

Regioselective Substitution of Phenols with Trifluoroacetaldehyde Ethyl Hemiacetal

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Phenol did not react directly with trifluoroacetaldehyde ethyl hemiacetal. In the presence of catalytic amounts of anhydrous potassium carbonate, however, the reaction readily occurred. The *p*-substituted product 4-(2,2,2-trifluoro-1-hydroxyethyl)phenol predominated. In contrast, the reaction catalyzed by zinc halide predominantly produced the *o*-substituted product. Corresponding reactions of several phenols were studied under the same catalytic conditions.

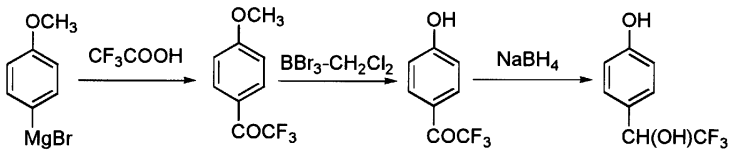
2,2,2-Trifluoroethanols are of great interest because of their unique physical, chemical, and biological properties.[1] The development of new preparation methods therefore continues to be an important area of research. Useful synthetic methods reported include the reduction of trifluoromethyl ketones,[2] addition of trifluoromethanide anion reagents to carbonyl compounds,[3] and electrochemical trifluoromethylation of carbonyl compounds.[4] Trifluoroacetaldehyde is a very efficient reagent for obtaining 2,2,2-trifluoroethanols.[5] Because it is unavailable commercially, its hemiacetal has been usually used to react with enamines,[6] enolates,[7] olefins,[8] alkylmetals[9] or arenes,[10] sometimes using Lewis acid catalyst.

We found that trifluoroacetaldehyde ethyl hemiacetal (TFAE) readily reacts with the various electron-rich heteroarenes, forming 1-hetereoaryl-2,2,2-trifluoroethanols in good yields.[11] In our continuing investigations, substitution reactions of TFAE with electron-rich benzene derivatives, in particularly phenol, have been used to prepare 1-(hydroxyphenyl)-2,2,2-trifluoroethanols.[12] 4-(2,2,2-Trifluoro-1-hydroxyethyl)phenol (**1**) is an important intermediate used in ferroelectric liquid crystals. Usually it is prepared by the Grignard reaction of trifluoroacetic acid, with subsequent demethylation and reduction[2c,13] (Scheme 1). We recently succeeded in achieving regioselective substitutions of phenols with TFAE by using potassium carbonate or zinc halide as the catalyst. This method provides a most convenient route to 1-(hydroxyphenyl)-2,2,2-trifluoroethanols (Chart 1). Details of the procedure are described hereafter.

Results

When a mixture of equimolar amounts of phenol and TFAE was heated at 120 °C for 8 h, no detectable substitution product was determined by TLC, but in the presence of 0.05 molar amount of anhydrous potassium carbonate, phenol readily reacted with TFAE even at 60 °C, giving a good yield of the *p*-substituted product 4-(2,2,2-trifluoro-1-hydroxyethyl)phenol (**1**) and a small amount of the *o*-substituted product 2-(2,2,2-trifluoro-1-hydroxyethyl)phenol (**2**).[12] Further experiments clearly showed that the ratio of **1**/**2** is comparatively low and that the disubstituted product (**3**), purified as its triacetylated product (**4**) (Chart 1), is generated simultaneously when the reaction takes place at a high temperature (Scheme 2). Moreover, the addition of a large excess of TFAE led to the formation of the trisubstituted product 2,4,6-tris(2,2,2-trifluoro-1-hydroxyethyl)phenol (**5**) in an excellent yield. The yields obtained are given in Table 1 (Entries 1–4).

Next the reaction of phenol with TFAE was studied with a Lewis acid as the catalyst. The first experiment done at 70 °C in the presence 0.05 molar amount of zinc chloride gave no substitution product, but when the temperature was raised to 130 °C, the reaction readily proceeded (Scheme 2). Product analysis by GC showed preferential formation of *o*-substituted product (**2**) rather than *p*-substituted product (**1**) (Table 1, Entry 6). In addition, about 5% of the corresponding ether, 2- or 4-(1-ethoxy-2,2,2-trifluoroethyl)phenol (**6**), was detected by GC/MS, but the product was not purified further. Similar results



Scheme 1.

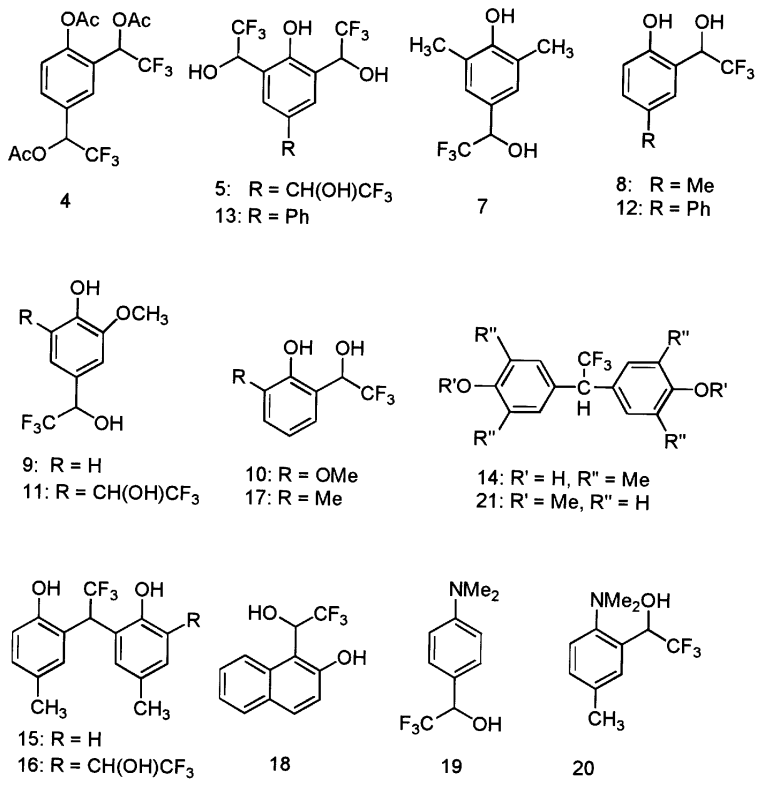
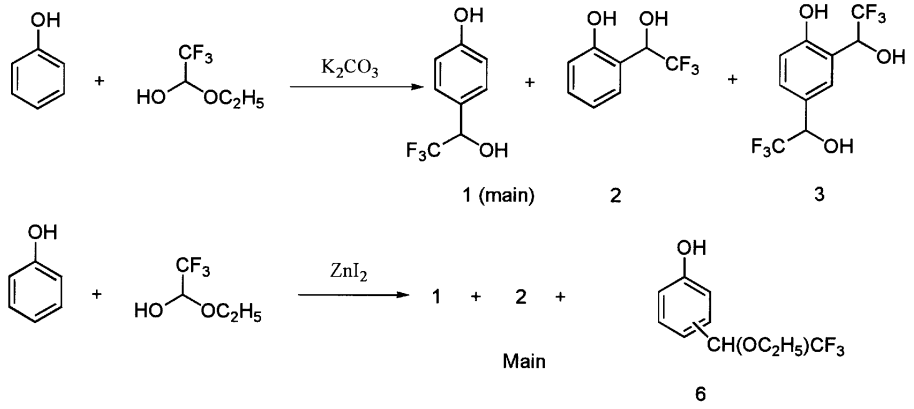


Chart 1.



Scheme 2.

Table 1. Reaction of Phenol with TFAE

Entry	Molar ratio[a)]	Catalyst[b)]	Conditions	Product (Yield/%)
1	1	none	120 °C, 8 h	none
2	1	K_2CO_3	60 °C, 12 h	**1** (65) **2**(10) [c)]
				1 (85) **2**(15) [d)]
3	1	K_2CO_3	120 °C, 6 h	**1** (48) **2**(20) **3** (7) [c)]
				1 (55) **2**(30) **3** (10) [d)]
4	5	K_2CO_3	120 °C, 6 h	**5** (92) [c)]
5	1.1	$ZnCl_2$	70 °C, 6 h	none
6	1.1	$ZnCl_2$	130 °C, 8 h	**1** (1) **2**(46) [d)]
7	1.1	ZnI_2	130 °C, 8 h	**1** (4) **2**(83) [d)]
8	1.1	$BF_3 \cdot Et_2O$	45 °C, 8 h	**1** (10) [d)]

a) TFAE/Phenol. b) Catalytic amounts: K_2CO_3 (0.05 mol amt.), ZnX_2 (0.05 mol amt.) and $BF_3 \cdot Et_2O$ (0.1 mol amt.). c) Isolated yields. d) GC yields .

were obtained when 0.05 molar amount of zinc iodide was used, but the catalytic activity was much higher than that of zinc chloride (Entry 7). In contrast, *p*-substitution occurred with low conversion when the reaction was catalyzed by boron trifluoride–diethyl ether, indicative of low catalytic efficiency (Entry 8). For this reason, the reactions of other phenols were studied using potassium carbonate or zinc halide as the catalyst.

The reaction of 2,6-dimethylphenol catalyzed by potassium carbonate afforded only the *p*-substituted product 2,6-dimethyl-4-(2,2,2-trifluoro-1-hydroxyethyl)phenol (**7**), whereas that of 4-methylphenol gave the *o*-substituted product 4-methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)phenol (**8**), both in high yields (Table 2, Entries 1–2).[12] With 2-methoxyphenol, mainly the *p*-substituted product 2-methoxy-4-(2,2,2-trifluoro-1-hydroxyethyl)phenol (**9**) was formed together with small amounts of the *o*-substituted and disubstituted products, 2-methoxy-6-(2,2,2-trifluoro-1-hydroxyethyl)phenol (**10**) and 2-methoxy-4,6-bis(2,2,2-trifluoro-1-hydroxyethyl)phenol (**11**) (Entry 3). The yields of (**10**) and (**11**) somewhat increased when the reaction temperature was raised to 120 °C (Entry 4). In the case of 4-phenylphenol, only the *o*-substituted products 4-phenyl-2-(2,2,2-trifluoro-1-hydroxyethyl)phenol (**12**) and 4-phenyl-2,6-bis(2,2,2-trifluoro-1-hydroxyethyl)phenol (**13**) were obtained (Entry 5), but no product substituted in the other phenyl ring was detected.

These phenols were also used to study the reaction catalyzed by 0.05 molar amount of zinc iodide. Results are given in Table 3. With 2,6-dimethylphenol, *p*-substituted product (**7**) was the main product (Entry 1), and a small amount of 4,4′-(2,2,2-trifluoroethylidene)bis(2,6-dimethylphenol) (**14**) was detected by ^{19}F NMR and MS. 4-Methylphenol, however, always gave the *o*-substitution (Entry 3). Besides the main product (**8**), small amounts of condensation products (**15**) and (**16**) were detected. Only *o*-substitution occurred in the reaction with 4-phenylphenol, disubstitution being markedly decreased (Entry 6) as compared with the reaction catalyzed by potassium carbonate (Table 2, Entry 5). The reaction promoted by boron trifluoride was also assessed. Only the *o*-substituted products (**12**) and (**13**) were produced under the conditions (Entry 7). Like phenol, 2-methylphenol reacted with TFAE, giving a high yield of the *o*-substituted product 2-methyl-6-(2,2,2-trifluoro-1-hydroxyethyl)phenol (**17**), but there was no detectable *p*-substituted product (Entry 4). The reaction of 2-methoxyphenol proceeded with relatively low regioselectivity, the *o*-substituted product (**10**) still being the main product (Entry 5).

As reported, zinc chloride also catalyzed the reaction of TFAE with phenol, but with relatively poor catalytic activity. For this reason, in the reaction with phenols we used a high molar ratio of zinc chloride. In the presence of 0.5 molar amount of zinc chloride, the reaction with phenol proceeded smoothly at 130 °C. Crude product analysis, however, clearly showed that very complicated products were afforded under those conditions, mainly because of successive condensation between 1-aryl-2,2,2-trifluoroethanols **1**–**3** and phenol. Similar results were obtained for the reactions with 4-methylphenol and with 2-methoxyphenol. In contrast, bisphenolic compound (**14**) was the main product in the corresponding reaction with 2,6-dimethylphenol, and it was easily purified by column chromatography (Table 3, Entry 2). The corresponding reaction with 1- or 2-naphthols was also investigated. In the presence of 0.05 molar amount of zinc iodide, the reaction with 2-naphthol gave only the 1-substituted product 1-(2,2,2-trifluoro-1-hydroxyethyl)-2-naphthol (**18**) (Table 4, Entry 1), whereas that of 1-naphthol afforded complicated products. Similar results were observed when 0.5 molar amount of zinc chloride was used instead (Table 4, Entry 2). In addition, the reaction with 1- or 2-naphthols carried out in the presence of 0.05 molar amount of potassium carbonate at 90 °C provided quite complicated products.

Table 2. Reaction of Substituted Phenols Catalyzed by K_2CO_3

Entry	Substituent	Conditions	Products (Yield/%[a)])		
1	2,6-di-Me	120 °C, 6 h	**7** (95)		
2	4-Me	120 °C, 6 h	**8** (91)		
3	2-MeO	60 °C, 72 h	**9** (48)	**10** (3)	**11** (6)
4	2-MeO	120 °C, 6 h	**9** (33)	**10** (11)	**11** (12)
5	4-Ph	120 °C, 30 h	**12** (43)	**13** (22)	

a) Isolated yields based on the substrate

Table 3. Reaction of Substituted Phenols Catalyzed by Lewis Acid at 130 °C

Entry	Substituent	Catalyst[a)]	Time /h	Product (Yield/%[b)])	
1	2,6-di-Me	ZnI_2	8	**7** (92)	**14** (3)
2	2,6-di-Me	$ZnCl_2$	8	**7** (19)	**14** (78)
3	4-Me	ZnI_2	8	**8** (86)	
4	2-Me	ZnI_2	8	**17** (92)	
5	2-MeO	ZnI_2	8	**9** (16)	**10** (46)
6	4-Ph[c)]	ZnI_2	12	**12** (63)	**13** (5)
7	4-Ph[c)]	BF_3	12	**12** (21)	**13** (2)

a) Catalyst: ZnI_2 (0.05 mol amt.), $ZnCl_2$ (0.5 mol amt.), BF_3 (0.2 mol amt.). b) Isolated yields based on the substrate. c) Toluene was the solvent.

Table 4. Reaction of Other Typical Arenes with TFAE

Entry	Substrate	Catalyst[a)]	Conditions	Product (Yield/%[b)])
1	2-naphthol	ZnI_2	130 °C, 8 h	**18** (14)
2	2-naphthol	$ZnCl_2$	130 °C, 8 h	**18** (57)
3	$PhNMe_2$	none	120 °C, 6 h	**19** (95)
4	*p*-$MePhNMe_2$	none	120 °C, 30 h	**20** (58)
5	PhOMe	ZnI_2	130 °C, 8 h	**21** (10)
6	PhOMe	$ZnCl_2$	130 °C, 8 h	**21** (21)
7	PhNHAc	$ZnCl_2$	130 °C, 8 h	trace

a) Catalytst: ZnI_2 (0.05 mol amt.), $ZnCl_2$ (0.5 mol amt.). b) Isolated yields based on the substrate.

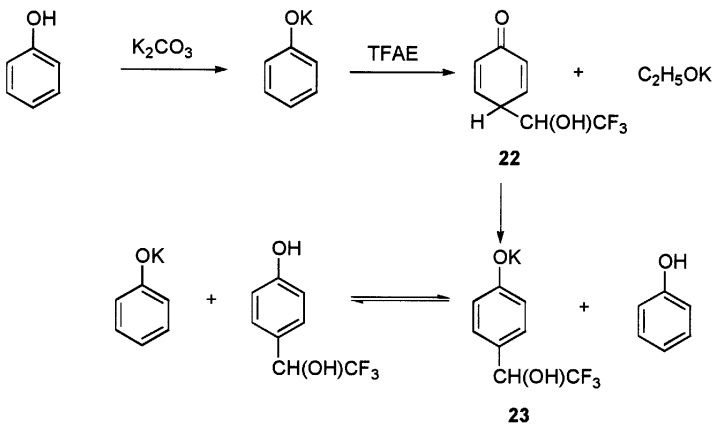
Next we extended our study to other typical benzene derivatives. *N*,*N*-dimethylaniline reacted smoothly with TFAE with no catalyst present at 120 °C, yielding 4-(2,2,2-trifluoro-1-hydroxyethyl)-*N*,*N*-dimethylaniline (**19**) in a high yield (Table 4, Entry 3). A similar reaction with *N*,*N*-dimethyl-*p*-toluidine provided a good yield of 4-methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)-*N*,*N*-dimethylaniline (**20**) (Entry 4).[12] Acetanilide, however, did not react with TFAE, and only a trace amount of substituted product was detected in the presence of zinc chloride (Entry 7). The reaction with anisole proceeded in the presence of 0.05 molar amount of zinc iodide with formation of 4,4′-(2,2,2-trifluoroethylidene)dianisole (**21**) (Entry 5), and the yield of (**21**) was markedly enhanced by using 0.5 molar amount of zinc chloride as the catalyst (Entry 6).

Discussion

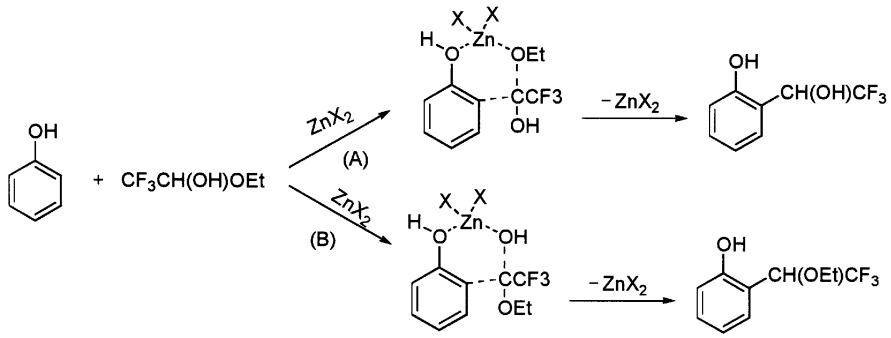
As reported above, direct substitution of TFAE with phenol did not occur due to the relatively low reactivity of phenol, but the reaction readily took place in the presence of a catalytic amount of potassium carbonate or zinc halide. The reaction catalyzed by potassium carbonate mainly produced *p*-substituted product (**1**), whereas that catalyzed by zinc halide preferentially formed *o*-substituted product (**2**). Moreover, bisphenolic compounds are mainly generated when a large amount of zinc chloride was used.

In interpreting these results, one must consider the role of the catalyst used. As known to us, *o*-substitution was usually preferred in some aromatic substitution reaction of sodium phenoxide such as in the Kolbe–Schmitt reaction. Although the mechanism is not clearly understood, apparently some kind of a complex is formed between the reactants.[14] In fact, potassium phenoxide, which is less likely to form such a complex, is chiefly attacked in the para position.[15] Therefore in the case of potassium carbonate, the reaction may have proceeded along the route shown in Scheme 3. Potassium carbonate, a strong Brønsted base, easily removed the weakly acidic proton of phenol, generating the much more reactive potassium phenoxide. Potassium phenoxide is mainly attacked by TFAE in the para position, affording an unstable intermediate **22**, which was quickly converted into the substituted phenolate anion **23**. This anion was consumed in the following ways: (a) abstracting one proton from phenol to form the final product (**1**) and a new phenolate anion; and (b) successive reaction with TFAE to form disubstituted or trisubstituted products. Eventually, trisubstituted product **5** was obtained in high yield when a large excess of TFAE was used.

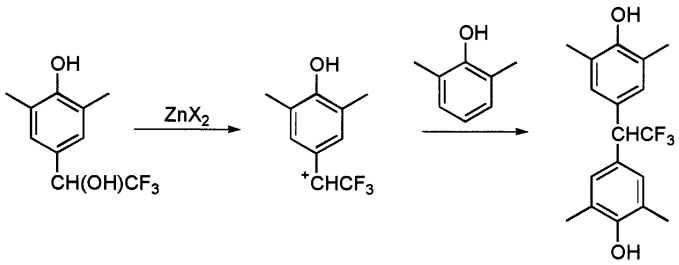
Lewis acids are widely used in the Friedel–Crafts reaction of TFAE with olefinic compounds.[8] Their catalytic effect is the enhancement of the reactivity of electrophile by coordination with one oxygen atom of TFAE. The catalytic role of zinc halide in the reaction with phenol can be considered similar. The preference for the *o*-substitution suggests that this reaction proceeds through a six-membered transition state involving a zinc halide (Scheme 4), as reported in the reactions of phenol or 1-naphthol with aldehydes catalyzed by aluminium or titanium complexes.[16] Moreover, preferential formation of 1-aryl-2,2,2-trifluoroethanol, rather than the corresponding ether **6**, indicates that the pathway (A) is much more important than path-



Scheme 3.



Scheme 4.



Scheme 5.

way (B) in the reaction. An alternative explanation for the preferential removal of ethoxy group in the presence of a Lewis acid has been already proposed by HSAB theory.[10b] Furthermore, formation of bisphenolic compounds, e.g. (**14**), may be due to a successive substitution of 1-aryl-2,2,2-trifluoroethanol with phenol; a possible pathway for this is suggested in Scheme 5. This means that the coordination of zinc halide may greatly weaken the C–O bond of 1-aryl-2,2,2-trifluoroethanol, and may eventually lead to the generation of a reactive species such as 1-aryl-2,2,2-trifluoroethyl cation.

Experimental

^{1}H NMR spectra were recorded at 90 MHz on a Hitachi R-90H FT spectrometer with tetramethylsilane (TMS) as an internal standard. ^{19}F NMR spectra were recorded at 84.7 MHz on the same spectrometer with hexafluorobenzene as an internal standard. Mass spectra (70 eV) were determined on a Hitachi M-80 instrument. Melting points were measured in a glass capillary on a heating block and are uncorrected. High-resolution mass spectra were recorded on a JEOL JMS-SX102A MS spectrometer.

Reaction with Phenol Catalyzed by K_2CO_3 (General Procedure): A mixture of 2.82 g (30 mmol) of phenol, 4.32 g (30 mmol) of trifluoroacetaldehyde ethyl hemiacetal and 0.21 g (1.5 mmol) of anhydrous potassium carbonate was heated with stirring at the temperatures and for the periods given in Tables 1 and 2. After being cooled, the mixture was dissolved in ethyl acetate (20 ml), and washed with aqueous ammonium chloride and distilled water, then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was isolated by silica gel column chromatography (hexane/ethyl acetate, v/v: 5:1 to 5:2) to give products (**1**) and (**2**).

Reaction of Phenol Catalyzed by Lewis Acid (General Procedure): A mixture of 2.82 g (30 mmol) of phenol, 4.75 g (33 mmol) of trifluoroacetaldehyde ethyl hemiacetal and 0.48 g (1.5 mmol) of zinc iodide was heated with stirring at 130 °C for the periods given in Tables 1 and 3. After being cooled, the mixture was dissolved in ethyl acetate (20 ml), and washed with water. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed by evaporation under reduced pressure. The residue was isolated by column chromatography eluted with hexane/ethyl acetate (v/v: 5/1 to 5/2).

In the case of 4-phenylphenol, about 10 ml of toluene dried over 4 Å molecular sieves was added to the mixture.

4-(2,2,2-Trifluoro-1-hydroxyethyl)phenol (1). Mp 123.5–125 °C, white needles. ^{1}H NMR (acetone-d_6) δ 2.95 (2H, br, s), 5.06 (1H, q, J = 7.4 Hz), 6.86 (2H, d, J = 8.5 Hz), 7.36 (2H, d, J = 8.5 Hz). ^{19}F NMR (acetone-d_6) δ 85.73 (3F, d, J = 7.4 Hz); MS m/z 192 (M^+, 38), 123 (100). HRMS Found: m/z 192.0398, Calcd for $C_8H_7O_2F_3$: 192.0398.

2-(2,2,2-Trifluoro-1-hydroxyethyl)phenol (2). Mp 118–118.5 °C, white needles. ^{1}H NMR (acetone-d_6) δ 2.87 (2H, br, s), 5.57 (1H, q, J = 7.4 Hz), 6.91 (2H, m), 7.17 (1H, dd, J = 7.0, 2.0 Hz), 7.50 (1H, d, J = 7.0 Hz). ^{19}F NMR (acetone-d_6) δ 85.94 (3F, d, J = 7.4 Hz); MS m/z 192 (M^+, 55), 174 (18), 146 (40), 123 (95), 77 (100). HRMS Found: m/z 192.0378, Calcd for $C_8H_7O_2F_3$: 192.0398.

2,4-Bis(1-acetoxy-2,2,2-trifluoroethyl)phenyl Acetate (4). Mp 109–110 °C, white plates. ^{1}H NMR ($CDCl_3$) δ 2.17 (3H, s), 2.20 (3H, s), 2.37 (3H, s), 6.19 (1H, q, J = 6.8 Hz), 6.51 (1H, q, J = 6.8 Hz), 7.27 (1H, dd, J = 8.1, 2.8 Hz), 7.58 (1H, d, J = 8.1 Hz), 7.65 (1H, d, J = 2.8 Hz). ^{19}F NMR ($CDCl_3$) δ 85.84 (3F, d, J = 6.8 Hz), 86.25 (3F, d, J = 6.8 Hz); MS m/z 416 (M^+, 12), 374 (100), 357 (13), 332 (76), 294 (17). HRMS Found: 416.0693, Calcd for $C_{16}H_{14}O_6F_6$: 416.0695.

2,4,6-Tris(2,2,2-trifluoro-1-hydroxyethyl)phenol (5). A colorless liquid. ^{1}H NMR (acetone-d_6) δ 3.30 (2H, br, s), 5.18 (1H, q, J = 7.3 Hz), 5.63 (2H, q, J = 7.3 Hz), 6.60 (1H, br,s), 7.64 (2H, s),

8.90 (1H, br, s). ^{19}F NMR (acetone-d_6) δ 85.69 (9F, d, J = 7.3 Hz); MS m/z 388 (M^+, 26), 319 (39), 301 (100), 281 (15). HRMS Found: m/z 388.0359, Calcd for $C_{12}H_9O_4F_9$: 388.0357.

2,6-Dimethyl-4-(2,2,2-trifluoro-1-hydroxyethyl)phenol (7). Mp 136–138 °C, white solid. ^{1}H NMR ($CDCl_3$) δ 2.25 (6H, s), 4.88 (1H, q, J = 7.2 Hz), 5.12 (2H, br, s), 7.07 (2H, s). ^{19}F NMR ($CDCl_3$) δ 85.91 (3F, d, J = 7.2 Hz); MS m/z 220 (M^+, 60), 151 (100). HRMS Found: m/z 220.0711, Calcd for $C_{10}H_{11}O_2F_3$: 220.0711.

4-Methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)phenol (8). Mp 106–107.5 °C, white needles. ^{1}H NMR ($CDCl_3$) δ 2.26 (3H, s), 4.51 (2H, br, s), 5.16 (1H, q, J = 6.7 Hz), 6.75 (1H, d, J = 8.1 Hz), 7.02 (2H, m). ^{19}F NMR ($CDCl_3$) δ 83.49 (3F, d, J = 6.7 Hz); MS m/z 206 (M^+, 39), 188 (21), 137 (20), 108 (100). HRMS Found: m/z 206.0551, Calcd for $C_9H_9O_2F_3$: 206.0555.

2-Methoxy-4-(2,2,2-trifluoro-1-hydroxyethyl)phenol (9). Mp 83–85 °C, white grains. ^{1}H NMR ($CDCl_3$) δ 2.85 (1H, br, s), 3.89 (3H, s), 4.92 (1H, q, J = 6.6 Hz), 5.70 (1H, br, s), 6.92 (2H, s), 6.99 (1H, s). ^{19}F NMR ($CDCl_3$) δ 83.46 (3F, d, J = 6.6 Hz); MS m/z 222 (M^+, 100), 204 (19), 184 (66), 153 (59), 124 (26), 93 (37). HRMS m/z Found: 222.0499, Calcd for $C_9H_9O_3F_3$: 222.0504.

2-Methoxy-6-(2,2,2-trifluoro-1-hydroxyethyl)phenol (10). A colorless liquid. ^{1}H NMR ($CDCl_3$) δ 3.64 (1H, br, s), 3.90 (3H, s), 5.29 (1H, q, J = 7.0 Hz), 6.10 (1H, br, s), 6.91 (3H, s). ^{19}F NMR ($CDCl_3$) δ 83.75 (3F, d, J = 7.0 Hz); MS m/z 222 (M^+, 79), 204 (19), 184 (100), 153 (15), 133 (13). HRMS Found: m/z 222.0504, Calcd for $C_9H_9O_3F_3$: 222.0504.

2-Methoxy-4,6-bis(2,2,2-trifluoro-1-hydroxyethyl)phenol (11). A colorless liquid. ^{1}H NMR ($CDCl_3$) δ 2.85 (1H, br, s), 3.89 (3H, s), 4.91 (1H, q, J = 6.2 Hz), 5.34 (1H, q, J = 6.2 Hz), 5.70 (2H, br, s), 7.04 (1H, s), 7.10 (1H, s). ^{19}F NMR ($CDCl_3$) δ 83.52 (6F, d, J = 6.2 Hz); MS m/z 320 (M^+, 100), 303 (37), 282 (32), 251 (38). HRMS Found: m/z 320.0492, Calcd for $C_{11}H_{10}O_4F_6$: 320.0483.

4-Phenyl-2-(2,2,2-trifluoro-1-hydroxyethyl)phenol (12). Mp 93–94 °C, white grains. ^{1}H NMR ($CDCl_3$) δ 5.10 (1H, br, s), 5.28 (1H, q, J = 6.9 Hz), 6.94 (1H, d, J = 7.3 Hz), 7.30 (1H, d, J = 7.3 Hz), 7.45 (6H, m). ^{19}F NMR ($CDCl_3$) δ 83.49 (3F, d, J = 6.9 Hz); MS m/z 268 (M^+, 100), 303 (37), 250 (69), 222 (33), 181 (28), 153 (14). HRMS Found: m/z 268.0703, Calcd for $C_{14}H_{11}O_2F_3$: 268.0711.

4-Phenyl-2,6-bis(2,2,2-trifluoro-1-hydroxyethyl)phenol (13). Mp 102–104 °C, white solid. ^{1}H NMR ($CDCl_3$) δ 5.31 (2H, q, J = 6.8 Hz), 7.42 (5H, m), 7.47 (2H, s). ^{19}F NMR ($CDCl_3$) δ 83.64 (6F, d, J = 6.8 Hz); MS m/z 366 (M^+, 100), 348 (34), 328 (17), 279 (82), 259 (32). HRMS Found: m/z 366.0680, Calcd for $C_{16}H_{12}O_3F_6$: 366.0691.

4,4′-(2,2,2-Trifluoroethylidene)bis(2,6-dimethylphenol) (14). Mp 85–86 °C, colorless needles. ^{1}H NMR ($CDCl_3$) δ 2.22 (12H, s), 4.40 (1H, q, J = 10.3 Hz), 4.60 (2H, br, s), 6.95 (4H, s). ^{19}F NMR ($CDCl_3$) δ 95.67 (3F, d, J = 10.3 Hz); MS m/z 324 (M^+, 36), 255 (100). HRMS Found: m/z 324.1344, Calcd for $C_{18}H_{19}O_2F_3$: 324.1337.

2-Methyl-6-(2,2,2-trifluoro-1-hydroxyethyl)phenol (17). A colorless liquid. ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s), 4.20 (2H, br, s), 5.17 (1H, q, J = 7.3 Hz), 6.80 (1H, t, J = 7.2 Hz), 6.98 (1H, d, J = 7.2 Hz), 7.15 (1H, d, J = 7.2 Hz). ^{19}F NMR ($CDCl_3$) δ 83.46 (3F, d, J = 7.3 Hz); MS m/z 206 (M^+, 100), 189 (5), 168 (62), 137 (39), 109 (27), 91 (38). HRMS Found: m/z 206.0555, Calcd for $C_9H_9O_2F_3$: 206.0555.

1-(2,2,2-Trifluoro-1-hydroxyethyl)-2-naphthol (18). The reaction of 2-naphthol was carried out according to the general procedure. The crude product was purified by column chromatography eluted with hexane/ethyl acetate (v/v 3:1). Mp 139–140 °C, white needles. ^{1}H NMR (acetone-d_6) δ 5.10 (2H, br, s), 6.29 (1H, q, J = 7.9 Hz), 7.18 (1H, d, J = 9.1 Hz), 7.45 (2H, m), 7.84 (2H, m), 8.27 (1H, m). ^{19}F NMR (acetone-d_6) δ 87.68 (3F, d, J = 7.9 Hz); MS m/z 242 (M^+, 52), 196 (26), 173 (100), 127 (59). HRMS Found: m/z 242.0554, Calcd for $C_{12}H_9O_2F_3$: 242.0555.

4-(2,2,2-Trifluoro-1-hydroxyethyl)-*N*,*N*-dimethylaniline (19). A mixture of 3.63 g (30 mmol) of *N*,*N*-dimethylaniline and 4.32 g (30 mmol) of trifluoroacetaldehyde ethyl hemiacetal was heated with continuous stirring at 120 °C for 6 h. After being cooled, the mixture became a solid cake. The crude product was then recrystallized from dichloromethane to give 6.24 g (95%) of the pure product (**19**). Mp 98–99 °C, white needles. ^{1}H NMR ($CDCl_3$) δ 2.55 (1H, s), 2.94 (6H,s), 4.85 (1H, q, J = 6.5 Hz), 6.70 (2H, d, J = 8.7 Hz), 7.29 (2H, d, J = 8.7 Hz). ^{19}F NMR (acetone-d_6) δ 85.81 (3F, d, J = 6.5 Hz); MS m/z 219 (M^+, 94), 150 (100). HRMS Found: m/z 219.0871, Calcd for $C_{10}H_{12}NOF_3$: 219.0871.

4-Methyl-2-(2,2,2-trifluoro-1-hydroxyethyl)-*N*,*N*-dimethylaniline (20). A mixture of 4.05 g (30 mmol) of *N*,*N*-dimethyl-*p*-toluidine and 4.32 g (30 mmol) of trifluoroacetaldehyde ethyl hemiacetal was heated with continuous stirring at 120 °C for 30 h. After being cooled, the mixture was distilled under reduced pressure, giving 4.05 g (58%) of the product (**20**), Bp 124–126 °C/ 9 mm Hg, a yellowish liquid. ^{1}H NMR ($CDCl_3$) δ 2.31 (3H, s), 2.66 (6H, s), 2.88 (1H, s), 5.04 (1H, q, J = 7.5 Hz), 6.99 (1H, d, J = 1.8 Hz), 7.20 (1H, d, J = 1.8 Hz), 7.27 (1H, s). ^{19}F NMR ($CDCl_3$) δ 83.67 (3F, d, J = 7.5 Hz); MS m/z 233 (M^+, 100), 218 (12), 164 (58), 162 (55), 134 (30). HRMS Found: m/z 233.1025, Calcd for $C_{11}H_{14}NOF_3$: 233.1027.

4,4′-(2,2,2-Trifluoroethylidene)dianisole (21). The product was purified by column chromatography eluted with hexane/ethyl acetate (v/v: 9:1). A colorless liquid. ^{1}H NMR (acetone-d_6) δ 3.78 (6H, s), 4.90 (1H, q, J = 10.5 Hz), 6.92 (4H, d, J = 8.8 Hz), 7.38 (4H, d, J = 8.8 Hz). ^{19}F NMR (acetone-d_6) δ 97.69 (3F, d, J = 10.5 Hz); MS m/z 296 (M^+, 26), 227 (100), 165 (14), 137 (36), 107 (15). HRMS Found: m/z 296.1019, Calcd for $C_{16}H_{15}O_2F_3$: 296.1024.

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