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Efficient and Reliable Iodination and *O*-Methylation of Fluorinated Phenols

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Fluorinated phenols and other electron-deficient phenolic substrates are efficiently and cleanly iodinated by an iodine/iodide mixture employing alkaline conditions. This protocol turned out to be the most practical for the generation of such highly fluorinated iodophenols. For later application in coupling processes the protection of the phenolic hydroxy moiety is often required. Therefore, a practical iodination and subsequent methylation sequence was elaborated providing the highly fluorinated anisoles with good to excellent yields. The developed method is applicable for a broad scope of fluorinated phenols and analogues.

Introduction

Iodo substituents offer the straightforward installation of various functionalities because of their outstanding reactivity.[1] Consequently, iodoarenes represent very valuable precursors for the synthesis of complex organic molecules. For example, transition-metal-catalyzed cross-coupling reactions of arenes represent an extremely powerful synthetic tool, wherein the iodo derivatives are usually considered as the preferred substrates.[2] Furthermore, the superior leaving nature of this specific functionality is beneficial in dehalometallations,[3] protodeiodinations[4] and metal-catalyzed homo-coupling reactions.[5] Among the latter, the copper-mediated Ullmann coupling is the most prominent transformation.[6] In addition, iodo-substituted aromatic systems are applied as contrast agents for X-ray diagnostics[7] or as radiolabelled compounds.[8] Fluoro substituents are known to enhance the metabolic and electrochemical stability.[9] Consequently, fluorinated compounds represent the key entities for pharmaceutical[10] and energy-storage applications.[11]

In general, phenols can be iodinated under basic or slightly basic conditions.[12] Common protocols involve the application of iodine/morpholine mixtures.[13] Alternatively, iodine can be provided as dichloroiodate in combination with organic cations[14] or as iodo amide in ionic liquids.[15] The reagent mixtures consisting of hypochlorite and iodide give direct access to simple iodophenols.[16] Treatment with iodine monochloride is mostly applied for periodination reactions.[17] The installation of iodo moieties in peptidic substrates is cleanly performed by the Barluenga reagent.[18] However, this powerful iodonium species has to be prepared with mercury salts and is therefore not preferable for larger applications.[19]

The installation of an iodo moiety in electron-deficient phenols turned out to be difficult.[20] In particular, fluorinated substrates seem to be challenging since the electron-withdrawing nature and good leaving-group properties of fluorine cause side reactions.[21] Here we present a reliable and efficient protocol for the iodination of fluorinated phenols with simple iodination reagents.

Results and Discussion

First tests for the iodination of some fluorinated phenols with several iodination reagents resulted in very low yields with a tremendously impure product or very slow conversion with many byproducts. In particular the conversion of **1m** with $BnNEt_3ICl_2/NaHCO_3$ lead to a yield of 31% (GC) in a very complex mixture, which was hardly separated. The use of iodine monochloride for the iodination of **1m** revealed even poorer results, namely a yield of 15% (GC), whereas the 6-chlorinated phenol was identified as the main product (GC/MS). The iodinated phenol **2m** was isolated in moderate yields (36%) after conversion of **1m** with I_2/morpholine. However, these reaction conditions are not applicable to more electron-deficient substrates, as the reaction of **1a** was very slow and aborted after 5 d (69% starting material, 31% product, GC). Treatment at elevated temperature rendered led to complete decomposition of the substrate. Consequently, a more drastic but still practical and environmentally benign method for the iodination of fluorinated phenols was desired. For this purpose the use of an aqueous iodine/iodide mixture in presence of NaOH (Scheme 1) proved to be the most convenient way.

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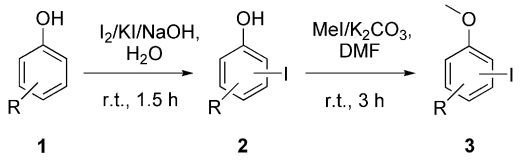


Scheme 1. Conversion of electron-deficient phenols to the corresponding iodinated anisoles (R = F, Cl, Br, NO_2).

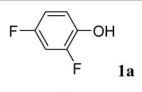
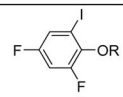
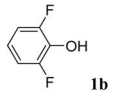
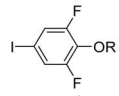
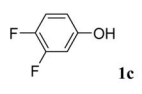
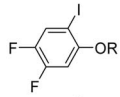
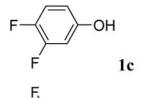
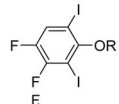
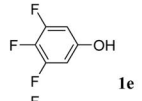
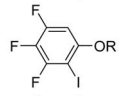
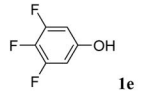
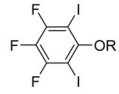
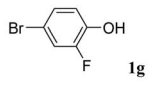
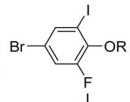
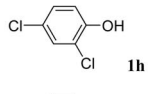
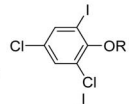
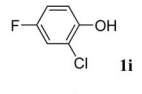
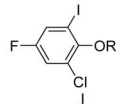
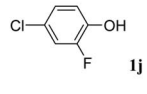
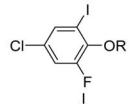
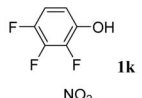
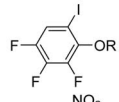
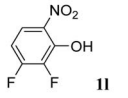
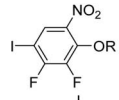
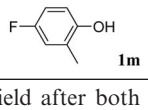
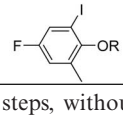
First, the installation of iodo moieties into difluorophenols was studied. 2,4-Difluorophenol (**1a**) was iodinated in position 6 in 66% yield. Subsequent methylation in the combined sequence provided 2,4-difluoro-6-iodoanisole in almost the same yield (Table 1, Entry 1). The isomeric difluorophenols result in the iodination reaction in considerably better yields. Iodination in position 4 provided the iodinated phenol **2b** in excellent yield, whereas the anisole derivative was obtained in 86% isolated yield (Entry 2). 3,4-Difluorophenol offers two positions for the installation of iodo groups. When applying only 1 equiv. of the iodination mixture to **1c**, the functionalization occurs on the less hindered position 6, and the corresponding phenol **2c** and anisole **3c** were isolated in 88% and 84% yield, respectively. A clean twofold installation *ortho* to the hydroxy group is achieved by treatment with 3 equiv. of the iodination mixture (Entry 4). Substrates exhibiting three fluoro groups in positions 3, 4 and 5 represent suitable substrates for the mono- and difunctionalization by altering the amount of the iodination reagent mixture. The corresponding anisoles are isolated in almost the same yield as the intermediate phenols (Entries 5 and 6). Analogous substrates involving bromo and fluoro moieties can be transformed to the iodo derivatives **2g** and **3g** in 90% and 87% isolated yields, respectively (Entry 7). Exchange of halogen substituents was not observed under the applied reaction conditions. The dichloro analogue **1h** as well as the chloro/fluoro-substituted substrates **1i** and **1j** are superb starting materials for these transformations (Entries 8–10). A chloro moiety in position 4 gives excellent yields, whereas a fluoro substituent in that particular position leads to slightly depressed yields in the iodination process (Entry 9). Phenols with a fluoro moiety in *para* position tend to give 4,4-disubstituted cyclohexadienones upon oxidative treatment,[22] which are prone to decomposition under the given reaction conditions. These side products were not isolated, but might reduce the yields during the iodination process. Employment of 2,3,4-trifluorophenol provides the 6-iodinated phenol **2k** and the corresponding anisole **3k** in 95% and 90% isolated yield, respectively (Entry 11).

Replacement of a fluoro moiety by a nitro functionality still allows the installation of an iodo group on a remaining activated position. For excellent to good yields the conversion requires harsher reaction conditions and prolonged treatment (Entry 12).

The installation of the iodo moiety in position 4 of product **2l** was verified by an X-ray analysis of a suitable single crystal. Interestingly, the intramolecular hydrogen bonding of the hydroxy functionality occurs to the adjacent nitro moiety and not to the competing fluoro group (Figure 1). However, by this arrangement the nitro moiety is brought into the plane of the aromatic core and consequently a dense layer-type packing is possible in the solid state.

Analogous conversion of 4-fluoro-2-methylphenol (**1m**) was less successful under the previously described conditions. Mostly decomposition was observed. Switching to aqueous methanol as reaction medium and a slow addition

Table 1. Synthesis of iodinated phenols and corresponding anisoles.

Entry	Starting material	Iodination pattern	Yield [%] iodinated phenol	Yield [%] iodination + methylation[a]
1	 **1a**		66 (**2a**)	60 (**3a**)
2	 **1b**		93 (**2b**)	86 (**3b**)
3	 **1c**		88[b] (**2c**)	84 (**3c**)
4	 **1c**		95[c] (**2d**)	90 (**3d**)
5	 **1e**		70*[b] (**2e**)	66 (**3e**)
6	 **1e**		94[c] (**2f**)	91 (**3f**)
7	 **1g**		90 (**2g**)	87 (**3g**)
8	 **1h**		90 (**2h**)	86 (**3h**)
9	 **1i**		79 (**2i**)	69 (**3i**)
10	 **1j**		96 (**2j**)	88 (**3j**)
11	 **1k**		95 (**2k**)	90 (**3k**)
12	 **1l**		95[d] (**2l**)	86[e] (**3l**)
13	 **1m**		64[f] (**2m**)	55 (**3m**)

[a] Yield after both steps, without purification after first step. [b] 1 equiv. I_2, 1 equiv. KI, stirred at 0 °C for 2 h. [c] 3 equiv. I_2, 3 equiv. KI. [d] 2 equiv. I_2, 2 equiv. KI, stirred at 85 °C for 8 h. [e] Stirred for 3 d, *16% of recovered starting material, 8% of diiodinated product. [f] Solvent mixture: MeOH/H_2O (1:1), dissolved I_2 (1.05 equiv.) and KI (1.05 equiv.) were added slowly.

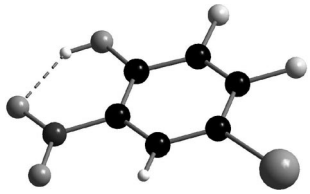


Figure 1. Molecular structure of **2l** by X-ray analysis of a single crystal.

of iodination reagent mixture led to synthetically acceptable amounts for **2m** and **3m** in 64% and 55% isolated yields, respectively (Entry 13).

The limit of the method is reached when electron-rich fluorophenols such as 4-fluoroguajacol are subjected to the reaction conditions. Only a dark residue was obtained without any indication of the desired product.

Conclusions

Fluorinated and other electron-deficient phenols are efficiently iodinated by an I_2/I^- mixture in alkaline media. The employed reagents for iodination are readily available and environmentally benign. The selectivity for mono- vs. multiple-iodination can be directed by the amount of applied iodination reagent. The elaborated protocol is the best way to iodinate fluorinated phenols and can be reliably used to prepare larger amounts. For the preparation of anisoles a telescoped reaction sequence provides similar yields without a purification of the intermediate iodinated phenols. The use of these building blocks in the synthesis of materials for energy-storage devices will be reported in due course.

Experimental Section

General Procedure for the Iodination of the Phenols: To a solution of iodine (1.90 g, 7.5 mmol), potassium iodide (1.25 g, 7.5 mmol) and the corresponding phenol (5 mmol) in water (25 mL) was added dropwise a solution of sodium hydroxide (0.4 g, 10 mmol) in water (25 mL) at 0 °C. The reaction mixture was warmed up to room temperature and then stirred for 1.5 h. After completion of the reaction, the mixture was neutralized with ammonium chloride, followed by addition of sodium thiosulfate until decolorization of the mixture. The aqueous phase was extracted three times with *tert*-butyl methyl ether (10 mL). The combined organic extracts were washed with brine (15 mL), dried with $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified either by sublimation, short-path distillation or column chromatography, depending on the substrate.

General Procedure for the Iodination/Methylation Sequence: The whole series of reactions starts wih of the phenol substrate **1** (5 mmol). The iodination was carried out as described above. The crude product was converted without further purification: A mixture of the corresponding iodinated phenol (5 mmol), potassium carbonate (0.83 g, 6 mmol) and methyl iodide (0.38 mL, 0.85 g, 6 mmol) in DMF (10 mL) was stirred at room temperature for 3 h. Then ammonia solution (10% in water, 25 mL) was added and the aqueous phase extracted two times with *tert*-butyl methyl ether (10 mL). The combined organic extracts were washed three times with water and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude product was purified either by column chromatography or short-path distillation, depending on the anisole.

2,4-Difluoro-6-iodophenol (2a): 2,4-Difluorophenol (1.02 g, 7.84 mmol), purified by column chromatography (cyclohexane/ethyl acetate, 4:1, R_F = 0.46), yielded **2a** (1.32 g, 5.17 mmol, 66%); m.p. 48 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.31 (br. s, 1 H, OH), 7.43 (ddd, J = 7.9, 3.0, 2.0 Hz, 1 H), 7.28 (ddd, J = 10.9, 8.7, 3.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 154.7 (dd, J = 241.6, 11.4 Hz), 149.5 (dd, J = 245.6, 13.0 Hz), 141.8 (dd, J = 15.4, 3.5 Hz), 120.3 (dd, J = 24.2, 3.7 Hz), 104.8 (dd, J = 27.0, 23.7 Hz), 86.83 (dd, J = 10.2, 2.6 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –117.29, –122.61 ppm. HRMS: calcd. for $C_6H_3F_2IO$ 255.9197; foun: 255.9198. $C_6H_3F_2IO$ (255.99): calcd. C 28.15, H 1.18; found C 28.17, H 1.33.

2,4-Difluoro-6-iodoanisole (3a): 2,4-Difluorophenol (**1a**) (2.08 g, 15.99 mmol), purified by column chromatography (cyclohexane, R_F = 0.43) yielded **3a** as a colorless liquid (2.59 g, 9.59 mmol, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (ddd, J = 10.9, 8.2, 3.0 Hz, 1 H), 6.86 (ddd, J = 7.4, 3.0, 2.1 Hz, 1 H), 3.86 (d, J = 1.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = = 158.4 (dd, J = 249.1, 11.6 Hz), 154.4 (dd, J = 254.0, 12.7 Hz), 144.9 (dd, J = 12.5, 4.2 Hz), 121.2 (dd, J = 24.5, 3.8 Hz), 105.9 (dd, J = 26.4, 22.4 Hz), 91.4 (dd, J = 10.4, 2.7 Hz), 61.7 (dd, J = 4.6, 1.1 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –115.7, 123.05 ppm. HRMS: calcd. for $C_7H_5F_2IO$ 269.9353; found 269.9351. $C_7H_5F_2IO$ (270.02): calcd. C 31.14, H 1.87; found C 31.05, H 1.86.

2,6-Difluoro-4-iodophenol (2b): 2,6-Difluorophenol (**1b**) (1.00 g, 7.69 mmol), purified by sublimation (65 °C, 4 mbar), yielded **2b** as a colorless solid (1.83 g, 7.15 mmol, 93%); m.p. 56–57 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.47 (br. s, 1 H, OH), 7.49–7.35 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 152.5 (dd, J = 246.8, 7,1 Hz), 134.14 (t, J = 15.8 Hz), 120.8 (dt, J = 12.1, 3.2 Hz), 77.8 (t, J = 9.3 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]-DMSO): δ = –130.45 ppm. HRMS: calcd. for $C_6H_3F_2IO$ 255.9197; found 255.9191. $C_6H_3F_2IO$ (255.99): calcd. C 28.15, H 1.18; found C 27.88, H 1.26.

2,6-Difluoro-4-iodoanisole (3b): 2,6-Difluorophenol (**1b**) (0.51 g, 3.92 mmol), purified by short-path distillation (55 °C, 2 mbar) yielded **3b** as a colorless liquid (0.91 g, 3.37 mmol, 86%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.42–7.60 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 155.1 (dd, J = 251.6, 6.0 Hz), 135.9 (t, J = 14.0 Hz), 122.7–120.8 (m), 84.3–84.5 (m), 61.7 ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –127.2 ppm. HRMS: calcd. for $C_7H_5F_2IO$ 269.9353; found 269.9358. $C_7H_5F_2IO$ (270.02): calcd. C 31.14, H 1.87; found C 31.10, H 1.91.

3,4-Difluoro-6-iodophenol (2c): 3,4-Difluorophenol (**1c**) (1.01 g, 7.76 mmol), iodine (1.97 g, 7.76 mmol), potassium iodide (1.29 g, 7.76 mmol), sodium hydroxide (0.62 g, 15.52 mmol), stirred at 0 °C for 2 h, purified by column chromatography (toluene, R_F = 0.38), yielded **2c** as a colorless liquid (1.75 g, 6.83 mmol, 88%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.76 (br. s, 1 H, OH), 7.83–7.61 (m, 1 H), 6.95–6.74 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 153.7 (dd, J = 8.9, 2.2 Hz), 149.4 (dd, J = 245.8, 13.5 Hz), 142.9 (dd, J = 240.3, 13.2 Hz), 126.0 (d, J = 19.8 Hz), 103.2 (d, J = 19.8 Hz), 77.1 (dd, J = 6.2, 3.6 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –136.26, –148.81 ppm. HRMS: calcd. for $C_6H_3F_2IO$ 255.9197; found 255.9201. $C_6H_3F_2IO$ (255.99): calcd. C 28.15, H 1.18; found C 27.95, H 1.32.

3,4-Difluoro-6-iodoanisole (3c): 3,4-Difluorophenol (**1c**) (0.79 g, 6.07 mmol), for equiv. of iodination reagents see **2c**, purified by

column chromatography after step 1 (see **2c**) and by short-path distillation after step 2 (70 °C, 1 mbar) yielded **3c** as a colorless liquid, which crystallized upon standing (1.38 g, 5.11 mmol, 84%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.87 (dd, J = 9.8, 9.1 Hz, 1 H), 7.19 (dd, J = 12.9, 7.0 Hz, 1 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 154.9 (dd, J = 8.1, 2.1 Hz), 149.8 (dd, J = 245.8, 13.3 Hz), 143.7 (dd, J = 242.1, 13.1 Hz), 126.4 (d, J = 19.4 Hz), 101.4 (d, J = 21.8 Hz), 78.6 (dd, J = 6.1, 3.9 Hz), 57.3 ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –135.17, –147.12 ppm. HRMS: calcd. for $C_7H_5F_2IO$ 269.9353; found 269.9352. $C_7H_5F_2IO$ (270.02): calcd. C 31.14, H 1.87; found C 31.05, H 1.98.

3,4-Difluoro-2,6-diiodophenol (2d): 3,4-Difluorophenol (**1c**) (1.00 g, 7.69 mmol), iodine (5.85 g, 23.06 mmol), potassium iodide (3.83 g, 23.06 mmol), sodium hydroxide (0.92 g, 23.06 mmol), purified by sublimation (60 °C, 1 mbar), yielded **2d** as a colorless solid (2.79 g, 7.30 mmol, 95%); m.p. 86 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.86 (br. s, 1 H, OH), 7.90 (dd, J = 9.6, 9.1 Hz) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 153.6–153.3 (m), 149.6 (dd, J = 241.4, 14.1 Hz), 143.2 (dd, J = 246.1, 15.9 Hz) 125.7 (d, J = 20.4 Hz), 79.6 (dd, J = 5.9, 3.8 Hz), 77.8 (d, J = 23.0 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –112.94, –143.64 ppm. HRMS: calcd. for $C_6H_2F_2I_2O$ 381.8163; found 381.8164. $C_6H_2F_2I_2O$ (381.89): calcd. C 18.87, H 0.53; found C 18.93, H 0.61.

3,4-Difluoro-2,6-diiodoanisole (3d): 3,4-Difluorophenol (**1c**) (0.72 g, 5.53 mmol), for equiv. of iodination reagents see **2d**, purified by short-path distillation (75 °C, 10^{-2} mbar) yielded **3d** (1.97 g, 4.98 mmol, 90%) as a colorless solid; m.p. 43 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.07–7.93 (m, 1 H), 3.74 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 156.1 (dd, J = 3.2, 3.2 Hz), 150.0 (dd, J = 243.8, 14.2 Hz), 145.7 (dd, J = 251.2, 15.7 Hz), 126.3 (d, J = 20.0 Hz), 84.3 (dd, J = 5.9, 4.0 Hz), 82.2 (d, J = 22.5 Hz), 60.5 ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –112.88, –138.08 ppm. HRMS: calcd. for $C_7H_4F_2I_2O$ 395.8320; found 395.8308. $C_7H_4F_2I_2O$ (395.91): calcd. C 21.24, H 1.02; found C 21.35, H 1.02.

3,4,5-Trifluoro-2-iodophenol (2e): 3,4,5-Trifluorophenol (**1e**) (1.07 g, 7.23 mmol), iodine (1.83 g, 7.23 mmol), potassium iodide (1.20 g, 7.23 mmol), sodium hydroxide (0.58 g, 14.46 mmol), stirred at 0 °C for 2.5 h, purified by column chromatography (toluene, R_F = 0.31), yielded **2e** as a colorless liquid (1.39 g, 5.06 mmol, 70%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.08 (br. s, 1 H, OH) 6.75 (ddd, J = 12.2, 6.4, 2.3 Hz) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 153.5 (ddd, J = 11.5, 7.2, 2.7 Hz), 150.7 (ddd, J = 238.8, 10.9, 6.3 Hz), 150.3 (ddd, J = 245.1, 10.5, 6.2 Hz) ppm. 132.3 (ddd, J = 242.1, 18.4, 16.3), 98.5 (d, J = 20.3), 69.1 (d, J = 24.4) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –114.13, –135.38, –170.74 ppm. HRMS: calcd. for $C_6H_2F_3IO$ 273.9102; found 273.9101. $C_6H_2F_3IO$ (273.98): calcd. C 26.30, H 0.74; found C 25.95, H 0.77.

3,4,5-Tifluoro-2-iodoanisole (3e): 3,4,5-Trifluorophenol (**1e**) (0.94 g, 6.32 mmol), for equiv. of iodination reagents see **2e**, purified by column chromatography after step 1 (see **2e**) and by short-path distillation after step 2 (60 °C, 2 mbar) yielded **3e** as a colorless solid (1.20 g, 4.17 mmol, 66%); m.p. 41 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.13 (ddd, J = 12.9, 6.3, 2.3 Hz, 1 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 154.6–154.3 (m), 150.7 (ddd, J = 245.0, 10.3, 5.9 Hz), 150.6 (ddd, J = 244.5, 18.5, 16.3 Hz) ppm. 133.2 (ddd, J = 244.5, 18.5, 16.3), 96.8 (d, J = 22.4), 70.4 (d, J = 22.9), 57.5 ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –113.68, –134.17, –168.62 ppm. HRMS: calcd. for $C_7H_4F_3IO$ 287.9259; found 287.9253. $C_7H_4F_3IO$ (288.01): calcd. C 29.19, H 1.40; found C 29.22, H 1.50.

3,4,5-Trifluoro-2,6-diiodophenol (2f): 3,4,5-Trifluorophenol (**1e**) (1.00 g, 6.75 mmol), iodine (5.15 g, 20.25 mmol), potassium iodide (3.36 g, 20.25 mmol), sodium hydroxide (0.81 g, 20.25 mmol), purified by sublimation (60 °C, 10^{-2} mbar), yielded **2f** as a colorless solid (2.54 g, 6.35 mmol, 94%); m.p. 81 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.22 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 152.9 (dd, J = 8.8, 5.7 Hz), 150.3 (ddd, J = 239.9, 11.1, 6.4 Hz), 132.4 (dt, J = 248.1, 19.1 Hz), 71.5 (d, J = 26.0 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –112.30, –165.00 ppm. HRMS: calcd. for $C_6HF_3I_2O$ 399.8069; found 399.8064. $C_6HF_3I_2O$ (399.88): calcd. C 18.02, H 0.25; found C 17.85, H 0.41.

3,4,5-Tifluoro-2,6-diiodoanisole (3f): 3,4,5-Trifluorophenol (**1e**) (0.94 g, 6.35 mmol), for equiv. of iodination reagents see **2f**, purified by column chromatography (cyclohexane/ethyl acetate, 99:1, R_F = 0.37) yielded **3f** as a colorless solid (2.39 g, 5.78 mmol, 91%); m.p. 73 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.75 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 155.4 (td, J = 5.3, 3.9 Hz), 150.6 (ddd, J = 242.1, 11.1, 5.9 Hz), 135.2 (dt, J = 253.4, 18.9 Hz), 76.6 (d, J = 25.6 Hz), 60.9 ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –112.15, –159.2 ppm. HRMS: calcd. for $C_7H_3F_3I_2O$ 413.8225; found 413.8222. $C_7H_3F_3I_2O$ (413.90): calcd. C 20.31, H 0.73; found C 20.34, H 0.90.

4-Bromo-2-fluoro-6-iodophenol (2g): 4-Bromo-2-fluorophenol (**1g**) (1.00 g, 5.24 mmol), purified by column chromatography (cyclohexane/ethyl acetate, 9:1, R_F = 0.33) yielded **2g** as a colorless solid (1.49 g, 4.71 mmol, 90%); m.p. 67 °C. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 10.75 (s, 1 H, OH), 7.68 (dd, J = 2.2, 1.8 Hz, 1 H), 7.51 (dd, J = 10.2, 2.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 149.9 (d, J = 247.8 Hz), 144.6 (d, J = 15.3 Hz), 135.61 (d, J = 3.5 Hz), 119.3 (d, J = 22.5 Hz), 110.3 (d, J = 8.9 Hz), 88.4 (d, J = 1.9 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –127.70 ppm. HRMS: calcd. for C_6H_3BrFIO 315.8396; found 315.8397. C_6H_3BrFIO (316.89): calcd. C 22.74, H 0.95; found C 22.65, H 1.01.

4-Bromo-2-fluoro-6-iodoanisole (3g): 4-Bromo-2-fluorophenol (**1g**) (0.65 g, 3.40 mmol), purified by short-path distillation (65 °C, 10^{-2} mbar) yielded **3g** as a colorless liquid (0.98 g, 2.98 mmol, 87%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.84–7.76 (m, 1 H), 7.65 (dd, J = 10.7, 2.2 Hz, 1 H), 3.82 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 153.9 (d, J = 254.5 Hz), 146.9 (d, J = 1.9 Hz), 136.1 (d, J = 3.6 Hz), 120.7 (d, J = 22.9 Hz), 116.2 (d, J = 9.3 Hz), 94.2 (d, J = 1.4 Hz), 61.2 ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –123.97 ppm. HRMS: calcd. for C_7H_5BrFIO 329.8552; found 329.8550. C_7H_5BrFIO (330.92): calcd. C 25.41, H 1.52; found C 25.33, H 1.62.

2,4-Dichloro-6-iodophenol (2h): 2,4-Dichlorophenol (**1h**) (2.00 g, 12.27 mmol), purified by sublimation (65 °C, 10^{-1} mbar) yielded **2h** as a colorless solid (3.19 g, 11.04 mmol, 90%); m.p. 62 °C (ref.[23] m.p. 62 °C). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.31 (br. s, 1 H, OH), 7.73 (d, J = 2.5 Hz, 1 H), 7.54 (d, J = 2.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 151.7, 136.6, 129.2, 124.5, 120.7, 88.7 ppm. HRMS: calcd. for $C_6H_3Cl_2IO$ 287.8606; found 287.8604. $C_6H_3Cl_2IO$ (288.90): calcd. C 24.94, H 1.05; found C 24.98, H 1.08.

2,4-Dichloro-6-iodoanisole (3h): 2,4-Dichlorophenol (**1h**) (1.25 g, 7.65 mmol), purified by column chromatography (cyclohexane/ethyl acetate, 99:1, R_F = 0.61) yielded **3h** as a colorless solid (1.99 g, 6.58 mmol, 86%); m.p. 36 °C (ref.[24] m.p. 35 °C). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.87 (d, J = 2.5 Hz, 1 H), 7.69 (d, J = 2.5 Hz, 1 H), 3.77 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 154.5, 137.1, 130.1, 129.7, 127.3, 94.3, 60.5 ppm. HRMS: calcd.

for $C_7H_5Cl_2IO$ 301.8762; found 301.8752. $C_7H_5Cl_2IO$ (302.92): calcd. C 27.75, H 1.66; found C 27.77, H 1.78.

2-Chloro-4-fluoro-6-iodophenol (2i): 2-Chloro-4-fluorophenol (**1i**) (1 g, 6.82 mmol), purified by short-path distillation (60 °C,10^{-2} mbar) yielded **2i** as a colorless oil, which solidified upon standing (1.47 g, 5.39 mmol, 79%); m.p. 37 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.94 (br. s, 1 H, OH), 7.61 (dd, J = 7.7, 3.0 Hz, 1 H) 7.42 (dd, J = 8.3, 3.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 155.0 (d, J = 243.3 Hz), 149.3 (d, J = 3.1 Hz), 124.1 (d, J = 24.2 Hz), 120.2 (d, J = 11.2 Hz), 116.8 (d, J = 25.9 Hz), 87.7 (d, J = 9.2 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]-DMSO): δ = –121.63 ppm. HRMS: calcd. for C_6H_3ClFIO 271.8901; found 271.8901. C_6H_3ClFIO (272.44): calcd. C 26.45, H 1.11; found C 26.47, H 1.16.

2-Chloro-4-fluoro-6-iodoanisole (3i): 2-Chloro-4-fluorophenol (**1i**) (0.47 g, 3.19 mmol), purified by column chromatography (cyclohexane/ethyl acetate, 99:1, R_F = 0.44) yielded **3i** as a colorless solid (0.63 g, 2.20 mmol, 69%); m.p. 33 °C. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 7.72 (dd, J = 7.7, 3.0 Hz, 1 H) 7.56 (dd, J = 8.3, 3.0 Hz, 1 H), 3.75 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 157.8 (d, J = 248.6 Hz), 152.2 (d, J = 3.6 Hz), 126.7 (d, J = 11.6 Hz), 124.6 (d, J = 24.4 Hz), 117.8 (d, J = 26.2 Hz), 93.3 (d, J = 9.4 Hz), 60.4 ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –115.41 ppm. HRMS: calcd. for C_7H_5ClFIO 285.9058; found 285.9055. C_7H_5ClFIO (286.47): calcd. C 29.35, H 1.76; found C 29.67, H 1.87.

4-Chloro-2-fluoro-6-iodophenol (2j): 4-Chloro-2-fluorophenol (**1j**) (1 g, 6.82 mmol), purified by sublimation (55 °C, 1.2×10^{-2} mbar) yielded **2j** as a colorless solid (1.78 g, 6.55 mmol, 96%); m.p. 65 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.72 (br. s, 1 H, OH), 7.61–7.53 (m, 1 H) ppm. 7.42 (dd, J = 10.5, 2.5, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 149.7 (d, J = 246.8 Hz), 144.3 (d, J = 15.4 Hz), 133.1 (d, J = 3.5 Hz), 123.5 (d, J = 9.6 Hz), 116.7 (d, J = 22.9 Hz), 87.8 (d, J = 2.3 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]-DMSO): δ = –127.89 ppm. HRMS: calcd. for C_6H_3ClFIO 271.8901; found 271.8902. C_6H_3ClFIO (272.44): calcd. C 26.45, H 1.11; found C 26.17, H 1.12.

4-Chloro-2-fluoro-6-iodoanisole (3j): 4-Chloro-2-fluorophenol (**1j**) (0.74 g, 5.06 mmol), purified by column chromatography (cyclohexane/ethyl acetate, 9:1, R_F = 0.47) yielded **3j** as a colorless liquid (1.28 g, 4.45 mmol, 88%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.70 (dd, J = 2.4, 1.8 Hz, 1 H), 7.55 (dd, J = 11.0, 2.5 Hz), 3.83 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 153.6 (d, J = 253.3 Hz), 146.5 (d, J = 11.9 Hz), 133.4 (d, J = 3.6 Hz), 128.8 (d, J = 10.3 Hz), 118.0 (d, J = 23.3 Hz), 93.6 (d, J = 1.7 Hz), 61.2 (d, J = 4.7 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –124.12 ppm. HRMS calcd. for C_7H_5ClFIO 285.9058; found 285.9055. C_7H_5ClFIO (286.47): calcd. C 29.35, H 1.76; found C 29.75, H 1.91.

2,3,4-Trifluoro-6-iodophenol (2k): 2,3,4-Trifluorophenol (**1k**) (1 g, 6.75 mmol), purified by short-path distillation (60 °C, 2 mbar) yielded **2k** as a colorless liquid which solidified upon standing (1.76 g, 6.42 mmol, 95%); m.p. 37 °C. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 10.91 (br. s, 1 H, OH), 7.71 (ddd, J = 9.9, 8.5, 2.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 143.7 (ddd, J = 242.4, 10.5, 2.3 Hz), 142.7 (dd, J = 12.2, 2.8 Hz), 139.7 (ddd, J = 248.4, 11.4, 3.8 Hz), 139.5 (ddd, J = 248.4, 16.4, 14.0 Hz), 120.0 (dd, J = 19.7, 3.6 Hz), 79.4 (dd, J = 7.3, 4.3 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –146.17, –151.55, –158.42 ppm. HRMS: calcd. for $C_6H_2F_3IO$ 273.9102; found 273.9102. $C_6H_2F_3IO$ (273.98): calcd. C 26.30, H 0.74; found C 26.15, H 0.98.

2,3,4-Trifluoro-6-iodoanisole (3k): 2,3,4-Trifluorophenol (**1k**) (1.00 g, 6.75 mmol), purified by short-path distillation (55 °C, 2 mbar) yielded **3k** as a colorless liquid (1.75 g, 6.08 mmol, 90%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.84 (ddd, J = 9.8, 8.4, 2.6 Hz, 1 H), 3.84 (d, J = 1.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 146.7 (ddd, J = 247.7, 10.3, 2.7 Hz), 145.0 (dd, J = 9.0, 4.1 Hz), 143.8 (ddd, J = 252.7, 10.9, 4.1 Hz), 139.5 (ddd, J = 250.6, 16.4, 14.0 Hz), 120.5 (dd, J = 19.9, 3.7 Hz), 84.9 (dd, J = 7.6, 4.0 Hz), 61.6 (d, J = 3.9 Hz, OMe) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –139.52, –147.53, –156.80 ppm. HRMS: calcd. for $C_7H_4F_3IO$ 287.9259; found 287.9259. $C_7H_4F_3IO$ (288.01): calcd. C 29.19, H 1.40; found C 29.23, H 1.50.

2,3-Difluoro-4-iodo-6-nitrophenol (2l): 2,3-Difluoro-6-nitrophenol (**1l**) (2.02 g, 11.54 mmol), iodine (5.85 g, 23.08 mmol), potassium iodide (3.30 g, 23.08 mmol), sodium hydroxide (0.92 g, 23.08 mmol), stirred at 85 °C for 8 h, purified by column chromatography (short column, cyclohexane/ethyl acetate, 1:1), yielded **2l** as a yellow solid (3.33 g, 10.96 mmol, 95%); m.p. 79 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.95 (dd, J = 7.6, 1.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 157.5 (dd, J = 14.6, 4.7 Hz), 152.6 (dd, J = 249.8, 12.4 Hz), 144.4 (dd, J = 242.8, 10.4 Hz), 136.1 (d, J = 4.9 Hz), 128.9 (dd, J = 5.2, 3.8 Hz), 56.4–55.7 (m) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –114.4, –153.4 ppm. HRMS: calcd. for $C_6H_2F_2INO_3$ 300.9047; found 300.9047. $C_6H_2F_2INO_3$ (300.99): calcd. C 23.94, H 0.67, N 4.65; found C 23.92, H 0.65, N 4.83.

2,3-Difluoro-4-iodo-6-nitroanisole (3l): 2,3-Difluoro-6-nitrophenol (**1l**) (1.39 g, 7.94 mmol), stirred for 3 d, purified by column chromatography (cyclohexane/toluene, 2:1, R_F = 0.38) yielded **3l** as a light yellow solid (2.15 g, 6.83 mmol, 86%); m.p. 46 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.28 (dd, J = 6.0, 2.5 Hz, 1 H), 4.03 (d, J = 2.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 153.3 (dd, J = 249.8, 11.9 Hz), 143.6 (dd, J = 255.1, 16.9 Hz), 143.0 (dd, J = 11.5, 2.7 Hz), 140.7–140.5 (m), 128.2 (dd, J = 3.7, 3.7 Hz), 75.9 (dd, J = 25.7, 1.5 Hz), 62.9 (d, J = 5.6 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –107.72, –146.76 ppm. HRMS: calcd. for $C_7H_4F_2INO_3$ 314.9204; found 314.9204. $C_7H_4F_2INO_3$ (315.01): calcd. C 26.69, H 1.28, N 4.45; found C 26.71, H 1.35, N 4.49.

4-Fluoro-6-iodo-2-methylphenol (2m): 4-Fluoro-2-methylphenol (**1m**) (1.07 g, 8.50 mmol), iodine (2.26 g, 8.92 mmol, 1.05 equiv.), potassium iodide (1.48 g, 8.92 mmol, 1.05 equiv.), sodium hydroxide (0.68 g, 17.00 mmol, 2 equiv.), purified by sublimation (55 °C, 4 mbar) yielded **2m** as a colorless solid (1.27 g, 5.06 mmol, 64%); m.p. 57 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.94 (s, 1 H, OH), 7.42–7.31 (m, 1 H), 7.00 (ddd, J = 9.1, 3.1, 0.6 Hz, 1 H), 2.21 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 155.9 (d, J = 239.6 Hz), 151.1 (d, J = 2.4 Hz), 127.1 (d, J = 8.0 Hz), 122.0 (d, J = 24.3 Hz), 117.1 (d, J = 22.3 Hz), 87.0 (d, J = 9.0 Hz), 17.5 (d, J = 1.3 Hz) ppm. ^{19}F NMR (282 MHz, [D$_6$]DMSO): δ = –123.46 ppm. HRMS: calcd. for C_7H_6FIO 251.9447; found 251.9456. C_7H_6FIO (252.02): calcd. C 33.36, H 2.40; found C 33.31, H 2.68.

4-Fluoro-6-iodo-2-methylanisole (3m): 4-Fluoro-2-methylphenol (**1m**) (1.00 g, 7.94 mmol), for equiv. of iodination reagents see **2m**, purified by short-path distillation (60 °C, 3 mbar) yielded 3**m** as a colorless liquid (1.16 g, 4.37 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (ddd, J = 7.5, 3.0, 0.5 Hz, 1 H), 6.86 (ddd, J = 8.7, 3.0, 0.7 Hz, 1 H), 3.72 (s, 3 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7 (d, J = 247.0 Hz), 154.7 (d, J = 3.6 Hz), 133.3 (d, J = 8.3 Hz), 123.6 (d, J = 24.9 Hz), 118.1 (d, J = 22.3 Hz), 91.2 (d, J = 9.5 Hz), 60.6 (s), 17.4 (d, J = 1.5 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –118.22 ppm. HRMS: calcd. for

C_8H_8FIO 265.9604; found 265.9600. C_8H_8FIO (266.05): calcd. C 36.12, H 3.03; found C 35.99, H 3.27.

Supporting Information (see footnote on the first page of this article): General remarks, detailed spectroscopic data with structural correlated assignments as well as details on X-ray analysis of compound **2l**.

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