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Regioselective Oxidative Trifluoromethylation of Imidazoheterocycles *via* C(sp^2)–H Bond Functionalization

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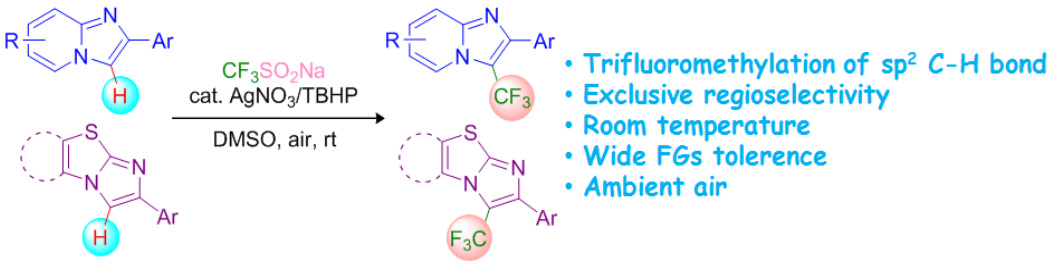


ABSTRACT:

Catalytic oxidative trifluoromethylation of imidazopyridines has been carried out at room temperature through the functionalization of sp^2 C-H bond employing Langlois reagent under ambient air. A library of 3-trifluoromethylimidazo[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.

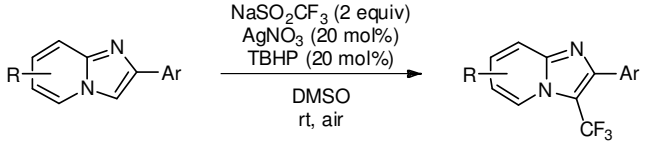
INTRODUCTION

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

Recently, much attention has been paid on 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 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 trifluoromethanesulphonate (Langlois reagent) as trifluoromethylating agent for trifluoromethylation of aromatic compounds under oxidative conditions.[7a] After that few methodologies for the trifluomethylation have been developed employing sodium trifluoromethanesulphonate 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 of this significant progress, the direct and catalytic trifluoromethylation of biologically active non-prefunctionalized heterocyles is still remained challenging.

Imidazopyridines show many interesting features towards 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] A considerable attention has been paid on 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 increase their bioactivities. Therefore, we turned our attention in synthesizing trifluoromethylimidazo[1,2-*a*]pyridine derivatives which might have 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 presence of catalytic amount of $AgNO_3$ and TBHP at room temperature in ambient air.

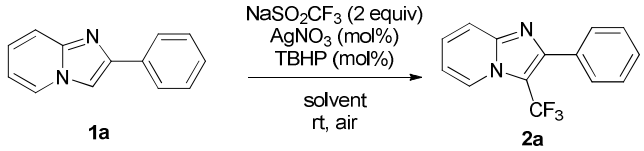
Scheme 1. Regioselective Trifluoromethylation of Imidazopyridines.



RESULTS AND DISCUSSION

First, 2-phenylimidazo[1,2-*a*]pyridine was selected as a model substrate to find the suitable reaction conditions employing sodium trifluoromethanesulphonate (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 $NaSO_2CF_3$ (2 equiv), $AgNO_3$ (20 mol %) and $K_2S_2O_8$ (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 were tested and the best result was achieved in DMSO at room temperature affording 67% yield (Table 1, entries 2-5). Then we turned our attention towards the role of oxidant. For this purpose we screened various oxidants e.g. TBHP, DTBP, BQ etc and it was found that TBHP showed the best result affording 74% yield after 12 h (Table 1, entries 6-8). Other metal salts like $AgNO_2$, Ag_2CO_3, Ag_2O, $Cu(OTf)_2$, $FeCl_3$ 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 decreasing the catalyst loading, lower yield was obtained even after 36 h (Table 1, entry 15). Trace amount of product was formed when only $AgNO_3$ was used as oxidant (Table 1, entry 16). However TBHP is not proficient of any conversion (Table 1, entry 17). Finally, the optimized reaction conditions were obtained using 2 equiv of $NaSO_2CF_3$, 20 mol % $AgNO_3$ and 20 mol % of TBHP as oxidant in DMSO at room temperature for 12 h under aerobic conditions (Table 1, entry 6).

Table 1. Optimization of the Reaction Conditions.[a]



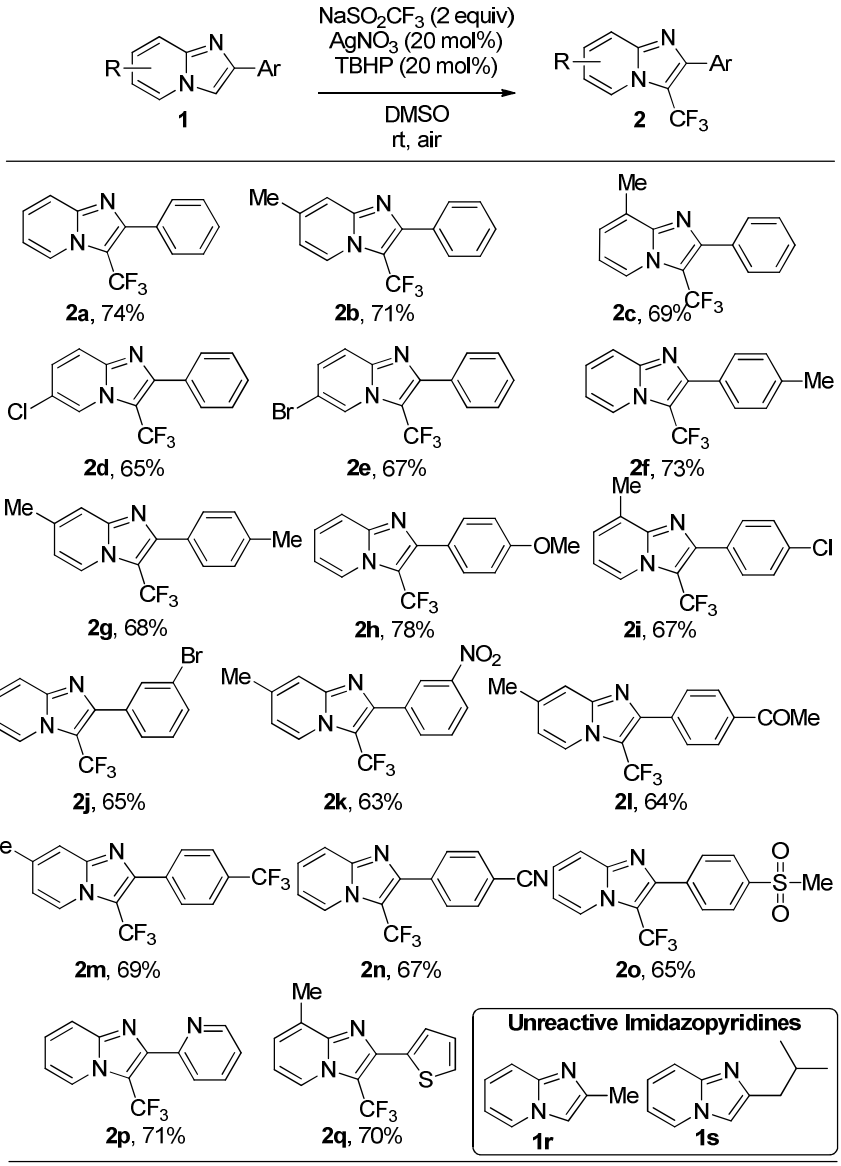
1a 2a

entry	metal salts (mol %)	oxidant (mol %)	solvent	yield (%)
1	$AgNO_3$ (20)	$K_2S_2O_8$ (20)	DMF	30
2	$AgNO_3$ (20)	$K_2S_2O_8$ (20)	1,2-DCE	20
3	$AgNO_3$ (20)	$K_2S_2O_8$ (20)	DMSO	67
4	$AgNO_3$ (20)	$K_2S_2O_8$ (20)	CH_3CN	25
5	$AgNO_3$ (20)	$K_2S_2O_8$ (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_2CO_3 (20)	TBHP (20)	DMSO	48
11	Ag_2O (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 $NaSO_2CF_3$ 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.

With the optimized reaction conditions in hand, we turned our attention towards 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 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, -Br on the pyridine ring successfully reacted to give the desired products (**2d** and **2e**). Phenyl group at 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-2n**). 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.

Scheme 2. Substrates Scope of Imidazopyridines.[a]

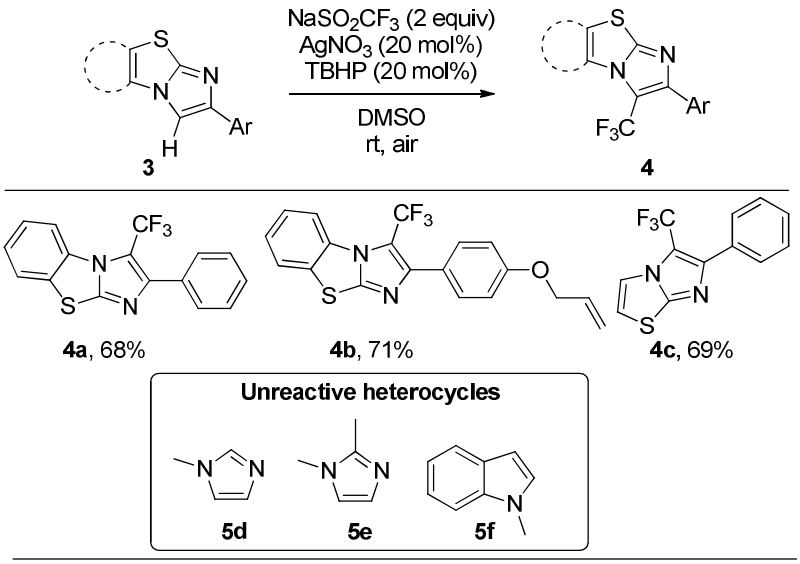


[a]Reaction conditions: 0.2 mmol of **1** and 0.4 mmol of $NaSO_2CF_3$ in the presence of $AgNO_3$ (20 mol%) and TBHP (5~6 M solution in decane) (20 mol%) in DMSO (1 mL) at room temperature under ambient air for 12 h.

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 was occurred at the alkene part (**4b**). In case of imidazothiazole only mono trifluoromethylation took place regioselectively (**4c**). The present protocol is highly selective for the trifluoromethylation of imidazofused heterocycles. Other heterocycles like *N*-methyl imidazole (**5d**), 1,2-dimethyl imidazole (**5e**), and *N*-methyl indoles (**5f**) were unreacted under the present reaction conditions.

Scheme 3. Substrates scope of Imidazoheterocycles.[a]

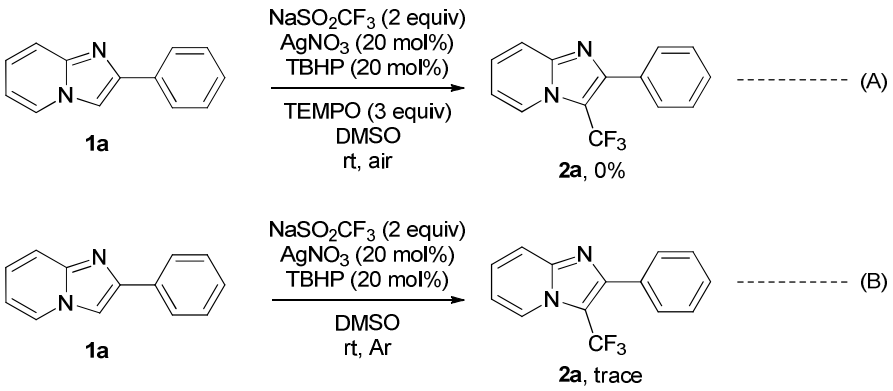


[a]Reaction conditions: 0.2 mmol of **3** or **5** and 0.4 mmol of $NaSO_2CF_3$ in the presence of $AgNO_3$ (20 mol%) and TBHP (5~6 M solution in decane) (20 mol%) in DMSO (1 mL) at room temperature under ambient air for 12 h.

To understand the mechanistic pathway of this reaction, few controlled experiments were carried out (Scheme 4). The reaction did not proceed at all in 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

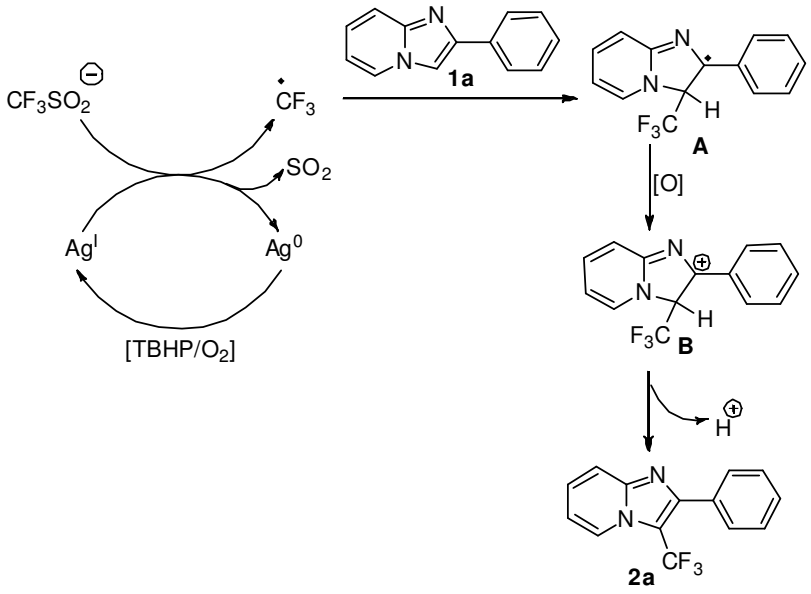
desired product was obtained. Thus the aerial oxygen plays a crucial role to fulfil the catalytic cycle (Scheme 4, Eq B).

Scheme 4. Controlled Experiments.



From these experiments and literature reports,[8a-c] the probable mechanism of the reaction is described in Scheme 5. At first the CF_3 radical is generated from the sodium trifluoromethanesulphonate 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**. 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.

Scheme 5. Plausible Mechanism.



CONCLUSIONS

In conclusion, we have developed a direct and straightforward method for regioselective trifluoromethylation of imidazopyridines through sp^2 C-H functionalization employing Langlois reagent in ambient air. To the best of our knowledge this is the first report for the direct trifluoromethylation of imidazopyridines. Catalytic amount of $AgNO_3$/TBHP is sufficient to perform the reactions. An array of 3-trifluoromethylimidazo[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 get much importance in medicinal chemistry.

Experimental section:

General Information:

^{1}H NMR spectra were determined on a 400 MHz spectrometer as solutions in $CDCl_3$. Chemical shifts are expressed in parts per million (δ) and are referenced to tetramethylsilane (TMS) as internal standard and the signals were reported as s (singlet), d (doublet), t (triplet), m (multiplet) and coupling constants *J* were given in Hz. ^{13}C NMR spectra and ^{19}F NMR spectra were recorded at 100 MHz and at 376 MHz respectively in $CDCl_3$ 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 ºC 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.[12a,e]

General procedure for trifluoromethylation of imidazoheterocycles (2 or 4):

A mixture of **1 (or 3)** (0.2 mmol), sodium trifluoromethanesulphonate (62 mg, 0.4 mmol) and $AgNO_3$ (7 mg, 20 mol%) was taken in sealed tube followed by drop wise 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 Na_2SO_4. After evaporation of solvent the crude product was purified by column chromatography on silica gel using petroleum ether/ethylacetate (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 report 81-83 °C). ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.7. Anal. Calc for $C_{14}H_9F_3N_2$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.4. Anal. Calc for $C_{15}H_{11}F_3N_2$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.8. Anal. Calc for $C_{15}H_{11}F_3N_2$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.69-7.66 (m, 3H), 7.49-7.44 (m, 3H), 7.38-7.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.6. Anal. Calc for $C_{14}H_8ClF_3N_2$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.6. Anal. Calc $C_{14}H_8BrF_3N_2$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.6. Anal. Calc $C_{15}H_{11}F_3N_2$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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); ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.4. Anal. Calc for $C_{16}H_{13}F_3N_2$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.6. Anal. Calc for $C_{15}H_{11}F_3N_2O$: 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. ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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. Calc for $C_{15}H_{10}ClF_3N_2$: 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. Calc for $C_{14}H_8BrF_3N_2$: 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. Calc for $C_{15}H_{10}F_3N_3O_2$: 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. Calc for $C_{17}H_{13}F_3N_2O$: 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. Calc for $C_{16}H_{10}F_6N_2$: 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)benzonitrile (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. Calc $C_{15}H_8F_3N_3$: 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. Calc for $C_{15}H_{11}F_3N_2O_2S$: 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. Calc for $C_{13}H_8F_3N_3$: C, 59.32; H, 3.06; N, 15.96%. Found: C, 59.34; H, 3.10; N, 15.89%.

7-Methyl-2-(thiophen-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. Calc for $C_{13}H_9F_3N_2S$: 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 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. Calc for $C_{16}H_9F_3N_2S$: 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. Calc for $C_{19}H_{13}F_3N_2OS$: 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. Calc for $C_{12}H_7F_3N_2S$: C, 53.73; H, 2.63; N, 10.44%; Found: C, 53.75; H, 2.69; N, 10.41%.

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Supporting Information. 1H and 13C 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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