

A practical ligand-free copper(I) bromide-catalyzed fluoroalkoxylation of unactivated aryl bromides

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Received: 4 June 2015 / Accepted: 4 July 2015 © Springer Science+Business Media Dordrecht 2015

Abstract An efficient ligand-free fluoroalkoxylation of unactivated aryl bromides has been developed, with special attention focused on practicability of the reaction. Without precious metal and organic ligand, the reaction was carried out under the catalytic system of inexpensive copper(I) bromide as a catalyst, N,N-dimethyl formamide as a cocatalyst, and the corresponding stoichiometric sodium fluoroalkoxide as a nucleophilic reagent. The facile approach avoids the drawbacks associated with cost, separation and pollution of ligand to enable sustainable access to aryl fluoroalkyl ethers from readily available bromoarenes.

Keywords Fluoroalkoxylation · Ligand-free catalysis · Unactivated aryl bromides · Copper(I) bromide · Aryl fluoroalkyl ethers

Introduction

Incorporation of various fluorinated moieties into organic molecules has been an attractive topic, due to the widespread applications of fluorine-containing compounds in materials science, agricultural chemicals and drug discovery [1–6]. In fact, substitution of hydrogen with fluorine will usually give rise to dramatic enhancement in the resulting compounds of physical, chemical and biological properties including solubility, lipophilicity, metabolic and oxidative stability, as well as bioavailability [7–10]. Remarkably, aryl fluoroalkyl ethers have emerged as common fluorinated building blocks in the pharmaceutical industry. For instance, trifluoroethoxylated aromatics have appeared in the commercial drugs with excellent metabolic stability and lipophilicity [11], such as the alpha

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1-adrenoreceptor antagonist silodosin [12], the atrial fibrillation therapeutic agent flecainide [13] and the proton pump inhibitor lansoprazole (Fig. 1) [14]. Furthermore, the compounds bearing aryl 2,2,3,3-tetrafluoropropyl ether moieties were disclosed as serotonin 5-HT6 antagonists [15] and cholesteryl ester transfer protein (CETP) inhibitors (Fig. 1) [16]. Therefore, the construction of aryl fluoroalkyl ethers has received considerable attention.

Owing to the unavoidable drawbacks involving cost, separation and pollution issues, substantial efforts have been devoted to approaches without the need for precious metals and organic ligands to the fluoroalkoxylated aromatics. Typically, fluoroalkyl sulfonates [15, 17] or halides [18, 19] as preinstalled electrophiles can easily condense with phenols to offer aryl fluoroalkyl ethers under basic conditions. Base-mediated nucleophilic reaction undergoing an aromatic SN1 mechanism between activated aryl halides and fluoroalkanols is another class of common methods [16, 20–22]. The use of prefunctionalized fluoroalkyl derivative and activated aryl halides greatly limits the substrate scope in the preparation of aryl ethers. In addition, the ligand-based copper-catalyzed etherifications of aryl halides and aryl trifluoroborate salts with fluoroalkanols also provide feasible access to fluoroethoxylated aromatics [23–25]. However, the employment of ligands, iodides or superstoichiometric fluoroalkanols raised the concerns of cost, separation and pollution.

In contrast, the ligand-free copper-catalyzed etherification strategies with stoichiometric fluoroalkanols are considered to be more economical in large-scale applications for fluoroalkoxylation of unactivated aryl bromides (no strong electron-withdrawing groups like NO₂, CN, CF₃, etc. on aromatic ring), due to less expensive substrates as well as omission of precious metals and organic ligands. Although having an example of ligand-free copper(I) iodide-catalyzed trifluoroethoxylation of iodobenzene [26], the use of iodides is still beyond our consideration. In this context, we report a practical and convenient ligand-free fluoroalkoxylation herein,



Fig. 1 Pharmaceutically active molecules bearing aryl fluoroalkyl ether moieties

which features the use of inexpensive aryl bromides and stoichiometric sodium fluoroalkoxides as reactants, along with copper(I) bromide as a catalyst and with *N*,*N*-dimethyl formamide (DMF) as a cocatalyst.

Results and discussion

Considering their high boiling points, troublesome workup and reproductive health hazards [27], the polar aprotic solvents DMF, *N*-methyl-2-pyrrolidinone (NMP) dimethylsulfoxide (DMSO) and hexamethylphosphoric triamide (HMPT) were only allowed as cocatalysts in the current study. Furthermore, DMF holding lower boiling point was preferentially used in the preliminary investigations [28, 29]. We commenced the optimization process with the trifluoroethoxylation of 1-bromo-3-methoxybenzene as a model reaction, employing copper(I) bromide (10 mol%) as a catalyst and DMF (1.5 equiv) as a cocatalyst under 110 °C (Table 1).

Firstly, the screening of solvents showed that acetonitrile worked poorly to provide the desired product **1** with 32 % yield (entry 1). Whereas, the ethereal solvent 2-methyltetrahydrofuran (2-MeTHF) proved to be a better choice furnishing **1** in 85 % yield (entry 2). Furthermore, tetrahydrofuran (THF) and 1,4-dioxane equally delivered excellent yield of 92 % (entries 3 and 4). Given better dissolving

	OCH ₃		Cu(I) salt (n ₁ mol%) DMF (n ₂ equiv)	OCH3	
	+ CF ₃ CH ₂ ONa Br		solvent (5 mL) 110 ^o C, T (h)	OCH ₂ CF ₃	
	model substrate	9		I	
Entry	Solvent	Cu salt $(n_1 \mod \%)$) DMF (n_2 equiv)	Time (h)	Yield (%) ^a
1	CH ₃ CN	CuBr (10)	1.5	6	32
2	2-MeTHF	CuBr (10)	1.5	6	85
3	THF	CuBr (10)	1.5	6	92
4	1,4-dioxane	CuBr (10)	1.5	6	92
5	1,4-dioxane	CuCl (10)	1.5	6	84
6 ^b	1,4-dioxane	CuBr (10)	1.5	6	90
7	1,4-dioxane	CuBr (10)	1.0	6	92
8	1,4-dioxane	CuBr (10)	0.75	6	78
9	1,4-dioxane	CuBr (8)	1.0	6	81
10	1,4-dioxane	CuBr (10)	1.0	5	88

Table 1 Optimization of the reaction conditions

Reaction conditions: a CF₃CH₂ONa solution [6.0 mmol, freshly prepared from CF₃CH₂OH (6.6 mmol) and Na (6.0 mmol) in solvent (5 mL)], 1-bromo-3-methoxybenzene (3.0 mmol), Cu(I) salt (n_1 mol%) and DMF (n_2 equiv) in a Teflon-lined sealed tube at 110 °C for specified time

Bold indicates the standard reaction condition

^a Isolated yield (%)

^b DMF replaced by NMP

capacity to the following sodium fluoroalkoxides, we gave preference to 1,4dioxane as the ideal solvent.

Afterwards, an attempt to replace copper(I) bromide by copper(I) chloride resulted in a diminished yield of 84 % (entry 5), indicating that copper(I) bromide possesses higher catalytic activity. Besides, a slightly reduced yield of 90 % was observed when using NMP as a cocatalyst instead of DMF (entry 6). The further survey of catalyst loadings identified the optimal amounts of copper(I) bromide and DMF at the levels of 10 mol% and 1.0 equiv, respectively (entry 7 vs. entries 8 and 9). Shortening reaction time to 5 h led to a slightly weakened efficiency (88 %, entry 10). On the basis of these results, the standard reaction conditions (entry 7) were established to probe the substrate scope of the fluoroalkoxylation.

Next, various commercially available unactivated aryl bromides and fluoroalkanols were assessed for this Ullmann-type C–O coupling reaction (Table 2). Primarily, with regard to the shortest carbon-chain trifluoroethanol, the substrates



Table 2	Substrate	scope	of the	fluoroalkoxylation
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Reaction conditions: a 1,4-dioxane solution of R_FONa [3.0(n + 1) mmol, freshly prepared from R_FOH (3.3(n + 1) mmol) and Na (3.0(n + 1) mmol) in 1,4-dioxane (5 mL)], ArBr_n (3.0 mmol), CuBr (0.3n mmol) and DMF (3.0n mmol) in a Teflon-lined sealed tube at 110 °C for 6 h

^a Isolated yield (%)

^b The substrate with phenolic hydroxyl group needing additional one equiv of R_FONa

containing both electron-donating and weak electron-withdrawing substituents all underwent the approach smoothly to achieve the corresponding products, with excellent yields of more than 90 % (1–6). A series of strong electron-donating substituents tending to impairment of the nucleophilic reaction, like methoxy, ethoxy and hydroxy groups, did not give rise to any detrimental influence. In all the cases, no significant amounts of byproducts were observed, validating an excellent functional group tolerance for this method. It was noteworthy that the dibromoarenes 2,4-dibromo-1-methoxybenzene and 2,6-dibromo-4-methylphenol also proceeded successfully to deliver the di-trifluoroethoxylated products with good yields of 85 and 86 %, respectively (7 and 8).

The scope of nucleophilic partners was further extended to sodium fluoropropoxides (9–16). Although 3,3,3-trifluoropropoxide anion owns the higher electron density at the oxygen atom and has stronger reductive ability to copper(I) ion among these fluoroalkoxide anions [28, 29], sodium 3,3,3-trifluoropropoxide was still compatible with the approach, offering the corresponding products in yields of 58 and 60 %, respectively (9 and 10). In contrast, for 2,2,3,3tetrafluoropropoxide anion owning lower electron density at the oxygen atom, the protocol efficiently submitted the tetrafluorinated ethers in excellent yields of 92–94 % with good functional group tolerance (11–15). These outcomes could illustrate the fact that sodium 2,2,3,3-tetrafluoropropoxide was more favorable to the fluoroalkoxylation than sodium 3,3,3-trifluoropropoxide, attributed to its distinct reductive capabilities to copper(I) ion [29]. Pleasingly, 2,4-dibromo-1-methoxybenzene was subjected to the di-2,2,3,3-tetrafluoropropoxylation, providing the target compound 16 in good yield of 83 %.

Finally, the fluoroalkanol containing five carbon atoms was investigated. With regard to the highly fluorinated sodium 2,2,3,3,4,4,5,5-octafluoropentyloxide, the bromoarenes smoothly suffered from the protocol to attain the octafluorinated ethers with satisfactory yields of 72 and 85 %, respectively (**17** and **18**). It was noted that the increase of alkoxide carbon chain would impair the reaction outcome. Obviously, weak electron-withdrawing substituent was liable to the reaction in comparison with electron-donating substituent (**18** vs. **17**).

Flecainide has clinically served as a classical anti-arrhythmic agent [13]. To evaluate the synthetic utility of this protocol, the synthesis of the key intermediate of flecainide, 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid (22, Scheme 1), was carried out on a multigram scale through a new route by virtue of our method. Gratifyingly, the commercially inexpensive 1,4-dibromobenzene (19) underwent the crucial difluoroalkoxylation to accomplish the fluorinated product 20 with good yield of



Scheme 1 Synthesis of the key intermediate of flecainide on a multigram scale

82 %. Then, the acylation of **20** presented a usual yield of 83 % to the acetophenones **21**, which was followed by the haloform reaction to efficiently access the desired product **22** at 89 % yield. Impressively, this ligand-free protocol unfolded a potential practicality for convenient preparation of high-value aryl fluoroalkyl ether derivatives.

Conclusion

In summary, we have developed a ligand-free transition metal-catalyzed fluoroalkoxylation of unactivated aryl bromides, utilizing inexpensive copper(I) bromide as a catalyst and DMF as a co-catalyst. The sustainable reaction is characterized by operational simplicity and reagent economy. Its synthetic utility was highlighted by a multigram-scale preparation of the key intermediate of flecainide. We anticipate that the approach developed here will provide a useful tool in academia and industry.

Experimental

Unless otherwise indicated, all reagents were obtained from commercial sources and used as received without further purification. All reactions were carried out in a Teflon-lined, stainless steel, sealed tube or autoclave. All solvents were only dried over 4 Å molecular sieves. Reaction products were purified via column chromatography on silica gel (300–400 mesh). Melting points were determined using an open capillaries and uncorrected. Nuclear magnetic resonance (NMR) spectra were determined on a Bruker AV400 in CDCl₃ or DMSO- d_6 with TMS as internal standard for ¹H NMR (400 MHz), ¹³C NMR (100 MHz) and ¹⁹F NMR (376 MHz), respectively. HRMS were measured on a QSTAR Pulsar I LC/TOF MS mass spectrometer or Micromass GCTTM gas chromatograph-mass spectrometer.

General fluoroalkoxylation procedure (Table 2)

The Teflon-lined sealed tube (20 mL) was charged with a 1,4-dioxane solution of sodium fluoroalkoxide R_FONa [freshly prepared from fluoroalkanol R_FOH (3.3 (n + 1) mmol) and Na (3.0 (n + 1) mmol) in 1,4-dioxane (5 mL)], unactivated aryl bromide ArBr_n (3.0 mmol), CuBr (0.3*n* mmol) and DMF (3.0*n* mmol). The sealed tube was heated to 110 °C and stirred for 6 h. After the completion of reaction, the concentration of the mixture in vacuo gave a residue, to which was added methyl *tert*-butyl ether (MTBE, 20 mL) and diluted hydrochloric acid (10 mL, 1.0 mol/L). The organic phase was separated, and the aqueous phase was extracted with MTBE (10 mL × 3). The combined organic layer was dried over anhydrous MgSO₄, and then concentrated in vacuo to supply a crude product. Lastly, the purification of the crude product provided the desired product via column chromatography on silica gel (eluents: petroleum ether/ethyl acetate 20:1).

1-methoxy-3-(2,2,2-trifluoroethoxy)benzene (1)

Pale yellow oil, 0.57 g (92 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 3.80 (s, 3H, OCH₃), 4.33 (q, ³J_{HF} = 8.0 Hz, 2H, CH₂), 6.51–6.54 (m, 2H, Ar), 6.59–6.63 (dd, J = 8.8 Hz, 2.4, 1H, Ar), 7.20–7.25 (m, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 55.3, 65.8 (q, ²J_{CF} = 35.5 Hz), 101.6, 106.6, 108.2, 123.4 (q, ¹J_{CF} = 276.3 Hz), 130.2, 158.6, 161.0; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -74.0 (t, ³J_{HF} = 8.2 Hz, 3F); HRMS (EI): m/z [M⁺] calcd. for C₉H₉O₂F₃ 206.0555, found 206.0551.

1-ethoxy-4-(2,2,2-trifluoroethoxy)benzene (2)

Pale yellow oil, 0.60 g (91 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 1.40 (t, J = 6.8 Hz, 3H, CH₃), 3.99 (q, J = 6.8 Hz, 2H, CH₂), 4.29 (q, ³ $J_{HF} = 8.0$ Hz, 2H, CH₂), 6.86 (q, J = 8.8 Hz, 4H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 14.9, 64.0, 67.0 (q, ² $J_{CF} = 35.1$ Hz), 115.5 (2C), 116.4 (2C), 123.4 (q, ¹ $J_{CF} = 276.7$ Hz), 151.6, 154.5; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -74.1 (t, ³ $J_{HF} = 8.2$ Hz, 3F); HRMS (EI): m/z [M⁺] calcd. for C₁₀H₁₁O₂F₃ 220.0711, found 220.0713.

2,4-dimethyl-1-(2,2,2-trifluoroethoxy)benzene (3)

Pale yellow oil, 0.56 g (92 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 2.23 (s, 3H, CH₃), 2.28 (s, 3H, CH₃), 4.32 (q, ³J_{HF} = 8.0 Hz, 2H, CH₂), 6.69 (d, J = 8.0 Hz, 1H, Ar), 6.96 (d, J = 8.0 Hz, 1H, Ar), 6.99 (s, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 15.8, 20.5, 66.5 (q, ²J_{CF} = 35.1 Hz), 112.1, 123.6 (q, ¹J_{CF} = 276.4 Hz), 127.1, 127.4, 131.7, 132.0, 153.7; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -74.2 (t, ³J_{HF} = 8.2 Hz, 3F); HRMS (EI): m/z [M⁺] calcd. for C₁₀H₁₁OF₃ 204.0762, found 204.0761.

1-methoxy-4-methyl-2-(2,2,2-trifluoroethoxy)benzene (4)

Pale yellow oil, 0.61 g (93 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 2.28 (s, 3H, CH₃), 3.84 (s, 3H, CH₃), 4.38 (q, ³*J*_{HF} = 8.4 Hz, 2H, CH₂), 6.82–6.86 (m, 3H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 20.6, 56.1, 68.1 (q, ²*J*_{CF} = 34.7 Hz), 112.7, 118.7, 123.6 (q, ¹*J*_{CF} = 277.0 Hz), 124.3, 130.7, 146.8, 148.3; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -74.1 (t, ³*J*_{HF} = 8.2 Hz, 3F); HRMS (EI): *m/z* [M⁺] calcd. for C₁₀H₁₁O₂F₃ 220.0711, found 220.0712.

4-methyl-2-(2,2,2-trifluoroethoxy)phenol (5)

Pale yellow oil, 0.57 g (93 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 2.29 (s, 3H, CH₃), 4.40 (q, ³J_{HF} = 8.0 Hz, 2H, CH₂), 5.35 (br s, 1H, OH), 6.68 (s, 1H, Ar), 6.77 (d, J = 8.0 Hz, 1H, Ar), 6.87 (d, J = 8.0 Hz, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 20.9, 60.8 (q, ²J_{CF} = 35.6 Hz), 113.7, 115.5, 123.2 (q, ¹J_{CF} = 276.4 Hz), 123.9, 130.0, 143.6, 144.2; ¹⁹F NMR (376 MHz, CDCl₃), δ

(ppm): -74.1 (t, ${}^{3}J_{\rm HF} = 8.2$ Hz, 3F); HRMS (EI): m/z [M⁺] calcd. for C₉H₉O₂F₃ 206.0555, found 206.0553.

1-chloro-4-(2,2,2-trifluoroethoxy)benzene (6)

White solid, 0.59 g (94 %), m.p. 31–33 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 4.32 (q, ³*J*_{HF} = 8.0 Hz, 2H, CH₂), 6.88 (d, *J* = 8.0 Hz, 2H, Ar), 7.28 (d, *J* = 8.0 Hz, 2H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 66.1 (q, ²*J*_{CF} = 35.6 Hz), 116.3 (2C), 123.2 (q, ¹*J*_{CF} = 276.4 Hz), 127.6, 129.7 (2C), 156.0; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -74.0 (t, ³*J*_{HF} = 8.2 Hz, 3F); HRMS (EI): *m/z* [M⁺] calcd. for C₈H₆ClOF₃ 210.0059, found 210.0061.

1-methoxy-2,4-bis(2,2,2-*trifluoroethoxy*)*benzene* (7)

Pale yellow oil, 0.77 g (85 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 3.84 (s, 3H, CH₃), 4.29 (q, ³*J*_{HF} = 8.0 Hz, 2H, CH₂), 4.39 (q, *J*_{HF} = 8.4 Hz, 2H, CH₂), 6.60 (d, *J* = 8.8 Hz, 1H, Ar), 6.67 (s, 1H, Ar), 6.86 (d, *J* = 8.8 Hz, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 56.5, 66.7 (q, ²*J*_{CF} = 35.3 Hz), 67.9 (q, ²*J*_{CF} = 35.1 Hz), 106.6, 109.0, 113.4, 123.3 (q, ¹*J*_{CF} = 276.5 Hz), 123.4 (q, ¹*J*_{CF} = 276.9 Hz), 146.0, 147.7, 151.7; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -74.1 to -74.0 (m, 6F); HRMS (EI): *m/z* [M⁺] calcd. for C₁₁H₁₀O₃F₆ 304.0534, found 304.0535.

4-methyl-2,6-bis(2,2,2-trifluoroethoxy)phenol (8)

White solid, 0.77 g (86 %), m.p. 49–51 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 2.27 (s, 3H, CH₃), 4.42 (q, ³*J*_{HF} = 8.0 Hz, 4H, CH₂), 5.32 (br s, 1H, OH), 6.52 (s, 2H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 21.1, 67.5 (q, ²*J*_{CF} = 35.3 Hz, 2C), 111.2 (2C), 123.3 (q, ¹*J*_{CF} = 276.7 Hz, 2C), 129.5, 134.6, 145.3 (2C); ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -74.2 (t, ³*J*_{HF} = 8.2 Hz, 6F); HRMS (ESI): *m/z* [M–H]⁻ calcd. for C₁₁H₉O₃F₆ 303.0456, found 303.0446.

1-methoxy-3-(3,3,3-trifluoropropoxy)benzene (9)

Pale yellow oil, 0.38 g (58 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 2.56–2.68 (m, 2H, CH₂), 3.80 (s, 3H, CH₃), 4.18 (t, ³J_{HF} = 6.8 Hz, 2H, CH₂), 6.46 (s, 1H, Ar), 6.48 (d, J = 8.4 Hz, 1H, Ar), 6.55 (d, J = 8.4 Hz, 1H, Ar), 7.20 (t, J = 8.4 Hz, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 34.1 (q, ²J_{CF} = 28.7 Hz), 55.3, 60.9 (q, ³J_{CF} = 3.7 Hz), 101.2, 106.5, 107.0, 125.9 (q, ¹J_{CF} = 275.0 Hz), 130.0, 159.3, 160.9; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -74.1 (t, ³J_{HF} = 8.2 Hz, 6F); HRMS (EI): m/z [M⁺] calcd. for C₁₀H₁₁O₂F₃ 220.0711, found 220.0712.

1-ethoxy-4-(3,3,3-trifluoropropoxy)benzene (10)

Pale yellow oil, 0.42 g (60 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 1.39 (t, J = 7.0 Hz, 3H, CH₃), 2.53–2.66 (m, 2H, CH₂), 3.98 (q, ³ $J_{HF} = 6.8$ Hz, 2H, CH₂),

4.15 (t, J = 7.0 Hz, 2H, CH₂), 6.83 (s, 4H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 14.9, 34.1 (q, ² $J_{CF} = 28.5$ Hz), 61.7 (q, ³ $J_{CF} = 3.6$ Hz), 64.0, 115.5 (2C), 115.7 (2C), 126.0 (q, ¹ $J_{CF} = 274.9$ Hz), 152.1, 153.7; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -64.7 (t, ³ $J_{HF} = 10.9$ Hz, 3F); HRMS (EI): m/z [M⁺] calcd. for C₁₁H₁₃O₂F₃ 234.0868, found 234.0869.

1-methoxy-3-(2,2,3,3-tetrafluoropropoxy)benzene (11)

Pale yellow oil, 0.66 g (92 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 3.80 (s, 3H, CH₃), 4.33 (t, ³J_{HF} = 11.6 Hz, 2H, CH₂), 6.07 (t, ²J_{HF} = 49.6 Hz, 1H, CHF₂), 6.49 (s, 1H, Ar), 6.51 (d, J = 8.4 Hz, 1H, Ar), 6.61 (d, J = 8.4 Hz, 1H, Ar), 6.86 (t, J = 8.4 Hz, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 55.4, 65.3 (t, ²J_{CF} = 29.7 Hz), 101.4, 106.5, 108.1, 109.0 (tt, ¹J_{CF} = 248.4 Hz, ²J_{CF} = 33.9 Hz), 114.6 (tt, ¹J_{CF} = 248.6 Hz, ²J_{CF} = 26.7 Hz), 130.2, 158.5, 161.0; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -139.6 (dt, ²J_{HF} = 53.0 Hz, ³J_{FF} = 3.8 Hz, 2F), -125.4 to -125.3 (m, 2F); HRMS (EI): *m*/*z* [M⁺] calcd. for C₁₀H₁₀O₂F₄ 238.0617, found 238.0618.

1-ethoxy-4-(2,2,3,3-tetrafluoropropoxy)benzene (12)

Pale yellow oil, 0.70 g (93 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 1.40 (t, J = 6.8 Hz, 3H, CH₃), 3.99 (q, J = 6.8 Hz, 2H, CH₂), 4.29 (t, ³ $J_{\rm HF} = 12.0$ Hz, 2H, CH₂), 6.06 (tt, ² $J_{\rm HF} = 53.2$ Hz, ³ $J_{\rm HF} = 4.8$ Hz, 1H, CHF₂), 6.85 (s, 4H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 14.9, 64.0, 66.3 (t, ² $J_{\rm CF} = 29.7$ Hz), 109.1 (tt, ¹ $J_{\rm CF} = 248.2$ Hz, ² $J_{\rm CF} = 33.9$ Hz), 114.6 (tt, ¹ $J_{\rm CF} = 248.4$ Hz, ² $J_{\rm CF} = 26.7$ Hz), 115.5 (2C), 116.0 (2C), 151.5, 154.4; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -139.7 (dt, ² $J_{\rm HF} = 53.0$ Hz, ³ $J_{\rm FF} = 3.8$ Hz, 2F), -125.5 to -125.4 (m, 2F); HRMS (EI): m/z [M⁺] calcd. for C₁₁H₁₂O₂F₄ 252.0773, found 252.0775.

1-methoxy-4-methyl-2-(2,2,3,3-tetrafluoropropoxy)-benzene (13)

Pale yellow oil, 0.69 g (92 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 2.28 (s, 3H, CH₃), 3.83 (s, 3H, CH₃), 4.36 (t, ³J_{HF} = 12.0 Hz, 2H, CH₂), 6.17 (t, ²J_{HF} = 53.2 Hz, 1H, CHF₂), 6.76–6.85 (m, 3H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 20.6, 56.0, 67.7 (t, ²J_{CF} = 29.4 Hz), 109.1 (tt, ¹J_{CF} = 248.0 Hz, ²J_{CF} = 33.1 Hz), 112.6, 114.6 (tt, ¹J_{CF} = 248.9 Hz, ²J_{CF} = 26.3 Hz), 117.9, 124.1, 130.7, 146.8, 148.2; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -139.7 (dt, ²J_{HF} = 53.0 Hz, ³J_{FF} = 3.8 Hz, 2F), -125.6 to -125.5 (m, 2F); HRMS (EI): *m*/z [M⁺] calcd. for C₁₁H₁₂O₂F₄ 252.0773, found 252.0777.

4-ethyl-2-(2,2,3,3-tetrafluoropropoxy)phenol (14)

Pale yellow oil, 0.70 g (93 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 1.21 (t, J = 7.6 Hz, 3H, CH₃), 2.58 (q, J = 7.6 Hz, 2H, CH₂), 4.43 (t, ³ $J_{\rm HF} = 12.0$ Hz, 2H, CH₂), 5.30 (br s, 1H, OH), 6.00 (tt, ² $J_{\rm HF} = 53.2$ Hz, ³ $J_{\rm HF} = 3.6$ Hz, 1H, CHF₂), 6.73 (d, J = 1.6 Hz, 1H, Ar), 6.80 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.6$ Hz, 1H, Ar), 6.89 (d,

 $J = 8.4 \text{ Hz}, 1\text{H}, \text{Ar}); {}^{13}\text{C} \text{ NMR} (100 \text{ MHz}, \text{CDCl}_3), \delta \text{ (ppm)}: 15.8, 28.4, 66.1 (t, {}^{2}J_{\text{CF}} = 28.6 \text{ Hz}), 109.5 (tt, {}^{1}J_{\text{CF}} = 248.7 \text{ Hz}, {}^{2}J_{\text{CF}} = 36.5 \text{ Hz}), 112.7, 114.4 (tt, {}^{1}J_{\text{CF}} = 248.4 \text{ Hz}, {}^{2}J_{\text{CF}} = 27.9 \text{ Hz}), 115.5, 122.7, 136.8, 143.7, 144.4; {}^{19}\text{F} \text{ NMR} (376 \text{ MHz}, \text{CDCl}_3), \delta \text{ (ppm)}: -139.5 (dt, {}^{2}J_{\text{HF}} = 53.0 \text{ Hz}, {}^{3}J_{\text{FF}} = 4.0 \text{ Hz}, 2\text{F}), -125.5 \text{ to} -125.4 (m, 2\text{F}); \text{HRMS} (\text{ESI}): m/z \text{ [M-H]}^{-} \text{ calcd. for C}_{11}\text{H}_{11}\text{O}_2\text{F}_4 251.0695, \text{ found } 251.0676.$

1-chloro-4-(2,2,3,3-tetrafluoropropoxy)benzene (15)

Pale yellow oil, 0.68 g (94 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 4.32 (tt, ³*J*_{HF} = 12.0 Hz, ⁴*J*_{HF} = 1.6 Hz, 2H, CH₂), 6.04 (tt, ²*J*_{HF} = 52.8 Hz, ³*J*_{HF} = 4.8 Hz, 1H, CHF₂), 6.87 (dt, *J*₁ = 3.6 Hz, *J*₂ = 8.8 Hz, 2H, Ar), 7.28 (dt, *J*₁ = 3.6 Hz, *J*₂ = 8.8 Hz, 2H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 65.5 (t, ²*J*_{CF} = 29.6 Hz), 109.0 (tt, ⁻¹*J*_{CF} = 248.4 Hz, ⁻²*J*_{CF} = 34.4 Hz), 114.4 (tt, ¹*J*_{CF} = 248.7 Hz, ²*J*_{CF} = 27.0 Hz), 116.1 (2C), 127.6, 129.7 (2C), 156.0; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -139.3 (dt, ²*J*_{HF} = 53.0 Hz, ³*J*_{FF} = 4.0 Hz, 2F), -125.0 to -124.9 (m, 2F); HRMS (EI): *m*/*z* [M⁺] calcd. for C₉H₇ClOF₄ 242.0122, found 242.0121.

1-methoxy-2,4-bis(2,2,3,3-tetrafluoropropoxy)benzene (16)

Pale yellow solid, 0.92 g (83 %), m.p. 29–31 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 3.82 (s, 3H, CH₃), 4.29 (t, ³J_{HF} = 12.0 Hz, 2H, CH₂), 4.37 (t, ³J_{HF} = 12.0 Hz, 2H, CH₂), 6.04 (tt, ²J_{HF} = 53.2 Hz, ³J_{HF} = 4.8 Hz, 1H, CHF₂), 6.13 (tt, ²J_{HF} = 53.2 Hz, ³J_{HF} = 4.8 Hz, 1H, CHF₂), 6.57 (dd, J₁ = 8.8 Hz, J₂ = 2.4 Hz, 1H, Ar), 6.60 (d, J = 2.4 Hz, 1H, Ar), 6.85 (d, J = 8.8 Hz, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 56.5, 66.1 (t, ²J_{CF} = 29.5 Hz), 67.4 (t, ²J_{CF} = 29.3 Hz), 105.7, 108.2, 109.1 (tt, ¹J_{CF} = 248.1 Hz, ²J_{CF} = 34.0 Hz, 2C), 113.2, 114.5 (tt, ¹J_{CF} = 248.7 Hz, ²J_{CF} = 26.7 Hz), 114.6 (tt, ¹J_{CF} = 248.8 Hz, ²J_{CF} = 26.6 Hz), 145.9, 147.8, 151.6; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -139.8 (dt, ²J_{HF} = 53.0 Hz, ³J_{FF} = 4.1 Hz, 2F), -139.3 (dt, ²J_{HF} = 53.0 Hz, ³J_{FF} = 4.0 Hz, 2F), -125.6 to -125.5 (m, 2F), -125.1 to -125.0 (m, 2F); HRMS (EI): m/z [M⁺] calcd. for C₁₃H₁₂O₃F₈ 368.0659, found 368.0660.

1-methoxy-3-((2,2,3,3,4,4,5,5-octafluoropentyl)oxy)-benzene (17)

Pale yellow oil, 0.73 g (72 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 3.84 (s, 3H, CH₃), 4.48 (t, ³*J*_{HF} = 12.8 Hz, 2H, CH₂), 6.04 (tt, ²*J*_{HF} = 52.0 Hz, ³*J*_{HF} = 5.6 Hz, 1H, CHF₂), 6.54–6.58 (m, 2H, Ar), 6.63–6.67 (m, 1H, Ar), 7.24–7.30 (m, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 55.4, 65.1 (t, ²*J*_{CF} = 26.4 Hz), 101.6, 107.0, 107.6 (t, ²*J*_{CF} = 30.0 Hz), 108.2, 110.0 (d, ²*J*_{CF} = 30.7 Hz), 112.2 (d, ²*J*_{CF} = 30.5 Hz), 114.9 (t, ²*J*_{CF} = 30.9 Hz), 130.2, 158.6, 161.0; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): –137.3 to –137.1 (m, 2F), –130.3 to –130.2 (m, 2F), –125.3 (quint, ³*J*_{FF} = 8.2 Hz, 2F), –119.8 to –119.7 (m, 2F); HRMS (EI): *m*/ z [M⁺] calcd. for C₁₂H₁₀O₂F₈ 338.0553, found 338.0555.

1-chloro-4-((2,2,3,3,4,4,5,5-octafluoropentyl)oxy)ben-zene (18)

Pale yellow oil, 0.87 g (85 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 4.44 (t, ³*J*_{HF} = 12.8 Hz, 2H, CH₂), 6.08 (tt, ²*J*_{HF} = 52.0 Hz, ³*J*_{HF} = 5.6 Hz, 1H, CHF₂), 6.89 (d, *J* = 8.8 Hz, 2H, Ar), 7.29 (d, *J* = 8.8 Hz, 2H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 65.5 (t, ²*J*_{CF} = 26.7 Hz), 104.9 (t, ²*J*_{CF} = 27.9 Hz), 107.6 (t, ²*J*_{CF} = 31.0 Hz), 110.1 (d, ²*J*_{CF} = 27.2 Hz), 114.6 (d, ²*J*_{CF} = 21.1 Hz), 116.3 (2C), 127.7, 129.7 (2C), 156.1; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -137.3 to -137.1 (m, 2F), -130.1 to -130.0 (m, 2F), -125.2 (quint, ³*J*_{FF} = 8.2 Hz, 2F), -119.8 to -119.7 (m, 2F); HRMS (EI): *m/z* [M⁺] calcd. for C₁₁H₇ClOF₈ 342.0058, found 342.0057.

Procedure for the synthesis of the key intermediate of flecainide on a multigram scale (Scheme 1)

1,4-bis(2,2,2-trifluoroethoxy)benzene (20)

The Teflon-lined autoclave (100 mL) was charged with CF₃CH₂ONa [freshly prepared from CF₃CH₂OH (3.58 mL, 1.382 g/mL, 49.5 mmol) and Na (1.04 g, 45 mmol) in 1,4-dioxane (35 mL)], CuBr (0.43 g, 3.0 mmol), DMF (2.3 mL, 0.944 g/mL, 30 mmol) and 1-bromo-3-methoxybenzene (19, 3.54 g, 15 mmol). The autoclave was heated to 110 °C and stirred for 6 h. After the completion of reaction, the mixture was concentrated in vacuo to give a residue. Diethyl ether (50 mL) and diluted hydrochloric acid (1.6 M, 50 mL) were added to the residue. The organic phase was separated, and the aqueous phase was extracted with diethyl ether $(20 \text{ mL} \times 3)$. The combined organic layer was dried over anhydrous MgSO₄, and then concentrated in vacuo to supply a crude product, which was separated via column chromatography on a silica gel (eluents: petroleum ether/ethyl acetate 20:1) to provide the desired product **20**. White solid, 3.37 g (82 %), m.p. 76–78 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 4.31 (q, ${}^{3}J_{HF} = 8.4$ Hz, 4H, CH₂), 6.91 (s, 4H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 66.8 (q, ² J_{CF} = 35.5 Hz, 2C), 116.4 (4C), 123.3 (q, ¹ J_{CF} = 276.6 Hz, 2C), 152.9 (2C); ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -74.1 (t, ${}^{3}J_{HF} = 8.2$ Hz, 6F); HRMS (EI): m/z [M⁺] calcd. for C₁₀H₈O₂F₆ 274.0428, found 274.0430.

1-(2,5-bis(2,2,2-trifluoroethoxy)phenyl)ethanone (21)

A three-necked flask was charged with the above product **20** (3.37 g, 12.3 mmol), anhydrous AlCl₃ (3.28 g, 24.6 mmol) and dichloromethane (DCM, 15 mL). Acetyl chloride (1.05 mL, 1.11 g/mL, 14.8 mmol) was added dropwise to the mixture at 0 °C. Then the mixture was further stirred at room temperature for 6 h. After completion of the reaction, the mixture was poured into diluted hydrochloric acid (1.6 M, 20 mL) at 0 °C. The organic phase was separated and the aqueous phase was extracted with DCE (10 mL \times 3). The combined organic layer was washed with brine (30 mL), dried over anhydrous MgSO₄, and then concentrated in vacuo to supply a crude product, which was separated via column chromatography on a

silica gel (eluents: petroleum ether/ethyl acetate 15:1) to provide the desired product **21**. White solid, 3.21 g (83 %), m.p. 91–92 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 2.64 (s, 3H, CH₃), 4.35 (q, ³J_{HF} = 8.4 Hz, 2H, CH₂), 4.42 (q, ³J_{HF} = 8.4 Hz, 2H, CH₂), 6.88 (d, J = 8.8 Hz, 1H, Ar), 7.13 (dd, J_1 = 8.8 Hz, J_2 = 3.2 Hz, 1H, Ar), 7.37 (d, J = 3.2 Hz, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 31.7, 66.1 (q, ²J_{CF} = 30.0 Hz), 66.8 (q, ²J_{CF} = 29.7 Hz), 114.4, 115.7, 121.5, 123.0 (q, ¹J_{CF} = 276.3 Hz), 123.2 (q, ¹J_{CF} = 276.6 Hz), 129.2, 151.7, 152.5, 197.8; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -74.0 (t, ³J_{HF} = 8.0 Hz, 3F), -73.6 (t, ³J_{HF} = 8.2 Hz, 3F); HRMS (ESI): *m*/z [M + Na⁺] calcd. for C₁₂H₁₀O₃F₆Na 339.0432, found 339.0435.

2,5-bis(2,2,2-trifluoroethoxy)benzoic acid (22)

A three-necked flask was charged with the above product 21 (3.21 g, 10.2 mmol), NaOH (0.61 g, 15.3 mmol) and water (15 mL), then the mixture was heated to 95 °C. To the mixture, aqueous sodium hypochlorite solution (45 g, 10 %, 61.2 mmol) was added dropwise over 1 h. Subsequently, the mixture was further stirred for 8 h at 95 °C. After completion of the reaction, the mixture was cooled to room temperature and hydrochloric acid (1.6 mL, 30 %) was added to give a precipitation. The precipitation was washed with water, and then dried in vacuo at 50 °C to supply the desired product 22. White solid, 2.89 g (89 %), m.p. 122–123 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 4.39 (q, ³J_{HF} = 8.0 Hz, 2H, CH₂), 4.51 (q, ${}^{3}J_{\text{HF}} = 8.0$ Hz, 2H, CH₂), 7.05 (d, J = 9.2 Hz, 1H, Ar), 7.21 (dd, $J_1 = 9.2$ Hz, $J_2 = 3.2$ Hz, 1H, Ar), 7.66 (d, J = 3.2 Hz, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 66.4 (q, ²J_{CF} = 35.7 Hz), 68.5 (q, ²J_{CF} = 35.6 Hz), 117.8, 118.0, 120.8, 122.7, 122.8 (q, ${}^{1}J_{CF} = 276.8$ Hz), 123.0 (q, ${}^{1}J_{CF} = 276.4$ Hz), 152.4, 153.1, 166.9; ¹⁹F NMR (376 MHz, CDCl₃), δ (ppm): -74.1 (t, ${}^{3}J_{\text{HF}} = 8.2 \text{ Hz}, 3\text{F}$, -73.5 (t, ${}^{3}J_{\text{HF}} = 8.2 \text{ Hz}, 3\text{F}$); HRMS (ESI): m/z [M + Na⁺] calcd. for C₁₁H₈O₄F₆Na 341.0224, found 341.0226.

Acknowledgments The authors are grateful to the National Natural Science Foundation of China (Project Nos. 21176074 and 21476074), and the Research Fund for the Doctoral Program of Higher Education of China (Project No. 20130074110009) for financial support.

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