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A Domino Azidation/C–H Amination Approach towards Trifluoromethylsubstituted Imidazoles

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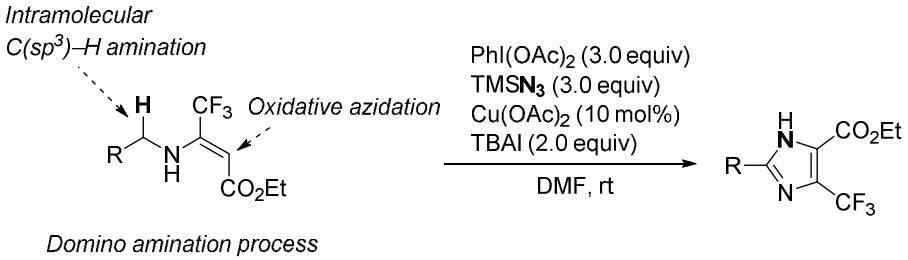
Graphic abstract



Abstract

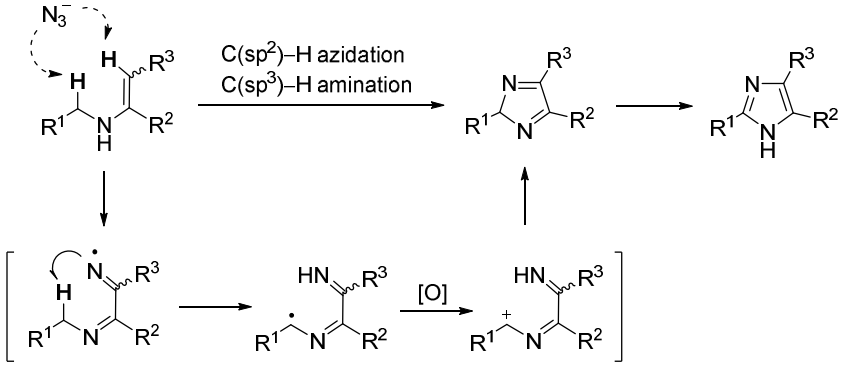
N-Alkyl enamines can be transformed into 2,4,5-trisubsituted imidazoles by reacting with (diacetoxyiodo) benzene and $TMSN_3$ under the catalysis of a copper salt such as $Cu(OAc)_2$. Tetrabutyl ammonium iodide was also capable of promoting the reaction. The transformation from *N*-alkyl enamines into 2,4,5-trisubsituted imidazoles took place in a domino azidation/intramolecular $C(sp^3)$–H amination pattern. The present reaction provides a new efficient method for the preparation of 5-(trifluoromethyl) imidazoles.

Key words: azidation; C–H amination; enamines; 5-(trifluoromethyl)imidazoles; (diacetoxyiodo) benzene.

The C–H amination reactions are of topical interest in the field of current organic synthesis.[1] In this context, azides have recently emerged as powerful reagents for the amination of both $C(sp^2)$–H bond and $C(sp^3)$–H bond.[2-4] Concurrent with the insurgence in the azide-involved amination reactions, many efforts have been made to develop new methods for the azidation of C–H bonds[5] as well as the carbon-carbon double bonds.[6] From the view point of synthetic efficiency, a domino process combining azidation with the azide-based C–H amination would be highly valuable

for the preparation of nitrogen-containing compounds because in this way two C–N bonds can be constructed in one synthetic operation.

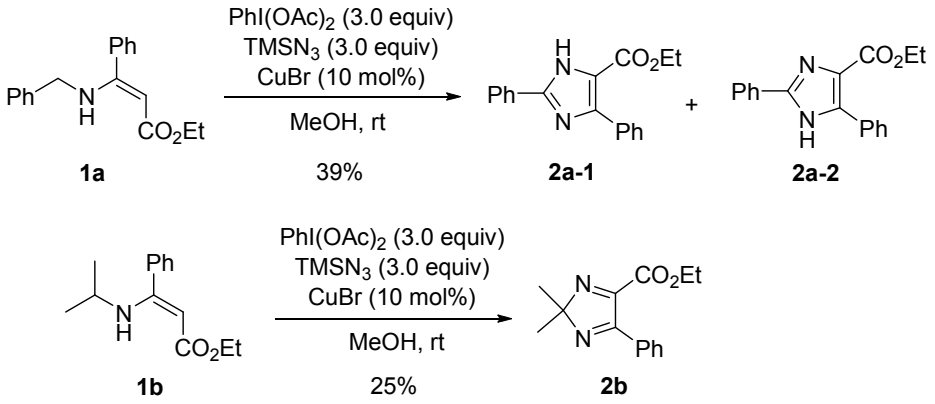
To implement this synthetic strategy recently we developed a new method for the preparation of quinoxalines from *N*-arylenamines.[7,8] This method takes advantage of the oxidative conditions of (diacetoxyiodo) benzene (DIB) and $TMSN_3$ to azidate the electron-rich *N*-arylenamines. The thus formed unstable azidated products then undergo dinitrogenative cyclization to afford quinoxaline products. The reactions were believed to follow a free radical mechanism which involves iminyl radicals as the key intermediates. On the basis of this study, we envisioned that this double amination strategy might be applied as well to realize a domino azidation/ $C(sp^3)$–H amination process (Scheme 1) through which the structurally important imidazole compounds would be generated.[9] It was anticipated that after the iminyl radical was formed, it would abstract an hydrogen atom from the methylene group adjacent to the other nitrogen atom to afford a α-amino radical. The latter would then be oxidized to the carbocation and trapped by the imine nitrogen to form the cyclization product. The 1,5-hydrogen atom transfer (HAT) reactions,[10] including those involving nitrogen-centered radicals,[11,12] have proved to be a powerful tool for C–H functionalization. However, the iminyl radical-mediated 1,5-HAT reactions are far less explored.[13] We hoped that by implementing this strategy, the efficacy of iminyl radicals to abstract the hydrogen atom from C–H bond could be further evaluated. Our subsequent investigation showed that the designed reaction did take place, and the expected imdazole products were obtained in good yields when 3-trifluromethyl substituted enamine esters were used as the substrates. Herein we wish to report this result.



Scheme 1 Designed strategy

Our investigation began by applying the reaction conditions of hypervalent(III) iodine reagent and $TMSN_3$ to compound **1a**. As expected, the desired transformation did take place when copper salts were used as catalyst, but the yield was low. After extensive screening of the reaction conditions, we found that by using CuBr as catalyst and methanol as solvent, the imidazole products **2a-1** and **2a-2** could be obtained in a

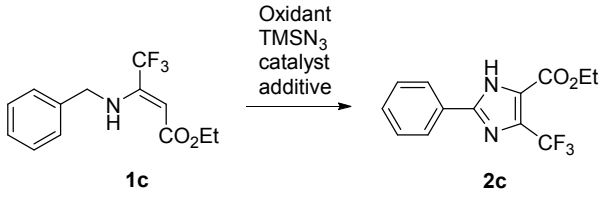
combined yield of 39% (Scheme 2). Besides **1a**, compound **1b** was also used as the substrate, which was transformed into **2b** in a moderate yield of 25%. Although these preliminary results were unsatisfactory, the formation of both compounds **2a** and **2b** did demonstrate the practicability of the designed strategy. We hoped that it might work well with other substrates. Thus compound **1c** was tested next, and the representative reaction conditions being applied to it are listed in Table 1.



Scheme 2 Preliminary result with **1a** and **1b** as the substrates

It can be seen from Table 1 that compound **1c** can be converted into the trifluomethyl-substituted imidazole **2c** smoothly in DMF under the conditions of $PhI(OAc)_2$, $TMSN_3$ and $Cu(OAc)_2$ (or CuI) . This transformation was also realized in methanol, but the yield was much lower. Using PhIO as oxidant also effected the reaction. The yield of **2c** can be considerably improved by adding tetrabutyl ammonium iodide (TBAI) into the reaction system (Table1, entries 4-9). The optimal amount of TBAI was found to be 2.0 equiv. As such, when 2.0 equiv. of TBAI was used along with 3.0 equiv. of $PhI(OAc)_2$, 3.0 equiv of $TMSN_3$ and 0.1 equiv $Cu(OAc)_2$, **2c** was generated in a yield of 84% in DMF (Table 1, entry 9). The reaction was also conducted by replacing TBAI with 1.0 equiv of CuI, but the yield of **2c** was much lower.

Table 1 Screening of the reaction conditions for the reaction of compound **1c**[a]

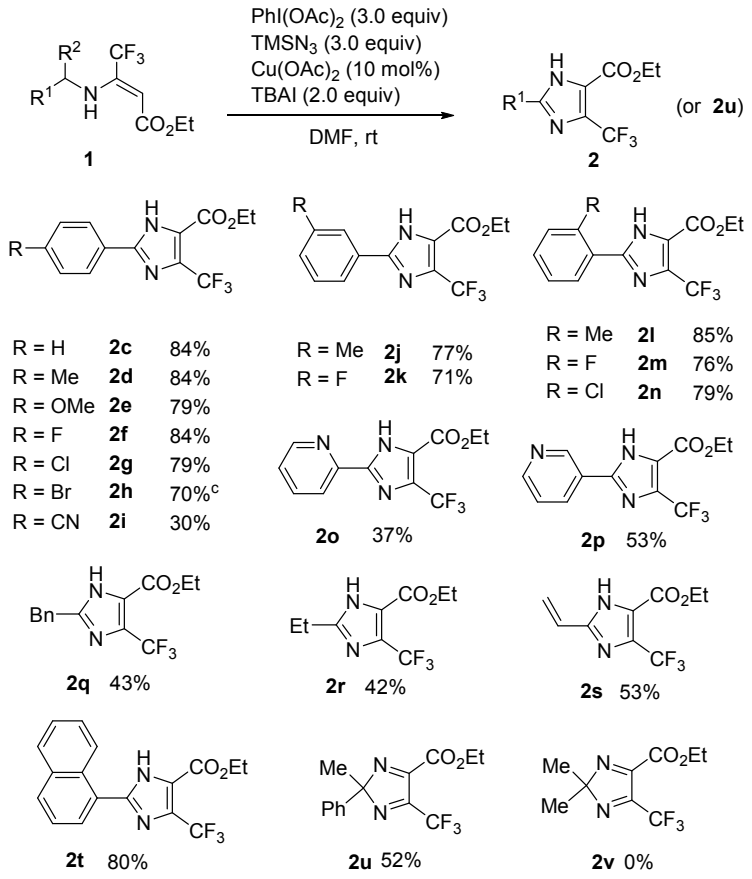


entry	oxidant	equiv of $TMSN_3$	cat	additive (equiv)	solvent	yield (%)
1[b]	$PhI(OAc)_2$	2.0	$CuBr_2$	none	MeOH	10

2	$PhI(OAc)_2$	3.0	CuBr	none	MeOH	19
3	PhIO	3.0	$Cu(OAc)_2$	none	MeOH	22
4	PhIO	3.0	$CuCl_2$	TBAI	MeOH	44
5	PhIO	3.0	CuBr	TBAI	MeOH	46
6	PhIO	3.0	$Cu(OTf)_2$	TBAI	MeOH	61
7	PhIO	3.0	$Cu(OAc)_2$	TBAI	MeOH	68
8	$PhI(OAc)_2$	3.0	$Cu(OAc)_2$	TBAI	MeOH	63
9	***$PhI(OAc)_2$***	***3.0***	***$Cu(OAc)_2$***	***TBAI***	***DMF***	***84***
10	$PhI(OAc)_2$	3.0	$Cu(OAc)_2$	none	DMF	46
11	$PhI(OAc)_2$	3.0	none	TBAI	DMF	51
12 [c]	$PhI(OAc)_2$	3.0	none	none	DMF	trace
13 [b]	$PhI(OAc)_2$	3.0	$Cu(OAc)_2$	TBAI	DMF	64
14 [d]	$PhI(OAc)_2$	3.5	$Cu(OAc)_2$	TBAI	DMF	79
15	$PhI(OAc)_2$	3.0	$Cu(OAc)_2$	TBAI (0.1)	DMF	70
16	$PhI(OAc)_2$	3.0	$Cu(OAc)_2$	TBAI (1.0)	DMF	72
17	$PhI(OAc)_2$	3.0	$Cu(OAc)_2$	TBAI (3.0)	DMF	81
18	PhIO	3.0	$Cu(OAc)_2$	TBAI	DMF	66
19	$PhI(OAc)_2$	3.0	CuI	TBAI	DMF	79
20 [e]	$PhI(OAc)_2$	3.0	CuI	none	DMF	40

[a]The reaction was carried out on a 0.2 mmol scale in 2 mL solvent at room temperature. 3.0 Equiv of hypervalent iodine reagent, 2.0 equiv. of TABI, and 10 mol% of copper salt were used unless otherwise specified. The reaction time was 2−4 h. [b]2.0 Equiv of $PhI(OAc)_2$ was used. [c]Complex mixture was generated. [d]3.5 Equiv of $PhI(OAc)_2$ was used. [e]1.0 Equiv of CuI was used. TBAI: tetrabutylammonium Iodide.

The trifluoromethyl group possesses important functions in pharmaceutically and medicinally significant compounds.[14] Despite the intense interest in the trifluoromethylated aromatic compounds,[15] however, the synthesis of trifluoromethyl attached imidazoles have only been scarcely reported.[16] We anticipated that the current protocol would provide an efficient approach towards this structural moiety. Thus, the optimal conditions were next applied to a variety of 3-trifluromethyl enamine esters, and the results are illustrated in Scheme 3.



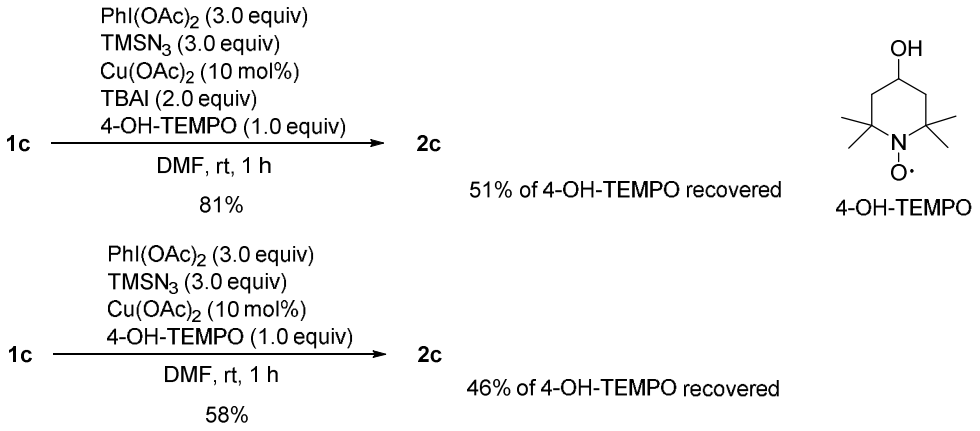
The Reaction was conducted on a 0.2 mmol scale. R^2 = H except for **1u** and **1v**.
The structures of **2h** and **2l** were confirmed by X-ray crystallographic analysis.[17]

Scheme 3 Examination of the reaction's scope

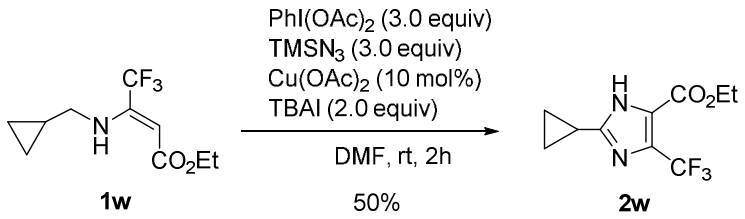
From Scheme 3, it can be seen that this protocol is well suitable for the preparation of 2-phenyl-5-(trifluoromethyl)-imidazoles, the yields were generally good except for those bearing a strong electron withdrawing group at the phenyl ring (**2i**). This result suggests that the benzyl position would bear some positive charge at certain stages during the reaction. Substituting an electron-deficient pyridyl ring for the phenyl ring lowered the yield as well (**2o** and **2p**). 2-Alkyl and 2-vinyl substituted imidazoles can also be prepared with this method, albeit in lower yields (**2q**-**2s**). When reactants bearing two substituents at the amino's α-position was used, the reaction delivered mixed result: while compound **2u** was generated in a yield of 52%, compound **2v** cannot be obtained in this way. The current conditions were also applied to compounds **1a** and **1b,** but the results were inferior to those shown in Scheme 2.

As shown in Scheme 1, our design was based on the assumption that the initial

azidation would produce a vinyl azide intermediate, which would be further oxidized to afford iminyl radicals. To verify this radical mechanism, some preliminary investigations were conducted. The results are shown in Schemes 4 and 5. It was found the commonly used radical scavenger TEMPO (4-OH-TEMPO was used in this case) had no inhibiting effect on the reaction, and when compound **1w** was used as the substrate, the imidazole product **2w** was obtained in a yield of 50%. In the latter case, no ring-opening product was obtained. These results did not support the assumed radical mechanism, but they also did not point to other alternative pathways. Further studies are needed to elucidate the mechanistic issues.



Scheme 4 Reactions conducted in the presence of 4-OH-TEMPO



Scheme 5 Reaction of *N*-cyclopropylmethyl enamine **1w**

In summary, a tandem azidation/C(sp^3)–H amination strategy has been developed to gain access to 2,4,5-trisubsituted imidazoles from the enamine precursors by using (diacetoxyiodo)benzene as oxidant and $TMSN_3$ as an azide source. This protocol is highly efficient for the preparation of 5-(trifluoromethyl)imidazoles. A copper salt or tetrabutyl ammonium iodide is required for the reaction to take place, and 5-(trifluoromethyl)imidazoles can be obtained in high yields when both of them were present in the reaction system. The present result demonstrates the synthetic value of

the domino azidation/C–H amination strategy in the synthesis of nitrogen heterocycles.

Experimental section

General information

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6 or acetone-d_6 on a 400 MHz spectrometer or a 300 MHz spectrometer. NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz), and integration. The chemical shifts in ^{1}H NMR spectra were determined with $Si(CH_3)_4$ as the internal standard (δ = 0.00 ppm). The chemical shifts in ^{13}C NMR spectra were determined based on the chemical shift of $CDCl_3$ (δ = 77.00 ppm), DMSO-d_6 (δ = 39.60 ppm) or acetone-d_6 (206.5 ppm). All the ^{13}CNMR spectra measured in this study were proton-decoupled. The high resolution mass spectra (HRMS) were measured on a TOF-MS instrument with an ESI source. X-ray crystallographic analysis was performed with a SMART CCD and a P4 diffractometer. Melting points were uncorrected. Flash column chromatography was carried out on silica gel (200-300 mesh) with petroleum ether (PE) and ethyl acetate as the eluent.

General procedure for the synthesis of 1 Compounds (*Z*)-ethyl 3-((arylmethyl)amino)-4,4,4-trifluorobut-2-enoate (**1c**-**1w**) were prepared according to the literature methods.[18]

As a typical procedure, to a 50 mL round-bottom flask equipped with a magnetic stirring bar were added benzylamine (5.5 mmol, 1.1 equiv), CH_3COOH (5.5 mmol, 1.1 equiv) and $CHCl_3$ (8 mL). The mixture was stirred at room temperature for 5 minutes. A solution of ethyl 4,4,4-trifluoroacetoacetate (5 mmol, 1.0 equiv) in $CHCl_3$ (10 mL) was then added into the mixture. After stirring for 5h under reflux, the solution was evaporated under reduced pressure, and the residual was filtered through a short silica column (PE/ethyl acetate) to give the **1c**.

Compounds **1a**, **1b** were prepared according to the literature methods.[19, 20]

General procedure for the reactions of 1 Into a 10 mL round-bottom flask equipped with a magnetic stirring bar were added sequentially **1** (0.2 mmol, 1.0 equiv),

$Cu(OAc)_2$ (3.6 mg, 0.02 mmol, 0.1 equiv), DMF (5 mL) , tetrabutyl ammonium iodide (147 mg, 0.4 mmol, 2.0 equiv), $TMSN_3$ (78.9 μL, 0.6 mmol, 3.0 equiv), and finally $PhI(OAc)_2$ (193 mg, 0.6 mmol, 3.0 equiv). The mixture was stirred at room temperature until the reaction was complete as indicated by TLC (generally 2-4 h). The reaction mixture was then poured into a saturated aqueous $NaHCO_3$ solution (20 mL), and was then extracted with ethyl acetate (4×10 mL). The combined organic layers were washed with brine (4×30 mL) and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residual was treated with silica gel chromatography (PE/ethyl acetate) to give product **2**.

Compounds **2a** and **2b** are obtained by a similar operation as described above.

Warning!

Under the present reaction conditions of $TMSN_3/PhI(OAc)_2/CuCl_2$, HN_3 and $Cu(N_3)_2$ might be formed as the by-products. These compounds are toxic and explosive; the reactions must be handled carefully with sufficient protection.

*(Z)-Ethyl 3-(benzylamino)-4,4,4-trifluorobut-2-enoate (**1c**):*[18] 75% yield (0.806 g), Colorless liquid; R_f = 0.25 (PE : EtOAc = 95 : 5); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.45 (s, 1H), 7.36–7.26 (m, 5H), 5.17 (s, 1H), 4.46 (d, *J* = 6.4 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.8, 148.1, 137.7, 128.8, 127.7, 127.2, 120.3 (q, *J* = 275 Hz), 85.2, 59.7, 48.0, 14.2.

*(Z)-Ethyl 4,4,4-trifluoro-3-((4-methylbenzyl)amino)but-2-enoate (**1d**):*[18] 75% yield (0.859 g), Yellow liquid; R_f = 0.26 (PE : EtOAc = 20 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.40 (s, 1H), 7.19–7.13 (m, 4H), 5.15 (s, 1H), 4.41 (d, *J* = 6.4 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.8, 148.1, 137.5, 134.6, 129.5, 127.4, 120.3 (q, *J* = 275 Hz), 85.0, 59.6, 47.8, 21.0, 14.2.

*(Z)-Ethyl 4,4,4-trifluoro-3-((4-methoxybenzyl)amino)but-2-enoate (**1e**):*[18] 80% yield (0.980 g), Orange oil; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.34 (s, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 9.2 Hz, 2H), 5.14 (s, 1H), 4.39 (d, *J* = 6.0 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.8, 159.2, 148.0, 129.7, 128.7, 120.3 (q, *J* = 275 Hz), 114.2, 84.9, 59.6, 55.2,

47.5,14.3.

*(Z)-Ethyl 4,4,4-trifluoro-3-((4-fluorobenzyl)amino)but-2-enoate (**1f**):* 49% yield (0.713 g), Colorless liquid; R_f = 0.64 (PE : EtOAc = 20 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.39 (s, 1H), 7.28–7.25 (m, 2H), 7.07–7.02 (m, 2H), 5.17 (s, 1H), 4.44 (d, *J* = 6.4 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.8, 162.4 (d, *J* = 244 Hz), 148.0 (d, *J* = 31 Hz), 133.5, 129.0, 120.3 (q, *J* = 275 Hz), 115.8, 85.6, 59.8, 47.4, 14.3; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{13}H_{14}F_4NO_2$ 292.0955; found 292.0952.

*(Z)-Ethyl 3-((4-chlorobenzyl)amino)-4,4,4-trifluorobut-2-enoate (**1g**):*[18] 78% yield (1.214 g); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.43 (s, 1H), 7.33–7.31 (m, 2H), 7.23–7.21 (m, 2H), 5.18 (s, 1H), 4.43 (d, *J* = 6.4 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.8, 147.9, 136.3, 133.6, 129.0, 128.5, 120.3 (q, *J* = 275 Hz), 85.8, 59.8, 47.3, 14.2.

*(Z)-Ethyl 3-((4-bromobenzyl)amino)-4,4,4-trifluorobut-2-enoate (**1h**):* 47% yield (0.828 g), Colorless liquid; R_f = 0.44 (PE : EtOAc = 20 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.44 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.18 (s, 1H), 4.41 (d, *J* = 6.4 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.7, 147.9, 136.8, 131.9, 128.8, 121.6, 120.3 (q, *J* = 275 Hz), 85.8, 59.8, 47.3, 14.2; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{13}H_{14}F_3BrNO_2$ 352.0155; found 352.0150.

*(Z)-ethyl 3-((4-cyanobenzyl)amino)-4,4,4-trifluorobut-2-enoate (**1i**):* 55% yield (0.819 g), yellow liquid; R_f = 0.20 (PE : EtOAc = 20 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.55 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 5.23 (s, 1H), 4.54 (d, *J* = 6.8 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.7, 147.7, 143.4, 132.6, 127.5, 120.3 (q, *J* = 275 Hz), 118.5, 111.6, 86.7, 60.0, 47.4, 14.2; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{14}H_{14}F_3N_2O_2$ 299.1002; found 299.0995.

*(Z)-Ethyl 4,4,4-trifluoro-3-((3-methylbenzyl)amino)but-2-enoate (**1j**):* 49% yield (0.703 g), yellow liquid; R_f = 0.56 (PE : EtOAc = 20 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.40 (s, 1H), 7.25–7.22 (m, 2H), 7.11–7.08 (m, 2H), 5.16 (s, 1H), 4.43 (d, *J* =

6.4 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.8, 148.1, 138.5, 137.5, 128.7, 128.6, 128.1, 124.3, 120.3 (q, *J* = 275 Hz), 85.0, 59.7, 48.1, 21.4, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{17}F_3NO_2$ 288.1206; found 288.1203.

*(Z)-Ethyl 4,4,4-trifluoro-3-((3-fluorobenzyl)amino)but-2-enoate (**1k**):* 88% yield (1.285 g), colorless liquid; R_f = 0.65 (PE : EtOAc = 20 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.47 (s, 1H), 7.34–7.29 (m, 1H), 7.08–7.06 (m, 1H), 7.01–6.96 (m, 2H), 5.19 (s, 1H), 4.46 (d, *J* = 6.4 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.8, 163.0 (d, *J* = 245 Hz), 147.9. 140.4, 130.3, 122.6, 120.3 (q, *J* = 275 Hz), 121.6, 114.7, 114.1, 85.9, 59.8, 47.5, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $C_{13}H_{14}F_4NO_2$ 292.0955; found 292.0952.

*(Z)-Ethyl 4,4,4-trifluoro-3-((2-methylbenzyl)amino)but-2-enoate (**1l**):* 61% (0.876 g), colorless liquid; R_f = 0.48 (PE : EtOAc = 20 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.27 (s, 1H), 7.25–7.17 (m, 4H), 5.17 (s, 1H), 4.43 (d, *J* = 6.0 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.8, 148.1, 136.3, 135.4, 130.6, 128.2, 128.1, 126.4, 120.3 (q, *J* = 275 Hz), 85.1, 59.7, 46.2, 18.8, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{17}F_3NO_2$ 288.1206; found 288.1203.

*(Z)-Ethyl 4,4,4-trifluoro-3-((2-fluorobenzyl)amino)but-2-enoate (**1m**):* 87% yield (1.274 g), colorless liquid; R_f = 0.68 (PE : EtOAc = 20 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.46 (s, 1H), 7.33–7.26 (m, 2H), 7.17–7.12 (m, 1H), 7.09–7.05 (m, 1H), 5.17 (s, 1H), 4.53 (d, *J* = 6.4 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.8, 160.6 (d, *J* = 246 Hz), 147.9, 129.5. 129.1, 124.9, 124.4, 120.3 (q, *J* = 275 Hz), 115.5, 85.7, 59.8, 41.9, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}F_4NO_2$ 292.0955; found 292.0957.

*(Z)-Ethyl 3-((2-chlorobenzyl)amino)-4,4,4-trifluorobut-2-enoate (**1n**):*[18] 81% yield (1.242 g); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.53 (s, 1H), 7.40–7.34 (m, 1H), 7.34–7.32 (m, 1H), 7.29–7.23 (m, 2H), 5.19 (s, 1H), 4. 57 (d, *J* = 6.8 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.8, 148.0, 135.4, 133.2, 129.7, 129.1, 128.8, 127.2, 120.3 (q, *J* = 275 Hz), 85.7, 59.8, 45.8,

14.3.

*(Z)-Ethyl 4,4,4-trifluoro-3-((pyridin-2-ylmethyl)amino)but-2-enoate (**1o**):* 39% yield (0.534 g), pale yellow liquid; R_f = 0.22 (PE : EtOAc = 3 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.09 (s, 1H), 8.64–8.63 (m, 1H), 7.70–7.66 (m, 1H), 7.26–7.20 (m, 2H), 5.21 (s, 1H), 4. 64 (d, *J* = 5.6 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.4, 156.0, 149.3, 147.4, 136.7, 122.4, 121.0, 120.3 (q, *J* = 275 Hz), 85.6, 59.6, 48.4, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{14}F_3N_2O_2$ 275.1002; found 275.1004.

*(Z)-Ethyl 4,4,4-trifluoro-3-((pyridin-3-ylmethyl)amino)but-2-enoate (**1p**):* 84% yield (1.156 g), pale yellow liquid; R_f = 0.17 (PE : EtOAc = 3 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.57–8.56 (m, 2H), 8.47 (s, 1H), 7.65–7.63 (m, 1H), 7.32–7.29 (m, 1H), 5.22 (s, 1H), 4. 50 (d, *J* = 6.4 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.7, 149.2, 148.8, 147.8, 134.8, 133.3, 123.6, 120.3 (q, *J* = 275 Hz), 86.4, 59.9, 45.5, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{14}F_3N_2O_2$ 275.1002; found 275.0999.

*(Z)-ethyl 4,4,4-trifluoro-3-(phenethylamino)but-2-enoate (**1q**):*[18] 53% yield (0.758 g, 5.0 mmol scale); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.23 (s, 1H), 7.34–7.30 (m, 2H), 7.26–7.20 (m, 3H), 5.09 (s, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.52 (d, *J* = 7.2 Hz, 2H), 2.88 (t , *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.8, 137.9, 128.7, 128.7, 126.7, 120.3 (q, *J* = 275 Hz), 84.7, 59.6, 45.6, 37.2, 14.3.

*(Z)-ethyl 4,4,4-trifluoro-3-(propylamino)but-2-enoate (**1r**):* 58% yield (0.658 g), colorless liquid; R_f = 0.76 (PE : EtOAc = 20 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.20 (s, 1H), 5.06 (s, 1H), 4.15 (q, *J* = 9.6 Hz, 2H), 3.26 (q, *J* = 9.2 Hz, 2H), 1.68-1.56 (m, 2H), 1.28 (t , *J* = 9.6 Hz, 3H), 0.99 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 170.1, 148.7, 120.3 (q, *J* = 275 Hz), 83.8, 59.5, 45.7, 23.7, 14.3, 11.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{15}F_3NO_2$; found 226.1050.

*(Z)-Ethyl 3-(allylamino)-4,4,4-trifluorobut-2-enoate (**1s**):*[21] 73% yield (0.818 g), colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.25 (s, 1H), 5.95–5.83 (m, 1H), 5.29–5.18 (m, 2H), 5.12 (s, 1H), 4.16 (q, *J* = 9.6 Hz, 2H), 3.91 (t, *J* = 7.6 Hz, 2H),

1.28 (t , J = 9.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.9, 148.2, 133.9, 120.3 (q, J = 275 Hz), 116.8, 85.0, 59.7, 46.4, 14.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{13}F_3NO_2$ 224.0893; found 224.0891.

*(Z)-Ethyl 4,4,4-trifluoro-3-((naphthalen-1-ylmethyl)amino)but-2-enoate (**1t**):* 89% yield (1.438 g), white solid, m.p. = 65–66 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.41 (s, 1H), 7.95–7.93 (m, 1H), 7.88–7.86 (m, 1H), 7.82–7.80 (m, 1H), 7.57–7.41 (m, 4H), 5.21 (s, 1H), 4. 89 (d, J = 5.6 Hz, 2H), 4.07 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.7, 148.0, 133.8, 132.8, 131.1, 128.9, 128.8, 126.7, 126.0, 125.9, 125.4, 124.6, 122.8, 120.3 (q, J = 275 Hz), 85.5, 59.7, 46.0, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}F_3NO_2$ 324.1206; found 324.1203.

*(Z)-Ethyl 4,4,4-trifluoro-3-((1-phenylethyl)amino)but-2-enoate (**1u**):*[22,23] 53% yield (0.758 g); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.66 (d, J = 9.6 Hz, 1H), 7.35–7.22 (m, 5H), 5.13 (s, 1H), 4.77–4.73 (m, 1H), 4.20–4.14 (m, 2H), 1.53 (d, J = 6.8 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 169.9, 147.6, 143.9, 128.7, 127.3, 125.3, 124.4, 120.3 (q, J = 275 Hz), 85.4, 59.7, 53.9, 24.9, 14.3.

*(Z)-Ethyl 4,4,4-trifluoro-2-(isopropylamino)but-2-enoate (**1v**):*[23] 56% yield (0.660 g);^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.09 (s, 1H), 5.03 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.82–3.71 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.23 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 170.1, 147.9, 120.4 (q, J = 275 Hz), 83.8, 59.5, 46.6, 24.6, 14.3.

(Z)-Ethyl-3-*((cyclopropylmethyl)amino)-4,4,4-trifluorobut-2-enoate (**1w**):* 59% yield (0.695 g), colorless liquid, R_f = 0.61 (PE : EtOAc = 10 : 1); 1H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.27 (s, 1H), 5.07 (s, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.15 (t, J = 6.4 Hz, 2H), 1.28 (t , J = 7.2 Hz, 3H), 1.08–1.03 (m, 1H), 0.61–0.57 (m, 2H), 0.28–0.24 (m, 2H); 13C NMR (CDCl3, 100 MHz, δ ppm): 169.9, 148.2, 120.3 (q, J = 275 Hz), 84.0, 59.5, 49.0, 14.3, 11.4, 3.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{15}F_3NO_2$ 238.1049; found 238.1046.

*Ethyl 2,4-diphenyl-1H-imidazole-5-carboxylate (**2a-1**), ethyl 2,5-diphenyl-1H -imidazole-4-carboxylate (**2a-2**):*[24] 39% yield (23 mg); ^{1}H NMR (DMSO-d_6, 400

MHz, δ ppm): 13.22–13.10 (d, 1H), 8.22–8.08 (m, 2H), 7.92–7.68 (m, 2H), 7.51–7.43 (m, 6H), 4.30–4.18 (m, 2H), 1.28–1.17 (m, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.0, 160.0, 147.9, 147.1, 145.9, 138.2, 133.9, 129.7, 129.5, 129.3, 129.0, 128.8, 128.5, 128.0, 127.9, 127.6, 126.5, 125.7, 60.4, 59.6, 14.2.

*Ethyl 2,2-dimethyl-5-phenyl-2H-imidazole-4-carboxylate (**2b**):* 25% yield (12 mg), pale yellow liquid, R_f = 0.39 (PE : EtOAc = 5 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.70–7.68 (m, 2H), 7.42–7.35 (m, 3H), 4.36 (q, *J* = 7.2 Hz, 2H), 1.55 (s, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 163.3, 162.1, 156.9, 131.1, 130.8, 128.5, 128.4, 103.3, 62.5, 23.3, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{17}N_2O_2$ 245.1285; found 245.1293.

*Ethyl 2-phenyl-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2c**):*[16a] 84% yield (48 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.07 (br, 1H), 8.17–8.15 (m, 2H), 7.52 (d, *J* = 6.8 Hz, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 158.0, 147.9, 134.1, 130.1, 128.9, 128.4, 126.7, 122.5, 121.3 (q, *J* = 266 Hz), 61.4, 14.0.

*Ethyl 2-(p-tolyl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2d**):* 84% yield (50 mg), white solid, m.p. = 190–192 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.90 (br, 1H), 8.02 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 158.1, 148.1, 140.0, 134.1, 129.5, 126.6, 125.8, 122.2, 121.4 (q, *J* = 266 Hz), 61.4, 21.0, 14.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{13}F_3N_2O_2Na$ 321.0821; found 321.0819.

*Ethyl 2-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2e**):*[16a] 79% yield (50 mg), white solid, m.p. = 194–197 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.80 (br, 1H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 160.8, 158.2, 148.1, 134.4, 128.3, 122.0, 121.4 (q, *J* = 267 Hz), 121.1, 114.3, 61.3, 55.4, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}F_3N_2O_3$ 315.0951, found: 315.0948.

*Ethyl 2-(4-fluorophenyl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2f**):* 84%

yield (51 mg) white solid, m.p. = 191–193 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.03 (br, 1H), 8.19–8.15 (m, 2H), 7.34–7.29 (m, 2H), 4.35 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 163.2 (d, J = 246 Hz), 158.1, 147.1, 134.1, 129.1, 125.1, 121.3 (q, J = 267 Hz), 116.0, 61.4, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}F_4N_2O_2$ 303.0751; found 303.0748.

*Ethyl 2-(4-chlorophenyl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2g**):* 79% yield (50 mg), white solid, m.p. = 206–208 °C; ^{1}H NMR (Acetone-d_6, 400 MHz, δ ppm): 8.15–8.11 (m, 2H), 7.55–7.52 (m, 2H), 4.37 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (Acetone-d_6, 100 MHz, δ ppm): 158.5, 147.5, 136.3, 129.8, 128.8, 128.2, 123.6, 122.0 (q, J = 266 Hz), 62.0, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}F_3ClN_2O_2$ 319.0456; found 319.0451.

*Ethyl 2-(4-bromophenyl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2h**):*[16a] 70% yield (50 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.11 (br, 1H), 8.06 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 4.35 (q, J = 6.8 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 158.0, 146.9, 134.1, 131.9, 128.6, 127.7, 122.8, 122.5, 121.2 (q, J = 267 Hz), 61.5, 14.0.

*Ethyl 2-(4-cyanophenyl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2i**):* 30% yield (19 mg), white solid, m.p. = 244–246 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.36 (br, 1H), 8.28 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 7.6 Hz, 2H), 4.36 (q, J = 6.8 Hz, 2H), 1.32 (t, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 157.9, 146.1, 134.5, 132.9, 132.5, 127.2, 123.7, 121.1 (q, J = 267 Hz), 118.5, 112.3, 61.6, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}F_3N_3O_2$ 310.0798; found 310.0804.

*Ethyl 2-(m-tolyl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2j**):* 77% yield (46 mg), white solid, m.p. = 138–139 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.99 (br, 1H), 7.98 (s, 1H), 7.93 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.2 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 158.1, 148.1, 138.3, 134.4, 130.8, 128.8, 128.4, 127.2, 123.8, 122.4, 121.3 (q, J = 266 Hz), 61.4, 21.0, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}F_3N_2O_2$ 299.1002; found 299.0998.

*Ethyl 2-(3-fluorophenyl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2k**):* 71% yield (43 mg), white solid, m.p. = 176–179 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.13 (br, 1H), 7.98–7.93 (m, 2H), 7.54–7.48 (m, 1H), 7.30–7.25 (m, 1H), 4.35 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 162.4 (d, J = 242 Hz), 158.0, 146.6, 134.6, 131.1, 130.6, 122.8, 121.3 (q, J = 267 Hz), 116.9, 113.3, 61.5, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. for $C_{13}H_{11}F_4N_2O_2$ 303.0751; found 303.0747.

*Ethyl 2-(o-tolyl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2l**):* 85% yield (51 mg), white solid, m.p. = 103–104 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.91 (br, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.41–7.29 (m, 3H), 4.35 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 158.1, 148.5, 137.2, 133.8, 131.0, 130.1, 129.9, 128.6, 125.9, 121.9, 121.3 (q, J = 267 Hz), 61.3, 20.4, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}F_3N_2O_2$ 299.1002; found 299.0997.

*Ethyl 2-(2-fluorophenyl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2m**):* **7**6% yield (46 mg), white solid, m.p. = 106–108 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.01 (br, 1H), 7.87–7.83 (m, 1H), 7.59–7.54 (m, 1H), 7.41–7.32 (m, 2H), 4.36 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 159.5 (d, J = 250 Hz), 157.9, 143.4, 134.0, 132.5, 132.4, 130.9, 124.9, 122.6, 121.3 (q, J = 266 Hz), 117.1, 116.4, 61.5, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}F_4N_2O_2$ 303.0751; found 303.0748.

*Ethyl 2-(2-chlorophenyl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2n**):* 79% yield (50 mg), white solid, m.p. = 91–92 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 14.16 (br, 1H), 7.68–7.66 (m, 1H), 7.64–7.62 (m, 1H), 7.57–7.53 (m, 1H), 7.49–7.46 (m, 1H), 4.35 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 157.9, 145.8, 133.8, 132.6, 132.3, 131.8, 130.1, 128.6, 127.3, 122.4, 121.3 (q, J = 266 Hz), 61.5, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}F_3ClN_2O_2$ 319.0456; found 319.0450.

*Ethyl 2-(pyridin-2-yl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2o**):* 37% yield (21 mg), white solid, m.p. = 138–140 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ

ppm): 14.35 (br, 1H), 8.72–8.70 (m, 1H), 8.14 (d, J = 8.0 Hz, 1H), 8.00–7.96 (m, 1H), 7.54–7.51 (m, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 157.9, 149.5, 147.4, 147.0, 137.8, 131.6, 128.8, 125.0, 121.6, 121.3 (q, J = 267 Hz), 61.4, 13.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{11}F_3N_3O_2$ 286.0798; found 286.0801.

*Ethyl 2-(pyridin-3-yl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2p**):* 53% yield (30 mg), pale yellow solid, m.p. = 204–205 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 9.26 (s, 1H), 8.63 (d, J = 4.0 Hz, 1H), 8.43 (d, J = 8.0 Hz, 1H), 7.52–7.49 (m, 1H), 4.35 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 158.1, 150.7, 147.7, 145.7, 134.4, 134.0, 124.8, 123.9, 122.6, 121.3 (q, J = 267 Hz), 61.5, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{11}F_3N_3O_2$ 286.0798; found 286.0792.

*Ethyl 2-benzyl-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2q**):* 43% yield (26 mg), white solid, m.p. = 143–144 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.73 (br, 1H), 7.32–7.22 (m, 4H), 7.21–7.19 (m, 1H), 4.30 (q, J = 7.2 Hz, 2H), 4.06 (s, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 157.9, 149.8, 137.3, 133.5, 128.7, 128.6, 126.7, 121.3 (q, J = 267 Hz), 121.1, 61.2, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}F_3N_2O_2$ 299.1002; found 299.0999.

*Ethyl 2-ethyl-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2r**):* 42% yield (20 mg), white solid, m.p. = 160–162 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.42 (br, 1H), 4.30 (q, J = 6.8 Hz, 2H), 3.35 (s, 1H), 2.68 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 158.0, 152.4, 133.1, 121.3 (q, J = 266 Hz), 120.7, 61.1, 21.0, 14.0, 12.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{12}F_3N_2O_2$ 237.0845; found 237.0842.

*Ethyl 4-(trifluoromethyl)-2-vinyl-1H-imidazole-5-carboxylate (**2s**):* 53% yield (25 mg), white solid, m.p. > 300 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.82 (br, 1H), 6.63 (dd, J = 17.6 Hz, 7.2Hz, 1H), 6.27 (d, J = 17.6 Hz, 1H), 5.61 (d, J = 11.6 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 157.9, 147.0, 134.0, 124.5, 121.6, 121.4, 121.3 (q, J = 267 Hz), 61.4, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{10}F_3N_2O_2$ 235.0689; found 235.0687.

*Ethyl 2-(naphthalen-1-yl)-4-(trifluoromethyl)-1H-imidazole-5-carboxylate (**2t**):* 80% yield (53 mg), white solid, m.p. = 194–195 °C; ^{1}H NMR (Acetone-d_6, 400 MHz, δ ppm): 12.98 (br, 1H), 8.71–8.69 (m, 1H), 8.06–8.04 (m, 1H), 8.00–7.89 (m, 1H), 7.88–7.87 (m, 1H), 7.63–7.55 (m, 3H), 4.41 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (Acetone-d_6, 100 MHz, δ ppm): 158.6, 148.5, 135.6, 135.3, 134.6, 131.6, 131.4, 129.1, 128.9, 127.8, 127.1, 126.8, 126.5, 125.7, 123.2, 122.2 (q, J = 266 Hz), 62.0,14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{14}F_3N_2O_2$ 335.1002; found 335.0995.

*Ethyl 2-methyl-2-phenyl-5-(trifluoromethyl)-2H-imidazole-4-carboxylate (**2u**):* 52% yield (31 mg), pale yellow liquid, R_f = 0.31 (PE : EtOAc = 20 : 1); ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 7.69–7.66 (m, 2H), 7.39–7.31 (m, 3H), 4.52–4.46 (m, 2H), 1.88 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 159.5, 153.8, 153.5, 136.6, 128.7, 128.6, 127.1, 118.6 (q, J = 272 Hz), 108.5, 63.1, 26.4, 13.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}F_3N_2O_2$ 299.1002; found 299.0999.

Ethyl 2-cyclopropyl-4-(trifluoromethyl)-1H-imidazole-5-carboxylate ***(2w):*** White solid, 50% yield (25 mg), m.p. = 99–102 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.48 (s, 1H), 4.30 (q, J = 7.2 Hz, 2H), 2.05–2.01 (m, 1H), 1.28 (t , J = 7.2 Hz, 3H), 1.01–0.95 (m, 2H), 0.94–0.90 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 157.8, 152.9, 133.8, 133.1, 120.3 (q, J = 266 Hz), 61.0, 14.0, 8.44, 8.39; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{12}F_3N_2O_2$ 249.0845; found 249.0844.

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Notes

The authors declare no competing financial interest.

Associated content

The Supporting Information:

^{1}H and ^{13}C NMR spectra for the reactants and products, X-ray crystal data (CIF) for compounds **2h** and **2l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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