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Copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes: Convenient synthesis of CF_3-containing alkyl nitriles

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ABSTRACT

A copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes has been developed, in which the less reactive Togni reagent **2** was used as a CF_3 source and TMSCN was employed as a cyano source. Both activated and unactivated alkenes were suitable for this transformation to give CF_3-containing organonitriles under mild conditions.

1. Introduction

Organonitriles have been widely recognized as important organic compounds and applied in organic synthesis as valuable intermediates and building blocks due to their versatile chemical property and bioactivities [1]. Elegant methodologies have been reported for the conversion of organonitrile to diverse organic compounds, such as organocarboxylic acid, which have extensively been applied in pharmaceuticals and agricultural chemicals [2]. Representative organonitriles and related carboxylic acid exhibited some bioactivity, such as enzyme inhibitor, anti HIV and hNK2 receptor [3] (Fig. 1). Therefore, many efforts have been paid to introduce nitrile group into organic molecules. On the other hand, trifluoromethyl group is prevalent in pharmaceuticals and agrochemicals due to its unique properties [4]. We speculated that, if both CF_3 and nitrile groups can be simultaneously introduced into organic compounds, efficient synthesis of trifluoromethylated organonitriles and related derivatives might be expected, which will shed a light to introduce CF_3 into original leading compounds or drugs to adjust their bioactivity. Herein we report a copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes to construct CF_3-containing organonitriles under very mild conditions [5].

Recently, a notable development of allylic trifluoromethylation of alkenes was reported independently by Buchwald, Liu, Wang and Sodeoka groups [6]. Since then, the trifluoromethylation of alkenes has been disclosed to allowing the effective formation of C_{sp3}–CF_3 bond [7]. Among them, three-component coupling trifluoromethylation reactions have received more and more attention [7c–g,k]. In 2012, our group reported the first difunctionalization of alkenes involving trifluoromethylation using a palladium catalyst [8]. As a continuation of our interest in difunctionalization of alkenes [9], our group recently discovered a copper-catalyzed intermolecular trifluoromethylazidation of alkenes [10], in which a carbon radical or carbon cation intermediate was proposed to be trapped by an azide reagent. Inspired by this result, we envisioned that this carbon radical or carbon cation intermediate might also be trapped by a cyano reagent to introduce both CF_3 and CN groups into the alkenes (Scheme 1). If so, a variety CF_3-containing organonitriles and their derivatives could be expected to achieve through a very efficient approach. Very recently, Szabó and Liang also independently reported copper-mediated or -catalyzed cyanotrifluoromethylation of alkenes with the same strategy using more reactive ester type Togni reagent [5].

2. Results and discussion

In our previous study, trimethylsilyl azide ($TMSN_3$) plays an important role to activate less active Togni reagent (**2**) to generate

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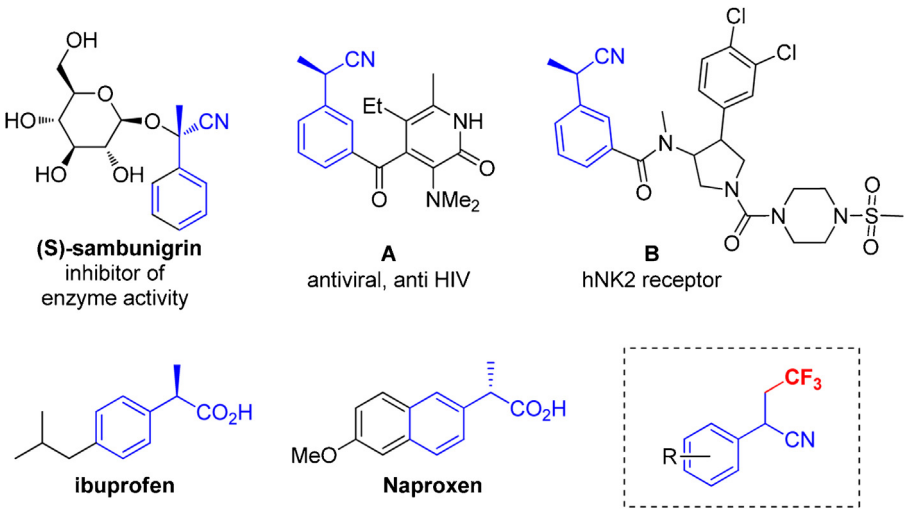
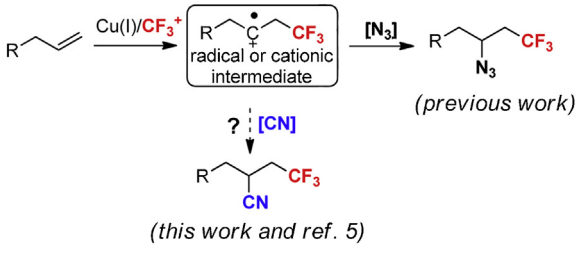


Fig. 1. Representative bioactive trifluoromethylated nitriles and derivative.

CF_3 radical in the presence of copper catalyst. Thus, the initial study was focused on the reaction of styrene (**1a**) with Togni reagent (**2**) in the presence of copper catalysts, and trimethylsilyl cyanide (TMSCN) was employed as a cyano source. As shown in Table 1, the reaction of **1a** did afford the desired cyanotrifluoromethylation product **3a** in the presence of 5 mol% $Cu(CH_3CN)_4PF_6$ in DMSO at room temperature (Table 1, entry 1). Solvent screening implied that DMSO was the best solvent for this reaction. Then different copper salts were applied into the reaction which showed that all listed copper salts could catalyze this reaction (entries 2–8). Firstly, copper catalysts, such as CuTc and $(CuOTf)_2{\cdot}C_6H_6$, were tested to give only moderate yield (entries 2 and 3). Secondly, when copper(II) catalyst was used, the yield was not improved (entry 4). And the copper powder was also used to catalyze this reaction, albeit in low yield (entry 5). Finally, copper complexes with bidentate nitrogen ligand **L1**–**L3** were used, and the yield was improved significantly to 93% in the presence of 10 mol% (**L3**)CuBr (entries 6–8). The yield was decreased to 85% with lowered catalyst loading (5%) (entry 9). The combination of CuBr and ligand **L3** to generate the copper complex *in situ* was not as effective as the prepared complex (entry 10). Control experiment showed that no reaction took place in the absence of a copper catalyst (entry 11).

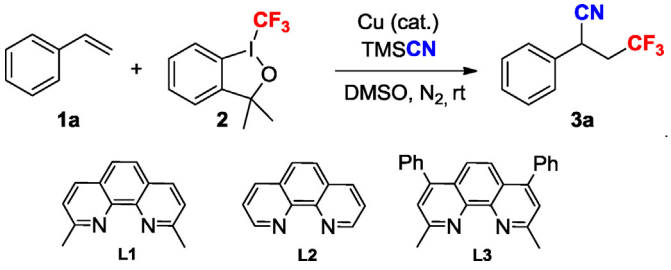
With the optimized reaction conditions in hand, the substrate scope was investigated and the results are summarized in Table 2. Styrenes **1a**–**1j** bearing various substituents on the aromatic ring, including electron-donating and electron-withdrawing groups, were compatible with this reaction condition to give **3a**–**j** in good to excellent yields. Among them, substrates **1c**–**1d**, **1g**–**1h** bearing halides gave the corresponding products **3c**–**d**, **3g**–**h** in 84–98% yield without loss of halides. In additional, the reaction of cyclic styrene **1k** afforded a desired product **3k** in 73% yield with excellent diastereoselectivity (>20:1).

Intrigued by the results of styrenes, we extended the substrate scope to aliphatic substituted alkenes. To our delight, the reaction of alkyl substituted alkenes proceeded smoothly to give desired products. For instance, simple alkene **1l** could be transformed to **3l** in 74% yield. Importantly, the reaction of enamine substrate **1m** proceeded well to give **3m** in good yield, which could be transformed to 2-amino-4,4,4-trifluorobutanenitrile as an important building block after deprotection. The reaction of **1n**–**p** with an imide group afforded **3n**–**p** in good yields. A free proton of *N*-allylaniline **1q** did



Scheme 1. Copper-catalyzed intermolecular difunctionalization of alkenes.

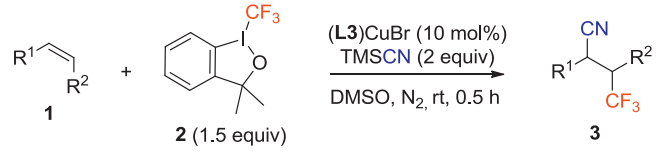
Table 1
Optimization of reaction condition.[a]

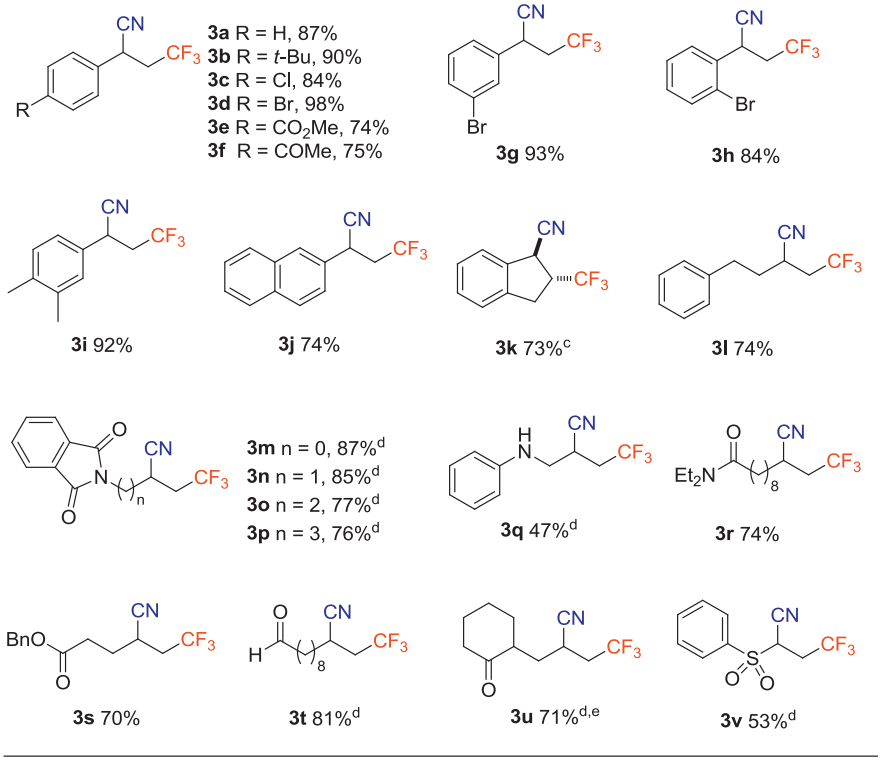


Entry	Catalyst (mol%)	Yield (%)[b]
1	$Cu(CH_3CN)_4PF_6$ (5)	76
2	CuTc (5)	50
3	$(CuOTf)_2{\cdot}C_6H_6$ (5)	61
4	$CuBr_2$ (10)	56
5	Cu powder (5)	27
6	(**L1**)CuBr (10)	76
7	(**L2**)CuBr (10)	80
8	(**L3**)CuBr (10)	93
9	(**L3**)CuBr (5)	85
10[c]	(**L3**)CuBr (10)	87
11[d]	-	0

[a] Reaction conditions: **1a** (0.1 mmol), Cu catalyst (10 mol%), TMSCN (0.2 mmol), Togni reagent **2** (0.15 mmol) in DMSO (0.5 mL) at room temperature in 0.5 h.
[b] NMR yield, determined by ^{19}F NMR spectroscopy using *N*,*N*-dimethyltrifluoroacetamide (DMA-CF_3) as an internal standard.
[c] CuBr and **L3** were added separately.
[d] Without copper catalyst.

Table 2
Copper-catalyzed cyanotrifluoromethylation of alkenes.[a,b]

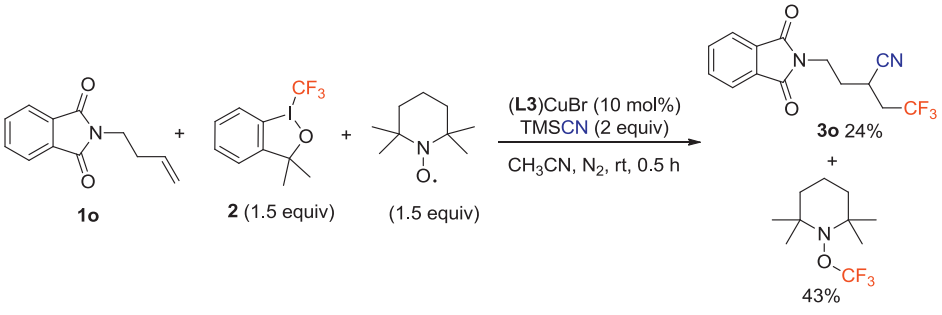




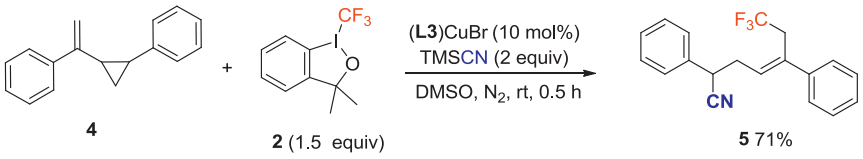
[a] Reaction conditions: **1** (0.2 mmol), (**L3**)CuBr (10 mol%), TMSCN (0.4 mmol), Togni reagent **2** (0.3 mmol) in DMSO (1.0 mL) at room temperature in 0.5 h.
[b] Isolated yield.
[c] d.r. > 20:1.
[d] CH_3CN was used as solvent instead of DMSO.
[e] d.r. = 1:1.

not affect the reaction to give product **3q**, rather than trifluoromethylated aziridine product [7k], albeit in 47% yield. Functional groups in the alkene substrates, such as amide, ester, aldehyde and ketone, were tolerated under the reaction condition to give **3r–u** in good yields. For the electron-deficient alkene, the reaction could also smoothly proceed to give product **3v** in moderate yield (53%).

To shed light on this transformation, some preliminary mechanism studies were conducted. When 1.5 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added into the reaction system, the desired product **3o** was partly inhibited to give in 24% yield and TEMPO–CF_3 adduct was observed by ^{19}F NMR (Eq. (1)). Furthermore, when vinyl cyclopropane **4**, a faster radical clock, was conducted under the standard reaction conditions, the ring-opening product **5** was obtained as a single product in 71% yield (Eq. (2)). Based on those observations, a mechanistic pathway was proposed that Togni reagent (**2**) was activated by TMS group and Cu(I) to give CF_3 radical, followed by the reaction with alkene to give a carbon radical or carbon cation intermediate which was trapped by TMSCN to yield the final product.



(1)



4 2 (1.5 equiv) 5 71% (2)

3. Conclusion

In this report, we have developed a copper-catalyzed intermolecular cyanotrifluoromethylation of alkenes, in which the less reactive Togni reagent **2** was used as a CF_3 source and TMSCN was employed as a cyano source under mild reaction conditions. Both activated and unactivated alkenes were suitable for this transformation with good functional groups tolerance. This reaction afforded a convenient way to trifluoromethylated nitriles for medicinal chemistry. Further application of this reaction is in progress.

4. Experimental

4.1. General

All reactions were carried out in an oven-dried glass tube with rubber stopper caps under nitrogen atmosphere. All commercially available compounds obtained from Aldrich, Alfa Aesar, Adamas are used as received. NMR spectra were recorded on Varian Inova 400 and Aglient 400 (400 MHz for ^1H; 376 MHz for ^{19}F; 100 MHz for ^{13}C) spectrometer. The chemical shifts (δ) are given in ppm relative to $CDCl_3$ (7.26 ppm for ^1H) and $CDCl_3$ (77.0 ppm for ^{13}C). Flash column chromatography was performed on silica gel (particle size 300–400 mesh, purchased from Canada) and eluted with petroleum ether/ethyl acetate. Dimethyl sulfoxide (DMSO) was distillated under reduced pressure over CaH_2 before using. Acetonitrile (CH_3CN) was dried by refluxing over CaH_2 and distillated before using.

4.2. Typical procedure for copper complex [11]

A mixture of CuBr (0.57 g, 4 mmol) and 2,9-dimethyl-1,10-phenanthroline (**L3**) (0.72 g, 2 mmol) in CH_3CN (30 ml) was stirred overnight under nitrogen atmosphere at room temperature. The copper complex was obtained as a brick-red solid in 90% yield.

4.3. Typical procedure for cyanotrifluoromethylation of alkenes

General procedure A: To a dried glass tube, Togni reagent **2** (99 mg, 0.3 mmol, 1.5 equiv), (**L3**)CuBr (10 mg, 0.02 mmol, 0.1 equiv) and DMSO (1.0 mL) were added under N_2 atmosphere, followed by substrate **1** (0.2 mmol, 1.0 equiv) and TMSCN (54 μL, 0.4 mmol, 2.0 equiv). After the reaction mixture was stirred at room temperature for 0.5 h, dichloromethane was added and the mixture was filtered through a short pad of celite. The filtrate was washed with water (15 mL × 3) and dried over anhydride Na_2SO_4. After the removal of solvent, the residue was purified by column chromatography on silica gel with a gradient eluent of petroleum ether and ethyl acetate to afford the product.

General procedure B: To a dried glass tube, Togni reagent **2** (99 mg, 0.3 mmol, 1.5 equiv), (**L3**)CuBr (10 mg, 0.02 mmol, 0.1 equiv) and CH_3CN (1.0 mL) were added under N_2 atmosphere, followed by substrate **1** (0.2 mmol, 1.0 equiv) and TMSCN (54 μL, 0.4 mmol, 2.0 equiv). After the reaction mixture was stirred at room temperature for 0.5 h, the mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel with a gradient eluent of petroleum ether and ethyl acetate to afford the product.

4.3.1. 4,4,4-Trifluoro-2-phenylbutanenitrile (**3a**)

General procedure A: Pale yellow liquid; 34.6 mg, 87%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.36 (m, 5H), 4.10 (dd, J = 9.6, 5.2 Hz, 1H), 2.90–2.77 (m, 1H), 2.66–2.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.4, 129.5, 128.9, 127.1, 124.6 (q, J = 276.3 Hz), 118.5, 39.7 (q, J = 29.7 Hz), 31.2 (q, J = 3.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.1 (t, J = 9.4 Hz); HRMS (EI), calcd. for $C_{10}H_8F_3N$ 199.0609 $[M]^+$; found 199.0610.

4.3.2. 2-(4-(Tert-butyl)phenyl)-4,4,4-trifluorobutanenitrile (**3b**)

General procedure A: Pale yellow solid; 46 mg, 90%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 4.08 (dd, J = 9.6, 4.8 Hz, 1H), 2.89–2.75 (m, 1H), 2.65–2.50 (m, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 130.4, 126.8, 126.5, 124.7 (q, J = 275.9 Hz), 118.6, 39.7 (q, J = 29 Hz), 34.6, 31.1, 30.7 (q, J = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.2 (t, J = 9.7 Hz); HRMS (EI), calcd. for $C_{14}H_{16}F_3N$ 255.1235 $[M]^+$, found 255.1233.

4.3.3. 2-(4-Chlorophenyl)-4,4,4-trifluorobutanenitrile (**3c**)

General procedure A: Pale yellow liquid; 39.2 mg, 84%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 4.09 (dd, J = 8.8, 5.2 Hz, 1H), 2.90–2.75 (m, 1H), 2.64–2.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 131.8, 129.8, 128.6, 124.4 (q, J = 276.3 Hz), 118.1, 39.5 (q, J = 29.4 Hz), 30.7 (q, J = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.9 (t, J = 9.4 Hz); HRMS (EI), calcd. for $C_{10}H_7ClF_3N$ 233.0219 $[M]^+$, found 233.0217.

4.3.4. 2-(4-Bromophenyl)-4,4,4-trifluorobutanenitrile (**3d**)

General procedure A: Pale yellow liquid; 54.5 mg, 98%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 4.08 (dd, J = 8.8, 5.2 Hz, 1H), 2.87–2.78 (m, 1H), 2.62–2.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.7, 132.4, 128.9, 124.4 (q, J = 276.2 Hz), 123.2, 118.0, 39.4 (q, J = 29.4 Hz), 30.8 (q, J = 3.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.9 (t, J = 9.4 Hz); HRMS (EI), calcd. for $C_{10}H_7BrF_3N$ 276.9714 $[M]^+$, found 276.9716.

4.3.5. Methyl 4-(1-cyano-3,3,3-trifluoropropyl)benzoate (**3e**)

General procedure A: Pale yellow liquid; 38.1 mg, 74%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 4.17 (dd, J = 8.8, 5.2 Hz, 1H), 3.93 (s, 3H), 2.95–2.77 (m, 1H), 2.70–2.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 138.0, 131.0, 130.8, 127.4, 124.5 (q, J = 276.3 Hz), 117.9, 52.4, 39.4 (q, J = 30 Hz), 31.2 (q, J = 3.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.9 (t, J = 9.4 Hz); HRMS (EI), calcd. for $C_{12}H_{10}F_3NO_2$ 257.0664 $[M]^+$, found 257.0668.

4.3.6. 2-(4-Acetylphenyl)-4,4,4-trifluorobutanenitrile (**3f**)

General procedure A: Pale yellow liquid; 36.1 mg, 75%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 4.18 (dd, J = 9.2, 5.2 Hz, 1H), 2.93–2.78 (m, 1H), 2.69–2.56 (m, 1H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 138.1, 137.5, 129.5, 127.6, 124.4 (q, J = 276.3 Hz), 117.9, 39.3 (q, J = 29.6 Hz), 31.1 (q, J = 3.1 Hz), 26.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.9 (t, J = 9.8 Hz); HRMS (ESI), m/z: calcd. for $C_{12}H_{11}F_3NO$ 242.0793 $[M+H]^+$, found 242.0793.

4.3.7. 2-(3-Bromophenyl)-4,4,4-trifluorobutanenitrile (**3g**)

General procedure A: Pale yellow liquid; 51.7 mg, 93%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56–7.50 (m, 2H), 7.35–7.28 (m, 2H), 4.07 (dd,

J = 9.6, 5.6 Hz, 1H), 2.90–2.76 (m, 1H), 2.66–2.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.4, 132.3, 131.1, 130.3, 125.9, 124.4 (q, *J* = 276.4 Hz), 123.4, 117.9, 39.8 (q, *J* = 31.1 Hz), 30.8 (q, *J* = 3.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.5 (t, *J* = 9.8 Hz); HRMS (EI), calcd. for $C_{10}H_7BrF_3N$ 276.9714 $[M]^+$, found 276.9710.

4.3.8. 2-(2-Bromophenyl)-4,4,4-trifluorobutanenitrile (**3 h**)

General procedure A: Pale yellow liquid; 46.7 mg, 84%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 4.63–4.58 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.80–2.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.8, 132.7, 130.7, 129.1, 128.7, 124.5 (q, *J* = 276.3 Hz), 122.6, 117.9, 37.9 (q, *J* = 29.6 Hz), 31.3 (q, *J* = 3.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.1 (t, *J* = 9.4 Hz); HRMS (EI), calcd. for $C_{10}H_7BrF_3N$ 276.9714 $[M]^+$, found 276.9712.

4.3.9. 2-(3,4-Dimethylphenyl)-4,4,4-trifluorobutanenitrile (**3i**)

General procedure A: Pale yellow liquid; 41.8 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, *J* = 7.6 Hz, 1H), 7.13 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 4.03 (dd, *J* = 10, 5.2 Hz, 1H), 2.87–2.74 (m, 1H), 2.63–2.51 (m, 1H), 2.29 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 137.6, 130.8, 130.6, 128.2, 124.6 (q, *J* = 276.3 Hz), 124.4, 118.8, 39.8 (q, *J* = 28.8 Hz), 30.8 (q, *J* = 3.0 Hz), 19.7, 19.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.1 (t, *J* = 10.2 Hz); HRMS (EI), calcd. for $C_{12}H_{12}F_3N$ 227.0922 $[M]^+$, found 227.0919.

4.3.10. 4,4,4-Trifluoro-2-(naphthalen-2-yl)butanenitrile (**3j**)

General procedure A: Pale yellow liquid; 184 mg, 74%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8 Hz, 1H), 7.89–7.83 (m, 3H), 7.59–7.53 (m, 2H), 7.42 (d, *J* = 8 Hz, 1H), 4.27 (dd, *J* = 9.6, 5.2 Hz, 1H), 2.99–2.84 (m, 1H), 2.76–2.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.2, 133.0, 130.5, 129.7, 127.9, 127.8, 127.1, 127.0, 126.6, 124.6 (q, *J* = 276.7 Hz), 124.0, 118.6, 39.6 (q, *J* = 29.6 Hz), 31.3 (q, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.0 (t, *J* = 9.4 Hz); HRMS (EI), calcd. for $C_{14}H_{10}F_3N$ 249.0765 $[M]^+$, found 249.0768.

4.3.11. 2-(Trifluoromethyl)-2,3-dihydro-1H-indene-1-carbonitrile (**3k**)

General procedure A: Pale yellow liquid; 30.8 mg, 74%, dr > 20:1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.43 (m, 1H), 7.38–7.32 (m, 2H), 7.31–7.25 (m, 1H), 4.35 (d, *J* = 9.2 Hz, 1H), 3.55–3.40 (m, 1H), 3.36–3.30 (m, 1H), 3.21–3.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 134.9, 129.4, 128.3, 126.2 (q, *J* = 275.5 Hz), 125.0, 124.4, 118.8, 48.2 (q, *J* = 28.7 Hz), 35.4 (q, *J* = 2.9 Hz), 31.8 (q, *J* = 2.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −68.5 (d, *J* = 7.9 Hz); HRMS (EI), calcd. for $C_{11}H_8F_3N$ 211.0609 $[M]^+$, found 211.0605.

4.3.12. 4,4,4-Trifluoro-2-phenethylbutanenitrile (**3l**)

General procedure A: Pale yellow liquid; 33.6 mg, 74%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, *J* = 6.8 Hz, 2H), 7.26 (d, *J* = 6.0 Hz, 1H), 7.20 (t, *J* = 6.8 Hz, 2H), 3.00–2.90 (m, 1H), 2.90–2.70 (m, 2H), 2.60–2.45 (m, 1H), 2.45–2.35 (m, 1H), 2.10–1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 128.8, 128.3, 126.7, 125.0 (q, *J* = 276.3 Hz), 119.4, 36.3 (q, *J* = 29.6 Hz), 33.6, 32.7, 24.9 (q, *J* = 2.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.8 (t, *J* = 10.2 Hz); HRMS (ESI), *m*/*z*: calcd. for $C_{12}H_{13}F_3N$ 228.0995 $[M+H]^+$, found 228.0991.

4.3.13. 2-(1,3-Dioxoisoindolin-2-yl)-4,4,4-trifluorobutanenitrile (**3m**)

General procedure B: Pale yellow solid; 46.6 mg, 87%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.82 (dd, *J* = 5.2, 3.2 Hz, 2H), 5.54 (dd, *J* = 8.4, 5.2 Hz, 1H), 3.33–3.17 (m, 1H), 3.06–2.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 135.1, 131.0, 124.3, 124.0 (q, *J* = 276.3 Hz), 114.0, 35.0 (q, *J* = 30.0 Hz), 33.9 (q, *J* = 3.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.1 (t, *J* = 10.0 Hz); HRMS (EI), calcd. for $C_{12}H_7F_3N_2O_2$ 268.0460 $[M]^+$, found 268.0456.

4.3.14. 2-((1,3-Dioxoisoindolin-2-yl)methyl)-4,4,4-trifluorobutanenitrile (**3n**)

General procedure B: Orange solid; 41.7 mg, 74%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92–7.86 (m, 2H), 7.81–7.74 (m, 2H), 4.15–4.05 (m, 1H), 3.94–3.89 (m, 1H), 3.51–3.42 (m, 1H), 2.70–2.55 (m, 1H), 2.55–2.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 134.6, 131.3, 124.7 (q, *J* = 276.3 Hz), 123.8, 117.2, 38.4, 34.3 (q, *J* = 30.4 Hz), 25.4 (q, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.8 (t, *J* = 10.2 Hz); HRMS (ESI), *m*/*z*: calcd. for $C_{13}H_{13}F_3N_3O_2$ 300.0954 $[M+NH_4]^+$, found 300.0958.

4.3.15. 2-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)-4,4,4-trifluorobutanenitrile (**3o**)

General procedure B: Pale yellow liquid; 45.6 mg, 77%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.81 (m, 2H), 7.75–7.70 (m, 2H), 3.93–3.84 (m, 2H), 2.99–2.93 (m, 1H), 2.65–2.56 (m, 1H), 2.56–2.42 (m, 1H), 2.17–2.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 134.2, 131.7, 124.8 (q, *J* = 276.3 Hz), 123.4, 118.8, 35.8 (q, *J* = 29.9 Hz), 34.8, 30.6, 23.3 (q, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.6 (t, *J* = 10.2 Hz); HRMS (EI), calcd. for $C_{14}H_{11}F_3N_2O_2$ 296.0773 $[M]^+$, found 296.0778.

4.3.16. 5-(1,3-Dioxoisoindolin-2-yl)-2-(2,2,2-trifluoroethyl)pentanenitrile (**3p**)

General procedure B: Pale yellow liquid; 45.6 mg, 77%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.72 (dd, *J* = 5.6, 3.2 Hz, 2H), 3.75 (t, *J* = 6.8 Hz, 2H), 3.04–2.94 (m, 1H), 2.59–2.44 (m, 1H), 2.39–2.26 (m, 1H), 2.04–1.91 (m, 1H), 1.91–1.81 (m, 1H), 1.81–1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 134.1, 131.8, 124.9 (q, *J* = 275.5 Hz), 123.3, 119.2, 36.5, 36.3 (q, *J* = 29.7 Hz), 29.2, 26.0, 25.0 (q, *J* = 2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.9 (t, *J* = 10.2 Hz); HRMS (EI), calcd. for $C_{15}H_{13}F_3N_2O_2$ 310.0929 $[M]^+$, found 310.0926.

4.3.17. 4,4,4-Trifluoro-2-((phenylamino)methyl)butanenitrile (**3q**)

General procedure B: Green liquid; 21.6 mg, 47%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, *J* = 8.4 Hz, 2H), 6.81 (t, *J* = 7.2 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 2H), 4.07 (t, *J* = 6.0 Hz, 1H), 3.54 (t, *J* = 6.8 Hz, 2H), 3.25–2.18 (m, 1H), 2.63–2.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 129.7, 125.1 (q, *J* = 274.4 Hz), 119.1, 118.7, 113.0, 45.1, 33.9 (q, *J* = 30.1 Hz), 26.1 (q, *J* = 2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.6 (t, *J* = 10.2 Hz); HRMS (ESI), *m*/*z*: calcd. for $C_{11}H_{12}F_3N_2$ 229.0947 $[M+H]^+$, found 229.0941.

4.3.18. 10-Cyano-N,N-diethyl-12,12,12-trifluorododecanamide (**3r**)

General procedure A: Pale yellow solid; 49.5 mg, 74%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34 (q, *J* = 7.2 Hz, 2H), 3.28 (q, *J* = 7.2 Hz, 2H), 2.87–2.80 (m, 1H), 2.59–2.42 (m, 1H), 2.35–2.30 (m, 1H), 2.26 (t, *J* = 7.6 Hz, 2H), 1.70–1.40 (m, 6H), 1.40–1.20 (m, 8H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 125.0 (q, *J* = 275.9 Hz), 119.6, 41.8, 39.9, 36.2 (q, *J* = 29.4 Hz), 32.9, 31.9, 29.2, 29.1, 28.9, 28.6, 26.5, 25.3 (q, *J* = 3.3 Hz), 25.2, 14.2, 12.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.0 (t, *J* = 10.2 Hz); HRMS (ESI), *m*/*z*: calcd. for $C_{17}H_{30}F_3N_2O$ 335.2305 $[M+H]^+$, found 335.2295.

4.3.19. Benzyl 3-cyano-5,5,5-trifluoropentanoate (**3s**)

General procedure A: Pale yellow liquid; 39.9 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.32 (m, 5H), 5.15 (d, *J* = 2.4 Hz, 2H), 3.10–3.00 (m, 1H), 2.70–2.60 (m, 2H), 2.60–2.45 (m, 1H), 2.45–2.30 (m, 1H), 2.15–2.00 (m, 1H), 2.00–1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 135.3, 128.6, 128.3, 124.9 (q, *J* = 275.9 Hz), 118.9, 66.8, 36.3 (q, *J* = 29.6 Hz), 30.9, 27.1, 24.8 (q, *J* = 2.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.8 (t, *J* = 10.2 Hz); HRMS (EI), calcd. for $C_{14}H_{14}F_3NO_2$ 285.0977 $[M]^+$, found 285.0980.

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*4.3.20. 11-Oxo-2-(2,2,2-trifluoroethyl)undecanenitrile (**3t**)*

General procedure B: Pale yellow liquid; 42.7 mg, 81%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 2.87–2.80 (m, 1H), 2.60–2.46 (m, 1H), 2.42 (t, J = 7.2 Hz, 2H), 2.36–2.26 (m, 1H), 1.74–1.52 (m, 5H), 1.40–1.26 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9, 125.1 (q, J = 275.8 Hz), 119.7, 43.8, 36.3 (q, J = 29.8 Hz), 32.0, 29.1, 29.0, 28.9, 28.7, 26.6, 25.5 (q, J = 3.0 Hz), 21.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.0 (t, J = 9.4 Hz); HRMS (ESI), m/z: calcd. for $C_{13}H_{18}F_3NO$ 261.1340 $[M-2H]^+$, found 261.1337.

*4.3.21. 4,4,4-Trifluoro-2-((2-oxocyclohexyl)methyl)butanenitrile (**3u**)*

General procedure B: Brown solid; 40.5 mg, 71%, dr = 1:1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32–3.23 (m, 1H), 2.71–2.61 (m, 1H), 2.55–2.32 (m, 4H), 2.17–2.00 (m, 3H), 1.90–1.60 (m, 3H), 1.50–1.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.0, 125.0 (q, J = 277.9 Hz), 119.9, 48.0, 42.3, 37.0 (q, J = 29.7 Hz), 35.3, 33.0, 28.1, 25.2, 24.3 (q, J = 2.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.6 (t, J = 9.8 Hz); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00–2.90 (m, 1H), 2.62–2.10 (m, 9H), 1.80–1.60 (m, 3H), 1.43–2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.9, 125.0 (q, J = 273.3 Hz), 119.3, 47.6, 42.0, 36.7 (q, J = 29.4 Hz), 33.2, 31.6, 27.7, 25.0, 22.9 (q, J = 3.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.9 (t, J = 9.8 Hz); HRMS (ESI), m/z: calcd. for $C_{11}H_{18}F_3N_2O$ 251.1366 $[M+NH_4]^+$, found 251.1364.

*4.3.22. 4,4,4-Trifluoro-2-(phenylsulfonyl)butanenitrile (**3v**)*

General procedure B: Brown solid; 27.9 mg, 53%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 7.2 Hz, 2H), 7.83 (t, J = 7.2 Hz, 1H), 7.69 (t, J = 8.0 Hz, 2H), 4.15 (dd, J = 12.0, 2.8 Hz, 1H), 3.15–3.02 (m, 1H), 2.82–2.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 134.2, 129.9, 129.8, 124.1 (q, J = 276.3 Hz), 112.3, 51.1 (q, J = 3 Hz), 31.6 (q, J = 32.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −64.4 (t, J = 10.2 Hz); HRMS (ESI), m/z: calcd. for $C_{10}H_9F_3NO_2S$ 264.0306 $[M+H]^+$, found 264.0309.

*4.3.23. (E)-7,7,7-Trifluoro-2,5-diphenylhept-4-enenitrile (**5**)*

General procedure A: Pale yellow liquid; 44.8 mg, 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.33 (m, 10H), 6.05 (t, J = 5.6 Hz, 1H), 3.97 (t, J = 7.2 Hz, 1H), 3.25 (q, J = 10.4 Hz, 2H), 2.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 134.7, 133.5 (q, J = 2.2 Hz), 129.2, 129.1, 128.4, 128.3, 127.8, 127.2, 126.4, 125.6 (q, J = 277.1 Hz), 120.1, 37.1, 35.1, 34.6 (q, J = 28.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.4 (t, J = 10.5 Hz); HRMS (EI), calcd. for $C_{19}H_{16}F_3N$: 315.1235 $[M]^+$, found 315.1240.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2014.04.004.

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