Selective and Facile Palladium-Catalyzed Amination of 2-Fluoro-4-iodopyridine in the 4-Position under Microwave Conditions

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Abstract: The selective C–N cross-coupling of 2-fluoro-4-iodopyridine with aromatic amines is reported. In contrast to conventional substitutions where C–N bond formation takes place at the 2-position (e.g., 2,4-dichloropyridine), the Buchwald–Hartwig cross-coupling was found to be complementary and exclusive for the 4-position. Reactions were carried out under microwave irradiation typically within 30 minutes. These conditions also allowed a decrease in the amount of base required to 3.5 equivalents compared to 20 equivalents in established protocols. Additionally, use of potassium carbonate as a mild base was sufficient, and good yields of the coupling products were obtained in all cases with the simple system $Pd(OAc)_2$/BINAP.

Key words: cross-coupling, heterocycles, catalysis, amines, regioselectivity

Transition-metal-catalyzed cross-coupling reactions are one of the most important tools for bond formation in modern synthesis.[1] Initially limited to the construction of C–C bonds, the utility of these methods was significantly broadened by the development of protocols to establish carbon–heteroatom bonds. Most importantly, the palladium-catalyzed amination reaction, independently developed by Buchwald and Hartwig, provided synthetic chemists with a powerful tool to construct C–N bonds.[2] Since its discovery, the amination protocol has successfully been applied in the synthesis of numerous arylamino-substituted arenes and heteroarenes.[3] Among heterocycles, pyridine certainly represents a privileged scaffold and is present in many biologically active compounds (e.g., alkaloids). In this context, C–N cross-coupling reactions at the 4-position are interesting from a synthetic point of view since this novel connection holds the prospect of enabling complementary access to compounds with diverse biological activity (Figure 1). Compounds of the general structure **I** were reported as a new class of antitumor agents,[4] substance **II** displayed inhibition of the vascular endothelial growth factor receptor (VEGFR-2) tyrosine kinase[5] and structure **III** was reported as a phosphodiester IV inhibitor.[6]

Consequently, methods for efficiently decorating the pyridine scaffold are highly important, and Buchwald–Hartwig reactions of pyridine halides have been investigated, in particular using chlorinated and brominated compounds.[7] However, only a few examples of amination reactions on dihalogenated pyridines have been reported in the literature using either palladium[8] or nickel catalysts.[9] 2,6-Dichloropyridine, 2,3-dichloropyridine, and 3,5-dichloropyridine were successfully applied in selective C–N cross-coupling reactions with aromatic amines.[10] In case of symmetric 2,6- and 3,5-dichloropyridine, only one C–N cross-coupling took place leading to a defined product, whereas 2,3-dichloropyridine reacted selectively at the more activated 2-position. Although regiospecific, these protocols have two major drawbacks: a large excess (usually approx. 20 equivalents) of base (K_2CO_3) is required to achieve complete conversion, and rather long reaction times (18 hours typically) are required. In general, C–N coupling reactions at the 4-position of pyridine are poorly covered in the literature,[11] and the conversion of a 2,4-dihalopyridine was reported only briefly;[12a,b] the selectivity and generality of this transformation was not further elaborated. To the best of our knowledge, the first detailed investigation on a selective amination reaction at the 4-position of a 2,4-dihalopyridine is reported within this contribution.

The most obvious and convenient dihalo starting material is 2,4-dichloropyridine (**1**) due to its commercial availability and reasonable price (~20/g, Aldrich). However, the 2- and the 4-positions in pyridine are quite similar in reactivity and the 2-position is usually only slightly fa-

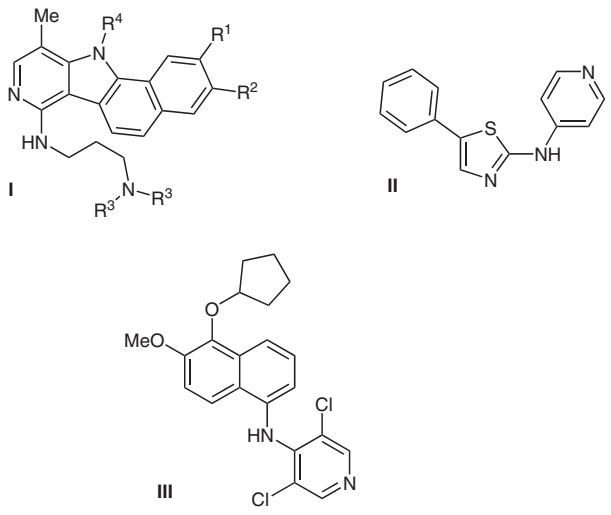

Figure 1

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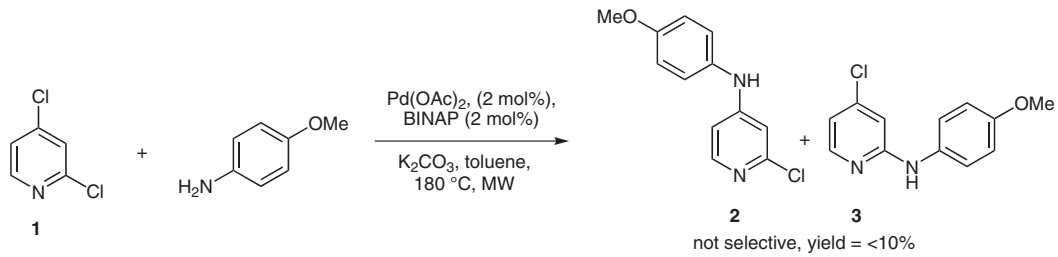
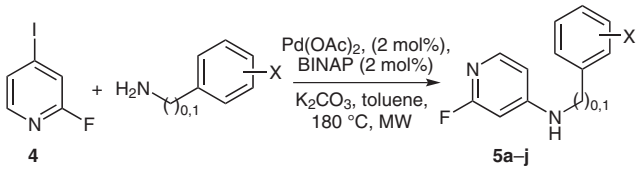


Scheme 1

vored.[13] Nevertheless, we investigated the C–N cross-coupling reaction of **1** (Scheme 1). As expected, the reaction of **1** with *p*-anisidine provided both 2- and 4-amino-substituted products **2** and **3** in approximately equimolar ratios (based on GC-MS), however, in less than 10% yield.

Consequently, 2-fluoro-4-iodopyridine (**4**) was prepared as an alternative substrate according to a literature protocol starting from 2-fluoropyridine in high yield (Scheme 2).[14] This compound bears iodine in the 4-position as a better leaving group for the cross-coupling process. Additionally, the fluorine atom in the 2-position is an excellent leaving group for subsequent nucleophilic substitution reactions, which could be a competing pathway to give 2-aminated side-products. We had elaborated these properties of building block **4** in a C–C coupling approach towards analogues of the cytostatic Gleevec.[14c,15] There, it was found that, under acidic nucleophilic substitution conditions, amination with 3-chloroaniline takes place preferentially at the 2-position (66%) accompanied by minor amounts of 2,4-bis-aminated product (9%).[15b] This selectivity should be inverted to favor amination at the 4-position under Buchwald–Hartwig conditions.

In analogy to an already successful amination protocol for pyridine halides,[10] $Pd(OAc)_2$ was used as metal source, (+/–) BINAP as the ligand, K_2CO_3 as base, and *p*-anisidine as the model amine component. As use of BINAP gave reasonably good yields as well as complete conversion in all cases, and since it is cheaper than other ligands used for Buchwald–Hartwig coupling reactions, we decided to stay with this readily available system. Reactions were accelerated by applying microwave irradiation at 180 °C to complete conversions within 30 minutes. A single reaction product was formed and identified as the C–N cross-coupled product **5b** with a good yield of 63% upon selective transformation at the 4-position (Scheme 2). Neither nucleophilic substitution at the 2-position nor formation of a 2,4-diaminated product was observed. Additionally, the use of 3.5 equivalents of the mild base K_2CO_3 proved to be sufficient under microwave conditions (compared to 20 equiv under classical heating according to reported protocols[10]). It is also noteworthy that the widely applied stronger bases *t*-BuONa or *t*-BuOK could be avoided. Although use of these stronger bases have been reported to give faster reactions, their high basicity has caused problems when base-sensitive substrates are employed.[3] Gratifyingly, microwave irradiation was successfully employed to overcome previous limitations of C–N coupling reactions at pyridine such as long reaction times and the need for a large excess of base. An additional advantage of this protocol is that none of the reagents are sensitive to air, hence, manipulation of all reaction partners can be conducted under ambient conditions, thus avoiding troublesome handling in a glove box; simple flushing of the reaction vessel with argon before sealing is sufficient to ensure reproducible yields.



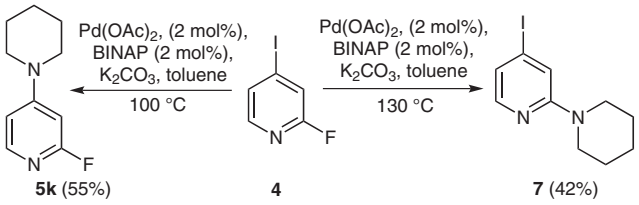
Scheme 2

A series of substituted aniline derivatives were coupled under the established conditions in order to assess the scope of the protocol. All reactions proceeded smoothly, affording reaction products **5a–j** in good yields (Table 1). It should be emphasized that, in every case, the mono-aminated product was formed exclusively and regioselectively in the 4-position; 2,4-bisamino products could not be detected even after prolonged reaction times in the presence of an excess of amine. As the 2-position is more activated towards nucleophilic substitution reactions in pyridine, and because fluorine is a better leaving group compared to iodine in case of nucleophilic aromatic substitutions, it can be concluded that the amination at the 4-position takes place exclusively via a palladium-catalyzed C–N cross-coupling reaction in which iodine is a better leaving group than fluorine.[3] This result was confirmed by a control experiment conducted in the absence of palladium-catalyst, which did not result in any formation of aminated products. This finding is also in agreement with previous reports in the literature for other cross-coupling reactions.[1]

The protocol is not sensitive to the nature of aniline reaction partner and both amines bearing electron-donating (compounds **5b/c** and **5g/h**) and electron-withdrawing substituents (compounds **5d–f**) were obtained in good yields. Furthermore, the presence of base-sensitive functional groups was well tolerated (compounds **5e/f**). The cross-coupling reaction proceeded with excellent yield when *o*-anisidine was used as the amine source (**5c**), indicating the applicability of sterically hindered amines in

this transformation. Using benzylamine (**5i**) or 4-methoxybenzylamine (**5j**) as examples of primary alkylamines also gave reasonable conversion and no side products were isolated. However, in these cases, the yield was somewhat lower (52 and 56%, respectively), and prolonged reaction times were required (45 min). Reaction with the secondary alkylamine piperidine (**5k**) also gave a reasonable yield at lower temperature (100 °C) under conventional heating (Scheme 3). However, at higher temperature (130 °C), nucleophilic substitution at the fluorine in the 2-position predominated over the substitution of iodine at the 4-position in a ratio of 5:1 (according to GC-MS); 4-iodo-2-(piperidin-1-yl)pyridine was isolated as the major product in this reaction with a yield of 42%.

It seems that at higher temperatures the activation energy barrier for the nucleophilic substitution is exceeded; under these conditions the reaction rate of the nucleophilic substitution is higher than the rate of the Buchwald–Hartwig cross-coupling process.[16] This is not surprising since it was reported that the nucleophilic substitution of fluorine in 2-fluoropyridine with piperidine can take place at room temperature even without base.[16a]



Scheme 3

Table 1 Scope of the Reaction

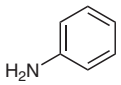
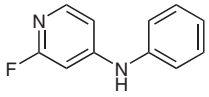
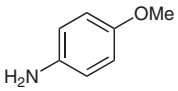
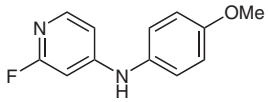
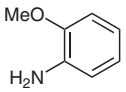
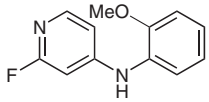
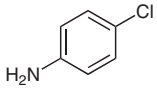
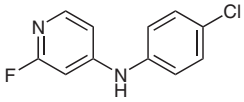
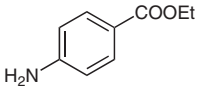
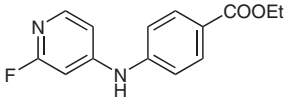
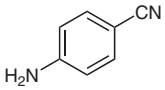
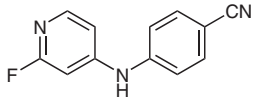
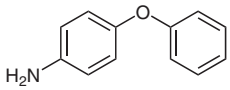
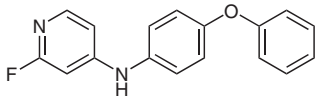
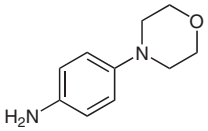
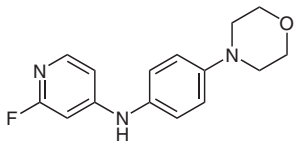
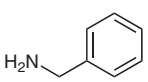
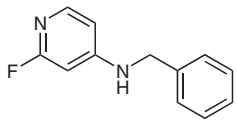
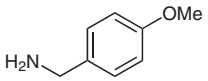
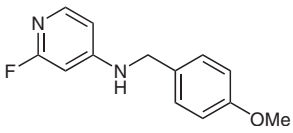
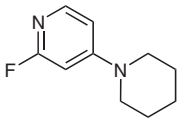
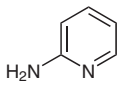
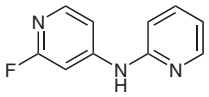
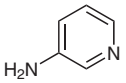
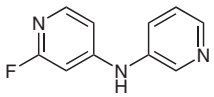
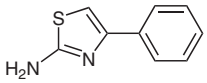
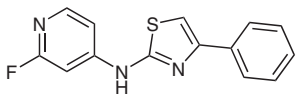
Amine	Product	Compound	Time (min)	Yield (%)
		**5a**	30	65
		**5b**	30	63
		**5c**	30	83
		**5d**	30	74
		**5e**	45	69
		**5f**	45	78
		**5g**	30	75
		**5h**	30	84
		**5i**	45	52

Table 1 Scope of the Reaction (continued)

Amine	Product	Compound	Time (min)	Yield (%)
		**5j**	45	56
		**5k**[a]	16 h	55
		**6a**	30	66
		**6b**	30	79
		**6c**	30	48

[a] Reaction was performed under conventional heating at 100 °C for 16 h.

This demonstrates that the developed protocol is suitable for both aromatic and aliphatic amines since even secondary aliphatic amines can be applied selectively as the C–N coupling component.

Finally, three heterocyclic amines were applied to this amination protocol. All these reactants provided access to C–N coupling products (**6a–c**) upon selective reaction at the 4-position in moderate to good yields. Furthermore, in the case of **6c** the reaction also worked smoothly and with complete conversion, however, in lower yield, which can be attributed to troublesome purification. Hence, this approach allows facile access to potentially interesting amino-bridged heterocyclic compounds.

In summary, the microwave-assisted C–N cross-coupling protocol described above can serve as a valuable procedure for the selective amination of pyridines at the 4-position.[17] The protocol gives access to useful intermediates for the synthesis of biologically active compounds and pharmaceuticals that contain the 4-anilino pyridine motif, and is complementary to nucleophilic substitution reactions with aniline derivatives that take place preferentially at the 2-position.[15b] The fluorine atom at the 2-position can be utilized for further functionalization, e.g., nucleophilic substitution. This procedure is superior to previous protocols due to the straightforward operational conditions (no glove box manipulation), drastically shorter reaction times, as well as substantially decreased amounts of base. The use of a mild base, K_2CO_3, is also advantageous in case of sensitive substrates. The synthesis of an array of 4-aniline-substituted pyridine derivatives was accomplished starting from 2-fluoro-4-iodopyridine. Presently, we are assessing the scope and limitations of the microwave-based protocol for the Buchwald–Hartwig C–N coupling reaction with other polyhalogenated nitrogen heterocycles.

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(17) **General Procedure**: 2-Fluoro-4-iodopyridine (**4**; 1 equiv), aryl/alkyl amine (1.2 equiv), K_2CO_3 (3.5 equiv), $Pd(OAc)_2$ (2 mol%), and BINAP (2 mol%) were charged into a microwave vial and anhydrous toluene (2 mL) was added. The vial was then sealed, evacuated and flushed with argon. Then the reaction mixture was irradiated at 180 °C in a CEM Explorer™ microwave unit for 30 min with stirring. After cooling to r.t., the solid material was removed by filtration and washed with CH_2Cl_2 (10 mL). The solvent was evaporated and the resulting crude product was purified by flash column chromatography.

2-Fluoro-*N*-phenylpyridin-4-amine (5a): Yellow solid; mp 148–150 °C; GC-MS: *m*/*z* (%) = 188 (100) $[M]^+$, 187 (65), 167 (20); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.45 (d, *J* = 1.7 Hz, 1 H), 6.67–6.78 (m, 2 H), 7.23 (d, *J* = 6.8 Hz, 3 H), 7.44 (t, *J* = 7.1 Hz, 2 H), 7.86 (d, *J* = 7.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 92.5 (q, $J_{C–F}$ = 44.1 Hz), 108.2 (q, $J_{C–F}$ = 3.1 Hz), 122.4 (d), 129.7 (d), 138.9 (s), 147.8 (d), 138.9 (s), 147.8 (q, $J_{C–F}$ = 16.6 Hz), 154.5 (d, $J_{C–F}$ = 3.1 Hz), 165.5 (d, $J_{C–F}$ = 221.5 Hz).

2-Fluoro-*N*-(4-methoxyphenyl)pyridin-4-amine (5b): Yellow crystals; mp 150 °C; GC-MS: *m*/*z* (%) = 218 (79)$[M]^+$, 203 (100), 155 (13); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.83 (s, 3 H), 6.20 (d, *J* = 1.7 Hz, 1 H), 6.31 (s, 1 H), 6.51 (td, J_1 = 5.9 Hz, J_2 = 1.9 Hz, 1 H), 6.95 (d, *J* = 8.9 Hz, 2 H), 7.14 (d, *J* = 8.8 Hz, 2 H), 7.81 (d, *J* = 8.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 55.5 (t), 91.6 (q, $J_{C–F}$ = 42.4 Hz), 107.5 (q, $J_{C–F}$ = 2.8 Hz), 114.9 (d), 125.8 (d), 131.4 (s), 147.4 (q, $J_{C–F}$ = 18.7 Hz), 156.5 (d, $J_{C–F}$ = 11.6 Hz), 157.6 (s), 165.5 (d, $J_{C–F}$ = 232.7 Hz).

2-Fluoro-*N*-(2-methoxyphenyl)pyridin-4-amine (5c): Brown oil; GC-MS: *m*/*z* (%) = 218 (100)$[M]^+$, 203 (83), 175 (33); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.85 (s, 3 H), 6.45 (d, *J* = 1.9 Hz, 1 H), 6.56 (s, 1 H), 6.70 (d, *J* = 5.8 Hz, 1 H), 6.96 (t, *J* = 6.9 Hz, 1 H), 7.04–7.17 (m, 1 H), 7.35 (d, *J* = 7.4 Hz, 1 H), 7.87 (d, *J* = 5.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 55.6 (t), 92.8 (q, $J_{C–F}$ = 42.4), 108.7 (q, $J_{C–F}$ = 2.5 Hz), 111.2 (d), 120.7 (d), 120.8 (d), 124.4 (d), 128.5 (s), 147.6 (q, $J_{C–F}$ = 18.4 Hz), 150.7 (s), 154.6 (d, $J_{C–F}$ = 10.2 Hz), 165.5 (d, $J_{C–F}$ = 232.1 Hz).

***N*-(4-Chlorophenyl)-2-fluoropyridin-4-amine (5d):** Colorless solid; mp 175–178 °C; GC-MS: *m*/*z* (%) = 222 (100)$[M]^+$, 224 (47), 186 (31); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.31 (s, 1 H), 6.35 (d, *J* = 1.9 Hz, 1 H), 6.63 (d, *J* = 5.8 Hz, 1 H), 7.14 (d, *J* = 8.8 Hz, 2 H), 7.35 (d, *J* = 8.6 Hz, 2 H), 7.9 (d, *J* = 5.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 92.9 (q, $J_{C–F}$ = 42.7 Hz), 108.2 (q, $J_{C–F}$ = 3.5 Hz), 123.8 (d), 129.9 (d), 130.3 (s), 137.5 (s), 148.1 (q, $J_{C–F}$ = 17.6 Hz), 154.8 (d, $J_{C–F}$ = 14.7 Hz), 165.5 (d, $J_{C–F}$ = 235.2 Hz).

Ethyl 4-(2-fluoropyridin-4-ylamino)benzoate (5e): Light-yellow solid; mp 170 °C; GC-MS: *m*/*z* (%) = 260 (67)$[M]^+$, 232 (25), 215 (100); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.40 (t, *J* = 7.1 Hz, 3 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 6.56 (d, *J* = 1.7 Hz, 1 H), 6.72 (s, 1 H), 6.79 (d, *J* = 5.6 Hz, 1 H), 7.19–7.26 (m, 2 H), 7.97 (d, *J* = 5.8 Hz, 1 H), 8.06 (d, *J* = 8.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.4 (q), 60.9 (t), 94.2 (q, $J_{C–F}$ = 41.3 Hz), 109.2 (q, $J_{C–F}$ = 3.5 Hz), 119.5 (d), 125.7 (s), 131.4 (d), 143.5 (s), 148.2 (q, $J_{C–F}$ = 19.2 Hz), 153.4 (d, $J_{C–F}$ = 11.3 Hz), 165.9 (d, $J_{C–F}$ = 234.3 Hz).

4-(2-Fluoropyridin-4-ylamino)benzonitrile(5f): Yellow solid; mp 195–197 °C; GC-MS: *m*/*z* (%) = 213 (100)$[M]^+$, 212 (45), 192 (16); ^{1}H NMR (CD_3OD, 200 MHz): δ = 6.68 (d, *J* = 1.7 Hz, 1 H), 6.98 (d, *J* = 5.8 Hz, 1 H), 7.35 (d, *J* = 8.6 Hz, 2 H), 7.70 (d, *J* = 8.6 Hz, 2 H), 7.92 (d, *J* = 6.6 Hz, 1 H). ^{13}C NMR (CD_3OD, 50 MHz): δ = 97.6 (q, $J_{C–F}$ = 39.9 Hz), 108.8 (d), 113.2 (q, $J_{C–F}$ = 3.2 Hz), 122.16 (s), 123.1 (d), 137.4 (d), 148.67 (d), 151.1 (q, $J_{C–F}$ = 15.8 Hz), 158.0 (d, $J_{C–F}$ = 11.6 Hz), 169.2 (d, $J_{C–F}$ = 234.1 Hz).

2-Fluoro-*N*-(4-phenoxyphenyl)pyridin-4-amine (5g): Brown crystals; mp 149 °C; GC-MS: *m*/*z* (%) = 280 (100)$[M]^+$, 203 (63), 77 (41); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.51 (d, *J* = 1.9 Hz, 1 H), 6.61 (s, 1 H), 6.81 (d, *J* = 5.8 Hz, 1 H), 7.23 (d, *J* = 2.1 Hz, 2 H), 7.37 (m, 3 H), 7.48 (s, 1 H), 7.57 (t, *J* = 7.9 Hz, 3 H), 8.80 (d, *J* = 5.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 92.0 (q, $J_{C–F}$ = 39.5 Hz), 107.8 (q, $J_{C–F}$ = 3.2 Hz), 118.9 (d), 119.9 (d), 123.5 (d), 125.0 (d), 129.9 (d), 133.9 (s), 147.9 (q, $J_{C–F}$ = 22.9 Hz), 154.8 (s), 155.8 (d, $J_{C–F}$ = 11.9 Hz), 157.0 (s), 165.6 (d, $J_{C–F}$ = 233.0 Hz).

2-Fluoro-*N*-(4-morpholinophenyl)pyridin-4-amine (5h): Colorless crystals; mp 154 °C; GC-MS: *m*/*z* (%) = 273 (100)$[M]^+$, 215 (80), 214 (21); ^{1}H NMR ($CDCl_3$, 200 MHz):

δ = 3.16 (s, 4 H), 3.88 (t, *J* = 4.8 Hz, 4 H), 6.21 (s, 1 H), 6.28 (s, 1 H), 6.50 (d, *J* = 5.6 Hz, 1 H), 6.93 (d, *J* = 6.9 Hz, 2 H), 7.10 (d, *J* = 8.6 Hz, 2 H), 7.81 (d, *J* = 6.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 49.4 (t), 66.8 (t), 91.7 (q, $J_{C–F}$ = 43.7 Hz), 107.6 (q, $J_{C–F}$ = 3.2 Hz), 116.6 (d), 125.2 (d), 130.9 (s), 147.4 (q, $J_{C–F}$ = 17.3 Hz), 149.1 (s), 156.4 (d, $J_{C–F}$ = 13.7 Hz), 165.5 (d, $J_{C–F}$ = 233.0 Hz).

***N*-Benzyl-2-fluoropyridin-4-amine (5i):** Yellow oil; GC-MS: *m*/*z* (%) = 202 (42)[M]$^+$, 91 (100), 65 (11); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.36 (d, *J* = 4.4 Hz, 2 H), 5.03 (s, 1 H), 6.00 (d, *J* = 1.8 Hz, 1 H), 6.32–6.40 (m, 1 H), 7.27–7.38 (m, 5 H), 7.75 (d, *J* = 5.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 45.2 (t), 88.5 (q, $J_{C–F}$ = 51.2 Hz), 104.9 (q, $J_{C–F}$ = 2.4 Hz), 125.8 (d), 126.1 (d), 135.5 (s), 145.1 (q, $J_{C–F}$ = 19.1 Hz), 155.5 (d, $J_{C–F}$ = 12.3 Hz), 161.3 (d), 165.8 (d, $J_{C–F}$ = 232.2 Hz).

2-Fluoro-*N*-(4-methoxybenzyl)pyridin-4-amine (5j): Yellow solid; mp 123–124 °C; GC-MS: *m*/*z* (%) = 121 (100), 122 (9), 232 (7)[M]$^+$; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.73 (s, 3 H), 4.20 (d, *J* = 5.3 Hz, 2 H), 4.75 (s, 1 H), 5.92 (d, *J* = 1.8 Hz, 1 H), 6.27 (td, J_1 = 5.9 Hz, J_2 = 1.8 Hz, 1 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 7.16 (d, *J* = 8.8 Hz, 2 H), 7.69 (d, *J* = 5.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 46.7 (t), 55.3 (q), 90.4 (q, $J_{C–F}$ = 42.7 Hz), 106.9 (q, $J_{C–F}$ = 2.5 Hz), 114.3 (d), 128.8 (d), 129.2 (s), 147.2 (q, $J_{C–F}$ = 18.7 Hz), 157.3 (d, $J_{C–F}$ = 12.0 Hz), 159.2 (s), 165.5 (d, $J_{C–F}$ = 232.1 Hz).

2-Fluoro-4-(piperidin-1-yl)pyridine (5k): Yellow oil. GC-MS: *m*/*z* (%) = 180 (59)[M]$^+$, 179 (100), 123 (22); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.51–1.63 (m, 6 H), 3.22–3.31 (m, 4 H), 6.11 (s, 1 H), 6.54 (dt, J_1 = 6.1 Hz, J_2 = 1.9 Hz, 1 H), 7.83 (d, *J* = 6.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 24.2 (t), 25.0 (t), 91.3 (q, $J_{C–F}$ = 42.0 Hz), 105.5 (s), 147.5 (q, $J_{C–F}$ = 10.1 Hz), 158.8 (q, $J_{C–F}$ = 11.7 Hz), 166.1 (d, $J_{C–F}$ = 232.1 Hz).

***N*-(2-Fluoropyridin-4-yl)pyridin-2-amine (6a):** Yellow solid; mp 143 °C; GC-MS: *m*/*z* (%) = 188 (100), 189 (30)[M]$^+$, 168 (8); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.80–6.90 (m, 2 H), 7.09 (d, *J* = 6.1 Hz, 1 H), 7.15 (s, 1 H), 7.32 (d, *J* = 1.8 Hz, 1 H), 7.64 (m, 1 H), 7.99 (d, *J* = 5.4 Hz, 1 H), 8.34 (d, *J* = 3.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 95.9 (q, $J_{C–F}$ = 43.2 Hz), 110.2 (q, $J_{C–F}$ = 3.1 Hz), 11.7 (d), 117.5 (d), 138.1 (d), 147.7 (q, $J_{C–F}$ = 17.3 Hz), 148.2 (d, $J_{C–F}$ = 12.6 Hz), 151.8 (d), 153.5 (s), 165.2 (d, $J_{C–F}$ = 233.4 Hz).

***N*-(2-Fluoropyridin-4-yl)pyridin-3-amine (6b):** Colorless crystals; mp 152 °C; GC-MS: *m*/*z* (%) = 189 (100)[M]$^+$, 188 (37), 168 (22); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.39 (d, *J* = 1.9 Hz, 1 H), 6.71 (d, *J* = 5.8 Hz, 1 H), 7.22–7.42 (m, 2 H), 7.61 (d, *J* = 8.8 Hz, 1 H), 7.91 (d, *J* = 5.9 Hz, 1 H), 8.40 (d, *J* = 4.1 Hz, 1 H), 8.51 (s, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 92.9 (q, $J_{C–F}$ = 43.0 Hz), 108.3 (q, $J_{C–F}$ = 3.1 Hz), 124.1 (d), 129.1 (d), 136.2 (s), 143.8 (d), 145.4 (d), 148.0 (q, $J_{C–F}$ = 18.0 Hz), 154.6 (d, $J_{C–F}$ = 12.0 Hz), 165.5 (d, $J_{C–F}$ = 234.0 Hz).

***N*-(2-Fluoropyridin-4-yl)-4-phenylthiazol-2-amine (6c):** Colorless crystals; mp 195 °C; GC-MS: *m*/*z* (%) = 271 (100)[M]$^+$, 134 (49), 270 (39); ^{1}H NMR (CD_3OD, 200 MHz): δ = 7.27 (s, 1 H), 7.39–7.49 (m, 4 H), 7.70 (d, *J* = 1.6 Hz, 1 H), 7.94 (d, *J* = 7.0 Hz, 2 H), 7.98 (d, *J* = 5.8 Hz, 1 H). ^{13}C NMR (CD_3OD, 50 MHz): δ = 95.9 (q, $J_{C–F}$ = 49.4 Hz), 111.1 (q, $J_{C–F}$ = 3.0 Hz), 127.0 (d), 128.9 (d), 143.8 (s), 148.0 (q, $J_{C–F}$ = 19.4 Hz), 152.9 (d), 153.7 (d), 155.2 (q, $J_{C–F}$ = 12.4 Hz), 165.2 (d, $J_{C–F}$ = 239.3 Hz).

4-Iodo-2-(piperidin-1-yl)pyridine (7): Yellow oil; GC-MS: *m*/*z* (%) = 288 (100)[M]$^+$, 258 (63), 204 (34); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.62 (s, 6 H), 3.50 (d, *J* = 5.5 Hz, 4 H), 6.89 (dd, J_1 = 5.1 Hz, J_2 = 1.2 Hz, 1 H), 6.99 (s, 1 H), 7.79 (d, *J* = 5.1 Hz, 1 H).^{13}C NMR ($CDCl_3$, 50 MHz): δ = 24.6 (t), 25.4 (t), 46.1 (t), 106.6 (s), 115.9 (d), 120.9 (d), 148.2 (d), 159.7 (s).