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Synthesis of polyfluorinated benzofurans

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ABSTRACT

A simple and efficient approach to the synthesis of fluorinated benzofurans including the Sonogashira cross-coupling of *o*-iodophenols with terminal Ph- and *n*-Bu-acetylenes, followed by intramolecular cyclization, in good to excellent yields is reported.

1. Introduction

Heterocyclic compounds have, of course, found many applications in all part of the chemical industry and significantly impact on our daily lives as components of medicines, agrochemicals, natural products and commodity chemicals. Among them, fluorinated heterocyclic compounds are known to modify their pharmacological properties and their therapeutical potency due to the particular properties of fluorine, in many cases, increased lipophilicity of fluorine containing organic molecules in a biological environment [1]. Therefore, synthesis of fluorine containing heterocyclic compounds came into the focus of organic chemists [2].

The broad spectrum of pharmacological activity of benzofurans indicates that the search for new biologically active compounds in this series of compounds is of undoubted interest [3]. Although several protocols for the production of monofluorinated derivatives have been reported [4], there are very a few examples for the synthesis of polyfluorinated benzofurans [5].

Previously, we have developed efficient strategies for preparation of polyfluorinated heterocyclic derivatives (indoles [6], indazoles [7] and 2,3-dihydroquinolinones [8]), via the common methods based on transformations of fluorinated iodoanilines into alkynylanilines with further heterocyclization. Herein we describe a simple, effective and universal pathway of conversion of fluorinated iodophenols into benzofurans.

2. Results and discussion

The starting materials for this study (a representative series of iodophenols **2a–f** with different fluorine contents) were prepared via the aromatic electrophilic substitution of a hydrogen atom with iodine in fluorophenols **1a–e** (Table 1). In the present work we used a simple and convenient iodination system, well proven earlier in obtaining fluorinated iodoanilines [8a] (compare [9]).

Phenols reacted with elemental iodine in aqueous medium in the presence of $NaHCO_3$ at room temperature. Since fluorinated phenolic derivatives are extremely volatile compounds, it is important that the reactions are carried out in a closed vessel. The carbon dioxide formed in the cause of interaction of HI with $NaHCO_3$ was released from the reaction flask through a needle inserted into the septa. Another important point in the preparation of fluorinated iodophenols is the thorough purification of the reaction products from the impurity of the elemental iodine by the action of a saturated aqueous solution of $Na_2S_2O_3$. Otherwise, elemental iodine, readily soluble in the aromatic substrates, increases the already high volatility of iodophenols, which dramatically decreases the yields of target products.

In order to obtain the monoiodinated derivatives of phenols **1a** and **1d** in the aqueous medium we carried out these reactions at 0 °C using the half amount of iodine in relation to aromatic substrates. However, our attempts failed: under these conditions, only products **2b** and **2e** were formed. For this reason, we replaced H_2O as a solvent with aqueous dioxane. This allowed us to obtain the target iodophenol **2a** even when the reaction proceeded at room temperature (Table 1, entry 1). A

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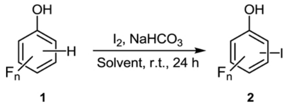
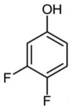
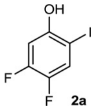
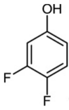
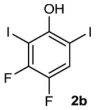
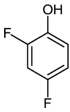
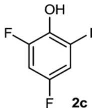
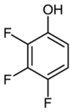
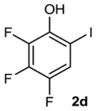
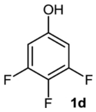
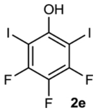
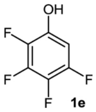
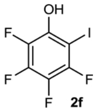
Table 1
Synthesis of fluorinated iodophenols **2a–f**.



Entry	Phenole **1**	Iodophenole **2**	I_2 (equiv)	Solvent	Yield (%)
1	 **1a**	 **2a**	0.9	dioxane (aq)	63
2	 **1a**	 **2b**	2.2	H_2O	98
3	 **1b**	 **2c**	1.1	H_2O	90
4	 **1c**	 **2d**	1.1	H_2O	93
5	 **1d**	 **2e**	2.2	H_2O	85
6	 **1e**	 **2f**	1.1	H_2O	82

possible reason for the decrease in the reactivity of phenol **1a** in dioxane compared to that in the water is a decrease in the degree of dissociation of the alcohol function with a decrease in the permittivity of the solvent. However, phenol **1d** interacted with the iodine giving diiodophenol **2e**, even when the reaction is carried out in dioxane.

At present there are a large number of examples of benzofurans production by the interaction of *o*-iodophenols with terminal alkynes [10]. It is noteworthy that Pd catalysts used in these cross-coupling reactions were overwhelmingly of unusual structure such as: graphene oxide-grafted aminobisphosphine – Pd(II) complex [10a], palladium nanoparticles (Pd-NPs) [10b], nanoparticles Pd^0-AmP-MCF [10c], Pd-NPs on N,O-dual-doped hierarchical porous carbon [10d], $[(PhCH_2O)_2PN^iPr_2]_2PdCl_2$ [10e], Pd(II) complex catalyst [10f] and so on.

In our work, we used the most common Sonogashira reaction conditions: bis(triphenylphosphine) palladium dichloride, copper(I) iodide, and triethylamine as catalysts in dry acetonitrile as a solvent caused the cross-coupling of iodophenols **2a–f** with the acetylene, followed by intramolecular cyclization thus yielding fluorinated benzofurans **3a–l** (Table 2). The reactions were carried out at room temperature in a tightly closed Schlenk flask in an argon atmosphere. Target compounds **3** were isolated by thin-layer chromatography (TLC).

The similar reaction conditions caused the cross-coupling of iodoanilines **2a**,**c** with trimethylsilylacetylene. Scheme 1 shows the products of these transformations. The yield of the target trimethylsilylethynylphenol **4a** is relatively small due to the high volatility of this fluorinated hydroxyderivative. The result of the interaction of trimethylsilylacetylene with **2c** was the formation in addition to **4b** more and dimeric benzofuran **3 m**, which was, apparently, a consequence of the dimerization of 2-ethynyl-4,6-difluorophenol (by-product), followed by subsequent cyclization reaction (Scheme 2).

3. Conclusion

In conclusion, we carried out a highly efficient and simple synthesis of polyfluorinated iodophenols using readily available reagents. On the basis of iodophenols we have realized the classic cross-coupling reaction with acetylene using the simplest catalysts (bis(triphenylphosphine) palladium dichloride, copper(I) iodide, triethylamine), which made it possible to obtain a representative series of fluorinated benzofurans.

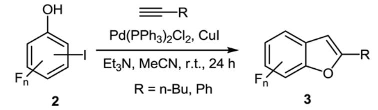
4. Experimental section

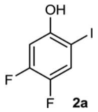
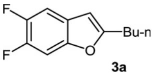
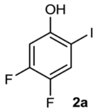
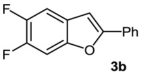
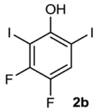
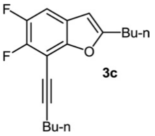
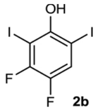
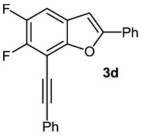
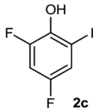
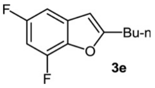
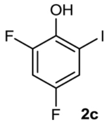
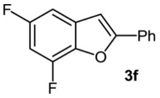
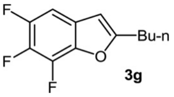
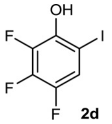
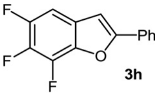
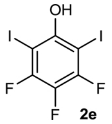
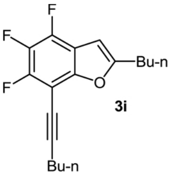
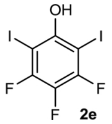
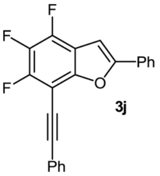
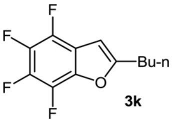
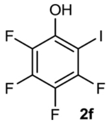
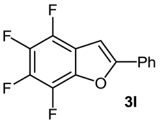
4.1. General

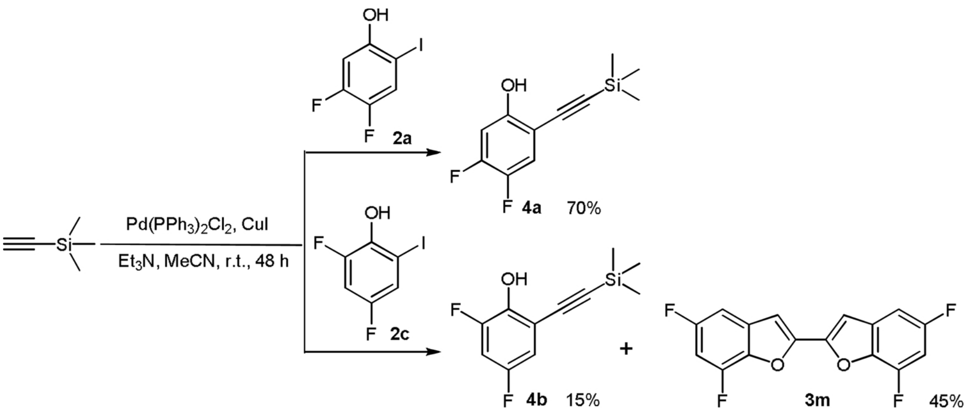
All solvents were purified using standard procedures. Et_3N, MeCN were distilled and kept over CaH_2 before to use. 2,3,4,5-Tetrafluorophenol **1e** was synthesized according to previously described methods [11]. Other chemicals were obtained from commercial sources and were used without further purification. Preparative thin-layer chromatography was performed on Merck precoated silica gel 60 PF_{254} containing gypsum. Visualization of the developed chromatograms was performed by UV light.

NMR spectra were recorded on a Bruker Avance-300 (300.13 MHz for ^1H and 282.37 MHz for ^{19}F), Avance-400 (400.13 MHz for ^1H, 376.44 MHz for ^{19}F and 100.62 MHz for ^{13}C) and DRX-500 (500.13 MHz for ^1H, 125.76 MHz for ^{13}C) spectrometers. Deuterochloroform ($CDCl_3$) and acetone-d_6 were used as solvents, with residual $CHCl_3$ (δ_H = 7.26 ppm) or $CDCl_3$ (δ_C = 77.0 ppm) and acetone (δ_H = 2.15 ppm) or acetone-d_6 (δ_C = 28.6 and 205.0 ppm) being employed as internal standards. C_6F_6 (δ_F 163.0 ppm) was used as external references (^{19}F NMR). ^{13}C NMR spectra were registered with C—H spin decoupling. Masses of molecular ions were determined by HRMS on a DFS Thermo scientific instrument (EI, 70 eV) Melting points were

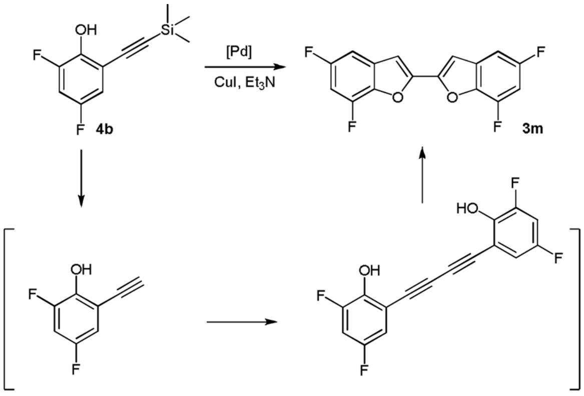
Table 2
Synthesis of fluorinated benzofurans **3a–l.**



Entry	Iodophenole **2**	Benzofurane **3**	Yield (%)
1	 **2a**	 **3a**	96
2	 **2a**	 **3b**	80
3	 **2b**	 **3c**	78
4	 **2b**	 **3d**	80
5	 **2c**	 **3e**	70
6	 **2c**	 **3f**	65
7	 **2d**	 **3g**	95
8	 **2d**	 **3h**	93
9	 **2e**	 **3i**	63
10	 **2e**	 **3j**	88
11	 **2f**	 **3k**	66
12	 **2f**	 **3l**	75



Scheme 1. The interaction of iodophenols **2a** and **2c** with trimethylsilylacetylene.



Scheme 2. The hypothetical scheme of **3 m** formation.

recorded on a Melter-Toledo FP81 Thermosystem apparatus. The IR spectra were recorded on a Bruker Vector 22 spectrometer (KBr or thin layer).

The structures of all polyfluorinated compounds prepared here were corroborated by their ^{19}F, ^{1}H and ^{13}C NMR, high-resolution mass spectrometry, and IR-spectroscopy data (see Supplementary data). Signals in the NMR spectra of **1e**, **2**, **3** and **4** were assigned on the basis of spin coupling constants, which are typical for polyfluorinated benzenes [6–8].

4.2. Synthetic procedures

*4.2.1. 2,3,4,5-Tetrafluorophenol (**1e**)*

To a stirred solution of 1,2,3,4-tetrafluorobenzene [11] (5.0 g, 33 mmol) in dry tetrahydrofuran (25 mL) 2.5 M solution of butyl-lithium in hexane (15 mL, 38 mmol)) in a Schlenk flask under argon at –70 °C was added. The mixture was stirred at –70 °C for 1.5 h, then a solution of trimethylborate (3.9 g, 38 mmol) in dry tetrahydrofuran (5 mL) was added over 0.5 h. The mixture was stirred at –70 °C for 1 h, then 45% w/w hydrogen peroxide (9 mL, ˜30 mmol) was added and the mixture was warmed to room temperature. A solution of NaOH (1.7 g, 40 mmol) in H_2O (20 mL) was added with stirring to obtain a three-layer system. Top layer was discarded, the two lower layers were extracted with CH_2Cl_2 (2 × 50 mL), acidified with hydrochloric acid (˜5 mL), washed with H_2O (50 mL) and dried ($MgSO_4$). The solvent was evaporated to small volume to obtain the target product (since **1f** is very volatile, its yield was determined based on the ^{19}F NMR spectrum recorded with a quantity of the internal standard – C_6F_6).

Colorless oil; yield: 2.9 g (53%). IR (neat): 3589, 3375, 2889, 1642, 1529, 1510, 1319, 1273, 1240, 1068, 953, 883, 837, 713 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.88 (s, 1 H, OH), 6.49 (m, J (H^6,F^5) = 11.5 Hz, J (H^6,F^4) = 7.3 Hz, 1 H, H^6). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.5 (ddt, ^{1}J (C^5,F^5) = 244.1 Hz, ^{2}J (C^5,F^4) = 10.6 Hz, C^5), 141.2 (dm, ^{1}J (C^3,F^3) = 249.6 Hz, ^{2}J (C^3,F^2) ≈ ^{2}J (C^3,F^4) = 13 Hz, C^3), 141.0 (tt, ^{2}J (C^1,F^2) = 11.8 Hz, C^1), 137.5 (dddd, ^{1}J (C^2,F^2) = 240.5 Hz, ^{2}J (C^2,F^3) = 11.9 Hz, C^2), 133.9 (dm, ^{1}J (C^4,F^4) = 244.0 Hz, ^{2}J (C^4,F^5) ≈ ^{2}J (C^4,F^3) = 15 Hz, C^4), 99.8 (d, ^{2}J (C^6,F^5) = 21.9 Hz, C^6). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –142.8 (m, J (F^5,F^4) = 22 Hz, J (F^5,H^6) = 11.5 Hz, 1 F, F^5), –159.1 (tm, J (F^3,F^2) ≈ J (F^3,F^4) = 20 Hz, 1 F, F^3); –165.7 (m, J (F^2,F^3) = 20.4 Hz, 1 F, F^2); –171.7 (tm, J (F^4,F^5) = 22.1 Hz, J (F^4,F^3) = 20.3 Hz, J (F^4,H^6) = 7.3 Hz, 1 F, F^4). HRMS (EI): *m/z* [M]$^+$ calcd for $C_6H_2F_4O$: 166.0036; found: 166.0037.

*4.2.2. 4,5-Difluoro-2-iodophenol (**2a**)*

To a stirred solution of phenol **1a** (2 g, 15 mmol) in dioxane (20 mL), a solution of $NaHCO_3$ (1.1 g, 13 mmol) in H_2O (7 mL) and then finely ground I_2 (3.3 g, 13 mmol) were added. The reaction flask was closed with rubber septa, in which a needle was inserted. The reaction mixture was stirred at room temperature for 24 h. Then saturated aqueous solutions of $Na_2S_2O_3$ (50 mL) was added and the mixture was stirred for 1 h. The reaction product was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with H_2O (70 mL), dried ($MgSO_4$) and filtered. Solvent was removed under vacuum to a constant weight.

Colorless oil; yield: 2.1 g (63%). IR (neat): 3591, 3487, 1601, 1516, 1502, 1489, 1408, 1319, 1300, 1238, 1198, 1142, 991, 960, 870, 802, 781, 735, 622, 567 cm^{-1}. NMR spectra are close to those published earlier [9]. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 9.44 (s, 1 H, OH), 7.65 (dd, J (H^3,F^4) = 9.9 Hz, J (H^3,F^5) = 9.0 Hz, 1 H, H^3), 6.88 (dd, J (H^6,F^5) = 12.0 Hz, J (H^6,F^4) = 7.1 Hz, 1 H, H^6). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 154.9 (dd, ^{2}J (C^1,F^2) = 8.8 Hz, C^1), 151.6 (dd, ^{1}J (C^5,F^5) = 246.8 Hz, ^{2}J (C^5,F^4) = 13.6 Hz, C^5), 145.3 (dd, ^{1}J (C^4,F^4) = 241.6 Hz, ^{2}J (C^4,F^5) = 13.4 Hz, C^4), 127.8 (dd, ^{2}J (C^3,F^4) = 20.2 Hz, C^3), 104.9 (d, ^{2}J (C^6,F^5) = 20.3 Hz, C^6), 76.9 (dd, ^{3}J (C^2,F^4) = 6.4 Hz, C^2). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –135.9 (m, J (F^5,F^4) = 21.0 Hz, J (F^5,H^6) = 12.0 Hz, J (F^5,H^3) = 9.0 Hz,1 F, F^5), –147.9 (m, J (F^4,F^5) = 21 Hz, J (F^4,H^3) = 9.9 Hz, J (F^4,H^6) = 7.1 Hz,1 F, F^4). HRMS (EI): *m/z* [M]$^+$ calcd for $C_6H_3F_2IO$: 255.9191; found: 255.9195.

*4.2.3. Iodophenols **2**; general procedure*

To a stirred solution of phenol **1** (20 mmol) in H_2O (40 mL), $NaHCO_3$ (2.2 g, 26 mmol or 4.4 g, 52 mmol for **2b,e**), I_2 (5.6 g, 22 mmol or 11.2 g, 44 mmol for **2b,e**) were added. The reaction flask was closed with rubber septa, in which a needle was inserted and reaction mixture was stirred at room temperature for 24 h. Then a saturated aqueous solutions of $Na_2S_2O_3$ (40 mL) was added and the mixture was stirred for 1 h. The reaction product was extracted with CH_2Cl_2 or Et_2O (2 × 100 mL). The combined organic layers were washed with saturated aqueous solutions of $Na_2S_2O_3$ (50 mL), H_2O (2 × 70 mL), dried ($MgSO_4$), filtered and solvent was removed under vacuum to a constant weight.

*4.2.3.1. 3,4-Difluoro-2,6-diiodophenol (**2b**).* White solid; yield: 7.5 g (98%); mp 82.1 °C (decomp.) (mp 86 °C [9]). IR (KBr): 3450, 2926, 1601, 1466, 1400, 1340, 1290, 1209, 1194, 1165, 1012, 860, 748, 700, 652, 619 cm^{-1}. NMR spectra are close to those published earlier [11]. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 8.44 (s, 1 H, OH), 7.78 (dd, J (H^{5},F^{4}) = 9.4 Hz, J (H^{5},F^{3}) = 8.8 Hz, 1 H, H^{5}). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 154.1 (t, ^{3}J (C^{1},F^{3}) = 3.1 Hz, C^{1}), 151.4 (dd, ^{1}J (C^{3},F^{3}) = 243.2 Hz, ^{2}J (C^{3},F^{4}) = 14.4 Hz, C^{3}), 144.6 (dd, ^{1}J (C^{4},F^{4}) = 246.9 Hz, ^{2}J (C^{4},F^{3}) = 15.8 Hz, C^{4}), 127.1 (dd, ^{2}J (C^{5},F^{4}) = 20.5 Hz, C^{5}), 76.3 (dd, ^{3}J (C^{6},F^{4}) = 6.3 Hz, C^{6}), 74.8 (d, ^{2}J (C^{2},F^{3}) = 24.1 Hz, C^{2}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –111.6 (dd, J (F^{3},F^{4}) = 23.2 Hz, J (F^{3},H^{5}) = 8.8 Hz, 1 F, F^{3}), –143.0 (dd, J (F^{4},F^{5}) = 23.2 Hz, J (F^{4},H^{5}) = 9.4 Hz, 1 F, F^{4}). HRMS (EI): m/z [M]$^{+}$ calcd for $C_6H_2F_2I_2O$: 381.8158; found: 381.8161.

*4.2.3.2. 2,4-Difluoro-6-iodophenol (**2c**).* White solid; yield: 4.6 g (90%); mp 36.6–41.7 °C (liquid [11]). IR (KBr): 3234, 30,91, 1695, 1599, 1489, 1431, 1394, 1294, 1209, 1165, 1103, 985, 850, 829, 779, 702, 592, 519, 457 cm^{-1}.

NMR spectra are close to those published earlier [9]. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 7.37 (dm, J (H^{5},F^{4}) = 7.8 Hz, J (H^{5},H^{3}) = 3.0 Hz, 1 H, H^{5}), 7.11 (m, J (H^{3},F^{2}) = 10.6 Hz, J (H^{3},F^{4}) = 8.5 Hz, J (H^{3},H^{5}) = 3.0 Hz, 1 H, H^{3}). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 156.1 (dd, ^{1}J (C^{4},F^{4}) = 242.8 Hz, ^{3}J (C^{4},F^{2}) = 11.2 Hz, C^{4}), 150.4 (dd, ^{1}J (C^{2},F^{2}) = 245.5 Hz, ^{3}J (C^{2},F^{4}) = 12.7 Hz, C^{2}), 142.7 (dd, ^{2}J (C^{1},F^{2}) = 15.6 Hz, C^{1}), 121.3 (dd, ^{2}J (C^{5},F^{4}) = 24.6 Hz, C^{5}), 105.2 (dd, ^{2}J (C^{3},F^{2}) = 27.0 Hz, ^{2}J (C^{3},F^{4}) = 23.5 Hz, C^{3}), 85.0 (dd, ^{3}J (C^{6},F^{4}) = 10.4 Hz, C^{6}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –121.1 (m, J (F^{4},H^{3}) = 8.5 Hz, J (F^{4},H^{5}) = 7.8 Hz,1 F, F^{4}), –128.2 (dm, J (F^{2},H^{3}) = 10.6 Hz, 1 F, F^{2}). HRMS (EI): m/z [M]$^{+}$ calcd for $C_6H_3F_2IO$: 255.9191; found: 255.9192.

*4.2.3.3. 2,3,4-Trifluoro-6-iodophenol (**2d**).* Colorless oil; yield: 5.1 g (93%). IR (neat): 3572, 3483, 1697, 1612, 1514, 1473, 1360, 1333, 1298, 1255, 1215, 1188, 1076, 997, 850, 798, 710, 652, 536, 469 cm^{-1}. NMR spectra are close to those published earlier [9]. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 9.91 (s, 1 H, OH), 7.51 (m, J (H^{5},F^{4}) = 9.7 Hz, J (H^{5},F^{3}) = 8.2 Hz, J (H^{5},F^{2}) = 2.6 Hz, 1 H, H^{5}). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 145.3 (ddd, ^{1}J (C^{4},F^{4}) = 243.8 Hz, ^{2}J (C^{4},F^{3}) = 10.6 Hz, C^{4}), 143.7 (dd, ^{2}J (C^{1},F^{2}) = 12.6 Hz, C^{1}), 141.0 (ddd, ^{1}J (C^{3},F^{3}) = 245.5 Hz, ^{2}J (C^{3},F^{2}) = 16.4 Hz, ^{2}J (C^{3},F^{4}) = 13.9 Hz, C^{3}), 140.8 (ddd, ^{1}J (C^{2},F^{2}) = 246.5 Hz, ^{2}J (C^{2},F^{3}) = 11.8 Hz, C^{2}), 121.1 (dd, ^{2}J (C^{5},F^{4}) = 20.2 Hz, C^{5}), 77.2 (dd, ^{3}J (C^{6},F^{4}) = 7.9 Hz, C^{6}). ^{19}F NMR (282 MHz, CDCl$_3$): δ = –145.5 (dd, J (F^{4},F^{3}) = 20.8 Hz, J (F^{4},H^{5}) = 9.2 Hz, 1 F, F^{4}), –153.9 (dd, J (F^{2},F^{3}) = 19.5 Hz, J (F^{2},H^{5}) = 2.6 Hz, 1 F, F^{2}), –158.2 (m, J (F^{3},F^{4}) = 20.8 Hz, J (F^{3},F^{2}) = 19.5 Hz, J (F^{3},H^{5}) = 8.2 Hz, 1 F, F^{3}). HRMS (EI): m/z [M]$^{+}$ calcd for $C_6H_2F_3IO$: 273.9097; found: 273.9096.

*4.2.3.4. 3,4,5-Trifluoro-2,6-diiodophenol (**2e**).* White solid; yield: 6.8 g (85%); mp 79.8–81.2 °C (mp 81 °C [11]). IR (KBr): 3437, 1583, 1483, 1441, 1381, 1294, 1228, 1207, 1066, 872, 723, 654, 465 cm^{-1}. NMR spectra are close to those published earlier [9]. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.83 (s, OH). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 153.6 (td, C^{1}), 152.1 (ddd, ^{1}J (C^{3},F^{3}) = 241.7 Hz, C^{3}), 133.8 (dt, ^{1}J (C^{4},F^{4}) = 2482.9 Hz, ^{2}J (C^{4},F^{3}) = 18.9 Hz, C^{4}), 68.3 (dm, ^{2}J (C^{2},F^{3}) = 27.2 Hz, C^{2}). ^{19}F NMR (282 MHz, CDCl$_3$): δ = –108.6 (d, J (F^{3},F^{4}) = 22.4 Hz, 2 F, F^{3}), –161.3 (t, J (F^{4},F^{3}) = 22.4 Hz, 1 F, F^{4}). HRMS (EI): m/z [M]$^{+}$ calcd for $C_6H_1F_3I_2O$: 399.8063; found: 399.8059.

*4.2.3.5. 2,3,4,5-Tetrafluoro-6-iodophenol (**2f**).* Colorless oil; yield: 4.8 g (82%). IR (neat): 3568, 3493, 1622, 1514, 1485, 1431, 1309, 1219, 1080, 972, 908, 796, 735, 650 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.23 (s, OH). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 147.1 (ddt, ^{1}J (C^{5},F^{5}) = 242.5 Hz, ^{2}J (C^{5},F^{4}) = 11.8 Hz, C^{5}), 141.2 (dtd, ^{1}J (C^{3},F^{3}) = 252.8 Hz, ^{2}J (C^{3},F^{2}) ≈ ^{2}J (C^{3},F^{4}) = 14 Hz, C^{3}), 140.8 (dm, ^{2}J (C^{1},F^{2}) = 12 Hz, C^{1}), 136.1 (dddd, ^{1}J (C^{2},F^{2}) = 245 Hz, ^{2}J (C^{2},F^{3}) = 12.8 Hz, C^{2}), 134.3 (dddd, ^{1}J (C^{4},F^{4}) = 250 Hz, ^{2}J (C^{4},F^{5}) ≈ ^{2}J (C^{4},F^{3}) = 19 Hz, C^{4}), 67.5 (dd, ^{2}J (C^{6},F^{5}) = 26.8 Hz, C^{6}). ^{19}F NMR (282 MHz, CDCl$_3$): δ = –120.1 (ddd, J (F^{5},F^{4}) = 23.7 Hz, J (F^{5},F^{2}) = 7.7 Hz, J (F^{5},F^{3}) = 2.3 Hz, 1 F, F^{5}), –155.7 (tm, J (F^{3},F^{2}) ≈ J (F^{3},F^{4}) = 20.4 Hz, J (F^{3},F^{5}) = 2.3 Hz, 1 F, F^{3}); –161.2 (ddd, J (F^{2},F^{3}) = 20.4 Hz, J (F^{2},F^{5}) = 7.7 Hz, J (F^{2},F^{4}) = 3.9 Hz, 1 F, F^{2}); –166.2 (tm, J (F^{4},F^{5}) = 24 Hz, J (F^{4},F^{3}) = 20.4 Hz, J (F^{4},F^{2}) = 3.9 Hz, 1 F, F^{4}). HRMS (EI): m/z [M]$^{+}$ calcd for $C_6H_1F_4IO$: 291.9003; found: 291.9005.

*4.2.4. Cross-coupling reactions of iodophenols **2** with acetylene; general procedure*

To a solution of iodophenol **2** (1.5 mmol) and acetylene (1.6 mmol or 3.3 mmol for **3c**,**d**,**i**,j) in MeCN (10 mL) in a Schlenk flask under argon, Pd(PPh$_3$)$_2$Cl$_2$ (52 mg, 0.07 mmol), CuI (28 mg, 0.15 mmol) and Et$_3$N (3 mL) were added. The mixture was stirred at room temperature for 24 ÷ 48 h. Then, the reaction suspension was placed directly onto a chromatography plates (silica gel) and air-dried. The reaction products were isolated by preparative TLC using hexane as an eluent.

*4.2.4.1. 2-Butyl-5,6-difluorobenzofuran (**3a**).* Colorless oil; yield: 0.30 g (96%); R_f = 0.75 (hexane). IR (neat): 2960, 2933, 2671, 1604, 1481, 1458, 1358, 1207, 1188, 1338, 1101, 947, 862, 764, 629 cm^{-1}. ^{1}H NMR (500 MHz, Acetone-d_6): δ = 7.42 (m, J (H^{7},F^{6}) = 10.4 Hz, J (H^{7},F^{5}) = 6.6 Hz, 1 H, H^{7}), 7.39 (dd, J (H^{4},F^{5}) = 10.4 Hz, J (H^{4},F^{6}) = 8.0 Hz, 1 H, H^{4}), 6.50 (m, 1 H, H^{3}), 2.75 (t, J (H^{8},H^{9}) = 7.6 Hz, 2 H, H^{8}), 1.72 – 1.66 (m, 2 H, H^{9}), 1.41 – 1.36 (m, 2 H, H^{10}), 0.93 (t, J (H^{11},H^{10}) = 7.3 Hz, 3 H, H^{11}). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 162.9 (d, C^{2}), 150.3 (dd, ^{3}J (C^{7a},F^{6}) = 11.4 Hz, C^{7a}), 148.6 (dd, ^{1}J (C^{6},F^{6}) = 241.7 Hz, ^{2}J (C^{6},F^{5}) = 15.7 Hz, C^{6}), 148.4 (dd, ^{1}J (C^{5},F^{5}) = 238.5 Hz, ^{2}J (C^{5},F^{6}) = 14.2 Hz, C^{5}), 125.7 (dd, ^{3}J (C^{3a},F^{5}) = 8.9 Hz, C^{3a}), 107.9 (d, ^{2}J (C^{4},F^{5}) = 20.6 Hz, C^{4}), 102.8 (dd, C^{3}), 100.7 (d, ^{2}J (C^{7},F^{6}) = 22.4 Hz, C^{7}), 30.4 (s, C^{8}), 29.5 (s, C^{9}), 22.8 (s, C^{10}), 14.0 (s, C^{11}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –142.5 (m, J (F^{6},F^{5}) = 18.3 Hz, J (F^{6},H^{7}) = 10.4 Hz, J (F^{6},H^{4}) = 8.0 Hz, 1 F, F^{6}), –144.9 (m, J (F^{5},F^{6}) = 18.3 Hz, J (F^{5},H^{4}) = 10.4 Hz, J (F^{5},H^{7}) = 6.6 Hz, 1 F, F^{5}). HRMS (EI): m/z [M]$^{+}$ calcd for $C_{12}H_{12}F_2O$: 210.0851; found: 210.0854.

*4.2.4.2. (E)-2,3,5,6-Tetrafluoro-4-(1-(2-(perfluorophenyl)hydrazono) ethyl)aniline (**3b**).* White solid; yield: 0.28 g (80%); R_f = 0.81 (hexane, twice); mp 137.6–140.8 °C. IR (KBr): 3106, 3058, 2926, 1602, 1566, 1480, 1461, 1441, 1356, 1273, 1230, 1191, 1143, 1112, 1073, 1020, 916, 863, 803, 765, 689, 636, 493 cm^{-1}. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 7.91 – 7.88 (m, 2 H, H$_m$), 7.60 (m, J (H^{7},F^{6}) = 10.3 Hz, J (H^{7},F^{5}) = 6.5 Hz, 1 H, H^{7}), 7.56 (dd, J (H^{4},F^{5}) = 10.4 Hz, J (H^{4},F^{6}) = 8.0 Hz, 1 H, H^{4}), 7.51 – 7.46 (m, 2 H, H$_o$), 7.41 (tm, J (H$_p$,H$_m$) = 7.3 Hz, 1 H, H$_p$), 7.29 (m, 1 H, H^{3}). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 157.7 (d, C^{2}), 149.6 (dd, ^{3}J (C^{7a},F^{6}) = 12 Hz, C^{7a}), 148.6 (dd, ^{1}J (C^{6},F^{6}) = 245.4 Hz, ^{2}J (C^{6},F^{5}) = 15.7 Hz, C^{6}), 148.0 (dd, ^{1}J (C^{5},F^{5}) = 241.3 Hz, ^{2}J (C^{5},F^{6}) = 14.3 Hz, C^{5}), 129.7 (s, C^{8}), 128.8 (s, C^{11}), 128.7 (s, C^{9}), 124.7 (s, C^{10}), 124.5 (dd, ^{3}J (C^{3a},F^{5}) = 8.8 Hz, C^{3a}), 107.3 (d, ^{2}J (C^{4},F^{5}) = 20.5 Hz, C^{4}), 100.9 (m, C^{3}), 100.3 (d, ^{2}J (C^{7},F^{6}) = 22.3 Hz, C^{7}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –140.3 (m, J (F^{6},F^{5}) = 19.8 Hz, J (F^{6},H^{7}) = 10.3 Hz, J (F^{6},H^{4}) = 8.0 Hz, 1 F, F^{6}), –143.8 (m, J (F^{5},F^{6}) = 19.8 Hz, J (F^{5},H^{4}) = 10.4 Hz, J (F^{5},H^{7}) = 6.5 Hz, 1 F, F^{5}). HRMS (EI): m/z [M]$^{+}$ calcd for $C_{14}H_8F_2O$: 230.0538; found: 230.0539.

*4.2.4.3. 2-Butyl-5,6-difluoro-7-(hept-1-ynyl)benzofuran (**3c**).* Colorless oil; yield: 0.34 g (78%); R_f = 0.65 (hexane). IR (neat): 2958, 2933, 2873, 2252, 1606, 1483, 1448, 1196, 1147, 1101, 955, 850, 746, 671 cm^{-1}. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 7.40 (dd, J (H^{4},F^{5}) = 10.2 Hz, J (H^{4},F^{6}) = 7.7 Hz, 1 H, H^{4}), 6.55 (m, 1 H, H^{3}), 2.79 (t, J (H^{14},H^{15}) = 9 Hz, 2 H, H^{14}), 2.57 (t, J (H^{8},H^{9}) = 6.4 Hz, 2 H, H^{8}), 1.76 – 1.36 (m, 8 H, 2H^{9} + 2H^{10} + 2H^{15} + 2H^{16}), 0.99 – 0.92 (m, 6 H, 3H^{11} + 3H^{17}). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 163.1 (d, C^{2}), 150.6

(dd, ^{3}J (C^{7a},F^{6}) = 5.4 Hz, C^{7a}), 149.0 (dd, ^{1}J (C^{6},F^{6}) = 245.8 Hz, ^{2}J (C^{6},F^{5}) = 16.1 Hz, C^{6}), 148.2 (dd, ^{1}J (C^{5},F^{5}) = 238.9 Hz, ^{2}J (C^{5},F^{6}) = 13.9 Hz, C^{5}), 124.9 (dd, ^{3}J (C^{3a},F^{5}) = 9.6 Hz, C^{3a}), 107.5 (d, ^{2}J (C^{4},F^{5}) = 20.9 Hz, C^{4}), 103.1 (dd, C^{3}), 102.0 (d, C^{12}), 99.3 (dd, ^{2}J (C^{7},F^{6}) = 17.9 Hz, C^{7}), 68.8 (dd, C^{13}), 31.2 (s, C^{14}), 30.3 (s, C^{8}), 28.4 (s, C^{9}), 22.8 (s, C^{10}), 22.5 (s, C^{15}), 19.7 (s, C^{16}), 13.9 (s, C^{17}), 13.8 (s, C^{11}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –141.9 (dd, J (F^{6},F^{5}) = 19.7 Hz, J (F^{6},H^{4}) = 10.2 Hz, 1 F, F^{6}), –144.0 (dd, J (F^{5},F^{6}) = 19.7 Hz, J (F^{5},H^{4}) = 10.2 Hz, 1 F, F^{5}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{18}H_{20}F_{2}O$: 290.1477; found: 290.1475.

4.2.4.4. 5,6-Difluoro-2-phenyl-7-(phenylethynyl)benzofuran (**3d**). White solid; yield: 0.40 g (80%); R_f = 0.50 (hexane); mp 119.1 °C (decomp.). IR (KBr): 3433, 3074, 3034, 2922, 2222, 1705, 1601, 1500, 1454, 1437, 1370, 1340, 1267, 1225, 1201, 1174, 1115, 1070, 1022, 937, 912, 856, 760, 740, 688, 582, 565, 490 cm^{-1}. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 7.96 – 7.93 (m, 2 H, H$_m$), 7.72 – 7.69 (m, 2 H, H'$_m$), 7.61 (dd, J (H^{4},F^{5}) = 10.0 Hz, J (H^{4},F^{6}) = 7.8 Hz, 1 H, H^{4}), 7.53 – 7.40 (m, 6 H, H'$_p$ + 2H$_o$ + 2H'$_o$ + H$_p$), 7.34 (s, 1 H, H^{3}).

^{13}C NMR (126 MHz, Acetone-d_6): δ = 159.1 (d, C^{2}), 150.5 (d, C^{7a}), 149.4 (dd, ^{1}J (C^{6},F^{6}) = 249.1 Hz, ^{2}J (C^{6},F^{5}) = 16.5 Hz, C^{6}), 148.6 (dd, ^{1}J (C^{5},F^{5}) = 240.5 Hz, ^{2}J (C^{5},F^{6}) = 13.8 Hz, C^{5}), 132.6 (s, C^{15}), 130.3 (s, C^{17}), 130.2 (s, C^{8}), 130.1 (s, C^{11}), 129.9 (s, C^{16}), 129.6 (s, C^{9}), 125.7 (s, C^{10}), 125.5 (dd, ^{3}J (C^{3a},F^{5}) = 9.8 Hz, C^{3a}), 122.9 (s, C^{14}), 109.1 (d, ^{2}J (C^{4},F^{5}) = 21.0 Hz, C^{4}), 102.7 (dd, C^{3}), 100.2 (d, C^{12}), 99.0 (dd, ^{2}J (C^{7},F^{6}) = 17.9 Hz, C^{7}), 77.0 (dd, C^{13}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –138.8 (dd, J (F^{6},F^{5}) = 19.6 Hz, J (F^{6},H^{4}) = 7.8 Hz, 1 F, F^{6}), –142.5 (dd, J (F^{5},F^{6}) = 19.6 Hz, J (F^{5},H^{4}) = 10.0 Hz, 1 F, F^{5}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{22}H_{12}F_{2}O$: 330.0851; found: 330.0847.

4.2.4.5. 2-Butyl-5,7-difluorobenzofuran (**3e**). Colorless oil; yield: 0.22 g (70%); R_f = 0.70 (hexane). IR (neat): 2960, 2933, 2674, 1641, 1606, 1487, 1439, 1360, 1213, 1182, 1144, 1111, 1078, 978, 945, 843, 733, 607 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.91 (dm, J (H^{4},F^{5}) = 8.3 Hz, J (H^{4},H^{6}) = 2.4 Hz, 1 H, H^{4}), 6.71 (m, J (H^{6},F^{7}) = 10.6 Hz, J (H^{6},F^{5}) = 9.5 Hz, J (H^{6},H^{4}) = 2.4 Hz, 1 H, H^{6}), 6.36 (dm, J (H^{3},F^{7}) = 3 Hz,1 H, H^{3}), 2.75 (t, J (H^{8},H^{9}) = 7.9 Hz, 2 H, H^{8}), 1.75 – 1.67 (m, 2 H, H^{9}), 1.45 – 1.37 (m, 2 H, H^{10}), 0.94 (t, J (H^{11},H^{10}) = 7.4 Hz, 3 H, H^{11}). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 162.5 (d, C^{2}), 158.3 (dd, ^{1}J (C^{5},F^{5}) = 239.8 Hz, ^{3}J (C^{5},F^{7}) = 9.2 Hz, C^{5}), 146.5 (dd, ^{1}J (C^{7},F^{7}) = 251.0 Hz, ^{3}J (C^{7},F^{5}) = 14.0 Hz, C^{7}), 137.9 (dd, ^{2}J (C^{7a},F^{7}) = 10.9 Hz, C^{7a}), 132.0 (dd, ^{3}J (C^{3a},F^{5}) = 12.0 Hz, C^{3a}), 102.5 (dd, C^{3}), 101.4 (dd, ^{2}J (C^{4},F^{5}) = 24.7 Hz, C^{4}), 98.7 (dd, ^{2}J (C^{6},F^{5}) = 29.7 Hz, ^{2}J (C^{6},F^{7}) = 20.4 Hz,C^{6}), 29.5 (s, C^{8}), 28.0 (s, C^{9}), 22.1 (s, C^{10}), 13.6 (s, C^{11}). ^{19}F NMR (282 MHz, CDCl$_3$): δ = –119.7 (m, J (F^{5},H^{6}) = 9.5 Hz, J (F^{5},H^{4}) = 8.3 Hz, J (F^{5},F^{7}) = 3 Hz, 1 F, F^{5}), –135.4 (dm, J (F^{7},H^{6}) = 10.6 Hz, J (F^{7},H^{3}) ≈ J (F^{7},F^{5}) = 3 Hz, 1 F, F^{7}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{12}H_{12}F_{2}O$: 210.0851; found: 210.0848.

4.2.4.6. 5,7-Difluoro-2-phenylbenzofuran (**3f**). White solid; yield: 0.22 g (65%); R_f = 0.75 (hexane); mp 67.3 °C (decomp.). IR (KBr): 3440, 3095, 2926, 1643, 1603, 1498, 1475, 1435, 1358, 1213, 1169, 1115, 1082, 1039, 978, 910, 858, 848, 827, 767, 731, 690, 605, 482 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.87 – 7.84 (m, 2 H, H$_m$), 7.48 – 7.36 (m, 3 H, H$_p$ + 2H$_o$), 7.02 (dm, J (H^{4},F^{5}) = 8.1 Hz, J (H^{4},H^{6}) = 2.3 Hz, 1 H, H^{4}), 7.00 (d, J (H^{3},F^{7}) = 2.8 Hz,1 H, H^{3}), 6.80 (m, J (H^{6},F^{7}) = 10.5 Hz, J (H^{6},F^{5}) = 9.4 Hz, J (H^{6},H^{4}) = 2.3 Hz, 1 H, H^{6}). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 158.5 (dd, ^{1}J (C^{5},F^{5}) = 240.9 Hz, ^{3}J (C^{5},F^{7}) = 9.1 Hz, C^{5}), 158.4 (d, C^{2}), 147.0 (dd, ^{1}J (C^{7},F^{7}) = 252.0 Hz, ^{3}J (C^{7},F^{5}) = 14.0 Hz, C^{7}), 138.3 (dd, ^{2}J (C^{7a},F^{7}) = 11.0 Hz, C^{7a}), 132.1 (dd, ^{3}J (C^{3a},F^{5}) = 12.1 Hz, C^{3a}), 129.2 (s, C^{8}), 128.8 (s, C^{9}), 128.3 (s, C^{11}), 125.1 (s, C^{10}), 102.0 (dd, ^{2}J (C^{4},F^{5}) = 24.8 Hz, C^{4}), 101.6 (dd, C^{3}), 99.9 (dd, ^{2}J (C^{6},F^{5}) = 29.8 Hz, ^{2}J (C^{6},F^{7}) = 20.2 Hz,C^{6}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –116.6 (m, J (F^{5},H^{6}) = 9.4 Hz, J (F^{5},H^{4}) = 8.1 Hz, J (F^{5},F^{7}) = 3 Hz, 1 F, F^{5}), –133.3 (dm, J (F^{7},H^{6}) = 10.5 Hz, J (F^{7},H^{3}) ≈ J (F^{7},F^{5}) = 3 Hz, 1 F, F^{7}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{14}H_{8}F_{2}O$: 230.0538; found: 230.0540.

4.2.4.7. 2-Butyl-5,6,7-trifluorobenzofuran (**3g**). Colorless oil; yield: 0.32 g (95%); R_f = 0.85 (hexane). IR (neat): 2960, 2935, 2874, 1637, 1610, 1514, 1471, 1385, 1329, 1196, 1149, 1080, 960, 941, 847, 796, 731, 673 cm^{-1}. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 7.32 (m, J (H^{4},F^{5}) = 9.8 Hz, J (H^{4},F^{6}) = 6.9 Hz, J (H^{4},H^{3}) = 2.1 Hz, 1 H, H^{4}), 6.64 (dm, J (H^{3},H^{4}) = 2.1 Hz, 1 H, H^{3}), 2.82 (t, J (H^{8},H^{9}) = 7.5 Hz, 2 H, H^{8}), 1.77 – 1.67 (m, 2 H, H^{9}), 1.48 – 1.38 (m, 2 H, H^{10}), 0.94 (t, J (H^{11},H^{10}) = 7.4 Hz, 3 H, H^{11}). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 164.2 (dd, C^{2}), 148.9 (ddd, ^{1}J (C^{5},F^{5}) = 240.6 Hz, ^{2}J (C^{5},F^{6}) = 11.6 Hz, C^{5}), 138.7 (dm, ^{2}J (C^{7a},F^{7}) = 8 Hz, C^{7a}), 138.0 (ddd, ^{1}J (C^{6},F^{6}) = 243.0 Hz, ^{2}J (C^{6},F^{5}) = 18.4 Hz, ^{2}J (C^{6},F^{7}) = 12.5 Hz, C^{6}), 137.8 (ddd, ^{1}J (C^{7},F^{7}) = 251.6 Hz, ^{2}J (C^{7},F^{6}) = 13.9 Hz, C^{7}), 126.5 (ddd, ^{3}J (C^{3a},F^{5}) = 10.3 Hz, C^{3a}), 103.4 (m, C^{3}), 103.0 (dd, ^{2}J (C^{4},F^{5}) = 20.8 Hz, C^{4}), 30.3 (s, C^{8}), 28.4 (s, C^{9}), 22.8 (s, C^{10}), 13.9 (s, C^{11}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –141.8 (m, J (F^{5},F^{6}) = 19.5 Hz, J (F^{5},H^{4}) = 9.8 Hz, 1 F, F^{5}), –158.2 (dm, J (F^{7},F^{6}) = 19.2 Hz, 1 F, F^{7}), –167.3 (tm, J (F^{6},F^{7}) ≈ J (F^{6},F^{5}) = 19.3 Hz, J (F^{6},H^{4}) = 6.9 Hz, 1 F, F^{6}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{12}H_{11}F_{3}O$: 228.0757; found: 228.0759.

4.2.4.8. 5,6,7-Trifluoro-2-phenylbenzofuran (**3h**). White solid; yield: 0.34 g (93%); R_f = 0.53 (hexane); mp 93.4–95.1 °C. IR (KBr): 3115, 3074, 2924, 2854, 1649, 1614, 1512, 1466, 1442, 1379, 1338, 1255, 1217, 1174, 1082, 1020, 953, 910, 858, 808, 767, 729, 690, 677, 594, 555, 499 cm^{-1}. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 7.91 – 7.88 (m, 2 H, H$_m$), 7.53 – 7.37 (m, 4 H, H$_p$ + 2H$_o$ + H^{4}), 7.34 (d, J (H^{3},H^{4}) = 3 Hz, 1 H, H^{3}). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 159.8 (dd, C^{2}), 149.3 (ddd, ^{1}J (C^{5},F^{5}) = 241.7 Hz, ^{2}J (C^{5},F^{6}) = 11.7 Hz, C^{5}), 139.0 (dm, C^{7a}), 138.9 (ddd, ^{1}J (C^{6},F^{6}) = 244.6 Hz, ^{2}J (C^{6},F^{5}) = 18.3 Hz, ^{2}J (C^{6},F^{7}) = 12.2 Hz, C^{6}), 138.0 (ddd, ^{1}J (C^{7},F^{7}) = 252.7 Hz, ^{2}J (C^{7},F^{6}) = 13.8 Hz, C^{7}), 130.4 (s, C^{9}), 130.0 (s, C^{8}), 129.9 (s, C^{11}), 126.7 (dt, ^{3}J (C^{3a},F^{5}) = 10.6 Hz, C^{3a}), 125.9 (s, C^{10}), 103.6 (dd, ^{2}J (C^{4},F^{5}) = 20.9 Hz, C^{4}), 102.7 (m, C^{3}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –143.6 (m, J (F^{5},F^{6}) = 19.4 Hz, J (F^{5},H^{4}) = 9.8 Hz, 1 F, F^{5}), –160.5 (dm, J (F^{7},F^{6}) = 19.0 Hz, 1 F, F^{7}), –168.2 (tm, J (F^{6},F^{7}) ≈ J (F^{6},F^{5}) = 19.1 Hz, J (F^{6},H^{4}) = 6.9 Hz, 1 F, F^{6}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{14}H_{7}F_{3}O$: 248.0444; found: 248.0446.

4.2.4.9. 2-Butyl-4,5,6-trifluoro-7-(hex-1-ynyl)benzofuran (**3i**). Colorless oil; yield: 0.29 g (63%); R_f = 0.68 (hexane). IR (neat): 2960, 2935, 2873, 2243, 1601, 1518, 1456, 1379, 1350, 1327, 1255, 1196, 1176, 1120, 1034, 987, 945, 897, 785, 742 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.42 (s, 1 H, H^{3}), 2.74 (t, J (H^{14},H^{15}) = 7.6 Hz, 2 H, H^{14}), 2.51 (t, J (H^{8},H^{9}) = 7.0 Hz, 2 H, H^{8}), 1.74 – 1.35 (m, 8 H, 2H^{9} + 2H^{10} + 2H^{15} + 2H^{16}), 0.96 – 0.91 (m, 6 H, 3H^{11} + 3H^{17}). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 161.6 (d, C^{2}), 149.6 (ddd, C^{7a}), 149.3 (ddd, ^{1}J (C^{6},F^{6}) = 248.4 Hz, ^{2}J (C^{6},F^{5}) = 12.8 Hz, C^{6}), 142.2 (ddd, ^{1}J (C^{4},F^{4}) = 253.5 Hz, ^{2}J (C^{4},F^{5}) = 12.5 Hz, C^{4}), 136.8 (ddd, ^{1}J (C^{5},F^{5}) = 242.9 Hz, ^{2}J (C^{5},F^{6}) = 16.7 Hz, ^{2}J (C^{5},F^{4}) = 14.7 Hz, C^{5}), 113.8 (dm, ^{2}J (C^{3a},F^{4}) = 18.6 Hz, C^{3a}), 100.5 (dd, C^{12}), 98.2 (m, C^{3}), 94.7 (dd, ^{2}J (C^{7},F^{6}) = 18.5 Hz, C^{7}), 67.3 (t, C^{13}), 30.4 (s, C^{14}), 29.4 (s, C^{8}), 27.9 (s, C^{9}), 22.1 (s, C^{10}), 21.8 (s, C^{15}), 19.4 (s, C^{16}), 13.6 (s, C^{17}), 13.4 (s, C^{11}). ^{19}F NMR (282 MHz, CDCl$_3$): δ = –137.5 (dd, J (F^{6},F^{5}) = 20.0 Hz, J (F^{6},F^{4}) = 2.0 Hz, 1 F, F^{6}), –140.6 (dd, J (F^{4},F^{5}) = 20.7 Hz, J (F^{4},F^{6}) = 2.0 Hz, 1 F, F^{4}), –166.3 (dd, J (F^{5},F^{4}) = 20.7 Hz, J (F^{5},H^{6}) = 20.0 Hz, 1 F, F^{5}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{18}H_{19}F_{3}O$: 308.1383; found: 308.1390.

4.2.4.10. 4,5,6-Trifluoro-2-phenyl-7-(phenylethynyl)benzofuran (**3j**). White solid; yield: 0.46 g (88%); R_f = 0.35 (hexane); mp 121.8 °C (decomp.). IR (KBr): 3115, 3078, 3032, 2220, 1622, 1597, 1520, 1458, 1346, 1267, 1203, 1132, 1115, 1041, 1024, 980, 912, 802, 764, 739, 688, 557, 524, 486 cm^{-1}. ^{1}H NMR (300 MHz, Acetone-d_6): 8.00 – 7.97 (m, 2 H, H$_m$), 7.71 – 7.68 (m, 2 H, H'$_m$), 7.55 – 7.46 (m, 7 H, H$_p$ + H'$_p$ + 2H$_o$ + 2H'$_o$ + H^{3}). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 159.7 (d, C^{2}), 151.0 (dd, C^{7a}), 150.8 (ddd, ^{1}J (C^{6},F^{6}) = 249.6 Hz, ^{2}J (C^{6},F^{5}) = 13.1 Hz, C^{6}), 144.7 (ddd, ^{1}J (C^{4},F^{4}) = 225.0 Hz, ^{2}J (C^{4},F^{5}) = 12.5 Hz, C^{4}), 138.6 (ddd, ^{1}J (C^{5},F^{5}) = 242.7 Hz, ^{2}J (C^{5},F^{6}) = 16.5 Hz, ^{2}J (C^{5},F^{4})

=14.7 Hz, C^{5}), 133.1 (s, C^{15}), 131.1 (s, C^{17}), 130.9 (s, C^{11}), 130.5 (s, C^{16}), 130.2 (s, C^{8}), 130.2 (s, C^{9}), 126.2 (s, C^{10}), 123.4 (s, C^{14}), 116.5 (d, ^{2}J (C^{3a},F^{4}) =18.7 Hz, C^{3a}), 100.5 (t, C^{12}), 99.1 (t, C^{3}), 96.1 (dd, ^{2}J (C^{7},F^{6}) =18.6 Hz, C^{7}), 76.7 (m, C^{13}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –136.6 (dd, *J* (F^{6},F^{5}) =19.5 Hz, *J* (F^{6},F^{4}) =2.6 Hz, 1 F, F^{6}), –140.0 (dd, *J* (F^{4},F^{5}) =20.2 Hz, *J* (F^{4},F^{6}) =2.6 Hz, 1 F, F^{4}), –166.8 (t, *J* (F^{5},F^{4}) ≈ *J* (F^{5},H^{6}) =19.8 Hz, 1 F, F^{5}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{22}H_{11}F_3O$: 348.0757; found: 348.0759.

4.2.4.11. 2-Butyl-4,5,6,7-tetrafluorobenzofuran ***(3k)***. Colorless oil; yield: 0.24 g (66%); *R$_f$* = 0.88 (hexane, twice). IR (neat): 2962, 2936, 2875, 1603, 1531, 1491, 1346, 1321, 1254, 1188, 1140, 1122, 1009, 993, 941, 798, 731, 634 cm^{-1}. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 6.46(m, 1 H, H^{3}), 2.73 (t, *J* (H^{8},H^{9}) =7.7 Hz, 2 H, H^{8}), 1.74 – 1.64 (m, 2 H, H^{9}), 1.45 – 1.35 (m, 2 H, H^{10}), 0.94 (t, *J* (H^{11},H^{10}) =7.3 Hz, 3 H, H^{11}). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 162.5 (d, C^{2}), 138.5 (dddd, ^{1}J (C^{4},F^{4}) =246.8 Hz, ^{2}J (C^{4},F^{5}) =12.3 Hz, C^{4}), 138.0 (dm, ^{1}J (C^{5},F^{5}) =246.1 Hz, ^{2}J (C^{5},F^{6}) =14.7 Hz, ^{2}J (C^{5},F^{4}) =13.4 Hz,C^{5}), 137.4 (m, C^{7a}), 136.9 (dm, ^{1}J (C^{6},F^{6}) =244.8 Hz, ^{2}J (C^{6},F^{5}) =16.7 Hz, ^{2}J (C^{6},F^{7}) =14.3 Hz, C^{6}), 133.7 (dddd, ^{1}J (C^{7},F^{7}) =250.5 Hz, ^{2}J (C^{7},F^{6}) =14.0 Hz, C^{7}), 114.9 (dm, ^{2}J (C^{3a},F^{4}) =19.6 Hz, C^{3a}), 98.3 (m, C^{3}), 29.3 (s, C^{8}), 27.8 (s, C^{9}), 22.0 (s, C^{10}), 13.4 (s, C^{11}). ^{19}F NMR (282 MHz, CDCl$_3$): δ = –149.9 (m, *J* (F^{4},F^{7}) =20.6 Hz, *J* (F^{4},F^{5}) =15.9 Hz, 1 F, F^{4}), –163.8 (m, *J* (F^{5},F^{6}) =19.7 Hz, *J* (F^{5},F^{4}) =15.9 Hz, 1 F, F^{5}), –165.2 (tm, *J* (F^{6},F^{7}) ≈ *J* (F^{6},F^{5}) =19.6 Hz, 1 F, F^{6}), –166.7 (m, *J* (F^{7},F^{4}) =20.6 Hz, *J* (F^{7},F^{6}) =19.5 Hz, 1 F, F^{7}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{12}H_{10}F_4O$: 246.0662; found: 246.0660.

4.2.4.12. 4,5,6,7-Tetrafluoro-2-phenylbenzofuran ***(3 l)***. White solid; yield: 0.30 g (75%); *R$_f$* = 0.78 (hexane); mp 113.5 °C (decomp.) (mp 112–114 °C [5e]). IR (KBr): 3118, 2926, 2854, 1527, 1483, 1446, 1346, 1311, 1265, 1217, 1134, 1043, 997, 908, 800, 763,7, 727, 688, 559 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.84 – 7.82 (m, 2 H, H$_m$), 7.48 – 7.39 (m, 3 H, H$_p$ + 2H$_o$), 7.08 (d, *J* (H^{3},F^{4}) = 2 Hz, 1 H, H^{3}). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 158.5 (d, C^{2}), 138.9 (ddm, ^{1}J (C^{4},F^{4}) =246.5 Hz, ^{2}J (C^{4},F^{5}) =12 Hz, C^{4}), 138.6 (dtm, ^{1}J (C^{5},F^{5}) =246.5 Hz, ^{2}J (C^{5},F^{6}) =14.8 Hz, ^{2}J (C^{5},F^{4}) =13 Hz,C^{5}), 137.6 (tm, C^{7a}), 137.4 (dtm, ^{1}J (C^{6},F^{6}) =246.1 Hz, ^{2}J (C^{6},F^{5}) =15.5 Hz, ^{2}J (C^{6},F^{7}) =13 Hz, C^{6}), 134.1 (dddd, ^{1}J (C^{7},F^{7}) =253.3 Hz, ^{2}J (C^{7},F^{6}) =16.1 Hz, C^{7}), 132.4 (s, C^{8}), 129.7 (s, C^{9}), 128.9 (s, C^{11}), 125.1 (s, C^{10}), 115.5 (dm, ^{2}J (C^{3a},F^{4}) =19.3 Hz, C^{3a}), 97.4 (m, C^{3}). ^{19}F NMR (282 MHz, Acetone-d_6: δ = –147.7 (m, *J* (F^{4},F^{7}) =20.0 Hz, *J* (F^{4},F^{5}) =15.8 Hz, 1 F, F^{4}), –162.0 (m, *J* (F^{5},F^{6}) =19 Hz, *J* (F^{5},F^{4}) =15.8 Hz, 1 F, F^{5}), –163.0 (tm, *J* (F^{6},F^{7}) ≈ *J* (F^{6},F^{5}) =19 Hz, 1 F, F^{6}), –164.8 (m, *J* (F^{7},F^{4}) =20 Hz, *J* (F^{7},F^{6}) =19 Hz, 1 F, F^{7}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{14}H_6F_4O$: 266.0349; found: 266.0345.

4.2.4.13. 5,5′,7,7′-Tetrafluoro-2,2′-bibenzofuran ***(3 m)***. White solid; yield: 0.20 g (45%); *R$_f$* = 0.72 (hexane, twice); mp 194.1–194.4 °C. IR (KBr): 3444, 3138, 3099, 2927, 2854, 1691, 1643, 1604, 1535, 1458, 1431, 1356, 1211, 1178, 1118, 1084, 1953, 982, 883, 848, 806, 727, 658, 602, 580, 501, 453 cm^{-1}. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 7.48 (d, *J* (H^{3},F^{7}) =2.8 Hz,2 H, H^{3}), 7.32 (dm, *J* (H^{4},F^{5}) =8.2 Hz, *J* (H^{4},H^{6}) =2.4 Hz, 2 H, H^{4}), 7.14 (m, *J* (H^{6},F^{7}) =10.8 Hz, *J* (H^{6},F^{5}) =9.6 Hz, *J* (H^{6},H^{4}) =2.4 Hz, 2 H, H^{6}). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 159.8 (dd, ^{1}J (C^{5},F^{5}) =240.7 Hz, ^{3}J (C^{5},F^{7}) =9.2 Hz, C^{5}), 149.7 (d, C^{2}), 147.9 (dd, ^{1}J (C^{7},F^{7}) =251.2 Hz, ^{3}J (C^{7},F^{5}) =14.1 Hz, C^{7}), 139.5 (dd, ^{2}J (C^{7a},F^{7}) =11.3 Hz, C^{7a}), 132.6 (dd, ^{3}J (C^{3a},F^{5}) =12.5 Hz, C^{3a}), 106.5 (dd, C^{3}), 104.2 (dd, ^{2}J (C^{4},F^{5}) =25.4 Hz, C^{4}), 102.2 (dd, ^{2}J (C^{6},F^{5}) =30.5 Hz, ^{2}J (C^{6},F^{7}) =20.3 Hz,C^{6}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –115.6 (m, *J* (F^{5},H^{6}) =9.6 Hz, *J* (F^{5},H^{4}) =8.2 Hz, *J* (F^{5},F^{7}) =3.4 Hz, 2 F, F^{5}), –132.8 (dm, *J* (F^{7},H^{6}) =10.8 Hz, *J* (F^{7},F^{5}) =3.4 Hz, *J* (F^{7},H^{3}) =2.8 Hz, 2 F, F^{7}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{16}H_6F_4O_2$: 306.0298; found: 306.0304.

4.2.4.14. 4,5-Difluoro-2-((trimethylsilyl)ethynyl)phenol ***(4a)***. Yellowish oil; yield: 0.24 g (70%); *R$_f$* = 0.34 (hexane, twice). IR (neat): 3510, 2950, 2900, 2150, 1610, 1581, 1527, 1504, 1481, 1425, 1400, 1325, 1252, 1219, 1192, 872, 845, 760, 729, 700, 633 cm^{-1}. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 7.25 (dd, *J* (H^{3},F^{4}) =10.8 Hz, *J* (H^{3},F^{5}) =9.1 Hz, 1 H, H^{3}), 6.83 (dd, *J* (H^{6},F^{5}) =12.0 Hz, *J* (H^{6},F^{4}) =7.0 Hz, 1 H, H^{6}), 0.21 (s, 9 H, CH$_3$). ^{13}C NMR (126 MHz, Acetone-d_6): δ = 156.4 (d, ^{3}J (C^{1},F^{5}) =9.7 Hz, C^{1}), 151.5 (dd, ^{1}J (C^{5},F^{5}) =249.3 Hz, ^{2}J (C^{5},F^{4}) =14.0 Hz, C^{5}), 144.2 (dd, ^{1}J (C^{4},F^{4}) =238.2 Hz, ^{2}J (C^{4},F^{5}) =13.4 Hz, C^{4}), 121.3 (dd, ^{2}J (C^{3},F^{4}) =19.3 Hz, C^{3}), 107.5 (ddd, ^{3}J (C^{2},F^{4}) =7.2 Hz, C^{2}), 105.5 (d, ^{2}J (C^{6},F^{5}) =20.2 Hz, C^{6}), 99.8 (m, C^{7} + C^{8}), –0.1 (s, C^{9}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –133.2 (m, *J* (F^{5},F^{4}) =22.0 Hz, *J* (F^{5},H^{6}) =12.0 Hz, *J* (F^{5},H^{3}) =9.1 Hz,1 F, F^{5}), –149.2 (m, *J* (F^{4},F^{5}) =22.0 Hz, *J* (F^{4},H^{3}) =10.8 Hz, *J* (F^{4},H^{6}) =7.0 Hz,1 F, F^{4}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{11}H_{12}F_2SiO$: 226.0620; found: 226.0615.

4.2.4.15. 2,4-Difluoro-6-((trimethylsilyl)ethynyl)phenol ***(4b)***. Yellowish oil; yield: 50 mg (15%); *R$_f$* = 0.65 (hexane). IR (neat): 3570, 3510, 3081, 2962, 2900, 2154, 1632, 1601, 1487, 1444, 1350, 1335, 1252, 1217, 1186, 1122, 1010, 991, 847, 794, 762, 729, 702, 677, 596, 528 cm^{-1}. ^{1}H NMR (300 MHz, Acetone-d_6): δ = 8.82 (s, 1 H, OH), 7.07 (m, *J* (H^{3},F^{2}) =10.9 Hz, *J* (H^{3},F^{4}) =8.6 Hz, *J* (H^{3},H^{5}) =3.0 Hz, 1 H, H^{3}), 6.94 (dm, *J* (H^{5},F^{4}) =8.7 Hz, *J* (H^{5},H^{3}) = 3.0 Hz, 1 H, H^{5}), 0.22 (s, 9 H, CH$_3$). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 154.8 (dd, ^{1}J (C^{4},F^{4}) =241.2 Hz, ^{3}J (C^{4},F^{2}) =11.4 Hz, C^{4}), 150.0 (dd, ^{1}J (C^{2},F^{2}) =246.7 Hz, ^{3}J (C^{2},F^{4}) =13.0 Hz, C^{2}), 141.9 (dd, ^{2}J (C^{1},F^{2}) =12.8 Hz, C^{1}), 113.0 (dd, ^{2}J (C^{5},F^{4}) =24.3 Hz, C^{5}), 111.7 (dd, ^{3}J (C^{6},F^{4}) =11.3 Hz, C^{6}), 106.0 (dd, ^{2}J (C^{3},F^{2}) =27.1 Hz, ^{2}J (C^{3},F^{4}) =21.9 Hz, C^{3}), 104.1 (s, C^{7}), 96.7 (m, C^{8}), –0.3 (s, C^{9}). ^{19}F NMR (282 MHz, Acetone-d_6): δ = –121.6 (td, *J* (F^{4},H^{3}) ≈ *J* (F^{4},H^{5}) =8.6 Hz, *J* (F^{4},F^{2}) =2.0 Hz,1 F, F^{4}), –130.9 (dm, *J* (F^{2},H^{3}) =10.9 Hz, *J* (F^{2},F^{4}) =2.0 Hz, 1 F, F^{2}). HRMS (EI): *m/z* [M]$^{+}$ calcd for $C_{11}H_{12}F_2SiO$: 226.0620; found: 226.0617.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jfluchem.2019.109371.

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