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Regioselective 2,2,2-Trifluoroethylation of Imidazopyridines by Visible Light Photoredox Catalysis

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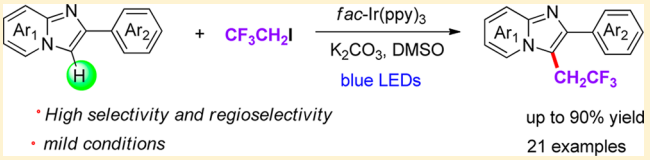
Supporting Information

ABSTRACT: A visible-light-induced C-3 selective trifluoroethylation of imidazoheterocycles using 1,1,1-trifluoro-2-iodoethane as trifluoroethyl radical sources was developed. The methodology enables the introduction of a trifluoroethyl group in a fast and efficient reaction under mild conditions with excellent regioselectivities and high functional group tolerance.



The incorporation of fluorinated functional groups into organic molecules has been widely recognized as a general strategy in pharmaceutical research and drug development. Fluorinated analogues of pharmaceutically relevant compounds often possess properties conducive to drug development, such as improved lipophilicity, metabolic stability, and bioavailability relative to their nonfluorinated counterparts.[1] Among diverse fluorine-containing molecules, trifluoroethyl-containing aromatic or azaheterocycle compounds are of current interest for their applications in the fields of medicinal chemistry and biochemistry.[2] In recent years, direct C(sp^2-aryl)−CH_2CF_3 bond formation has received much attention as a new synthetic route to trifluoroethylated compounds.[3] Transition-metal-catalyzed cross-coupling trifluoroethylation reactions starting from aryl halides[4] and boronic acids[5] have since been disclosed by several groups, allowing the effective formation of a C(sp^2-aryl)−CH_2CF_3 bond. However, a few methods have been exploited to date for the construction of a C(sp^2)−CH_2CF_3 bond via direct aryl C(sp^2)−H functionalization.[6] For example, Ackermann developed the first nickel-catalyzed trifluoroethylation process utilizing an 8-aminoquinoline directing group and trifluoroethyl iodide as alkyl sources.[6b] Liu and co-workers report a palladium-catalyzed selective *ortho*-C−H trifluoroethylation of aryl iodides for the synthesis of olefinated trifluoroethyl arenes.[6a] Although CF_3CH_2 can be introduced to aromatic molecules, most approaches either suffer from poor substrate scope or require use of prefunctionalized substrates. Recently, Baran et al. reported direct C−H trifluoroethylation of nitrogen-containing heterocyclic compounds with the combination of $(CF_3CH_2SO_2)_2Zn$ and ^{t}BuOOH.[6c] Unfortunately, these radical transformations result in the trifluoroethylated products with poor regioselectivity and require Baran's expensive $(CF_3CH_2SO_2)_2Zn$ reagents. Therefore, the development of mild and straightforward methodologies, capable of tolerating a wide range of functional groups, for the incorporation of trifluoroethyl moieties through direct C−H functionalization is highly desirable.

In the past few years, visible-light photoredox catalysis has attracted substantial attention because of its environmental compatibility and versatility in promoting a large number of synthetically important reactions.[7] Although great progress has been made in photoredox fluoroalkylation, especially trifluoromethylation, until recently, there were rather few practical methods for related visible-light photocatalyzed trifluoroethylation.[8] For instance, Dolbier et al. have shown that the trifluoroethyl radical can be generated from $CF_3CH_2SO_2Cl$ via photoredox catalysis.[9] In our previous work, we demonstrated the reduction of CF_3CH_2I based on iridium(III) photocatalyst release of a trifluoroethyl radical, which can be added to various unsaturated bonds to construct complex organic skeletons.[10]

Imidazopyridines are an important structural motif that is found in many biological molecules and pharmaceutical products.[11] In particular, installation of the fluorine atom or fluorinated groups might render these compounds more valuable in the subject of drug discovery. However, a few methods have been exploited to date for the construction of imidazopyridines with the introduction of fluorinated groups. Very recently, the Hajra group reported a silver-catalyzed regioselective trifluoromethylation of imidazopyridines using Langlois reagent.[12] Sun and co-workers reported an efficient regioselective fluorination of imidazo[1,2-*a*]pyridines with Selectfluor.[13] Until the present work, there have been no methods for the introduction of a trifluoroethyl group into this kind of N-heterocycle. Consistent with our ongoing research on the visible-light photocatalytic synthesis of fluorinated hetero-

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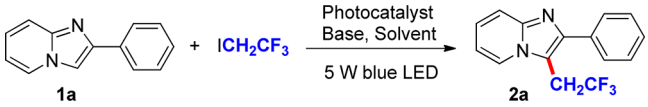
cycles,[14] we hereby report a direct and regioselective trifluoroethylation of imidazopyridines with trifluoroethyl iodide via visible-light photocatalysis.

In our initial studies, the reaction between 2-phenylimidazo-[1,2-*a*]pyridine **1a** and 1,1,1-trifluoro-2-iodoethane (CF_3CH_2I) was applied as a model reaction to investigate the optimal conditions (Table 1). We examined the reaction conditions,

Table 1. Optimization of Reaction Conditions for 2a[a]



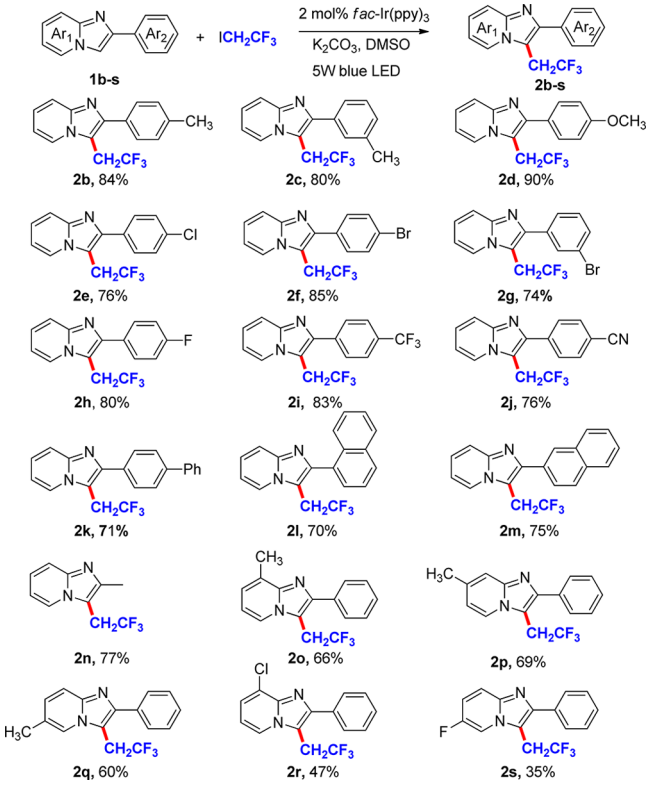
entry	catalyst	base	solvent	yield[b] (%)
1	*fac*-Ir(ppy)$_3$	K_2CO_3	DMF	25
2	*fac*-Ir(ppy)$_3$	K_2CO_3	CH_3CN	72
3	*fac*-Ir(ppy)$_3$	K_2CO_3	DMSO	83
4	*fac*-Ir(ppy)$_3$	K_2CO_3	CH_2Cl_2	38
5	*fac*-Ir(ppy)$_3$	Cs_2CO_3	DMSO	66
6	*fac*-Ir(ppy)$_3$	KOAc	DMSO	77
7	*fac*-Ir(ppy)$_3$	K_3PO_4	DMSO	68
8	*fac*-Ir(ppy)$_3$	Na_2HPO_4	DMSO	80
9	Ir(ppy)$_2$(dtbbpy)]PF_6	K_2CO_3	DMSO	60
10	Ru(bpy)$_3$(PF_6)$_2$	K_2CO_3	DMSO	31
11	Eosin Y	K_2CO_3	DMSO	0
12[c]	*fac*-Ir(ppy)$_3$	K_2CO_3	DMSO	84
13[d]		K_2CO_3	DMSO	0
14[e]	*fac*-Ir(ppy)$_3$	K_2CO_3	DMSO	0

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), ICH_2CF_3 (0.6 mmol, 3.0 equiv), base (0.4 mmol, 2.0 equiv), and photocatalyst (0.004 mmol, 2.0 mol %) in indicated solvent (2.0 mL) were irradiated with a 5 W blue LED for 36 h. [b]Isolated yield. [c]With 5.0 equiv of ICH_2CF_3. [d]Without photocatalyst. [e]Without visible-light irradiation.

which were developed for photocatalyzed trifluoroethylation of *N*-arylacrylamides[10b] (Table 1, entry 1). The desired product **2a** was obtained in 25% yield (Table 1, entry 1) after 36 h irradiation with a 5 W blue light-emitting diode (LED) bulb in the presence of *fac*-Ir(ppy)$_3$ and K_2CO_3 at room temperature in DMF. Several solvents such as CH_3CN, DMSO, and CH_2Cl_2 were used to replace DMF (Table 1, entries 2–4), and DMSO was chosen as the ideal organic solvent for the reaction. We next investigated different bases including Cs_2CO_3, KOAc, K_3PO_4, and Na_2HPO_4 and found that K_2CO_3 was the best choice (Table 1, entries 5–8). We then explored the effects of the photocatalysts on the reaction. To our disappointment, none of them gave better results than *fac*-Ir(ppy)$_3$ (Table 1, entries 9–11). The use of 3.0 equiv of CF_3CH_2I gave a good yield, but if the amount of CF_3CH_2I was increased to 5.0 equiv, the yield of **2a** did not increase further (Table 1, entriy 12). Control experiments suggested that the photocatalyst and light irradiation are all indispensable for the success of the reaction, and no reaction occurred in its absence (Table 1, entries 13 and 14).

The scope of the photocatalyzed trifluoroethylation was surveyed using the optimized reaction conditions. It was found that various imidazo[1,2-*a*]pyridines could be trifluoroethylated smoothly using this transformation with excellent regioselectivities (Table 2). The effect of substituents on the arene (Ar_2) undergoing the trifluoroethylation reaction was first examined. A variety of substituents on the aromatic ring were compatible under the standard conditions, indicating that the reaction has a

Table 2. Regioselective Trifluoroethylation of Different Imidazo[1,2-*a*]pyridines under Visible-Light Irradiation[a,b]



[a]Reaction conditions: **1** (0.2 mmol), ICH_2CF_3 (0.6 mmol, 3.0 equiv), K_2CO_3 (0.4 mmol, 2.0 equiv), and *fac*-Ir(ppy)$_3$ (0.004 mmol, 2.0 mol %) in DMSO (2.0 mL) were irradiated with a 5 W blue LED for 36 h. [b]Isolated yield.

broad substrate scope. In addition to the normal electron-neutral (**2b,c**) and electron-rich (**2d**) substituents, halo substituents (**2e–h**) were well-tolerated in this reaction, leading to products which could be further structurally characterized. Meanwhile, electron-deficient groups (**2i,j**) were compatible under the standard conditions, as well. The polyphenyl-substituted substrates also performed well under the optimal conditions, and the corresponding trifluoroethylated products (**2k–m**) were obtained in reasonable yield. It is noteworthy that the aliphatic substituted substrate 2-methylimidazo[1,2-*a*]pyridine was proven to be a good candidate for this transformation (**2n**), which was unambiguously determined by X-ray crystallographic analysis (see the Supporting Information). We then examined the effect of the substituents on the pyridine ring. Substrates with normal electron-neutral group (**1o–q**) proceeded smoothly to give the corresponding products **2o–q** in moderate yields. In comparison, substrate bearing a halogen (**2r,s**) atom on the pyridine ring resulted in relatively poor yield.

To expand the potential utility of this reaction for medicinal chemistry, other imidazoheterocycles, such as benzo[*d*]-imidazo[2,1-*b*]thiazole derivatives, were also subjected to this reaction protocol (**3a,b**). The desired trifluoroethylated products (**4a,b**) were nevertheless produced in good yields under the developed conditions (Scheme 1).

To figure out whether the in situ generated trifluoroethyl radical species [$\bullet CH_2CF_3$] would be involved in the reaction, we conducted an inhibition experiment of 2-phenylimidazo-[1,2-*a*]pyridine **1a** with the addition of the known radical

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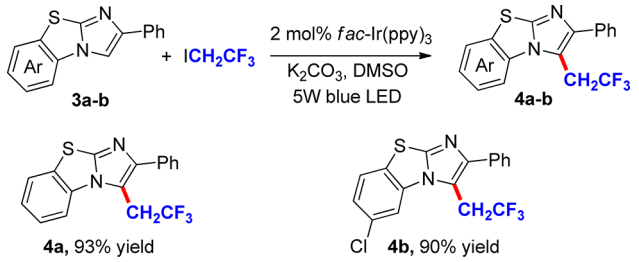
Scheme 1. Regioselective Trifluoroethylation of Imidazoheterocycles



scavenger of TEMPO (3.0 equiv) under the standard reaction conditions (Scheme 2). The formation of the corresponding product **2a** was completely suppressed, and TEMPO−CH_2CF_3 was detected in 100% yield by ^{19}F NMR spectroscopy analysis, thus suggesting that the present reaction might involve a radical process. Furthermore, the reduction potential of trifluoroethyl iodide was measured to be between −1.4 and −2.0 V versus SCE (see the Supporting Information). We inferred that this trifluoroethylation reaction involves the oxidative quenching cycle of the photocatalyst.

Based on these observations and the reports of others on the mechanism of the radical addition of imidazoheterocycles,[15] a possible catalytic cycle is proposed for this transformation, as shown in Scheme 3. First, the excited state [*fac*-Ir(III)$(ppy)_3$*] is formed under light irradiation, which is next oxidized by CF_3CH_2I to generate a [*fac*-Ir(IV)$(ppy)_3$]$^+$ complex and a •CH_2CF_3 radical species **A**. Subsequently, the •CH_2CF_3 radical adds to imidazo[1,2-*a*]pyridine **1a** to produce the radical intermediate **B**, which is then oxidized by [*fac*-Ir(IV)$(ppy)_3$]$^+$ to form the carbocation intermediate **C** with the concurrent regeneration of [*fac*-Ir(III)$(ppy)_3$]. Finally, deprotonation assisted by base yields the desired product **2a**.

In conclusion, we developed a visible-light-catalyzed C-3 regioselective trifluoroethylation of imidazo[1,2-*a*]pyridines using commercially available 1,1,1-trifluoro-2-iodoethane (CF_3CH_2I) under mild conditions. The reaction is very generally applicable to a wide range of substrates, and most functional groups are tolerated. It would be useful in industrial processes, laboratory methods, and applications in drug discovery research.

EXPERIMENTAL SECTION

General. All reactions were performed in a 20 mL tube equipped with a rubber septum at room temperature. Photoirradiation was carried out with a 5 W blue LED (460−470 nm). Solvents were purified or dried in a standard manner. Column chromatography was performed on silica gel (200−300 mesh). ^1H NMR spectra, ^{13}C NMR spectra, and ^{19}F NMR spectra were measured in $CDCl_3$ and recorded on 500 MHz NMR spectrometers with TMS as an internal standard. HRMS analyses was recorded on a Q-TOF global mass spectrometer.

General Procedure for Trifluoroethylation of Imidazo[1,2-*a*]pyridine. To a mixture of imidazo[1,2-*a*]pyridine **1a**−**s** (0.20 mmol), CF_3CH_2I (0.6 mmol), and K_2CO_3 (0.4 mmol) in 2.0 mL of DMSO was added *fac*-Ir$(ppy)_3$ (0.004 mmol, 2.0 mol %) under N_2 atmosphere. The solution was stirred at room temperature under 5 W blue LED irradiation for 36 h. Then the reaction mixture was diluted by adding EtOAc and brine. The aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to give the desired products **2a**−**s**.

*2-Phenyl-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2a**):* Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (45.8 mg, 83%); mp 113−114 °C; ^1H NMR (500 MHz, $CDCl_3$dn't) δ 8.09 (d, 1 H, J = 7.0 Hz), 7.79−7.76 (m, 2 H), 7.70 (dt, 1 H, J_1 = 4.0 Hz, J_2 = 1.0 Hz), 7.51−7.48 (m, 2 H), 7.44−7.40 (m, 1 H), 7.30−7.27 (m, 1 H), 6.92 (dt, 1 H, J_1 = 7.0 Hz, J_2 = 1.0 Hz), 3.88 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9, 145.7, 133.7, 128.7, 128.6, 128.3, 125.7 (q, J = 277.1 Hz), 125.1, 123.5 (d, J = 2.4 Hz), 117.9, 112.8, 109.3, 30.1 (q, J = 32.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.2; HRMS (ESI) calcd for $[M + H]^+$ $C_{15}H_{12}F_3N_2$ 277.0947, found 277.0938.

*2-(p-Tolyl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2b**):* Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (48.7 mg, 84%); mp 126−128 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.08 (d, 1 H, J = 7.0 Hz), 7.70−7.66 (m, 3 H), 7.31−7.26 (m, 3 H), 6.92−6.89 (m, 1 H), 3.87 (q, 2 H, J = 10.0 Hz), 2.42 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9, 145.6, 138.2, 130.7, 129.5, 128.4, 125.8 (q, J = 277.1 Hz), 125.0, 123.5 (d, J = 2.4 Hz), 117.8, 112.7, 109.0 (d, J = 3.4 Hz), 30.1 (q, J = 31.9 Hz), 21.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.2; HRMS (ESI) calcd for $[M + H]^+$ $C_{16}H_{14}F_3N_2$ 291.1104, found 291.1101.

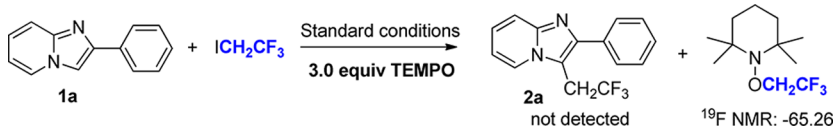
*2-(m-Tolyl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2c**):* Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (46.4 mg, 80%); mp 115−116 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, 1 H, J = 7.0 Hz), 7.72 (d, 1 H, J = 8.0 Hz), 7.65 (s, 1 H), 7.56 (d, 1 H, J = 8.0 Hz), 7.40 (t, 1 H, J = 8.0 Hz), 7.31−7.25 (m, 2 H), 6.93 (dt, 1 H, J_1 = 7.0 Hz J_2 = 1.0 Hz), 3.90 (q, 2 H, J = 10.0 Hz), 2.46 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 145.6, 138.5, 133.5, 129.5, 129.1, 128.6, 125.8 (q, J = 277.1 Hz), 125.4, 125.1, 123.5, 117.9, 112.8, 109.2 (d, J = 3.3 Hz), 30.1 (q, J = 31.8 Hz), 21.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.2; HRMS (ESI) calcd for $[M + H]^+$ $C_{16}H_{14}F_3N_2$ 291.1104, found 291.1109.

*2-(4-Methoxyphenyl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2d**):* Purified by column chromatography (petroleum ether/EtOAc, 3/1) as a white solid (55.1 mg, 90%); mp 130−132 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, 1 H, J = 7.0 Hz), 7.75−7.69 (m, 3 H), 7.30−7.27 (m, 1 H), 7.05−7.03 (m, 2 H),6.92 (dt, 1 H, J_1 = 7.0 Hz J_2 = 1.0 Hz), 3.89 (s, 3 H), 3.87 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 146.7, 145.5, 129.8, 126.1, 125.8 (q, J = 277.3 Hz), 125.0, 123.4, 117.7, 114.2, 112.7, 108.7 (d, J = 3.1 Hz), 55.3, 30.1 (q, J = 31.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.2; HRMS (ESI) calcd for $[M + H]^+$ $C_{16}H_{14}F_3N_2O$ 307.1053, found 307.1061.

*2-(4-Chlorophenyl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2e**):* Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (47.1 mg, 76%); mp 157−158 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, 1 H, J = 7.0 Hz), 7.73−7.69 (m, 3 H), 7.48−7.46 (m, 2 H), 7.32−7.29 (m, 1 H), 6.94 (dt, 1 H, J_1 = 7.0 Hz J_2 = 1.0 Hz), 3.85 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7, 145.67, 134.4, 132.2, 129.8, 129.0, 126.7, 125.6 (q, J = 277.1 Hz), 125.4, 123.5 (d, J = 2.1 Hz), 117.9, 113.0, 109.4 (d, J = 3.3 Hz), 30.1 (q, J = 32.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.3; HRMS (ESI) calcd for $[M + H]^+$ $C_{15}H_{11}ClF_3N_2$ 311.0558, found 311.0550.

*2-(4-Bromophenyl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2f**):* Purified by column chromatography (petroleum ether/EtOAc, 4/

Scheme 2. Experiment for Mechanistic Study



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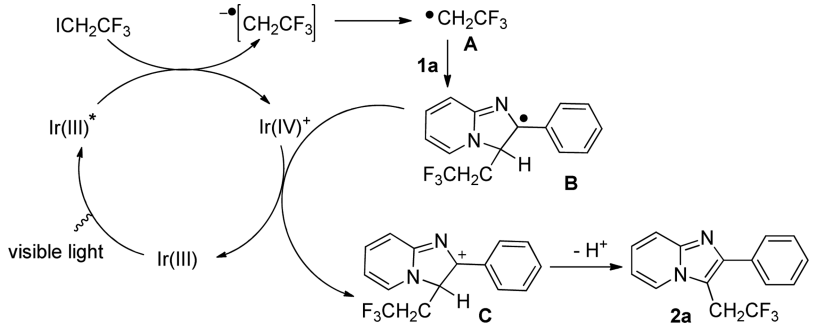
Scheme 3. Plausible Reaction Mechanism



1) as a white solid (60.2 mg, 85%); mp 140−141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, 1 H, J = 7.0 Hz), 7.71−7.62 (m, 5 H), 7.31 (t, 1 H, J = 8.0 Hz), 6.95 (t, 1 H, J = 7.0 Hz), 3.88 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.71, 145.67, 132.7, 131.9, 130.1, 125.6 (q, J = 277.1 Hz), 125.4, 123.5 (d, J = 2.1 Hz), 117.9, 113.0, 109.4 (d, J = 2.8 Hz), 30.1 (q, J = 32.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.3; HRMS (ESI) calcd for $[M + H]^+$ $C_{15}H_{11}BrF_3N_2$ 355.0052, found 355.0045.

2-(3-Bromophenyl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2g**): Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (52.4 mg, 74%); mp 133−135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, 1 H, J = 7.0 Hz), 7.99 (t, 1 H, J = 2.0 Hz), 7.73−7.70 (m, 2 H), 7.58−7.56 (m, 1 H), 7.39−7.31 (m, 2 H), 6.96 (dt, 1 H, J_1 = 7.0 Hz J_2 = 1.0 Hz), 3.89 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7, 145.3, 135.8, 131.7, 131.3, 130.2, 126.9, 125.6 (q, J = 277.1 Hz), 125.5, 123.6 (d, J = 2.1 Hz), 122.9, 118.0, 113.1, 109.6 (d, J = 3.5 Hz), 30.0 (q, J = 32.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.3; HRMS (ESI) calcd for $[M + H]^+$ $C_{15}H_{11}BrF_3N_2$ 355.0052, found 355.0048.

2-(4-Fluorophenyl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2h**): Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (47.1 mg, 80%); mp 138−140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, 1 H, J = 7.0 Hz), 7.76−7.73 (m, 2 H), 7.69 (d, 1 H, J = 9.0 Hz), 7.31−7.28 (m, 1 H), 7.20−7.16 (m, 2 H), 6.92 (dt, 1 H, J_1 = 7.0 Hz J_2 = 1.0 Hz), 3.84 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (d, J = 246.3 Hz), 146.0, 145.6, 130.3 (d, J = 7.5 Hz), 129.8 (d, J = 3.8 Hz), 125.7 (q, J = 277.1 Hz), 125.2, 123.5 (d, J = 2.3 Hz), 117.9, 115.7 (d, J = 21.5 Hz), 112.9, 109.2 (d, J = 2.9 Hz), 30.0 (q, J = 32.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.3, −113.5; HRMS (ESI) calcd for $[M + H]^+$ $C_{15}H_{11}F_4N_2$ 295.0853, found 295.0864.

3-(2,2,2-Trifluoroethyl)-2-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyridine (**2i**): Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (57.1 mg, 83%); mp 152−153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, 1 H, J = 6.5 Hz), 7.93 (d, 1 H, J = 8.0 Hz), 7.78−7.73 (m, 3 H), 7.37−7.33 (m, 1 H), 6.98 (dt, 1 H, J_1 = 7.0 Hz J_2 = 1.0 Hz), 3.90 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8, 145.3, 137.3, 130.3 (d, J = 3.3 Hz), 128.8, 125.6 (q, J = 277.0 Hz), 125.7 (q, J = 8.8 Hz), 125.6, 124.2 (q, J = 270.4 Hz), 123.6, 118.1, 113.2, 109.9 (d, J = 2.5 Hz), 30.0 (q, J = 32.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −62.6, −63.3; HRMS (ESI) calcd for $[M + H]^+$ $C_{16}H_{11}F_6N_2$ 345.0821, found 345.0818.

4-(3-(2,2,2-Trifluoroethyl)imidazo[1,2-a]pyridin-2-yl)benzonitrile (**2j**): Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (45.8 mg, 76%); mp 172−173 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, 1 H, J = 6.5 Hz), 7.93 (d, 2 H, J = 8.0 Hz), 7.79 (d, 2 H, J = 8.0 Hz), 7.72 (d, 1 H, J = 9.0 Hz), 7.36 (t, 1 H, J = 7.5 Hz), 6.99 (t, 1 H, J = 7.0 Hz), 3.91 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9, 144.6, 138.3, 132.5, 129.0, 125.9, 125.5 (q, J = 277.1 Hz), 123.6 (d, J = 2.1 Hz), 118.8, 118.1, 113.4, 111.9, 110.2 (d, J = 2.9 Hz), 30.1 (q, J = 32.1 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.2; HRMS (ESI) calcd for $[M + H]^+$ $C_{16}H_{11}F_3N_3$ 302.0900, found 302.0910.

2-([1,1′-Biphenyl]-4-yl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]-pyridine (**2k**): Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (50.0 mg, 71%); mp 142−143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, 1 H, J = 6.5 Hz), 7.90 (d, 1 H, J = 7.5 Hz), 7.77−7.69 (m, 5 H), 7.51−7.48 (m, 2 H), 7.42−7.39 (m, 1 H), 7.34−7.30 (m, 1 H), 6.95 (dt, 1 H, J_1 = 7.0 Hz, J_2 = 1.0 Hz), 3.95 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 145.7, 141.0, 140.6, 132.0, 128.92, 128.86, 127.5, 127.1, 125.8 (q, J = 277.1 Hz), 125.1, 123.5 (d, J = 2.5 Hz), 117.9, 112.9, 109.3 (d, J = 3.8 Hz), 30.2 (q, J = 31.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.1; HRMS (ESI) calcd for $[M + H]^+$ $C_{21}H_{16}F_3N_2$ 353.1260, found 353.1267.

2-(Naphthalen-1-yl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]-pyridine (**2l**): Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (45.6 mg, 70%); mp 118−120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, 1 H, J = 6.5 Hz), 7.97 (d, 1 H, J = 8.0 Hz), 7.94 (d, 1 H, J = 8.0 Hz), 7.85 (d, 1 H, J = 8.5 Hz), 7.77 (d, 1 H, J = 9.0 Hz), 7.62−7.57 (m, 2 H), 7.54−7.51 (m, 1 H), 7.48−7.44 (m, 1 H), 7.37−7.33 (m, 1 H), 3.73 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 145.6, 133.8, 132.6, 130.9, 129.1, 128.4, 128.2, 126.5, 126.0, 125.4 (q, J = 277.1 Hz), 125.1, 125.0, 123.7, 118.0, 112.9, 111.5 (d, J = 3.8 Hz), 29.5 (q, J = 32.5 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.8; HRMS (ESI) calcd for $[M + H]^+$ $C_{19}H_{14}F_3N_2$ 327.1104, found 327.1095.

2-(Naphthalen-2-yl)-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]-pyridine (**2m**): Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (48.9 mg, 75%); mp 137−138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 8.15 (d, 1 H, J = 7.0 Hz), 8.00−7.91 (m, 4 H), 7.77 (d, 1 H, J = 9.0 Hz), 7.56−7.54 (m, 2 H), 7.35−7.32 (m, 1 H), 6.96 (dt, 1 H, J_1 = 7.0 Hz, J_2 = 1.0 Hz), 3.97 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 145.8, 133.4, 133.1, 131.1, 128.47, 128.45, 127.74, 127.72, 126.43, 126.38, 125.8 (q, J = 277.3 Hz), 125.2, 123.6 (d, J = 2.4 Hz),, 117.9, 112.9, 109.6 (d, J = 3.4 Hz), 30.2 (q, J = 31.8 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.1; HRMS (ESI) calcd for $[M + H]^+$ $C_{19}H_{14}F_3N_2$ 327.1104, found 327.1101.

2-Methyl-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2n**): Purified by column chromatography (petroleum ether/EtOAc, 1/1) as a white solid (32.9 mg, 77%); mp 103−105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, 1 H, J = 7.0 Hz), 7.58 (d, 1 H, J = 9.0 Hz), 7.23−7.20 (m, 1 H), 6.87−6.85 (m, 1 H), 3.71 (q, 2 H, J = 10.0 Hz), 2.48 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 143.8, 125.6 (q, J = 276.8 Hz), 124.3, 122.8, 117.1, 112.3, 109.3, 29.0 (q, J = 32.3 Hz), 13.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −65.4; HRMS (ESI) calcd for $[M + H]^+$ $C_{10}H_{10}F_3N_2$ 215.0791, found 215.0798.

8-Methyl-2-phenyl-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2o**): Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (38.3 mg, 66%); mp 115−117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, 1 H, J = 7.0 Hz), 7.80−7.78 (m, 2 H), 7.52−7.42 (m, 3 H), 7.09 (d, 1 H, J = 7.0 Hz), 6.84 (t, 1 H, J = 7.0 Hz), 3.86 (q, 2 H, J = 10.0 Hz), 2.70 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 146.1, 134.0, 128.8, 128.7, 128.2, 127.9, 125.8 (q, J = 277.1 Hz), 123.8, 124.3 (d, J = 2.1 Hz), 112.8, 109.7 (d, J = 3.1 Hz), 30.1 (q, J = 31.9 Hz), 17.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.3; HRMS (ESI) calcd for $[M + H]^+$ $C_{16}H_{14}F_3N_2$ 291.1104, found 291.1113.

7-Methyl-2-phenyl-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2p**): Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (40.0 mg, 69%); mp 127−128 °C; ^{1}H NMR (500

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MHz, $CDCl_3$) δ 7.96 (d, 1 H, J = 7.0 Hz), 7.76 (d, 1 H, J = 7.5 Hz), 7.49−7.39 (m, 4 H), 6.74 (d, 1 H, J = 7.0 Hz), 3.84 (q, 2 H, J = 10.0 Hz), 2.43 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 146.1, 136.2, 133.8, 128.7, 128.5, 128.2, 125.8 (q, J = 277.1 Hz), 122.7 (d, J = 2.3 Hz), 116.2, 115.4, 108.7 (d, J = 2.9 Hz), 30.1 (q, J = 31.9 Hz), 21.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.4 (s, 3 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{16}H_{14}F_3N_2$ 291.1104, found 291.1106.

*6-Methyl-2-phenyl-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2q**):* Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (34.8 mg, 60%); mp 121−123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.80−7.78 (m, 2 H), 7.62 (d, 1 H, J = 9.0 Hz), 7.52−7.42 (m, 3 H), 7.17−7.15 (m, 1 H), 3.88 (q, 2 H, J = 10.0 Hz), 2.42 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 144.7, 133.8, 128.7, 128.5, 128.2, 126.1, 125.8 (q, J = 277.3 Hz), 122.6, 121.2, 117.2, 109.0 (d, J = 3.1 Hz), 30.1 (q, J = 31.9 Hz), 18.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.2; HRMS (ESI) calcd for $[M + H]^+$ $C_{16}H_{14}F_3N_2$ 291.1104, found 291.1112.

*8-Chloro-2-phenyl-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2r**):* Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (29.1 mg, 47%); mp 109−111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, 1 H, J = 7.0 Hz), 7.81−7.78 (m, 2 H), 7.53−7.38 (m, 4 H), 6.89 (t, 1 H, J = 7.0 Hz), 3.89 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 143.1, 133.1, 128.9, 128.7, 128.6, 125.6 (q, J = 277.1 Hz), 124.1, 123.8, 122.3, 112.4, 111.1 (d, J = 3.6 Hz), 30.2 (q, J = 32.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.1; HRMS (ESI) calcd for $[M + H]^+$ $C_{15}H_{11}ClF_3N_2$ 311.0558, found 311.0564.

*6-Fluoro-2-phenyl-3-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridine (**2s**):* Purified by column chromatography (petroleum ether/EtOAc, 4/1) as a white solid (20.6 mg, 35%); mp 130−132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (t, 1 H, J = 3.0 Hz), 7.78−7.77 (m, 2 H), 7.70 (dd, 1 H, J_1 = 10.0 Hz J_2 = 5.5 Hz), 7.54−7.51 (m, 2 H), 7.47−7.44 (m, 1 H), 7.26−7.22 (m, 1 H), 3.87 (q, 2 H, J = 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6 (d, J = 236.8 Hz), 148.2 (d, J = 2.1 Hz), 143.3, 133.3, 128.8, 128.5, 127.2, 125.6 (q, J = 277.0 Hz), 118.4 (d, J = 9.0 Hz), 117.2 (d, J = 25.4 Hz), 110.8, 110.5 (d, J = 41.1 Hz), 30.2 (q, J = 32.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.1 (s, 3 F), −138.9 (s, 1 F); HRMS (ESI) calcd for $[M + H]^+$ $C_{15}H_{11}F_4N_2$ 295.0853, found 295.0846.

*2-Phenyl-3-(2,2,2-trifluoroethyl)benzo[d]imidazo[2,1-b]thiazole (**4a**):* Purified by column chromatography (petroleum ether/EtOAc, 9/1) as a white solid (61.8 mg, 93%); mp 152−154 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, 1 H, J = 8.0 Hz), 7.76−7.74 (m, 3 H), 7.51−7.47 (m, 3 H), 7.44−7.38 (m, 2 H), 4.08 (q, 2 H, J = 9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 148.1, 133.5, 133.1, 130.5, 128.7, 128.14, 128.10, 126.1, 125.2 (q, J = 277.0 Hz), 124.8, 124.5, 113.2 (d, J = 2.5 Hz), 113.0 (d, J = 3.8 Hz), 30.9 (q, J = 31.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.2; HRMS (ESI) calcd for $[M + H]^+$ $C_{17}H_{12}F_3N_2S$ 333.0668, found 333.0661.

*6-Chloro-2-phenyl-3-(2,2,2-trifluoroethyl)benzo[d]imidazo[2,1-b]thiazole (**4b**):* Purified by column chromatography (petroleum ether/EtOAc, 9/1) as a white solid (65.9 mg, 90%); mp 178−180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73−7.71 (m, 3 H), 7.68 (d, 1 H, J = 9.0 Hz), 7.50−7.47 (m, 2 H), 7.45−7.40 (m, 2 H), 4.03 (q, 2 H, J = 9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 148.4, 133.2, 132.0, 131.6, 130.4, 128.8, 128.2, 128.1, 126.4, 125.1 (q, J = 277.0 Hz), 124.2, 113.8 (d, J = 2.4 Hz), 113.1 (d, J = 3.4 Hz), 30.8 (q, J = 32.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.3; HRMS (ESI) calcd for $[M + H]^+$ $C_{17}H_{11}ClF_3N_2S$ 367.0278, found 367.0280.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00950.

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra of new compounds (PDF)

Crystallographic data for **2n** (CIF)

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Notes

The authors declare no competing financial interest.

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