloro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile 23

# 22 (crude, 2.0 g, ~8 mmol) was reacted according to General Synthetic Procedure B. Purification (Biotage isolera, 50–100% ethyl acetate/hexanes) gave the title compound as an orange powder (1.14 g, 56%); mp 226–227 °C; νmax (film)/cm-1 3089, 2228, 1597; δH (200 MHz; DMSO-*d6*) 9.53 (s, 1 H), 8.14 (s, 1 H), 8.08–7.93 (m, 4 H); δC (75 MHz; DMSO-*d6*) 147.1, 146.1, 142.7, 132.3, 132.0, 131.6, 129.4, 121.9, 118.4, 113.1; *m/z* (APCI) 256 (MH+, 100%); HRMS (ESI) 256.03845 ([M+H]+), calcd. for C12H7N5Cl+ 256.03845.

# 5-Chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine 26

# 25 (pure, 250 mg, 0.94 mmol) was reacted according to General Synthetic Procedure B. Purification (Biotage isolera, 7–85% ethyl acetate/hexanes) gave the title compound as pale yellow crystals (207 mg, 83%); mp 172–173 °C; νmax (film)/cm-1 3089, 1601, 1465; δH (200 MHz; CDCl3) 9.35 (s, 1 H), 7.89 (s, 1 H), 7.56–7.49 (m, 4 H); δC (101 MHz; DMSO-*d6*) 147.1, 146.5, 142.7, 135.5, 133.2, 129.3, 127.9, 126.2, 121.9; *m/z* (APCI) 265 (MH+, 100%); HRMS (ESI) 265.00440 ([M+H]+), calcd. for C11H7Cl2N4+ 265.00423.

# 5-Chloro-3-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyrazine 35

# 34 (550 mg, 2.4 mmol) was reacted according to General Synthetic Procedure B. Purification (Biotage isolera, 60–100% ethyl acetate/hexanes) gave the title compound as a pale yellow powder (406 mg, 75%); mp 165–167 °C; νmax (film)/cm-1 3036, 3003, 1593; δH (200 MHz; DMSO-*d6*) 9.54 (s, 1 H), 8.81–8.78 (m, 2 H), 8.16 (s, 1 H), 7.79–7.76 (m, 2 H); δC (101 MHz; DMSO-*d6*) 149.1, 147.2, 145.4, 142.7, 135.3, 129.5, 125.8, 121.9; *m/z* (APCI) 232 (MH+, 100%); HRMS (APCI) 232.03834 ([M+H]+), calcd. for C10H7ClN5+ 232.03845.

# 5-Chloro-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine 37

Prepared according to General Synthetic Procedures A and B. **21** (crude, 1.0 g, ~7.0 mmol, 1.0 equiv.) and 4-(difluoromethoxy)benzaldehyde (0.9 mL, 1.2 g, 7.0 mmol, 1.0 equiv.) were used to synthesise the hydrazone intermediate, **36**. The identity of the major product in the crude material (2.2 g, ~7 mmol, 104%) was verified by 1H NMR spectroscopy (DMSO-*d6*) before carrying through to the next step without purification. **36** (crude, 2.01 g, ~7 mmol) was used in part B. Purification (30–100% ethyl acetate/hexanes) gave the title compound as brown plates (829 mg, 40%); mp 122–123 °C; νmax (film)/cm-1 3086, 1612, 1467, 1235, 1122, 1045; δH (400 MHz; DMSO-*d6*) 9.49 (s, 1 H), 8.09 (s, 1 H), 7.81–7.77 (m, 2 H), 7.41 (t, *J*HF = 73.6 Hz, 1 H), 7.37–7.33 (m, 2 H); δC (101 MHz; DMSO-*d6*) 152.6, 147.1, 146.7, 142.8, 133.4, 129.2, 124.0, 121.9, 117.4, 116.2 (t, *J*CF = 259 Hz); *m/z* (APCI) 297 (MH+, 100%); HRMS (APCI) 297.03484 ([M+H]+), calcd. for C12H8ClF2N4O+ 297.03492.

# General Synthetic Procedure C: SN2 Displacement

# This procedure was adapted from the literature.60 Compounds 28–32 and 38–40 were prepared using this procedure. To a stirred solution of the appropriate alcohol, amine or thiol (1.0–1.2 equiv.) and the appropriate triazolopyrazine (1.0 equiv.) in toluene (to 0.40 M of triazolopyrazine) was added potassium hydroxide (3.3 equiv.) and 18-crown-6 (0.050 equiv.). The reaction mixture was heated at 40 °C (bath temperature) for 1–2 h and allowed to cool to rt. The mixture was diluted with water and the aqueous fraction was extracted with ethyl acetate. The combined organic fractions were washed with water until neutral (pH 10 for the amines) followed by brine. The organic fractions were dried (Na2SO4), concentrated under reduced pressure and dried *in vacuo*. The crude material was purified by flash chromatography over silica to yield the title compounds.

# 4-(5-Phenethoxy-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile 28

# Phenethyl alcohol (60 μL, 60 mg, 0.5 mmol, 1.2 equiv.) and 23 (96 mg, 0.4 mmol, 1.0 equiv.) were reacted according to General Synthetic Procedure C. Purification (manual, 50–100% ethyl acetate/hexanes) gave the title compound as pale brown needles (33 mg, 26%); mp 142–143 °C; νmax (film)/cm-1 3063, 2228, 1610, 1507, 1297; δH (400 MHz; DMSO-*d6*) 9.09 (s, 1 H), 7.94–7.89 (m, 4 H), 7.67 (s, 1 H), 7.19–7.18 (m, 3 H), 6.92–6.90 (m, 2 H), 4.54 (t, 2 H, *J* = 6.4 Hz), 2.89 (t, 2 H, *J* = 6.4 Hz); δC (101 MHz; DMSO-*d6*) 147.6, 144.9, 143.9, 137.2, 134.9, 132.4, 131.5, 131.5, 128.7, 128.2, 126.4, 118.6, 112.2, 109.3, 71.1, 33.7; *m/z* (APCI) 342 (MH+, 100%); HRMS (ESI) 342.13477 ([M+H]+), calcd. for C20H16N5O+ 342.13494.

# 4-(5-(2-Chlorophenethoxy)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile 29

# 2-Chlorophenethyl alcohol (60 μL, 60 mg, 0.4 mmol, 1 equiv.) and 23 (107 mg, 0.4 mmol, 1 equiv.) were reacted according to General Synthetic Procedure C. Purification (manual, 50–100% ethyl acetate/hexanes) gave the title compound as pearlescent cream needles (78 mg, 53%); mp 183–185 °C; νmax (film)/cm-1 2229, 1611, 1507, 1369, 1298; δH (400 MHz; DMSO-*d6*) 9.10 (s, 1 H), 7.87–7.81 (m, 4 H), 7.72 (s, 1 H), 7.40 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.24 (tdapp, *J* = 7.7, 1.7 Hz, 1 H), 7.13 (tdapp, *J* = 7.5, 1.3 Hz, 1 H), 6.90 (dd, *J* = 7.7, 1.6 Hz, 1 H), 4.58 (t, *J* = 6.4 Hz, 2 H), 2.99 (t, *J* = 6.4 Hz, 2 H); δC (101 MHz; DMSO-*d6*) 147.6, 144.9, 143.8, 135.1, 134.4, 133.1, 132.4, 131.4, 131.3, 130.3, 129.2, 128.5, 127.1, 118.5, 112.2, 109.3, 68.9, 31.3; *m/z* (APCI) 376 (MH+, 100%); HRMS (ESI) 376.09585 ([M+H]+), calcd. for C20H15ClN5O+ 376.09596.

# 4-(5-(Phenethylthio)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile 30

# Phenylethyl mercaptan (60 μL, 60 mg, 0.4 mmol, 1 equiv.) and 23 (103 mg, 0.4 mmol, 1 equiv.) were reacted according to General Synthetic Procedure C. Purification (manual, 50–100% ethyl acetate/hexanes) gave the title compound as pearlescent cream stars (55 mg, 38%); mp 237–238 °C; νmax (film)/cm-1 2324, 1450, 1273; δH (500 MHz; DMSO-*d6*) 8.43 (d, *J* = 5.0 Hz, 1 H), 8.16–8.10 (m, 4 H), 7.89 (d, *J* = 5.0 Hz, 1 H), 7.34–7.23 (m, 5 H), 3.61 (tapp, *J* = 8.0, 7.5 Hz, 2 H), 3.06 (t, *J* = 7.5 Hz, 2 H); δC (126 MHz; DMSO-*d6*) 153.1, 146.4, 144.1, 139.9, 133.2, 130.1, 129.9, 129.0, 128.6, 128.4, 126.4, 118.3, 113.5, 112.8, 54.9, 34.4; *m/z* (APCI) 358 (MH+, 100%); HRMS (ESI) 358.11199 ([M+H]+), calcd. for C20H16N5S+ 358.11209.

# 4-(5-((3-Chlorophenethyl)amino)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile 31

2-­(3-Chlorophenyl)ethylamine (0.06 μL, 67 mg, 0.43 mmol, 1.1 equiv) and **23** (101 mg, 0.39 mmol, 1.0 equiv) were reacted together according to General Synthetic Procedure C. Purification (Biotage isolera, 17–100% ethyl acetate/hexanes) gave the title compound as a cream powder (25 mg, 17%); mp 246–248 °C; νmax (film)/cm-1 3250, 2923, 2227, 1573; δH (400 MHz; DMSO-*d6*) 8.40 (t, *J* = 5.6 Hz, 1 H), 8.14–8.08 (m, 4 H), 7.85 (d, *J* = 4.8 Hz, 1 H), 7.41 (d, *J* = 4.8 Hz, 1 H), 7.37–7.23 (m, 4 H), 3.75 (qapp, *J* = 6.8, 6.4 Hz, 2 H), 2.99 (t, *J* = 7.6 Hz, 2 H); δC (101 MHz; DMSO-*d6*) 161.1, 147.9, 146.5, 142.2, 141.9, 139.9, 133.2, 132.9, 130.7, 130.6, 130.2, 128.7, 128.6 127.5, 126.1, 118.4, 112.5, 106.3; *m/z* (APCI) 375 (MH+, 100%); HRMS (ESI) 375.11174 ([M+H]+), calcd. for C20H16ClN6+ 375.11195.

# N-(3-chlorophenethyl)-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-amine 32

2-­(3-Chlorophenyl)ethylamine (50 μL, 56 mg, 0.36 mmol, 1.0 equiv.) and **26** (103 mg, 0.39 mmol, 1.1 equiv.) were reacted together according to General Synthetic Procedure C. Purification (Biotage isolera, 12–100% ethyl acetate/hexanes) gave the title compound as a cream powder (46 mg, 33% yield); mp 191–193 °C; νmax (film)/cm-1 3248, 3111, 2917, 2034, 1975, 1613, 1582; δH (400 MHz; DMSO-*d6*) 8.35 (t, *J* = 5.6 Hz, 1 H), 7.94–7.91 (m, 2 H), 7.77 (d, *J* = 4.8 Hz, 1 H), 7.71–7.67 (m, 2 H), 7.37–7.23 (m, 5 H), 3.75 (m, 2 H), 2.99 (t, *J* = 7.1 Hz, 2 H); δC (101 MHz; DMSO-*d6*) 147.9, 146.8, 142.2, 139.7, 135.0, 132.9, 130.3, 130.2, 129.9, 129.4, 128.6, 127.5, 126.1, 125.1, 106.1, 41.2, 33.9; *m/z* (APCI) 384 (MH+, 100%); HRMS (ESI) 384.07772 ([M+H]+), calcd. for C19H16ClN5+ 384.07773.

# 3-(4-Chlorophenyl)-5-((3,4-difluorobenzyl)oxy)-[1,2,4]triazolo[4,3-a]pyrazine 38

Part 1 of this procedure was adapted from a procedure developed by Ms Katrina Badiola.78 To a dry flask was added 3,4-difluorobenzaldehyde (0.4 mL, 520 mg, 3.7 mmol, 1.0 equiv.) and tetrahydrofuran (10 mL). The mixture was cooled in an ice bath (0 °C) under argon. Sodium borohydride (500 mg, 13.0 mmol, 3.5 equiv.) was added carefully in portions. The reaction mixture was stirred for 15 min on ice before warming to room temperature and stirring for a further 25 min. The solution was adjusted to pH 7 with hydrochloric acid (1 M) and extracted with dichloromethane (3 × 15 mL). The combined organic fractions were dried (MgSO4) and concentrated under reduced pressure and dried *in vacuo* to give the crude material ((3,4-difluorophenyl)methanol) as a pale yellow oil (620 mg, 116%). The identity of the crude material was verified by 1H NMR (CDCl3) and carried through to the next step without purification. (3,4-difluorophenyl)methanol (80 μL, 100 mg, 0.7 mmol, 1.2 equiv) and **26** (154 mg, 0.6 mmol, 1.0 equiv) were reacted together according to General Synthetic Procedure C. Purification (Biotage isolera, 30–100% ethyl acetate/hexanes) gave the title compound as fluffy white needles (86 mg, 38%); mp 181–182 °C; νmax (film)/cm-1 3070, 1612, 1509, 1303; δH (500 MHz; DMSO-*d6*) 9.11 (s, 1 H), 7.67 (s, 1 H), 7.66–7.64 (m, 2 H), 7.36–7.33 (m, 2 H), 7.13–7.05 (m, 3 H), 5.29 (s, 2 H); δC (126 MHz; DMSO-*d6*) 147.4, 145.4, 143.8, 135.4, 134.6, 132.4, 127.4, 126.7, 131.7 (2C), 125.4 (2C), 117.4, 117.3, 109.2, 70.9; *m/z* (APCI) 373 (MH+, 100%), 345 (52%) 318 (23%); HRMS (APCI) 373.06609 ([M+H]+), calcd. for C18H12ClF2N4O+ 373.06622.

# 3-(4-(Difluoromethoxy)phenyl)-5-(3,4-difluorophenethoxy)-[1,2,4]triazolo[4,3-a]pyrazine 39

2-(3,4-Difluorophenyl)ethan-1-ol (98 mg, 0.62 mmol, 1.1 equiv.) and **37** (159 mg, 0.54 mmol, 1.0 equiv.) were reacted together according to General Synthetic Procedure C. Purification (Biotage isolera, 50–100% ethyl acetate/hexanes) did not yield pure product. The product was purified a second time by flash chromatography over silica (20% ethanol/hexanes) before recrystallisation from ethyl acetate (washed with cold methanol) to give the title compound as white needles (43 mg, 19%); mp 111–112 °C; νmax (film)/cm-1 3074, 2956, 1612, 1508, 1118, 1046; δH (200 MHz; DMSO-*d6*) 9.05 (s, 1 H), 7.79–7.73 (m, 2 H), 7.60 (s, 1 H), 7.36 (t, *J*HF = 73.6 Hz, 1 H), 7.30–6.69 (m, 5 H), 4.51 (t, *J* = 6.2, 2 H), 2.90 (t, *J* = 6.2, 6.0 Hz, 2 H); δC (75 MHz; DMSO-*d6*) 151.9, 147.4, 146.4, 145.4, 143.8, 135.1, 132.5, 125.3 (2C), 124.7, 117.5, 117.3, 117.0, 116.9, 116.1 (t, *J*CF = 256.7 Hz), 108.8, 70.6, 32.8; *m/z* (APCI) 419 (MH+, 100%); HRMS (APCI) 419.11215 ([M+H]+), calcd. for C20H15F4N4O+ 419.11256.

# 5-(2-Chlorophenethoxy)-3-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyrazine 40

# 2-Chlorophenethyl alcohol (0.18 mL, 210 mg, 1.3 mmol, 1.0 equiv.) and 35 (300 mg, 1.3 mmol, 1.0 equiv.) were reacted together according to General Synthetic Procedure C. Purification (Biotage isolera, 15–80% ethanol/hexanes/1% TEA) gave the title compound as light brown plates (56 mg, 12%); mp 132–134 °C; νmax (film)/cm-1 2959, 2926, 1602, 1507, 1465, 1359, 1239, 824; δH (200 MHz; DMSO-*d6*) 9.11 (s, 1 H), 8.67–8.64 (m, 2 H), 7.75 (s, 1 H), 7.71–7.68 (m, 2 H), 7.41 (dd, *J* = 7.8, 7.6, 1.2, 1.0 Hz, 1 H), 7.24 (tdapp, *J* = 7.8, 7.6, 7.4, 1.8, 1.6 Hz, 1 H) 7.14 (tdapp, *J* = 7.4, 7.2, 1.2 Hz, 1 H) 6.90 (dd, *J* = 7.4, 1.6 Hz, 1 H), 4.58 (t, *J* = 6.6, 6.4 Hz, 2 H), 3.03 (t, *J* = 6.6, 6.4 Hz, 2 H); δC (75 MHz; DMSO-*d6*) 148.9, 147.7, 144.2, 143.6, 135.5, 135.0, 134.3, 133.1, 130.7, 129.3, 128.6, 127.2, 124.9, 109.5, 69.3, 31.4; *m/z* (APCI) 352 (MH+, 100%) 324 (25%); HRMS (APCI) 352.09599 ([M+H]+), calcd. for C18H15ClN5O+ 352.09596.

# Procedures and characterisation for fluoroalkene synthesis

# 2-Bromo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine 50

This procedure was adapted from the literature.69 To a solution of ~1.7 M solution of *n*-BuLi (2.9 mL, ~5.0 mmol, ~1.2 equiv.) in freshly distilled tetrahydrofuran (40 mL) under argon, cooled to -78 °C, was added a solution of **47** (1.0 g, 4.2 mmol, 1.0 equiv.) in THF (20 mL). The reaction was stirred at -78 °C for 45 min. A solution of triethylborate (730 mg, 0.85 mL, 5.0 mmol, 1.2 equiv.) in THF (8 mL) was added and the dark mixture stirred at rt for 3 h. A solution of pinacol (670 mg, 5.7 mmol, 1.35 equiv) in THF (8 mL) was added, followed by glacial acetic acid (0.25 mL, 265 mg, 4.4 mmol, 1.05 equiv) after 5 min.  The mixture was filtered through CeliteTM and quenched by slow addition of 2.5% aqueous NaOH solution (100 mL). The aqueous layer was separated and acidified down to pH 6 by careful addition of 3M HCl, keeping the internal temperature below 5 °C. The solution was extracted with ethyl acetate (3 × 50 mL), dried (MgSO4), concentrated under reduced pressure and dried *in vacuo*. The crude material was an orange solid (370 mg, 36%); mp 103-106 °C; νmax (film)/cm-1 2978, 2929, 1547, 1390, 1347, 1318, 1143, 1125, 1105; δH (500 MHz; DMSO-*d6*) 7.73–7.67 (m, 3 H), 1.31 (s, 12 H); *m/z* (GC-EI) 157 (MH+-BO2C6H12, 32%) 159 (MH+-BO2C6H12, 32%). This data was consistent with the literature.69

# (2-Bromo-2-fluorovinyl)benzene 51

This procedure was adapted from the literature.68 A dry 250 mL three neck flask fitted with a reflux condenser was flushed with nitrogen before adding triphenylphosphine (20.4 g, 78 mmol, 2.5 equiv.) and anhydrous diglyme (120 mL, dried over molecular sieves). The reaction mixture was heated to 70 °C before injecting tribromofluoromethane (8.4 g, 3.05 mL, 31 mmol, 1.0 equiv.). The solution turned yellow and a precipitate formed. At 90 °C benzaldehyde (3.29 g, 31 mmol, 1.0 equiv.) was added and the reaction was stirred at 120 °C for 3 h. The reaction was stopped and cooled to room temperature before transferring to a clean 500 mL flask. The product and diglyme were co-distilled with water (125 mL) at 90–102 °C (temperature at connection). The crude material was a pale yellow oil and was washed with water to remove the diglyme. The crude material was extracted with ether, dried (MgSO4), concentrated under reduced pressure and dried *in vacuo*. It was distilled under vacuum (~0–1 mbar) at 40–46 °C (temperature at connection) to remove impurities. Purified was further attempted by flash chromatography (Biotage isolera, 100% hexanes) to obtain a mixture of isomers as a crude colourless oil (110 mg, 2%) in a 6:1 ratio of isomers; νmax (film)/cm-1 3211, 3092, 3063, 2954, 2924, 2854, 1719, 1648, 1495, 1449, 1044, 747, 691; δH (400 MHz; CDCl3) 7.42–7.26 (m, 6 H), 6.67 (d, *J*HF*cis* = 15.2 Hz, 0.16 H), 5.98 (d, *J*HF*trans* = 32.8 Hz, 1 H); *m/z* (GC-EI) 200 (MH+, 62%). This data was consistent with the literature.**68, 72**

# 2-Bromo-6-styrylpyridine 53

This procedure was adapted from the literature.50 **52** (100 mg, 0.55 mmol, 1 equiv.), **50** (200 mg, 0.7 mmol, 1.3 equiv.), potassium carbonate (228 mg, 1.65 mmol, 3 equiv.) were stirred into toluene (7.5 mL), ethanol (1.5 mL) and water (1.5 mL). Argon was bubbled through to remove oxygen. 1,4-Bis(diphenylphosphino)butane-palladium(II) chloride (18 mg, 0.03 mmol, 0.05 equiv.) was added and the mixture heated at reflux overnight. The mixture was filtered through CeliteTM (washed with ethyl acetate), dried (MgSO4), and dried *in vacuo*. Clean product was not obtained following an initial purification by flash chromatography over silica (Biotage isolera, 20% ethyl acetate/hexanes). The crude material was bright yellow crystals (32 mg, 22%) as a 7:1 mixture of isomers. The following data was obtained and indicates the formation of the desired product: δH (500 MHz; CDCl3) 7.67–7.27 (m, 11 H), 7.07 (d, *J* = 16.0 Hz, 1 H) 6.87 (d, *J* = 12.5 Hz, 0.14H); *m/z* (APCI) 260 (MH+, 100%); HRMS (APCI) 260.00707 ([M+H]+), calcd. for C13H11BrN+ 260.00694.

# 2-Bromo-6-(1-fluoro-2-phenylvinyl)pyridine 54

This procedure was adapted from the literature.50 **51** (~20–30 mg, flask was washed out, ~0.1–0.15 mmol, 1 equiv.), **50** (85 mg, 0.3 mmol, 2 equiv), potassium carbonate (104 mg, 0.75 mmol, 6 equiv.) were stirred into toluene (3.75 mL), ethanol (0.75 mL) and water (0.75 mL). Argon was bubbled through to remove oxygen. 1,4-Bis(diphenylphosphino)butane-palladium(II) chloride (12 mg, 0.02 mmol, 0.2 equiv) was added and the mixture heated at reflux overnight. The mixture was filtered through CeliteTM (washed with ethyl acetate), dried (MgSO4), and dried *in vacuo*. Clean product was not obtained following an initial purification by flash column chromatography over silica (Biotage isolera, 20% ethyl acetate/hexanes). The crude material was bright yellow crystals (8 mg, 30%) as a 5:1 mixture of isomers. The following data was obtained and indicates the formation of the desired product: δH (500 MHz; CDCl3) 7.76–7.31 (m, 15 H), 7.12 (d, *J*HF = 39.5 Hz, 1 H), 6.73 (d, *J*HF = 23.0 Hz, 0.2 H); *m/z* (APCI) 278 (MH+, 68%); HRMS (APCI) 277.99759 ([M+H+]), calcd. for C13H10BrFN+ 277.99752.