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Synthesis of Pentafluoroethyl Ethers by Silver-Mediated Oxidative Pentafluoroethylation of Alcohols and Phenols

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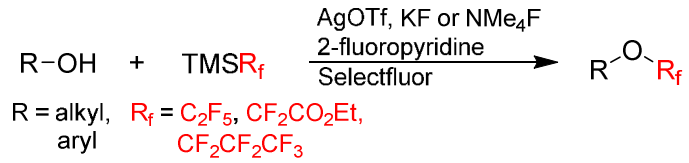
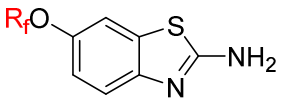


Abstract

A silver triflate (AgOTf)-mediated oxidative pentafluoroethylation of alcohols and phenols with nucleophilic (pentafluoroethyl)trimethylsilane ($TMSCF_2CF_3$) using Selectfluor as oxidant under mild reaction conditions was developed. This oxidative coupling protocol utilizes broadly available substrates and easily handled reagents to afford various pentafluoroethyl ethers in moderate to excellent yields. Furthermore, this method was extended to the oxidative heptafluoropropylation and ethoxycarbonyldifluoromethylation of alcohols and phenols for preparation of the corresponding fluoroalkyl ethers.

Introduction

The demand for organofluorine compounds is rapidly increasing because of their prevalence in pharmaceuticals, agrochemicals and material science.[1] Consequently, research interests are ever increasing concerning not only the fluorine atom, but also the fluoroalkyl, fluoroalkylthio, and fluoroalkoxy groups.[2] As a typical fluoroalkoxy group, trifluoromethoxy (OCF_3) is prevalent in bioactive compounds and functional materials.[3] Thus, various methods have been reported for the preparation of OCF_3-containing compounds.[4] Compared with the well studied OCF_3 group, its bulkier analogue, pentafluoroethoxy (OC_2F_5) group, has been much less explored. In fact, OC_2F_5 has similar properties to OCF_3 in electronic effect, lipophilicity, and metabolic stability,[5] which makes it attractive in drugs and agrochemicals discovery process. For example, Jimonet and co-workers evaluated the effect of different polyfluoroalkoxy substituents in the 6-position of 2-benzothiazolamine on the in vivo "antiglutamate" activity.[6] The ED_{50} values, the doses of drugs (mg/kg) that totally protected 50% of the rats from clonic convulsions, clearly showed that the OC_2F_5-substituted compound is more active than Riluzole and other polyfluoroalkoxy (OCF_2H,[7] OCH_2CF_3,[8] and OCF_2CF_2H[9]) substituted derivatives (Figure 1).



Riluzole ($R_f = CF_3$)
(treatment of neurological diseases)

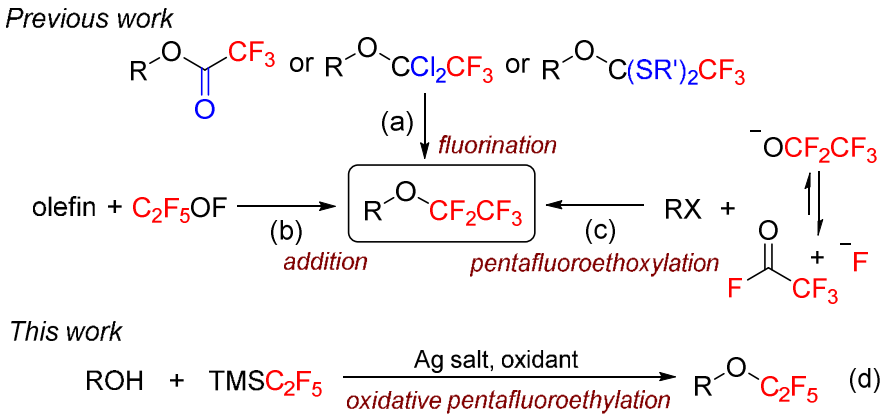
R_f	CF_3	CF_2H	CH_2CF_3	CF_2CF_3	CF_2CF_2H
ED_{50}	**3.2**	7.5	6.5	**2.5**	8.5

Figure 1. "Antiglutamate" activities of 6-fluoroalkoxy-2-benzothiazolamines.

Traditionally, pentafluoroethyl ethers are synthesized by nucleophilic fluorination of trifluoroacetates,[10a] fluorohaloalkyl ethers[10b] or trifluoromethyl dithioorthoesters[10c] with toxic fluorinating reagents (Scheme 1a), all of which suffer from the necessity of prefunctionalized substrates

and/or harsh reaction conditions. In 1980, Lerman and Rozen disclosed a novel method for the introduction of OC_2F_5 group by the addition of C_2F_5OF to olefins (Scheme 1b).[11] But this protocol also employed poisonous and corrosive C_2F_5OF. Recently, the reaction of alkyl halides with pentafluoroethoxide has been reported as an alternative synthetic method (Scheme 1c),[12] however, the reversible decomposition of pentafluoroethoxide anion hampered the wide application of this method. It is noteworthy that pentafluoroethyl ethers cannot be prepared by nucleophilic substitution of pentafluoroethyl iodide, which is attacked on the iodine atom rather than the carbon atom of pentafluoroethyl group because of the reversed electron density.[13] Obviously, the efficient and practical synthesis of pentafluoroethyl ethers remains a big challenge. Inspired by our recent discoveries on silver-mediated oxidative trifluoromethylation of phenols and alcohols for direct synthesis of trifluoromethyl ethers,[4e,4g] we envisioned that oxidative pentafluoroethylation of alcohols and phenols would provide a potentially valuable strategy for the preparation of pentafluoroethyl ethers. Herein, we disclose the preparation of these compounds by silver-mediated oxidative pentafluoroethylation of alcohols and phenols with safe and stable $TMSC_2F_5$ (Scheme 1d).

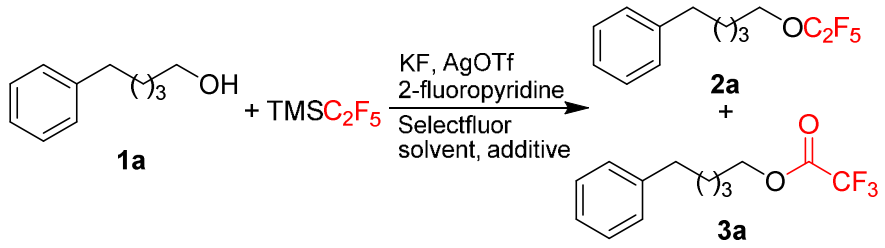
Scheme 1. Approaches to Pentafluoroethyl Ethers



Results and Discussion

Initially, we investigated the oxidative pentafluoroethylation of 5-phenylpentan-1-ol (**1a**) with $TMSC_2F_5$ in the presence of KF, AgOTf, 2-fluoropyridine and Selectfluor in EtOAc according to the optimized reaction conditions of oxidative trifluoromethylation of alcohols.[4g] However, the desired pentafluoroethyl ether (**2a**) was obtained in only 19% yield along with a byproduct trifluoroacetate ester (**3a**) in 27% yield (Table 1, entry 1). We reasoned that the byproduct **3a** was formed by the reaction of alcohol **1a** with trifluoroacetyl fluoride. To change the ratio of **2a** and **3a**, a number of reaction conditions were screened. First, the reaction was carried out at lower concentration, and **2a** was produced in higher yield (entry 2). However, further decreasing the concentration did not improve the yield (entry 3). Then, the less-polar solvents $PhCH_3$ and $PhCF_3$ or more polar solvent DMF were examined (entries 4-6). No better result was obtained. A binary solvent mixture was beneficial for the chemoselectivity of this reaction (entries 7-11), and EtOAc/$PhCF_3$ (1:1) was the ideal solvent system to give **2a** in 53% yield (entry 9). The observed solvent effect might be due to the solubility of reagents. To improve the reaction yield further, we increased the amounts of reagents. Although a higher yield of **2a** was observed, a larger amount of byproduct **3a** was simultaneously formed (entry 12). Finally, different additives including LiBr, LiOTf, NaOTf, and $LiNTf_2$ were added to the reaction mixture (entries 13-16). Among these salts, only LiOTf was beneficial for this reaction to afford compound **2a** in 84% yield (entry 14). However, the exact role of LiOTf for promoting the reaction is unclear at the present stage.

Table 1. Optimization of Reaction Conditions[a]



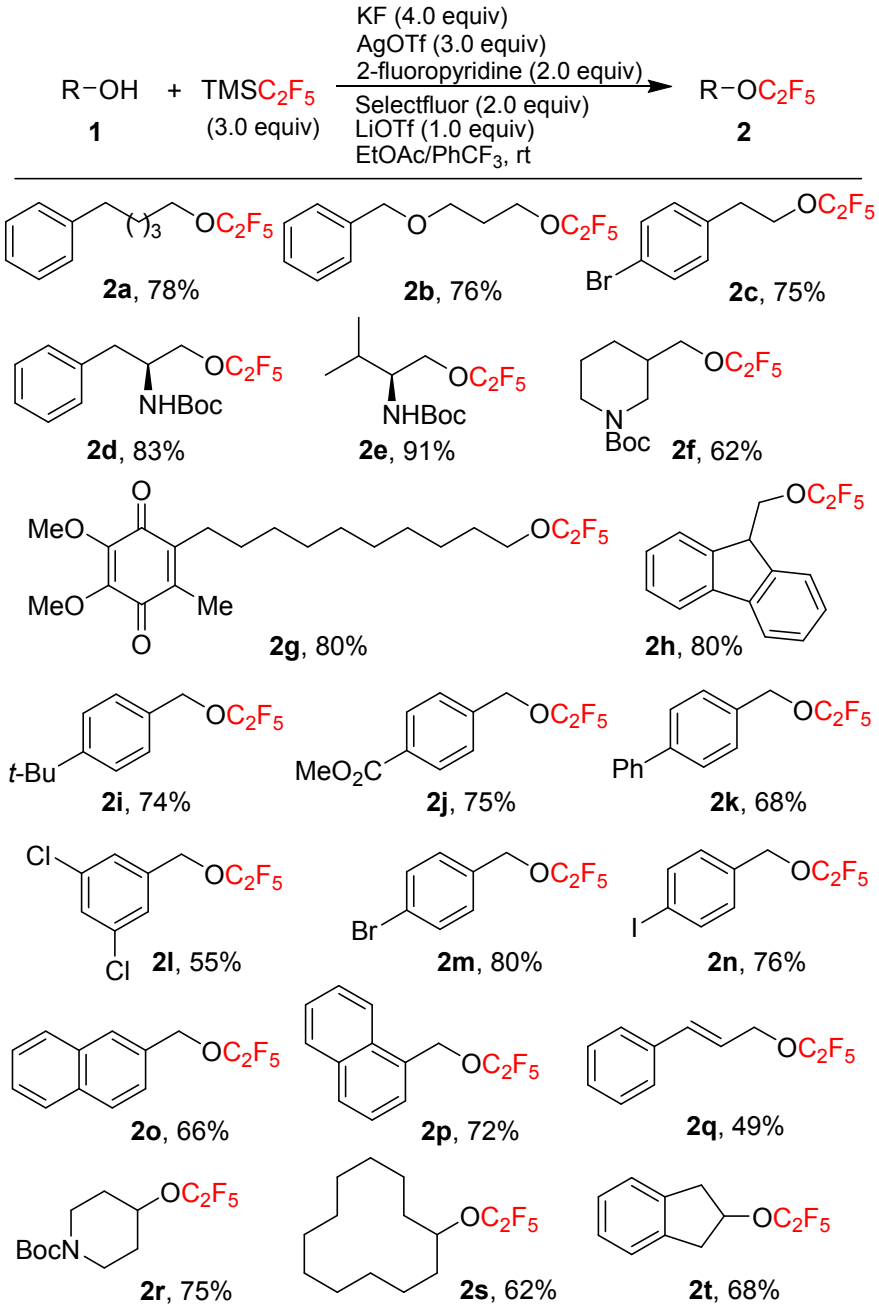
Entry	Solvent	Additive	yield (**2a**/**3a**, %)[b]
1[c]	EtOAc	—	19/27
2	EtOAc	—	30/16
3[d]	EtOAc	—	29/15
4	$PhCH_3$	—	29/14
5	$PhCF_3$	—	trace/31
6	DMF	—	8/4
7	EtOAc/$PhCH_3$ (1:1)	—	44/8
8	EtOAc/CH_2Cl_2 (1:1)	—	36/2
9	EtOAc/$PhCF_3$ (1:1)	—	53/2
10	EtOAc/$PhCF_3$ (2:1)	—	42/2
11	EtOAc/$PhCF_3$ (1:2)	—	48/2
12[e]	EtOAc/$PhCF_3$ (1:1)	—	68/16
13[e]	EtOAc/$PhCF_3$ (1:1)	LiBr	51/19
14[e]	EtOAc/$PhCF_3$ (1:1)	LiOTf	84/14
15[e]	EtOAc/$PhCF_3$ (1:1)	NaOTf	38/10
16[e]	EtOAc/$PhCF_3$ (1:1)	$LiNTf_2$	32/54

[a]Reaction conditions: **1a** (0.1 mmol), $TMSC_2F_5$ (0.2 mmol), KF (0.3 mmol), Selectfluor (0.15 mmol), AgOTf (0.2 mmol), 2-fluoropyridine (0.2 mmol), additive (0.1 mmol), solvent (1.0 mL), under N_2, rt, 12 h. [b]Yields determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. [c]Solvent (0.5 mL). [d]Solvent (2.0 mL). [e]$TMSC_2F_5$ (0.3 mmol), KF (0.4 mmol), Selectfluor (0.2 mmol), AgOTf (0.3 mmol).

Under the optimized reaction conditions (Table 1, entry 14), the scope of this oxidative pentafluoroethylation was next investigated. As shown in Scheme 2, a variety of alcohols were transformed to the corresponding alkyl pentafluoroethyl ethers in moderate to excellent yields. In most cases the undesired trifluoroacetate esters were formed in low yields, and in some cases the oxidation products (aldehydes) were detected. The primary (**1a-h**), benzyl (**1i-p**), and secondary (**1r-t**) alcohols are almost equally effective in this protocol. The allylic alcohol (**1q**) underwent this reaction to give ether **2q** in low yield (49%). However, the tertiary alcohols are not suitable substrates for this reaction.

Different functional groups, such as ether, ketone, ester, amide, chloro, bromo, and iodo, are well tolerated under the mild reaction conditions.

Scheme 2. Oxidative Pentafluoroethylation of Alcohols[a]

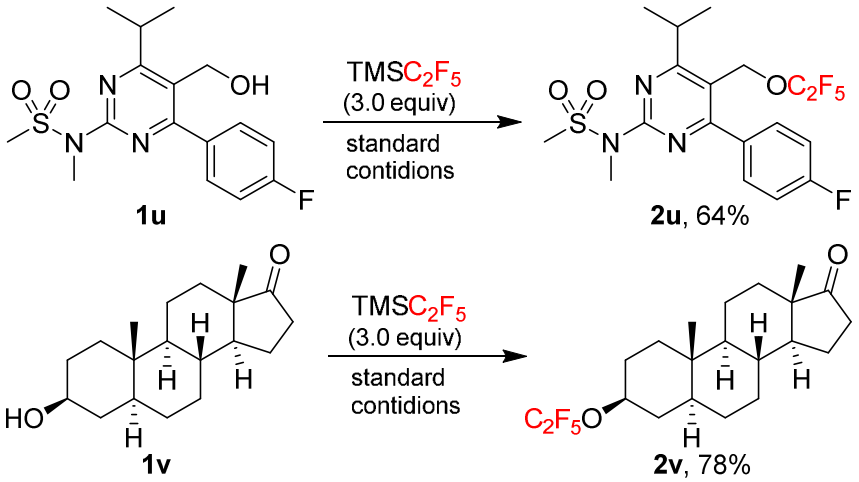


[a]Reaction conditions: **1** (0.5 mmol), $TMSC_2F_5$ (1.5 mmol), KF (2.0 mmol), Selectfluor (1.0 mmol), AgOTf (1.5 mmol), 2-fluoropyridine (1.0 mmol), LiOTf (0.5 mmol), EtOAc/$PhCF_3$ (1:1, 5.0 mL), under N_2, rt, 12 h, isolated yields.

Notably, complex substrates including rosuvastatin derivative and epiandrosterone were compatible with the reaction conditions to afford pentafluoroethyl ethers (**2u** and **2v**) in good yields (Scheme 3).

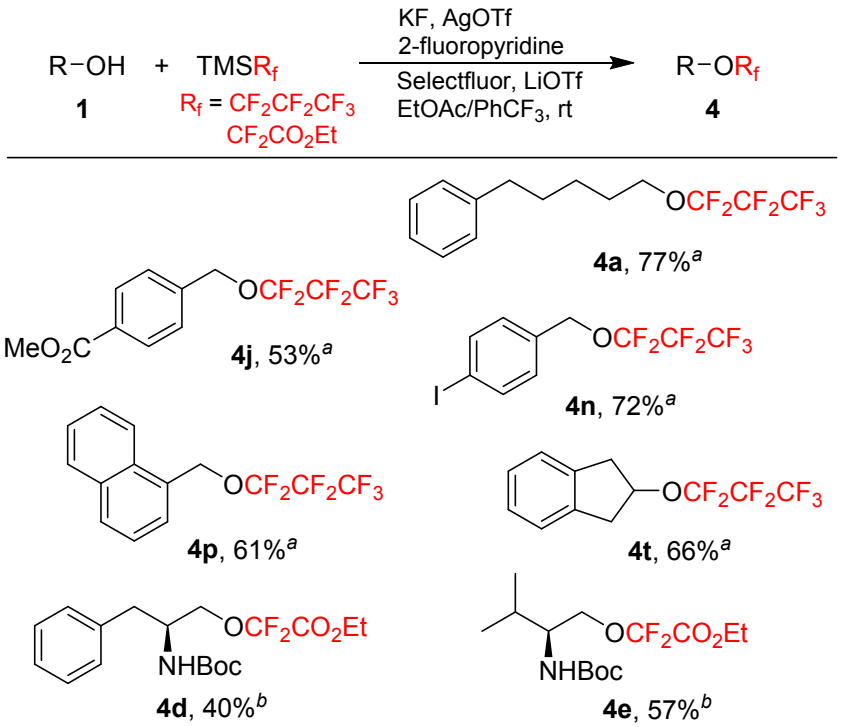
These results demonstrated that this oxidative pentafluoroethylation protocol could be applied in the late-stage drug development.

Scheme 3. Late-Stage Oxidative Pentafluoroethylation



Subsequently, we explored the oxidative heptafluoropropylation of alcohols (Scheme 4). The reaction of several primary, benzyl, and secondary alcohols with $TMSCF_2CF_2CF_3$ proceeded well to give the corresponding heptafluoropropyl ethers **4** in moderate to high yields. Similar to the oxidative pentafluoroethylation, this reaction also gave the byproducts (pentafluoropropanoate esters) in low yields. Moreover, the oxidative ethoxycarbonyldifluoromethylation of alcohols **1d** and **1e** with $TMSCF_2CO_2Et$ afforded ethers **4d** and **4e** in moderate yields. However, the analogous oxidative difluoromethylation with $TMSCF_2H$ failed to give the desired product.

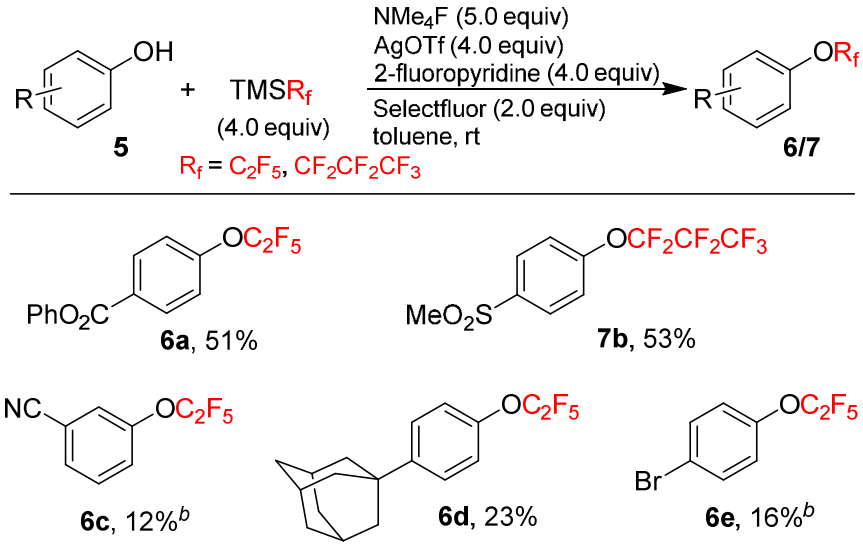
Scheme 4. Oxidative Heptafluoropropylation and Ethoxycarbonyldifluoromethylation of Alcohols



[a]Reaction conditions: **1** (0.5 mmol), $TMSCF_2CF_2CF_3$ (1.25 mmol), KF (2.0 mmol), Selectfluor (1.0 mmol), AgOTf (1.5 mmol), 2-fluoropyridine (1.0 mmol), LiOTf (0.5 mmol), EtOAc/$PhCF_3$ (1:1, 5.0 mL), under N_2, rt, 12 h, isolated yields. [b]Reaction conditions: **1** (0.5 mmol), $TMSCF_2CO_2Et$ (1.5 mmol), KF (2.0 mmol), Selectfluor (1.0 mmol), AgOTf (1.5 mmol), EtOAc/$PhCF_3$ (1:1, 5.0 mL), under N_2, rt, 12 h, isolated yields.

The phenols were also applicable to this oxidative perfluoroalkylation protocol (Scheme 5). For example, the reaction of phenols **5a** and **5b** with $TMSCF_2CF_3$ and $TMSCF_2CF_2CF_3$ gave the corresponding aryl perfluoroalkyl ethers **6a** and **7b** in moderate yields respectively (for the optimization of reaction conditions: see Table S1 in the Supporting Information). However, the *meta*-substituted phenol (**5c**) was converted to pentafluoroethylated product **6c** in low yield. In the cases of the phenols substituted with an electron-donating group (**5d**) or bromine (**5e**), the desired products (**6d** and **6e**) were also obtained in low yields.

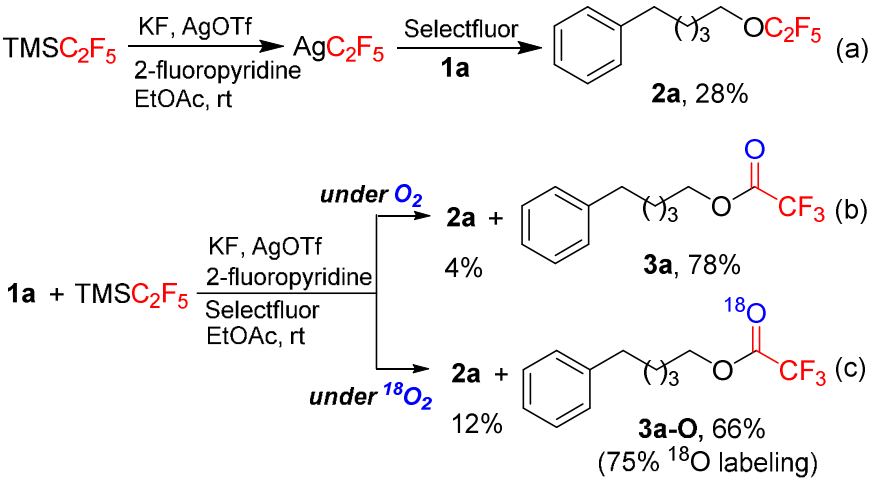
Scheme 5. Oxidative Perfluoroalkylation of Phenols[a]



[a]Reaction conditions: **5** (0.5 mmol), $TMSR_f$ (2.0 mmol), NMe_4F (2.5 mmol), Selectfluor (1.0 mmol), AgOTf (2.0 mmol), 2-fluoropyridine (1.0 mmol), toluene (7.5 mL), under air, rt, 16 h, isolated yields. [b]Yields determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard.

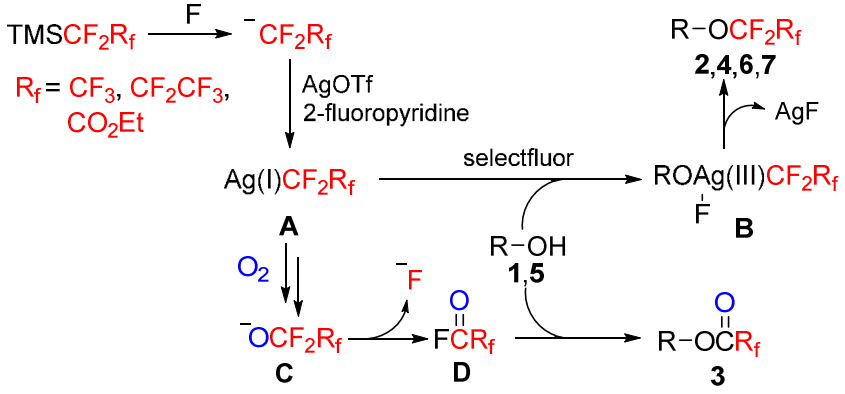
To probe for the possible reaction mechanism, preliminary mechanistic experiments were performed. First, treatment of $TMSC_2F_5$ with KF, AgOTf and 2-fluoropyridine in EtOAc generated AgC_2F_5 (^{19}F NMR: δ -84.9 ppm, s, 3F; -109.0 ppm, s, 2F).[14] Unlike $AgCF_3$ which easily disproportionates to $Ag(CF_3)_4$ anion,[4g,15] the AgC_2F_5 in solution is stable under inert atmosphere. Then, AgC_2F_5 reacted with **1a** in the presence of Selectfluor to give product **2a** in 28% yield (Scheme 6a). This result revealed that AgC_2F_5 probably is the reaction intermediate. Furthermore, the reaction of **1a** and $TMSC_2F_5$ in EtOAc under O_2 gave ester **3a** in 78% yield (Scheme 6b), which indicated that O_2 was the source of the oxygen atom of trifluoroacetyl group. This result was further confirmed by the ^{18}O-labeling experiment (Scheme 6c).

Scheme 6. Mechanistic Investigations



Based on the above results and previous reports, we proposed a plausible reaction mechanism (Scheme 7). First, the initiation of $TMSCF_2R_f$ by fluoride and subsequent reaction with AgOTf produced $Ag(I)CF_2R_f$ **A**. Then the oxidation of **A** with Selectfluor followed by ligand exchange with alcohol **1** or phenol **5** afforded silver complex **B**, which underwent reductive elimination to give the desired products **2**, **4**, **6** and **7**. On the other hand, intermediate **A** might be converted into acyl fluoride **D** after several transformations in the presence of oxygen. The byproduct **3** was formed by the reaction of alcohol **1** with **D**.

Scheme 7. Proposed Reaction Mechanism



Conclusion

In summary, we have developed a new method for the preparation of potentially useful but less explored pentafluoroethyl (heptafluoropropyl) ethers. The silver-mediated oxidative coupling of simple alcohols and phenols with safe and stable nucleophilic $TMSCF_2CF_3$ ($TMSCF_2CF_2CF_3$) reagents provides a convenient access to the target compounds. Further investigation of the reaction mechanism and extension of oxidative fluoroalkylation reactions are currently in progress.

Experimental Section

General Experimental Methods. ^1H NMR (TMS as the internal standard), ^{13}C NMR, and ^{19}F NMR spectra ($CFCl_3$ as the outside standard and low field is positive) were recorded on a 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HRMS data using EI were obtained on a GC-TOF mass spectrometer. Substrates were purchased from commercial sources and used as received. Unless otherwise noted, all reagents were obtained commercially and used without further purification.

General procedure for pentafluoroethylation of alcohols

To a reaction tube that was equipped with a stirring bar, AgOTf (385.4 mg, 1.5 mmol, 3.0 equiv), Selectfluor (354.3 mg, 1.0 mmol, 2.0 equiv), KF (116.5 mg, 2.0 mmol, 4.0 equiv), and LiOTf (78.0 mg, 0.5 mmol, 1.0 equiv) were added in a nitrogen-filled glovebox. Then the reaction tube was removed from the glovebox. Alcohol (0.5 mmol, 1.0 equiv), ethyl acetate (2.5 mL), $PhCF_3$ (2.5 mL), $TMSCF_2CF_3$ (288.3 mg, 1.5 mmol, 3.0 equiv), and 2-fluoropyridine (145.5 mg, 1.5 mmol, 3.0 equiv) were added successively under N_2 atmosphere. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a plug of silica (eluted with ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography on silica gel to give the alkyl pentafluoroethyl ether.

(5-(Perfluoroethoxy)pentyl)benzene (2a). Compound **2a** was obtained as a colorless liquid (110.0 mg, 78%), hexane as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.31-7.17 (m, 5H), 4.01 (t, *J* = 6.4 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.77-1.63 (m, 4H), 1.48-1.40 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.2 (s, 3F), -90.7 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.2, 128.4, 128.3, 125.8, 116.8 (qt, *J* = 282.5, 45.3 Hz), 115.3 (tq, *J* = 267.6, 41.1 Hz), 65.4 (t, *J* = 4.8 Hz),

35.7, 30.9, 28.7, 25.1. IR (thin film) *v* 3028, 2938, 2861, 1454, 1217, 1102, 1031, 735, 698 cm^{-1}. MS (EI): *m/z* 282 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{13}H_{15}F_5O$: 282.1043; Found: 282.1031.

((3-(Perfluoroethoxy)propoxy)methyl)benzene (2b). Compound **2b** was obtained as a colorless liquid (108.1 mg, 76%), hexane/Et_2O = 10:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.35-7.28 (m, 5H), 4.50 (s, 2H), 4.15 (t, *J* = 6.0 Hz, 2H), 3.56 (t, *J* = 5.8 Hz, 2H), 2.01-1.95 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.2 (s, 3F), -90.8 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.1, 128.4, 127.7, 127.6, 116.8 (qt, *J* = 282.5, 45.4 Hz), 115.3 (tq, *J* = 268.1, 41.1 Hz), 73.2, 65.6, 62.5 (t, *J* = 5.3 Hz), 29.3. IR (thin film) *v* 3033, 2929, 2864, 1496, 1479, 1454, 1216, 1101, 735, 698 cm^{-1}. MS (EI): *m/z* 284 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{12}H_{13}F_5O_2$: 284.0836; Found: 284.0841.

1-Bromo-4-(2-(perfluoroethoxy)ethyl)benzene (2c). Compound **2c** was obtained as a colorless liquid (120.8 mg, 75%), hexane as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 4.17 (t, *J* = 6.8 Hz, 2H), 2.95 (t, *J* = 6.8 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.1 (s, 3F), -90.9 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 135.6, 131.7, 130.6, 120.9, 116.6 (qt, *J* = 283.1, 44.8 Hz), 115.1 (tq, *J* = 268.4, 41.0 Hz), 65.4 (t, *J* = 5.3 Hz), 34.8. IR (thin film) *v* 3028, 2972, 2926, 2855, 1594, 1490, 1422, 1218, 1104, 1074, 1013, 964, 818, 736, 517 cm^{-1}. MS (EI): *m/z* 318 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{10}H_8BrF_5O$: 317.9679; Found: 317.9683.

Tert-butyl (S)-(1-(perfluoroethoxy)-3-phenylpropan-2-yl)carbamate (2d). Compound **2d** was obtained as a white solid (154.2 mg, 83%), hexane/ethyl acetate = 7:1 as eluent for the column chromatography. Mp: 72-74 °C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.32-7.17 (m, 5H), 4.65 (s, 1H), 4.08-3.89 (m, 3H), 2.88-2.81 (m, 2H), 1.41 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -85.9 (s, 3F), -90.3-(-91.2) (m, 2F). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 155.1, 136.7, 129.2, 128.7, 126.9, 116.7 (qt, *J* = 282.8, 45.0 Hz), 115.1 (tq, *J* = 268.4, 41.0 Hz), 79.9, 65.3, 50.5, 37.1, 28.2. IR (thin film) *v* 3350, 3030, 2979, 1712, 1498, 1421, 1393, 1250, 1177, 1059, 968, 878, 700 cm^{-1}. MS (EI): *m/z* 369 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{16}H_{20}F_5NO_3$: 369.1363; Found: 369.1372.

Tert-butyl (S)-(3-methyl-1-(perfluoroethoxy)butan-2-yl)carbamate (2e). Compound **2e** was obtained as a yellow oil (145.5 mg, 91%), hexane/ethyl acetate = 7:1 as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.62-4.60 (m, 1H), 4.05-4.01 (m, 2H), 3.60 (s, 1H), 1.85-1.80 (m, 1H), 1.42 (s, 9H), 0.96-0.93 (m, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.0 (s, 3F), -90.5-(-91.3) (m, 2F). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 155.5, 116.6 (qt, *J* = 282.6, 45.5 Hz), 115.1 (tq, *J* = 268.4, 41.1 Hz), 79.5, 65.3, 54.4, 28.9, 28.1, 19.1, 18.3. IR (thin film) *v* 3347, 2972, 2879, 1707, 1502, 1421, 1393, 1231, 1174, 1101, 1024 cm^{-1}. MS (EI): *m/z* 306 [M-CH_3]$^+$. HRMS (EI-TOF): *m/z* [M-CH_3]$^+$ Calculated for $C_{11}H_{17}F_5NO_3$: 306.1129; Found: 306.1135.

Tert-butyl 3-((perfluoroethoxy)methyl)piperidine-1-carboxylate (2f). Compound **2f** was obtained as a colorless liquid (101.4 mg, 62%), hexane/Et_2O = 3:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.89-3.82 (m, 4H), 2.86 (s, 2H), 1.90-1.84 (m, 1H), 1.80-1.76 (m, 1H), 1.68-1.60 (m, 1H), 1.42 (s, 10H), 1.30-1.20 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.1 (s, 3F), -91.0 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 154.8, 116.7 (qt, *J* = 282.5, 44.9 Hz), 115.1 (tq, *J* = 267.6, 41.1 Hz), 79.6, 66.9, 46.3, 44.0, 35.2, 28.2, 26.7, 23.8. IR (thin film) *v* 2978, 2860, 1696, 1423, 1393, 1212, 1152, 1100, 972, 736 cm^{-1}. MS (EI): *m/z* 333 [M$^+$]. HRMS (EI-TOF): *m/z* [M$^+$] Calculated for $C_{13}H_{20}F_5NO_3$: 333.1363; Found: 333.1354.

2,3-Dimethoxy-5-methyl-6-(10-(perfluoroethoxy)decyl)cyclohexa-2,5-diene-1,4-dione (2g). Compound **2g** was obtained as a yellow oil (182.5 mg, 80%), hexane/Et_2O = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.00-3.97 (m, 7H), 2.45-2.41 (m, 2H), 1.99 (s, 3H), 1.71-1.64 (m, 2H), 1.33-1.19 (m, 14H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.2 (s, 3F), -90.7 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 184.7, 184.1, 144.3, 143.0, 138.6, 116.7 (qt, *J* = 282.5, 45.4 Hz), 115.2 (tq, *J* = 267.6, 41.1 Hz), 65.5 (t, *J* = 4.8 Hz), 61.0, 29.7, 29.3, 29.2, 29.1, 28.9, 28.7, 28.6, 26.3, 25.3, 11.7. IR (thin film) *v* 2930, 2857, 1651, 1611, 1458, 1380, 1266, 1214, 1157, 1096, 1003, 948, 744 cm^{-1}. MS (EI): *m/z* 456 [M$^+$]. HRMS (EI-TOF): *m/z* [M$^+$] Calculated for $C_{21}H_{29}F_5O_5$: 456.1935; Found: 456.1926.

9-((Perfluoroethoxy)methyl)-9H-fluorene (2h). Compound **2h** was obtained as a colorless liquid **(**125.7 mg, 80%), hexane as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.82 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.50-7.47 (m, 2H), 7.41-7.37 (m, 2H), 4.30 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -85.9 (s, 3F), -90.9 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.8, 141.4, 128.2, 127.4, 125.2, 120.2, 117.1 (qt, *J* = 282.2, 45.2 Hz), 115.4 (tq, *J* = 269.1, 41.3 Hz), 67.6 (t, *J* = 4.8 Hz), 46.7. IR (thin film) *v* 3069, 1610, 1478, 1420, 1324, 1216, 1099, 810, 737 cm^{-1}. MS (EI): *m/z* 314 [M$^+$]. HRMS (EI-TOF): *m/z* [M$^+$] Calculated for $C_{16}H_{11}F_5O$: 314.0730; Found: 314.0728.

1-(Tert-butyl)-4-((perfluoroethoxy)methyl)benzene (2i). Compound **2i** was obtained as a colorless liquid **(**130.1 mg, 74%), hexane as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.02 (s, 2H), 1.34 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -85.9 (s, 3F), -90.1 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 152.1, 130.9, 128.1, 125.7, 116.8 (qt, *J* = 282.5, 44.3 Hz), 115.4 (tq, *J* = 268.6, 41.2 Hz), 66.9 (t, *J* = 6.8 Hz), 34.6, 31.2. IR (thin film) *v* 2966, 2871, 1518, 1466, 1365, 1216, 1100, 1020, 818, 732, 669 cm^{-1}. MS (EI): *m/z* 282 [M$^+$]. HRMS (EI-TOF): *m/z* [M$^+$] Calculated for $C_{13}H_{15}F_5O$: 282.1043; Found: 282.1046.

Methyl 4-((perfluoroethoxy)methyl)benzoate (2j). Compound **2j** was obtained as a yellow liquid **(**106.5 mg, 75%), hexane/ethyl acetate = 8:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 5.07 (s, 2H), 3.90 (s, 3H). ^{19}F NMR

(376 MHz, $CDCl_3$) δ ppm -86.2 (s, 3F), -90.7 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.5, 138.8, 130.6, 129.9, 127.4, 116.8 (qt, *J* = 282.2, 44.1 Hz), 115.3 (tq, *J* = 269.1, 41.3 Hz), 66.1 (t, *J* = 5.5 Hz), 52.0. IR (thin film) *v* 2958, 2849, 1727, 1580, 1418, 1220, 1021, 967, 841, 757 cm^{-1}. MS (EI): *m/z* 284 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{11}H_9F_5O_3$: 284.0472; Found: 284.0466.

4-((Perfluoroethoxy)methyl)-1,1'-biphenyl (2k). Compound **2k** was obtained as a white solid **(**102.7 mg, 68%), hexane as eluent for the column chromatography. Mp: 54-56 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.63-7.58 (m, 4H), 7.47-7.34 (m, 5H), 5.08 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -85.9 (s, 3F), -90.1 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 141.9, 140.4, 132.8, 128.9, 128.6, 127.6, 127.5, 127.2, 116.8 (qt, *J* = 283.2, 44.8 Hz), 115.4 (tq, *J* = 269.6, 41.8 Hz), 66.9 (t, *J* = 5.7 Hz). IR (thin film) *v* 3033, 2965, 1489, 1467, 1216, 1100, 1008, 826, 743 cm^{-1}. MS (EI): *m/z* 302 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{15}H_{11}F_5O$: 302.0730; Found: 302.0741.

1,3-Dichloro-5-((perfluoroethoxy)methyl)benzene (2l). Compound **2l** was obtained as a colorless liquid **(**80.8 mg, 55%), hexane as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.37 (t, *J* = 1.6 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 2H), 4.98 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.0 (s, 3F), -90.7 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 137.1, 135.4, 129.0, 126.0, 116.6 (qt, *J* = 283.2, 44.0 Hz), 115.2 (tq, *J* = 270.2, 41.8 Hz), 65.2 (t, *J* = 5.7 Hz). IR (thin film) *v* 3084, 2927, 2856, 1575, 1413, 1220, 1108, 855, 740 cm^{-1}. MS (EI): *m/z* 294 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_9H_5Cl_2F_5O$: 293.9638; Found: 293.9644.

1-Bromo-4-((perfluoroethoxy)methyl)benzene (2m). Compound **2m** was obtained as a colorless liquid **(**121.6 mg, 80%), hexane as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.52 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.98 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.0 (s, 3F), -90.3 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 132.9, 131.9, 129.6, 123.1, 116.6 (qt, *J* = 283.2, 44.8 Hz), 115.2 (tq, *J* = 270.3, 41.0 Hz), 66.2 (t, *J* = 5.7Hz). IR (thin film) *v* 2964, 2927, 2855, 1598, 1491, 1408, 1217, 1102, 1014, 806, 736 cm^{-1}. MS (EI): *m/z* 304 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_9H_6BrF_5O$: 303.9522; Found: 303.9516.

1-Iodo-4-((perfluoroethoxy)methyl)benzene (2n). Compound **2n** was obtained as a colorless liquid **(**133.8 mg, 76%), hexane as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.72 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 4.96 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.0 (s, 3F), -90.3 (s, 2F).^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 137.9, 133.6, 129.8, 116.7 (qt, *J* = 282.5, 44.6 Hz), 115.3 (tq, *J* = 269.1, 41.1 Hz), 94.8, 66.4 (t, *J* = 5.6 Hz). IR (thin film) *v* 2963, 2925, 2854, 1594, 1404, 1218, 1101, 1009, 951, 803 cm^{-1}. MS (EI): *m/z* 352 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_9H_6F_5IO$: 351.9384; Found: 351.9382.

2-((Perfluoroethoxy)methyl)naphthalene (2o). Compound **2o** was obtained as a white solid **(**91.1 mg, 66%), hexane as eluent for the column chromatography. Mp: 58-60 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ

ppm 7.87-7.81 (m, 4H), 7.52-7.49 (m, 2H), 7.46-7.43 (m, 1H), 5.18 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -85.9 (s, 3F), -90.0 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 133.4, 133.1, 131.3, 128.7, 128.1, 127.8, 127.5, 126.7, 126.6, 125.4, 116.8 (qt, J = 282.5, 44.9 Hz), 115.4 (tq, J = 269.1, 41.1 Hz), 67.3 (t, J = 5.6 Hz). IR (thin film) v 3060, 3029, 2966, 1603, 1511, 1420, 1272, 1100, 961, 857, 743 cm^{-1}. MS (EI): m/z 276 [M$^+$]. HRMS (EI-TOF): m/z [M$^+$] Calculated for $C_{13}H_9F_5O$: 276.0574; Found: 276.0563.

1-((Perfluoroethoxy)methyl)naphthalene (2p). Compound **2p** was obtained as a colorless liquid **(**99.4 mg, 72%), hexane as eluent for the column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.05 (d, J = 8.5 Hz, 1H), 7.96-7.93 (m, 2H), 7.66-7.53 (m, 3H), 7.51-7.49 (m, 1H), 5.54 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -85.9 (s, 3F), -90.6 (s, 2F). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 133.8, 131.4, 130.1, 129.4, 128.8, 127.6, 127.0, 126.2, 125.2, 123.0, 116.9 (qt, J = 283.0, 44.6 Hz), 115.6 (tq, J = 269.2, 41.7 Hz), 65.6 (t, J = 6.2 Hz). IR (thin film) v 3052, 1601, 1513, 1420, 1216, 1101, 930 744 cm^{-1}. MS (EI): m/z 276 [M$^+$]. HRMS (EI-TOF): m/z [M$^+$] Calculated for $C_{13}H_9F_5O$: 276.0574; Found: 276.0582.

(E)-(3-(Perfluoroethoxy)prop-1-en-1-yl)benzene (2q). Compound **2q** was obtained as a colorless liquid **(**61.8 mg, 49%), hexane as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42-7.24 (m, 5H), 6.70 (d, J = 16.0 Hz, 1H), 6.30-6.23 (m, 1H), 4.69 (d, J = 6.8 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.1 (s, 3F), -90.1 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 135.7, 135.4, 128.7, 128.5, 126.8, 116.8 (qt, J = 282.2, 44.5 Hz), 115.4 (tq, J = 269.1, 41.2 Hz), 66.1 (t, J = 7.3 Hz). IR (thin film) v 3086, 3031, 2960, 1498, 1450, 1217, 1098, 966, 745, 691 cm^{-1}. MS (EI): m/z 252 [M$^+$]. HRMS (EI-TOF): m/z [M$^+$] Calculated for $C_{11}H_9F_5O$: 252.0574; Found: 252.0573.

Tert-butyl 4-(perfluoroethoxy)piperidine-1-carboxylate (2r). Compound **2r** was obtained as a colorless liquid (118.1 mg, 75%), hexane/Et_2O = 4:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.58-4.52 (m, 1H), 3.67-3.61 (m, 2H), 3.28-3.22 (m, 2H), 1.88-1.82 (m, 2H), 1.75-1.67 (m, 2H), 1.41 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.5 (s, 3F), -88.4 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 154.6, 116.6 (qt, J = 282.5, 45.9 Hz), 115.5 (tq, J = 268.6, 41.7 Hz), 79.8, 73.1(t, J = 5.0 Hz), 40.2, 31.6, 28.2. IR (thin film) v 2976, 2934, 2873, 1701, 1421, 1325, 1248, 1136, 1016, 734 cm^{-1}. MS (EI): m/z 319 [M$^+$]. HRMS (EI-TOF): m/z [M$^+$] Calculated for $C_{12}H_{18}F_5NO_3$: 319.1207; Found: 319.1215.

(Perfluoroethoxy)cyclododecane (2s). Compound **2s** was obtained as a colorless liquid **(**150.0 mg, 62%), hexane as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.59-4.53 (m, 1H), 1.86-1.77(m, 2H), 1.66-1.58 (m, 2H), 1.59-1.36 (m, 18H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.5 (s, 3F), -87.7 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 116.8 (qt, J = 282.9, 45.4 Hz), 115.5 (tq, J = 266.9, 40.9 Hz), 30.0, 23.9, 23.8, 23.2, 23.1, 20.5. IR (thin film) v 2934, 2866, 1471, 1447, 1251,

1214, 1152, 1095, 733 cm^{-1}. MS (EI): *m/z* 302 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{14}H_{23}F_5O$: 302.1665; Found: 302.1669.

2-(Perfluoroethoxy)-2,3-dihydro-1H-indene (2t). Compound **2t** was obtained as a colorless liquid **(**85.7mg, 68%), hexane as eluent for the column chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.27-7.22 (m, 4H), 5.30-5.25 (m, 1H), 3.38-3.32 (m, 2H), 3.23-3.17 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.3 (s, 3F), -88.6 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 139.2, 127.2, 124.6, 116.8 (qt, *J* = 283.0, 45.2 Hz), 115.5 (tq, *J* = 268.3, 41.1 Hz), 77.6 (t, *J* = 5.4 Hz), 39.9. IR (thin film) *v* 3029, 2962, 1484, 1414, 1250, 1216, 1097, 998, 824, 738 cm^{-1}. MS (EI): *m/z* 252 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{11}H_9F_5O$: 252.0574; Found: 252.0571.

N-(4-(4-fluorophenyl)-6-isopropyl-5-((perfluoroethoxy)methyl)pyrimidin-2-yl)-N-methylmethanesulfonamide (2u). Compound **2u** was obtained as a white solid **(**149.8 mg, 64%), hexane/ethyl acetate = 5:1 as eluent for the column chromatography. Mp: 128-130 °C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.63-7.60 (m, 2H), 7.17 (t, *J* = 8.6 Hz, 2H), 5.00 (s, 2H), 3.56 (s, 3H), 3.50 (s, 3H), 3.35-3.28 (m, 1H), 1.32 (d, *J* = 6.8 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.1 (s, 3F), -91.5 (s, 2F), -110.4-(-110.5) (m, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 178.7, 167.7, 163.9 (d, *J* = 249.2 Hz), 158.9, 133.2(d, *J* = 3.6 Hz), 131.1 (d, *J* = 8.1 Hz), 116.6 (qt, *J* = 282.6, 44.2 Hz), 115.0 (tq, *J* = 270.8, 41.6 Hz), 115.7 (d, *J* = 21.7 Hz), 114.5, 60.7 (t, *J* = 11.7 Hz), 42.5, 33.1, 31.7, 22.0. IR (thin film) *v* 3079, 2877, 1605, 1510, 1420, 1336, 1209, 1095, 998, 821 cm^{-1}. MS (EI): *m/z* 471 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{18}H_{19}F_6N_3O_3S$: 471.1051; Found: 471.1054.

(3S,5S,8R,9S,10S,13S,14S)-10,13-Dimethyl-3-(perfluoroethoxy)hexadecahydro-17H-cyclopenta[a]phenanthren-17-one (2v). Compound **2v** was obtained as a white solid **(**159.3 mg, 78%), hexane/ethyl acetate = 7:1 as eluent for the column chromatography. Mp: 153-155 °C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.33-4.25 (m, 1H), 2.44-2.37 (m, 1H), 2.08-1.99 (m, 1H), 1.93-1.42 (m, 11H), 1.35-0.90 (m, 8H), 0.83 (s, 6H), 0.71-0.64 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.4 (s, 3F), -87.2-(-88.0) (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 221.0, 116.8 (qt, *J* = 282.6, 46.1 Hz), 115.4 (tq, *J* = 267.3, 41.5 Hz), 77.0 (t, *J* = 26.2 Hz), 54.3, 51.4, 47.7, 44.7, 36.7, 35.8, 35.4, 35.2, 35.0, 31.5, 30.7, 28.6, 28.2, 21.7, 20.4, 13.8, 12.1. IR (thin film) *v* 2960, 2856, 1740, 1474, 1384, 1214, 1092, 958, 734 cm^{-1}. MS (EI): *m/z* 408 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{21}H_{29}F_5O_2$: 408.2088; Found: 408.2082.

General procedure for heptafluoropropylation of alcohols

To a reaction tube that was equipped with a stirring bar, AgOTf (385.4 mg, 1.5 mmol, 3.0 equiv), Selectfluor (354.3 mg, 1.0 mmol, 2.0 equiv), KF (116.5 mg, 2.0 mmol, 4.0 equiv), and LiOTf (78.0 mg, 0.5 mmol, 1.0 equiv) were added successively in a nitrogen-filled glovebox. Then the reaction tube was removed from the glovebox. Alcohol (0.5 mmol, 1.0 equiv), ethyl acetate (2.5 mL), $PhCF_3$ (2.5 mL),

$TMSCF_2CF_2CF_3$ (303.0 mg, 1.25 mmol, 2.5 equiv), and 2-fluoropyridine (145.5 mg, 1.5 mmol, 3.0 equiv) were added successively under N_2 atmosphere. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a plug of silica (eluted with ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography on silica gel to give the alkyl haptafluoropropyl ether.

(5-(Perfluoropropoxy)pentyl)benzene (4a). Compound **4a** was obtained as a colorless liquid (127.1 mg, 77%), hexane as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.33-7.20 (m, 5H), 4.05 (t, *J* = 6.4 Hz, 2H), 2.66 (t, *J* = 7.6 Hz, 2H), 1.79-1.65 (m, 4H), 1.49-1.42 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -81.5-(-81.6) (m, 3F), -86.6-(-86.7) (m, 2F), -129.6-(-129.7) (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.3, 128.4, 128.3, 125.8, 122.2-103.9 (m), 65.5 (t, *J* = 5.1 Hz), 35.7, 30.8, 28.6, 25.0. IR (thin film) *v* 3065, 2938, 2861, 1496, 1341, 1236, 1097, 992, 744 cm^{-1}. MS (EI): *m/z* 332 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{14}H_{15}F_7O$: 332.1011; Found: 332.1006.

Methyl 4-((Perfluoropropoxy)methyl)benzoate (4j). Compound **4j** was obtained as a yellow liquid (88.6 mg, 53%), hexane/ethyl acetate = 8:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.05 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.10 (s, 2H), 3.91 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -81.4-(-81.5) (m, 3F), -86.4-(-86.5) (m, 2F), -129.4-(-129.5) (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.6, 138.7, 130.6, 130.0, 127.3, 122.1-104.2 (m), 66.3 (t, *J* = 5.7 Hz), 52.2. IR (thin film) *v* 2958, 1727, 1617, 1438, 1340, 1284, 1192, 1109, 998, 785 cm^{-1}. MS (EI): *m/z* 334 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{12}H_9F_7O_3$: 334.0440; Found: 334.0436.

1-Iodo-4-((perfluoropropoxy)methyl)benzene (4n). Compound **4n** was obtained as a colorless liquid **(**143.3 mg, 72%), hexane as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (d, *J* = 6.8 Hz, 2H), 7.10 (d, *J* = 6.8 Hz, 2H), 5.02 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -81.7-(-81.8) (m, 3F), -86.5-(-86.6) (m, 2F), -129.8 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.0, 133.5, 129.6, 121.7-103.8 (m), 94.7, 66.4 (t, *J* = 5.9Hz). IR (thin film) *v* 2965, 2911, 1594, 1487, 1385, 1231, 1105, 1060, 997, 801, 742 cm$^{-1.}$ MS (EI): *m/z* 402 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{10}H_6F_7IO$: 401.9352; Found: 401.9364.

1-((Perfluoropropoxy)methyl)naphthalene (4p). Compound **4p** was obtained as a colorless liquid (100.0 mg, 61%), hexane as eluent for the column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.00-7.89 (m, 3H), 7.62-7.45 (m, 4H), 5.53(s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -81.3-(-81.4) (m, 3F), -86.4-(-86.5) (m, 2F), -129.3-(-129.4) (m, 2F). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 133.7, 131.3, 130.1, 129.3, 128.8, 127.4, 126.8, 126.2, 125.2, 122.9, 119.8-103.8 (m), 65.6 (t, *J* = 6.2 Hz). IR (thin film) *v* 3035, 1513, 1336, 1235, 1190, 1102, 993, 773 cm^{-1}. MS (EI): *m/z* 326 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{14}H_9F_7O$: 326.0542; Found: 326.0545.

2-(Perfluoropropoxy)-2,3-dihydro-1H-indene (4t). Compound **4t** was obtained as a colorless liquid (100.0 mg, 66%), hexane as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28-7.23 (m, 4H), 5.34-5.30 (m, 1H), 3.40-3.36 (m, 2H), 3.23-3.19 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -81.4-(-81.5) (m, 3F), -84.5-(-84.6) (m, 2F), -129.6 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 139.2, 127.2, 124.6, 121.8-104.2 (m), 77.7 (t, *J* =4.6 Hz), 39.9. IR (thin film) *v* 3088, 2963, 1484, 1382, 1251, 1100, 981, 778 cm^{-1}. MS (EI): *m/z* 302 [M$^+$]. HRMS (EI-TOF): *m/z* [M$^+$] Calculated for $C_{12}H_9F_7O$: 302.0542; Found: 302.0541.

General procedure for ethoxycarbonyldifluoromethylation of alcohols

To a reaction tube that was equipped with a stirring bar, AgOTf (385.4 mg, 1.5 mmol, 3.0 equiv), Selectfluor (354.3 mg, 1.0 mmol, 2.0 equiv), and KF (116.5 mg, 2.0 mmol, 4.0 equiv) were added successively in a nitrogen-filled glovebox. Then the reaction tube was removed from the glovebox. Alcohol (0.5 mmol, 1.0 equiv), ethyl acetate (2.5 mL), $PhCF_3$ (2.5 mL), and $TMSCF_2CO_2Et$ (294.4 mg, 1.5 mmol, 3.0 equiv) were added successively under N_2 atmosphere. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a plug of silica (eluted with ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography on silica gel to give the corresponding ether.

Ethyl (S)-2-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-2,2difluoroacetate (4d). Compound **4d** was obtained as a yellow oil (74.6 mg, 40%), hexane/ethyl acetate = 5:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30-7.19 (m, 5H), 4.75 (s, 1H), 4.38-4.32 (m, 2H), 4.04 (s, 1H), 3.93-3.83 (m, 2H), 2.87-2.83 (m, 2H), 1.40-1.35 (m, 12H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -79.9 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.1 (t, *J* = 42.5 Hz), 155.1, 137.1, 129.4, 128.6, 126.7, 114.7 (t, *J* = 268.6 Hz), 79.7, 64.8, 63.4, 50.7, 37.3, 28.3, 13.9. IR (thin film) *v* 3336, 2933, 1714, 1498, 1368, 1169, 1061, 855, 701 cm^{-1}. MS (EI): *m/z* 317 [M-C_4H_8]$^+$. HRMS (EI-TOF): *m/z* [M$^+$] Calculated for $C_{14}H_{17}F_2NO_5$: 317.1075; Found: 317.1074.

Ethyl (S)-2-(2-((tert-butoxycarbonyl)amino)-3-methylbutoxy)-2,2-difluoroacetate (4e). Compound **4e** was obtained as a yellow oil (92.5 mg, 57%), hexane/ethyl acetate = 6:1 as eluent for the column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.66-4.64 (m, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.03-3.92 (m, 2H), 3.58-3.55 (m, 1H), 1.86-1.81 (m, 1H), 1.41(s, 9H), 1.35-1.32 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -80.2 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.0 (t, *J* = 41.7 Hz), 155.6, 114.6 (t, *J* = 268.4 Hz), 79.4, 64.9, 63.3, 54.6, 29.0, 28.3, 19.3, 18.5, 13.9. IR (thin film) *v* 3346, 2976, 1777, 1506, 1342, 1175, 973, 778 cm^{-1}. MS (EI): *m/z* 282 [M-C_3H_7]$^+$. HRMS (EI-TOF): *m/z* [M$^+$] Calculated for $C_{11}H_{18}F_2NO_5$: 282.1153; Found: 282.1161.

Phenyl 4-(perfluoroethoxy)benzoate (6a). To a reaction tube that was equipped with a stirring bar, AgOTf (513.9 mg, 2.0 mmol, 4.0 equiv), Selectfluor (354.3 mg, 1.0 mmol, 2.0 equiv), NMe_4F (232.9

mg, 2.5 mmol, 5.0 equiv), and phenyl 4-hydroxybenzoate (107.1 mg, 0.5 mmol, 1.0 equiv) were added in a nitrogen-filled glovebox. Then the reaction tube was removed from the glovebox. $PhCH_3$ (7.5 mL), $TMSCF_2CF_3$ (384.4 mg, 2.0 mmol, 4.0 equiv), and 2-fluoropyridine (194.2 mg, 2.0 mmol, 4.0 equiv) were added successively under Air atmosphere. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through a plug of silica (eluted with ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography (silica gel, hexane/ethyl acetate = 15:1) to give compound **6a** as a white solid **(**85.3 mg, 51%). Mp: 78-80 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.26 (d, J = 8.8 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 8.26 (d, J = 7.6 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.1 (s, 3F), -87.9 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.0, 152.4, 150.7, 132.1, 129.5, 128.2, 126.1, 121.6, 121.2, 116.5 (qt, J = 283.5, 43.4 Hz), 114.3 (tq, J = 275.0, 41.8 Hz). IR (thin film) v 3017, 2929, 2854, 2258, 1592, 1493, 1409, 1321, 1235, 1149, 989, 909, 768 cm^{-1}. MS (EI): m/z 332 [M^+]. HRMS (EI-TOF): m/z [M^+] Calculated for $C_{15}H_9F_5O_3$: 332.0472; Found: 332.0460.

(3r,5r,7r)-1-(4-(Perfluoroethoxy)phenyl)adamantine (6d). To a reaction tube that was equipped with a stirring bar, AgOTf (513.9 mg, 2.0 mmol, 4.0 equiv), Selectfluor (354.3 mg, 1.0 mmol, 2.0 equiv), NMe_4F (232.9 mg, 2.5 mmol, 5.0 equiv), and 4-(1-adamantyl)phenol (114.2 mg, 0.5 mmol, 1.0 equiv) were added in a nitrogen-filled glovebox. Then the reaction tube was removed from the glovebox. $PhCH_3$ (7.5 mL), $TMSCF_2CF_3$ (384.4 mg, 2.0 mmol, 4.0 equiv), and 2-fluoropyridine (194.2 mg, 2.0 mmol, 4.0 equiv) were added successively under Air atmosphere. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through a plug of silica (eluted with ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography (silica gel, hexane) to give compound **6d** as a white solid **(**40.1 mg, 23%). Mp: 40-42 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.36 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 2.10 (s, 3H), 1.89 (s, 6H), 1.76 (q, J = 11.7 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -86.1 (s, 3F), -87.7 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.1, 146.1, 126.2, 121.0, 116.8 (qt, J = 283.4, 44.2 Hz), 114.3 (tq, J = 271.9, 41.5 Hz), 43.1, 36.6, 36.0, 28.8. IR (thin film) v 2909, 2360, 1508, 1345, 1213, 1085, 835, 807 cm^{-1}. MS (EI): m/z 346 [M^+]. HRMS (EI-TOF): m/z [M^+] Calculated for $C_{18}H_{19}F_5O$: 346.1356; Found: 346.1359.

1-(Methylsulfonyl)-4-(perfluoropropoxy)benzene (7b). To a reaction tube that was equipped with a stirring bar, AgOTf (513.9 mg, 2.0 mmol, 4.0 equiv), Selectfluor (354.3 mg, 1.0 mmol, 2.0 equiv), NMe_4F (232.9 mg, 2.5 mmol, 5.0 equiv), and 4-(methylsulfonyl)phenol (86.1 mg, 0.5 mmol, 1.0 equiv) were added in a nitrogen-filled glovebox. Then the reaction tube was removed from the glovebox. $PhCH_3$ (7.5 mL), $TMSCF_2CF_2CF_3$ (484.4 mg, 2.0 mmol, 4.0 equiv), and 2-fluoropyridine (194.2 mg, 2.0 mmol, 4.0 equiv) were added successively under Air atmosphere. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through a plug of silica (eluted with ethyl

acetate). The filtrate was concentrated, and the product was purified by column chromatography (silica gel, hexane/ethyl acetate = 2:1) to give compound **7b** as a white solid **(**90.6 mg, 53%). Mp: 96-98 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 (d, *J* = 8.8 Hz, 2H), 7.39(d, *J* = 8.4 Hz, 2H), 3.06 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm -81.6-(-81.7) (m, 3F), -84.0 (s, 2F), -129.7-(-129.8) (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 152.2, 139.2, 129.7, 122.1, 119.1-104.4 (m), 44.5. IR (thin film) *v* 3020, 2930, 2258, 1493, 1340, 1232, 1208, 1150, 989, 768, 738 cm^{-1}. MS (EI): *m/z* 340 [M^+]. HRMS (EI-TOF): *m/z* [M^+] Calculated for $C_{10}H_7F_7O_3S$: 340.0004; Found: 340.0007.

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Supporting Information Available: Optimization of reaction conditions for oxidative pentafluoroethylation of phenols, preliminary mechanistic experiments, as well as copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra. These material are available free of charge via the Internet at http://pubs.acs.org.

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