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Copper-Mediated Halotrifluoromethylation of Unactivated Alkenes

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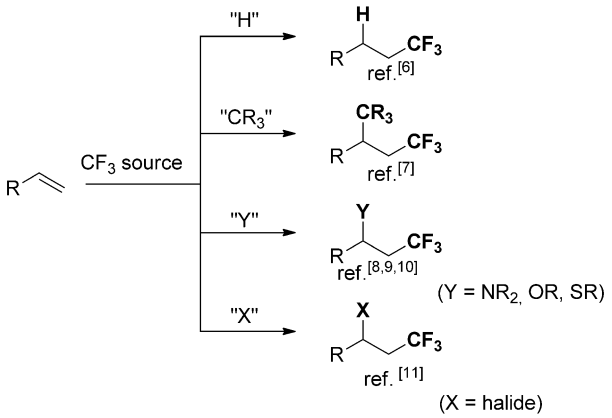
Abstract: A copper-mediated halotrifluoromethylation of unactivated alkenes using Umemoto's reagent and copper(I) halide (CuX, X = Cl, Br, and I) was developed. The CuX species (CuI, CuBr, and CuCl) were chosen as the source for both copper and halides because of their benchtop stability, commercial availability, and relatively low cost. Simple exchange of the copper salt provided the desired simultaneous and regioselective incorporation of the halogen atom and of the CF_3 group to various alkenes. This protocol offers an efficient and practical route to various β-halotrifluoromethylated alkanes. Further modifications of the C–Br bond to C–B, C–N and C–S bonds were performed. These derivatizations show the feasibility of late-stage modifications.

Keywords: copper-mediated reaction; halotrifluoromethylation; late stage modification; trifluoromethyl group (CF_3); unactivated alkenes

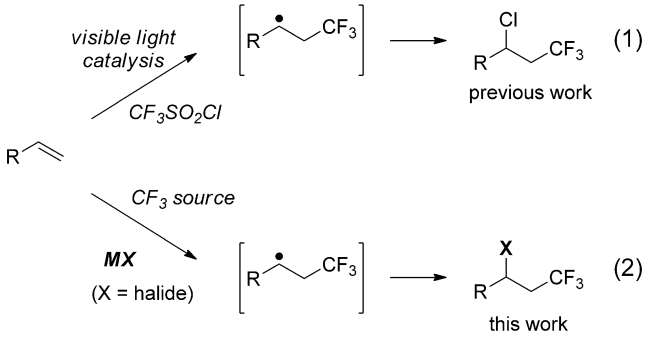
Introduction

Because of their unique properties, fluorine-containing molecules are of great importance in pharmaceutical, agricultural, and materials science, and efforts have been directed toward the development of new organic transformations for the introduction of fluorine.[1] In particular, for many years, the introduction of a CF_3 group has been one of the main focuses in medicinal chemistry because of the great impact of this moiety on biological properties such as lipophilicity, metabolic stability, and binding selectivity.[2] However, because of the characteristic chemical reactivity of fluorine and the limited commercial availability of the sources, conventional methods for introducing CF_3 groups showed limited application in the preparation of organofluorine compounds.[3] In order to overcome these drawbacks, several new types of reactions have been developed and various sources of CF_3 have been employed photochemically, oxidatively, reductively, and electrochemically.[4] Among the synthetic methods using active CF_3-containing species, trifluoromethylation of alkenes has been extensively studied because, in many cases, at the same time a variety of functional groups are easily introduced into the β position to the CF_3 group.[5] For example, C–H,[6] C–C,[7] C–N,[8] C–O,[9] C–S,[10] or C–X[11] (X = halogen) bonds were simultaneously formed along with the C–CF_3 bond (Scheme 1). This strategy has many advantages from the synthetic point of view because it allows the preparation of various CF_3-containing multi-functional aliphatic derivatives from a common alkene intermediate. In particular, the halotrifluoromethylation of alkenes has been an important focus of study not only because of its versatility but also because halogen atoms are useful handles for further manipulations. In spite of the importance of the vicinal halotrifluoromethylation, most methodologies were directed towards the development of iodotrifluoromethylation. Only a few methods introduce other halogen elements, with narrow substrate scopes and harsh reaction conditions.[9g,11b] Thus, a new reaction for incorporation of



Scheme 1. Various vicinal difunctionalizations of alkenes (C–H, C–C, C–N, C–O, C–S, and C–X bond formation along with the introduction of CF_3).

different halogen atoms from a common intermediate is needed. Our group previously reported the vicinal chlorotrifluoromethylation of alkenes using CF_3SO_2Cl and visible light catalysis [Eq. (1), Scheme 2].[11j] In the course of this study, we assumed that the same alkyl radical intermediate could be a new useful platform for the incorporation of different halogen atoms. In particular, we speculated that a transition metal halide that can generate the active CF_3 species and serve as the halogen source would be a good candidate to address this issue [Eq. (2), Scheme 2].



Scheme 2. Strategy for the transition metal-mediated halotrifluoromethylation of alkenes.

Results and Discussion

As a proof of concept, Cu(I)X species (CuI, CuBr, and CuCl) were chosen as the source for both copper and halides because of their benchtop stability, commercial availability, and relatively low cost.[12a] Moreover, CuX has been used as halide source in the Sandmeyer reaction.[13] In addition, these species generate a CF_3 radical from commercial CF_3 sources such as

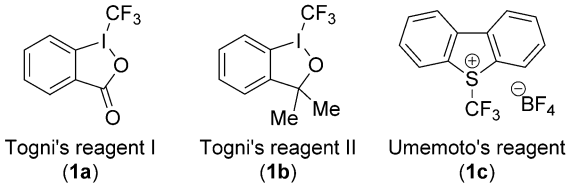
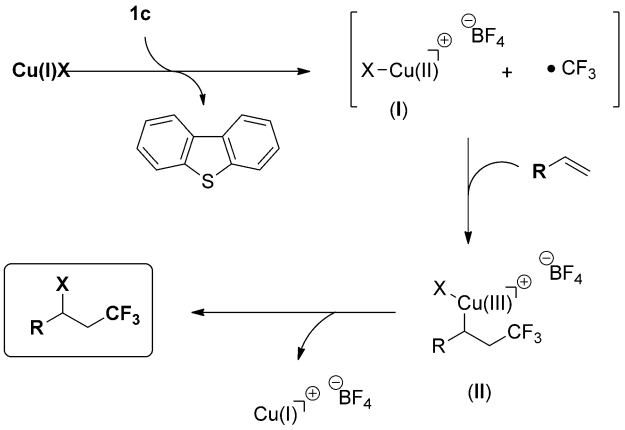


Figure 1. CF_3 sources.

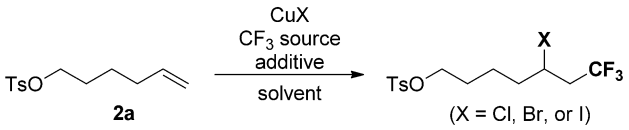
Togni's reagent[14] I (**1a**), II (**1b**) and Umemoto's reagent[15] (**1c**) (Figure 1).

Our hypothesized reaction design is described in Scheme 3. When Cu(I)X activates the CF_3 source, e.g., Umemoto's reagent (**1c**), Cu(I) will be oxidized to Cu(II) species (**I**) and the CF_3 radical will be formed. This CF_3 radical would be easily trapped by an alkene to give an alkyl radical, which will recombine with Cu(II) to produce the Cu(III) species (**II**). Reductive elimination will eventually generate the desired product. On the basis of our hypothesis, we first tested the bromotrifluoromethylation of alkene **2a** using the three different CF_3 reagents (**1a**, **1b**, and **1c**). Pleasingly, using **1c**, the desired product containing vicinal Br- and CF_3 moieties was obtained regioselectively in 80% yield (entry 3, Table 1). However Togni's reagents **1a** and **1b** showed little or no reactivity (entries 1 and 2). Solvent screening revealed that MeCN was the optimal solvent (entries 3–5). To validate our strategy of simply changing the Cu salt, CuI was applied instead of CuBr. As expected, CuI showed very high reactivity to generate the target iodotrifluoromethylated product (entry 6). However, when CuCl was employed, the desired product was obtained in only 40% yield (entry 7). In order to improve the low efficiency of CuCl, various reaction parameters were screened. During investigation of the effect of additives, 2,2′-bipyridyl was found to improve the reaction to 59% yield (entry 8). Encour-



Scheme 3. Hypothesized reaction scheme.

Table 1. Optimization of halotrifluoromethylation of alkenes.[a]



Entry	CuX	CF_3	Additive[b]	Solvent	Yield[c]
1	CuBr	**1a**	-	MeCN	36%
2	CuBr	**1b**	-	MeCN	trace
3	CuBr	**1c**	-	MeCN	80%
4	CuBr	**1c**	-	DCE	49%
5	CuBr	**1c**	-	THF	46%
6	CuI	**1c**	-	MeCN	89%
7	CuCl	**1c**	-	MeCN	40% (25%)[d]
8	CuCl	**1c**	2,2'-bipryidyl	MeCN	59%
9	CuCl	**1c**	PCy_3	MeCN	75%
10	CuCl	**1c**	B_2pin_2	MeCN	84% (72%)[d]
11	CuBr	**1c**	B_2pin_2	MeCN	93% (85%)[d]
12	CuI	**1c**	B_2pin_2	MeCN	95% (90%)[d]

[a] The reactions were carried out under an N_2 atmosphere at 65 °C for 20 h using **2a** (0.25 mmol), CuX (1.5 equiv.), CF_3 source (2 equiv.) and K_2HPO_4 (1 equiv.).
[b] 0.1 equiv.
[c] Yields were determined by ^1H NMR.
[d] Isolated yield.

aged by this result, different additives were tested. In the event, PCy_3 and B_2pin_2 (10 mol%) were found to be very efficient, producing the corresponding chlorotrifluoromethylated product in 75% and 84% yield, respectively (entries 9 and 10).

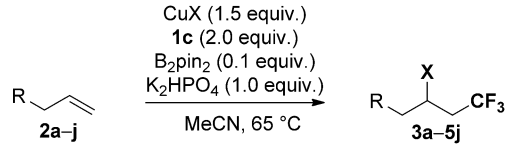
A similar ligand effect was found in related copper chemistry.[16] When B_2pin_2 was applied with CuBr, the product yield increased from 80% to 93%, as expected (entry 11). This effect was consistent in the case of CuI (from 89% to 95% yield; entry 12). Therefore, by simply changing the copper halide salt, after optimization we achieved I-, Br-, and Cl-trifluoromethylation of the unactivated alkene **2a**.[12b]

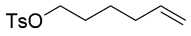
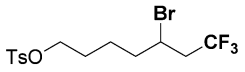
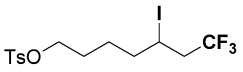
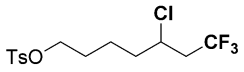
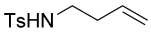
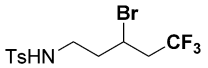
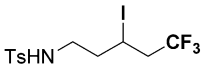
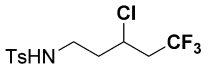
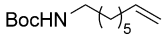
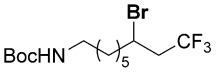
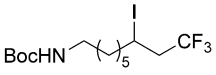
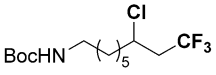
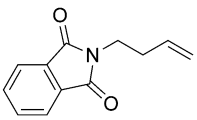
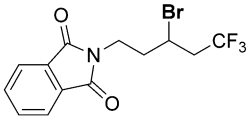
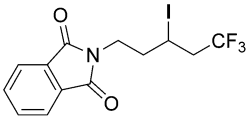
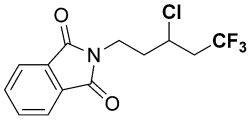
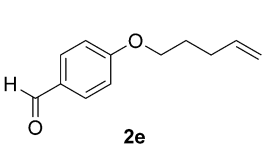
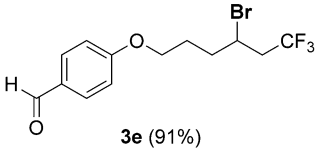
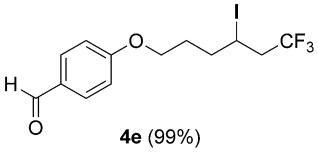
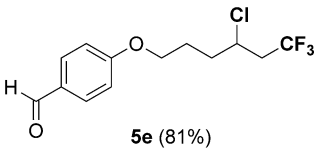
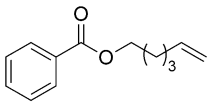
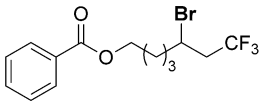
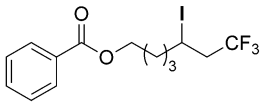
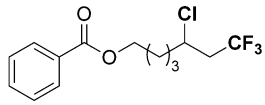
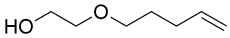
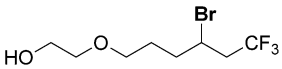
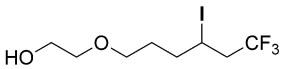
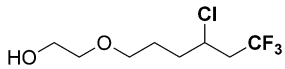
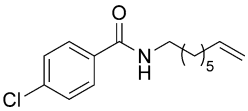
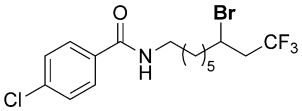
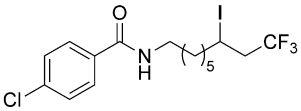
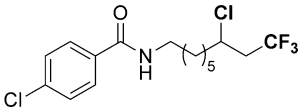
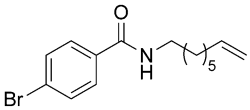
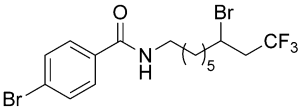
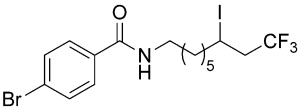
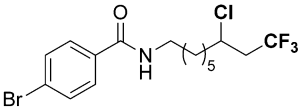
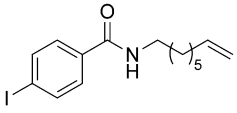
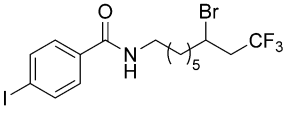
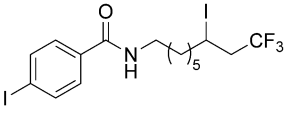
With the optimized conditions in hand, we examined the scope of the bromotrifluoromethylation of terminal alkenes. Various terminal alkenes showed high reactivity and regioselectivity under the optimized conditions (Table 2). The *O*-tosylated alcohol **2a** was converted into the corresponding bromotrifluoromethylated product **3a** in very high yield (85%). Also, *N*-tosyl (**2b**) and Boc (**2c**) protected amine-containing alkenes were efficiently transformed into the desired products in 77% (**3b**) and 83% (**3c**) yield, respectively. Moreover, the phthalimide-containing bromotrifluoromethylated product **3d** was obtained from the corresponding terminal alkene **2d** with comparable efficiency (74%). Notably, unprotected aldehyde **2e** participated smoothly in the reaction (91%). In addition, the ester functional group (**2f**) was well tolerated by this procedure (93%). Surprisingly, the unprotected primary alcohol-containing alkene **2g** was smoothly converted into the desired product **3g** (70%). Moreover, alkenes bearing an amide group (**2h**, **2i**, and **2j**) afforded the desired products in high yields. Interestingly, aromatic halogens, such as Cl, Br, and I, showed high stability under the reaction conditions (81%, 74%, and 78%, respectively). Thus, this transformation proved to be highly tolerant of a variety of functional groups. Notably, this is the first report of vicinal bromotrifluoromethylation of unactivated alkenes with broad substrate scope.[17] Because the bromo group is a very useful functional handle for further manipulations, the products could serve as building blocks for various derivatizations.

Next, in order to expand the scope of the reaction CuI was employed using the optimized condition. The same set of terminal alkenes **2a–j** was employed. The general reactivity of the reaction is similar to that of CuBr. Iodotrifluoromethylated alkanes containing OTs (**4a**, 90%), NHTs (**4b**, 88%), NHBoc (**4c**, 83%), and phthalimide (**4d**, 64%) moieties were produced in high yields and selectivity. Products containing aldehyde (**4e**, 99%), ester (**4f**, 85%), unprotected alcohol (**4g**, 60%), and amide (**4h–4j**; 81%, 83%, and 82%, respectively) moieties were obtained with comparable functional group tolerance. This type of product in particular has been extensively produced in recently developed methodologies with the use of CF_3I.[4] However, the handling of gaseous CF_3I is inconvenient and problematic. The combination of CuI and Umemoto's reagent can therefore provide an alternative way to access the iodotrifluoromethylated products. Finally, chlorotrifluoromethylation was performed on the same substrates **2a–j** using CuCl. The products **5a–j** were obtained with similar yields and selectivities.

After the scope of terminal alkenes was explored, other types of alkenes, such as 1,1-disubstituted and internal alkenes, were subjected to the reaction conditions (Table 3). The 1,1-disubstituted alkene **6a** was converted into the corresponding halotrifluoromethylated products **7a** (I, 71%), **8a** (Br, 71%), and **9a** (Cl, 74%) in high yields (entry 1) by simply changing the copper halide source. (*S*)-Carvone **6b** reacted smoothly to afford the desired iodo- (**7b**, 68%), bromo- (**8b**, 72%), and chloro- (**9b**, 63%) trifluoromethylated products. In addition, (*S*)-(−)-perillaldehyde **6c** was easily transformed into the desired products **7c** (I, 62%), **8c** (Br, 64%), and **9c** (Cl, 53%) in moderate yields (entry 3). These results showed the tolerance of α,β-unsaturated ketones (**6b**) and aldehydes (**6c**) under the optimized protocol. Moreover, a biologically active natural compound (+)-nootkatone **6d** was tested and the iodo- (**7d**, 84%), bromo- (**8d**, 71%), and chloro- (**9d**, 69%) derivatives were formed in

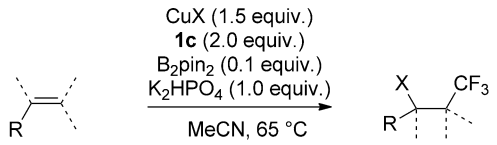
Table 2. Reaction scope of halotrifluoromethylation of terminal alkenes.[a]



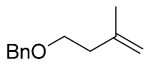
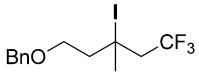
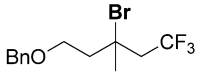
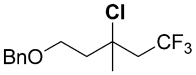
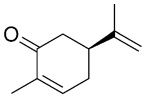
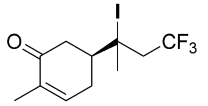
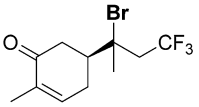
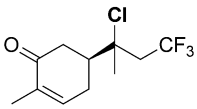
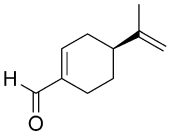
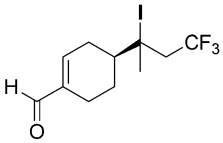
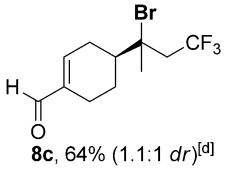
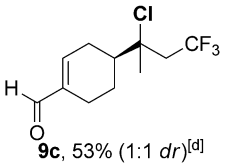
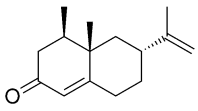
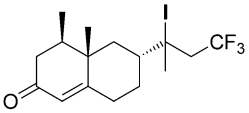
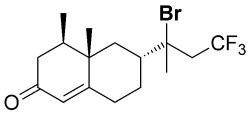
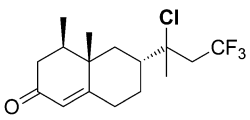
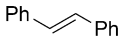
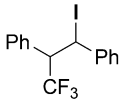
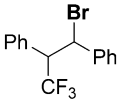
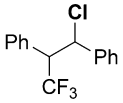
Entry	Substrate	Products[b]		
1	 **2a**	 **3a** (85%)	 **4a** (90%)	 **5a** (72%)
2	 **2b**	 **3b** (77%)	 **4b** (88%)	 **5b** (75%)
3	 **2c**	 **3c** (83%)	 **4c** (83%)	 **5c** (77%)
4	 **2d**	 **3d** (74%)	 **4d** (64%)	 **5d** (75%)
5	 **2e**	 **3e** (91%)	 **4e** (99%)	 **5e** (81%)
6	 **2f**	 **3f** (93%)	 **4f** (85%)	 **5f** (75%)
7	 **2g**	 **3g** (70%)	 **4g** (60%)	 **5g** (55%)
8	 **2h**	 **3h** (81%)	 **4h** (81%)	 **5h** (72%)
9	 **2i**	 **3i** (74%)	 **4i** (83%)	 **5i** (71%)
10	 **2j**	 **3j** (78%)	 **4j** (82%)	**5j** (68%)

[a] The reactions were carried out under an N_2 atmosphere for 20 h using **2a–j** (0.25 mmol) in MeCN (0.125 M).
[b] Isolated yield.

Table 3. Reaction scope of 1,1-disubstituted and internal alkenes.[a]

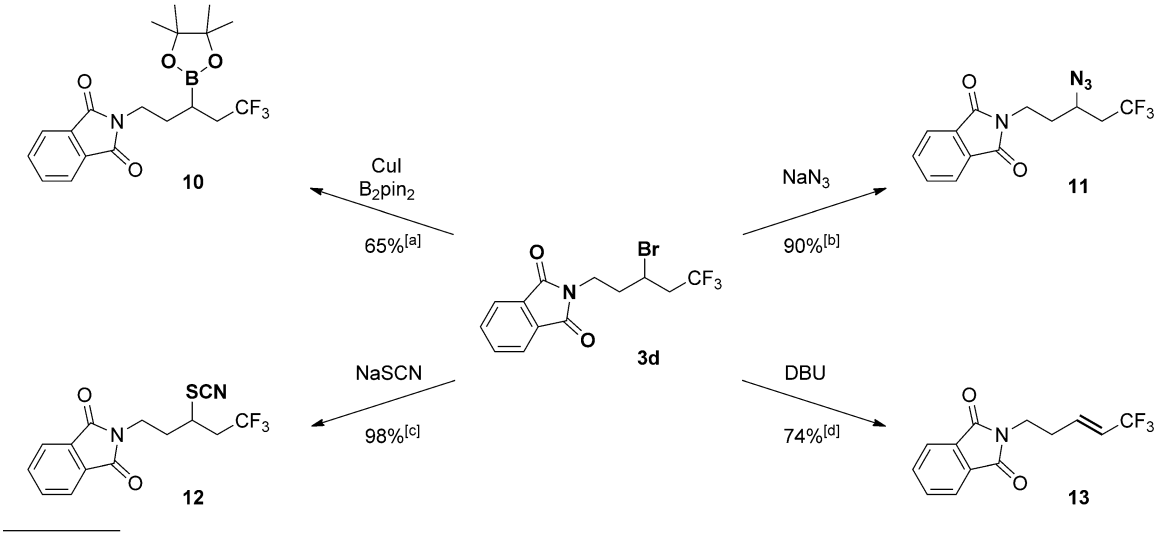


6a–e **7a–9e**

Entry	Substrate	Products[b]		
1	 **6a**	 **7a.** 0% (71%)[c]	 **8a**, 71%	 **9a**, 74%
2	 **6b**	 **7b**, 68% (1:1 *dr*)[d]	 **8b**, 72% (1.1:1 *dr*)[d]	 **9b**, 63% (1:1 *dr*)[d]
3	 **6c**	 **7c**, 0% (62%)[c]	 **8c**, 64% (1.1:1 *dr*)[d]	 **9c**, 53% (1:1 *dr*)[d]
4	 **6d**	 **7d**, 0% (84%)[c]	 **8d**, 71% (1:1 *dr*)[d]	 **9d**, 69% (1:1 *dr*)[d]
5	 **6e**	 **7e**, 37% (83%)[c] (1:0.8 *dr*)[d]	 **8e**, 80% (1.5:1 *dr*)[d]	 **9e,** 73% (2:1 *dr*)[d]

[a] The reactions were carried out under an N_2 atmosphere for 20 h using **6a–e** (0.25 mmol) in MeCN (0.125 M).
[b] Isolated yield.
[c] The yields were determined by ^{1}H NMR and the products decomposed during purification.
[d] The *dr* was determined by ^{1}H NMR.

high yields (entry 4). When the symmetric internal alkene **6e** was employed, in all cases, internal C–CF_3 and C–X bonds were formed simultaneously (**7e**, **8e**, and **9e**, entry 5). Notably, whereas tertiary bromo- (**8a–d**) and chloro-containing products (**9a–d**) showed high stability, tertiary iodo-containing compounds (**7a–d**) were readily decomposed during purification. Thus, investigation of the substrate scope (Table 2 and Table 3) showed that various alkenes were smoothly converted to the desired products by simple change of the Cu salt. Having established the scope of the reaction, various modifications were performed on the halotrifluoromethylated products to demonstrate the potential of the halogen atom for further derivatization (Scheme 4). Under copper-catalyzed borylation conditions,[18] **3d** was efficiently converted to boronic ester **10** (65% yield), which is a useful synthetic intermediate for transition metal-catalyzed cross-coupling reactions. An azide group can be easily introduced in high yield by treatment with NaN_3 (**11**, 90% yield), proving the efficient formation of a C–N bond. In addition, nucleophilic substitution reaction with NaSCN was performed to achieve C–S bond formation (**12**, 98%). Treatment of **3d** with a base such as DBU generated the elimination product **13** in high yield (74%) and selectivity (*E*-alkene). These various derivatization examples showed the possibility of late-stage modifications of the halotrifluoromethylated



[a] The reaction was carried out under an N_2 atmosphere for 24 h using **3d** (0.50 mmol), CuI (0.05 mmol), PPh_3 (0.065 mmol), LiOEt (1.0 mmol) and B_2pin_2 (0.75 mmol) in DMF (0.125 M) at 37 ° C.
[b] The reaction was carried out under an N_2 atmosphere for 4 h using **3d** (0.25 mmol), NaN_3 (0.5 mmol) and NaI (0.05 mmol) in DMF (0.125 M) at 80 °C.
[c] The reaction was carried out under an N_2 atmosphere for 4 h using **3d** (0.25 mmol), NaSCN (0.5 mmol), NaI (0.05 mmol) in DMF (0.125 M) at 80 °C.
[d] The reaction was carried out under an N_2 atmosphere for 1 h using **3d** (0.25 mmol) and DBU (0.25 mmol) in DCM (0.2 M) at 0 °C.

Scheme 4. Derivatization of the bromotrifluoromethylated product.

product, which can be highly valuable in medicinal chemistry.

Conclusions

We have developed a copper-mediated halotrifluoromethylation of alkenes using inexpensive and stable CuX salts (X = Cl, Br, and I). This reaction provided an efficient and practical route to various β-halotrifluoromethylated alkanes by simple change of CuX salt. The regioselectivity and the wide substrate scope make this protocol a very convenient strategy. In addition, the possibility of further manipulations of the halogen group is highly attractive in the field of medicinal chemistry.

Experimental Section

General Remarks

All of the Cu reactions were carried out under an N_2 atmosphere using pre-dried screw-capped sealed tubes. Chemical reagents were purchased from Aldrich and TCI. Commercially available alkenes were purified immediately prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (Merck TLC Silica gel 60 F254). Flash chromatography was performed on silica gel 60 (200–400 mesh). NMR spectra were recorded on a Varian 300 and Bruker 300 NMR spectrophotometer operating at 300 MHz and 500 MHz. High resolution mass spectra were obtained on a Varian 1200L quadrupole MS (EI) spectrophotometer. FT-IR spectra were obtained using an FT-IR Smiths Identify IR. Melting points were obtained on a Mettler Toledo MP50 apparatus and are uncorrected.

Typical Experimental Procedure for Halotrifluoromethylation Reactions of Alkenes and Characterization for Selected Examples

In a 4-mL pre-dried screw-capped sealed tube, a suspension of alkene (0.25 mmol), Umemoto's reagent **1c** (0.50 mmol), CuX (0.38 mmol), B_2pin_2 (0.03 mmol) and K_2HPO_4 (0.25 mmol) in MeCN (0.125 M) was stirred at 65 °C for 20 h under an N_2 atmosphere. The reaction mixture was concentrated under vacuum. Purification was achieved by column chromatography on SiO_2 gel using hexanes/ethyl acetate.

5-Bromo-7,7,7-trifluoroheptyl 4-ethylbenzenesulfonate (3a): Yield: 85%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.82$ (d, $J = 8.0$ Hz, 2H), 7.38 (d, $J = 8.0$ Hz, 2H), 4.13–4.05 (m, 3H), 2.79–2.59 (m, 2H), 2.48 (s, 3H), 1.89–1.61 (m, 5H), 1.51–1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 144.85$, 132.98, 129.87, 127.88, 125.17 (q, $J = 276.4$ Hz), 69.91, 44.33 (q, $J = 2.8$ Hz), 42.96 (q, $J = 28.3$ Hz), 37.62, 27.99, 23.25, 21.63; ^{19}F NMR (470 MHz, $CDCl_3$): $\delta = -64.83$ (t, $J = 9.4$ Hz); HR-MS: (EI): $m/z = 402.0120$, calcd. for $C_{14}H_{18}Br_1F_3O_3S_1$ $[M]^+$: 402.0112; IR (neat): $\nu = 2926$, 1354, 1253, 1173, 1143, 1094, 934, 908, 814, 778, 730, 662 cm^{-1}.

***N*-(3-Bromo-5,5,5-trifluoropentyl)-4-methylbenzenesulfonamide (3b):** Yield: 77%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 4.61 (t, J = 6.3 Hz, 1H), 4.21–4.12 (m, 1H), 3.23–3.08 (m, 2H), 2.83–2.53 (m, 2H), 2.44 (s, 3H), 2.19–1.85 (m, 2H);^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.78, 136.44, 129.84, 127.05, 124.99 (q, J = 276.5 Hz), 42.92 (q, J = 28.5 Hz), 41.48 (q, J = 2.6 Hz), 41.10, 38.09, 21.48; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.56 (t, J = 9.4 Hz); HR-MS (EI): m/z = 372.9957, calcd. for $C_{12}H_{15}Br_1F_3N_1O_2S_1$ $[M]^+$: 374.9939; mp 60–62 °C; IR (neat): ν = 3283, 2925, 1597, 1417, 1325, 1240, 1142, 938, 835, 811, 658 cm^{-1}.

***tert*-Butyl (7-bromo-9,9,9-trifluorononyl)carbamate (3c):** Yield: 83%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.51 (br, 1H), 4.17–4.08 (m, 1H), 3.13–3.06 (q, J = 6.5 Hz, 2H), 2.83–2.60 (m, 2H), 1.89–1.79 (m, 2H), 1.51–1.43 (m, 13H), 1.38–1.32 (q, J = 8.2 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.94, 125.28 (q, J = 276.4 Hz), 79.03, 45.02 (q, J = 2.5 Hz), 43.03 (q, J = 28.2 Hz), 40.43, 38.32, 29.93, 28.38, 27.00, 26.50; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.84 (t, J = 9.4 Hz); HR-MS (EI): m/z = 375.1026, calcd. for $C_{14}H_{25}Br_1F_3N_1O_2$ $[M]^+$: 375.1021; IR (neat): ν = 2975, 2930, 2859, 1696, 1510, 1365, 1252, 1164, 1147 cm^{-1}.

2-(3-Bromo-5,5,5-trifluoropentyl)isoindoline-1,3-dione (3d): Yield: 74%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.83 (m, 2H), 7.77–7.71 (m, 2H), 4.21–4.12 (m, 1H), 4.00–3.83 (m, 2H), 2.90–2.71 (m, 2H), 2.42–2.15 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.15, 134.15, 131.92, 125.05 (q, J = 276.5 Hz), 123.42, 42.87 (q, J = 28.5 Hz), 41.01 (q, J = 2.8 Hz), 36.84, 36.10; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.61 (t, J = 9.4 Hz); HR-MS (EI): m/z = 348.9923, calcd. for $C_{13}H_{11}Br_1F_3N_1O_2$ $[M]^+$: 348.9925; mp 61–63 °C; IR (neat): ν = 2921, 1767, 1700, 1391, 1356, 1260, 1237, 1174, 1145, 1084, 1042, 1000, 714 cm^{-1}.

4-[(4-Bromo-6,6,6-trifluorohexyl)oxy]benzaldehyde (3e): Yield: 91%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.88 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 4.23 (br, 1H), 4.10 (t, J = 4.8 Hz, 2H), 2.93–2.64 (m, 2H), 2.18–2.10 (m, 2H), 2.06–1.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.77, 163.73, 132.00, 130.03, 125.18 (q, J = 276.38), 114.67, 67.08, 44.40 (q, J = 3.0 Hz), 43.11 (q, J = 67.5 Hz), 35.04, 26.92; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.79 (t, J = 9.4 Hz); HR-MS (EI): m/z = 338.0132, calcd. for $C_{13}H_{14}Br_1F_3O_2$ $[M]^+$: 338.0129; IR (neat): ν = 2954, 2877, 2732, 1686, 1600, 1250, 1152, 1064, 937, 846, 769 cm^{-1}.

5-Bromo-7,7,7-trifluoroheptyl benzoate (3f): Yield: 93%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.05 (m, 2H), 7.62–7.56 (m, 1H), 7.47 (d, J = 7.5 Hz, 2H), 4.37 (t, J = 6.4 Hz, 2H), 4.37 (t, J = 6.4 Hz, 2H), 4.24–4.15 (m, 1H), 2.89–2.66 (m, 2H), 2.03–1.74 (m, 5H), 1.71–1.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.53, 132.91, 130.22, 129.50, 128.34, 125.22 (q, J = 276.4 Hz), 64.41, 44.65 (q, J = 2.8 Hz), 42.94 (q, J = 28.3 Hz), 37.95, 27.86, 23.81; ^{19}F NMR (470 MHz, $CDCl_3$): δ −64.78 (t, J = 9.4 Hz); HR-MS (EI): m/z = 352.0285, calcd. for $C_{14}H_{16}Br_1F_3O_2$ $[M]^+$: 352.0286; IR (neat): ν = 2953, 1714, 1451, 1388, 1313, 1270, 1255, 1174, 1143, 1113, 1069, 1026, 711, 687 cm^{-1}.

5-Bromo-7,7,7-trifluoroheptyl benzoate (3g): Yield: 70%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.24–4.15 (m, 1H), 3.73 (m, 2H), 3.56–3.48 (m, 4H), 2.87–2.64 (m, 2H), 1.91–1.83 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 125.25 (q, J = 276.3 Hz), 71.86, 70.03, 61.85, 44.79 (q, J = 2.6 Hz), 43.12 (q, J = 28.3 Hz), 35.32, 27.36; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.83 (t, J = 9.4 Hz); HR-MS (EI): m/z = 278.0122, calcd. for $C_8H_{14}Br_1F_3O_2$ $[M]^+$: 278.0129; IR (neat): ν = 3419, 2925, 2867, 1388, 1369, 1257, 1225, 1145, 1121, 1062, 889, 680 cm^{-1}.

***N*-(7-Bromo-9,9,9-trifluorononyl)-4-chlorobenzamide (3h):** Yield: 81%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 2H), 7.44- 7.39 (m, 2H), 6.20 (br, 1H), 4.20–4.11 (m, 1H), 3.49–3.42 (m, 2H), 2.86–2.64 (m, 2H), 1.93–1.80 (m, 2H), 1.69–1.58 (m, 2H), 1.50–1.35 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.45, 137.53, 133.04, 128.75, 128.26, 125.26 (q, J = 276.4 Hz), 42.03 (q, J = 2.8 Hz), 42.96 (q, J = 28.3 Hz), 40.02, 38.27, 29.49, 28.36, 26.98, 26.70; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.80 (t, J = 9.4 Hz); HR-MS (EI): m/z = 413.0367, calcd. for $C_{16}H_{20}Br_1Cl_1F_3N_1O_1$ $[M]^+$: 413.0369; mp 71–74 °C; IR (neat): ν = 3299, 2933, 2857, 1625, 1535, 1481, 1385, 1306, 1253, 1233, 1149, 1089, 1059, 1014, 842, 758, 726, 664 cm^{-1}.

***N*-(7-Bromo-9,9,9-trifluorononyl)-4-chlorobenzamide (3i):** Yield: 74%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 2H), 7.44–7.39 (m, 2H), 6.20 (br, 1H), 4.20–4.11 (m, 1H), 3.49–3.42 (m, 2H), 2.86–2.64 (m, 2H), 1.93–1.80 (m, 2H), 1.69–1.58 (m, 4H), 1.50–1.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.51, 133.53, 131.77, 128.44, 126.01, 125.26 (q, J = 276.4 Hz), 45.01 (q, J = 2.8 Hz), 42.98 (q, J = 28.3 Hz), 40.04, 38.30, 29.52, 28.38, 26.99, 26.71; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.80 (t, J = 9.4 Hz); HR-MS (EI): m/z = 413.0367, calcd. for $C_{16}H_{20}Br_1Cl_1F_3N_1O_1$ $[M]^+$: 413.0369; mp 71–74 °C; IR (neat): ν = 3299, 2933, 2857, 1625, 1535, 1481, 1385, 1306, 1253, 1233, 1149, 1089, 1059, 1014, 842, 758, 726, 664 cm^{-1}.

***N*-(7-Bromo-9,9,9-trifluorononyl)-4-iodobenzamide (3j):** Yield: 78%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 6.24 (br, 1H), 4.20–4.11 (m, 1H), 3.47–3.41 (m, 2H), 2.89–2.60 (m, 2H), 1.92–1.79 (m, 2H), 1.61–1.55 (m, 2H), 1.49–1.27 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.70, 137.70, 134.09, 128.44, 125.26 (q, J = 276.4 Hz), 98.22, 45.01 (q, J = 2.6 Hz), 43.02 (q, J = 28.3 Hz), 40.02, 38.28, 29.48, 28.36, 26.98, 26.70; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.79 (t, J = 9.4 Hz); HR-MS (EI): m/z = 504.8937, calcd. for $C_{16}H_{20}Br_1Cl_1F_3N_1O_1$ $[M]^+$: 504.9725; mp 78–80 °C; IR (neat): ν = 3303, 2929, 2852, 1632, 1585, 1539, 1413, 1367, 1313, 1259, 1235, 1143, 1123, 1079, 1062, 1002, 844, 670 cm^{-1}.

4-Methyl-*N*-(5,5,5-trifluoro-3-iodopentyl)benzenesulfonamide (4b): Yield: 88%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.83 (m, 2H), 7.77–7.70 (m, 2H), 4.20–4.12 (t, J = 6.3 Hz, 1H), 3.97–3.86 (m, 2H), 2.73–2.58 (m, 2H), 2.32–2.08 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.81, 136.52, 129.86, 127.10, 125.28 (q, J = 277.3 Hz), 44.79 (q, J = 28.4 Hz), 43.41, 39.20, 21.52, 17.03 (q, J = 2.6 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.62 (t, J = 11.8 Hz); HR-MS (EI): m/z = 420.9801, calcd. for $C_{12}H_{15}F_3N_1O_2S_1I_1$ $[M]^+$: 420.9820; IR (neat): ν = 3275, 2928, 1425, 1321, 1255, 1224, 1137, 1093, 1080, 941, 896, 857, 833, 813, 764, 705 cm^{-1}.

***tert*-Butyl (9,9,9-trifluoro-7-iodononyl)carbamate (4c):** Yield: 83%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.51 (s, 1H), 4.18 (s, 1H), 3.10 (s, 2H), 2.90–2.79 (m, 2H), 1.76 (s, 2H), 1.44 (s, 13H), 1.32 (s, 4H);^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.95, 125.56 (q, J = 277.0 Hz), 79.06, 44.88 (q, J = 28.1 Hz), 40.46, 39.50, 29.96, 29.35, 28.41, 28.16, 26.52, 21.70 (q, J = 2.5 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.79 (t, J = 9.4 Hz); HR-MS (EI): m/z = 423.0858, calcd. for

$C_{14}H_{25}I_1F_3N_1O_2$ [M]$^+$: 423.0882 ; IR (neat): ν = 2973, 2928, 2857, 1697, 1509, 1365, 1251, 1169, 1145 cm^{-1}.

2-(5,5,5-Trifluoro-3-iodopentyl)isoindoline-1,3-dione (4d): Yield: 64%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.83 (m, 2H), 7.76–7.71 (m, 2H), 4.21–4.11 (m, 1H), 3.94–3.76 (m, 2H), 2.99–2.80 (m, 2H), 2.27–2.19 (m, 2H);^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.15, 134.15, 131.90, 125.35 (q, J = 277.5 Hz), 123.42, 44.67 (q, J = 28.4 Hz), 38.14, 38.10, 15.49 (q, J = 2.5 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.71 (t, J = 9.4 Hz); HR-MS (EI): m/z = 396.9772, calcd. for $C_{13}H_{11}I_1F_3N_1O_1$ [M]$^+$: 396.9787; IR (neat): ν = 2941, 1771, 1709, 1432, 1396, 1257, 1187, 1145, 721 cm^{-1}.

4-[(6,6,6-Trifluoro-4-iodohexyl)oxy]benzaldehyde (4e): Yield: 99%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.91 (s, 1H), 7.88–7.85 (m, 2H), 7.12 (d, J = 8.7 Hz, 2H), 4.31–4.27 (m, 1H), 4.14–4.08 (m, 2H), 3.04–2.80 (m, 2H), 2.17–1.95 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.79, 163.75, 132.00, 130.02, 125.48 (q, J = 277.2 Hz), 114.68, 66.92, 44.93 (q, J = 28.2 Hz), 36.20, 29.20, 20.57 (q, J = 2.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.85 (t, J = 9.4 Hz); HR-MS (EI): m/z = 385.9988, calcd. for $C_{13}H_{14}F_3O_2I_1$ [M]$^+$: 358.9991; IR (neat): ν = 2925, 2736, 1686, 1598, 1577, 1508, 1350, 1213, 1156, 1143, 1109, 1076, 831 cm^{-1}.

4-Chloro-*N*-(9,9,9-trifluoro-7-iodononyl)benzamide (4g): Yield: 60%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.28–4.19 (m, 1H), 3.76–3.71 (m, 2H), 3.56–3.51 (m, 4H), 2.98–2.74 (m, 2H), 1.91–1.81 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 125.52 (q, J = 277.1 Hz), 71.87, 69.85, 61.84, 44.93 (q, J = 28.1 Hz), 36.50, 29.62, 21.18 (q, J = 2.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.92 (t, J = 11.8 Hz); HR-MS (EI): m/z = 325.9959, calcd. for $C_8H_{14}F_3O_2I_1$ [M]$^+$: 325.9991; IR (neat): ν = 6411, 2918, 2865, 1433, 1365, 1253, 1213, 1143, 1119, 1075, 1061, 889 cm^{-1}.

4-Chloro-*N*-(9,9,9-trifluoro-7-iodononyl)benzamide (4h): Yield: 81%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 7.8 Hz, 2H), 6.27 (br, 1H), 4.25–4.11 (m, 1H), 3.46–3.40 (m, 2H), 2.94–2.71 (m, 2H), 1.90–1.74 (m, 2H), 1.90–1.54 (m, 2H), 1.49–1.30 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.45, 137.49, 137.03, 128.71, 128.27, 125.51 (q, J = 277.2 Hz), 44.81 (q, J = 28.0 Hz), 40.02, 39.41, 29.48, 29.29, 28.14, 26.69, 21.66 (q, J = 2.5 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.87 (t, J = 9.4 Hz); HR-MS (EI): m/z = 461.0227, calcd. for $C_{16}H_{20}Cl_1F_3I_1N_1O_1$ [M]$^+$: 461.0230; mp 72–75 °C; IR (neat): ν = 3309, 2936, 2858, 1627, 1592, 1528, 1484, 1470, 1363, 1335, 1302, 1255, 1243, 1143, 1130, 1106, 1089, 1067, 1015, 843, 763, 726, 661 cm^{-1}.

4-Bromo-*N*-(9,9,9-trifluoro-7-iodononyl)benzamide (4i): Yield: 83%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 6.20 (br, 1H), 4.25–4.16 (m, 1H), 3.49–3.42 (m, 2H), 2.93–2.78 (m, 2H), 1.83–1.75 (m, 2H), 1.69–1.50 (m, 3H), 1.50–1.29 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.54, 133.51, 131.69, 128.46, 125.94, 125.52 (q, J = 277.1 Hz), 44.82 (q, J = 28.0 Hz), 40.03, 39.42, 29.48, 29.30, 28.15, 26.69, 21.64 (q, J = 2.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.87 (t, J = 9.4 Hz); HR-MS (EI): m/z = 504.9732, calcd. for $C_{16}H_{20}Br_1F_3I_1N_1O_1$ [M]$^+$: 504.9725; mp 85–88 °C; IR (neat): ν = 3304, 2936, 2857, 1626, 1587, 1528, 1480, 1469, 1363, 1334, 1300, 1255, 1244, 1143, 1129, 1104, 1066, 1011, 840, 760, 711, 662 cm^{-1}.

4-Iodo-*N*-(9,9,9-trifluoro-7-iodononyl)benzamide (4j): Yield: 82%; ^{1}H NMR (300 MHz, $CDCl_3$)::δ = 7.80 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 6.12 (br, 1H), 4.25–4.16 (m, 1H), 3.49–3.43 (m, 2H), 2.93–2.79 (m, 2H), 1.84–1.74 (m, 2H), 1.66–1.62 (m, 2H), 1.49–1.33 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.67, 137.75, 134.11, 128.44, 125.51 (q, J = 277.1 Hz), 98.24, 44.89 (q, J = 28.0 Hz), 40.03, 39.45, 29.53, 29.33, 28.17, 26.71, 21.65 (q, J = 2.2 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.89 (t, J = 9.4 Hz); HR-MS (EI): m/z = 552.9588, calcd. for $C_{16}H_{20}F_3I_2N_1O_1$ [M]$^+$: 552.9587; mp 91–95 °C; IR (neat): ν = 3304, 2935, 2855, 1731, 1625, 1584, 1528, 1168, 1364, 1300, 1128, 1142, 1128, 1245, 1065, 1007, 879, 856, 768, 708, 663 cm^{-1}.

5-Chloro-7,7,7-trifluoroheptyl 4-methylbenzenesulfonate (5a): Yield: 72%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 4.08–4.00 (m, 3H), 2.69–2.41 (m, 2H), 2.39 (s, 3H), 1.85–1.57 (m, 5H), 1.54–1.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.85, 132.93, 129.85, 127.83, 125.11 (q, J = 275.9 Hz), 69.93, 53.65 (q, J = 2.8 Hz), 42.26 (q, J = 28.3 Hz), 37.16, 28.05, 21.99, 21.57; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.81 (t, J = 9.4 Hz); HR-MS (EI): m/z = 358.0616, calcd. for $C_{14}H_{18}Cl_1F_3O_3S_1$ [M]$^+$: 358.0617; IR (neat): ν = 2956, 1597, 13.56, 1268, 1188, 1175, 1145, 1097, 939, 910, 814, 733, 665 cm^{-1}.

***N*-(3-Chloro-5,5,5-trifluoropentyl)-4-methylbenzenesulfonamide (5b):** Yield: 75%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 4.65 (t, J = 6.3 Hz, 1H), 4.21–4.12 (m, 1H), 3.21–3.14 (m, 2H), 2.65–2.45 (m, 2H), 2.44 (s, 3H), 2.15–2.04 (m, 1H), 1.89–1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.82, 136.51, 129.87, 127.07, 125.17 (q, J = 276.4 Hz), 51.17 (q, J = 2.2 Hz), 42.33 (q, J = 28.3 Hz), 40.0, 37.73, 21.52; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.83 (t, J = 9.4 Hz); HR-MS (EI): m/z = 402.0120, calcd. for $C_{14}H_{18}Br_1F_3O_3S_1$ [M]$^+$: 402.0112; mp 87–89 °C; IR (neat): ν = 2926, 1354, 1253, 1173, 1143, 1094, 934, 908, 814, 778, 730, 662 cm^{-1}.

***N*-(3-Chloro-5,5,5-trifluoropentyl)-4-methylbenzenesulfonamide (5c):** Yield: 77%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.51 (s, 1H), 4.11–4.04 (m, 1H), 3.13–3.07 (m, 2H), 2.60–2.46 (m, 2H), 1.86–1.63 (m, 2H), 1.50–1.22 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.95, 125.24 (q, J = 275.9 Hz), 54.09 (q, J = 2.5 Hz), 42.38 (q, J = 28.1 Hz), 40.43, 37.89, 29.93, 28.47, 28.38, 26.52, 25.80; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.83 (t, J = 9.4 Hz); HR-MS (EI): m/z = 331.1519, calcd. for $C_{14}H_{25}Cl_1F_3N_1O_2$ [M]$^+$: 331.1526; IR (neat): ν = 2930, 2859, 1697, 1510, 1365, 1265, 1244, 1168, 1147 cm^{-1}.

4-[(4-Chloro-6,6,6-trifluorohexyl)oxy]benzaldehyde (5e): Yield: 81%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.89 (s, 1H), 7.84 (d, J = 9 Hz, 2H), 6.99 (d, J = 9 Hz, 2H), 4.24–4.17 (m, 1H), 4.10 (t, J = 5.7 Hz, 2H), 2.64–2.55 (m, 2H), 2.14–2.07 (m, 2H), 2.02–1.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.79, 163.74, 132.00, 130.03, 125.12 (q, J = 275.9 Hz), 114.67, 67.20, 53.73 (q, J = 2.0 H), 42.48 (q, J = 28.4 Hz), 34.62, 25.73; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.75 (t, J = 9.4 Hz); HR-MS (EI): m/z = 294.0634, calcd. for $C_{13}H_{14}Cl_1F_3O_2$ [M]$^+$; 294.0609; IR (neat): ν = 2955, 2878, 2841, 1687, 1603, 1578, 1245, 1146, 1115, 1031, 830 cm^{-1}.

2-[(4-Chloro-6,6,6-trifluorohexyl)oxy]ethan-1-ol (5g): Yield: 55%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.17–4.12 (m, 1H), 3.76–3.71 (m, 2H), 3.56–3.50 (m, 4H), 2.66–2.50 (m,

2H), 1.93–1.75 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 125.19 (q, J=276.5 Hz), 71.83, 70.13, 61.83, 53.96 (q, J=2.0H), 42.45 (q, J=28.3 Hz), 34.86, 26.16; ^{19}F NMR (470 MHz, $CDCl_3$): δ −64.81 (t, J=9.4 Hz); HRMS (EI): m/z Calcd for $C_8H_{14}Cl_1F_3O_2$ $[M]^+$234.0634, found 234.0631; IR (neat): 3419, 2922, 2867, 1389, 1263, 1243, 1145, 1119, 1063, 664 cm^{-1}.

***N*-(7-Chloro-9,9,9-trifluorononyl)-4-chlorobenzamide (5h):** Yield: 72%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.70 (d, J=8.6 Hz, 2H), 7.40 (d, J=8.6 Hz, 2H), 6.17 (br, 1H), 4.14–4.06 (m, 1H), 3.47–3.40 (m, 2H), 2.68–2.47 (m, 2H), 1.89–1.71 (m, 2H), 1.65–1.58 (m, 2H), 1.48–1.33 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.44, 137.55, 133.07, 128.77, 128.26, 125.22 (q, J=275.9 Hz), 54.08 (q, J=2.8 Hz), 42.39 (q, J=28.1 Hz), 40.03, 37.86, 29.51, 28.49, 26.72, 25.78; ^{19}F NMR (470 MHz, $CDCl_3$): δ=−64.80 (t, J=9.4 Hz); HR-MS (EI): m/z=369.0874, calcd. for $C_{16}H_{20}Cl_2F_3N_1O_1$ $[M]^+$: 369.0813; mp 67–70 °C; IR (neat): ν=3299, 2935, 2857, 1625, 1535, 1481, 1386, 1310, 1257, 1240, 1151, 1091, 1060, 1014, 861, 843, 758, 726, 665 cm^{-1}.

***N*-(7-Chloro-9,9,9-trifluorononyl)-4-bromobenzamide (5i):** Yield: 71%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.63 (d, J=8.6 Hz, 2H), 7.56 (d, J=8.6 Hz, 2H), 6.16 (br, 1H), 4.15–4.06 (m, 1H), 3.47–3.40 (m, 2H), 2.68–2.49 (m, 2H), 1.87–1.69 (m, 2H), 1.64–1.60 (m, 2H), 1.48–1.33 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.53, 133.53, 131.75, 128.45, 125.99, 125.24 (q, J=275.9 Hz), 54.09 (q, J=2.8 Hz), 42.39 (q, J=28.1 Hz), 40.04, 37.87, 29.50, 28.49, 26.73, 25.79; ^{19}F NMR (470 MHz, $CDCl_3$): δ=−64.80 (t, J=9.4 Hz); HR-MS (EI): m/z=413.0340, calcd. for $C_{16}H_{20}Br_1Cl_1F_3N_1O_1$ $[M]^+$: 413.0369; mp 67–70 °C; IR (neat): ν=3296, 3055, 2934, 2856, 1625, 1590, 1535, 1479, 1387, 1307, 1258, 1241, 1150, 1095, 1070, 1005, 841, 665 cm^{-1}.

***N*-(7-Chloro-9,9,9-trifluorononyl)-4-iodobenzamide (5j):** Yield: 68%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.80 (d, J=8.4 Hz, 2H), 7.50 (d, J=8.4 Hz, 2H), 6.12 (br, 1H), 4.18–4.08 (m, 1H), 3.49–3.42 (m, 2H), 2.70–2.49 (m, 2H), 1.89–1.75 (m, 2H), 1.70–1.56 (m, 2H), 1.50–1.35 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.68, 137.75, 134.10, 128.43, 125.13 (q, J=275.9 Hz), 98.24, 54.08 (q, J=2.0 Hz), 42.40 (q, J=28.1 Hz), 40.02, 37.87, 29.51, 28.50, 26.72, 25.79; ^{19}F NMR (470 MHz, $CDCl_3$): δ=−64.80 (t, J=9.4 Hz); HR-MS (EI): m/z=461.0223, calcd. for $C_{16}H_{20}I_1Cl_1F_3N_1O_1$ $[M]^+$: 461.0230; mp 64–67 °C; IR (neat): ν=3302, 3066, 2929, 2852, 1637, 1586, 1539, 1436, 1385, 1314, 1264, 1238, 1138, 1057, 1001, 885, 760, 667 cm^{-1}.

(*S*)-2-Methyl-5-(4,4,4-trifluoro-2-iodobutan-2-yl)cyclohex-2-en-1-one (7b): Yield: 68% (1:1 *dr*); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.74–6.76 (m, 1H), 3.02–3.21 (m, 2H), 2.66–2.72 (m, 1H), 2.53–2.61 (m, 1H), 2.34–2.44 (m, 2H), 2.17–1.81 (m, 3H), 1.80–1.81 (m, 3H), 1.09–1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=199.1, 198.7, 144.3, 144.1, 134.8, 124.95 (q, J=279.2 Hz), 53.97, 53.69, 48.49, 48.35, 45.38, 45.02, 43.54, 43.32, 33.33, 31.30, 31.04, 15.91, 15.89; ^{19}F NMR (470 MHz, $CDCl_3$): δ=−60.97 (t, J=11.8 Hz); HR-MS (EI): m/z=346.0747, calcd. for $C_{11}H_{14}F_3O_1I_1$ $[M]^+$: 346.0042; IR (neat): ν=2978, 2927, 1670, 1358, 1249, 1222, 1194, 1172, 1134, 1115, 1073, 904, 673 cm^{-1}.

{[(5,5,5-Trifluoro-3-bromo-3-methylpentyl)oxy]methyl}-benzene (8a): Yield: 71%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.41–7.32 (m, 5H), 4.55 (s, 2H), 3.85–3.78 (m, 2H), 3.00–2.86 (m, 2H), 2.37–2.24 (m, 2H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=137.98, 128.43, 127.69, 127.57, 125.07 (q, J=277.6 Hz), 73.17, 68.09, 60.84, 48.18 (q, J=28.6 Hz), 44.54, 32.13; ^{19}F NMR (470 MHz, $CDCl_3$): δ=−61.46 (t, J=9.4 Hz); HR-MS (EI): m/z=324.0326, calcd. for $C_{13}H_{16}Br_1F_3O_1$ $[M]^+$: 324.0337; IR (neat): ν=2927, 2859, 1453, 1363, 1255, 1207, 1140, 1100, 1027, 736, 698, 677 cm^{-1}.

(*S*)-5-(2-Bromo-4,4,4-trifluorobutan-2-yl)-2-methylcyclohex-2-en-1-one (8b): Yield: 72% (1.1:1 *dr*); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.78 (s, 1H), 3.06–2.87 (m, 2H), 2.77–2.70 (m, 1H), 2.59–2.51 (m, 3H), 2.25–2.19 (m, 1H), 1.98–1.86 (m, 3H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=198.25, 197.91, 143.43, 143.30, 135.39, 124.90 (q, J=278.1 Hz), 124.87 (q, J=278.1 Hz), 66.67, 66.61, 46.14 (q, J=27.4 Hz), 46.09 (q, J=27.4 Hz), 45.16, 45.06, 40.99, 40.80, 29.85, 29.77, 28.82, 28.63, 15.52; ^{19}F NMR (470 MHz, $CDCl_3$): δ=−61.35 (t, J=9.4 Hz), −61.37 (t, J=9.4 Hz); HR-MS (EI): m/z=298.0173, calcd for $C_{16}H_{20}I_1Cl_1F_3N_1O_1$ $[M]^+$: 298.0180; IR (neat): ν=2925, 1671, 1433, 1365, 1252, 1177, 1137, 1115, 1076, 906, 733, 673 cm^{-1}.

(*R*)-4-(2-Bromo-4,4,4-trifluorobutan-2-yl)cyclohex-1-ene-1-carbaldehyde (8c): Yield: 64% (1.1:1 *dr*); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.45 (s, 1H), 6.83–6.82 (m, 1H), 3.20–2.90 (m, 2H), 2.69–2.58 (m, 2H), 2.45–2.43 (m, 1H), 2.19–2.07 (m, 2H), 2.02–1.98 (m, 3H), 1.82–1.73 (m, 1H), 1.53–1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=193.30, 148.88, 148.72, 141.19, 141.13, 126.16 (q, J=279.5 Hz), 123.94 (q, J=279.5 Hz), 67.41, 67.08, 46.36 (q, J=27.5 Hz), 46.30 (q, J=27.5 Hz), 44.31, 43.83, 30.41, 29.88, 29.54, 29.47, 24.65, 24.28, 21.61, 1.47; ^{19}F NMR (470 MHz, $CDCl_3$): δ=−61.27 (t, J=10.4 Hz), −61.51 (t, J=10.4 Hz); HR-MS (EI): m/z=298.0176, calcd. for $C_{11}H_{14}Br_1F_3O_1$ $[M]^+$: 298.0180; IR (neat): ν=2928, 1682, 1648, 1434, 1359, 1252, 1102, 1197, 1132, 1083, 1026, 738, 679 cm^{-1}.

(4*R*,4a*S*,6*R*)-6-(2-bromo-4,4,4-trifluorobutan-2-yl)-4,4a-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (8d): Yield: 71% (1:1 *dr*); ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.78 (s, 1H), 3.03–2.82 (m, 2H), 2.53–2.39 (m, 2H), 2.30–2.26 (m, 2H), 2.13–2.03 (m, 3H), 1.96–1.93 (m, 3H), 1.90–1.81 (m, 1H), 1.50–1.12 (m, 2H), 1.11–1.09 (m, 3H), 1.01–0.99 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=199.24, 199.21, 168.86, 168.75, 125.18 (q, J=278.1 Hz), 125.10 (q, J=278.1 Hz), 124.78, 124.74, 67.57, 67.05, 46.29 (q, J=27.4 Hz), 46.07 (q, J=27.4 Hz), 43.69, 43.02, 41.94, 40.71, 40.60, 40.33, 40.29, 39.07, 32.15, 32.08, 30.59, 30.25, 28.87, 28.64, 15.01, 14.98; ^{19}F NMR (470 MHz, $CDCl_3$): δ=−61.14 (t, J=10.4 Hz), −61.15 (t, J=10.4 Hz); HR-MS (EI): m/z=366.0805, calcd. for $C_{16}H_{22}Br_1F_3O_1$ $[M]^+$: 366.0806; IR (neat): ν=2962, 2938, 2881, 1663, 1619, 1434, 1370, 1355, 1304, 1254, 1190, 1137, 1100, 1080, 1028, 998, 886, 680, 661 cm^{-1}.

(1-Bromo-3,3,3-trifluoropropane-1,2-diyl)dibenzene (8e): Yield: 80% (1.5:1 *dr*); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.49–7.35 (m, 4H), 7.22–7.06 (m, 6H), 5.44–5.39 (m, 1H), 4.22–4.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=139.44, 138.86, 134.04, 132.39, 129.39, 128.93, 128.84, 128.62, 128.59, 128.41, 128.38, 128.31, 128.23, 128.20, 127.86, 126.69, 125.57 (q, J=280.4 Hz), 124.74 (q, J=281.0 Hz), 58.08 (q, J=26.1 Hz), 58.24 (q, J=26.1 Hz), 52.10, 48.42; ^{19}F NMR (470 MHz, $CDCl_3$): δ=−64.45 (d, J=8.6 Hz), −64.69 (d, J=8.6 Hz); HR-MS (EI): m/z=328.0080, calcd. for $C_{15}H_{12}Br_1F_3$ $[M]^+$: 328.0074; mp 84–88 °C; IR (neat): ν=1492, 1454,

1370, 1322, 1239, 1150, 1171, 1031, 1001, 939, 823, 774, 759, 670, 651 cm^{-1}.

{[(3-Chloro-5,5,5-trifluoro-3-methylpentyl)oxy]methyl}-benzene (9a): Yield: 74%; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.31 (m, 5H), 4.54 (s, 2H), 3.83–3.71 (m, 2H), 2.89–2.66 (m, 2H), 2.31–2.16 (m, 2H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.98, 137.98. 128.43, 127.69, 127.57, 125.07 (q, J = 277.0 Hz), 73.15, 66.69, 66.19, 46.93 (q, J = 27.5 Hz), 43.59, 30.41; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −60.49 (t, J = 10.6 Hz); HR-MS (EI): m/z = 280.0842, calcd. for $C_{13}H_{16}Br_1F_3O_1$ $[M]^+$: 280.0842; IR (neat): ν = 2864, 1453, 1355, 1293, 1258, 1208, 1176, 1142, 1101, 1027, 736, 699, 678 cm^{-1}.

(1-Chloro-3,3,3-trifluoropropane-1,2-diyl)dibenzene (9e): Yield: 73% (2:1 *dr*); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.37 (m, 3H), 7.20–7.03 (m, 7H), 5.45–5.35 (m, 1H), 4.08–3.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.80, 138.34, 132.23, 132.17, 129.72, 129.35, 128.86, 128.78, 128.50, 128.44, 128.41, 128.39, 128.21, 127.85, 127.51, 125.66 (q, J = 280.3 Hz), 125.12 (q, J = 280.3 Hz), 60.84, 59.46, 58.13 (q, J = 26.0 Hz), 58.09 (q, J = 25.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.24 (d, J = 8.6 Hz), −65.34 (d, J = 8.6 Hz); HR-MS (EI): m/z = 284.0554, calcd. for $C_{15}H_{12}Cl_1F_3$ $[M]^+$: 284.0580; mp 73–76 °C; IR (neat): ν = 1491,1455, 1370, 1276, 1244, 1162, 1153, 1108, 1074, 761, 727, 697, 684 cm^{-1}.

Derivatization of the Bromotrifluoromethylated Product

2-[5,5,5-Trifluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]isoindoline-1,3-dione (10): 2-(3-Bromo-5,5,5-trifluoropentyl)isoindoline-1,3-dione (175 mg, 0.50 mmol), B_2pin_2(190.5 mg, 0.75 mmol), CuI (10.0 mg, 0.05 mmol), PPh_3 (17 mg, 0.065 mmol) and LiOEt (52.0 mg, 1.0 mmol) were dissolved in DMF (4 mL, 0.125 M). The reaction mixture was stirred for 12 h at 37 °C. Then the mixture was cooled to room temperature and poured into a separatory funnel containing 50 mL of EtOAc and H_2O (20 mL). The aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. Purification by column chromatography on SiO_2 gel (EtOAc : hexanes = 2:8) gave the desired product as an oily liquid; yield: 65%; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.82 (m, 2H), 7.74–7.69 (m, 2H), 3.80–3.69 (m, 2H), 2.43–2.19 (m, 2H), 1.90–1.76 (m, 2H), 1.26–1.24 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.26, 133.88, 132.17, 127.27 (q, J = 275.5 Hz), 123.18, 83.87, 36.77, 34.65 (q, J = 27.9 Hz), 29.24, 24.67, 24.64; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −65.72 (t, J = 11.5 Hz); HR-MS (EI): m/z = 397.1663, calcd. for $C_{14}H_{16}F_3N_1O_2$ $[M]^+$: 397.1676; IR (neat): ν = 2980, 2935, 1773, 1710, 1392, 1371, 1332, 1259, 1138, 1084, 721 cm^{-1}.

***N*-{4-[(4-Azido-6,6,6-trifluorohexyl)oxy]pheny}acetamide (11):** In a 4-mL pre-dried screw-capped sealed tube, a suspension of 2-(3-bromo-5,5,5-trifluoropentyl)isoindoline-1,3-dione (88 mg, 0.25 mmol), NaN_3 (33 mg, 0.5 mmol), and NaI (7.5 mg, 0.05 mmol) in DMF (2 mL, 0.125 M) was stirred at 80 °C for 4 h. The reaction mixture was cooled and concentrated under vacuum. A white solid precipitated out after addition of Et_2O. The white solid was filtered and dried to give the desired product as an oily liquid; yield: 90%; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.85 (m, 2H), 7.77–7.73 (m, 2H), 3.94–3.80 (m, 2H), 3.78–3.68 (m, 1H), 2.45–2.31 (m, 2H), 2.03–1.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.25, 134.20, 131.90, 123.45 (q, J = 275.3 Hz), 54.75, 38.75 (q, J = 28.1 Hz), 34.45, 33.56; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.39 (t, J = 9.9 Hz); HR-MS (EI): m/z = 284.0763, calcd. for $C_{13}H_{11}F_3N_2O_2$ $[M-N_2]^+$: 284.2377; IR (neat): ν = 2925, 2118, 2018, 1395, 1379, 1282, 1258, 1138, 117, 719 cm^{-1}.

2-(5,5,5-Trifluoro-3-thiocyanatopentyl)isoindoline-1,3-dione (12): In a 4-mL pre-dried screw-capped sealed tube, a suspension of 2-(3-bromo-5,5,5-trifluoropentyl)isoindoline-1,3-dione (88 mg, 0.25 mmol), NaSCN (41 mg, 0.5 mmol), and NaI (7.5 mg, 0.05 mmol) in DMF (2 mL, 0.125 M) was stirred at 80 °C for 4 h. The reaction mixture was cooled and concentrated under vacuum. A white solid precipitated out after addition of Et_2O. The white solid was filtered and dried to give the desired product as oily liquid; yield: 98%; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.85 (m, 2H), 7.79–7.74 (m, 2H), 3.97–3.89 (m, 2H), 3.32–3.22 (m, 1H), 2.82–2.61 (m, 2H), 2.37–2.12 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.26, 134.38, 131.71, 124.73 (q, J = 272.7 Hz), 123.59, 109.21, 40.61, 39.56 (q, J = 29.0 Hz), 34.96, 34.16; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −64.39 (t, J = 9.4 Hz); HR-MS (EI): m/z = 328.0486, calcd. for $C_{14}H_{11}F_3N_2O_2S_1$ $[M]^+$: 328.3092; IR (neat): ν = 2945, 2155, 1774, 1707, 1357, 1266, 1247, 1211, 1018, 715 cm^{-1}.

(*E*)-2-(5,5,5-Trifluoropent-3-en-1-yl)isoindoline-1,3-dione (13): 2-(3-Bromo-5,5,5-trifluoropentyl)isoindoline-1,3-dione (175 mg, 0.25 mmol) was dissolved in DCM (0.2 M). The solution was cooled to 0 °C and DBU (77 mg, 0.25 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h. H_2O was added to the reaction mixture. The solution was extracted with Et_2O and dried over Na_2SO_4. The crude was purified by silica gel column chromatography (EtOAc:kexane = 1:4) to give the desired product as a solid; Yield: 74%; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87–7.85 (m, 2H), 7.74–7.72 (m, 2H), 6.41–6.34 (m, 1H), 5.73–5.66 (m, 1H), 3.83 (t, J = 7.1 Hz, 2H), 2.59–2.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.13, 136.29 (q, J = 6.2 Hz), 134.13, 131.85, 123.38, 121.01 (q, J = 34.8 Hz), 36.20, 30.62; ^{19}F NMR (470 MHz, $CDCl_3$): δ = −65.46 (d, J = 4.0 Hz); HR-MS (EI): m/z = 269.0674, calcd. for $C_{13}H_{10}F_3N_1O_2$ $[M]^+$: 269.0664; M.P.: 91.7–92.6 °C; IR (neat): ν = 2948, 2920, 2851, 1699, 1101, 872, 719 cm^{-1}.

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