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Synthesis of polyfluorinated *ortho*-alkynylanilines

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ABSTRACT

A series of polyfluorinated *ortho*-alkynylanilines – the versatile building blocks for diverse polyfluorobenzo azaheterocycles – have been synthesized by the Sonogashira reaction of polyfluorinated *ortho*-iodanilines with terminal alkynes.

1. Introduction

Fluorinated benzoazaheterocycles are molecular cores of many bioactive compounds, including active substances of medicines [1–5]. Therefore, fluorine introduction in the benzene moiety of a benzoheterocycle is an important structural modification in the molecular design of bioactive compounds. In this respect compounds of this type with a polyfluorinated benzene ring are of their own importance as accumulation of fluorine atoms can both essentially modify bioactivity and also afford nice opportunities to functionalize the scaffold by nucleophilic substitution of fluorine. However, until recently this area was in its infancy, obviously, because of a small accessibility of one of the versatile precursor types for the diversity of polyfluorobenzo azaheterocycles – anilines containing 3–4 fluorine atoms and a nonsubstituted position *ortho* to the amino group. This obstacle was recently substantially minimized by developing the selective *ortho*-defluorination of polyfluoroaniline N-acetyl derivatives [6,7] and dechlorination of polyfluorochloroanilines [8]. In particular, this allowed starting the systematic exploration of quinolines polyfluorinated on the benzene ring [7–11].

The scope of methods for azaheteroannelation can appreciably be extended by incorporating various structural units suitable for heterocyclization in the position *ortho* to the amino group. Among those, the alkynyl groups are especially attractive because can serve for diverse constructions of both five- and six-membered azaheterocycles. This is of special importance for synthesis of indoles polyfluorinated on the benzene ring, as above achievements in the synthesis of *ortho*-unsubstituted polyfluoroanilines are not sufficient to surmount their scarce accessibility by virtue of difficulty of the Fisher indole assembling on the basis of polyfluorinated anilines [12,13] which originates from the very nature of these building blocks as polyfluoroarenes. As a consequence, though the Fisher indole syntheses from anilines containing up to 2 fluorine atoms are amply presented in literature [14–16], to the best of our knowledge, only two indoles with the perfluorinated benzene ring were prepared till now, both with the substituted pyrrole moiety [17]. 4,5,6,7-Tetrafluoroindole itself was synthesized from hexafluorobenzene via a different multistep course [18], applicability of which for a wide range of similar compounds being at least not obvious.

By virtue of aforementioned, the methods draw attention which are based on reactions catalysed by transition metal complexes, the cyclizations of *ortho*-alkynylanilines [19–25] or their N-derivatives [19,20,26–32] seeming most attractive. Such starting materials can be got from the catalytic cross-condensation of *ortho*-haloanilines (preferably, iodoanilines) with terminal alkynes [32,33] and used for synthesis of a vast diversity of benzoazaheterocycles [34,35]. Only few applications of the approach to the polyfluorinated building blocks of this type were reported [25,32–34], apparently, owing to their previous poor accessibility. Fortunately, the above development of a general concise route to the *ortho*-nonsubstituted polyfluoroanilines cancels this restriction, thus rendering the corresponding polyfluorinated *ortho*-halonanilines and, potentially, *ortho*-alkynylanilines, on their ground, quite accessible.

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In this connection, the purpose of the present work is to examine a possibility to synthesize polyfluorinated *ortho*-alkynylanilines from corresponding *ortho*-haloanilines via the Sonogashira reaction.

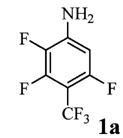
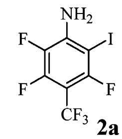
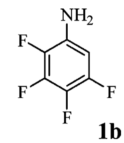
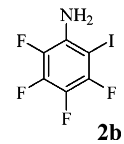
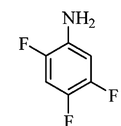
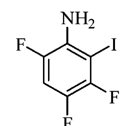
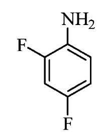
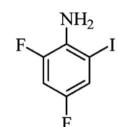
2. Results and discussion

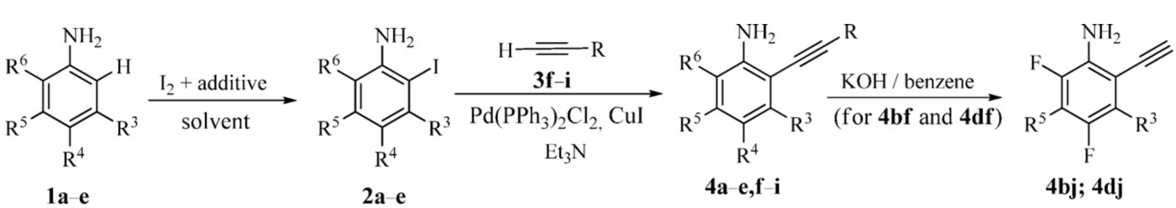
2.1. Iodination of polyfluoroanilines

As starting materials we used 2,3,5-trifluoro-4-(trifluoromethyl)aniline **1a** [6], 2,3,4,5-tetrafluoroaniline **1b** [6], 2,4,5-trifluoroaniline **1c** [11], 2,4-difluoroaniline **1d** [36] and commercial 3,4-difluoroaniline **1e**. To iodinate these amines [37], iodine was preferred to use as more convenient in comparison with iodine chloride which was applied earlier to prepare 2-iodo-4,5-difluoroaniline (**2e**) [32] and 2-iodo-3,4,5,6-tetrafluoroaniline (**2b**) [38] from amines **1e** and **1b**, respectively. Although 2-iodo-4,5-difluoroaniline **2e** was smoothly prepared from aniline **1e** by the protocol [39] (I_2–$NaHCO_3$–H_2O, r.t.), aniline **1d** gave no a iodination product with this reagent even at reflux. Therefore, the silver sulfate additive (I_2–Ag_2SO_4–EtOH, reflux) was used in iodination of aniline **1a** to obtain 2-iodo-3,5,6-trifluoro-4-(trifluoromethyl)aniline (**2a**) in 93% yield (Scheme 1). However, probably owing to a high reactivity, this system turned out nonselective in iodination of aniline **1c**: even at an incomplete consumption of the starting compound (14% in the resulting mixture) a GC–MS analysis revealed the formation of both isomeric mono-(43% *ortho* and 8% *meta*) and diiodinated (32%) products. Proceeding from these results, the combination of iodine and iodic acid in aqueous dioxane was found nicely appropriate for the selective monoiodination of anilines **1a**–**d** to afford anilines **2a**, **2b**, 2-iodo-3,4,6-trifluoroaniline (**2c**) and 2-iodo-4,6-difluoroaniline (**2d**) in 88–97% yields (Scheme 1 and Table 1). The structures of **2a**–**e** are unequivocally evidenced from their ^{1}H and ^{19}F NMR characteristics which are discussed below.

Besides the synthetic value, the above results are of interest to compare the reactivity of the iodination systems and substrates. It seems obvious that, in all the cases, the iodination is electrophilic, so that the respective reagents should be considered as equivalents of the cationic I^+ synthon (actually, solvated I_3^+) with a reactivity depending on a nature of the counterion and solvent. The relatively high basicity of the I_2–$NaHCO_3$–H_2O system causes the strongest I^+ association with the counterion and the solvent among the iodination systems we used. As a result, its lowest reactivity among the used iodination systems allows to iodinate only aniline **1e** – certainly most reactive of the substrates under study. In turn, the fact that isomeric aniline **1d** failed to be iodinated by this system elucidates clearly the reaction to be crucially retarded by switching from an activating electron-donating effect of the fluorine *para* to the reaction site to a deactivating electron-withdrawing effect of the *meta* fluorine. As mentioned above, the I_2–Ag_2SO_4–EtOH system appeared most active among the iodination systems under application, likely due to strong counterion binding by an Ag^+ cation, the I^+ cation thus being relatively weakly associated with I_2 or solvent molecules. The I_2–HIO_3–aq. dioxane system manifests the medium reactivity obviously due to the association of the I^+ cation with counterion and solvent in this system is weaker compared with the more basic I_2–$NaHCO_3$–H_2O system and stronger compared with the less basic I_2–Ag_2SO_4–EtOH system. The high reactivity and, consequently, low selectivity of the I_2–Ag_2SO_4–alcohol system is probably responsible for the comparably low and unnaturally substituent-dependent yields of the selective *ortho* iodination products obtained from 4-X-anilines (X = H 46%, Me 41%, Cl 73%, NO_2 75%) by using the I_2–Ag_2SO_4–1,2-ethanediol system [40]. In turn, the high selectivity of the I_2–HIO_3 system is in line with numerous examples of the selective iodination of substituted phenols [41,42] and 5- or 6-amino-1,4-naphthoquinones [43] at the positions *ortho* or *para* to the OH and NH_2 group, accordingly.

Table 1
Iodination of anilines **1a**–**d** (I_2 + HIO_3, aq. dioxane, 70 °C).

Entry	Substrate	Product	Time (h)	Yield (%)
1	 **1a**	 **2a**	4	97
2	 **1b**	 **2b**	3	88
3	 **1c**	 **2c**	3	97
4	 **1d**	 **2d**	3	95



	R^3	R^4	R^5	R^6	additive	solvent
a	F	CF_3	F	F	$AgSO_4$	EtOH
					HIO_3	dioxane (aq)
b	F	F	F	F	HIO_3	dioxane (aq)
c	F	F	H	F	HIO_3	dioxane (aq)
d	H	F	H	F	HIO_3	dioxane (aq)
e	H	F	F	H	$NaHCO_3$	H_2O

R = $C(CH_3)_2OH$ (**f**), *n*-Bu (**g**), Ph (**h**), CH_2OTHP (**i**), H (**j**)

Scheme 1.

Table 2
Synthesis of alkynylanilines **4a–e**,**f–i**.

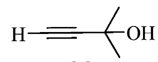
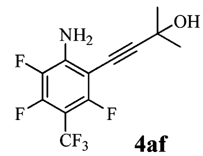
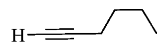
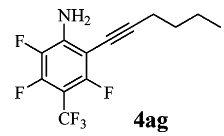
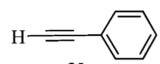
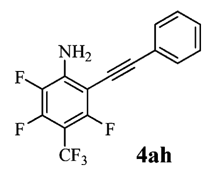
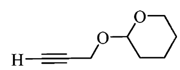
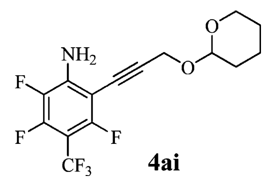
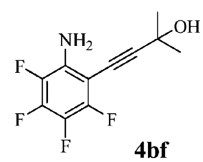
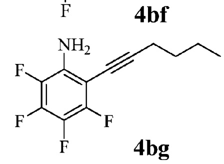
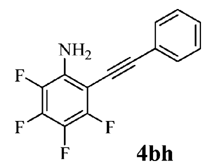
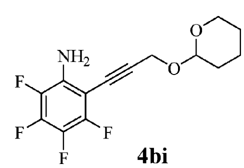
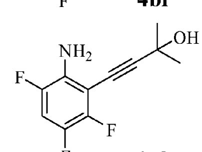
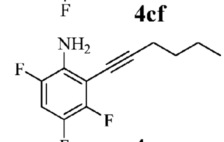
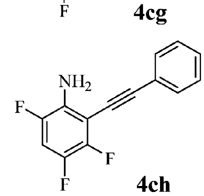
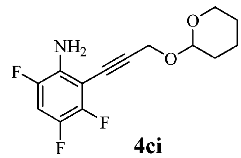
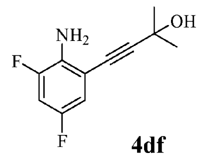
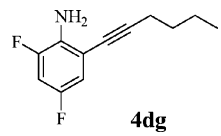
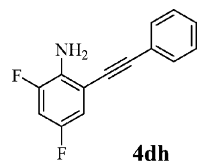
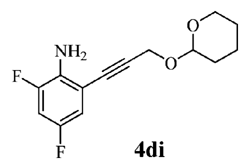
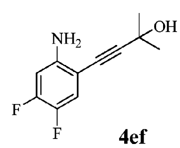
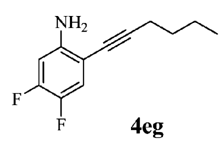
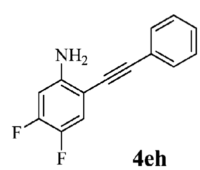
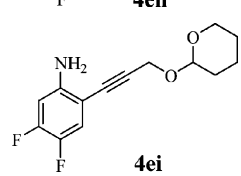
Entry	Substrate	Alkyne	Product	Time (h)	Yield (%)
1	**2a**	 **3f**	 **4af**	3	73
2	**2a**	 **3g**	 **4ag**	3	78
3	**2a**	 **3h**	 **4ah**	3	81
4	**2a**	 **3i**	 **4ai**	3	76
5	**2b**	**3f**	 **4bf**	3	89
6	**2b**	**3g**	 **4bg**	3	80
7	**2b**	**3h**	 **4bh**	3	82
8	**2b**	**3i**	 **4bi**	3	85
9	**2c**	**3f**	 **4cf**	3	90
10	**2c**	**3g**	 **4cg**	3	80
11	**2c**	**3h**	 **4ch**	3	91

Table 2 (*Continued*)

Entry	Substrate	Alkyne	Product	Time (h)	Yield (%)
12	**2c**	**3i**	 **4ci**	3	83
13	**2d**	**3f**	 **4df**	3	72
14	**2d**	**3g**	 **4dg**	3	73
15	**2d**	**3h**	 **4dh**	3	77
16	**2d**	**3i**	 **4di**	3	70
17	**2e**	**3f**	 **4ef**	3	74
18	**2e**	**3g**	 **4eg**	3	95
19	**2e**	**3h**	 **4eh**	3	92
20	**2e**	**3i**	 **4ei**	3	73

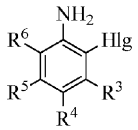
Summing up, we demonstrate a high efficiency of the I_2–HIO_3 system in the selective iodination of polyfluorinated 2-H-anilines affording respective polyfluorinated 2-iodoanilines which are believed to be valuable versatile starting materials to synthesize a wide diversity of *ortho* functionalized polyfluoroanilines.

2.2. Polyfluorinated 2-iodoanilines in the Sonogashira coupling

In development of the latter possibility, all the *ortho*-iodoanilines **2a**–**e** were subjected to cross-coupling with terminal alkynes **3f–i** in Et_3N with $Pd(PPh_3)_2Cl_2$ (4 mol.%) and CuI (9 mol.%) as catalysts (Scheme 1). According to ^{19}F NMR and GC–MS analyses, conversion of all the starting compounds to the *ortho*-alkynylanilines **4a**–**e**,**f**–**i** was complete, and the corresponding diynes derived by alkynes homo-coupling (cf. [44]) were present in the product mixtures. The target compounds **4** were isolated by TLC (Table 2).

Though the principal goal of the work has been achieved by the synthesis of alkynylanilines **4a**–**e**,**f**–**i**, the evaluation of substituent effects in the Sonogashira coupling is of interest. 2-Bromo-4,6-difluoroaniline, 2-bromo-4-nitro-6-chloroaniline and 2-bromo-5-(trifluoromethyl)aniline were reported to react with ethynyltrimethylsilane in the presence of $Pd(PPh_3)_2Cl_2$, CuI and Et_3N in

Table 3
^{1}H and ^{19}F NMR chemical shifts (ppm) and coupling constants (Hz) for anilines **2a–e** and **5** ($CDCl_3$).



	R^3	R^4	R^5	R^6
a, 5	F	CF_3	F	F
b	F	F	F	F
c	F	F	H	F
d	H	F	H	F
e	H	F	F	H

	Hlg
2a–e	I
5	Br

Compound	NH_2	R^3	R^4	R^5	R^6
2a	4.93 (s)	−95.2 (qd, 1F) $J_{F3,CF3}$ = 21.6 $J_{F3,F6}$ = 9.8	−56.4 (dd, 3F) $J_{CF3,F3}$, $J_{CF3,F5} \approx 22$	−141.6 (dq, 1F) $J_{F5,CF3}$, $J_{F5,F6} \approx 22$	−161.0 (dd, 1F) $J_{F6,F5}$ = 19.4 $J_{F6,F3}$ = 9.9
2b	4.13 (s)	−119.5 (ddd, 1F) $J_{F3,F4}$ = 23.7 $J_{F3,F6}$ = 7.9 $J_{F3,F5}$ = 3.0	−171.0 (ddd, 1F) $J_{F4,F3}$ = 23.7 $J_{F4,F5}$ = 20.7 $J_{F4,F6}$ = 5.4	−157.6 (ddd, 1F) $J_{F5,F6}$, $J_{F5,F4} \approx 20.5$ $J_{F5,F3}$ = 3.0	−159.1 (ddd, 1F) $J_{F6,F5}$ = 19.9 $J_{F6,F3}$ = 7.9 $J_{F6,F4}$ = 5.4
2c	4.08 (s, 2H)	−121.6 (ddd, 1F) $J_{F3,F4}$ = 23.4 $J_{F3,F6}$ = 11.5 $J_{F3,H5}$ = 7.2	−148.0 (ddd, 1F) $J_{F4,F3}$ = 23.5 $J_{F4,H5}$ = 9.7 $J_{F4,F6}$ = 2.5	6.96 (ddd, 1H) $J_{H5,F4}$, $J_{H5,F6} \approx 10$ $J_{H5,F3}$ = 7.2	−134.2 (ddd, 1F) $J_{F6,F3}$, $J_{F6,H5} \approx 11$ $J_{F6,F4}$ = 2.5
2d	3.96 (s, 2H)	7.11 (ddd, 1H) $J_{H3,F4}$ = 7.8 $J_{H3,H5}$ = 2.7 $J_{H3,F6}$ = 2.1	−125.5 (dd, 1F) $J_{F4,H3}$, $J_{F4,H5} \approx 8$	6.74 (ddd, 1H) $J_{H5,F6}$ = 10.9 $J_{H5,F4}$ = 8.3 $J_{H5,H3}$ = 2.8	−126.9 (dd, 1F) $J_{F6,H5}$ = 10.9 $J_{F6,H3} \approx 2$
2e	4.00 (s, 2H)	7.41 (dd, 1H) $J_{H3,F4}$ = 9.5 $J_{H3,F5}$ = 8.4	−150.6 (ddd, 1F) $J_{F4,F5}$ = 21.0 $J_{F4,H3}$ = 9.5 $J_{F4,H6}$ = 7.1	−137.7 (ddd, 1F) $J_{F5,F4}$ = 21.0 $J_{F5,H6}$ = 11.8 $J_{F5,H3}$ = 8.4	6.54 (dd, 1H) $J_{F6,F5}$ = 11.8 $J_{H6,F4} \approx 7$
5	4.77 (s)	−110.2 (qd, 1F) $J_{F3,CF3}$ = 21.5 $J_{F3,F6}$ = 9.7	−56.4 (dd, 3F) $J_{CF3,F3}$, $J_{CF3,F5} \approx 21.5$	−139.6 (dq, 1F) $J_{F5,CF3}$, $J_{F5,F6} \approx 21.5$	−161.7 (dd, 1F) $J_{F6,F5}$ = 20.0 $J_{F6,F3}$ = 9.7

DMF at 50 °C for 8 h [25]. We found out that 2-bromo-3,5,6-trifluoro-4-(trifluoromethyl)aniline (**5**) (synthesized by bromination of **1a**) remained intact after exposing with alkyne **3f**, $Pd(PPh_3)_2Cl_2$, CuI and Et_3N in DMF at 90 °C for 7 h (^{19}F NMR data). Matching this result with the above literature data, one may infer that the simultaneous fluorine implacement in the 3- and 5-positions and fluorine substitution by a trifluoromethyl group in the 4-position retard the Sonogashira coupling crucially. However, basing on the current notion of the mechanism of this reaction [45], the increased electron withdrawing substitution should benefit the reaction. Thus, it turns out that only an electron-donating effect of the F^5 atom is responsible for the retardation, but a special study is necessary for the firm conclusion.

Being potential precursors for corresponding indoles with unsubstituted heterocyclic moiety, polyfluorinated 2-ethynylanilines are of principal importance, to obtain which anilines **4a–e**,**f** are likely appropriate starting materials. In this connection, anilines **4bf** and **4df** were shown to smoothly afford 2-ethynyltetrafluoroaniline (**4bj**) and known [25] 2-ethynyl-4,6-difluoroaniline (**4dj**) in the 71 and 78% isolated yields, accordingly, upon interaction with KOH in boiling benzene (the conditions are similar to those used for preparation of 2-ethynylanthraquinone [46]) (Scheme 1).

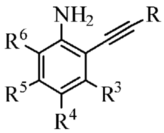
2.3. Spectral data

The structures of all compounds obtained for the first time are obvious enough from their synthesis and corroborated by their ^{19}F, ^{1}H and ^{13}C NMR and IR characteristics. The ^{19}F and ^{1}H NMR spectral data of polyfluorinated 2-haloanilines are presented in Table 3. The observed ^{19}F NMR chemical shifts and spin coupling constants are fully consistent with their structures and typical for polyfluorinated benzene derivatives [47]. For example, in the ^{19}F NMR spectrum of aniline **2b** observed are four signals of equal intensity, shifted to low field by $\Delta\delta_F$ 23.0, 3.0, 1.6 and 4.3 ppm, from the similar signals of the starting aniline **1b** (δ_F −142.5 (F^3), −174.0 (F^4), −159.2 (F^5) and −163.5 (F^6) ppm), respectively. These $\Delta\delta_F$ values are characteristic for all pairs of anilines **1a–e–2a–e**, being in good conformity with those between pentafluorobenzene and iodopentafluorobenzene [48]. Besides, the F^3 $\Delta\delta_F$ value between anilines **2a** and **5** (−15.0 ppm) is close to the *ortho*-F $\Delta\delta_F$ value (−13.4 ppm) between iodo- and bromo-pentafluorobenzene [48] (the negative $\Delta\delta_F$ values correspond to a high-field shift).

The ^{19}F and ^{1}H NMR spectral data of polyfluorinated 2-ethynylanilines are presented in Table 4. Four equally intensive signals observable in a ^{19}F NMR spectrum of aniline **4bg** are shifted from their counterparts of aniline **2b** by −17.7 for *ortho*, −0.5 and −1.6 for *meta* and 1.9 ppm for *para* positions to the site of iodine atom replacement by an alkynyl radical. These $\Delta\delta_F$ values are typical for all pairs of the respective *ortho*-iodo- and -alkynylanilines and correspond to those between iodo- and ethynylpentafluorobenzene [48], the signal spin-coupling structures being virtually identical. Moreover, the ^{19}F NMR spectra of **4e**,**f–i** coincide practically with that of 4,5-difluoro-2-[2-(trimethylsilyl)ethynyl]aniline [34].

The ^{13}C NMR spectral data of polyfluorinated 2-halo- and 2-alkynylanilines are given in Table 5. The signals are assigned with taking into account the ^{13}C NMR data reported for pentafluorophenylethynylbenzene and its halogen derivatives [49], keeping in mind that absolute J_{C-F} values change in a sequence $^1J_{C,F} \gg {}^2J_{C,F} > {}^3J_{C,F} > {}^4J_{C,F}$ [50]. The ^{13}C NMR characteristics of anilines **4d**,**f–i** and **4e**,**f–i** are reasonably close with those of 2-ethynyl-4,6-difluoroaniline [25] and 2-[2-(trimethylsilyl)ethynyl]-4,5-difluoroaniline [34]. Besides, the assignments of carbons of the C–F fragments are confirmed by comparing the respective $^1J_{C,F}$ values with those observed in satellite signals of the corresponding fluorine resonances in the ^{19}F NMR spectra. To assign ethynyl

Table 4
^{1}H and ^{19}F NMR chemical shifts (ppm) and coupling constants (Hz) for anilines **4a–e**,**f–j** ($CDCl_3$).



4a-e,f-j

	R^3	R^4	R^5	R^6		R
a	F	CF_3	F	F	**f**	$C(CH_3)_2OH$
b	F	F	F	F	**g**	n-Bu
c	F	F	H	F	**h**	Ph
d	H	F	H	F	**i**	CH_2OTHP
e	H	F	F	H	**j**	H

Compound	NH_2	R^3	R^4	R^5	R^6	Others
4af	4.84 (s, 2H)	−114.5 (dq, 1F) $J_{F3,CF3}$ = 21.6 $J_{F3,F6}$ = 11.2	−56.4 (dd, 3F) $J_{CF3,F3}$, $J_{CF3,F5}$ ≈ 21	−137.5 (dq, 1F) $J_{F5,CF3}$, $J_{F5,F6}$ ≈ 21	−164.9 (dd, 1F) $J_{F6,F5}$ = 20.2 $J_{F6,F3}$ = 11.2	1.63 (s, 6H, CH_3) 2.52 (s, 1H, OH)
4ag	4.74 (s, 2H)	−115.5 (dq, 1F) $J_{F3,CF3}$ = 21.5 $J_{F3,F6}$ = 11.2	−56.4 (dd, 3F) $J_{CF3,F3}$, $J_{CF3,F5}$ ≈ 21	−139.0 (dq, 1F) $J_{F5,CF3}$, $J_{F5,F6}$ ≈ 21	−165.3 (dd, 1F) $J_{F6,F5}$ = 20.3 $J_{F6,F3}$ = 11.2	0.94 (t, 3H, CH_3) $J_{H,H}$ = 7.2 1.47 (m, 2H, CH_2CH_3) 1.61 (m, 2H, $CH_2CH_2CH_3$) 2.49 (t, 2H (CH_2C(C) $J_{H,H}$ = 6.8
4ah	3.91 (s, 2H)	−114.3 (dq, 1F) $J_{F3,CF3}$ = 21.6 $J_{F3,F6}$ = 11.1	−56.0 (dd, 3F) $J_{CF3,F3}$, $J_{CF3,F5}$ ≈ 21	−138.1 (dq, 1F) $J_{F5,CF3}$, $J_{F5,F6}$ ≈ 21	−164.7 (dd, 1F) $J_{F6,F5}$ = 20.1 $J_{F6,F3}$ = 11.3	7.18–7.27 (m, 3H, Ph) 7.40–7.45 (m, 2H, Ph)
4ai	4.93 (s, 2H)	−111.3 (dq, 1F) $J_{F3,CF3}$ = 21.6 $J_{F3,F6}$ = 11.3	−53.4 (dd, 3F) $J_{CF3,F3}$, $J_{CF3,F5}$ ≈ 21	−134.4 (dq, 1F) $J_{F5,CF3}$, $J_{F5,F6}$ ≈ 21	−162.1 (dd, 1F) $J_{F6,F5}$ = 20.1 $J_{F6,F3}$ = 11.3	1.54–1.83 (m, 6H, $CH_2CH_2CH_2$) 3.54 (m, 1H, OCH_2), 3.87 (m, 1H, OCH_2), 4.53 (s, 2H, CH_2C(C) 4.85 (m, 1H, CH)
4bf	4.26 (s, 2H)	−139.3 (ddd, 1F) $J_{F3,F4}$ = 22.0 $J_{F3,F6}$ = 9.7 $J_{F6,F5}$ = 3.0	−174.1 (ddd, 1F) $J_{F4,F3}$, $J_{F4,F5}$ ≈ 22 $J_{F4,F6}$ = 5.5	−157.0 (ddd, 1F) $J_{F5,F6}$, $J_{F5,F4}$ ≈ 21 $J_{F5,F3}$ = 3.0	−163.3 (ddd, 1F) $J_{F6,F5}$ = 20.4 $J_{F6,F3}$ = 9.7 $J_{F6,F4}$ = 5.5	1.63 (s, 6H, CH_3) 2.52 (s, 1H, OH)
4bg	4.19 (s, 2H)	−137.2 (ddd, 1F) $J_{F3,F4}$ = 22.1 $J_{F3,F6}$ = 9.5	−171.5 (ddd, 1F) $J_{F4,F3}$, $J_{F4,F5}$ ≈ 22 $J_{F4,F6}$ = 5.6	−155.7 (ddd, 1F) $J_{F5,F4}$, $J_{F5,F6}$ ≈ 21	−160.7 (ddd, 1F) $J_{F6,F5}$ = 20.4 $J_{F6,F3}$ = 9.5 $J_{F6,F4}$ = 5.6	0.93 (t, 3H, CH_3) $J_{H,H}$ = 7.3 1.46 (m, 2H, CH_2CH_3) 1.60 (m, 2H, $CH_2CH_2CH_3$) 2.49 (t, 2H, CH_2C(C) $J_{H,H}$ = 6.9
4bh	4.43 (s, 2H)	−138.9 (ddd, 1F) $J_{F3,F4}$ = 22.2 $J_{F3,F6}$ = 9.6 $J_{F3,F5}$ = 2.8	−174.0 (ddd, 1F) $J_{F4,F3}$, $J_{F4,F5}$ ≈ 22 $J_{F4,F6}$ = 5.5	−157.0 (ddd, 1F) $J_{F5,F4}$, $J_{F5,F6}$ ≈ 21 $J_{F5,F3}$ = 2.8	−163.3 (ddd, 1F) $J_{F6,F5}$ = 20.4 $J_{F6,F3}$ = 9.6 $J_{F6,F4}$ = 5.5	7.34–7.39 (m, 3H, Ph) 7.51–7.56 (m, 2H, Ph)
4bi	4.34 (s, 2H)	−139.0 (ddd, 1F) $J_{F3,F4}$ = 22.0 $J_{F3,F6}$ = 9.6 $J_{F3,F5}$ = 2.7	−174.4 (ddd, 1F) $J_{F4,F3}$, $J_{F4,F5}$ ≈ 22 $J_{F4,F6}$ = 5.5	−156.9 (ddd, 1F) $J_{F5,F6}$, $J_{F5,F4}$ ≈ 21 $J_{F5,F3}$ = 2.7	−163.5 (ddd, 1F) $J_{F6,F5}$ = 20.3 $J_{F6,F3}$ = 9.6 $J_{F6,F4}$ = 5.5	1.51–1.83 (m, 6H, $CH_2CH_2CH_2$) 3.54 (m, 1H, OCH_2), 3.86 (m, 1H, OCH_2), 4.53 (s, 2H, CH_2C(C) 4.85 (m, 1H, CH)
4bj	4.32 (s, 2H)	−139.1 (ddd, 1F) $J_{F3,F4}$ = 22.0 $J_{F3,F6}$ = 9.6 $J_{F3,F5}$ = 3.1	−174.2 (ddd, 1F) $J_{F4,F3}$, $J_{F4,F5}$ ≈ 22 $J_{F4,F6}$ = 5.5	−156.3 (ddd, 1F) $J_{F5,F6}$, $J_{F5,F4}$ ≈ 21 $J_{F5,F3}$ = 3.1	−163.3 (ddd, 1F) $J_{F6,F5}$ = 20.0 $J_{F6,F3}$ = 9.6 $J_{F6,F4}$ = 5.5	3.63 (s, 1H, C(CH)
4cf	4.14 (s, 2H)	−141.5 (ddd, 1F) $J_{F3,F4}$ = 21.3 $J_{F3,F6}$ = 13.4 $J_{F3,H5}$ = 7.1	−151.1 (ddd, 1F) $J_{F4,F3}$ = 21.8 $J_{F4,H5}$ = 10.0 $J_{F4,F6}$ = 2.2	6.82 (ddd, 1H) $J_{H5,F4}$, $J_{H5,F6}$ ≈ 10 $J_{H5,F3}$ = 7.1	−138.1 (ddd, 1F) $J_{F6,F3}$ = 13.1 $J_{F6,H5}$ = 11.0 $J_{F6,H4}$ = 2.2	1.62 (s, 6H, CH_3) 2.74 (s, 1H, OH)
4cg	4.06 (s, 2H)	−142.2 (ddd, 1F) $J_{F3,F4}$ = 21.3 $J_{F3,F6}$ = 13.4 $J_{F3,H5}$ = 7.1	−151.2 (ddd, 1F) $J_{F4,F3}$ = 21.9 $J_{F4,H5}$ = 9.9 $J_{F4,F6}$ = 2.5	6.79 (ddd, 1H) $J_{H5,F4}$, $J_{H5,F6}$ ≈ 10 $J_{H5,F3}$ = 7.1	−138.5 (ddd, 1F) $J_{F6,F3}$ = 13.4 $J_{F6,H5}$ = 10.6 $J_{F6,H4}$ = 2.5	0.93 (t, 3H, CH_3) $J_{H,H}$ = 7.3 1.47 (m, 2H, CH_2CH_3) 1.61 (m, 2H, $CH_2CH_2CH_3$) 2.50 (t, 2H, CH_2C(C) $J_{H,H}$ = 7.0
4ch	4.25 (s, 2H)	−140.7 (ddd, 1F) $J_{F3,F4}$ = 21.7 $J_{F3,F6}$ = 13.4 $J_{F3,H5}$ = 7.0	−150.5 (ddd, 1F) $J_{F4,F3}$ = 21.9 $J_{F4,H5}$ = 10.0 $J_{F4,F6}$ = 2.5	6.92 (ddd, 1H) $J_{H5,F4}$, $J_{H5,F6}$ ≈ 10 $J_{H5,F3}$ = 7.0	−137.7 (ddd, 1F) $J_{F6,F3}$ = 13.4 $J_{F6,H5}$ = 10.5 $J_{F6,F4}$ = 2.5	7.40–7.42 (m, 3H, Ph) 7.58–7.61 (m, 2H, Ph)
4ci	4.19 (s, 2H)	−141.2 (ddd, 1F) $J_{F3,F4}$ = 21.2 $J_{F3,F6}$ = 13.4 $J_{F3,H5}$ = 7.1	−151.2 (ddd, 1F) $J_{F4,F3}$ = 21.8 $J_{F4,H5}$ = 10.0 $J_{F4,F6}$ = 2.4	6.84 (ddd, 1H) $J_{H5,F4}$, $J_{H5,F6}$ ≈ 10 $J_{H5,F3}$ = 7.1	−138.3 (ddd, 1F) $J_{F6,F3}$ = 13.4 $J_{F6,H5}$ = 10.9 $J_{F6,F4}$ = 2.4	1.52–1.88 (m, 6H, $CH_2CH_2CH_2$) 3.55 (m, 1H, OCH_2), 3.87 (m, 1H, OCH_2), 4.55 (s, 2H, CH_2C(C) 4.87 (m, 1H, CH)
4df	4.07 (s, 2H)	6.68–6.75 (m, 1H)	−126.0 (dd, 1F) $J_{F4,H3}$, $J_{F4,H5}$ ≈ 8	6.68–6.75 (m, 1H)	−131.3 (d, 1F) $J_{F6,H5}$ ≈ 10	1.59 (s, 6H, CH_3) 3.08 (s, 1H, OH)

Table 4 (*Continued*)

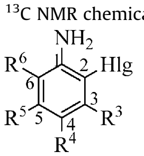
Compound	NH_2	R^3	R^4	R^5	R^6	Others
4dg	4.00 (s, 2H)	6.76 (dm, 1H) $J_{H}3,_{F}4 = 8.9$	−125.5 (dd, 1F) $J_{F}4,_{H}3$, $J_{F}4,_{H}5 \approx 9$	6.70 (ddd, 1H) $J_{H}5,_{H}6 \approx 11$ $J_{H}5,_{F}4 \approx 9$ $J_{H}5,_{H}3 \approx 3$	−130.7 (d, 1F) $J_{F}6,_{H}5 = 10.8$	0.93 (t, 3H, CH_3) $J_{H,H} = 7.3$ 1.46 (m, 2H, CH_2CH_3) 1.58 (m, 2H, $CH_2CH_2CH_3$) 2.45 (t, 2H, CH_2C(C) $J_{H,H} = 7.1$
4dh	4.18 (s, 2H)	6.93 (dm, 1H) $J_{H}3,_{F}4 = 8.8$ $J_{H}3,_{F}5 = 2.8$	−126.0 (dd, 1F) $J_{F}4,_{H}3$, $J_{F}4,_{H}5 \approx 9$	6.81 (ddd, 1H) $J_{H}5,_{H}6 = 11.0$ $J_{H}5,_{F}4 = 8.6$ $J_{H}5,_{H}3 = 2.8$	−131.3 (d, 1F) $J_{F}6,_{H}5 = 10.8$	7.38–7.39 (m, 3H, Ph) 7.54–7.57 (m, 2H, Ph)
4di	4.09 (s, 2H)	6.74–6.9 (dm, 1H) $J_{H}3,_{F}4 \approx 8$	−126.4 (dd, 1F) $J_{F}4,_{H}3$, $J_{F}4,_{H}5 \approx 8$	6.74–6.79 (ddd, 1H) $J_{H}5,_{H}6 \approx 11$ $J_{H}5,_{F}4 \approx 9$ $J_{H}5,_{H}3 \approx 3$	−131.5 (d, 1F) $J_{F}6,_{H}5 = 10.7$	1.51–1.83 (m, 6H, $CH_2CH_2CH_2$) 3.56 (m, 1H, OCH_2), 3.86 (m, 1H, OCH_2), 4.51 (s, 2H, CH_2C(C) 4.85 (m, 1H, CH)
4dj	4.15 (s, 2H)	6.75–6.87 (m, 1H)	−126.0 (dd, 1F) $J_{F}4,_{H}3$, $J_{F}4,_{H}5 \approx 9$	6.75–6.87 (m, 1H)	−131.0 (d, 1F) $J_{F}6,_{H}5 = 10.8$	3.45 (s, 1H, C(CH)
4ef	4.17 (s, 2H)	7.00 (dd, 1H) $J_{H}3,_{F}4 = 10.4$ $J_{H}3,_{F}5 = 8.7$	−152.6 (ddd, 1F) $J_{F}4,_{F}5 = 22.1$ $J_{F}4,_{F}3 = 10.4$ $J_{F}4,_{H}6 = 7.2$	−135.6 (ddd, 1F) $J_{F}5,_{F}4 = 22.1$ $J_{F}5,_{H}6 = 11.8$ $J_{F}5,_{H}3 = 8.7$	6.45 (dd, 1H) $J_{H}6,_{F}5 = 11.8$ $J_{H}6,_{F}4 = 7.2$	1.59 (s, 6H, CH_3) 2.71 (s, 1H, OH)
4eg	4.10 (s, 2H)	6.99 (dd, 1H) $J_{H}3,_{F}4 = 10.7$ $J_{H}3,_{F}5 = 8.7$	−153.2 (ddd, 1F) $J_{F}4,_{F}5 = 22.3$ $J_{F}4,_{H}3 = 10.7$ $J_{F}4,_{H}6 = 7.2$	−137.3 (ddd, 1F) $J_{F}5,_{F}4 = 22.3$ $J_{F}5,_{H}6 = 11.8$ $J_{F}5,_{H}3 = 8.7$	6.43 (dd, 1H) $J_{H}6,_{F}5 = 11.8$ $J_{H}6,_{F}4 = 7.2$	0.92 (t, 3H, CH_3) $J_{H,H} = 7.3$ 1.47 (m, 2H, CH_2CH_3) 1.57 (m, 2H, $CH_2CH_2CH_3$) 2.42 (t, 2H, CH_2C(C) $J_{H,H} = 6.8$
4eh	4.30 (s, 2H)	7.21 (dd, 1H) $J_{H}3,_{F}4 = 10.5$ $J_{H}3,_{F}5 = 8.8$	−152.5 (ddd, 1F) $J_{F}4,_{H}5 = 22.1$ $J_{F}4,_{H}3 = 10.5$ $J_{F}4,_{H}6 = 7.1$	−135.4 (ddd, 1F) $J_{F}5,_{F}4 = 22.1$ $J_{F}5,_{H}6 = 11.8$ $J_{F}5,_{H}3 = 8.8$	6.54 (dd, 1H) $J_{H}6,_{F}5 = 11.8$ $J_{H}6,_{F}4 = 7.1$	7.40–7.42 (m, 3H, Ph) 7.56–7.59 (m, 2H, Ph)
4ei	4.19 (s, 2H)	7.04 (dd, 1H) $J_{H}3,_{F}4 = 10.5$ $J_{H}3,_{F}5 = 8.7$	−152.8 (ddd, 1F) $J_{F}4,_{H}5 = 22.2$ $J_{F}4,_{H}3 = 10.5$ $J_{F}4,_{H}6 = 7.0$	−135.3 (ddd, 1F) $J_{F}5,_{F}4 = 22.2$ $J_{F}5,_{H}6 = 11.8$ $J_{F}5,_{H}3 = 8.7$	6.43 (dd, 1H) $J_{H}6,_{F}5 = 11.8$ $J_{H}6,_{F}4 = 7.0$	1.52–1.83 (m, 6H, $CH_2CH_2CH_2$) 3.54 (m, 1H, OCH_2), 3.86 (m, 1H, OCH_2), 4.48 (s, 2H, CH_2C(C) 4.85 (m, 1H, CH)

carbons of **4a**–**e**,**f**–**j**, informative was that in the ^{13}C spectrum of **4bj**, registered without C–H spin decoupling, the C^8 exhibits a doublet with $^1J_{C}8,_{H} = 255.6$ Hz, whereas the C^7 signal appears as a doublet with $^2J_{C}7,_{H} = 50.6$ Hz. Accordingly, the signals at $\delta_C = 67$–84 ppm in the ^{13}C NMR spectra of **4a**–**e**,**f**–**j** are assigned to C^7 adjacent to the polyfluorinated benzene ring. Only the J values most structurally informative for the ^{13}C signals assignment are shown in Table 5.

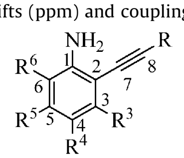
That low-field location of the C^2 resonances of **2a** and **2b** is caused by polyfluorination of the benzene ring is illustrated by the respective values for 1-fluoro-4-iodobenzene (87.1 ppm) and pentafluoroiodobenzene (66.1 ppm) [51]. Interestingly, a dependence is observed of the ethynyl δ_C values on substitution both in the fluorinated benzene ring and at the ethynyl β-C-atom. Thus, in going from anilines **4a**–**e**,**f**–**i**, containing fluorine *ortho* to the ethynyl fragment, to **4d**–**e**,**f**–**i**, having no substituent at the 3-position, the two ethynyl signals approach each other as a result of the α-C drift to a high field and of the β-C signals – to a low field, both moving towards the ethynyl δ_C values reported for 2-ethynyl-4,6-difluoroaniline [25] and nonfluorinated tolanes [52,53]. The similar takes place in going from anilines with β-substituents CMe_2OH (**f**) and *n*-Bu (**g**) to those with β-substituents Ph (**h**) and CH_2OTHP (**i**).

Table 5

^{13}C NMR chemical shifts (ppm) and coupling constants (Hz) for anilines **2a**–**e**, **4a**–**e**,**f**–**j** and **5** ($CDCl_3$).



2a–e, 5



4a–e,f–j

	R^3	R^4	R^5	R^6		R		Hlg
a, 5	F	CF_3	F	F	**f**	$C(CH_3)_2OH$	**2**	I
b	F	F	F	F	**g**	n-Bu	**5**	Br
c	F	F	H	F	**h**	Ph		
d	H	F	H	F	**i**	CH_2OTHP		
e	H	F	F	H	**j**	H		

	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	Others
2a	141.2 $^2J_{C}1,_{F}6 = 11.1$	65.5 $^2J_{C}2,_{F}3 = 32.1$	154.7 $^1J_{C}3,_{F}3 = 248.7$ $^3J_{C}3,_{CF3} = 1.6$	96.7 $^2J_{C}4,_{CF3} = 34.6$ $^2J_{C}4,_{F}3 = 19.6$ $^2J_{C}4,_{F}5 = 12.5$	148.3 $^1J_{C}5,_{F}5 = 257.2$ $^2J_{C}5,_{F}6 = 13.5$ $^3J_{C}5,_{CF3} = 1.6$	134.5 $^1J_{C}6,_{F}6 = 241.8$ $^2J_{C}6,_{F}5 = 15.5$			121.5 (CF_3) $^1J_{CF3,F} = 272.7$
2b	133.0 $^2J_{C}1,_{F}6 = 11.9$	65.2 $^2J_{C}2,_{F}3 = 27.2$	147.2 $^1J_{C}3,_{F}3 = 239.8$ $^2J_{C}3,_{F}4 = 11.5$	132.3 $^1J_{C}4,_{F}4 = 246.0$ $^2J_{C}4,_{F}3 = 19.3$ $^2J_{C}4,_{F}5 = 13.5$	141.0 $^1J_{C}5,_{F}5 = 250.0$ $^2J_{C}5,_{F}4 = 14.1$ $^2J_{C}5,_{F}6 = 13.4$	135.2 $^1J_{C}6,_{F}6 = 242.4$ $^2J_{C}6,_{F}5 = 12.8$			
2c	133.2	72.9	146.9	141.1	105.1	144.5			

Table 5 (*Continued*)

	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	Others
	$^2J_{C1,F6}=15.2$	$^2J_{C2,F3}=26.6$	$^1J_{C3,F3}=239.5$; $^2J_{C3,F4}=14.2$	$^1J_{C4,F4}=243.6$ $^2J_{C4,F3}=16.7$ $^3J_{C4,F6}=11.8$	$^2J_{C5,F4}=25.0$ $^2J_{C5,F6}=22.2$	$^1J_{C6,F6}=241.7$ $^3J_{C6,F4}=9.6$			
2d	133.0 $^2J_{C1,F6}=14.0$	82.3 $^3J_{C2,F4}=10.5$	120.3 $^2J_{C3,F4}=24.2$	154.4 $^1J_{C4,F4}=242.4$ $^3J_{C4,F6}=11.9$	104.2 $^2J_{C5,F4}=26.3$ $^2J_{C5,F6}=23.5$	148.9 $^1J_{C6,F6}=245.9$ $^3J_{C6,F4}=12.0$			
2e	144.0 $^3J_{C1,F5}=8.7$	74.9 $^3J_{C2,F4}=6.5$	126.5 $^2J_{C3,F4}=20.0$	143.1 $^1J_{C4,F4}=243.0$ $^2J_{C4,F5}=13.5$	150.9 $^1J_{C5,F5}=246.6$ $^2J_{C5,F4}=13.3$	102.6 $^2J_{C6,F5}=21.0$			
5	138.7 $^2J_{C1,F6}=11.9$	91.8 $^2J_{C2,F3}=26.4$	152.8 $^1J_{C3,F3}=252.0$ $^3J_{C3,CF3}=1.9$	97.2 $^2J_{C4,CF3}=34.7$ $^2J_{C4,F3}=17.7$ $^2J_{C4,F5}=12.6$	147.4 $^1J_{C5,F5}=257.2$ $^2J_{C5,F6}=13.5$ $^3J_{C5,CF3}=1.8$	135.5 $^1J_{C6,F6}=241.0$ $^2J_{C6,F5}=15.6$			121.7 (CF_3) $^1J_{CF3,F}=273.0$
4af	141.1 $^2J_{C1,F6}=11.1$	94.3 $^2J_{C2,F3}=21.8$	156.3 $^1J_{C3,F3}=256.8$ $^3J_{C3,CF3}\approx 2$	96.8 $^2J_{C4,CF3}=34.7$ $^2J_{C4,F3}=16.3$ $^2J_{C4,F5}=12.6$	148.0 $^1J_{C5,F5}=259.2$ $^2J_{C5,F6}=13.2$ $^3J_{C5,CF3}\approx 2$	135.4 $^1J_{C6,F6}=238.4$ $^2J_{C6,F5}=15.2$	69.6	106.1	31.4 (CH_3) 65.9 (COH) 121.7 (CF_3) $^1J_{CF3,F}=272.4$
4ag	141.0 $^2J_{C1,F6}=11.4$	95.8 $^2J_{C2,F3}=21.8$	156.3 $^1J_{C3,F3}=255.8$ $^3J_{C3,CF3}\approx 2$	96.8 $^2J_{C4,CF3}=34.7$ $^2J_{C4,F3}=16.3$ $^2J_{C4,F5}=12.6$	147.5 $^1J_{C5,F5}=258.1$ $^2J_{C5,F6}=15.0$ $^3J_{C5,CF3}\approx 2$	135.5 $^1J_{C6,F6}=237.7$ $^2J_{C6,F5}=15.3$	67.8	103.0	13.6 (CH_3) 19.4 (CH_2) 22.0 (CH_2) 30.6 (CH_2) 121.8 (CF_3) $^1J_{CF3,F}=272.6$
4ah	140.9 $^2J_{C1,F6}=11.7$	95.2 $^2J_{C2,F3}=21.7$	156.2 $^1J_{C3,F3}=257.1$ $^3J_{C3,CF3}\approx 2$	97.1 $^2J_{C4,CF3}=34.7$ $^2J_{C4,F3}=16.3$ $^2J_{C4,F5}=12.6$	148.1 $^1J_{C5,F5}=258.8$ $^2J_{C5,F6}=13.1$ $^3J_{C5,CF3}\approx 2$	135.5 $^1J_{C6,F6}=238.5$ $^2J_{C6,F5}=15.2$	76.1	101.0	121.7 (CF_3) $^1J_{CF3,F}=272.8$ 121.8 (Ph) 128.6 (Ph) 129.3 (Ph) 131.7 (Ph)
4ai	141.8 $^2J_{C1,F6}=11.7$	94.3 $^2J_{C2,F3}=21.9$	156.5 $^1J_{C3,F3}=257.3$ $^3J_{C3,CF3}\approx 2$	96.5 $^2J_{C4,CF3}=34.7$ $^2J_{C4,F3}=16.3$ $^2J_{C4,F5}=12.6$	148.2 $^1J_{C5,F5}=259.2$ $^2J_{C5,F6}=13.4$ $^3J_{C5,CF3}\approx 2$	135.4 $^1J_{C6,F6}=238.2$ $^2J_{C6,F5}=15.2$	73.2	97.5	19.0 (CH_2) 25.3 (CH_2) 30.3 (CH_2) 55.2 (CH_2) 62.3 (CH_2) 97.8 (CH) 121.7 (CF_3) $^1J_{CF3,F}=272.3$
4bf	133.4 $^2J_{C1,F6}=11.5$	93.8 $^2J_{C2,F3}=17.5$	147.8 $^1J_{C3,F3}=247.7$ $^2J_{C3,F4}=11.2$	132.7 $^1J_{C4,F4}=242.1$ $^2J_{C4,F3}=16.3$ $^2J_{C4,F5}=13.4$	141.5 $^1J_{C5,F5}=252.0$ $^2J_{C5,F4}$, $^2J_{C5,F6}\approx 14$	136.0 $^1J_{C6,F6}=238.8$ $^2J_{C6,F5}=12.6$	69.9	105.8	31.4 (CH_3) 65.9 (COH)
4bg	133.2 $^2J_{C1,F6}=11.5$	95.2 $^2J_{C2,F3}=17.7$	148.0 $^1J_{C3,F3}=246.5$ $^2J_{C3,F4}=11.1$	132.8 $^1J_{C4,F4}=241.6$ $^2J_{C4,F3}=16.7$ $^2J_{C4,F5}=13.3$	140.9 $^1J_{C5,F5}=250.8$ $^2J_{C5,F4}$, $^2J_{C5,F6}\approx 14$	136.1 $^1J_{C6,F6}=238.2$ $^2J_{C6,F5}=12.7$	68.1	102.9	13.5 (CH_3) 19.5 (CH_2) 22.0 (CH_2) 30.6 (CH_2)
4bh	133.2 $^2J_{C1,F6}=11.8$	94.4 $^2J_{C2,F3}=17.7$	147.6 $^1J_{C3,F3}=247.9$ $^2J_{C3,F4}=11.1$	132.7 $^1J_{C4,F4}=242.3$ $^2J_{C4,F3}=16.6$ $^2J_{C4,F5}=13.5$	141.3 $^1J_{C5,F5}=252.2$ $^2J_{C5,F4}$, $^2J_{C5,F6}\approx 14$	135.9 $^1J_{C6,F6}=236.3$ $^2J_{C6,F5}=12.3$	76.4	100.7	121.9 (Ph) 128.4 (Ph) 129.1 (Ph) 131.5 (Ph)
4bi	134.0 $^2J_{C1,F6}=11.6$	93.6 $^2J_{C2,F3}=17.7$	148.0 $^1J_{C3,F3}=248.1$ $^2J_{C3,F4}=11.1$	132.5 $^1J_{C4,F4}=241.8$ $^2J_{C4,F3}=16.6$ $^2J_{C4,F5}=13.5$	141.6 $^1J_{C5,F5}=252.3$ $^2J_{C5,F4}$, $^2J_{C5,F6}\approx 14$	136.0 $^1J_{C6,F6}=238.8$ $^2J_{C6,F5}=12.8$	73.5	97.4	19.0 (CH_2) 25.3 (CH_2) 30.3 (CH_2) 55.1 (CH_2) 62.3 (CH_2) 97.6 (CH)
4bj	134.5 $^2J_{C1,F6}=11.7$	93.4 $^2J_{C2,F3}=17.5$	148.5 $^1J_{C3,F3}=249.0$ $^2J_{C3,F4}=11.2$	132.8 $^1J_{C4,F4}=242.4$ $^2J_{C4,F3}=16.4$ $^2J_{C4,F5}=13.8$	142.0 $^1J_{C5,F5}=253.0$ $^2J_{C5,F4}$, $^2J_{C5,F6}\approx 14$	136.2 $^1J_{C6,F6}=239.0$ $^2J_{C6,F5}=12.6$	71.6 $^2J_{C7,H}=50.6$	89.0 $^1J_{C8,H}=255.6$	
4cf	133.3 $^2J_{C1,F6}=15.1$	99.5 $^2J_{C2,F3}=17.5$	147.0 $^1J_{C3,F3}=245.8$ $^2J_{C3,F4}=13.7$	141.1 $^1J_{C4,F4}=239.2$ $^2J_{C4,F3}=13.9$ $^2J_{C4,F5}=12.7$	105.4 $^2J_{C5,F4}=24.4$ $^2J_{C5,F6}=22.3$	145.3 $^1J_{C6,F6}=238.0$ $^3J_{C6,F4}=10.4$	70.9	106.1	31.4 (CH_3) 65.8 (COH)
4cg	133.1 $^2J_{C1,F6}=14.9$	101.0 $^2J_{C2,F3}=17.6$	147.4 $^1J_{C3,F3}=245.3$ $^2J_{C3,F4}=13.7$	141.3 $^1J_{C4,F4}=238.9$ $^2J_{C4,F3}$, $^2J_{C4,F5}\approx 14$	104.5 $^2J_{C5,F4}$, $^2J_{C5,F6}\approx 23$	145.4 $^1J_{C6,F6}=237.2$ $^3J_{C6,F4}=10.5$	69.3	103.2	13.6 (CH_3) 19.5 (CH_2) 22.0 (CH_2) 30.6 (CH_2)
4ch	133.4	100.2	147.2	141.5	105.5	145.5	77.9	100.9	122.4 (Ph)

Table 5 (*Continued*)

	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	Others
	$^2J_{C1,F6}=15.7$	$^2J_{C2,F3}=17.5$	$^1J_{C3,F3}=246.8$ $^2J_{C3,F4}=13.6$	$^1J_{C4,F4}=239.3$ $^2J_{C4,F3}$, $^2J_{C4,F5}\approx 13$	$^2J_{C5,F4}$, $^2J_{C5,F6}\approx 23$	$^1J_{C6,F6}=237.8$ $^3J_{C6,F4}=10.5$			128.7 (Ph) 129.9 (Ph) 131.9 (Ph)
4ci	133.8 $^2J_{C1,F6}=15.1$	99.4 $^2J_{C2,F3}=17.7$	147.4 $^1J_{C3,F3}=246.9$ $^2J_{C3,F4}=13.8$	141.0 $^1J_{C4,F4}=239.2$ $^2J_{C4,F3}=13.6$ $^2J_{C4,F5}=12.4$	105.6 $^2J_{C5,F4}$, $^2J_{C5,F6}\approx 23$	145.2 $^1J_{C6,F6}=237.8$ $^3J_{C6,F4}=10.4$	74.6	97.6	19.1 (CH_2) 25.3 (CH_2) 30.3 (CH_2) 55.0 (CH_2) 62.2 (CH_2) 97.5 (CH)
4df	133.0 $^2J_{C1,F6}=13.7$	109.4 $^3J_{C2,F4}=11.0$	113.3 $^2J_{C3,F4}=23.4$	153.8 $^1J_{C4,F4}=237.9$ $^3J_{C4,F6}=12.3$	104.6 $^2J_{C5,F4}=26.8$ $^2J_{C5,F6}=22.9$	150.6 $^1J_{C6,F6}=241.6$ $^3J_{C6,F4}=12.7$	76.8	101.3	31.5 (CH_3) 65.6 (COH)
4dg	132.9 $^2J_{C1,F6}=13.5$	110.9 $^3J_{C2,F4}=11.0$	113.3 $^2J_{C3,F4}=23.2$	153.9 $^1J_{C4,F4}=237.4$ $^3J_{C4,F6}=12.5$	103.8 $^2J_{C5,F4}=26.8$ $^2J_{C5,F6}=22.9$	150.5 $^1J_{C6,F6}=241.0$ $^3J_{C6,F4}=12.9$	75.3	97.9	13.6 (CH_3) 19.3 (CH_2) 22.1 (CH_2) 30.8 (CH_2)
4dh	133.2 $^2J_{C1,F6}=13.7$	109.8 $^3J_{C2,F4}=11.0$	113.3 $^2J_{C3,F4}=23.3$	153.9 $^1J_{C4,F4}=237.9$ $^3J_{C4,F6}=12.4$	104.7 $^2J_{C5,F4}=26.9$ $^2J_{C5,F6}=22.8$	150.6 $^1J_{C6,F6}=241.6$ $^3J_{C6,F4}=12.7$	83.8	96.4	122.5 (Ph) 128.5 (Ph) 128.9 (Ph) 131.6 (Ph)
4di	133.7 $^2J_{C1,F6}=13.8$	109.0 $^3J_{C2,F4}=10.9$	113.5 $^2J_{C3,F4}=23.3$	153.6 $^1J_{C4,F4}=237.8$ $^3J_{C4,F6}=12.3$	104.9 $^2J_{C5,F4}=26.8$ $^2J_{C5,F6}=22.8$	150.4 $^1J_{C6,F6}=241.6$ $^3J_{C6,F4}=12.7$	80.5	92.5	19.0 (CH_2) 25.3 (CH_2) 30.3 (CH_2) 54.9 (CH_2) 62.2 (CH_2) 97.3 (CH)
4ef	144.9 $^3J_{C1,F5}=9.4$	102.9 $^3J_{C2,F4}=7.0$	120.0 $^2J_{C3,F4}=19.0$	142.8 $^1J_{C4,F4}=238.1$ $^2J_{C4,F5}=13.4$	151.2 $^1J_{C5,F5}=249.1$ $^2J_{C5,F4}=13.7$	103.0 $^2J_{C6,F5}=20.9$	84.0	99.7	31.6 (CH_3) 65.7 (COH)
4eg	144.8 $^3J_{C1,F5}=9.1$	104.5 $^3J_{C2,F4}=6.9$	119.8 $^2J_{C3,F4}=18.6$	142.7 $^1J_{C4,F4}=237.4$ $^2J_{C4,F5}=13.5$	150.6 $^1J_{C5,F5}=247.6$ $^2J_{C5,F4}=13.7$	102.7 $^2J_{C6,F5}=20.8$	75.3	96.3	13.6 (CH_3) 19.2 (CH_2) 22.1 (CH_2) 30.9 (CH_2)
4eh	144.9 $^3J_{C1,F5}=9.4$	103.1 $^3J_{C2,F4}=7.3$	119.5 $^2J_{C3,F4}=18.9$	142.5 $^1J_{C4,F4}=237.9$ $^2J_{C4,F5}=13.6$	151.0 $^1J_{C5,F5}=249.1$ $^2J_{C5,F4}=13.8$	102.6 $^2J_{C6,F5}=20.9$	83.8	94.7	122.4 (Ph) 128.2 (Ph) 128.3 (Ph) 131.2 (Ph)
4ei	145.5 $^3J_{C1,F5}=9.4$	102.5 $^3J_{C2,F4}=7.3$	120.2 $^2J_{C3,F4}=18.9$	142.7 $^1J_{C4,F4}=238.0$ $^2J_{C4,F5}=13.5$	151.4 $^1J_{C5,F5}=249.3$ $^2J_{C5,F4}=13.8$	102.8 $^2J_{C6,F5}=20.9$	80.8	91.0	19.1 (CH_2) 25.3 (CH_2) 30.3 (CH_2) 54.9 (CH_2) 62.2 (CH_2) 97.2 (CH)

In the IR spectra of all anilines synthesized the valence vibrations of the N–H (3354–3496 cm^{-1}) and C(C (2206–2235 cm^{-1}) bonds are observed. Characteristic for compound **4bj** are the ethynyl C–H vibration at 3304 cm^{-1} and the high-frequency shift (~100 cm^{-1}) of the C(C band from that of anilines **4a**–**e**,**f**–**i** (cf [46]).

3. Conclusion

By means of the Pd-catalysed condensation of polyfluorinated *ortho*-iodoanilines with terminal alkynes the corresponding *ortho*-alkynylanilines – base building blocks for assembling polyfluorobenzoazaheterocycles and molecular design of their functional derivatives were obtained.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AV-300 (300.13 for ^1H and 282.37 MHz for ^{19}F) and AV-400 (400.13 for ^1H, 376.44 for ^{19}F and 100.62 MHz for ^{13}C) spectrometers in $CDCl_3$ using residual $CHCl_3$ (δ_H 7.24 ppm), $CDCl_3$ (δ_C 76.9 ppm) as internal references and C_6F_6 ($\delta_F = -163.0$ ppm) as an external reference. ^{13}C NMR spectra were registered with C–H spin decoupling, while the another is not stated.

Masses of molecular ions were determined by HRMS on a DFS Thermo scientific instrument (EI, 70 eV), or by Hybrid Quadrupole Time of Flight mass spectrometer (microTOF-Q, Bruker) equipped with Atmospheric Pressure Chemical Ionization (APCI) and Atmospheric Pressure Electrostatic Spray Ionization (API-ES). GC–MS was performed in a Hewlett–Packard instrument with a HP 5890 Series II gas chromatograph and HP 5971 (EI, 70 eV) mass-selective detector using a HP5MS capillary column (30 mm × 0.25 mm × 0.25 mm); the carrier gas was He et 1 mL/min. IR spectra were recorded with a Bruker V-22 spectrometer. The starting 2-(prop-2-in-1-yloxy)oxane **3i** [54] and $Pd(PPh_3)_2Cl_2$ [55] were prepared by the reported protocols. 3,4-Difluoroaniline, other materials and solvents were of a commercial supply, the solvents having been distilled. Sorbfil plates were used for products isolation by TLC (eluent: hexane–EtOAc, 10 ÷ 5: 1) as an oils. According to ^{19}F NMR data with calibration of peak intensities by C_6F_6 as an internal standard the first synthesized compounds had purity ≥95% (Table 6).

Table 6
Exact values of molecular ion masses and IR data of anilines **2a**–**d** and **4a**–**e**,**f**–**j**.

Compound	*m*/*z*	Calcd for	$[M]^+$ (calcd)	$[M]^+$ (found)	IR spectra, ν (cm^{-1})		
					OH (C(C–H)	NH_2	C(C
2a	$[M]^+$	$C_7H_2F_6IN$	340.9131	340.9133		3507, 3402	
2c	$[M]^+$	$C_6H_3F_3IN$	272.9257	272.9258		3480, 3383	
2d	$[M]^+$	$C_6H_4F_2IN$	254.9351	254.9350		3465, 3369	
4af	$[M]^+$	$C_{12}H_9F_6NO$	297.0583	297.0584	3609	3411, 3358	2232
4ag	$[M]^+$	$C_{13}H_{11}F_6N$	295.0790	295.0793		3515, 3408	2232
4ah	$[M]^+$	$C_{15}H_7F_6N$	315.0477	315.0475		3511, 3405	2214
4ai	$[M]^+$	$C_{15}H_{13}F_6NO_2$	353.0845	353.0847		3474, 3339	2231
4bf	$[M+H^+-H_2O]^+$	$C_{11}H_8F_4N$	230.0587	230.0586	3604	3355	2227
4bg	$[M]^+$	$C_{12}H_{11}F_4N$	245.0822	245.0821		3496, 3396	2235
4bh	$[M-H^+]^-$	$C_{14}H_6F_4N$	264.0442	264.0440		3473, 3386	2211
4bi	$[M]^+$	$C_{14}H_{13}F_4NO_2$	303.0877	303.0876		3470, 3354	2233
4bj	$[M]^+$	$C_8H_3F_4N$	189.0196	189.0200	3304 (C(CH)	3503, 3402	2112
4cf	$[M]^+$	$C_{11}H_{10}F_3NO$	229.0709	229.0711	3599	3359	2227
4cg	$[M]^+$	$C_{12}H_{12}F_3N$	227.0916	227.0915		3472, 3396	2230
4ch	$[M+H^+]^+$	$C_{14}H_9F_3N$	248.0682	248.0690		3473, 3392	2206
4ci	$[M]^+$	$C_{14}H_{14}F_3NO_2$	285.0971	285.0968		3475, 3354	2231
4df	$[M]^+$	$C_{11}H_{11}F_2NO$	211.0803	211.0800	3568	3350	2223
4dg	$[M]^+$	$C_{12}H_{13}F_2N$	209.1011	209.1016		3481, 3384	2229
4dh	$[M]^+$	$C_{14}H_9F_2N$	229.0698	229.0699		3476, 3386	2206
4di	$[M+H^+]^+$	$C_{14}H_{16}F_2NO_2$	268.1144	268.1132		3469, 3357	2229
4ef	$[M]^+$	$C_{11}H_{11}F_2NO$	211.0803	211.0802	3568	3408, 3301	2218
4eg	$[M+H^+]^+$	$C_{12}H_{14}F_2N$	210.1089	210.1085		3477, 3384	2225
4eh	$[M-H^+]^-$	$C_{14}H_8F_2N$	228.0630	228.0623		3452, 3361	2206
4ei	$[M+H^+]^+$	$C_{14}H_{16}F_2NO_2$	268.1144	268.1141		3469, 3361	2223

4.2. Synthetic procedures

4.2.1. 2-Iodo-3,5,6-trifluoro-4-(trifluoromethyl)aniline (2a). Method I (typical procedure for anilines 2a–d).

To a stirred solution of aniline **1a** (0.52 g, 2.4 mmol) in dioxane (18 mL) at 70 °C were added 0.31 г (1.2 mmol) fine-ground iodine and a solution of iodic acid (0.43 g, 2.4 mmol) in H_2O (3 mL). The reaction mixture was refluxed for 4 h, cooled to r.t., poored into H_2O (50 mL) and extracted with $CHCl_3$ (3 × 30 mL). The extract was washed with sat. $Na_2S_2O_3$ (2 × 30 mL) and NaCl (30 mL) solutions, then with H_2O (30 mL), dried ($MgSO_4$), and purified by flash chromatography on Al_2O_3 to afford **2a** (0.79 g, 97%) as an oil.

Method II. A solution of 2,3,5-trifluoro-4-(trifluoromethyl)aniline **1a** (0.34 g, 1.57 mmol) in EtOH (3 mL) was added during 15 min to a stirred mixture of I_2 (0.51 g, 2.0 mmol), Ag_2SO_4 (0.62 g, 2.0 mmol) and EtOH (10 mL). The mixture was boiled for 4 h, filtered, solvent was evaporated. The residue was dissolved in $CHCl_3$ (40 mL), the solution was washed with sat. aq. solutions of $Na_2S_2O_3$ (2 × 30 mL) and NaCl (30 mL), then with H_2O (30 mL), dried ($MgSO_4$), and purified by flash chromatography on Al_2O_3 to afford **2a** (0.49 g, 93%) as an oil.

4.2.2. 2,3,4,5-Tetrafluoro-6-(hex-1-yn-1-yl)aniline (4bg) (typical procedure for anilines 4a–e,f–i)

To a stirred mixture of aniline **2b** (0.100 g, 0.344 mmol), hex-1-yne **3g** (0.084 g, 1.031 mmol) and Et_3N (3 mL) under argon added were $Pd(PPh_3)_2Cl_2$ (0.010 g, 0.014 mmol), CuI (0.006 g, 0.031 mmol) and, additionally, Et_3N (3 mL). Stirring was continued at 70 °C for 3 h, the mixture was cooled to r.t., diluted by $CHCl_3$ (10 mL) and poured into a mixture of H_2O (30 mL) and $CHCl_3$ (20 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 30 mL), the collected organic solution was washed with H_2O (3 × 30 mL) and dried ($MgSO_4$). Evoparation of the solvent and chromatography (TLC) of the crude product (eluent: hexane–EtOAc, 10:1 → 10:1 → 10:1, R_f = 0.54) gave aniline **4bg** (0.067 g, 80%) as an oil.

4.2.3. 2-Ethynyl-tetrafluoroaniline (4bj) (typical procedure for anilines 4bj, 4dj)

The crude product (**4bf**), obtained by reaction of aniline **2b** (0.202 g, 0.693 mmol) with alkyne **3f** (see typical procedure for anilines **4a**–**e**,**f**–**i**), and powdered KOH (0.078 g, 1.4 mmol) in absolute benzene (8 mL) were refluxed with stirring for 40 min. The mixture was cooled to r.t. and poured into a mixture of H_2O (30 mL) and $CHCl_3$ (20 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 30 mL), the collected organic solution was washed with H_2O (3 × 30 mL) and dried ($MgSO_4$). Evoparation of the solvent and chromatography (TLC) of the crude product (eluent: hexane–EtOAc, 15:1 → 15:1 → 15:1, R_f = 0.46) gave aniline **4bj** (0.093 g, 71% on **2b**) as an oil.

4.2.4. 2-Bromo-3,5,6-trifluoro-4-(trifluoromethyl)aniline (5)

To a stirred solution of aniline **1a** (2.0 g, 9.3 mmol) in glycial AcOH (7 mL) were added powdered iron (0.07 g, 1.3 mmol) and anhydrous AcONa (1.0 g, 12.1 mmol). The mixture was warmed to 45 °C and a solution of Br_2 (2.7 g, 16.8 mmol) in AcOH (7 mL) was dropwise added for 1 h. The mixture was stirred at 60 °C for 2 h, then cooled to r.t. and decolorized by adding a sat. aq. solution of $Na_2S_2O_3$ and steam distilled. The distillate was extracted with $CHCl_3$ (3 × 50 mL), the extract was washed with H_2O (50 mL), dried ($MgSO_4$), evaporated to afford the title aniline (2.3 g, 85%) as a colorless solid. m.p.: 33–34 °C. IR (KBr): 3510 and 3414 (NH_2) cm^{-1}. Anal. Calcd. for $C_7H_2F_6BrN$: C, 28.60; H, 0.69, Br, 27.18; N, 4.76. Found: C, 28.42; H, 0.70; Br, 27.15; N, 4.72.

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