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Base-mediated [3+2] annulation of trifluoroacetimidoyl chlorides and isocyanides: An improved approach for regioselective synthesis of 5-trifluoromethyl-imidazoles

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ABSTRACT

A *t*-BuOK-mediated [3 + 2] cycloaddition reaction of trifluoroacetimidoyl chlorides and active methylene isocyanides for the synthesis of 5-trifluoromethyl-imidazoles has been developed. Under mild reaction conditions, the transformation proceeds smoothly in the presence of *t*-BuOK to afford an array of structurally diverse 5-trifluoromethyl-imidazoles with high efficiency.

1. Introduction

Imidazoles, especially multi-functionalized imidazoles, as a kind of highly privileged structural motifs, are much prevalent in biological and pharmaceutical fields, ligand chemistry as well as functional materials [1]. Imidazole motifs exist in several commercial drugs, such as losartan, eprosartan, etomidate, flumazenil, econazole and clotrimazole [2]. Therefore, a great amount of efforts have been devoted to investigate the synthetic methods for imidazoles over the past decades [3]. In this context, the mainstream and frequently-used pathways to imidazoles lie in the [3 + 2] cycloaddition of active methylene isocyanides and "C=N" subunits, including imines (Scheme 1a), carbodiimides/isothiocynates/ketenimines (Scheme 1b), benzothiazoles (Scheme 1c), and isocyanides (Scheme 1d) [4,5]. Isocyanides are identified as a kind of important and powerful building blocks for the synthesis of diverse heterocyclic compounds [6]. Besides that, there are several seminal multicomponent reactions and visible-light-induced reactions involving isocyanides to construct trisubstituted imidazoles [7]. As an option, the [3 + 2] cycloaddition of isocyanides with trifluoromethyl synthons represents an interesting pathway for the construction of trifluoromethyl-substituted imidazoles. Although Bunev and coworkers realized NaH-promoted synthesis of 5-trifluoromethyl-imidazoles from trifluoroacetimidoyl chlorides and isocyanides, limited imidazole products (only 9 examples) were obtained with moderate yields [8]. The development of more general and efficient routes for the rapid construction of trifluoromethyl substituted imidazoles is still desirable.

The significance of trifluoromethyl-substituted nitrogen-containing heterocycles has aroused considerable attention due to their extensive applications in the fields of organic synthesis, pharmaceuticals, agrochemicals, and materials science [9]. The existence of the trifluoromethyl group could greatly improve the properties of the parent molecule. The efficient and atom-economical methods for the synthesis of trifluoromethyl-substituted *N*-heterocycles mostly focus on the reaction of diverse trifluoromethyl-containing synthons with suitable coupling substrates. It is worth mentioning that trifluoroacetimidoyl chloride has been applied as a versatile synthon to construct trifluoromethyl-substituted *N*-heterocycles, and numerous related works have been reported [10]. Very recently, our group developed a metal-free approach for the assembly of 5-

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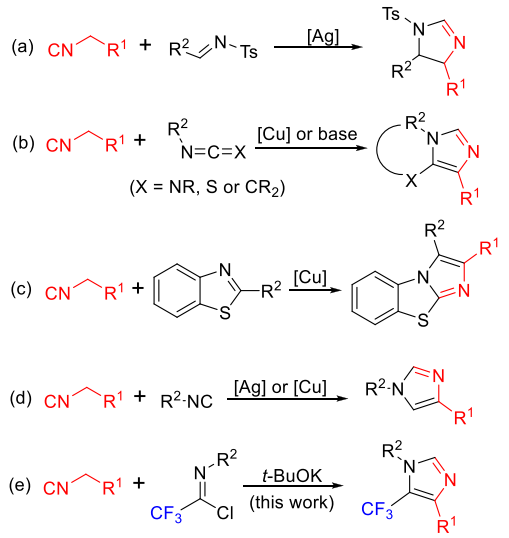
0040-4020/



Scheme 1. Isocyanides-"C=N" [3 + 2] Cycloaddition for the Synthesis of Imidazole Derivatives.

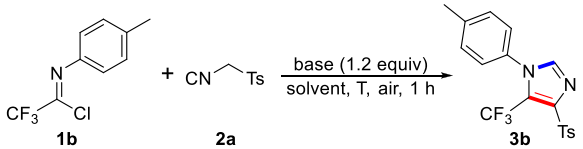
trifluoromethyl-1,2,4-triazoles from I_2-mediated annulation of trifluoroacetimidoyl chlorides and hydrazones [10b]. Inspired by the relevant impressive achievement and our continuous efforts on the synthesis of diverse nitrogen-containing heterocycles [11], we herein disclosed a *t*-BuOK-mediated [3 + 2] cycloaddition reaction of active methylene isocyanides and trifluoroacetimidoyl chlorides for the direct formation of 5-trifluoromethyl-imidazoles with broad substrate scope and high efficiency (Scheme 1e).

2. Results and discussion

We chose 2,2,2-trifluoro-*N*-(*p*-tolyl)acetimidoyl chloride **1b** and tosylmethylisocyanide (TosMIC) **2a** as the model substrates to initiate the investigations. The reaction proceeded smoothly with **1b** and **2a** in the presence of Cs_2CO_3 in DMF at 80 °C for 1 h. To our delight, the 5-trifluoromethyl-imidazole product **3b** was obtained in 83% yield (Table 1, entry 1). A series of bases were next screened, and the results indicated that *t*-BuOK showed the best reactivity to give rise to the desired product **3b** in 90% yield (Table 1, entries 2–7). Noteworthy was that the reaction did not occur in the absence of base (Table 1, entry 8). The study towards different solvents revealed the reaction proceeded well in CH_3CN, DMSO or THF and only trace of product was detected with respect to toluene or 1,4-dioxane (Table 1, entries 9–13). When the reaction was carried out at room temperature, 83% yield of **3b** was afforded, whereas the optimal reaction temperature was 60 °C, which could enable the desired product in the highest yield (Table 1, entries 14–15). Further increasing the reaction temperature to 100 °C resulted in the reduced efficiency (Table 1, entry 16).

With the optimized reaction conditions in hand, the scope and generality of this [3 + 2] annulation reaction was surveyed by the employment of a range of fluorinated imidoyl chlorides to react with TosMIC (Table 2). To our delight, broad substrate scope of the protocol was shown, as demonstrated by the obtained good to excellent yields with regard to *N*-aryl-trifluoroacetimidoyl chlorides bearing electron-donating or -withdrawing groups (Table 2, **3a-3r**). The steric hindrance of trifluoroacetimidoyl chlorides had a slightly impact on the reaction (Table 2, **3b-3d**). It was found that the electronic factors did not exert an obvious influence on the transformation and comparable reactivity was observed upon the trifluoroacetimidoyl chlorides (Table 2, **3a-3r**). Noteworthy was

Table 1
Optimization of reaction conditions[a].



1b **2a** **3b**

Entry	Base (equiv)	Solvent (mL)	Temp (°C)	Yield (%)[b]
1	Cs_2CO_3	DMF	80	83
2	K_2CO_3	DMF	80	37
3	Ag_2CO_3	DMF	80	70
4	DBU	DMF	80	67
5	*t*-BuONa	DMF	80	79
6	*t*-BuOK	DMF	80	90
7	NaOH	DMF	80	72
8	/	DMF	80	ND
9	*t*-BuOK	toluene	80	trace
10	*t*-BuOK	CH_3CN	80	80
11	*t*-BuOK	1,4-dioxane	80	trace
12	*t*-BuOK	DMSO	80	88
13	*t*-BuOK	THF	80	85
14	*t*-BuOK	DMF	RT	83
15	***t*-BuOK**	**DMF**	**60**	**98**
16	*t*-BuOK	DMF	100	89

Bold indicated It the optimized conditions.
[a] Reaction conditions: **1b** (0.45 mmol), **2a** (0.3 mmol), and base (1.2 equiv) in solvent (2.0 mL) under air at specified temperature for 1 h.
[b] Isolated yields. ND = No detection of the product.

that the halogen atoms, strong electron-withdrawing groups as well as di-substituted substrates were all smoothly tolerated under the standard conditions (Table 2, **3j-3r**), implying the good compatibility of the reaction. Furthermore, the naphthalene ring could be attached into the trifluoromethyl-substituted imidazole product **3s** in 79% yield. Gratifyingly, trifluoroacetimidoyl chloride derived from aliphatic amine was also employed as a reactive substrate to furnish the target product **3t** in acceptable yield. However, in the case of low molecular weight amines, we failed to get the desired imidoyl chlorides which might due to the low boiling point after substituted with fluoro group. As for other different fluorinated imidoyl chlorides, the transformation proceeded well to lead to the corresponding fluoroalkyl-imidazoles **3u-3y** with high efficiency. In addition, the scope of active methylene isocyanides under the current reaction conditions was next examined. Undoubtedly, alkyl isocyanoacetates were viable reactive substrates to react with trifluoroacetimidoyl chloride **1b** to enable the formation of ester-substituted imidazoles **3z-3aa** in reasonable yields. Benzylisocyanide could also participate in the reaction to give the corresponding imidazole products **3 ab** in 73% yield upon the replacement of *t*-BuOK with NaH. The exact structure of the obtained 5-trifluoromethyl-imidazole **3l** was unambiguously confirmed by single X-ray diffraction analysis (Fig. 1) [12].

In order to gain better understanding of the mechanism, a series of control experiments were conducted (Scheme 2). The radical trapping experiments were carried out by the addition of different radical scavengers. The yield of the reaction was not sharply decreased with the addition of 2.0 equiv. of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) or BHT (2,4-di-*tert*-butyl-4-methylphenol) into the reaction (Scheme 2a), which indicated that a single electron transfer (SET) pathway was not involved in the transformation. Furthermore, the reaction in the presence of 2.0 equiv. of D_2O resulted in the deuterated imidazole [D]-**3b** in 84% yield with moderate deuterium incorporation (60%) (Scheme 2b). This result implied that the hydrogen atom of imidazole partly came from trace amount of water in DMF. However, we can not

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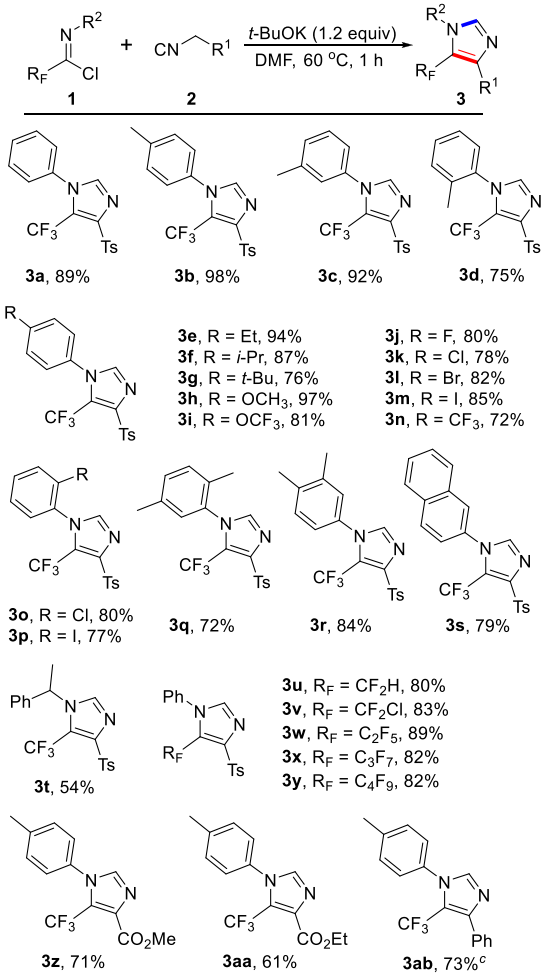
Table 2
Scope of fluorinated imidoyl chlorides and isocyanides[a,b].



[a] Reaction conditions: **1** (0.45 mmol), **2** (0.3 mmol), and *t*-BuOK (1.2 equiv) in DMF (2.0 mL) under air at 60 °C for 1 h.
[b] Isolated yields.
[c] NaH was used instead of *t*-BuOK.

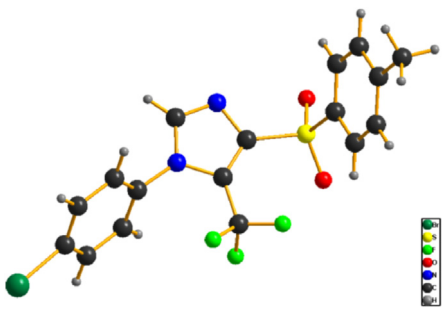
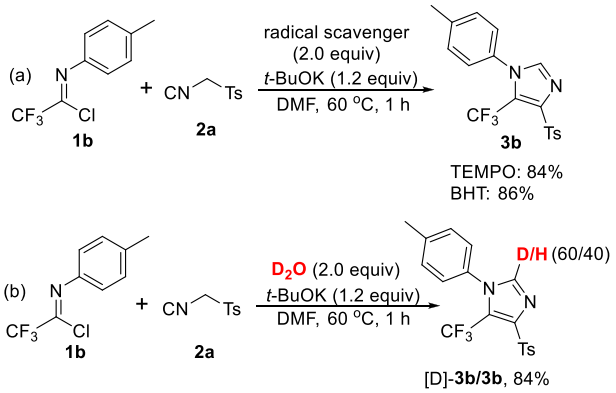


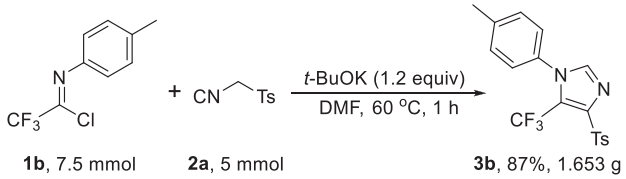
Fig. 1. The X-ray structure of product **3l**.

exclude that the hydrogen was exchanged after the reaction in the presence of base as the proton is quite reactive.

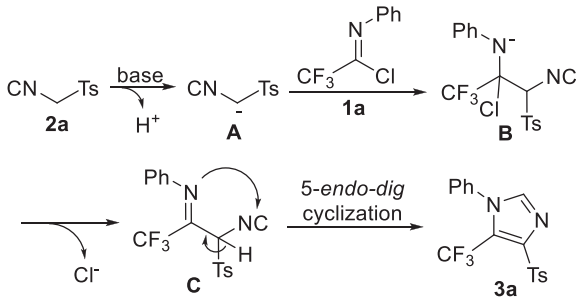
To further illustrate the practical utility of the methodology, the gram-scale reaction of **1b** and **2a** was conducted under the standard reaction conditions in 5.0 mmol scale (Scheme 3). Notably, the



Scheme 2. Control experiments.



Scheme 3. Scale-up reaction.



Scheme 4. Plausible reaction mechanism.

imidazole product **3b** could be isolated in 87% yield, highlighting the great synthetic potential of the reaction.

On the basis of the preliminary experimental results and related literatures [4d,13], a plausible mechanistic pathway is proposed as outlined in Scheme 4. At first, the active carbanionic intermediate **A** was formed upon base-mediated deprotonation of TosMIC **2a**. The nucleophilic addition of intermediate **A** into **1a** could give intermediate **B**, followed by the elimination of chloride ion to lead to **C**. Subsequently, a 5-*endo-dig* cyclization of intermediate **C** and the following 1,3-*H* shift or protonation occurred to afford the final imidazole product **3a**. Of note, the hydrogen atom of imidazole product possibly originated from active methylene of isocyanides or trace amount of water in DMF. In addition, a concerted [3 + 2]-cycloaddition [14] of base-promoted isocyanides with trifluoroacetimidoyl chlorides cannot be entirely excluded because the attempt to isolate or detect the coupling product **C** during the reaction process failed.

3. Conclusions

In conclusion, we have disclosed a facile and practical catalyst-free approach for the preparation of 5-trifluoromethyl-imidazoles through base-mediated [3 + 2] annulation of active methylene

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isocyanides with trifluoroacetimidoyl chlorides. Notable features of the current methodology include mild reaction conditions, readily accessible reagents, broad substrate scope, high efficiency and scalability. The present protocol offers an efficient alternative for the synthesis of trifluoromethyl-substituted imidazoles. Further investigations of the application of trifluoromethyl synthons to construct more trifluoromethyl-containing heterocyclic compounds are in progress.

4. Experimental details

Unless otherwise stated, all reactions were performed under air in a flame-dried reaction flask. Toluene, THF, 1,4-Dioxane, CH_3CN and DMF were dried by calcium hydride and freshly distilled. DMSO was used without further purification. The isocyanides, other materials and solvents were purchased from Adamas-beta and other commercial suppliers and used without additional purification. For chromatography, 200–300 mesh silica gel (Qingdao, China) was employed. ^{1}NMR spectra were recorded on a Bruker Avance operating at for ^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz and ^{19}F NMR at 377 MHz using TMS as internal standard. Mass spectroscopy data of the products were collected on an HRMS-TOF instrument or Waters TOFMS GCT Premier using EI or ESI ionization. Melting points were measured with WRR digital point apparatus and not corrected. The trifluoroacetimidoyl chlorides were synthesized according to the previous literatures [15].

4.1. General procedure for the synthesis of 5-trifluoromethyl-imidazoles (3)

t-BuOK (40.3 mg, 0.36 mmol) were added to a solution of fluorinated imidoyl chlorides **1** (0.45 mmol) and isocyanides **2** (0.3 mmol) in DMF (2.0 mL). The mixture was stirred at 60 °C under air for 1 h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature, quenched by water and extracted with ethyl acetate (3 × 15 mL). The extract was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo to provide a crude product, which was purified by column chromatography on silica gel with petroleum ether/EtOAc as eluent to afford the imidazole products **3**.

4.2. General procedure for the radical trapping experiments

t-BuOK (40.3 mg, 0.36 mmol) was added to a solution of 2,2,2-trifluoro-*N*-(*p*-tolyl)acetimidoyl chloride **1b** (0.45 mmol) and tosylmethylisocyanide **2a** (0.3 mmol) in DMF (2.0 mL). Then, the radical scavenger TEMPO (93.6 mg, 0.6 mmol) or BHT (132 mg, 0.6 mmol) was added into the reaction, respectively. The mixture was stirred at 60 °C under air for 1 h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature, quenched by water and extracted with ethyl acetate (3 × 15 mL). The extract was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo to provide a crude product, which was purified by column chromatography on silica gel with petroleum ether/EtOAc as eluent to afford the imidazole product **3b** as white solid in 84% or 86% yield, respectively.

4.3. General procedure for the deuterium labelling experiments

t-BuOK (40.3 mg, 0.36 mmol) and D_2O (12 mg, 0.6 mmol) were added to a solution of 2,2,2-trifluoro-*N*-(*p*-tolyl)acetimidoyl chloride **1b** (0.45 mmol) and tosylmethylisocyanide **2a** (0.3 mmol) in DMF (2.0 mL). The mixture was stirred at 60 °C under air for 1 h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature, quenched by water and extracted with ethyl acetate (3 × 15 mL). The extract was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo to provide a crude product, which was purified by column chromatography on silica gel with petroleum ether/EtOAc as eluent to afford the imidazole product [D]-**3b** as white solid in 84% yield with 60% deuterium incorporation.

4.4. General procedure for the scale-up reaction

t-BuOK (672 mg, 6 mmol) was added to a solution of 2,2,2-trifluoro-*N*-(*p*-tolyl)acetimidoyl chloride **1b** (7.5 mmol) and tosylmethylisocyanide **2a** (5 mmol) in DMF (20 mL). The mixture was stirred at 60 °C under air for 1 h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature, quenched by water and extracted with ethyl acetate (3 × 50 mL). The extract was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo to provide a crude product, which was purified by column chromatography on silica gel with petroleum ether/EtOAc as eluent to afford the imidazole product **3b** as white solid in 87% yield (1.653 g).

4.4.1. Characterization data of the corresponding products

*4.4.1.1. 1-Phenyl-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3a**).* Yield: 89%; 98.2 mg, white solid; m.p = 146–148 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, 2H, *J* = 8.4 Hz), 7.60 (s, 1H), 7.57–7.48 (m, 3H), 7.36 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 7.2 Hz), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 143.9, 139.7, 137.0, 134.5, 130.6, 129.8, 129.7, 128.7, 126.2, 122.6 (q, *J* = 41.2 Hz), 119.0 (q, *J* = 268.9 Hz), 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.1. HRMS (EI-TOF) calcd for $C_{17}H_{14}F_3N_2O_2S^+$ (M + H) $^+$: 367.0723, found: 367.0737.

*4.4.1.2. 1-(p-tolyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3b**).* Yield: 98%; 111.8 mg, white solid; m.p = 197–199 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, 2H, *J* = 8.0 Hz), 7.57 (s, 1H), 7.36 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 7.18 (d, 2H, *J* = 8.0 Hz), 2.43 (s, 3H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 143.9, 141.0, 139.8, 137.1, 131.9, 130.3, 129.8, 128.7, 126.0, 122.6 (q, *J* = 41.0 Hz), 119.0 (q, *J* = 268.8 Hz), 21.7, 21.2. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.2. HRMS (EI-TOF) calcd for $C_{18}H_{15}F_3N_2O_2SNa^+$ (M + Na) $^+$: 403.0699, found: 403.0714.

*4.4.1.3. 1-(m-tolyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3c**).* Yield: 92%; 105.5 mg, white solid; m.p = 189–191 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, 2H, *J* = 8.0 Hz), 7.59 (s, 1H), 7.39–7.33 (m, 4H), 7.11–7.09 (m, 2H), 2.43 (s, 3H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 143.9, 140.1, 139.7, 137.1, 134.4, 131.3, 129.8, 129.4, 128.9, 128.7, 126.7, 123.2, 122.5 (q, *J* = 40.8 Hz), 119.0 (q, *J* = 265.6 Hz), 21.7, 21.2. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.1. HRMS (EI-TOF) calcd for $C_{18}H_{16}F_3N_2O_2S^+$ (M + H) $^+$: 381.0879, found: 381.0898.

*4.4.1.4. 1-(o-tolyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3d**).* Yield: 75%; 86.0 mg, white solid; m.p = 179–181 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, 2H, *J* = 8.0 Hz), 7.51 (s, 1H), 7.44 (t, 1H, *J* = 7.6 Hz), 7.39–7.34 (m, 3H), 7.31 (t, 1H, *J* = 7.6 Hz), 7.20 (d, 1H, *J* = 7.6 Hz), 2.45 (s, 3H), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 143.8, 139.7, 137.1, 135.2, 131.3, 130.9, 129.8, 128.7, 127.4, 127.0, 122.7 (q, *J* = 41.0 Hz), 119.0 (q, *J* = 268.9 Hz), 21.7, 17.0. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −54.5. HRMS (EI-TOF) calcd for $C_{18}H_{16}F_3N_2O_2S^+$ (M + H) $^+$: 381.0879, found: 381.0898.

*4.4.1.5. 1-(4-ethylphenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3e**).* Yield: 94%; 111.2 mg, white solid; m.p = 195–197 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, 2H, *J* = 8.4 Hz), 7.58 (s, 1H), 7.36 (d, 2H,

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J = 8.4 Hz), 7.31 (d, 2H, J = 8.4 Hz), 7.20 (d, 2H, J = 8.4 Hz), 2.27–2.69 (m, 2H), 2.43 (s, 3H), 1.26 (t, 3H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.1, 145.0, 143.9, 137.1, 132.0, 129.6, 129.1, 128.7, 126.1, 122.6 (q, J = 41.2 Hz), 119.0 (q, J = 268.9 Hz), 28.5, 21.7, 15.2. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.2. HRMS (EI-TOF) calcd for $C_{19}H_{18}F_3N_2O_2S^+$(M + H) $^+$: 395.1036, found: 395.1050.

*4.4.1.6. 1-(4-isopropylphenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3f**).* Yield: 87%; 107.1 mg, white solid; m.p = 200–201 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (d, 2H, J = 8.0 Hz), 7.62 (s, 1H), 7.39 (t, 4H, J = 8.4 Hz), 7.25 (d, 2H, J = 8.4 Hz), 3.03–2.98 (m, 1H), 2.47 (s, 3H), 1.30 (d, 6H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.7, 145.0, 143.9, 139.8, 137.1, 132.0, 129.8, 128.7, 127.7, 126.1, 122.6 (q, J = 40.9 Hz), 119.0 (q, J = 269.1 Hz), 33.9, 23.8, 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.2. HRMS (EI-TOF) calcd for $C_{20}H_{20}F_3N_2O_2S^+$(M + H) $^+$: 409.1192, found: 409.1209.

*4.4.1.7. 1-(4-(tert-butyl)phenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3g**).* Yield: 76%; 97.1 mg, white solid; m.p = 196–197 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, 2H, J = 8.4 Hz), 7.63 (s, 1H), 7.54 (d, 2H, J = 8.8 Hz), 7.40 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.8 Hz), 2.48 (s, 3H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.0, 145.0, 143.9, 139.8, 137.1, 131.8, 129.8, 128.7, 126.6, 125.7, 122.6 (q, J = 41.1 Hz), 119.0 (q, J = 268.9 Hz), 35.0, 31.2, 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.1. HRMS (EI-TOF) calcd for $C_{21}H_{22}F_3N_2O_2S^+$(M + H) $^+$: 423.1349, found: 423.1358.

*4.4.1.8. 1-(4-methoxyphenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3h**).* Yield: 97%; 115.8 mg, white solid; m.p = 193–194 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, 2H, J = 8.0 Hz), 7.64 (s, 1H), 7.43 (d, 2H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.0 Hz), 7.05 (d, 2H, J = 8.0 Hz), 3.92 (s, 3H), 2.50 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.0,145.0, 143.9, 140.0, 137.1, 129.8, 128.7, 127.5, 127.0, 122.7 (q, J = 41.1 Hz), 119.0 (q, J = 269.0 Hz), 114.8, 55.7, 21.8. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.3. HRMS (EI-TOF) calcd for $C_{18}H_{16}F_3N_2O_3S^+$ (M + H) $^+$:397.0828, found: 397.0837.

*4.4.1.9. 4-Tosyl-1-(4-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)-1H-imidazole (**3i**).* Yield:81%; 109.1 mg, white solid; m.p = 185–187 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, 2H, J = 8.4 Hz), 7.65 (s, 1H), 7.44–7.42 (m, 6H), 2.50 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.5, 145.2, 144.5, 139.6, 136.8, 132.6, 130.0, 128.9, 128.1, 121.9, 120.2 (q, J = 258.2 Hz), 118.9 (q, J = 271.2 Hz), 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.0, −57.9. HRMS (EI-TOF) calcd for $C_{18}H_{13}F_6N_2O_3S^+$ (M + H) $^+$: 451.0546, found: 451.0551.

*4.4.1.10. 1-(4-fluorophenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3j**).* Yield: 80%; 91.8 mg, white solid; m.p = 188–189 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, 2H, J = 8.4 Hz), 7.60 (s, 1H), 7.36 (d, 2H, J = 8.0 Hz), 7.33–7.30 (m, 2H), 7.22–7.17 (m, 2H, J = 8.0 Hz), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5 (d, J = 250 Hz), 145.1, 144.2, 139.8, 136.9, 130.3, 129.8, 128.7, 128.4 (d, J = 9.0 Hz), 122.6 (q, J = 41.3 Hz), 119.0 (q, J = 268.9 Hz), 116.8 (d, J = 23.4 Hz), 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.1, −108.8. HRMS (EI-TOF) calcd for $C_{17}H_{13}F_4N_2O_2S^+$ (M + H) $^+$: 385.0628, found: 385.0643.

*4.4.1.11. 1-(4-chlorophenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3k**).* Yield: 78%; 92.1 mg, white solid; m.p = 199–200 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, 2H, J = 8.4 Hz), 7.59 (s, 1H), 7.49 (d, 2H, J = 8.8 Hz), 7.37 (d, 2H, J = 8.0 Hz), 7.28–7.26 (m, 2H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.1, 144.4, 139.5, 136.9, 136.8, 132.9, 130.0, 129.8, 128.7, 127.6, 122.5 (q, J = 41.2 Hz), 119.0 (q, J = 269.0 Hz), 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.0. HRMS (EI-TOF) calcd for $C_{17}H_{13}ClF_3N_2O_2S^+$(M + H) $^+$: 401.0333, found: 401.0347.

*4.4.1.12. 1-(4-bromophenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3l**).* Yield: 82%; 109.9 mg, white solid; m.p = 194–195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, 2H, J = 8.0 Hz), 7.65 (d, 2H, J = 8.4 Hz), 7.59 (s, 1H), 7.57 (d, 2H, J = 8.0 Hz), 7.20 (d, 2H, J = 8.0 Hz), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.2, 144.4, 139.5, 136.9, 133.4, 133.1, 129.7, 128.8, 127.8, 124.9, 122.5 (q, J = 41.3 Hz), 119.0 (q, J = 268.7 Hz), 21.8. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.0. HRMS (EI-TOF) calcd for $C_{17}H_{13}BrF_3N_2O_2S^+$(M + H) $^+$: 444.9828, found: 444.9836.

*4.4.1.13. 1-(4-iodophenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3m**).* Yield: 85%; 125.7 mg, white solid; m.p = 200–201 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, 2H, J = 8.4 Hz), 7.85 (d, 2H, J = 8.8 Hz), 7.58 (s, 1H), 7.37 (d, 2H, J = 8.0 Hz), 7.06 (d, 2H, J = 8.4 Hz), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.1, 144.5, 139.4, 139.0, 136.9, 134.1, 129.8, 128.7, 127.9, 122.4 (q, J = 41.6 Hz), 119.0 (q, J = 269.0 Hz), 96.5, 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.0. HRMS (EI-TOF) calcd for $C_{17}H_{13}F_3IN_2O_2S^+$(M + H) $^+$: 492.9689, found: 492.9699.

*4.4.1.14. 4-Tosyl-5-(trifluoromethyl)-1-(4-(trifluoromethyl)phenyl)-1H-imidazole (**3n**).* Yield: 72%; 93.6 mg, white solid; m.p = 185–186 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, 2H, J = 8.4 Hz), 7.80 (d, 2H, J = 8.8 Hz), 7.64 (s, 1H), 7.49 (d, 2H, J = 8.4 Hz), 7.37 (d, 2H, J = 8.4 Hz), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.3, 144.7, 139.4, 137.4, 136.7, 132.8 (q, J = 33.1 Hz), 129.9, 128.7, 127.1, 126.9, 123.2(q, J = 271.0 Hz), 122.4 (q, J = 41.4 Hz), 119.0 (q, J = 269.1 Hz), 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.2, −55.4. HRMS (EI-TOF) calcd for $C_{18}H_{13}F_6N_2O_2S^+$(M + H) $^+$: 435.0596, found: 435.0613.

*4.4.1.15. 1-(2-chlorophenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3o**).* Yield: 80%; 96.6 mg, white solid; m.p = 187–188 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, 2H, J = 8.4 Hz), 7.58–7.50 (m, 3H), 7.42 (t, 1H, J = 7.6 Hz), 7.38–7.36 (m, 3H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.1, 143.6, 139.8, 137.0, 132.3, 132.1, 132.0, 130.6, 129.9, 128.9, 128.7, 127.9, 122.8 (q, J = 41.7 Hz), 119.0 (q, J = 269.2 Hz), 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.2. HRMS (EI-TOF) calcd for $C_{17}H_{13}ClF_3N_2O_2S^+$(M + H) $^+$: 401.0333, found: 401.0346.

*4.4.1.16. 1-(2-iodophenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3p**).* Yield: 77%; 113.7 mg, white solid; m.p = 195–196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99–7.94 (m, 3H), 7.53 (s, 1H), 7.49 (t, 1H, J = 7.6 Hz), 7.37–7.34 (m, 3H), 7.27–7.25 (m, 1H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 143.8, 140.0, 139.7, 137.1, 132.2, 129.8, 129.4, 128.6, 128.3, 122.6 (q, J = 41.0 Hz), 119.0 (q, J = 269.2 Hz), 97.0, 21.8. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.9. HRMS (EI-TOF) calcd for $C_{17}H_{13}F_3IN_2O_2S^+$(M + H) $^+$: 492.9689, found: 492.9690.

*4.4.1.17. 1-(2,5-dimethylphenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3q**).* Yield: 72%; 85.2 mg, white solid; m.p = 189–190 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, 2H, J = 8.0 Hz), 7.49 (s, 1H), 7.36 (d, 2H, J = 8.4 Hz), 7.23–7.21 (m, 2H), 6.99 (s, 1H), 2.44 (s, 3H), 2.33 (s, 3H),1.97 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 143.6, 139.7, 137.1, 133.4, 131.9, 131.6, 131.0, 129.8, 128.6, 127.8, 122.7 (q, J = 40.7 Hz), 119.0 (q, J = 269.1 Hz), 21.7, 20.6, 16.5. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −54.5. HRMS (EI-TOF) calcd for $C_{19}H_{18}F_3N_2O_2S^+$(M + H) $^+$:395.1036, found: 395.1051.

*4.4.1.18. 1-(3,4-dimethylphenyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3r**).* Yield: 84%; 99.4 mg, white solid; m.p = 181–182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, 2H, J = 8.4 Hz), 7.56 (s, 1H), 7.36 (d, 2H, J = 8.0 Hz), 7.23 (d, 1H, J = 8.0 Hz), 7.06–7.03 (m, 2H), 2.44 (s,

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3H), 2.32 (s, 3H),2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 143.8, 139.8, 139.5, 138.5, 137.2, 132.1, 130.6, 129.8, 128.7, 127.0, 123.4, 122.6 (q, J = 41.2 Hz), 119.0 (q, J = 269.0 Hz), 21.7, 19.8, 19.6. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.2. HRMS (EI-TOF) calcd for $C_{19}H_{18}F_3N_2O_2S^+$(M + H) $^+$: 395.1036, found: 395.1049.

*4.4.1.19. 1-(Naphthalen-2-yl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3s**).* Yield: 79%; 98.7 mg, white solid; m.p = 179−181 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, 2H, J = 8.4 Hz), 7.97 (d, 1H, J = 8.8 Hz), 7.94−7.87 (m, 2H), 7.81 (s, 1H), 7.70 (s, 1H), 7.64−7.59 (m, 2H), 7.38−7.34 (m, 3H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.1, 144.2, 140.0, 1371, 133.5, 132.7, 131.8, 130.0, 129.9, 128.7, 128.3, 128.1, 128.0, 127.9, 125.4, 123.2, 122.8 (q, J = 40.9 Hz), 119.0 (q, J = 269.0 Hz), 21.8. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.0. HRMS (EI-TOF) calcd for $C_{21}H_{16}F_3N_2O_2S^+$(M + H) $^+$: 417.0879, found: 417.0890.

*4.4.1.20. 1-(1-phenylethyl)-4-tosyl-5-(trifluoromethyl)-1H-imidazole (**3t**).* Yield: 54%; 63.9 mg, white solid; m.p = 169−171 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, 2H, J = 8.0 Hz), 7.56 (s, 1H), 7.38−7.32 (m, 5H), 7.18−7.16 (m, 2H), 5.64−5.59 (m, 1H), 2.43 (s, 3H), 1.88 (d, 3H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.8, 143.7, 138.6, 137.3, 137.1, 129.7, 129.3, 129.2, 129.0, 128.7, 126.2, 120.9 (q, J = 41.3 Hz), 119.0 (q, J = 268.5 Hz), 57.5, 22.4, 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −54.2. HRMS (EI-TOF) calcd for $C_{19}H_{18}F_3N_2O_2S^+$(M + H) $^+$: 395.1036, found: 395.1042.

*4.4.1.21. 5-(difluoromethyl)-1-phenyl-4-tosyl-1H-imidazole (**3u**).* Yield: 80%; 83.6 mg, white solid; m.p = 194−195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, 2H, J = 8.4 Hz), 7.65 (t, 1H, J = 52 Hz), 7.61 (s, 1H), 7.54−7.48 (m, 3H), 7.39−7.37 (m, 4H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.1, 140.8, 137.1, 135.0, 130.2, 130.0, 129.5, 128.3, 127.2 (t, J = 24.3 Hz), 126.4, 107.6 (t, J = 235.0 Hz), 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −110.8 (d, J = 56.0 Hz). HRMS (EI-TOF) calcd for $C_{17}H_{15}F_2N_2O_2S^+$(M + H) $^+$: 349.0817, found: 349.0832.

*4.4.1.22. 5-(chlorodifluoromethyl)-1-phenyl-4-tosyl-1H-imidazole (**3v**).* Yield: 83%; 81.8 mg, white solid; m.p = 191−192 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, 2H, J = 8.0 Hz), 7.55−7.48 (m, 4H), 7.37−7.34 (m, 4H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 141.8, 139.5, 137.2, 134.5, 130.6, 129.8, 129.6, 128.7, 127.4 (t, J = 34.8 Hz), 126.7, 119.8 (t, J = 287.4 Hz), 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −42.3. HRMS (EI-TOF) calcd for $C_{17}H_{14}ClF_2N_2O_2S^+$(M + H) $^+$: 383.0427, found: 383.0444.

*4.4.1.23. 5-(perfluoroethyl)-1-phenyl-4-tosyl-1H-imidazole (**3w**).* Yield: 89%; 111.2 mg, white solid; m.p = 190−191 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, 2H, J = 8.4 Hz), 7.60 (s, 1H), 7.55 (t, 1H, J = 7.6 Hz), 7.48 (t, 2H, J = 7.6 Hz), 7.38 (d, 2H, J = 8.4 Hz), 7.29 (d, 2H, J = 7.6 Hz), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.2, 145.0, 141.4, 137.3, 134.5, 130.7, 129.8, 129.2, 128.9, 127.4, 118.4 (q, J = 251.8 Hz) 116.7 (t, J = 251.8 Hz), 110.0 (t, J = 41.4 Hz), 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −82.7, −104.0. HRMS (EI-TOF) calcd for $C_{18}H_{14}F_5N_2O_2S^+$(M + H) $^+$: 417.0691, found: 417.0702.

*4.4.1.24. 5-(perfluoropropyl)-1-phenyl-4-tosyl-1H-imidazole (**3x**).* Yield: 82%; 114.7 mg, white solid; m.p = 201−202 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, 2H, J = 8.4 Hz), 7.61 (s, 1H), 7.54 (t, 1H, J = 7.2 Hz), 7.47 (t, 2H, J = 7.2 Hz), 7.37 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 7.6 Hz), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.5, 145.0, 141.5, 137.3, 134.5, 130.7, 129.7, 129.2, 128.9, 127.5, 122.0 (t, J = 33.5 Hz), 117.6 (qt, J_1 = 286.3 Hz, J_2 = 34.5 Hz), 112.38, 108.2 (tt, J_1 = 264.1 Hz, J_2 = 39.5 Hz), 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −80.0 (t, 3F, J = 10.4 Hz), −100.8 (q, 2F, J = 10.0 Hz), −122.5 (s, 2F). HRMS (EI-TOF) calcd for $C_{19}H_{14}F_7N_2O_2S^+$(M + H) $^+$: 467.0659, found: 467.0667.

*4.4.1.25. 5-(perfluorobutyl)-1-phenyl-4-tosyl-1H-imidazole (**3y**).* Yield: 82%; 127.0 mg, white solid; m.p = 205−207 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, 2H, J = 8.0 Hz), 7.60 (s, 1H), 7.55 (t, 1H, J = 7.6 Hz), 7.48 (t, 2H, J = 7.6 Hz), 7.37 (d, 2H, J = 8.4 Hz), 7.29 (d, 2H, J = 7.6 Hz), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.7, 145.0, 141.5, 137.3, 134.5, 130.7, 129.7, 129.2, 128.9, 127.5, 120.6 (t, J = 31.8 Hz), 118.7 (t, J = 33.3 Hz), 115.5 (q, J = 19.6 Hz), 113.0 (t, J = 35.1 Hz), 110.4, 21.7. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −80.9 (t, 3F, J = 9.2 Hz), −100.3 (t, 2F, J = 15.6 Hz), −119.0 (m, 2F), −125.9 (m, 2F). HRMS (EI-TOF) calcd for $C_{20}H_{14}F_9N_2O_2S^+$(M + H) $^+$: 517.0627, found: 517.0634.

*4.4.1.26. Methyl 1-(p-tolyl)-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3z**).* Yield: 71%; 60.5 mg, white solid; m.p = 172−174 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (s, 1H), 7.29 (d, 2H, J = 8.4 Hz), 7.21 (d, 2H, J = 8.4 Hz), 3.95 (s, 3H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.6, 140.5, 140.0, 134.7, 132.5, 130.1, 125.9, 124.8 (q, J = 39.8 Hz), 119.6 (q, J = 268.3 Hz), 52.5, 21.2. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −54.7. HRMS (EI-TOF) calcd for $C_{13}H_{11}F_3N_2O_2$ Na^+ (M + Na) $^+$: 307.0665, found: 307.0685.

*4.4.1.27. Ethyl 1-(p-tolyl)-5-(trifluoromethyl)-1H-imidazole-4-carboxylate (**3aa**).* Yield: 61%; 54.6 mg, white solid; m.p = 188−189 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (s, 1H), 7.29 (d, 2H, J = 8.4 Hz), 7.20 (d, 2H, J = 8.4 Hz), 4.42 (q, 2H, J = 6.8 Hz), 2.43 (s, 3H), 1.40 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.3, 140.5, 140.0, 135.1, 132.5, 130.1, 125.9, 124.6 (q, J = 39.8 Hz), 119.6 (q, J = 268.5 Hz), 61.6, 21.2, 14.1. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −54.6. HRMS (EI-TOF) calcd for $C_{14}H_{14}F_3N_2O_2$+(M + H) $^+$: 299.1002, found: 299.1010.

*4.4.1.28. 4-Phenyl-1-(p-tolyl)-5-(trifluoromethyl)-1H-imidazole (**3 ab**).* Yield: 73%; 66.2 mg, white solid; m.p = 167−169 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66−7.65 (m, 3H), 7.46−7.40 (m, 3H), 7.31 (s, 4H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 140.2, 139.8, 133.2, 132.9, 130.0, 19.0, 128.5, 128.2, 126.0, 121.5 (q, J = 266.7 Hz), 117.7 (q, J = 37.4 Hz), 21.2. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −53.5. HRMS (EI-TOF) calcd for $C_{17}H_{14}F_3N_2^+$(M + H) $^+$: 303.1104, found: 303.1112.

Declaration of competing interest

We have no conflict of interest to declaration!

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131168.

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[12] Compound 3l was determined by X-ray crystallography. See the Supporting Information for full details. CCDC 1978368 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre viawww.ccdc.cam.ac.uk/data_request/cif

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