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Synthesis of aryl 2-bromo-2-chloro-1,1-difluoroethyl ethers mediated by a reaction between phenols and halothane

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Abstract

An efficient and convenient method for the synthesis of structurally unique and highly functionalized aryl 2-bromo-2-chloro-1,1-difluoroethyl ethers has been developed. This approach exhibited a broad reaction scope, simple operation, and no need for any expensive transition-metal catalysts, or highly toxic reagents. Notably, we demonstrated the potential utility of halothane for obtaining such aryl *gem*-difluoroalkyl ethers containing a bromochloromethyl group.

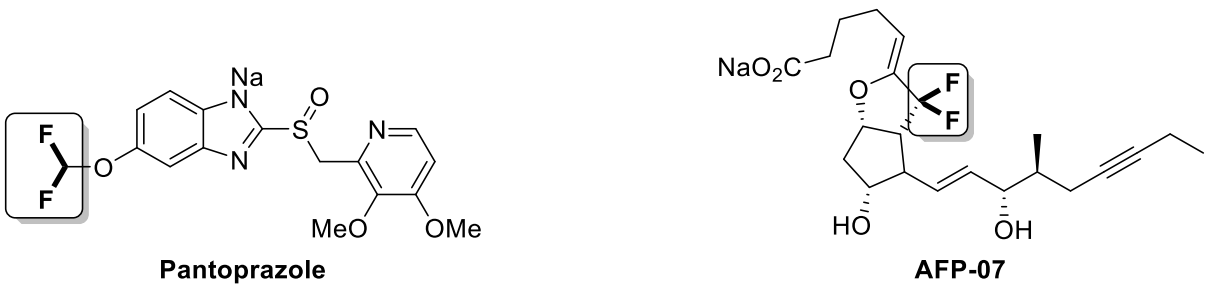
Keywords

aryl 1,1-difluoroethyl ether; 1,1-difluoroethene; fluorine compound; halothane; phenol.

Introduction

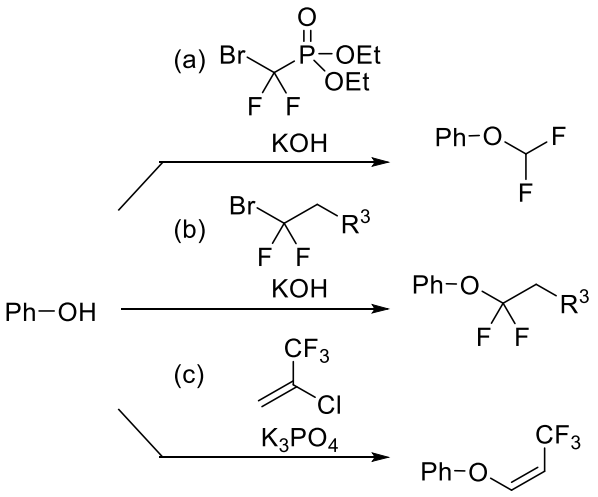
Molecules containing fluoroalkyl groups are of interest in pharmaceutical and agrochemical sciences because deliberately incorporated fluorine atoms often change the chemical properties of the parent molecules, thereby improving their absorption, resistance to metabolism, and pharmacological activities. To date, difluoromethyl or difluoromethylene compounds have been studied extensively as well as monofluorinated and trifluoromethylated arenes or aliphatics. [1-4] Recent progress in difluoromethylene chemistry has successfully led to the discovery of bioactive compounds such as pantoprazole, a proton pump inhibitor [5], and AFP-07, a prostaglandin I2 receptor-selective agonist [6-8], which highlights the importance of the difluoromethylene unit in drug discovery (Figure 1). There have been many reports on the construction of difluoromethylene units, such as deoxygenating and conversion of a carbonyl to a difluoromethylene unit using N,N-diethylaminosulfur trifluoride (DAST) [9-14], a Reformatsky reaction of ethyl bromodifluoroacetate [15-23], and transformations of tetrafluoroethylene with appropriate metal catalysts [24-31]. Additionally, recent advances in difluoromethylene chemistry have allowed the synthesis of aryl fluoroalkyl ethers, as shown in Scheme 1. For example, the reactions of phenols with “gem-difluorocarbene precursors (route (a))” or “bromodifluoroalkyl compounds (route (b))” have been typically used to obtain a variety of aryl gem-difluoromethyl ethers. The latter approach is particularly useful for obtaining liquid crystal materials. [32-36] In the case of using the 2-chloro-3,3,3-trifluoroprop-1-ene route (route (c), Scheme 1), an aryl enol ether with a trifluoromethyl group was obtained. [37,38] Based on our previous reports, we focused on halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) because the treatment of halothane with several bases has been found to give highly electrophilic 2-bromo-2-chloro-1,1-difluoroethene. [39,40]

Additionally, other reports discussed the carbocationic character of the gem-difluorovinyl carbon, which can be explained by the orbital interaction between the n orbital (fluorine) and the π orbital. [41] Considering these, we envisioned that the reaction of phenols with halothane in the presence of a suitable base would proceed via the addition of the phenoxide oxygen to the electrophilic *gem*-difluoromethylene carbon, which would lead to highly functionalized aryl 2-bromo-2-chloro-1,1-difluoroethyl ethers. In this paper, we discuss the synthetic approach to obtain such structurally unique and highly functionalized aryl *gem*-difluoroalkyl ethers with a bromochloromethyl group.



Pantoprazole **AFP-07**

Figure 1: Medical compounds having a difluoromethyl group

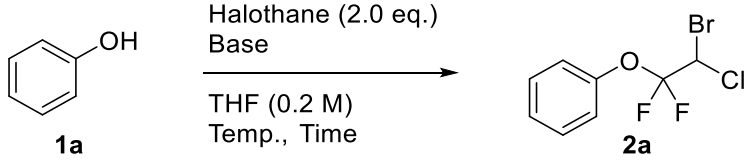


Scheme 1: Methods for the synthesis of ethers containing fluorine substituents

Results and Discussion

We began our study to optimize the reaction conditions (Table 1). When two equivalents of halothane and sodium hydride (NaH) were treated with phenol at room temperature, the reaction proceeded to provide the ether product (**2a**) in 39% yield (entry 1, Table 1). In this case, there was unreacted phenol starting material in the reaction mixture. Therefore, the reaction was conducted with an increased amount of halothane to 2.5 and 4.0 equivalents; however, in both reactions, the yields of **2a** were not improved despite a significant decrease in the starting material (entries 2, 3). Next, as shown in entry 4, when the reaction was conducted with a lower loading of NaH, 2a was obtained in the same yield as that of entry 1. The result in entry 5 shows that when the reaction time was prolonged to 52 h, the yield of **2a** was somewhat better (55%), which suggests this may be a sluggish reaction. However, when the reaction temperature was raised to 40 or 60 °C, the product yield was gradually improved (entries 6, 7). It is worth noting that when the base was changed to potassium hydroxide (KOH), a dramatic improvement was observed in the reaction efficiency to give **2a** in 74%, in a remarkably short reaction time (entry 8). Conversely, the reaction did not occur at all when potassium carbonate was used because the deprotonation of phenol was much slower (entry 9).

Table 1: Screening the reaction conditions with phenol.



Entry	Base (eq.)	Temp. (°C)	Time (h)	Yield (%)[a]
1	NaH (2.0)	rt	20	39

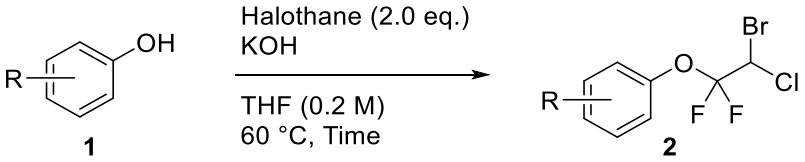
2[b]	NaH (2.0)	rt	23	37
3[c]	NaH (2.0)	rt	23	32
4	NaH (1.5)	rt	24	39
5	NaH (1.5)	rt	52	55
6	NaH (1.5)	40	25	54
7	NaH (1.5)	60	13	74
8	KOH (1.5)	60	1.5	74
9	K_2CO_3 (1.5)	60	24	0

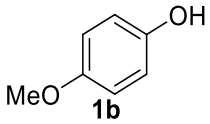
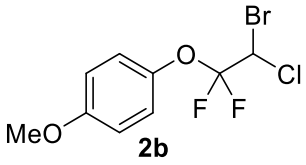
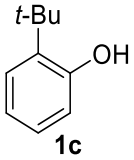
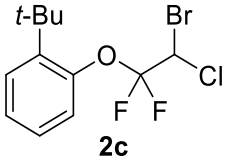
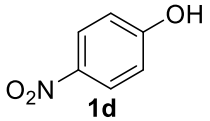
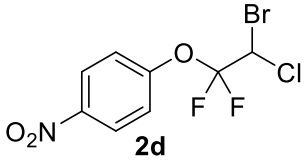
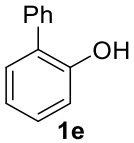
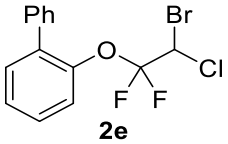
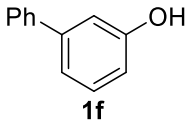
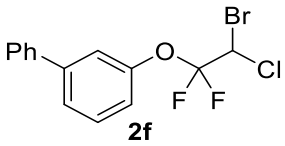
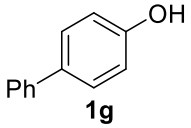
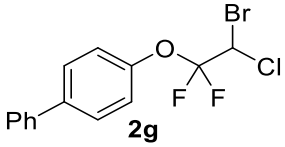
[a]Isolated yields.; [b]Halothane (2.5 eq.) was used; [c]Halothane (4.0 eq.) was used.

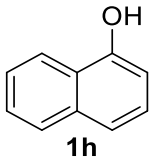
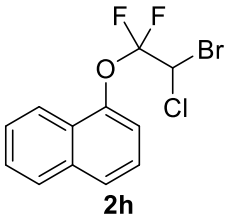
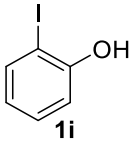
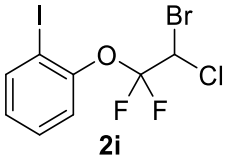
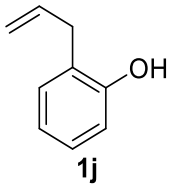
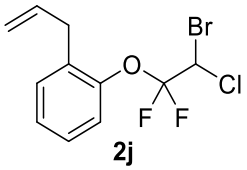
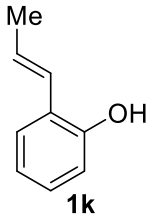
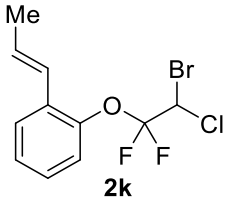
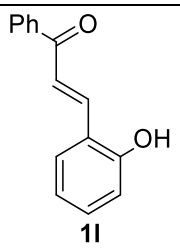
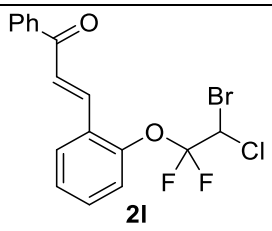
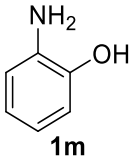
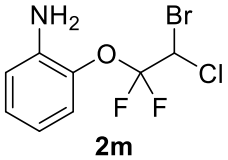
With the optimal reaction condition in hand, we examined the scope of this reaction (Table 2). When an electron-rich phenol, *p*-methoxyphenol (**1b**), was used, the reaction proceeded to afford **2b** in 79% yield (entry 1, Table 2). *Ortho*-substitution with a bulkier *t*-butyl group slightly affected the reaction to give **2c** in an acceptable yield (entry 2). *p*-Nitrophenol (**1d**), an electron-poor phenol, was converted into **2d** only in a trace amount (entry 3). A phenyl group at *ortho* position, a compound **1e**, did not affect the reaction, and the positional isomers, **1f** and **1g**, gave the corresponding products in good yields (entries 4 to 6). 1-Naphthol (**1h**) was also compatible with the reaction and gave **2h** in good yield (entry 7). When a strongly electronegative nitro group was at the ortho-position, the reaction appeared to become slow, and the yield decreased to 39% (entry 7). As shown in entries 8 to 10, iodide (**1i**) and alkenyl chains (**1j** and **1k**), which are more susceptible to radical conditions, were all intact, suggesting that the reaction proceeds in an ionic manner. 2-Hydroxychalcone (**1l**), a good Michael acceptor, was able to participate in the reaction to give **2l** in 43% yield, without any Michael reaction byproduct formation (entry 11). When *o*-aminophenol was used as

the substrate, the coupling reaction occurred on the hydroxyl group exclusively to give **2m** (entry 12).

Table 2: The reaction scope with various phenols.



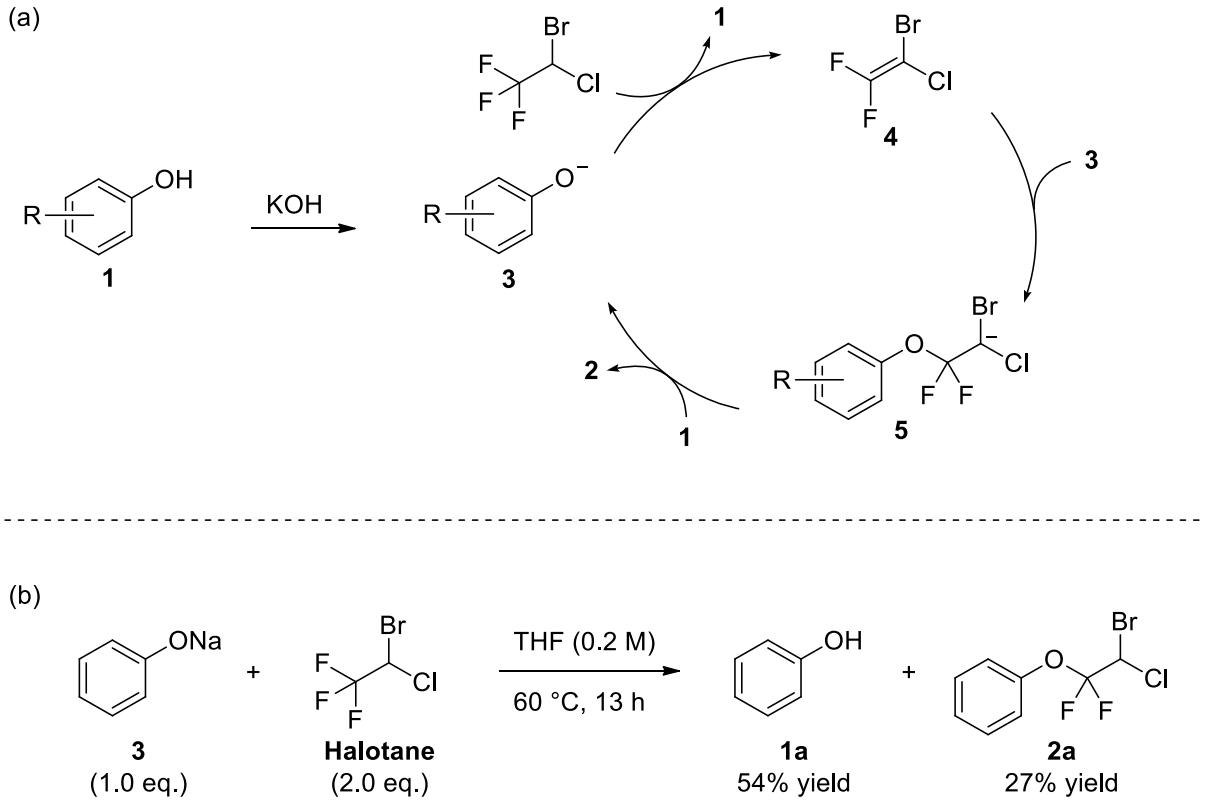
Entry	Substrates	Products	Time (h)	Yield (%)[a]
1			2.5	79
2			0.5	47
3			28	–
4			3.0	71
5			1.5	79
6			5.0	88

7	 **1h**	 **2h**	3.5	85
8	 **1i**	 **2i**	6.5	67
9	 **1j**	 **2j**	1.5	81
10[b]	 **1k**	 **2k**	1.0	71
11	 **1l**	 **2l**	23	43
12	 **1m**	 **2m**	19	51

[a]Isolated yield.; [b]**1k** and **2k** were *cis-trans* mixtures.

Regarding the reaction mechanism, we initially speculated that the phenoxide was generated first, and the potassium hydroxide remaining in the reaction mixture could deprotonate halothane to provide fully halogenated ethylene **4** that appeared to be a key intermediate for this reaction (Scheme 2 (a)). Recent studies have

demonstrated that *gem*-difluorovinyl carbons have electrophilic character because of the overlapping fluorine lone pairs and adjacent π orbital favor the generation of difluoromethyl cation species. [41] Considering these reports, a phenoxide attack on the *gem*-difluorovinyl carbon is a plausible next step in the reaction, which generates carbanion 5. Finally, the protonation of **5** by **1** or other acidic compounds, including a water molecule, would provide **2**. To gain further insight into the reaction mechanism, we conducted the reaction with only sodium phenoxide and halothane as shown in Scheme 2 (a). Indeed, the reaction occurred to give **2a** in 27% yield, which suggested that the phenoxide anion could also deprotonate halothane to promote the reaction. This result is reasonable because the reaction with *p*-nitrophenoxide (entry 3, Table 2) did not occur at all, probably because of the low basicity of the *p*-nitrophenoxide anion.



Scheme 2: Proposed reaction mechanism.

Conclusion

We have developed the first example to synthesize structurally unique and highly functionalized aryl 2-bromo-2-chloro-1,1-difluoroethyl ethers, which contain a gem-difluoroalkyl ether unit in addition to a bromochloromethyl group. The reaction is mild and compatible with various phenols to give the products in moderate to good yields. Additionally, the products are expected to undergo a variety of functionalization using ionic and radical processes; further studies based on such chemical transformations of the ether products are currently underway.

Experimental

General information

^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded on JEOL ECZ 400S spectrometers. Chemical shifts of ^{1}H NMR are reported in ppm from tetramethylsilane (TMS) as an internal standard. Chemical shifts of ^{13}C NMR are reported in ppm from the center line of a triplet at 77.16 ppm for deuterochloroform. Chemical shifts of ^{19}F NMR are reported in ppm from $CFCl_3$ as an internal standard. All data are reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, br = broad, brd = broad-doublet, m = multiplet), coupling constants (Hz). Mass spectra were obtained on JEOL JMS-700T spectrometer (EI).

Materials

All commercially available materials were used as received without further purification. All experiments were carried out under argon atmosphere in flame-dried

glassware using standard inert techniques for introducing reagents and solvents unless otherwise noted.

Typical procedure for the reaction between various phenols and halothane.

To a solution of phenol (1.0 mmol) in THF (5.0 mL) was added KOH (1.5 mmol) and halothane (2.0 mmol) dropwise at 0 °C. The solution was heated to 60 °C until the reaction was completed with monitoring by TLC analysis. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl (20 mL) at 0 °C and extracted with AcOEt. The organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to afford **2**.

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2-Bromo-2-chloro-1,1-difluoroethyl phenyl ether (2a): The title product (**2a**) was purified by column chromatography and preparative TLC (hexane only). **2a** was obtained in 74% yield (199.6 mg). A pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.91 (1H, t, *J* = 5.2 Hz), 7.20-7.31 (5H, m), 7.35-7.42 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.5 (t, *J* = 41.7 Hz), 119.7 (t, *J* = 267.1 Hz), 121.8, 126.5, 129.7, 149.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -77.9 (1F, dd, *J* = 136.9, 5.2 Hz), -78.2 (1F, dd, *J* = 136.9, 5.2 Hz); MS (EI) *m/z*: 270, 272 (M^+); HRMS (EI) Calcd. for $C_8H_6BrClF_2O$: 269.9259, 271.9238 ($M^{+)}$, Found: 269.9264, 271.9233.

2-Bromo-2-chloro-1,1-difluoroethyl p-methoxyphenyl ether (2b): The title product (**2c**) was purified by column chromatography (hexane:$CHCl_3$ = 19:1 to hexane:AcOEt = 9:1) and was obtained in 79% yield (237.2 mg). A yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.81 (3H, s), 5.90 (1H, t, *J* = 5.0 Hz), 6.88 (2H, d, *J* = 9.1 Hz), 7.15 (2H, d, *J* = 9.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.5 (t, *J* = 42.1 Hz), 55.7, 114.6, 119.7 (t, *J* = 267.1 Hz), 123.2, 142.9, 157.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -78.2 (1F, dd, *J* = 137.5, 5.0 Hz), -78.5 (1F, dd, *J* = 137.5, 5.0 Hz); MS (EI) *m/z*: 300 (M^+); HRMS (EI) Calcd. for $C_9H_8BrClF_2O_2$: 299.9364 (M^+), Found: 299.9361.

2-Bromo-2-chloro-1,1-difluoroethyl *o*-*t*-butylphenyl ether (2c): The title product (**2c**) was purified by column chromatography and preparative TLC (hexane only). **2c** was obtained in 47% yield (155.2 mg). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41 (9H, s), 5.97 (1H, t, *J* = 5.2 Hz), 7.13 (1H, ddd, *J* = 7.5, 7.5, 1.2 Hz), 7.18-7.24 (1H, m), 7.37-7.43 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.5, 35.0, 54.0 (t, *J* = 42.1 Hz), 119.1 (t, *J* = 3.6 Hz), 120.0 (t, *J* = 270.8 Hz), 125.0, 127.2, 127.8, 140.0, 149.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -76.9 (1F, ddd, *J* = 134.3, 5.2, 2.1 Hz), -77.2 (1F, ddd, *J* = 134.3, 5.2, 2.1 Hz); MS (EI) *m/z*: 326 (M^+); HRMS (EI) Calcd. for $C_{12}H_{14}BrClF_2O$: 325.9885 (M^+), Found: 325.9879.

2-Bromo-2-chloro-1,1-difluoroethyl *o*-phenylphenyl ether (2e): The title product (**2e**) was purified by column chromatography and preparative TLC (hexane only). **2e** was obtained in 71% yield (247.1 mg). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.64 (1H, t, *J* = 5.2 Hz), 7.30-7.49 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.4 (t, *J* = 41.2 Hz), 119.6 (t, *J* = 268.8 Hz), 122.4, 126.7, 127.6, 128.2, 128.6, 129.7, 131.5, 135.9, 137.4, 146.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -77.5 (2F, dd, *J* = 5.2, 3.1 Hz); MS (EI) *m/z*: 346 (M^+); HRMS (EI) Calcd. for $C_{14}H_{10}BrClF_2O$: 345.9572 (M^+), Found: 345.9562.

2-Bromo-2-chloro-1,1-difluoroethyl *m*-phenylphenyl ether (2f): The title product (**2f**) was purified by column chromatography and preparative TLC (hexane only). **2f** was obtained in 79% yield (275.9 mg). A pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.94 (1H, t, *J* = 5.1 Hz), 7.19-7.24 (1H, m), 7.35-7.53 (6H, m), 7.56-7.61 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.5 (t, *J* = 41.7 Hz), 119.7 (t, *J* = 269.6 Hz), 120.5, 120.6, 125.3, 127.3, 128.0, 129.1, 130.0, 140.0, 143.2, 150.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -77.7 (1F, dd, *J* = 136.9, 5.1 Hz), -78.1 (1F, dd, *J* = 136.9, 5.1 Hz); MS (EI) *m/z*: 346 (M^+); HRMS (EI) Calcd. for $C_{14}H_{10}BrClF_2O$: 345.9572 (M^+), Found: 345.9567.

2-Bromo-2-chloro-1,1-difluoroethyl *p*-phenylphenyl ether (2g): The title product (**2g**) was purified by column chromatography (hexane only) and was obtained in 88% yield (304.4 mg). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.93 (1H, t, *J* = 4.8 Hz), 7.30 (2H, d, *J* = 7.9 Hz), 7.37 (1H, t, *J* = 7.2 Hz), 7.45 (2H, dd, *J* = 7.9, 7.2 Hz), 7.58 (4H, t, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.5 (t, *J* = 41.6 Hz), 119.7 (t, *J* = 267.7 Hz), 122.1, 127.2, 127.7, 128.4, 129.0, 139.7, 140.1, 149.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -78.0 (1F, dd, *J* = 137.1, 4.8 Hz), -78.1 (1F, dd, *J* = 137.1, 4.8 Hz); MS (EI) *m/z*: 346 (M^+); HRMS (EI) Calcd. for $C_{14}H_{10}BrClF_2O$: 345.9572 (M^+), Found: 345.9566.

2-Bromo-2-chloro-1,1-difluoroethyl 1-naphthyl ether (2h): The title product (**2h**) was purified by column chromatography (hexane only). **2h** was obtained in 85% yield (275.3 mg). A colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.09 (1H, t, *J* = 4.8 Hz), 7.39-7.49 (2H, m), 7.51-7.60 (2H, m), 7.74-7.80 (1H, m), 7.84-7.91 (1H, m), 8.21-8.29 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.7 (t, *J* = 41.7 Hz), 117.4, 120.1 (t, *J* = 268.1 Hz), 122.0, 125.3, 126.5, 126.8, 126.9, 127.7, 127.9, 134.8, 145.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -77.5 (1F, dd, *J* = 136.6, 4.8 Hz), -78.0 (1F, dd, *J* = 136.6, 4.8 Hz); MS (EI) *m/z*: 320 (M^+); HRMS (EI) Calcd. for $C_{12}H_8BrClF_2O$: 319.9415 (M^+), Found: 319.9416.

2-Bromo-2-chloro-1,1-difluoroethyl *o*-iodophenyl ether (2i): The title product (**2i**) was purified by column chromatography (hexane only) and was obtained in 67% yield (266.7 mg). A yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.01 (1H, t, *J* = 5.6 Hz), 6.97-7.03 (1H, m), 7.30-7.40 (2H, m), 7.86 (1H, dd, *J* = 8.4, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.5 (t, *J* = 40.3 Hz), 89.9, 119.9 (t, *J* = 270.5 Hz), 122.0, 127.9, 129.6, 140.3, 149.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -77.4 (1F, ddd, *J* = 135.0, 5.8, 1.1 Hz), -77.8 (1F, ddd, *J* = 135.0, 5.8, 1.1 Hz); MS (EI) *m/z*: 396 (M^+); HRMS (EI) Calcd. for $C_8H_5BrClF_2IO$: 395.8225 (M^+), Found: 395.8231.

***o*-Allylphenyl 2-bromo-2-chloro-1,1-difluoroethyl ether (2j):** The title product (**2j**) was purified by column chromatography (hexane only) and was obtained in 81% yield

(253.4 mg). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.49 (2H, d, *J* = 6.8 Hz), 5.06-5.14 (2H, m), 5.95 (1H, t, *J* = 4.6 Hz), 5.96 (1H, ddt, *J* = 17.6, 9.4, 6.7 Hz), 7.17-7.32 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.2, 53.7 (t, *J* = 41.8 Hz), 116.5 , 119.9 (t, *J* = 268.9 Hz), 121.8, 126.5, 127.5, 130.8, 133.2, 136.2, 147.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -77.3 (1F, dd, *J* = 137.1, 4.6 Hz), -77.6 (1F, dd, *J* = 137.1, 4.6 Hz); MS (EI) *m*/*z*: 310 (M^+); HRMS (EI) Calcd. for $C_{11}H_{10}BrClF_2O$: 309.9572 (M^+), Found: 309.9568.

2-Bromo-2-chloro-1,1-difluoroethyl *o*-propenylphenyl ether (2k): The title product (**2k**) was purified by column chromatography and preparative TLC (hexane only). **2k** was obtained an inseparable mixture of *cis*-*trans* isomers (1:2.2) in 71% yield (219.9 mg). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.81 (dd, *J* = 7.0, 1.7 Hz, *cis*-isomer) and 1.91 (dd, *J* = 6.7, 1.7 Hz, *trans*-isomer) (3H), 5.88 (dq, *J* = 11.4, 7.0 Hz, *cis*-isomer) and 6.26 (dd, *J* = 15.7, 6.7 Hz, *trans*-isomer) (1H), 5.93 (t, *J* = 5.0 Hz, *cis*-isomer) and 5.98 (t, *J* = 4.8 Hz, *trans*-isomer) (1H), 6.54 (dq, *J* = 11.4, 1.7 Hz, *cis*-isomer) and 6.76 (d, *J* = 15.7 Hz, *trans*-isomer) (1H), 7.17-7.31 (3H, m) , 7.33-7.38 (m, *cis*-isomer) and 7.49-7.57 (m, *trans*-isomer) (1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.7 (*cis*-isomer), 19.0 (*trans*-isomer), 53.6 (t, *J* = 41.8 Hz, *cis*-isomer), 53.7 (t, *J* = 41.8 Hz, *trans*-isomer), 119.77 (t, *J* = 267.9 Hz, *cis*-isomer), 119.81 (t, *J* = 268.0 Hz, *trans*-isomer), 122.2 (*cis*-isomer), 122.4 (*trans*-isomer), 124.5, 126.0 (*cis*-isomer), 126.4 (*trans*-isomer), 126.6 (*trans*-isomer), 127.7 (*trans*-isomer), 127.9 (*cis*-isomer), 128.4 (*trans*-isomer), 128.8 (*cis*-isomer), 130.9 (*cis*-isomer), 131.4 (*cis*-isomer), 131.9 (*trans*-isomer), 146.1 (*trans*-isomer), 147.2 (*cis*-isomer); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -77.2 (1F, dd, *J* = 137.1, 4.8 Hz, *trans*-isomer), -77.6 (1F, dd, *J* = 137.1, 4.8 Hz, *trans*-isomer), -77.51 (1F, dd, *J* = 9.0, 5.0 Hz, *cis*-isomer), -77.53 (1F, dd, *J* = 9.0, 5.0 Hz, *cis*-isomer); MS (EI) *m*/*z*: 310 (M^+); HRMS (EI) Calcd. for $C_{11}H_{10}BrClF_2O$: 309.9572 (M^+), Found: 309.9568.

(*E*)-2'-(2-Bromo-2-chloro-1,1-difluoroethoxy)-chalcone (2l): The title product (**2l**) was purified by column chromatography and preparative TLC (hexane: AcOEt = 9:1).

2l was obtained in 43% yield (170.9 mg). A yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.97 (1H, t, *J* = 4.8 Hz), 7.32-7.39 (2H, m), 7.41-7.54 (4H, m), 7.55-7.62 (1H, m), 7.79-7.84 (1H, m), 7.96-8.01 (2H, m), 8.14 (1H, d, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.2 (t, *J* = 41.0 Hz), 119.9 (t, *J* = 269.4 Hz), 122.7, 125.0, 126.9, 127.7, 128.6, 128.8, 129.0, 131.5, 132.9, 138.1, 138.5, 148.4, 191.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -77.2 (1F, dd, *J* = 136.4, 4.8 Hz), -77.8 (1F, dd, *J* = 136.4, 4.8 Hz); MS (EI) *m*/*z*: 400 (M^+); HRMS (EI) Calcd. for $C_{17}H_{12}BrClF_2O_2$: 399.9677 (M^+), Found: 399.9670.

***o*-Aminophenyl 2-bromo-2-chloro-1,1-difluoroethyl ether (2m):** The title product (**2m**) was purified by column chromatography (hexane: AcOEt = 9:1) and was obtained in 51% yield (145.3 mg). A yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.93 (2H, br s), 5.98 (1H, t, *J* = 4.4 Hz), 6.72 (1H, dd, *J* = 7.6, 1.2 Hz), 6.79 (1H, dd, *J* = 8.0, 1.6 Hz), 7.06 (1H, dd, *J* = 7.6, 1.6 Hz), 7.16 (2H, dd, *J* = 8.0, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.7 (t, *J* = 41.9 Hz), 116.7, 118.4, 120.2 (t, *J* = 267.4 Hz), 122.6, 127.4, 136.5, 139.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -77.7 (1F, dd, *J* = 137.1, 4.4 Hz), -78.5 (1F, dd, *J* = 137.1, 4.4 Hz); MS (EI) *m*/*z*: 285 (M^+); HRMS (EI) Calcd. for $C_8H_7BrClF_2NO$: 284.9368 (M^+), Found: 284.9363.

Supporting Information

Supporting Information File 1: ^{1}H and ^{13}C NMR spectra.

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