Magnesium Metal-Mediated Reductive Trifluoromethylation of Aldehydes with Phenyl Trifluoromethyl Sulfone

Yanchuan Zhao, Jieming Zhu, Chuanfa Ni, Jinbo Hu*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, P. R. of China
E-mail: jinbohu@sioc.ac.cn

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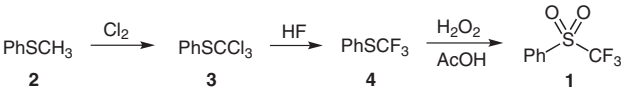
Abstract: An unprecedented reductive nucleophilic trifluoromethylation of aldehydes by using phenyl trifluoromethyl sulfone is reported. Mercury(II) chloride efficiently activates magnesium metal to induce the desulfonylative trifluoromethylation process. The new reductive trifluoromethylation provides an alternative method for efficient trifluoromethylation of non-enolizable or enolizable aldehydes with readily available phenyl trifluoromethyl sulfone reagent.

Key words: alkylations, aldehydes, alcohols, trifluoromethylations, phenyl trifluoromethyl sulfone

The selective introduction of a trifluoromethyl (CF_3) group into an organic molecule is a strategy that is frequently used in drug design and agrochemical development because of the profound changes in bioactivity that occur when a methyl group is replaced by a trifluoromethyl group.[1] As a result, a variety of nucleophilic, electrophilic, and free-radical trifluoromethylation methods have been developed,[2] among which the nucleophilic trifluoromethylation reactions have been most extensively studied.[2a–g] Because the trifluoromethyl anion (CF_3^-) is highly unstable, various compounds with the structure XCF_3 [X = H, Br, I, SPh, TMS, SO_2Ph, C(O)Y; Y = NR^1R^2, OR, Ph][3] are normally used as synthons for the trifluoromethyl anion in nucleophilic trifluoromethylation reactions. The strategies for transferring the CF_3 group and breaking the X–C bond in XCF_3 can be generally categorized into two types: a) electron transfer from a suitable reducing agent to XCF_3 (X = Br, I, SPh, SO_2Ph),[2h,3a,b] and b) nucleophilic attack of X in XCF_3 [X = H, SPh, TMS, SO_2Ph, C(O)Y (Y = NR^1R^2, OR, Ph)][3c–g] to cleave the X–C bond of XCF_3. Because of the relatively low bond-dissociation energy of XCF_3 (X = I, TMS) and the ease with which these undergo reduction or nucleophilic attack, trifluoro(iodo)methane and trimethyl(trifluoromethane)silane (Ruppert–Prakash reagent) are considered to be the most versatile reagents of types a) and b), respectively.

Previously, we were interested in the exploration of synthetic applications of fluorinated sulfones.[4] Although the reductive trifluoromethylation of chlorosilanes by using phenyl trifluoromethyl sulfone (**1**) was successfully achieved in 2003, reactions with carbonyl compounds under the reductive conditions appeared to be more challenging.[3b] Although an alkoxide-induced nucleophilic trifluoromethylation with **1** has been developed, the method is only suitable for non-enolizable carbonyl compounds.[3f] Because of the low cost and ready availability of phenyl trifluoromethyl sulfone (**1**) (Scheme 1), which is also a precursor of trimethyl(trifluoromethane)silane,[3b] further exploration of the synthetic applications of the sulfone under milder conditions is desirable. Here, we report a reductive nucleophilic trifluoromethylation of carbonyl compounds by using phenyl trifluoromethyl sulfone (**1**), which is commercially available and can also be prepared from methyl phenyl sulfide (**2**) through chlorination, fluorination, and oxidation (Scheme 1).[5]



Scheme 1 Synthesis of phenyl trifluoromethyl sulfone (**1**)

Reductive alkylation through desulfonylation remains a relatively poorly studied reaction (especially when compared with Barbier-type and Grignard-type reactions), partly because of the greater dissociation energy of the C–S bond compared with the C–X (X = Br, I) bond.[6] As a result, reductive desulfonylation generally requires harsher reaction conditions than do reductive dehalogenation reactions. Indeed, the known desulfonylative alkylation reactions usually employ relatively expensive samarium diiodide[7] or lithium naphthalenide[8] as a reducing agent, which hampered their widespread adoption. We envisaged that phenyl trifluoromethyl sulfone (**1**) might act as a good electron acceptor because of the high electron-withdrawing ability of the trifluoromethyl group and that the consequent reductive trifluoromethylation should proceed smoothly.

Initial results were, however, quite discouraging. We found that reducing agents such as magnesium, aluminum, zinc, or samarium diiodide in various solvents led to recovery of phenyl trifluoromethyl sulfone (**1**). After screening of several metal salts as additives for activating the reducing metals, we found that mercury(II) chloride efficiently activates magnesium to induce the required desulfonylation reaction (Table 1). The solvent also plays an important role in the desulfonylation reaction, as the reaction only occurs in highly polar solvents such as *N*,*N*-

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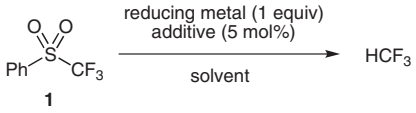
dimethylformamide or dimethyl sulfoxide, which facilitate the electron-transfer process and stabilize the anionic intermediate.

Table 1 Effects of the Reaction Conditions on the Reductive Desulfonylation of Phenyl Trifluoromethyl Sulfone (**1**)[a]



1

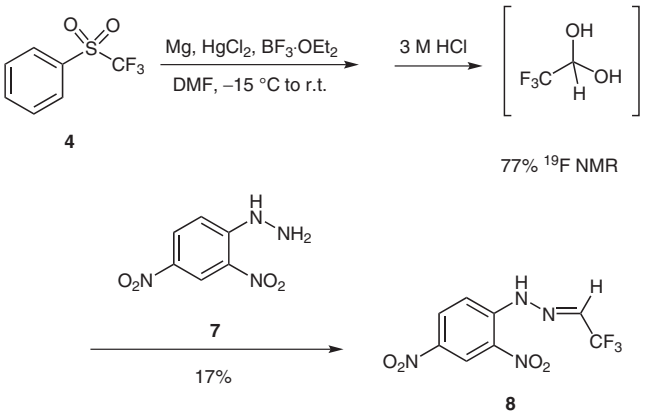
Entry	Reducing metal	Solvent	Additive	Conv.[b] (%)
1	Mg	DMF	$NiCl_2$	0
2	Mg	DMF	$PbCl_2$	0
3	Mg	DMF	$CuBr_2$	0
4	Mg	DMF	$HgCl_2$	>99
5	Mg	THF	$HgCl_2$	0
6	Mg	DMSO	$HgCl_2$	>99
7	Zn	DMF	$HgCl_2$	0
8	Al	DMF	$HgCl_2$	0

[a] For all cases, $PhSO_2CF_3$ was added to a mixture of reducing metal, additive, and solvent at r.t.
[b] Determined by ^{19}F NMR of the crude reaction mixture, and based on the consumption of **1**.

Next, we chose anisaldehyde (**5a**) as a model compound to optimize the reactant ratio and reaction temperature (Table 2). We found that when the reactant ratio **1**/**5a**/Mg/$HgCl_2$ was 2:1:2:0.06 and the reaction temperature ranged between –15 °C and room temperature, the corresponding trifluoromethylated product **6a** was obtained in 88% yield (Table 2, entry 4).

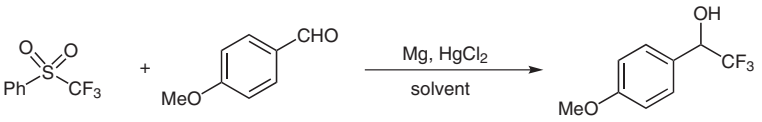
Having determined the optimal reaction conditions (Table 2, entry 4), we evaluated the scope and limitations of this new nucleophilic trifluoromethylation reaction between **1** and carbonyl compounds **5a–l**. On treatment with sulfone **1**, various aldehydes reacted smoothly to the corresponding trifluoromethyl carbinols **6** in moderate-to-good yields (Table 3; entries 1–8, 10–12). Aldehydes with strong electron-withdrawing groups gave lower yields because of the rapid reduction and pinacol coupling of these substrates under the reductive conditions (entries 3, 5, 8, and 9). Moreover, under the reductive trifluoromethylation conditions, the enolizable aldehyde **5l** gave an acceptable yield that was superior to that of the previously developed alkoxide-induced nucleophilic trifluoromethylation.[3f] Note that the magnesium–mercury(II) chloride–methanol system is used extensively in reductive desulfonylation reactions,[9] but, to the best of our knowledge, the corresponding desulfonylative alkylation reaction in a nonprotic solvent has never been reported.

Note that, unlike fluoride-induced nucleophilic trifluoromethylation with trimethyl(trifluoromethyl) silane, our method generates the CF_3^- species (or its synthetic equivalent) in the presence of a strong Lewis acid, so that substrates with a low electrophilicity (such as *N*,*N*-



Scheme 2 Synthesis and trapping of the hydrated form of the trifluoroacetaldehyde (fluoral)

Table 2 Effects of the Reaction Conditions for Reductive Desulfonylation Trifluoromethylation with Phenyl Trifluoromethyl Sulfone (**1**)

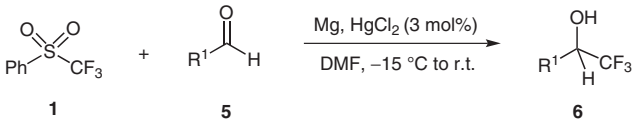


1 **5a** **6a**

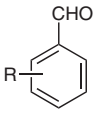
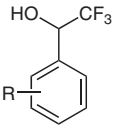
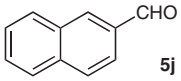
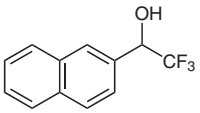
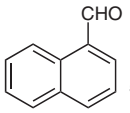
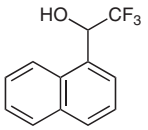
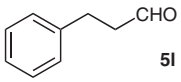
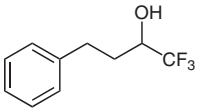
Entry	Temp (°C)	Molar ratio **1**/**5a**/Mg	$HgCl_2$ (mol%)[a]	Solvent	Yield (%)[b]
1	–50 °C to r.t.	1:1:1	3	DMF	50
2	–50 °C to r.t.	2:1:2	3	DMF	80
3	0 °C to rt	1.5:1:1.5	6	DMF	79
4	–15 °C to r.t.	2:1:2	3	DMF	88
5	r.t.	1:1:2	2	DMSO	28[c]

[a] Relative to the amount of Mg metal used.
[b] Isolated yield.
[c] Determined by ^{19}F NMR spectroscopy.

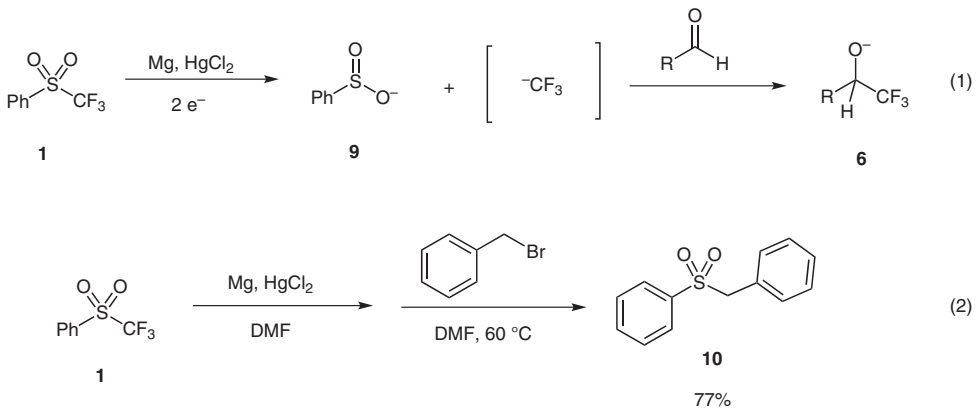
Table 3 Reductive Desulfonylation–Trifluoromethylation of Aldehydes with Phenyl Trifluoromethyl Sulfone (**1**)



1 **5** **6**

Entry[a]	Substrate	Product		Yield (%)[b]
1	 **5a–i**		**6a** R = 4-MeO	88
2			**6b** R = 3,4-$(MeO)_2$	82
3			**6c** R = 2-Cl	60
4			**6d** R = 4-Ph	72
5			**6e** R = 3-Cl	53
6			**6f** R = 4-*t*-Bu	69
7			**6g** R = 4-BnO	78
8			**6h** R = 2,4-Cl_2	45
9			**6i** R = 4-O_2N	28
10	 **5j**		**6j**	55
11	 **5k**		**6k**	60
12[c]	 **5l**		**6l**	45

[a] In all cases, the molar ratio of reactants was **1/5**/Mg/$HgCl_2$ = 2.0:1.0:2.0:0.06.
[b] Isolated yield.
[c] $MgCl_2$ was added to neutralize the basicity of the reaction system.



1 **9** **6** **10**

77%

Scheme 3 Proposed mechanism for the trifluoromethylation reaction

dimethylformamide) can also be trifluoromethylated. Indeed, we found that in the absence of aldehydes, the reaction mixture produced the hydrated form of the trifluoroacetaldehyde (fluoral) in 77% yield (determined by ^{19}F NMR). The formation of trifluoroacetaldehyde was confirmed by the observation that when we treated the reaction mixture with (2,4-dinitrophenyl)hydrazine **7**, the condensed product **8** could be isolated and characterized (Scheme 2). The low yield (17%) is partially due to decomposition of compound **8** during purification by column chromatography on silica gel (Scheme 2).

With regard to the reaction mechanism of the trifluoromethylation with trifluoromethyl sulfone **1**, we propose that a single-electron transfer from magnesium metal to **1** facilitates reductive desulfonylation to form an anionic trifluoromethyl species and magnesium benzenesulfinate **9** (Scheme 3, equation 1). The formation of benzenesulfinate species **9** is supported by the fact that when we treated the reaction mixture with (bromomethyl)benzene, the benzylated product **10** was isolated in 77% yield (Scheme 3, equation 2).

In conclusion, we have developed a novel nucleophilic trifluoromethylation method for aldehydes by using phenyl trifluoromethyl sulfone through a magnesium metal-mediated reductive desulfonylation process. The method provides an alternative approach for efficient trifluoromethylation of both nonenolizable and enolizable aldehydes with a readily available reagent.

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. DMF was distilled from CaH_2, and THF was distilled from Na. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a 300-MHz NMR spectrometer (Bruker AM300). ^1H NMR chemical shifts were determined relative to internal TMS (δ = 0.0) or to the signals of solvent $CDCl_3$ (δ = 7.26). ^{13}C NMR chemical shifts were determined relative to internal TMS (δ = 0.0) or solvent $CDCl_3$ (δ = 77.0). ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ (δ = 0.0). Mass spectra were recorded on a HP5973N (Agilent) mass spectrometer. HRMS were recorded on a Saturn 2000 high-resolution mass spectrometer in the EI or ESI mode.

Trifluoromethylation of Aldehydes 5; General Procedure

$PhSO_2CF_3$ (**1**; 210 mg, 1 mmol) and aldehyde **5** (0.5 mmol) in DMF (2 mL) were added dropwise to a suspension of $HgCl_2$ (8 mg, 0.03 mmol) and Mg (24 mg, 1 mmol) in DMF (2 mL) at –15 °C. The mixture was allowed to warm to r.t. and, upon disappearance of Mg (~2 h), the reaction was quenched with 3 N HCl (1.5 mL). The mixture was then extracted with Et_2O (3 × 15 mL). The combined organic phase was washed with brine then dried ($MgSO_4$), filtered, and concentrated under vacuum to give a crude product that was purified by silica gel chromatography (EtOAc–petroleum ether).

2,2,2-Trifluoro-1-(4-methoxyphenyl)ethanol (6a)

The physical and spectroscopic data were identical to those reported in the literature.[10]

^1H NMR: δ = 7.40 (d, *J* = 8.3 Hz, 2 H), 6.93 (d, *J* = 8.6 Hz, 2 H), 4.97 (q, *J* = 6.6 Hz, 1 H), 3.83 (s, 3 H), 2.39 (br s, 1 H).

^{19}F NMR: δ = –78.66 (d, *J* = 6.6 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 206 (2.7) [M^+], 137 (100.0), 109 (38.2).

1-(3,4-Dimethoxyphenyl)-2,2,2-trifluoroethanol (6b)

The physical and spectroscopic data were identical to those reported in the literature.[11]

^1H NMR: δ = 6.94 (m, 1 H), 6.89 (m, 2 H), 5.23 (q, *J* = 7.2 Hz, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.61 (br s, 1 H).

^{19}F NMR: δ = –78.39 (d, *J* = 6.5 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 236 (100.0) [M^+], 219 (41.6), 167 (81.7), 139 (80.7).

1-(2-Chlorophenyl)-2,2,2-trifluoroethanol (6c)

The physical and spectroscopic data were identical to those reported in the literature.[12]

^1H NMR: δ = 7.70 (m, 1 H), 7.43–7.33 (m, 3 H), 5.65 (m, 1 H), 2.74 (d, *J* = 3.7 Hz, 1 H).

^{19}F NMR: δ = –77.96 (d, *J* = 6.1 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 210 (34.0) [M^+], 141 (100.0), 113 (18.3), 77 (87.2), 51 (15.4).

1-Biphenyl-4-yl-2,2,2-trifluoroethanol (6d)

The physical and spectroscopic data were identical to those reported for this compound.[3f]

^1H NMR: δ = 7.66–7.57(m, 6 H), 7.48–7.35 (m, 3 H), 5.09 (q, *J* = 6.1 Hz, 1 H), 1.93 (br s, 1 H).

^{19}F NMR: δ = –78.25 (d, *J* = 6.5 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 252 (39.3) [M^+], 183 (100.0), 155 (80.6), 77 (13.0).

1-(3-Chlorophenyl)-2,2,2-trifluoroethanol (6e)

The physical and spectroscopic data were identical to those reported in the literature.[12]

^1H NMR: δ = 7.50 (s, 1 H), 7.43–7.31 (m, 3 H), 5.01 (q, *J* = 7.0 Hz, 1 H), 2.73 (br s, 1 H).

^{19}F NMR: δ = –78.33 (d, *J* = 6.2 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 210 (13.7) [M^+], 141 (81.9), 113 (43.3), 77 (100.0).

1-(4-*tert*-Butylphenyl)-2,2,2-trifluoroethanol (6f)

The physical and spectroscopic data were identical to those reported in the literature.[13]

^1H NMR: δ = 7.44 (d, *J* = 8.7 Hz, 2 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 4.99 (q, *J* = 6.6 Hz, 1 H), 2.30 (br s, 1 H), 1.33 (s, 9 H).

^{19}F NMR: δ = –78.39 (d, *J* = 6.8 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 232 (17.6) [M^+], 217 (100.0), 189 (15.9), 91 (14.0).

1-[4-(Benzyloxy)phenyl]-2,2,2-trifluoroethanol (6g)

The physical and spectroscopic data were identical to those reported in the literature.[14]

^1H NMR: δ = 7.44–7.27 (m, 7 H), 6.96 (d, *J* = 8.2 Hz, 2 H), 5.02 (s, 2 H), 4.84 (q, *J* = 6.6 Hz, 1 H), 2.78 (br s, 1 H).

^{19}F NMR: δ = –78.95 (d, *J* = 6.6 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 282 (12.3) [M^+], 278 (5.4), 139 (8.1), 91 (100.0).

1-(2,4-Dichlorophenyl)-2,2,2-trifluoroethanol (6h)

IR (film): 1708, 1593, 1477, 1385, 1269, 1178, 1133, 1108, 1085, 1046, 871, 849, 817, 778, 691, 459 cm^{-1}.

^1H NMR: δ = 7.63 (d, *J* = 8.6 Hz, 1 H), 7.43 (d, *J* = 1.7 Hz, 1 H), 7.34 (dd, *J* = 8.3 Hz, *J* = 1.7 Hz 1 H), 5.58 (q, *J* = 6.5 Hz, 1 H), 2.88 (br s, 1 H).

^{19}F NMR: δ = –78.56 (d, *J* = 6.1 Hz, 3 F).

^{13}C NMR: δ = 136.1, 134.4, 130.4, 129.9, 129.4, 127.7, 123.9 (q, *J* = 282.7 Hz), 68.3 (q, *J* = 33.4 Hz).

MS (EI, 70 eV): *m/z* (%) = 244 (24.9) [M^+], 175 (100.0), 111 (65.5), 75 (24.5).

HRMS (EI): *m/z* calcd for $C_8H_5Cl_2F_3O$: 243.9670; found: 243.9671.

2,2,2-Trifluoro-1-(4-nitrophenyl)ethanol (6i)

The physical and spectroscopic data were identical to those reported in the literature.[15]

^1H NMR: δ = 8.29 (d, *J* = 8.7 Hz, 2 H), 7.70 (d, *J* = 8.6 Hz, 2 H), 5.19 (q, *J* = 6.6 Hz, 1 H), 2.79 (br s, 1 H).

^{19}F NMR: δ = –78.73 (d, *J* = 6.3 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 221 (89.5) [M^+], 152 (100.0), 127 (32.5), 78 (39.3).

2,2,2-Trifluoro-1-(2-naphthyl)ethanol (6j)

The physical and spectroscopic data were identical to those reported in the literature.[15]

^1H NMR: δ = 7.96 (s, 1 H), 7.93–7.83 (m, 3 H), 7.61–7.45 (m, 3 H), 5.20 (q, *J* = 6.8 Hz, 1 H), 2.38 (br s, 1 H).

^{19}F NMR: δ = –78.08 (d, *J* = 6.6 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 226 (47.8) [M$^+$], 209 (15.0), 157 (63.0), 129 (100.0).

2,2,2-Trifluoro-1-(1-naphthyl)ethanol (6k)
The physical and spectroscopic data were identical to those reported in the literature.[15]

^{1}H NMR: δ = 8.04 (d, *J* = 8.7 Hz, 1 H), 7.95–7.85 (m, 2 H), 7.82 (d, *J* = 7.1 Hz, 1 H), 7.62–7.46 (m, 3 H), 5.87 (q, *J* = 6.5 Hz, 1 H), 2.47 (br s, 1 H).

^{19}F NMR: δ = –77.31 (d, *J* = 6.6 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 226 (41.8) [M$^+$], 209 (7.5), 157 (66.8), 129 (100.0).

1,1,1-Trifluoro-4-phenylbutan-2-ol (6l)
The physical and spectroscopic data were identical to those reported in the literature.[10]

^{1}H NMR: δ = 7.37–7.27 (m, 2 H), 7.27–7.16 (m, 3 H), 3.89 (m, 1 H), 2.91 (m, 1 H), 2.77 (m, 1 H), 2.00 (m, 3 H).

^{19}F NMR: δ = –79.87 (d, *J* = 6.4 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 204 (12.7) [M$^+$], 117 (31.4), 91 (100.0), 65 (13.9).

(2*E*)-1-(2,4-dinitrophenyl)-2-(2,2,2-trifluoroethylidene)hydrazine (8)
The physical and spectroscopic data were identical to those in the literature.[16]

^{1}H NMR: δ = 11.37 (s, 1 H), 9.12 (s, 1 H), 8.44 (dd, *J* = 9.6 Hz, *J* = 2.7 Hz, 1 H), 8.04 (d, *J* = 9.6 Hz, 1 H), 7.50 (q, *J* = 3.8 Hz, 1 H).

^{19}F NMR: δ = –66.51 (d, *J* = 3.8 Hz, 3 F).

MS (EI, 70 eV): *m/z* (%) = 278 (67.1) [M$^+$], 259 (15.7), 79 (100.0), 75 (43.3), 63 (57.6), 51 (43.0).

Benzyl Phenyl Sulfone (10)
The physical and spectroscopic data were identical to those reported in the literature.[17]

^{1}H NMR: δ = 7.96–7.56 (m, 3 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.36–7.21 (m, 3 H), 7.10 (d, *J* = 7.6 Hz, 2 H), 4.31 (s, 2 H).

MS (EI, 70 eV): *m/z* (%) = 232 (3.9) [M$^+$], 91 (100.0).

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