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Divergent synthesis of arylated pyridin-2(1*H*)-one derivatives via metal-catalysed cross-coupling processes

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ABSTRACT

1,5-Di(hetero)arylated-pyridin-2(1*H*)-one derivatives have been readily obtained in good yields starting from 2-fluoro-5-pyridylboronic acid. The sequence comprises three steps: (i) palladium-catalysed Suzuki-Miyaura reaction; (ii) base-catalysed hydrolysis; (iii) copper-catalysed C–N coupling. X-ray crystal structures are reported for selected pyridin-2(1*H*)-one derivatives. These compounds are of interest as new scaffolds for drug discovery.

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1. Introduction

Functionalised pyridones are of continued interest due to their prevalence in naturally occurring compounds,[1–3] bioactive compounds and drugs,[4–14] coordination chemistry[15] and their catalytic acitivity.[16] New routes for their synthesis and functionalisation continue to be developed.[17,18] Metal-catalysed cross-coupling reactions have revolutionised the modification of pyridones[19] and related heterocycles, with C–C, C–N, C–O bond forming processes now widely utilised.[20,21] Notably, Suzuki-Miyaura, Buchwald-Hartwig and Ullmann type reactions have become ubiquitous in the post-functionalisation of heterocycles. Access to *N*-arylpyridones was traditionally achieved using harsh Ullmann-Goldberg conditions[22] resulting in low yields and poor functional group tolerance. Ligand-accelerated and copper-catalysed approaches have led to much milder coupling conditions.[23–28] Other methods for *N*-arylating pyridones and related heterocycles include: copper-mediated coupling with arylboronic acids,[24,29,30] lead-mediated coupling to aryl halides[31,32] and HATU-mediated coupling of arylamides to 4-hydroxyquinazolines.[33] There is interest in sequential metal-catalysed routes to functionalised heteroaryl systems.[34–39] The aim of the present work was to develop an efficient divergent route to tri-(hetero)aryl systems based on the pyridin-2(1*H*)-one framework starting from the commercially-available 2-fluoro-5-pyridylboronic acid **1**.[40] We also report related reactions of 2,6-difluoro-5-pyridylboronic acid.

2. Results and discussion

An overview of our methodology is shown in Scheme 1. Suzuki-Miyaura cross-coupling of 2-fluoro-5-pyridylboronic acid **1** with (hetero)aryl bromides **2**–**4** furnished compounds **5**–**7** under standard conditions[41,42] in high isolated yields (Table 1).

Conversion of **5**–**7** into the 2-pyridone derivatives **8**–**10** was achieved in high yields by hydrolysis under basic conditions (Table 1).[43] Compounds **6** and **7** reacted faster than **5**, presumably due to the electron withdrawing effect of the quinolyl and pyridyl substituents, respectively.

It has previously been observed that the copper-catalysed coupling of 2-pyridones can lead to both C–N and C–O arylated products.[28,44] To explore this reaction, pyridone derivative **8** was reacted with **11** (Scheme 2). After isolation of the *N*-heteroarylated product **12a** vide infra, a comparison with the crude ^{1}H NMR

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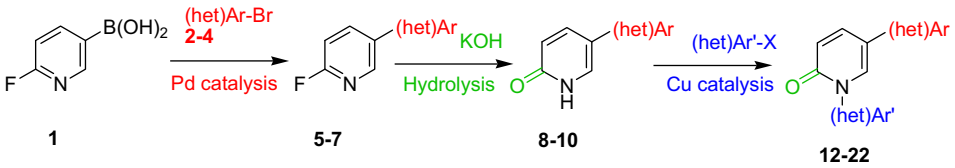
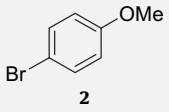
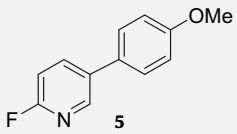
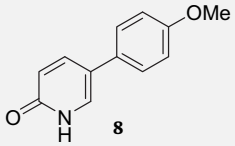
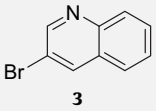
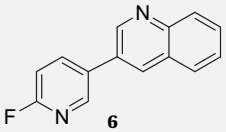
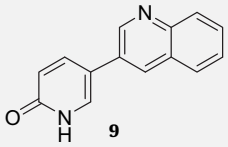
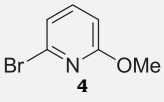
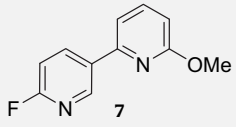
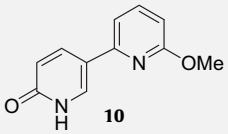
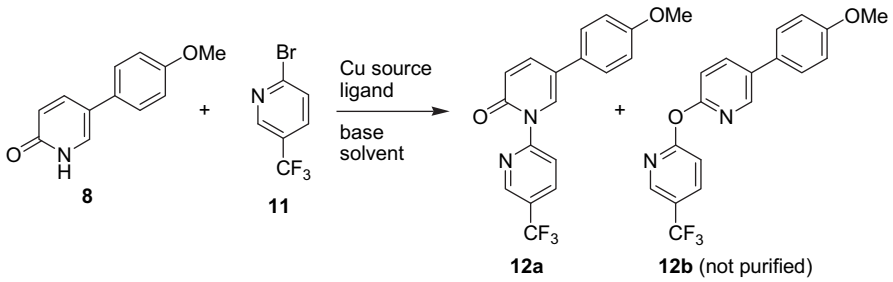


Scheme 1. Protocol for the three-step synthesis of 1,5-di(hetero)arylpyridin-2(1*H*)-one derivatives.

Table 1
Synthesis of fluoropyridines **5**–**7** and pyridones **8**–**10**

Entry	(het)Ar–Br	Cross-coupling product[c]	Yield[a] (%)	Hydrolysis product[d]	Yield[b] (%)
1	 **2**	 **5**	98	 **8**	83
2	 **3**	 **6**	89	 **9**	88
3	 **4**	 **7**	97	 **10**	92

[a] The quoted yields are for isolated product after purification by chromatography and/or recrystallisation.
[b] The quoted yields are for isolated product after acidification and filtration.
[c] Reagents and conditions: **1** (1.2–1.5 equiv), (hetero)arylbromide (1.0 equiv), $Pd(PPh_3)_2Cl_2$, Na_2CO_3 (3 equiv, 1 M in H_2O), 1,4-dioxane, reflux, 1–20 h under argon.
[d] Reagents and conditions: compound **5**, **6** or **7**, KOH (1 M in H_2O), 1,4-dioxane, reflux, 24–66 h.



Scheme 2. Coupling of **8** and **11**. For conditions see Table 2.

spectrum and GC–MS traces confirmed that **12a** was the major product. The other product, presumed to be **12b**, could not be obtained pure. An initial screening was undertaken utilising commonly employed conditions and ligands for the C–N coupling of 2-pyridones, 2-pyridazinones and NH-heterocycles (Table 2). Using 1,10-phenanthroline (1,10-phen) with conditions used previously for the N-heteroarylation of benzimidazole and other NH-heterocycles,[39] conversion was complete after 24 h with a 79:21 ratio of **12a**:**12b** (Table 2, entry 1). Buchwald's 4,7-dimethoxy-1,10-phenanthroline ligand has proved to be effective for the copper-catalysed N-arylation of 2-pyridone;[28] however, the high cost of the ligand led us to try cheaper alternatives. Whilst keeping the same base (Cs_2CO_3), the solvent was changed to dioxane, 8-hydroxyquinoline (8-HQ) was employed as the ligand and PEG was added as a solid–liquid transfer catalyst.[45] However, despite 8-HQ being previously used to *N*-arylated pyridones[44] and pyridazinones,[27] these conditions resulted in a low conversion and a reduced ratio

Table 2
Screening of conditions for arylation of **8** with **11**

Entry	Cu source	Ligand	Base	Solvent	GC–MS analysis **11**:**12a**:**12b**
1	CuI	1,10-phen	Cs_2CO_3	DMF	0:79:21
2	CuI	8-HQ	Cs_2CO_3	dioxane[a]	69:20:11
3	CuI	DMCDA	K_2CO_3	toluene	0:95:5
4	CuI	DMCDA	K_2CO_3	DMSO	3:97:0
5	Cu_2O	Chxn–Py–Al	Cs_2CO_3	MeCN	39:50:11

Conditions and reagents: **8** (0.735 mmol), **11** (0.700 mmol), Cu source (0.07 mmol), ligand (0.140 mmol), base (1.40 mmol), anhydrous solvent (2 mL), 100 °C, 36 h under argon.
[a] PEG (43 mg) additive used.

Table 3
Copper-catalysed C–N cross-coupling reactions of pyridone derivatives

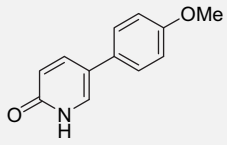
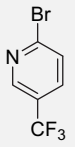
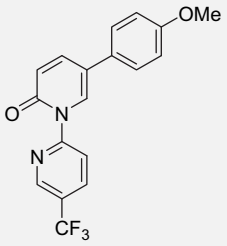
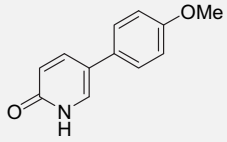
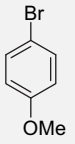
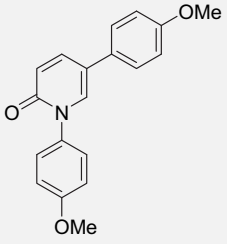
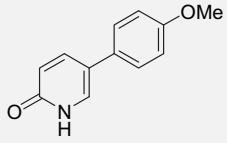
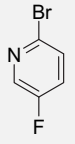
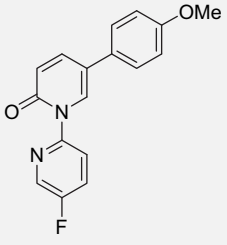
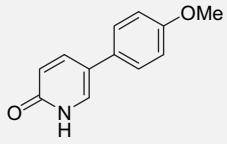
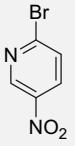
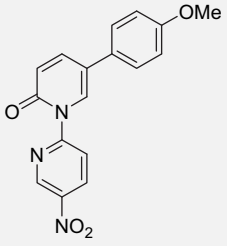
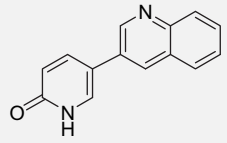
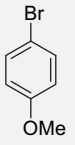
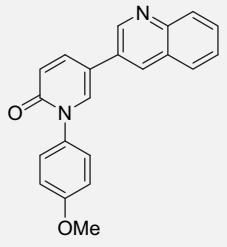
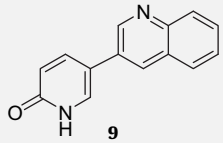
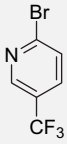
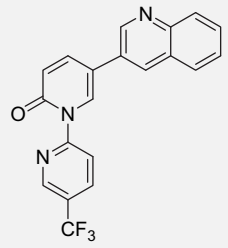
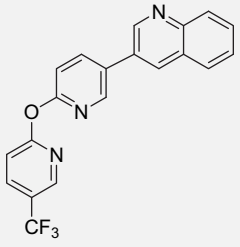
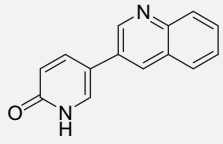
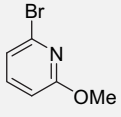
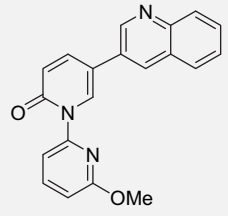
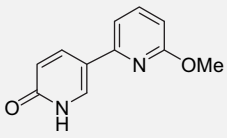
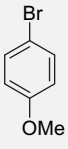
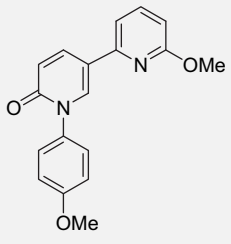
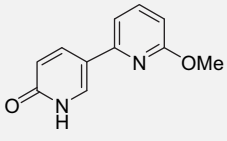
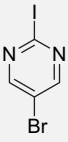
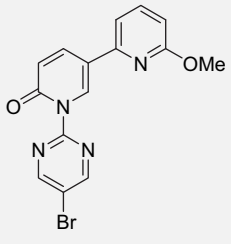
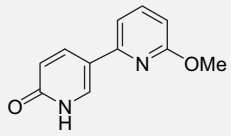
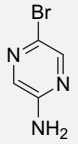
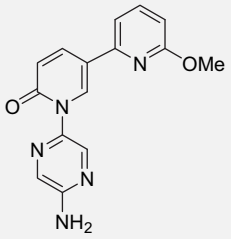
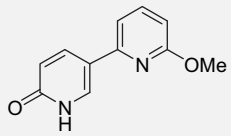
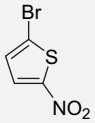
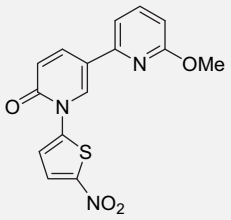
Entry	Pyridone	(het)Ar–X	Product	Yield[a] (%)
1	 **8**	 **11**	 **12a**	80
2	 **8**	 **2**	 **13**	82
3	 **8**	 **23**	 **14**	77
4	 **8**	 **24**	 **15**	83
5	 **9**	 **2**	 **16**	66

Table 3 (*continued*)

Entry	Pyridone	(het)Ar–X	Product	Yield[a] (%)
6	 **9**	 **11**	 **17a**	72
			 **17b**	5
7	 **9**	 **4**	 **18**	70
9	 **10**	 **2**	 **19**	74
10	 **10**	 **25**	 **20**	51

(*continued on next page*)

Table 3 (*continued*)

Entry	Pyridone	(het)Ar–X	Product	Yield[a] (%)
11	 **10**	 **26**	 **21**	40
12	 **10**	 **27**	 **22**	60

[a] The quoted yields are for isolated product after purification by chromatography and/or recrystallisation. Conditions and reagents: Pyridone, (hetero)aryl halide, CuI, DMCDA, K_2CO_3, anhydrous toluene, 100 °C, 20–88 h under argon.

of **12a**:**12b** (Table 2, entry 2). When *N*,*N*′-dimethylcyclohexane-1,2-diamine (DMCDA) was employed using K_2CO_3 in toluene[26] (Table 2, entry 3) the conversion was complete with a high ratio (95:5) of **12a**:**12b** and **12a** was isolated in 80% yield (Table 3, entry 3). By changing the solvent to DMSO,[28] **12a** was the sole product observed (Table 2, entry 4). It has been observed previously that more polar solvents favour the 2-(1*H*)pyridone tautomer.[25] Utilising the potentially tetradentate Schiff base ligand Chxn–Py–Al with conditions developed by Cristau et al., for the N-arylation of 2-pyridone,[25] conversion was improved compared to 8-HQ with an enhanced **12a**:**12b** ratio of 50:11 (Table 2, entry 5).

4-Bromoanisole **2** was used as a more challenging substrate with pyridone **8**. Using the best conditions from Table 2 (entry 3: CuI, DMCDA, K_2CO_3 in toluene) gave clean conversion to **13**, which was isolated in 82% yield: no other product was detected by GC analysis (Table 3, entry 2) (Scheme 3). However, when using the same base, solvent and copper source, but changing the ligands to those used in the previous screening (Table 2, entries 1, 2 and 5), no reaction of **8** with **2** was observed. The structure of **13** was confirmed by single crystal X-ray analysis (Fig. 1).

Having found suitable conditions for N-arylation, 2-pyridone derivatives **8**, **9** and **10** were coupled with a variety of aryl and heteroaryl halides to give the functionalised 2-pyridones **12**–**22**

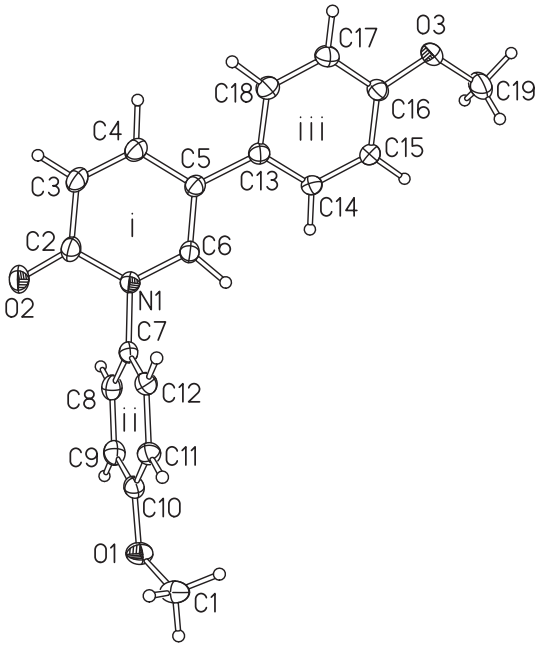
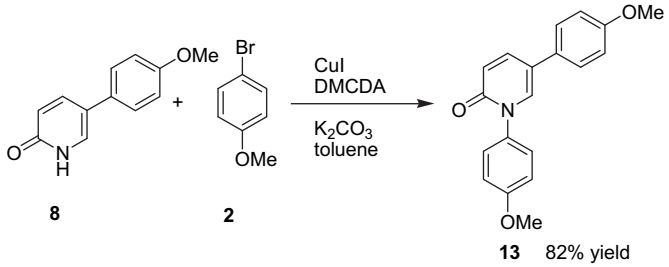
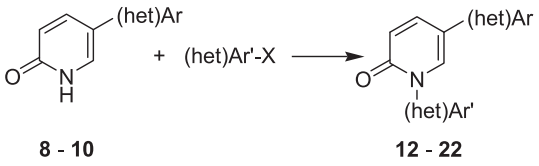


Figure 1. X-ray molecular structure of **13**. Interplanar angles: i/ii 68.6, i/iii 28.7°. Henceforth thermal ellipsoids are drawn at the 50% probability level.



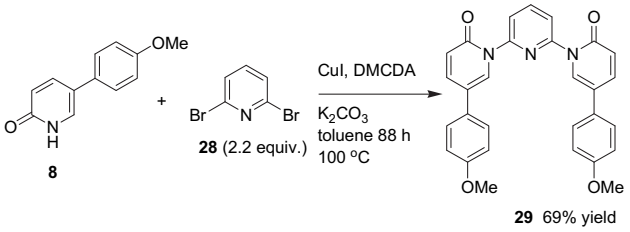
Scheme 3. Coupling of **8** and **2** to yield **13**.

(Table 3, entries 1–12 and Scheme 4). High yields were also obtained when using more activated heteroaryl bromides (Table 3, entries **1**, **3** and **4**). Pyridone **9** coupled with both 4-bromoanisole **2** and 2-bromo-5-(trifluoromethyl)pyridine **11** giving **16** (66%) and **17a** (72%), respectively (Table 3, entries 5 and 6). Alongside the major product **17a**, the C–O coupled product **17b** was isolated in low yield (Table 3, entry 6). Coupling of **9** was also performed with **4** giving **18** in a good yield. Pyridone **10** coupled to **2** under the same conditions, giving **19** in 74% isolated yield. Coupling at the iodo site of **25** afforded **20** (entry 10) leaving an active bromo



Scheme 4. Synthesis of **12**–**22**. For conditions see Table 3.

group for further functionalisation. Aminopyrazine derivative **26** coupled to **10** to give **21** in 40% yield (entry 11). 2-Bromo-5-nitrothiophene **27** coupled to **10** to give **22** in 60% yield. Functional group tolerance is notable, with fluoro, trifluoromethyl, methoxy, primary amino and nitro-substituted (hetero)aryl bromides coupling in good yields.



Scheme 5. Synthesis of **29** via two-fold N-arylation.

Two-fold coupling of **8** with 2,6-dibromopyridine **28** (2.2 equiv) provided the penta-aryl system **29** in 69% yield (Scheme 5). X-ray crystallographic analysis of **29** confirmed the bis-C–N coupled structure, with both amide carbonyls lying parallel to each other, facing away from the lone pair of the pyridyl nitrogen and out of the plane of the pyridine ring (Fig. 2).

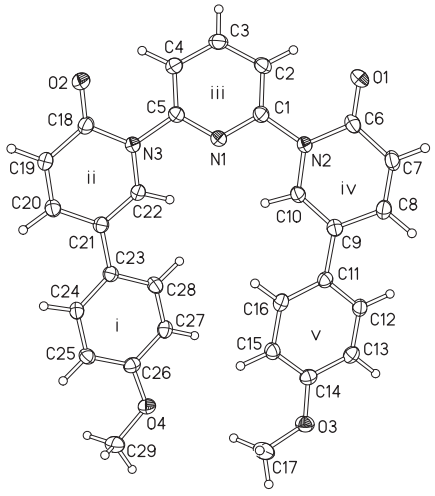
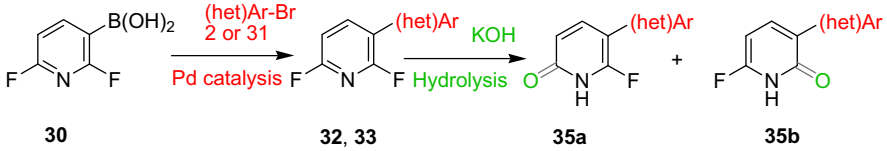


Figure 2. X-ray molecular structure of **29**. Interplanar angles (°): i/ii 36.0, ii/iii 25.1, iii/iv 34.6, iv/v 10.9, i/v 4.3.

3-Aryl-2,6-difluoropyridines **32** and **33** were synthesised via Suzuki cross-coupling of 2,6-difluoro-3-pyridylboronic acid **30** with **2** and **31** in good yields (Scheme 6 and Table 4). Hydrolysis of **32** gave a 1:1.4 ratio of **35a** and **35b**, as judged by ^{1}H NMR analysis of the crude mixture, indicating a slight preference for nucleophilic attack by the hydroxide anion at the less hindered C(6) site of **32**. The isolated crude yield of **35a**+**35b** was ca. 80%. Separation was very difficult and the two isomers were isolated pure in 10 and 8% yields, respectively. The parent compound **36**[46] was synthesised from 2,6-difluoropyridine **34** via basic hydrolysis (Table 4, entry 3); the reaction was sluggish, giving **36** in 62% yield after 114 h at reflux (Scheme 7). Similar isomers of 2- and 5-arylpyridone derivatives have been synthesised by Cheng et al.[43] Fluoropyridones have been reported as potential bioactive compounds in previous studies.[5,47]

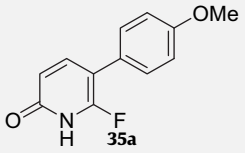
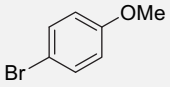
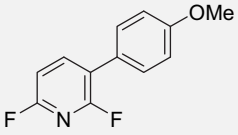
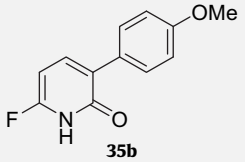
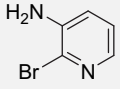
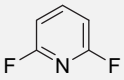
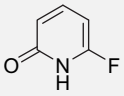
X-ray crystal structure determinations of fluoropyridone derivatives **35b** and **36** (Fig. 3) revealed that both exist as lactim (2-hydroxypyridine) tautomers. In both structures, pairs of hydroxypyridine groups related by a crystallographic inversion centre and practically coplanar, are linked together by pairs of strong linear hydrogen bonds O–H···N, with the proton unequivocally localised at the oxygen. Tautomerism of 2-pyridones has been extensively investigated.[48–53] In the solid state the parent 2-pyridone exists as the lactam tautomer as do 5-chloro-2-pyridone, 2-thiopyridone, 4-hydroxy-2-pyridone and 5-nitro-2-pyridone.[51,52] Functionalisation of 2-pyridones at C-6 with inductively electron withdrawing groups affects the acidity of the O–H group (in the 2-hydroxypyridine form) and the N–H group (in the 2-pyridone form) via a bimolecular proton transfer mechanism leading to the lactim tautomer.[52] Polar solvents favour the lactam tautomer and interaction with another non-solvent species can have an effect on the tautomeric equilibrium.[16,53]

Arylation of 5-fluoro-2-pyridone **36** was attempted using the optimised conditions for the arylation of 2-pyridone **8** (Table 2, entry 3). However, no reaction was observed after 72 h at reflux and starting material was recovered. Copper-catalysed arylation of amides is known to be very dependent on base strength with the optimal pK_a below that of the amide.[54] Although the solubility of K_2CO_3 in toluene is expected to be low, if the acidity of the 6-fluoro-2-pyridone is significantly greater than 2-pyridone (pK_a=17.0 in DMSO),[55] then deprotonation could occur faster than arylation leading to inactive cuprate complexes. A screening of different bases was carried out whilst keeping all other conditions unchanged. Despite changing to weak inorganic bases such as $KHCO_3$ and weak organic bases such as Et_3N (pK_a=9.0 in DMSO)[56] and pyridine (pK_a=3.4 in DMSO)[56] no reaction was observed after 48 h at reflux. On the basis of these results it is more likely that the steric effect of a 6-fluoro substituent hampers the arylation of **36**, as well as the electron withdrawing effect of the fluorine atom resulting in a reduced nucleophilicity.[44] An attempt to arylate **36** by copper-catalysed coupling with phenylboronic acid (DCM, room temperature, 48 h)[24] gave an intractable reaction mixture.

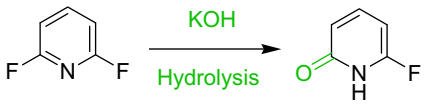


Scheme 6. Synthesis of **32**, **33**, **35a**, **35b**. For conditions see Table 4.

Table 4
Synthesis of difluoropyridines **32** and **33** and fluoropyridones **35a**, **35b** and **36**

Entry	(het)Ar–Br	Cross-coupling product/difluoropyridine	Yield[a] (%)	Hydrolysis product[c]	Yield[a] (%)
				 **35a**	(80)[d] 10
1	 **2**	 **32**	76[b]	 **35b**	8
2	 **31**	 **33**	83[c]	—	—
3	—	 **34**	—	 **36**	92[d]

[a] The quoted yields are for isolated product after purification by chromatography and/or recrystallisation. Yield in parenthesis refers to combined isolated yield of both isomers **35a** and **35b** before purification.
[b] Reagents and conditions: **30** (1.2 equiv), **2** (1.0 equiv), $Pd(PPh_3)_2Cl_2$, Na_2CO_3 (3 equiv, 1 M in H_2O), 1,4-dioxane, reflux, 1 h under argon.
[c] Reagents and conditions: **30** (1.5 equiv), **31** (1.0 equiv), $Pd_2(dba)_3$, PCy_3, Na_2CO_3 (3 equiv, 1 M in H_2O), 1,4-dioxane, reflux, 22 h under argon.
[d] Reagents and conditions: KOH (1–6 M in H_2O), 1,4-dioxane, reflux, 16–114 h.



Scheme 7. Synthesis of **36**. For conditions see Table 4.

On the premise that a compound with complementary hydrogen bonding sites could form host–guest complexes with **36**, we have investigated the interaction of this compound with diaminopyridine derivative **37** (Fig. 4a). DFT calculations (Fig. 4b) performed on structure **36** predict that although the carbonyl oxygen possess a significantly larger negative electrostatic potential than the fluoride, this derivative could have the propensity to form complementary hydrogen bonds with **37** (principally through the carbonyl oxygen and N*H* components of the pyridinone moiety with the amide N–*H* and pyridyl nitrogen of **37**, respectively).[57] We have investigated the ability of **36** to form hydrogen bonding interactions with **37** using ^1H and ^{19}F NMR spectroscopy in $CDCl_3$. A 1:1 admixture of **36** and **37** resulted in a broadening and a small downfield shift (−0.2 ppm) of the pyridinone N*H* resonance using ^1H NMR spectroscopy, features, which are characteristic of weak hydrogen bonding interactions. The proton-decoupled ^{19}F spectrum of the admixture revealed a 2 ppm shift from −75 ppm to −73 ppm in the single fluorine resonance,[58] suggesting that weak F···H–N interactions may be occuring.[59] Thus, the data are consistent with the formation of a low-affinity complex between **36** and **37** in $CDCl_3$.

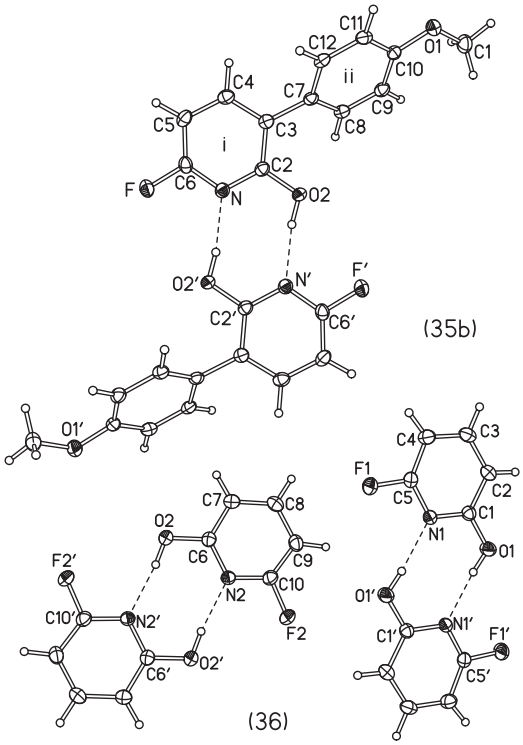


Figure 3. X-ray molecular structures of **35b** and **36**, showing independent molecules, their inversion equivalents (primed) and hydrogen bonds (dashed lines). Interplanar angle i/ii 50.1°. Bond distances (Å): C(2)–O(2) 1.337(2), N–C(2) 1.339(2), N–C(6) 1.323 (2), O(2)···N′ 2.758(2), O(2)–H 0.92(2) in **35b**; C(1)–O(1) 1.330(1), N(1)–C(1) 1.342(1), N(1)–C(5) 1.320, C(6)–O(2) 1.335(1), N(2)–C(6) 1.342(1), N(2)–C(10) 1.323(1), O(1)···N(1′) 2.735(1), O(1)–H 0.88(2), O(2)···N(2′) 2.760(1), O(2)–H 0.89(2) in **36** indicate 2-hydroxypyridine tautomeric structures.

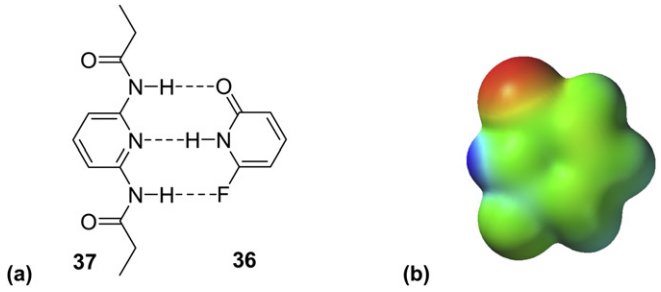


Figure 4. (a) Possible hydrogen bonding interactions between **37** and **36**. (b) DFT (B3LYP-/6-31G*) derived electrostatic potential map for compound **36**.

3. Conclusion

We have described efficient and flexible procedures that afford a range of 1,5-di(hetero)arylated-pyridin-2(1*H*)-one derivatives starting from the readily-available 2-fluoro-5-pyridylboronic acid **1**. These protocols are amenable to further exploitation in the synthesis of libraries of functionalised heterocycles of high diversity derived from **1**, especially compounds of potential utility as new pharmacophores and scaffolds for drug discovery.

4. Experimental

4.1. General

All cross-coupling reactions were performed under an argon atmosphere, which was dried by passage through a column of phosphorus pentoxide. All reagents used were of standard reagent grade, used as supplied unless otherwise stated and purchased from Sigma–Aldrich or Alfa Aesar, except for (2-fluoro-5-pyridyl)boronic acid **1**,[40] (2,6-difluoro-3-pyridyl)boronic acid **30**,[60] 5-bromo-2-iodopyrimidine **25**,[61] 2-amino-5-bromopyrazine **26**,[62] Chxn–Py–Al[63] and $Pd(PPh_3)_4$ which were prepared in-house. Anhydrous toluene, DMSO, DMF and MeCN were dried through a HPLC column on an Innovative Technology Inc. solvent purification system. 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). GC–MS analysis was recorded on a Thermo-Finnigan Trace mass spectrometer with positive ionisation mode. 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 parts per million, relative to the residual solvent as internal reference for ^{1}H and ^{13}C. The following abbreviations are used in listing NMR spectra: s=singlet, d=doublet, dd=doublet of doublets, ddd=doublet of doublet of doublets, dt=doublet of triplets, t=triplet, td=triplet of doublets, m=multiplet, br=broad. *J* values are quoted in hertz. 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. AP^+ mass spectra were obtained on a Waters LCT Classic spectrometer equipped with an atmospheric pressure chemical ionisation source. High resolution AP^+ spectra were obtained on a Waters Xevo QToF spectrometer equipped with an atmospheric solids analysis probe. GC–MS analysis was obtained using a Thermo-Finnigan Trace GC–MS with EI ionisation. IR spectra were recorded on a Perkin Elmer Paragon 1000 FTIR instrument. Elemental analyses were obtained on an Exeter analytical Inc. CE-440 elemental analyser.

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

To an argon purged flask was added the (hetero)aryl halide, 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 (1–20 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.

4.3. General method for pyridone C–N cross-coupling reactions

To an argon purged flask was added the pyridone, aryl halide, copper source, ligand, additive (where applicable), base and dry degassed solvent. The mixture was heated to 100 °C under argon and monitored by TLC. Upon completion, the reaction mixture was allowed to cool to room temperature and passed through a silica plug, eluting with EtOAc. The concentrated residue was purified via column chromatography.

*4.3.1. 2-Fluoro-5-(4-methoxyphenyl)pyridine **5**.* In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted (2-fluoro-5-pyridyl)boronic acid **1** (1.18 g, 8.40 mmol), 4-bromoanisole **2** (1.31 g, 7 mmol), $Pd(PPh_3)_2Cl_2$ (0.122 g, 0.18 mmol) and Na_2CO_3 (21 mL, 21 mmol, 1 M in water) in 1,4-dioxane (50 mL) at reflux for 14 h. Standard work-up and concentration gave a brown solid, which was purified via column chromatography (SiO_2, eluent 5:1 EtOAc:hexane) yielding **5** as a white solid (1.39 g, 98%); mp: 69.8–70.9 °C; δ_H (400 MHz, $CDCl_3$) 8.35 (1H, d, *J* 2.6), 7.90 (1H, ddd, *J* 8.5, 7.7, 2.6), 7.45 (2H, d, *J* 8.9), 7.03–6.92 (3H, m), 3.84 (3H, s); δ_C (126 MHz, $CDCl_3$) 162.9 (d, J_{CF} 238.4), 159.9, 145.5 (d, J_{CF} 14.7), 139.5 (d, J_{CF} 7.8), 134.7 (d, J_{CF} 4.6), 129.3, 128.4, 114.8, 109.5 (d, J_{CF} 37.5), 55.6. Anal. Calcd for $C_{12}H_{10}FNO$: C, 70.93; H, 4.96; N, 6.89. Found: C, 70.99; H, 4.94; N, 6.85; *m*/*z* (EI) 203 (M^+, 100%); ν_{max} (film)/cm^{-1} 2939, 2833, 1612, 1594, 1518, 1476, 1373, 1246, 1187, 1047, 1013, 1000, 826, 813, 796.

*4.3.2. 3-(6-Fluoropyridin-3-yl)quinoline **6**.* In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted (2-fluoro-5-pyridyl)boronic acid **1** (2.03 g, 14.4 mmol), 3-bromoquinoline **3** (2.40 g, 12.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.126 g, 0.180 mmol) and Na_2CO_3 (36 mL, 36 mmol, 1 M in water) in 1,4-dioxane (65 mL) at reflux for 20 h. Standard work-up and concentration yielded an off-white solid, which was purified via column chromatography (SiO_2, eluent 1:1 EtOAc:hexane) yielding **6** as an off-white solid (2.39 g, 89%); mp: 265 °C (decomp.); δ_H (700 MHz, $CDCl_3$) 9.10 (1H, d, *J* 2.3), 8.55 (1H, d, *J* 2.6), 8.29 (1H, d, *J* 8.4), 8.15 (1H, d, *J* 8.4), 8.10 (1H, ddd, *J* 8.4, 7.5, 2.6), 7.89 (1H, d, *J* 8.2), 7.76 (1H, ddd, *J* 8.4, 6.9, 1.4), 7.61 (1H, ddd, *J* 8.4, 6.9, 1.4), 7.10 (1H, dd, *J* 8.5, 3.1); δ_C (176 MHz, $CDCl_3$) 163.8 (d, J_{CF} 241.1), 149.1, 147.7, 146.5 (d, J_{CF} 15.1), 140.2 (d, J_{CF} 8.1), 134.0, 132.0 (d, J_{CF} 4.7), 130.4, 129.8, 129.5, 128.2, 128.0, 127.8, 110.3 (d, J_{CF} 37.6); *m*/*z* (EI) 224 (M^+, 100%). Anal. Calcd for

$C_{14}H_9FN_2$: C, 74.99; H, 4.05; N, 12.49. Found: C, 74.97; H, 4.13; N, 12.23; ν_{max} (film)/cm^{-1} 3041, 2921, 2845, 1597, 1583, 1570, 1491, 1394, 1345, 1298, 1255, 1124, 1052, 1023, 954, 913, 825, 788, 741, 668.

4.3.3. 2-(6-Fluoropyridin-3-yl)-6-methoxypyridine ***7***. In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted (2-fluoro-5-pyridyl)boronic acid **1** (1.69 g, 12.0 mmol), 2-bromo-6-methoxypyridine **4** (1.88 g, 10 mmol), $Pd(PPh_3)_2Cl_2$ (0.176 g, 0.25 mmol) and Na_2CO_3 (30 mL, 30 mmol, 1 M in water) in 1,4-dioxane (60 mL) at reflux for 14 h although completion by TLC noted after 10 min at reflux. Standard work-up and concentration gave a black residue, which was purified via column chromatography (SiO_2, eluent 5:1 EtOAc:hexane) yielding **7** as a white solid (1.98 g, 97%); mp: 67.2–67.7 °C; δ_H (700 MHz, $CDCl_3$) 8.83 (1H, d, *J* 2.5), 8.43 (1H, ddd, *J* 8.5, 7.8, 2.5), 7.64 (1H, dd, *J* 8.3, 7.4), 7.29 (1H, d, *J* 7.4), 7.00 (1H, ddd, *J* 8.5, 3.0, 0.6), 6.73 (1H, d, *J* 8.3), 4.00 (3H, s); δ_C (176 MHz, $CDCl_3$) 164.2, 164.1 (d, J_{CF} 240.5), 151.2, 146.4 (d, J_{CF} 15.3), 139.7 (d, J_{CF} 8.1), 139.6, 133.0 (d, J_{CF} 4.7), 112.8, 110.5, 109.5 (d, J_{CF} 37.5), 53.56 (3H, s); *m*/*z* (EI) 204 (M^+, 68%), 203 (100, M^+–H). Anal. Calcd for $C_{11}H_9FN_2O$: C, 64.70; H, 4.44; N, 13.72. Found: C, 64.82; H, 4.50; N, 13.63; ν_{max} (film)/cm^{-1} 2957, 1607, 1579, 1494, 1463, 1434, 1372, 1329, 1291, 1245, 1165, 1029, 797, 685.

4.3.4. 5-(4-Methoxyphenyl)pyridin-2(1H)-one ***8***. To **5** (1.40 g, 6.89 mmol) was sequentially added 1,4-dioxane (26 mL) and KOH (1 M, 40 mL) and the resulting mixture was heated at reflux and judged complete by TLC (SiO_2, eluent 2:1 hexane:EtOAc, R_f=0) after 66 h. The mixture was cooled to room temperature and acidified to pH 6 with 4 M HCl. The precipitate was filtered and washed with hexane (2×50 mL), water (2×50 mL) and acetone (2×20 mL) followed by drying in vacuo yielding **8** as a white solid (1.145 g, 83%); mp: 191 °C (decomp.); δ_H (400 MHz, $CDCl_3$) 13.04 (1H, s), 7.72 (1H, dd, *J* 9.4, 2.6), 7.52 (1H, d, *J* 2.6), 7.32 (2H, d, *J* 8.7), 6.94 (2H, d, *J* 8.7), 6.66 (1H, d, *J* 9.4), 3.82 (3H, s); δ_C (176 MHz, DMSO-d_6) 161.6, 158.3, 140.0, 131.8, 128.6, 126.4, 119.9, 117.7, 114.3, 55.1; *m*/*z* (AP^+) 202 (M^++H, 100%), 201 (69, M^+). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.47; H, 5.89; N, 6.78; ν_{max} (film)/cm^{-1} 2843, 1738, 1657, 1622, 1514, 1468, 1283, 1244, 1183, 1037, 1020, 950, 881, 821.

4.3.5. 5-(Quinolin-3-yl)pyridin-2(1H)-one ***9***. To **6** (2.24 g, 10 mmol) was sequentially added 1,4-dioxane (26 mL) and KOH (1 M, 50 mL) and the resulting mixture was heated at reflux and judged complete by TLC (SiO_2, eluent 2:1 hexane:EtOAc, R_f=0) after 24 h. The mixture was cooled to room temperature and acidified to pH 6 with 4 M HCl. The precipitate was filtered and washed with hexane (2×50 mL), water (2×50 mL) and acetone (2×20 mL) followed by drying in vacuo yielding **9** as an off-white solid (1.95 g, 88%); mp: 290 °C (decomp.); δ_H (700 MHz, DMSO-d_6) 12.03 (1H, s), 9.17 (1H, d, *J* 2.3), 8.52 (1H, d, *J* 2.2), 8.06–7.99 (3H, m), 7.97 (1H, d, *J* 7.9), 7.73 (1H, t, *J* 7.6), 7.62 (1H, t, *J* 7.4), 6.52 (1H, d, *J* 9.5); δ_C (176 MHz, DMSO-d_6) 161.7, 148.5, 146.3, 139.9, 133.8, 130.7, 129.1 (2C), 128.6, 128.0, 127.6, 127.0, 120.4, 114.8; *m*/*z* (AP^+) 223 (M^++H). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 7.20. Found: C, 75.56; H, 4.53; N, 7.03; ν_{max} (film)/cm^{-1} 2823, 1659, 1618, 1590, 1435, 1316, 1297, 1258, 1122, 952, 866, 832, 784, 752, 672.

4.3.6. 5-(6-Methoxypyridin-2-yl)pyridin-2(1H)-one ***10***. To **7** (2.04 g, 10 mmol) was sequentially added 1,4-dioxane (26 mL) and KOH (1 M, 40 mL) and the resulting mixture was heated at reflux and judged complete by TLC (SiO_2, eluent 2:1 hexane:EtOAc, R_f=0) after 24 h. The mixture was cooled to room temperature and acidified to pH 6 with 4 M HCl. The precipitate was filtered and washed with hexane (2×50 mL), water (2×50 mL) and acetone (2×20 mL) followed by drying in vacuo yielding **10** as a white solid (1.85 g, 92%); mp: 277 °C (decomp.); δ_H (500 MHz, $CDCl_3$) 13.25 (1H, s), 8.24 (1H, d, *J* 2.2), 8.13 (1H, dd, *J* 9.5, 2.6), 7.58 (1H, dd, *J* 8.2, 7.5), 7.08 (1H, d, *J* 7.4), 6.68 (1H, d, *J* 9.5), 6.63 (1H, d, *J* 8.2), 3.96 (3H, s); δ_C (126 MHz, $CDCl_3$) 165.4, 164.0, 150.8, 140.2, 139.6, 133.8, 119.9, 119.7, 110.9, 109.5, 53.5; *m*/*z* (ES^+) 202 (M^++H, 100%). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.47; H, 5.04; N, 13.66; ν_{max} (film)/cm^{-1} 2842, 1666, 1576, 1466, 1433, 1327, 1263, 1123, 1077, 1029, 790, 745, 693.

4.3.7. 1-(5-(Trifluoromethyl)pyridin-2-yl)-5-(4-methoxyphenyl)pyridin-2(1H)-one ***12a***. In accordance with the general procedure for pyridone C–N cross-coupling, **8** (0.211 g, 1.05 mmol), 2-bromo-6-(trifluoromethyl)pyridine **11** (0.226 g, 1.00 mmol), CuI (0.038 g, 0.200 mmol), DMCDA (0.057 g, 0.400 mmol) and K_2CO_3 (0.276 g, 2.00 mmol) in toluene (6 mL) were reacted for 20 h. Standard work-up and column chromatography (SiO_2, eluent 1:1 EtOAc:hexane) yielded **12a** as a white solid (0.276 g, 80%); mp: 101.1–102.7 °C; δ_H (400 MHz, $CDCl_3$) 8.83 (1H, dd, *J* 1.6, 0.8), 8.26 (1H, d, *J* 8.6), 8.12 (1H, dd, *J* 2.7, 0.6), 8.07 (1H, dd, *J* 8.6, 2.4), 7.67 (1H, dd, *J* 9.5, 2.7), 7.39 (2H, d, *J* 8.9), 6.95 (2H, d, *J* 8.9), 6.72 (1H, dd, *J* 9.5, 0.7), 3.83 (4H, s); δ_C (176 MHz, $CDCl_3$) 161.6, 159.6, 154.5, 146.1 (q, J_{CF} 4.1), 141.0, 135.3 (q, J_{CF} 3.2), 131.7 (d, J_{CF} 14.6), 128.8, 127.3, 126.0 (q, J_{CF} 33.6), 123.4 (q, J_{CF} 272.4), 122.4, 121.4, 120.9, 114.7, 55.6; *m*/*z* (AP^+) 347.1006 (M^++H, $C_{18}H_{13}F_3N_2O_2$ requires 347.1007); ν_{max} (film)/cm^{-1} 3056, 2801, 1659, 1600, 1587, 1269, 1248, 1297, 1156, 1001, 809.

4.3.8. 1,5-Bis(4-methoxyphenyl)pyridin-2(1H)-one ***13***. In accordance with the general procedure for pyridone C–N cross-coupling, **8** (0.211 g, 1.05 mmol), 4-bromoanisole **2** (0.187 g, 1.00 mmol), CuI (0.019 g, 0.100 mmol), DMCDA (0.029 g, 0.200 mmol) and K_2CO_3 (0.276 g, 2.00 mmol) in toluene (3 mL) were reacted for 20 h. Standard work-up and column chromatography (SiO_2, eluent EtOAc) yielded **13** as a white solid, which was recrystallised from hexane/DCM (0.251 g, 82%); mp: 147.0–148.2 °C; δ_H (400 MHz, $CDCl_3$) 7.64 (1H, dd, *J* 9.5, 2.7), 7.46 (1H, d, *J* 2.7), 7.33 (4H, dd, *J* 8.7, 1.5), 6.99 (2H, d, *J* 8.9), 6.92 (2H, d, *J* 8.7), 6.71 (1H, d, *J* 9.5), 3.83 (3H, s), 3.81 (3H, s); δ_C (176 MHz, $CDCl_3$) 162.1, 159.7, 159.4, 139.9, 135.0, 134.2, 129.0 (2C), 127.9 (2C), 127.2, 121.8, 120.0, 114.8 (2C), 114.7 (2C), 55.8, 55.6; *m*/*z* (EI) 307 (M^+, 100%). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.34; H, 5.60; N, 4.49; ν_{max} (film)/cm^{-1} 3058, 2834, 1662, 1610, 1598, 1514, 1275, 1249, 1180, 1026, 818. *Crystal data*: $C_{19}H_{17}NO_3$, *M*=307.34, *T*=120 K, monoclinic, space group $P2_1/c$ (no. 14), *a*=10.6471(4), *b*=12.5157(5), *c*=11.4966(4) Å, β=93.900(8)°, *V*=1528.4(1) Å^3, *Z*=4, *R*(*F*)=0.049 on 3602 data with $I \geq 2\sigma(I)$, CCDC 767480.

4.3.9. 1-(5-Fluoropyridin-2-yl)-5-(4-methoxyphenyl)pyridin-2(1H)-one ***14***. In accordance with the general procedure for pyridone C–N cross-coupling, **8** (0.423 g, 2.10 mmol), 2-bromo-5-fluoropyridine **23** (0.352 g, 2.00 mmol), CuI (0.038 g, 0.200 mmol), DMCDA (0.057 g, 0.400 mmol) and K_2CO_3 (0.553 g, 4.00 mmol) in toluene (6 mL) were reacted for 20 h. Standard work-up and column chromatography (SiO_2, eluent EtOAc) yielded **14** as a white solid (0.533 g, 77%); mp: 140.9–142.2 °C; δ_H (500 MHz, $CDCl_3$) 8.40 (1H, d, *J* 2.6), 8.01 (1H, dd, *J* 8.9, 4.0), 7.98 (1H, dd, *J* 2.7, 0.6), 7.66 (1H, dd, *J* 9.5, 2.7), 7.56 (1H, ddd, *J* 8.9, 7.5, 3.0), 7.38 (2H, d, *J* 8.9), 6.94 (2H, d, *J* 8.8), 6.71 (1H, dd, *J* 9.5, 0.6), 3.82 (3H, s); δ_C (126 MHz, $CDCl_3$) 161.6, 159.4, 158.8 (d, J_{CF} 257.1), 148.0 (d, J_{CF} 2.9), 140.8, 136.9 (d, J_{CF} 25.8), 132.6, 129.0, 127.3 (2C), 125.0 (d, J_{CF} 19.8), 122.9 (d, J_{CF} 5.0), 122.2, 120.7, 114.7 (2C), 55.6; *m*/*z* (EI) 296 (M^+, 100%). Anal. Calcd for $C_{17}H_{13}FN_2O_2$: C, 68.91; H, 4.42; N, 9.45. Found: C, 69.07; H, 4.39; N, 9.21; ν_{max} (film)/cm^{-1} 3076, 2940, 2834, 1674, 1619, 1514, 1473, 1394, 1286, 1248, 1184, 1024, 819.

4.3.10. 5-(4-Methoxyphenyl)-1-(5-nitropyridin-2-yl)pyridin-2(1H)-one ***15***. In accordance with the general procedure for pyridone C–N

cross-coupling, **8** (0.211 g, 1.05 mmol), 2-bromo-5-nitropyridine **24** (0.203 g, 1.00 mmol), CuI (0.019 g, 0.100 mmol), DMCDA (0.028 g, 0.200 mmol) and K_2CO_3 (0.276 g, 2.00 mmol) in toluene (2 mL) were reacted for 20 h. Standard work-up and column chromatography (SiO_2, eluent 1:1 hexane:EtOAc) yielded **15** as a yellow solid, which was precipitated from EtOAc (0.268 g, 83%); mp: 184.9–185.5 °C; δ_H (400 MHz, $CDCl_3$) 9.38 (1H, dd, *J* 2.7, 0.6), 8.60 (1H, dd, *J* 9.0, 2.7), 8.44 (1H, dd, *J* 9.0, 0.6), 8.22 (1H, dd, *J* 2.6, 0.6), 7.68 (1H, dd, *J* 9.5, 2.6), 7.40 (2H, d, *J* 8.9), 6.96 (2H, d, *J* 8.9), 6.73 (1H, dd, *J* 9.5, 0.6), 3.84 (3H, d, *J* 3.7); δ_C (126 MHz, $CDCl_3$) 161.6, 159.7, 155.6, 149.1, 144.7, 141.3, 133.3, 131.1, 128.61, 127.4, 122.6, 121.4, 121.3, 114.8, 55.6; *m*/*z* (AP^+) 323 (M^+, 100%). Anal. Calcd for $C_{17}H_{13}N_3O_4$: C, 68.16; H, 4.05; N, 13.00. Found: C, 68.06; H, 4.19; N, 12.70; ν_{max} (film)/cm^{-1} 3073, 2839, 1680, 1610, 1576, 1513, 1464, 1393, 1348, 1298, 1248, 1230, 1191, 1142, 1119, 1038, 1019, 858, 814, 770.

4.3.11. 1-(4-Methoxyphenyl)-5-(quinolin-3-yl)pyridin-2(1H)-one ***16****.* In accordance with the general procedure for pyridone C–N cross-coupling, **9** (0.355 g, 1.60 mmol), 4-bromoanisole **2** (0.285 g, 1.52 mmol), CuI (0.058 g, 0.304 mmol), DMCDA (0.087 g, 0.609 mmol) and K_2CO_3 (0.421 g, 3.04 mmol) in toluene (4.5 mL) were reacted for 72 h. Standard work-up and precipitation from EtOAc yielded **16** as an off-white solid (0.328 g, 66%); mp: 179.8–181.2 °C; δ_H (500 MHz, $CDCl_3$) 9.05 (1H, d, *J* 2.3), 8.19 (1H, d, *J* 2.3), 8.15 (1H, d, *J* 8.1), 7.87 (1H, d, *J* 7.8), 7.83 (1H, dd, *J* 9.5, 2.8), 7.79–7.72 (2H, m), 7.61 (1H, ddd, *J* 8.0, 7.0, 0.9), 7.41 (2H, d, *J* 9.0), 7.06 (2H, d, *J* 9.0), 6.86 (1H, dd, *J* 9.5, 0.6), 3.89 (3H, s); δ_C (126 MHz, $CDCl_3$) 162.1, 159.9, 148.6, 147.5, 146.4, 141.1, 139.5, 136.5, 133.8, 132.0, 129.8, 129.5, 128.0, 127.9 (2C), 127.6, 122.6, 117.0, 115.0 (2C), 55.8; *m*/*z* (EI) 328 (M^+, 100%). Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 77.08; H, 4.99; N, 8.32; ν_{max} (film)/cm^{-1} 3061, 2830, 1650, 1613, 1587, 1510, 1282, 1247, 1175, 1020, 809.

4.3.12. 1-(5-(Trifluoromethyl)pyridin-2-yl)-5-(quinolin-3-yl)pyridin-2(1H)-one ***17a*** *and 3-(6-(5-(trifluoromethyl)pyridin-2-yloxy)pyridin-3-yl)quinoline* ***17b****.* In accordance with the general procedure for pyridone C–N cross-coupling, **9** (0.233 g, 1.05 mmol), 2-bromo-5-(trifluoromethyl)pyridine **11** (0.226 g, 1.00 mmol), CuI (0.038 g, 0.200 mmol), DMCDA (0.057 g, 0.400 mmol) and K_2CO_3 (0.276 g, 2.00 mmol) in toluene (3 mL) were reacted for 48 h. Standard work-up and column chromatography (SiO_2, eluent 4:1 EtOAc:hexane) yielded **17a** as a white solid (0.264 g, 72%) followed by **17b** as a white solid (0.017 g, 5%).

Compound **17a** mp: 156.0–157.8 °C; δ_H (700 MHz, $CDCl_3$) 9.04 (1H, d, *J* 2.3), 8.37 (1H, d, *J* 2.6), 8.28 (1H, d, *J* 8.6), 8.19 (1H, d, *J* 2.0), 8.13–8.04 (2H, m), 7.83 (1H, d, *J* 8.1), 7.79 (1H, dd, *J* 9.5, 2.7), 7.71 (1H, ddd, *J* 8.3, 6.9, 1.3), 7.61–7.54 (1H, m), 6.81 (1H, d, *J* 9.5); *m*/*z* (EI) 367 (M^+, 100%); δ_C (176 MHz, $CDCl_3$) 161.4, 154.1, 148.5, 147.6, 146.2 (q, J_{CF} 4.1), 140.3, 135.5 (q, J_{CF} 3.2), 133.3, 132.3, 129.9, 129.5, 129.2, 127.98, 127.95, 127.6, 126.4 (q, J_{CF} 33.6), 123.3 (q, J_{CF} 272.4), 123.2, 121.3, 118.0; *m*/z (AP^+) 367 (M^+, 100%). Anal. Calcd for $C_{20}H_{12}F_3N_3O$: C, 65.40; H, 3.29; N, 11.44. Found: C, 65.73; H, 3.50; N, 11.42; ν_{max} (film)/cm^{-1} 3033, 2858, 1609, 1583, 1299, 1280, 1235, 1177, 1016.

Compound **17b** mp: 127.8–128.3 °C; δ_H (700 MHz, $CDCl_3$) 9.13 (1H, d, *J* 2.2), 8.65 (1H, d, *J* 2.2), 8.54 (1H, s), 8.30 (1H, s), 8.14 (1H, d, *J* 8.7), 8.13 (1H, dd, *J* 8.4, 2.6), 8.00 (1H, dd, *J* 8.6, 2.2), 7.89 (1H, d, *J* 8.1), 7.75 (1H, t, *J* 7.5), 7.60 (1H, t, *J* 7.5), 7.28 (1H, d, *J* 8.4), 7.23 (1H, d, *J* 8.6); δ_C (176 MHz, $CDCl_3$) 164.4, 161.0, 149.33, 147.9, 147.0, 145.9 (q, J_{CF} 4.3), 138.9, 137.3 (q, J_{CF} 3.2), 133.7, 131.4, 130.2, 130.1, 129.6, 128.2, 128.0, 127.6, 123.7 (q, J_{CF} 271.7), 123.3 (q, J_{CF} 33.4), 115.2, 113.7. Anal. Calcd for $C_{20}H_{12}F_3N_3O$: C, 65.40; H, 3.29; N, 11.44. Found: C, 65.48; H, 3.20; N, 11.09; ν_{max} (film)/cm^{-1} 3023, 2836, 1628, 1555, 1304, 1281, 1257, 1220, 1183, 1002.

4.3.13. 1-(6-Methoxypyridin-2-yl)-5-(quinolin-3-yl)pyridin-2(1H)-one ***18****.* In accordance with the general procedure for pyridone C–N cross-coupling, **9** (0.233 g, 1.05 mmol), 2-bromo-6-methoxypyridine **4** (0.188 g, 1.00 mmol), CuI (0.038 g, 0.200 mmol), DMCDA (0.057 g, 0.400 mmol) and K_2CO_3 (0.276 g, 2.00 mmol) in toluene (6 mL) were reacted for 20 h. Standard work-up and column chromatography (SiO_2, eluent EtOAc) yielded **18** as a white solid (0.230 g, 70%); mp: 187 °C (decomp.); δ_H (700 MHz, $CDCl_3$) 9.07 (1H, d, *J* 2.3), 8.28 (1H, d, *J* 2.6), 8.19 (1H d, *J* 2.2), 8.11 (1H, d, *J* 8.5), 7.84 (1H, d, *J* 8.0), 7.77 (1H, dd, *J* 9.5, 2.7), 7.76–7.73 (1H, m), 7.71 (1H, ddd, *J* 8.3, 6.9, 1.4), 7.62–7.53 (2H, m), 6.85–6.76 (2H, m), 3.94 (3H, s); δ_C (176 MHz, $CDCl_3$) 164.1, 161.6, 148.9, 148.7, 147.5, 140.5, 139.5, 134.2, 132.1, 129.8, 129.7, 129.6, 128.1, 128.0, 127.6, 123.1, 117.1, 113.7, 110.6, 54.0; *m*/*z* (AP^+) 330.1252 (M^++H, $C_{20}H_{15}N_3O_2$ requires 330.1243); ν_{max} (film)/cm^{-1} 2983, 2892, 1680, 1620, 1574, 1470, 1434, 1414, 1321, 1286, 1249, 1215, 1148, 1073, 918, 821, 739.

4.3.14. 1-(4-Methoxyphenyl)-5-(6-methoxypyridin-2-yl)pyridin-2(1H)-one ***19****.* In accordance with the general procedure for pyridone C–N cross-coupling, **10** (0.302 g, 1.49 mmol), 4-bromoanisole **2** (0.266 g, 1.42 mmol), CuI (0.054 g, 0.285 mmol), DMCDA (0.081 g, 0.569 mmol) and K_2CO_3 (0.393 g, 2.85 mmol) in toluene (4.5 mL) were reacted for 72 h. Standard work-up and column chromatography (SiO_2, eluent EtOAc) yielded **19** as a white solid (0.326 g, 74%); mp: 62.9–64.0 °C; δ_H (500 MHz, $CDCl_3$) 8.13 (1H, d, *J* 2.5), 8.02 (1H, dd, *J* 9.6, 2.6), 7.57 (1H, dd, *J* 8.1, 7.6), 7.34 (2H, d, *J* 8.9), 7.07 (1H, d, *J* 7.4), 7.00 (2H, d, *J* 8.9), 6.71 (1H, d, *J* 9.6), 6.62 (1H, d, *J* 8.2), 3.92 (3H, s), 3.84 (3H, s); δ_C (126 MHz, $CDCl_3$) 164.0, 162.7, 159.8, 151.0, 139.7, 138.5, 137.5, 134.1, 127.9 (2C), 121.3, 118.5, 114.9 (2C), 111.1, 109.2, 55.8, 53.5; *m*/*z* (EI) 308 (M^+, 100%). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.27; H, 5.39; N, 9.34; ν_{max} (film)/cm^{-1} 3010, 2949, 1736, 1664, 1588, 1575, 1506, 1409, 1314, 1244, 1124, 1023, 901, 830, 799.

4.3.15. 1-(5-Bromopyrimidin-2-yl)-5-(6-methoxypyridin-2-yl)pyridin-2(1H)-one ***20****.* In accordance with the general procedure for pyridone C–N cross-coupling, **10** (0.202 g, 1.000 mmol), 5-bromo-2-iodopyrimidine **25** (0.313 g, 1.10 mmol), CuI (0.042 g, 0.220 mmol), DMCDA (0.063 g, 0.440 mmol) and K_2CO_3 (0.304 g, 2.22 mmol) in toluene (4 mL) were reacted for 28 h. Standard work-up and column chromatography (SiO_2, eluent 1:1 hexane:EtOAc) yielded **20** as an off-white solid (0.203 g, 51%); mp: 172.3–173.9 °C; δ_H (400 MHz, $CDCl_3$) 9.06 (1H, s), 8.38 (1H, d, *J* 2.6), 8.06 (1H, ddd, *J* 9.7, 2.6, 1.7), 7.58 (1H, td, *J* 7.4, 3.7), 7.10 (1H, ddd, *J* 7.4, 1.0, 0.6), 6.73 (1H, ddd, *J* 9.7, 1.7, 0.7), 6.64 (1H, dt, *J* 8.2, 0.7), 3.94 (3H, s); δ_C (126 MHz, $CDCl_3$) 164.8, 164.0, 161.6, 161.6, 160.0, 150.5, 139.6, 139.2, 134.4, 122.3, 118.9, 111.2, 109.6, 53.5; *m*/*z* (EI) 359 (M^+, 60%), 279 (100, M^+–Br). Anal. Calcd for $C_{15}H_{11}BrN_4O_2$: C, 50.16; H, 3.09; N, 15.60. Found: C, 50.44; H, 3.30; N, 15.37; ν_{max} (film)/cm^{-1} 2937, 2899, 1707, 1645, 1573, 1549, 1509, 1387, 1234, 1100, 1094, 1006, 914, 824.

4.3.16. 1-(5-Aminopyrazin-2-yl)-5-(6-methoxypyridin-2-yl)pyridin-2(1H)-one ***21****.* In accordance with the general procedure for pyridone C–N cross-coupling, **10** (0.425 g, 2.10 mmol), 2-amino-5-bromopyrazine **26** (0.348 g, 2 mmol), CuI (0.076 g, 0.400 mmol), DMCDA (0.114 g, 0.800 mmol) and K_2CO_3 (0.553 g, 4.00 mmol) in toluene (6 mL) were reacted for 42 h. The reaction mixture was quenched by stirring in saturated ammonium chloride solution (50 mL) for 1 h then the organic component was extracted into EtOAc (3×250 mL) and washed with brine (2×50 mL). After drying over Na_2SO_4, filtration, concentration and a precipitation from EtOAc, the yellow solid was purified twice consecutively by column chromatography (SiO_2, eluent 20:1 EtOAc:MeOH & SiO_2, eluent 20:1 DCM:MeOH) yielding **21** as a yellow solid (0.238 g, 40%); mp: 169 °C

(decomp.); δ_H (500 MHz, DMSO-d_6) 8.48 (1H, d, J 2.4), 8.28–8.24 (2H, m), 7.85 (1H, d, J 1.3), 7.72 (1H, t, J 7.8), 7.43 (1H, d, J 7.5), 6.81 (2H, br s), 6.70 (1H, d, J 8.1), 6.61 (1H, d, J 9.6), 3.88 (3H, s); δ_C (126 MHz, DMSO-d_6) 163.1, 161.0, 155.6, 150.3, 140.3, 140.1, 138.8, 137.5, 136.3, 129.8, 120.1, 117.2, 111.4, 108.6, 52.9; m/z (AP^+) 295 (M^+, 100%), 296 (69, M^++H). Anal. Calcd for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 61.33; H, 4.60; N, 23.65; ν_{max} (film)/cm^{-1} 3333, 3174, 1666, 1577, 1538, 1465, 1398, 1331, 1269, 1156, 1125, 1013, 826, 788.

4.3.17. 5-(6-Methoxypyridin-2-yl)-1-(5-nitrothiophen-2-yl)pyridin-2(1H)-one ***22****.* In accordance with the general procedure for pyridone C–N cross-coupling, **10** (0.212 g, 1.05 mmol), 2-bromo-5-nitrothiophene **27** (0.208 g, 1.00 mmol), CuI (0.038 g, 0.200 mmol), DMCDA (0.057 g, 0.400 mmol) and K_2CO_3 (0.276 g, 2.00 mmol) in toluene (6 mL) were reacted for 20 h. Standard work-up and column chromatography (SiO_2, eluent 3:2 hexane:EtOAc) yielded **22** as a yellow solid (0.196 g, 60%); mp: 227 °C (decomp.); δ_H (400 MHz, DMSO-d_6) 8.93 (1H, d, J 2.1), 8.38 (1H, dd, J 9.6, 2.3), 8.21 (1H, d, J 5.0), 7.94 (1H, d, J 5.1), 7.87–7.76 (1H, m), 7.70 (1H, d, J 7.4), 6.90 (1H, d, J 9.6), 6.79 (1H, d, J 8.1), 3.96 (3H, s); δ_C (126 MHz, $CDCl_3$) 164.2, 162.9, 160.2, 149.2, 144.3, 139.9, 138.3, 130.4, 126.1, 121.5, 121.4, 114.4, 111.8, 110.6, 53.6; m/z (AP^+) 329 (M^+ 66%), 330 (100, M^++H). Anal. Calcd for $C_{15}H_{11}N_3O_4S$: C, 54.71; H, 3.37; N, 12.76. Found: C, 55.00; H, 3.56; N, 12.40; ν_{max} (film)/cm^{-1} 2924, 2848, 1667, 1611, 1575, 1542, 1494, 1460, 1425, 1334, 1284, 1258, 1017, 800, 701.

4.3.18. 2,6-Di(5-(4-methoxyphenyl)-2-oxopyridin-1(2H)-yl)pyridine ***29****.* In accordance with the general procedure for pyridone C–N cross-coupling, **8** (0.460 g, 2.28 mmol), 2,6-dibromopyridine **28** (0.246 g, 1.04 mmol), CuI (0.079 g, 0.415 mmol), DMCDA (0.118 g, 0.830 mmol) and K_2CO_3 (0.574 g, 4.15 mmol) in toluene (12 mL) were reacted for 88 h. Standard work-up and column chromatography (SiO_2, eluent 19:1 EtOAc:Et_3N) yielded **29** as a white solid, which was recrystallised from hot EtOAc/hexane (0.340 g, 69%); mp: 229.9–231.1 °C; δ_H (700 MHz, $CDCl_3$) 8.06–7.98 (3H, m), 7.96 (2H, d, J 2.5), 7.68 (2H, dd, J 9.5, 2.7), 7.35 (4H, d, J 8.8), 6.92 (4H, d, J 8.8), 6.74 (2H, d, J 9.5), 3.80 (6H, s); δ_C (176 MHz, $CDCl_3$) 161.5, 159.5, 151.3, 140.8, 139.8, 132.5, 128.8, 127.3, 122.2, 121.1, 120.7, 114.7, 55.5; m/z (AP^+) 478 (M^+, 100%). Anal. Calcd for $C_{29}H_{23}FN_3O_4$: C, 72.94; H, 4.85; N, 8.80. Found: C, 73.02; H, 4.5.13; N, 8.69; ν_{max} (film)/cm^{-1} 2959, 1683, 1610, 1516, 1436, 1295, 1246, 1205, 1181, 1025, 821, 798. *Crystal data*: $C_{29}H_{23}N_3O_4$, M=477.50, T=120 K, orthorhombic, space group *Pbca* (no. 61), a=22.0189(6), b=7.5416(2), c=26.8158(9) Å, V=4453.0 (2) Å^3, Z=8, $R(F)$=0.040 on 4292 data with $I \geq 2\sigma(I)$, CCDC 767481.

4.3.19. 2,6-Difluoro-3-(4-methoxyphenyl)pyridine ***32****.* In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted (2,6-difluoro-3-pyridyl)boronic acid **30** (0.953 g, 6 mmol), 4-bromoanisole **2** (0.935 g, 5 mmol), Pd(PPh_3)$_2Cl_2$ (0.175 g, 0.25 mmol) and Na_2CO_3 (15 mL, 15 mmol, 1 M in water) in 1,4-dioxane (40 mL) at reflux for 1 h. Standard work-up and concentration followed by column chromatography (SiO_2, eluent 1:3 EtOAc:hexane) yielded **32** as a white solid (0.839 g, 76%); mp: 33.4–34.9 °C; δ_H (700 MHz, DMSO-d_6) 8.18 (1H, dd, J 17.9, 8.0), 7.48 (2H, dd, J 8.6, 1.2), 7.14 (1H, dd, J 8.1, 2.6), 7.02 (2H, d, J 8.8), 3.80 (3H, s); δ_C (176 MHz, DMSO-d_6) 157.8, 157.6 (dd, J_{CF} 243.2, 13.9), 155.3 (dd, J_{CF} 245.4, 14.5), 144.0, 128.2, 122.9 (d, J_{CF} 4.8), 118.3 (dd, J_{CF} 25.4, 5.8), 112.5, 105.3 (dd, J_{CF} 40.1, 9.3), 53.5; m/z (EI) 221 (M^+, 100%). Anal. Calcd for $C_{12}H_9F_2NO$: C, 65.16; H, 4.10; N, 6.33. Found: C, 65.05; H, 4.11; N, 6.20; (film)/cm^{-1} 3095, 1642, 1602, 1589, 1511, 1370, 1245, 1176, 1053, 1004, 995, 831, 780.

4.3.20. 2-(2,6-Difluoropyridin-3-yl)-3-aminopyridine ***33****.* In accordance with the general method for Suzuki-Miyaura cross-coupling reactions outlined above was reacted (2,6-difluoro-3-pyridyl)boronic acid **30** (1.50 g, 9.44 mmol), 3-amino-2-bromopyridine **31** (1.09 g, 6.29 mmol), $Pd_2(dba)_3$ (0.144 g, 0.157 mmol), PCy_3 (0.088 g, 0.315 mmol) and Na_2CO_3 (18.9 mL, 18.9 mmol, 1 M in water) in 1,4-dioxane (45 mL) at reflux for 22 h. Standard work-up and concentration followed by column chromatography (SiO_2, eluent 2:1 EtOAc:hexane) yielded **33** as a white solid (1.09 g, 83%); mp: 156.9–157.7 °C; δ_H (400 MHz, DMSO-d_6) 8.16 (1H, dt, J 9.5, 8.1), 7.86 (1H, dd, J 4.2, 1.8), 7.25 (1H, ddd, J 8.1, 2.5, 0.8), 7.18–7.03 (2H, m), 5.25 (2H, s); δ_C (126 MHz, DMSO-d_6) 160.0 (dd, J_{CF} 243.0, 14.0), 157.7 (dd, J_{CF} 245.4, 14.6), 147.8 (dd, J_{CF} 8.0, 5.1), 143.2, 137.2, 135.8 (d, J_{CF} 4.1), 124.3, 121.8, 118.7 (dd, J_{CF} 28.7, 5.6), 106.8 (dd, J_{CF} 34.6, 5.3); m/z (AP^+) 208 (M^++H, 100%). Anal. Calcd for $C_{10}H_7F_2N_3$: C, 57.97; H, 3.41; N, 20.28. Found: C, 58.31; H, 3.77; N, 20.08; ν_{max} (film)/cm^{-1} 3384, 3308, 3201, 1640, 1602, 1587, 1478, 1458, 1444, 1402, 1307, 1274, 1254, 1226, 1211, 1106, 1023, 997, 972, 846, 834, 804, 736.

4.3.21. 6-Fluoro-5-(4-methoxyphenyl)pyridin-2(1H)-one ***35a*** *and 6-fluoro-3-(4-methoxyphenyl)pyridin-2(1H)-one* ***35b****.* To **32** (0.481 g, 2.17 mmol) was sequentially added 1,4-dioxane (4 mL) and KOH (1 M, 11 mL) and the resulting mixture was heated at reflux and judged complete by TLC (SiO_2, eluent 2:1 hexane:EtOAc, R_f=0.33, 0.29) after 16 h. The mixture was cooled to room temperature and acidified to pH 6 with 4 M HCl. The mixture was extracted into EtOAc, dried over Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography (SiO_2, eluent 2:1 hexane:EtOAc) to give a pure mixture of **35a** and **35b** as a white solid (0.383 g, 80%). The mixture was separated by column chromatography (SiO_2, eluent 3:1 hexane:EtOAc) followed by preparative TLC (SiO_2, eluent 3:1 hexane:EtOAc) giving **35b** as a white solid, which was recrystallised from hexane (0.036 g, 8%). Further column chromatography provided **35a** as a white solid, which was recrystallised from hexane (0.046 g, 10%).

Compound **35a** mp: 195 °C (decomp.); δ_H (400 MHz, $CDCl_3$) 7.80 (4H, dd, J 10.1, 8.2), 7.42 (9H, dd, J 8.9, 1.5), 6.96 (9H, d, J 8.9), 6.72 (4H, dd, J 8.2, 0.9), 3.84 (15H, s); δ_C (176 MHz, DMSO-d_6) 161.4 (d, J 15.7), 158.6, 157.7 (d, J 238.1), 143.4 (d, J 4.6), 129.4 (d, J 3.0), 126.0 (d, J 5.1), 114.1, 112.4 (d, J 27.0), 106.9 (d, J 4.8), 55.1; m/z (AP^+) 220 (M^++H, 100%). Anal. Calcd for $C_{12}H_{10}FNO_2$: C, 65.75; H, 4.60; N, 6.39. Found: C, 65.70; H, 4.60; N, 6.41; ν_{max} (film)/cm^{-1} 2936, 1613, 1591, 1509, 1448, 1390, 1290, 1200, 1192, 1104, 1003, 855, 817, 760, 707.

Compound **35b** mp: 200 °C (decomp.); δ_H (700 MHz, $CDCl_3$) 10.32 (1H, s), 7.73 (1H, t, J 8.0), 7.53 (2H, d, J 8.9), 6.97 (2H, d, J 8.8), 6.53 (1H, dd, J 8.0, 1.7), 3.84 (3H, s); δ_C (126 MHz, $CDCl_3$) 160.5 (d, J 244.7), 159.4, 159.4 (d, J 11.2), 143.9 (d, J 8.1), 130.3, 127.8, 120.3 (d, J 5.3), 114.2, 100.4 (d, J 32.3), 55.6; m/z (AP^+) 220 (M^++H, 100%). Anal. Calcd for $C_{12}H_{10}FNO_2$: C, 65.75; H, 4.60; N, 6.39. Found: C, 65.89; H, 4.87; N, 6.23; ν_{max} (film)/cm^{-1} 2927, 1613, 1590, 1516, 1448, 1379, 1285, 1253, 1217, 1178, 1100, 1034, 1019, 841, 806, 773, 742. *Crystal data*: $C_{12}H_{10}FNO_2$, M=219.21, T=120 K, triclinic, space group $P\bar{1}$ (no. 2), a=5.9326(6), b=9.2981(9), c=9.5566(10) Å, α=90.95(1), β=97.56(1), γ=104.41(1)°, V=505.5(1) Å^3, Z=2, $R(F)$=0.041 on 1656 data with $I \geq 2\sigma(I)$, CCDC 767482.

4.3.22. 6-Fluoropyridin-2(1H)-one ***36****.* To 2,6-difluoropyridine **34** (2.24 g, 10 mmol) was sequentially added 1,4-dioxane (26 mL) and KOH (6 M, 50 mL) and the resulting mixture was heated at reflux and judged complete by TLC (SiO_2, eluent EtOAc, R_f=0) after 114 h. The mixture was cooled to room temperature, concentrated in vacuo and acidified to pH 6 with 4 M HCl. After extraction into DCM (2×200 mL) and washing with brine (2×50 mL) the organic layer was dried over Na_2SO_4, filtered and concentrated. The resulting residue was recrystallised from a mixture of DCM and hexane yielding **36** as white needles (0.703 g, 62%); mp: 127.2–128.2 °C; δ_H (400 MHz, $CDCl_3$) 11.87 (1H, s), 7.71 (1H, dd, J 16.2, 8.1), 6.73–6.53 (1H, m), 6.53–6.35 (1H, m); δ_C (101 MHz, $CDCl_3$) 163.7 (d, J_{CF} 11.7), 161.8 (d, J_{CF} 245.7), 144.6 (d, J_{CF} 8.7), 107.4 (d, J_{CF} 5.0), 99.5 (d, J_{CF} 31.6); m/z (AP^+) 114 (M^++H, 100%), 113 (35, M^+). Anal. Calcd for C_5H_4FNO:

C, 53.10; H, 3.57; N, 16.80. Found: C, 52.86; H, 3.39; N, 17.11; ν_{max} (film)/cm^{-1} 3320, 2696, 1632, 1596, 1574, 1486, 1456, 1344, 1242, 1143, 1070, 1017, 996, 787, 744, 723. *Crystal data*: C_5H_4FNO, M=113.09, T=120 K, monoclinic, space group $P2_1/n$ (no. 14), a=16.023(1), b=3.6830(2), c=16.910(1) Å, β=103.41(1)°, V=970.7 (1) Å^3, Z=8, $R(F)$=0.038 on 2279 data with $I \geq 2\sigma(I)$, CCDC 767483.

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Supplementary data

Supplementary data for this article can be found in the online version, at doi:10.1016/j.tet.2010.05.108.

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