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Iterative and regioselective cross-couplings of 2-chloro-3,4-diiodopyridine leading to 2,3,4-triheteroarylpyridines

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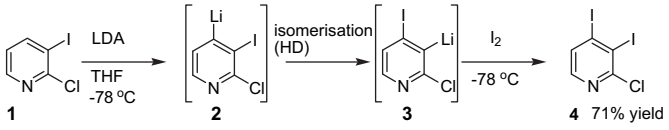
ABSTRACT

A one-pot synthesis of 2-chloro-3,4-diiodopyridine from 2-chloropyridine is described via a Directed *ortho* Metallation (DoM)/Halogen Dance (HD) mechanism in 26–28% yields. By performing sequential, iterative Suzuki–Miyaura cross-couplings using a variety of functionalised heteroaryl and arylboronic acids, a series of novel 2,3,4-triheteroarylpyridine scaffolds have been accessed in synthetically viable yields, including sterically hindered derivatives. 2-Chloro-4-heteroaryl-3-iodopyridines and 2-chloro-3,4-diheteroarylpyridines are also reported. The synthesis of 5-[3,4-bis(2-phenylethynyl)pyridin-2-yl]-2-fluoropyridine via a two-step Sonogashira/Suzuki–Miyaura reaction sequence from 2-chloro-3,4-diiodopyridine, phenylacetylene and 6-fluoropyridin-3-yl-3-boronic acid has been achieved in 48% overall yield.

1. Introduction

Highly-substituted pyridine scaffolds are of contemporary interest due to their prevalence in bioactive compounds,[1] as ligands for organometallics[2] and in materials chemistry applications.[3] In recent years, metal-catalysed cross-coupling methodologies have expanded the scope of substitutions on heteroaryls by giving access to aryl–aryl, aryl–alkyl, aryl–alkenyl, aryl–alkynyl and aryl–heteroatom bond formations.[4] These substitutions have also been achieved via rhodium catalysed CH activation[5] and iridium catalysed borylations,[6] as well as palladium catalysed direct arylations.[7]

The more commonly used coupling reactions, require pre-activation in the form of a halide or other leaving group on the electrophilic substrate. Many such halogenated heteroaryl compounds are commercially available; however, the 2,3,4-trihalopyridine substitution pattern is not well exploited. 4-Bromo-2-chloro-3-iodopyridine has recently been employed in the preparation of naphthyridone p38 MAP kinase inhibitors[8] and 2-chloro-3-fluoro-4-iodo-5,6-dimethylpyridine has been used in the synthesis of Streptonigrin analogues.[9] Organometallic bases regioselectively deprotonate aryl rings by Directed *ortho* Metallation (DoM) allowing electrophilic halogenation and access to a range of halogenated products.[10] It has been well documented that 'halogen dance' (HD) reactions are amenable to the regioselective synthesis of multihalogenated pyridines.[11] For example, Rocca et al.[12] reported that 2-chloro-3-iodopyridine **1** can be selectively deprotonated *ortho* to iodine with LDA leading to the 4-lithio species **2**. Subsequent isomerism (HD) gave the 3-lithio species **3** (with stability imparted by a strongly inductive electron withdrawing effect of chlorine and chelation of the lithium to chlorine in the intermediate **3**).[11d,11e,12] Electrophilic attack by molecular iodine on **3** then leads to 2-chloro-3,4-diiodopyridine **4** in 71% yield (Scheme 1).[12]



Scheme 1. The halogen dance (HD) mechanism for the synthesis of **4** from **1**.[12]

We now report the synthesis of **4** in a one-pot reaction from cheap and readily available[13] 2-chloropyridine using combined DoM and HD methodology. We also demonstrate the first utilisation of **4** in metal-catalysed cross-couplings leading to the regioselective synthesis of novel 2,3,4-triheteroarylpyridines.

2. Results and discussion

The overview of our synthetic strategy is shown in Scheme 2. Lithiation of 2-chloropyridine **5** at −78 °C or −100 °C using 2 equiv

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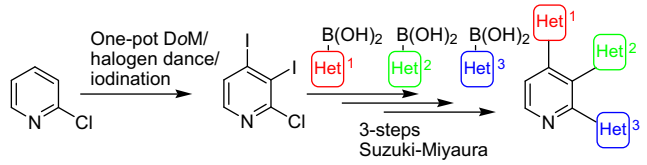
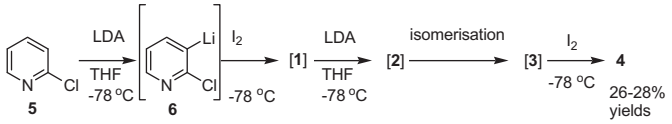
of LDA (prepared in situ from *n*-butyllithium or *n*-hexyllithium and diisopropylamine) followed by addition of iodine (2.9 equiv) and aqueous workup reproducibly afforded 2-chloro-3,4-diiodopyridine **4** in 26–28% yields for ca. 4–5 g batches of product. Lower yields of **4** were obtained under the following conditions: (i) scale-up of the reaction; (ii) use of 2,2,6,6-tetramethylpiperidine as base at −100 to −85 °C. It is presumed that initial directed *ortho* lithiation of 2-chloropyridine **5** gives the 3-lithio intermediate **6** and electrophilic attack by I_2 then gives 2-chloro-3-iodopyridine **1**.[14] Subsequent directed lithiation and HD as reported previously[12] and a final electrophilic attack affords product **4** (Scheme 3).

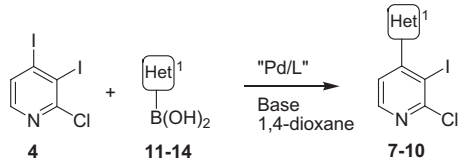


Scheme 2. Reaction scheme for the four-step synthesis of 2,3,4-triheteroarylpyridines from 2-chloropyridine.



Scheme 3. Proposed mechanism for the one-pot synthesis of **4** from **5**.

Suzuki–Miyaura[15] cross-coupling reactions were performed on **4** using a variety of heteroarylboronic acids[16] to give a range of functional mono-heteroarylated products **7**–**10** (Scheme 4 and Table 1).



Scheme 4. General reaction scheme for the mono-couplings of **4**.

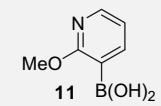
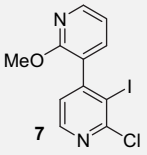
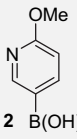
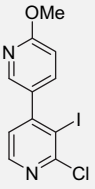
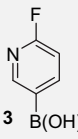
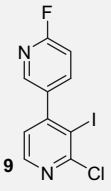
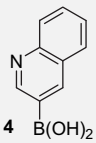
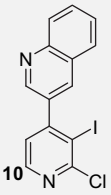
When using less than 1 equiv of the boronic acid a mixture of unreacted **4**, mono- and bis-coupled products was obtained. In attempts to optimise the conversion of **4** (Table 1, entries 3 and 4) by using 2.5 equiv of boronic acids **12** and **13**, products **8** and **9** were obtained in 38% and 50% yields, respectively, along with bis-coupled side-products observed via GC–MS. Performing the Suzuki–Miyaura reaction on **4** using 2.5 equiv of **11** yielded the bis-coupled product **15** in 47% (see Table 2, entry 1) with **7** also observed via GC–MS. The increased yield for the more electron deficient fluoropyridylboronic acid **13** compared to the methoxypyridylboronic acid **12** is consistent with the S_E2 (coordination) mechanism for the transmetalation to palladium.[15a] The activated 4-position of **4** reacts first, followed by reaction at the less electronically active and more sterically hindered 3-position.[17] X-ray diffraction studies confirmed the regioselectivity for mono- and bis-coupled products **7** and **19** (see Fig. 1). A higher isolated yield of **7** was obtained for the reaction of **4** when using $Pd(PPh_3)_4$ as catalyst rather than the air stable $Pd(PPh_3)_2Cl_2$ (Table 1, entry 1).[18]

Twofold cross-coupling of the boronic acids **11**, **12** or **21** at both the 4- and 3-positions of **4** gave **15**–**17** in optimised yields of 47–64% (Scheme 5 and Table 2, entries 1–3). Tris-coupled products were not observed in any of the reactions shown in Schemes 4–6.

Entries 4–6 in Table 2 show the products of stepwise reactions where the pyridyl substituents at C3 and C4 are different in each case. This was achieved by further reaction of **7**–**9** with a selection of pyridylboronic acids under the standard conditions furnishing compounds **18**–**20** in variable yields. The inherent regioselectivity, vide supra, led to the second coupling occurring exclusively at the 3-position giving excellent control over the substitution pattern on the pyridine core. When using boronic acid **11** the resulting product **19** was obtained in only 23% yield (Table 2, entry 5) presumably due to the added steric hindrance of the *ortho*-methoxy group on **11**. The X-ray molecular structure of **19** is shown in Figure 1. Compound **18** does not suffer this steric interference and furthermore, the electron withdrawing fluoropyridine substituent at C4 of **9** would be expected to enhance reactivity at C3, thus explaining the high yield in this case (Table 2, entry 4). In attempts to mitigate anticipated low yields for the coupling of the sterically encumbered **7** with boronic acid **12**, Fu's conditions (which have been reported to provide excellent yields for sterically crowded substrates)[19] were employed. Using **12** (1.1 equiv) we were gratified to obtain **20** in 74% yield (Table 2, entry 6).

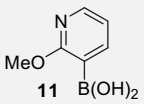
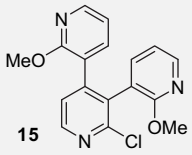
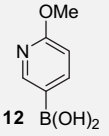
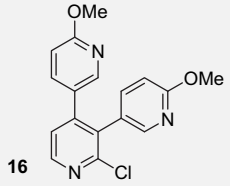
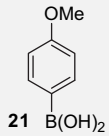
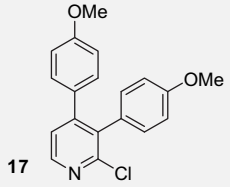
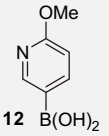
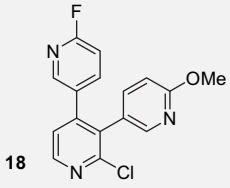
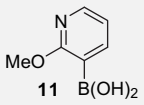
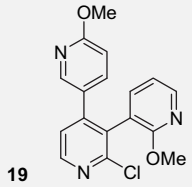
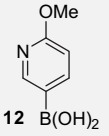
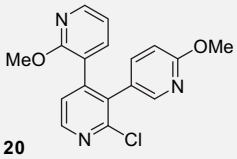
As stated above, on no occasion was a tris-coupled product observed in the reactions shown in Schemes 4–6 (Tables 1 and 2). This provided the opportunity to introduce regioselectively a third heteroaryl substituent into the pyridine core by reactions of the remaining 2-chloro functionality.[20] For this purpose a selection of the bis-coupled products (**18**, **19** and **20**) were reacted with a range of aryl and heteroarylboronic acids to gain access to 2,3,4-tri(hetero)arylpyridines **22**–**25** in 23–51% yields (Scheme 7 and Table 3). The reactions were performed using the conditions designed for coupling heteroaryl chlorides with nitrogen-containing heteroarylboronic acids[21]

Table 1
Suzuki–Miyaura cross-couplings of 2-chloro-3,4-diiodopyridine **4** with heteroarylboronic acids to yield mono-coupled products

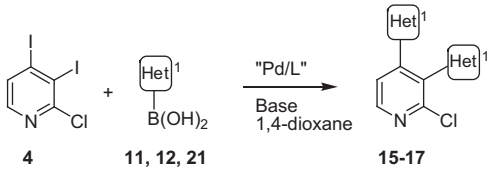
Entry	R-X	Boronic acid	Product	Yield[a] (%)
1	**4**	 **11** (0.9 equiv.)	 **7**	44[b] 22[c]
3	**4**	 **12** (2.5 equiv.)	 **8**	38[b]
4	**4**	 **13** (2.5 equiv)	 **9**	50[b]
5	**4**	 **14** (0.75 equiv.)	 **10**	13[c]

[a] Isolated yields after purification via chromatography and/or recrystallisation.
[b] Reagents and conditions: $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane, reflux, 20–24 h.
[c] Reagents and conditions: $Pd(PPh_3)_2Cl_2$, Na_2CO_3, 1,4-dioxane, reflux, 19–70 h.

Table 2
Suzuki–Miyaura cross-couplings with pyridylboronic acids to yield bis-coupled products

Entry	R-X	Boronic acid	Product	Yield[a] (%)
1	**4**	 **11** (2.5 equiv.)	 **15**	47[b]
2	**4**	 **12** (2.5 equiv.)	 **16**	64[b]
3	**4**	 **21** (2.5 equiv.)	 **17**	50[b]
4	**9**	 **12** (1.5 equiv.)	 **18**	90[c]
5	**8**	 **11** (1.5 equiv.)	 **19**	23[c]
6	**7**	 **12** (1.1 equiv.)	 **20**	74[d]

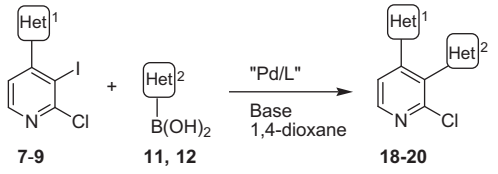
[a] Isolated yields after purification via chromatography and/or recrystallisation.
[b] Reagents and conditions: $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane, reflux, 20 h.
[c] Reagents and conditions: $Pd(PPh_3)_2Cl_2$, Na_2CO_3, 1,4-dioxane, reflux, 18–70 h.
[d] Reagents and conditions: $Pd_2(dba)_3$, P(*t*-Bu)$_3$.HBF_4, 1,4-dioxane, KF, 80 °C, 7 h.



4 **11, 12, 21** **15-17**

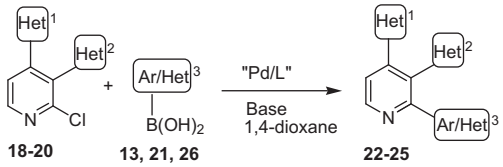
Scheme 5. General reaction scheme for bis-couplings of **4**.

[viz. $Pd_2(dba)_3$, PCy_3, K_3PO_4, 1,4-dioxane, H_2O, reflux]. However, a similar yield of **25** was obtained on the one occasion when $Pd(PPh_3)_4/Na_2CO_3$ was used (Table 3, entry 4).



7-9 **11, 12** **18-20**

Scheme 6. General reaction scheme for mono-couplings of **7**–**9**.



18-20 **13, 21, 26** **22-25**

Scheme 7. General reaction scheme for the mono-couplings of **18**–**20**.

Suzuki–Miyaura reactions are known to be tolerant to unprotected amine functionality,[22] and accordingly, coupling of 2-aminopyrimidin-5-yl-5-boronic acid **26** with **18** gave **23** in 23% yield. With all of these third couplings (Scheme 7) a varying amount of dechlorinated side-product was observed via GC–MS thus accounting for the modest yields of **22**–**25**. This can be explained by the steric crowding in the bis-coupled substrate **18**–**20** inhibiting transmetalation of the boronic acid in the transition state leading to competing protodechlorination.

It is noteworthy that to our knowledge compounds **23**–**25** represent the first reported 2,3,4-triheteroarylpyridine derivatives. 2,3,4-Triphenylpyridine has been synthesised by the nickel catalysed annulation of 2-iodobenzaldimine,[23] 3-[2-(pyridin-2-yl)-3-(pyridin-3-yl)phenyl]pyridine and 5-[2-(pyridin-2-yl)-3-(pyrimidin-5-yl)-phenyl]pyrimidine were synthesised via the ruthenium catalysed *ortho*-arylation of 2-phenylpyridine.[24] The phenyl core analogue 3-[2,3-di(pyridin-3-yl)phenyl]pyridine has been used as an electron

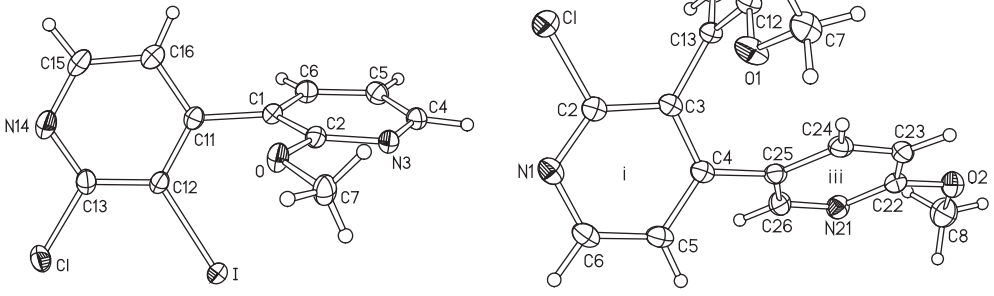
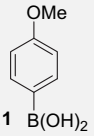
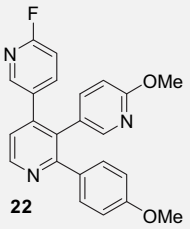
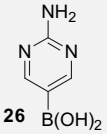
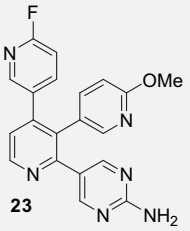
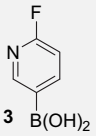
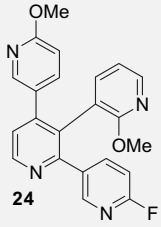
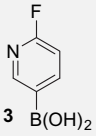
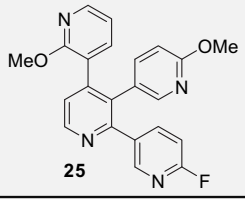


Figure 1. X-ray molecular structures of **7** (left) and **19**, showing thermal ellipsoids at 50% probability level. Dihedral angles between pyridyl rings: 72.4° in **7**, i/ii 85.3° and i/iii 52.8° in **19**.

Table 3
Suzuki–Miyaura cross-couplings of (hetero)arylboronic acids with compounds **18**, **19** and **20**

Entry	R-X	Boronic acid	Product	Yield[a] (%)
1	**18**	 **21** (1.2 equiv.)	 **22**	30[b]
2	**18**	 **26** (1.2 equiv.)	 **23**	23[b]
3	**19**	 **13** (1.2 equiv.)	 **24**	45[b]
4	**20**	 **13** (1.2 equiv.)	 **25**	51[b] 50[c]

[a] Isolated yields after purification via chromatography and/or recrystallisation.
[b] Reagents and conditions: $Pd_2(dba)_3$, PCy_3, 1,4-dioxane, K_3PO_4, 100 °C, 2–20 h.
[c] Reagents and conditions: $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane, reflux, 24 h.

transport material in electroluminescent devices.[25] Related bis(pyridyl)pyridines and linear quaterpyridines have recently been synthesised via Suzuki–Miyaura reactions by Burzicki et al. starting from dihalopyridines.[26]

To extend further the scope of **4** in cross-coupling reactions a Sonogashira reaction[27] was performed (Scheme 8). Compound **4** reacted with phenylacetylene (2.05 equiv) under standard conditions [5 mol % $Pd(PPh_3)_2Cl_2$, 5 mol % CuI, Et_3N] to give **27** in 72% yield. No dehalogenation was observed in this case. A subsequent Suzuki–Miyaura reaction of **13** on the remaining 2-chloro substituent of **27** gave **28** in 66% yield. The higher yield in this case when comparing to the reaction of the same boronic acid **13** with the chloro substituent of **20** (Table 3, entry 4) can be attributed to the reduced steric hindrance in **27** compared to **20**. We note that (arylethynyl)pyridines have been synthesised for pharmacological applications[28] and bis(arylethynyl)pyridines are of interest for their optoelectronic properties.[29]

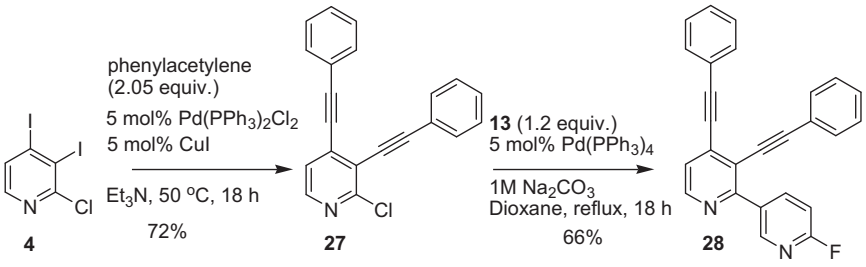
3. Conclusion

We have described a new one-pot synthesis of 2-chloro-3,4-diiodopyridine **4** in 4–5 g batches from 2-chloropyridine via a Directed *ortho* Metallation–Halogen Dance–iodination sequence. Utilising **4** as a starting material has led to a versatile range of mono-, bis- and triheteroarylpyridine derivatives in a series of iterative and regioselective Suzuki–Miyaura cross-coupling reactions. These procedures have provided the first examples of pyridine derivatives bearing heteroaryl units in the 2, 3 and 4 positions. The yields of the products are synthetically viable, even for the more sterically hindered derivatives, especially in view of the known challenges of cross-coupling heteroaryl halides with heteroarylboronic acids/esters.[20,21] We have also established that compound **4** is a suitable reagent for Sonogashira reactions. These protocols are versatile and can be further exploited in the synthesis of libraries of small molecules derived from **4** for drug discovery and for materials chemistry applications.

4. Experimental

4.1. General

All reactions were performed under an argon atmosphere, which was dried by passage through a column of phosphorus pentoxide. Glassware was flame dried prior to use for moisture sensitive reactions. All reagents used were of standard reagent grade, used as supplied unless otherwise stated and purchased from Sigma–Aldrich or Alfa Aesar, except for methoxypyridylboronic acid derivatives **11**[22,30] and **12**,[22,30] which were supplied by Vertellus Specialities UK Ltd., 2-fluoro-5-pyridylboronic acid **13**,[31] 2-amino-5-pyrimidylboronic acid **26**,[32] $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$,[33] which were prepared in-house. Anhydrous THF was dried through a HPLC column on an Innovative Technology Inc. solvent purification system. Anhydrous triethylamine was dried over calcium hydride, distilled and stored under dry nitrogen prior to use. All other solvents were used without prior purification. Solvents were degassed by bubbling dry argon at a steady rate through the solvent for ca. 20 min. Column chromatography was carried out using 40–63 μm mesh silica. Thin-layer chromatography (TLC) was performed on 20 mm pre-coated plates of silica gel (Merck, silica gel $60F_{254}$), visualisation was made using ultraviolet light (254 nm). NMR spectra were recorded on: a Bruker Avance-400 spectrometer [^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz)], a Varian Inova-500 spectrometer [^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz)] and a Varian NMR system 700 spectrometer using deuterated solvent as a lock. Chemical shifts are quoted in ppm, relative to the residual solvent as internal reference for ^{1}H and ^{13}C. The



Scheme 8. Synthesis of **28** via sequential twofold Sonogashira and Suzuki–Miyaura reactions.

following abbreviations are used in listing NMR spectra: s=singlet, d=doublet, dd=doublet of doublets, t=triplet, m=multiplet, br=broad. *J* values are quoted in Hz. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Electron Impact (EI) mass spectra were recorded on a Thermo-Finnigan Trace mass spectrometer with positive ionisation mode. Electrospray (ES^+) mass spectra were recorded on a Thermo-Finnigan LTQ FT mass spectrometer or a Micromass Autospec LCT mass spectrometer. High resolution ES^+ mass spectra were recorded on a Thermo-Finnigan LTQ FT mass spectrometer. High resolution $APCI^+$ mass spectra were obtained courtesy of Mr Liam Brady of Waters Ltd on a Waters LCT Premier XE using atmospheric pressure chemical ionisation with an ASAP probe or on a Waters Xevo QToF equipped with Atmospheric Pressure Gas Chromatography (APGC). Elemental analyses were obtained on an Exeter analytical Inc. CE-440 elemental analyser.

4.1.1. 2-Chloro-3,4-diiodopyridine **4**.

4.1.1.1. Method A. A solution of diisopropylamine (12.33 mL, 88 mmol) and anhydrous THF (100 mL) was cooled to −10 °C under an argon atmosphere. To this *n*-hexyllithium (2.3 M in hexane, 35.2 mL, 88 mmol) was added dropwise over 10 min. Following the addition, the reaction was stirred at 0 °C for 0.5 h, yielding a clear yellow solution. The solution was cooled to −78 °C and treated dropwise over 0.5 h with 2-chloropyridine **1** (4.2 mL, 44 mmol) in THF (50 mL). The solution was stirred for 1 h and became clear orange. To this solution iodine (32.4 g, 128 mmol) in THF (100 mL) was added over 45 min after which the reaction was stirred at −78 °C for further 30 min. The solution was allowed to warm to 0 °C before quenching with water (200 mL), followed by addition of saturated solution of sodium sulfite (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered and then concentrated to yield a dark brown crude solid (10.4 g). This product was dried and precipitated from acetonitrile yielding 2-chloro-3,6-diiodopyridine **4** as a white solid (4.42 g, 28%); mp: 161.1–162.5 °C; δ_H (700 MHz, $CDCl_3$) 7.96 (1H, d, *J* 5.0), 7.67 (1H, d, *J* 5.0); δ_C (176 MHz, $CDCl_3$) 155.0, 148.4, 133.2, 122.5, 110.5; *m*/*z* (EI) 365 (M^+), 238 (62%, M^+-I). Anal. Calcd for $C_5H_2ClI_2N$: C, 16.44; H, 0.55; N, 3.83. Found: C, 16.32; H, 0.56; N, 3.68; ν_{max} (film)/cm^{-1} 2359, 2337, 1535, 1408, 1331, 1180, 1141, 1001, 828.

4.1.1.2. Method B. The experimental procedure of Method A was followed using *n*-butyllithium (2.5 M in hexane, 35.2 mL, 88 mmol) instead of *n*-hexyllithium. The crude solid (13.1 g) was recrystallised from acetonitrile yielding **4** as a white solid (4.18 g, 26%). Scale-up using diisopropylamine (24.67 mL, 180 mmol), *n*-butyllithium (70.50 mL, 176 mmol), 2-chloropyridine **1** (8.30 mL, 88 mmol), iodine (65.0 g, 260 mmol), THF (350 mL) gave **4** (5.50 g, 17%). Analytical data were consistent with those obtained by Method A.

4.1.1.3. Method C. Method B was followed but with the temperature maintained between −100 and −85 °C during the addition of 2-chloropyridine and iodine. Iodine was added over 1.25 h. This gave **4** as a white solid (4.16 g, 26%). Analysis was consistent with that obtained by Method A.

4.2. General method for Suzuki–Miyaura cross-coupling reactions

To an argon purged flask was added the halopyridine, boronic acid, palladium source and additional ligand (when applicable). Degassed 1,4-dioxane and aqueous base were added and the mixture was heated to reflux, with stirring. The reaction was monitored by TLC and on completion (2–70 h) the reaction was cooled to room temperature and the solvent was removed in vacuo. The residue was extracted into ethyl acetate and washed with brine. The organic layers were dried over Na_2SO_4, filtered and then concentrated in vacuo. Purification was achieved by flash chromatography on a silica gel column followed in some cases by recrystallisation.

4.2.1. 3-(2-Chloro-3-iodopyridin-4-yl)-2-methoxypyridine **7**.

4.2.1.1. Method A. Compound **4** (2.0 g, 5.5 mmol), **11** (0.754 g, 4.9 mmol), $Pd(PPh_3)_4$ (5 mol %, 0.316 g, 0.27 mmol), 1,4-dioxane (20 mL), Na_2CO_3 (1 M, 10.94 mL, 10.94 mmol) reflux for 24 h. Chromatography (SiO_2, hexane/ethyl acetate, 4:1 v/v) yielded **7** as a white solid (0.75 g, 44%) used in subsequent reactions without further purification. A sample was recrystallised from hexane and ethyl acetate; mp: 169.5–171.0 °C; δ_H (500 MHz, $CDCl_3$) 8.32 (1H, d, *J* 4.8), 8.26 (1H, dd, *J* 5.1, 1.9), 7.37 (1H, dd, *J* 7.3, 1.9), 7.04 (1H, d, *J* 4.8), 6.99 (1H, dd, *J* 7.3, 5.1), 3.91 (3H, s); δ_C (126 MHz, $CDCl_3$) 159.8, 156.0, 154.9, 148.5, 148.1, 138.4, 125.9, 123.7, 116.8, 101.6, 53.9; *m*/*z* (EI) 346 (M^+, 45%), 219 (100, M^+-I). Anal. Calcd for $C_{11}H_8ClIN_2O$: C, 38.12; H, 2.33; N, 8.08. Found: C, 38.14; H, 2.34; N, 7.97; ν_{max} (film)/cm^{-1} 3032, 2993, 2949, 1581, 1463, 1402, 1342, 1017, 840, 783.

4.2.1.2. Method B. Compound **4** (5.80 g, 16 mmol), **11** (2.20 g, 14 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %, 0.557 g, 0.79 mmol), 1,4-dioxane (30 mL), Na_2CO_3 (1 M, 29.0 mL, 29 mmol) reflux for 19 h. Chromatography (SiO_2, hexane/ethyl acetate, 4:1 v/v) yielded **7** (1.05 g, 22%). *Crystal data*: $C_{11}H_8ClIN_2O$, *M*=346.54, *T*=120 K, monoclinic, space group $P2_1/c$ (no. 14), *a*=10.3846(7), *b*=8.0785(6), *c*=13.6228(9) Å, *β*=99.452(3)°, *V*=1127.3(1) $Å^3$, *Z*=4, D_x=2.042 g cm^{-3}, *μ*(Mo *Kα*)=3.06 mm^{-1}, 20,013 reflections (3291 unique), absorption correction by numerical integration, R_{int}=0.066, $R[I\geq 2\sigma(I)]$=0.022. CCDC-745858.

4.2.2. 5-(2-Chloro-3-iodopyridin-4-yl)-2-methoxypyridine **8**.

Compound **4** (3.0 g, 8.0 mmol), **12** (3.10 g, 21 mmol), $Pd(PPh_3)_4$ (5 mol %, 0.474 g, 0.41 mmol), 1,4-dioxane (30 mL), Na_2CO_3 (1 M, 41 mL, 41 mmol) reflux for 20 h. Chromatography (SiO_2, hexane/ethyl acetate, 3:1 v/v) yielded **8** as a cream solid (1.05 g, 38%), used in subsequent reactions without further purification. A sample was recrystallised from hexane and ethyl acetate; mp: 130.1–130.6 °C; δ_H (700 MHz, $CDCl_3$) 8.31 (1H, d, *J* 4.8), 8.13 (1H, dd, *J* 2.5, 0.6), 7.57 (1H, dd, *J* 8.6, 2.5), 7.07 (1H, d, *J* 4.8), 6.82 (1H, dd, *J* 8.5, 0.6), 3.98 (3H, s); δ_C (176 MHz, $CDCl_3$) 164.5, 156.6, 155.6, 148.7, 146.5, 139.1, 131.6, 123.3, 110.7, 100.8, 54.0; *m*/*z* (EI) 346 (M^+). Anal. Calcd for $C_{11}H_8ClIN_2O$: C, 38.12; H, 2.33; N, 8.08. Found: C, 38.07; H, 2.32; N, 7.90; ν_{max} (film)/cm^{-1} 3038, 3012, 2950, 1599, 1490, 1372, 1061, 1002, 828.

4.2.3. 5-(2-Chloro-3-iodopyridin-4-yl)-2-fluoropyridine **9**.

Compound **4** (1.61 g, 4.4 mmol), **13** (1.60 g, 11 mmol), $Pd(PPh_3)_4$ (5 mol %, 0.255 g, 0.22 mmol), 1,4-dioxane (20 mL), Na_2CO_3 (1 M, 22 mL, 22 mmol) reflux for 24 h. Chromatography (SiO_2, 0–50% ethyl acetate in hexane) yielded **9** as a white solid (0.740 g, 50%), used in subsequent reactions without further purification. A sample was recrystallised from hexane and DCM; mp: 152.9–153.9 °C; δ_H (700 MHz, $CDCl_3$) 8.36 (1H, d, *J* 4.8), 8.19 (1H, d, *J* 2.5), 7.78 (1H, ddd, *J* 8.4, 7.5, 2.6), 7.09 (1H, d, *J* 4.8), 7.04 (1H, dd, *J* 8.4, 2.5); δ_C (176 MHz, $CDCl_3$) 163.7 (d, J_{CF} 242.5), 156.8, 154.2, 148.9, 147.3 (d, J_{CF} 15.4), 141.6 (d, J_{CF} 8.3), 136.2 (d, J_{CF} 4.8), 123.2, 109.6 (d, J_{CF} 37.6), 100.6; *m*/*z* (EI) 334 (M^+, 32%), 207 (15, M^+-I), 127 (100, $M^+-C_{10}H_5ClFN_2$). Anal. Calcd for $C_{10}H_5ClFIN_2$: C, 35.90; H, 1.51; N, 8.37. Found: C, 35.73; H, 1.50; N, 8.31; ν_{max} (film)/cm^{-1} 3048, 1588, 1485, 1376, 1260, 850, 828.

4.2.4. 3-(2-Chloro-3-iodopyridin-4-yl)quinoline **10**.

Compound **4** (2.80 g, 7.7 mmol), **14** (0.994 g, 5.75 mol), $Pd(PPh_3)_2Cl_2$ (5 mol %, 0.269 g, 0.383 mmol), 1,4-dioxane (30 mL), Na_2CO_3 (1 M, 11 mL,

11 mmol) reflux for 67 h. Chromatography (SiO_2, ethyl acetate/hexane, 4:1 v/v) and recrystallisation from hexane and DCM yielded **10** as a white solid (0.277 g, 13%); mp: 199.1–199.9 °C; δ_H (700 MHz, $CDCl_3$) 8.90 (1H, d, *J* 2.3), 8.40 (1H, d, *J* 4.7), 8.17 (1H, d, *J* 8.5), 8.11 (1H, d, *J* 2.2), 7.88 (1H, d, *J* 8.1), 7.81 (1H, ddd, *J* 8.4, 6.9, 1.4), 7.63 (1H, ddd, *J* 8.1, 6.9, 1.1), 7.19 (1H, d, *J* 4.7); δ_C (176 MHz, $CDCl_3$) 156.7, 155.5, 149.7, 148.9, 148.0, 135.7, 135.5, 130.8, 129.8, 128.4, 127.8, 127.2, 123.5, 100.6; *m*/*z* (ES$^+$) 366.94959 (M^++H, $C_{14}H_9{}^{35}Cl^{127}IN_2$ requires 366.94935); ν_{max} (film)/cm^{-1} 3060, 3036, 1565, 1329, 850, 786.

*4.2.5. 3-[2-Chloro-3-(2-methoxypyridin-3-yl)pyridin-4-yl]-2-methoxypyridine **15**.* Compound **4** (2.00 g, 5.5 mmol), **11** (2.09 g, 13.69 mmol), $Pd(PPh_3)_4$ (5 mol %, 0.316 g, 0.274 mmol), 1,4-dioxane (20 mL), Na_2CO_3 (1 M, 10.95 mL, 10.95 mmol) reflux for 20 h. Chromatography (SiO_2, hexane/ethyl acetate, 2:1 v/v) yielded **15** as a pale yellow waxy solid (0.897 g, 47%), used in subsequent reactions without further purification. A sample was recrystallised from hexane/ethyl acetate; mp: 111.5–112.2 °C; δ_H (500 MHz, $CDCl_3$) 8.42 (1H, d, *J* 5.0), 8.05 (1H, dd, *J* 5.0, 1.9), 8.03 (1H, dd, *J* 5.0, 1.9), 7.29–7.25 (2H, m), 7.23 (1H, d, *J* 5.0), 6.78–6.75 (2H, m), 3.77 (3H, s), 3.69 (3H, s); δ_C (126 MHz, $CDCl_3$) 160.9, 160.0, 151.8, 148.6, 148.5, 147.5, 147.3, 139.7, 138.8, 131.7, 124.3, 121.4, 119.7, 116.5, 116.3, 53.6, 53.5; *m*/*z* (EI) 327 (M^+, 60%), 292 (100, M^+−Cl). Anal. Calcd for $C_{17}H_{14}ClN_3O_2$: C, 62.30; H, 4.31; N, 12.82. Found: C, 62.19; H, 4.32; N, 12.78; ν_{max} (film)/cm^{-1} 2989, 2952, 1578, 1468, 1400, 1366, 1300, 1188, 1017.

*4.2.6. 2-Chloro-3,4-bis(6-methoxypyridin-3-yl)pyridine **16**.* Compound **4** (0.500 g, 1.37 mmol), **12** (0.419 g, 2.74 mmol), $Pd(PPh_3)_4$ (5 mol %, 0.081 g, 0.07 mmol), 1,4-dioxane (20 mL) and Na_2CO_3 (1 M, 5.5 mL, 5.5 mmol) reflux for 20 h. Chromatography (SiO_2, petroleum ether/ethyl acetate, 1:1 v/v) yielded **16** as a white powder (0.255 g, 50%); mp: 145.6–147.9 °C; δ_H (400 MHz, $CDCl_3$) 8.44 (1H, d, *J* 5.0), 7.97 (1H, d, *J* 2.7), 7.91 (1H, d, *J* 2.5), 7.39 (1H, dd, *J* 2.5, 8.6), 7.29 (1H, d, *J* 5.1), 7.20 (1H, dd, *J* 2.6, 8.7), 6.73 (1H, d, *J* 8.0), 6.60 (1H, d, *J* 8.0), 3.93 (3H, s) 3.90 (3H, s); δ_C (100 MHz, $CDCl_3$) 163.8, 163.5, 152.3, 149.0, 148.7, 148.2, 147.0, 140.6, 139.1, 131.9, 127.7, 126.9, 124.8, 123.7, 110.6, 53.6, 53.5; *m*/*z* (ES$^+$) 328.08469 (M^+, $C_{17}H_{14}{}^{35}ClN_3O_2$ requires 328.08473); ν_{max} (film)/cm^{-1} 3039, 3010, 2945, 1602, 1560, 1498, 1456, 1359, 1302, 1289, 1257, 1188, 1012, 830, 776.

*4.2.7. 2-Chloro-3,4-bis(4-methoxyphenyl)pyridine **17**.* Compound **4** (0.500 g, 1.37 mmol), **21** (0.416 g, 2.74 mmol), $Pd(PPh_3)_4$ (5 mol %, 0.081 g, 0.07 mmol), 1,4-dioxane (20 mL) and Na_2CO_3 (1 M, 5.5 mL, 5.5 mL) reflux for 20 h. Chromatography (SiO_2, petroleum ether/ethyl acetate, 3:2 v/v) yielded **17** as a white crystalline powder (0.288 g, 64%); mp: 126.4–129.9 °C; δ_H (400 MHz, $(CD_3)_2CO$) 8.37 (1H, d, *J* 4.9), 7.39 (1H, d, *J* 5.2), 6.80 (2H, d, *J* 8.8), 7.10 (4H, d, *J* 9.1), 6.88 (2H, d, *J* 8.8), 6.80 (2H, d, *J* 8.8), 3.78 (3H, s), 3.75 (3H, s); δ_C (100 MHz, $(CD_3)_2CO$) 160.4, 160.1, 152.6, 152.4, 148.8, 135.6, 132.5, 131.6, 131.4, 129.8, 125.0, 114.4, 114.3, 55.53, 55.48; *m*/*z* (APCI$^+$) 326.0938 (M^++H, $C_{19}H_{17}{}^{35}ClNO_2$ requires 326.0948); ν_{max} (film)/cm^{-1} 2963, 2838, 1606, 1577, 1511, 1454, 1371, 1289, 1246, 1173, 1110, 1060, 1027, 998, 812, 767.

*4.2.8. 5-[2-Chloro-3-(6-methoxypyridin-3-yl)pyridin-4-yl]-2-fluoropyridine **18**.* Compound **9** (0.480 g, 1.43 mmol), **12** (0.330 g, 2.2 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %, 0.0504 g, 0.072 mmol), 1,4-dioxane (20 mL), Na_2CO_3 (1 M, 4.0 mL, 4.0 mmol) reflux for 18 h. Chromatography (SiO_2, hexane/ethyl acetate, 2:1 v/v) yielded **18** as a yellow oil (0.410 g, 90%) used in subsequent reactions without further purification; δ_H (700 MHz, $CDCl_3$) 8.45 (1H, d, *J* 5.0), 7.97 (1H, d, *J* 2.2), 7.84 (1H, d, *J* 1.8), 7.42 (1H, td, *J* 8.4, 2.5), 7.33 (1H, dd, *J* 8.5, 2.4), 7.27 (1H, d, *J* 5.0), 6.79 (1H, dd, *J* 8.5, 2.6), 6.68 (1H, dd, *J* 8.5, 0.5), 3.88 (3H, s); δ_C (176 MHz, $CDCl_3$) 163.8, 163.2 (d, J_{CF} 242.3), 152.7, 149.1, 148.3, 147.8 (d, J_{CF} 15.2), 147.8, 141.8 (d, J_{CF} 8.2), 140.6, 132.4, 131.9 (d, J_{CF} 4.8), 124.4, 123.8, 111.0, 109.6 (d, J_{CF} 37.6), 53.8; *m*/*z* (APCI$^+$) 315.05770 (M^+, $C_{16}H_{11}{}^{35}ClFN_3O$ requires 315.05692); ν_{max} (film)/cm^{-1} 2950, 1594, 1498, 1362, 1286, 1250, 1017, 830.

*4.2.9. 5-[2-Chloro-3-(2-methoxypyridin-3-yl)pyridin-4-yl]-2-methoxypyridine **19**.* Compound **8** (0.680 g, 1.96 mmol), **11** (0.450 g, 2.9 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %, 0.0689 g, 0.0981 mmol), 1,4-dioxane (20 mL), Na_2CO_3 (1 M, 6.0 mL, 6.0 mmol) reflux for 70 h. Chromatography (SiO_2, diethyl ether/petroleum ether, 2:1 v/v) yielded **19** as a white solid (0.146 g, 23%). A sample was recrystallised from hexane and ethyl acetate; mp: 149.6–150.2 °C; δ_H (500 MHz, $CDCl_3$) 8.42 (1H, d, *J* 5.0), 8.13 (1H, dd, *J* 5.0, 1.9), 7.93 (1H, d, *J* 2.4), 7.30 (1H, dd, *J* 7.3, 1.9), 7.25 (1H, d, *J* 5.1), 7.20 (1H, dd, *J* 8.6, 2.5), 6.84 (1H, dd, *J* 7.3, 5.0), 6.55 (1H, d, *J* 8.6), 3.86 (3H, s), 3.78 (3H, s); δ_C (126 MHz, $CDCl_3$) 164.0, 161.0, 152.3, 149.4, 148.9, 147.6, 146.6, 140.2, 138.7, 130.9, 127.3, 123.5, 119.7, 116.8, 110.5, 53.8, 53.8; *m*/*z* (EI) 327 (M^+), 292 (100, M^+−Cl). Anal. Calcd for $C_{17}H_{14}ClN_3O_2$: C, 62.30; H, 4.31; N, 12.82. Found: C, 62.32; H, 4.37; N, 12.73; ν_{max} (film)/cm^{-1} 2978, 2939, 1574, 1492, 1464, 1376, 1287, 1016, 784. *Crystal data*: $C_{17}H_{14}ClN_3O_2$, *M*=327.76, *T*=120 K, triclinic, space group $P\bar{1}$ (no. 2), *a*=8.3074(11), *b*=10.0536(14), *c*=10.0793(14) Å, α=68.25(2), β=78.16(2), γ=79.04(2)°, *V*=759.2(2) Å^3, *Z*=2, D_x=1.434 g cm^{-3}, μ(Mo Kα)=0.27 mm^{-1}, 9263 reflections (4187 unique), R_{int}=0.015, $R[I\geq 2\sigma(I)]$=0.032. CCDC-745859.

*4.2.10. 3-[2-Chloro-3-(6-methoxypyridin-3-yl)pyridin-4-yl]-2-methoxypyridine **20**.* Compound **7** (2.00 g, 5.77 mmol), **12** (0.970 g, 6.3 mmol), $Pd_2(dba)_3$ (3 mol %, 0.159 g, 0.173 mol), P(*t*-Bu)$_3\cdot$HBF$_4$ (6 mol %, 0.100 g, 0.346 mmol) 1,4-dioxane (20 mL), KF (1.10 g, 19 mmol) reflux for 6 h. Chromatography (SiO_2, hexane/ethyl acetate, 4:1 v/v) yielded **20** as a white solid (1.40 g, 74%); mp: 102.7–105.3 °C; δ_H (700 MHz, $CDCl_3$) 8.41 (1H, d, *J* 4.9), 8.06 (1H, dd, *J* 5.0, 1.8), 7.83 (1H, s), 7.35 (1H, d, *J* 7.3), 7.30 (1H, dd, *J* 7.2, 1.7), 7.22 (1H, d, *J* 4.9), 6.82 (1H, dd, *J* 7.2, 5.0), 6.62 (1H, d, *J* 8.5), 3.86 (3H, s), 3.68 (3H, s); δ_C (176 MHz, $CDCl_3$) 163.6, 159.8, 151.8, 148.6, 148.4, 147.7 (2C), 140.4, 139.1, 133.3, 125.3, 124.6, 121.5, 116.8, 110.1, 53.7, 53.5; *m*/*z* (ES$^+$) 328.08494 (M^++H, $C_{17}H_{15}{}^{35}ClN_3O_2$ requires 328.08473); ν_{max} (film)/cm^{-1} 2952, 1469, 1400, 1375, 1284, 1016, 839, 788.

*4.2.11. 2-Fluoro-5-[2-(4-methoxyphenyl)-3-(6-methoxypyridin-3-yl)pyridin-4-yl]pyridine **22**.* Compound **18** (0.175 g, 0.554 mmol), **21** (0.100 g, 0.67 mmol), $Pd_2(dba)_3$ (2 mol %, 0.010 g, 0.011 mmol), PCy_3 (4.8 mol %, 0.008 g, 0.027 mmol) 1,4-dioxane (7 mL), K_3PO_4 (1.27 M, 0.74 mL, 0.94 mmol) reflux for 20 h. Chromatography (SiO_2, ethyl acetate/hexane, 3:1 v/v) yielded **22** as a pale yellow solid (0.0640 g, 30%); mp: 139.2–140.2 °C; δ_H (700 MHz, $CDCl_3$) 8.72 (1H, d, *J* 5.0), 7.98 (1H, d, *J* 1.9), 7.63 (1H, d, *J* 2.3), 7.40 (1H, td, *J* 8.0, 2.4), 7.25 (1H, d, *J* 5.0), 7.17 (2H, d, *J* 8.7), 7.04 (1H, dd, *J* 8.5, 2.4), 6.79 (1H, dd, *J* 8.4, 2.6), 6.73 (2H, d, *J* 8.8), 6.50 (1H, d, *J* 8.5), 3.83 (3H, s), 3.74 (3H, s); δ_C (176 MHz, $CDCl_3$) 163.1, 163.0 (d, J_{CF} 241.2), 159.6, 159.2, 149.0, 148.8, 147.9 (d, J_{CF} 15.0), 145.8, 142.0 (d, J_{CF} 8.0), 141.3, 133.1 (d, J_{CF} 4.7), 132.3, 131.4 (2C), 130.9, 126.1, 123.3, 113.7 (2C), 110.8, 109.4 (d, J_{CF} 37.5), 55.4, 53.6; *m*/*z* (EI) 387 (M^+, 85%), 386 (100, M^+−H). Anal. Calcd for $C_{23}H_{18}FN_3O_2$: C, 71.31; H, 4.68; N, 10.85. Found: C, 70.88; H, 4.74; N, 10.67; ν_{max} (film)/cm^{-1} 3030, 2940, 1604, 1499, 1252, 1178, 1016, 836.

*4.2.12. 5-[4-(6-Fluoropyridin-3-yl)-3-(6-methoxypyridin-3-yl)pyridin-2-yl]pyrimidin-2-amine **23**.* Compound **18** (0.175 g, 0.5543 mmol), **26** (0.0920 g, 0.67 mmol), $Pd_2(dba)_3$ (2 mol %, 0.0102 g, 0.011 mmol), PCy_3 (4.8 mol %, 0.00750 g, 0.027 mmol) 1,4-dioxane (7 mL), K_3PO_4 (1.27 M, 0.742 mL, 0.942 mmol) reflux for 2 h. Chromatography (SiO_2, ethyl acetate/methanol, 4:1 v/v) yielded **23** as a white solid (0.0470 g, 23%); mp: 200.2–202.5 °C; ν_{max} (film)/cm^{-1} 3454 and 3305 (NH_2), 3184, 1638, 1585, 1487, 1410, 1285, 1251, 828; δ_H (700 MHz, $CDCl_3$) 8.76 (1H, d, *J* 4.9), 8.24 (2H, s), 7.99 (1H, d, *J* 1.6), 7.72 (1H, d, *J* 1.8), 7.40 (1H, td, *J* 8.4, 2.4), 7.30 (1H, d, *J* 4.9), 7.12 (1H, dd, *J* 8.5, 2.5), 6.81 (1H, dd, *J* 8.4, 2.6), 6.60 (1H, d, *J* 8.5), 5.20 (2H, br s), 3.86 (3H, s); δ_C (176 MHz, $CDCl_3$) 163.6, 163.2 (d, J_{CF} 242.0), 161.5, 159.2 (2C), 154.1, 149.7, 148.8, 147.9 (d,

J_{CF} 15.1), 146.3, 141.9 (d, J_{CF} 8.0), 141.0, 132.6 (d, J_{CF} 5.0), 131.1, 125.1, 124.2, 123.9, 111.5, 109.5 (d, J_{CF} 37.5), 53.8; *m/z* (ES^+) 375.13660 (M^++H), $C_{20}H_{16}FN_6O$ requires 375.13641.

*4.2.13. 5-[2-(6-Fluoropyridin-3-yl)-3-(2-methoxypyridin-3-yl)pyridin-4-yl]-2-methoxypyridine **24**.* Compound **19** (0.100 g, 0.31 mmol), **13** (0.052 g, 0.37 mmol), $Pd_2(dba)_3$ (2 mol %, 0.0056 g, 0.0061 mmol), PCy_3 (4.8 mol %, 0.0041 g, 0.015 mmol) 1,4-dioxane (5 mL), K_3PO_4 (1.27 M, 0.4 mL, 0.052 mmol) reflux for 5 h. Chromatography (SiO_2, ethyl acetate/hexane, 3:1 v/v) yielded **24** as a clear colourless oil (0.0540 g, 45%); δ_H (700 MHz, $CDCl_3$) 8.73 (1H, d, *J* 5.0), 8.07 (1H, d, *J* 1.8), 8.01 (1H, dd, *J* 5.0, 1.7), 7.93 (1H, d, *J* 1.9), 7.66 (1H, td, *J* 8.3, 2.4), 7.33 (1H, d, *J* 5.0), 7.16 (1H, dd, *J* 8.6, 2.5), 7.09 (1H, dd, *J* 7.3, 1.7), 6.76 (1H, dd, *J* 8.4, 2.5), 6.70 (1H, dd, *J* 7.2, 5.0), 6.55 (1H, d, *J* 8.6), 3.87 (3H, s), 3.56 (3H, s); δ_C (176 MHz, $CDCl_3$) 163.9, 163.0 (d, J_{CF} 240.4), 160.7, 155.3, 149.3, 148.2 (d, J_{CF} 15.1), 147.8, 147.5, 146.6, 141.8 (d, J_{CF} 8.0), 140.9, 138.8, 134.4 (d, J_{CF} 4.6), 130.3, 127.7, 124.2, 120.3, 117.0, 110.4, 108.7 (d, J_{CF} 37.4), 53.8, 53.5; *m/z* (ES^+) 389.14105 (M^++H, $C_{22}H_{18}FN_4O_2$ requires 389.14083); ν_{max} (film)/cm^{-1} 2963, 1592, 1488, 1462, 1397, 1369, 1286, 1257, 1097, 1015, 827, 797, 732.

*4.2.14. 3-[2-(6-Fluoropyridin-3-yl)-3-(6-methoxypyridin-3-yl)pyridin-4-yl]-2-methoxypyridine **25**.*

4.2.14.1. Method A. Compound **20** (0.500 g, 1.5 mmol), **13** (0.260 g, 1.8 mmol), $Pd_2(dba)_3$ (2 mol %, 0.0279 g, 0.0305 mmol), PCy_3 (4.8 mol %, 0.0205 g, 0.073 mmol) 1,4-dioxane (15 mL), K_3PO_4 (1.27 M, 2.04 mL, 2.59 mmol) reflux for 17 h. Chromatography (SiO_2, ethyl acetate/hexane, 3:1 v/v) yielded **25** as a clear colourless oil (0.302 g, 51%); δ_H (700 MHz, $CDCl_3$) 8.69 (1H, d, *J* 4.9), 8.06 (1H, d, *J* 2.2), 8.04 (1H, dd, *J* 5.0, 1.8), 7.71 (1H, td, *J* 8.3, 2.4), 7.61 (1H, s), 7.32 (1H, dd, *J* 7.2, 1.6), 7.27 (1H, d, *J* 4.9), 7.02 (1H, d, *J* 7.5), 6.81 (1H, dd, *J* 7.2, 5.1), 6.77 (1H, dd, *J* 8.5, 2.5), 6.43 (1H, d, *J* 8.5), 3.76 (3H, s), 3.60 (3H, s); δ_C (176 MHz, $CDCl_3$) 163.1, 162.9 (d, J_{CF} 240.8), 159.9, 154.4, 149.1, 149.0 (d, J_{CF} 15.1), 148.1, 147.4, 146.8, 142.6 (d, J_{CF} 8.0), 140.5, 139.1, 134.1 (d, J_{CF} 4.4), 132.5, 125.9, 124.8, 121.9, 116.8, 110.3, 108.9 (d, J_{CF} 37.4), 53.5, 53.3; *m/z* (ES^+) 389.14105 (M^++H, $C_{22}H_{18}FN_4O_2$ requires 389.14083); ν_{max} (film)/cm^{-1} 2949, 1592, 1463, 1400, 1285, 1249, 1016, 830.

4.2.14.2. Method B. Compound **20** (0.250 g, 0.763 mmol), **13** (0.130 g, 0.92 mmol), $Pd(PPh_3)_4$ (5 mol %, 0.0441 g, 0.038 mmol), 1,4-dioxane (12 mL), Na_2CO_3 (1 M, 1.8 mL, 1.8 mmol), reflux for 24 h. Chromatography (SiO_2, ethyl acetate/hexane, 3:1 v/v) yielded **25** as a clear colourless oil (0.150 g, 50%).

*4.2.15. 2-Chloro-3,4-bis(2-phenylethynyl)pyridine **27**.* To a flask fitted with a septum was added 2-chloro-3,4-diiodopyridine **4** (1.500 g, 4.11 mmol), $Pd(PPh_3)_2Cl_2$ (0.144 g, 0.21 mmol) and CuI (0.039 g, 0.21 mmol). The flask was evacuated and backfilled with dry argon three times. Dry, degassed triethylamine (40 mL) was added via a cannula and phenylacetylene (0.860 g, 8.42 mmol) was added via syringe. The reaction was heated to 50 °C for 18 h by which time the reaction was complete by TLC. The reaction was cooled to room temperature, triethylamine was removed in vacuo and the residue was passed through a silica plug eluting with ethyl acetate (300 mL). After concentration, the residue was purified by flash chromatography (SiO_2, DCM/hexane, 1:1 v/v) followed by recrystallisation from methanol yielding **27** as a white solid (1.01 g, 72%); mp: 100.5–101.7 °C; δ_H (400 MHz, $CDCl_3$) 8.26 (1H, d, *J* 5.1), 7.63–7.53 (4H, m), 7.44–7.31 (7H, m); δ_C (176 MHz, $CDCl_3$) 152.9, 147.3, 136.2, 132.3, 132.0, 129.9, 129.5, 128.8, 128.7, 124.1, 122.7, 122.11, 122.07, 101.0, 99.5, 85.9, 84.1; *m/z* (ES^+) 314.07294 (M^++H, $C_{21}H_{13}{}^{35}ClN$ requires 314.07310); ν_{max} (film)/cm^{-1} 3046, 2365, 2323, 2235, 2202, 1596, 1567, 1519, 1490, 1442, 1389, 1279, 1160, 901, 841, 754.

*4.2.16. 5-[3,4-Bis(2-phenylethynyl)pyridin-2-yl]-2-fluoropyridine **28**.* The general method for Suzuki–Miyaura cross-couplings was followed. Compound **27** (0.400 g, 1.38 mmol), **13** (0.216 g, 1.53 mmol), $Pd(PPh_3)_4$ (5 mol %, 0.074 g, 0.06 mmol), 1,4-dioxane (20 mL), Na_2CO_3 (1 M, 2.55 mL, 2.55 mmol) heated at reflux for 18 h. Chromatography (SiO_2, ethyl acetate/hexane, 1:2 v/v) followed by recrystallisation from hexane and DCM yielded **28** as white needles (0.314 g, 66%); mp: 124.3–124.9 °C; δ_H (700 MHz, $CDCl_3$) 8.95 (1H, d, *J* 2.4), 8.58 (1H, d, *J* 5.0), 8.50–8.37 (1H, m), 7.65–7.51 (2H, m), 7.50–7.28 (9H, m), 7.04 (1H, dd, *J* 8.5, 2.7); δ_C (176 MHz, $CDCl_3$) 163.9 (d, J_{CF} 241.2), 156.1, 148.8 (d, J_{CF} 15.4), 148.2, 142.3, 135.6, 133.4 (d, J_{CF} 4.6), 132.2, 131.7, 129.8, 129.4, 128.80, 128.77, 124.4, 122.6, 122.3, 119.8, 108.9 (d, J_{CF} 37.4), 99.8, 98.9, 86.4, 85.9; *m/z* ($APCI^+$) 375.1294 (M^++H, $C_{26}H_{16}N_2F$ requires 375.1298); ν_{max} (film)/cm^{-1} 3056, 2360, 2339, 2212, 1590, 1552, 1491, 1442, 1408, 1367, 1256, 1130, 1023, 899, 831, 740, 684.

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13. At present (September 2009) Sigma–Aldrich sell 100 g of 2-chloropyridine **5** for £9.40. A price of 2-chloro-3-iodopyridine could not be found in the catalogues available to us. The synthesis of **1** from **5**, as reported by Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 1371–1376 was accomplished in 76% yield, making an overall literature yield of 54% for the two-step synthesis of **4** from **1**, compared to 26–28% for our one-pot method.
14. In the GC–MS analysis of the crude product mixture, along with the signal for **4**, two smaller signals were observed both of *m/z* 238.9 which are consistent with 2-chloro-3-iodopyridine and 2-chloro-4-iodopyridine as minor products.
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