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Facile Access to Fluorinated Aryl and Vinyl Ethers through Copper-Catalysed Reaction of Fluoro Alcohols

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Fluorinated alcohols react with aryl and vinyl halides by copper-catalysed cross-coupling reactions to afford the corresponding ethers. With trifluoroethanol (TFE) the reaction proceeds with both iodides and bromides and a wide range of aromatic substituents are tolerated. When higher fluorinated homologues such as $C_7F_{15}CH_2OH$ were used, the corresponding products were obtained in good yields, thus offering an interesting entry to fluorous tagging.

Introduction

Fluorinated molecules find widespread applications in numerous areas, for example, in materials science,[1] agrochemistry[2] and pharmaceuticals.[3] In recent years, trifluoroethyl aryl ethers have emerged as useful groups and are present in some important drugs described in the pharmacopoeia, such as Silodosin, Flecainide or the blockbuster drug Lansoprazole.[3] In fact, Lansoprazole differs from the original proton pump inhibitor Omeprazole largely by the replacement of an ethoxy group by a trifluorinated analogue (Figure 1).[4] It is generally acknowledged that CF_3CH_2O brings metabolic stability and lipophilicity.[3,5] On the other hand, it has also been recently reported that trifluoroethoxy-coated phthalocyanines are promising candidates for the development of phototherapeutic drugs.[6]

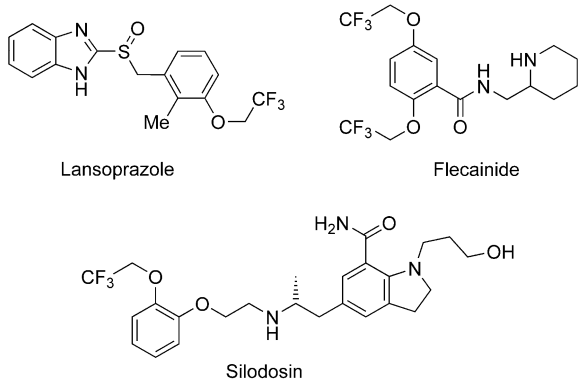

Figure 1. Examples of drugs with the trifluoroethoxyarene motif.

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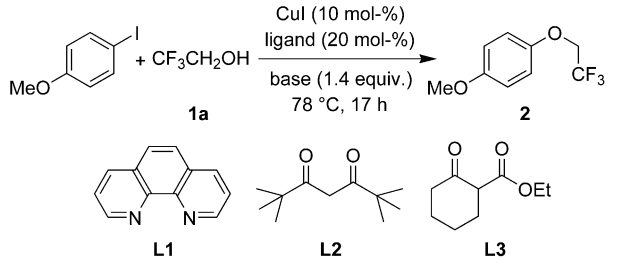
The main method used to attach a trifluoroethoxy moiety onto an arene involves the nucleophilic addition of a phenol onto a trifluoroethyl electrophile, such as trifluoroethyl iodide[7] or trifluoroethyl mesylate,[8] the latter being prepared from trifluoroethanol (TFE). In these reports, reactions proceed at elevated temperatures in DMSO or HMPA. An interesting alternative approach would involve a reaction in which trifluoroethanol is coupled to aromatic halides.[9] Such a pathway has two main advantages: TFE can be purchased in bulk quantities and there is a wide range of aryl halides commercially available, or easily accessible. Since the pioneering work of Ullmann, who reported the copper-promoted cross-coupling of phenols with aryl halides,[10] several efficient catalytic methods have been reported in recent years with palladium,[11] copper[12] and iron[13] complexes.[14] Furthermore, the scope of the reaction has been successfully extended to aliphatic alcohols,[15] and there are also some rare examples in which the latter also react with vinyl partners to afford enol ethers.[16] Although two articles have described the synthesis of trifluoroethyl aryl ethers from aryl halides and TFE, they both reported harsh conditions (with an excess of copper salt in hot HMPT on one hand[17] and a temperature of 110 °C for 5 d on the other[18]), probably due to the poor nucleophilicity of the fluorinated alcohol. Thus, there is still a need for mild and efficient reaction conditions. In this context, we now report on a general process for the synthesis of aryl and vinyl trifluoroethyl ethers by copper catalysis, as well as its extension to higher fluorinated homologues.

Results and Discussion

In recent years, Buchwald has described the cross-coupling reaction of aliphatic alcohols with aryl iodides using copper(I) iodide as a catalyst precursor, 1,10-phenanthrolines as ligands and caesium carbonate as a base.[15c,15d]

Thus, we started our investigations by treating 4-iodoanisole with trifluoroethanol (**1a**) in excess (7 equiv.) without solvent at the reflux temperature of TFE (78 °C) with CuI/phenanthroline (**L1**) as catalyst and Cs_2CO_3 as base (Table 1, entry 1). After 17 h, 75% conversion to the product **2** was obtained. The replacement of **L1** by dicarbonyl ligands **L2** and **L3** gave superior results with complete conversion of the starting iodide (entries 2 and 3). Our attempts to decrease the amount of trifluoroethanol failed: with 4 equiv., only 80% conversion was afforded. Further experiments showed that, as previously reported, the base Cs_2CO_3 was also essential for the success of the reaction (entries 5–7).

Table 1. Optimization of the reaction conditions for the Cu-catalysed cross-coupling between TFE (**1a**) and 4-iodoanisole.



Entry	Ligand	TFE [equiv.]	Base	% Conversion[a]
1	**L1**	7	Cs_2CO_3	75
2	**L2**	7	Cs_2CO_3	100
3	**L3**	7	Cs_2CO_3	100
4	**L3**	4	Cs_2CO_3	80
5	**L3**	7	K_2CO_3	12
6	**L3**	7	K_3PO_4	0
7	**L3**	7	*t*BuONa	0

[a] The conversion was monitored by ^{1}H NMR spectroscopy.

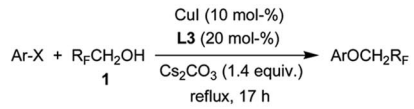
From these optimal conditions (CuI, **L3**, Cs_2CO_3 and 7 equiv. of TFE at reflux), the scope of the reaction was studied by varying the structure of the arene partner. The results are presented in Table 2. Under these conditions, iodobenzene also reacted very well (72% yield, entry 1). As reported above, 4-iodoanisole underwent complete conversion and **2** was isolated in 86% yield (entry 2). Aryl bromides were also excellent coupling partners: 4-bromoanisole reacted in the same way as its iodo analogue (85% yield, entry 3), although it has been reported that bromide substrates require much harsher conditions or did not even react with aliphatic alcohols.[15d] In contrast, with 4-chloroanisole no transformation occurred (entry 4). Various aryl iodides were then assessed and it was revealed that many substituents were very well tolerated. Thus, with *ortho*-methyl and -methoxy substituents, the desired products were obtained in good yields (67 and 83%, entries 5 and 6, respectively), whereas with *m*-CF_3, the yield was only moderate (60%, entry 7). Electron-poor 4-iodonitrobenzene also afforded the coupled product in an excellent 93% yield (entry 8). In addition, in contrast to the results of a previous report,[15d] the reaction with bromobenzonitrile did not require special care to avoid hydrolysis of the CN group, and thus **8** was isolated in 60% yield under the usual conditions (entry 9). Moreover, the nature of the aromatic ring itself can also be changed, as shown by the formation of 3-(trifluoroethoxy)pyridine (80% yield, entry 10). Finally, we focussed our attention on the preparation of bis(trifluoroethoxy)benzene from which the synthesis of the antiarrhythmic drug Flecainide (Flécaine™, Tambocor™) has been reported.[19] Thus, with twice the quantity of TFE (14 equiv.), diiodobenzene reacted at both halogen sites to afford the target molecule **10** in a good 75% yield (entry 11).

Next, because the length of a fluorinated chain can influence the properties of the molecule to which it is bonded, the scope of this reaction was explored with higher fluorinated homologues of TFE: 1,1-H-pentafluoropropanol (**1b**) and 1,1-H-perfluorooctanol (**1c**). Owing to the nature of the alcohols **1b** and **1c** (price and availability), the reaction conditions were slightly modified. Thus, by using 3 equiv. of **1b** (instead of 7 equiv. of **1a**) under the catalytic conditions used for **1a** the aryl ether products **11** and **12** were obtained in good yields (63 and 75%, respectively, entries 12 and 13). In contrast to **1a** and **1b**, the highly fluorinated alcohol **1c** is a solid (m.p. 44–47 °C), albeit with a reasonable boiling point (b.p. 163 °C). With 1.5 equiv. of **1c** the reaction required strong heating to proceed (reflux temperature). However, even under these harsh conditions the reaction with **1c** also gave satisfactory results with moderate-to-good yields of the ethers (45–75%, entries 14–18). Owing to the high fluorine content of the perfluoroalkoxy moiety, this reaction offers an attractive entry to fluorous compounds.[20]

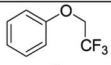
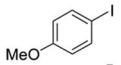
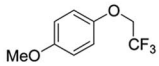
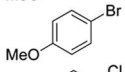
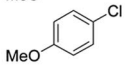
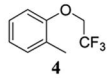
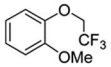
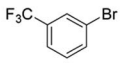
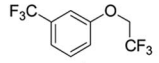
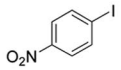
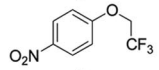
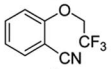
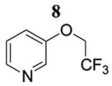
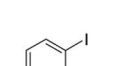
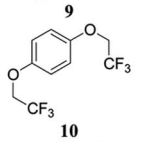
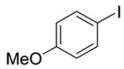
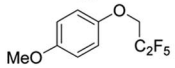
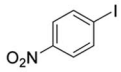
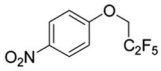
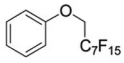
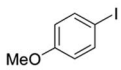
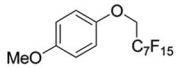
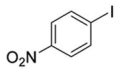
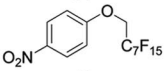
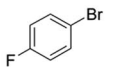
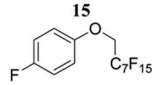
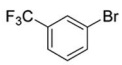
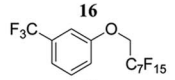
Note that alcohol **1a** behaved differently to **1b**,**c** with 4-bromo-1-iodobenzene as the reaction partner (Scheme 1). With 7 equiv. of TFE (**1a**), the reaction afforded the double coupling product **10** in 72% yield. Moreover, even with 1 equiv. of **1a** both bromo and iodo sites of 4-bromoiodobenzene reacted to afford a mixture of mono- and bis(trifluoroethoxy) products along with large amounts of unreacted starting dihalide. In contrast, with **1b** or **1c** (3 and 1.5 equiv., respectively), 4-bromoiodobenzene reacted almost exclusively at the iodinated site to yield the corresponding 4-bromo-1-fluoroalkoxybenzenes (82 and 72% yields, respectively). In the absence of any explanation, this suggests that the introduction of a long fluoroalkoxy chain into the aromatic ring modifies its reactivity and thus hinders the oxidative addition of copper at the bromo position.

Finally, the cross-coupling of vinyl bromides with fluorinated alcohols **1a**–**c** was assessed. Vinyl ethers find industrial applications as monomers in the production of oxygen-containing vinyl polymers,[21] and it is thus of interest to find an easy access to fluorinated series. In fact, the use of vinyl halides as coupling partners with aliphatic alcohols for the synthesis of enol ethers has also been documented in the literature, albeit to a considerably lesser extent.[16] Thus, under the conditions reported in Table 3, the cross-coupling between **1** and alkenyl bromides took place very easily. With TFE (**1a**), (*E*)-β-bromostyrene, α-bromostyrene and the sterically hindered olefin bromotriphenylethylene afforded the corresponding enol ethers **20**–**22** in very good

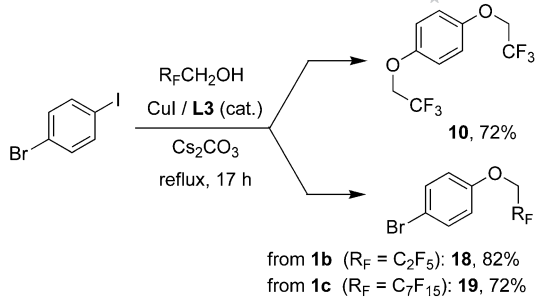
Table 2. Copper-catalysed cross-coupling reaction of fluoro alcohols **1a**–**c** with aryl halides.[a,b]



R_F = CF_3 (**1a**), C_2F_5 (**1b**), C_7F_{15} (**1c**)

Entry	R–X	Product	% Yield
1		 **3**	72
2		 **2**	86
3			85
4		-	–
5		 **4**	67
6		 **5**	83
7		 **6**	60
8		 **7**	93
9		 **8**	60
10		 **9**	80
11		 **10**	75
12		 **11**	75
13		 **12**	63
14		 **13**	75
15		 **14**	60
16		 **15**	45
17		 **16**	45
18		 **17**	50

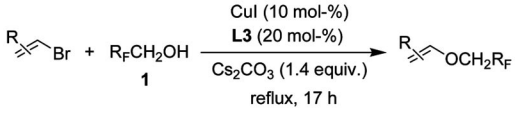
[a] Reactions were performed on a 1 mmol scale. [b] Reflux temperatures of **1a**, **1b** and **1c** are 78, 80 and 163 °C, respectively.



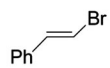
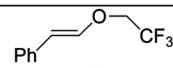
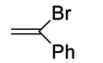
Scheme 1.

yields (71–95% yields, entries 1–3). Bromotrimethylethylene also reacted very well with **1a** (85% conversion by ^{1}H NMR), however, due to the high volatility of product **23**, we did not succeed in isolating it (entry 4).[22] Finally, the cross-coupling between **1b** and **1c** and bromotriphenylethylene also occurred to yield the vinyl ethers **24** and **25** (entries 5 and 6, respectively).

Table 3. Copper-catalysed cross-coupling reaction of fluoro alcohols **1a**–**c** with vinyl bromides.



R_F = CF_3 (**1a**), C_2F_5 (**1b**), C_7F_{15} (**1c**)

Entry	R–X	Product	% Yield
1		 **20**	95
2		**21**	71
3		**22**	95
4		**23**	85% conv.[a]
5		**24**	87
6		**25**	70

[a] Conversion was calculated by direct ^{1}H NMR analysis of the reaction medium. Product **23** was too volatile to be isolated.

In comparison with the results reported in the literature, the cross-coupling reactions of aryl/vinyl bromides with fluoro alcohols **1a**–**c** is much more successful than with their non-fluorinated counterparts. In a recent article, Buchwald and co-workers suggested that the efficiency of the coupling was connected to the acidity of the alcohol as BnOH behaved better than *n*-hexanol or ethanol (pK_a values in DMSO: BnOH = 26.9, EtOH = 29.8).[15d] Thus, the higher acidity of TFE (pK_a in DMSO: TFE = 23.5)[23] could account for its good reactivity with bromide partners.

Conclusions

We have reported an efficient process for the synthesis of fluorinated aryl and vinyl ethers by the copper-catalysed cross-coupling reaction of trifluoroethanol and higher fluorinated homologues with the corresponding halide partner (I or Br).[24] In the trifluoromethyl series, this simple procedure offers a very attractive alternative for the synthesis of motifs that are found in various bioactive molecules. Moreover, the success of this reaction with a perfluoro alcohol has potential for fluorous labelling.

Experimental Section

General: All chemicals were used as provided without further purification, except for CuI.[25] NMR spectra were obtained with a Bruker 200, 300 or 400 spectrometer. Chemical shifts (δ) are given in ppm. The chemical shifts in the ^{19}F NMR spectra are referenced to external $CFCl_3$, and in the ^1H and ^{13}C NMR spectra to TMS. Coupling constants J are measured in Hz. Elemental analyses were performed by the Service de Microanalyses at the Faculté de Pharmacie, Châtenay-Malabry.

General Procedure for the Synthesis of Fluorinated Aryl and Vinyl Ethers 2–25: A 5-mL round-bottomed flask equipped with a reflux condenser was charged with CuI (0.1 mmol, 19 mg), ethyl 2-oxocyclohexanecarboxylate (0.2 mmol, 34 mg), Cs_2CO_3 (1.4 mmol, 456 mg) and the halide (1.0 mmol). Then the fluoro alcohol was added to the mixture: trifluoroethanol (**1a**; 7 mmol, 700 mg; b.p. 78 °C), 1,1-H-pentafluoropropanol (**1b**; 3 mmol, 450 mg; b.p. 80 °C) or 1,1-H-perfluorooctanol (**1c**; 1.5 mmol, 600 mg; b.p. 163 °C) without any solvent. The mixture was then heated at reflux whilst stirring. After 17 h, the reaction mixture was cooled to room temperature, dichloromethane was added to the residue and the mixture was filtered through silica. If necessary, the crude product was finally purified by chromatography on silica gel (petroleum ether/Et_2O, 9:1).

4-Methoxy-1-(2,2,2-trifluoroethoxy)benzene (2):[26] Yellow oil, 117 mg, 86% yield. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.78 (s, 3 H, Me), 4.30 (q, J = 8.2 Hz, 2 H, CH_2), 6.81–6.95 (m, 4 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.6, 66.8 (q, J = 35.2 Hz), 114.7, 116.3, 124.4 (q, J = 278.0 Hz), 151.1, 155.6 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –74.5 (t, J = 8.2 Hz) ppm. $C_9H_9F_3O_2$ (206.16): calcd. C 52.43, H 4.40; found C 52.21, H 4.22.

1-(2,2,2-Trifluoroethoxy)benzene (3):[27] Yellow oil, 127 mg, 72% yield. ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.36 (q, J = 8.2 Hz, 2 H, CH_2), 6.95 (d, J = 7.7 Hz, 2 H, Ar), 7.06 (t, J = 7.3 Hz, 1 H, Ar), 7.34 (t, J = 7.6 Hz, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 65.8 (q, J = 36.0 Hz), 114.9, 122.5, 123.4 (q, J = 278.0 Hz), 129.7, 157.4 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –74.4 (t, J = 8.2 Hz) ppm. $C_8H_7F_3O$ (176.14): calcd. C 54.55, H 4.01; found C 54.74, H 4.21.

2-Methyl-1-(2,2,2-trifluoroethoxy)benzene (4): Yellow liquid, 127 mg, 67% yield. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.37 (s, 3 H, Me), 4.40 (q, J = 8.2 Hz, 2 H, CH_2), 6.85 (d, J = 7.9 Hz, 1 H, Ar), 7.06 (t, J = 7.4 Hz, 1 H, Ar), 7.26 (t, J = 7.4 Hz, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.7, 66.1 (q, J = 36.0 Hz), 111.8, 120.2 (q, J = 278.0 Hz), 122.3, 126.9, 127.6, 131.2, 155.7 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –74.6 (t, J = 8.2 Hz) ppm. $C_9H_9F_3O$ (190.16): calcd. C 56.84, H 4.77; found C 57.02, H 4.95.

2-Methoxy-1-(2,2,2-trifluoroethoxy)benzene (5): Yellow oil, 142 mg, 83% yield. ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.88 (s, 3 H, Me), 4.39 (q, J = 8.4 Hz, 2 H, CH_2), 6.86–7.11 (m, 4 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.7, 67.9 (q, J = 35.0 Hz), 112.6, 117.7, 120.9, 123.6 (q, J = 278.0 Hz), 124.1, 147.0, 150.4 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –74.5 (t, J = 8.4 Hz) ppm. $C_9H_9F_3O_2$ (206.16): calcd. C 52.43, H 4.40; found C 52.68, H 4.69.

1-(2,2,2-Trifluoroethoxy)-3-(trifluoromethyl)benzene (6): Orange liquid, 146 mg, 60% yield. ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.32 (q, J = 8.0 Hz, 2 H, CH_2), 7.13 (d, J = 8.3 Hz, 1 H, Ar), 7.19 (s, 1 H, Ar), 7.32 (d, J = 7.70 Hz, 1 H, Ar), 7.45 (t, J = 8.01 Hz, 1 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 66.0 (q, J = 36.0 Hz), 123.1 (q, J = 278.0 Hz), 123.7 (q, J = 272.0 Hz), 111.9, 118.4, 119.4, 130.4, 132.1 (q, J = 32 Hz), 157.4 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –74.3 (t, J = 8.0 Hz, 3 F), –63.23 (s, 3 F) ppm. $C_9H_6F_6O$ (244.13): calcd. C 44.28, H 2.48; found C 44.50, H 2.72.

4-Nitro-1-(2,2,2-trifluoroethoxy)benzene (7): Yellow solid, 205 mg, 93% yield, m.p. 76 °C (lit.[28] 75.5–76.5 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.46 (q, J = 7.8 Hz, 2 H, CH_2), 7.04 (d, J = 9.3 Hz, 2 H, Ar), 8.25 (d, J = 9.3 Hz, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 65.8 (q, J = 36.0 Hz), 114.9, 122.8 (q, J = 278.0 Hz), 126.0, 142.8, 161.8 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –74.1 (t, J = 7.9 Hz) ppm. $C_8H_6F_3NO_3$ (221.13): calcd. C 43.45, H 2.73, N 6.33; found C 43.38, H 2.74, N 6.20.

2-(2,2,2-Trifluoroethoxy)benzonitrile (8): Yellow solid, 121 mg, 60% yield, m.p. 58 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.49 (q, J = 7.9 Hz, 2 H, CH_2), 7.00 (d, J = 8.5 Hz, 1 H, Ar), 7.14 (t, J = 7.6 Hz, 1 H, Ar), 7.55–7.65 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 66.3 (q, J = 36 Hz), 103.2, 113.0, 115.3, 122.7 (q, J = 278 Hz), 122.9, 134.2, 134.4, 158.6 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –73.7 (t, J = 8.0) ppm. $C_8H_6F_3NO$ (189.14): calcd. C 53.74, H 3.01, N 6.96; found C 53.47, H 2.92, N 7.11.

3-(2,2,2-Trifluoroethoxy)pyridine (9): Yellow oil, 142 mg, 80% yield. ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.40 (q, J = 8.0 Hz, 2 H, CH_2), 7.26 (m, 2 H, Ar), 8.37 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 65.9 (q, J = 36.0 Hz), 121.9, 122.9 (q, J = 278.0 Hz), 123.9, 138.0, 143.8, 153.6 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –74.1 (t, J = 8.0 Hz) ppm. $C_7H_6F_3NO$ (177.12): calcd. C 47.47, H 3.41, N 7.91; found C 47.54, H 3.22, N 7.72.

1,4-Bis(2,2,2-trifluoroethoxy)benzene (10): The reaction was performed with 1,4-diiodobenzene (1 mmol, 330 mg), TFE (14 mmol), Cs_2CO_3 (2.8 mmol, 912 mg), CuI (0.2 mmol, 38 mg) and ethyl 2-oxocyclohexanecarboxylate (0.4 mmol, 68 mg). Yellow solid, 206 mg, 75% yield, m.p. 70 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.31 (q, J = 8.2 Hz, 4 H, 2×CH_2), 6.92 (s, 4 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 66.7 (q, J = 35.4 Hz), 116.4, 123.3 (q, J = 278.0 Hz), 152.9 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –74.1 (t, J = 8.2) ppm. $C_{10}H_8F_6O_2$ (274.16): calcd. C 43.81, H 2.94; found C 44.09, H 3.08.

4-Methoxy-1-(2,2,3,3,3-pentafluoropropoxy)benzene (11): White solid, 190 mg, 75% yield, m.p. 100–103 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.11 (s, 3 H, Me), 4.70 (tq, J = 12.5, J = 1.3 Hz, 2 H, CH_2), 7.21 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.5, 66.0 (t, J = 27.4 Hz), 114.8, 116.3, 111–121 (m), 151.7, 155.2 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –83.9 (t, J = 1.3 Hz, 3 F), –124.0 (t, J = 12.5 Hz, 2 F) ppm. $C_{10}H_9F_5O_2$ (256.17): calcd. C 46.89, H 3.54; found C 46.58, H 3.32.

4-Nitro-1-(2,2,3,3,3-pentafluoropropoxy)benzene (12): Brown solid, 170 mg, 63% yield, m.p. 51–54 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.53 (t, J = 12.2 Hz, 2 H, CH_2), 7.04 (d, J = 9.3 Hz, 2 H, Ar), 8.24 (d, J = 9.3 Hz, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 64.8 (t, J = 28.2 Hz), 114.8, 126.0, 109–121 (m), 142.8, 161.8 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –83.9 (s, 3 F), –123.7

(t, J = 12.2 Hz, 2 F) ppm. $C_9H_6F_5NO_3$ (271.14): calcd. C 39.87, H 2.23, N 5.17; found C 39.60, H 2.21, N 4.95.

1-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Pentadecafluorooctyloxy)benzene (13): Yellow oil, 355 mg, 75% yield. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.48 (tt, J = 12.9, J = 1.5 Hz, 2 H, CH_2), 6.94–7.13 (m, 3 H, Ar), 7.30–7.37 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 65.4 (t, J = 27.3 Hz), 103–123 (m), 115.0, 122.6, 129.8, 157.6 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –81.6 (tt, J = 9.7, J = 2.0 Hz, 3 F), –120.1 (m, 2 F), –122.6 (m, 4 F), –123.4 (m, 2 F), –123.7 (m, 2 F), –126.8 (m, 2 F) ppm. $C_{14}H_7F_{15}O$ (476.18): calcd. C 35.31, H 1.48; found C 35.57, H 1.32.

4-Methoxy-1-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyloxy)-benzene (14): Yellow solid, 305 mg, 60% yield, m.p. 36 °C. ^{1}H NMR ([D$_6$]acetone, 200 MHz): δ = 3.76 (s, 3 H, Me), 4.68 (tt, J = 13.4, J = 1.5 Hz, 2 H, CH_2), 7.8 (d, J = 9.3 Hz, 2 H, Ar), 7.02 (d, J = 9.3 Hz, 2 H, Ar) ppm. ^{13}C NMR ([D$_6$]acetone, 75 MHz): δ = 56.9, 67.8 (t, J = 27.2 Hz), 105–121 (m), 116.6, 118.1, 153.7, 157.3 ppm. ^{19}F NMR ([D$_6$]acetone, 188 MHz): δ = –81.6 (tt, J = 10.2, J = 2.2 Hz, 3 F), –119.9 (m, 2 F), –122.4 (m, 4 F), –123.2 (m, 4 F), –126.6 (m, 2 F) ppm. $C_{15}H_9F_{15}O_2$ (506.21): calcd. C 35.59, H 1.79; found C 35.37, H 1.74.

4-Nitro-1-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyloxy)benzene (15): Orange solid, 235 mg, 45% yield, m.p. 50 °C (lit.[28] 49.5–50.0 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.57 (tt, J = 12.5, J = 1.3 Hz, 2 H, CH_2), 7.04 (d, J = 9.4 Hz, 2 H, Ar), 8.24 (d, J = 9.4 Hz, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 65.3 (t, J = 27.4 Hz), 104–121 (m), 114.9, 126.0, 142.9, 161.8 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –81.2 (m, 3 F), –119.7 (m, 2 F), –122.5 (m, 4 F), –123.4 (m, 4 F), –126.6 (m, 2 F) ppm. $C_{14}H_6F_{15}NO_3$ (521.18): calcd. C 32.26, H 1.16, N 2.69; found C 31.94, H 1.02, N 2.95.

4-Fluoro-1-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyloxy)benzene (16): Yellow oil, 200 mg, 45% yield. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.42 (tt, J = 12.9, J = 1.5 Hz, 2 H, CH_2), 6.85–7.08 (m, 4 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 66.2 (t, J = 26.9 Hz), 105–121 (m), 116.2 (d, J = 23.6 Hz), 116.4 (d, J = 8.2 Hz), 153.8, 156.9 (d, J = 241.0 Hz) ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –81.6 (tt, J = 10.2, J = 2.1 Hz, 3 F), –120.2 (m, 2 F), –121.9 (m, 1 F), –122.6 (m, 4 F), –123.6 (m, 4 F), –126.8 (m, 2 F) ppm. $C_{14}H_6F_{16}O$ (494.17): calcd. C 34.03, H 1.22; found C 35.97, H 1.54.

1-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Pentadecafluorooctyloxy)-3-(trifluoromethyl)benzene (17): Orange oil, 270 mg, 50% yield. ^{1}H NMR ([D$_6$]-acetone, 200 MHz): δ = 4.95 (tt, ^1J = 13.3, ^2J = 1.4 Hz, 2 H, CH_2), 7.38 (m, 1 H, Ar), 7.42 (m, 2 H, Ar), 7.60 (t, J = 7.8 Hz, 1 H, Ar) ppm. ^{13}C NMR ([D$_6$]acetone, 75 MHz): δ = 67.1 (t, J = 27.4 Hz), 105–121 (m), 113.7, 121.0, 126.0 (q, J = 271.7 Hz), 132.7 (q, J = 32 Hz), 159.7 ppm. ^{19}F NMR ([D$_6$]acetone, 188 MHz): δ = –63.2 (s, 3 F), –81.6 (tt, J = 10.1, J = 2.2 Hz, 3 F), –119.9 (m, 2 F), –122.4 (m, 4 F), –123.2 (m, 4 F), –126.7 (m, 2 F) ppm. $C_{15}H_6F_{18}O$ (544.18): calcd. C 33.11, H 1.11; found C 33.37, H 1.43.

4-Bromo-1-(2,2,3,3,3-pentafluoropropoxy)benzene (18): Orange oil, 250 mg, 82% yield. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.73 (tq, J = 12.2, J = 1.2 Hz, 2 H), 7.17 (d, J = 9.1 Hz, 2 H), 7.77 (d, J = 9.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 65.2 (t, J = 28.0 Hz), 115.1, 116.8, 112–121 (m), 132.6, 156.5 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –83.9 (t, J = 1.2 Hz, 3 F), –123.9 (t, J = 12.2 Hz, 2 F) ppm. $C_9H_6BrF_5O$ (305.04): calcd. C 35.44, H 1.98; found C 35.67, H 2.13.

4-Bromo-1-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyloxy)-benzene (19): Yellow solid, 400 mg, 72% yield, m.p. 65 °C. ^{1}H NMR ([D$_6$]acetone, 200 MHz): δ = 4.79 (tt, ^1J = 13.2, ^2J = 1.5 Hz, 2 H, 2 × CH_2), 7.05 (d, J = 9.2 Hz, 2 H, Ar), 7.49 (d, J = 9.2 Hz, 2 H, Ar) ppm. ^{13}C NMR ([D$_6$]acetone, 75 MHz): δ = 67.1 (t, J = 26.8 Hz), 105–122 (m), 118.2, 119.0, 134.5, 158.8 ppm. ^{19}F NMR ([D$_6$]acetone, 188 MHz): δ = –81.6 (t, J = 10.2 Hz, 3 F), –119.8 (m, 2 F), –122.3 (m, 4 F), –123.2 (m, 4 F), –126.6 (m, 2 F) ppm. $C_{14}H_6F_{15}O$ (475.17): calcd. C 30.29, H 1.09; found C 30.49, H 0.95.

1-[(*E*)-2-(2,2,2-Trifluoroethoxy)vinyl]benzene (20): Yellow oil, 192 mg, 95% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.20 (q, J = 8.2 Hz, 2 H, CH_2), 6.01 (d, J = 12.8 Hz, 1 H, H vinyl), 6.94 (d, J = 12.8 Hz, 1 H, H vinyl), 7.18–7.34 (m, 5 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 66.9 (q, J = 35.0 Hz), 108.8, 123.3 (q, J = 278.0 Hz), 125.4, 126.5, 128.7, 134.9, 146.2 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –74.1 (t, J = 8.1 Hz) ppm. $C_{10}H_9F_3O$ (202.17): calcd. C 59.41, H 4.49; found C 59.25, H 4.62.

1-(2,2,2-Trifluoroethoxy)vinylbenzene (21): Brown oil, 143 mg, 71% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.19–4.27 (m, 3 H), 4.81 (dt, J = 3.6 Hz, 1 H, H vinyl), 7.34–7.39 (m, 3 H, Ar), 7.60–7.64 (m, 2 H, Ar) ppm. ^{13}C NMR ($CDCl_3$,75 MHz): δ = 65.3 (q, J = 36.0 Hz), 84.1, 123.8 (q, J = 280 Hz), 125.4, 128.3, 129.0, 134.8, 158.9 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –73.7 (t, J = 7.8 Hz) ppm. $C_{10}H_9F_3O$ (202.17): calcd. C 59.41, H 4.49; found C 59.65, H 4.54.

1,2,2-Triphenyl-1-(2,2,2-trifluoroethoxy)ethylene (22): Yellow solid, 335 mg, 95% yield, m.p. 74 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.99 (q, J = 8.5 Hz, 2 H, CH_2), 7.00–7.45 (m, 15 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 66.8 (q, J = 35.0 Hz), 123.4 (q, J = 278.0 Hz), 126.5, 127.1, 127.8, 128.1, 128.3, 129.5, 129.8, 130.3, 131.1, 134.0, 139.9, 140.7, 141.0, 143.7, 150.6 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –73.5 (t, J = 8.6 Hz) ppm. $C_{22}H_{17}F_3O$ (354.36): calcd. C 74.57, H 4.84; found C 74.89, H 4.73.

1-(2,2,3,3,3-Pentafluoropropoxy)-1,2,2-triphenylethylene (24): White solid, 350 mg, 87% yield, m.p. 92–94 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.94 (t, J = 13.2 Hz, 2 H, CH_2), 6.87–7.38 (m, 15 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 65.9 (t, J = 26.8 Hz), 112–121 (m), 126.9, 127.5, 127.8, 127.9, 128.1, 129.5, 130.2, 130.3, 131.0, 133.8, 139.8, 140.5, 141.0, 143.7, 150.4 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –83.7 (s, 3 F), –123.5 (t, J = 13.2 Hz, 2 F) ppm. $C_{23}H_{17}F_5O$ (404.37): calcd. C 68.31, H 4.24; found C 68.58, H 4.30.

1-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Pentadecafluorooctyloxy)-1,2,2-triphenylethylene (25): Brown solid, 455 mg, 70% yield, m.p. 105–107 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.12 (t, J = 13.9 Hz, 2 H, CH_2), 7.02–7.52 (m, 15 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 66.3 (t, J = 25.5 Hz), 105–121 (m), 126.9, 127.5, 127.8, 127.9, 128.2, 129.5, 129.7, 130.3, 131.1, 133.9, 139.9, 140.6, 141.1, 143.8, 150.7 ppm. ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –81.6 (t, J = 10.0 Hz, 3 F), –119.8 (m, 2 F), –122.3 (m, 4 F), –123.1 (m, 2 F), –123.3 (m, 2 F), –126.5 (m, 2 F) ppm. $C_{28}H_{17}F_{15}O$ (654.41): calcd. C 51.39, H 2.62; found C 51.59, H 2.94.

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