JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00009 • Publication Date (Web): 30 Mar 2018

ACS Publications

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Synthesis of Trifluoroethyl Pyrazolines via Trichloroisocyanuric Acid Promoted Cascade Cyclization/Trifluoromethylation of *β,γ*-Unsaturated Hydrazones

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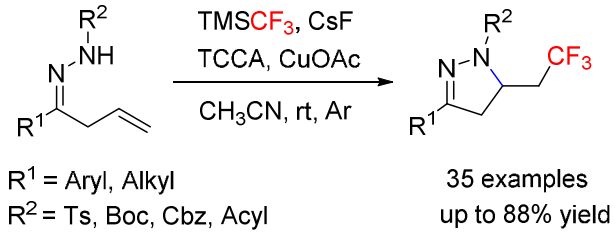
Abstract



A novel and efficient protocol for the construction of trifluoroethyl pyrazolines has been developed by cascade cyclization/trifluoromethylation reaction of *β,γ*-unsaturated hydrazones. This strategy uses cheap and commercially available trichloroisocyanuric acid as promoter and $TMSCF_3$ as the trifluoromethylating reagent, which make trifluoromethylating process much cheaper. A wide range of substrates can be applied in this process to afford the trifluoroethyl pyrazolines in good yield.

INTRODUCTION

Trifluoromethyl group is the most prevalent fluorine-containing group appeared in pharmaceuticals,[1] agrochemicals[2] and material science[3] owing to its unique properties such as

significantly enhanced lipophilicity, metabolic stability, and bioactivities comparing to their parent compounds. Thus, strategies to introduce CF_3 group into organic compounds have been greatly investigated in recent years.[1d,4] Among existed methods, trifluoromethylation reagents such as Togni,[4a,5] Umemoto,[6] Ruppert-Prakash reagent (Me_3SiCF_3),[4b,4g,7] Langlois/Baran reagent (CF_3SO_2M; M = Na, Zn)[8] and others provide direct and effective ways to introduce CF_3 group into organic compounds. Due to its advantages such as easy handling and storage, low cost and commercially availability in large quantity, Me_3SiCF_3 has been widely applied in trifluoromethylation process. Except its traditional nucleophilic trifluoromethylation process, the radical trifluoromethylation protocol with Me_3SiCF_3 is another interesting way.[9] For instance, combinations of Me_3SiCF_3 with $PhI(OAc)_2$, silver or copper salts have been demonstrated as an effective way for the formation of C-CF_3 bond.[9a,9b,9d] Despite such achievements, a more cheap and practical method for the synthesis of trifluoromethyl organic compound is still highly desirable.

Trichloroisocyanuric acid (TCCA) has been produced on large scale in 100000 t/year and used for many purposes, such as disinfecting swimming pools, nonshrinking treatment of wool, cleaning and sterilizing bathrooms, laundry bleach and other purpose.[10] In organic synthesis, TCCA has been mainly applied as chlorination and oxidation reagents.[11] In our research works on fluorine chemistry, we find that TCCA can successfully induce the trifluoromethylation reaction of allylic oximes by using Me_3SiCF_3 as trifluoromethyl source.[12] Obviously, low cost and easy availability of TCCA and Me_3SiCF_3 make it a very interesting trifluoromethylation process.

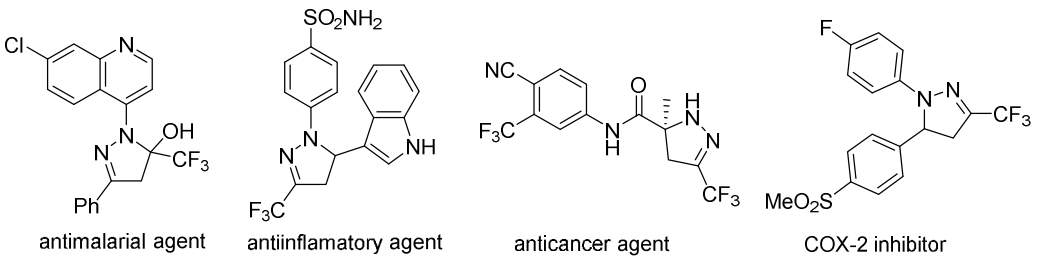
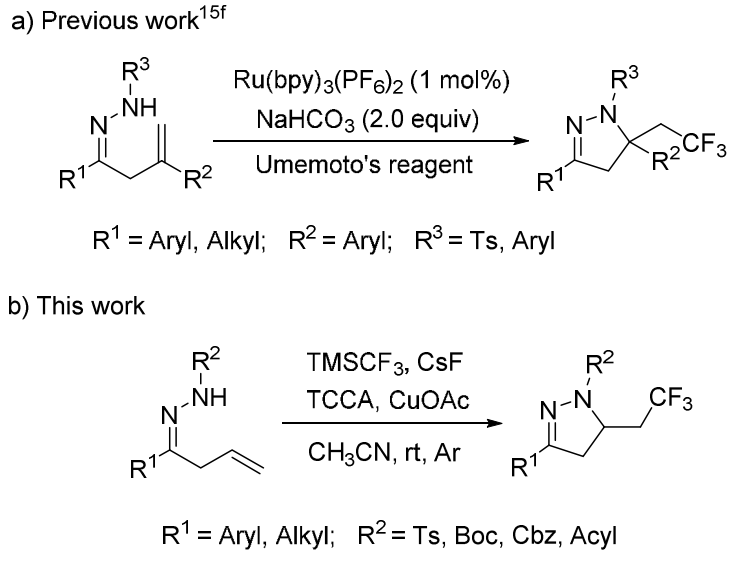


Figure 1. Examples of biologically active CF_3-containing pyrazolines.

On the other hand, pyrazolines play an important role in drug discovery and organic synthesis.[13] As for their fluorine derivatives, CF_3-containing pyrazolines have been proven to possess remarkable bioactivities (Figure 1).[14] However, efficient methods for the synthesis of CF_3-containing pyrazoline derivatives have been scarce in literature.[15] [3+2] Cycloadditions of $CF_3CH_2N_2$ with electron-deficient olefins are reported to give CF_3-substituted pyrazolines.[15a-c] Cyclocondensations of hydrazines with trifluoromethylated *α,β*-unsaturated ketones or 1,3-dicarbonyl compounds are other ways to obtain CF_3-substituted pyrazolines.[15d-e] Recently, a cascade photocatalytic radical trifluoromethylation/cyclization of *β,γ*-unsaturated hydrazones was reported to afford trifluoroethyl pyrazolines by using Umemoto's reagent as trifluoromethyl source in the presence of $Ru(bpy)_3(PF_6)_2$ as photocatalyst (Scheme 1, a).[15f] Herein, we would like to report that TCCA promoted cascade cyclization/trifluoromethylation of *β,γ*-unsaturated hydrazones by using Me_3SiCF_3 as trifluoromethyl source to give trifluoroethyl pyrazolines in good yields (Scheme 1, b).

Scheme 1. Synthesis of Trifluoroethyl Pyrazolines.

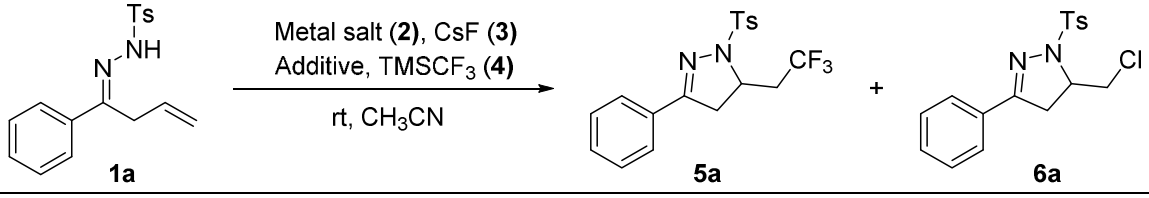


RESULTS AND DISCUSSION

The initial investigation commenced with the reaction of *N*-*p*-toluenesulfonyl-*β,γ*-unsaturated hydrazones **1a** between $TMSCF_3$ and TCCA in the presence of CsF and CuCl in acetonitrile (CH_3CN) under argon atmosphere at room temperature. After the reaction finished, the desired trifluoroethyl pyrazoline **5a** was formed in 55% yield along with chlorinated by-product **6a** in 23% yield (Table 1, entry 1). As reported in literature, metal salts usually have great influence on the trifluoromethylation by using $TMSCF_3$ as trifluoromethyl reagent due to the formation of trifluoromethyl organometallic reagents (MCF_3).[16] Thus, different metal salts were firstly examined in order to improve the selectivity for desired trifluoromethylated product **5a**. When CuCN was used, the reaction did not occur, and only starting material hydrazones **1a** was recovered in 86% yield (Table 1, entry 2). If $Cu(OAc)_2$, $CuCl_2$ or $ZnCl_2$ was applied in the reaction, there were no trifluoromethylated product **5a** formed, but only the chlorinated product **6a** was produced in moderate yield (Table 1, entries 3−5). Silver acetate could only give the product **5a** without the formation of by-product **6a**, but the yield of **5a** was low (Table 1, entry 6). However, the yield of **5a** was not elevated when the amount of TCCA was further increased (Table 1, entry 7). Finally, when copper(I) acetate was used in the reaction, the yield of **5a** could be improved to 75% meanwhile the starting material **1a** was recovered in 13% and trace amount of by-product **6a** could be seen on TLC (Table 1, entry 8). Afterwards, the amount of TCCA was examined to improve the yield of trifluoromethylated product **5a**. It was found that the amount of TCCA also have some influence on the reaction. When its amount was increased from 0.5 equiv to 0.67 equiv, the yield of **5a** went up to 83%, meanwhile the starting material **1a** disappeared and trace amount of by-product **6a** could be seen on TLC (Table 1, entries 8 and 9). However, further increasing of the TCCA amount to 0.84 equiv led to the decreasing of yield of **5a** down to 15%, and the yield of by-product **6a** went up to 56% at the same time (Table 1, entry 10). Next, other additives such as *N*-Cl-phthalimide,

N-Chlorosuccinimide (NCS), *N*-Bromosuccinimide (NBS) and *N*-Iodosuccinimide (NIS) were tested for the reaction, but the yield and selectivity for **5a** were not improved (Table 1, entries 11-14). Finally, it was found both of copper(I) acetate and TCCA were crucial in the reaction to obtain the desired product **5a**. For instance, only chlorinated product **6a** was obtained if there was no copper(I) acetate in the reaction (Table 1, entry 15), and the reaction could not occur neither without TCCA (Table 1, entry 16). Therefore, the optimized reaction conditions were found to be the use of **1a**, CuOAc, CsF, $TMSCF_3$ and TCCA in a molar ratio of 1:3.5:4.2:4.2:0.67 in MeCN at room temperature under argon atmosphere.

Table 1 Optimization of Reaction Conditions[a]



1a **5a** **6a**

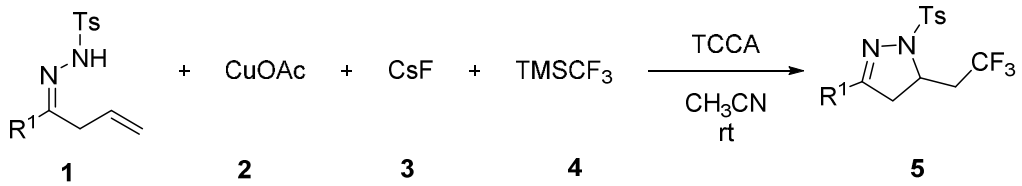
entry	metal salt **2**	additive (equiv)	time	yield (%)	
				5a	**6a**
1	CuCl	TCCA (0.5)	0.5 h	55	23
2	CuCN	TCCA (0.5)	4 h	–	–
3	$Cu(OAc)_2$	TCCA (0.5)	5 h	–	58
4	$CuCl_2$	TCCA (0.5)	1.5 h	–	78
5	$ZnCl_2$	TCCA (0.5)	1.5 h	–	63
6	AgOAc	TCCA (0.5)	0.5 h	35	–
7	AgOAc	TCCA (0.67)	20 min	33	–
8	CuOAc	TCCA (0.5)	4 h	75	trace
9	CuOAc	TCCA (0.67)	1.5 h	83	trace
10	CuOAc	TCCA (0.84)	15 min	15	56
11	CuOAc	*N*-Cl-phthalimide (2.0)	4 h	14	24
12	CuOAc	NCS (2.0)	0.5 h	54	23
13	CuOAc	NIS (2.0)	0.5 h	37	(44)[b]
14	CuOAc	NBS (2.0)	0.5 h	32	(53)[c]

15	–	TCCA (0.67)	15 min	–	46
16	CuOAc	–	4 h	–	–

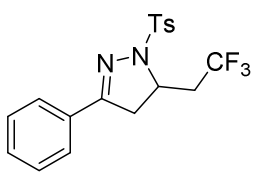
[a] Unless otherwise noted, the reactions were performed with **1a** (0.3 mmol), additive (0.15-0.6 mmol, 0.5-2.0 equiv), **2** (1.1 mmol, 3.5 equiv), **3** (1.3 mmol, 4.2 equiv), and **4** (1.3 mmol, 4.2 equiv) in 6 mL CH_3CN at room temperature. [b] Yield of 5-(iodomethyl)-3-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrazole (**6b**). [c] Yield of 5-(bromomethyl)-3-phenyl-1-tosyl-4,5-dihydro-1*H*-pyrazole (**6c**).

With the optimized reaction conditions in hand, the substrate scope was then investigated. The *β,γ*-unsaturated hydrazones derived from homoallylic ketones **1** were examined firstly. As shown in Table 2, both of aromatic and aliphatic *β,γ*-unsaturated hydrazones **1** could produce the corresponding products **5** in good yields. As for the aromatic ketone-derived *β,γ*-unsaturated hydrazones, electronic properties of substituents on the phenyl rings had little effect on the yields of the products. The *β,γ*-unsaturated hydrazones with both of electron-donating and electron-withdrawing groups on phenyl rings could afford the products in reasonable to good yields (Table 2, **5a**–**5j**). However, if the substituents on the phenyl rings were the same, the *ortho*-substituted ones gave the product in lowest yields (Table 2, **5e**–**5g**). Heterocyclic *β,γ*-unsaturated hydrazones such as 2-thiophenehydrazone and Boc-protected 3-indolehydrazone were also suitable for this reaction to give the desired product **5k** and **5l** in 47% and 75% yields, respectively. In addition, this protocol could be further applied successfully to a range of linear and branched aliphatic *β,γ*-unsaturated hydrazones **1m**–**1p**; and the desired products **5m**–**5p** were obtained in moderate to high yields (Table 2, **5m**–**5p**).

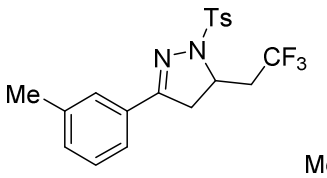
Table 2. Scope of *β,γ*-Unsaturated Hydrazones[a]



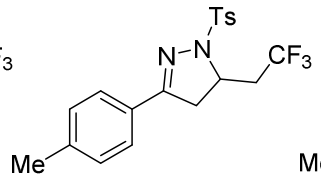
1 **2** **3** **4** **5**



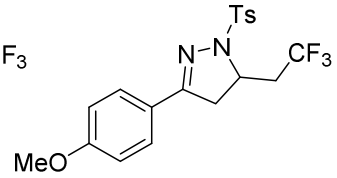
5a: 80% yield, 1h



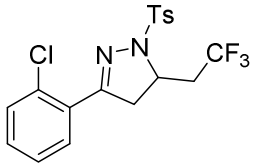
5b: 65% yield, 2 h



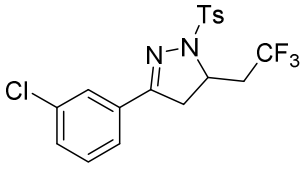
5c: 65% yield 2.5 h



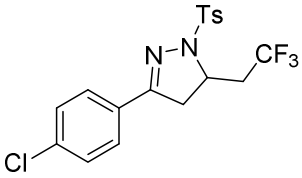
5d: 73% yield, 3 h



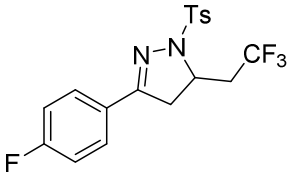
5e: 56% yield, 2 h



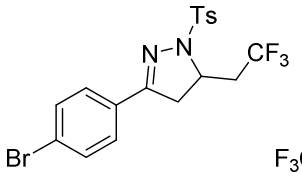
5f: 74% yield, 2 h



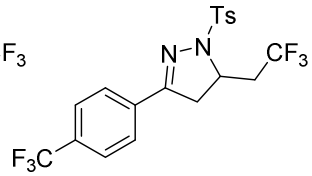
5g: 75% yield, 1.5 h



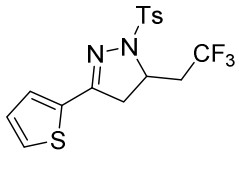
5h: 63% yield, 20 min



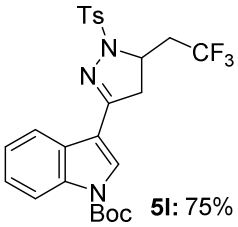
5i: 76% yield 1.5 h



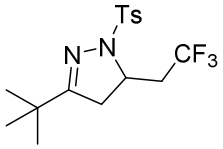
5j: 72% yield 2.5 h



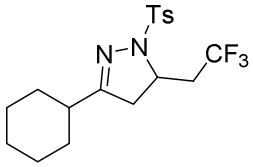
5k: 47% yield, 4 h



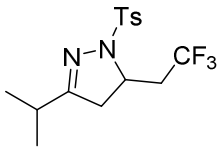
5l: 75% yield, 5 h



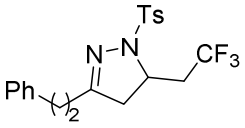
5m: 88% yield, 2 h



5n: 59% yield, 2 h



5o: 69% yield, 2 h

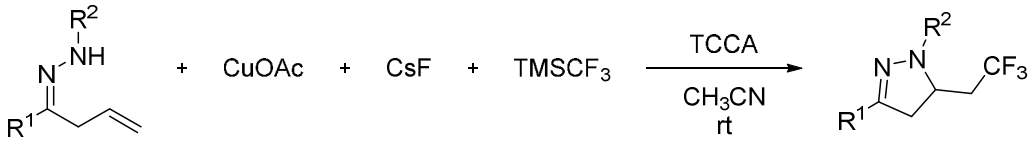


5p: 61% yield, 2.5 h

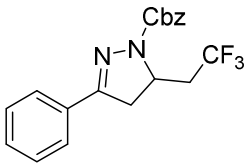
[a]All reactions were carried out using 0.3 mmol of **1a**, 0.2 mmol of TCCA (0.67 equiv), 1.1 mmol of CuOAc (3.5 equiv), 1.3 mmol of $TMSCF_3$ (4.2 equiv), 1.3 mmol of CsF (4.2 equiv), and 4 mL of CH_3CN.

In order to examine the generality of the reaction further, the hydrazones with other *N*-protecting groups (R^2) such as benzyloxycarbonyl (Cbz), methyl carbonate, *tert*-butoxycarbonyl (Boc) and acyl groups had been investigated (Table 3). It was indicated that the Cbz, carbonate and Boc groups were compatible in the reactions to allow the corresponding products formed in good yields. However, when aliphatic acyl groups such as acetyl and isobutyryl groups were used, the yields of the products were low. For instance, the products **5ar** and **5as** were obtained in only 27% and 34% yields (Table 3, **5ar** and **5as**).

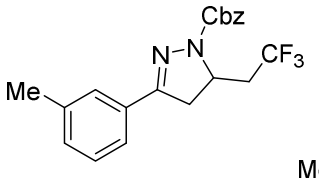
Table 3. Scope of *N*-Protected Hydrazones[a]



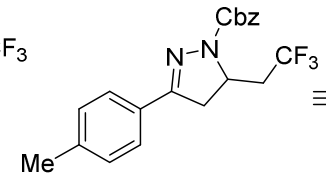
1 **2** **3** **4** **5**



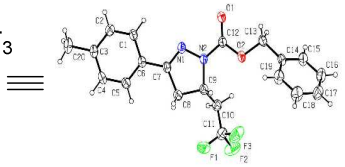
5aa: 68% yield, 26 h



5ab: 55% yield, 18 h



5ac: 62% yield, 16 h



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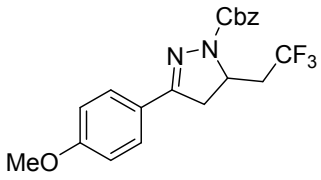
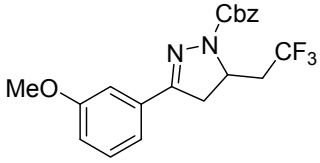
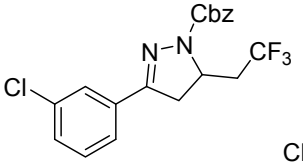


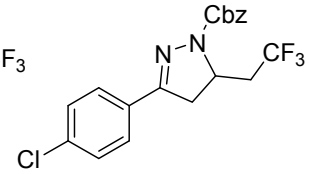
5ad: 57% yield, 16 h



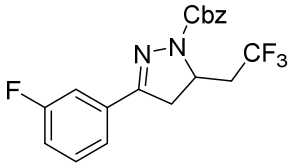
5ae: 63% yield, 16h



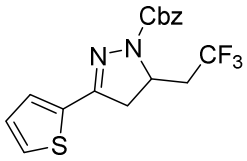
5af: 50% yield, 16 h



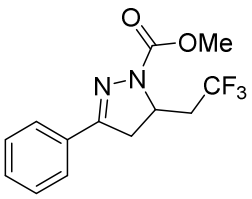
5ag: 58% yield, 17 h



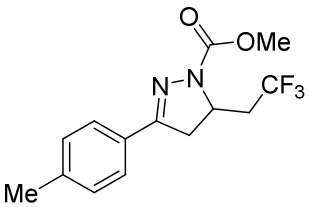
5ah: 35% yield, 16 h



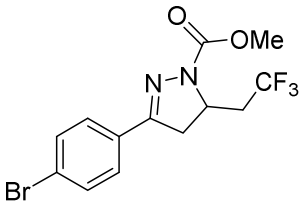
5ai: 58% yield, 17 h



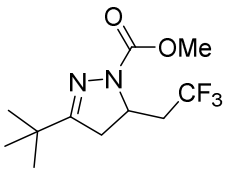
5aj: 61% yield, 19 h



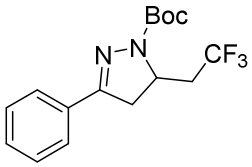
5ak: 55% yield, 17 h



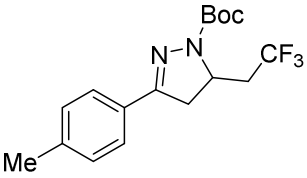
5al: 56% yield, 17 h



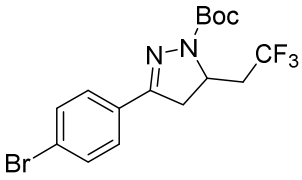
5am: 45% yield, 17 h



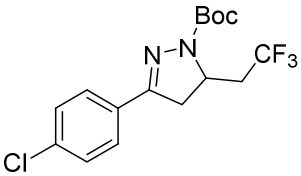
5an: 67% yield, 23 h



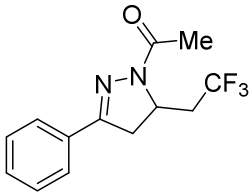
5ao: 58% yield, 17 h



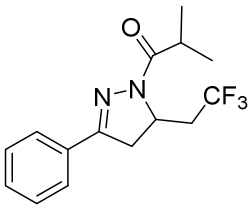
5ap: 55% yield, 17 h



5aq: 53% yield, 17h



5ar: 27% yield, 17 h

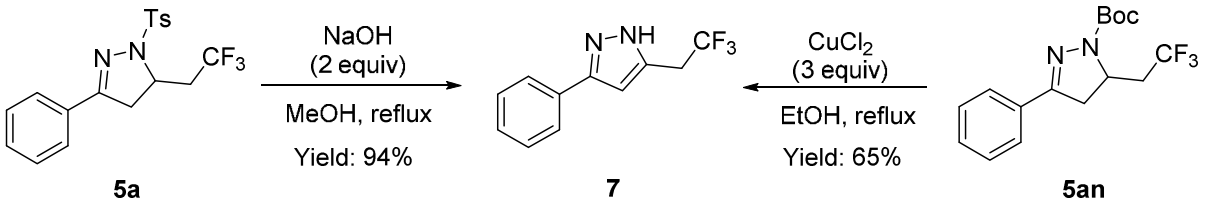


5as: 34% yield, 17 h

[a]All reactions were carried out using 0.3 mmol of **1a**, 0.2 mmol of TCCA (0.67 equiv), 1.1 mmol of CuOAc (3.5 equiv), 1.3 mmol of $TMSCF_3$ (4.2 equiv), 1.3 mmol of CsF (4.2 equiv), and 4 mL of CH_3CN.

The products obtained in above reaction could be further transformed into pyrazoles. For instance, when compound **5a** was refluxed in methanol in the presence of sodium hydroxide, pyrazole **7** could be produced in 94% yield. Boc-protected compound **5an** could also be transformed into pyrazole **7** in the presence of $CuCl_2$ under reflux in ethanol (Scheme 2).

Scheme 2. Transformation of the Products

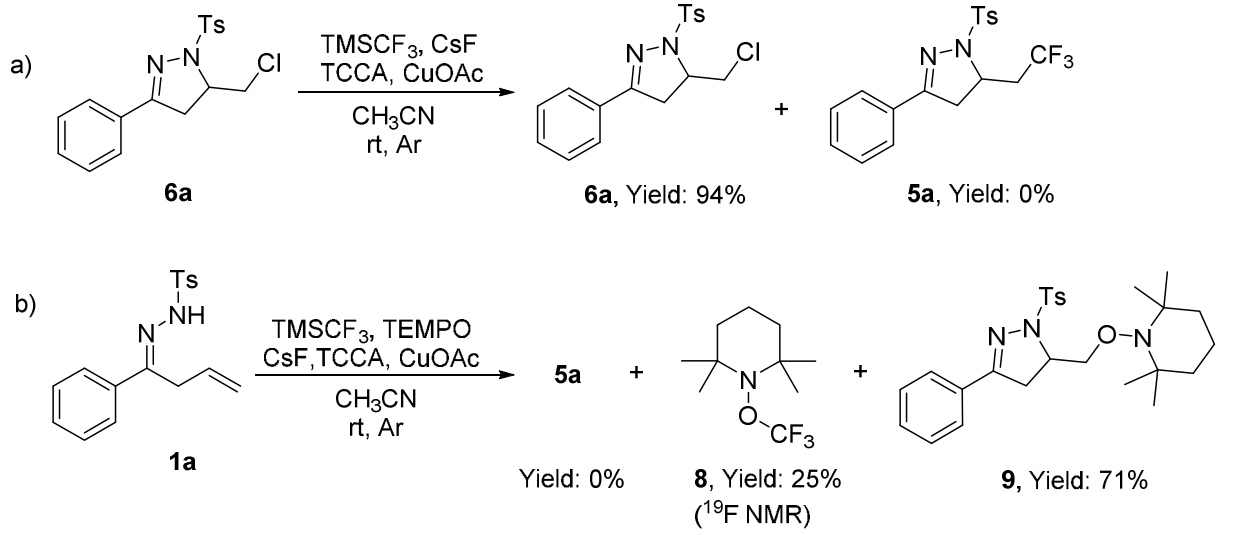


5a **7** **5an**

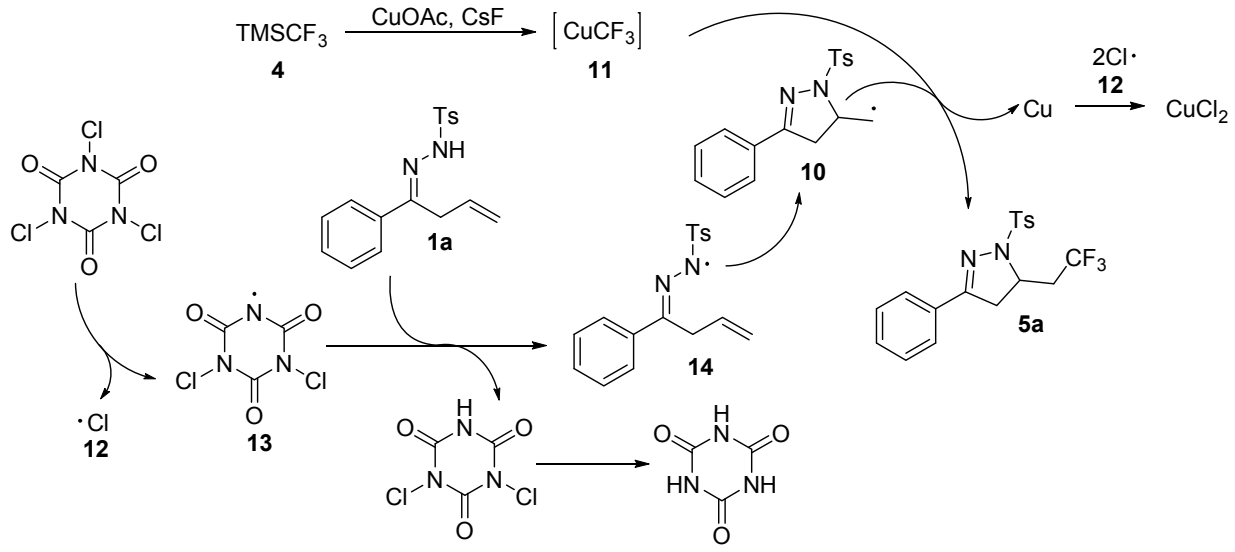
To consider the reaction mechanism, some control experiments were carried out (Scheme 3). Firstly, chlorinated product **6a** obtained at the beginning of this work was used as substrate to carry out the reaction under the standard reaction conditions, but there was no trifluoromethylated product **5a** formed, and **6a** was recovered in 94% yield (Scheme 3, a). This result indicated that desired product **5a** was not produced from the **6a**. Next, TEMPO was added into the reaction of hydrazones **1a** under the standard conditions. The product **5a** was not produced, but products **8** and **9** were formed in 25% and 71% yields, respectively (Scheme 3, b). This meant that the reaction proceeded in radical manner, and the radical **10** was the major intermediate (Scheme 4).

Based on the experimental results and literature,[17] a mechanism was proposed finally. As showed in Scheme 4, a trifluoromethyl copper complex **11** was formed firstly when $TMSCF_3$ was stirred with CuOAc and CsF.[18] The decomposition of TCCA afforded chlorine radical **12** and radical **13**, which abstracted a hydrogen from hydrazone **1a** to produce radical **14**. TCCA was finally converted into isocyanuric acid, which was detected from reaction mixture. Cyclization of radical **14** afforded carbon radical **10**, which combined the trifluoromethyl group from complex **11** to give the final product **5a**.

Scheme 3. Control Experiments for Mechanism



Scheme 4. Proposed Mechanism



CONCLUSIONS

In summary, an efficient cascade cyclization/trifluoromethylation reaction of *β,γ*-unsaturated hydrazones has been developed by using $TMSCF_3$ as CF_3 source and TCCA acid as promoter. Both

of the low cost and commercial availability of $TMSCF_3$ and TCCA make this process practical for preparation of trifluoroethyl pyrazolines. It is further demonstrated that TCCA can be an effective promoter for trifluoromethylation by using $TMSCF_3$ as trifluoromethylating reagent.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in flame-dried glassware with magnetic stirring bar and sealed with a rubber septum. The solvents were distilled by standard methods. Reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Silica gel column chromatography was carried out using silica Gel 60 (230–400 mesh). Analytical thin layer chromatography (TLC) was done using silica Gel (silica gel 60 F254). TLC plates were analyzed by an exposure to ultraviolet (UV) light and/or submersion in phosphomolybdic acid solution or submersion in $KMnO_4$ solution or in Iodine vapor. NMR experiments were carried out in deuterochloroform ($CDCl_3$) or deuterated acetone ($(CD_3)_2CO$). ^1H NMR, $^{13}C\{^1H\}$ NMR spectra were recorded at 400 MHz or 600 MHz and 100 MHz or 150 MHz spectrometers, respectively.^{19}F NMR spectra were recorded at 376 MHz or 564 MHz spectrometers. Chemical shifts are reported as δ values relative to internal TMS (δ 0.00 for ^1H NMR), chloroform (δ 7.26 for ^1H NMR), acetone (δ 2.05 for ^1H NMR), chloroform (δ 77.00 for $^{13}C\{^1H\}$ NMR), and acetone (δ 206.26 for $^{13}C\{^1H\}$ NMR) in parts per million (ppm). The following abbreviations are used for the multiplicities: s: singlet, d: doublet, dd: doublet of doublet, t: triplet, q: quartet, m: multiplet, br: broad signal for proton spectra; Coupling constants (J) are reported in Hertz (Hz). Melting points were uncorrected. High resolution mass spectra (HRMS) were recorded on MicroTOF-QII mass instrument (ESI).

General Procedure for the Synthesis of CF_3-Containing Pyrazolines 5. Under argon atmosphere, $TMSCF_3$ (179.0 mg, 1.3 mmol, 4.2 equiv) was added into a suspension of CuOAc

(129.0 mg, 1.1 mmol, 3.5 equiv) and CsF (191.0 mg, 1.3 mmol, 4.2 equiv) in dried MeCN (4 mL) at room temperature. After the reaction mixture was stirred at room temperature for 30 min, TCCA (0.2 mmol, 0.67 equiv) was added into the reaction mixture followed by addition of hydrazones **1** (0.3 mmol) immediately. The mixture was stirred at room temperature, and the reaction was monitored by thin layer chromatography (TLC) until the starting material was not detected. The reaction mixture was then quenched with water and extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was evaporated off under vacuum. The residue was purified by silica gel column chromatography (petroleumether : EtOAc = 3 : 1) to afford the desired products **5** and by-products **6**.

3-Phenyl-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5a)****:* 92 mg, 80% yield, white solid, mp 167−169 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4, 2H), 7.66 (d, J = 7.2, 2H), 7.44−7.38 (m, 3H), 7.31 (d, J = 7.8, 2H), 3.93−3.87 (m, 1H), 3.51−3.42 (m, 1H), 3.30 (dd, J = 17.4, 10.8 Hz, 1H), 3.01 (dd, J = 17.4, 10.2 Hz, 1H), 2.61−2.52 (m, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 157.6, 144.8, 130.9, 130.8, 130.2, 129.7, 128.9, 128.7, 126.9, 125.6 (q, J = 275.4 Hz), 56.8 (q, J = 3.0 Hz), 40.1 (q, J = 27.0 Hz), 40.0, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.55 (t, J = 10.9 Hz); HRMS (ESI): calcd for $C_{18}H_{17}F_3N_2O_2SNa$ $[M + Na]^+$ 405.0855, found 405.0854.

3-(m-Tolyl)-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5b)****:* 77 mg, 65% yield, white solid, mp 151−153 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4, 2H), 7.50 (s, 1H), 7.43 (d, J = 7.8, 1H), 7.31 (d, J = 7.8, 2H), 7.27 (t, J = 7.8, 1H), 7.24 (d, J = 7.2, 1H), 3.90−3.84 (m, 1H), 3.50−3.41 (m, 1H), 3.29 (dd, J = 17.4, 10.8 Hz, 1H), 2.99 (dd, J = 17.4, 10.8 Hz, 1H), 2.60−2.50 (m, 1H), 2.40 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 157.7, 144.7, 138.5, 131.7, 130.8, 130.1, 129.7, 128.9, 128.6, 127.4, 125.6 (q, J = 275.3 Hz), 124.1, 56.7 (q, J = 3.0 Hz), 40.1 (q, J = 27.6 Hz), 40.0, 21.6, 21.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.55 (t, J = 10.9 Hz); HRMS (ESI): calcd for $C_{19}H_{19}F_3N_2O_2SNa$ $[M + Na]+$ 419.1012, found 419.1017.

3-(p-Tolyl)-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5c)****:* 77 mg, 65% yield, white solid, mp 170−171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4, 2H), 7.55 (d, J = 8.4, 2H), 7.30 (d, J = 8.0, 2H), 7.19 (d, J = 8.0, 2H), 3.90−3.81 (m, 1H), 3.52−3.39 (m, 1H), 3.28 (dd, J = 17.2, 10.8 Hz, 1H), 2.98 (dd, J = 17.2, 10.4 Hz, 1H), 2.63−2.51 (m, 1H), 2.39 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 157.6, 144.7, 141.4, 130.8, 129.7, 129.4, 128.4, 127.5, 126.9, 125.6 (q, J = 275.7 Hz), 56.7 (q, J = 2.9 Hz), 40.1 (q, J = 27.2 Hz), 40.0, 21.6, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.56 (t, J = 10.9 Hz); HRMS (ESI): calcd for $C_{19}H_{19}F_3N_2O_2SNa$ $[M + Na]^+$ 419.1012, found 419.1021.

3-(4-Methoxyphenyl)-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5d)****:* 90 mg, 73% yield, white solid, mp 191−193 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4, 2H), 7.60 (d, J = 8.4, 2H), 7.30 (d, J = 8.4, 2H), 6.89 (d, J = 8.4, 2H), 3.88−3.84 (m, 1H), 3.83 (s, 3H), 3.49−3.40 (m, 1H), 3.26 (dd, J = 17.4, 10.8 Hz, 1H), 2.98 (dd, J = 17.4, 10.8 Hz, 1H), 2.59−2.50 (m, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 161.7, 157.3, 144.7, 130.8, 129.6, 128.9, 128.6, 125.6 (q, J = 275.6 Hz), 122.8, 114.1, 56.7 (q, J = 3.0 Hz), 55.4, 40.1 (q, J = 27.2 Hz), 40.0, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.56 (t, J = 10.9 Hz); HRMS (ESI): calcd for $C_{19}H_{19}F_3N_2O_3SNa$ $[M + Na]^+$ 435.0961, found 435.0968.

3-(2-Chlorophenyl)-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5e)****:* 70 mg, 56% yield, white solid, mp 125−127 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, J = 8.4, 2H), 7.56−7.54 (m, 1H), 7.38−7.32 (m, 4H), 7.29−7.26 (m, 1H), 3.94−3.88 (m, 1H), 3.51−3.45 (m, 1H), 3.42 (dd, J = 18.0, 10.2 Hz, 1H), 3.01 (dd, J = 17.4, 10.8 Hz, 1H), 2.64−2.57 (m, 1H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 157.8, 145.0, 132.8, 131.3, 130.8, 130.6, 130.4, 129.7, 129.6, 129.0, 126.9, 125.5 (q, J = 275.4 Hz), 57.4 (q, J = 3.0 Hz), 43.0, 39.9 (q, J = 27.5 Hz), 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.60 (t, J = 10.9 Hz); HRMS (ESI): calcd for $C_{18}H_{16}ClF_3N_2O_2SNa$ $[M + Na]^+$ 439.0465, found 439.0470.

3-(3-Chlorophenyl)-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5f)****:* 92 mg, 74% yield, white solid, mp 165−166 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4, 2H), 7.64 (t, J = 1.8 Hz, 1H), 7.52−7.50 (m, 1H), 7.40−7.38 (m, 1H), 7.33−7.31 (m, 3H), 3.95−3.89 (m, 1H), 3.50−3.41 (m, 1H), 3.28 (dd, J = 17.4, 10.8 Hz, 1H), 3.01 (dd, J = 17.4, 10.8 Hz, 1H), 2.60−2.54 (m, 1H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 156.3, 145.0, 134.9, 132.0, 130.8, 130.7, 130.0, 129.8, 128.8, 126.8, 125.5 (q, J = 275.6 Hz), 125.0, 56.9 (q, J = 3.0 Hz), 40.0 (q, J = 27.5 Hz), 39.8, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.53 (t, J = 10.9 Hz); HRMS (ESI): calcd for $C_{18}H_{16}ClF_3N_2O_2SNa$ $[M + Na]^+$ 439.0465, found 439.0469.

3-(4-Chlorophenyl)-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5g)****:* 94 mg, 75% yield, white solid, mp 136−138 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4, 2H), 7.59 (d, J = 8.4, 2H), 7.36 (d, J = 8.4, 2H), 7.32 (d, J = 7.8, 2H), 3.93−3.87 (m, 1H), 3.50−3.42 (m, 1H), 3.28 (dd, J = 16.8, 10.8 Hz, 1H), 2.98 (dd, J = 16.8, 10.8 Hz, 1H), 2.61−2.52 (m, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 156.5, 144.9, 137.0, 130.8, 129.7, 129.0, 128.9, 128.7, 128.1, 125.5 (q, J = 272.6 Hz), 57.0 (q, J = 3.0 Hz), 40.0 (q, J = 27.5 Hz), 39.8, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.56 (t, J = 10.5 Hz); HRMS (ESI): calcd for $C_{18}H_{16}ClF_3N_2O_2SNa$ $[M + Na]^+$ 439.0465, found 439.0468.

3-(4-Fluorophenyl)-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5h)****:* 76 mg, 63% yield, white solid, mp 206−207 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4, 2H), 7.67−7.63 (m, 2H), 7.32 (d, J = 8.4, 2H), 7.09−7.05 (m, 2H), 3.93−3.87 (m, 1H), 3.50−3.41 (m, 1H), 3.28 (dd, J = 17.4, 10.8 Hz, 1H), 2.99 (dd, J = 17.4, 10.8 Hz, 1H), 2.61−2.51 (m, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.8 (d, J = 250.7), 156.5, 144.9, 130.8, 129.7, 128.9 (d, J = 8.7), 128.8, 126.5 (d, J = 3.0 Hz), 125.6 (q, J = 275.4 Hz), 115.9 (d, J = 21.9), 56.9 (q, J = 3.3 Hz), 40.0 (q, J = 27.3 Hz), 39.9, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.55 (t, J = 10.5 Hz), -108.77; HRMS (ESI): calcd for $C_{18}H_{16}F_4N_2O_2SNa$ $[M + Na]^+$ 423.0761, found 423.0763.

3-(4-Bromophenyl)-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5i)****:* 105 mg, 76% yield, white solid, mp 197−198 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8, 2H), 7.52 (s, 4H), 7.32 (d, J = 7.8, 2H), 3.93−3.88 (m, 1H), 3.50−3.42 (m, 1H), 3.28 (dd, J = 17.4, 10.8 Hz, 1H), 2.98 (dd, J = 17.4, 10.8 Hz, 1H), 2.61−2.51 (m, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 156.6, 144.9, 132.0, 130.8, 129.7, 129.1, 128.9, 128.3, 125.5 (q, J = 275.7 Hz), 125.4, 57.0 (q, J = 2.0 Hz), 40.0 (q, J = 27.5 Hz), 39.8, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.55 (t, J = 10.5 Hz); HRMS (ESI): calcd for $C_{18}H_{16}BrF_3N_2O_2SNa$ $[M + Na]^+$ 482.9960, found 482.9967.

1-Tosyl-5-(2,2,2-trifluoroethyl)-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole ***(5j)****:* 97 mg, 72% yield, white solid, mp 152−154 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 7.8 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 3.98−3.93 (m, 1H), 3.52−3.44 (m, 1H), 3.33 (dd, J = 16.8, 10.8 Hz, 1H), 3.02 (dd, J = 16.8, 10.2 Hz, 1H), 2.63−2.54 (m, 1H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 156.1, 145.1, 133.5, 132.5 (q, J = 32.7 Hz), 130.8, 129.8, 128.8, 127.1, 125.7 (q, J = 3.6 Hz), 125.5 (q, J = 275.1 Hz), 123.7 (q, J = 271.0 Hz), 57.1 (q, J = 3.2 Hz), 40.0 (q, J = 27.5 Hz), 39.8, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.39, -64.54 (t, J = 10.5 Hz); HRMS (ESI): calcd for $C_{19}H_{16}F_6N_2O_2SNa$ $[M + Na]^+$ 473.0729, found 473.0735.

3-(Thiophen-2-yl)-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5k)****:* 54 mg, 46% yield, white solid, mp 124−125 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8 Hz, 2H), 7.44−7.43 (m, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.18−7.17 (m, 1H), 7.03−7.02 (m, 1H), 3.90−3.84 (m, 1H), 3.47−3.39 (m, 1H), 3.26 (dd, J = 17.4, 10.8 Hz, 1H), 3.01 (dd, J = 16.8, 10.8 Hz, 1H), 2.60−2.51 (m, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 153.1, 144.8, 133.6, 130.6, 129.7, 129.6, 129.4, 129.0, 127.5, 125.5 (q, J = 275.6 Hz), 56.9 (q, J = 3.2 Hz), 40.6, 39.9 (q, J = 27.5 Hz), 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.57 (t, J = 10.5 Hz); HRMS (ESI): calcd for $C_{16}H_{15}F_3N_2O_2S_2Na$ $[M + Na]^+$ 411.0419, found 411.0434.

tert-Butyl 3-(1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazol-3-yl)-1H-indole-1-

carboxylate ***(5l)****:* 117 mg, 75% yield, white solid, mp 165−167 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d, J = 7.2 Hz, 1H), 8.12 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.66 (s, 1H), 7.43−7.38 (m, 2H), 7.26 (d, J = 6.6 Hz, 2H), 3.89−3.83 (m, 1H), 3.53−3.45 (m, 1H), 3.30 (dd, J = 16.8, 10.8 Hz, 1H), 3.04 (dd, J = 16.8, 10.8 Hz, 1H), 2.62−2.52 (m, 1H), 2.36 (s, 3H), 1.67 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 153.1, 149.0, 144.7, 135.7, 130.7, 129.7, 128.9, 127.8, 126.9, 125.7, 125.6 (q, J = 275.7 Hz), 124.1, 122.9, 115.1, 112.8, 85.0, 55.9 (q, J = 3.3 Hz), 40.7, 40.0 (q, J = 27.2 Hz), 28.1, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.54 (t, J = 10.5 Hz); HRMS (ESI): calcd for $C_{25}H_{26}F_3N_3O_4SNa$ $[M + Na]^+$ 544.1488, found 544.1490.

3-(tert-Butyl)-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5m)****:* 96 mg, 88% yield, white solid, mp 119−120 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 3.66−3.61 (m, 1H), 3.37−3.28 (m, 1H), 2.82 (dd, J = 17.4, 10.2 Hz, 1H), 2.56 (dd, J = 17.4, 10.8 Hz, 1H), 2.49−2.44 (m, 1H), 2.43 (s, 3H), 1.06 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 169.8, 144.6, 130.3, 129.3, 129.1, 125.6 (q, J = 275.4 Hz), 56.8 (q, J = 3.0 Hz), 40.0 (q, J = 27.3 Hz), 39.0, 34.2, 27.7, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.69 (t, J = 10.9 Hz); HRMS (ESI): calcd for $C_{16}H_{21}F_3N_2O_2SNa$ $[M + Na]^+$ 385.1171, found 385.1168.

3-Cyclohexyl-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5n)****:* 69 mg, 59% yield, white solid, mp 144−145 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 3.67−3.61 (m, 1H), 3.37−3.29 (m, 1H), 2.78 (dd, J = 17.4, 10.2 Hz, 1H), 2.57 (dd, J = 17.4, 10.2 Hz, 1H), 2.48−2.39 (m, 4H), 2.28−2.24 (m, 1H), 1.75−1.65 (m, 5H), 1.30−1.13 (m, 5H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 166.6, 144.6, 130.5, 129.4, 129.0, 125.6 (q, J = 275.6 Hz), 56.0 (q, J = 3.0 Hz), 40.5, 40.0 (q, J = 27.3 Hz), 39.1, 30.2, 29.8, 25.7, 25.6, 25.5, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.69 (t, J = 10.5 Hz); HRMS (ESI): calcd for $C_{18}H_{23}F_3N_2O_2SNa$ $[M + Na]^+$ 411.1325, found 411.1332.

3-Isopropyl-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5o)****:* 72 mg, 69% yield,

white solid, mp 118−119 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 3.69−3.63 (m, 1H), 3.38−3.29 (m, 1H), 2.79 (dd, J = 17.4, 10.2 Hz, 1H), 2.60−2.54 (m, 2H), 2.50−2.40 (m, 4H), 1.05 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 167.4, 144.6, 130.5, 129.4, 129.0, 125.6 (q, J = 275.4 Hz), 56.3 (q, J = 3.0 Hz), 40.1, 40.0 (q, J = 27.3 Hz), 29.7, 21.6, 19.9, 19.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.71 (t, J = 10.9 Hz); HRMS (ESI): calcd for $C_{15}H_{19}F_3N_2O_2SNa$ $[M + Na]^+$ 371.1012, found 371.1009.

3-Phenethyl-1-tosyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole ***(5p)****:* 75 mg, 61% yield, white solid, mp 64−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.26−7.20 (m, 3H), 7.05 (d, J = 7.2 Hz, 2H), 3.72−3.63 (m, 1H), 3.39−3.26 (m, 1H), 2.90−2.81 (m, 1H), 2.76 (dd, J = 14.0, 7.6 Hz, 1H), 2.69 (dd, J = 17.6, 10.4, Hz, 1H), 2.62−2.49 (m, 3H), 2.45 (s, 3H), 2.43−2.34 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 162.2, 144.7, 140.1, 130.7, 129.6, 128.9, 128.5, 128.1, 126.4, 125.5 (q, J = 275.3 Hz), 56.1 (q, J = 3.2 Hz), 42.7, 39.9 (q, J = 27.2 Hz), 32.4, 31.5, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.70 (t, J = 10.5 Hz); HRMS (ESI): calcd for $C_{20}H_{21}F_3N_2O_2SNa$ $[M + Na]^+$ 433.1168, found 433.1175.

Benzyl 3-phenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5aa)****:* 74 mg, 68% yield, white solid, mp 119−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.73 (m, 2H), 7.47−7.32 (m, 8H), 5.37−5.29 (m, 2H), 4.75−4.67 (m, 1H), 3.52 (dd, J = 18.0, 11.2 Hz, 1H), 3.18 (dd, J = 17.6, 5.6 Hz, 1H), 3.04 (br, 1H), 2.41−2.24 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.3, 152.7, 135.9, 130.8, 130.5, 128.6, 128.5, 128.3, 128.2, 126.7, 125.6 (q, J = 275.9 Hz), 67.8, 53.0, 38.4, 37.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.71; HRMS (ESI): calcd for $C_{19}H_{17}F_3N_2O_2Na$ $[M + Na]^+$ 385.1134, found 385.1141.

Benzyl 3-(m-tolyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5ab)****:* 62 mg, 55% yield, white solid, mp 140−141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.2 Hz, 2H), 7.35−7.32 (m, 1H), 7.29 (t, J = 7.8 Hz,

1H), 7.23 (d, *J* = 7.8 Hz, 1H), 5.36−5.30 (m, 2H), 4.72−4.67 (m, 1H), 3.50 (dd, *J* = 17.4, 11.4 Hz, 1H), 3.17 (dd, *J* = 18.0, 5.4 Hz, 1H), 3.03 (br, 1H), 2.38 (s, 3H), 2.35−2.28 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 154.5, 152.7, 138.4, 136.0, 131.3, 130.7, 128.6, 128.5, 128.3, 128.2, 127.2, 125.6 (q, *J* = 275.4 Hz), 124.0, 67.9. 53.0, 38.5, 37.5, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.45; HRMS (ESI): calcd for $C_{20}H_{19}F_3N_2O_2Na$ $[M + Na]^+$ 399.1291, found 399.1293.

Benzyl 3-(p-tolyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5ac)****:* 70 mg, 62% yield, white solid, mp 158−159 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.35−7.32 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 5.36-5.30 (m, 2H), 4.71-4.66 (m, 1H), 3.48 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.15 (dd, *J* = 17.4, 5.4 Hz, 1H), 3.04 (br, 1H), 2.38 (s, 3H), 2.35−2.25 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 154.4, 152.7, 140.8, 136.0, 129.3, 128.5, 128.3, 128.2, 128.1, 126.7, 125.6 (q, *J* = 275.9 Hz), 67.8, 53.0, 38.4, 37.5, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.47; HRMS (ESI): calcd for $C_{20}H_{19}F_3N_2O_2Na$ $[M + Na]^+$ 399.1291, found 399.1294.

Benzyl 3-(4-methoxyphenyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5ad)****:* 67 mg, 57% yield, white solid, mp 151−152 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.40−7.33 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.36-5.29 (m, 2H), 4.71-4.65 (m, 1H), 3.84 (s, 3H), 3.49 (dd, *J* = 17.6, 11.2 Hz, 1H), 3.14 (dd, *J* = 18.0, 5.6 Hz, 1H), 3.04 (br, 1H), 2.37−2.23 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 161.5, 154.1, 152.4, 136.0, 128.5, 128.4, 128.3, 128.2, 128.1, 125.6 (q, *J* = 275.9 Hz), 123.4, 67.8, 55.4, 52.9, 38.5, 37.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.72; HRMS (ESI): calcd for $C_{20}H_{20}F_3N_2O_3$ $[M + H]^+$ 393.1421, found 393.1417.

Benzyl 3-(3-methoxyphenyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5ae)****:* 74 mg, 63% yield, white solid, mp 135−136 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.39−7.36 (m, 2H), 7.34−7.30 (m, 3H), 7.26−7.25 (m, 1H), 6.98−6.96 (m, 1H), 5.35−5.30 (m,

2H), 4.72−4.67 (m, 1H), 3.84 (s, 3H), 3.50 (dd, J = 17.4, 11.4 Hz, 1H), 3.16 (dd, J = 17.4, 5.4 Hz, 1H), 3.02 (br, 1H), 2.35−2.26 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 159.7, 154.3, 152.5, 135.9, 132.1, 129.7, 128.6, 128.3, 128.2, 125.6 (q, J = 275.7 Hz), 119.4, 116.8, 111.5, 67.9, 55.4, 53.0, 38.5, 37.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.72; HRMS (ESI): calcd for $C_{20}H_{19}F_3N_2O_3Na$ [M + Na]$^+$ 415.1240, found 415.1236.

Benzyl 3-(3-chlorophenyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5af)****:* 60 mg, 50% yield, white solid, mp 120−121 ^{o}C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.45 (d, J = 7.8 Hz, 2H), 7.40−7.38 (m, 3H), 7.35−7.33 (m, 2H), 5.36−5.30 (m, 2H), 4.74−4.69 (m, 1H), 3.49 (dd, J = 18.0, 11.4 Hz, 1H), 3.14 (dd, J = 18.0, 5.4 Hz, 1H), 3.03 (br, 1H), 2.37−2.28 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 152.9, 152.6, 135.8, 134.8, 132.6, 130.4, 129.9, 128.6, 128.4, 128.3, 126.7, 125.5 (q, J = 275.9 Hz), 124.8, 68.0, 53.3, 38.3, 37.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.45; HRMS (ESI): calcd for $C_{19}H_{16}ClF_3N_2O_2Na$ [M + Na]$^+$ 419.0745, found 419.0749.

Benzyl 3-(4-chlorophenyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5ag)****:* 69 mg, 58% yield, white solid, mp 136−137 ^{o}C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 6.8 Hz, 2H), 7.41−7.32 (m, 5H), 5.36−5.29 (m, 2H), 4.75−4.67 (m, 1H), 3.49 (dd, J = 18.0, 11.2 Hz, 1H), 3.15 (dd, J = 18.0, 5.6 Hz, 1H), 3.03 (br, 1H), 2.39−2.25 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 153.2, 152.5, 136.5, 135.9, 129.4, 129.0, 128.6, 128.4, 128.3, 128.0, 125.6 (q, J = 276.0 Hz), 68.0, 53.2, 38.4, 37.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.47; HRMS (ESI): calcd for $C_{19}H_{16}ClF_3N_2O_2Na$ [M + Na]$^+$ 419.0745, found 419.0748.

Benzyl 3-(3-fluorophenyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5ah)****:* 40 mg, 35% yield, white solid, mp 114−115 ^{o}C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.49−7.45 (m, 4H), 7.40−7.33 (m, 4H), 7.13−7.10 (m, 1H), 5.35-5.30 (m, 2H), 4.75−4.70 (m, 1H), 3.50 (dd, J = 17.4, 10.8 Hz, 1H), 3.15 (dd, J = 18.0, 5.4 Hz, 1H), 3.04 (br, 1H), 2.37−2.28 (m, 1H); $^{13}C\{^1H\}$ NMR (150

MHz, $CDCl_3$) δ 162.8 (d, J = 245.4 Hz), 153.1, 152.6, 135.8, 133.0 (d, J = 8.1 Hz), 130.3 (d, J = 8.1 Hz), 128.6, 128.4, 128.3, 125.5 (q, J = 275.9 Hz), 122.5 (d, J = 3.0 Hz), 117.4 (d, J = 21.3 Hz), 113.5 (d, J = 23.1 Hz), 68.0, 53.2, 38.3, 37.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.72, -112.59; HRMS (ESI): calcd for $C_{19}H_{16}F_4N_2O_2Na$ $[M + Na]^+$ 403.1040, found 403.1048.

Benzyl 3-(thiophen-2-yl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5ai)****:* 64 mg, 58% yield, white solid, mp 124−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.42 (m, 3H), 7.40−7.31 (m, 3H), 7.26 (d, J = 3.2 Hz, 1H), 7.07−7.05 (m, 1H), 5.35−5.27 (m, 2H), 4.73−4.65 (m, 1H), 3.52 (dd, J = 17.6, 11.2 Hz, 1H), 3.17 (dd, J = 17.6, 5.6 Hz, 1H), 3.02 (br, 1H), 2.38−2.24 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 152.5, 149.9, 135.9, 134.3, 129.0, 128.8, 128.5, 128.3, 128.2, 127.5, 125.5 (q, J = 275.9 Hz), 67.9, 53.1, 39.2, 37.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.73; HRMS (ESI): calcd for $C_{17}H_{15}F_3N_2O_2SNa$ $[M + Na]^+$ 391.0699, found 391.0708.

Methyl 3-phenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5aj)****:* 52 mg, 61% yield, white solid, mp 122−123 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, J = 7.8 Hz, 2H), 7.44−7.39 (m, 3H), 4.72−4.67 (m, 1H), 3.90 (s, 3H), 3.53 (dd, J = 18.0, 11.4 Hz, 1H), 3.01 (dd, J = 18.0, 5.4 Hz, 1H), 3.08 (br, 1H), 2.37−2.28 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.4, 153.3, 130.7, 130.5, 128.7, 126.7, 125.6 (q, J = 275.7 Hz), 53.4, 53.0 (q, J = 2.9 Hz), 38.3, 37.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.68 (t, J = 10.9 Hz); HRMS (ESI): calcd for $C_{13}H_{13}F_3N_2O_2Na$ $[M + Na]^+$ 309.0821, found 309.0811.

Methyl 3-(p-tolyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5ak)****:* 50 mg, 55% yield, white solid, mp 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 4.72−4.64 (m, 1H), 3.90 (s, 3H), 3.51 (dd, J = 17.6, 11.2 Hz, 1H), 3.16 (dd, J = 18.0, 5.6 Hz, 1H), 3.08 (br, 1H), 2.38 (s, 3H), 2.36−2.67 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.5, 153.3, 140.9, 129.4, 127.9, 125.7, 125.6 (q, J = 275.9 Hz), 53.4, 52.9 (q, J = 3.3 Hz), 38.4, 37.4, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.88 (t, J = 10.5 Hz); HRMS (ESI): calcd for

$C_{14}H_{15}F_3N_2O_2Na$ $[M + Na]^+$ 323.0978, found 323.0978.

Methyl 3-(4-bromophenyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5al)****:* 61 mg, 56% yield, white solid, mp 112−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 4.74−4.67 (m, 1H), 3.90 (s, 3H), 3.51 (dd, J = 18.0, 11.2 Hz, 1H), 3.16 (dd, J = 18.0, 5.6 Hz, 1H), 3.08 (br, 1H), 2.40−2.26 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 153.3, 153.2, 131.9, 129.7, 128.1, 125.6 (q, J = 275.9 Hz), 124.9, 53.5, 53.0 (q, J = 3.2 Hz), 38.2, 37.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.67 (t, J = 10.5 Hz); HRMS (ESI): calcd for $C_{13}H_{12}BrF_3N_2O_2Na$ $[M + Na]^+$ 386.9926, found 386.9917.

Methyl 3-(tert-butyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5am)****:* 36 mg, 45% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55−4.48 (m, 1H), 3.83 (s, 3H), 3.11 (dd, J = 18.0, 11.2 Hz, 1H), 2.95 (br, 1H), 2.78 (dd, J = 18.0, 5.2 Hz, 1H), 2.28−2.14 (m, 1H), 1.21 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 166.0, 153.4, 125.6 (q, J = 275.9 Hz), 53.3, 52.6 (q, J = 2.9 Hz), 37.3, 37.0 (q, J = 23.1 Hz), 34.0, 27.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.66 (t, J = 10.5 Hz); HRMS (ESI): calcd for $C_{11}H_{17}F_3N_2O_2Na$ $[M + Na]^+$ 289.1134, found 289.1128.

tert-Butyl 3-phenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5an)****:* 66 mg, 67% yield, white solid, mp 113−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 3.6 Hz, 2H), 7.41−7.39 (m, 3H), 4.68−4.62 (m, 1H), 3.51 (dd, J = 18.0, 11.6 Hz, 1H), 3.14 (dd, J = 18.0, 5.2 Hz, 1H), 2.97 (br, 1H), 2.37−2.24 (m, 1H), 1.58 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 153.3, 151.7, 131.1, 130.2, 128.6, 126.6, 125.7 (q, J = 272.4 Hz), 82.1, 52.8 (q, J = 3.0 Hz), 38.6, 38.0, 28.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.75; HRMS (ESI): calcd for $C_{16}H_{19}F_3N_2O_2Na$ $[M + Na]^+$ 351.1291, found 351.1297.

tert-Butyl 3-(p-tolyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5ao)****:* 60 mg, 58% yield, white solid, mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.6 Hz, 2H), 7.63 (d, J = 7.6 Hz, 2H), 4.65−4.60 (m, 1H), 3.48 (dd, J = 17.6, 11.2 Hz, 1H), 3.12 (dd, J = 17.6, 5.6 Hz,

1H), 2.95 (br, 1H), 2.37 (s, 3H), 2.33−2.22 (m, 1H), 1.57 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 153.3, 151.6, 140.5, 129.8, 128.3, 126.6, 125.7 (q, J = 275.8 Hz), 82.0, 52.7 (q, J = 2.5 Hz), 38.7, 37.8, 28.3, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.01; HRMS (ESI): calcd for $C_{17}H_{21}F_3N_2O_2Na$ $[M + Na]^+$ 365.1447, found 365.1449.

tert-Butyl 3-(4-bromophenyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5ap)****:* 67 mg, 55% yield, white solid, mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 4.68−4.61 (m, 1H), 3.48 (dd, J = 17.6, 11.2 Hz, 1H), 3.11 (dd, J = 17.6, 5.6 Hz, 1H), 2.96 (br, 1H), 2.38−2.24 (m, 1H), 1.57 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 152.2, 151.4, 131.8, 130.1, 128.1, 125.6 (q, J = 275.9 Hz), 124.6, 82.3, 53.0 (q, J = 3.3 Hz), 38.5, 38.0, 28.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.99; HRMS (ESI): calcd for $C_{16}H_{18}BrF_3N_2O_2Na$ $[M + Na]^+$ 429.0396, found 429.0408.

tert-Butyl 3-(4-chlorophenyl)-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxylate ***(5aq)****:* 65 mg, 53% yield, white solid, mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 4.69−4.61 (m, 1H), 3.48 (dd, J = 17.6, 11.2 Hz, 1H), 3.11 (dd, J = 17.6, 5.2 Hz, 1H), 2.97 (br, 1H), 2.38−2.24 (m, 1H), 1.57 (s, 9H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 152.1, 136.2, 129.6, 128.9, 127.9, 125.6 (q, J = 275.9 Hz), 82.3, 53.0 (q, J = 3.2 Hz), 38.5, 38.0, 28.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.97; HRMS (ESI): calcd for $C_{16}H_{18}ClF_3N_2O_2Na$ $[M + Na]^+$ 385.0901, found 385.0902.

1-(3-Phenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one ***(5ar)****:* 22 mg, 27% yield, white solid, mp 120−121 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.46−7.42 (m, 3H), 4.86−4.81 (m, 1H), 3.49 (dd, J = 18.0, 11.4 Hz, 1H), 3.20 (dd, J = 18.0, 5.4 Hz, 1H), 3.17−3.11 (m, 1H), 2.39 (s, 3H), 2.33−2.24 (m, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 169.5, 154.3, 131.0, 130.6, 128.8, 126.5, 125.7 (q, J = 275.7 Hz), 51.6 (q, J = 3.2 Hz), 38.0, 36.4 (q, J = 26.9 Hz), 22.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.20 (t, J = 10.9 Hz); HRMS (ESI): calcd for

$C_{13}H_{13}F_3N_2ONa$ $[M + Na]^+$ 293.0872, found 293.0881.

2-Methyl-1-(3-phenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one ***(5as)****:* 30 mg, 34% yield, white solid, mp 86−87 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74−7.72 (m, 2H), 7.46−7.41 (m, 3H), 4.85−4.80 (m, 1H), 3.50−3.42 (m, 2H), 3.18 (dd, J = 18.0, 5.4 Hz, 1H), 3.15−3.06 (m, 1H), 2.33−2.24 (m, 1H), 1.23 (d, J = 7.2 Hz, 3H), 1.18 (d, J = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 176.0, 154.0, 131.1, 130.4, 128.7, 126.5, 125.8 (q, J = 275.9 Hz), 51.7 (q, J = 3.0 Hz), 37.7, 36.4 (q, J = 26.9 Hz), 32.0, 18.9, 18.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.54 (t, J = 10.9 Hz); HRMS (ESI): calcd for $C_{15}H_{18}F_3N_2O$ $[M + H]^+$ 299.1366, found 299.1366.

5-(Chloromethyl)-3-phenyl-1-tosyl-4,5-dihydro-1H-pyrazole ***(6a)****:* 24 mg, 23% yield (Table 1, Entry 1), white solid, mp 126−127 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 7.2 Hz, 2H), 7.43−7.37 (m, 3H), 7.29 (d, J = 7.8 Hz, 2H), 4.19−4.12 (m, 2H), 3.80−3.77 (m, 1H), 3.24 (dd, J = 17.4, 10.8 Hz, 1H), 3.17 (dd, J = 17.4, 8.4 Hz, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 157.5, 144.6, 131.9, 130.8, 130.4, 129.6, 128.6, 128.5, 126.9, 61.9, 46.6, 38.6, 21.6; HRMS (ESI): calcd for $C_{17}H_{17}ClN_2O_2SNa$ $[M + Na]^+$ 371.0591, found 371.0599.

5-(Iodomethyl)-3-phenyl-1-tosyl-4,5-dihydro-1H-pyrazole ***(6b)****:* 58 mg, 44% yield, white solid, mp 141−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 6.8 Hz, 2H), 7.44−7.36 (m, 3H), 7.30 (d, J = 8.0 Hz, 2H), 4.08−4.00 (m, 1H), 3.83 (dd, J = 10.0, 3.2 Hz, 1H), 3.45 (t, J = 10.0 Hz, 1H), 3.32 (dd, J = 17.2, 10.8 Hz, 1H), 3.00 (dd, J = 17.6, 9.2 Hz, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.6, 144.6, 131.9, 130.8, 130.4, 129.7, 128.6, 128.5, 126.9, 62.2, 41.6, 21.6, 9.8; HRMS (ESI): calcd for $C_{17}H_{17}IN_2O_2SNa$ $[M + Na]^+$ 462.9948, found 462.9947.

5-(Bromomethyl)-3-phenyl-1-tosyl-4,5-dihydro-1H-pyrazole ***(6c)****:* 62 mg, 53% yield, white solid, mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 7.2 Hz, 2H), 7.44−7.37 (m, 3H), 7.30 (d, J = 8.0 Hz, 2H), 4.20−4.12 (m, 1H), 4.00 (dd, J = 10.0, 3.2 Hz, 1H),

3.62 (t, J = 9.6 Hz, 1H), 3.28 (dd, J = 17.6, 11.2 Hz, 1H), 3.12 (dd, J = 17.6, 8.8 Hz, 1H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.3, 144.6, 131.7, 130.8, 130.3, 129.7, 128.6, 128.5, 126.9, 61.8, 39.7, 35.2, 21.6; HRMS (ESI): calcd for $C_{17}H_{17}BrN_2O_2SNa$ $[M + Na]^+$ 415.0086, found 415.0094.

General Procedure I for the Synthesis of Compound 7. Substrate **5a** (76.48 mg, 0.20 mmol), NaOH (16.00 mg, 0.40 mmol, 2.0 equiv) and MeOH (3.0 mL) were added to a flask equipped with a magnetic stir bar under argon atmosphere. The mixture was stirred at 90 ^oC until the reaction was completed as monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleumether : EtOAc = 3 : 1) directly to give the corresponding product **7** in 94% yield as a white solid.

General Procedure II for the Synthesis of Compound 7. A solution of trifluoroethyl pyrazoline **5an** (65.67 mg, 0.20 mmol) and $CuCl_2$ (80.67 mg, 0.60 mmol, 3.0 equiv) in EtOH (4.0 mL) was stirred under reflux for 8 h. The reaction process was monitored by TLC until the starting material disappeared. The reaction mixture was then cooled to room temperature, and the solid was filtered off from the reaction mixture. The filtrate was concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (petroleumether : EtOAc = 3 : 1) directly to give the corresponding product **7** in 65% yield as a white solid.

*3-Phenyl-5-(2,2,2-trifluoroethyl)-1H-pyrazole **(7)**:* 42 mg, 94% yield (Synthesized by Procedure I), white solid, mp 118−120 ^oC; ^1H NMR (600 MHz, $CDCl_3$) δ 11.35 (br, 1H), 7.60 (d, J = 7.2 Hz, 2H), 7.43−7.40 (m, 2H), 7.37−7.34 (m, 1H), 6.54 (s, 1H), 3.45−3.41 (m, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 146.1, 141.6, 129.7, 129.1, 128.7, 125.5, 125.3 (q, J = 274.8 Hz), 103.4, 32.9 (q, J = 31.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.78 (t, J = 10.9 Hz); HRMS (ESI): calcd for $C_{11}H_9F_3N_2Na$ $[M + Na]^+$ 249.0610, found 249.0613.

Control Experiments.

Reaction of 6a with TCCA, Me_3SiCF_3, CsF, CuOAc.

Under argon atmosphere, Me_3SiCF_3 (179.0 mg, 1.3 mmol, 4.2 equiv) was added to a suspension of CuOAc (129.0 mg, 1.1 mmol, 3.5 equiv) and CsF (191.0 mg, 1.3 mmol, 4.2 equiv) in dried MeCN (4 mL) at room temperature. After the reaction mixture was stirred at room temperature for 30 min, TCCA (47 mg, 0.2 mmol, 0.67 equiv) was added to the reaction mixture. Subsequently, **6a** (0.3 mmol) was added to the system. The mixture was stirred at room temperature and monitored by thin layer chromatography (TLC). No desired product **5a** was observed and **6a** was recovered in 94% yield.

Reaction of TEMPO with TCCA, Me_3SiCF_3, CsF, CuOAc, and 1a.

Under argon atmosphere, $TMSCF_3$ (179.0 mg, 1.3 mmol, 4.2 equiv) was added to a suspension of CuOAc (129.0 mg, 1.1 mmol, 3.5 equiv) and CsF (191.0 mg, 1.3 mmol, 4.2 equiv) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 94.0 mg, 0.6 mmol, 2.0 equiv) in dried MeCN (4 mL) at room temperature. After the reaction mixture was stirred at room temperature for 30 min, *α*,*α*,*α*-trifluorotoluene (internal standard, 44.0 mg, 0.3 mmol) and TCCA were added to the reaction mixture. Subsequently, hydrazones **1a** (0.3 mmol) was added to the system. ^{19}F NMR analysis of this reaction mixture showed that TEMPO-CF_3 were formed in 25% and no desired product **5a** was observed. Then the reaction mixture was quenched with water and extracted with ethyl acetate (3 × 5 mL). The organic layer was dried over Na_2SO_4, and evaporated in vacuum. The residue was purified by silica gel column chromatography (petroleumether : EtOAc = 5 : 1) to afford the compound **9** in 71% yield.

2,2,6,6-Tetramethyl-1-((3-phenyl-1-tosyl-4,5-dihydro-1H-pyrazol-5-yl)methoxy)piperidine **(9)**: 102 mg, 71% yield, white solid, mp 169−170 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 2H), 7.71−7.68 (m, 2H), 7.44−7.36 (m, 3H), 7.27 (d, J = 8.4 Hz, 2H), 4.31 (dd, J = 9.2, 3.6 Hz, 1H), 4.12 (dd, J = 9.6, 7.2 Hz, 1H), 4.00−3.92 (m, 1H), 3.21−3.06 (m, 2H), 2.38 (s, 3H), 1.51−1.45 (m,

5H), 1.32−1.31 (m, 1H), 1.23 (s, 6H), 1.08 (s, 6H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 158.3, 144.1, 132.2, 130.9, 130.5, 129.5, 128.6, 128.5, 126.9, 59.9, 39.6, 37.4, 33.2, 33.0, 21.6, 20.1, 17.0; HRMS (ESI): calcd for $C_{26}H_{35}N_3O_3SNa$ $[M + Na]^+$ 492.2300, found 492.2291.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of the ^{1}H NMR, ^{19}F NMR, $^{13}C\{^{1}H\}$ NMR and HRMS spectra of **5**, **6**, **7**, **9** and crystallography of **5ac** (PDF).

Crystallographic data for **5ac**

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are thankful for financial support from the National Natural Science Foundation of China (Grant Nos. 21662030 and 21462037); Key Laboratory Polymer Materials of Gansu Province

(Northwest Normal University); Bioactive Product Engineering Research Center for Gansu Distinctive Plants; and State Key Laboratory of Applied Organic Chemistry, Lanzhou University.

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