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Preparation of Alkyl and Aryl Chlorodifluoromethyl Ethers Using BrF_3

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Both alkyl and aryl chlorothioformates could readily be obtained from the corresponding alcohols and thiophosgene. These families of compounds were treated with BrF_3 to form the corresponding alkyl and aryl chlorodifluoromethyl ethers in 60–85 % yields. The method is suitable for constructing a variety of aliphatic as well as electron-deficient aromatic chlorodifluoromethyl ethers. The reactions proceed under mild conditions and short reaction times.

Introduction

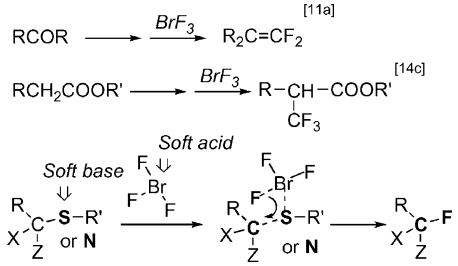
The chlorodifluoromethoxy group, OCF_2Cl, has wide applications in the realm of biologically interesting compounds. It can be found in anesthetics,[1] in antimalarial drugs,[2] in various inhibitors,[3] and more. Incorporation of this moiety into organic molecules can often modify the biological and physiological activities and properties. These modifications are associated with increasing stability and lipophilicity without gross steric distortion. In addition, the interest in preparing the OCF_2Cl moiety is also based on its ability to serve as a starting point for further chemical transformations. For instance, substitution of the chlorine atom with trimethylsilane in aromatic chlorodifluoro ethers, forms a reactive intermediate used to incorporate the CF_2 group in different substrates.[4] The chlorine atom in OCF_2Cl can also be replaced by fluorine to access trifluoromethyl ethers that can serve as potential anesthetics among other useful functions.[5]

$ROCF_2Cl$ ethers are usually prepared by treatment of the corresponding trichloromethyl derivatives – $ROCCl_3$ with HF,[6,7] or SbF_3.[1,8] The main disadvantage of these methods is the difficulty to stop at the chlorodifluoromethoxylation stage and the main product of these reactions is often the trifluoromethyl ether.

Additional methods for the preparation of this group rely on radical chlorination of difluoromethyl ethers[9] or reactions of aryl (but not alkyl) alcohols with CF_2Cl_2.[10] Invariably, all these methods were demonstrated on aromatic or heavily halogenated alkyl compounds.

The preparation of regular alkyl chlorodifluoromethyl ethers is suspiciously lacking in the literature. We describe here a general method for the preparation of these ethers applicable for most types of alcohols and especially for aliphatic ones.

For the last 10 years or so, we have investigated the versatility of BrF_3 as a nucleophilic fluorinating agent, especially in constructing and attaching the CF_2[11,12] and the CF_3[13,14] groups to various sites in organic molecules (Scheme 1). The main feature of the mechanism governing most reactions with BrF_3 involves complexation of the soft acidic bromine around a soft base (e.g., sulfur or nitrogen atoms) in the target molecule. The naked fluorides react then selectively with the activated carbon, forming the desired products and minimizing undesired radical destructive reactions (Scheme 1).



Scheme 1. Examples and mechanism for selective fluorination with BrF_3.

Results and Discussion

The reaction between octanol (**1a**), triethylamine (Et_3N) and thiophosgene in THF provided octyl chlorothioformate (**2a**)[15] in good yield. Applying 2 molar equiv. of BrF_3, for about a minute, led to the yet unknown chlorodifluoromethyl octyl ether (**3a**) in 70% yield (Scheme 2).

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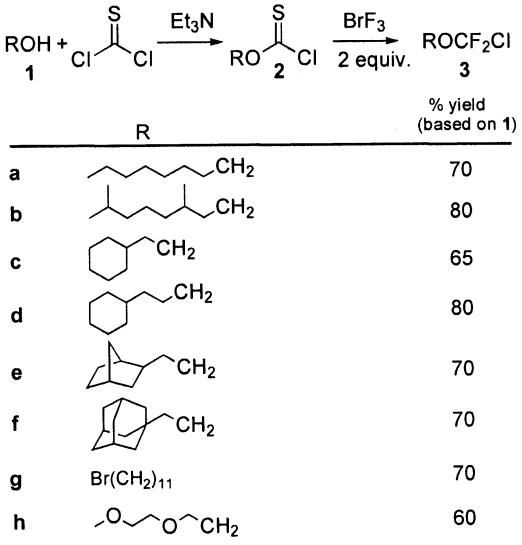


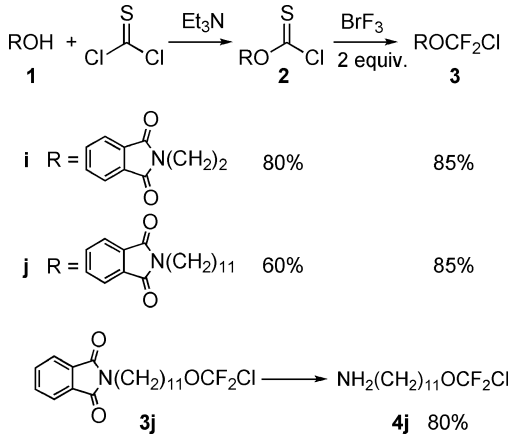
Scheme 2. Conversion of alipathic alcohols to alkyl chlorodifluoromethyl ethers.

Similarly, the branched and cyclic aliphatic alcohols **1b**–**d**, were converted into the corresponding chlorothioformate derivatives **2b**–**d**. After fast reactions with BrF_3, chlorodifluoromethyl 3,7-dimethyloctyl ether (**3b**), chlorodifluoromethyl 2-cyclohexylethyl ether (**3c**) and chlorodifluoromethyl 3-cyclohexylpropyl ether (**3d**) were formed in 80%, 65% and 80% yields respectively. Bi- and tricyclic compounds, such as 2-norbornylethanol (**1e**) and 1-adamantaneethanol (**1f**) also provided, after treatment with thiophosgene, the corresponding 2-norbornylethyl chlorothioformate (**2e**) and 1-adamantylethyl chlorothioformate (**2f**). Both materials were successfully reacted with 2 molar equiv. of BrF_3, to produce the desired chlorodifluoromethyl 1-norbornylethyl ether (**3e**) and chlorodifluoromethyl 1-adamantylethyl ether (**3f**) in 70% yields.

It was documented that the fluorine atoms in BrF_3 can, in certain cases, act as electrophiles[16] and substitute tertiary hydrogen atoms similarly to F_2.[17] Because no such process took place with the above examples, it was clear that the reaction around the sulfur atom were much faster. In addition, BrF_3 is known to substitute bromine atoms,[18] but again the complexation and the fast reaction with the sulfur atoms in the reaction of **2g** was far more selective, and the bromine stays intact to yield chlorodifluoromethyl 11-bromoundecyl ether (**3g**) in 70% yield.

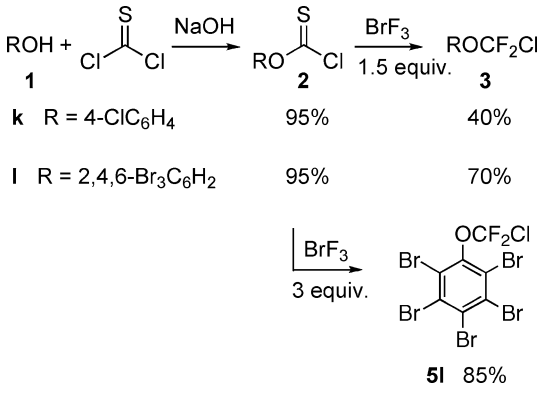
The polyether alcohol **1h** too was converted into the (2-methoxyethoxy)ethyl chlorothioformate (**2h**) and treated with BrF_3. The hard basic oxygen atoms in the alkyl chain did not complex themselves with the bromine atom of the reagent and hence only chlorodifluoromethyl (2-methoxyethoxy)ethyl ether (**3h**) was obtained in 60% yield.

Because the amine moiety can also react with thiophosgene as well as with BrF_3, it has to be protected and one option is to form the phthalimide derivative.[19] Indeed, the reaction of such derivatives, e.g. *N*-(2-hydroxyethyl)phthalimide (**1i**) and *N*-(11-hydroxyundecyl)phthalimide (**1j**) with thiophosgene followed by treatment with BrF_3 led to the formation of **3i** and **3j** in 85% yield (Scheme 3). The protecting group can then be removed[19] with hydrazine hydrate without affecting the OCF_2Cl group as demonstrated for **3j**, converted to 11-(aminoundecyl) chlorodifluoromethyl ether (**4j**) in 80% yield.



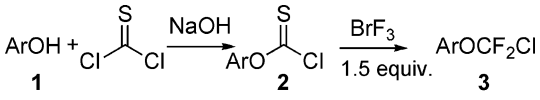
Scheme 3. Preparation of chlorodifluoromethyl *N*-phthalimidoalkyl ethers and chlorodifluoromethyl alkylamine ethers.

The presence of aromatic rings, especially ones with electron-donating groups, can pose a problem because the electrophilic bromine in BrF_3 tends to brominate the electron-rich ring and compete with the fluorination process around the carbon–sulfur bond.[20] This is expressed, for example, when deactivated 4-chlorophenyl chlorothioformate (**2k**)[21] was treated with BrF_3. Analysis of the crude reaction mixture revealed that in addition to the formation of the desired 4-chloro-1-(chlorodifluoromethoxy)benzene (**3k**),[9] a variety of brominated products were also formed, reducing the yield of **3k** to 40%. Somewhat similar results were obtained when 2,4,6-tribromophenyl chlorothioformate (**2l**) was treated with BrF_3 (Scheme 4). Lowering the amount of BrF_3 to 1 molar equiv. led to **3l** in 70% yield, accompanied with 15% of unreacted starting material **2l**. Increasing the amount of BrF_3 up to 3 molar equiv., resulted in a full bromination of the aromatic ring, and 2,3,4,5,6-pentabromo-1-(chlorodifluoromethoxy)benzene (**5l**) was obtained in 85% yield.



Scheme 4. Conversion of slightly deactivated phenol derivatives to aryl chlorodifluoromethyl ethers.

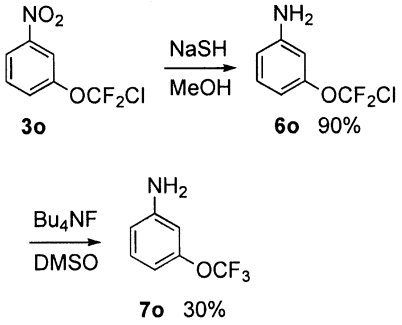
Phenol derivatives with strong electron-withdrawing group (EWG), such as cyano or nitro, do not suffer from the above limitations. The aryl chlorothioformate derivatives (**2m**,[22] **2n**,[21] **2o**[21] and **2p**[21]) were formed and isolated in high yields (90–95%) using thiophosgene and NaOH as a base.[23] After a fast reaction with 1.5 molar equiv. of BrF_3, 4-(chlorodifluoromethoxy)benzonitrile (**3m**) [9] was obtained in 65% yield (Scheme 5). The three isomers of nitrophenyl chlorothioformate (**2n**, **2o**, **2p**) were also converted successfully to 1-(chlorodifluoromethoxy)-2-, -3-, or -4-nitrobenzene (**3n**, **3o**, **3p**[21]), each in 80% yields.



	Ar		% yield
m	4-CNC_6H_4	90	65
n	2-$NO_2C_6H_4$	95	80
o	3-$NO_2C_6H_4$	95	80
p	4-$NO_2C_6H_4$	95	80

Scheme 5. Conversion of deactivated aromatics to aryl chlorodifluoromethyl ethers.

It should be emphasized that the nitro groups can be reduced without affecting the OCF_2Cl moiety forming the respective amino derivatives. Thus, 1-(chlorodifluoromethoxy)-3-nitrobenzene (**3o**) was reduced by NaSH to produce 3-(chlorodifluoromethoxy)aniline (**6o**)[21] in 90% yield (Scheme 6). This opens, of course, new avenues for making practically any aromatic chlorodifluoromethyl ethers at will.



Scheme 6. Reduction of (chlorodifluoromethoxy)nitrobenzenes to the corresponding anilines and its transformation to the (trifluoromethoxy)anilines.

Although the CF_3 group is present in large numbers of drugs, only a few examples in the literature deal with the incorporation of the positron emitter radionuclide ^{18}F into this moiety for imaging using positron emitting tomography (PET).[24] When 3-(chlorodifluoromethoxy)aniline (**6o**) was treated with tetrabutylammonium fluoride in conditions suitable for ^{18}F labeling, the desired 3-(trifluoromethoxy)-aniline (**7o**)[21] was produced, but in only 30% yield (Scheme 6).

This preliminary result may suggest that the aryl or alkyl chlorodifluoromethyl ether derivatives **3** can serve as candidates for ^{18}F containing compounds targeted for PET studies.

Conclusions

In conclusion, this work describes a general method for the preparation of aromatic and especially aliphatic chlorodifluoromethyl ethers **3** in reasonable yield under fast and uncomplicated reaction conditions. When properly used, BrF_3 could serve as an excellent fluorinating agent for hard to prepare fluorinated compounds.

Experimental Section

^1H NMR spectra were recorded using a 200 MHz or 400 MHz spectrometer with $CDCl_3$ as a solvent and Me_4Si as an internal standard. The ^{19}F NMR spectra were measured at 188.1 MHz with $CFCl_3$, serving as an internal standard. The proton broad-band decoupled ^{13}C NMR spectra were recorded at 50.2 MHz or at 100.5 MHz. Here, $CDCl_3$ served as a solvent and Me_4Si as an internal standard. MS was measured under CI, EI, or ESI-QqTOF conditions. In case that these methods could not detect the molecular ion, we have successfully used the Amirav's supersonic GC-MS developed in our department. The main feature of this method is to provide electron ionization while the sample is vibrationally cooled in a supersonic molecular beam. This considerably enhances the relative abundance of molecular ions.[25] Silica gel 60H (Merck) and petroleum ether/ethyl acetate were used for flash chromatography.

Preparing and Handling of BrF_3: Although commercially available, we prepare BrF_3 simply by passing 0.6 mol of commercially available fluorine (ca. 95%) through 0.2 mol of bromine placed in a copper reactor that is held at temperatures between 4–10 °C. Under these conditions, the higher oxidation state of bromine, BrF_5, does not form in appreciable amounts.[26] The reagent can be stored in Teflon® containers indefinitely. BrF_3 tends to react very exothermically with water and oxygenated organic solvents such as acetone or THF. Alkanes, like petroleum ether, cannot serve as solvents because they react fast with BrF_3. Solvents such as $CHCl_3$, CH_2Cl_2, $CFCl_3$ or, if solubility is not an issue, any perfluoroalkane or perfluoroether may be used. Any use of BrF_3 should be conducted in a well-ventilated area, and caution and common sense should be exercised.

At this point we would like to clarify that when dealing with BrF_3 all molar equiv. values given are approximates because the reagent is never completely pure and usually contains some bromine. Furthermore, regardless of the nature of the solvent, it will slowly react with the reagent, effectively reducing the amount of bromine trifluoride reaching the substrate.

Some of the starting compounds are known and referenced, but frequently not adequately described. In such cases their spectral properties are given below.

General Procedure for the Preparation of Alkyl Chlorothioformate Derivatives 2a–j: A solution of the appropriate alcohol **1** (16.6 mmol) and 2.3 mL of triethylamine (16.6 mmol) in 10 mL of THF was added dropwise to a stirred solution of 5 mL thiophosgene (49.8 mmol) in 10 mL THF at 0 °C. Stirring was continued for 20 min, precipitated salt filtered, and the red liquid evaporated to provide a crude mixture containing the corresponding alkyl chlorothioformate (**2**) in 80–90% yield (based on ^1H NMR). The

latter compounds were treated with BrF_3 without further purification with the exceptions of **2i** and **2j**, which were purified by flash chromatography before reacted with BrF_3.

3,7-Dimethyloctyl Chlorothioformate (2b): This compound was prepared from 3,7-dimethyloctanol (**1b**) (2.6 g), as described above: 3.5 g crude mixture, red oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.61 (t, J = 7 Hz, 2 H, CH_2), 1.92–1.18 [m, 10 H, $(CH)CH_2CH_2CH_2$-(CH) CH_2], 0.92 [t, J = 7 Hz, 9 H, $(CH_3)_3$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.1, 76.6, 45.9, 38.8, 36.7, 34.4, 29.3, 27.6, 24.4, 22.4, 19.3 ppm.

2-Cyclohexylethyl Chlorothioformate (2c): This compound was prepared from 2-cyclohexylethanol (**1c**) (2.1 g) as described above: 2.9 g of crude mixture, red oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.54 (t, J = 7 Hz, 2 H, CH_2), 1.68–0.75 [m, 13 H, $(CH_2)_5(CH)CH_2$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.5, 76.3, 67.9, 35.5, 33.0, 26.2, 26.0 ppm.

3-Cyclohexylpropyl Chlorothioformate (2d): This compound was prepared from 3-cyclohexylpropanol (**1d**) (2.3 g) as described above: 3.3 g of crude mixture, red oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.57 (t, J = 7 Hz, 2 H, CH_2), 1.76–0.91 [m, 15 H, $(CH_2)_5(CH)$-CH_2CH_2] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.3, 79.3, 65.9, 34.7, 32.1, 26.8, 25.9 ppm.

2-Nonbornylethyl Chlorothioformate (2e): This compound was prepared from 2-norbornanylethanol (**1e**) (2.3 g) as described above: 3.3 g of crude mixture, red oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.53 (t, J = 7 Hz, 2 H, CH_2), 2.23 (s, 1 H, CH), 1.99 (s, 1 H, CH), 1.85 (s, 1 H, CH), 1.61–1.05 [m, 10 H, $(CH_2)_5$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.3 76.8, 40.1, 38.0, 37.3, 36.5, 31.0, 29.9, 28.2 ppm.

1-Adamantylethyl Chlorothioformate (2f): This compound was prepared from 1-adamantylethanol (**1f**) (2.9 g) as described above: 3.8 g of crude mixture, red oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.62 (t, J = 7 Hz, 2 H, CH_2), 1.97 [s, 3 H, $(CH)_3$], 1.74–1.33 [m, 14 H, $(CH_2)_7$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.4, 74.8, 42.6, 42.3, 37.0, 25.6 ppm.

11-Bromoundecyl Chlorothioformate (2g): This compound was prepared from 11-bromoundecan-1-ol (**1g**) (2.8 g) as described above: 3.1 g of crude mixture, red oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.81 (t, J = 7 Hz, 2 H, CH_2), 3.67 (t, J = 7 Hz, 2 H, CH_2), 2.16–2.05 [m, 4 H, $(CH_2)_2$], 1.70–1.57 [m, 14 H, $(CH_2)_7$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.3, 78.1, 33.9, 32.8, 29.4, 29.1, 28.7, 28.1, 27.8, 25.7 ppm.

(2-Methoxyethoxy)ethyl Chlorothioformate (2h): This compound was prepared from (2-methoxyethoxy)methanol (**1g**) (1.9 g) as described above: 2.9 g of crude mixture, red oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.68 (t, J = 5 Hz, 2 H, CH_2), 3.70–3.55 [m, 6 H, $(CH_2)_2$], 3.86 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.3, 76.3, 71.1, 70.0, 67.7, 58.8 ppm.

***N*-Phthalimidoethyl Chlorothioformate (2i):** This compound was prepared from *N*-(2-hydroxyethyl)phthalimide (**1i**) (3.2 g) as described above. Yield 80% (3.6 g), red oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.60 [m, 4 H, $(CH)_4$], 4.65 (t, J = 7 Hz, 2 H, CH_2), 3.98 (t, J = 7 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.4, 167.5, 134.2, 131.6, 123.4, 73.3, 35.7 ppm.

Procedure for Preparation of *N*-Phthalimidoundecyl Chlorothioformate (2j): 11-Bromoundecan-1-ol (**1g**) (3.7 g, 14.7 mmol), potassium phthalimide (2.8 g, 15.0 mmol), and DMF (20 mL) were heated at 130 °C for 3 h. The DMF was removed under reduced pressure and the crude product dissolved in diethyl ether (30 mL), washed twice with water (40 mL), and dried with $MgSO_4$ to yield pure *N*-(2-hydroxyundecyl)phthalimide (**1j**) in 90% (4.2 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.87–7.69 [m, 4 H, $(CH)_4$], 3.66 [m, 4 H, $(CH_2)_2$], 1.66–1.53 [m, 4 H, $(CH_2)_2$], 1.27 [s, 14 H, $(CH_2)_7$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.3, 134.0, 131.9, 123.0, 62.7, 37.9, 32.6, 29.3, 29.0, 28.4, 26.7, 25.6 ppm.

***N*-Phthalimidoundecyl Chlorothioformate (2j):** This compound was prepared from *N*-(2-hydroxyundecyl)phthalimide (**1j**) (1.2 g) as described above. Yield 60% (900 mg), red oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.81–7.68 [m, 2 H, $(CH)_2$], 7.87–7.81 [m, 2 H, $(CH)_2$], 4.53 (t, J = 7 Hz, 2 H, CH_2), 3.62 (t, J = 7 Hz, 2 H, CH_2), 1.70–1.59 [m, 4 H, $(CH_2)_2$], 1.27 [s, 14 H, $(CH_2)_7$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 186.3, 168.2, 133.6, 132.0, 122.9 77.9, 37.8, 32.4, 29.3, 28.7, 28.4, 27.7, 26.7, 25.5 ppm.

General Procedure for the Preparation of Aryl Chlorothioformate Derivatives 2k–p:[23] The phenol derivative **1** (6.7 mmol) in 6 mL of 5% NaOH solution in water was added to a thiophosgene (6.7 mmol) in 4 mL of $CHCl_3$ at 0 °C. The reaction was stirred for 1 h at 0–5 °C. The chloroform layer was washed with 3 M HCl, water, dried with $MgSO_4$ and evaporated to provide a crude oil which was homogenized by flash chromatography to the corresponding aryl chlorothioformate **2** in almost quantitative yield (90–95%).

2,4,6-Tribromophenyl Chlorothioformate (2l): This compound was prepared from 2,4,6-tribromophenol (**1l**, 2.2 g) as described above. Yield 95% (2.6 g), yellow crystals, m.p. 48.8–49.30 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.73 [s, 2 H, $(CH)_2$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 181.4, 148.3, 134.6, 121.3, 117.8 ppm.

4-Cyanophenyl Chlorothioformat (2m):[22] This compound was prepared from 4-hydroxybenzonitrile (**1m**, 0.8 g) as described above. Yield 90% (1.2 g), yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.73 [d, J = 7 Hz, 2 H, $(CH)_2$], 7.25 [d, J = 7 Hz, 2 H, $(CH)_2$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 184.6, 156.8, 134.2, 123.2, 117.6, 111.5 ppm.

General Procedure for the Preparation of Chlorodifluoromethyl Alkyl or Aryl Ether Derivatives 3a–p with BrF_3: The alkyl or aryl chlorothioformate derivative **2** (usually 3 mmol) was dissolved in 20–25 mL of dry $CFCl_3$ and cooled to 0 °C. Approximately 4.5–6.0 mmol of BrF_3 (1.5–2.0 molar equiv.) was dissolved in 10–15 mL of dry $CFCl_3$, cooled to 0 °C, and added dropwise (about 1 min) to the alkyl or aryl chlorothioformate **2** solution at the same temperature. The reaction mixture was then washed with aqueous Na_2SO_3 till colorless, the aqueous layer extracted three times with CH_2Cl_2 and the combined organic layers dried with $MgSO_4$. Evaporation of the solvent followed by flash chromatography yielded the desired fluorinated compounds **3**.

Chlorodifluoromethyl Octyl Ether (3a): This compound was prepared from **2a** (3.1 g) as described above with 1.8 molar equiv. of BrF_3 in 70% yield (2.5 g), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.99 (t, J = 7 Hz, 2 H, CH_2), 1.71 (quint, J = 7 Hz, 2 H, CH_2), 1.42–1.36 (m, 2 H, CH_2), 1.32–1.29 [m, 8 H, $(CH_2)_4$], 0.89 (t, J = 7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 125.7 (t, J = 286 Hz, CF_2), 69.1, 31.6, 28.9, 28.8, 28.3, 25.4, 22.5, 13.9 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –27.5 (s) ppm. MS (ESI-Qq TOF): m/z = 215.1254 $[MH]^+$. $C_9H_{17}ClF_2O$ (214.68): calcd. C 50.35; H, 7.98; Cl, 16.51; F, 17.70; found: C, 49.57; H, 7.73; Cl, 16.45; F, 16.98.

Chlorodifluoromethyl 3,7-Dimethyloctyl Ether (3b): This compound was prepared from **2b** (3.5 g) as described above with 1.8 molar equiv. of BrF_3 in 80% yield (3.2 g), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (t, J = 7 Hz, 2 H, CH_2), 1.76–1.66 [m, 4 H, CH_2, $(CH)_2$], 1.37–1.18 [m, 6 H, $(CH_2)_3$], 0.89 [t, J = 7 Hz, 9 H, $(CH_3)_3$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 125.8 (t, J =

285 Hz, CF_2), 67.6, 39.1, 37.0, 35.3, 29.3, 27.9, 24.5, 22.6, 22.5, 19.2 . ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –27.6 (s) ppm. $C_{11}H_{21}ClF_2O$ (242.73): calcd. C 54.43, H 8.72; found C 54.06, H 8.98.

Chlorodifluoromethyl 2-Cyclohexylethyl Ether (3c): This compound was prepared from **2c** (2.9 g) as described above with 1.9 molar equiv. of BrF_3 in 65% yield (2.3 g), colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.03 (t, J = 7 Hz, 2 H, CH_2), 1.75–0.95 [m, 13 H, $(CH_2)_5(CH)CH_2$] ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = NMR 125.9 (t, J = 287 Hz, CF_2), 67.4, 35.9, 34.1, 33.1, 26.6, 26.2 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –27.5 (s) ppm. MS (ESI-Qq TOF): m/z = 213.1548 $[MH]^+$.

Chlorodifluoromethyl 3-Cyclohexylpropyl Ether (3d): This compound was prepared from **2d** (3.3 g) as described above with 1.7 molar equiv. of BrF_3 in 80% yield (3.0 g), colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.93 (t, J = 7 Hz, 2 H, CH_2), 1.78–1.69 [m, 7 H, $CH_2CH_2(CH)CH_2$], 1.27–1.23 [m, 6 H, $(CH_2)_3$], 0.98–0.93 (m, 2 H, CH_2) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 125.5 (t, J = 285 Hz, CF_2), 68.9, 36.7, 33.1, 26.6, 26.2, 25.8 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –27.7 (s) ppm. For MS, the usual methods fail to show any molecular peak. However, using Amirav's method provided the solution and indeed a strong molecular ion peak of m/z 226 $(M)^+$ was observed. $C_{10}H_{17}ClF_2O$ (226.69): calcd. C 52.98, H 7.56, F 16.76; found C 52.92, H 7.60, F 16.34.

Chlorodifluoromethyl 2-Norbornylethyl Ether (3e): This compound was prepared from **2e** (3.3 g) as described above with 1.9 molar equiv. of BrF_3 in 70% yield (2.6 g), colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.99 (t, J = 7 Hz, 2 H, CH_2), 2.23 (s, 1 H, CH), 1.98 (s, 1 H, CH), 1.74 (s, 1 H, CH), 1.54–1.49 [m, 4 H, $(CH_2)_2$], 1.31–1.29 (m, 2 H, CH_2), 1.19–1.10 [m, 4 H, $(CH_2)_2$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 125.8 (t, J = 285 Hz, CF_2), 69.7, 40.9, 38.1, 37.9, 36.6, 35.5, 31.6, 29.7, 28.6 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –27.5 (s) ppm. For MS, the usual methods fail to show any molecular peak. However, using Amirav's method provided the solution and indeed a strong molecular ion peak of m/z 224 $[M]^+$ was observed. $C_{10}H_{15}ClF_2O$ (224.68): calcd. C 53.46, H 6.73, F 16.91; found C 53.56, H 6.91, F 16.55.

Chlorodifluoromethyl 1-Adamantylethyl Ether (3f): This compound was prepared from **2f** (3.8 g) as described above with 1.9 molar equiv. of BrF_3 in 70% yield (3.1 g), colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.05 (t, J = 7 Hz, 2 H, CH_2), 1.96 [s, 3 H, $(CH)_3$], 1.69–1.47 [m, 14 H, $(CH_2)_7$] ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 125.7 (t, J = 285 Hz, CF_2), 65.6, 42.3, 42.0, 36.8, 28.4 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –27.4 (s) ppm. For MS, the usual methods fail to show any molecular peak. However, using Amirav's method provided the solution and indeed a strong molecular ion peak of m/z 264 $[M]^+$ was observed. $C_{13}H_{19}ClF_2O$ (264.74): calcd. C 58.98, H 7.23, F 14.35, Cl 13.39; found C 59.10, H 7.30, F 14.62, Cl 13.64.

Chlorodifluoromethyl 11-Bromoundecyl Ether 3g: This compound was prepared from **2g** (3.1 g) as described above with 1.5 molar equiv. of BrF_3 in 70% yield (2.6 g), colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.98 (t, J = 7 Hz, 2 H, CH_2), 3.39 (t, J = 7 Hz, 2 H, CH_2), 1.88–1.67 [m, 4 H, $(CH_2)_2$], 1.30 [s, 14 H, $(CH_2)_7$] ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 125.7 (t, J = 285 Hz, CF_2), 69.1, 33.7, 32.7, 29.3, 28.9, 28.6, 28.3, 28.1, 25.4 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –27.5 (s) ppm. For MS, the usual methods fail to show any molecular peak. However, using Amirav's method provided the solution and indeed a strong molecular ion peak of m/z 336 $[M]^+$ was observed. $C_{12}H_{22}BrClF_2O$ (335.66): calcd. C 42.94, H 6.61, F 11.32; found C 43.02, H 6.69, F 11.70.

Chlorodifluoromethyl (2-Methoxyethoxy)ethyl Ether (3h): This compound was prepared from **2h** (2.9 g) as described above with 1.7 molar equiv. of BrF_3 in 60% (2.0 g), colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.16 (t, J = 5 Hz, 2 H, CH_2), 3.77 (t, J = 5 Hz, 2 H, CH_2), 3.69–3.66 (m, 2 H, CH_2), 3.59–3.56 (m, 2 H, CH_2), 3.39 (s, 3 H, CH_3) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 125.7 (t, J = 286 Hz, CF_2), 71.6, 70.5, 68.1, 67.9, 58.6 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –28.4 (s) ppm. HRMS (ESI-Qq TOF) m/z calcd. for $C_6H_{11}ClF_2NaO_3$ 227.0256 $(MNa)^+$, found 227.0259 $(MNa)^+$. $C_6H_{11}ClF_2O_3$ (204.60): calcd. C 35.22, H 5.42; found C 34.98, H 4.97.

Chlorodifluoromethyl *N*-Phthalimidoethyl Ether (3i): This compound was prepared from **2i** (3.6 g) as described above with 1.8 molar equiv. of BrF_3 in 85% yield (3.1 g); white crystals; m.p. 54.2–55.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 [t, J = 5 Hz, 2 H, $(CH)_2$], 7.78 [t, J = 5 Hz, 2 H, $(CH)_2$], 4.29 (t, J = 7 Hz, 2 H, CH_2), 4.06 (t, J = 7 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 125.7 (t, J = 285 Hz, CF_2), 167.8, 134.2, 131.7, 123.7, 65.3, 40.7 . ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –28.5 (s) ppm. HRMS (CI) m/z calcd. for $C_{11}H_9ClF_2NO_3$ 276.023903 $[MH]^+$, found 276.022870 $[MH]^+$. $C_{11}H_8ClF_2NO_3$ (275.64): calcd. C 47.93, H 2.93, F 13.79; found C 48.16, H 2.67, F 13.96.

Chlorodifluoromethyl *N*-Phthalimidoundecyl Ether (3j): This compound was prepared from **2j** (900 mg) as described above with 1.5 mol equiv. of BrF_3 in 85% yield (810 mg); white crystals; m.p. 33 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 [t, J = 5 Hz, 2 H, $(CH)_2$], 7.71 [t, J = 5 Hz, 2 H, $(CH)_2$], 3.98 (t, J = 7 Hz, 2 H, CH_2), 3.67 (t, J = 7 Hz, 2 H, CH_2), 1.69–1.63 [m, 4 H, $(CH_2)_2$], 1.27 [s, 14 H, $(CH_2)_7$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 125.7 (t, J = 285 Hz, CF_2), 168.2, 134.1, 133.7, 123.8, 69.2, 37.9, 29.0, 28.7, 28.6, 28.4, 26.7, 25.4 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –27.5 (s) ppm. HRMS (CI) m/z calcd. for $C_{20}H_{26}ClF_2NO_3$ 401.156928 $[M]^+$, found 401.156860 $[M]^+$. $C_{20}H_{26}ClF_2NO_3$ (401.88): calcd. C 59.77, H 6.52, N 3.49; found C 60.07, H 6.60, N 3.48.

Preparation of Chlorodifluoromethyl 11-Aminoundecyl Ether 4j: Compound **3j** (400 mg, 0.96 mmol) was dissolved in 15 mL of ethanol, hydrazine hydrate (0.5 mL) was added, and the mixture was heated at reflux for 1.5 h. The reaction mixture was cooled and 0.2 mL of concentrated hydrochloric acid was added. The white precipitate formed was filtered, the filtrate neutralized with 30% sodium hydroxide, extracted with chloroform and dried with $MgSO_4$. The solvent removed under reduced pressure to yield the **chlorodifluoromethyl 11-aminoundecyl ether (4j)** in 80% yield (208 mg), yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.91 (t, J = 7 Hz, 2 H, CH_2), 2.55 (t, J = 7 Hz, 2 H, CH_2), 1.73–1.64 (m, 2 H, CH_2), 1.47–1.25 [m, 16 H, 2 H br, $(CH_2)_8$, NH_2] ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 125.6 (t, J = 284 Hz, CF_2), 69.0, 41.6, 33.2, 29.3, 28.8, 28.2, 27.2, 26.6, 25.3 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –27.6 (s) ppm. For MS, the usual methods fail to show any molecular peak. However, using Amirav's method provided the solution and indeed a strong molecular ion peak of m/z 271 $[M]^+$ was observed.

4-Chloro-1-(chlorodifluoromethoxy)benzene (3k):[9] This compound was prepared from **2k** (621 mg) as described above with 1.9 molar equiv. of BrF_3 in 40% yield (256 mg), colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.40 [d, J = 8 Hz, 2 H, $(CH)_2$], 7.22 [d, J = 8 Hz, 2 H, $(CH)_2$] ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 124.9 (t, J = 289 Hz, CF_2), 148.5, 141.9, 132.5, 129.7, 122.7 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –26.4 (s) ppm.

2,4,6-Tribromo-1-(chlorodifluoromethoxy)benzene (3l): This compound was prepared from **2l** (1.1 g) as described above with 1 mo-

lar equiv. of BrF_3 in 70% yield (850 mg), colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.75 [s, 2 H, $(CH)_2$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 124.8 (t, J = 296 Hz, CF_2), 145.9, 135.6, 121.3, 119.8 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –21.6 (s) ppm. HRMS (CI) *m/z* calcd. for $C_7H_2Br_3ClF_2O$ 415.727140 $[M]^+$, found 415.726944 $[M]^+$. $C_7H_2Br_3ClF_2O$ (415.25): calcd. C 20.25; H, 0.49; F, 9.15; found: C, 20.49; H, 0.50; F, 9.10.

2,3,4,5,6-Pentabromo-1-(chlorodifluoromethoxy)benzene (5l): This compound was prepared by treatment **2l** (1.1 g) as described above with up to 3 molar equiv. of BrF_3 in 85% yield (1.3 g); white crystals, m.p. 69 °C. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 125.7 (t, J = 296 Hz, CF_2), 146.8, 128.6, 122.5, 119.8 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –20.7 (s) ppm. HRMS (EI) *m/z* calcd. for $C_7Br_5ClF_2O$ 573.546116 $[M]^+$, found 573.547668 $[M]^+$. $C_7Br_5ClF_2O$ (573.04): calcd. C 14.67, H 0.00; found C 14.72, H 0.00.

4-(Chlorodifluoromethoxy)benzonitrile (3m):[9] This compound was prepared from **2m** (593 mg) as described above with 1.5 molar equiv. of BrF_3 in 65% yield (400 mg), yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 [d, J = 8.7 Hz, 2 H, $(CH)_2$], 7.25 [d, J = 8.7 Hz, 2 H, $(CH)_2$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 124.7 (t, J = 291 Hz, CF_2), 153.8, 134.4, 121.8, 117.6, 111.3 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –26.5 (s) ppm. HRMS (CI) *m/z* calcd. for $C_8H_5ClF_2NO$ 204.002773 $[MH]^+$, found 204.002677 $[MH]^+$.

1-(Chlorodifluoromethoxy)-2-nitrobenzene (3n): This compound was prepared from **2n** (651 mg) as described above with 1.9 molar equiv. of BrF_3 in 80% yield (500 mg), yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8 Hz, 1 H, CH), 7.72 (td, J_1 = 8, J_2 = 2 Hz, 1 H, CH), 7.53–7.48 [m, 2 H, $(CH)_2$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 124.9 (t, J = 292 Hz, CF_2), 142.6, 141.9, 134.1, 127.6, 124.9, 123.5 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –26.5 (s) ppm. HRMS (CI) *m/z* calcd. for $C_7H_5ClF_2NO_3$ 223.992602 $[MH]^+$, found 223.992447 $[MH]^+$. $C_7H_4ClF_2NO_3$ (223.56): calcd. C 37.61, H 1.80, Cl 15.86, F 17.00, N 6.27; found C 37.32, H 1.77, Cl 16.20, F 18.10, N 6.13.

1-(Chlorodifluoromethoxy)-3-nitrobenzene (3o): This compound was prepared from **2o** (651 mg) as described above with 1.9 molar equiv. of BrF_3 in 80% yield (500 mg), yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8 Hz, 1 H, CH), 8.09 (s, 1 H, CH), 7.73–7.58 [m, 2 H, $(CH)_2$] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 125.4 (t, J = 291 Hz, CF_2), 150.2, 148.8, 130.7, 127.8, 122.1, 117.4 ppm. ^{19}F NMR (188.1 MHz, $CDCl_3$): δ = –27.1 (s) ppm. HRMS (CI) *m/z* calcd. for $C_7H_5ClF_2NO_3$ 223.992602 $[MH]^+$, found 223.993132 $[MH]^+$. $C_7H_4ClF_2NO_3$ (223.56): calcd. C 37.61, H 1.80, F 17.00; found C 37.39, H 1.57, F 17.48.

Preparation of 3-(Chlorodifluoromethoxy)aniline (6o):[21] $NaHCO_3$ (2 g, 0.024 mol) was added to the solution of sodium sulfide ($Na_2S{\cdot}9H_2O$, 6 g, 0.025 mol) dissolved in 20 mL of water. When the carbonate has dissolved completely, 20 mL of methanol were added. Filtration of the precipitated sodium carbonate left a methanol solution of sodium hydrogen sulfide (NaSH). This solution was added to a solution of 1-(chlorodifluoromethoxy)-3-nitrobenzene (**3o**, 2.6 g, 0.012 mol) in 20 mL of methanol and refluxed for 1 h. Purification by flash chromatography led to the desired **6o** in 90% yield (2 g), yellow oil.

Preparation of 3-(Trifluoromethoxy)aniline (7o):[21] Tetrabutylammonium fluoride (3.9 mL, 3.85 mmol, 1.0 M solution in THF) was added to 3-(difluorochloromethoxy)aniline (**6o**, 150 mg, 0.77 mmol) dissolved in 3 mL of anhydrous dimethyl sulfoxide. Reflux for 2 h followed by purification by flash chromatography, led to 3-(trifluoromethoxy)aniline (**7o**) in 30% yield (41 mg), yellow oil.

Supporting Information (see also the footnote on the first page of this article): All NMR spectra of the new chlorodifluoromethyl ethers described in this work.

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