Alkylation of *in situ* generated fluorinated alkoxides: novel synthesis of partially fluorinated ethers

G. K. Surya Prakash*, Jinbo Hu and George A. Olah

Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, University Park, Los Angeles, CA 90089-1661
E-mail: gprakash@usc.edu

Abstract

Fluorinated ethers R_fCF_2OR were prepared from acyl chlorides R_fCOCl, alkylating agents (such as dimethyl sulfate, alkyl triflates, alkyl mesylates and tosylates, etc.) and potassium fluoride in diglyme at 80~100 ^oC. The success and the efficiency of the reaction are affected by two factors: the stability and nucleophilicity of the fluorinated alkoxide generated *in situ*; and the other is the electrophilicity of the alkylating agents used.

Keywords: Fluoroethers, fluoroacyl halides, fluoride ion, alkylation

Introduction

In general, carbon-fluorine bonds (C-F, ~116 kcal/mol) are stronger than carbon-hydrogen bonds (C-H, ~99 kcal/mol).[1] However, not all organofluorine compounds are more stable than their non-fluorinated analogs, and sometimes they are even less stable. For instance, if a partially or fully fluorinated organic compounds contains an acidic hydrogen at the β position, HF elimination is observed. This is the main reason that α-fluoro alcohols are thermally unstable and difficult to be synthesized or isolated.[2] Formation of fluoromethanol (FCH_2OH) from ethyl fluoroformate and from formyl fluoride was first reported by Olah and Pavlath[3] in 1953, and Weinmayer[4] in 1963 claimed the formation of fluoromethanol (25-30% in equilibrium) from a solution of paraformaldehyde in excess hydrogen fluoride. But both research groups were unable to isolate and characterize the pure compound. Trifluoromethanol (CF_3OH) has been prepared, purified and characterized from trifluoromethyl hypochlorite and hydrogen chloride by Kloter and Seppelt[5] in 1979, but it decomposes readily above -20 ^oC. Stable protonated α-fluoro alcohols in condensed state or in crystalline state have been known, such as protonated fluoromethanol ($FCH_2OH_2^+$) by Olah and Mateescu,[6] protonated heptafluoroisopropanol

{$(CF_3)_2C(F)OH_2^+$} by Minkwitz and Reinemann,[7] and protonated trifluoromethanol ($CF_3OH_2^+$) by Christe and co-workers.[8] However, to our knowledge, the only reported α-fluoro alcohol stable in the pure state at ambient temperature is heptafluorocyclobutanol (C_4F_7OH), which was prepared from hexafluorocyclobutanone and hydrogen fluoride by Andreades and England[9] in 1961. All these difficulties in the preparation and isolation of α-fluoro alcohols make them not practical as reagents for organic synthesis, especially for the generation of α-fluoro alkoxide (R_fO^-) synthon.

α-Fluoroalkoxides, particularly perfluoroalkoxides, have been reported for more than thirty years. The first preparations of reasonably stable, crystalline perfluoroalkoxides of alkali metals, i.e. R_fOM ($R_f = CF_3$, M = K, Rb or Cs; $R_f = CF_3$, C_2F_5, C_3F_7 or perfluoroisopropyl group, M=Cs or Rb), were reported by Redwood and Willis[10] in 1965 and 1966. Pittman,[11] Evans[12] and their coworkers also reported the formation of adducts between fluorinated ketones and metal fluorides in 1965 and 1968, respectively. Above room temperature (20 ^oC), these metal perfluoroalkoxides decompose into metal fluorides and acyl fluorides or ketones,[10] which indicates their relatively lower nucleophilicity compared with their non-fluorinated alkoxide analogs. And in the following twenty years, only few synthetic applications of these perfluoroalkoxides have been explored, such as reactions with unsaturated acyl chloride,[13] with allyl bromide,[10b] with olefin in the presence of a halogen,[14] with epibromohydrin[11] and fluoroolefin epoxides.[15] Tris(dimethylamino)sulfonium trifluoromethoxide ($TAS^+ CF_3O^-$) was also reported as a stable crystalline compound by Farnham and co-workers in 1985,[16] but its synthetic application has not been well investigated.

In the last decade, partially fluorinated ethers, or so-called "hydrofluoroethers (HFE)", have attracted increasing attention as refrigerants especially in industry as promising substitutes for the ozone-depleting chlorofluorocarbons (CFCs). According to Montreal Protocol and its appended amendments, the production and use of CFCs must be discontinued.[17] Partially fluorinated ethers (R_fOR), as a class of compounds, are particularly spotlighted as promising replacements for CFCs, not only because of their zero ozone depleting potential and low toxicity, but also they exhibit excellent solvent properties—they dissolve both hydrocarbon based and fluorocarbon based materials.[18] These partially fluorinated ethers can be extensively used as detergents, solvents, lubricants, heat-transfer media, and so on.[19,20] These fluoroethers can be synthesized by two categories of methods: direct fluorination (with elemental fluorine) of the hydrocarbon ether compound, and methods wherein the ether linkage is formed during the reaction with a fluorinated precursor.[18,21] The latter methods are more popular, such as acid catalyzed alkylation of perfluoroacyl fluoride with alkyl fluoride,[18] and alkylation of perfluorinated alkoxides prepared by the reaction of the corresponding perfluorinated acyl halide or perfluorinated ketone with an anhydrous metal fluoride in anhydrous polar, aprotic solvent.[19,22-24] Since the acid catalyzed alkylation of perfluoroacyl fluorides normally gives low yields and complex isomerization products,[18] non-catalytic alkylation of perfluoroalkoxides shows the more attractive practical features for industrial applications. Although in the recent years there have been several disclosures on this methodology using different alkylating agents

(such as alkyl fluorovinylalkyl ether,[25] dimethyl sulfate[19] and alkyl triflate[26]); gaseous short-chain perfluoroacyl halides are often used, and the results are only recorded in industrial patents without full characterization or experimental details.

Recently, we were interested in developing new types of fluorinated compounds as low temperature lithium battery electrolyte co-solvents. Partially fluorinated ethers were some of our prime candidates, since these compounds can increase the battery's discharge capacity during charge/discharge cycle, by forming a stable coating on the surface of the negative electrode and suppressing the degradation of the non-aqueous electrolyte.[27,28] Herein, we wish to report the synthesis of these partially fluorinated ethers by alkylating fluorinated alkoxides generated *in situ* by treating short or long chain fluorinated acyl chlorides with potassium fluoride.

Results and Discussion

1. Dimethyl sulfate as the alkylating agent

Dimethyl sulfate is a powerful alkylating agent and has been used for the methylation of almost every imaginable nucleophile.[29] Using dimethyl sulfate as the methylating agent, we successfully synthesized fluoroalkyl methyl ethers **2** (see Scheme 1).

$$R_fC(=O)-Cl \xrightarrow[\text{2) Me}_2\text{SO}_4]{\text{1) KF/diglyme}} R_fCF_2OCH_3$$

1   **2**
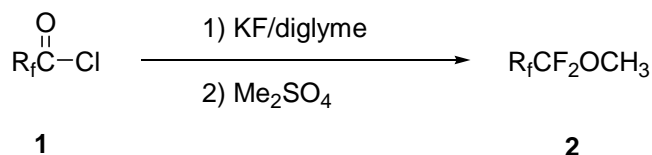
Scheme 1

Fluorinated acyl chlorides **1** are the preferred precursors for the generation of 1,1-difluoroalkoxides, since fluoroacyl chlorides have higher boiling points than the corresponding fluoroacyl fluorides.
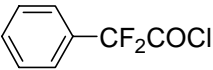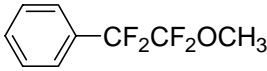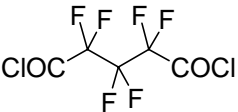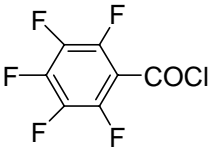

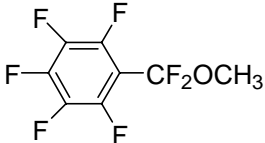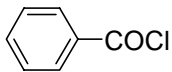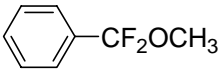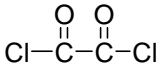**1**   **3**   **4**   **5**

Me$_2$SO$_4$

2
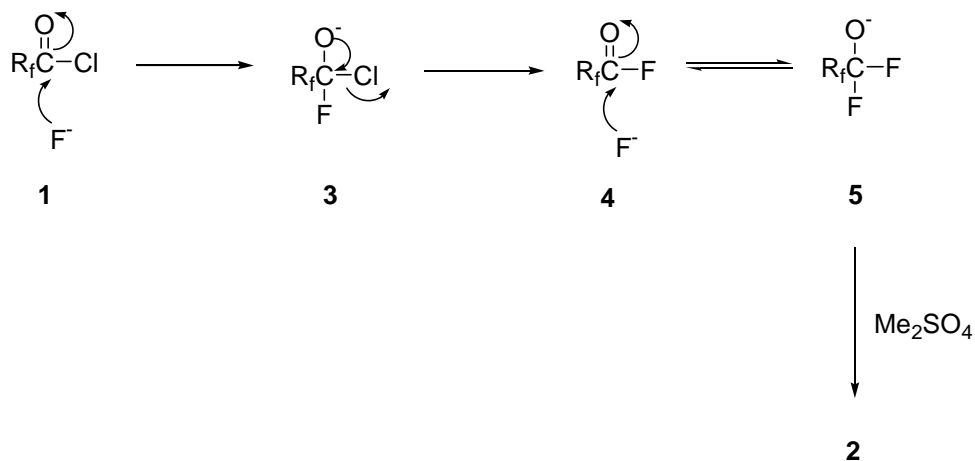
Scheme 2

During the reaction, fluoroacyl chloride can be fluorinated by KF to fluoroacyl fluoride **4** *in situ*,[19] and the latter is easily transformed into fluoroalkoxide **5** (see scheme 2). Diglyme is the solvent of choice due to it's high polarity and excellent solvation of the *in situ* generated fluorinated alkoxides **5**.[19,25]

Typical reaction condition is as follows: perfluorooctanoyl chloride **1a** (30 mmol) is reacted with anhydrous KF (90 mmol) in dry diglyme at 50 ^{0}C for 30 minutes, followed by a slow drop-wise addition of dimethyl sulfate (60 mmol) at 70 ^{0}C. The reaction mixture was kept at 70 ~100 ^{0}C for another 1 hour, cooled to room temperature and stirred overnight. The ester by-product (R_fCOOMe) can be removed from the ether product **2** simply by stirring the reaction mixture with NaOH aqueous solution. After workup, perfluorooctyl methyl ether **2a** can be isolated in 80% yield.

As shown in table 1, both short chain perfluoroacyl (C_1~C_4)[19] and long chain perfluoroacyl chlorides (C_7~C_9) gave good yields of methylated products **2a**~**2c**. For the other non-perfluorinated substrates **1d** and **1e,** the reactions gave lower yields. For the substrates without fluorine atoms at the α-carbon to the carbonyl group (see **1g** and **1h**), the reaction did not take place. Varying yields of fluoroethers can be roughly explained by the stability and the nucleophilicity of each fluoroalkoxide **5** ($R_fCF_2O^-$) generated *in situ* in the reaction. Since these fluoroalkoxides exist in equilibrium with metal fluoride and fluoroacyl fluorides under the reaction conditions, as shown in scheme 2, the weaker fluoroalkoxide would have a higher tendancy to decompose into the metal fluoride and acyl fluoride. Among these fluoroalkoxides **5**, the trifluoromethoxide ion (i.e. R_f = F) is the most stable one, because the negative charge on the trifluoromethoxide ion rests formally on the oxygen atom, with the negative charge being shared to some extent by the three fluorine atoms because of their greater electronegativity.[10] When the R_f is changed to a perfluoroalkyl group, such as in **1a**, **1b** and **1c**, the longer the perfluoroalkane chain makes the carbon atom connecting to CF_2O^- less electronegative, resulting in the lower stability of the resulting alkoxide and then somewhat lower yields of the ethers. When R_f = Cl (**1d**), the ether yield is moderate; and when R_f = phenyl group (**1e**), the yield of ether is much lower because the phenyl group has even weaker electron-withdrawing ability than the chlorine atom. In the case of **1g-1i**, although these acyl chlorides can be transformed into corresponding acyl fluorides **4g-4i** (characterized by NMR), they failed to produce the ether product **2g**, **2h** or **2i** indicating that these acyl fluorides **4g-4i** are not further fluorinated into alkoxides **5g-5i**, probably due to their instability. Finally, it is also remarkable that the diacyl chloride **1f** can be transformed into the diether **2f** in good yield.

Table 1. Preparation of fluoroethers **2** from fluorinated acyl chlorides **1**, KF and dimethyl sulfate in diglyme

	Reactants	Products	
	1	**2**	Yields (%)[a]
a	$n\text{-}C_7F_{15}COCl$	$n\text{-}C_8F_{17}OCH_3$	80
b	$n\text{-}C_8F_{17}COCl$	$n\text{-}C_9F_{19}OCH_3$	71
c	$n\text{-}C_9F_{19}COCl$	$n\text{-}C_{10}F_{21}OCH_3$	62
d	$CClF_2COCl$	$CClF_2CF_2OCH_3$	48
e	Ph–CF_2COCl	Ph–$CF_2CF_2OCH_3$	23
f	$ClOC$–$CF_2CF_2CF_2$–$COCl$	$CH_3OCF_2CF_2CF_2CF_2OCH_3$	50
g	C_6F_5–$COCl$	C_6F_5–CF_2OCH_3	0[b]
h	Ph–$COCl$	Ph–CF_2OCH_3	0
i	$Cl\text{-}C(O)\text{-}C(O)\text{-}Cl$	$CH_3OCF_2CF_2OCH_3$	0

[a] All are isolated yields; [b] methyl triflate was also tried as methylating reagent, but the reaction was not successful.

The relative stability and nucleophilicity of fluoroalkoxide **5** can also be explained by the *negative hyperconjugation* (HCJ)[30] as shown in Scheme 3. Farnham and coworkers have explained the structural parameters of $(Me_2N)_3S^+$ CF_3O^- by HCJ. Their evidence for HCJ is that the X-ray structure shows the C-O bond to be unusually short (1.227 Å) and the C-F bond is extraordinarily long (1.390-1.397 Å).[16a] Thus we can derive that for the other fluorinated alkoxides ($R_f \neq F$), strong electron-withdrawing property of R_f group may facilitate the HCJ between **5a**, **5b** and **5c,** which stabilizes the corresponding alkoxides and increases their propensity to react with alkylating agents such as dimethyl sulfate.

(a)

C-O: 1.227 Å
C-F: 1.390-1.397 Å

(b)
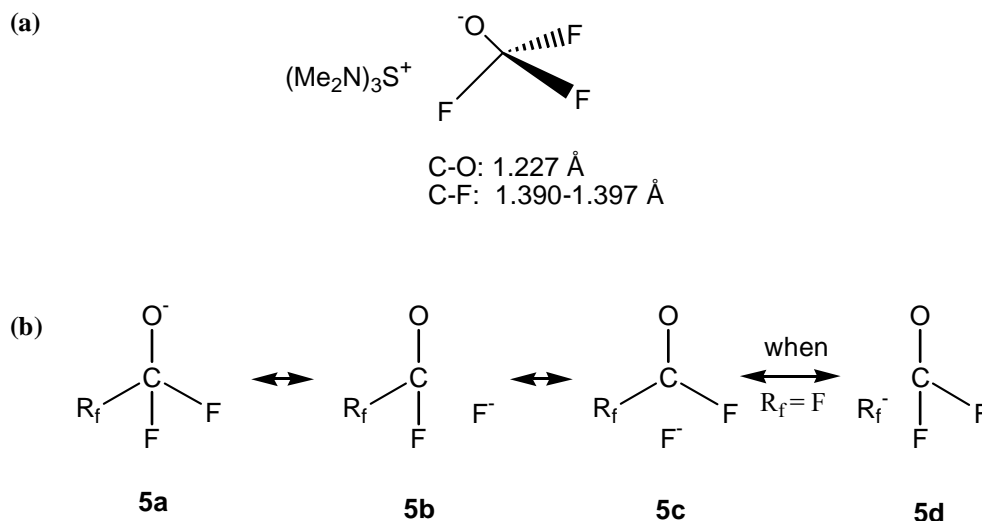
Scheme 3. (a) C-O and C-F Bond lengths from $(Me_2N)_3S^+ CF_3O^-$ X-ray crystal structure;[16a] (b) Negative hyperconjugation in fluorinated alkoxide (**5**).

2. Alkyl sulfonates as alkylating agents

Besides dimethyl sulfate, we also attempted to use other strong alkylating agents to prepare partially fluorinated ethers, such as methyl trifluoromethanesulfonate (methyl triflate), ethyl triflate, hexyl triflate, methyl methanesulfonate (methyl mesylate) and methyl *p*-toluenesulfonate (methyl tosylate). The reaction conditions were similar to previously studied reactions with dimethyl sulfate (Scheme 4).
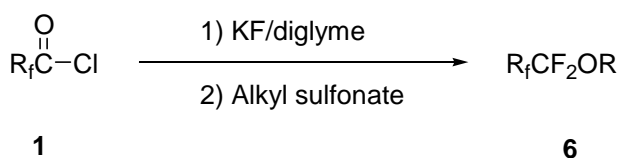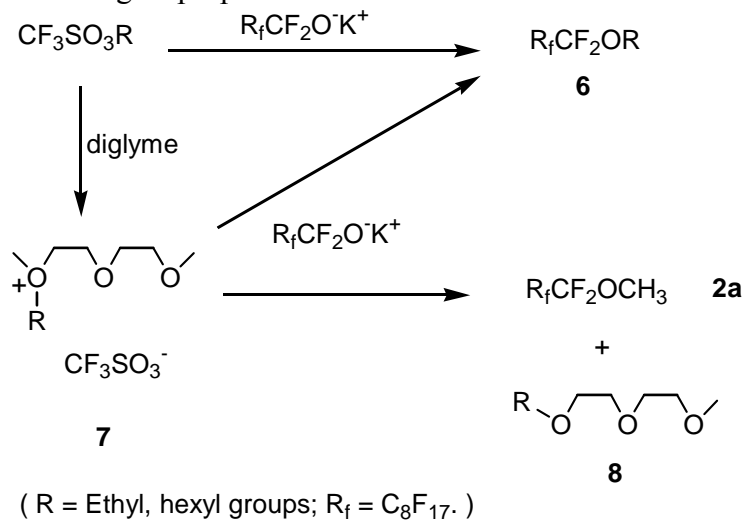

Scheme 4

The results are summarized in Table 2.

Table 2. Preparation of fluoroethers **6** from *n*-perfluorooctanoyl chloride, **1**, KF and alkyl sulfonates in diglyme

Alkyl sulfonate	Products 6	Yields (%)[a]
$CF_3SO_3CH_3$	$n\text{-}C_8F_{17}OCH_3$	82
Methyl mesylate	$n\text{-}C_8F_{17}OCH_3$	29
Methyl tosylate	$n\text{-}C_8F_{17}OCH_3$	17
CF_3SO_3Et	$n\text{-}C_8F_{17}OCH_2CH_3$ 34 $n\text{-}C_8F_{17}OCH_3$ 51	85
$CF_3SO_3C_6H_{13}\text{-}n$	$n\text{-}C_8F_{17}OC_6H_{13}\text{-}n$ 60 $n\text{-}C_8F_{17}OCH_3$ 15	75

[a] All are isolated yields.

The effect of different alkylating agents on the yields of ether product **6** can be clearly seen from Table 2 (entries **a-c**). Since the order of methylating ability is methyl triflate > methyl mesylate > methyl tosylate, the yields of methyl perfluorooctyl ether are in the same order. It is interesting note that in the case of ethylation and hexylation reactions using ethyl triflate and hexyl triflate, respectively (entries **d** and **e**), each reaction gives the methyl ether ($n\text{-}C_8F_{17}OCH_3$) besides expected product (**6d** or **6e**). The mechanism of formation of methyl ether is proposed as shown in Scheme 5 involving disproportionation reactions.
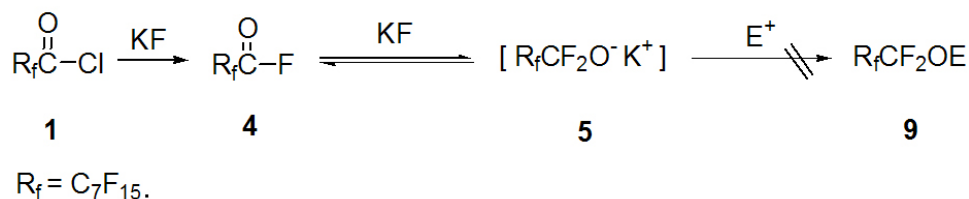

(R = Ethyl, hexyl groups; $R_f = C_8F_{17}$.)

Scheme 5

At first, ethyl or hexyl triflate can react with diglyme solvent to form Meerwein-type[31] oxonium ion **7**, which can further methylate the fluorinated alkoxide to form **2a**.

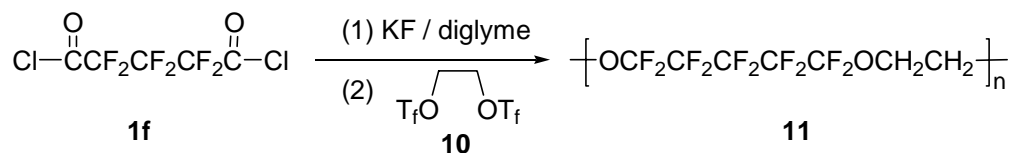## 3. Attempted reactions with other electrophiles

We have also attempted to react fluorinated alkoxide **5a** with other electrophiles, such as methyl iodide, acetyl chloride, benzoyl chloride, triflic anhydride, allyl bromide, acryloyl chloride, methyl chloroformate, propyl chloroformate, and *N,N*-carbonyl diimidazole (Scheme 6). Unfortunately, all these reactions did not give the expected products. This means that besides the facile formation of perfluoroalkoxides **5**, very strong electrophilicity of the alkylating agents is also necessary (Scheme 6).

$$R_fC\overset{\overset{\displaystyle O}{\|}}{}-Cl \xrightarrow{KF} R_fC\overset{\overset{\displaystyle O}{\|}}{}-F \underset{}{\overset{KF}{\rightleftharpoons}} [\,R_fCF_2O^-K^+\,] \xrightarrow{E^+} R_fCF_2OE$$

$$\quad\quad \mathbf{1} \quad\quad\quad\quad \mathbf{4} \quad\quad\quad\quad\quad\quad \mathbf{5} \quad\quad\quad\quad \mathbf{9}$$

$$R_f = C_7F_{15}.$$

Scheme 6

4. Attempted synthesis of partially fluorinated polyether

With similar ether formation methodology methioned above, we also attempted to synthesize polyether **11** using ethylene glycol bistriflate **10** and hexafluoroglutaryl chloride **1f** (Scheme 7).

$$Cl-\overset{\overset{\displaystyle O}{\|}}{C}CF_2CF_2CF_2\overset{\overset{\displaystyle O}{\|}}{C}-Cl \xrightarrow[\substack{(2) \\ T_fO \quad OT_f}]{(1)\ KF\ /\ diglyme} \left[OCF_2CF_2CF_2CF_2CF_2OCH_2CH_2\right]_n$$

$$\quad\quad\quad \mathbf{1f} \quad\quad\quad\quad\quad\quad\quad \mathbf{10} \quad\quad\quad\quad\quad\quad\quad \mathbf{11}$$

Scheme 7

Hexafluorofluoroglutaryl chloride (3.6 mmol) was reacted with KF (21.6 mmol) in diglyme at 50 ^{o}C for 30 min, followed by addition of ethylene glycol bistriflate **10** (3.6 mmol) and the resulting reaction mixture was stirred at 70 ^{o}C for 20 h. It turns out that the major products are some oligomeric compounds, and only around 5 % yield of relatively high molecular weight polymer was obtained as an oily liquid (average molecular weight = 1,413 according to SEC measurement using poly(ethylene oxide), PEO as a standard).

Conclusions

In conclusion, we have synthesized partially fluorinated ethers by the direct alkylation of fluorinated alkoxides generated *in situ* from fluoroacyl chlorides with potassium fluoride in diglyme. The success and yields of the reaction are affected by two factors: the stability and nucleophilicity of the fluorinated alkoxide generated *in situ*; and the other is the electrophilicity

of alkylating agents. The new fluoroethers prepared have been found to be promising candidates for the lithium battery applications.[38]

Experimental Section

General Procedures. KF was dried at 300 ^{o}C under high vacuum for 10 hours and stored under argon. Diglyme was distilled over calcium hydride. Dimethyl sulfate was purchased from Aldrich chemical Co., and other fluoroacyl chlorides were purchased from Synquest laboratories, Inc. or prepared from the corresponding carboxylic acid with PCl_5 or $SOCl_2$.

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker AMX 500 and AM 360 NMR spectrometers. ^{1}H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ 0.0 or to the signal of a residual protonated solvent: $CDCl_3$ δ 7.26. ^{13}C NMR chemical shifts were determined relative to internal TMS at δ 0.0 or to the ^{13}C signal of solvent: $CDCl_3$ δ 77.0. ^{19}F NMR chemical shifts were determined relative to internal $CFCl_3$ at δ 0.0. Infrared spectra were obtained on a Perkin-Elmer Spectrum 2000 FT-IR spectrophotometer. Mass spectra were recorded on Hewlett Packard 5890 Gas Chromatograph with a Hewlett Packard 5971 Mass Selective Detector at 70 eV.

Methyl perfluorooctyl ether (2a). In a 200 ml three-neck flask equipped with a dropping funnel, a magnetic stirring bar and condenser, was added 5.23 g of anhydrous KF (90 mmol) and 16 ml of freshly distilled diglyme under argon atmosphere. The temperature was raised to 50 ^{o}C, and 13.0 g perfluorooctanoyl chloride was added in slowly via dropping funnel over 30 minutes period. Then the temperature was raised to 70 ^{o}C and 7.57 g dimethyl sulfate (60 mmol) was dropped in slowly, and the reaction mixture was kept stirring at 70~100 ^{o}C for another 1 hour. The mixture was cooled and stirred overnight at room temperature. The volatile material (~25 g) was distilled into a liquid nitrogen trap under high vacuum, followed by washing with cold 10 % NaOH aqueous solution, brine and water respectively. After drying over anhydrous sodium sulfate, the crude product mixture was fractionally distilled. Totally 10.8 g (80% yield) of **2a** was isolated as colorless liquid, b.p. 61 ^{0}C/26 mmHg. ^{1}H NMR($CDCl_3$): δ 3.73 (s, 3H); ^{13}C NMR($CDCl_3$): δ 51.25 (t, J = 7.7 Hz), 109.38~120.15 (m); ^{19}F NMR($CDCl_3$): δ -81.49 (t, J = 9.2 Hz, 3F), -88.76 (m, 2F), -122.57 (m, 4F), -122.87 (m, 2F), -123.33 (m, 2F), -125.85 (m, 2F), -126.77 (m, 2F). IR (neat): 2976, 1793, 1460, 1349, 1206, 1010, 879, 723, 704, 659, 561, 529 cm^{-1}. MS (relative intensity): 449 (0.7, M$^+$-1), 431 (30, M$^+$- F), 381 (18), 331 (6), 281 (2), 231 (6), 181 (9), 169 (20), 131 (35), 119 (21), 100 (15), 81 (100), 59 (50).

Methyl perfluorononanoyl ether (2b). In a 50 ml three-neck flask equipped with a condenser, a stirring bar and two rubber septa, was added 2.41 g anhydrous KF (41 mmol) and 10 ml of dry diglyme under argon atmosphere. At 50 ^{o}C, 5.0 g perfluorononanoyl chloride (10 mmol) was added in slowly via a syringe. After 30 minutes at 50 ^{o}C, the temperature was raised to 70 ^{0}C slowly, followed by slow addition of 3.92 g dimethyl sulfate (30 mmol). The reaction mixture

was stirred at 70 ^{o}C for 1 hour, then at 100 ^{o}C for another 1 hour. The reaction mixture was cooled, and stirred overnight at room temperature. The reaction mixture was mixed with 20 ml of ether and washed with cold 10% NaOH aqueous solution for 3 times. The ether layer was washed with brine and water 3 times, respectively. The ether phase was dried over magnesium sulfate. After filtration, the solvent was evaporated. The crude product was fractionally distilled and 3.66 g (71 %) of **2b** was isolated, b.p. 80-81 ^{o}C/36 mmHg. ^{1}H NMR(CDCl$_3$): δ 3.73 (s, 3H); ^{13}C NMR(CDCl$_3$): δ 51.40 (t, J = 7.0 Hz); 105.28 - 122.00 (m); ^{19}F NMR(CDCl$_3$): δ -81.54 (t, J = 9.3 Hz, 3F), -88.81 (m, 2F), -122.56 (m, 6F), -122.88 (m, 2F), -123.34 (m, 2F), -125.88 (m, 2F), -126.81 (m, 2F). MS (relative intensity): 481 (0.1, M^{+}- F), 463 (9), 413 (4), 281 (0.7), 231 (4), 181 (4), 169 (4), 151 (3), 131 (15), 119 (6), 100 (7), 81 (100), 69 (22), 51 (22).

Methyl perfluorodecanoyl ether (2c). In a 200 ml three-neck flask equipped with a stirring bar, a condenser and two rubber septa, was added 5.0 g of anhydrous KF (86 mmol) and 20 ml of dry diglyme under argon atmosphere. At 50 ^{o}C, 12.0 g perfluorononanoyl chloride (22 mmol) made from perfluorononanoic acid and thionyl chloride, was dissolved in 10 ml diglyme and added in reaction mixture slowly via a syringe. After 30 minutes at 50 ^{o}C, the temperature was raised up to 70 ^{o}C slowly, followed by the slow addition of 8.51 g dimethyl sulfate (66 mmol). The reaction mixture was stirred at 70 ^{o}C for 1 hour, then at 100 ^{o}C for another hour. The reaction mixture was cooled, and stirred overnight at room temperature. The reaction mixture was added in 20 ml of ether and washed with cold 10% NaOH aqueous solution for 3 times. The ether layer was washed with brine and water 3 times, respectively. The ether phase was dried over magnesium sulfate. After filtration, the solvent was evaporated. The crude product was fractionally distilled and 7.68 g of **2c** (62%) was isolated, b.p. 84-85 ^{o}C/27 mmHg. ^{1}H NMR (acetone-d$_6$): δ 3.83 (s, 3H); ^{13}C NMR(acetone-d$_6$): δ 51.49 (t, J = 6.4 Hz); 106.14-123.16 (m); ^{19}F NMR(acetone-d$_6$): δ -81.29 (t, J = 9.2 Hz, 3F), -87.84 (m, 2F), -121.74 (m, 8F), -122.19 (m, 2F), -122.70 (m, 2F), -125.32 (m, 2F), -126.28 (m, 2F).

Chlorodifluoroacetyl chloride (1d). Chlorodifluoroacetic acid (100 g, 0.766 mol) reacts with 1.5 equiv. PCl$_5$ (239 g) at 90-100 ^{o}C for 3h, and the product was distilled out to give 40.5 g (36 % yield) **1d**,[34] b.p. 28-29 ^{o}C, ^{19}F NMR (CDCl$_3$): δ -63.30. It was re-distilled before use.

2-Chloro-1,1,2,2-tetrafluoroethyl methyl ether (2d). In a 200 ml three-neck flask equipped with a dry ice condenser, a stirring bar and two rubber septa, was added 20.0 g of anhydrous KF (430 mmol) and 20 ml of dry diglyme under an argon atmosphere. At 50 ^{o}C, 6.0 g chlorodifluoroacetyl chloride (40 mmol) made from chlorodifluoroacetic acid and phosphorus pentachloride, was added into the reaction mixture slowly via a syringe. After 30 minutes at 50 ^{o}C, the temperature was raised to 70 ^{o}C slowly, followed by slow addition of 8.51 g dimethyl sulfate (66 mmol). Reaction mixture was kept at 70 ^{o}C for 1 hour and then cooled down to room temperature, followed by stirring overnight. 10 ml of 10% NaOH aqueous solution was added into the reaction mixture, and the volatile product was fractionally distilled. Totally 3.24 g (48%) **3d** was isolated. ^{1}H NMR(CDCl$_3$, ppm): δ 3.73 (s, 3H); ^{13}C NMR(CDCl$_3$): δ 51.77 (t, J = 6.1 Hz), 117.18 (tt, ^{1}J$_{C-F}$ = 271.5 Hz, ^{2}J$_{C-F}$ = 34.2 Hz), 120.77 (tt, ^{1}J$_{C-F}$ = 299.1 Hz, ^{2}J$_{C-F}$ = 45.2 Hz); ^{19}F NMR(CDCl$_3$): δ -73.11 (t, J = 3.0 Hz, 2F), - 93.09 (t, J=3.0 Hz, 2F).

2-Phenyl-2,2-difluoroacetyl chloride (1e)[35,36]**.** At 0 °C, into 21.95 g (0.13 mol) methyl benzoylformate, was slowly added 25.85 g (0.16 mol) (diethylamino)sulfur trifluoride (DAST). The reaction mixture was stirred at 0 °C for 0.5 h and then at 40 °C for another 4 h. The reaction mixture was cooled to room temperature and poured into 50 ml of ice water, followed by extraction with 50 ml CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$ aqueous solution and water. After drying over $MgSO_4$ and solvent removal, 22.9 g crude *methyl 1,1-difluorobenzylformate* as a wine-red liquid, yield 92 %. ^{1}H NMR shows the purity to be above 96 %. ^{1}H NMR(CDCl$_3$): δ 3.84 (s, 3H), 7.40 (m, 3H), 7.61 (d, 2H); ^{13}C NMR (CDCl$_3$): δ 53.60, 113.41 (t), 125.42, 128.60, 131.03, 132.65 (t), 164.7; ^{19}F NMR(CDCl$_3$): δ - 104.25.

Into 22.84 g (0.122 mol) methyl 1,1-difluorobenzylformate was added 100 ml of 2.5 M aqueous NaOH solution and 60 ml of THF, then the mixture was refluxed for 4 h. The reaction mixture was cooled and extracted with 200 ml of ether. The aqueous phase was acidified with 5 % HCl until pH paper test showed acidic. The aqueous phase was extracted with 100 ml ether twice, and the combined ether phase was dried over $MgSO_4$. After solvent removal, 18.05 g yellow liquid was obtained, into which 150 ml hexane was added. The hexane solution was stored in refrigerator at -10 °C overnight. and 9.06 g Needle-like crystalline product *2-phenyl-2,2-difluoroacetic acid*, was isolated by suction filtraction, 9.06 g, yield 46 %. ^{1}H NMR(CDCl$_3$): δ 7.55 (m, 3H), 7.62 (d, 2H), 10.08 (b, 1H); ^{13}C NMR (CDCl$_3$): δ 112.99 (t, J = 252.3 Hz), 125.52, 128.79, 131.43, 131.85 (t, J = 25.1 Hz), 169.25 (t, J = 36.1 Hz); ^{19}F NMR(CDCl$_3$): δ - 105.85.

Into 9.31 g (54 mmol) of 2-phenyl-2,2-difluoroacetic acid was added 35 ml of thionyl chloride, and the mixture was refluxed for 10 h under argon. Fractional distillation gave 9.4 g *2-phenyl-2,2-difluoroacetyl chloride* (**1e**), yield 91 %, b.p. 67 °C/15 mmHg. ^{1}H NMR(CDCl$_3$): δ 7.51 (t, 3H), 7.58 (t, 1H), 7.63 (d, 2H); ^{13}C NMR (CDCl$_3$): δ 114.41 (t, J = 259.0 Hz), 125.95 (t, J = 6.0 Hz), 129.03, 130.02, (t, J = 26.1 Hz), 131.95, 167.31 (t, J = 50 Hz); ^{19}F NMR(CDCl$_3$): δ - 101.32.

Methyl 2-phenyl-1,1,2,2-tetrafluoroethyl ether (2e). In a 200 ml three-neck flask equipped with a stirring bar, a condenser and two rubber septa, was added 8.6 g of anhydrous KF (148 mmol) and 20 ml of dry diglyme under an argon atmosphere. At 50 °C, 8.5 g **1e** (44 mmol) was added into the reaction mixture slowly via syringe. After 30 minutes at 50 °C, the temperature was raised up to 70 °C slowly, followed by slow addition of 11.25 g dimethyl sulfate (89 mmol). The reaction mixture was stirred at 70 °C for 1 hour, then at 100 °C for another 2 hours. The reaction mixture was cooled, and stirred overnight at room temperature. The reaction mixture was mixed with 20 ml of CH_2Cl_2 and washed with cold 10% NaOH aqueous solution trice. The organic layer was washed with brine and water trice, respectively. The organic phase was dried over magnesium sulfate and the solvent was evaporated off. After column chromatography using hexanes as eluent, 2.10 g (23%) of **2e** was isolated as a corlorless liquid. [1]H (CDCl$_3$): δ 3.61 (s, 3H), 7.45 (t, 2H), 7.51 (t, 1H), 7.59 (d, 2H); [13]C (CDCl$_3$): δ 51.03 (t, J = 6.7 Hz), 119.24(tt, $^1J_{C-F}$ = 271 Hz, $^2J_{C-F}$ = 36 Hz), 114.44 (tt, $^1J_{C-F}$ = 271 Hz, $^2J_{C-F}$ = 36 Hz), 130.86 (t, J=24.5Hz), 126.61 (t, J = 6.7 Hz), 128.18, 130.98; [19]F (CDCl$_3$): δ -93.81 (t, J = 4.9 Hz, 2F), -114.08 (t, J = 4.9 Hz).

MS (relative intensity): 208 (27, M$^+$), 189 (4, M$^+$ - F), 177 (0.3, PhCF$_2$CF$_2$$^+$), 127 (100, PhCF$_2$$^+$), 81 (21, CH$_3OCF_2$$^+$), 77 (9, Ph$^+$), 51 (4).

1,5-Dimethoxy-perfluoropentane (2f). In a 50 ml three-neck flask equipped with a dropping funnel, a magnetic stirring bar and a condenser, was added 6.22 g of anhydrous KF (107 mmol) and 10 ml of freshly distilled diglyme under an argon atmosphere. The temperature was raised to 50 ^{o}C, and 1.64 g (5.92 mmol) **1f** was added in slowly via syringe. Then the temperature was raised to 70 ^{o}C and 3.78 g dimethyl sulfate (30 mmol) was dropped in slowly, and the reaction was kept stirred at 70~100 ^{o}C for another 1 hour. The reaction mixture was cooled and stirred overnight at room temperature. The reaction mixture was washed with 10% NaOH aqueous solution and extracted with CH$_2$Cl$_2$, and the organic phase was washed with brine and water, respectively. After drying over magnesium sulfate, the solvent was evaporated. After fractional distillation, about 5 g crude product was isolated, which contains diglyme. The diglyme was removed by washing with water and extracted with diethyl ether 10 times. After drying and removal of the solvent, 0.92 g (50% yield) of **2f** was isolated as a colorless liquid. ^{1}H (CDCl$_3$): δ 3.72 (s, 3H); ^{13}C (CDCl$_3$): δ 51.44 (t, J = 6.8 Hz), 105.58~120.22 (m); ^{19}F (CDCl$_3$): δ -88.80 (t, J = 9.2 Hz, 4F), -123.36 (m, 2F), -126.01 (m, 4F). MS (relative intensity): 311 (0.07, M$^+$), 293 (18), 243 (2), 231 (5), 197 (0.7), 181 (3), 169 (10), 131 (9), 119 (3), 112 (4), 100 (7), 81 (100, CH$_3$OCF$_2$$^+$), 69 (10).

Methyl triflate as the alkylating agent. In a 50 ml three-neck flask equipped with a magnetic stirring bar and a condenser, was added 0.54 g (9.3 mmol) of anhydrous KF and 10 ml of freshly distilled diglyme under argon atmosphere. The temperature was raised to 50 ^{o}C, and 1.0 g (2.3 mmol) perfluorooctanoyl chloride was slowly added in via a syringe. Then the temperature was raised to 70 ^{o}C and 0.76 g methyl triflate (4.6 mmol) was added in via syringe, and the reaction was kept stirred at 70~100 ^{o}C for another 2 hours. The reaction mixture was cooled and stirred overnight at room temperature. The reaction mixture was stirred in cold 30 % NaOH aqueous solution (10 ml) for 30 min, followed by extraction with 15 ml ether twice. The ether phase was washed with brine and water respectively. After drying over anhydrous sodium sulfate, the crude product mixture was fractionally distilled to afford 0.85 g (82% yield) of the product as a colorless liquid. ^{1}H, ^{13}C, ^{19}F NMR and MS spectra indicate the product to be *Methyl perfluorooctyl ether* **2a**.

The reaction conditions for the *methyl mesylate* and *methyl tosylate* as alkylating agents are similar, except that the reaction times are longer (~20 h). The isolated yields of **2a** are 29 % and 17 % respectively.

Ethyl triflate as alkylating agent. In a 100 ml three-neck flask equipped with a magnetic stirring bar and a condenser, was added 2.69 g (46.2 mmol) of anhydrous KF and 10 ml of freshly distilled diglyme under an argon atmosphere. The temperature was raised to 50 ^{o}C, and 5.0 g (11.6 mmol) perfluorooctanoyl chloride was slowly added in via a syringe. Then the temperature was raised to 70 ^{o}C and 2.06 g ethyl triflate (11.6 mmol) was added in via syringe, and the reaction was kept stirred at 70~100 ^{o}C for another 2 hours. Then another 5g of ethyl triflate (28 mmol) was added into the reaction mixture and stirred at 100 ^{o}C for another 2 h. The

reaction mixture was cooled and stirred at room temperature. The reaction mixture was treated with cold 30 % NaOH aqueous solution (15 ml) for 30 min, followed by extraction with 15 ml ether thrice. The ether phase was washed with brine and water respectively. After drying over anhydrous sodium sulfate, the crude product mixture was fractionally distilled to afford 4.54 g (85% yield) of the product as a colorless liquid, b.p. 50-52 ^{o}C/17 mmHg. ^{1}H, ^{19}F NMR and GCMS showed that it contains two compounds: *ethyl perfluorooctyl ether* **6d** and *methyl perfluorooctyl ether* **2a.** The ratio of **6d** : **2a** = 2: 3. For **6d**, ca. 34 % yield. ^{1}H NMR (CDCl$_3$): δ 1.36 (t, 3H), 4.13 (q, 2H); ^{13}C NMR (CDCl$_3$): δ 14.54, 61.79 (t, J = 5.9 Hz), 104 ~120 (m); ^{19}F NMR (CDCl$_3$): δ -81.47 (t, J = 9.2 Hz, 3F), -85.80 (m, 2F), -122.61 (m, 4F), -122.89 (m, 2F), -123.40 (m, 2F), -125.86 (m, 2F), -126.77 (m, 2F). MS (relative intensity): 463 (7, M$^+$-1), 449 (13), 331 (4), 232 (7), 219 (13), 181 (15), 169 (36), 131 (55), 119 (34), 100 (33), 95 (40), 69 (100). For **2a,** ca. 51 % yield. The characterization data are same as above.

Hexyl triflate as the alkylating agent. In a 200 ml three-neck flask equipped with a magnetic stirring bar and a condenser, was added 2.0 g (34 mmol) of anhydrous KF and 30 ml of freshly distilled diglyme under an argon atmosphere. The temperature was raised to 50 ^{o}C, and 5.0 g (11.6 mmol) perfluorooctanoyl chloride was slowly added in via a syringe. Then the temperature was raised to 70 ^{o}C and 4.06 g (17.4 mmol) of hexyl triflate was added in via syringe, and the reaction was kept stirred at 70~100 ^{o}C for another 2 hours. Then another 1.4 g (6 mmol) of hexyl triflate was added into the reaction mixture, and stirred at 90 ^{o}C overnight. The reaction mixture was cooled and stirred with cold 30 % NaOH aqueous solution (20 ml) for 30 min, followed by extraction with 15 ml ether thrice. The ether phase was washed with brine and water respectively. After drying over anhydrous sodium sulfate and removal of the solvent, the crude product was further purified by silica gel column chromatography (hexanes as eluent) to afford 3.6 g (60 % yield) of *hexyl perfluorooctyl ether* **6e** as a colorless liquid, and 0.78 g (15 % yield) **2a.** For **6e**, ^{1}H NMR (CDCl$_3$): δ 0.90 (t, J= 6.6 Hz, 3H), 1.26-1.42 (m, 6H), 1.69 (m, 2H), 4.04 (t, J = 6.6 Hz, 2H); ^{13}C NMR (CDCl$_3$): δ 13.78, 22.43, 25.06, 28.73, 31.17, 65.72 (t, J = 5.1 Hz), 108.63-118.36 (m); ^{19}F NMR (CDCl$_3$): δ -81.26 (t, J = 9.5 Hz, 3F), -85.68 (2F), -122.46 (b, 4F), -122.74 (b, 2F), -123.24 (b, 2F), -125.74 (b, 2F), -126.62 (b, 2F). MS (relative intensity): 475 (0.7), 449 (0.7), 231 (1), 219 (2), 181 (3), 169 (10), 131 (30), 119 (16), 100 (12), 85 (15), 69 (100), 55 (73). For **2a,** the characterization data are same as above.

Attempted reactions with other electrophiles. The reaction conditions for other electrophiles, such as methyl iodide, acetyl chloride, benzoyl chloride, triflic anhydride, allyl bromide, acryloyl chloride, methyl chloroformate, propyl chloroformate, and *N,N*-carbonyl diimidazole, are similiar as above. For some volatile substrates, dry ice condenser was used.

Attempted synthesis of partially fluorinated polyether (11): Ethylene glycol bistriflate (10)[37]**.** A mixture of dry ethylene glycol (1 g, 16.1 mmol) and anhydrous pyridine (3 ml) in dry methylene chloride (30 ml), was added dropwise into an ice-cooled, stirred solution of triflic anhydride (9.1 g, 32.2 mmol) in 20 ml of methylene chloride under argon. The solution was stirred for an additional 2h, then washed with water (100 ml) and dried over MgSO$_4$. After removal of the solvent, 4.5 g product **10** was obtained as a pale yellow crystalline solid, yield 86

%. ^1H NMR (CDCl$_3$): δ 4.77 (s, C$\underline{H}_2$-C$\underline{H}_2$); ^{13}C NMR (CDCl$_3$): δ 71.72, 118.53 (q, J = 319.5 Hz); ^{19}F NMR (CDCl$_3$): δ -74.77.

Fluorinated polyether (11). In a 100 ml three-neck round bottom flask, was added 1.26 g (21.7 mmol) of dry KF and 10 ml of dry diglyme. At 50 °C, 1.0 g hexafluoroglutaryl chloride (3.6 mmol) was added via a syringe, and the reaction mixture was stirred for 30 min. Then the temperature was raised to 70 °C and 1.18 g ethylene glycol bistriflate (3.6 mmol) was added into the reaction mixture. The reaction mixture was stirred at 70 °C for another 1 h and then at 100 °C overnight. The reaction mixture was cooled and stirred with 30 % NaOH aqueous solution (10 ml), and then extracted with 15 ml ether thrice. Combined ether phase was washed with water twice. After drying over MgSO$_4$ and solvent removal, the crude product was treated with high vacuum for 10 h to give 0.12 g of oily liquid (~ 5 % yield). ^{19}F NMR (CDCl$_3$): δ -85.8 (-OC$\underline{F}_2$-, 4F), -123.1 (m, 2F), -125.9 (m, 4F). Size Exclusion Chromatography measurement with PEO standard curve gave the average molecular weight M_w = 1,413; M_n = 1,316; M_w/M_n = 1.07.

Acknowledgments

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