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Regioselective Fluorination of Imidazo[1,2-*a*]pyridines with Selectfluor in Aqueous Condition

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Supporting Information

ABSTRACT: A regioselective synthesis of 3-fluorinated imidazo[1,2-*a*]pyridines using 1-chloromethyl-4-fluoro-1,4-diazoniabi cyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) as the fluorinating reagent in aqueous condition is described. In the presence of DMAP, the reaction mainly gave monofluorinated product via electrophilic fluorinated process in moderate to good yields.

Imidazo[1,2-*a*]pyridine moiety is recognized as a "drug prejudice" scaffold because of its diverse biological activities and occurring in a variety of clinical drugs or agricultural chemicals (Figure 1),[1] such as zolpidem,[2] alpidem,[3] olprinone,[4]

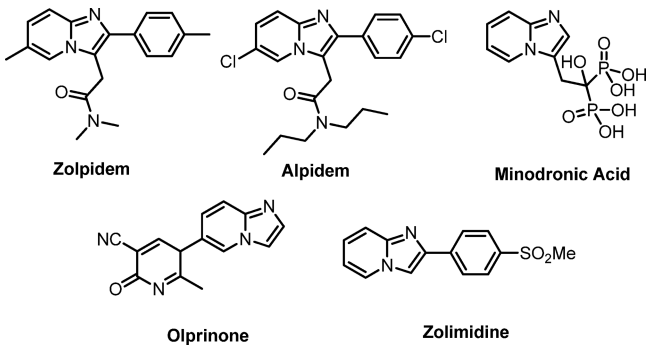

Figure 1. Some clinical drugs based on imidazo[1,2-*a*]pyridine.

minodronic acid,[5] and zolimidine,[6] etc. Thus, the synthesis of imidazo[1,2-*a*]pyridine derivatives with a variety of substituents has aroused much attention. Significant efforts have been made in the area of developing novel strategies for the construction of imidazo[1,2-*a*]pyridines scaffold, and the rapid development in this field was reviewed by Hajra et al. recently.[7] Meanwhile, a set of synthetic methods have been established for the functionalization of imidazo[1,2-*a*]pyridine derivatives. The C-3 position of the imidazo[1,2-*a*]pyridine moiety is electron-rich, which enables it to be attacked by electrophiles or radicals. Thus, a series of metal-catalyzed C−H functionalization reactions on C-3 position to form C−C bonds, including regioselective arylation,[8] alkenylation,[9] formylation,[10] and trifluoromethylation,[11] were achieved. The methods for the formation of C−heteroatom bonds at the same position were also developed in due course, e.g., C-3 halogenation,[12] sulfenylation,[13] hydrazination,[14] and nitrosylation.[15]

It is well-known that fluorine's electronegativity, size, and lipophilicity can dramatically improve metabolic stability and bioavailability for some medical compounds.[16] So the fluorination of organic compounds is continuously the attractive research subject to organic chemists. Selectfluor is commercially available, exceptionally stable, and useful for the incorporation of fluorine into organic molecules.[17] By using 1-chloromethyl-4-fluoro-1,4-diazoniabi cyclo[2.2.2]octane bis-(tetrafluoroborate) (Selectfluor) as the electrophilic fluorinating reagent, several heterocyclic molecules were fluorinated efficiently to provide mono- or difluorinated derivatives. For example, difluorohydroxylation of substituted indoles,[18a] Au[18b] or Ag[18c]-catalyzed cyclization/fluorination of 2-alkynylanilines to synthesize 3,3-difluoro-2-substituted-3*H*-indoles or fluorinated indole derivatives, fluorination of 2-substituted benzo-[*b*]furans,[18d] and fluorination of 3,5-diarylpyrazoles.[18e] Expanding the application of Selectfluor in the fluorination of organic molecule as well as to getting the useful organofluorine compounds are still challenging works. We herein report an efficient method on regioselective fluorination of imidazo[1,2-*a*]pyridines with Selectfluor.

2-Phenylimidazo[1,2-*a*]pyridine (**1a**) was chosen as the model substrate for the optimization of reaction conditions (Table 1). Selectfluor (2 equiv) was used as fluorinated reagent. To our surprise, the desired product 3-fluoro-2-phenylimidazo-[1,2-*a*]pyridine (**2a**) was obtained in 32% yield, accompanied by a 53% yield of the difluorohydroxylated product (**3a**) when the reaction proceeded in the presence of 0.2 equiv $AgNO_3$ in $CHCl_3/H_2O$ (1:1) (entry 1). In the absence of $AgNO_3$, the result showed no obvious difference (entry 2), which indicated that metal might not be involved in this transformation. Increasing the temperature resulted in higher conversion of **1a**, but lowered the total yields of **2a** and **3a** (entries 3, 4). The polar aprotic solvents were also screened, and $CHCl_3$ was

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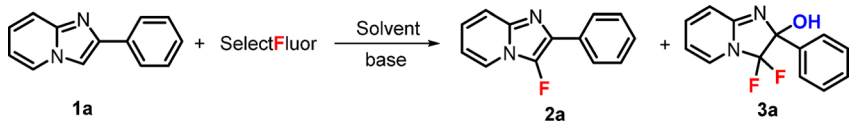
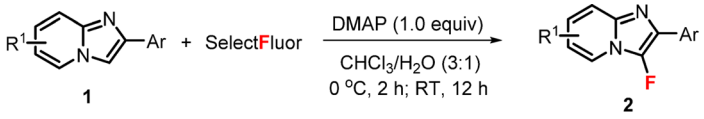
Table 1. Optimization of Reaction Conditions[a]

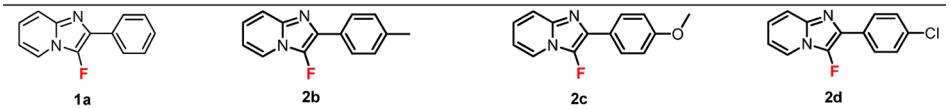


entry	catalyst (equiv)	base	solvent	temperature (°C)	yield (%) 2a	yield (%) 3a (1a)[b]
1	$AgNO_3$ (0.2)	_	$CHCl_3/H_2O$ (1:1)	RT	32	53 (11)
2	_	_	$CHCl_3/H_2O$ (1:1)	RT	35	56 (5)
3	_	_	$CHCl_3/H_2O$ (1:1)	60	28	56
4	_	_	$CHCl_3/H_2O$ (1:1)	100	27	52
5	_	_	CH_2Cl_2/H_2O (1:1)	RT	17	60 (19)
6	_	_	CH_3CN/H_2O (1:1)	RT	23	25 (46)
7	_	_	THF/H_2O (1:1)	RT	17	15 (61)
8	_	_	$CHCl_3/H_2O$ (3:1)	RT	37	57 (trace)
9	_	_	$CHCl_3/H_2O$ (5:1)	RT	32	58 (5)
10	_	_	$CHCl_3$	RT	27	38 (29)
11	_	$NaHCO_3$	$CHCl_3/H_2O$ (3:1)	RT	49	31 (16)
12	_	Et_3N	$CHCl_3/H_2O$ (3:1)	RT	38	trace (57)
13	_	DMAP	$CHCl_3/H_2O$ (3:1)	RT	65	33
14	_	**DMAP**	**$CHCl_3/H_2O$ (3:1)**	**0, 2 h, then RT**	**83**	**15**
15[c]	_	DMAP	$CHCl_3/H_2O$ (3:1)	0, 2 h, then RT	67	9 (21)

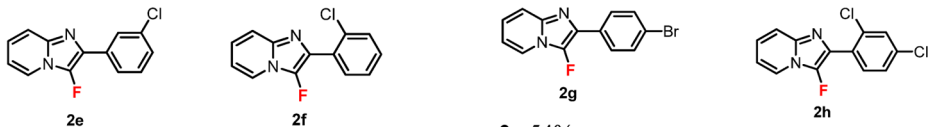
[a]Unless otherwise specified, the reactions were carried out in the presence of **1a** (0.2 mmol), Selectfluor (0.4 mmol), and base (0.2 mmol) in solvent (2 mL) under ambient air for 12 h. All listed yields are isolated ones. [b]The recovered yield of **1a** in parentheses. [c]Selectfluor (0.3 mmol) was used.

Table 2. Regioselective Monofluorination of Aryl Substituted Imidazo[1,2-*a*]pyridines[a]

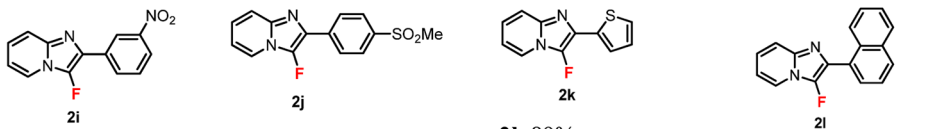




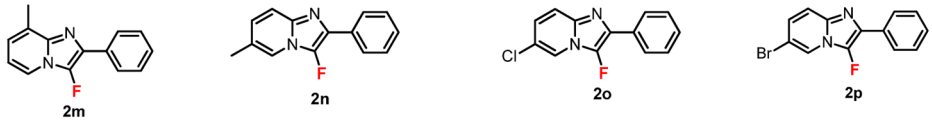
2a 83% **2b** 81% **2c** 75% **2d** 74%



2e 89% **2f** 84% **2g** 54% **2h** 57%



2i 92% **2j** 87% **2k** 89% **2l** 69%



2m 77% **2n** 82% **2o** 86% **2p** 78%

[a]Reaction conditions: **1** (0.20 mmol), Selectfluor (0.40 mmol) and DMAP (0.20 mmol) in $CHCl_3/H_2O$ (3:1, 2 mL) was stirred at 0 °C for 2 h, then at room temperature for 12 h. All listed yields are isolated ones.

proved to be the best one (entries 2, 5–7). The ratio of **1a**, **2a**, and **3a** in the final reaction mixture was obviously influenced by the water content of the solvent. Concerning both the yield of **2a** and the conversion of **1a**, a 3:1 volume ratio of $CHCl_3$ and water was proved to be the best (entries 2, 8–10), in which both **1a** and Selectfluor were well dissolved. The addition of 1.0

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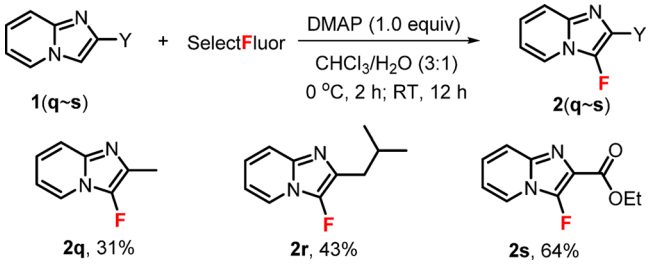
equiv $NaHCO_3$ was helpful for the formation of the 3-fluorinated product **2a** and improved the yield to 49% (entry 11). Other bases were then investigated (entries 12, 13). To our delight, the addition of 4-dimethylaminopyridine (DMAP) dramatically improved both the yield of **2a** (65%) and the conversion of **1a** (~100%). In expectation, lowering the reaction temperature inhibited the formation of the difluorohydroxylation product **3a** and afforded the **2a** in 83% yield (entry 14). In addition, decreasing the amounts of Selectfluor lowered the yield of **2a** and **3a** and the conversion of **1a** (entry 15).

Thus, the optimized conditions were employed to explore the scope and limitations of the fluorination reaction of imidazo[1,2-*a*]pyridines (**1**). The results are summarized in Table 2. First, a wide range of 2-aryl substituted imidazo[1,2-*a*]pyridines were investigated. The results showed that the reaction of imidazo[1,2-*a*]pyridines with electron-donating substituents, such as methyl, methoxyl on the benzene ring, proceeded smoothly and gave the corresponding 3-fluorinated products in good yields (**2a**–**2c**). The para-, meta-, or ortho-halogenated and 2,4-dichloro phenyl substrates were also suitable to the reaction and gave the desired products in moderate to high yields (**2d**–**2h**). Notably, benzene ring bearing strong electron-withdrawing groups were more effective, e.g., nitro-substituted substrates gave excellent yield (**2i**), which might be due to inhibit the second electrophilic fluorinated reaction. The anti-ulcer drug zolimidine bearing electron-withdrawing methylsulfonyl also afforded the corresponding monofluorinated product (**2j**) in 87% yield. Moreover, the reaction of heteroaromatic and polycyclic compounds (**1k** and **1l**) was also suitable to provide monofluorinated product (**2k** and **2l**) in 89% and 69% yield, respectively. In addition, imidazo[1,2-*a*]pyridines with various substituents, such as Me, Cl, and Br, at different positions on the pyridine ring were compatible under these reaction conditions to yield the desired products **2m**–**2p** in satisfactory yields.

Scheme 1. Fluorination of Alkyl or Ethoxycarbonyl Substituted Imidazo[1,2-*a*]pyridines

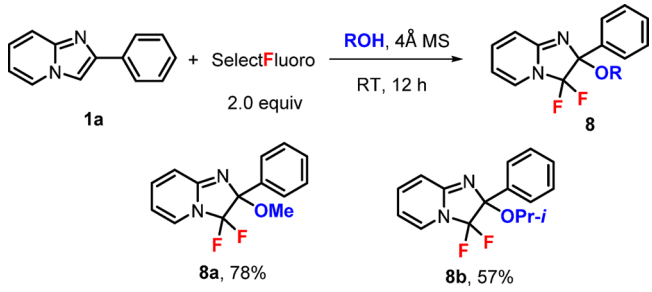


Subsequently, the alkyl or ethoxycarbonyl groups on 2-position of imidazopyridines (**1q** and **1r**) were investigated under the same reaction condition. Electron-poor scaffold seemed more reactive than electron-rich substrates for the monofluorination. As shown in Scheme 1, methyl- and isopropyl-substituted reactants gave monofluorinated products **2q** and **2r** in 31% and 43% yield, respectively, while the electron-withdrawing ethoxycarbonyl group afforded the monofluorinated product **2s** in 64% yield.

Next, we explored the scope with respect to imidazoheterocycles 2-phenylimidazo[1,2-*a*]pyrimidine (**4a**) and 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (**6a**) (Scheme 2). Further optimization of reaction conditions revealed that slightly decreased amounts of Selectfluor reagent was beneficial for the reaction of **4a** and gave monofluorinated product **5a** in 71% yield. In the case of 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole, increasing the temperature to 70 °C and in the absence of DMAP, the monofluorinated product **7a** was obtained in 63% yield.

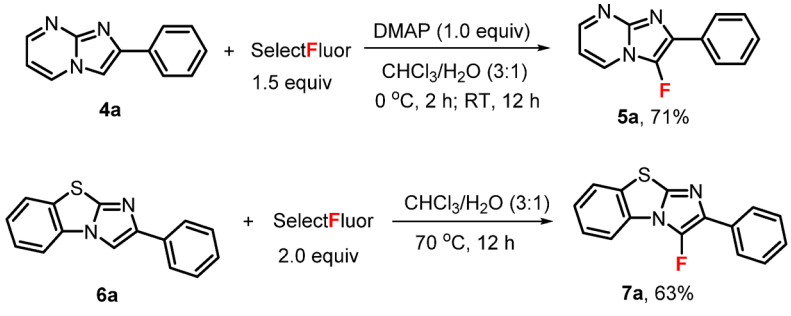
Furthermore, like electrophilic fluorination of indole and benzo[*b*]furan rings,[18] when methanol or isopropanol was used as the nucleophile in the absence of DMAP at room temperature, the corresponding 3,3-difluoroalkoxylation product **8a** or **8b** was obtained in moderate yield (Scheme 3).

Scheme 3. Difluoroalkoxylation of 1a Using Alcohols as Nucleophiles



For understanding the processes of this fluorination, some control experiments were designed (Scheme 4). The regioisomer **9a** bearing phenyl group on 3-position of imidazo[1,2-*a*]pyridine could not afford 2-fluorinated product **10a** under the standard reaction condition, which showed that the reaction proceeded at 3-position with excellent regioselectivity (Scheme 4, eq 1). In order to elucidate the role of DMAP in the fluorinated process, we also conducted several

Scheme 2. Regioselective Monofluorination of Imidazoheterocycles



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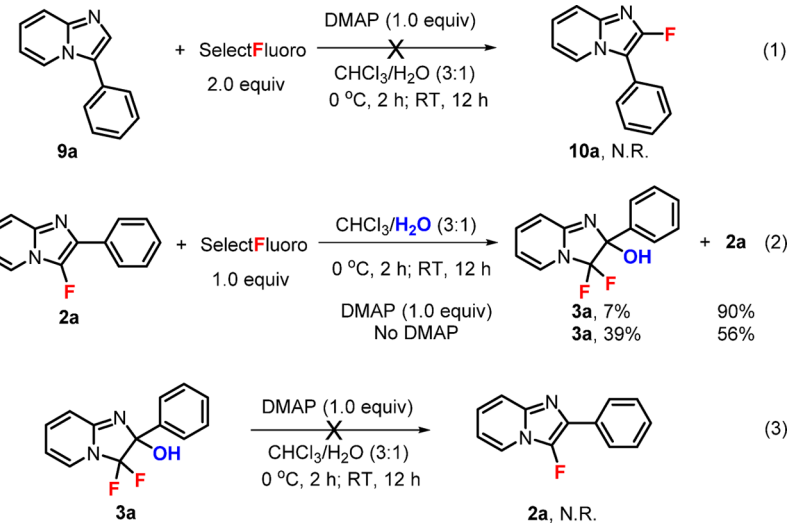
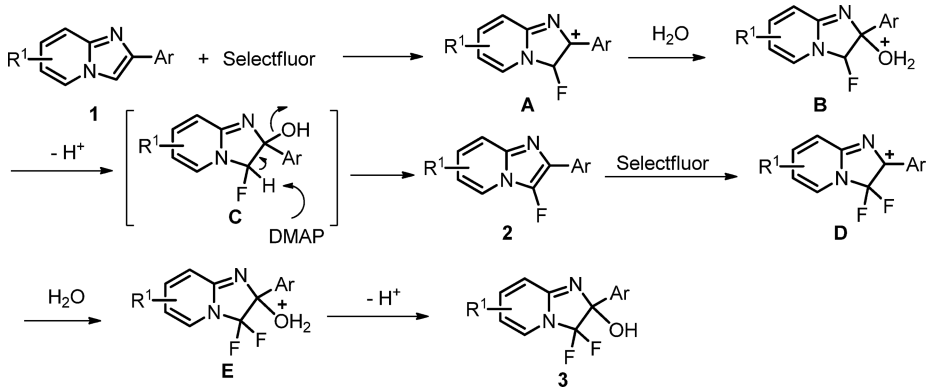
Scheme 4. Control Experiments



Scheme 5. Plausible Mechanism for Regioselective Fluorination of Imidazo[1,2-*a*]pyridines



control experiments. When the monofluorinated product **2a** was performed in the presence of a stoichiometric amount of DMAP and Selectfluor, only 7% yield of difluorinated product **3a** was obtained, compared with 39% yield in the absence of DMAP (Scheme 4, eq 2), suggesting that DMAP caused obvious suppression to the difluorination process. The monofluorinated product **2a** could not completely convert to **3a** in 12 h, and the elimination reaction of **3a** was also ruled out, which showed that the transformation from **2a** to **3a** was not a reversible process (Scheme 4, eq 3).

Based on the above results and the related reports,[17,18] we proposed that the reaction proceeded through an electrophilic fluorinated mechanism (Scheme 5). Initially, reaction of imidazo[1,2-*a*]pyridine **1** with Selectfluor yielded the unstable 3-fluorinated cation **A**, followed by addition to water to form B. Next, deprotonation took place to generate intermediate C, and then the proton was extracted by the base DMAP quickly to furnish the monofluorinated product **2**. We also assumed that DMAP as a Lewis base limited the activity of Selectfluor in a certain extent. When the reaction was run without DMAP, the compound **2** would undergo a similar process to produce the unstable 3,3-difluorinated cation **D**, which was then attacked by H_2O to generate the difluorohydroxylated product **3**.

In summary, we have successfully developed an efficient method for regioselective monofluorination of imidazo[1,2-*a*]pyridine with Selectfluor in aqueous condition. Various substituents on the aryl ring at 2-position of imidazo[1,2-*a*]pyridines tolerated the reaction and gave the corresponding products in moderate to good yields. DMAP was a benefit to the electrophilic monofluorinated transformation and caused obvious suppression to the difluorinated product. The mild reaction conditions and convenient operation would be helpful for the drug development of imidazo[1,2-*a*]pyridines. The strategy is expected to get the application in pharmaceutical synthesis.

EXPERIMENTAL SECTION

General. All reactions were run in a sealed tube with a Teflon-lined cap under air. Chemicals were commercially available and were used without purification. Imidazo[1,2-*a*]pyridines and imidazoheterocycles were prepared according to the literature procedures.[19] Melting points are uncorrected. NMR spectra were recorded at 400 MHz (^{1}H), 100 MHz (^{13}C), and 376 MHz (^{19}F) in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, dt = doublet of triplet, td = triplet of doublet, q = quartet, m = multiplet. For the HRMS measurements, Q-TOF was used.

General Experimental Procedures for the Synthesis of Fluorinated Product. Imidazo[1,2-*a*]pyridine **1a** (38.8 mg, 0.2 mmol), Selectfluor (141.7 mg, 0.4 mmol, 2.0 equiv), and DMAP (24.4 mg, 0.2 mmol, 1.0 equiv) were added in $CHCl_3/H_2O$ (3:1, 2 mL) at 0 °C under ambient air. The mixture was stirred for 2 h at 0 °C, then warmed to room temperature, and stirred for another 12 h. The reaction mixture was quenched with saturated aqueous Na_2CO_3

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solution (5 mL) and extracted with EtOAc (15 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel (300−400 mesh) column chromatography using hexane/EtOAc (10:1, v/v) as eluent to afford the desired product **2a**.

General Experimental Procedures for the Synthesis of Difluoroalkoxylation Product. Imidazo[1,2-*a*]pyridine **1a** (38.8 mg, 0.2 mmol), Selectfluor (141.7 mg, 0.4 mmol, 2.0 equiv), and 4 Å MS (50 mg) in ROH (1 mL) was stirred for 12 h at room temperature under ambient air. The reaction mixture was then diluted with DCM (20 mL) and filtered. The filtrate was concentrated in vacuo, and the residue was purified by silica gel (300−400 mesh) column chromatography using hexane/EtOAc (10:1, v/v) as eluent to afford the desired product **8**.

*3-Fluoro-2-phenylimidazo[1,2-a]pyridine (**2a**).* Yellow solid (35.2 mg, 83% yield); mp 96−98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.01 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 6.8 Hz, 1H), 7.52 (dt, J = 9.2, 0.8 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 7.34−7.30 (m, 1H), 7.11 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 6.81 (td, J = 6.8, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.7 (d, J = 273.7 Hz), 136.9 (d, J = 5.8 Hz), 131.7 (d, J = 5.0 Hz), 128.8, 127.8, 126.3 (d, J = 4.3 Hz), 123.8 (d, J = 1.9 Hz), 122.7, 120.4, 117.9, 112.6; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −154.9; HRMS-ESI (m/z): calcd for $C_{13}H_{10}FN_2$ $[M + H]^+$ 213.0823, found 213.0814.

*3-Fluoro-2-(p-tolyl)imidazo[1,2-a]pyridine (**2b**).* Yellow solid (36.7 mg, 81% yield); mp 95−97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.90 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 6.8 Hz, 1H), 7.51 (d, J = 9.2 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.12−7.08 (m, 1H), 6.80 (t, J = 6.8 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.5 (d, J = 273.1 Hz), 137.6, 136.8 (d, J = 5.9 Hz), 129.5, 128.9 (d, J = 5.1 Hz), 126.2 (d, J = 4.2 Hz), 123.6 (d, J = 2.1 Hz), 122.9, 120.4, 117.8, 112.5, 21.4; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −155.4; HRMS-ESI (m/z): calcd for $C_{14}H_{12}FN_2$ $[M + H]^+$ 227.0980, found 227.0975.

*3-Fluoro-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine (**2c**).* White solid (36.3 mg, 75% yield); mp 103−105 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.94 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 6.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.12−7.09 (m, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.81 (t, J = 6.8 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 159.4, 138.2 (d, J = 264.3 Hz), 136.8, 127.6 (d, J = 4.1 Hz), 124.4 (d, J = 5.1 Hz), 123.5, 122.7, 120.3, 117.7, 114.3, 112.4, 55.3; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −156.4; HRMS-ESI (m/z): calcd for $C_{14}H_{12}FN_2O$ $[M + H]^+$ 243.0929, found 243.0923.

*2-(4-Chlorophenyl)-3-fluoroimidazo[1,2-a]pyridine (**2d**).* White solid (36.5 mg, 74% yield); mp 131−132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.93 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 6.8 Hz, 1H), 7.51 (d, J = 9.2 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 1H), 6.84 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.7 (d, J = 274.1 Hz), 137.0 (d, J = 5.8 Hz), 133.6 (d, J = 0.4 Hz), 130.3 (d, J = 5.2 Hz), 129.0, 127.5 (d, J = 4.3 Hz), 124.1 (d, J = 1.9 Hz), 121.7, 120.5, 118.0, 112.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −154.4; HRMS-ESI (m/z): calcd for $C_{13}H_9ClFN_2$ $[M + H]^+$ 247.0433, found 247.0428.

*2-(3-Chlorophenyl)-3-fluoroimidazo[1,2-a]pyridine (**2e**).* White solid (43.9 mg, 89% yield); mp 107−108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.00 (s, 1H), 7.87 (t, J = 8.0 Hz, 2H), 7.51 (d, J = 9.2 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.29−7.27 (m, 1H), 7.16−7.12 (m, 1H), 6.84 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.8 (d, J = 274.4 Hz), 137.0 (d, J = 5.7 Hz), 134.9, 133.5 (d, J = 5.2 Hz), 130.0, 127.8, 126.2 (d, J = 4.3 Hz), 124.3 (d, J = 4.6 Hz), 124.2 (d, J = 1.8 Hz), 121.4, 120.5, 118.0, 112.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −153.8; HRMS-ESI (m/z): calcd for $C_{13}H_9ClFN_2$ $[M + H]^+$ 247.0433, found 247.0429.

*2-(2-Chlorophenyl)-3-fluoroimidazo[1,2-a]pyridine (**2f**).* Light yellow solid (41.4 mg, 84% yield); mp 67−68 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.95 (d, J = 6.8 Hz, 1H), 7.74 (dd, J = 7.6, 2.0 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.50 (dd, J = 7.6, 1.6 Hz, 1H), 7.39−7.31 (m, 2H), 7.19−7.15 (m, 1H), 6.88 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.2 (d, J = 273.0 Hz), 137.2 (d, J = 4.9 Hz), 133.1, 132.1, 131.0 (d, J = 4.2 Hz), 130.0, 129.6, 126.9, 123.9 (d, J = 1.9 Hz), 120.9 (d, J = 3.2 Hz), 120.7, 118.2, 112.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −148.7; HRMS-ESI (m/z): calcd for $C_{13}H_9ClFN_2$ $[M + H]^+$ 247.0433, found 247.0428.

*2-(4-Bromophenyl)-3-fluoroimidazo[1,2-a]pyridine (**2g**).* Light yellow solid (31.4 mg, 54% yield); mp 146−147 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.87−7.84 (m, 3H), 7.57−7.54 (m, 2H), 7.49 (dt, J = 9.2, 0.8 Hz, 1H), 7.15−7.11 (m, 1H), 6.83 (td, J = 6.8, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.7 (d, J = 274.5 Hz), 137.0 (d, J = 5.8 Hz), 131.9, 130.7 (d, J = 5.2 Hz), 127.7 (d, J = 4.4 Hz), 124.1 (d, J = 1.9 Hz), 121.7 (d, J = 1.5 Hz), 121.7, 120.5, 117.9, 112.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −154.1; HRMS-ESI (m/z): calcd for $C_{13}H_9BrFN_2$ $[M + H]^+$ 290.9928, found 290.9924.

*2-(2,4-Dichlorophenyl)-3-fluoroimidazo[1,2-a]pyridine (**2h**).* White solid (32.0 mg, 57% yield); mp 151−152 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.94 (d, J = 6.8 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 9.2 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 8.4, 2.4 Hz, 1H), 7.20−7.16 (m, 1H), 6.88 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.2 (d, J = 272.2 Hz), 137.3 (d, J = 4.9 Hz), 134.8, 133.7, 132.8, 129.8, 129.7 (d, J = 4.3 Hz), 127.3, 124.1, 120.7, 119.9, 118.2, 112.9; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −147.8; HRMS-ESI (m/z): calcd for $C_{13}H_8Cl_2FN_2$ $[M + H]^+$ 281.0043, found 281.0038.

*3-Fluoro-2-(3-nitrophenyl)imidazo[1,2-a]pyridine (**2i**).* Yellow solid (47.3 mg, 92% yield); mp 193−195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.85 (s, 1H), 8.34 (d, J = 7.2 Hz, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.96 (d, J = 6.4 Hz, 1H), 7.65−7.55 (m, 2H), 7.23−7.19 (m, 1H), 6.93−6.90 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 148.4, 138.9 (d, J = 276.8 Hz), 136.7 (d, J = 5.5 Hz), 133.3 (d, J = 5.4 Hz), 131.8 (d, J = 4.7 Hz), 130.8, 125.5, 122.3, 122.1, 119.8 (d, J = 4.0 Hz), 119.3, 117.3, 113.3; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −153.0; HRMS-ESI (m/z): calcd for $C_{13}H_9FN_3O_2$ $[M + H]^+$ 258.0674, found 258.0672.

*3-Fluoro-2-(4-(methylsulfonyl)phenyl)imidazo[1,2-a]pyridine (**2j**).* Light yellow solid (50.5 mg, 87% yield); mp 176−178 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.32 (d, J = 6.8 Hz, 1H), 8.13 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 9.2 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.02 (t, J = 6.8 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 139.4, 139.0 (d, J = 276.2 Hz), 136.7 (d, J = 5.8 Hz), 136.5 (d, J = 5.1 Hz), 127.7, 126.2 (d, J = 4.5 Hz), 125.3, 122.0, 119.7, 117.3, 113.2, 43.6; ^{19}F NMR (DMSO-d_6, 376 MHz): δ (ppm) −151.2; HRMS-ESI (m/z): calcd for $C_{14}H_{12}FN_2O_2S$ $[M + H]^+$ 291.0598, found 291.0598.

*3-Fluoro-2-(thiophen-2-yl)imidazo[1,2-a]pyridine (**2k**).* Light yellow solid (38.8 mg, 89% yield); mp 76−77 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.89 (d, J = 6.8 Hz, 1H), 7.53−7.51 (m, 2H), 7.35 (dd, J = 5.2, 1.2 Hz, 1H), 7.16−7.11 (m, 2H), 6.85 (td, J = 6.8, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 137.3 (d, J = 274.3 Hz), 137.0 (d, J = 5.2 Hz), 134.6 (d, J = 6.2 Hz), 127.9, 125.3 (d, J = 2.3 Hz), 124.5 (d, J = 4.3 Hz), 124.0 (d, J = 2.1 Hz), 120.4, 119.2 (d, J = 2.7 Hz), 117.8, 112.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −155.5; HRMS-ESI (m/z): calcd for $C_{11}H_8FN_2S$ $[M + H]^+$ 219.0387, found 219.0379.

*3-Fluoro-2-(naphthalen-1-yl)imidazo[1,2-a]pyridine (**2l**).* Yellow oil (34.8 mg, 69% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.45 (d, J = 7.6 Hz, 1H), 7.93−7.89 (m, 3H), 7.79 (d, J = 7.2 Hz, 1H), 7.61−7.58 (m, 1H), 7.57−7.48 (m, 3H), 7.15−7.11 (m, 1H), 6.82 (td, J = 6.8, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.8 (d, J = 271.3 Hz), 137.0 (d, J = 5.5 Hz), 134.0, 131.4, 128.9, 128.6 (d, J = 4.1 Hz), 128.3, 128.2 (d, J = 2.2 Hz), 126.5, 125.9, 125.9 (d, J = 2.0 Hz), 125.3, 123.7 (d, J = 2.0 Hz), 122.7 (d, J = 2.6 Hz), 120.5, 118.0, 112.6; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −155.2; HRMS-ESI (m/z): calcd for $C_{17}H_{12}FN_2$ $[M + H]^+$ 263.0980, found 263.0976.

*3-Fluoro-8-methyl-2-phenylimidazo[1,2-a]pyridine (**2m**).* Light yellow oil (36.2 mg, 77% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.02 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 6.8 Hz, 1H), 7.47−7.43 (m, 2H), 7.32−7.28 (m, 1H), 6.88 (dt, J = 6.8, 1.2 Hz, 1H), 6.90 (t, J = 6.8 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 139.0 (d, J = 273.6 Hz), 137.2 (d, J = 5.5 Hz), 132.0 (d, J = 5.0 Hz), 128.7, 127.8, 127.6, 126.4 (d, J = 4.2 Hz), 122.4 (d, J = 1.4 Hz), 122.1,

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118.3, 112.6, 16.2; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −154.3; HRMS-ESI (m/z): calcd for $C_{14}H_{12}FN_2$ $[M + H]^+$ 227.0980, found 227.0975.

3-Fluoro-6-methyl-2-phenylimidazo[1,2-a]pyridine (**2n**). Yellow solid (37.1 mg, 82% yield); mp 119−120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.99 (d, J = 8.0 Hz, 2H), 7.64 (s, 1H), 7.47−7.40 (m, 3H), 7.31 (t, J = 7.4 Hz, 1H), 6.95 (dd, J = 9.2, 1.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.5 (d, J = 273.5 Hz), 136.1 (d, J = 5.9 Hz), 132.0 (d, J = 5.1 Hz), 128.7, 127.6, 127.1 (d, J = 1.9 Hz), 126.2 (d, J = 4.2 Hz), 122.5, 122.4, 117.9, 117.2, 18.3; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −154.7; HRMS-ESI (m/z): calcd for $C_{14}H_{12}FN_2$ $[M + H]^+$ 227.0980, found 227.0976.

6-Chloro-3-fluoro-2-phenylimidazo[1,2-a]pyridine (**2o**). Yellow solid (42.4 mg, 86% yield); mp 136−138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.96 (d, J = 8.0 Hz, 2H), 7.90 (s, 1H), 7.46−7.43 (m, 3H), 7.32 (t, J = 7.4 Hz, 1H), 7.06 (dd, J = 9.6, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.5 (d, J = 275.8 Hz), 135.2 (d, J = 5.9 Hz), 131.2 (d, J = 5.0 Hz), 128.8, 128.1, 126.3 (d, J = 4.3 Hz), 125.3 (d, J = 2.1 Hz), 124.0, 121.1, 118.3, 118.2; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −153.0; HRMS-ESI (m/z): calcd for $C_{13}H_9ClFN_2$ $[M + H]^+$ 247.0433, found 247.0428.

6-Bromo-3-fluoro-2-phenylimidazo[1,2-a]pyridine (**2p**). Light yellow solid (45.4 mg, 78% yield); mp 128−129 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.99−7.94 (m, 3H), 7.46−7.42 (m, 2H), 7.40−7.37 (m, 1H), 7.34−7.30 (m, 1H), 7.15 (dd, J = 9.6, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 138.3 (d, J = 276.1 Hz), 135.2 (d, J = 6.0 Hz), 131.2 (d, J = 5.0 Hz), 128.8, 128.1, 127.3 (d, J = 2.1 Hz), 126.3 (d, J = 4.2 Hz), 123.8, 120.4, 118.5, 107.5; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −153.1; HRMS-ESI (m/z): calcd for $C_{13}H_9BrFN_2$ $[M + H]^+$ 290.9928, found 290.9924.

3-Fluoro-2-methylimidazo[1,2-a]pyridine (**2q**). Orange oil (9.3 mg, 31% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.82 (d, J = 6.4 Hz, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.10−7.05 (m, 1H), 6.81−6.77 (m, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 139.1 (d, J = 265.7 Hz), 136.5 (d, J = 5.7 Hz), 122.9 (d, J = 2.0 Hz), 120.1, 119.8 (d, J = 5.4 Hz), 117.3, 112.0, 11.3 (d, J = 3.7 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −162.6; HRMS-ESI (m/z): calcd for $C_8H_8FN_2$ $[M + H]^+$ 151.0667, found 151.0664.

3-Fluoro-2-isobutylimidazo[1,2-a]pyridine (**2r**). Orange oil (16.5 mg, 43% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.85 (d, J = 6.8 Hz, 1H), 7.45 (dt, J = 9.2, 1.2 Hz, 1H), 7.11−7.07 (m, 1H), 6.81 (td, J = 6.8, 0.8 Hz, 1H), 2.64 (dd, J = 7.2, 0.8 Hz, 2H), 2.19−2.09 (m, 1H), 0.98 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 139.4 (d, J = 265.7 Hz), 136.6 (d, J = 5.6 Hz), 123.5 (d, J = 5.2 Hz), 122.9 (d, J = 2.4 Hz), 120.2, 117.5, 112.1, 35.3 (d, J = 3.8 Hz), 28.5 (d, J = 1.2 Hz), 22.5; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −162.1; HRMS-ESI (m/z): calcd for $C_{11}H_{14}FN_2$ $[M + H]^+$ 193.1136, found 193.1132.

Ethyl 3-fluoroimidazo[1,2-a]pyridine-2-carboxylate (**2s**). White solid (26.6 mg, 64% yield); mp 79−80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.96 (d, J = 6.8 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.26−7.22 (m, 1H), 6.94 (t, J = 6.8 Hz, 1H), 4.48 (q, J = 7.2 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 161.6 (d, J = 4.9 Hz), 143.1 (d, J = 285.3 Hz), 136.6 (d, J = 4.9 Hz), 125.6, 121.0, 119.2, 114.8, 113.9, 61.1, 14.3; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −143.5; HRMS-ESI (m/z): calcd for $C_{10}H_{10}FN_2O_2$ $[M + H]^+$ 209.0721, found 209.0720.

3,3-Difluoro-2-phenyl-2,3-dihydroimidazo[1,2-a]pyridin-2-ol (**3a**). Yellow solid (26.3 mg, 53% yield, Table 1, entry1); mp 166−168 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.51−7.48 (m, 2H), 7.46 (dt, J = 6.8, 1.2 Hz, 1H), 7.39−7.32 (m, 3H), 7.17 (ddd, J = 9.6, 6.4, 1.2 Hz, 1H), 6.91 (s, 1H), 6.54 (d, J = 9.6 Hz, 1H), 6.02 (t, J = 6.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 155.9 (dd, J = 6.2, 3.1 Hz), 139.3, 138.5 (d, J = 2.0 Hz), 129.1, 128.3, 127.7, 126.5, 124.4 (dd, J = 271.6, 262.5 Hz), 116.2, 106.1, 95.3 (dd, J = 27.1, 15.6 Hz); ^{19}F NMR (DMSO-d_6, 376 MHz): δ (ppm) −82.3 (d, J = 181.6 Hz), −102.2 (d, J = 182.0 Hz); HRMS-ESI (m/z): calcd for $C_{13}H_{11}F_2N_2O$ $[M + H]^+$ 249.0834, found 249.0829.

3-Fluoro-2-phenylimidazo[1,2-a]pyrimidine (**5a**). Light yellow solid (30.3 mg, 71% yield); mp 133−135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.47−8.43 (m, 1H), 8.22−8.20 (m, 1H), 8.06−8.04 (m, 2H), 7.48−7.42 (m, 2H), 7.36−7.32 (m, 1H), 6.90−6.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 149.1 (d, J = 3.0 Hz), 139.1 (d, J = 3.2 Hz), 136.5 (d, J = 278.8 Hz), 131.0 (d, J = 5.0 Hz), 128.7, 128.3, 128.1, 126.7 (d, J = 4.1 Hz), 124.2 (d, J = 5.6 Hz), 108.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −154.4; HRMS-ESI (m/z): calcd for $C_{12}H_9FN_3$ $[M + H]^+$ 214.0776, found 214.0773.

3-Fluoro-2-phenylbenzo[d]imidazo[2,1-b]thiazole (**7a**). White solid (33.8 mg, 63% yield); mp 145−147 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.85 (d, J = 7.6 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.43−7.37 (m, 3H), 7.31−7.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 141.9 (d, J = 275.5 Hz), 138.9 (d, J = 7.2 Hz), 131. Nine (d, J = 5.4 Hz), 130.9 (d, J = 2.5 Hz), 129.8, 128.7, 127.1, 126.3, 125.3 (d, J = 4.6 Hz), 125.2, 124.1, 123.5 (d, J = 2.6 Hz), 113.0 (d, J = 3.0 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −150.5; HRMS-ESI (m/z): calcd for $C_{15}H_{10}FN_2S$ $[M + H]^+$ 269.0543, found 269.0541.

3,3-Difluoro-2-methoxy-2-phenyl-2,3-dihydroimidazo[1,2-a]-pyridine (**8a**). Yellow solid (40.9 mg, 78% yield); mp 96−98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.65−7.62 (m, 2H), 7.43−7.38 (m, 3H), 7.08−7.03 (m, 2H), 6.61 (d, J = 10.0 Hz, 1H), 5.93 (t, J = 6.8 Hz, 1H), 3.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 157.7 (dd, J = 6.5, 2.2 Hz), 139.2, 135.0 (d, J = 2.7 Hz), 129.2, 128.3 (d, J = 1.7 Hz), 128.2, 127.7 (d, J = 0.8 Hz), 124.1 (dd, J = 274.8, 263.0 Hz), 117.3, 106.3, 99.3 (dd, J = 29.2, 13.4 Hz), 51.6; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −77.6 (d, J = 183.5 Hz), −108.0 (d, J = 183.5 Hz); HRMS-ESI (m/z): calcd for $C_{14}H_{13}F_2N_2O$ $[M + H]^+$ 263.0990, found 263.0993.

3,3-Difluoro-2-isopropoxy-2-phenyl-2,3-dihydroimidazo[1,2-a]-pyridine (**8b**). Yellow solid (33.1 mg, 57% yield); mp 136−137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.71−7.66 (m, 2H), 7.41−7.37 (m, 3H), 7.05−7.01 (m, 2H), 6.58 (d, J = 9.6 Hz, 1H), 5.90 (t, J = 6.8 Hz, 1H), 4.00−3.91 (m, 1H), 1.23 (d, J = 6.4 Hz, 3H), 1.05 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 157.1 (dd, J = 6.5, 2.2 Hz), 138.9, 136.7 (d, J = 2.6 Hz), 129.0, 128.4 (d, J = 1.6 Hz), 127.9, 127.8 (d, J = 0.9 Hz), 124.2 (dd, J = 274.1, 263.4 Hz), 117.2, 106.0, 99.4 (dd, J = 28.9, 13.5 Hz), 67.8, 24.8, 24.2; ^{19}F NMR ($CDCl_3$, 376 MHz): δ (ppm) −77.7 (d, J = 182.7 Hz), −107.5 (d, J = 182.4 Hz); HRMS-ESI (m/z): calcd for $C_{16}H_{17}F_2N_2O$ $[M + H]^+$ 291.1303, found 291.1301.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01961.

Copies of ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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