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Synthesis of trifluoromethyl ethers and difluoro(methylthio)methyl ethers by the reaction of dithiocarbonates with IF_5-pyridine-HF

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ABSTRACT

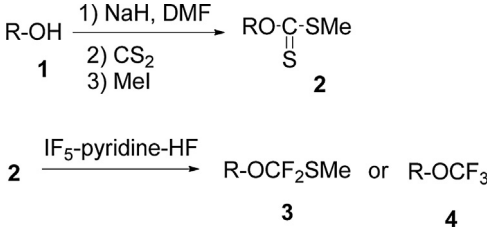
Trifluoromethyl ether and difluoro(methylthio)methyl ether of phenols and aliphatic alcohols were selectively synthesized from the corresponding dithiocarbonates. When IF_5-pyridine-HF was used alone in the reaction of the dithiocarbonate, the difluoro(methylthio)methyl ether was selectively formed. On the other hand, by the additional use of Et_3N-6HF with IF_5-pyridine-HF, trifluoromethyl ether was formed selectively. Various functional groups such as ester, ether, amide, and acetonide could tolerate the reaction conditions, and various functionalized difluoro(methylthio)methyl ethers and trifluoromethyl ethers were synthesized.

1. Introduction

Recently, bioactive compounds [1] and functional materials [2] having a trifluoromethoxy group are becoming important, and many methods for their synthesis have been developed [1–3]. Among them, conversion from dithiocarbonates has been frequently used to synthesize the trifluoromethoxy group, because the starting material can be easily prepared, and fluorine atoms can be introduced under mild conditions using an oxidant such as NBS, NIS, and DBH, and a fluorinating reagent such as pyridinium poly(hydrogen fluoride) [4]. However, pyridinium poly(hydrogen fluoride) is toxic, hygroscopic, and corrosive liquid, and a special care is required for its use. Furthermore, undesired side reaction such as bromination of aromatic ring was observed during the reaction [**4a** and **d**]. Therefore, more reliable and safer method for the conversion of dithiocarbonates to trifluoromethyl ether was desired. Recently, we reported an air-stable fluorinating reagent, IF_5-pyridine-HF, and its application to various fluorination reactions [5]. IF_5-pyridine-HF is a non-hygroscopic white solid, and special care is not required for its use. Therefore, we applied IF_5-pyridine-HF to the reaction with dithiocarbonates of phenols and aliphatic alcohols (Scheme 1).

2. Results and discussion

When the dithiocarbonate of 4-isopropylphenol **2a** was reacted with 1.1 eq of IF_5-pyridine-HF at room temperature for 50 min, difluoro(methylthio)methyl ether **3a** was obtained in 74% yield (Entry 1 in Table 1). By performing the reaction for 3 h, the yield was increased to 87% (Entry 2). Neither further extension of the reaction time nor additional use of IF_5-pyridine-HF was effective in improving the yield further (Entries 3 and 4). Under the employed reaction conditions, the trifluoromethoxy compound **4a** was not formed at all. On the other hand, when the reaction was performed using 2.0 eq of IF_5-pyridine-HF in 1,2-dichloroethane at 60 °C for 24 h, **4a** was formed in 5% yield with 32% of **3a** (Entry 5). By performing the reaction at 84 °C for 24 h, **4a** was selectively formed in moderate yield (Entry 6). The additional use of Et_3N-6HF was found to be effective to activate IF_5-pyridine-HF, and by performing the reaction in a mixture of 5 eq of Et_3N-6HF and 2.0 eq of IF_5-pyridine-HF at 60 °C for 15 h, **4a** was obtained in 66% yield with 7% of **3a** (Entry 7). Finally, **4a** was obtained in the highest yield by performing the reaction in 1,2-dichloroethane at 60 °C for 9 h using 5 eq of Et_3N-6HF and 2.0 eq of IF_5-pyridine-HF (Entry 8).



Scheme 1. Synthesis of trifluoromethyl ethers and difluoro(methylthio)methyl ethers from alcohols or phenols.

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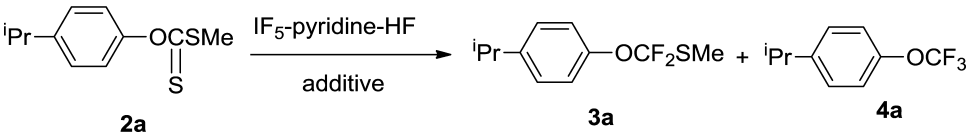
0022-1139/

Table 1
The reaction of dithiocarbonate **2a** with IF_5-pyridine-HF[a]



2a **3a** **4a**

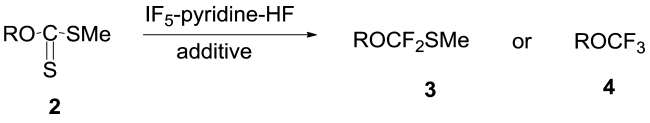
.

Entry	Additive (Additive/**2a**)	Solvent	Reaction conditions	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1[c]	none	CH_2Cl_2	rt, 50 min	74	0
2[c]	none	CH_2Cl_2	rt, 3 h	87	0
3[c]	none	CH_2Cl_2	rt, 24 h	76	0
4[d]	none	CH_2Cl_2	rt, 50 min	67	0
5	none	$(CH_2Cl)_2$	60 °C, 24 h	32	5
6	none	$(CH_2Cl)_2$	84 °C, 24 h	0	45
7	Et_3N-6HF (5)	none	60 °C, 15 h	7	66
8	Et_3N-6HF (5)	$(CH_2Cl)_2$	60 °C, 9 h	0	74

[a] If otherwise not mentioned, 2.0 eq of IF_5-pyridine-HF was used.
[b] ^{19}F NMR yield based on **2a**. Fluorobenzene was used as an internal standard.
[c] 1.1 eq of IF_5-pyridine-HF was used.
[d] 1.5 eq of IF_5-pyridine-HF was used.

The difluoro(methylthio)methyl ether and trifluoromethyl ether of various phenols and alcohols were synthesized from the corresponding dithiocarbonate (Table 2). The difluoro(-methylthio)methyl ether of phenols **3** were generally synthesized by the reaction with IF_5-pridine-HF at room temperature for 3 h. However, when an electron withdrawing group was attached, a longer reaction time was required (Entries 5 and 7). The difluoro(methylthio)methyl ether of aliphatic alcohols (**3f**–**3j**), which are difficult to synthesize in reasonable yield by conventional methods [**4a** and **d**], were also prepared from the corresponding dithiocarbonates (**2f**–**2j**). On the other hand, the trifluoromethyl ethers of phenols and alcohols were synthesized from the corresponding dithiocarbonates by the reaction with IF_5-pyridine-HF and Et_3N-6HF. Various functional groups such as ester

Table 2
Synthesis of difluoro(methylthio)methyl ethers **3** and trifluoromethyl ethers **4** from the corresponding dithiocarbonates **2** by the reaction with IF_5-pyridine-HF



2 **3** **4**

.

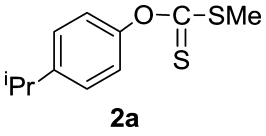
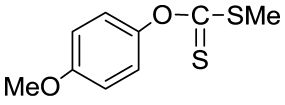
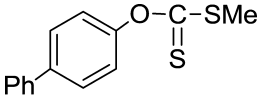
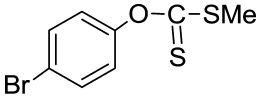
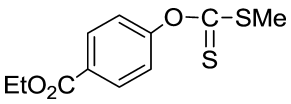
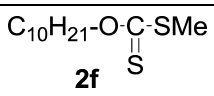
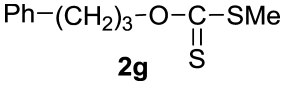
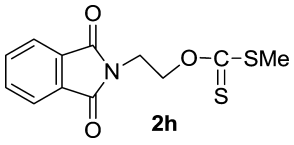
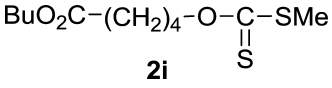
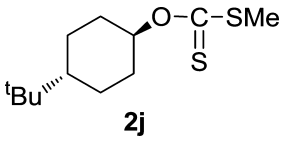
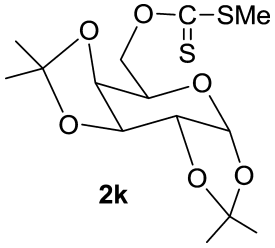
Entry	Substrate **2**	Reaction time (h)	Method[a]	Product	Yield (%)[b]
1	 **2a**	rt, 3 h	A	**3a**	83(87)
2[c]	**2a**	60 °C, 9 h	B	**4a**	(74)
3	 **2b**	rt, 3 h	A	**3b**	78
4	 **2c**	rt, 3 h	A	**3c**	64
5	 **2d**	rt, 24 h	A	**3d**	68
6[c]	**2d**	60 °C, 24 h	B	**4d**	(71)
7	 **2e**	rt, 24 h	A	**3e**	54
8[c]	**2e**	60 °C, 24 h	B	**4e**	55

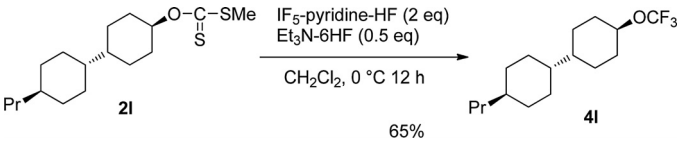
Table 2 (*Continued*)

Entry	Substrate **2**	Reaction time (h)	Method[a]	Product	Yield (%)[b]
9	 **2f**	rt, 3 h	A	**3f**	(98)
10	**2f**	rt, 2 h	B	**4f**	91
11	 **2g**	rt, 3 h	A	**3g**	(100)
10	**2g**	rt, 3 h	B	**4g**	67
11	 **2h**	rt, 3 h	A	**3h**	76
12	**2h**	rt, 3 h	B	**4h**	72
13	 **2i**	rt, 3 h	A	**3i**	(100)
14[d]	**2i**	rt, 3 h	B	**4i**	77
15	 **2j**	0 °C, 24 h	A	**3j**	(88)
16	**2j**	0 °C, 24 h	B	**4j**	53
17	 **2k**	rt, 3 h	B	**4k**	50

[a] Method A: the reaction was carried out in CH_2Cl_2 using 1.1 eq of IF_5-pyridine-HF. Method B: the reaction was carried out in CH_2Cl_2 using 2.0 eq of IF_5-pyridine-HF and 5.0 eq of Et_3N-6HF.
[b] Isolation yield based on substrate. In parentheses, ^{19}F NMR yield based on **2a**, using fluorobenzene as an internal standard.
[c] 1,2-Dichloroethane was used as solvent.
[d] 1.0 eq of Et_3N-6HF was used.

(**4e**, **4i**), amide (**4h**), and acetonide (**4k**) could tolerate the reaction conditions, and introduction of the trifluoromethoxy group to various substrates is possible by using this method. The trifluoromethyl ether of *sec*-alcohol is difficult to synthesize by conventional methods [**4b, d** and **h**], because of instability of the starting dithiocarbonate under acidic conditions. The trifluoromethyl ether of 4-*tert*-butylcyclohexanol **4j** was synthesized from the corresponding dithiocarbonate **2j** in a reasonable yield by performing the reaction using 5 eq of Et_3N-6HF and 2.0 eq of IF_5-pyridine-HF at 0 °C for 24 h (Entry 16).

Trifluoromethoxy group substituted bi(cyclohexane) derivatives are expected as a novel liquid crystalline material, and 1-(4-propylcyclohexyl)-4-trifluoromethoxycyclohexane **4l** was previously prepared from the corresponding dithiocarbonate **2l** by using NBS and 70% HF/pyridine in 40% yield [**4e**]. As our method is applicable to the synthesis of the trifluoromethyl ether of *sec*-alcohol, IF_5-pyridine-HF/Et_3N-6HF was used in the reaction with **2l**, and **4l** was obtained in 65% isolated yield from **2l** (Scheme 2).



Scheme 2. Synthesis of 1-(4-propylcyclohexyl)-4-trifluoromethoxycyclohexane **4l**.

3. Conclusion

We showed that an air-stable fluorination reagent, IF_5-pyridine-HF, can be used for the selective synthesis of various difluoro(methylthio)methyl ethers and trifluoromethyl ethers of phenols and alcohols from the corresponding dithiocarbonates. The present method has some advantages over the previously reported methods. IF_5-pyridine-HF is easy to use and special care is not required, and can be used for the synthesis of the difluoro(methylthio)methyl ethers and trifluoromethyl ethers which were difficult to synthesize previously. Furthermore, undesired side reaction such as halogenation of aromatic ring was not observed during the reaction. We also used the reagent for the synthesis of the trifluoromethyl ether of 4′-propyl-[1,1′-bi(cyclohexan)]-4-ol, which is expected to be a new ionic liquid material.

4. Experimental

4.1. General

The melting points were measured with a Yanagimoto micro melting-point apparatus. The IR spectra were recorded using a JASCO FT/IR-410. The ^1H NMR (400 MHz) spectra, ^{19}F NMR (376 MHz) spectra, and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, is

referred to TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. IF_5 in a cyclinder was supplied by Daikin industries, Ltd. Anhydrous HF in a cyclider was purchaed from Stella Chemifa Corporation. IF_5-pyridine-HF is air-stable and non-hygroscopic white solid. The reaction using IF_5-pyridine-HF can be carried out in glass vessel, but use of Teflon or polyethylene vessel is recommended. It was prepared from IF_5 and pyridine-HF by the previously reported method [5]. Dithiocarbonates **2** were prepared from the corresponding phenols or alcohols **1**, according to the literature [**4d**].

4.1.1. Preparation of Et_3N-6HF

Anhydrous HF (10 g, 0.5 mole) was collected in a Teflon bottle from a cylider. The anhydrous HF in the Teflon bottle was cooled to 0 °C and freshly distilled Et_3N (8.42 g, 0.083 mole) was added slowly. As it is highly exothermal, slow and careful additon of Et_3N is required. After the addition, the mixture was stirred for 30 min. The resulting clear solution of Et_3N-6HF was used without further purification and kept in the Teflon bottle with a screw cap. Anhydrous HF is highly hazadrous and should be handled with rubber gloves in a bench hood.

4.2. Reaction of dithiocarbonate with IF_5-pyridine-HF

4.2.1. 1-Isopropyl-4-[difluoro(methylthio)methoxy]benzene (**3a**)

To a CH_2Cl_2 solution (2 mL) of **2a** (113 mg, 0.5 mmol) was added IF_5-pyridine-HF (193 mg, 0.6 mmol) at room temperature, and the mixture was stirred at room temperature for 3 h. The resulting dark red solution was poured into water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with aq $NaHCO_3$ and aq $Na_2S_2O_3$, and dried over $MgSO_4$. After concentration under reduced pressure, **3a** was isolated in 83% yield by column chromatography (silica gel/hexane); IR (neat) 2291, 1507, 1199, 1135, 1053 434 cm^{-1}; ^{1}H NMR δ 7.20 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 2.96–2.85 (m, 1H), 2.38 (s, 3H), 1.24 (d, J = 8.0 Hz, 6H); ^{19}F NMR δ—46.74 (s, 2F); ^{13}C NMR δ 148.5, 146.6, 129.8 (t, $^1J_{C-F}$ = 294.0 Hz), 127.3 (2C), 121.3 (2C), 33.5, 24.0 (2C), 12.4 (t, $^3J_{C-F}$ = 2.0 Hz); HRMS (EI) calcd for $C_{11}H_{14}F_2OS$ 232.07330, found 232.07350.

4.2.2. 1-Methoxy-4-[difluoro(methylthio)methoxy]benzene (**3b**)

IR (neat) 1507, 1193, 1143, 1034, 478 cm^{-1}; ^{1}H NMR δ 7.13 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 3.80 (s, 3H), 2.73 (s, 3H); ^{19}F NMR δ—46.35 (s, 2F) (lit. [**4d**]—46.84 (s)); ^{13}C NMR δ 157.5, 144.0, 129.9 (t, $^1J_{C-F}$ = 291.6 Hz), 122.8 (2C), 114.3 (2C), 55.5, 12.3 (t, $^3J_{C-F}$ = 3.0 Hz).

4.2.3. 4-[Difluoro(methylthio)methoxy]-1,1′-biphenyl (**3c**)

White solid. *Mp* 29.3–30.8 °C; IR (KBr) 1487, 1134, 1086, 1039, 756 cm^{-1}; ^{1}H NMR δ 7.58–7.55 (m, 4H), 7.44 (d, J = 8.0 Hz, 2H), 7.37–7.34 (m, 1H), 7.23 (d, J = 12.0 Hz, 2H), 2.40 (s, 3H); ^{19}F NMR δ—46.72 (s, 2F) (lit. [**4d**]—47.91 (s)); ^{13}C NMR δ 150.0, 140.0, 139.1, 129.9 (t, $^1J_{C-F}$ = 292.5 Hz), 128.8 (2C), 128.1 (2C), 127.4, 127.0 (2C), 121.7 (2C), 12.4 (t, $^3J_{C-F}$ = 3.0 Hz).

4.2.4. 1-Bromo-4-[difluoro(methylthio)methoxy]benzene (**3d**)

IR (neat) 1484, 1200, 1143, 1067, 1012, 445 cm^{-1}; ^{1}H NMR δ 7.50–7.46 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 2.73 (s, 3H); ^{19}F NMR δ—47.16 (s, 2F) (lit. [**4d**]—46.96 (s)); ^{13}C NMR δ 149.6 (t, $^3J_{C-F}$ = 2 Hz), 132.5 (2C), 129.7 (t, $^1J_{C-F}$ = 298.0 Hz), 123.2 (2C), 119.2, 12.3 (t, $^3J_{C-F}$ = 3.0 Hz).

4.2.5. Ethyl 4-[difluoro(methylthio)methoxy]benzoate (**3e**)

IR (neat) 2983, 1720 (C=O), 1606, 1505 cm^{-1}; ^{1}H NMR δ 8.07–8.05 (m, 2H), 7.27–7.25 (m, 2H), 4.38 (q, J = 7.3 Hz, 2H), 2.38 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H); ^{19}F NMR δ—46.94 (s, 2F); ^{13}C NMR δ 165.8, 154.2, 131.4 (2C), 129.9 (t, $^1J_{C-F}$ = 295.0 Hz), 128.1, 120.8 (2C), 61.3, 14.4, 12.5; HRMS (EI) calcd for $C_{11}H_{12}F_2O_3S$ 262.04750, found 262.04700.

4.2.6. 1-[Difluoro(methylthio)methoxy]decane (**3f**)

IR (neat) 2926, 2855, 1179, 1074, 1035, 1006, 445 cm^{-1}; ^{1}H NMR δ 3.91 (t, J = 4.0 Hz, 2H), 2.30 (s, 3H), 1.69–1.62 (m, 2H), 1.37–1.27 (m, 14H), 0.88 (t, J = 6.9 Hz, 3H); ^{19}F NMR δ—50.53 (s, 2F); ^{13}C NMR δ 130.2 (t, $^1J_{C-F}$ = 293.0 Hz), 66.4 (t, $^3J_{C-F}$ = 4.0 Hz), 31.9, 29.5, 29.5, 29.3, 29.2, 29.0, 25.7, 22.7, 14.1, 12.2 (t, $^3J_{C-F}$ = 2.0 Hz); HRMS (EI) calcd for $C_{12}H_{24}F_2OS$ 254.15159, found 254.15166.

4.2.7. 3-[Difluoro(methylthio)methoxy]-1-phenylpropane (**3g**)

IR (neat) 2936, 1177, 1029, 756 cm^{-1}; ^{1}H NMR δ 7.32–7.19 (m, 5H), 3.93 (t, J = 6.4 Hz, 2H), 2.73 (t, J = 7.6 Hz, 2H), 2.31 (s, 3H), 2.02–1.95 (m, 2H); ^{19}F NMR δ—50.61 (s, 2F) (lit. [**4d**]—50.51 (s)); ^{13}C NMR δ 149.9, 141.1, 128.6 (4C), 126.2 (t, $^1J_{C-F}$ = 230.9 Hz), 65.6 (t, $^3J_{C-F}$ = 4.4 Hz), 32.0, 30.8, 12.4; HRMS (EI) calcd for $C_{11}H_{14}F_2OS$ 232.07334, found 232.07291.

4.2.8. N-2-[difluoro(methylthio)methoxy]ethylphthalimide (**3h**)

White solid. *Mp* 48.0–50.9 °C; IR (KBr) 2968, 1772, 1714 (C=O), 1395, 1198, 1082, 978 cm^{-1}; ^{1}H NMR δ 7.89–7.85 (m, 2H), 7.76–7.73 (m, 2H), 4.18 (t, J = 5.7 Hz, 2H), 3.99 (t, J = 5.7 Hz, 2H), 2.25 (s, 3H); ^{19}F NMR δ—51.26 (s, 2F); ^{13}C NMR δ 167.8 (2C), 134.1 (2C), 131.8 (2C), 130.1 (t, $^1J_{C-F}$ = 292.0 Hz), 123.3 (2C), 62.9 (t, $^3J_{C-F}$ = 4.4 Hz), 37.1, 12.2; HRMS (ESI) calcd for $C_{12}H_{11}F_2NO_3SNa$ (M^+ + Na) 310.03250 found 310.03200.

4.2.9. Butyl 5-[difluoro(methylthio)methoxy]pentanoate (**3i**)

IR (neat) 2960, 1735 (C=O), 1154 cm^{-1}; ^{1}H NMR δ 4.08 (t, J = 6.6 Hz, 2H), 3.93 (t, J = 6.0 Hz, 2H), 2.35 (t, J = 7.0 Hz, 2H), 2.30 (s, 3H), 1.78–1.69 (m, 4H), 1.65–1.58 (m, 2H), 1.43–1.33 (m, 2H), 0.94 (t, J = 7.6 Hz, 3H); ^{19}F NMR δ—50.81 (s, 2F); ^{13}C NMR δ 173.4, 130.3 (t, $^1J_{C-F}$ = 290.8 Hz), 65.8 (t, $^3J_{C-F}$ = 4.4 Hz), 64.4, 33.8, 30.7, 28.5, 21.4, 19.2, 13.8, 12.3; HRMS (FTMS) calcd for $C_{11}H_{20}F_2O_3SNa$ 293.09930, found 293.09970.

4.2.10. 1-tert-Butyl-4-[difluoro(methylthio)methoxy]cyclohexane (**3j**)

IR (neat) 2952, 1200, 1077 cm^{-1}; ^{1}H NMR δ 4.17–4.12 (m, 1H), 2.31 (s, 3H), 2.08 (d, J = 9.1 Hz, 2H), 1.81 (d, J = 11.0 Hz, 2H), 1.43–1.40 (m, 2H), 1.09 -1.00 (m, 3H), 0.85 (s, 9H); ^{19}F NMR δ—47.29 (s, 2F); ^{13}C NMR δ 130.2 (t, $^1J_{C-F}$ = 291.3 Hz), 77.5 (t, $^3J_{C-F}$ = 3.2 Hz), 46.7, 33.4 (2C), 32.3, 27.6 (3C), 25.6 (2C), 12.4 (t, $^3J_{C-F}$ = 2.5 Hz); MS (EI) m/z 41 (40), 56 (22), 57 (100), 67 (27), 81 (28), 94 (20), 123 (11), 138 (5).

4.2.11. 1-Isopropyl-4-(trifluoromethoxy)benzene (**4a**)

To IF_5-pyridine-HF (321 mg, 1.0 mmol) in dichloroethane (2 mL), were added Et_3N-6HF (553 mg, 2.5 mmol) and **2a** (113 mg, 0.5 mmol) successively at room temperature. The mixture was stirred at 60 °C for 9 h. The resulting dark red solution was poured into water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with aq $NaHCO_3$ and aq $Na_2S_2O_3$, and dried over $MgSO_4$. The yield of **4a** was determined to be 74% by ^{19}F NMR using fluorobenzene as an internal standard. Pure **4a** was obtained by column chromatography (silica gel/hexane); IR (neat) 2963, 1256, 1212 cm^{-1}; ^{1}H NMR δ 7.23 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 2.95–2.85 (m, 1H), 1.24 (d, J = 6.8 Hz, 6H); ^{19}F NMR δ—58.53 (s, 3F); ^{13}C NMR δ 147.7, 147.3, 127.8 (2C), 121.0 (2C), 120.7 (q, $^1J_{C-F}$ = 257.7 Hz), 33.7, 24.1 (2C); HRMS (EI) calcd for $C_{10}H_{11}F_3O$ 204.07620, found 204.07606.

4.2.12. 1-Bromo-4-(trifluoromethoxy)benzene (**4d**)

IR (neat) 2961, 1743, 1380, 1227 cm^{-1}; ^{1}H NMR δ 7.52 (d, J = 9.2 Hz, 2H), 7.10 (d, J = 9.2 Hz, 2H); ^{19}F NMR δ—58.70

(s, 3F) (lit. [**4d**]—58.63 (s)); ^{13}C NMR δ 148.4, 133.1 (2C), 122.9 (2C), 120.4 (q, $^{1}J_{C-F}$ = 257.7 Hz), 120.3.

*4.2.13. Ethyl 4-(trifluoromethoxy)benzoate (**4e**)*

IR (neat) 2986, 1721 (C=O), 1259, 1169, 1105 cm^{-1}; ^{1}H NMR δ 8.10 (d, J = 9.2 Hz, 2*H*), 7.23 (d, J = 8.4 Hz, 2*H*), 4.39 (q, J = 7.2 Hz, 2*H*), 1.40 (t, J = 7.2 Hz, 3*H*); ^{19}F NMR δ—58.23 (s, 3F) (lit. [6]—58.1); ^{13}C NMR δ 165.5, 152.7, 131.6 (2C), 129.0, 120.4 (q, $^{1}J_{C-F}$ = 260.0 Hz), 120.3 (2C), 61.4, 14.3.

*4.2.14. 1-(Trifluoromethoxy)decane (**4f**)*

IR (neat) 1724, 1442, 1281 cm^{-1}; ^{1}H NMR δ 3.95 (t, J = 6.6 Hz, 2*H*), 1.72–1.65 (m, 2*H*), 1.45–1.12 (m, 14*H*), 0.83 (t, J = 7.0 Hz 3*H*); ^{19}F NMR δ—61.23 (s, 3F) (lit. [**4d**]—61.14 (s)); ^{13}C NMR δ 121.9 (q, $^{1}J_{C-F}$ = 255.0 Hz), 67.7 (d, $^{3}J_{C-F}$ = 2.9 Hz), 32.0, 29.7, 29.6, 29.5, 29.2, 28.9, 25.6, 22.8, 14.2.

*4.2.15. 3-(Trifluoromethoxy)-1-phenylpropane (**4g**)*

IR (neat) 2927, 2857, 1467, 1408, 1275, 1141 cm^{-1}; ^{1}H NMR δ 7.32–7.28 (m, 2*H*), 7.21–7.18 (m, 3*H*), 3.96 (t, J = 6.4 Hz, 2*H*), 2.73 (t, J = 8.4 Hz, 2*H*), 2.04–1.97 (m, 2*H*); ^{19}F NMR δ—61.23 (s, 3F) (lit. [7]—60.3); ^{13}C NMR δ 140.7, 128.7, 128.6 (2C), 126.3 (2C), 121.9 (q, $^{1}J_{C-F}$ = 254.8 Hz), 66.6 (q, $^{3}J_{C-F}$ = 3.8 Hz), 31.7, 30.4.

*4.2.16. N-2-(trifluoromethoxy)ethylphthalimide (**4h**)*

White solid. *Mp* 70.0–72.0 °C (lit. [**4g**] 77.0–77.4 °C); IR (KBr) 1775, 1716 (C=O), 1392, 1225 cm^{-1}; ^{1}H NMR δ 7.91–7.87 (m, 2*H*), 7.78–7.72 (m, 1*H*), 4.23 (t, J = 6.0 Hz, 2*H*), 4.02 (t, J = 5.2 Hz, 2*H*); ^{19}F NMR δ—61.6 (s, 3F) (lit. [**4g**]—61.4); ^{13}C NMR δ 168.0 (2C), 134.4 (2C), 131.9 (2C), 123.7 (2C), 121.6 (q, $^{1}J_{C-F}$ = 256.8 Hz), 64.0 (q, $^{3}J_{C-F}$ = 2.9 Hz).

*4.2.17. Butyl 5-(trifluoromethoxy)pentanoate (**4i**)*

IR (neat) 2964, 1737 (C=O), 1273, 1142 cm^{-1}; ^{1}H NMR δ 4.08 (t, J = 7.0 Hz, 2*H*), 3.99–3.96 (m, 2*H*), 2.37–2.34 (m, 2*H*), 1.78–1.73 (m, 4*H*), 1.65–1.57 (m, 2*H*), 1.43–1.33 (m, 2*H*), 0.938 (t, J = 7.6 Hz, 3*H*); ^{19}F NMR δ—61.40 (s, 3F); ^{13}C NMR δ 173.3, 121.8 (q, $^{1}J_{C-F}$ = 255.0 Hz), 67.0 (d, $^{3}J_{C-F}$ = 2.9 Hz), 64.5, 33.7, 30.8, 28.2, 21.1, 19.3, 13.8; HRMS (EI) calcd for $C_{10}H_{18}F_3O_3$ (M^+ + H) 243.12026, found 243.12050.

*4.2.18. 1-*tert*-Butyl-4-(trifluoromethoxy)cyclohexane (**4j**)*

IR (neat) 2955, 1288, 1214, 1133 cm^{-1}; ^{1}H NMR δ 4.11–4.04 (m, 1*H*), 2.12 (d, J = 10.8 Hz, 2*H*), 1.84 (d, J = 12.0 Hz, 2*H*), 1.49–1.39 (m, 2*H*), 1.11–0.99 (m, 3*H*), 0.86 (s, 9*H*); ^{19}F NMR δ—58.14 (s, 3F); ^{13}C NMR δ 121.8 (q, $^{1}J_{C-F}$ = 254.9 Hz), 78.7, 46.8, 33.0 (2C), 32.4, 27.7(3C), 25.5 (2C); MS (EI) *m/z* 123(18), 81(23), 69 (21), 67 (18), 57 (100), 56 (84), 41 (67).

*4.2.19. 1,2:3,4-Di-*O*-isopropylidene-6-*O*-trifluoromethyl-α-*D*-galactopyranose (**4k**)*

White solid. *Mp*. 53.0–56.0 °C (lit. [8] 53.5–55.5 °C); IR (KBr) 2997, 1218, 1146, 1065, 1005, 871 cm^{-1}; ^{1}H NMR δ 5.54 (d, J = 5.5 Hz, 1*H*), 4.62 (dd, J = 2.4, 8.0 Hz, 1*H*), 4.35 (dd, J = 2.4, 5.2 Hz, 1*H*), 4.25 (dd, J = 1.8, 8.0 Hz, 1*H*), 4.15–4.02 (m, 3*H*), 1.54 (s, 3*H*), 1.43 (s, 3*H*), 1.34 (s, 6*H*); ^{19}F NMR δ—61.45 (s, 3F); ^{13}C NMR δ 121.8 (q, $^{1}J_{C-F}$ = 256.0 Hz), 109.9, 109.0, 96.3, 70.7, 70.5, 66.1, 66.0, 65.9, 26.1, 26.0, 25.0, 24.5; HRMS (ESI) calcd for $C_{13}H_{19}O_6F_3Na$ (M^+ + Na) 351.10259 found 351.10262.

*4.2.20. 4-Propyl-4′-(trifluoromethoxy)-1,1′-bi(cyclohexane) (**4l**)*

White solid. *Mp* 28.8–29.2 °C (lit. [**4e**] 30.8–31.1 °C); IR (KBr) 2925, 1297, 1125 cm^{-1}; ^{1}H NMR δ 4.07 (tt, J = 4.8, 10.8 Hz, 1*H*), 2.11–2.07 (m, 2*H*), 1.81–1.67 (m, 6*H*), 1.44–0.82 (m, 19*H*), 0.87 (t, J = 7.4 Hz, 3*H*); ^{19}F NMR δ—58.12 (s, 3F) (lit. [**4e**]—58.0 (s, 3F)); ^{13}C NMR δ 121.8 (q, $^{1}J_{C-F}$ = 254.8 Hz), 78.7, 42.7, 42.0, 37.9, 37.7, 33.6 (2C), 32.9 (2C), 32.4, 30.3 (2C), 28.0 (2C), 26.8, 22.9, 14.3; HRMS (EI) calcd for $C_{18}H_{31}OF_3$ 320.23270 found 320.23274.

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