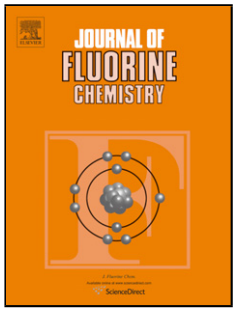

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Authors: Wei Zhang, Jin-Hong Lin, Ji-Chang Xiao

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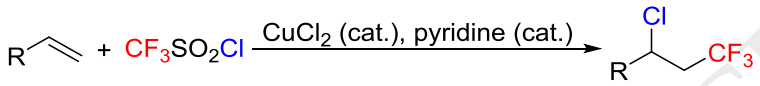
Cu-catalyzed Chlorotrifluoromethylation of Alkenes with CF_3SO_2Cl

Wei Zhang, Jin-Hong Lin,* and Ji-Chang Xiao*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. Fax: +86-21-6416-6128; Tel: +86-21-5492-5340; Email: jlin@sioc.ac.cn, jchxiao@sioc.ac.cn.

Graphical abstract



Chlorotrifluoromethylation of various alkenes, including aryl alkenes, α,β-unsaturated alkenes and alkyl alkenes, with CF_3SO_2Cl catalyzed by a simple Cu complex is described.

Highlights

- **Chlorotrifluoromethylation with CF_3SO_2Cl catalyzed by simple system consisting of $CuCl_2$ and pyridine was achieved.**
- **A wide substrate scope and good functional group tolerance were observed.**
- High yields were obtained under mild conditions.

Abstract: Although CF_3SO_2Cl is an efficient chlorotrifluoromethylation reagent, an expensive transition metal complex usually has to be used. We found that $CuCl_2$-catalyzed chlorotrifluoromethylation of alkenes with CF_3SO_2Cl occurred smoothly under mild conditions. A wide substrate scope and good functional group compatibility were observed.

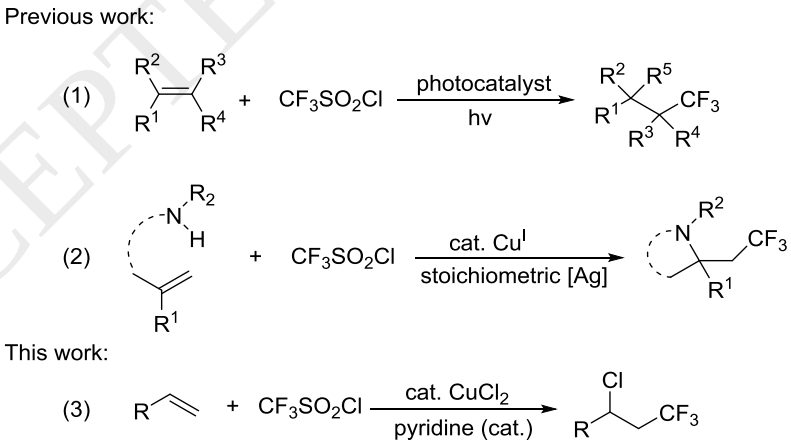
Keywords: Chlorotrifluoromethylation, Alkenes, Catalysis, Copper, Fluorine

1. Introduction

Due to its strong electron-withdrawing nature (Hammett constants $\sigma_p = 0.43$, $\sigma_m = 0.54$) and high lipophilicity (Hansch constant $\pi = 0.88$) [1, 2], trifluoromethyl group (CF_3) has proven to be a valuable functionality in medicinal chemistry and agrochemistry [3-6], and many CF_3-containing pharmaceuticals and agrochemicals have been developed, such as Fluoxetine, Efavirenz, Pleconaril and Acifluorfen. The high demand for the biologically active CF_3-molecules has stimulated significant efforts to develop efficient methods for the installation of CF_3 group [7-10]. Difunctionalization-type trifluoromethylation of alkenes [11, 12], including hydrotrifluoromethylation [13-15], oxtrifluoromethylation [16-18], carbotrifluoromethylation

[19-22], aminotrifluoromethylation [23-25], and halotrifluoromethylation [26-28], has emerged as an important synthetic tool for CF_3 incorporation. Halotrifluoromethylation is apparently an attractive protocol as the presence of the halo substituent allows for further transformation. The reaction could be achieved by the combined use of a trifluoromethylation reagent and a halogen source [29-34], or by the use of a single halotrifluoromethylation reagent. Obviously, the use of a single halotrifluoromethylation reagent is more straightforward and would therefore be highly desirable.

The most commonly used halotrifluoromethylation reagents are CF_3I and CF_3SO_2Cl. CF_3I (bp: -22 ^oC) is gaseous and the need to manipulate this gas may limit its applicability [35-38]. As CF_3SO_2Cl could be easily reduced to generate active trifluoromethyl radical ($CF_3\cdot$) intermediate, it has served a versatile reagent to achieve various trifluoromethylation reactions [39-48], such as chlorotrifluoromethylation [39-43] and aminotrifluoromethylation [45, 46]. Compared with the widely used trifluoromethylation reagents including Togni's reagents and Umemoto reagent [9], CF_3SO_2Cl is an easily available and inexpensive reagent. As CF_3SO_2Cl is usually reduced under photocatalytic conditions, the use of an expensive transition metal complex as the photocatalyst is usually required (Scheme 1, eq 1) [40-44, 48]. Recently, Liu found that CuI complex could also reduce CF_3SO_2Cl and Cu-catalyzed radical aminotrifluoromethylation of alkenes was then achieved [45, 46], but the stoichiometric use of a silver salt was required to suppress side reactions (eq 2). We have been interested in the development of efficient methods for the incorporation of fluoroalkyl groups [49-58]. We found that a simple catalyst system consisting of copper dichloride ($CuCl_2$) and pyridine could catalyze chlorotrifluoromethylation of alkenes with CF_3SO_2Cl (eq 3). A series of alkenes including aryl alkenes, α,β-unsaturated alkenes and alkyl alkenes could all be converted smoothly, demonstrating a wide substrate scope of this protocol. It is noteworthy that general methods for chlorotrifluoromethylation of all of these alkenes are scarce.



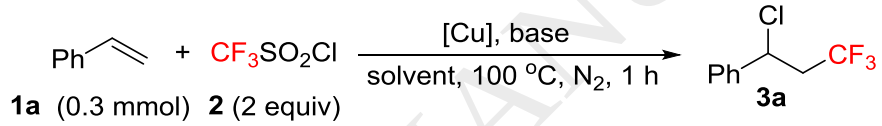
Scheme 1. Difunctionalization of alkenes with CF_3SO_2Cl

2. Results and discussion

Although monovalent copper complex (Cu^I) is a good reducing reagent and Liu has shown that CF_3SO_2Cl could be reduced by a Cu^I complex [45, 46], our initial attempts indicated that divalent

copper source was also an effective catalyst albeit with low efficiency (Table 1, entry 1). Further brief survey revealed that the reaction solvent played a crucial role (entries 1-7) and a good yield was obtained in 1,4-dioxane (entry 7). The concentration has an important effect on the reaction. Increasing the concentration and decreasing the loadings of both the copper source and the pyridine to 10 mol % gave the desired product in a high yield (entry 8). Slightly decreasing the loading of CF_3SO_2Cl to 1.8 equiv did not lead to the decrease in the yield (entry 9 vs. entry 8). The product was isolated in a lower yield (83%) due to its high volatility (entry 9). Other bases such as Et_3N (triethylamine) and DMAP (4-dimethylaminopyridine) are also quite effective (entries 10-11), but the yield was dramatically decreased by using 4,4'-bpy (4,4'-bipyridine) as a base (entry 12). Besides $CuCl_2$, other copper sources such as $Cu(OAc)_2$, $Cu(OTf)_2$ and CuCl were all good catalyst for this chlorotrifluoromethylation reaction (entries 12-15). Lowering the reaction temperature from 100 °C to 90 °C decreased the yield significantly to 73% (entry 9 vs. entry 16). The absence of the pyridine could still give the expected product in 45% yield (entry 17). No chlorotrifluoromethylation was observed in the absence of the copper catalyst (entry 18).

Table 1. The optimization of reaction conditions [a]



1a (0.3 mmol) **2** (2 equiv) **3a**

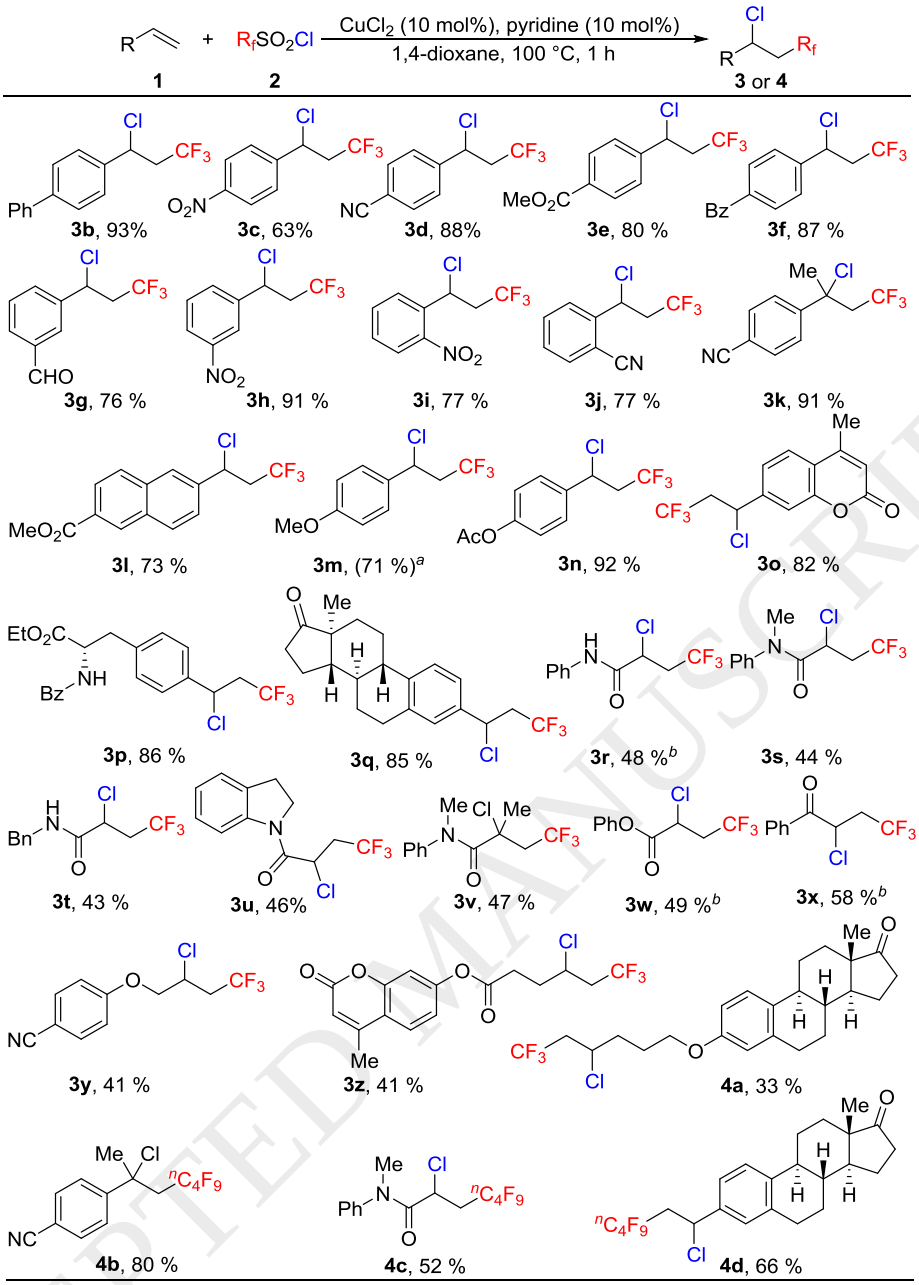
entry	[Cu] (mol %)	base (mol %)	solvent	yield (%)[b]
1	$CuCl_2$ (20)	pyridine (60)	DMF	7
2	$CuCl_2$ (20)	pyridine (60)	MeCN	46
3	$CuCl_2$ (20)	pyridine (60)	$MeNO_2$	73
4	$CuCl_2$ (20)	pyridine (60)	$CHCl_3$	trace
5	$CuCl_2$ (20)	pyridine (60)	DCE	73
6	$CuCl_2$ (20)	pyridine (60)	THF	66
7	$CuCl_2$ (20)	pyridine (60)	1,4-dioxane	84
8[c]	$CuCl_2$ (10)	pyridine (10)	1,4-dioxane	96
9[d]	$CuCl_2$ (10)	pyridine (10)	1,4-dioxane	95 (83)[e]
10[d]	$CuCl_2$ (10)	Et_3N (10)	1,4-dioxane	81
11[d]	$CuCl_2$ (10)	DMAP (10)	1,4-dioxane	95
12[d]	$CuCl_2$ (10)	4,4'-bpy (10)	1,4-dioxane	22
13[d]	$Cu(OAc)_2$ (10)	pyridine (10)	1,4-dioxane	88
14[d]	$Cu(OTf)_2$ (10)	pyridine (10)	1,4-dioxane	89
15[d]	CuCl (10)	pyridine (10)	1,4-dioxane	91
16[df]	$CuCl_2$ (10)	pyridine (10)	1,4-dioxane	73
17[d]	$CuCl_2$ (10)	-	1,4-dioxane	45

18[d]	-	pyridine (10)	1,4-dioxane	ND

[a]Reaction conditions: **1a** (0.3 mmol), **2** (2.0 equiv), copper source, base, solvent (2.0 mL), under N_2; DCE = $ClCH_2CH_2Cl$; 4,4'-bpy = 4,4'-bipyridine; ND = not detected; [b]The yields were determined by ^{19}F NMR spectroscopy; [c]0.5 mmol of **1a** was used; [d]0.5 mmol of **1a** and 1.8 equiv of **2** were used; [e]The yield in parentheses was an isolated yield; [f]The reaction was performed at 90 °C.

With the optimized reaction conditions in hand (Table 1, entry 9), we then investigated the substrate scope of this chlorotrifluoromethylation of alkenes. As shown in Scheme 2, a wide substrate scope and a high level of functional group tolerance were observed. Electron-deficient, -neutral, and –rich aryl alkenes could all be converted well into the expected products in moderate to good yields (**3b-3q**). In the case of substrates containing a strong electron-donating group (**3m**), the products are too unstable to be isolated, because benzyl cation would be easily formed by elimination of a chloride anion. Radical halotrifluoromethylation of electron-deficient alkenes is challenging, because the electrophilic nature of the radical intermediate formed by the addition of trifluoromethyl radical to electron-deficient alkene would suppress the abstraction of a halogen atom from electrophilic CF_3X or CF_3SO_2Cl by the radical intermediate. To our delight, chlorotrifluoromethylation of α,β-unsaturated amides (**3r-3v**), ester (**3w**) and ketone (**3x**) proceeded smoothly under these conditions. Alkyl alkenes showed lower reactivity and low yields were obtained (**3y-4a**). The protocol could also be applied to chloroperfluoroalkylation (**4b-4d**).

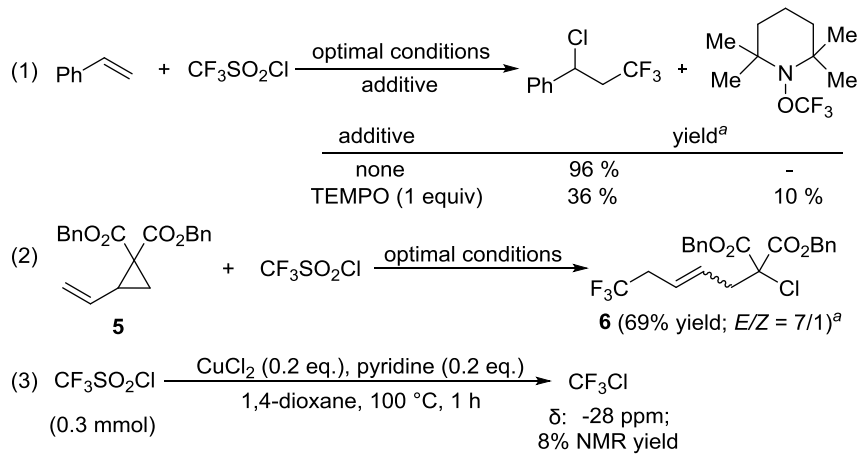
Scheme 2 Chlorotrifluoromethylation of alkenes.



Isolated yields. Reaction conditions: **1** (0.5 mol), **2** (1.8 eq.), $CuCl_2$ (10 mol%), pyridine (10 mol%), 1,4-dioxane (2 mL), under N_2 atmosphere. [a]The yield of **3m** was determined by ^{19}F NMR spectroscopy; [b]3 equiv of **2** was used.

More experimental evidence was collected to gain more mechanistic insights into this process. The chlorotrifluoromethylation was suppressed by the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) and the TEMPO-CF_3 product was detected by ^{19}F NMR spectroscopy (Scheme 3, eq 1). The conversion of vinylcyclopropane **5** with CF_3SO_2Cl under optimal conditions gave ring-opening products **6** (eq 2). Without the presence of a substrate, the $CuCl_2$/pyridine catalyst system could lead to the complete conversion of CF_3SO_2Cl and CF_3Cl was observed (eq 3) (See Supporting Information). These results suggest that a radical mechanism may be operative.

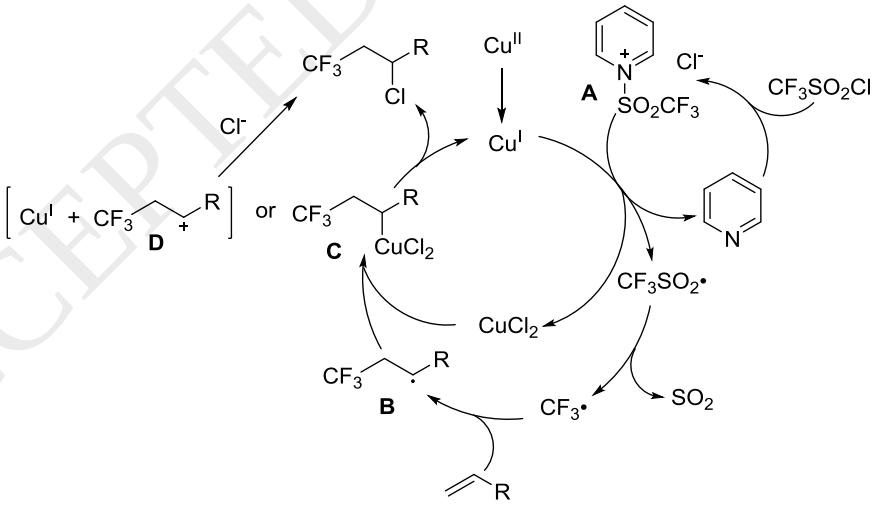
Scheme 3 Experimental evidences for radical mechanism.



[a]The yields and the *E/Z* ratio were determined by ^{19}F NMR spectroscopy.

On the basis of the above results, we propose that the reaction mechanism shown in Scheme 4 is plausible. Cu^{II} is a strong oxidant and would be easily reduced to Cu^{I} in the reaction system [59]. Cu^{I} should be the real catalyst for the chlorotrifluoromethylation process [45, 46]. CF_3SO_2Cl is activated by pyridine via forming pyridinum salt **A**. The redox reaction of salt **A** with Cu^{I} produces $CF_3SO_2^{\bullet}$ radical, $Cu^{II}Cl_2$ and pyridine. $CF_3SO_2^{\bullet}$ radical would readily undergo desulfonation to generate $CF_3^{\bullet}$ radical, which is trapped by alkenes to afford radical intermediate **B**. The capture of radical **B** by $CuCl_2$ gives Cu^{III} species **C**, the reductive elimination of which provides the final product and re-generates the catalyst Cu^{I}. Radical **B** and $CuCl_2$ may also undergo a single electron transfer process to form cation **D** and the catalyst Cu^{I}. The attack of a chloride anion at cation **D** also furnishes the final product.

Scheme 4 The plausible reaction mechanism.



3. Conclusions

In summary, we have described Cu-catalyzed chlorotrifluoromethylation of various alkenes, including aryl alkenes, α,β-unsaturated alkenes and alkyl alkenes, with CF_3SO_2Cl. A wide

substrate scope and good functional group compatibility were observed. This work represents the first efficient protocol for chlorotrifluoromethylation with CF_3SO_2Cl catalyzed by a simple Cu^{II} complex. The Cu/CF_3SO_2Cl system may find synthetic utility in other trifluoromethylation chemistry.

4. Experimental section

4.1 General remark

^1H, ^{13}C and ^{19}F NMR spectra were detected on a 400 MHz or 300 MHz NMR spectrometer. Data for ^1H NMR, ^{13}C NMR and ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, coupling constant (s) in Hz). Mass spectra were obtained on GC-MS (EI) or LC-MS (ESI). High resolution mass data were recorded on a high resolution mass spectrometer in the EI, ESI or DART mode.

4.2 General procedure for chlorotrifluoromethylation of alkenes:

$CuCl_2$ (7 mg, 10 mol%), alkene (0.5 mmol), 1,4-dioxane (2 mL), CF_3SO_2Cl (152 mg, 1.8 eq.) and pyridine (4 mg, 10 mol%) were added into a Schlenk tube under a N_2 atmosphere. The reaction mixture was stirred at 100 °C for 1 h. After being cooled to room temperature, the solid was removed by filtration and washed with DCM (30 mL). The combined organic solution was evaporated, and the resulting crude product was purified by flash column chromatography to give the products **3** or **4**.

4.3 Compound data of chlorotrifluoromethylation products:

(**3a**) [31]: Colorless oil, 83% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 5H), 5.10 (t, *J* = 7.0 Hz, 1H), 3.15-2.80 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.1 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 129.0, 128.9, 126.8, 124.7 (q, *J* = 276.5 Hz), 54.8 (q, *J* = 3.4 Hz), 43.7 (q, *J* = 28.2 Hz). GC-MS (EI): Calculated for $C_9H_8ClF_3$ [M]: 208.0; Found: 208.0.

(**3b**) [31]: White solid, 93% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.53 (m ,4H), 7.42-7.39 (m, 4H), 7.35-7.31 (m, 1H), 5.12 (t, *J* = 7.0 Hz, 1H), 3.05-2.79 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.8 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 140.1, 138.6, 128.8, 127.7, 127.6, 127.2, 127.1, 124.8 (q, *J* = 276.3 Hz), 54.5 (q, *J* = 3.4 Hz), 43.6 (q, *J* = 28.2 Hz). GC-MS(EI): Calculated for $C_{15}H_{12}ClF_3$ [M]: 284.1; Found: 284.1.

(**3c**) [31]: Yellow oil, 63% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 5.20 (t, *J* = 7.0 Hz, 1H), 3.11-2.85 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.9 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 146.2, 128.0, 124.3 (q, *J* = 276.3 Hz), 124.2, 53.2 (q, *J* = 3.4 Hz), 43.4 (q, *J* = 28.5 Hz). GC-MS (EI): Calculated for $C_9H_7ClF_3NO_2$[M]: 253.0; Found: 253.0.

(**3d**) [31]: Colorless oil, 88% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 5.14 (t, *J* = 7.2 Hz, 1H), 3.08-2.82 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.9 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 132.7, 127.7, 124.3 (q, *J* = 276.3 Hz), 118.0, 112.9, 53.5 (q, *J* = 3.4 Hz), 43.3 (q, *J* = 28.6 Hz). GC-MS (EI): Calculated for

$C_{10}H_7ClF_3N$[M]: 233.0; Found: 233.1.

(**3e**) [31]: Colorless oil, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 5.14 (t, *J* = 7.0 Hz, 1H), 3.92 (s, 3H), 3.07-2.82 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.0 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 144.1, 130.7, 130.2, 126.9, 124.5 (q, *J* = 276.2 Hz), 53.92 (q, *J* = 3.4 Hz), 52.2, 43.4 (q, *J* = 28.4 Hz). GC-MS (EI): Calculated for $C_{11}H_{10}ClF_3O_2$ [M]: 266.0; Found: 266.1.

(**3f**) [32]: Colorless oil, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.77 (m, 4H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.52-7.45 (m, 4H), 5.17 (t, *J* = 7.0 Hz, 1H), 3.09-2.85 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.9 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 143.6, 138.0, 137.1, 132.6, 130.5, 129.9, 128.3, 126.8, 124.5 (q, *J* = 276.3 Hz), 53.95 (q, *J* = 3.5 Hz), 43.4 (q, *J* = 28.4 Hz). GC-MS (EI): Calculated for $C_{16}H_{12}ClF_3O$ [M]: 312.1; Found: 312.1.

(**3g**): Colorless oil, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.94 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 5.20 (t, *J* = 7.0 Hz, 1H), 3.11-2.86 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.9 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 140.8, 136.9, 132.7, 130.5, 129.7, 127.5, 124.5 (q, *J* = 276.3 Hz), 53.8 (q, *J* = 3.4 Hz), 43.5 (q, *J* = 28.4 Hz). HRMS (EI): Calculated for $C_{10}H_8ClF_3O$[M]: 236.0216; Found: 236.0219. IR: 3446, 1701, 1607, 1427, 1386, 1264, 1141, 1111, 1047, 910, 847, 799, 758, 698, 640, 589 cm^{-1}.

(**3h**) [39]: Pale yellow oil, 91 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 5.22 (t, *J* = 7.2 Hz, 1H), 3.13-2.88 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.9 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 141.5, 132.9, 130.1, 124.4 (q, *J* = 276.2 Hz), 123.9, 122.0, 53.3 (q, *J* = 3.4 Hz), 43.5 (q, *J* = 28.5 Hz). GC-MS (EI): Calculated for $C_9H_7ClF_3NO_2$ [M]: 253.0; Found: 253.0

(**3i**) [32]: Yellow oil, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 5.87 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 3.08-2.88 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.0 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 134.4, 133.8, 129.8, 129.7, 124.7, 124.5 (q, *J* = 276.3 Hz), 49.085 (q, *J* = 3.5 Hz), 43.43 (q, *J* = 28.9 Hz).

(**3j**): Pale yellow oil, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.65 (m, 3H), 7.51-7.46 (m, 1H), 5.51 (t, *J* = 7.2 Hz, 1H), 3.15-2.94 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.0 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 133.5, 133.3, 129.5, 128.0, 124.3 (q, *J* = 276.3 Hz), 116.4, 111.1, 51.4 (q, *J* = 3.4 Hz), 42.74 (q, *J* = 28.7 Hz). HRMS (EI): Calculated for $C_{10}H_7ClF_3N$ [M]: 233.0219; Found: 233.0223. IR: 3446, 2228, 1634, 1601, 1489, 1451, 1430, 1381, 1334, 1303, 1262, 1146, 1089, 1041, 935, 859, 762, 642, 597, 555, 505 cm^{-1}.

(**3k**): Colorless oil, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 7.72-7.67 (m, 4H), 3.17-3.0 (m, 2H), 2.15 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 147.8, 132.1, 126.8, 124.1 (q, *J* = 277.3 Hz), 118.1, 112.1, 65.4 (q, *J* = 2.2 Hz), 49.0 (q, *J* = 27.6 Hz), 30.3 (q, *J* = 1.5 Hz). HRMS (EI): Calculated for $C_{11}H_9ClF_3N$ [M]: 247.0376; Found: 247.0378. IR: 3413, 2995, 2232, 1610, 1506, 1364, 1310, 1259, 1235, 1149, 1122, 1064, 1035, 842, 750, 710, 624, 560 cm^{-1}.

(**3l**): White solid, 73% yield, m.p. 59-62 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 5.28 (t, *J* = 7.0 Hz, 1H), 3.96 (s, 3H), 3.14-2.90 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.9 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 139.1, 135.0, 132.4, 130.6, 130.4, 128.3, 126.1, 125.9, 124.66, 124.65 (q, *J* = 276.3 Hz), 54.7 (q, *J* = 3.4 Hz), 52.2, 43.4 (q, *J* = 28.3 Hz). HRMS (EI): Calculated for $C_{15}H_{12}ClF_3O_2$ [M]: 316.0478; Found: 316.0470. IR (KBr): 3412, 3075, 3025, 3970, 1716, 1633, 1439, 1384, 1348, 1282, 1256, 1226, 1205, 1130, 1109, 1047, 989, 920, 895, 855, 818, 752, 683, 670, 574, 486 cm^{-1}.

(**3n**) [31]: White solid, 92% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2 H), 5.10 (dd, J_1 = 7.4 Hz, J_2 = 6.6 Hz, 1H), 3.03-2.76 (m, 2H), 2.27 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.0 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 150.9, 137.1, 127.9, 124.7 (q, *J* = 276.2 Hz), 122.1, 54.0 (q, *J* = 3.5 Hz), 43.7 (q, *J* = 28.4 Hz), 20.9. GC-MS (EI): Calculated for $C_{11}H_{10}ClF_3O_2$ [M]: 266.0; Found: 266.0.

(**3o**): White solid, 82% yield, m.p. 124-126 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.8 Hz, 1H), 7.37-7.36 (m, 2H), 6.31 (s, 1H), 5.18 (t, *J* = 7.0 Hz, 1H), 3.11-2.87 (m, 2H), 2.45 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.87 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 153.4, 151.7, 143.3, 125.3, 124.4 (q, *J* = 276.3 Hz), 122.5, 120.3, 115.5, 115.3, 53.5 (q, *J* = 3.4 Hz), 43.2 (q, *J* = 28.5 Hz), 18.4. HRMS (EI): Calculated for $C_{13}H_{10}ClF_3O$ [M]: 290.0321; Found: 290.0324. IR (KBr): 3093, 2993, 1727, 1622, 1560, 1510, 1421, 1386, 1257, 1135, 1104, 1070, 1048, 1017, 982, 913, 885, 864, 740, 709, 672, 656, 582, 522, 463, 438 cm^{-1}.

(**3p**) [31]: White solid, 86% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.2 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 6.8 Hz, 1H), 5.09-5.02 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.31-3.19 (m, 2H), 3.02-2.77 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.8 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 166.8, 138.3, 137.1, 133.7, 131.6, 129.8, 128.4, 126.9, 126.8, 124.6 (q, *J* = 276.3 Hz), 61.5, 54.3 (q, *J* = 3.4 Hz), 53.4 (d, *J* = 2.1 Hz), 43.4 (q, *J* = 28.2 Hz), 37.4, 13.9. MS (ESI^+): Calculated for $C_{21}H_{22}ClF_3NO_3^+$ $[M+H]^+$: 428.1; Found: 428.0.

(**3q**) [31]: 1:1 stereoisomers were obtained. Colorless oil, 85% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.11 (s, 1H), 5.07 (t, *J* = 7.0 Hz, 1H), 3.05-2.79 (m, 4H), 2.53-2.46 (m, 1H), 2.44-2.39 (m, 1H), 2.32-2.26 (m, 1H), 2.18-1.93 (m, 4H), 1.68-1.39 (m, 6H), 0.90 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.0 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.4, 140.70, 140.69, 137.13, 137.12, 137.06, 137.04, 127.2, 127.1, 125.9, 125.8, 124.7 (q, *J* = 276.2 Hz), 123.91, 123.86, 54.6-54.5 (m), 50.3, 47.7, 44.2, 43.40 (q, *J*

= 28.2 Hz), 43.35 (q, *J* = 28.1 Hz), 37.8, 35.6, 31.4, 29.18, 29.16, 26.2, 25.5, 21.4, 13.7.

(**3r**) [42]: White solid, 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 4.64 (dd, J_1 = 8.8 Hz, J_2 = 3.6 Hz, 1H), 3.31-3.19 (m, 1H), 2.82-2.69 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.1 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 136.4, 129.1, 125.6, 122.1 (q, *J* =275.6 Hz), 120.4, 52.2 (q, *J* = 3.0 Hz), 38.9 (q, *J* = 29.7 Hz). GC-MS (EI): Calculated for $C_{10}H_9ClF_3NO$ [M]: 251.0; Found: 251.0.

(**3s**) [42]: Colorless oil, 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.42 (m, 3H), 7.29-7.27 (m, 2H), 4.33 (dd, J_1 = 9.0 Hz, J_2 = 4.6 Hz, 1H), 3.33 (s, 3H), 3.28-3.14 (m, 1H), 2.63-2.51 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.7 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 142.1, 130.1, 128.8, 127.1, 124.7 (q, *J* =276.1 Hz), 45.8 (q, *J* = 3.2 Hz), 38.9 (q, *J* = 28.8 Hz), 38.0. GC-MS (EI): Calculated for $C_{11}H_{11}ClF_3NO$ [M]: 265.0; Found: 265.0.

(**3t**): White solid, 43% yield, m.p. 80-81 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 7.06 (s, 1H), 4.52 (dd, J_1 = 8.8 Hz, J_2 = 3.6 Hz, 1H), 4.45 (d, *J* = 4 Hz, 2H), 3.25-3.13 (m, 1H), 2.74-2.61 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.1 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 136.9, 128.8, 127.9, 127.7, 125.1 (q, *J* = 275.7 Hz), 51.9 (q, *J* = 3.1 Hz), 44.2, 39.0 (q, *J* = 29.6 Hz). HRMS (EI): Calculated for $C_{11}H_{11}ClF_3NO$ [M]: 265.0481; Found: 265.0478. IR (KBr): 3293, 3071, 2993, 2945, 1655, 1557, 1456, 1424, 1402, 1367, 1340, 1298, 1266, 1232,1143, 1070, 1042, 858, 749, 698, 658, 623, 579, 511, 468 cm^{-1}.

(**3u**): White solid, 46% yield, m.p. 113-115 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.0 Hz, 1H), 7.24-7.20 (m, 2H), 7.09 (t, *J* = 8.0 Hz, 1H), 4.64 (t, *J* = 6.8 Hz, 1H), 4.40-4.33 (m, 1H), 4.14-4.07 (m, 1H), 3.32-3.18 (m, 3H), 2.89-2.76 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.1 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 142.2, 131.5, 127.7, 125.1 (q, *J* = 275.8 Hz), 124.9, 124.7, 117.5, 48.3 (q, *J* = 3.1 Hz), 47.8, 38.3 (q, *J* = 29.2 Hz), 28.0. HRMS (EI): Calculated for $C_{12}H_{11}ClF_3NO$ [M]: 277.0481; Found: 277.0479. IR (KBr): 3027, 2935, 2864, 1652, 1597, 1484, 1464, 1429, 1385, 1285, 1243, 1221, 1204, 1143, 1068, 937, 857, 760, 648, 591, 546, 492, 424 cm^{-1}.

(**3v**) [42]: Colorless oil, 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.32 (m ,5H), 3.34 (s, 3H), 3.19-3.07 (m, 1H), 2.78-2.67 (m, 1H), 1.63 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.3 (t, *J* = 10.5 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 143.8, 129.4, 128.39, 128.37, 124.6 (q, *J* = 277.1 Hz), 63.4 (q, *J* = 2.5 Hz), 46.7 (q, *J* = 28.0 Hz), 42.0, 29.0. GC-MS (EI): Calculated for $C_{12}H_{13}ClF_3NO$ [M]: 279.1; Found: 279.1.

(**3w**) [42]: Colorless oil, 49% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 4.70 (t, J = 6.9 Hz, 1H), 3.25-3.08 (m, 1H), 2.93-2.76 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.9 (t, *J* = 9.9 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 150.1, 129.7, 126.7, 124.6 (q, *J* = 275.8 Hz), 120.9, 48.8 (q, *J* = 3.3 Hz), 39.1 (q, *J* = 29.7 Hz). GC-MS (EI): Calculated for $C_{10}H_8ClF_3O_2$ [M]: 252.0; Found: 252.0.

(**3x**) [42]: Colorless oil, 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 5.32 (t, *J* = 6.4 Hz, 1H), 3.27-3.14 (m, 1H), 2.89-2.75 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.0 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 134.3, 133.2, 129.4, 129.1, 125.3 (q, *J* = 275.5 Hz), 48.3 (q, *J* = 2.9 Hz), 37.4 (q, *J* = 29.2 Hz). GC-MS (EI): Calculated for $C_{10}H_8ClF_3O$ [M]: 236.0; Found: 236.0.

(**3y**): Pale yellow oil, 41% yiled. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.46-4.40 (m, 1H), 4.28 (dd, J_1 = 10.0 Hz, J_2 = 4.8 Hz, 1H), 4.18 (dd, J_1 = 10.0 Hz, J_2 = 6.0 Hz, 1H), 2.99-2.86 (m, 1H), 2.75-2.62 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.9 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 134.1, 125.1 (q, *J* = 275.6 Hz), 118.7, 115.3, 105.2, 70.4, 50.0 (q, *J* = 3.2 Hz), 38.8 (q, *J* = 29.2 Hz). HRMS (EI): Calculated for $C_{11}H_9ClF_3NO$ [M]: 263.0325; Found: 263.0328. IR: 3429, 2952, 2227, 1607, 1577, 1509, 1462, 1430, 1394, 1254, 1154, 1090, 1042, 945, 835, 737, 679, 636, 549, 512, 431 cm^{-1}.

(**3z**): White solid, 41% yield, m.p. 96-98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 1H), 7.12-7.07 (m, 2H), 6.27 (s, 1H), 4.32-4.25 (m, 1H), 2.97-2.83 (m, 2H), 2.79-2.56 (m, 2H), 2.44 (s, 3H), 2.42-2.34 (m, 1H), 2.16-2.06 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.7 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 160.3, 154.0, 152.7, 151.9, 125.4, 124.9 (q, *J* = 275.9 Hz), 117.9, 117.8, 114.5, 110.2, 53.0 (q, *J* = 3.2 Hz), 42.4 (q, *J* = 28.5 Hz), 32.6, 30.7, 18.6. HRMS (ESI): Calculated for $C_{16}H_{15}ClF_3O_4^+$ $[M+H]^+$: 363.0605; Found:363.0601. IR (KBr): 3081, 2923, 1739, 1615, 1574, 1389, 1265, 1137, 1018, 982, 929, 883, 866, 821, 797, 741, 707, 662, 633, 562, 525, 476, 453, 413 cm^{-1}.

(**4a**): White solid, m.p.: decomposes before melting as determined by DSC measurements, 33% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.8 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 6.64 (s, 1H), 4.20-4.16 (m, 1H), 3.97 (s, 2H), 2.95-2.72 (m, 2H), 2.72-2.46 (m, 3H), 2.43-2.31 (m, 1H), 2.29-2.21 (m, 1H), 2.18-1.82 (m, 8H), 1.67-1.37 (m, 6H), 0.90 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.9 (t, *J* = 11.3 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.7, 156.7, 137.7, 132.2, 126.3, 125.2 (q, *J* = 276.0 Hz), 114.4, 112.0, 66.7, 53.8 (q, *J* = 3.1 Hz), 50.3, 47.9, 43.9, 42.4 (q, *J* = 28.3 Hz), 38.3, 35.8, 34.8, 31.5, 29.6, 26.5, 25.9, 25.8, 21.5, 13.8. HRMS (EI): Calculated for $C_{24}H_{30}ClF_3O_2$ [M]: 442.1886; Found: 442.1893. IR (KBr): 3454, 2934, 2866, 1735, 1610, 1571, 1500, 1390, 1342, 1243. 1187, 1150, 1063, 1006, 959, 879, 823, 787, 732, 628, 879, 439 cm^{-1}.

(**4b**): Colorless oil, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.68 (m, 4 H), 3.23-2.97 (m, 2H), 2.22 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.3--81.4 (m, 3F), -110.8--112.6 (m, 2F), -124.77--124.79 (m, 2F), -126.0--126.1 (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 132.2, 126.7, 118.1, 112.3, 121.8-105.3 (m), 66.0, 45.2 (t, *J* = 19.5 Hz), 30.8. HRMS (EI): Calculated for $C_{14}H_9ClF_9N$ [M]: 397.0280; Found: 397.0285. IR: 3080, 2995, 2953, 2233, 1610, 1506, 1410, 1353, 1227, 1135, 1079, 1053, 1019, 939, 873, 846, 745, 723, 694, 591, 571, 532 cm^{-1}.

(**4c**): Colorless oil, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.42 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 2H), 4.44 (dd, J_1 = 9.2 Hz, J_2 = 3.6 Hz, 1H), 3.41-3.25 (m, 4 H), 2.58-2.44 (m, 1H). ^{19}F

NMR (376 MHz, $CDCl_3$) δ -81.2--81.3 (m, 3F), -112.4--114.6 (m, 2F), -124.70--124.73 (m, 2F), -126.1--126.2 (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 142.1, 130.1, 128.9, 127.18, 121.9-105.3 (m), 45.18 (t, *J* = 2.7 Hz), 38.0, 36.1 (t, *J* = 20.3 Hz). HRMS (EI): Calculated for $C_{14}H_{11}ClF_9NO$ [M]: 415.0385; Found: 415.0378. IR: 3340, 3066, 2962, 1679, 1597, 1497, 1432, 1354, 1236, 1135, 1075, 1037, 880, 848, 774, 700, 670, 564, 530, 483, 411 cm^{-1}.

(**4d**): 1:1 stereoisomers were obtained. White solid, m.p.: decomposes before melting as determined by DSC measurements, 66% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.14 (s, 1H), 5.20 (t, *J* = 6.8 Hz, 1H), 3.07-2.81 (m, 4H), 2.54-2.27 (m, 3 H), 2.19-1.96 (m, 4H), 1.69-1.41 (m, 6H), 0.91 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.2 (t, *J* = 11.3 Hz, 3F), -113.7--114.0 (m, 2F), -124.61--124.64 (m, 2F), -125.98--126.04 (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.4, 140.81, 140.80, 137.6, 137.3, 127.21, 127.15, 126.0, 123.93, 123.88, 121.9-105.4 (m), 53.69-53.64 (m), 50.4, 47.8, 44.3, 40.31 (t, *J* = 20.3 Hz), 40.28 (t, *J* = 20.4 Hz), 37.9, 35.7, 31.5, 29.3, 29.2, 26.3, 25.5, 21.5, 13.7. HRMS (EI): Calculated for $C_{24}H_{24}ClF_9O$ [M]: 534.1372; Found: 534.1361. IR (KBr): 3460, 2933, 2863, 1740, 1500, 1456, 1355, 1233, 1134, 1102, 1053, 1013, 881, 850, 824, 747, 713, 678, 591, 527 cm^{-1}.

(**6**) [60]: Colorless oil, 57% isolated yield. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 10H), 5.73-5.61 (m, 1H), 5.46-5.36 (m, 1H), 5.21-5.10 (m, 4H), 3.00 (d, *J* = 7.2, Hz, 2H), 2.75-2.62 (m, 2H); ^{19}F NMR: (376 MHz, $CDCl_3$) δ -66.4 (t, *J* = 10.5 Hz, 3F) (*E* configuration); HRMS (DART): Calculated for $C_{22}H_{21}ClF_3O_4^+$ $[M+H]^+$:441.1075; Found: 441.1073.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version.

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