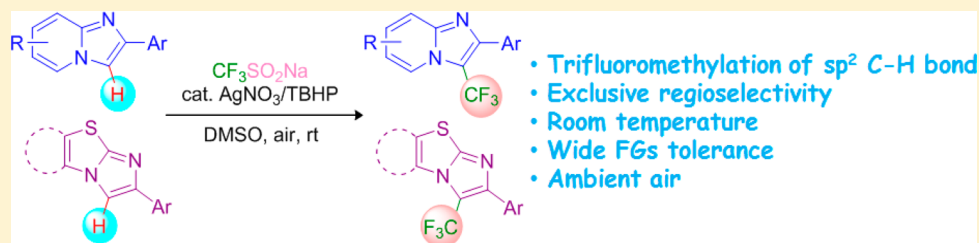# Regioselective Oxidative Trifluoromethylation of Imidazoheterocycles via C(sp^2)−H Bond Functionalization

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S *Supporting Information*

ABSTRACT: Catalytic oxidative trifluoromethylation of imidazopyridines has been carried out at room temperature through the functionalization of the sp^2 C−H bond employing Langlois reagent under ambient air. A library of 3-(trifluoromethyl)imidazo-[1,2-a]pyridines with broad functionalities have been synthesized regioselectively. This methodology is also applicable to imidazo[2,1-b]thiazole and benzo[d]imidazo[2,1-b]thiazole.

INTRODUCTION

The incorporation of a trifluoromethyl group into organic molecules brings alteration of their properties such as solubility, metabolic stability, and bioavailability.[1] Because of these features fluorinated compounds have gained significant interest in the pharmaceutical industry, the agrochemical industry, as well as material science.[2] In addition, a number of F-containing drugs are also available in the market.[3]

Recently, much attention has been paid to the trifluoromethylation of arenes and heterocycles due to the importance of trifluoromethyl group in drug development.[4] Consequently, a number of methods have been developed for the synthesis of trifluoromethylated organic compounds.[5] Among these, the direct trifluoromethylation of heterocycles via C−H functionalization is the most appealing as no prefunctionalization is required.[6] In addition, it is a straightforward and more economical method. Direct trifluoromethylations have been carried out employing various radical, nucleophilic, and electrophilic trifluoromethylating agents like Togni's reagent,[6d−g] Umemoto's reagent,[6i,j] Ruppert's reagent,[6k,l] Langlois' reagent,[6m] etc. Among these, Langlois' reagent is the most preferable as it is inexpensive and easy to handle.[7] In 1991, Langlois first employed sodium trifluoromethanesulfonate (Langlois reagent) as trifluoromethylating agent for trifluoromethylation of aromatic compounds under oxidative conditions.[7a] After that, few methodologies for the trifluomethylation have been developed that employ sodium trifluoromethanesulfonate as the source of CF$_3$ radical in the presence of certain oxidants.[8,9] Recently, Baran et al. reported an elegant method for the direct trifluoromethylation of aromatic heterocycles using Langlois reagent.[6m] Despite this significant progress, the direct and

catalytic trifluoromethylation of biologically active non-prefunctionalized heterocyles is still remained challenging.

Imidazopyridines show many interesting features toward the biological activities, for instance, antiviral, antimicrobial, antitumor, antiinflammatory, antiparasitic, hypnotic, etc.[10] In addition, some marketed drugs like alpidem, zolpidem, necopidem, saripidem, olprinone, zolimidine, etc. contain this scaffold. These are also very useful in material science.[11] Considerable attention has been paid to the synthesis and functionalization of imidazopyridines.[12] Recently, we have also reported some graceful methodologies for the synthesis of functionalized imidazo[1,2-a]pyridine derivatives from readily available materials.[13] It is well-known that incorporation of fluorine atoms into medicinally active compounds increases their bioactivities. Therefore, we turned our attention toward synthesizing trifluoromethylimidazo[1,2-a]pyridine derivatives that might have an influence in biological activities. Recently, Xiao et al. reported a method for the synthesis of various trifluoromethylated heteroaromatic compounds from their iodo-substituted derivatives.[14] However, there is no such method for the trifluoromethylation of imidazo[1,2-a]pyridine derivatives. Based on our research experiences on imidazopyridines,[12a,13] we envisaged that the trifluoromethylation of imidazopyridines could be carried out under suitable conditions. Herein, we report a direct and regioselective method for trifluoromethylation of imidazopyridines using Langlois' reagent in the presence of catalytic amount of AgNO$_3$ and TBHP at room temperature in ambient air.

Scheme 1. Regioselective Trifluoromethylation of Imidazopyridines
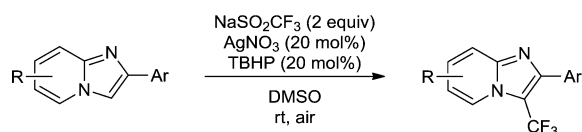
RESULTS AND DISCUSSION

First, 2-phenylimidazo[1,2-a]pyridine was selected as a model substrate to find suitable reaction conditions employing sodium trifluoromethanesulfonate (Langlois' reagent) as the trifluoromethylating agent. The reaction was carried out using various oxidants and solvents. The results are summarized in Table 1. Initially, the reaction was carried out employing

Table 1. Optimization of the Reaction Conditions[a]

entry	metal salts (mol %)	oxidant (mol %)	solvent	yield (%)
1	AgNO$_3$ (20)	K$_2$S$_2$O$_8$ (20)	DMF	30
2	AgNO$_3$ (20)	K$_2$S$_2$O$_8$ (20)	1,2-DCE	20
3	AgNO$_3$ (20)	K$_2$S$_2$O$_8$ (20)	DMSO	67
4	AgNO$_3$ (20)	K$_2$S$_2$O$_8$ (20)	CH$_3$CN	25
5	AgNO$_3$ (20)	K$_2$S$_2$O$_8$ (20)	THF	0
6	AgNO$_3$ (20)	TBHP (20)[b]	DMSO	74
7	AgNO$_3$ (20)	DTBP (20)	DMSO	27
8	AgNO$_3$ (20)	BQ (20)	DMSO	22
9	AgNO$_2$ (20)	TBHP (20)	DMSO	56
10	Ag$_2$CO$_3$ (20)	TBHP (20)	DMSO	48
11	Ag$_2$O (20)	TBHP (20)	DMSO	31
12	Cu(OTf)$_2$ (20)	TBHP (20)	DMSO	0
13	FeCl$_3$ (20)	TBHP (20)	DMSO	ND
14	AgNO$_3$ (30)	TBHP (30)	DMSO	71
15	AgNO$_3$ (10)	TBHP (10)	DMSO	49[c]
16	AgNO$_3$ (20)		DMSO	<10
17		TBHP (20)	DMSO	0

[a]Reaction conditions: 0.2 mmol of **1a** and 0.4 mmol of NaSO$_2$CF$_3$ in the presence of catalyst (20 mol %) and oxidant (20 mol %) in solvent (1 mL) at room temperature under ambient air for 12 h. [b]TBHP (5−6 M solution in decane). [c]Stirred for 36 h. ND: Not detected in TLC.

NaSO$_2$CF$_3$ (2 equiv), AgNO$_3$ (20 mol %), and K$_2$S$_2$O$_8$ (20 mol %) as oxidant in DMF solvent at room temperature under aerobic reaction conditions (Table 1, entry 1). The desired product was obtained only in 30% yield after 24 h, and the remaining starting material was successfully isolated. Further, no improvement of the yield was observed even after 48 h. Inspired by this initial result, the effect of different solvents such as 1,2-dichloroethane, DMSO, acetonitrile, THF was tested, and the best result was achieved in DMSO at room temperature affording 67% yield (Table 1, entries 2−5). We then turned our attention toward the role of oxidant. For this purpose we screened various oxidants, e.g., TBHP, DTBP, BQ, etc., and it was found that TBHP gave the best result, affording 74% yield after 12 h (Table 1, entries 6−8). Other metal salts like AgNO$_2$, Ag$_2$CO$_3$, Ag$_2$O, Cu(OTf)$_2$, and FeCl$_3$ were also tested, but these were not effective like AgNO$_3$ (Table 1, entries 9−13). No substantial increase in the yield

was observed by increasing the oxidant loading (Table 1, entry 14), whereas when the catalyst loading was decreased, a lower yield was obtained even after 36 h (Table 1, entry 15). A trace amount of product was formed when only AgNO$_3$ was used as oxidant (Table 1, entry 16). However, TBHP is not optimal for conversion (Table 1, entry 17). Finally, the optimized reaction conditions were obtained using 2 equiv of NaSO$_2$CF$_3$, 20 mol % of AgNO$_3$, and 20 mol % of TBHP as oxidant in DMSO at room temperature for 12 h under aerobic conditions (Table 1, entry 6).

With the optimized reaction conditions in hand, we turned our attention toward the scope of the reaction, and the results are shown in Scheme 2. A wide range of substituted imidazo[1,2-a]pyridines were subjected to prove the general applicability of the present procedure. Imidazopyridines substituted with a methyl group at different positions efficiently react with trifluoromethylating agent to afford the corresponding products with good yields (**2b** and **2c**). The imidazopyridines bearing halogens like −Cl and −Br on the pyridine ring successfully reacted to give the desired products (**2d** and **2e**). Phenyl groups at the 2-position of imidazopyridines with different functionalities were also tested. The phenyl moiety with electron-donating substituents gave higher yields compared to the electron-withdrawing groups (**2f−n**). The zolimidine (antiulcer drug) afforded the corresponding trifluoromethylated product (**2o**), which might have greater bioactivity. 2-Heteroaryl imidazopyridines also reacted well to afford the corresponding products with good yields (**2p** and **2q**). The trifluoromethylation occurred regioselectively in imidazole moiety only. However, the alkyl-group-containing imidazopyridines (**1r** and **1s**) did not afford the trifluoromethylated product, which signifies the necessity of the aryl group at the 2-position.

Next, we explored our present methodology to other imidazoheterocycles (**3**) like imidazo[2,1-b]thiazole and benzo[d]imidazo[2,1-b]thiazole to prove the general applicability of the present protocol (Scheme 3). To our delight, the corresponding trifluoromethylated products (**4**) were obtained regioselectively in good yields. It is worthy to mention that no trifluomethylation occurred at the alkene part (**4b**). In the case of imidazothiazole, only mono-trifluoromethylation took place regioselectively (**4c**). The present protocol is highly selective for the trifluoromethylation of imidazo-fused heterocycles. Other heterocycles like N-methylimidazole (**5d**), 1,2-dimethylimidazole (**5e**), and N-methylindoles (**5f**) were unreacted under the present reaction conditions.

To understand the mechanistic pathway of this reaction, a few controlled experiments were carried out (Scheme 4). The reaction did not proceed at all in the presence of radical scavenger TEMPO (3 equiv), which signifies that the reaction proceeds through a radical pathway (Scheme 4, eq A). When the reaction was carried out under argon atmosphere, only trace amount of desired product was obtained. Thus, the aerial oxygen plays a crucial role to fulfill the catalytic cycle (Scheme 4, eq B).

From these experiments and literature reports,[9a−c] the probable mechanism of the reaction is described in Scheme 5. At first, the CF$_3$ radical is generated from the sodium trifluoromethanesulfonate by the reaction with AgNO$_3$ and subsequently reacts with the imidazopyridines to form the radical intermediate **A**. This radical intermediate **A** on further oxidation transformed into carbocation intermediate **B**.

Scheme 2. Substrate Scope of Imidazopyridines[a]
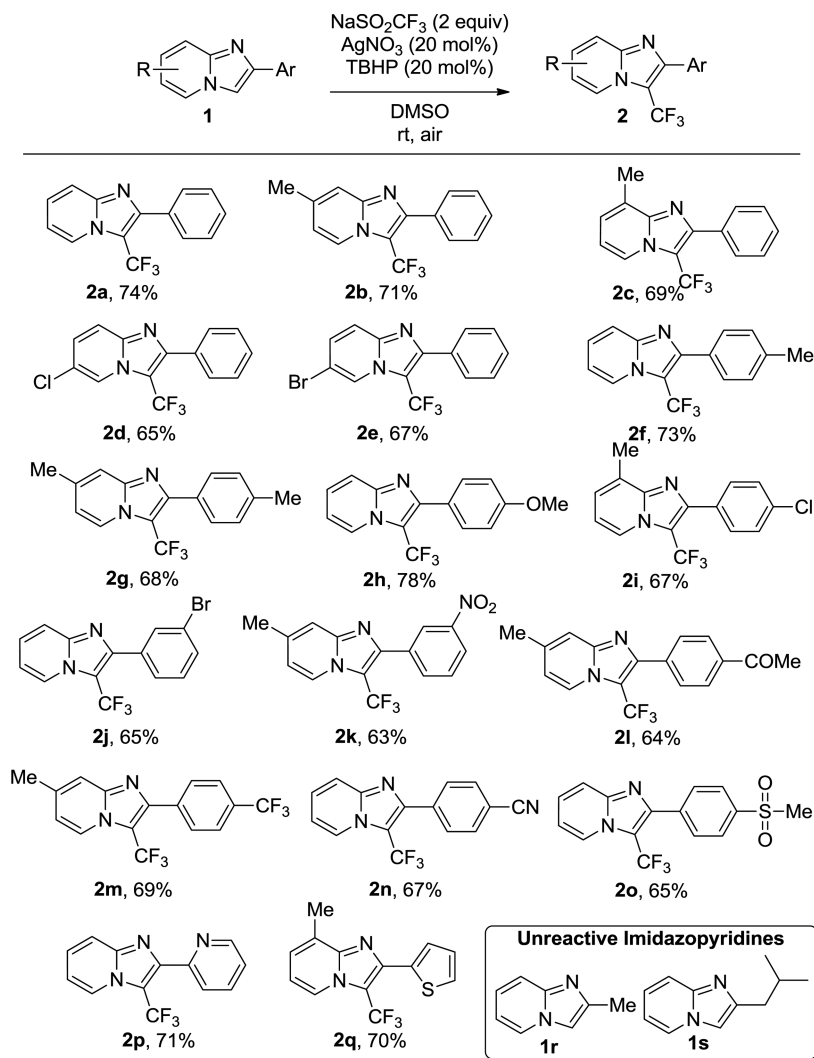
[a]Reaction conditions: 0.2 mmol of **1** and 0.4 mmol of NaSO$_2$CF$_3$ in the presence of AgNO$_3$ (20 mol %) and TBHP (5−6 M solution in decane) (20 mol %) in DMSO (1 mL) at room temperature under ambient air for 12 h.

Scheme 3. Substrates Scope of Imidazoheterocycles[a]
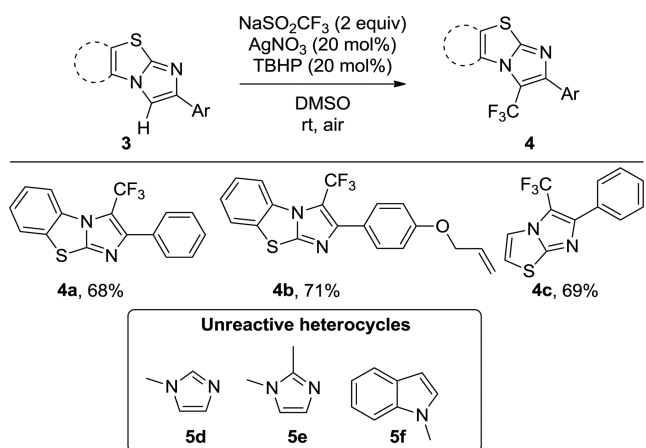
[a]Reaction conditions: 0.2 mmol of **3** or **5** and 0.4 mmol of NaSO$_2$CF$_3$ in the presence of AgNO$_3$ (20 mol %) and TBHP (5−6 M solution in decane) (20 mol %) in DMSO (1 mL) at room temperature under ambient air for 12 h.

Scheme 4. Controlled Experiments
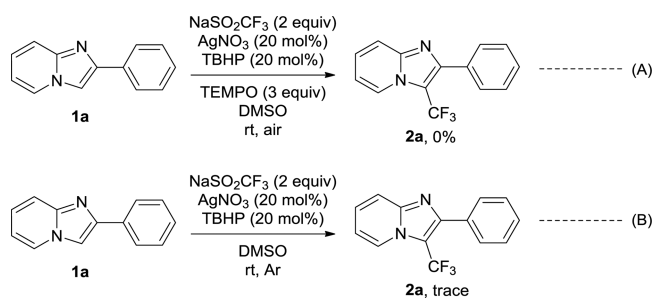
Probably both the intermediates **A** and **B** are stabilized by the presence of adjacent phenyl group. Finally, the intermediate **B** affords the product through the elimination of H$^+$. Ag(I) is regenerated from Ag(0) by TBHP and O$_2$.

■ CONCLUSIONS

In conclusion, we have developed a direct and straightforward method for regioselective trifluoromethylation of imidazopyridines through sp^2 C−H functionalization employing Langlois

Scheme 5. Plausible Mechanism
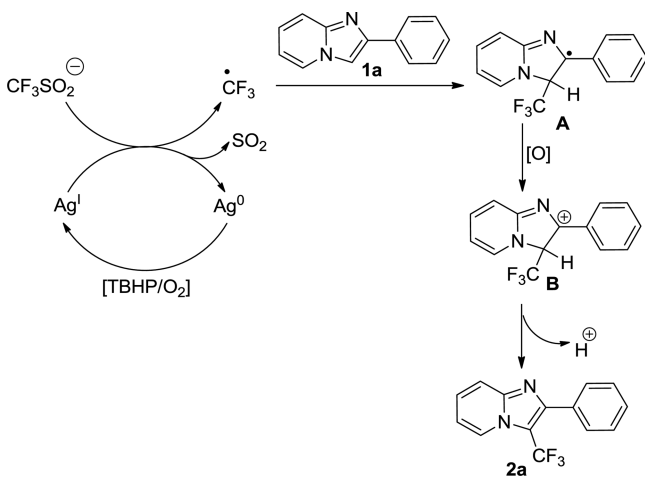
reagent in ambient air. To the best of our knowledge, this is the first report for the direct trifluoromethylation of imidazopyridines. A catalytic amount of AgNO₃/TBHP is sufficient to perform the reactions. An array of 3-(trifluoromethyl)imidazo[1,2-a]pyridine derivatives with broad functionalities were synthesized at room temperature. The present protocol is also applicable for other imidazoheterocycles like imidazo[2,1-b]thiazole and benzo[d]imidazo-[2,1-b]thiazole. Mild reaction conditions, employment of cheap trifluoromethylating agent, regioselectivity, aerobic reaction conditions, and broad substrates scope are the attractive features of this methodology. We believe these trifluoromethylated imidazopyridine derivatives will be of much importance in medicinal chemistry.

■ EXPERIMENTAL SECTION

General Information. ¹H NMR spectra were determined on a 400 MHz spectrometer as solutions in CDCl₃. Chemical shifts are expressed in parts per million (δ) and are referenced to tetramethylsilane (TMS) as internal standard, the signals are reported as s (singlet), d (doublet), t (triplet), and m (multiplet), and coupling constants J are given in hertz. ¹³C and ¹⁹F NMR spectra were recorded at 100 MHz and at 376 MHz, respectively in CDCl₃ solution. TLC was done on silica gel coated glass slide. Silica gel (60−120 mesh) was used for column chromatography. Petroleum ether refers to the fraction boiling in the range of 60−80 °C unless otherwise mentioned. All solvents were dried and distilled before use. Commercially available substrates were freshly distilled before the reaction. All reactions involving moisture-sensitive reactants were executed using oven-dried glassware. All the imidazoheterocycles were prepared by our reported methods.[13a,e]

General Procedure for Trifluoromethylation of Imidazoheterocycles (2 or 4). A mixture of **1** (or **3**) (0.2 mmol), sodium trifluoromethanesulfonate (62 mg, 0.4 mmol), and AgNO₃ (7 mg, 20 mol %) was taken in sealed tube followed by dropwise addition of TBHP (5−6 M solution in decane, 8 μL, 20 mol %) in DMSO (1 mL) and stirred at room temperature for 12 h. After completion (TLC), the reaction mixture was extracted with dichloromethane (10 mL) followed by washing with brine (5 mL) and dried over Na₂SO₄. After evaporation of solvent, the crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (9:1 to 3:1) as an eluent.

2-Phenyl-3-(trifluoromethyl)imidazo[1,2-a]pyridine (2a):[14] 74% yield (38 mg), white solid; mp 79−81 °C (lit.[14] mp 81−83 °C); ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, J = 7.2 Hz, 1H), 7.67−7.61 (m, 3H), 7.41−7.29 (m, 4H), 6.94−6.90 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 148.1, 146.2, 132.9, 129.7, 129.0, 128.3, 127.1,

126.0, 125.6 (q, $J_{C−F}$ = 4 Hz),121.0 (q, $J_{C−F}$ = 266 Hz), 118.0, 114.0; ¹⁹F NMR (376 MHz, CDCl₃) δ −57.7. Anal. Calcd for C₁₄H₉F₃N₂: C, 64.12; H, 3.46; N, 10.68. Found: C, 64.14; H, 3.48; N, 10.66.

7-Methyl-2-phenyl-3-(trifluoromethyl)imidazo[1,2-a]-pyridine (2b): 71% yield (39 mg), gummy mass; ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, J = 7.2 Hz, 1H), 7.61−7.60 (m, 2H), 7.40−7.34 (m, 4H), 6.76−6.73 (m, 1H), 2.38 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 148.0, 146.7, 138.4, 133.1, 129.6, 129.0, 128.2, 126.1, 124.7 (q, $J_{C−F}$ = 4 Hz), 119.5 (q, $J_{C−F}$ = 263 Hz,), 116.7, 116.5, 21.4; ¹⁹F NMR (376 MHz, CDCl₃) δ −57.4. Anal. Calcd for C₁₅H₁₁F₃N₂: C, 65.21; H, 4.01; N, 10.14. Found: C, 65.23; H, 4.03; N, 10.12.

8-Methyl-2-phenyl-3-(trifluoromethyl)imidazo[1,2-a]-pyridine (2c): 69% yield (38 mg), gummy mass; ¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, J = 6.8 Hz, 1H), 7.61 (d, J = 7.2 Hz, 2H), 7.39−7.34 (m, 3H), 7.08 (d, J = 6.8 Hz, 1H), 6.82−6.79 (m, 1H), 2.59 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.6, 146.6, 133.3, 129.8, 128.9, 128.7, 128.3, 128.3, 125.7, 123.3 (q, $J_{C−F}$ = 3 Hz), 122.1 (q, $J_{C−F}$ = 265 Hz), 114.0, 17.3; ¹⁹F NMR (376 MHz, CDCl₃) δ −57.8. Anal. Calcd for C₁₅H₁₁F₃N₂: C, 65.21; H, 4.01; N, 10.14. Found: C, 65.24; H, 4.02; N, 10.15.

6-Chloro-2-phenyl-3-(trifluoromethyl)imidazo[1,2-a]-pyridine (2d): 65% yield (38 mg), gummy mass; ¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 7.69−7.66 (m, 3H), 7.49−7.44 (m, 3H), 7.38−7.35 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 148.9, 144.6, 132.5, 129.6, 129.3, 129.0, 128.6, 128.4, 123.6 (q, $J_{C−F}$ = 3 Hz), 122.5, 121.8 (q, $J_{C−F}$ = 266 Hz), 118.5; ¹⁹F NMR (376 MHz, CDCl₃) δ −57.6. Anal. Calcd for C₁₄H₈ClF₃N₂: C, 56.68; H, 2.72; N, 9.44. Found: C, 56.70; H, 2.74; N, 9.42.

6-Bromo-2-phenyl-3-(trifluoromethyl)imidazo[1,2-a]-pyridine (2e): 67% yield (45 mg), gummy mass; ¹H NMR (400 MHz, CDCl₃) δ 8.44 (s, 1H), 7.68−7.66 (m, 2H), 7.63 (d, J = 9.6 Hz, 1H), 7.48−7.44 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 148.7, 144.6, 132.5, 130.7, 129.6, 129.3, 128.4, 127.3, 125.7 (q, $J_{C−F}$ = 3 Hz), 121.7 (q, $J_{C−F}$ = 265 Hz), 118.7, 108.9; ¹⁹F NMR (376 MHz, CDCl₃) δ −57.6. Anal. Calcd for C₁₄H₈BrF₃N₂: C, 49.29; H, 2.36; N, 8.21. Found: C, 49.31; H, 2.38; N, 8.23.

2-p-Tolyl-3-(trifluoromethyl)imidazo[1,2-a]pyridine (2f): 73% yield (40 mg), gummy mass; ¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 9.2 Hz, 1H), 7.51 (d, J = 7.6 Hz, 2H), 7.31−7.27 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 6.92−6.88 (m, 2H), 2.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 148.3, 146.2, 139.0, 130.1, 129.6, 129.0, 126.9, 125.6 (q, $J_{C−F}$ = 3 Hz), 122.1 (q, $J_{C−F}$ = 265 Hz), 118.1, 114.3, 113.9, 21.5; ¹⁹F NMR (376 MHz, CDCl₃) δ −57.6. Anal. CalcdC₁₅H₁₁F₃N₂: C, 65.21; H, 4.01; N, 10.14. Found: C, 65.23; H, 4.04; N, 10.12.

7-Methyl-2-p-tolyl-3-(trifluoromethyl)imidazo[1,2-a]-pyridine (2g): 68% yield (39 mg), gummy mass; ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, J = 7.2 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.40 (s, 1H), 7.19−7.17 (m, 2H), 6.75−6.73 (m, 1H), 2.38 (s, 3H), 2.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 148.1, 146.6, 138.9, 138.3, 136.0, 130.1, 129.5, 129.0, 124.8 (q, $J_{C−F}$ = 4 Hz), 122.2 (q, $J_{C−F}$ = 265 Hz), 116.6, 116.4, 21.4 (2C); ¹⁹F NMR (376 MHz, CDCl₃) δ −57.4. Anal. Calcd for C₁₆H₁₃F₃N₂: C, 66.20; H, 4.51; N, 9.65. Found: C, 66.22; H, 4.52; N, 9.63.

2-(4-Methoxyphenyl)-3-(trifluoromethyl)imidazo[1,2-a]-pyridine (2h): 78% yield (45 mg), gummy mass; ¹H NMR (400 MHz, CDCl₃) δ 8.30 (d, J = 6.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.40−7.36 (m, 1H), 7.01−6.96 (m, 3H), 3.86 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.0, 147.7, 145.9, 130.8, 126.9, 125.4 (q, $J_{C−F}$ = 3 Hz), 125.0, 121.9 (q, $J_{C−F}$ = 265 Hz), 119.4, 117.8, 113.8, 113.6, 55.2; ¹⁹F NMR (376 MHz, CDCl₃) δ −57.6. Anal. Calcd for C₁₅H₁₁F₃N₂O: C, 61.64; H, 3.79; N, 9.59. Found: C, 61.66; H, 3.81; N, 9.57.

2-(4-Chlorophenyl)-8-methyl-3-(trifluoromethyl)imidazo-[1,2-a]pyridine (2i): 67% yield (41 mg), gummy mass; ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, J = 6.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.44−7.41 (m, 2H), 7.18 (d, J = 7.2 Hz, 1H), 6.92−6.89 (m, 1H), 2.66 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 146.6, 146.2, 134.9, 131.7, 130.9, 128.9, 128.4, 128.2, 125.8, 123.2 (q, $J_{C−F}$ = 3

Hz), 121.8 (q, J_{C-F} = 265 Hz), 114.1, 17.0; ^{19}F NMR (376 MHz, CDCl$_3$) δ −57.7. Anal. Calcd for C$_{15}$H$_{10}$ClF$_3$N$_2$: C, 57.99; H, 3.24; N, 9.02. Found: C, 58.00; H, 3.22; N, 9.00.

2-(3-Bromophenyl)-3-(trifluoromethyl)imidazo[1,2-*a*]-pyridine (2j): 65% yield (44 mg), gummy mass; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.24 (d, *J* = 7.2 Hz, 1H), 7.79 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.54−7.48 (m, 2H), 7.35−7.30 (m, 1H), 7.27−7.23 (m, 1H), 7.19−6.93 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.4, 146.2, 138.0, 135.0, 132.6, 132.1, 129.8, 128.3, 127.4, 125.6 (q, J_{C-F} = 3 Hz), 121.8 (q, J_{C-F} = 265 Hz), 118.2, 114.3, 94.0; ^{19}F NMR (376 MHz, CDCl$_3$) δ −57.6. Anal. Calcd for C$_{14}$H$_8$BrF$_3$N$_2$: C, 49.29; H, 2.36; N, 8.21. Found: C, 49.31; H, 2.38; N, 8.20.

7-Methyl-2-(3-nitrophenyl)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2k): 63% yield (40 mg), gummy mass; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.51 (s, 1H), 8.24−8.21 (m, 1H), 8.13 (d, *J* = 6.8 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.43 (s, 1H), 6.82 (d, *J* = 6.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.1, 146.8, 145.1, 145.0, 135.4, 134.7, 129.1, 127.3, 124.6 (q, J_{C-F} = 4 Hz), 123.6, 121.6 (q, J_{C-F} = 267 Hz), 117.1, 116.5, 115.5, 21.3; ^{19}F NMR (376 MHz, CDCl$_3$) δ −57.7. Anal. Calcd for C$_{15}$H$_{10}$F$_3$N$_3$O$_2$: C, 56.08; H, 3.14; N, 13.08. Found: C, 56.10; H, 3.12; N, 13.06.

1-(4-(7-Methyl-3-(trifluoromethyl)imidazo[1,2-*a*]pyridin-2-yl)phenyl)ethanone (2l): 64% yield (40 mg), gummy mass; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.12 (d, *J* = 7.2 Hz, 1H), 7.98−7.96 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.42 (s, 1H), 6.79−6.77 (m, 1H), 2.57 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.7, 146.6, 146.5, 138.7, 137.5, 137.1, 129.8, 128.1, 124.6 (q, J_{C-F} = 4 Hz), 121.8 (q, J_{C-F} = 265 Hz), 116.9, 116.4, 109.3, 26.6, 21.3; ^{19}F NMR (376 MHz, CDCl$_3$) δ −57.4. Anal. Calcd for C$_{17}$H$_{13}$F$_3$N$_2$O: C, 64.15; H, 4.12; N, 8.80. Found: C, 64.17; H, 4.14; N, 8.81.

7-Methyl-3-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)-imidazo[1,2-*a*]pyridine (2m): 69% yield (47 mg), gummy mass; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.12 (d, *J* = 6.8 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.41 (s, 1H), 6.79−6.77 (m, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.6, 146.2, 138.7, 136.5, 130.9, 130.5, 129.8, 125.1 (q, J_{C-F} = 4 Hz), 124.6 (q, J_{C-F} = 3 Hz), 124.0 (q, J_{C-F} = 268 Hz), 121.7 (q, J_{C-F} = 267 Hz), 116.9, 116.4, 21.3; ^{19}F NMR (376 MHz, CDCl$_3$) δ −57.5, −62.6. Anal. Calcd for C$_{16}$H$_{10}$F$_6$N$_2$: C, 55.82; H, 2.93; N, 8.14. Found: C, 55.84; H, 2.95; N, 8.12.

4-(3-(Trifluoromethyl)imidazo[1,2-*a*]pyridin-2-yl)benzo-nitrile (2n): 67% yield (38 mg), gummy mass; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.34 (d, *J* = 7.2 Hz, 1H), 7.83−7.74 (m, 5H), 7.47−7.43 (m, 1H), 7.08−7.05 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.2, 145.7, 137.3, 132.1, 131.9, 130.2, 127.6, 125.5 (q, J_{C-F} = 4 Hz), 121.5 (q, J_{C-F} = 265 Hz), 118.5, 118.2, 114.5, 112.7; ^{19}F NMR (376 MHz, CDCl$_3$) δ −57.6. Anal. Calcd for C$_{15}$H$_8$F$_3$N$_3$: C, 62.72; H, 2.81; N, 14.63. Found: C, 62.74; H, 2.83; N, 14.61.

2-(4-(Methylsulfonyl)phenyl)-3-(trifluoromethyl)imidazo-[1,2-*a*]pyridine (2o): 65% yield (44 mg), gummy mass; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (d, *J* = 6.8 Hz, 1H), 8.06−8.04 (m, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 9.2 Hz, 1H), 7.48−7.44 (m, 1H), 7.10−7.06 (m, 1H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.4, 145.7, 140.8, 138.3, 130.7, 127.8, 127.5, 127.3, 125.6 (q, J_{C-F} = 4 Hz), 121.6 (q, J_{C-F} = 265 Hz), 118.3, 114.8, 44.6; ^{19}F NMR (376 MHz, CDCl$_3$) δ −57.6. Anal. Calcd for C$_{15}$H$_{11}$F$_3$N$_2$O$_2$S: C, 52.94; H, 3.26; N, 8.23. Found: C, 52.95; H, 3.28; N, 8.21.

2-(Pyridin-2-yl)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2p): 71% yield (37 mg), gummy mass; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.69 (d, *J* = 4.4 Hz, 1H), 8.29 (d, *J* = 6.8 Hz, 1H), 7.79−7.68 (m, 3H), 7.35−7.25 (m, 2H), 6.97−6.93 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.8, 149.5, 146.7, 145.9, 136.2, 133.7, 127.0, 125.6 (q, J_{C-F} = 4 Hz), 124.4, 123.4, 121.6 (q, J_{C-F} = 266 Hz), 118.4, 114.2; ^{19}F NMR (376 MHz, CDCl$_3$) δ −57.5. Anal. Calcd for C$_{13}$H$_8$F$_3$N$_3$: C, 59.32; H, 3.06; N, 15.96. Found: C, 59.34; H, 3.10; N, 15.89.

7-Methyl-2-(thiophene-2-yl)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine (2q): 70% yield (39 mg), gummy mass; ^{1}H NMR (400

MHz, CDCl$_3$) δ 8.08 (d, *J* = 6.8 Hz, 1H), 7.41−7.37 (m, 3H), 7.05−7.03 (m, 1H), 6.73−6.71 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 146.3, 138.4, 135.0, 127.8 (q, J_{C-F} = 4 Hz), 127.6, 127.6, 124.6 (q, J_{C-F} = 4 Hz), 122.0 (q, J_{C-F} = 266 Hz), 117.1, 116.6, 116.2, 21.3; ^{19}F NMR (376 MHz, CDCl$_3$) δ −57.4. Anal. Calcd for C$_{13}$H$_9$F$_3$N$_2$S: C, 55.31; H, 3.21; N, 9.92. Found: C, 55.33; H, 3.23; N, 9.90.

2-Phenyl-3-(trifluoromethyl)benzo[*d*]imidazo[2,1-*b*]thiazole (4a):[14] 68% yield (43 mg), white solid; mp 152−154 °C (lit[14] report 154−156 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.70−7.64 (m, 3H), 7.49−7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 150.8, 149.9, 132.8, 132.0, 130.0, 129.5, 128.9, 128.6, 128.1, 126.7, 125.5, 124.2, 121.4 (q, J_{C-F} = 265 Hz), 114.6 (q, J_{C-F} = 4 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ −54.9. Anal. Calcd for C$_{16}$H$_9$F$_3$N$_2$S: C, 60.37; H, 2.85; N, 8.80. Found: C, 60.30; H, 2.90; N, 8.85.

2-(4-(Allyloxy)phenyl)-3-(trifluoromethyl)benzo[*d*]imidazo-[2,1-*b*]thiazole (4b): 71% yield (53 mg), gummy mass; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.76−7.74 (m, 1H), 7.58−7.54 (m, 2H), 7.52−7.50 (m, 1H), 7.44−7.40 (m, 1H), 7.01−6.98 (m, 2H), 6.12−6.05 (m, 1H), 5.44 (d, *J* = 17.2 Hz, 1H), 5.31 (d, *J* = 10.4 Hz, 1H), 4.61−4.59 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.2, 149.9, 147.9, 133.0, 132.2, 130.7, 130.7, 130.1, 126.7, 125.4, 124.2, 121.5 (q, J_{C-F} = 265 Hz), 117.7, 114.6 (q, J_{C-F} = 4 Hz), 114.5, 114.3, 68.7; ^{19}F NMR (376 MHz, CDCl$_3$) δ −54.9. Anal. Calcd for C$_{19}$H$_{13}$F$_3$N$_2$OS: C, 60.96; H, 3.50; N, 7.48. Found: C, 60.92; H, 3.56; N, 7.45.

6-Phenyl-5-(trifluoromethyl)imidazo[2,1-*b*]thiazole (4c): 69% yield (37 mg), gummy mass; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70 (d, *J* = 6.8 Hz, 2H), 7.59 (d, *J* = 4.8 Hz, 1H), 7.48−7.40 (m, 3H), 6.98 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 151.5, 149.1, 132.7, 128.9, 128.9, 128.4, 121.7 (q, J_{C-F} = 266 Hz), 119.0 (q, J_{C-F} = 3 Hz), 114.3, 112.0; ^{19}F NMR (376 MHz, CDCl$_3$) δ −56.3. Anal. Calcd for C$_{12}$H$_7$F$_3$N$_2$S: C, 53.73; H, 2.63; N, 10.44. Found: C, 53.75; H, 2.69; N, 10.41.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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