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# Direct and regioselective C(sp<sup>3</sup>)-H bond fluorination of 2-alkyl azaarenes with selectfluor

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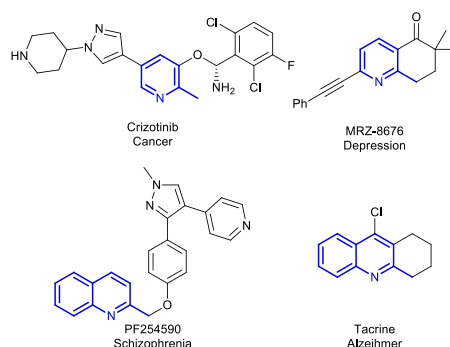
## Abstract

Herein, a regioselective and direct mono-fluorination strategy of pyridylic and quinolinic C(sp<sup>3</sup>)-H bonds was developed under transition metal free conditions with Selectfluor. The reaction was performed under smooth conditions and afforded fluorinated azaheterocycles including 2-methylpyridines and quinolines in moderate to good yields.

Keywords : Fluorination, azaheterocycle, Selectfluor, 2-methylpyridines, 2-methylquinolines

## Introduction

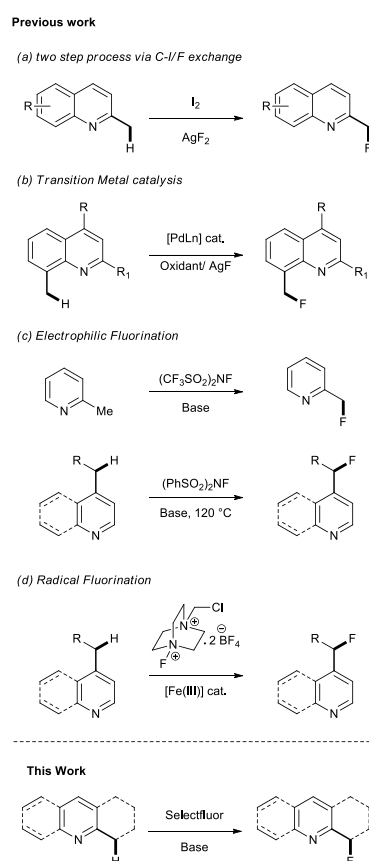
Nitrogen-containing aromatic heterocycles are abundant and ubiquitous scaffolds found in a large variety of natural products, agrochemicals, synthetic drugs and pharmaceuticals.



**Figure 1.** Selective examples of bioactive compounds bearing 2-alkyl substituted pyridine and quinoline core.

In particular, C2-substituted pyridines and quinolines exhibit a wide range of biological properties such as antimalarial,<sup>2</sup> anticancer,<sup>3</sup> anti-inflammatory<sup>4</sup> or antidepressant activities<sup>5</sup> as exemplified by compounds shown in Figure 1: Crizotinib,<sup>6</sup> PF254590,<sup>7</sup> MRZ-8676<sup>8</sup> and Tacrine<sup>9</sup> a well-known acetyl and butyrylcholinesterase inhibitor for the treatment of Alzheimer's disease withdrawn from its clinical use due to its liver toxicity.<sup>10</sup> Additionally, they are versatile structural synthons in molecular synthesis. Since the introduction of fluorine atom into azaarenes hugely impacts their pharmacokinetic properties, prevents oxidative metabolism and more generally the overall biological activities of parent molecules,<sup>11</sup> the development of novel methodologies for the late stage fluorination of 2-alkylpyridines and 2-alkylquinolines is still highly desirable. Numerous strategies were developed for the direct functionalization of a carbon adjacent to the quinoline or pyridine ring<sup>12</sup> surprisingly, fluorination methods are limited. The classical synthetic approach for the monofluorination of alkylated pyridines and quinolines is based on fluorine displacement of a leaving group at the reaction site typically under harsh conditions (Figure 2, a).<sup>13</sup> Recently, Shibatomi's group reported a decarboxylative fluorination of substituted 2-pyridylacetate to 2-(fluoroalkyl)pyridine, the main drawback of this method being the

use of prefunctionalized substrates.<sup>14</sup> During the last decade, significant progress has been made on the direct site selective fluorination of benzylic and aliphatic C(sp<sup>3</sup>)-H bonds proceeding *via* transition metal catalysis, radical or photosensitized activation,<sup>15</sup> however direct fluorination of pyridylic and quinolinic C(sp<sup>3</sup>)-H bonds remains sparse. In this context, efficient late-stage fluorination of 2-alkylpyridine and 2-alkylquinoline under mild conditions is a particularly appealing and highly challenging task. Sandford and co-workers<sup>16</sup> described the first pallado-catalyzed C-H fluorination of 8-methylquinoline (Figure 2, b). Under this condition no fluorination was observed at the C2 positions of the quinoline ring. Pioneering work by the group of DesMarteau<sup>17</sup> demonstrated that fluoro-methylpyridines can be generated by electrophilic fluorination from 2- and 4-methyl pyridines in the presence of N-fluoro-bis[(trifluoromethyl)sulfonyl]imide as fluorinated agent via an ionic mechanism. Since this seminal report, Britton and co-workers<sup>18</sup> reported an elegant electrophilic mono-fluorination of 4-alkylpyridines including annulated pyridines and 4-alkylquinolines with N-fluorobenzenesulfonimide (NFSI), however only a single example of fluorination of 2-annulated pyridine is described (Figure 2, c). Soon afterward, the group of Humbeck<sup>19</sup> developed an efficient benzylic fluorination of 4-alkylquinolines through an unusual single-electron transfer thanks to the formation of a selectfluor/pyridine charge transfer complex (Figure 2, d). Nevertheless, only 4-alkylquinolines were employed and to the best of our knowledge no direct fluorination of 2-alkylquinolines or 2-alkylpyridines have been described previously. Herein, we report a regioselective and direct fluorination on the C2 pyridylic or quinolinic carbon atoms under mild conditions.



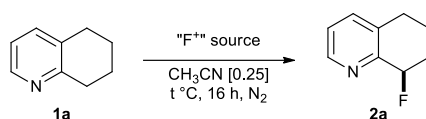
**Figure 2.** Direct fluorination of pyridylic and quinolinic C(sp<sup>3</sup>)-H bonds.

## Results and discussion

At the outset of the study, 2,3-cyclohexenopyridine (**1a**) was selected as model substrate to investigate the direct fluorination of 2-alkylazaarenes. Interestingly, fluorination with NFSI as fluorine source in acetonitrile under reflux, which is an effective system for direct fluorination of C4-alkylpyridines,<sup>18</sup> was

inefficient since no reaction was observed (Table 1, entry 1). To our pleasure, the use of one equivalent of selectfluor was found to be effective furnishing **2a** after stirring in acetonitrile at 60 °C and inert atmosphere for 16 h albeit in low yield (Table 1, entry 2). Encouragingly, a reduced reaction temperature provided higher yield (Table 1, entry 3). Further optimization was then performed, starting from an investigation of the performance of different bases. The reaction efficiency was further enhanced when performed with NaHCO<sub>3</sub> (Table 1, entry 4) whereas poorer results were obtained with Li<sub>2</sub>CO<sub>3</sub> or Na<sub>2</sub>CO<sub>3</sub> (Table 1, entries 7-8). The addition of catalytic amount of AIBN as radical initiator or the iron(III) complex [FeCl<sub>4</sub>][FeCl<sub>2</sub>-(dmf)<sub>3</sub>]<sup>19</sup> did not further improve the fluorination process (Table 1, entries 5-6). The loading of the base was also tested and the use of 2 equivalent resulted in a slightly better yield (Table 1, entry 9). To our delight, we found that 62 % of the desired product **2a** could be obtained when both reactants are introduced simultaneously over 4 h to the reaction mixture (Table 1, entries 10).

Table 1 Optimization of the reaction conditions for the monofluorination of compound **1a**<sup>a</sup>

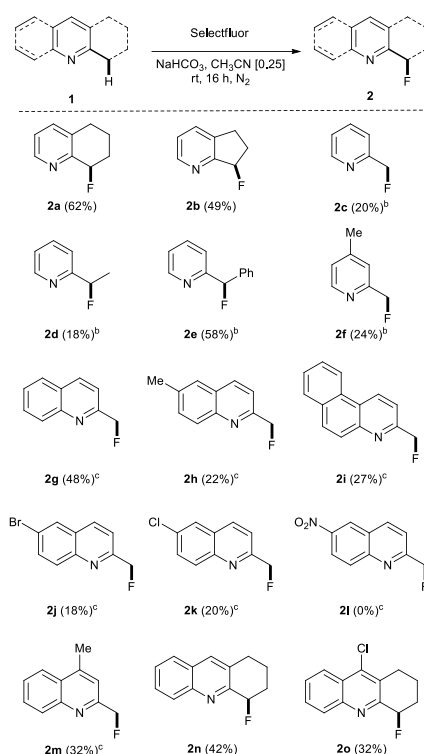


Entry	Fluorine source	Base (x eq)	T (°C)	Yield (%) <sup>b</sup>
1	NFSI	-	80	Traces
2	Selectfluor	-	60	21
3	Selectfluor	-	25	28
4	Selectfluor	NaHCO <sub>3</sub> (1)	25	37
5 <sup>c</sup>	Selectfluor	NaHCO <sub>3</sub> (1)	25	25
6 <sup>d</sup>	Selectfluor	NaHCO <sub>3</sub> (1)	25	22
7	Selectfluor	Li <sub>2</sub> CO <sub>3</sub> (1)	25	28
8	Selectfluor	Na <sub>2</sub> CO <sub>3</sub> (1)	25	21
9	Selectfluor	NaHCO <sub>3</sub> (2)	25	41
10 <sup>e</sup>	Selectfluor	NaHCO <sub>3</sub> (2)	25	62

<sup>a</sup>All reactions unless specified were carried out using **1a** (0.38 mmol, 1 eq), Fluorine source (1 eq) and Base (1 eq), in CH<sub>3</sub>CN ([0.25 M]) under N<sub>2</sub> during 16 h. <sup>b</sup>Isolated yields. <sup>c</sup>10 mol % 1,1'-azobis(cyclohexanecarbonitrile) as a radical initiator. <sup>d</sup>10 mol % [FeCl<sub>4</sub>][FeCl<sub>2</sub>-(dmf)<sub>3</sub>] as catalyst. <sup>e</sup>co-addition of solutions of Selectfluor and **1a** over 4 h.

The generality and limitations of the direct fluorination of 2-alkylazaarenes were then investigated (scheme 1). Firstly, various pyridine derivatives were employed to react with selectfluor with yields ranging from 18 to 62% (scheme 1, **2a-f**). We were pleased to find that 6,7-dihydro-5H-cyclopenta[b]pyridine afforded the monofluorinated product **2b** in decent yield. When very challenging 2-methylpyridine was employed as substrate the reaction could proceed to provide the desired product **2c** albeit in low yield but within the same yield range than the procedure using the highly reactive fluorinating agent (CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>NF. It was observed that 2-fluoro-ethylpyridine **2d** was obtained with lower yield compared to 2-fluoro-methylpyridine however when the benzylic position is stabilized fluorinated adduct **2e** could be obtained with good yield. Interestingly, fluorination of 2,4-dimethylpyridine provided 4-methyl-2-fluoromethylpyridine **2d** with a complete regioselectivity. Thus, this methodology could represent an interesting opportunity for a late stage site selective fluorination in case of another benzylic position was present in the molecule. To further explore the scope of the reaction, various quinolines were employed. 2-methylquinolines proved to be reactive toward selectfluor with a slight modification of the reaction conditions providing the corresponding fluorinated products in low to good yields (18-48%). 2-methylquinolines bearing electron donating group (-Me, -Ph) **1h** and **1i** on the phenyl ring gave the desired product in higher yields compared to those with electro-withdrawing substituents (-Br, -Cl) **1j** and **1k**. Unfortunately, strong electro-

withdrawing group (NO<sub>2</sub>) containing 2-methylquinoline **1e** was not tolerated under the reaction conditions. Though 2-methylquinolines deliver fluorinated compounds with low to moderate yields this represent the first example of direct fluorination of 2-methylquinoline derivatives. As for pyridines, the reaction also proceed with complete regioselectivity to give **2m** in 32% yield. The fluorination was also compatible with 1,2,3,4-tetrahydroacridines **1n** and **1o**, decent yield could be obtained and halogen bearing substrate **1o** could offer an opportunity to further functionalize the product. In any case, the formation of by-products was not observed and the unreacted remaining 2-alkylazaarenes can be recoverable.

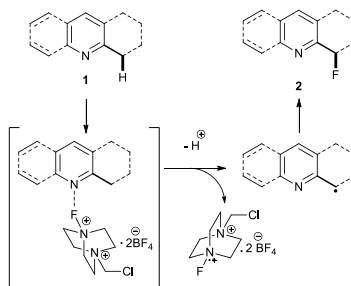


**Scheme 1.** <sup>a</sup>All reactions unless specified were carried out using **1a** (0.38 mmol, 1 eq), Fluorine source (1 eq) and Base (2 eq), in CH<sub>3</sub>CN ([0.25 M]) under N<sub>2</sub> during 16 h. <sup>b</sup>NMR yields. <sup>c</sup>**1a** (0.38 mmol, 1 eq), Fluorine source (2 eq) and Base (3 eq), in CH<sub>3</sub>CN ([0.25 M]) at 35 °C under N<sub>2</sub> during 16 h.

To gain insights into the fluorination mechanism, we conducted some control experiment under the standard conditions. 2-alkylazaarenes usually serve as nucleophilic coupling partner toward fluorinated agents such as NFSI.<sup>18</sup> Ended, 2-azaheterocycles can be first converted to the corresponding N-fluoropyridinium salt *via* addition to the fluorinating agent. Then, after the loss of one proton on the methylene site the corresponding tautomer can react with selectfluor to provide the pyridylic C-F bond. Finally, 2-alkylpyridines can attack the resulting pyridinium to deliver fluoroalkylazaarenes and the pyridinium intermediate.<sup>19</sup> However, the reaction did not proceed with N-fluoropyridinium triflate as fluorine source. These results suggested that a radical pathway rather than an ionic pathway<sup>16</sup> might be involved. As also described by Humbeck<sup>19</sup> we evaluated the formation of pyridine/Selectfluor charge-transfer complex in solution using UV/Vis spectroscopy. The 2,3-cyclohexenopyridine solution showed a maximum absorbance at a wavelength of 269 nm, however the absorbance of the reaction mixture under identical concentration was more intense, with its wavelength nearly identical to the 2,3-cyclohexenopyridine maximum.

On the basis of these investigations and literature precedents for benzylic fluorination of C4-alkylated N-heterocycles with selectfluor<sup>17</sup> a plausible mechanism is given in scheme 3. At first, a charge-transfer complex between alkylquinolines or alkylpyridines and selectfluor is formed. Then, the complex

exhibits a stepwise single electron transfer or a concerted proton-coupled electron transfer to generate the C2 pyridylic or quinolinic radical which undergoes a fluorine atom transfer to yield the desired fluorinated compound.



**Scheme 2.** Mechanistic proposal for the fluorination of pyridylic and quinolinic C(sp<sup>3</sup>)-H bonds.

In conclusion, we successfully developed the direct and regioselective fluorination of the C(sp<sup>3</sup>)-H bonds of 2-alkylpyridine and 2-alkylquinoline derivatives under mild condition with selectfluor. Various fluorinated N-heterocycles were synthesized in low to good yields. The mechanistic study suggested that the fluorination might proceed via a radical pathway. This work provides a useful tool for the synthesis of C2-fluoromethylazaarenes which are versatile skeletons for medicinal chemistry.

## Experimental section

All reagents were purchased from commercial suppliers (Strem Chemicals Inc., Sigma-Aldrich or Alfa Aesar) and were used without further purification unless otherwise indicated. Thin-layer chromatography plates (Silica gel 60 F254, Merck) and visualized under UV (254 nm). Chromatographic purifications were performed using PuriFlash® 215 equipped with UV (90-840 nm) and ELSD detectors purchased from Interchim. Pre-packed flash chromatography Silica HP columns (30 μm) were used. <sup>1</sup>H and <sup>13</sup>C were recorded on a Bruker AVANCE 300 spectrometer at 300 MHz (75 MHz). High-resolution mass spectra (HRMS) were performed on a Thermo LTQ orbitrap mass spectrometer.

### Procedures

#### General procedure A

To an oven-dried flask, NaHCO<sub>3</sub> was added (0.750 mmol, 2 equiv.) followed by a co-addition over 4 h of a solution of nitrogen heterocycles (0.375 mmol, 1 equiv.) and a solution of selectfluor (0.375 mmol, 1 equiv.) in dry acetonitrile (1.5 mL, [0.25]). The reaction mixture was then stirred for 16 h at room temperature gradually forming an orange brown solution. The reaction mixture was diluted with dichloromethane, washed with a saturated NaHCO<sub>3</sub> solution and extracted with dichloromethane. The combined organic layers were dried with MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether/EtOAc = 100:0 to 95:5) to give fluorinated nitrogen heterocycles.

#### General procedure B

To an oven-dried flask, to a solution of nitrogen heterocycles (0.375 mmol, 1 equiv.) in dry acetonitrile (3.0 mL, [0.12]) was added NaHCO<sub>3</sub> (1.12 mmol, 3 equiv.) and selectfluor (0.75 mmol, 2 equiv.). The reaction mixture was then stirred for 16 h at 35 °C gradually forming an orange brown solution. The reaction mixture was diluted with dichloromethane, washed with a saturated NaHCO<sub>3</sub> solution and extracted with dichloromethane. The combined organic layers were dried with MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether/EtOAc = 100:0 to 90:10) to give fluorinated nitrogen heterocycles.

### 8-Fluoro-5,6,7,8-tetrahydroquinoline (2a)

Procedure A; Yellow oil, yield: 35.1 mg (62%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 8.54 (dd,  $J$  = 4.6, 0.7 Hz, 1H), 7.48 (d,  $J$  = 7.8 Hz, 1H), 7.21 (ddd,  $J$  = 7.7, 4.7, 2.0 Hz, 1H), 5.56 (dt,  $J$  = 49.8, 3.3 Hz, 1H), 2.90-2.69 (m, 2H), 2.4-2.32 (m, 2H), 2.06-1.81 (m, 3H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 152.4, 148.2 (d,  $J$  = 2.5 Hz), 137.4, 133.8, 124.0 (d,  $J$  = 3.5 Hz), 88.9 (d,  $J$  = 168.0 Hz), 29.8 (d,  $J$  = 21.4 Hz), 28.4, 17.6.

$^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282.2 MHz):  $\delta$  = -163.0-163.3 (m, 1F).

HRMS:  $m/z$   $[\text{M}+\text{H}]^+$  calc. for  $\text{C}_9\text{H}_{11}\text{FN}$ , 152.0870 found 152.0868.

### 7-Fluoro-6,7-dihydro-5H-cyclopenta[b]pyridine (2b)<sup>18a</sup>

Procedure A; Yellow oil, yield: 25.2 mg (49%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 8.53 (d,  $J$  = 4.6 Hz, 1H), 7.62 (d,  $J$  = 7.7 Hz, 1H), 5.91 (ddd,  $J$  = 56.5, 6.3, 2.8 Hz, 1H), 3.15 (ddd,  $J$  = 10.8, 8.0, 3.4 Hz, 1H), 3.01 – 2.74 (m, 1H), 2.64 – 2.19 (m, 2H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 160.0 (d,  $J$  = 15.8 Hz), 149.1, 138.2 (d,  $J$  = 4.0 Hz), 133.5, 124.3, 95.7 (d,  $J$  = 175.2 Hz), 30.8 (d,  $J$  = 22.7 Hz), 27.9.

$^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282.2 MHz):  $\delta$  = 167.7 (dt,  $J$  = 56.5, 28.0 Hz).

HRMS:  $m/z$   $[\text{M}+\text{H}]^+$  calc. for  $\text{C}_8\text{H}_9\text{FN}$ , 131.0165 found 131.0163.

### 2-(Fluoromethyl)pyridine (2c)<sup>17</sup>

Procedure A; Yellow oil, Yield determined by analysis of  $^1\text{H}$ -NMR spectra of crude reaction product using 4-fluorotoluene as internal standard: 20 % yield.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 8.57 (d,  $J$  = 4.8 Hz, 1H), 7.74 (td,  $J$  = 7.7, 1.7 Hz, 1H), 7.45 (d,  $J$  = 7.9 Hz, 1H), 7.26 - 7.19 (m, 1H), 5.48 (d,  $J$  = 46.9 Hz, 2H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 156.5 (d,  $J$  = 21.2 Hz), 149.3, 137.1, 123.2, 120.7 (d,  $J$  = 5.7 Hz), 84.5 (d,  $J$  = 169.6 Hz).

$^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282.2 MHz):  $\delta$  = -221.1 (t,  $J$  = 46.9 Hz).

HRMS:  $m/z$   $[\text{M}+\text{H}]^+$  calc. for  $\text{C}_6\text{H}_7\text{FN}$ , 112.0557 found 112.0555.

### 2-(1-Fluoroethyl)pyridine (2d)

Procedure A; Yield determined by analysis of  $^1\text{H}$ -NMR spectra of crude reaction product using 4-fluorotoluene as internal standard: 16 % yield.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 8.64-8.63 (m, 2H), 7.28 (d, 1H,  $J$  = 6.0 Hz), 5.63 (dt, 1H,  $J$  = 47.4, 6.6 Hz), 1.64 (dd, 3H,  $J$  = 24.3, 6.6 Hz).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 152.3 (d,  $J$  = 16.0 Hz), 147.9 (d,  $J$  = 2.5 Hz), 137.2, 133.6, 128.8 (d,  $J$  = 3.6 Hz), 88.8 (d,  $J$  = 168.0 Hz), 29.6 (d,  $J$  = 21.8 Hz), 28.2, 17.4 (d,  $J$  = 2.0 Hz).

$^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282.2 MHz):  $\delta$  = -176.9 (dq, 1F,  $J$  = 24.3, 47.4 Hz).

HRMS:  $m/z$   $[\text{M}+\text{H}]^+$  calc. for  $\text{C}_7\text{H}_9\text{FN}$ , 126.0714 found 126.0712.

### 2-(Fluoro(phenyl)methyl)pyridine (2e)

Procedure A; Yellow oil, yield: 40.6 mg (58%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 8.38 (d,  $J$  = 4.8 Hz, 1H), 7.50 (t,  $J$  = 7.7 Hz, 1H), 7.36 (d,  $J$  = 7.8 Hz, 1H), 7.33 – 7.11 (m, 5H), 6.97 (dd,  $J$  = 17.2, 9.9 Hz, 1H), 6.38 (d,  $J$  = 46.7 Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 159.1 (d,  $J$  = 26.6 Hz), 149.1 (d,  $J$  = 2.2 Hz), 138.8 (d,  $J$  = 21.1 Hz), 136.9, 128.7 (d,  $J$  = 2.2 Hz), 128.5, 126.6 (d,  $J$  = 6.5 Hz), 123.0, 120.0 (d,  $J$  = 5.6 Hz), 94.7 (d,  $J$  = 174.2 Hz).

$^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282.2 MHz):  $\delta$  = -174.62 (d,  $J$  = 46.7 Hz).

HRMS:  $m/z$   $[\text{M}+\text{H}]^+$  calc. for  $\text{C}_{12}\text{H}_{11}\text{FN}$ , 188.0870 found 188.0873.

### 2-(Fluoromethyl)-4-methylpyridine (2f)

Procedure A; Yield determined by analysis of <sup>1</sup>H-NMR spectra of crude reaction product using 4-fluorotoluene as internal standard: 24 % yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 8.41 (d, J = 5.0 Hz, 1H), 7.34 - 7.20 (m, 1H), 7.13 - 6.93 (m, 1H), 5.44 (d, J = 47.0 Hz, 2H), 2.37 (s, 3H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): δ = 156.2 (d, J = 21.0 Hz), 149.1, 148.3, 124.1, 121.6 (d, J = 5.5 Hz), 84.6 (d, J = 169.4 Hz), 21.2.

<sup>19</sup>F NMR (CDCl<sub>3</sub>, 282.2 MHz): δ = -220.8 (t, J = 47.0 Hz).

HRMS: m/z [M+H]<sup>+</sup> calc. for C<sub>7</sub>H<sub>9</sub>FN, 126.0714 found 126.0715.

### 2-(Fluoromethyl)quinoline (2g)<sup>13</sup>

Procedure B; Brown solid, yield: 29.0 mg (46%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 8.11 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.63 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.53 - 7.39 (m, 2H), 5.56 (d, J = 47.0 Hz, 2H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): δ = 156.9 (d, J = 21.8 Hz), 147.5, 137.2, 130.0, 129.1, 127.8, 127.8, 126.8, 118.3 (d, J = 5.1 Hz), 85.1 (d, J = 170.3 Hz).

<sup>19</sup>F NMR (CDCl<sub>3</sub>, 282.2 MHz): δ = -221.30 (t, J = 47.0 Hz).

HRMS: m/z [M+H]<sup>+</sup> calc. for C<sub>10</sub>H<sub>9</sub>FN, 162.07135 found 162.07112.

### 2-(Fluoromethyl)-6-methylquinoline (2h)<sup>13</sup>

Procedure B; Brown solid, yield: 14.4 mg (22%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.96 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.44 (m, 3H), 5.56 (d, J = 47.1 Hz, 2H), 2.42 (s, 3H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): δ = 155.6 (d, J = 21.5 Hz), 145.8, 136.5, 136.3, 132.1, 128.5, 127.6, 126.4, 118.2 (d, J = 4.9 Hz), 85.0 (d, J = 169.8 Hz), 21.4.

<sup>19</sup>F NMR (CDCl<sub>3</sub>, 282.2 MHz): δ = -220.30 (td, J = 47.0, 3.3 Hz).

HRMS: m/z [M+H]<sup>+</sup> calc. for C<sub>11</sub>H<sub>11</sub>FN, 176.0870 found 176.0871.

### 3-(fluoromethyl)benzo[f]quinoline (2i)<sup>13</sup>

Procedure B; Brown solid, yield: 21.4 mg (27%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 8.92 (d, J = 8.6 Hz, 1H), 8.58 - 8.49 (m, 1H), 7.98-7.89 (m, 3H), 7.72 - 7.61 (m, 3H), 5.69 (d, J = 47.0 Hz, 2H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): δ = 156.2 (d, J = 21.9 Hz), 147.5 (d, J = 1.7 Hz), 131.8, 131.7, 131.5, 129.5, 128.8, 127.8, 127.5, 127.3, 124.9 (d, J = 0.9 Hz), 122.7, 118.4 (d, J = 5.4 Hz), 84.9 (d, J = 170.0 Hz).

HRMS: m/z [M+H]<sup>+</sup> calc. for C<sub>14</sub>H<sub>11</sub>FN, 212.0870 found 212.0869.

### 6-Bromo-2-(Fluoromethyl)quinoline (2j)<sup>13</sup>

Procedure B; Brown solid, yield: 16 mg (18%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 8.10 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.76 (dd, J = 9.0, 2.2 Hz, 1H), 7.59 (dd, J = 8.5, 0.9 Hz, 1H), 5.61 (d, J = 46.9 Hz, 2H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 300 MHz): δ = 157.4 (d, J = 21.9 Hz), 146.0, 136.2, 133.5, 130.8, 129.8, 128.8, 120.7, 119.1 (d, J = 5.2 Hz), 84.9 (d, J = 170.8 Hz).

<sup>19</sup>F NMR (CDCl<sub>3</sub>, 282.2 MHz): δ = -221.94 (t, J = 47.0 Hz).

HRMS: m/z [M+H]<sup>+</sup> calc. for C<sub>10</sub>H<sub>8</sub>FN, 239.9819 found 239.9818.

### 6-Chloro-2-(Fluoromethyl)quinoline (2k)<sup>13</sup>

Procedure B; Yellow solid, yield: 14.6 mg (20%).



$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 8.09 (d,  $J$  = 8.5 Hz, 1H), 7.95 (d,  $J$  = 9.0 Hz, 1H), 7.76 (d,  $J$  = 2.0 Hz, 1H), 7.67 - 7.53 (m, 2H), 5.61 (d,  $J$  = 46.9 Hz, 2H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 157.2 (d,  $J$  = 21.9 Hz), 145.8, 136.3, 132.6, 131.0, 130.7, 128.3, 126.4, 119.2 (d,  $J$  = 5.2 Hz).

$^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282.2 MHz):  $\delta$  = -221.81 (t,  $J$  = 46.9 Hz).

HRMS:  $m/z$   $[\text{M}+\text{H}]^+$  calc. for  $\text{C}_{10}\text{H}_8\text{ClFN}$ , 196.0324 found 196.0322.

#### 6-Chloro-2-(Fluoromethyl)quinoline (2m)<sup>13</sup>

Procedure B; Yellow solid, yield: 21.0 mg (32%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 8.01 - 7.92 (m, 1H), 7.87 (dd,  $J$  = 8.4, 1.0 Hz, 1H), 7.60 (ddd,  $J$  = 8.4, 6.9, 1.4 Hz, 1H), 7.45 (ddd,  $J$  = 8.2, 6.9, 1.2 Hz, 1H), 7.31 (s, 1H), 5.50 (d,  $J$  = 47.1 Hz, 2H), 2.61 (s, 3H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 156.49 (d,  $J$  = 21.2 Hz), 147.3, 145.6, 129.6 (2C), 127.7, 126.6, 123.9, 119.0 (d,  $J$  = 4.9 Hz), 85.1 (d,  $J$  = 170.0 Hz), 18.9.

$^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282.2 MHz):  $\delta$  = -221.22 (t,  $J$  = 46.9 Hz).

HRMS:  $m/z$   $[\text{M}+\text{H}]^+$  calc. for  $\text{C}_{10}\text{H}_8\text{ClFN}$ ,  $\text{C}_{11}\text{H}_{11}\text{FN}$ , 177.0948 found 177.0950.

#### 4-Fluoro-1,2,3,4-tetrahydroacridine (2n)

Procedure B; Yellow oil, yield: 31.6 mg (42%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 8.15 (d,  $J$  = 8.5 Hz, 1H), 7.95 (s, 1H), 7.75 (d,  $J$  = 8.2 Hz, 1H), 7.67 (ddd,  $J$  = 8.4, 6.9, 1.4 Hz, 1H), 7.52 (dd,  $J$  = 8.0, 7.0 Hz, 1H), 5.76 (dt,  $J$  = 7.5, 3.4 Hz, 1H), 3.09 (dt,  $J$  = 16.0, 4.2 Hz, 1H), 2.98 - 2.86 (m, 1H), 2.61 - 2.35 (m, 1H), 2.27 - 2.04 (m, 2H), 1.91 (dd,  $J$  = 9.1, 3.2 Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 153.4 (d,  $J$  = 15.2 Hz), 146.6, 136.3, 130.8, 129.2, 129.1, 128.4, 128.3 (d,  $J$  = 1.5 Hz), 127.1 (d,  $J$  = 21.4 Hz), 89.1 (d,  $J$  = 169.4 Hz), 29.9 (d,  $J$  = 21.3 Hz), 28.5, 17.6 (d,  $J$  = 2.2 Hz).

$^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282.2 MHz):  $\delta$  = -162.92 (ddd,  $J$  = 41.0, 29.9, 15.2 Hz, 1F).

HRMS:  $m/z$   $[\text{M}+\text{H}]^+$  calc. for  $\text{C}_{13}\text{H}_{13}\text{FN}$ , 202.1027 found 202.1023.

#### 6-Chloro-2-(Fluoromethyl)quinoline (2o)

Procedure B; Yellow oil, yield: 28.2 mg (32%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 8.22 (d,  $J$  = 8.4 Hz, 1H), 8.15 (d,  $J$  = 8.4 Hz, 1H), 7.80 - 7.69 (m, 1H), 7.63 (dd,  $J$  = 8.0, 7.2 Hz, 1H), 5.72 (dt,  $J$  = 7.5, 3.5 Hz, 1H), 3.34 - 3.16 (m, 1H), 2.87 (dq,  $J$  = 10.4, 4.3 Hz, 1H), 2.48 (ddd,  $J$  = 19.7, 10.8, 4.4 Hz, 1H), 2.19 - 1.93 (m, 3H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 153.7 (d,  $J$  = 15.4 Hz), 147.1, 142.1, 129.8 (d,  $J$  = 7.8 Hz), 129.0, 128.0, 126.4, 123.7, 89.4 (d,  $J$  = 170.8 Hz), 29.2 (d,  $J$  = 21.4 Hz), 26.8, 16.9 (d,  $J$  = 2.6 Hz).

$^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282.2 MHz):  $\delta$  = -164.27 - -164.79 (m, 1F).

HRMS:  $m/z$   $[\text{M}+\text{H}]^+$  calc. for  $\text{C}_{13}\text{H}_{12}\text{ClFN}$ , 236.0637 found 236.0636.

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#### **Supporting Information**

YES

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