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N-Arylation of nitrogen heterocycles with 2,4-difluoroiodobenzene

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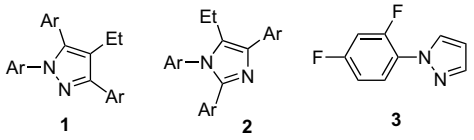
ABSTRACT

Arylation reactions of NH-heterocycles [specifically, pyrazole, 3-(trifluoromethyl)pyrazole, imidazole and pyrrole] with 2,4-difluoroiodobenzene in the absence and presence of copper catalysis are described. The combination of fluoro and iodo substituents in the same aryl substrate has facilitated both S_NAr reactions at the C–F bonds and copper-catalysed Ullmann-type coupling reactions at the C–I bond. Products arising from regioselective reactions and multiple substitutions have been isolated, providing a range of new *N*-arylated pyrazole, imidazole and pyrrole derivatives.

1. Introduction

Arylated nitrogen heterocycles are common motifs in biological and pharmaceutical science.[1] For example, a range of arylpyrazole[2] and arylimidazole derivatives[3] have promising medicinal properties; specifically, compounds **1** and **2** have been studied recently for their gene-activating properties on estrogen receptor alpha positive MCF-7 breast cancer cells.[2a] Arylazoles are also valuable building blocks in materials science due to their fluorescence properties, for example, pyrazole derivative **3** (which was a target that inspired the present study) is a ligand for blue-emitting iridium complexes.[4] There is, therefore, broad interest in developing methods for the synthesis and modification of such compounds.



Aryl substrates which possess both fluoro and iodo substituents offer unique scope for both S_NAr reactions at the C–F bond(s) and Ullmann-type coupling reactions at the C–I bond(s)—a scenario that has not been widely explored. S_NAr reactions where the nucleophile is an *N*-heteroatom generally require activated aryl halides (halogen=F or Cl) electron-withdrawing substituents and/or quite forcing reaction conditions.[5] The copper-promoted Ullmann reaction is most efficient for aryl iodides. The scope of this reaction has recently been enhanced by the addition of ligands, such as diamines,[6] pipecolinic acid,[7] sterically-hindered phosphines,[8] a mixture of 1,10-phenanthroline and dibenzylideneacetone,[9] 4,7-dimethoxy-1,10-phenanthroline,[10] (*S*)-pyrrolidinylmethylimidazole,[11] *N*-hydroxyimides,[12] ninhydrin,[13] benzotriazole,[14] D-glucosamine,[15] hippuric acid[16] and (−)-sparteine.[17] Arylbromides and electron-deficient arylchlorides can also be substrates under these conditions,[16] although high selectivity in favour of displacement of iodide is generally observed, e.g., for 4-bromo-iodobenzene.[6d] You et al. have shown that imidazoles can be *N*-arylated with aryl halides in the presence of base and a catalytic amount of CuI: the imidazole substrate may also function as a ligand in this process.[18] The CuOAc-mediated N-arylation of indoles and carbazole with aryl iodides under base-free and ligandless conditions has been developed.[19] These metal-catalysed processes have recently been extended to N-heteroarylations to obtain bi(heteroaryl) systems.[20]

Herein, we explore the reactions of NH-heterocycles (viz. pyrazoles, imidazole and pyrrole) with 2,4-difluoroiodobenzene **4** in the absence and presence of copper catalysis. The rationale was that the C–I bond should readily participate in Ullmann-type coupling reactions, whereas the C–F bonds would activate the system to S_NAr reactions. Using 2,4-difluoroiodobenzene **4** as a substrate also enabled the regioselectivity of the S_NAr processes to be explored.[21] It was also of interest to see if a second S_NAr reaction would occur on the initial S_NAr products, which would be deactivated by the electron-donating *N*-heteroaryl substituent. To our knowledge,

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reactions of 2,4-difluoroiodobenzene **4** have not been studied previously in this context.

2. Results and discussion

We initially studied the S_NAr reactions of **4** with pyrazole, 3-(trifluoromethyl)pyrazole, imidazole and pyrrole under basic conditions using 1.5 equiv of the heterocycle. The results are shown in Table 1.

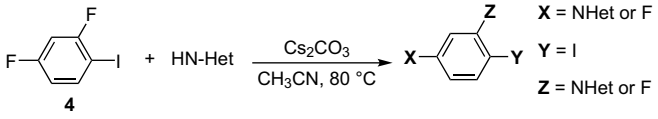
Under these conditions all the reactions (entries 1–4, conditions b) yielded mixtures of products, which were generally straightforward to separate by column chromatography. In all cases the S_NAr reaction occurred preferentially at C-2 rather than C-4 (based on both ^1H NMR analysis of the crude mixtures and the relative yields of purified isomers). It is interesting to note that the di(pyrazolyl) product **7** was also isolated in 22% yield (entry 1) whereas analogous disubstituted products were not observed with the less nucleophilic reagents (entries 2–4). The electron-withdrawing effect of the trifluoromethyl group reducing the nucleophilicity of the pyrazole nitrogen accounts for the lack of disubstituted product in entry 2. Using 3.0 equiv of pyrazole increased the yield of **7** to 56%. Using 1.0 equiv of pyrazole raised the yield of **5** to 50%. ^{19}F NMR spectra were especially useful in assigning the regiochemistry of the mono-substituted product—with additional confirmation from the X-ray crystal structure of **21** (see below).[22] The fluorine *ortho* to the iodine substituent was observed in the range δ_F −90 to −98 ppm (compounds **6**, **9**, **11** and **13**); *para* to the iodine at δ_F ca. −112 ppm (compounds **5**, **8**, **10** and **12**). For analysis of the ^1H NMR spectra see Supplementary data.

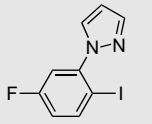
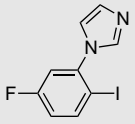
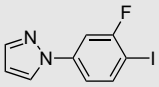
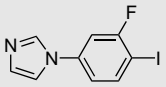
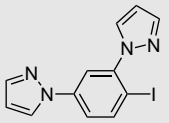
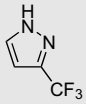
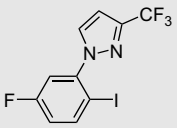
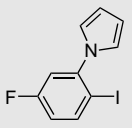
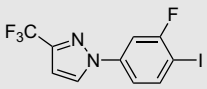
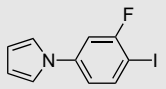
To study the copper-catalysed N-arylation, we adopted the conditions reported by Taillefer et al., viz. Cu_2O (5 mol %) 20% salicylaldoxime (20 mol %) and Cs_2CO_3 (2 equiv) in acetonitrile.[6c] The results are shown in Table 2. For all the systems studied, when using 1.5 equiv of the heterocycle competing substitution at C–I and C–F sites was observed, with C–I substitution being the major product (entries 1–4). Moreover, disubstituted products (**14** and **17**) and trisubstituted product **15** were also isolated from the pyrazole reactions (entries 1 and 2). An X-ray crystal structure (see below) confirmed unambiguously the structure of product **17**.[22] Using 3.5 equiv of pyrazole increased the yields of **14** and **15** to 35% and 13%, respectively.

The ratio of products did not change significantly when a mixture of pyrazole (1.5 equiv), Cu_2O and salicylaldoxime was stirred for 10 min at 20 °C (to preform the catalyst) before adding reagent **4**.

The general trend seen in Table 2 is consistent with the order of reactivity observed previously in Ullmann-type reactions in the azole series with aryl iodides, viz. pyrazole>imidazole>pyrrole.[6d]

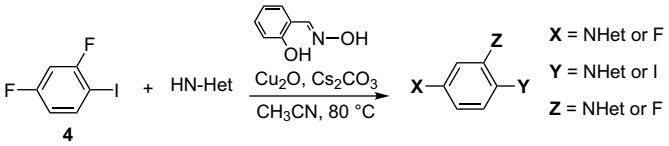
Table 1
Arylation of *N*-heterocycles with **4** without Cu(I) catalysis

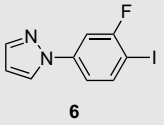
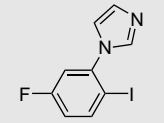
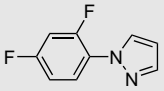
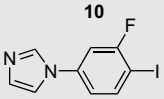
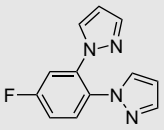
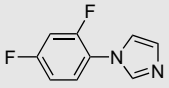
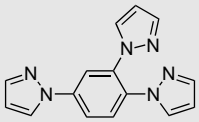
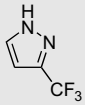
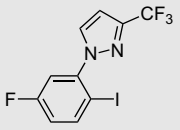
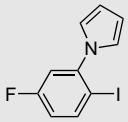
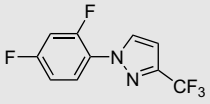
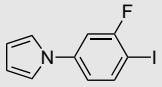
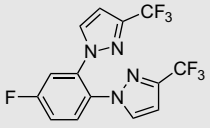
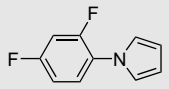


Entry	HN-Het	Product	Yield[a] (%)	Entry	HN-Het	Product	Yield[a] (%)
1		 **5**	34[b] 50[c,d] 16[c,e]	3		 **10**	66[b]
		 **6**	18[b] 15[c,d] 2[c,e]			 **11**	4[b]
		 **7**	22[b] 15[c,d] 56[c,e]				
2		 **8**	45[b]	4		 **12**	55[b]
		 **9**	6[b]			 **13**	10[c]

[a] Isolated yield of product, unless otherwise noted.
[b] Standard conditions: compound **4** (1.0 equiv), the *N*-heterocycle (1.5 equiv) and Cs_2CO_3 (2 equiv) in CH_3CN at 80 °C, 12 h.
[c] Yield based on ^1H NMR analysis of the product mixture after column chromatography.
[d] Pyrazole (1.0 equiv), 80 °C, 12 h.
[e] Pyrazole (3.0 equiv), 80 °C, 24 h.

Table 2
Arylation of *N*-heterocycles with **4** with Cu(I) catalysis



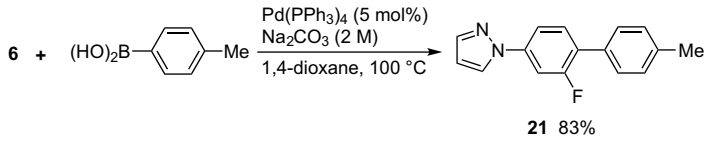
Entry	HN-Het	Product	Yield[a] (%)	Entry	HN-Het	Product	Yield[a] (%)
1		 **6**	2[b] 0[c,d]	3		 **10**	20[b]
		 **3**	13[b] 0[c,d]			 **11**	3[b]
		 **14**	20[b] 35[c,d]			 **18**	32[b]
		 **15**	4[b] 13[c,d]				
2		 **8**	5[b]	4		 **12**	20[c]
		 **16**	10[b]			 **13**	5[c]
		 **17**	41[b]			 **20**	35[b]

[a] Isolated yield of product, unless otherwise noted.
[b] Standard conditions: compound **4** (1.0 equiv), the *N*-heterocycle (1.5 equiv), Cs_2CO_3 (2.0 equiv), salicylaldoxime (20%) and CuO_2 (5%) in CH_3CN at 80 °C, 12 h.
[c] Yield based on ^1H NMR analysis of the product mixture after column chromatography.
[d] Pyrazole (3.5 equiv), 80 °C, 24 h.

To extend the application of our methodology product **6** was reacted further in a Suzuki–Miyaura reaction with *p*-toluene-boronic acid to obtain the linear triaryl product **21** in high yield (Scheme 1). The X-ray crystal structure of **21** (Fig. 1) provided additional support for the NMR assignment of the structure of regioisomer **6** discussed earlier.[22]

3. Conclusion

The functionalisation of aryl halides is a key topic in modern aromatic chemistry. In this context 2,4-difluoroiodobenzene **4** has been exploited as a substrate for both S_NAr reactions at the C–F bond(s) and copper-catalysed coupling reactions at the C–I bond. In this context NH-heterocycles (specifically, pyrazoles, imidazole and pyrrole) have been reacted with **4** in the absence and presence of copper catalysis to afford *N*-heterocycles bearing fluoroaryl and iodoaryl substituents. The general trend in reactivity in both these processes is pyrazole>imidazole>pyrrole. Regioselectivity in the S_NAr reactions and, in some cases, multiple substitutions have been observed. These products offer scope for drug discovery and material chemistry applications. The combination of a C–N coupling and a subsequent Suzuki–Miyaura reaction has led to compound



Scheme 1. Suzuki-Miyaura reaction of **6**.

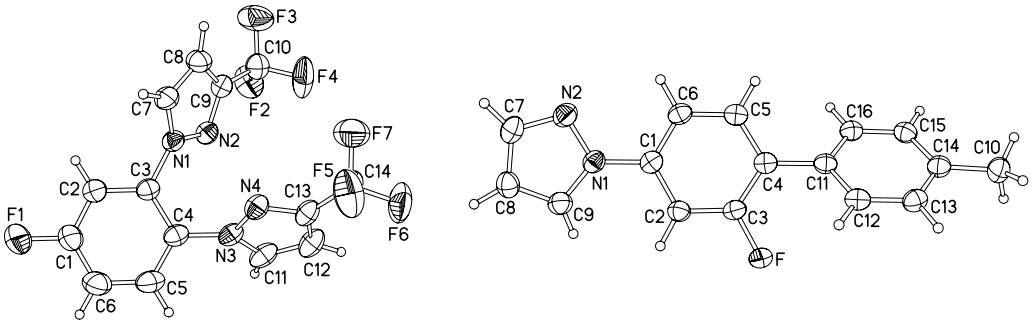


Figure 1. X-ray molecular structures of compounds **17** at room temperature (left) and **21** at 120 K (right). Thermal ellipsoids are drawn at the 30% (**17**) and 50% (**21**) probability levels; rotational disorder of CF_3 groups is not shown.

21, which illustrates that such protocols can provide a diversity of functionalised aryl/heteroaryl products. There is considerable scope for extension to other mixed-halogen substrates and optimisation of the selectivity of the reactions by using different nucleophiles, metal catalysts[23] and ligands.

4. Experimental

4.1. General

2,4-Difluoroiodobenzene, pyrazole, 3-(trifluoromethyl)pyrazole, imidazole, pyrrole salicylaldoxime and Cs_2CO_3 (anhydrous, 99%) were purchased from Alfa Aesar and used without further purification. Acetonitrile was purified using a PureSolv solvent purification system. Copper(I) oxide and tetrakis(triphenylphosphine)palladium(0) were purchased from Aldrich. Most ^1H and ^{19}F NMR spectra were recorded either on a Varian Unity-400 spectrometer operating at 399.96 MHz for ^1H and 376.33 MHz for ^{19}F or on a Bruker Avance 400 spectrometer operating at 400.13 MHz for ^1H and 100.61 MHz for ^{13}C, respectively. Chemical shifts are quoted downfield from TMS. MS data were obtained using a Thermo Finnigan LTQFT instrument for ES low and high resolution mass, and a Micromass AutoSpec spectrometer operating at 70 eV for electron impact (EI). Elemental analyses were obtained on an Exeter Analytical Inc. CE-440 elemental analyzer. Melting points were measured in open-end capillaries using a Stuart Scientific SMP3 melting point apparatus. The temperatures at the melting points were ramped at 2.5 °C/min and were uncorrected.

4.2. Reactions without Cu(I) catalysis

*4.2.1. Compounds **5**, **6**, **7***

The reaction of pyrazole (0.85 g, 12.5 mmol), 2,4-difluoroiodobenzene **4** (1.0 mL, 8.3 mmol) and Cs_2CO_3 (5.4 g, 16.7 mmol) in acetonitrile (10 mL) and column chromatography (SiO_2, eluent ether/DCM, 0:1 to 1:5 v/v) gave the following products in order of elution.

*4.2.1.1. 1-(3-Fluoro-4-iodophenyl)-1H-pyrazole **6**.* Yield 0.43 g, 18%; a white solid; mp 76.0–77.5 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.39 (dd, J=1.5, 2.5 Hz, 1H), 7.17 (dd, J=2.5, 8.5 Hz, 1H), 7.48 (dd, J=2.5 Hz, J_{HF}=9.0 Hz, 1H), 7.71 (d, J=1.5 Hz, 1H), 7.76 (dd, J_{HF}=7.0 Hz, J=8.5 Hz, 1H), 7.88 (d, J=2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 106 (d, J_{CF}=27.8 Hz), 108.5, 115.9 (d, J_{CF}=2.9 Hz), 126.7, 139.7, 139.8 (d, J_{CF}=2.9 Hz), 141.6, 141.7 (d, J_{CF}=9.0 Hz), 162.2 (d, J_{CF}=246 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −91.7; IR (neat) 3114, 2522, 2359, 1599, 1517, 1389, 1028, 752 cm^{-1}; MS (ES+) m/z (%): 288 (M^+, 100); HRMS calcd for $C_9H_6FIN_2$ (MH^+): 288.96326, found: 288.96327. Anal. Calcd for $C_9H_6FIN_2$: C, 37.53; H, 2.10; N, 9.72. Found: C, 37.40; H, 2.09; N, 9.67%.

*4.2.1.2. 1-(5-Fluoro-2-iodophenyl)-1H-pyrazole **5**.* Yield 0.81 g, 34%; a colourless liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.40 (dd, J=1.8, 2.4 Hz, 1H), 6.85 (ddd, J=3.0, 8.8 Hz, J_{HF}=11.6 Hz, 1H), 7.13 (dd, J=3.0 Hz, J_{HF}=9.2 Hz, 1H), 7.68 (d, J=1.8 Hz, 1H), 7.71 (d, J=2.4 Hz, 1H), 7.81 (dd, J_{HF}=5.8 Hz, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 86.5 (d, J_{CF}=4.4 Hz), 106.7, 115.5 (d, J_{CF}=23.4 Hz), 117.1 (d, J_{CF}=20.5 Hz), 130.8, 140.8 (d, J_{CF}=8.8 Hz), 140.9, 144.2 (d, J_{CF}=10.2 Hz), 162.5 (d, J_{CF}=250 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −112.1; IR (neat) 3726, 3102, 3102, 2360, 1583, 1468, 1191, 861, 749 cm^{-1}; MS (ES+) m/z (%): 289.1 (MH^+, 100); HRMS calcd for $C_9H_6FIN_2$ (MH^+): 288.96326, found: 288.96333.

*4.2.1.3. 2,4-Di(1-1H-pyrazolyl)-iodobenzene **7**.* Yield 0.61 g, 22%; white solid; mp 96.0–98.0 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.44 (dd, J=1.5, 2.5 Hz, 1H), 6.46 (dd, J=1.5, 2.5 Hz, 1H), 7.52 (dd, J=2.5, 8.5 Hz, 1H), 7.69 (d, J=1.5 Hz, 1H), 7.74 (d, J=1.5 Hz, 1H), 7.75 (d, J=2.5 Hz, 1H), 7.77 (d, J=2.5 Hz, 1H), 7.91 (d, J=2.5 Hz, 1H), 7.96 (d, J=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 89.4, 106.8, 108.4, 118.2, 120.2, 120.0, 126.6, 131.0, 140.7, 140.8, 141.0, 141.7, 144.0; IR (neat) 3735, 2360, 1524, 1267, 963, 847, 749 cm^{-1}; MS (ES+) m/z (%): 337.0 (MH^+, 100); HRMS calcd for $C_{12}H_9IN_4$ (MH^+) 336.99448, found: 336.99447.

The analogous reaction using pyrazole (1.0 equiv) gave **5** (50%), **6** (15%) and **7** (15%).

The analogous reaction using pyrazole (3.0 equiv) at 80 °C for 24 h gave **5** (16%), **6** (2%) and **7** (56%).

*4.2.2. Compounds **8**, **9***

The reaction of 3-(trifluoromethyl)pyrazole (1.7 g, 12.5 mmol), 2,4-difluoroiodobenzene **4** (1.0 mL, 8.3 mmol) and Cs_2CO_3 (5.4 g, 16.7 mmol) in acetonitrile (10 mL) and column chromatography (SiO_2, eluent DCM/hexane, 1:1 v/v) gave the following products in order of elution.

4.2.2.1. 1-(5-Fluoro-2-iodophenyl)-3-trifluoromethyl-1H-pyrazole ***8***. Yield 1.33 g, 45%; a colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.74 (dd, J_{HF}=0.6 Hz, J=2.4 Hz, 1H), 6.99 (ddd, J=3.0, 8.8 Hz, J_{HF}=11.9 Hz, 1H), 7.40 (dd, J=3.0 Hz, J_{HF}=8.5 Hz, 1H), 7.80 (qd, J_{HF}=0.9 Hz, J=2.4 Hz, 1H), 7.92 (dd, J=8.8 Hz, J_{HF}=5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 86.9 (d, J_{CF}=3.8 Hz), 105.5 (q, J_{CF}=1.9 Hz), 116.3 (d, J_{CF}=24.9 Hz), 118.7 (d, J_{CF}=22.0 Hz), 121.1 (q, J_{CF}=270 Hz), 132.8, 141.3 (d, J_{CF}=7.7 Hz), 143.6 (d, J_{CF}=9.6 Hz), 144.7 (q, J_{CF}=38.4 Hz), 162.9 (d, J_{CF}=252 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −111.6, −62.5; IR (neat) 3732, 2359, 1532, 1258, 968, 843, 747 cm^{-1}; MS (EI) *m*/*z* (%): 356 (M^+, 100), 337 (M^+−F, 10), 229 (M^+−I, 100); MS (ES+) *m*/*z* (%): 356.8 (MH^+, 100); HRMS calcd for $C_{10}H_6F_4I_2N_2$ (MH^+): 356.95064, found: 356.95060.

4.2.2.2. 1-(3-Fluoro-4-iodophenyl)-4-trifluoromethyl-1H-pyrazole ***9***. Yield 0.18 g, 6%; a colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.77 (dd, J_{HF}=0.5 Hz, J=2.4 Hz, 1H), 7.61 (dd, J_{HF}=2.6 Hz, J=8.6 Hz, 1H), 7.85 (dd, J=0.5 Hz, J_{HF}=8.8 Hz, 1H), 8.00–8.01 (m, 1H), 8.07 (dd, J=0.5, 8.6 Hz, 1H); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −97.8, −62.8; IR (neat) 3730, 2360, 1518, 1267, 845, 751 cm^{-1}; MS (EI) *m*/*z* (%): 356 (M^+, 100), 337 (M^+−F, 10), 229 (M^+−I, 100); MS (ES+) *m*/*z* (%): 356.8 (MH^+, 100); HRMS calcd for $C_{10}H_6F_4I_2N_2$ (MH^+): 356.95064, found: 356.95063. ^{1}H NMR showed that **9** was not completely separated from traces of **8**.

4.2.3. Compounds ***10***, ***11***

The reaction of imidazole (0.85 g, 12.5 mmol), 2,4-difluoro-iodobenzene **4** (1.0 mL, 8.3 mmol) and Cs_2CO_3 (5.4 g, 16.7 mmol) and column chromatography (SiO_2, eluent haxane/DCM, 4:1 to 1:1 v/v) gave the following products in order of elution.

4.2.3.1. 1-(5-Fluoro-2-iodophenyl)-1H-imidazole ***10***. Yield 1.8 g, 66%; a white solid; mp 67.0–68.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.97 (ddd, J=3.0, 8.5 Hz, J_{HF}=11.6 Hz, 1H), 7.07 (d, J=1.0 Hz, 1H), 7.08 (dd, J=3.0 Hz, J_{HF}=8.5 Hz, 1H), 7.21 (d, J=1.0 Hz, 1H), 7.64 (s, 1H), 7.91 (dd, J_{HF}=5.0 Hz, J=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 88.8 (d, J_{CF}=2.9 Hz), 115.8 (d, J_{CF}=23.4 Hz), 118.1 (d, J_{CF}=21.9 Hz), 120.4, 129.9, 137.4, 141.1 (d, J_{CF}=8.8 Hz), 141.5 (d, J_{CF}=10.2 Hz), 162.9 (d, J_{CF}=252 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −111.7; IR (neat) 3733, 2360, 1496, 1243, 1189, 1051, 846, 748 cm^{-1}; MS (ES+) *m*/*z* (%): 289.0 (MH^+, 100); HRMS calcd for $C_9H_6FIN_2$ (MH^+, 100): 288.96326, found: 288.96320.

4.2.3.2. 1-(3-Fluoro-4-iodophenyl)-1H-imidazole ***11***. Yield 80 mg, 4%; a white solid; mp 106.5–108.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.98 (dd, J=2.5 Hz, $^2J_{HF}$=9.0 Hz, 1H), 7.11 (dd, J=2.5, 8.5 Hz, 1H), 7.19 (s, 1H), 7.24 (s, 1H), 7.81 (dd, J_{HF}=7.0 Hz, J=8.5 Hz, 1H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 78.9 (d, J_{CF}=24.9 Hz), 109.0 (d, J_{CF}=26.3 Hz), 117.8, 118.2 (d, J_{CF}=4.4 Hz), 131.0, 135.2, 138.8 (d, J_{CF}=8.8 Hz), 140.4, 162.2 (d, J_{CF}=247 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −90.5; IR (neat) 2518, 2359, 1571, 1179, 852, 753 cm^{-1}; MS (EI) *m*/*z* (%): 287.9 (M^+, 100), 260.8 (M^+−I, 30); MS (ES+) *m*/*z* (%): 289.0 (MH^+, 100); HRMS calcd for $C_9H_6FIN_2$ (MH^+): 288.96326, found: 288.96322.

4.2.4. Compounds ***12***, ***13***

The reaction of pyrrole (0.85 mL, 12.5 mmol), 2,4-difluoro-iodobenzene **4** (1.0 mL, 8.3 mmol) and Cs_2CO_3 (5.4 g, 16.7 mmol) and column chromatography (SiO_2, eluent hexane) gave a mixture of **12** and **13** (1.55 g, 65%, ca. 5:1 ratio by ^{1}H NMR analysis of the crude mixture). Crystallisation of the mixture from hexane gave the following compounds.

4.2.4.1. 1-(5-Fluoro-2-iodophenyl)-1H-pyrrole ***12***. Yield 1.31 g, 55%; a white solid; mp 70–71.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.34 (t, J=2.0 Hz, 2H), 6.82 (t, J=2.0 Hz, 2H), 6.89 (ddd, J=3.0, 8.5 Hz, J_{HF}=11.6 Hz, 1H), 7.06 (d, J=3.0 Hz, J_{HF}=9.0 Hz, 1H), 7.88 (dd, J_{HF}=5.5 Hz, J=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 88.6 (d, J_{CF}=3.8 Hz), 109.7 (2C), 115.8 (d, J_{CF}=23.0 Hz), 116.9 (d, J_{CF}=21.0 Hz), 122.1 (2C), 140.9 (d, J_{CF}=8.6 Hz), 145.2 (d, J_{CF}=10.5 Hz), 162.9 (d, J_{CF}=250 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −112.7; IR (neat) 3140, 2798, 1530, 1480, 1125, 768 cm^{-1}; MS (ES+) *m*/*z* (%): 287.1 (MH^+, 100); HRMS calcd for $C_{10}H_7FIN$ (MH^+): 287.96801, found: 287.96825.

4.2.4.2. 1-(3-Fluoro-4-iodophenyl)-1H-pyrrole ***13***. Yield 0.24 g, 10%; a colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.39 (t, J=2.1 Hz, 2H), 7.00 (t, J_{12}=2.4 Hz, J_{13}=8.5 Hz, 1H), 7.07 (t, J=2.1 Hz, 2H), 7.14 (d, J_{12}=2.4 Hz, $^2J_{HF}$=9.1 Hz, 1H), 7.77 (dd, $^3J_{HF}$=7.0 Hz, J_{13}=8.5 Hz, 1H); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −91.8; IR (neat) 3148, 2787, 1532, 1485, 1120, 765 cm^{-1}; MS (EI) *m*/*z* (%): 287 (M^+, 100), 160 (M^+−I, 100). ^{1}H NMR showed that **13** was not completely separated from traces of **12**.

4.3. Reactions with Cu(I) catalysis

4.3.1. Compounds ***3***, ***6***, ***14***, ***15***

The reaction of pyrazole (0.85 g, 12.5 mmol), 2,4-difluoro-iodobenzene **4** (1.0 mL, 8.3 mmol), salicylaldoxime (0.23 g, 1.67 mmol), Cs_2CO_3 (5.4 g, 16.7 mmol) and Cu_2O (60 mg, 0.42 mmol) and column chromatography (SiO_2, eluent ether/DCM, 0:1 to 1:5 v/v) gave the following compounds in order of elution.

Compound **6** (39 mg, 2%) was eluted first, which was spectroscopically identical with the sample above.

4.3.1.1. 1-(2,4-Difluorophenyl)-1H-pyrazole ***3***. Yield 0.25 g, 13%; a colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.45 (t, J=1.5 Hz, 1H), 6.93–6.99 (m, 2H), 7.71 (d, J=1.5 Hz, 1H), 7.83 (td, J_{HF}=6.0 Hz, J=8.0 Hz, 1H), 7.90 (t, J_{HF}=2.4 Hz 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 105.0 (dd, J_{CF}=24.9, 26.3 Hz), 107.5, 112.1 (dd, J_{CF}=21.9, 4.4 Hz), 125.2 (dd, J_{CF}=8.8, 2.9 Hz), 125.6 (dd, J_{CF}=7.3, 10.2 Hz), 130.6 (d, J_{CF}=8.7 Hz), 140.9, 151.7 (dd, J_{CF1}=251.8 Hz, J_{CF}=11.7 Hz), 161.3 (dd, J_{CF}=250.3, 11.7 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −121.2, −112.0; IR (neat) 3730, 3109, 2360, 1583, 1474, 1390, 1193, 863, 748 cm^{-1}; MS (EI) *m*/*z* (%): 180 (M^+, 100); MS (ES+) *m*/*z* (%): 181.1 (MH^+, 100); HRMS calcd for $C_9H_7F_2N_2$ (MH^+): 181.05718, found: 181.05715.

4.3.1.2. 3,4-Di(1H-pyrazolyl)fluorobenzene ***14***. Yield 0.36 g, 20%; a colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.25 (s, 1H), 6.31 (s, 1H), 6.82 (s, 1H), 7.08 (s, 1H), 7.15 (td, J=8.8, 2.3 Hz, 1H), 7.50 (dd, J=2.3 Hz, J_{HF}=8.8 Hz, 1H), 7.58 (dd, J_{HF}=5.5 Hz, J=8.8 Hz, 1H), 7.67 (s, 1H), 7.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0 (d, J_{CF}=250 Hz), 141.5, 141.3, 136.5 (d, J_{CF}=11.0 Hz), 130.9, 130.2, 129.9 (d, J_{CF}=3.7 Hz), 129.2 (d, J_{CF}=9.5 Hz), 115.4 (d, J_{CF}=17.7 Hz), 113.5 (d, J_{CF}=26.0 Hz), 108.0, 107.7; ^{19}F NMR ($CDCl_3$, 376 MHz): δ −110.5; IR (neat) 3725, 3111, 2360, 1580, 1465, 1382, 1158, 870, 745 cm^{-1}; MS (ES+) *m*/*z* (%): 229.2 (MH^+, 100); HRMS calcd for $C_{12}H_{10}N_4F$ (MH^+): 229.08840, found: 229.08848.

4.3.1.3. 1,2,4-Tris(1H-pyrazolyl)benzene ***15***. Yield 80 mg, 4%; a colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.26 (t, J=2.5 Hz, 1H), 6.28 (t, J=2.0 Hz, 1H), 6.45 (t, J=2.5 Hz, 1H), 6.95 (d, J=2.5 Hz, 1H), 7.01 (d, J=2.0 Hz, 1H), 7.67–7.71 (m, 4H), 7.83 (dd, J=2.5, 8.5 Hz, 1H), 7.98 (d, J=2.5 Hz, 1H), 8.02 (d, J=2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 107.7, 107.8, 108.4, 116.6, 118.5, 126.9, 128.2, 130.4, 130.6, 131.8, 135.4, 140.0, 141.3, 141.4, 141.8; IR (neat) 3727, 2360, 1586, 1479, 1275, 1129, 865, 764 cm^{-1}; MS (ES+) *m*/*z* (%): 277.2 (MH^+, 32), 299.2 (M^++Na^+, 100); HRMS calcd for $C_{15}H_{12}N_6$ (M^++Na^+): 299.10157, found: 299.10169.

The analogous reaction using pyrazole (3.5 equiv) at 80 °C for 24 h gave **14** (35%) and **15** (13%).

*4.3.2. Compounds **8**, **16**, **17***

The reaction of 3-(trifluoromethyl)pyrazole (1.7 g, 12.5 mmol), 2,4-difluoroiodobenzene **4** (1.0 mL, 8.3 mmol), salicylaldoxime (0.23 g, 1.67 mmol), Cs_2CO_3 (5.4 g, 16.7 mmol) and Cu_2O (60 mg, 0.42 mmol) and column chromatography (SiO_2, eluent DCM/hexane, 1:1 v/v) gave the following compounds in order of elution.

Compound **8** (0.15 g, 5%) was eluted first, which was spectroscopically identical with the sample above, followed by compounds **17** and **16**.

*4.3.2.1. 3,4-Bis(4-trifluoromethyl-1H-pyrazolyl)fluorobenzene **17**.* Yield 1.24 g, 41%; a white solid; mp 83.4–84.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.58 (d, J=2.5 Hz, 1H), 6.61 (d, J=2.0 Hz, 1H), 7.14 (d, J=2.0 Hz, 1H), 7.27 (d, J=2.5 Hz, 1H), 7.31 (ddd, J=2.5, 8.5 Hz, J_{HF}=11.6 Hz, 1H), 7.50 (dd, J=2.5 Hz, J_{HF}=8.5 Hz, 1H), 7.67 (dd, J_{HF}=5.0 Hz, J=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 106.3 (d, J_{CF}=1.9 Hz), 114.5 (d, J_{CF}=25.9 Hz), 117.1 (d, J_{CF}=22.1 Hz), 119.8 (q, J_{CF}=277 Hz), 121.9 (q, J_{CF}=277 Hz), 129.5 (d, J_{CF}=9.6 Hz), 130.1 (d, J_{CF}=3.9 Hz), 132.1, 132.8, 136.1 (d, J_{CF}=10.5 Hz), 144.7–145.2 (m, 2C), 162.6 (d, J_{CF}=254 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −107.9, −62.8, −62.7; IR (neat) 3730, 3115, 2360, 1512, 1272, 1130, 755 cm^{-1}; MS (EI) m/z (%): 364.0 (M^+, 100); 295.0 (M^+-CF_3, 70); MS (ES+) m/z (%): 365.1 (MH^+, 100); HRMS calcd for $C_{14}H_7F_7N_4$ (M^++Na^+): 387.04512, found: 387.04505.

*4.3.2.2. 1-(2,4-Difluorophenyl)-3-trifluoromethyl-1H-pyrazole **16**.* Yield 0.2 g, 10%; a white solid; mp 29–30 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.73 (d, J=1.9 Hz, 1H), 6.97–7.01 (m, 2H), 7.85 (td, J_{HF}=5.8 Hz, J=8.1 Hz, 1H), 7.95 (d, J=1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 105.4 (t, $^2J_{CF}$=26.9 Hz), 106.0, 112.6 (dd, J_{CF1}=22.2 Hz, J_{CF2}=3.2 Hz), 121.4 (q, J_{CF}=269.5 Hz), 124.5–124.6 (m), 126.4 (d, J_{CF}=9.5 Hz), 132.4 (d, J_{CF}=9.5 Hz), 144.4 (d, J_{CF}=38.0 Hz), 154.4 (dd, J_{CF1}=252.0 Hz, J_{CF2}=12.7 Hz), 161.5 (dd, J_{CF1}=252.0 Hz, $^3J_{CF2}$=11.0 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −120.9, −109.6, −62.7; IR (neat) 3731, 3110, 2360, 1512, 1275, 1120, 861, 752 cm^{-1}; MS (EI) m/z (%): 248 (M^+, 100); 229 (M^+-F, 10), 179 (M^+-CF_3, 10); MS (ES+) m/z (%): 349.0 (MH^+, 100); HRMS calcd for $C_{10}H_6F_5N_2$ (MH^+): 249.04511, found: 249.04515.

*4.3.3. Compounds **10**, **11**, **18***

The reaction of imidazole (0.85 g, 12.5 mmol), 2,4-difluoroiodobenzene **4** (1.0 mL, 8.3 mmol), salicylaldoxime (0.23 g, 1.67 mmol), Cs_2CO_3 (5.4 g, 16.7 mmol) and Cu_2O (60 mg, 0.42 mmol) and column chromatography (SiO_2, eluent ether/DCM, 0:1 to 1:1 v/v) gave the following compounds in order of elution.

Compounds **10** (0.48 g, 20%) and **11** (70 mg, 3%) were eluted first, which were spectroscopically identical with the samples above, followed by compound **18**.

*4.3.3.1. 1-(2,4-Difluorophenyl)-1H-imidazole **18**.* Yield 0.48 g, 32%; a white solid; mp 60.0–62.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.97–7.06 (m, 2H), 6.20 (s, 1H), 6.22 (s, 1H), 7.37 (td, J_{HF}=6.1 Hz, J=8.8 Hz 1H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 175 MHz): δ 105.4 (dd, J_{CF}=23.8, 26.5 Hz), 112.1 (dd, J_{CF}=3.9, 22.5 Hz), 119.6 (d, J_C=1.6 Hz), 121.8 (dd, J_{CF}=3.9, 11.8 Hz), 126.2 (dd, J_{CF}=1.9, 9.9 Hz), 129.8, 136.9 (d, J_{CF}=3.3 Hz), 155.3 (dd, J_{CF}=12.3, 254 Hz), 161.5 (dd, J_{CF1}=11.0, 251 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −119.7, −109.5; IR (neat) 3735, 3109, 2360, 1581, 1425, 1243, 1185, 1052, 823, 745 cm^{-1}; MS (EI) m/z (%): 180 (M^+, 100); MS (ES+) m/z (%): 181.1 (MH^+, 100); HRMS calcd for $C_9H_6F_2N_2$ (MH^+): 181.05718, found: 181.05714.

*4.3.4. Compounds **12**, **13**, **20***

The reaction of pyrrole (0.85 mL, 12.5 mmol), 2,4-difluoroiodobenzene **4** (1.0 mL, 8.3 mmol), salicylaldoxime (0.23 g, 1.67 mmol), Cs_2CO_3 (5.4 g, 16.7 mmol) and Cu_2O (60 mg, 0.42 mmol) and column chromatography (SiO_2, eluent hexane) gave the following compounds in order of elution.

Compounds **12** and **13** (57 mg, 25%, 4:1 ratio by ^{1}H NMR), which were not separated, followed by compound **20**.

*4.3.4.1. 1-(2,4-Difluorophenyl)-1H-pyrrole **20**.* Yield 0.60 g, 35%; a colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.43 (t, J=2.0 Hz, 2H), 6.96–7.05 (m, 3H), 7.07–7.15 (m, 1H), 7.40 (td, J_{HF}=5.7 Hz, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 105.6 (dd, J_{CF}=24.2, 26.3 Hz), 109.7, 112.7 (dd, J_{CF}=3.9, 21.5 Hz), 121.5, 123.2 (dd, J_{CF}=2.0, 8.9 Hz), 124.9 (d, J_{CF}=10.5 Hz), 156.5 (dd, J_{CF}=11.5, 250 Hz), 161.0 (dd, J_{CF}=10.1, 251 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −112.7, −120.6; IR (neat) 3138, 2854, 2755, 1540, 1482, 1124, 1075, 748 cm^{-1}; MS (ES+) m/z (%): 287.1 (MH^+, 100); HRMS calcd for $C_{10}H_7F_2N$ (MH^+): 180.06248, found: 180.06240.

4.4. 1-(2-Fluoro-4′-methylbiphenyl-4-yl)-1*H*-pyrazole 21

A mixture of $Pd(PPh_3)_4$ (40 mg, 0.03 mmol), compound **6** (0.20 g, 0.69 mmol), Na_2CO_3 (2 M, 2.0 mL) and *p*-tolueneboronic acid (0.11 g, 0.83 mmol) in degassed 1,4-dioxane (20 mL) was stirred and heated in an oil bath at 100 °C overnight. The reaction mixture was cooled to room temperature, diluted with dichloromethane and water. The resulting organic layer was washed with water and saturated NaCl solution, separated and dried over $MgSO_4$. The solvent was removed in vacuo to yield the crude product, which was purified by column chromatography (SiO_2, eluent ether/DCM, 1:5 v/v) to give **21** (0.14 g, 83%); a white solid; mp 115.5–117 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 6.50 (t, J=2.4 Hz, 1H), 7.27 (d, J=7.6 Hz, 2H), 7.46 (d, J=2.0 Hz, 1H), 7.48 (d, J=2.0 Hz, 1H), 7.52–7.60 (m, 3H), 7.44 (d, J=2.4 Hz, 1H), 7.94 (d, J=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 107.4 (d, J_{CF}=28.8 Hz), 108.2, 114.6 (d, J_{CF}=3.8 Hz), 126.8, 127.0 (d, J_{CF}=13.4 Hz), 128.8, 128.9, 129.4 (2C), 131.5 (d, J_{CF}=4.8 Hz), 132.2, 137.9, 140.3 (d, J_{CF}=10.5 Hz), 160.5 (d, J_{CF}=248 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ −115.8; IR (neat) 3728, 2928, 2524, 2359, 1500, 1390, 1267, 1037, 850, 751 cm^{-1}; MS (ES+) m/z (%): 253.1 (MH^+, 100); HRMS calcd for $C_{16}H_{14}FN_2$ (MH^+): 253.11355, found: 253.11351.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.036.

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