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Synthesis of dioxin-like monofluorinated PCBs: for the use as internal standards for PCB analysis

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Abstract

Monofluorinated polychlorinated biphenyls (fluoro-PCBs) have been prepared using the Suzuki-coupling, for use as analytical standards for PCB measurements. Seven of these fluoro-PCBs are analogues of the dioxin-like PCBs, listed by the WHO as the most toxic PCB congeners. Four highly chlorinated fluoro-PCBs have been prepared by Suzuki-coupling of 2,3,5,6-tetrachloro-bromoaniline with various substituted arylboronic acids. The resulting amino-fluoro-PCBs are chlorinated using the Sandmeyer reaction or deaminated to yield tetra-, penta- and hexa-chlorinated fluoro-PCBs. The fluoro-PCBs elute just before the corresponding PCBs in the GC chromatogram, which strongly indicates their potential as analytical standards.

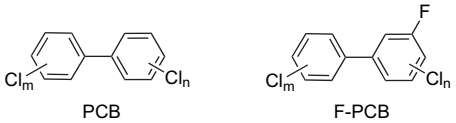
Keywords: Fluoro-PCB; Suzuki-coupling; Internal standards; Dioxin-like PCB

1. Introduction

Polychlorinated biphenyls (PCBs) constitute a major class of persistent environmental contaminants, despite a ban on production since the 1970s. Mixtures of PCB isomers were produced for a wide array of applications, such as capacitors and transformers, hydraulic fluids, paints, plastics and fire retardants.[1] Properties such as chemical stability, low flammability and electrical insulating properties led to worldwide use. Unfortunately, their chemical stability has also caused accumulation of PCBs in higher organisms of the food chain.[2]

PCBs are toxic pollutants whose toxicity depends largely on the number of *ortho*-substituents in the biphenyl molecule. The most toxic congeners are those which can adopt a partially co-planar conformation, which holds for PCBs with only one or no chlorine atoms in the *ortho*-position. These congeners show similar toxic properties to those observed for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, and are therefore known as dioxin-like PCBs.[3]

Traditionally, ^{13}C labelled PCB congeners are used as internal standards for PCB analysis, which are easily identified in a GC–MS chromatogram. However, these standards are expensive and may not be suitable when detection methods other than mass spectrometry are used, such as an electron capture detector (ECD). Fluorinated PCBs (fluoro-PCBs) may be used as alternative analytical standards. Fluorinated polyaromatic hydrocarbons (PAHs) have proven useful as standards for PAH analysis,[4] and a recent report from our laboratory shows the potential of difluorinated polybrominated diphenyl ethers as internal analytical standards.[5] Preliminary results from our lab show that fluoro-PCBs meet the criteria for the use as internal standards. They have similar chemical properties to their corresponding PCBs, and they elute close to the parent PCB with baseline resolution.



In this work, monofluorinated analogues of the dioxin-like PCBs were prepared by Suzuki cross-coupling of different substituted arylboronic acids and aryl bromides (Scheme 1).[6]

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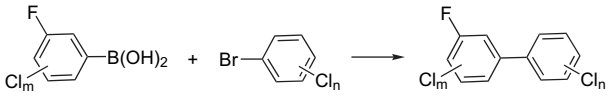
The Suzuki-coupling has previously been successfully used for syntheses of PCBs and hydroxy-PCBs.[7,8] The properties of the PCB molecule seem only to be slightly modified by the fluorine atom, so the fluoro-PCB is expected to elute close to the corresponding PCB in the GC chromatogram. The aim is to produce fluoro-PCB analogues of the dioxin-like PCBs, and highly chlorinated fluoro-PCB congeners with GC retention times close to the parent PCB congeners.



Scheme 1.

2. Results and discussion

Ten different fluoro-PCBs have been prepared using the Suzuki-coupling. Seven of these are analogues of the dioxin-like PCBs. In this article we have numbered the fluoro-PCBs according to their corresponding PCB IUPAC numbers.[9] For instance, the monofluorinated PCB 77 is termed fluoro-PCB 77. The fluoro-PCBs have been *meta*-fluorinated for two reasons. The *para*-fluorinated PCB is avoided because it overlaps with the corresponding PCB in the GC chromatogram while the *meta*- and *ortho*-fluorinated PCBs elute just before the corresponding PCB (Fig. 1). Fluoro-PCBs with fluorine in the *ortho*-position may affect the PCB so that it no longer meets the criteria for a dioxin-like PCB. Therefore all the fluoro-PCBs in this article are *meta*-fluorinated in order to be as similar as possible to the dioxin-like PCBs, and therefore useful as analytical standards.

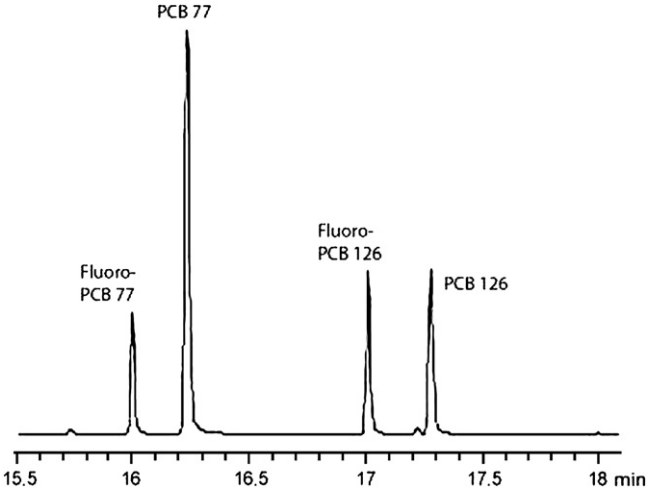
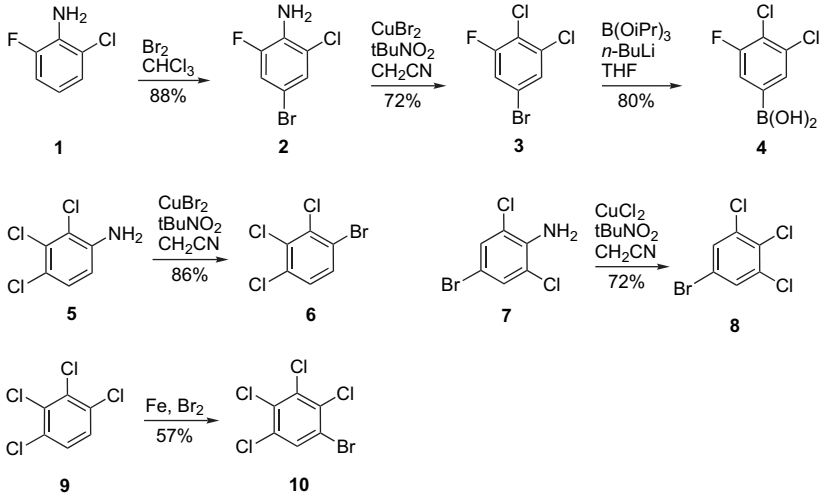


Figure 1. GC–MS chromatogram of the mixture of fluoro-PCB 77, fluoro-PCB 126, PCB 77 and PCB 126 (30–50 μg/mL).

2.1. Synthesis of dioxin-like fluoro-PCBs

One of the major challenges in the synthesis of highly chlorinated fluoro-PCBs is to prepare starting materials for the Suzuki-coupling. The syntheses of the substituted arylboronic acids and bromobenzenes are outlined in Scheme 2. The 3,4-dichloro-5-fluorophenylboronic acid (**4**) was prepared from 2-chloro-6-fluoroaniline (**1**) in a good overall yield. Bromination of **1** in $CHCl_3$ yielded **2**, followed by reaction with *tert*-butyl nitrite and copper(II)chloride producing **3**, using a modified Sandmeyer reaction reported by Doyle and co-workers.[10] Compound **3** was converted to the phenylboronic acid **4** by the use of triisopropyl borate and *n*-BuLi in THF. Unfortunately, **4** could not be purified to more than 95% purity by NMR, and 93% purity according to GC (prior to analysis, **4** was treated with H_2O_2 in diethyl ether, yielding 3,4-dichloro-5-fluorophenol), which caused the characterization by HRMS to fail. Bromo-2,3,4-trichlorobenzene (**6**) was prepared by conversion of 2,3,4-trichloroaniline (**5**) using copper(II)bromide. Sandmeyer reaction of 4-bromo-2,6-dichloroaniline (**7**) using *tert*-butyl nitrite and copper(II)chloride yielded 3,4,5-trichloroaniline (**8**). Bromination of 1,2,3,4-tetrachlorobenzene (**9**) yielded 1-bromo-2,3,4,5-tetrachlorobenzene (**10**) in a moderate yield.

The Suzuki-coupling reactions were performed in toluene under argon at 80 °C, using 3 mol % of either $Pd(PPh_3)_4$ or a recyclable polymer bound $Pd(PPh_3)_4$ as catalyst, and Na_2CO_3



Scheme 2.

(2 M) as base. The number of chlorine substituents, and especially the number of *ortho*-substituents, affects both yields and reaction times. While the tetrachlorinated fluoro-PCB congeners are synthesized in moderate to good yields (30–60%) in less than 6 h, the preparation of the penta- and hexachloro-fluoro-PCBs requires longer reaction times and results in moderate or poor yields (11–51%). The purity of the fluoro-PCBs is 97–99% according to GC–MS and NMR spectroscopy (Table 1).

Oxygen is reported to accelerate the self-coupling of the arylboronic acid.[11] In order to minimize this in the Suzuki-couplings, the mixtures were degassed under reduced pressure prior to use. The self-coupling product was avoided in all cases except for fluoro-PCB 77. The Suzuki-coupling of 3,4-dichlorophenylboronic acid and **3** resulted in 4–8% of by-product PCB 77, despite our efforts to exclude oxygen. Fortunately, when **4** and 3,4-dichloro-iodobenzene were used, the synthesis of fluoro-PCB 77 resulted in a higher yield and with less than 1% of the self-coupling product.

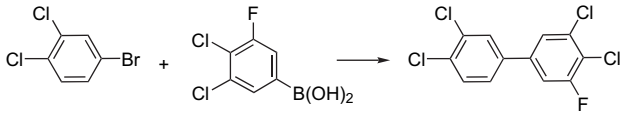
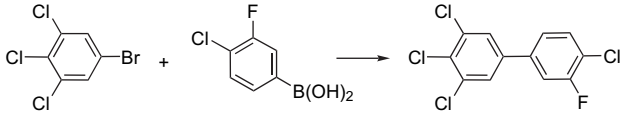
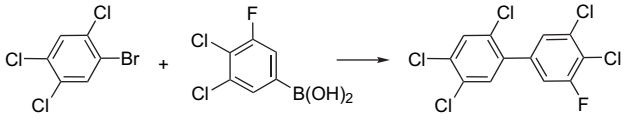
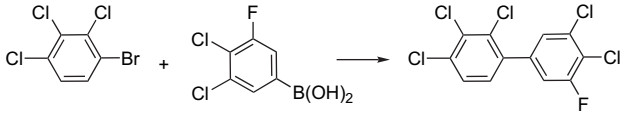
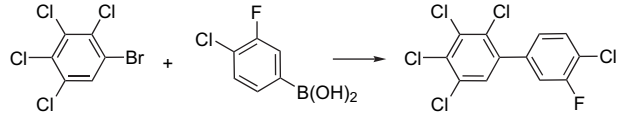
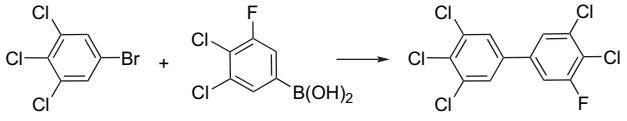
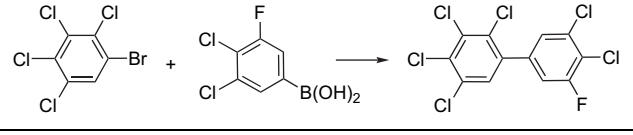
2.1.1. Dioxin-like fluoro-PCBs as analytical standards

Fluoro-PCB 77 and 126 were mixed with PCB congeners 77 and 126 and the mixture was analyzed by GC–MS. The resulting chromatogram shows that the fluoro-PCBs are well separated from their corresponding PCBs (Fig. 1), which indicates that these compounds are suitable as analytical standards for PCB analysis. Further analytical studies will tell whether the fluoro-PCBs are suitable standards in more complex mixtures of PCB congeners.

2.2. Highly chlorinated fluoro-PCBs prepared from 2,3,5,6-tetrachloro-bromoaniline

In order to synthesize fluoro-PCBs with five chlorine substituents in one of the biphenyl rings, pentachloro-iodobenzene was used in the Suzuki-couplings with 3-fluorophenylboronic acid and 3-fluoro-4-chlorophenylboronic acid, respectively. These

Table 1
Synthesis of dioxin-like fluoro-PCBs

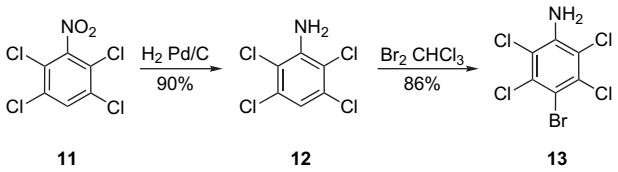
Fluoro-PCB[a]	Synthesis	Reaction time (h)	Yield (%)	Purity[b] (%)
77		6	43	97
81		2	66	99
105		42	11	97
114		18	26	99
118		18	40	97
126		18	51	97
156		18	26	99

[a] The fluoro-PCB is numbered according to their corresponding PCB IUPAC numbers.
[b] Purity calculated from the GC signal areas.

syntheses failed, producing only small amounts of highly contaminated products. Fortunately, this was solved by the use of 2,3,5,6-tetrachloro-bromoaniline (**13**) for the Suzuki-coupling, yielding the crude amino-fluoro-PCB which was deaminated or chlorinated in a Sandmeyer reaction (Scheme 3).[10,12] A similar strategy has previously been used by Bolgar and co-workers for PCB synthesis,[13] and it enables the synthesis of two different fluoro-PCBs from the same starting material, with four or five chlorines in one of the biphenyl rings. The only drawback is the debromination of **13** into **12**, a side reaction that was reduced by using 1.2–1.5 equiv of arylboronic acid. After the conversion of the fluoro-PCB-amine the resulting product was purified by recrystallization in methanol or by column chromatography.

Fluoro-PCBs 117 and 166 were prepared from the Suzuki-coupling of 3-fluoro-4-chlorophenylboronic acid and **13**. The resulting crude amino-fluoro-PCB 65 (**14**) was treated with *tert*-butyl nitrite and copper(II)chloride to yield fluoro-PCB 166 in 4% overall yield. Suzuki-coupling followed by deamination with *tert*-butyl nitrite in DMF yielded fluoro-PCB 117 in 7% overall yield (Table 2). Fluoro-PCB 65 was prepared in a similar manner, yielding the tetrachlorinated fluoro-PCB 117 (**15**) in 28%. The Suzuki-couplings yielding the crude **14** and **15** were completed after 18 h. The use of $Ba(OH)_2$ instead of Na_2CO_3 increased the reaction rate, but it also favoured the formation of the by-products **12** and **13**. The preparation of the three fluoro-PCBs from **13** resulted in moderate to poor yields, however, this synthetic route enables the preparation of tetra- up to hexa-chlorinated fluoro-PCBs, and potentially even higher chlorinated PCB congeners.

Compound **13** was prepared in two steps from 2,3,5,6-tetrachloro-nitrobenzene (**11**), using Pd/C in ethyl acetate under hydrogen at 40 Psi, yielding **12**. The following bromination of **12** in $CHCl_3$ yielded **13** in a total yield of 77% (Scheme 4).

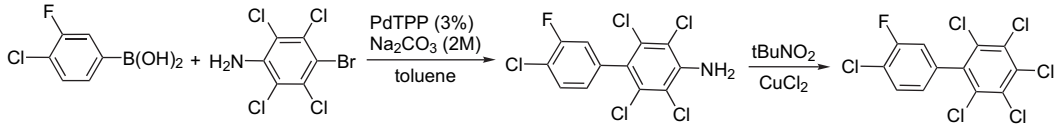


11 **12** **13**

Scheme 4. Synthesis of **13**.

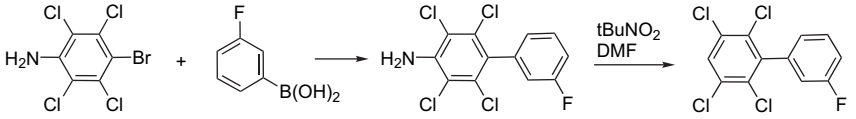
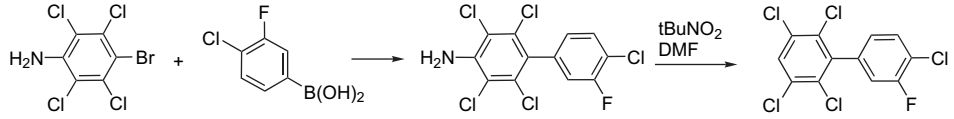
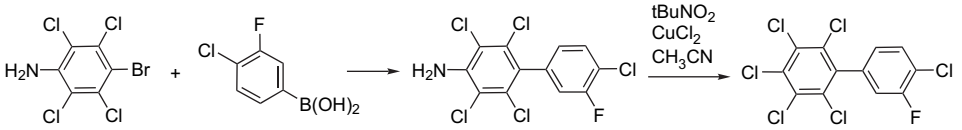
2.3. NMR spectroscopy of the fluoro-PCBs

The NMR spectra of the fluoro-PCBs all have in common the couplings caused by the ^{19}F nucleus, which is a useful tool for the assignment of the proton signals. Carbon signals were assigned by HSQC spectra of fluoro-PCBs 77 and 81. The ^{1}H spectra show that the vicinal $^{1}H-^{19}F$ couplings are 7–9 Hz, while the long range couplings lie between 1 and 6 Hz, depending on the proton position. $^{13}C-^{19}F$ couplings of 1–252 Hz are found in the ^{13}C spectra. The largest coupling in these compounds is the one-bond $^{13}C-^{19}F$ coupling of 249–252 Hz, found for the carbon signal at δ 160.



Scheme 3. Suzuki-coupling of 3-fluoro-4-chlorophenylboronic acid and **13**, followed by conversion of amino-fluoro-PCB 117, yielding fluoro-PCB 166.

Table 2
Synthesis of fluoro-PCBs from 2,3,5,6-tetrachloro-bromoaniline (**13**)

Fluoro-PCB[a]	Synthesis	Yield[b] (%)	Purity[c] (%)
65		26	97
117		7	98
166		4	97

[a] The fluoro-PCB is numbered according to their corresponding PCB IUPAC numbers.
[b] Two-step yield, starting from **13**.
[c] Purity calculated from the GC signal areas.

3. Conclusion

In conclusion, 10 monofluorinated tetra-, penta- and hexachlorinated biphenyls have been prepared, using the Suzuki-coupling. Seven of these fluoro-PCBs are analogues to the dioxin-like PCBs, and preliminary GC–MS measurements indicate that fluoro-PCBs are suitable as standards for PCB analysis. Further analytical studies are under way, telling us whether fluoro-PCBs are suitable as standards in complex mixtures of PCB congeners.

4. Experimental

4.1. NMR spectroscopy studies

All NMR spectra were recorded using a Bruker Avance DPX 400. The ^{1}H and ^{13}C spectra were referenced to the solvent signals at δ 7.27 and δ 77.23, respectively, in $CDCl_3$ and the solvent signals at δ 4.87 and δ 49.15, respectively, in CD_3OD.

4.2. GC analysis

All GC (GC–MS) analysis was performed on a HP-5MSi Advanced Inertness MS Column from Agilent technologies, using a temperature programme that runs 2 min at 50 °C followed by heating at a rate of 15 °C/min up to the temperature of 300 °C.

4.3. Synthesis of the fluoro-PCBs

4.3.1. 4-Bromo-2-chloro-6-fluoroaniline (2). General procedure for the bromination reactions

Bromine (27.5 g, 172 mmol) was added to a solution of 2-chloro-6-fluoroaniline (25 g, 172 mmol) dissolved in chloroform (400 mL). The bromoaniline precipitated within a minute and the mixture was stirred for 30–60 min, followed by GC. $Na_2S_2O_3$ (100 mL, 5%) and dichloromethane (200 mL) was added, the phases were separated, the organic phase was washed with water (50 mL) and dried over $MgSO_4$. The mixture was concentrated on the rotary evaporator, yielding **2** as a crude orange solid (90% purity). The product was recrystallized from methanol, yielding 33.9 g of **2** as a white solid (151 mmol, 88% yield, 98% purity). Mp=61–62 °C. ^{1}H NMR ($CDCl_3$) δ 4.1 (s, 2H, NH_2), 7.05 (dd, J_1=10.0 Hz, J_2=2.3 Hz, 1H, CFC*H*), 7.21 (dd, J_1=2.3 Hz, J_2=1.4 Hz, 1H, CClC*H*). ^{13}C NMR ($CDCl_3$) δ 107.7 (d, J=10.5 Hz, *C*Br), 117.5 (d, J=22.2 Hz, *C*H), 120.9 (d, J=5.7 Hz, *C*Cl), 127.5 (d, J=3.4 Hz, *C*H), 151.3 (d, J=245.1 Hz, *C*F). IR (KBr ν_{max}) 3500, 3404, 3017, 1622, 1584, 1492, 1413, 1215, 902, 0851, 742, 699 cm^{-1}. HRMS *m/z* calcd 224.9177, found 224.9175.

4.3.2. 3,4-Dichloro-5-fluoro-bromobenzene (3). General procedure for the Sandmeyer reactions[8]

To a mixture of copper(II)chloride (bromide) (24.35 g, 181.2 mmol), dry acetonitrile (200 mL) and *tert*-butyl nitrite (25.7 mL, 226.5 mmol), a solution of 4-bromo-2-chloro-5-fluoroaniline (33.9 g, 151 mmol) in dry acetonitrile (200 mL) was added at 60 °C under nitrogen. The mixture was stirred for 30 min at 60 °C, followed by cooling to room temperature and addition of HCl (400 mL, 2 M). The phases were separated, and the water phase was extracted with diethyl ether (150 mL). The combined organic phases were washed with water and dried over $MgSO_4$. Compound **3** was concentrated on the rotary evaporator and was distilled at 150 °C/20 mbar, yielding 30 g of colourless oil (111 mmol, 72% yield, 90% purity). Further purification by column chromatography, using *n*-hexane on Al_2O_3 gave **3** in 99% purity. ^{1}H NMR ($CDCl_3$) δ 7.24 (dd, J_1=8.0 Hz, J_2=2.4 Hz, 1H, CFC*H*), 7.43 (dd, J_1=2.4 Hz, J_2=1.4 Hz, 1H, CClC*H*). ^{13}C NMR ($CDCl_3$) δ 118.8 (d, J=24.8 Hz, *C*H), 120.0 (d, J=10.2 Hz, *C*Br), 120.5 (d, J=19.6 Hz, *C*Cl), 128.8 (d, J=3.7 Hz, *C*H), 135.2 (d, J=1.4 Hz, *C*Cl), 158.9 (d, J=255.4 Hz, *C*F). IR (thin film ν_{max}) 1572, 1442, 1402, 1116, 930, 850, 807, 560 cm^{-1}. HRMS *m/z* calcd 243.8677, found 243.8689.

4.3.3. 3,4-Dichloro-5-fluorophenylboronic acid (4)

To a mixture of **2** (5.35 g, 22 mmol), triisopropyl borate (7.6 mL, 33 mmol) and dry THF (100 mL), *n*-BuLi (14.5 mL, 2.5 M, 36.3 mmol) was added dropwise at −78 °C under nitrogen. The mixture was stirred for 30 min at −78 °C, and HCl (50 mL, 2 M) was added. The phases were separated, the water phase was extracted with diethyl ether (2×20 mL), and the combined organic phases were extracted with NaOH (3×20 mL, 2 M). The water phase was acidified to pH 4–5 by addition of HCl (6 M). The water phase was extracted with diethyl ether (3×50 mL), the combined organic phases were dried over $MgSO_4$ and **4** was concentrated on the rotary evaporator. The resulting 3.5 g white solid was washed with *n*-hexane (16 mmol, 72% yield, 94% purity by NMR). Mp=256–258 °C. ^{1}H NMR (CD_3OD) δ 7.46 (d, J=9.1 Hz, 1H, CFC*H*), 7.65 (s, 1H, CClC*H*). ^{13}C NMR (CD_3OD) δ 112.3 (d, J=24 Hz, *C*H), 122.4 (d, J=3 Hz, *C*H), 128.6 (d, J=20 Hz, *C*Cl), 140.2 (d, J=3 Hz, *C*Cl), 142.5 (d, J=12 Hz, *C*B), 160.5 (d, J=247 Hz, *C*F). IR (KBr ν_{max}) 3357, 3017, 2981, 2945, 1345, 1320, 1221, 1028, 736, 668 cm^{-1}.

4.3.4. Bromo-2,3,4-trichlorobenzene (6)[14]

Compound **6** was prepared according to the general method for the Sandmeyer reaction, using 2,3,4-trichloroaniline (**5**) (4.2 g, 21 mmol) copper(II)bromide (5.6 g, 25.2 mmol), acetonitrile (100 mL) and *tert*-butyl nitrite (3.6 mL, 31.5 mmol). Recrystallization from methanol yielded 5.0 g of **6** as orange crystals (18 mmol, 86% yield, 97% purity). Mp=58–60 °C (lit. mp=57.5–59.5 °C). ^{1}H NMR ($CDCl_3$) δ 7.22 (d, J=8.7 Hz, 1H, CClC*H*), 7.44 (dd, J=8.7 Hz, 1H, CBrC*H*). ^{13}C NMR ($CDCl_3$) δ 122.2 (*C*Br), 129.0 (*C*H), 131.8 (*C*H), 133.19 (*C*Cl), 133.55 (*C*Cl), 135.2 (*C*Cl). IR (KBr ν_{max}) 3018, 1425, 1214, 743, 669 cm^{-1}. HRMS *m/z* calcd 259.8381, found 259.8392.

4.3.5. Bromo-3,4,5-trichlorobenzene (8)[15]

Compound **8** was prepared according to the general method for the Sandmeyer reaction, using 4-bromo-2,6-dichloroaniline

(**7**) (4.5 g, 19 mmol), copper(II)chloride (3.0 g, 22 mmol), dry acetonitrile (50 mL) and *tert*-butyl nitrite (3.15 mL, 27 mmol). Recrystallizations from methanol gave 3.5 g of **8** as white needle crystals (14 mmol, 72% yield, 97% purity). Mp=60 °C (lit. mp=58 °C). ^{1}H NMR ($CDCl_3$) δ 7.54 (s, C*H*). ^{13}C NMR ($CDCl_3$) δ 120.0 (*C*Br), 131.16 (*C*H), 131.65 (*C*Cl), 135.2 (*C*Cl). IR (KBr ν_{max}) 3019, 1421, 1212, 738, 669 cm^{-1}. HRMS *m/z* calcd 259.8381, found 259.8383.

4.3.6. Bromo-2,3,4,5-tetrachlorobenzene (*10*)[16]

To 1,2,3,4-tetrachlorobenzene (**9**) (6.4 g, 29.3 mmol) were added Fe (0.41 g, 7.3 mmol) and Br_2 (4.8 g, 31 mmol) in three portions over 30 min at 80–100 °C. When reaction was completed, monitored by GC, $Na_2S_2O_3$ (20 mL, 5%) and CH_2Cl_2 (100 mL) were added. The phases were separated, the organic phase was washed with water (20 mL) and dried over $MgSO_4$. The organic phase was concentrated to yield **10**, which was recrystallized from methanol, yielding 5.08 g of white crystals (16.7 mmol, 57% yield, 97% purity). Mp=103.5–104.5 °C (lit. mp=98 °C). ^{1}H NMR ($CDCl_3$) δ 7.70 (s, C*H*).

4.3.7. 2,3,5,6-Tetrachloroaniline (*12*)[17]

2,3,5,6-Tetrachloro-nitrobenzene (**11**) (4.0 g, 33 mmol), Pd/C (1.1 g, 10%) and ethyl acetate (140 mL) were stirred under hydrogen (40 Psi) for 1 h. The mixture was filtered through Celite eluted with diethyl ether (150 mL), washed with water and dried over $MgSO_4$. The organic phase was concentrated to yield 7.7 g of **12** as a white solid (33.4 mmol, 97% yield, 96% purity). Mp=106–107.5 °C (lit. mp=106–108 °C). ^{1}H NMR ($CDCl_3$) δ 4.7 (s, 2H, NH_2), 7.34 (s, 1H, C*H*).

4.3.8. 4-Bromo-2,3,5,6-tetrachloroaniline (*13*)[18]

General procedure for bromination reactions was followed using Br_2 (2.2 g, 14 mmol), **12** (3.2 g, 14 mmol) and $CHCl_3$ (80 mL) yielding 3.9 g of **13** (12.2 mmol, 86% yield, 97% purity). Mp=231–232 °C (lit. mp=236–236.5 °C). ^{1}H NMR ($CDCl_3$) δ 4.8 (s, NH_2). ^{13}C NMR ($CDCl_3$) δ 111.3 (*C*Br), 111.8 (*C*Cl), 133.1 (*C*Cl), 141.3 (*C*N).

4.3.9. General procedure for the Suzuki-coupling

A solution of substituted arylboronic acid (5 mmol) in ethanol (10 mL) was slowly added to a mixture of substituted bromobenzene (5 mmol), polymer-encapsulated $Pd(PPh_3)_4$ (0.30 g, ≤0.15 mmol), toluene (25 mL) and sodium carbonate (5 mL, 2 M) under argon atmosphere at 80 °C. Traces of oxygen were removed in a sonic bath under vacuum prior to addition. The reaction mixture was maintained at 80 °C overnight. Hydrogen peroxide (0.5 mL, 30%) was added slowly to the warm reaction mixture, which was stirred at room temperature for 1 h. To the mixture was added diethyl ether (50 mL), the organic phase was washed with NaOH (30 mL, 2 M), and water (2×20 mL), dried over $MgSO_4$ and concentrated on the rotary evaporator to yield the crude product as an oil or solid. Column chromatography followed by recrystallization in methanol yielded the desired fluoro-PCB congener.

4.3.10. Fluoro-PCB 65 (2,3,5,6-tetrachloro-3′-fluorobiphenyl). General procedure for the deamination of amino-PCBs[15]

Compound **14** was prepared according to the general procedure for the Suzuki-coupling, using **13** (3.2 mmol), toluene (15 mL), sodium carbonate (3 mL, 2 M), $Pd(PPh_3)_4$ (0.13 g, 0.11 mmol), 3-fluorophenylboronic acid (3.2 mmol) and ethanol (6 mL). Purification by column chromatography (80:20 *n*-hexane/acetone on Al_2O_3) yielded 1.2 g of crude **14** (80% purity), which was converted into fluoro-PCB 65 by adding **14** (1.2 g crude) in DMF (2 mL) to a solution of *tert*-butyl nitrite (0.63 mL, 5.6 mmol) in dry DMF (2 mL) at 65 °C. After 2 h of stirring, HCl (50 mL, 2 M) and diethyl ether (50 mL) were added, the phases were separated, and the organic phase was washed with HCl (2×20 mL, 2 M) and water (20 mL), dried over $MgSO_4$ and concentrated on the rotary evaporator to yield the crude product as an oil. Column chromatography, using *n*-hexane on Al_2O_3 followed by short-path distillation at 100 °C/4×10^{-2} mbar yielded 0.28 g of fluoro-PCB 65 as a colourless oil (0.9 mmol, 28% yield, 97% purity). ^{1}H NMR ($CDCl_3$) δ 6.96 (dd, J_1=9.3 Hz, J_2=2 Hz, 1H, C′PhC′*H*C′F), 7.01 (dd, J_1=8.0 Hz, J_2=2 Hz, 1H, C′HC′*H*), 7.17 (dd, J_1=8.0 Hz, J_2=2.3 Hz, 1H, C′PhC′*H*), 7.48 (m, J_1=8.0 Hz, J_2=6.1 Hz, J_3=2.3 Hz, 1H, C′FC′*H*), 7.68 (1H, CClC*H*). ^{13}C NMR ($CDCl_3$) δ 115.7 (d, J=21.0 Hz, *C*H), 116.2 (d, J=22.0 Hz, *C*H), 124.7 (d, J=3 Hz, *C*H), 130.3 (d, J=8.2 Hz, *C*H), 130.5 (*C*H), 131.9 (*C*Cl), 132.1 (*C*Cl), 139.0 (d, J=8.2 Hz, *C*C), 141.3 (d, J=2 Hz, *C*C), 162.7 (d, J=247 Hz, *C*F). IR (thin film ν_{max}) 3016, 1614, 1588, 1455, 1215, 747, 667 cm^{-1}. HRMS *m/z* calcd 307.9129, found 307.9123.

4.3.11. Fluoro-PCB 77 (3,3′,4,4′-tetrachloro-5-fluorobiphenyl)

Fluoro-PCB 77 was prepared according to the general procedure for the Suzuki-coupling, using **3** (1.0 mmol), toluene (5 mL), sodium carbonate (1 mL, 2 M), polymer-encapsulated $Pd(PPh_3)_4$ (0.06 g, ≤0.03 mmol), **4** (1.5 mmol) and ethanol (2 mL), which yielded 0.06 g of fluoro-PCB 77 (0.19 mmol, 19% yield, 96% purity). Mp=121–121.5 °C. ^{1}H NMR ($CDCl_3$) δ 7.23 (dd, J_1=9.4 Hz, J_2=2.1 Hz, 1H, CFC*H*), 7.34 (dd, J_1=8.3 Hz, J_2=2.3 Hz, 1H, C′HC′*H*C′Ph), 7.43 (dd, J_1=2.1 Hz, J_2=1.5 Hz, 1H, CClC*H*CPh), 7.50 (d, J=8.3 Hz, 1H, C′HC′*H*C′Cl), 7.59 (d, J=2.1 Hz, 1H, C′ClC′*H*C′Ph). ^{13}C NMR ($CDCl_3$) δ 113.4 (d, J=22.8 Hz, *C*H), 120.8 (d, J=19.5 Hz, *C*Cl), 124.2 (d, J=3.4 Hz, *C*H), 126.2 (*C*H), 129.0 (*C*H), 131.3 (*C*H), 133.3 (*C*C), 133.6 (*C*Cl), 135.0 (*C*Cl), 138.0 (d, J=2.6 Hz, *C*C), 139.8 (d, J=8.5 Hz, *C*Cl), 159.2 (d, J=251.7 Hz, *C*F). IR (KBr ν_{max}) 3019, 1215, 777, 745, 669 cm^{-1}. HRMS *m/z* (M−2) calcd 307.9129, found 307.9117.

4.3.12. Fluoro-PCB 81 (3,4,4′,5-tetrachloro-3′-fluorobiphenyl)

Fluoro-PCB 81 was prepared according to the general procedure for the Suzuki-coupling, using **8** (2 mmol), toluene (10 mL), sodium carbonate (2 mL, 2 M), polymer-encapsulated $Pd(PPh_3)_4$ (0.12 g, ≤0.06 mmol), 3-fluoro-4-chlorophenylboronic acid (1.0 mmol) and ethanol (4 mL), which

yielded 0.41 g of fluoro-PCB 81 (1.32 mmol, 66% yield, 99% purity). Mp=143–144 °C. ^{1}H NMR ($CDCl_3$) δ 7.26 (ddd, J_1=0.9 Hz, J_2=2.1 Hz, J_3=8.2 Hz, 1H, C′PhC′*H*C′H), 7.33 (dd, J_1=2.1 Hz, J_2=9.9 Hz, 1H, C′PhC′*H*C′F), 7.48 (dd, J_1=7.6 Hz, J_2=8.2 Hz, 1H, C′PhC′*H*C′Cl), 7.55 (s, 2H, CClC*H*CPh). ^{13}C NMR ($CDCl_3$) δ 115.3 (d, J=22.2 Hz, *C*H), 121.8 (d, J=17.7 Hz, *C*Cl), 123.4 (d, J=3.7 Hz, *C*H), 127.2 (*C*H), 131.5 (*C*C), 131.6 (*C*Cl), 135.1 (*C*Cl), 138.4 (d, J=6.8 Hz, *C*H), 139.1 (d, J=2.0 Hz, *C*C), 158.7 (d, J=250.0 Hz, *C*F). IR (KBr ν_{max}) 3018, 1542, 1436, 1215, 778, 742, 669 cm^{-1}. HRMS *m/z* calcd 309.9096, found 309.9098.

4.3.13. Fluoro-PCB 105 (2,3,3′,4,4′-pentachloro-5′-fluorobiphenyl)

Fluoro-PCB 105 was prepared according to the general procedure for the Suzuki-coupling, using **6** (2 mmol), toluene (10 mL), sodium carbonate (2 mL, 2 M), polymer-encapsulated $Pd(PPh_3)_4$ (0.12 g, ≤0.06 mmol), **4** (1.0 mmol) and ethanol (4 mL), which yielded 0.08 g of fluoro-PCB 81 (0.23 mmol, 11% yield, 97% purity). Mp=109.5–111 °C. ^{1}H NMR ($CDCl_3$) δ 7.14 (dd, J_1=8.8 Hz, J_2=1.9 Hz, 1H, C′PhC′*H*C′F), 7.16 (d, J=8.5 Hz, 1H, CClC*H*CH), 7.31 (dd, J_1=1.9 Hz, J_2=1.5 Hz, 1H, C′PhC′*H*C′Cl), 7.47 (d, J=8.5 Hz, 1H, CHC*H*CPh). ^{13}C NMR ($CDCl_3$) δ 116.1 (d, J=22.8 Hz, *C*H), 121.1 (d, J=19.6 Hz, *C*Cl), 126.7 (d, J=3.4 Hz, *C*H), 128.7 (*C*H), 129.0 (*C*H), 132.9 (*C*C), 133.1 (*C*Cl), 134.3 (*C*Cl), 134.7 (*C*Cl), 138.0 (d, J=2.0 Hz, *C*H), 138.7 (d, J=8.8 Hz, *C*Cl), 158.6 (d, J=251.9 Hz, *C*F). IR (KBr ν_{max}) 3020, 1518, 1215, 750, 669 cm^{-1}. HRMS *m/z* calcd 343.8711, found 343.8714.

4.3.14. Fluoro-PCB 114 (2,3,4,4′,5-pentachloro-3′-fluorobiphenyl)

Fluoro-PCB 114 was prepared according to the general procedure for the Suzuki-coupling, using **10** (2 mmol), toluene (10 mL), sodium carbonate (2 mL, 2 M), $Pd(PPh_3)_4$ (0.08 g, 0.06 mmol), 3-fluoro-4-chlorophenylboronic acid (2.0 mmol) and ethanol (4 mL), which yielded 0.17 g of fluoro-PCB 114 (0.49 mmol, 25% yield, 99% purity). Mp=107–108 °C. ^{1}H NMR ($CDCl_3$) δ 7.10 (dd, J_1=2.1 Hz, J_2=8.1 Hz, 1H, C′HC′*H*C′Ph), 7.18 (dd, J_1=2.1 Hz, J_2=9.6 Hz, 1H, C′PhC′*H*C′F), 7.36 (s, 1H, CClC*H*Ph), 7.47 (dd, J_1=8.1 Hz, J_2=8.2 Hz, 1H, C′HC′*H*C′Cl). ^{13}C NMR ($CDCl_3$) δ 117.8 (d, J=22.2 Hz, *C*H), 121.9 (d, J=17.7 Hz, *C*Cl), 125.9 (d, J=3.7 Hz, *C*H), 129.8 (*C*H), 130.9 (*C*C), 131.3 (*C*Cl), 132.5 (*C*Cl), 133.0 (*C*Cl), 134.4 (*C*Cl), 138.0 (d, J=7.4 Hz, *C*H), 139.0 (d, J=1.7 Hz, *C*C), 157.9 (d, J=250.2 Hz, *C*F). IR (KBr ν_{max}) 3019, 1517, 1215, 750, 669 cm^{-1}. HRMS *m/z* (M−2) calcd 341.8740, found 341.8742.

4.3.15. Fluoro-PCB 117 (2,3,4′,5,6-pentachloro-3′-fluorobiphenyl)

Fluoro-PCB 166 was prepared according to the general procedure for the Suzuki-coupling, using **13** (5.0 mmol), toluene (20 mL), sodium carbonate (5 mL, 2 M), $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol), **12** (6.0 mmol) and ethanol (10 mL). Purification by column chromatography (80:20 *n*-hexane/acetone on Al_2O_3) yielded 1.7 g of crude **15** (90% purity), which was converted into fluoro-PCB 166 according to the general procedure for the deamination of amino-PCBs, using *tert*-butyl nitrite (0.9 mL, 7.9 mmol) and DMF (2 mL). The overall yield starting from **13** was 7% (98% purity). Mp=130–131 °C. ^{1}H NMR ($CDCl_3$) δ 6.96 (dd, J_1=8.2 Hz, J_2=2 Hz, 1H, C′PhC′*H*C′H), 7.05 (dd, J_1=9.3 Hz, J_2=2 Hz, 1H, C′FC′*H*C′Ph), 7.53 (dd, J_1=8.2 Hz, J_2=7.6 Hz, 1H, C′HC′*H*C′Cl), 7.68 (s, 1H, CClC*H*CCl). ^{13}C NMR ($CDCl_3$) δ 117.8 (d, J=22.2 Hz, *C*H), 121.9 (d, J=17.4 Hz, *C*Cl), 125.9 (d, J=3.7 Hz, *C*H), 130.9 (*C*H), 131.2 (*C*C), 132.0 (*C*Cl), 132.5 (*C*Cl), 137.4 (d, J=7.4 Hz, *C*H), 140.5 (d, J=1.7 Hz, *C*C), 158.3 (d, J=250.5 Hz, *C*F). IR (KBr ν_{max}) 3018, 1215, 740, 669 cm^{-1}. HRMS *m/z* (M−1) calcd 342.8797, found 342.8711.

4.3.16. Fluoro-PCB 118 (2,3′,4,4′,5-pentachloro-5′-fluorobiphenyl)

Fluoro-PCB 118 was prepared according to the general procedure for the Suzuki-coupling, using 2,4,5-trichlorobenzene (1.3 mmol), toluene (5 mL), sodium carbonate (1 mL, 2 M), polymer-encapsulated $Pd(PPh_3)_4$ (0.08 g, ≤0.04 mmol), **4** (1.9 mmol) and ethanol (2 mL), which yielded 0.18 g of fluoro-PCB 118 (0.52 mmol, 40% yield, 97% purity). Mp=120.5–121.5 °C. ^{1}H NMR ($CDCl_3$) δ 7.17 (dd, J_1=2.0 Hz, J_2=8.8 Hz, 1H, C′FC′*H*C′Ph), 7.34 (dd, J_1=1.5 Hz, J_2=2.0 Hz, 1H, C′PhC′*H*C′Cl), 7.43 (s, 1H, CClC*H*CCl), 7.62 (s, 1H, CClC*H*CPh). ^{13}C NMR ($CDCl_3$) δ 116.1 (d, J=22.8 Hz, *C*Cl), 121.3 (d, J=19.6 Hz, *C*Cl), 126.7 (d, J=3.4 Hz, *C*H), 131.28 (*C*H), 131.76 (*C*H), 131.83 (*C*C), 132.12 (*C*Cl), 133.7 (*C*Cl), 134.4 (*C*Cl), 137.20 (d, J=2.0 Hz, *C*C), 137.27 (d, J=9.0 Hz, *C*Cl), 158.7 (d, J=251.7 Hz, *C*F). IR (KBr ν_{max}) 3019, 1209, 786, 731, 669 cm^{-1}. HRMS *m/z* (M−2) calcd 341.8740, found 341.8742.

4.3.17. Fluoro-PCB 126 (3,3′,4,4′,5-pentachloro-5′-fluorobiphenyl)

Fluoro-PCB 126 was prepared according to the general procedure for the Suzuki-coupling, using **8** (2 mmol), toluene (10 mL), sodium carbonate (2 mL, 2 M), polymer-encapsulated $Pd(PPh_3)_4$ (0.12 g, ≤0.06 mmol), **4** (1.0 mmol) and ethanol (4 mL), which yielded 0.35 g of fluoro-PCB 126 (1.02 mmol, 51% yield, 94% purity). Mp=164.5–165.5 °C. ^{1}H NMR ($CDCl_3$) δ 7.25 (dd, J_1=9.2 Hz, J_2=2.2 Hz, 1H, C′FC′*H*C′Ph), 7.44 (dd, J_1=2.2 Hz, J_2=1.5 Hz, 1H, C′PhC′*H*C′Cl), 7.54 (s, 2H, CPhC*H*CCl). ^{13}C NMR ($CDCl_3$) δ 113.5 (d, J=23.2 Hz, *C*H), 124.3 (d, J=3.3 Hz, *C*H), 127.1 (*C*H), 138.2 (*C*C), 135.3 (*C*Cl), 138.0 (*C*Cl), 138.1 (d, J=8.3 Hz, *C*Cl), 159.0 (d, J=252.1 Hz, *C*F). IR (KBr ν_{max}) 3020, 3019, 2400, 1427, 1208, 1203, 787, 730, 669 cm^{-1}. HRMS *m/z* calcd 343.8711, found 343.8718.

4.3.18. Fluoro-PCB 156 (2,3,3′,4,4′,5-hexachloro-5′-fluorobiphenyl)

Fluoro-PCB 156 was prepared according to the general procedure for the Suzuki-coupling, using **10** (2 mmol), toluene (10 mL), sodium carbonate (2 mL, 2 M), $Pd(PPh_3)_4$ (0.08 g,

0.06 mmol), **4** (2.0 mmol) and ethanol (4 mL), which yielded 0.20 g fluoro-PCB 156 (0.52 mmol, 26% yield, 99% purity). Mp=120–120.5 °C. ^{1}H NMR ($CDCl_3$) δ 7.12 (dd, J_1= 2.0 Hz, J_2=9.1 Hz, 1H, C′FC′*H*C′Ph), 7.29 (dd, J_1=1.8 Hz, J_2=2.0 Hz, 1H, C′PhC′*H*C′C), 7.35 (s, 1H, CClC*H*CPh). ^{13}C NMR ($CDCl_3$) δ 116.0 (d, J=23.1 Hz, *C*H), 121.6 (d, J=19.6 Hz, *C*Cl), 126.6 (d, J=3.4 Hz, *C*H), 129.66 (*C*H), 131.2 (*C*C), 132.7 (*C*Cl), 133.5 (*C*Cl), 134.54 (*C*Cl), 134.61 (*C*Cl), 137.6 (d, J=8.8 Hz, *C*Cl), 137.9 (d, J=2.0 Hz, *C*C), 158.7 (d, J=252.5 Hz, *C*F). IR (KBr ν_{max}) 3019, 1215, 778, 744, 669 cm^{-1}. HRMS *m*/*z* (M+2) calcd 379.8293, found 379.8292.

4.3.19. Fluoro-PCB 166 (2,3,4,4′,5,6-hexachloro-3′-fluorobiphenyl)

Fluoro-PCB 166 was prepared according to the general procedure for the Suzuki-coupling, using **13** (5.0 mmol), toluene (20 mL), sodium carbonate (5 mL, 2 M), $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol), **12** (6.0 mmol) and ethanol (10 mL). Purification by column chromatography (80:20 *n*-hexane/acetone on Al_2O_3) yielded 1.7 g of crude **15** (90% purity), which was converted into fluoro-PCB 166 according to the general method for the Sandmeyer reaction, using *tert*-butyl nitrite (0.9 mL, 7.9 mmol), copper(II)chloride (0.85 g, 6.32 mmol) and dry acetonitrile (10 mL). The overall yield starting from **13** was 4% (97% purity). Mp=121–122 °C. ^{1}H NMR ($CDCl_3$) δ 6.96 (ddd, J_1=0.9 Hz, J_2=1.9 Hz, J_3=8.3 Hz, 1H, C′PhC′*H*C′H), 7.04 (dd, J_1=1.9 Hz, J_2=9.4 Hz, 1H, C′FC′*H*C′Ph), 7.55 (dd, J_1=7.6 Hz, J_2=8.2 Hz, 1H, C′HC′*H*C′Cl). ^{13}C NMR ($CDCl_3$) δ 117.8 (d, J=22.2 Hz, *C*H), 122.1 (d, J=17.7 Hz, *C*Cl), 125.8 (d, J=3.9 Hz, *C*H), 131.3 (*C*C), 132.5 (*C*Cl), 132.8 (*C*Cl), 134.2 (*C*Cl), 137.1 (d, J=7.4 Hz, *C*Cl), 138.3 (d, J=1.6 Hz, *C*C), 158.3 (d, J=250.5 Hz, *C*F). IR (KBr ν_{max}) 3018, 1215, 779, 772, 669 cm^{-1}. HRMS *m*/*z* calcd 377.8317, found 377.8321.

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