Synthesis of Bis-heteroaryls using Grignard Reagents and Pyridylsulfonium Salts

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1. General experimental

Chemicals were purchased and used without further purification unless otherwise stated. Solvents were dried using a Grubbs-type still, a Pure Solv-400-3-MD solvent purification system supplied by Innovative Technology Inc. design and stored in Strauss flasks over activated 4Å molecular sieves. Diphenyliodonium trifluoromethanesulfonate was prepared according to literature procedure.¹ Pyridylsulfides 1ai-1gi and sulfonium salts 1a-1g were prepared as previously described.² TMPMgCl•LiCl was prepared according to literature procedure.³ i-PrMgCl•LiCl and TMPMgCl•LiCl were titrated prior to use.⁴

Reactions requiring anhydrous conditions were performed under N₂; glassware was flame-dried immediately prior to use and allowed to cool under reduced pressure. Reaction monitoring by TLC was performed on Merck pre-coated Kieselgel 60 F₂₅₄ aluminium plates. Visualization was accomplished under UV light (254 nm). Flash column chromatography (FCC) was performed using either silica gel [Davisil, 230-400 mesh (40-63 µm)] or using a Biotage Isoleraᵀᴹ UV-VIS Flash Purification System Version 2.3.1 with SNAP Ultra (25 µm), SNAP KP-Sil (50 µm) or SNAP KP-NH (50 µm) prepacked silica cartridges. High-resolution mass spectra were run on a Waters Micromass GCT system or on an Agilent 6546 QTOF system in electrospray ionization mode (ESI). Extracts were concentrated in vacuo using both a rotary evaporator (bath temperatures up to 55 °C), and a high vacuum line at room temperature. ¹H NMR and ¹³C NMR spectra were measured in the solvent stated at 300 MHz, 400 MHz or 500 MHz or 100 – 126 MHz, respectively. ¹⁹F spectra was measured in the solvent stated at 376 – 470 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to residual solvent peak (e.g., CDCl₃: ¹H – 7.26 ppm and ¹³C – 77.16 ppm) or TMS (¹H – 0.00 ppm) and coupling constants (J) are given in Hertz. Multiplicities are abbreviated as: b (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or combinations thereof. Assignments were made, where necessary, with the aid of COSY, HSQC, HMBC and NOESY NMR experiments.

2. Synthesis of sulfides

**General procedure A**: 4-methylbenzenethiol (1 equiv.) was added to a round bottomed flask, followed by halopyridine (1 equiv.) and H₂O (0.5 M). The reaction was heated under reflux for 24 h (the flask sitting in an aluminium block placed on a stirrer hotplate). Then, the reaction was allowed to cool, followed by extraction with EtOAc. The combined organic layers were washed with water and brine and dried over Na₂SO₄. The solvent was evaporated, and the product was isolated by FCC.

**General procedure B**: 4-methylbenzenethiol (1 equiv.) was added to a crimp-top vial followed by halopyridine (1 equiv.) and K₂CO₃ (1.1 equiv.) and closed. The vial was evacuated and purged with N₂ three times. Anhydrous DMF (0.8–1 M wrt thiol/halopyridine) was added. The reaction was heated to 100 °C for 24 h (the flask sitting in an aluminium block placed on a stirrer hotplate). Then the reaction
was allowed to cool, followed by the addition of water and extraction with EtOAc. The combined organic layers were washed with water and brine and dried over Na₂SO₄. Details of purification are given below for each compound.

2-Methyl-6-(p-tolylthio)pyridine 1hi

![Chemical Structure]

Prepared from General procedure B with 4-methylbenzenethiol (0.62 g, 5.0 mmol), 2-bromo-6-methylpyridine (0.57 mL, 5.0 mmol), K₂CO₃ (0.88 g, 6.0 mmol) and DMF (6 mL). The reaction was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL) and dried over Na₂SO₄. The solvent was evaporated to give pyridylsulfide 1hi as a clear oil (1.05 g, 98%).

TLC: Rᵣ = 0.3(10% Et₂O in pentane).

¹H NMR (500 MHz, Chloroform-d) δ 7.50 – 7.46 (m, 2H, ArH), 7.28 (t, J = 7.8 Hz, 1H, ArH), 7.24 – 7.18 (m, 2H, ArH), 6.81 (d, J = 7.6 Hz, 1H, ArH), 6.55 (d, J = 8.0 Hz, 1H, ArH), 2.49 (s, 3H, CH₃), 2.38 (s, 3H, CH₃) ppm.

¹³C NMR (126 MHz, Chloroform-d) δ 161.9 (C), 158.5 (C), 139.5 (C), 137.0 (CH), 135.4 (CH), 130.5 (CH), 127.6 (C), 119.2 (CH), 117.7 (CH), 24.4 (CH₃), 21.4 (CH₃) ppm.

HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₁₃H₁₄NS: 216.0841; Found: 216.0844.

2-(p-Tolylthio)-6-(trifluoromethyl)pyridine 1ii

![Chemical Structure]

Prepared from General procedure B with slight modifications, with 4-methylbenzenethiol (0.56 g, 4.5 mmol), 2-bromo-6-(trifluoromethyl)pyridine (0.68 g, 3.0 mmol), K₂CO₃ (0.50 g, 3.6 mmol) and DMF (1.9 mL). The reaction was heated to 140 °C for 7 h. The reaction was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (3 x 30 mL) and brine (3 x 30 mL) and dried over Na₂SO₄. The solvent was evaporated and purification by FCC (5% Et₂O in pentane) gave pyridylsulfide 1ii as a white solid (0.52 g, 64%).

TLC: Rᵣ = 0.50 (5% Et₂O in pentane).

¹H NMR (500 MHz, Chloroform-d) δ 7.57 (t, J = 7.9 Hz, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.7 Hz, 1H), 7.28 (d, J = 7.8 Hz, 2H), 6.93 (d, J = 8.1 Hz, 1H), 2.43 (s, 3H, CH₃).
13C NMR (101 MHz, Chloroform-\textit{d}) \( \delta \) 164.3 (C), 147.9 (q, \( J = 34.8 \) Hz, CCF\(_3\)), 140.3 (C), 137.7 (CH), 135.7 (CH), 130.9 (CH), 126.1 (C), 123.2 (CH), 121.3 (d, \( J = 274.3 \) Hz, CF\(_3\)), 116.1 (q, \( J = 2.7 \) Hz, CH), 21.5 (CH\(_3\)).

19F NMR (282 MHz, Chloroform-\textit{d}) \( \delta \) -68.2.

HRMS (ESI-TOF) \( m/z \): [M+H]\(^+\) Calcd for C\(_{13}\)H\(_{11}\)F\(_3\)NS: 270.0559; Found: 270.0561.

6-(\textit{p}-Tolylthio)nicotinonitrile 1ji

Prepared from General procedure B with slight modifications, with 4-methylbenzenethiol (1.65 g, 13.3 mmol), 2-bromo-5-cyanopyridine (2.03 g, 11.1 mmol), K\(_2\)CO\(_3\) (2.31 g, 16.7 mmol) and DMF (5.6 mL). The reaction was heated to 140 °C for 16 h. The reaction was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (3 x 30 mL) and brine (3 x 30 mL) and dried over Na\(_2\)SO\(_4\). The solvent was evaporated and purification by FCC (20% Et\(_2\)O in pentane) gave pyridylsulfide 1ji as a white solid (1.60 g, 64%).

TLC: \( R_f = 0.37 \) (20% Et\(_2\)O in pentane).

\(^1\)H NMR (400 MHz, Chloroform-\textit{d}) \( \delta \) 8.62 (d, \( J = 2.1 \) Hz, 1H), 7.61 (dd, \( J = 8.5, 2.3 \) Hz, 1H), 7.48 (d, \( J = 8.0 \) Hz, 2H), 7.29 (d, \( J = 7.8 \) Hz, 2H), 6.87 (d, \( J = 8.4 \) Hz, 1H), 2.42 (s, 3H, CH\(_3\)).

13C NMR (101 MHz, Chloroform-\textit{d}) \( \delta \) 168.7, 152.2, 140.9, 138.9, 135.7, 131.0, 125.0, 120.0, 117.0, 105.0, 21.5 (CH\(_3\)).

Spectra were consistent with literature data.\(^5\)

5-Bromo-2-(\textit{p}-tolylthio)pyridine 1ki

Prepared from General procedure B with slight modifications, with 4-methylbenzenethiol (0.37 g, 3.0 mmol), 2,5-dibromopyridine (0.71 g, 3.0 mmol), K\(_2\)CO\(_3\) (0.5 g, 3.6 mmol) and DMF (1.9 mL). The reaction was heated to 140 °C for 7 h. The reaction was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (3 x 30 mL) and brine (3 x 30 mL) and dried over Na\(_2\)SO\(_4\). The solvent was evaporated and purification by FCC (5% Et\(_2\)O in pentane) gave pyridylsulfide 1ki as a white solid (0.36 g, 43%).

TLC: \( R_f = 0.36 \) (5% Et\(_2\)O in pentane).
\[ ^1H \text{NMR (400 MHz, Chloroform-}d \text{)} \delta 8.45 (d, J = 2.4 \text{ Hz, 1H}), 7.52 (dd, J = 8.6, 2.4 \text{ Hz, 1H}), 7.47 (d, J = 7.9 \text{ Hz, 2H}), 7.24 (d, J = 7.8 \text{ Hz, 2H}), 6.73 (dd, J = 8.6, 0.6 \text{ Hz, 1H}), 2.40 (s, 3H, CH}_3 \text{).} \]

\[ ^{13}C \text{NMR (101 MHz, Chloroform-}d \text{)} \delta 161.1 (C), 150.4 (CH), 140.0 (C), 139.2 (CH), 135.4 (CH), 130.7 (CH), 126.9 (C), 122.3 (CH), 116.3 (C), 21.5 (CH}_3 \text{).} \]

HRMS (ESI-TOF) \( m/z \): [M+H]\(^+\) Calcd for \( \text{C}_{12}\text{H}_{11}\text{BrNS} \): 279.9790, 281.9770; Found: 279.9792, 281.9771.

### 5-Chloro-2-(p-tolylthio)pyridine 1li

Prepared from General procedure B with slight modifications, with 4-methylbenzenethiol (0.5 g, 400 mmol), 2-bromo-5-chloropyridine (0.77 g, 4.0 mmol), \( \text{K}_2\text{CO}_3 \) (0.66 g, 4.8 mmol) and DMF (2.5 mL). The reaction was heated to 140 °C for 7 h. The reaction was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (3 x 30 mL) and brine (3 x 30 mL) and dried over \( \text{Na}_2\text{SO}_4 \). The solvent was evaporated and purification by FCC (5% \( \text{Et}_2\text{O} \) in pentane) gave pyridylsulfide 1li as a white solid (0.75 g, 79%).

TLC: \( R_f = 0.23 \) (5% \( \text{Et}_2\text{O} \) in pentane).

\[ ^1H \text{NMR (400 MHz, Chloroform-}d \text{)} \delta 8.37 – 8.36 (m, 1H), 7.47 (d, J = 8.1 \text{ Hz, 2H}), 7.39 (dd, J = 8.6, 2.7 \text{ Hz, 1H}), 7.24 (d, J = 8.2 \text{ Hz, 2H}), 6.79 (dd, J = 8.6, 0.6 \text{ Hz, 1H}), 2.40 (s, 3H, CH}_3 \text{).} \]

\[ ^{13}C \text{NMR (101 MHz, Chloroform-}d \text{)} \delta 160.5 (C), 148.3 (CH), 139.9 (C), 136.5 (CH), 135.3 (CH), 130.7 (CH), 128.1 (C), 127.0 (C), 121.8 (CH), 21.5 (CH}_3 \text{).} \]

HRMS (ESI-TOF) \( m/z \): [M+H]\(^+\) Calcd for \( \text{C}_{12}\text{H}_{11}\text{BrNS} \): 236.0295, 238.0266; Found: 236.0297, 238.0265.

### 2-(p-Tolylthio)pyrimidine 1mi

Prepared from General procedure B with slight modifications, with 4-methylbenzenethiol (1.91 g, 15.4 mmol), 2-bromopyrimidine (2.04 g, 12.8 mmol), \( \text{K}_2\text{CO}_3 \) (2.65 g, 19.2 mmol) and DMF (6.4 mL). The reaction was heated to 140 °C for 7 h. The reaction was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (3 x 30 mL) and brine (3 x 30 mL) and dried over \( \text{Na}_2\text{SO}_4 \). The solvent was evaporated and purification by FCC (20% \( \text{Et}_2\text{O} \) in pentane) gave pyridylsulfide 1mi as a white solid (1.81 g, 70%).
TLC: $R_f = 0.25$ (20% Et$_2$O in pentane).

$^1$H NMR (400 MHz, Chloroform-$_d$) $\delta$ 8.46 (d, $J = 5.0$ Hz, 2H), 7.50 (d, $J = 8.1$ Hz, 2H), 7.23 (d, $J = 7.7$ Hz, 2H), 6.93 (t, $J = 4.9$ Hz, 1H), 2.38 (s, 3H, CH$_3$).

$^{13}$C NMR (101 MHz, Chloroform-$_d$) $\delta$ 173.4 (C), 157.7 (CH), 139.7 (C), 135.4 (CH), 130.3 (CH), 125.9 (C), 117.0 (CH), 21.5 (CH$_3$).

HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{11}$H$_{11}$N$_2$S: 203.0637; Found: 203.0638.
3. Synthesis of sulfonium salts

**General procedure C:** Sulfide (1.1 equiv.), Ph$_2$IOTf (1.0 equiv.) and Cu(OTf)$_2$ (5 mol%) were added to a crimp-top vial and sealed. The vial was evacuated and purged with N$_2$ three times. Dry DCE (0.6 M) was added to the vial and the reaction was heated to 95 °C for 16 h (the vial sitting in an aluminium block placed on a stirrer hotplate). Then the reaction was allowed to cool and sat. aq. NH$_4$Cl (20 mL) was added. The product was extracted using CH$_2$Cl$_2$ (3 x 20 mL) and washed with H$_2$O (2 x 20 mL) and brine (20 mL). The solvent was evaporated and product was isolated by FCC.

**(6-Methylpyridin-2-yl)(phenyl)(p-tolyl)sulfonium trifluoromethanesulfonate 1h**

Product 1h was synthesised *via* General procedure C with sulfide 1hi (1.0 g, 4.6 mmol), Ph$_2$IOTf (1.81 g, 4.2 mmol) and Cu(OTf)$_2$ (76 mg, 0.21 mmol). Purification by FCC (5% MeOH in CH$_2$Cl$_2$) gave sulfonium salt 1h as a yellow oil (575 mg, 31%).

$^1$H NMR (500 MHz, Chloroform-d) δ 8.13 – 8.09 (m, 1H), 7.97 (t, $J = 7.8$ Hz, 1H), 7.91 – 7.85 (m, 2H), 7.84 – 7.79 (m, 2H), 7.77 – 7.69 (m, 1H), 7.69 – 7.63 (m, 2H), 7.52 – 7.44 (m, 3H), 2.60 (s, 3H), 2.46 (s, 3H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 162.8 (C), 146.4 (C), 146.1 (CH), 140.7 (CH), 134.5 (CH), 132.1 (CH), 132.0 (CH), 131.6 (CH), 131.3 (CH), 128.5 (C), 126.9 (CH), 125.4 (C), 121.0 (C), 24.5 (CH$_3$), 21.9 (CH$_3$). Peak for SO$_3$CF$_3$ not observed.

HRMS (ESI$^+$): [M-OTf]$^+$ Calcd for C$_{19}$H$_{18}$NS$^+$: 292.1154; found: 292.1156.

**Phenyl(p-tolyl)(6-(trifluoromethyl)pyridin-2-yl)sulfonium trifluoromethanesulfonate 1i**

Product 1i was synthesised *via* General procedure C with sulfide 1ii (0.65 g, 2.42 mmol), Ph$_2$IOTf (1.04 g, 2.42 mmol) and Cu(OTf)$_2$ (43 mg, 0.12 mmol). Purification by FCC (10% MeOH in CH$_2$Cl$_2$) gave sulfonium salt 1i as a brown oil (1.03 g, 86%).

TLC: $R_f = 0.30$ (10% MeOH in CH$_2$Cl$_2$).
$^1$H NMR (400 MHz, Chloroform-$d$) δ 8.50 (d, $J = 8.1$ Hz, 1H), 8.37 (t, $J = 8.0$ Hz, 1H), 8.02 (d, $J = 7.8$ Hz, 1H), 7.86 (dd, $J = 7.7$, 1.7 Hz, 2H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.78 – 7.69 (m, 1H), 7.69 – 7.61 (m, 2H), 7.47 (d, $J = 8.2$ Hz, 2H), 2.43 (s, 3H, CH$_3$).

$^{13}$C NMR (101 MHz, Chloroform-$d$) δ 150.2 (q, $J = 37.0$ Hz, CCF$_3$), 147.6 (C), 147.1 (C), 143.3 (CH), 135.0 (CH), 132.3 (CH), 132.0 (2 x CH), 131.6 (CH), 131.5 (CH), 125.2 (q, $J = 2.4$ Hz, CH), 124.4 (C), 120.8 (q, $J = 320.8$ Hz, OTf), 120.2 (q, $J = 274.9$ Hz, CF$_3$), 119.9 (C), 21.7 (CH$_3$).

$^{19}$F NMR (376 MHz, Chloroform-$d$) δ -68.1, -78.3.

HRMS (ESI-TOF) $m/z$: [M-OTf]$^+$ Caled for C$_{19}$H$_{15}$F$_3$NS: 346.0872; Found: 346.0874.

(5-Cyanopyridin-2-yl)(phenyl)(p-tolyl)sulfonium trifluoromethanesulfonate 1j

![Structure](image)

Product 1j was synthesised via General procedure C with sulfide 1ji (1.52 g, 6.73 mmol), Ph$_2$OTf (2.90 g, 6.73 mmol) and Cu(OTf)$_2$ (122 mg, 0.34 mmol). Purification by FCC (10% MeOH in CH$_2$Cl$_2$) gave sulfonium salt 1j as a brown oil (1.63 g, 53%).

TLC: $R_f = 0.36$ (10% MeOH in CH$_2$Cl$_2$).

$^1$H NMR (500 MHz, Chloroform-$d$) δ 8.92 (d, $J = 2.1$ Hz, 1H), 8.51 (d, $J = 8.2$ Hz, 1H), 8.35 (dd, $J = 8.3$, 2.3 Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 2H), 7.83 (d, $J = 8.3$ Hz, 2H), 7.76 (t, $J = 7.5$ Hz, 1H), 7.68 (t, $J = 7.8$ Hz, 2H), 7.50 (d, $J = 8.2$ Hz, 2H), 2.47 (s, 3H, CH$_3$).

$^{13}$C NMR (126 MHz, Chloroform-$d$) δ 153.8 (CH), 151.0 (C), 147.3 (C), 144.1 (CH), 135.1 (CH), 132.5 (CH), 132.3 (CH), 132.0 (CH), 131.7 (CH), 129.5 (CH), 124.0 (C), 120.8 (q, $J = 320.3$ Hz, OTf), 119.6 (C), 114.7 (CN), 114.5 (CCN), 21.9 (CH$_3$).

$^{19}$F NMR (470 MHz, Chloroform-$d$) δ -78.3.

HRMS (ESI-TOF) $m/z$: [M-OTf]$^+$ Caled for C$_{19}$H$_{15}$N$_2$S: 303.0950; Found: 303.0954.
(5-Bromopyridin-2-yl)(phenyl)(p-tolyl)sulfonium trifluoromethanesulfonate 1k

Product 1k was synthesised via General procedure C with sulfide 1ki (2.48 g, 8.85 mmol), Ph₂IOTf (3.17 g, 7.38 mmol) and Cu(OTf)₂ (133 mg, 0.37 mmol). Purification by FCC (10% MeOH in CH₂Cl₂) gave sulfonium salt 1k as a brown oil (2.87 g, 77%).

TLC: \( R_f = 0.36 \) (10% MeOH in CH₂Cl₂).

\(^1\)H NMR (500 MHz, Chloroform-\(d_2\)) \( \delta \) 8.77 (d, \( J = 2.1 \text{ Hz}, 1\text{H} \)), 8.55 – 8.47 (m, 1H), 8.25 – 8.18 (m, 1H), 7.90 (d, \( J = 7.9 \text{ Hz}, 2\text{H} \)), 7.85 (d, \( J = 8.3 \text{ Hz}, 2\text{H} \)), 7.73 (t, \( J = 7.4 \text{ Hz}, 1\text{H} \)), 7.65 (t, \( J = 7.5 \text{ Hz}, 2\text{H} \)), 7.45 (d, \( J = 7.5 \text{ Hz}, 2\text{H} \)), 2.45 (s, 3H, CH₃).

\(^{13}\)C NMR (126 MHz, Chloroform-\(d_2\)) \( \delta \) 153.4 (CH), 146.7 (C), 145.5 (C), 143.2 (CH), 134.7 (CH), 132.19 (CH), 132.17 (CH), 131.8 (CH), 131.4 (CH), 131.2 (CH), 126.9 (C), 124.9 (C), 120.9 (q, \( J = 320.5 \text{ Hz}, \text{OTf}) \), 120.6 (C), 21.8 (CH₃).

\(^{19}\)F NMR (470 MHz, Chloroform-\(d_2\)) \( \delta \) -78.2.

HRMS (ESI-TOF) \( m/z \): [M-OTf]⁺ Calcd for C₁₈H₁₅BrNS: 356.0103, 358.0083; Found: 356.0104, 358.0083.

(5-Chloropyridin-2-yl)(phenyl)(p-tolyl)sulfonium trifluoromethanesulfonate 1l

Product 1l was synthesised via General procedure C with sulfide 1li (0.32 g, 1.35 mmol), Ph₂IOTf (0.58 g, 1.35 mmol) and Cu(OTf)₂ (25 mg, 0.07 mmol). Purification by FCC (10% MeOH in CH₂Cl₂) gave sulfonium salt 1l as a brown oil (0.410 g, 66%).

TLC: \( R_I = 0.30 \) (10% MeOH in CH₂Cl₂).

\(^1\)H NMR (500 MHz, Chloroform-\(d_2\)) \( \delta \) 8.67 (d, \( J = 2.2 \text{ Hz}, 1\text{H} \)), 8.37 (d, \( J = 8.4 \text{ Hz}, 1\text{H} \)), 8.05 (d, \( J = 8.3, 2.5 \text{ Hz}, 1\text{H} \)), 7.88 – 7.82 (m, 2H), 7.80 (d, \( J = 8.4 \text{ Hz}, 2\text{H} \)), 7.76 – 7.70 (m, 1H), 7.69 – 7.62 (m, 2H), 7.46 (d, \( J = 8.3 \text{ Hz}, 2\text{H} \)), 2.44 (s, 3H, CH₃).
$^{13}$C NMR (101 MHz, Chloroform-$d$) δ 151.3 (CH), 146.8 (C), 144.7 (C), 140.2 (CH), 137.9 (C), 134.7 (CH), 132.2 (CH), 131.9 (CH), 131.6 (CH), 131.4 (CH), 130.6 (CH), 124.8 (C), 120.9 (q, $J = 320.6$ Hz, OTf), 120.4 (C), 21.8 (CH₃).

$^{19}$F NMR (376 MHz, Chloroform-$d$) δ -78.2.

HRMS (ESI-TOF) m/z: [M-OTf]$^+$ Calcd for C₁₈H₁₅ClNS: 312.0608, 314.0579; Found: 312.0610, 314.0578.

**Phenyl(pyrimidin-2-yl)(p-tolyl)sulfonium trifluoromethanesulfonate 1m**

Product 1m was synthesised via General procedure C with sulfide 1mi (1.71 g, 8.45 mmol), Ph₂IOTf (3.64 g, 8.45 mmol) and Cu(OTf)$_2$ (153 mg, 0.42 mmol). Purification by FCC (10% MeOH in CH₂Cl₂) gave sulfonium salt 1m as a brown solid (2.50 g, 69%).

TLC: $R_f$ = 0.32 (10% MeOH in CH₂Cl₂).

$^1$H NMR (500 MHz, Chloroform-$d$) δ 8.89 (d, $J = 4.8$ Hz, 2H), 7.87 (d, $J = 7.6$ Hz, 2H), 7.78 (d, $J = 8.5$ Hz, 2H), 7.77 – 7.75 (m, 1H), 7.72 (t, $J = 7.4$ Hz, 1H), 7.68 – 7.63 (m, 2H), 7.47 (d, $J = 8.3$ Hz, 2H), 2.42 (s, 3H, CH₃).

$^{13}$C NMR (126 MHz, Chloroform-$d$) δ 161.0 (CH), 160.1 (C), 147.0 (C), 135.0 (CH), 132.5 (CH), 132.3 (CH), 132.2 (CH), 131.5 (CH), 124.9 (CH), 124.4 (C), 120.8 (q, $J = 320.8$ Hz, OTf), 120.0 (C), 21.8 (CH₃).

$^{19}$F NMR (376 MHz, Chloroform-$d$) δ -78.2.

HRMS (ESI-TOF) m/z: [M-OTf]$^+$ Calcd for C₁₇H₁₅N₂S: 279.0950; Found: 279.0953.
4. Synthesis of bis-heteroaryls

**General procedure D:** Halopyridine (0.45 mmol, 1.5 equiv.) was added to an oven-dried crimp top vial and sealed. The vial was evacuated and purged with N\textsubscript{2} three times. The halopyridine was dissolved in dry THF (1.5 mL) and heated/cooled to a given temperature. \textit{i}-PrMgCl\textbullet LiCl (0.38 mL, 0.45 mmol, 1.5 equiv., 1.2 M in THF) was added dropwise to the stirring solution over 2 min. The reaction was allowed to stir for a given time at the specified temperature. Sulfonium salt (0.3 mmol, 1.0 equiv.) was added to a separate oven-dried crimp top vial and dissolved in dry THF (1.5 mL). The solution of sulfonium salt was added dropwise down the side of the vial to the Grignard reagent solution over 2 min. The reaction was allowed to stir for 2 h. Sat. aq. NH\textsubscript{4}Cl (3 mL) was added slowly to quench any excess Grignard reagent. The product was extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with H\textsubscript{2}O (20 mL) and brine (20 mL). The solvent was evaporated, and the product was isolated by FCC.

**General procedure E:** Pyridine (0.45 mmol, 1.5 equiv.) was added to an oven-dried crimp top vial and sealed. The vial was evacuated and purged with N\textsubscript{2} three times. The pyridine was dissolved in dry THF (1.5 mL) and heated/cooled to a given temperature. TMPMgCl\textbullet LiCl (0.41 mL, 0.45 mmol, 1.5 equiv., 1.1 M in THF) was added dropwise to the stirring solution over 2 min. The reaction was allowed to stir for a given time at the specified temperature. Sulfonium salt (0.3 mmol, 1.0 equiv.) was added to a separate oven-dried crimp top vial and dissolved in dry THF (1.5 mL). The solution of sulfonium salt was added dropwise down the side of the vial to the Grignard reagent solution over 2 min. The reaction was allowed to stir for 2 h. Sat. aq. NH\textsubscript{4}Cl (3 mL) was added slowly to quench any excess Grignard reagent. The product was extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with H\textsubscript{2}O (20 mL) and brine (20 mL). The solvent was evaporated, and the product was isolated by FCC.

**2,2’-Bipyridine 2**

![2,2’-Bipyridine 2](image)

Product 2 was synthesised via General procedure D using 2-iodopyridine (32 µL, 0.45 mmol) and sulfonium salt 1a (128.2 mg, 0.3 mmol). The Grignard reagent was formed at 0 °C for 30 min and the ligand coupling reaction was stirred at 0 °C. Purification by FCC (80% Et\textsubscript{2}O in pentane) gave bipyridine 2 as a white solid (24.8 mg, 53%).

\(^1\text{H} \text{NMR} \ (400 \text{ MHz, Chloroform-}d) \ \delta \ 8.74 - 8.61 \text{ (m, 2H), 8.40 (d, } J = 8.0 \text{ Hz, 2H), 7.82 (td, } J = 7.7, 1.8 \text{ Hz, 2H), 7.31 (ddd, } J = 7.6, 4.8, 1.2 \text{ Hz, 2H) ppm.}
^{13}C NMR (101 MHz, Chloroform-\textit{d}) \( \delta \) 156.3, 149.4, 137.1, 123.9, 121.2 ppm.

Spectra are consistent with literature data.\(^6\)

\textbf{2,3'-Bipyridine 3}

![2,3'-Bipyridine 3](image)

Product 3 was synthesised \textit{via} General procedure D using 3-iodopyridine (93 mg, 0.45 mmol) and sulfonium salt 1a (128.2 mg, 0.3 mmol). The Grignard reagent was formed at rt for 30 min and the ligand coupling reaction was stirred at rt. Purification by FCC (80% Et\textsubscript{2}O in pentane) gave bipyridine 3 as a yellow oil (46.0 mg, 98%).

^{1}H NMR (400 MHz, Chloroform-\textit{d}) \( \delta \) 9.20 (d, \( J = 2.3 \) Hz, 1H), 8.76 – 8.70 (m, 1H), 8.66 (dd, \( J = 4.9, 1.7 \) Hz, 1H), 8.33 (dt, \( J = 8.1, 2.0 \) Hz, 1H), 7.85 – 7.72 (m, 2H), 7.41 (dd, \( J = 7.9, 4.9 \) Hz, 1H), 7.33 – 7.26 (m, 1H) ppm.

^{13}C NMR (101 MHz, Chloroform-\textit{d}) \( \delta \) 154.9, 150.2, 150.0, 148.3, 137.1, 135.0, 134.5, 123.7, 123.0, 120.7 ppm.

Spectra are consistent with literature data.\(^7\)

\textbf{2,4'-Bipyridine 4}

![2,4'-Bipyridine 4](image)

Product 4 was synthesised \textit{via} General procedure D using 4-iodopyridine (93 mg, 0.45 mmol) and sulfonium salt 1a (128.2 mg, 0.3 mmol). The Grignard reagent was formed at rt for 30 min and the ligand coupling reaction was stirred at rt. Purification by FCC (70% Et\textsubscript{2}O in pentane) gave bipyridine 4 as a yellow oil (34.6 mg, 74%).

^{1}H NMR (500 MHz, Chloroform-\textit{d}) \( \delta \) 8.80 – 8.61 (m, 3H), 7.95 – 7.86 (m, 2H), 7.85 – 7.78 (m, 2H), 7.34 (ddd, \( J = 6.4, 4.8, 2.3 \) Hz, 1H) ppm.

^{13}C NMR (126 MHz, Chloroform-\textit{d}) \( \delta \) 154.8, 150.6, 150.3, 146.5, 137.2, 123.9, 121.2, 121.0 ppm.

Spectra are consistent with literature data.\(^8\)
4-Methyl-4'-{(trifluoromethyl)}-2,2'-bipyridine 5

![Methyl-4'-{(trifluoromethyl)}-2,2'-bipyridine 5](image)

Product 5 was synthesised via General procedure D using 2-bromo-4-methylpyridine (50.1 µL, 0.45 mmol) and sulfonium salt 1c (148.8 mg, 0.3 mmol). The Grignard reagent was formed at 30 °C for 2 h and the ligand coupling reaction was stirred at rt. Purification by FCC (5% Et₂O in pentane) gave bipyridine 5 as a white solid (46.2 mg, 64%).

TLC: R_t = 0.18 (10% Et₂O in pentane).

^{1}H NMR (500 MHz, Chloroform-d) δ 8.84 (dt, J = 5.0, 0.7 Hz, 1H, NCHCHCCF₃), 8.68 (dt, J = 1.7, 0.8 Hz, 1H, CF₃CCHC), 8.56 (dd, J = 4.9, 0.8 Hz, 1H, CH₃CCHCH), 8.27 (dt, J = 1.7, 0.8 Hz, 1H, CH₃CCH), 7.51 (ddd, J = 5.0, 1.8, 0.8 Hz, 1H, NCHCHCCF₃), 7.19 (ddd, J = 5.0, 1.7, 0.8 Hz, 1H, CH₃CCHCH), 2.46 (s, 3H, CH₃) ppm.

^{13}C NMR (126 MHz, Chloroform-d) δ 157.9 (C), 154.3 (C), 150.1 (NCHCHCCF₃), 149.3 (CH₃CCHCH), 148.6 (CH₃C), 139.5 (q, J = 34.2 Hz, CF₃C), 125.6 (CH₃CCHCH), 123.1 (q, J = 273.2 Hz, CF₃C), 122.3 (CH₃CCH), 119.2 (q, J = 3.5 Hz, CF₃CCHCH), 117.2 (q, J = 3.6 Hz, CF₃CCHCH), 21.4 ppm.

^{19}F NMR (470 MHz, CDCl₃) δ -64.8 ppm.

Spectra are consistent with literature data.⁹

4-Fluoro-4'-{(trifluoromethyl)}-2,2'-bipyridine 6

![4-Fluoro-4'-{(trifluoromethyl)}-2,2'-bipyridine 6](image)

Product 6 was synthesised via General procedure D using 2-bromo-4-fluoropyridine (46.6 µL, 0.45 mmol) and sulfonium salt 1c (148.8 mg, 0.3 mmol). The Grignard reagent was formed at rt for 1 h and the ligand coupling reaction was stirred at rt. Purification by FCC (7.5% Et₂O in pentane) gave bipyridine 6 as a yellow oil (52.8 mg, 73%).

TLC: R_t = 0.55 (10% Et₂O in pentane).
\[ 1\text{H NMR (500 MHz, Chloroform-}\text{d}) \delta 8.84 (dt, J = 5.0, 0.7 \text{ Hz, 1H, NCHCHCCF}_3), 8.69 (dt, J = 1.7, 0.8 \text{ Hz, 1H, F}_3\text{CCCH}), 8.66 (dd, J = 8.4, 5.5 \text{ Hz, 1H, NCHCHCF}), 8.20 (dd, J = 10.2, 2.5 \text{ Hz, 1H, FCCHC}), 7.59 – 7.51 (m, 1H, NCHCHCCF)_3, 7.10 (ddd, J = 8.1, 5.5, 2.5 \text{ Hz, 1H, FCCCH}) \text{ ppm.} \]

\[ 13\text{C NMR (126 MHz, Chloroform-}\text{d}) \delta 169.7 (d, J = 262.3 \text{ Hz, CF}), 158.2 (d, J = 7.4 \text{ Hz, FCCHC}), 156.5 (d, J = 3.8 \text{ Hz, NCHCHCCF}_3), 151.8 (d, J = 6.9 \text{ Hz, FCCHCHN}), 150.3 (NCHCHCCF)_3, 139.6 (q, J = 34.2 \text{ Hz, CF}_3\text{C}), 123.0 (q, J = 273.4 \text{ Hz, CF}_3), 119.8 (q, J = 3.4 \text{ Hz, CF}_3\text{CCH}), 117.3 (q, J = 3.7 \text{ Hz, CF}_3\text{CCH}), 112.4 (d, J = 16.8 \text{ Hz, FCCCH}), 109.3 (d, J = 18.7 \text{ Hz, FCCCH}) \text{ ppm.} \]

\[ 19\text{F NMR (470 MHz, Chloroform-}\text{d}) \delta -64.9 (\text{CF}_3), -101.3 (\text{app. dt, J = 10.3, 8.2 Hz, CF}) \text{ ppm.} \]

\[ \text{HRMS (ESI-TOF) m/z: [M+H]}^+ \text{ Calcd for C}_{11}\text{H}_{7}\text{F}_4\text{N}_2: 243.0540; \text{ found: 243.0539 ppm.} \]

**1-(5-Methoxypyridin-2-yl)isoquinoline 7**

Product 7 was synthesised via General procedure D using 2-bromo-5-methoxypyridine (56 \muL, 0.45 mmol) and sulfonium salt 1b (143.3 mg, 0.3 mmol). The Grignard reagent was formed at rt for 3 h and the ligand coupling reaction was stirred at rt. Purification by FCC (50% Et\text{2}O in pentane) gave bipyridine 7 as a white solid (55.3 mg, 78%).

**TLC:** \( R_f = 0.1 \) (50% Et\text{2}O in pentane).

\[ 1\text{H NMR (500 MHz, Chloroform-}\text{d}) \delta 8.67 (dd, J = 8.6, 1.0 \text{ Hz, 1H, NCCCH}), 8.60 (d, J = 5.6 \text{ Hz, 1H, NCH}), 8.49 (d, J = 2.9 \text{ Hz, 1H, NCHCOCH}_3), 7.99 (dd, J = 8.6, 0.7 \text{ Hz, 1H, CH}_3\text{OCCH}_3\text{H}), 7.88 – 7.83 (m, 1H, NCCCHCH), 7.72 – 7.65 (m, 2H, ArH), 7.59 (ddd, J = 8.3, 6.8, 1.3 \text{ Hz, 1H, NCCCHCH}), 7.41 (dd, J = 8.6, 3.0 \text{ Hz, 1H, CH}_3\text{OCCH}_3\text{H}), 3.97 (s, 3H, OCH\text{3}) \text{ ppm.} \]

\[ 13\text{C NMR (126 MHz, Chloroform-}\text{d}) \delta 157.4 (\text{NCC}), 155.7 (\text{COCH}_3), 151.1 (\text{C}), 142.0 (\text{NCH}), 137.4 (\text{C}), 136.4 (\text{NCHCO}), 130.1 (\text{CH}), 128.1 (\text{NCHCH}), 127.6 (\text{NCCCHCHCH}), 127.0 (\text{NCCCHCH}), 126.8 (\text{C}), 125.9 (\text{CH}_3\text{OCCH}_3\text{H}), 121.4 (\text{CH}_3\text{OCCH}_3\text{H}), 120.9 (\text{CH}), 55.9 (\text{OCH}_3) \text{ ppm.} \]

\[ \text{HRMS (ESI-TOF) m/z: [M+H]}^+ \text{ Calcd for C}_{15}\text{H}_{13}\text{N}_2\text{O}: 237.1022; \text{ found: 237.1023.} \]
5'-Bromo-2,3'-bipyridine 8

Product 8 was synthesised via General procedure D using 3,5-dibromopyridine (106.6 mg, 0.45 mmol) and sulfonium salt 1a (128.2 mg, 0.3 mmol). The Grignard reagent was formed at rt for 1 h and the ligand coupling reaction was stirred at rt. Purification by FCC (40% Et₂O in pentane) gave bipyridine 8 as a yellow solid (43.7 mg, 62%).

TLC: Rᵣ = 0.22 (40% Et₂O in pentane)

¹H NMR (500 MHz, Chloroform-d) δ 9.09 (d, J = 1.9 Hz, 1H), 8.72 (dt, J = 4.8, 1.3 Hz, 1H), 8.70 (d, J = 2.2 Hz, 1H), 8.51 (t, J = 2.0 Hz, 1H), 7.81 (dd, J = 7.7, 1.8 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.32 (ddd, J = 7.3, 4.7, 0.8 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-d) δ 153.4, 151.0, 150.4, 146.3, 137.3, 137.1, 136.5, 123.5, 121.3, 120.9.

Spectra were consistent with literature data.¹⁰

6-Bromo-2,3'-bipyridine 9

Product 9 was synthesised via General procedure D using 3-iodopyridine (92.3 mg, 0.45 mmol) and sulfonium salt 1g (151.9 mg, 0.3 mmol). The Grignard reagent was formed at rt for 45 min and the ligand coupling reaction was stirred at rt. Purification by FCC (80% Et₂O in pentane) gave bipyridine 9 as a yellow solid (46.8 mg, 66%).

TLC: Rᵣ = 0.19 (80% Et₂O in pentane)

¹H NMR (500 MHz, Chloroform-d) δ 9.15 (d, J = 2.3 Hz, 1H), 8.65 (dd, J = 4.9, 1.6 Hz, 1H), 8.32 (dt, J = 7.9, 2.1 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.39 (dd, J = 8.0, 4.8 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-d) δ 156.0, 150.6, 148.2, 142.7, 139.3, 134.6, 133.4, 127.3, 123.8, 119.2.

Spectra were consistent with literature data.¹¹
6′-Bromo-6-(trifluoromethyl)-2,3′-bpyridine 10

Product 10 was synthesised via General procedure D using 2,5-dibromopyridine (106.6 mg, 0.45 mmol) and sulfonium salt 1i (148.6 mg, 0.3 mmol). The Grignard reagent was formed at rt for 1 h and the ligand coupling reaction was stirred at rt. Purification by FCC (20% Et₂O in pentane) gave bipyridine 10 as a yellow solid (45.0 mg, 50%).

TLC: $R_f = 0.19$ (20% Et₂O in pentane)

$^1$H NMR (400 MHz, Chloroform-d) δ 8.96 (d, $J = 2.5$ Hz, 1H, CHN), 8.29 (dd, $J = 8.3, 2.7$ Hz, 1H), 7.99 (t, $J = 7.8$ Hz, 1H), 7.93 (d, $J = 7.6$ Hz, 1H), 7.69 (dd, $J = 7.5, 1.1$ Hz, 1H), 7.61 (dd, $J = 8.3, 0.5$ Hz, 1H).$^{13}$C NMR (101 MHz, Chloroform-d) δ 154.2 (C), 148.9 (q, $J = 35.0$ Hz, CCF₃), 148.6 (CH), 143.7 (CBr), 138.8 (CH), 137.3 (CH), 132.8 (C), 128.5 (CH), 122.8 (CH), 121.4 (q, $J = 276.6$ Hz, CF₃), 119.8 (q, $J = 2.7$ Hz, CH).

$^{19}$F NMR (282 MHz, Chloroform-d) δ -68.2.

HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C₁₁H₇BrF₃N₂: 302.9739, 304.9719; Found: 302.9741, 304.9721.

5-Chloro-2,3′-bpyridine 11

Product 11 was synthesised via General procedure D using 3-iodopyridine (92.3 mg, 0.45 mmol) and sulfonium salt 1i (138.6 mg, 0.3 mmol). The Grignard reagent was formed at rt for 45 min and the ligand coupling reaction was stirred at rt. Purification by FCC (80% Et₂O in pentane) gave bipyridine 11 as a white solid (31.9 mg, 56%).

TLC: $R_t = 0.27$ (80% Et₂O in pentane)

$^1$H NMR (400 MHz, Chloroform-d) δ 9.17 – 9.14 (m, 1H), 8.67 – 8.64 (m, 2H), 8.28 (dt, $J = 7.9, 2.0$ Hz, 1H), 7.76 (dd, $J = 8.4, 2.5$ Hz, 1H), 7.70 (dd, $J = 8.6, 0.6$ Hz, 1H), 7.40 (ddd, $J = 7.8, 4.7, 0.6$ Hz, 1H).
$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 153.0, 150.3, 149.1, 148.2, 136.8, 134.3, 133.9, 131.6, 123.8, 121.2.

Spectra were consistent with literature data.$^{12}$

**5,5'-Dibromo-2,3'-bipyridine 12**

![5,5'-Dibromo-2,3'-bipyridine 12](image)

Product 12 was synthesised via General procedure D using 3,5-dibromopyridine (106.6 mg, 0.45 mmol) and sulfonium salt 1k (151.9 mg, 0.3 mmol). The Grignard reagent was formed at rt for 1 h and the ligand coupling reaction was stirred at 45 °C for 3.5 h. Purification by FCC (40% Et$_2$O in pentane) gave bipyridine 12 as a white solid (63.5 mg, 67%).

TLC: $R_t = 0.23$ (40% Et$_2$O in pentane)

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.07 (d, $J = 1.9$ Hz, 1H), 8.77 (d, $J = 2.3$ Hz, 1H), 8.72 (d, $J = 2.3$ Hz, 1H), 8.49 (t, $J = 2.1$ Hz, 1H), 7.93 (dd, $J = 8.5$, 2.4 Hz, 1H), 7.65 (d, $J = 8.3$ Hz, 1H).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 151.8 (C), 151.5 (CH), 151.3 (CH), 146.0 (CH), 139.9 (CH), 136.9 (CH), 135.4 (C), 121.8 (CH), 121.4 (C), 121.0 (C).

HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{10}$H$_7$Br$_2$N$_2$: 312.8970, 314.8950, 316.8931; Found: 312.8971, 314.8952, 316.8930.

**[2,3'-Bipyridine]-5-carbonitrile 13**

![5,5'-Dibromo-2,3'-bipyridine 12](image)

Product 13 was synthesised via General procedure D using 3-iodopyridine (92.3 mg, 0.45 mmol) and sulfonium salt 1j (135.7 mg, 0.3 mmol). The Grignard reagent was formed at rt for 45 min and the ligand coupling reaction was stirred at rt. Purification by FCC (80% Et$_2$O in pentane) gave bipyridine 13 as a yellow solid (28.4 mg, 52%).

TLC: $R_t = 0.14$ (80% Et$_2$O in pentane)

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 9.25 (s, 1H), 8.97 (d, $J = 2.0$ Hz, 1H), 8.73 (d, $J = 4.8$ Hz, 1H), 8.37 (dt, $J = 7.9$, 1.9 Hz, 1H), 8.06 (dd, $J = 8.3$, 2.0 Hz, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.46 (dd, $J = 8.0$, 4.8 Hz, 1H).
$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 158.1 (C), 152.8 (CH), 151.5 (CH), 148.7 (CH), 140.3 (CH), 134.9 (CH), 133.1 (C), 124.0 (CH), 120.2 (CH), 116.7 (CN), 108.9 (CCN).

HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{11}$H$_8$N$_3$: 182.0713; Found: 182.0714.

5-Methoxy-2,3'-bipyridine 14

Product 14 was synthesised via General procedure D using 3-iodopyridine (92.3 mg, 0.45 mmol) and sulfonium salt 1f (137.2 mg, 0.3 mmol). The Grignard reagent was formed at rt for 45 min and the ligand coupling reaction was stirred at rt. Purification by FCC (80% Et$_2$O in pentane) gave bipyridine 14 as a white solid (23.1 mg, 41%).

TLC: $R_f$ = 0.10 (80% Et$_2$O in pentane)

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 9.12 (d, $J$ = 2.3 Hz, 1H), 8.59 (dd, $J$ = 4.8, 1.6 Hz, 1H), 8.41 (d, $J$ = 2.9 Hz, 1H), 8.25 (dt, $J$ = 8.1, 2.1 Hz, 1H), 7.68 (dd, $J$ = 8.5 Hz, 1H), 7.36 (dd, $J$ = 7.9, 4.7 Hz, 1H), 7.29 (dd, $J$ = 8.7, 3.0 Hz, 1H), 3.90 (s, 3H, OMe).

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 155.5 (C), 149.3 (CH), 147.9 (CH), 147.4 (C), 137.9 (CH), 134.7 (C), 133.9 (CH), 123.7 (CH), 121.3 (CH), 121.0 (CH), 55.8 (OMe).

HRMS (ESI-TOF) $m/z$: [M+H]$^+$ Calcd for C$_{11}$H$_{11}$N$_2$: 187.0866; Found: 187.0867.

2'-Fluoro-2,4'-bipyridine 15

Product 15 was synthesised via General procedure D using 4-bromo-2-fluoropyridine (46.2 µL, 0.45 mmol) and sulfonium salt 1a (128.2 mg, 0.3 mmol). The Grignard reagent was formed at rt for 30 min and the ligand coupling reaction was stirred at rt. Purification by FCC (70% Et$_2$O in pentane) gave bipyridine 15 as a yellow oil (46.0 mg, 88%).

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.74 (ddd, $J$ = 4.8, 1.8, 1.0 Hz, 1H), 8.31 (dt, $J$ = 5.3, 0.7 Hz, 1H), 7.83 (td, $J$ = 7.7, 1.8 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.62 – 7.52 (m, 1H), 7.37 (ddd, $J$ = 7.4, 4.8, 1.3 Hz, 1H) ppm.
$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 164.9 (d, $J = 237.9$ Hz, CF), 153.5 (d, $J = 3.8$ Hz), 152.2 (d, $J = 8.1$ Hz), 150.3, 148.3 (d, $J = 15.2$ Hz), 137.3, 124.5, 121.1, 119.0 (d, $J = 4.2$ Hz), 107.1 (d, $J = 39.1$ Hz) ppm.

$^{19}$F NMR (470 MHz, Chloroform-$d$) $\delta$ -67.8 ppm.

Spectra are consistent with literature data.$^{10}$

**2'-Fluoro-6-methyl-2,4'-bipyridine 16**

![2'-Fluoro-6-methyl-2,4'-bipyridine](image)

Product 16 was synthesised via General procedure D using 4-bromo-2-fluoropyridine (46.2 µL, 0.45 mmol) and sulfonium salt 1h (132.4 mg, 0.3 mmol). The Grignard reagent was formed at 0 °C for 30 min and the ligand coupling reaction was stirred at 0 °C. Purification by FCC (20% Et₂O in pentane) gave bipyridine 16 as a white solid (38.7 mg, 69%).

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.30 (d, $J = 5.2$ Hz, 1H), 7.77 (dt, $J = 5.3$, 1.7 Hz, 1H), 7.71 (t, $J = 7.7$ Hz, 1H), 7.61 – 7.55 (m, 2H), 7.23 (d, $J = 7.6$ Hz, 1H), 2.64 (s, 3H) ppm.

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 164.9 (d, $J = 237.9$ Hz, CF), 159.3, 152.9 (d, $J = 3.8$ Hz), 152.6 (d, $J = 8.2$ Hz), 148.2 (d, $J = 15.2$ Hz), 137.4, 124.1, 119.1 (d, $J = 4.2$ Hz), 118.2, 107.2 (d, $J = 38.9$ Hz), 24.8 ppm.

$^{19}$F NMR (376 MHz, Chloroform-$d$) $\delta$ -68.1 ppm.

Spectra are consistent with literature data.$^{10}$

**1-(2-Fluoropyridin-4-yl)isoquinoline 17**

![1-(2-Fluoropyridin-4-yl)isoquinoline](image)

Product 17 was synthesised via General procedure D using 4-bromo-2-fluoropyridine (46.2 µL, 0.45 mmol) and sulfonium salt 1b (143.3 mg, 0.3 mmol). The Grignard reagent was formed at 0 °C for 30 min and the ligand coupling reaction was stirred at 0 °C. Purification by FCC (50% Et₂O in pentane) gave bipyridine 17 as a white solid (67.2 mg, quant. yield).
The reaction was scaled up and product 17 was synthesized via General procedure D using 4-bromo-2-fluoropyridine (1.13 mL, 11.0 mmol) and sulfonium salt 1b (3.50 g, 7.3 mmol). Purification by FCC (50% Et2O in pentane) gave bipyridine 17 as a white solid (1.57 g, 96%).

TLC: \( R_f = 0.33 \) (35% EtO in pentane).

\(^1\)H NMR (500 MHz, Chloroform-\(d\)) \( \delta \) 8.64 (d, \( J = 5.6 \) Hz, 1H, NCH), 8.40 (dt, \( J = 5.1, 0.8 \) Hz, 1H, FCNCH), 8.02 (dt, \( J = 8.6, 1.0 \) Hz, 1H, NCHCHCCH), 7.97 – 7.92 (m, 1H, ArH), 7.79 – 7.72 (m, 2H, ArH), 7.62 (ddd, \( J = 8.2, 6.8, 1.2 \) Hz, 1H, NCCCHCH), 7.53 (dd, \( J = 5.1, 2.0 \) Hz, 1H, NCCCHCHN), 7.27 (d, \( J = 1.9 \) Hz, FCCH) ppm.

\(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) \( \delta \) 163.9 (d, \( J = 239.4 \) Hz, CF), 156.7 (d, \( J = 3.3 \) Hz, FCCHC), 152.8 (d, \( J = 8.1 \) Hz, FCCHC), 147.9 (d, \( J = 15.1 \) Hz, FCNCH), 142.5 (NCH), 136.9 (C), 130.6 (CH), 128.1 (NCCCHCH), 127.4 (CH), 126.11 (NCCCH), 126.10 (C), 122.5 (d, \( J = 4.3 \) Hz, FCNCHCH), 121.5 (C), 110.7 (d, \( J = 38.1 \) Hz, FCCH) ppm.

\(^{19}\)F NMR (470 MHz, Chloroform-\(d\)) \( \delta \) -67.4 ppm.

HRMS (ESI-TOF) \( m/z \): [M+H]+ Calcd for C\(_{14}\)H\(_{10}\)FN\(_2\): 225.0823; found: 225.0820.

**1-(2-Methoxypyridin-4-yl)isoquinoline 18**

[Diagram of 1-(2-Methoxypyridin-4-yl)isoquinoline]

Product 18 was synthesised via General procedure D using 4-bromo-2-methoxypyridine (84.6 mg, 0.45 mmol) and sulfonium salt 1b (143.3 mg, 0.3 mmol). The Grignard reagent was formed at 40 °C for 2 h and the ligand coupling reaction was stirred at rt. Purification by FCC (25% Et2O in pentane) gave bipyridine 18 as a white solid (44.7 mg, 63%).

TLC: \( R_t = 0.11 \) (20% EtO in pentane).

\(^1\)H NMR (500 MHz, Chloroform-\(d\)) \( \delta \) 8.61 (d, \( J = 5.7 \) Hz, 1H, NCH), 8.33 (dd, \( J = 5.2, 0.8 \) Hz, 1H, CH\(_3\)OCNCH), 8.05 (dd, \( J = 8.6, 1.0 \) Hz, 1H, NCCCH), 7.89 (dt, \( J = 8.2, 1.0 \) Hz, 1H, NCHCHCCH), 7.79 – 7.65 (m, 2H, ArH), 7.55 (dd, \( J = 8.3, 6.9, 1.3 \) Hz, 1H, NCHCHCCH), 7.19 (dd, \( J = 5.2, 1.4 \) Hz, 1H, OCNCH), 7.05 (dd, \( J = 1.4, 0.8 \) Hz, 1H, OCCH), 4.02 (s, 3H, OCH\(_3\)) ppm.

\(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) \( \delta \) 164.5 (C), 158.2 (C), 150.0 (C), 147.2 (OCNCH), 142.4 (NCH), 136.9 (app. d, \( J = 1.3 \) Hz, CH\(_3\)OC), 130.4 (CH), 127.8 (NCHCHCCH), 127.3 (NCHCHCCH), 126.8 (NCCCH), 126.4 (C), 121.0 (CH), 118.1 (OCNCH), 111.9 (OCCH), 53.8 (OCH\(_3\)) ppm.
HRMS (ESI-TOF) m/z: [M+H]^+ Calcd for C_{15}H_{14}N_2O: 237.1022; found: 237.1020.

4-(Trifluoromethyl)-2,4'-bipyridine 19

Product 19 was synthesised via General procedure D using 4-iodopyridine (93 mg, 0.45 mmol) and sulfonium salt 1c (148.8 mg, 0.3 mmol). The Grignard reagent was formed at 0 °C for 30 min and the ligand coupling reaction was stirred at 0 °C warming to rt. Purification by FCC (50% Et₂O in pentane) gave bipyridine 19 as a yellow oil (37.0 mg, 55%).

TLC: R_f = 0.27 (25% Et₂O in pentane).

^1H NMR (500 MHz, Chloroform-d) δ 8.93 (dt, J = 5.0, 0.7 Hz, 1H, NCHCCHCF₃), 8.83 – 8.71 (m, 2H, ArH), 7.99 (dt, J = 1.6, 0.7 Hz, 1H, CF₃CCH), 7.96 – 7.91 (m, 2H, ArH), 7.56 (ddd, J = 5.0, 1.6, 0.7 Hz, 1H, NCHCCHCF₃) ppm.

^13C NMR (126 MHz, Chloroform-d) δ 156.3 (NCC), 151.3 (NCHCHCCF₃), 150.8 (CH), 145.1 (NCC), 139.7 (q, J = 34.2 Hz, CF₃C), 122.8 (q, J = 273.2 Hz, CF₃), 121.2 (CH), 119.4 (q, J = 3.5 Hz, CF₃CCH), 116.6 (q, J = 3.7 Hz, CF₃CCH) ppm.

^19F NMR (470 MHz, CDCl₃) δ -64.8 ppm.

HRMS (ESI-TOF) m/z: [M+H]^+ Calcd for C_{11}H₈F₃N₂: 225.0634; found: 225.0635.

2'-Methoxy-4-(trifluoromethyl)-2,4'-bipyridine 20

Product 20 was synthesised via General procedure D using 4-bromo-2-methoxypyridine (84.6 mg, 0.45 mmol) and sulfonium salt 1c (148.8 mg, 0.3 mmol). The Grignard was formed at 40 °C for 2 h and the ligand coupling reaction was stirred at rt. Purification by FCC (15% Et₂O in pentane) gave bipyridine 20 as a white solid (49.0 mg, 64%).

TLC: R_f = 0.46 (20% Et₂O in pentane).

^1H NMR (500 MHz, Chloroform-d) δ 8.91 (dt, J = 5.0, 0.8 Hz, 1H, NCHCCHCF₃), 8.31 (dd, J = 5.4, 0.8 Hz, 1H, OCNCH), 7.94 (dt, J = 1.6, 0.8 Hz, 1H, F₃CCCH), 7.54 (ddd, J = 5.0, 1.7, 0.8 Hz,
NCHCHCCF₃, 7.50 (dd, J = 5.4, 1.5 Hz, OCNCHCH), 7.37 (dd, J = 1.5, 0.7 Hz, 1H, OCCH), 4.00 (s, 3H, OCH₃) ppm.

¹³C NMR (126 MHz, Chloroform-d) δ 165.4 (H₃COC), 156.4 (F₃CCCHCN), 151.1 (NCHCHCCF₃), 148.0 (OCNCH), 147.98 (NCC), 139.6 (q, J = 34.3 Hz, CF₃C), 122.9 (q, J = 273.2 Hz, CF₃), 119.3 (q, J = 3.6 Hz, CF₃CCCH), 116.7 (q, J = 3.7 Hz, CF₃CCHC), 114.6 (OCNCHCH), 108.7 (OCCH), 53.9 (OCH₃) ppm.

HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₁₁H₁₀F₃N₂O: 254.0661; found: 254.0676.

2',6'-Dichloro-3-methyl-2,4'-bipyridine 21

![2',6'-Dichloro-3-methyl-2,4'-bipyridine 21](image)

Product 21 was synthesised via General procedure E using 2,6-dichloropyridine (50.1 µL, 0.45 mmol) and sulfonium salt 1d (132.4 mg, 0.3 mmol). The Grignard reagent was formed at rt for 10 min and the ligand coupling reaction was stirred at rt. Purification by FCC (5% Et₂O in pentane) gave bipyridine 21 as a white solid (46.2 mg, 64%).

TLC: Rᵣ = 0.35 (20% Et₂O in pentane).

¹H NMR (500 MHz, Chloroform-d) δ 8.54 (ddd, J = 4.7, 1.6, 0.7 Hz, 1H, NCH), 7.64 (ddd, J = 7.8, 1.7, 0.8 Hz, 1H, NCHCHC₂H), 7.45 (s, 2H, ArH), 7.29 (dd, J = 7.8, 4.7 Hz, 1H, NCHC₂H), 2.39 (s, 3H, CH₃) ppm.

¹³C NMR (126 MHz, Chloroform-d) δ 153.5 (C), 153.4 (C), 150.7 (CH₃C), 147.8 (NCH), 139.4 (NCHCHC₂H), 131.4 (NCC), 124.1 (NCHCH), 123.2 (NCCICH), 19.8 (CH₃) ppm.

HRMS (ESI-TOF) m/z: [M+H]⁺ Calcd for C₁₁H₁₀Cl₂N₂: 239.0137, 240.0167, 241.0109, 242.0138 and 243.0082; found: 239.0140, 240.0173, 241.0110, 242.0142 and 243.0080.

2'-Fluoro-6-(trifluoromethyl)-2,4'-bipyridine 22

![2'-Fluoro-6-(trifluoromethyl)-2,4'-bipyridine 22](image)

Product 22 was synthesised via General procedure D using 4-bromo-2-fluoropyridine (46 µL, 0.45 mmol) and sulfonium salt 1i (148.6 mg, 0.3 mmol). The Grignard reagent was formed at rt for 1 h and
the ligand coupling reaction was stirred at rt. Purification by FCC (20% Et₂O in pentane) gave bipyridine 22 as a white solid (41.1 mg, 57%).

TLC: \( R_f = 0.14 \) (20% Et₂O in pentane).

\(^1\)H NMR (500 MHz, Chloroform-\( d \)) \( \delta \) 8.35 (d, \( J = 5.3 \) Hz, 1H), 8.04 (t, \( J = 7.8 \) Hz, 1H), 7.99 (d, \( J = 8.0 \) Hz, 1H), 7.85 – 7.82 (m, 1H), 7.76 (d, \( J = 7.7 \) Hz, 1H), 7.62 (s, 1H).

\(^{13}\)C NMR (126 MHz, Chloroform-\( d \)) \( \delta \) 164.9 (d, \( J = 238.7 \) Hz, CF), 153.9 (d, \( J = 3.3 \) Hz, C), 150.5 (d, \( J = 8.3 \) Hz, C), 148.9 (q, \( J = 35.0 \) Hz, CCF₃), 148.7 (d, \( J = 15.2 \) Hz, CH), 139.0 (CH), 123.5 (CH), 121.3 (q, \( J = 274.4 \) Hz, CCF₃), 121.0 (q, \( J = 2.8 \) Hz, CH), 119.0 (d, \( J = 3.9 \) Hz, CH), 107.4 (d, \( J = 39.1 \) Hz, CH).

\(^{19}\)F NMR (470 MHz, Chloroform-\( d \)) \( \delta \) -67.2, -68.2.

HRMS (ESI-TOF) \( m/z \): [M+H]+ Calcd for C₁₁H₇F₄N₂: 243.0540; Found: 243.0542.

**5-Bromo-2'-fluoro-2,4'-bipyridine 23**

![5-Bromo-2'-fluoro-2,4'-bipyridine 23](image)

Product 23 was synthesised via General procedure D using 4-bromo-2-fluoropyridine (46 µL, 0.45 mmol) and sulfonium salt 1k (151.9 mg, 0.3 mmol). The Grignard reagent was formed at 45 °C for 1 h and the ligand coupling reaction was stirred at 45 °C for 4.5 h. Purification by FCC (40% Et₂O in pentane) gave bipyridine 23 as a white solid (43.3 mg, 57%).

TLC: \( R_f = 0.44 \) (40% Et₂O in pentane).

\(^1\)H NMR (400 MHz, Chloroform-\( d \)) \( \delta \) 8.80 (dd, \( J = 2.3, 0.6 \) Hz, 1H), 8.33 (d, \( J = 5.3 \) Hz, 1H), 7.97 (dd, \( J = 8.6, 2.3 \) Hz, 1H), 7.75 (dt, \( J = 5.4, 1.7 \) Hz, 1H), 7.69 (d, \( J = 8.3 \) Hz, 1H), 7.54 (t, \( J = 1.7 \) Hz, 1H).

\(^{13}\)C NMR (126 MHz, Chloroform-\( d \)) \( \delta \) 164.9 (d, \( J = 238.4 \) Hz, CF), 151.9 (d, \( J = 3.8 \) Hz, C), 151.5 (CH), 151.0 (d, \( J = 8.5 \) Hz, C), 148.6 (d, \( J = 15.2 \) Hz, CH), 139.9 (CH), 122.2 (CH), 122.0 (CBr), 118.7 (d, \( J = 3.8 \) Hz, CH), 107.0 (d, \( J = 39.1 \) Hz, CH).

\(^{19}\)F NMR (376 MHz, Chloroform-\( d \)) \( \delta \) -67.4.

HRMS (ESI-TOF) \( m/z \): [M+H]+ Calcd for C₁₀H₇BrFN₂: 252.9771, 254.9751; Found: 252.9772, 254.9751.
2-(Pyridin-3-yl)pyrimidine 24

![Chemical structure of 2-(Pyridin-3-yl)pyrimidine 24](image)

Product 24 was synthesised via General procedure D using 3-iodopyridine (92.3 mg, 0.45 mmol) and sulfonium salt 1m (128.5 mg, 0.3 mmol). The Grignard reagent was formed at rt for 45 min and the ligand coupling reaction was stirred at rt. Purification by FCC (80% Et₂O in pentane) gave bis-heteroaryl 24 as a brown solid (33.1 mg, 70%).

TLC: \( R_f = 0.24 \) (80% Et₂O in pentane)

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \( \delta \) 9.65 (d, \( J = 2.2 \) Hz, 1H), 8.84 (d, \( J = 4.8 \) Hz, 2H), 8.74 – 8.66 (m, 2H), 7.45 – 7.40 (m, 1H), 7.26 (t, \( J = 4.9 \) Hz, 1H).

\(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \( \delta \) 163.2, 157.5, 151.5, 150.0, 135.6, 133.2, 123.5, 119.9.

Spectra were consistent with literature data.\(^{13}\)

2-(6-(Trifluoromethyl)pyridin-2-yl)pyrimidine 25

![Chemical structure of 2-(6-(Trifluoromethyl)pyridin-2-yl)pyrimidine 25](image)

Product 25 was synthesised via General procedure D using 2-bromo-6-(trifluoromethyl)pyridine (101.7 mg, 0.45 mmol) and sulfonium salt 1m (128.5 mg, 0.3 mmol). The Grignard reagent was formed at 45 °C for 2 h and the ligand coupling reaction was stirred at -78 °C. Purification by FCC (60% Et₂O in pentane) gave bis-heteroaryl 25 as an orange solid (27.2 mg, 40%).

TLC: \( R_f = 0.16 \) (60% Et₂O in pentane)

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \( \delta \) 8.97 (d, \( J = 4.8 \) Hz, 2H), 8.70 (d, \( J = 8.0 \) Hz, 1H), 8.06 (t, \( J = 7.9 \) Hz, 1H), 7.81 (d, \( J = 7.8 \) Hz, 1H), 7.37 (t, \( J = 4.8 \) Hz, 1H).

\(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \( \delta \) 162.8 (C), 158.0 (CH), 155.6 (C), 148.8 (q, \( J = 34.8 \) Hz, CCF₃), 138.6 (CH), 126.5 (CH), 121.7 (q, \( J = 3.0 \) Hz, CH), 121.6 (d, \( J = 274.6 \) Hz, CF₃), 121.0 (CH).

\(^{19}\)F NMR (376 MHz, Chloroform-\(d\)) \( \delta \) -67.5.

HRMS (ESI-TOF) \( m/z \) : [M+H]⁺ Calcd for C₁₀H₇F₃N₃: 226.0587; Found: 226.0589.
**2-Bromo-4-(4-(trifluoromethyl)pyridin-2-yl)pyrimidine 26**

![Chemical structure of 26]

Product 26 was synthesised via General procedure A using 2,4-dibromopyrimidine (71.5 mg, 0.45 mmol) and sulfonium salt 1c (148.8 mg, 0.3 mmol). The Grignard reagent was formed at -45 °C for 2 h. Purification by FCC (10% Et2O in pentane) gave bis-heteroaryl 26 as a white solid (58.1 mg, 64%).

TLC: Rf = 0.35 (20% Et2O in pentane).

1H NMR (500 MHz, Chloroform-d) δ 8.90 (dt, J = 5.0, 0.7 Hz, 1H), 8.73 (d, J = 5.1 Hz, 1H), 8.72 – 8.70 (m, 1H), 8.39 (d, J = 5.0 Hz, 1H), 7.67 (ddd, J = 5.0, 1.7, 0.8 Hz, 1H).

13C NMR (126 MHz, Chloroform-d) δ 164.5 (CBr), 160.8 (CH), 154.0 (C), 153.4 (C), 150.8 (CH), 140.05 (q, J = 34.8 Hz, CF3), 122.7 (t, J = 273.8 Hz, CF3), 121.7 (q, J = 3.4 Hz, CH), 118.1 (q, J = 3.5 Hz, CH), 116.5 (CH).

19F NMR (470 MHz, Chloroform-d) δ -64.8.

HRMS (ESI+): [M+H]+ Calcd for C10H5BrF3N3: 303.9692 and 305.9672; found: 303.9694 and 305.9676.

**2-(5-(Trifluoromethyl)pyridin-2-yl)pyrazine 27**

![Chemical structure of 27]

Product 27 was synthesised via General procedure E with a slight modification using iodopyrazine (44.4 µL, 0.45 mmol), sulfonium salt 1e (148.8 mg, 0.3 mmol) and n-butylmagnesium chloride (0.23 mL, 2.0 M in ether). The Grignard reagent was formed at -78 °C for 30 min and the ligand coupling reaction was stirred at -78 °C for 8 h. Purification by FCC (25% Et2O in pentane) gave bis-heteroaryl 27 as a white solid (39.6 mg, 59%).

TLC: Rf = (25% Et2O in pentane).

1H NMR (500 MHz, Chloroform-d) δ 9.69 (d, J = 1.4 Hz, 1H, NCHCN), 8.97 (dt, J = 2.0, 0.9 Hz, 1H, NCHCCF3), 8.73 – 8.58 (m, 2H, ArH), 8.52 (dt, J = 8.3, 0.8 Hz, 1H, F3CCCHCH), 8.15 – 8.03 (m, 1H, F3CCCHCH) ppm.
13C NMR (126 MHz, Chloroform-d) δ 157.6 (app. d, J = 2.4 Hz, NCCCH), 149.9 (NCCCH), 146.6 (q, J = 3.9 Hz, NCHCCF3), 145.6 (CH), 143.92 (CH), 143.91 (NCHCN), 134.4 (q, J = 3.5 Hz, F3CCHCH), 127.1 (q, J = 33.0 Hz, CF3C), 123.6 (q, J = 272.4 Hz, CF3), 121.2 (CNCHCH) ppm.

19F NMR (470 MHz, Chloroform-d) δ -62.5 ppm.

HRMS (ESI-TOF) m/z: [M+H]+ Calcd for C10H7F3N3: 226.0587; found: 226.0588.

2-(Benzothien-2-yl)pyridine 28

Product 28 was synthesised via General procedure E using benzothiophene (60.0 mg, 0.45 mmol) and sulfonium salt 1a (128.2 mg, 0.3 mmol). The Grignard reagent was formed at rt for 24 h and the ligand coupling reaction was stirred at 45 °C. Purification by FCC (100% Et2O) gave bis-heteroaryl 28 as a yellow solid (44.3 mg, 70%).

TLC: Rf = 0.05 (100% Et2O)

1H NMR (400 MHz, Chloroform-d) δ 8.64 (dd, J = 4.5, 1.6 Hz, 1H), 7.90 – 7.85 (m, 1H), 7.83 (s, 1H), 7.82 – 7.77 (m, 2H), 7.72 (td, J = 7.7, 1.9 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.20 (dd, J = 7.4, 4.8 Hz, 1H).

13C NMR (101 MHz, Chloroform-d) δ 152.7, 149.8, 144.9, 140.8, 140.6, 136.7, 125.2, 124.6, 124.2, 122.7, 121.2, 119.7.

Spectra were consistent with literature data.14

3,5-Dimethyl-4-(pyridin-2-yl)isoxazole 29

Product 29 was synthesised via General procedure D using 4-iodo-3,5-dimethylisoxazole (100.4 mg, 0.45 mmol) and sulfonium salt 1a (128.2 mg, 0.3 mmol). The Grignard reagent was formed at 45 °C for 2 h and the ligand coupling reaction was stirred at 45 °C. Purification by FCC (30% Et2O in pentane) gave bis-heteroaryl 29 contaminated with an impurity (8%) as a yellow oil (27.0 mg, 48%).

TLC: Rf = 0.24 (30% Et2O in pentane).

1H NMR (400 MHz, Chloroform-d) δ 8.69 – 8.65 (m, 1H), 7.74 (td, J = 7.8, 1.9 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.22 (dd, J = 7.6, 4.9 Hz, 1H), 2.56 (s, 3H, CH3), 2.42 (s, 3H, CH3).
$^{13}\text{C NMR} \ (101 \text{ MHz, Chloroform-}d) \ \delta \ 167.5, \ 158.8, \ 151.0, \ 150.1, \ 136.6, \ 123.0, \ 121.9, \ 116.2, \ 12.5 \ (\text{CH}_3), \ 11.6 \ (\text{CH})$.

Spectra were consistent with literature data.$^{15}$

2-Phenylpyridine 30

Product 30 was synthesised via General procedure D using phenylmagnesium bromide (2.6 M in diethyl ether, 0.17 mL, 0.45 mmol) and sulfonium salt 1a (128.2 mg, 0.3 mmol). The ligand coupling reaction was stirred at rt. Purification by FCC (80% Et$_2$O in pentane) gave product 30 as a yellow oil (32.1 mg, 69%).

TLC: $R_t = 0.45$ (20% Et$_2$O in pentane).

$^1\text{H NMR} \ (400 \text{ MHz, Chloroform-}d) \ \delta \ 8.70 \ (dt, \ J = 4.7, \ 1.4 \text{ Hz, 1H}), \ 8.02 - 7.98 \ (m, \ 2\text{H}), \ 7.78 - 7.70 \ (m, \ 2\text{H}), \ 7.52 - 7.45 \ (m, \ 2\text{H}), \ 7.45 - 7.39 \ (m, \ 1\text{H}), \ 7.23 \ (dd, \ J = 6.0, \ 4.7, \ 2.4 \text{ Hz, 1H})$.

$^{13}\text{C NMR} \ (101 \text{ MHz, Chloroform-}d) \ \delta \ 157.6, \ 149.8, \ 139.5, \ 136.9, \ 129.1, \ 128.9, \ 127.0, \ 122.2, \ 120.7$.

Spectra were consistent with literature data.$^{16}$

5. Synthesis of caerulomycin E and A

6-Bromo-4-methoxy-2,2'-bipyridine 36

Product 36 was synthesised via General procedure D using 2,6-dibromo-4-methoxypyridine (88.0 mg, 0.33 mmol) and sulfonium salt 1a (128.2 mg, 0.3 mmol). The Grignard reagent was formed at 45 °C for 2 h and the ligand coupling reaction was stirred at rt for 1 h and then at 30 °C for 1 h. Purification by FCC (50% Et$_2$O in pentane) gave bipyridine 36 as a white solid (73.3 mg, 92%).

TLC: $R_t = 0.50$ (50% Et$_2$O in pentane).

$^1\text{H NMR} \ (400 \text{ MHz, Chloroform-}d) \ \delta \ 8.64 \ (dd, \ J = 4.7, \ 1.7 \text{ Hz, 1H}), \ 8.39 \ (dt, \ J = 8.1, \ 1.3 \text{ Hz, 1H}), \ 7.94 \ (d, \ J = 2.2 \text{ Hz, 1H}), \ 7.80 \ (td, \ J = 7.7, \ 1.8 \text{ Hz, 1H}), \ 7.31 \ (ddd, \ J = 7.6, \ 4.8, \ 1.2 \text{ Hz, 1H}), \ 7.01 \ (d, \ J = 2.3 \text{ Hz, 1H}), \ 3.93 \ (s, \ 3\text{H, OMe})$. 
$^{13}$C NMR (101 MHz, Chloroform-$d$) δ 167.9, 158.4, 154.5, 149.2, 142.3, 137.1, 124.5, 121.8, 114.1, 106.2, 56.0 (OMe).

Spectra were consistent with literature data.$^{17}$

4-Methoxy-[2,2'-bipyridine]-6-carbaldehyde, caerulomycin E 37

An oven-dried crimptop vial was evacuated and purged with N$_2$ three times. A solution of $n$-BuLi (0.15 mL, 0.31 mmol, 2.1 M in hexanes) in dry Et$_2$O (1.0 mL) was prepared and cooled to -78 °C. A solution of 6-bromo-4-methoxy-2,2'-bipyridine (73 mg, 0.28 mmol) in dry Et$_2$O (0.5 mL) was prepared in a separate oven-dried crimptop vial and added dropwise to the $n$-BuLi solution. Stirring was continued at -78 °C for 30 min. Dimethylformamide (42 µL, 0.54 mmol) in dry Et$_2$O (0.3 mL) was prepared in a separate oven-dried crimptop vial and then added dropwise to the reaction flask and stirred for 90 min. The reaction was quenched at -78 °C with sat. NH$_4$Cl (2 mL). The reaction mixture was extracted with Et$_2$O (3 x 10 mL), the combined organic layers were washed with water (20 mL) and brine (20 mL), and then dried over anhydrous Na$_2$SO$_4$. Purification by FCC (10% MeOH in CH$_2$Cl$_2$) gave caerulomycin E as a yellow solid (35.6 mg, 60%).

TLC: $R_t = 0.08$ (10% MeOH in CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, Chloroform-$d$) δ 10.13 (s, 1H, CHO), 8.70 (dt, $J = 4.9$, 1.5 Hz, 1H), 8.58 – 8.50 (m, 1H), 8.19 (d, $J = 2.6$ Hz, 1H), 7.86 (td, $J = 7.7$, 1.8 Hz, 1H), 7.49 (d, $J = 2.4$ Hz, 1H), 7.36 (ddd, $J = 7.5$, 4.9, 1.2 Hz, 1H), 4.00 (s, 3H, OMe).

$^{13}$C NMR (101 MHz, Chloroform-$d$) δ 193.8 (CHO), 167.8, 158.6, 155.1, 154.3, 149.4, 137.2, 124.5, 121.6, 110.7, 107.8, 56.0 (OMe).

Spectra were consistent with literature data.$^{17}$
(E)-4-Methoxy-[2,2'-bipyridine]-6-carbaldehyde oxime, caerulomycin A 38

Caerulomycin A was prepared following a procedure adapted from Quéguiner and co-workers.\textsuperscript{17} Caerulomycin E (0.025 g, 0.12 mmol), hydroxylamine hydrochloride (0.041 g, 0.59 mmol), pyridine (0.041 mL, 0.50 mmol) and EtOH (0.84 mL) were added to a crimtop vial, which was sealed and heated under reflux for 1 h. Solvent was removed under vacuum and purification by FCC (10% MeOH in CH$_2$Cl$_2$) gave caerulomycin A as a white solid (24.1 mg, 90%).

TLC: $R_f = 0.07$ (10% MeOH in CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.72 (s, 1H), 8.69 (ddd, $J = 4.8$, 1.8, 0.9 Hz, 1H), 8.39 (dt, $J = 8.0$, 1.1 Hz, 1H), 8.15 (s, 1H), 7.96 (td, $J = 7.7$, 1.8 Hz, 1H), 7.91 (d, $J = 2.5$ Hz, 1H), 7.48 (ddd, $J = 7.5$, 4.8, 1.2 Hz, 1H), 7.33 (d, $J = 2.5$ Hz, 1H), 3.95 (s, 3H, OMe).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 166.6, 156.9, 154.5, 153.4, 149.3, 148.8, 137.3, 124.5, 120.7, 106.5, 105.6, 55.6.

Spectra were consistent with literature data.\textsuperscript{17}
6. NMR Spectra

$^1$H NMR (500 MHz, CDCl$_3$): 1hi

$^{13}$C NMR (101 MHz, CDCl$_3$): 1hi
$^1$H NMR (500 MHz, CDCl$_3$): 1ii

$^{13}$C NMR (101 MHz, CDCl$_3$): 1ii
$^1$H NMR (400 MHz, CDCl$_3$): 1ji

$^{13}$C NMR (101 MHz, CDCl$_3$): 1ji
$^1$H NMR (400 MHz, CDCl$_3$): 1ki

$^{13}$C NMR (101 MHz, CDCl$_3$): 1ki
$^1$H NMR (400 MHz, CDCl$_3$): 1li

$^{13}$C NMR (101 MHz, CDCl$_3$): 1li
$^1$H NMR (400 MHz, CDCl$_3$): 1mi

$^{13}$C NMR (101 MHz, CDCl$_3$): 1mi
$^1$H NMR (500 MHz, CDCl$_3$): \(1\) h

$^{13}$C NMR (126 MHz, CDCl$_3$): \(1\) h
$^1$H NMR (400 MHz, CDCl$_3$): 1i

$^{13}$C NMR (101 MHz, CDCl$_3$): 1i
$^1$H NMR (500 MHz, CDCl$_3$): 1j

$^{13}$C NMR (126 MHz, CDCl$_3$): 1j
$^1$H NMR (500 MHz, CDCl$_3$): 1k

$^{13}$C NMR (126 MHz, CDCl$_3$): 1k
$^1$H NMR (500 MHz, CDCl₃): 1

$^{13}$C NMR (101 MHz, CDCl₃): 1
$^1$H NMR (500 MHz, CDCl$_3$): 1m

$^{13}$C NMR (126 MHz, CDCl$_3$): 1m
$^1$H NMR (400 MHz, CDCl$_3$): 2

$^{13}$C NMR (101 MHz, CDCl$_3$): 2
$^1$H NMR (400 MHz, CDCl$_3$): 3

$^{13}$C NMR (101 MHz, CDCl$_3$): 3
$^1$H NMR (500 MHz, CDCl$_3$): 4

$^{13}$C NMR (126 MHz, CDCl$_3$): 4
$^{1}H$ NMR (500 MHz, CDCl$_3$): 5

$^{13}$C NMR (126 MHz, CDCl$_3$): 5
$^1$H NMR (500 MHz, CDCl$_3$): 6

$^{13}$C NMR (126 MHz, CDCl$_3$): 6
$^1$H NMR (500 MHz, CDCl$_3$): 7

$^{13}$C NMR (126 MHz, CDCl$_3$): 7
$^1$H NMR (500 MHz, CDCl$_3$): 8

$^{13}$C NMR (126 MHz, CDCl$_3$): 8
$^1$H NMR (500 MHz, CDCl$_3$): 9

$^{13}$C NMR (126 MHz, CDCl$_3$): 9
$^1$H NMR (400 MHz, CDCl$_3$): 10

$^{13}$C NMR (101 MHz, CDCl$_3$): 10
$^1$H NMR (400 MHz, CDCl$_3$): 11

$^{13}$C NMR (101 MHz, CDCl$_3$): 11
$^1$H NMR (400 MHz, CDCl$_3$): 12

$^{13}$C NMR (101 MHz, CDCl$_3$): 12
$^1$H NMR (500 MHz, CDCl$_3$): 13

$^{13}$C NMR (126 MHz, CDCl$_3$): 13
$^1$H NMR (500 MHz, CDCl$_3$): 14

$^{13}$C NMR (126 MHz, CDCl$_3$): 14
$^1$H NMR (500 MHz, CDCl$_3$): 15

$^{13}$C NMR (126 MHz, CDCl$_3$): 15
$^1$H NMR (500 MHz, CDCl$_3$): 16

$^{13}$C NMR (126 MHz, CDCl$_3$): 16
$^1$H NMR (500 MHz, CDCl$_3$): 17

$^{13}$C NMR (126 MHz, CDCl$_3$): 17
$^1$H NMR (500 MHz, CDCl$_3$): 18

$^{13}$C NMR (126 MHz, CDCl$_3$): 18
$^1$H NMR (500 MHz, CDCl$_3$): 19

$^{13}$C NMR (126 MHz, CDCl$_3$): 19
$^1$H NMR (500 MHz, CDCl$_3$): 20

$^{13}$C NMR (126 MHz, CDCl$_3$): 20
$^1$H NMR (500 MHz, CDCl$_3$): 21

$^{13}$C NMR (126 MHz, CDCl$_3$): 21
$^1$H NMR (500 MHz, CDCl$_3$): 22

$^{13}$C NMR (126 MHz, CDCl$_3$): 22
$^1$H NMR (400 MHz, CDCl$_3$): 23

$^{13}$C NMR (126 MHz, CDCl$_3$): 23
$^1$H NMR (400 MHz, CDCl$_3$): 24

$^{13}$C NMR (101 MHz, CDCl$_3$): 24
$^1$H NMR (400 MHz, CDCl$_3$): 25

$^{13}$C NMR (101 MHz, CDCl$_3$): 25
$^1$H NMR (500 MHz, CDCl$_3$): 26

$^{13}$C NMR (101 MHz, CDCl$_3$): 26
$^1$H NMR (400 MHz, CDCl$_3$): 27

$^{13}$C NMR (101 MHz, CDCl$_3$): 27
$^1$H NMR (400 MHz, CDCl$_3$): 28

$^{13}$C NMR (101 MHz, CDCl$_3$): 28
\(^1\)H NMR (400 MHz, CDCl\(_3\)): 29

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): 29
$^1$H NMR (400 MHz, CDCl$_3$): 30

$^{13}$C NMR (101 MHz, CDCl$_3$): 30
$^1$H NMR (400 MHz, CDCl$_3$): 36

$^{13}$C NMR (101 MHz, CDCl$_3$): 36
$^1$H NMR (400 MHz, CDCl$_3$): 37

$^{13}$C NMR (101 MHz, CDCl$_3$): 37
$^1$H NMR (400 MHz, DMSO-$d_6$): 38

$^{13}$C NMR (101 MHz, DMSO-$d_6$): 38
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