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FIFTY YEARS OF PCB RESEARCH: NEW APPROACHES AND DISCOVERIES AND STILL SO MUCH MORE TO LEARN

Synthesis of mono- and dimethoxylated polychlorinated biphenyl derivatives starting from fluoroarene derivatives

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Abstract

Polychlorinated biphenyls (PCBs) are environmental pollutants implicated in a variety of adverse health effects, including cancer and noncancer diseases in animals and humans. PCBs are metabolized to hydroxylated compounds, and some of these PCB metabolites are more toxic than the parent PCBs. Unfortunately, most PCB metabolites needed for toxicological studies are not available from commercial sources. Moreover, it is challenging to synthesize PCB metabolites because starting materials with suitable substitution patterns are not readily available. Here, we report the novel synthesis of a variety of mono- and dimethoxyarene derivatives from commercially available fluoroarenes via nucleophilic aromatic substitution with sodium methoxide. This reaction provided good to excellent yields of the desired methoxylated products. Suzuki coupling of selected mono- and dimethoxy haloarenes with chlorinated phenylboronic acids yielded methoxylated derivatives of PCB 11, 12, 25, 35, and 36 in low to good yields. Crystal structures of 3,3′-dichloro-2,5-dimethoxy-1,1′-biphenyl and 3′,5-dichloro-2,3-dimethoxy-1,1′-biphenyl confirmed the substitution pattern of both compounds. This synthesis strategy provides straightforward access to a range of mono- and dimethoxylated PCB derivatives that were not readily accessible previously.

Keywords Environmental contaminants · Fluoroarenes · Methoxylated PCBs · PCB metabolites · Suzuki coupling · Nucleophilic aromatic substitution · X-ray crystallography

Introduction

Polychlorinated biphenyls (PCBs) remain a significant public health concern because of their persistence in the environment, the continuing human exposure to these chemicals through diet and inhalation of indoor and outdoor air, and their adverse environmental and human health effects (ATSDR 2000; EPA 2018; IARC 2016). Although their industrial production was banned in the late 1970s, PCBs are still used in closed applications, such as in transformers and light ballasts. PCBs are also formed inadvertently by a variety of processes and, as a consequence, are present in consumer products, such as paints and others (Anezaki and Nakano 2014; Herkert et al. 2018; Hu and Hornbuckle 2010). In mammals, PCBs are metabolized by cytochrome P450 enzymes to hydroxylated PCBs (OH-PCBs) (Dhakal et al. 2018; Grimm et al. 2015; Kania-Korwel and Lehmler 2016; Tehrani et al. 2014). As a result, complex OH-PCB metabolite profiles are present in environmental samples, wildlife, and humans. OH-PCBs can be further oxidized to dihydroxylated metabolites or are converted into glucuronidated or sulfated metabolites. Growing evidence demonstrates that OH-PCB metabolites can be more toxic than the parent PCBs. Therefore, well-authenticated and highly pure OH-PCBs and their methoxylated derivatives (MeO-PCBs) are needed as test compounds to study their toxicity and as analytical standards for environmental and

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human biomonitoring studies (Li et al. 2018; Saktrakulkla et al. 2019).

OH-PCBs are typically prepared by demethylation of the corresponding MeO-PCB intermediates with BBr_3 or HBr (Bauer et al. 1995; Lehmler and Robertson 2001b; Waller et al. 1999). MeO-PCBs, in turn, can be synthesized using the Suzuki, Cadogan, or Ullmann coupling reactions. The Suzuki coupling is a powerful reaction for the synthesis of MeO-PCB congeners with ≤ 3 *ortho* chlorine substituents (Joshi et al. 2011a; Kania-Korwel et al. 2004; Lehmler and Robertson 2001b; Song et al. 2008; Telu et al. 2010). Suitable starting materials for the Suzuki coupling are (a) chlorinated bromo- and iodobenzenes and methoxybenzene boronic acids or (b) brominated methoxy benzenes and chlorobenzene boronic acids. The Cadogan coupling (Cadogan et al. 1966), a modification of the Gomberg-Bachmann reaction, can alternatively be used to synthesize some MeO-PCB congeners from a suitable chloroaniline and a large excess of a (chlorinated) methoxybenzene derivative. The Ullmann reaction is the third approach that can be employed for the synthesis of MeO-PCBs by coupling chlorinated iodobenzenes with methoxylated iodobenzenes (Telu et al. 2010; Waller et al. 1999). The Cadogan and Ullmann coupling reactions are not regioselective, and the yields of the desired MeO-PCB congener can be very low. Thus, the Suzuki coupling reaction currently offers the most straightforward approach for the synthesis of MeO-PCBs, the corresponding OH-PCBs, and other PCB metabolites.

A major limitation of the Suzuki coupling reaction is the availability of starting materials with substitution patterns suitable for the synthesis of specific MeO-PCBs. While many chlorinated benzeneboronic acids are available for commercial sources or can be synthesized from the corresponding chlorinated bromo- or iodobenzenes, suitable methoxylated precursors are frequently not available from commercial sources or need to be prepared in a multistep synthesis. For example, both 2,3,5-trichloro-4-iodo-methoxybenzene and 2,4,5-trichloro-3-iodo-methoxybenzene, precursors of hydroxylated PCB 136 metabolites, can be prepared in a four-step synthesis from the corresponding trichloromethoxybenzenes (Waller et al. 1999). A recent advance in the synthesis of MeO-PCBs is the regioselective iodination of chlorinated methoxybenzenes with different silver salts, a reaction that offers straightforward access to several relevant methoxylated building blocks (Joshi et al. 2011b). In contrast, the regioselective introduction of a hydroxy or methoxy group into chlorinated bromo- or iodobenzenes has not been used for the synthesis of OH- or MeO-PCB precursors. One exception is the conversion of an aromatic amino group into an OH group, a reaction that suffers from an exceedingly low yield (Waller et al. 1999).

A large number of chlorinated fluorobenzene derivatives are commercially available, and these fluorobenzene derivatives can be transformed into the corresponding methoxy derivatives by nucleophilic displacement reactions (S_NAr). Although different methods can be used to convert fluoroarene derivatives into the corresponding methoxy derivatives (Amii and Uneyama 2009; Su et al. 2018), this reaction has not been systematically explored for the synthesis of the methoxylated precursors needed for the synthesis of specific MeO-PCBs. Herein, we report the conversion of chlorinated mono-fluoroarenes **1**, **2**, and **3** to the corresponding methoxyarenes **4** to **6**, and of difluoroarenes **7** to dimethoxyarene **6** and **8**. The Suzuki coupling of selected methoxylated bromoarene derivative **5**, **6**, **8**, or **9** with benzene boronic acids **10** was used to synthesize a variety of mono- and dimethoxylated PCB derivatives **11** that can be difficult to synthesize by other approaches.

Experimental

Chemicals, reagents, and instruments

All chemicals and solvents were purchased from commercial sources and used directly without further purification. Column chromatography was carried out on silica gel (100–200 mesh; Sorbent Technologies, Atlanta, GA, USA). NMR spectra were recorded on a Bruker AV500 spectrometer in the University of Iowa Central NMR Research Facility (Iowa City, IA, USA) in $CDCl_3$. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^1H, δ 7.26 ppm; ^{13}C, δ 77.16 ppm). Gas chromatographic analyses were performed on an Agilent 6850 gas chromatograph (Agilent Technologies, CA, USA) equipped with flame ionization detector (GC-FID) using an HP-5MS column (30 m length, 250 μm inner diameter, 0.25 μm film thickness). The following conditions were used for the gas chromatographic analysis: starting temperature 50 °C, 20 °C/min to 250 °C, and hold for 5 min. The injector temperature and detector temperatures were 300 and 250 °C, respectively. Helium was used as the carrier gas with a flow rate of 1.9 mL/min. Mass spectra of all compounds were recorded on an Agilent 7890A gas chromatograph (GC) equipped with an Agilent 5975C Inert Mass Selective Detector (Agilent Technologies, CA, USA). A capillary Supelco SLB-5MS GC column (30 m length, 250 μm inner diameter, 0.25 μm film thickness; Sigma-Aldrich, St. Louis, MO, USA) was used with the following temperature program: starting at 80 °C, 10 °C/min to 150 °C, 5 °C/min to 300 °C, and hold for 5 min. The injector temperature was 280 °C, and the temperatures of the transfer line, source, and quadrupole were 280, 230, and 150 °C, respectively (Li et al. 2018). Accurate mass determinations were performed by gas chromatography with time-of-flight mass spectrometry in the High-Resolution Mass Spectrometry Facility of the University of Iowa (Iowa City, IA, USA). Elemental analyses were carried out by Atlantic

Microlab (Atlanta, GA, USA). The melting points were determined with a MEL-TEMP apparatus and are uncorrected. Representative ^{1}H NMR, ^{13}C NMR, and mass spectra of all reported compounds are included in the Supplemental information (Figs. S1 to S83).

General procedure for the optimization of the synthesis of 1-bromo-3-chloro-5-methoxybenzene and 2-chloro-4-iodo-1-methoxybenzene

Small-scale reactions (1 mmol starting material) were initially carried out to optimize the reaction of 1-bromo-3-chloro-5-fluorobenzene (**2d**) to 1-bromo-3-chloro-5-methoxybenzene (**5d**) (Table 1) and 2-chloro-1-fluoro-4-iodobenzene (**2f**) to 2-chloro-4-iodo-1-methoxybenzene (**5f**) (Table 2). Briefly, fluorobenzene **2d** or **2f** (0.125 mL, 1 mmol) was added to a mixture of varying amounts of sodium methoxide in 5 mL of dimethylformamide (DMF), methanol, tetrahydrofuran (THF), 1,4-dioxane, or N-methyl-2-pyrrolidone (NMP). The reaction mixture was stirred for 0.5 to 3 h at temperatures ranging from room temperature to 100 °C. The reaction in methanol was carried out in a sealed pressure vessel to avoid the evaporation of the solvent. The reaction mixture was quenched with cold water (5 mL) and extracted three times with hexane (4, 4, and 2 mL). The internal standard (diethylene glycol di-*n*-butyl ether, 20 μL, 17.7 mg) was added to the combined organic phase, and the reaction mixture was washed with saturated NaCl solution (5 mL). An aliquot of the organic phase (200 μL) was diluted with hexane (800 μL) before quantification of the starting material (**2d** or **2f**), target product (**5d** or **5f**), and possible side products (i.e., **1c** and **4c**) by GC-FID (Shaikh et al. 2006). The relative response factor (RRF_A) of the respective analyte was calculated from a calibration standard containing known amounts of the internal standard and the respective analytes using the formula $RRF_A = A_{IS} \cdot m_A/(A_A \cdot m_{IS})$, where A_{IS} is the peak area of the internal standard, A_A is the peak area of analyte, m_A is the known mass of the analyte, and m_{IS} is the known mass of the internal standard. The mass of the analytes in the reaction mixture was determined using the formula: $m_A = RRF_A \cdot A_A \cdot m_{IS}/A_{IS}$. All samples were analyzed in triplicate.

General experimental procedure for the synthesis of methoxyarenes

A fluoroarene compound **1**, **2**, or **3** (1 mmol) was added to the mixture of sodium methoxide (108 mg, 2 mmol, 2 equiv. [equivalent]) and DMF (5 mL). The reaction mixture was stirred at 110 °C for 3 h. The reaction mixture was quenched with cold water (5 mL) and extracted three times with hexane (4, 4, and 2 mL). The extract was washed with saturated NaCl solution (5 mL), and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified by silica gel flash chromatography with hexane as eluent to give the desired methoxyarenes **4**, **5**, or **6**.

1-Bromo-2-methoxybenzene (**4a**) (Quibell et al. 2018; Singh et al. 2017; Vajpayee et al. 2013): Yield 48% (88 mg), colorless oil from 1-bromo-2-fluorobenzene (**1a**). $R_f = 0.64$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, $J = 7.9$, 1.4 Hz, 1H), 7.28 (pseudo t, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 8.2$ Hz, 1H), 6.84 (pseudo t, $J = 7.6$ Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.99, 133.46, 128.62, 121.91, 112.13, 111.81, 56.25. MS *m*/*z* calcd for $[C_7H_7BrO]^+$: 186.0, found: 186.0.

1-Bromo-3-methoxybenzene (**4b**) (Blencowe et al. 2006; Gibson et al. 2005; Leas et al. 2017; Zilberman 2003): Yield 59% (111 mg), colorless oil from 1-bromo-3-fluorobenzene (**1b**). $R_f = 0.65$ in hexane/EtOAc = 19:1.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (pseudo t, $J =$ 8.0 Hz, 1H), 7.11–7.04 (m, 2H), 6.84 (dd, $J = 8.2$, 1.7 Hz, 1H), 3.80 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 130.5, 123.8, 122.8, 117.2, 113.1, 55.4. MS *m*/*z* calcd for $[C_7H_7BrO]^+$: 186.0, found: 186.0.

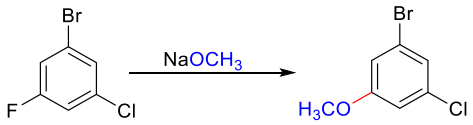
2-Chloro-1-methoxybenzene (**4c**) (Dhakshinamoorthy et al. 2010; Holloway et al. 2010; Maraš et al. 2008; Wu and Hynes 2010): Reaction of **1c** (25 mmol, 3.26 g) with sodium methoxide (2 equiv., 50 mmol, 2.70 g) in the presence of DMF (20 mL) for 3 h at 110 °C provided **4c** as a greenish yellow oil in 80% (2.84 g) yield; 70% yield (2.49 g), colorless oil after charcoal filtration. $R_f = 0.51$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.22 (pseudo t, $J = 7.9$ Hz, 1H), 6.94–6.87 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 130.2, 127.8, 122.4, 121.3, 112.2, 56.0. MS *m*/*z* calcd for $[C_7H_7ClO]^+$: 142.0, found: 142.0.

1-Bromo-2-chloro-3-methoxybenzene (**5a**) (Miyaji et al. 2017): Yield 90% (200 mg), colorless oil from 1-bromo-2-chloro-3-fluorobenzene (**2a**). $R_f = 0.58$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, $J = 8.1$, 1.2 Hz, 1H), 7.08 (pseudo t, $J = 8.2$ Hz, 1H), 6.86 (dd, $J =$ 8.3, 0.9 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 128.0, 125.6, 124.0, 123.5, 110.8, 56.6. MS *m*/*z* calcd for $[C_7H_6BrClO]^+$: 221.9, found: 222.0.

2-Bromo-1-chloro-4-methoxybenzene (**5b**) (Miyaji et al. 2017; Zhai et al. 2011): Yield 83% (184 mg), colorless oil from 2-bromo-1-chloro-4-fluorobenzene (**2b**). $R_f = 0.62$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, $J = 8.9$ Hz, 1H), 7.14 (d, $J = 2.9$ Hz, 1H), 6.79 (dd, $J =$ 8.9, 2.9 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 130.55, 125.9, 122.7, 119.0, 114.8, 55.8. MS *m*/*z* calcd for $[C_7H_6BrClO]^+$: 221.9, found: 221.9.

1-Bromo-3-chloro-2-methoxybenzene (**5c**) (Balko et al. 2007): Yield 75% (167 mg), colorless oil from 1-bromo-3-chloro-2-fluorobenzene (**2c**). Reaction of **2c** (58.91 mmol,

Table 1 Optimization of the reaction of 1-bromo-3-chloro-5-fluorobenzene (**2d**) to 1-bromo-3-chloro-5-methoxybenzene (**5d**)



2d **5d**

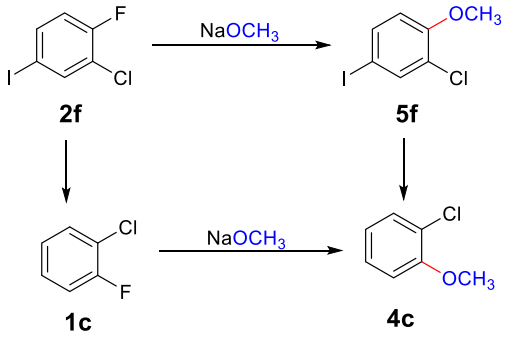
Entry	Solvent	NaOMe (equiv)	Temperature (°C)	Time (h)	Yield (%)	Conversion (%)	Mass balance (%)
			Solvent				
1.1.	DMF	2	80	3	96	97	98
1.2.	Methanol	2	80	3	1	4	98
1.3.	THF	2	80	3	61	62	99
1.4.	1,4-Dioxane	2	80	3	12	16	96
1.5.	NMP	2	80	3	79	93	86
			Equivalents of sodium methoxide				
1.6.	DMF	1	80	3	46	57	89
1.7.	DMF	1.5	80	3	77	81	96
1.8.	DMF	2	80	3	96	97	98
1.9.	DMF	3	80	3	93	95	98
			Temperature				
1.10.	DMF	2	RT (23)	3	89	93	96
1.11.	DMF	2	50	3	95	96	99
1.12.	DMF	2	80	3	97	97	99
1.13.	DMF	2	110	3	99	100	99
			Reaction time				
1.14.	DMF	2	110	0.5	93	97	96
1.15.	DMF	2	110	1	96	99	97
1.16.	DMF	2	110	2	98	99	99
1.17.	DMF	2	110	3	99	100	99

Note: (1) Reactions were carried out with 1-bromo-3-chloro-5-fluorobenzene (**2d**, 0.125 mL, 1.0 mmol) as described under "Experimental"; (2) all yields were determined by gas chromatography using diethylene glycol di-*n*-butyl ether (20 μL, 17.7 mg) as an internal standard (Shaikh et al. 2006); and (3) data are the average of triplicate analyses

12.34 g) with sodium methoxide (2 equiv., 117.82 mmol, 6.36 g) in the presence of DMF (20 mL) for 3 h at 110 °C provided **5c** in 74% (9.67 g) yield. $R_f = 0.71$ in hexane/EtOAc = 19:1 ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 8.1, 1.3 Hz, 1H), 7.33 (dd, J = 8.0, 1.3 Hz, 1H), 6.92 (pseudo t, J = 8.1 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 132.0, 129.8, 129.4, 125.8, 118.7, 60.7. MS m/z calcd for $[C_7H_6BrClO]^+$: 221.9, found: 222.0.

1-Bromo-3-chloro-5-methoxybenzene (**5d**) (Murphy et al. 2007): Yield 80% (176 mg), colorless liquid from 1-bromo-3-chloro-5-fluorobenzene (**2d**). Reaction of **2d** (90.62 mmol, 18.98 g) with sodium methoxide (2 equiv., 181 mmol, 9.79 g) in the presence of DMF (60 mL) for 3 h at 110 °C provided **5d** in 71% (13.77 g) yield. $R_f = 0.67$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (pseudo t, J = 1.6 Hz, 1H), 6.95 (pseudo t, J = 1.9 Hz, 1H), 6.83 (pseudo t, J = 2.0 Hz,

Table 2 Optimization of the reaction of 2-chloro-1-fluoro-4-iodobenzene (**2f**) to 2-chloro-4-iodo-1-methoxybenzene (**5f**)



Entry	Solvent	NaOMe (equiv)	Temp (°C)	Time (h)	Yield (%)			Conversion (%)	Mass balance (%)
					1c	4c	5f		
Solvent									
2.1.	DMF	2	80	3	2	1	83	89	97
2.2.	Methanol	2	80	3	0	1	1	16	85
2.3.	THF	2	80	3	2	1	74	75	101
2.4.	1,4-Dioxane	2	80	3	2	1	14	27	89
2.5.	NMP	2	80	3	0	14	52	100	59
Equivalents of sodium methoxide									
2.6.	DMF	1	80	3	1	0	37	44	94
2.7.	DMF	1.5	80	3	2	1	66	71	98
2.8.	DMF	2	80	3	2	1	83	89	97
2.9.	DMF	3	80	3	2	8	89	100	99
Temperature									
2.10.	DMF	2	RT (23)	3	3	1	60	72	93
2.11.	DMF	2	50	3	3	1	72	75	101
2.12.	DMF	2	80	3	2	1	83	89	97
2.13.	DMF	2	110	3	2	1	90	93	100
Reaction time									
2.14.	DMF	2	110	0.5	2	1	73	84	92
2.15.	DMF	2	110	1	2	1	77	78	102
2.16.	DMF	2	110	2	2	1	78	86	96
2.17.	DMF	2	110	3	2	1	90	93	100

Note: (1) Reactions were carried out with 3-chloro-4-fluoro-1-iodobenzene (**3**, 0.125 mL, 0.78 mmol) as described under "Experimental"; (2) all yields were determined by gas chromatography using diethylene glycol di-*n*-butyl ether (20 μL, 17.7 mg) as an internal standard (Shaikh et al. 2006); and (3) data are the average of triplicate analyses

1H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9, 135.7, 123.9, 123.0, 116.1, 113.8, 55.9. MS *m*/*z* calcd for $[C_7H_6BrClO]^+$: 221.9, found: 221.9.

2,4-Dichloro-1-methoxybenzene (**5e**) (Bovonsombat et al. 2015; Tay and Nicewicz 2017; Thongsornkleeb et al. 2014; Wang et al. 2018; Xin et al. 2017; Zhang and Hu 2017): Yield 82% (144 mg), colorless oil from 2,4-dichloro-1-fluorobenzene (**2e**). R_f = 0.66 in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 2.5 Hz, 1H), 7.20 (dd, J = 8.8, 2.5 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 130.1, 127.7, 125.8, 123.4, 112.9, 56.5. MS *m*/*z* calcd for $[C_7H_6BrClO]^+$: 176.0, found: 176.0.

2-Chloro-4-iodo-1-methoxybenzene (**5f**) (Chen et al. 2011; Gavryushin et al. 2012; Podgorsek and Iskra 2010; Tilve and Kanetkar 2005): Yield 73% (195 mg), white solid from 2-chloro-1-fluoro-4-iodobenzene (**2f**). $R_f = 0.54$ in hexane/EtOAc = 19:1; Mp. 81–82 °C (lit. mp. 89.1–93.7 °C (Gavryushin et al. 2012)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, $J = 2.0$ Hz, 1H), 7.51 (dd, $J = 8.6$, 2.0 Hz, 1H), 6.68 (d, $J = 8.7$ Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3, 138.4, 136.7, 124.0, 114.1, 82.0, 56.3. MS *m/z* calcd for $[C_7H_6ClIO]^+$: 267.9, found: 267.9.

1-Bromo-2-chloro-4-methoxybenzene (**5g**) (Pramanick et al. 2017; Quibell et al. 2018; Tajik et al. 2007): Yield 41% (91 mg), colorless oil from 1-bromo-2-chloro-4-fluorobenzene (**2g**). $R_f = 0.67$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, $J = 8.9$ Hz, 1H), 7.00 (d, $J = 2.9$ Hz, 1H), 6.68 (dd, $J = 8.9$, 2.9 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 134.9, 133.9, 115.8, 114.5, 112.9, 55.7. MS *m/z* calcd for $[C_7H_6BrClO]^+$: 221.9, found: 221.9.

2-Bromo-4-chloro-1-methoxybenzene (**5h**) (Mostafa et al. 2017; Pramanick et al. 2017; Quibell et al. 2018; Tang et al. 2018): Yield 85% (188 mg), colorless oil from 2-bromo-4-chloro-1-fluorobenzene (**2h**). Reaction of **2h** (63.84 mmol, 13.37 g) with sodium methoxide (2 equiv., 127.68 mmol, 6.90 g) in the presence of DMF (60 mL) for 3 h at 110 °C provided **5h** in 73% (10.29 g) crude yield (> 96.84% purity, as determined by GC–MS). For characterization, a small amount of compound was purified by passing through charcoal in a cotton plug pasture pipette. $R_f = 0.56$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, $J = 2.6$ Hz, 1H), 7.19 (dd, $J = 8.8$, 2.5 Hz, 1H), 6.76 (d, $J = 8.8$ Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 132.8, 128.3, 125.9, 112.6, 112.1, 56.4. MS *m/z* calcd for $[C_7H_6BrClO]^+$: 221.9, found: 221.9.

4-Bromo-1-chloro-2-methoxybenzene (**5i**) (Zhai et al. 2011): Yield 87% (193 mg), colorless oil from 4-bromo-1-chloro-2-fluorobenzene (**2i**). $R_f = 0.69$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, $J = 8.3$ Hz, 1H), 7.05–7.00 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 131.2, 124.3, 121.8, 120.8, 115.7, 56.4. MS *m/z* calcd for $[C_7H_6BrClO]^+$: 221.9, found: 221.9.

4-Bromo-2-chloro-1-methoxybenzene (**5j**) (Pramanick et al. 2017; Wang et al. 2018): Yield 84% (186 mg), white solid from 4-bromo-2-chloro-1-fluorobenzene (**2j**). A second reaction of **2j** (19.196 mmol, 4.02 g) with sodium methoxide (2 equiv., 38.39 mmol, 2.07 g) in the presence of DMF (20 mL) for 3 h at 110 °C provided **5j** in 78% (3.26 g) yield. $R_f = 0.65$ in hexane/EtOAc = 19:1; Mp. 61–62 °C (lit. mp. 68–70 °C (Pramanick et al. 2017)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, $J = 2.4$ Hz, 1H), 7.33 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.80 (d, $J = 8.8$ Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 132.8, 130.7, 123.8, 113.5, 112.6, 56.5. MS *m/z* calcd for $[C_7H_6BrClO]^+$: 221.9, found: 222.0.

4-Bromo-1,2-dimethoxybenzene (**6a**) (Liu et al. 2011; Narender et al. 2013; Ren et al. 2015; Xiong et al. 2017): Yield 86% (184.3 mg), colorless oil from 4-bromo-2-fluoro-1-methoxybenzene (**3a**). Reaction of **3a** (22.57 mmol, 4.63 g) with sodium methoxide (2 equiv., 45.15 mmol, 2.44 g) in the presence of DMF (15 mL) for 3 h at 110 °C provided **6a** in 78% (3.73 g) yield. $R_f = 0.31$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03–6.98 (m, 1H), 6.95 (dd, $J = 5.0$, 2.2 Hz, 1H), 6.71 (dd, $J = 8.5$, 6.0 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.9, 148.4, 123.45, 114.9, 112.8, 112.6, 56.2, 56.1. MS *m/z* calcd for $[C_8H_9BrO_2]^+$: 216.0, found: 216.0.

4-Chloro-1,2-dimethoxybenzene (**6b**) (Beekman and Barrow 2014; Beil et al. 2018; Wang et al. 2013): Yield 87% (149.5 mg), colorless oil from 4-chloro-2-fluoro-1-methoxybenzene (**3b**). Or, yield 88% (151 mg) from 4-chloro-1-fluoro-2-methoxybenzene (**3c**). $R_f = 0.36$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (dd, $J =$ 8.5, 2.4 Hz, 1H), 6.84 (d, $J = 2.3$ Hz, 1H), 6.76 (d, $J = 8.5$ Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7, 148.0, 125.7, 120.4, 112., 112.1, 56.2, 56.1. MS *m/z* calcd for $[C_8H_9ClO_2]^+$, 172.0, found: 172.0.

General experimental procedure for the synthesis of dimethoxyarene derivatives

A difluoroarene compound **7** (1 mmol, 1 equiv.) was added to a mixture of sodium methoxide (4 mmol, 4 equiv.) and DMF (8 mL). The reaction mixture was stirred at 110 °C for 3 h, quenched with cold water (5 mL) and extracted with hexane (3 × 4 mL). The combined extracts were washed with a saturated NaCl solution (5 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified by silica gel flash chromatography with ethyl acetate:hexane (5:95, *v*/v) as eluent to give the desired dimethoxy compounds **6a** and **8**.

4-Bromo-1,2-dimethoxybenzene (**6a**): Yield 87% (151 mg), colorless oil from 4-chloro-1,2-difluorobenzene (**7a**). See above for the analytical data of **6a**.

5-Bromo-1-chloro-2,3-dimethoxybenzene (**8b**): Yield 74% (162 mg), colorless oil from 5-bromo-1-chloro-2,3-difluorobenzene (**7b**). $R_f = 0.52$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, $J = 2.2$ Hz, 1H), 6.92 (d, $J = 2.2$ Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 145.0, 129.3, 124.5, 116.2, 114.7, 60.8, 56.4. MS *m/z* calcd for $[C_8H_8BrClO_2]^+$: 251.9, found: 252.0.

1-Bromo-5-chloro-2,3-dimethoxybenzene (**8c**): Yield 89% (224 mg) white solid from 1-bromo-5-chloro-2,3-difluorobenzene (**7c**); Mp. = 28–29 °C. $R_f = 0.46$ in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, $J =$ 2.3 Hz, 1H), 6.84 (d, $J = 2.3$ Hz, 1H), 3.85 (s, 3H), 3.83 (s,

3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 145.6, 129.8, 124.3, 118.0, 112.6, 60.8, 56.4. MS *m/z* calcd for $[C_8H_8BrClO_2]^+$: 251.9, found: 252.0.

General experimental procedure for the Suzuki coupling reaction

A mixture of a bromoarene derivative **5**, **8**, or **9** (1.0 equiv.), $Pd(dppf)Cl_2$ (0.005 equiv.) and aqueous Na_2CO_3 (2 N, 1.5 mL) was placed in a flame-dried flask (Kania-Korwel et al. 2004). The mixture was dissolved in dioxane (6 mL) under a nitrogen atmosphere. A solution of the phenylboronic acid **10** (1.2 equiv.) in ethanol (1.5 mL) was added dropwise to the reaction mixture. The mixture was heated under reflux for 16 h, allowed to cool to room temperature, and quenched with water (3 mL). The mixture was extracted by ethyl acetate (3 × 5 mL), and the combined organic phases were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the residue was purified by silica gel flash chromatography with ethyl acetate:hexane (5:95, v/v) as eluent to give the corresponding methoxylated biphenyl derivative **11**.

3,3′-Dichloro-2-methoxy-1,1′-biphenyl (**11a**) (Li et al. 2018; Zhu et al. 2013): Yield 26% (351 mg), colorless oil from 1-bromo-3-chloro-2-methoxybenzene (**5c**) and 3-chlorophenylboronic acid (**10a**). R_f = 0.67 in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (m, 1H), 7.47–7.44 (m, 1H), 7.40 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.38–7.34 (m, 2H), 7.23 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.12 (pseudo t, *J* = 7.8 Hz, 1H), 3.54 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 139.4, 135.7, 134.3, 130.2, 129.7, 129.4, 129.3, 128.8, 127.8, 127.4, 125.05, 60.8. MS *m/z* calcd for $[C_{13}H_{10}Cl_2O]^+$: 252.0, found: 252.0.

3,3′-Dichloro-4-methoxy-1,1′-biphenyl (**11b**) (Li et al. 2018; Zhu et al. 2013): Yield 68% (197 mg), white solid from 1-bromo-3-chloro-4-methoxybenzene (**5j**) and 3-chlorophenylboronic acid (**10a**). R_f = 0.45 in hexane/EtOAc = 19:1; Mp. 43–44 °C (lit. mp. 44–45 °C (Zhu et al. 2013)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 2.3 Hz, 1H), 7.51 (pseudo t, *J* = 1.6 Hz, 1H), 7.42 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.40 (dm, *J* = 7.7 Hz, 1H), 7.35 (pseudo t, *J* = 7.7 Hz, 1H), 7.30 (dm, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 141.5, 134.9, 133.3, 130.2, 129.0, 127.4, 127.0, 126.4, 125.0, 123.2, 112.5, 56.4. MS *m/z* calcd for $[C_{13}H_{10}Cl_2O]^+$: 252.0, found: 252.0.

3,3′-Dichloro-5-methoxy-1,1′-biphenyl (**11c**) (Li et al. 2018): Yield 57% (236 mg), colorless oil from 4-bromo-2-chloro-1-methoxybenzene (**5d**) and 3-chlorophenylboronic (**10a**). R_f = 0.61 in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 1H), δ 7.42 (d, pseudo t, *J* = 6.9, 1.9 Hz, 1H), 7.38–7.32 (m, 2H), 7.13 (pseudo t, *J* = 1.6 Hz, 1H), 6.96 (pseudo t, *J* = 1.9 Hz, 1H), 6.91 (pseudo t, *J* = 1.9 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.8, 142.5, 141.8, 135.5, 134.9, 130.2, 128.1, 127.4, 125.4, 119.9, 113.6, 111.8, 55.6. MS *m/z* calcd for $[C_{13}H_{10}Cl_2O]^+$: 252.0, found: 252.0.

3,3′-Dichloro-6-methoxy-1,1′-biphenyl (**11d**) (Li et al. 2018; Zhu et al. 2013): Yield 38% (690 mg), colorless oil from 2-bromo-4-chloro-1-methoxybenzene (**5h**) and 3-chlorophenylboroic acid (**10a**). R_f = 0.55 in hexane/EtOAc = 19:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 1H), 7.42–7.27 (m, 5H), 6.91 (dm, *J* = 9.0 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 139.1, 134.0, 130.8, 130.5, 129.6, 129.4, 128.8, 127.7, 127.6, 125.9, 112.7, 56.0. MS *m/z* calcd for $[C_{13}H_{10}Cl_2O]^+$: 252.0, found: 252.0.

3,3′-Dichloro-2,5-dimethoxy-1,1′-biphenyl (**11e**): Yield 23% (73 mg), white solid from 3-bromo-1-chloro-2,5-dimethoxybenzene (**9b**; Sigma-Aldrich) and 3-chlorophenylboronic acid (**10a**). R_f = 0.59 in hexane/EtOAc = 19:1; Mp. 80–80 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.56 (m, 1H), 7.48–7.43 (m, 1H), 7.34–7.38 (m, 2H), 6.95 (d, *J* = 3.1 Hz, 1H), 6.76 (d, *J* = 3.1 Hz, 1H), 3.80 (s, 3H), 3.47 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 147.4, 139.5, 135.9, 134.3, 129.7, 129.2, 129.2, 127.9, 127.4, 115.2, 115.0, 61.0, 56.0. HRMS (ESI) *m/z*: $[M\text{-}H]^+$ calcd for $[C_{14}H_{12}Cl_2O_2]^+$: 282.0214, found: 282.0212.

3′,5-Dichloro-2,3-dimethoxy-1,1′-biphenyl (**11f**): Yield 15% (107 mg), white solid from 1-bromo-5-chloro-2,3-dimethoxybenzene (**8c**) and 3-chlorophenylboronic acid (**10a**). R_f = 0.48 in hexane/EtOAc = 19:1; Mp. 49–50 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 1H), 7.43–7.38 (m, 1H), 7.36–7.32 (m, 2H), 6.91–6.92 (m, 2H), 3.90 (s, 3H), 3.58 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9, 145.4, 139.0, 135.5, 134.2, 129.6, 129.3, 129.2, 127.8, 127.5, 122.1, 112.7, 61.0, 56.3. Elemental analysis calcd for $C_{14}H_{12}Cl_2O_2$: C, 59.39; H, 4.27; found: C, 59.66; H, 4.22. HRMS (ESI) *m/z*: $[M\text{-}H]^+$ calcd for $[C_{14}H_{12}Cl_2O_2]^+$: 282.0214, found: 282.0221.

3,4-Dichloro-3′,4′-dimethoxy-1,1′-biphenyl (**11g**) (Bauer et al. 1995): Crude yield 45% (482 mg), white solid from 4-bromo-1,2-dimethoxybenzene (**6a**) and 3,4-dichlorophenylboronic acid (**10b**). R_f = 0.28 in hexane/EtOAc = 19:1; Mp. 88–89 °C (lit. mp. 93–94 °C (Bauer et al. 1995)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.1 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.36 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.08 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 149.4, 141.2, 132.8, 131.8, 130.9, 130.7, 128.7, 126.1, 119.5, 111.7, 110.2, 56.14, 56.11. Elemental analysis calcd for $C_{14}H_{12}Cl_2O_2$: C, 59.39; H, 4.27; found: C, 59.20; H, 4.20. MS *m/z* calcd for $[C_{14}H_{12}Cl_2O_2]^+$: 282.0, found: 282.0.

2,3′,4-Trichloro-5′-methoxy-1,1′-biphenyl (**11h**): Yield 40% (87 mg) white solid from 1-bromo-3-chloro-5-methoxybenzene (**5d**) and 2,4-dichlorophenylboronic acid (**10c**). R_f = 0.67 in hexane/EtOAc = 19:1; Mp. 55–56 °C. ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 8.3, 2.0 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 6.98 (m, 1H), 6.93 (pseudo t, J = 2.0 Hz, 1H), 6.83 (pseudo t, J = 1.7 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 140.7, 137.9, 134.8, 134.4, 133.3, 132.0, 130.0, 127.4, 122.0, 114.1, 113.9, 55.8. MS m/z calcd for $[C_{13}H_9Cl_3O]^+$: 286.0, found: 286.0.

3,3′,4-Trichloro-4′-methoxy-1,1′-biphenyl (**11i**) (Lehmler and Robertson 2001a): Yield 86% (374 mg), white solid from 4-bromo-2-chloro-1-methoxybenzene (**5j**) and 3,4-dichlorophenylboronic acid (**10b**). R_f = 0.45 in hexane/EtOAc = 19:1; Mp. 120–121 °C (lit. mp. 110–111 °C (Lehmler and Robertson 2001a)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 2.1 Hz, 1H), 7.56 (d, J = 2.3 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.40 (dd, J = 8.5, 2.3 Hz, 1H), 7.35 (dd, J = 8.3, 2.1 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 139.7, 133.1, 132.3, 131.5, 130.9, 128.8, 128.6, 126.3, 126.0, 123.3, 112.5, 56.4. MS m/z calcd for $[C_{13}H_9Cl_3O]^+$: 286.0, found: 286.0.

3,3′,5-Trichloro-4-methoxy-1,1′-biphenyl (**11j**) (Lehmler and Robertson 2001a): Yield 68% (368 mg), white crystalline solid from 5-bromo-1,3-dichloro-2-methoxybenzene (**9a**; Sigma-Aldrich) and 3-chlorophenylboronic acid (**10a**). R_f = 0.72 in hexane/EtOAc = 19:1; Mp. 82–83 °C (lit. mp. 73–75 °C (Lehmler and Robertson 2001a)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.48 (m, 1H), 7.48 (s, 2H), 7.41–7.30 (m, 3H), 3.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.2, 140.2, 137.4, 135.1, 130.4, 130.0, 128.3, 127.6, 127.2, 125.2, 61.0. MS m/z calcd for $[C_{13}H_9Cl_3O]^+$: 286.0, found: 286.0.

Crystal structure analysis

Crystals of 3,3′-dichloro-2,5-dimethoxy-1,1′-biphenyl (**11e**) and 3′,5-dichloro-2,3-dimethoxy-1,1′-biphenyl (**11f**) suitable for crystal structure analysis were obtained by slow evaporation of a solution of the compound in hexane:methanol (3:1, v/v). X-ray diffraction data were collected at 90 K on a Bruker D8 Venture dual source in the X-ray Crystallography Facility in the Department of Chemistry at the University of Kentucky (Lexington, KY, USA) as described previously (Li et al. 2014). All crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC deposition numbers 1961507 and 1961508.

Result and discussion

Optimization of the synthesis of 1-bromo-3-chloro-5-methoxybenzene (**5d**).

Initially, the reaction conditions for the conversion of 1-bromo-3-chloro-5-fluorobenzene (**2d**) to 1-bromo-3-chloro-5-methoxybenzene (**5d**) were optimized (Table 1). The total conversion of the starting material **2d** and the mass balance were >98 and > 97%, respectively, for all reaction conditions investigated, suggesting that no major side products were formed. Moreover, no additional products were observed in the gas chromatographic analyses of the crude reaction mixture. The reaction of **2d** with two equivalents of sodium methoxide in anhydrous N,N-dimethylformamide (DMF) for 3 h at 80 °C gave the desired product **5d** in 96% yield (Table 1, entry 1.1). Under the same conditions, lower yields of **5d** ranging from 1 to 79% were observed when the reaction was performed in methanol, THF, 1,4-dioxane, or N-methyl-2-pyrrolidone as solvent (Table 1, entries 1.2–1.5). These findings suggest that, out of the solvents investigated, DMF is the best solvent for the reaction of **2d** to **5d** in the presence of excess sodium methoxide.

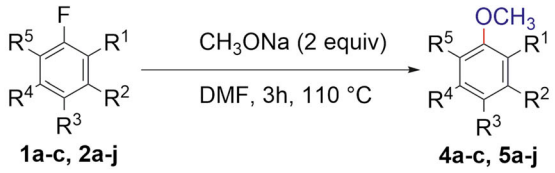
To determine the optimal amount of sodium methoxide for the synthesis of **5d**, a series of reactions were carried out with 1 to 3 equivalents of sodium methoxide in DMF for 3 h at 80 °C (Table 1, entries 1.6–1.9). Yields of **5d** slightly increased from 89 to 98% when the amount of sodium methoxide was increased from 1 to 2 equivalents. Similarly, yields of **5d** increased from 89 to 99% when the reaction temperature was increased from 23 °C (ambient temperature) to 110 °C using 2 equiv. of sodium methoxide in DMF for 3 h (Table 1, entries 1.10–1.13). Reactions carried out with 2 equivalents of sodium methoxide in DMF at 110 °C for 0.5 to 3 h (Table 1, entries 1.14–1.17) gave **5d** in yields of 93 to 99%, with reaction times of 3 h giving the best yield (99%; Table 1, entry 1.17). Overall, these experiments suggest that **2d** is converted near quantitatively to **5d** in the presence of 2 equivalents of sodium methoxide in DMF at 110 °C for 3 h.

Optimization of the synthesis of 2-chloro-4-iodo-1-methoxybenzene (5f)

We were also interested in optimizing the reaction of iodoarene derivatives with sodium methoxide to provide the corresponding methoxyiodoarene derivatives. Therefore, we first treated 2-chloro-1-fluoro-4-iodobenzene (**2f**) with 2 equivalents of sodium methoxide in DMF for 3 h at 80 °C (Table 2, entry 2.1). This reaction provided 2-chloro-4-iodo-1-methoxybenzene (**5f**) in 83% yield. We also observed side products resulting from the loss of iodine, such as 2-chloro-1-fluorobenzene (**1c**) in 2% yield and 2-chloro-1-methoxybenzene (**4c**) in 1% yield. The overall conversion and the yields of **5f** were much lower when the reaction was performed in methanol, THF, or 1,4-dioxane (Table 2, entries 2.2–2.4). Complete conversion of **2f** was observed in NMP; however, the yield of **5f** was only 52% (Table 2, entry 2.5). The poor mass balance (59%) of this reaction suggests that other, nonidentified products were formed in reactions with NMP as the solvent.

Additional experiments in DMF were performed to optimize the reaction of **2f** to **5f**, while at the same time

Scheme 1 Synthesis of mono-methoxy compounds **4a–c** and **5a–j** from mono-fluoroarenes. See Tables 3 and 4 for additional information



1a-c, 2a-j **4a-c, 5a-j**

Disubstituted Compounds:

1a, 4a: R^1 = Br, R^2, R^3, R^4, R^5 = H

1b, 4b: R^2 = Br, R^1, R^3, R^4, R^5 = H

1c, 4c: R^1 = Cl, R^2, R^3, R^4, R^5 = H

Trisubstituted Compounds:

2a, 5a; R^1 = Cl, R^2 = Br, R^3, R^4, R^5 = H

2b, 5b; R^3 = Cl, R^2 = Br, R^1, R^4, R^5 = H

2c, 5c; R^1 = Br, R^5 = Cl, R^2, R^3, R^4 = H

Trisubstituted Compounds (cont.):

2d, 5d; R^2 = Cl, R^4 = Br, R^1, R^3, R^5 = H

2e, 5e; R^1 = Cl, R^3 = Cl, R^2, R^4, R^5 = H

2f, 5f; R^1 = Cl, R^3 = I, R^2, R^4, R^5 = H

2g, 5g; R^3 = Br, R^2 = Cl, R^1, R^2, R^5 = H

2h, 5h; R^1 = Br, R^3 = Cl, R^2, R^4, R^5 = H

2i, 5i; R^1 = Cl, R^4 = Br, R^2, R^3, R^5 = H

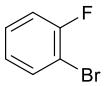
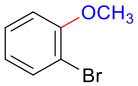
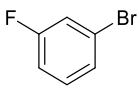
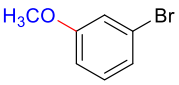
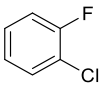
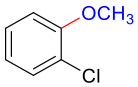
2j, 5j; R^1 = Cl, R^3 = Br, R^2, R^4, R^5 = H

minimizing the formation of undesired by-products (i.e., **1c** and **4c**). Increasing the amount of sodium methoxide from 1 to 3 equivalents increased the overall conversion from 44 to 100% and the yields of **5f** from 37 to 89% (Table 2, entries 2.6–2.9). The formation of by-products, in particular, 2-chloro-1-methoxybenzene (**4c**), was relatively high in reactions with 3 equivalents of sodium methoxide, suggesting that 2 equivalents of sodium methoxide are optimal for this reaction. In the presence of 2 equivalents of sodium methoxide, an increase in the reaction temperature from 23 °C (ambient temperature) to 110 °C increased the conversion of **2f** from 72 to 93% (Table 2, entries 2.10–2.13). The yield of the desired product **5f** also increased with increasing temperature, whereas the formation of deiodination products **1c** and **4c** was not affected by the reaction temperature. Finally, the reaction of **2f** at 110 °C in the presence of 2 equivalents of sodium methoxide gave both overall conversions and yields of **5f** that improved from 0.5 to 3 h without increasing the formation of undesired side products (Table 2, entries 2.14–2.17). Overall, the optimal reaction conditions for the synthesis of **5f** from the corresponding fluoroiodoarene **2f** are essentially identical to those described for the synthesis of 1-bromo-3-chloro-5-methoxybenzene (**5d**) described above.

General synthesis of monomethoxyarene derivatives

To expand the scope of the synthesis of bromo- or chloro-substituted methoxyarenes (i.e., **5d** and **5f**) from the corresponding fluoroarenes, a series of monomethoxyarene derivatives was prepared from di- and trisubstituted fluoroarenes using the optimized reaction conditions described above (Scheme 1). Two bromofluorobenzenes, **1a** and **1b**, reacted with 2 equivalents of sodium methoxide in DMF for 3 h at 110 °C to provide the corresponding bromomethoxybenzenes

Table 3 Reaction of disubstituted fluoroarenes **1a–c** with 2 equiv. of sodium methoxide yields the corresponding methoxyarenes **4a–c**

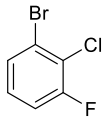
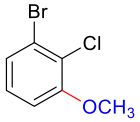
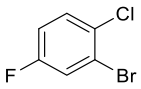
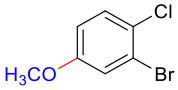
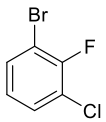
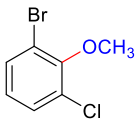
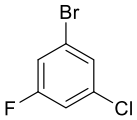
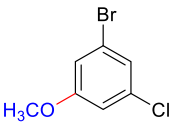
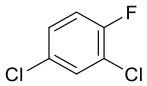
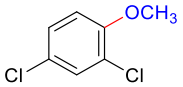
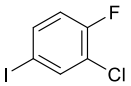
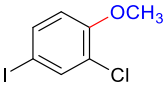
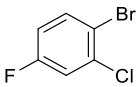
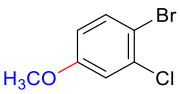
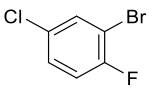
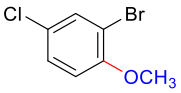
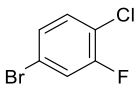
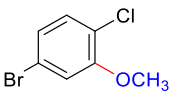
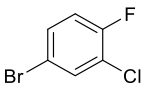
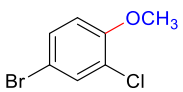
Entry	Fluoro Compound	Methoxy Compounds	Yield[a]
3.1.	 **1a**	 **4a**	48%
3.2.	 **1b**	 **4b**	59%
3.3.	 **1c**	 **4c**	80%[b]

See "Experimental" section for additional details

[a] Reaction was carried out at a 1-mmol scale

[b] Reaction was carried out only in a 25-mmol scale to provide product **4c**

Table 4 Reaction of trisubstituted fluoroarenes **2a-j** with 2 equiv. of sodium methoxide yields the corresponding methoxyarenes **5a-j**

Entry	Fluoro Compound	Methoxy Compound	Yield
4.1.	 **2a**	 **5a**	90%[a]
4.2.	 **2b**	 **5b**	83%[a]
4.3.	 **2c**	 **5c**	75%[a,b]
4.4.	 **2d**	 **5d**	80%[a,c]
4.5.	 **2e**	 **5e**	82%[a]
4.6.	 **2f**	 **5f**	73%[a]
4.7.	 **2g**	 **5g**	41%[a]
4.8.	 **2h**	 **5h**	85%[a,d]
4.9.	 **2i**	 **5i**	87%[a]
4.10.	 **2j**	 **5j**	84%[a,e]

See "Experimental" section for additional details

[a] Reactions were carried out at a 1-mmol scale

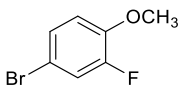
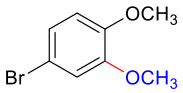
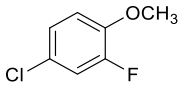
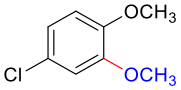
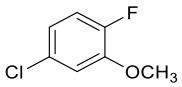
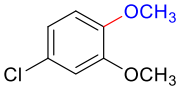
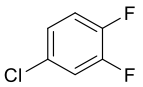
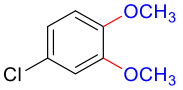
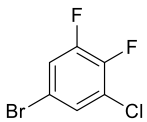
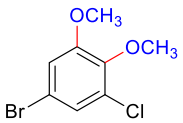
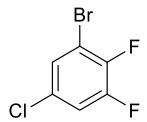
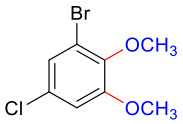
[b] Reaction was also carried out at a 58.9-mmol scale to provide product **5c** in 74% yield

[c] Reaction was carried out at a 90.6-mmol scale to provide product **5d** in 71%

[d] Reaction was also carried out at a 63.8-mmol scale to provide product **5 h** in 73% crude yield

[e] Reaction was also carried out at a 19.2-mmol scale to provide product **5j** in 78%

Table 5 Synthesis of dimethoxyarene derivatives from mono- and difluoroarenes

Entry	Fluoro Compound	Dimethoxy Compound	Yield
5.1.	 **3a**	 **6a**	86%[a,b,c]
5.2.	 **3b**	 **6b**	87%[a,c]
5.3.	 **3c**	 **6b**	88%[a,c]
5.4.	 **7a**	 **6b**	87%[a,d]
5.5.	 **7b**	 **8b**	74%[a,d]
5.6.	 **7c**	 **8c**	89%[a,d]

See "Experimental" section for additional details

[a] Reactions were carried out at a 1-mmol scale

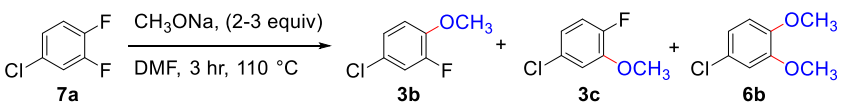
[b] Reaction was also carried out at a 22.6-mmol scale to provide product **6a** in 78% yield

[c] Reaction was carried out with 2 equiv. of the base

[d] Reaction was carried out with 4 equiv. of the base

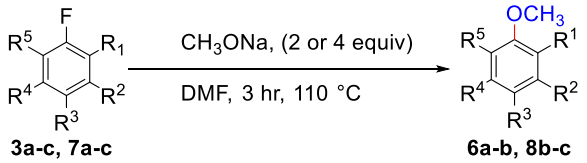
4a and **4b** in moderate yields (Table 3, entries 3.1 and 3.2). The conversion of 2-chloro-1-fluorobenzene (**1c**) gave the desired monomethoxyarene **4c** in good yield (80%; Table 3, entry 3.3).

Trisubstituted fluoroarene derivatives **2a–j** also underwent nucleophilic aromatic substitution with sodium methoxide to give a variety of methoxyhaloarene derivatives in good yields ranging from 73 to 90% (Table 4, entries 4.1–4.10). As shown for several examples in Table 4, the yields were similar when the reactions were scaled up and performed in the gram scale. The synthesis of 1-bromo-2-chloro-4-methoxybenzene (**5g**) from 1-bromo-2-chloro-4-fluorobenzene (**2g**) was one exception, with reproducibly poor yields (Table 4, entry 4.7). Overall, the nucleophilic substitution reaction provides easy



Scheme 2 Reaction of difluoroarene **7a** with 2 and 3 equivalents of sodium methoxide yields mixtures of mono- and dimethoxylated compounds. The reaction products were identified by comparison of their retention times in the GC-FID analysis with authentic standards

Scheme 3 Synthesis of dimethoxy compounds **6a–b** and **8b–c** from methoxylated mono-fluoroarenes **3a–c** or difluoroarenes **7a–c**. See Table 3 for additional information



3a-c, 7a-c **6a-b, 8b-c**

3a, 6a; $R^1 = OCH_3$; R^4 = Br; R^2,R^3,R^5 = H
3b, 6b; $R^1 = OCH_3$; R^4 = Cl; R^2,R^3,R^5 = H
3c, 6b; $R^1 = OCH_3$; R^3 = Cl; R^2,R^4,R^5 = H
7a; R^1 = F; R^3 = Cl; R^2,R^4,R^5 = H / **6b;** $R^1 = OCH_3$; R^3 = Cl; R^2,R^4,R^5 = H
7b; R^1 = F; R^2 = Cl; R^4 = Br; R^3,R^5 = H / **8b;** $R^1 = OCH_3$; R^2 = Cl; R^4 = Br; R^3,R^5 = H
7c; R^1 = F; R^2 = Br; R^4 = Cl; R^3,R^5 = H / **8c;** $R^1 = OCH_3$; R^2 = Br; R^4 = Cl; R^3,R^5 = H

access to structurally diverse bromochloro-substituted methoxyarenes that could be important precursors to synthesize a wide variety of methoxylated polychlorinated biphenyls via the Suzuki coupling.

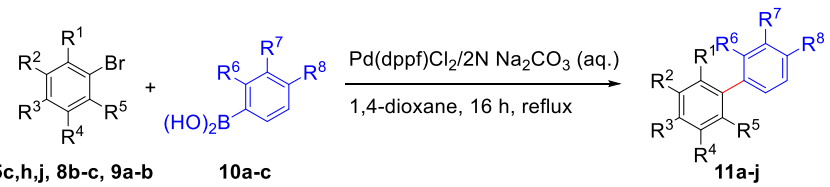
Both small- and large-scale reactions provided the desired mono-methoxyarenes in good to excellent yields. Although some metal-catalyzed reactions (Amii and Uneyama 2009; Keegstra et al. 1992) undergo a selective replacement of a bromine group by a methoxide group, we did not detect any replacement of bromine and chlorine substituents by a methoxide group, or other by-products, based on GC–MS analysis.

General synthesis of dimethoxyarene derivatives

In addition to monomethoxyarenes, diverse bromo(chloro)-substituted dimethoxyarene derivatives are valuable starting materials for the synthesis of dimethoxylated PCB derivatives. These compounds are useful as analytical standards (Haraguchi et al. 2004; Kania-Korwel et al. 2017; Lu et al. 2013; McLean et al. 1996) or can be demethylated to yield dihydroxylated PCB derivatives needed for in vitro and in vivo toxicological studies (Espandiari et al. 2004; Srinivasan et al. 2001). Therefore, we investigated if bromo(chloro)-substituted dimethoxyarene derivatives can be prepared from fluoro-substituted methoxybenzenes or difluoro-substituted bromo(chloro)benzenes (Scheme 3). The reaction of 4-bromo-2-fluoro-1-methoxybenzene (**3a**) with sodium methoxide afforded 4-bromo-1,2-dimethoxybenzene (**6a**) in 86% yield (Table 5, entry 5.1). When the reaction was scaled up to 4.63 g starting material, **6a** was obtained in 78% yield. Reaction of 4-chloro-2-fluoro-1-methoxybenzene (**3b**) or 4-chloro-1-fluoro-2-methoxybenzene (**3c**) with 2 equivalents of sodium methoxide also yielded 4-chloro-1,2-dimethoxybenzene (**6b**) in good yields (87 and 88%, respectively; Table 5, entries 5.2 and 5.3).

Reaction of 2 or 3 equivalents of sodium methoxide with 4-chloro-1,2-difluorobenzene (**7a**) as a model compound resulted in a mixture of 4-chloro-2-fluoro-1-methoxybenzene (**3b**), 4-chloro-1-fluoro-2-methoxybenzene (**3c**), and 4-chloro-1,2-dimethoxybenzene (**6b**) (Scheme 2). However, 4 equivalents of the base provided the desired product (**6b**) in 88% yield (Table 5, entry 5.4). Analogously, difluorobenzenes **7b** and **7c** afforded the desired bromo(chloro)-substituted dimethoxyarene

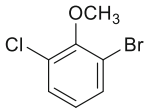
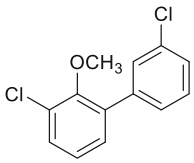
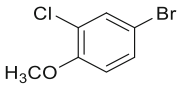
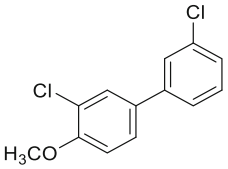
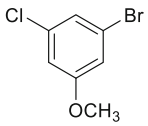
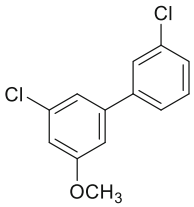
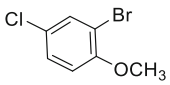
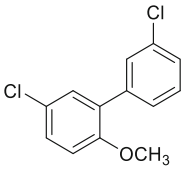
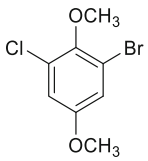
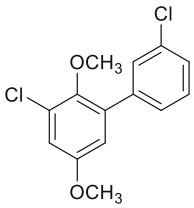
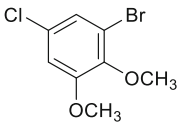
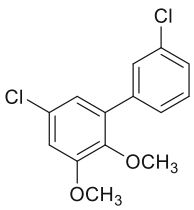
Scheme 4 Synthesis of a variety of methoxylated derivatives of PCB 11, PCB 12, PCB 25, PCB 35, and PCB 36 (**11a–j**) from selected methoxylated starting materials via the Suzuki coupling reaction. See Tables 6 and 7 for additional details



5c,h,j, 8b-c, 9a-b **10a-c** **11a-j**

5c, 10a, 11a; R^2,R^7 = Cl; $R^1 = OCH_3$; R^3,R^4,R^5, R^6,R^8 = H
5j, 10a, 11b; R^2,R^7 = Cl; $R^3 = OCH_3$; R^1,R^4,R^5, R^6,R^8 = H
5d, 10a, 11c; R^2,R^7= Cl; $R^4 = OCH_3$; R^1,R^3,R^5, R^6,R^8 = H
5h, 10a, 11d; R^2,R^7 = Cl; $R^5 = OCH_3$; R^1,R^3,R^4, R^6,R^8 = H
9b, 10a, 11e; R^2,R^7 = Cl; $R^1,R^4 = OCH_3$; R^3,R^5,R^6, R^8 = H
8c, 10a, 11f; R^2,R^7 = Cl; $R^4,R^5 = OCH_3$; R^1,R^3,R^6, R^8 = H
6a, 10b, 11g; R^7,R^8 = Cl; R^2, $R^3 = OCH_3$; R^1,R^4,R^5, R^6 = H
5d, 10c, 11h; R^2,R^6,R^8 = Cl; $R^4 = OCH_3$; R^1,R^3,R^5, R^7 = H
5j, 10b, 11i; R^2,R^7,R^8 = Cl; $R^3 = OCH_3$; R^1,R^4,R^5, R^6 = H
9a, 10a, 11j; R^2,R^4,R^7 = Cl; $R^3 = OCH_3$; R^1,R^5,R^6, R^8 = H

Table 6 Synthesis of methoxylated PCB 11 derivatives **11a–f** from methoxylated starting materials and 3-chlorobenzene boronic acid (**10a**) using the Suzuki coupling reaction

Entry	Methoxy Compound	Product	Yield[a]
6.1.	 **5c**	 **11a**	26%
6.2.	 **5j**	 **11b**	68%
6.3.	 **5d**	 **11c**	57%
6.4.	 **5h**	 **11d**	38%
6.5.	 **9b**	 **11e**	23%
6.6.	 **8c**	 **11f**	15%

[a] Isolated yields

derivatives **8b** and **8c** in 74 to 89% yield, respectively (Table 5, entries 5.5–5.6). This reaction provides facile access to structurally diverse dimethoxyarenes (i.e., **6b**, **8b–c**) that are difficult to synthesize by other routes (Scheme 3).

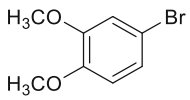
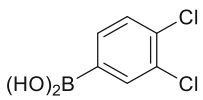
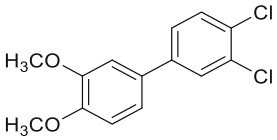
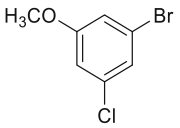
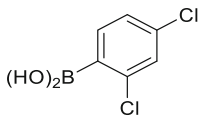
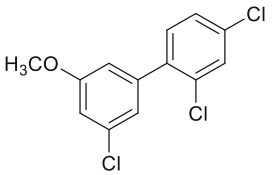
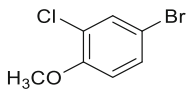
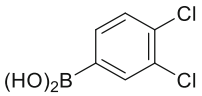
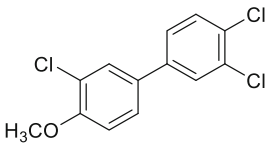
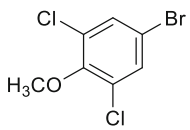
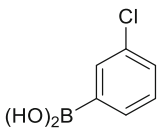
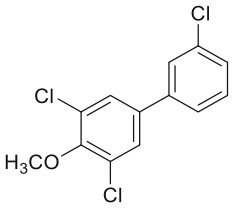
Synthesis of methoxylated PCB derivatives via Suzuki coupling

Several building blocks prepared from fluoroarene precursors were used to synthesize mono- and dimethoxylated PCB derivatives (Scheme 4). These efforts included a series of PCB 11 derivatives that are needed as analytical standards to study the metabolism of PCB 11, an environmentally prevalent, non-Aroclor PCB congener, and the toxicity of the corresponding hydroxylated PCB 11 derivatives. The mono-methoxylated PCB derivatives **11a–d** were prepared using the Suzuki coupling reaction of the corresponding mono-methoxybromoarene derivatives with 3-chlorophenyl boronic acid (**10a**) in the presence of $Pd(dppf)Cl_2$ and an aqueous solution of sodium carbonate (Table 6) (Kania-Korwel et al. 2004). The yields of mono-methoxylated PCB 11 derivatives **11a–d** ranged from 26 to 68% (Table 6, entries 6.1–6.4). Also, we prepared two dimethoxylated PCB 11 derivatives, **11e** and **11f**, with poor, isolated yields (23 and 15%, respectively; Table 6, entries 6.5–6.6). Besides, we synthesized a series of mono- and dimethoxy derivatives of PCB 12 (**11g**), PCB 25 (**11h**), PCB 35 (**11i**), and PCB 36 (**11j**) with the Suzuki coupling reaction in moderate to good yields (Table 7, entries 7.1–7.4).

Solid-state structure of 3,3′-dichloro-2,5-dimethoxy-1,1′-biphenyl (11e) and 3′,5-dichloro-2,3-dimethoxy-1,1′-biphenyl (11f)

The three-dimensional structure of PCBs and their metabolites is an important determinant in their interactions with different cellular targets, such as nuclear transcription factors (Lehmler et al. 2002; Shaikh et al. 2008; Song et al. 2011). To add to the available information about the three-dimensional structure of PCBs (Table S1), we obtained single-crystal structures of two dimethoxylated PCB 11 derivatives, 3,3′-dichloro-2,5-dimethoxy-1,1′-biphenyl (**11e**) and 3′,5-dichloro-2,3-dimethoxy-1,1′-biphenyl (**11f**). Crystal data, bond lengths, bond angles, and torsion angles for both compounds are presented in Tables 8 and 9. Dimethoxy derivative **11e** crystallized in the space group $P\bar{1}$ with two molecules in the

Table 7 Synthesis of a variety of methoxylated derivatives of PCB 12, 25, 35, and 36 (**11g–j**) from methoxylated starting materials via the Suzuki coupling reaction

Entry	Methoxy Compound	Boronic Acid	Product	Yield[a]
7.1.	 **6a**	 **10b**	 **11g**	45%
7.2.	 **5d**	 **10c**	 **11h**	40%
7.3.	 **5j**	 **10b**	 **11i**	86%
7.4.	 **9a**	 **10a**	 **11j**	68%

[a] Isolated yields

Table 8 Crystal data of 3,3′-dichloro-2,5-dimethoxy-1,1′-biphenyl (**11e**) and 3′,5-dichloro-2,3-dimethoxy-1,1′-biphenyl (**11f**)

Data	3,3′-Dichloro-2,5-dimethoxy-1,1′-biphenyl (**11e**)	3′,5-Dichloro-2,3-dimethoxy-1,1′-biphenyl (**11f**)
Crystal data		
Chemical formula	$C_{14}H_{12}Cl_2O_2$	$C_{14}H_{12}Cl_2O_2$
Molecular weight	283.14	283.14
Cell setting, space group	Triclinic, $P\bar{1}$	Monoclinic, $P2_1/c$
a (Å), b (Å), c (Å)	7.3327(2), 9.2656(3), 19.1081(5)	11.2311(5), 14.0879(6), 8.4982(3)
α, β, γ	83.273(1)°, 86.301(1)°, 89.476(1)°	90°, 104.1765(12)°, 90°
V (Å^3)	1286.61(6)	1303.66(9)
Z	4	4
F(000)	584	584
Dx (Mg m^{-3})	1.462 Mg m^{-3}	1.443
Radiation type	Mo Kα	Mo Kα
μ (mm^{-1})	0.494	0.488
Temperature (K)	90.0(2)	90.0(2)
Crystal form, color	Solvent-rounded cut block, colorless	Solvent-rounded slab, colorless
Crystal size (mm)	0.200 × 0.180 × 0.130	0.280 × 0.200 × 0.120
Data collection		
Diffractometer	Bruker D8 Venture dual source	Bruker D8 Venture dual source
Scan	ϕ and ω scans	ϕ and ω scans
Absorption correction	Multiscan	Multiscan
T_{min}, T_{max}	0.906, 0.958	0.865, 0.971
No. of measured reflections	25,149	21,142
No. of independent reflections	5903	2991
No. of observed reflections	5361	2713
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}, θ_{min}, θ_{max}	0.029, 2.571°, 27.491°	0.0326, 2.864°, 27.487°
h, k, l	− 9→9, − 12→12, − 24→24	− 14→14, − 18→18, − 10→11
Refinement		
Refinement on $R[F^2 > 2\sigma(F^2)]$	0.0265	0.0268
$wR(F^2)$	0.0659	0.0619
S	1.058	1.056
No. of reflections	5903	2991
No. of parameters	330	165
Restraint	0	0
H-atom treatment	Constrained	Constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.412, − 0.232	0.291, − 0.236

asymmetric unit (Fig. 1). The two molecules, A and B, display π–π stacking of the methoxylated rings, with the distance between the centers of gravity of Cg(C1A–C6A) to Cg(C1B–C6B) of 3.7280(16) Å. Moreover, CH–π interactions were present between C6A′–H6A′ and ring C1B′–C6B, with a distance from C6A′ to the mean plane of C1B′–C6B′ of 3.6900(14) Å. Dimethoxy PCB derivative **11f** crystallized in the space group $P2_1/c$ (Fig. 2). The packing suggests Cl–π interactions between glide-related molecules with a C1–C6 mean plane distance to Cl1(x,0.5–y,x–0.5) of 3.3309(6) Å.

The dihedral angle between the two phenyl rings plays an important role in the three-dimensional structure of PCB derivatives. The solid-state dihedral angles between the two benzene rings of **11e** were 47.64(4)° and 47.17(4)° for the two molecules in the asymmetric unit (Fig. 1). The dihedral angle of **11f** was slightly smaller, at 40.82(5)°. 4-Chloro-2′,3′-dimethoxybiphenyl, another PCB derivative with one *ortho* methoxy substituent, and 4-chloro-biphenyl-2,5-diol had comparable solid-state dihedral angles of 40.05° and 43.3°, respectively (Song et al. 2008; Song et al. 2011; Vyas et al. 2006b). For comparison, PCB derivatives without *ortho* chlorine substituents typically have solid-state dihedral angles ranging from 18.52(10)° to 43.94(6)°, whereas PCB derivatives with one *ortho* chlorine substituent typically have much

Table 9 Summary of bond length, bond angles, and torsion angles of 3,3′-dichloro-2,5-dimethoxy-1,1′-biphenyl (**11e**) and 3′,5-dichloro-2,3-dimethoxy-1,1′-biphenyl (**11f**)

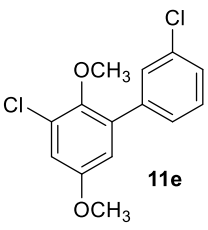
3,3′-Dichloro-2,5-dimethoxy-1,1′-biphenyl (**11e**)				3′,5-Dichloro-2,3-dimethoxy-1,1′-biphenyl (**11f**)	
Bond length					
Cl1A–C3A	1.7375(13)	Cl1B–C3B	1.7401(12)	Cl1–C5	1.7443(13)
Cl2A–C3A′	1.7458(13)	Cl2B–C3B′	1.7456(13)	Cl2–C3′	1.7425(13)
O1A–C2A	1.3743(14)	O1B–C2B	1.3735(14)	O1–C2	1.3802(14)
O1A–C7A	1.4405(16)	O1B–C7B	1.4368(16)	O1–C7	1.4371(15)
O2A–C5A	1.3659(15)	O2B–C5B	1.3670(14)	O2–C3	1.3640(14)
O2A–C8A	1.4308(16)	O2B–C8B	1.4305(15)	O2–C8	1.4298(16)
C1A–C6A	1.3904(17)	C1B–C6B	1.3905(17)	C1–C2	1.3938(17)
C1A–C2A	1.4044(17)	C1B–C2B	1.4054(17)	C1–C6	1.4029(17)
C1A–C1A′	1.4884(16)	C1B–C1B′	1.4880(17)	C1–C1′	1.4871(17)
C2A–C3A	1.3867(17)	C2B–C3B	1.3886(17)	C2–C3	1.4057(17)
C3A–C4A	1.3900(17)	C3B–C4B	1.3891(17)	C3–C4	1.3879(17)
C4A–C5A	1.3872(18)	C4B–C5B	1.3847(17)	C4–C5	1.3900(17)
C5A–C6A	1.3973(17)	C5B–C6B	1.3966(17)	C5–C6	1.3759(17)
C1A′–C2A′	1.3949(17)	C1B′–C2B′	1.3960(17)	C1′–C2′	1.3985(17)
C1A′–C6A′	1.3958(17)	C1B′–C6B′	1.3982(17)	C1′–C6′	1.4004(17)
C2A′–C3A′	1.3850(17)	C2B′–C3B′	1.3848(17)	C2′–C3′	1.3844(17)
C3A′–C4A′	1.3869(18)	C3B′–C4B′	1.3872(18)	C3′–C4′	1.3844(18)
C4A′–C5A′	1.3897(19)	C4B′–C5B′	1.3883(19)	C4′–C5′	1.3851(18)
C5A′–C6A′	1.3880(18)	C5B′–C6B′	1.3887(18)	C5′–C6′	1.3855(18)
Bond angles					
C2A–O1A–C7A	113.15(10)	C2B–O1B–C7B	112.99(10)	C2–O1–C7	112.19(9)
C5A–O2A–C8A	117.59(10)	C5B–O2B–C8B	117.56(10)	C3–O2–C8	117.27(10)
C6A–C1A–C2A	119.00(11)	C6B–C1B–C2B	119.24(11)	C2–C1–C6	118.64(11)
C6A–C1A–C1A′	119.63(11)	C6B–C1B–C1B′	119.49(11)	C2–C1–C1′	122.47(11)
C2A–C1A–C1A′	121.36(11)	C2B–C1B–C1B′	121.26(11)	C6–C1–C1′	118.88(11)
O1A–C2A–C3A	120.02(11)	O1B–C2B–C3B	120.06(11)	O1–C2–C1	120.87(11)
O1A–C2A–C1A	121.28(11)	O1B–C2B–C1B	121.40(11)	O1–C2–C3	118.45(11)
C3A–C2A–C1A	118.69(11)	C3B–C2B–C1B	118.52(11)	C1–C2–C3	120.67(11)
C2A–C3A–C4A	122.82(11)	C2B–C3B–C4B	122.66(11)	O2–C3–C4	124.33(11)
C2A–C3A–Cl1A	118.69(10)	C2B–C3B–Cl1B	118.89(9)	O2–C3–C2	115.13(11)
C4A–C3A–Cl1A	118.49(9)	C4B–C3B–Cl1B	118.45(9)	C4–C3–C2	120.54(11)
C5A–C4A–C3A	118.09(11)	C5B–C4B–C3B	118.32(11)	C3–C4–C5	117.77(11)
O2A–C5A–C4A	124.30(11)	O2B–C5B–C4B	124.13(11)	C6–C5–C4	122.83(12)
O2A–C5A–C6A	115.51(11)	O2B–C5B–C6B	115.59(11)	C6–C5–Cl1	118.82(10)
C4A–C5A–C6A	120.19(11)	C4B–C5B–C6B	120.28(11)	C4–C5–Cl1	118.35(10)
C1A–C6A–C5A	121.19(12)	C1B–C6B–C5B	120.96(11)	C5–C6–C1	119.55(11)
C2A′–C1A′–C6A′	119.12(11)	C2B′–C1B′–C6B′	118.99(11)	C2′–C1′–C6′	118.78(11)
C2A′–C1A′–C1A	120.39(11)	C2B′–C1B′–C1B	120.69(11)	C2′–C1′–C1	121.21(11)
C6A′–C1A′–C1A	120.48(11)	C6B′–C1B′–C1B	120.29(11)	C6′–C1′–C1	119.98(11)
C3A′–C2A′–C1A′	119.40(11)	C3B′–C2B′–C1B′	119.44(11)	C3′–C2′–C1′	119.27(11)
C2A′–C3A′–C4A′	122.10(12)	C2B′–C3B′–C4B′	122.07(12)	C2′–C3′–C4′	122.19(12)
C2A′–C3A′–Cl2A	118.57(10)	C2B′–C3B′–Cl2B	118.57(10)	C2′–C3′–Cl2	119.01(10)
C4A′–C3A′–Cl2A	119.32(10)	C4B′–C3B′–Cl2B	119.35(10)	C4′–C3′–Cl2	118.8(1)
C3A′–C4A′–C5A′	118.10(12)	C3B′–C4B′–C5B′	118.24(12)	C3′–C4′–C5′	118.42(12)
C6A′–C5A′–C4A′	120.81(12)	C4B′–C5B′–C6B′	120.74(12)	C4′–C5′–C6′	120.61(12)
C5A′–C6A′–C1A′	120.45(12)	C5B′–C6B′–C1B′	120.50(12)	C5′–C6′–C1′	120.72(12)
Dihedral angles					
C7A–O1A–C2A–C3A	93.99(13)	C7B–O1B–C2B–C3B	− 95.62(13)	C7–O1–C2–C1	97.54(13)
C7A–O1A–C2A–C1A	− 87.22(14)	C7B–O1B–C2B–C1B	85.63(14)	C7–O1–C2–C3	− 83.35(14)
C6A–C1A–C2A–O1A	− 177.21(11)	C6B–C1B–C2B–O1B	177.54(11)	C6–C1–C2–O1	179.10(11)
C1A′–C1A–C2A–O1A	3.71(18)	C1B′–C1B–C2B–O1B	− 3.23(18)	C1′–C1–C2–O1	−1.09(18)
C6A–C1A–C2A–C3A	1.60(17)	C6B–C1B–C2B–C3B	− 1.23(17)	C6–C1–C2–C3	0.01(18)
C1A′–C1A–C2A–C3A	− 177.48(11)	C1B′–C1B–C2B–C3B	178.00(11)	C1′–C1–C2–C3	179.81(11)
O1A–C2A–C3A–C4A	178.11(11)	O1B–C2B–C3B–C4B	− 178.46(11)	C8–O2–C3–C4	− 5.22(18)
C1A–C2A–C3A–C4A	−0.72(18)	C1B–C2B–C3B–C4B	0.33(18)	C8–O2–C3–C2	175.28(11)

Table 9 (continued)

3,3′-Dichloro-2,5-dimethoxy-1,1′-biphenyl (**11e**)				3′,5-Dichloro-2,3-dimethoxy-1,1′-biphenyl (**11f**)	
O1A–C2A–C3A–Cl1A	− 2.36(16)	O1B–C2B–C3B–Cl1B	1.35(16)	O1–C2–C3–O2	0.16(16)
C1A–C2A–C3A–Cl1A	178.82(9)	C1B–C2B–C3B–Cl1B	− 179.86(9)	C1–C2–C3–O2	179.28(11)
C2A–C3A–C4A–C5A	− 0.28(18)	C2B–C3B–C4B–C5B	0.23(18)	O1–C2–C3–C4	− 179.36(11)
Cl1A–C3A–C4A–C5A	− 179.82(9)	Cl1B–C3B–C4B–C5B	−179.58(9)	C1–C2–C3–C4	− 0.25(18)
C8A–O2A–C5A–C4A	0.16(17)	C8B–O2B–C5B–C4B	0.16(17)	O2–C3–C4–C5	− 179.51(11)
C8A–O2A–C5A–C6A	− 179.92(11)	C8B–O2B–C5B–C6B	− 179.96(11)	C2–C3–C4–C5	− 0.03(18)
C3A–C4A–C5A–O2A	− 179.70(11)	C3B–C4B–C5B–O2B	179.99(11)	C3–C4–C5–C6	0.57(19)
C3A–C4A–C5A–C6A	0.39(18)	C3B–C4B–C5B–C6B	0.12(18)	C3–C4–C5–Cl1	− 179.10(9)
C2A–C1A–C6A–C5A	− 1.53(18)	C2B–C1B–C6B–C5B	1.60(18)	C4–C5–C6–C1	− 0.81(19)
C1A′–C1A–C6A–C5A	177.56(11)	C1B′–C1B–C6B–C5B	− 177.64(11)	Cl1–C5–C6–C1	178.85(9)
O2A–C5A–C6A–C1A	− 179.40(11)	O2B–C5B–C6B–C1B	179.07(11)	C2–C1–C6–C5	0.50(18)
C4A–C5A–C6A–C1A	0.53(18)	C4B–C5B–C6B–C1B	− 1.04(18)	C1′–C1–C6–C5	− 179.31(11)
C6A–C1A–C1A′–C2A′	132.37(12)	C6B–C1B–C1B′–C2B′	− 132.34(12)	C2–C1–C1′–C2′	42.47(17)
C2A–C1A–C1A′–C2A′	− 48.55(17)	C2B–C1B–C1B′–C2B′	48.44(17)	C6–C1–C1′–C2′	−137.72(12)
C6A–C1A–C1A′–C6A′	− 46.31(17)	C6B–C1B–C1B′–C6B′	45.65(17)	C2–C1–C1′–C6′	−139.75(12)
C2A–C1A–C1A′–C6A′	132.76(13)	C2B–C1B–C1B′–C6B′	− 133.57(13)	C6–C1–C1′–C6′	40.06(17)
C6A′–C1A′–C2A′–C3A′	0.77(18)	C6B′–C1B′–C2B′–C3B′	− 0.89(18)	C6′–C1′–C2′–C3′	0.42(18)
C1A–C1A′–C2A′–C3A′	− 177.94(11)	C1B–C1B′–C2B′–C3B′	177.12(11)	C1–C1′–C2′–C3′	178.23(11)
C1A′–C2A′–C3A′–C4A′	− 1.36(19)	C1B′–C2B′–C3B′–C4B′	1.57(19)	C1′–C2′–C3′–C4′	− 1.44(19)
C1A′–C2A′–C3A′–Cl2A	177.40(9)	C1B′–C2B′–C3B′–Cl2B	− 177.03(9)	C1′–C2′–C3′–Cl2	178.49(9)
C2A′–C3A′–C4A′–C5A′	0.97(19)	C2B′–C3B′–C4B′–C5B′	− 1.1(2)	C2′–C3′–C4′–C5′	1.19(19)
Cl2A–C3A′–C4A′–C5A′	− 177.78(10)	Cl2B–C3B′–C4B′–C5B′	177.52(10)	Cl2–C3′–C4′–C5′	−178.74(10)
C3A′–C4A′–C5A′–C6A′	0.0(2)	C3B′–C4B′–C5B′–C6B′	− 0.1(2)	C3′–C4′–C5′–C6′	0.08(19)
C4A′–C5A′–C6A′–C1A′	− 0.5(2)	C4B′–C5B′–C6B′–C1B′	0.7(2)	C4′–C5′–C6′–C1′	− 1.1(2)
C2A′–C1A′–C6A′–C5A′	0.16(19)	C2B′–C1B′–C6B′–C5B′	− 0.23(19)	C2′–C1′–C6′–C5′	0.80(19)
C1A–C1A′–C6A′–C5A′	178.86(12)	C1B–C1B′–C6B′–C5B′	− 178.26(12)	C1–C1′–C6′–C5′	− 177.03(12)

larger solid-state dihedral angles ranging from 47.25(4)° to 59.92(9)° due to the steric demand of the chlorine substituent (Table S1). It is important to emphasize that intermolecular interactions in the solid state allow biphenyl molecules to adopt dihedral angles that would otherwise be energetically unfavorable.

The dihedral angle between the phenyl ring and the methoxy groups is an additional factor influencing the three-dimensional structure of methoxylated PCB derivatives. For biphenyl derivative **11e**, the dihedral angles for the *ortho* C-O-Me group relative to the mean plane of the phenyl ring are 86.82(8)° and 85.21(8)° for C2A–O1A–



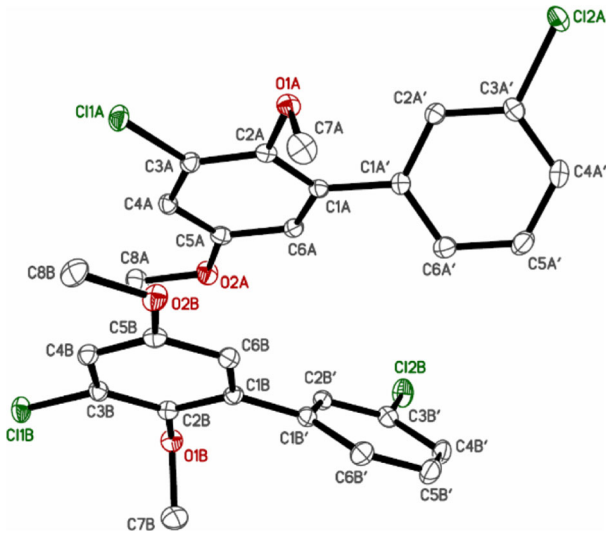


Fig. 1 Crystal structure showing two molecules in the crystallographic asymmetric unit of 3,3′-dichloro-2,5-dimethoxy-1,1′-biphenyl (**11e**) with atom-labeling scheme. Displacement ellipsoids are drawn at 50% probability

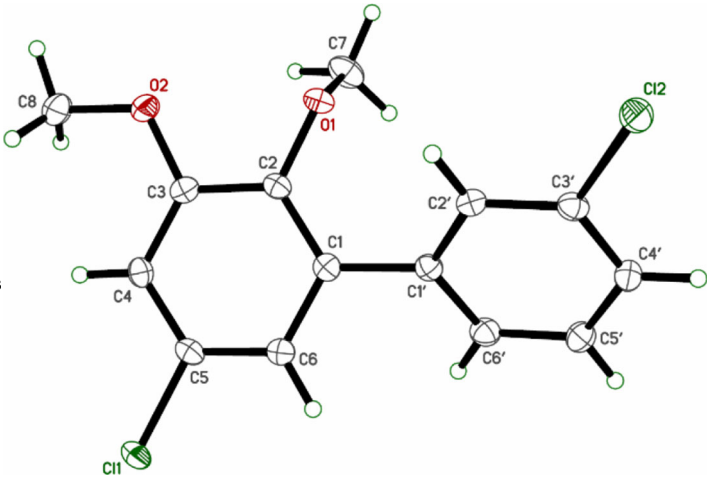
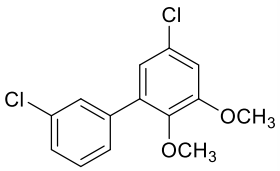


Fig. 2 Crystal structure of 3′,5-dichloro-2,3-dimethoxy-1,1′-biphenyl (**11f**) with atom-labeling scheme. Displacement ellipsoids are drawn at 50% probability



11f

C7A to C1A–C6A and C2B–O1B–C7B to C1B–C6B, respectively. In contrast, the *meta* C–O–Me group of **11f** essentially lies within the mean plane of the phenyl ring, with dihedral angles of 0.14(1)° and 0.38(1)° for the C5A–O2A–C8A to C1A–C6A and C5B-O2B-C8B to C1B–C6B dihedral angles. Dihedral angles between the planes of the methoxy groups and the phenyl ring for PCB derivative **11e** are 82.62(7)° for C2–O1–C7 to C1–C6 and 4.88(19)° for C3–O2–C8 to C1–C6. Analogously, methoxyarenes with no or one substituent *ortho* to the methoxy group, including PCB derivatives, adopt a conformation in the solid state where the C-O-Me group is near coplanar with the mean plane of the phenyl ring (Lehmler et al. 2013; Song et al. 2007; Song et al. 2010; Tan et al. 2005; Vyas et al. 2006a). In contrast, methoxyarenes with two substituents *ortho* to the methoxy group adopt a conformation where the C–O–Me group is nearly at a 90° angle relative to the mean plane of the phenyl ring.

Conclusions

We synthesized a number of mono- and dimethoxyarene derivatives starting from commercially available and relatively inexpensive fluoroarenes. This method provided good to excellent yields and can easily scale up to prepare gram quantities of mono- and dimethoxyarene derivatives **4**, **5**, **6**, and **8**. These mono- and dimethoxyarene derivatives provide facile access to a variety of mono- and dimethoxylated PCB congeners that are difficult to synthesize by other routes, thus expanding the available strategies for the synthesis of specific mono- and dimethoxylated PCB congeners needed as analytical standards, study compounds, and precursors for the preparation of hydroxylated and other PCB metabolites.

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References

Amii H, Uneyama K (2009) C-F bond activation in organic synthesis. Chem Rev 109:2119–2183. https://doi.org/10.1021/cr800388c

Anezaki K, Nakano T (2014) Concentration levels and congener profiles of polychlorinated biphenyls, pentachlorobenzene, and hexachlorobenzene in commercial pigments. Environ Sci Pollut Res 21:998–1009. https://doi.org/10.1007/s11356-013-1977-2

ATSDR (2000) Toxicological profile for polychlorinated biphenyls (PCBs). U.S. Department of Health & Human Services, Atlanta, GA https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=142&tid=26

Balko TW, Schmitzer PR, Daeuble JF, Yerkes CN, Siddall TL, Yerkes CN (2007) 6-(Poly-substituted aryl)-4-aminopicolinates and their use as herbicides. USA Patent 7314849, PCT Int Appl, July 19, 2007

Bauer U, Amaro AR, Robertson LW (1995) A new strategy for the synthesis of polychlorinated biphenyl metabolites. Chem Res Toxicol 8:92–95. https://doi.org/10.1021/tx00043a012

Beekman AM, Barrow RA (2014) Syntheses of the fungal metabolites boletopsins 7, 11, and 12 from the Papua New Guinea medicinal mushroom *Boletopsis* sp. J Organomet Chem 79:1017–1024. https://doi.org/10.1021/jo402492d

Beil SB, Uecker I, Franzmann P, Muller T, Waldvogel SR (2018) Mild, fast, and easy to conduct $MoCl_5$-mediated dehydrogenative coupling reactions in flow. Org Lett 20:4107–4110. https://doi.org/10.1021/acs.orglett.8b01664

Blencowe A, Cosstick K, Hayes W (2006) Surface modification of nylon 6,6 using a carbene insertion approach. New J Chem 30:53–58. https://doi.org/10.1039/b514205a

Bovonsombat P, Sophanpanichkul P, Pandey A, Tungsirisurp S, Limthavornlit P, Chobtumskul K, Kuhataparuk P, Sathityatiwat S, Teecomegaet P (2015) Regioselective iodination of activated arenes using phenyl trimethylammonium dichloroiodate in ionic liquid under microwave irradiation. Tetrahedron Lett 56:2193–2196. https://doi.org/10.1016/j.tetlet.2015.03.034

Cadogan JIG, Roy DA, Smith DM (1966) An alternative to the Sandmeyer reaction. J Chem Soc C:1249-1250. https://doi.org/10.1039/J39660001249

Chen J-M, Zeng X-M, Middleton K, Zhdankin VV (2011) Facile preparation and reactivity of polystyrene-supported (dichloroiodo)benzene: a convenient recyclable reagent for chlorination and oxidation. Tetrahedron Lett 52:1952–1955. https://doi.org/10.1016/j.tetlet.2011.02.065

Dhakal K, Gadupudi GS, Lehmler H-J, Ludewig G, Duffel MW, Robertson LW (2018) Sources and toxicities of phenolic polychlorinated biphenyls (OH-PCBs). Environ Sci Pollut Res 25:16277–16290. https://doi.org/10.1007/s11356-017-9694-x

Dhakshinamoorthy A, Sharmila A, Pitchumani K (2010) Layered double hydroxide-supported l-methionine-catalyzed chemoselective o-methylation of phenols and esterification of carboxylic acids with dimethyl carbonate: a "green" protocol. Chem Eur J 16:1128–1132. https://doi.org/10.1002/chem.200902626

EPA (2018). Polychlorinated biphenyls (PCBs) USA. https://www.epa.gov/pcbs

Espandiari P, Glauert HP, Lehmler HJ, Lee EY, Srinivasan C, Robertson LW (2004) Initiating activity of 4-chlorobiphenyl metabolites in the resistant hepatocyte model. Toxicol Sci 79:41–46. https://doi.org/10.1093/toxsci/kfh097

Gavryushin A, Malysheva Y, Combes S, Fedorov A, Knochel P (2012) New method of synthesis and biological evaluation of some combretastatin A-4 analogues. Synlett 23:1205–1208. https://doi.org/10.1055/s-0031-1290899

Gibson SL, Holt JJ, Ye M, Donnelly DJ, Ohulchanskyy TY, You Y, Detty MR (2005) Structure-activity studies of uptake and phototoxicity with heavy-chalcogen analogues of tetramethylrosamine in vitro in chemosensitive and multidrug-resistant cells. Bioorg Med Chem 13:6394–6403. https://doi.org/10.1016/j.bmc.2005.06.056

Grimm FA, Hu D, Kania-Korwel I, Lehmler H-J, Ludewig G, Hornbuckle KC, Duffel MW, Bergman A, Robertson LW (2015) Metabolism and metabolites of polychlorinated biphenyls. Crit Rev Toxicol 45:245–272. https://doi.org/10.3109/10408444.2014.999365

Haraguchi K, Kato Y, Koga N, Degawa M (2004) Metabolism of polychlorinated biphenyls by gunn rats: identification and serum retention of catechol metabolites. Chem Res Toxicol 17:1684–1691. https://doi.org/10.1021/tx0498096

Herkert NJ, Jahnke JC, Hornbuckle KC (2018) Emissions of tetrachlorobiphenyls (PCBs 47, 51, and 68) from polymer resin on kitchen cabinets as a non-aroclor source to residential air. Environ Sci Technol 52:5154–5160. https://doi.org/10.1021/acs.est.8b00966

Holloway GA, Parisot JP, Novello PM, Watson KG, Armstrong T, Thompson RC, Street IP, Baell JB (2010) Discovery of novel and potent benzhydryl-tropane trypanocides highly selective for *Trypanosoma cruzi*. Bioorg Med Chem Lett 20:1816–1818. https://doi.org/10.1016/j.bmcl.2010.02.022

Hu D, Hornbuckle K (2010) Inadvertent polychlorinated biphenyls in commercial paint pigments. Environ Sci Technol 44:2822–2827

IARC, ed. (2016). Polychlorinated biphenyls and polybrominated biphenyls. Lyon, France. https://publications.iarc.fr/131

Joshi SN, Vyas SM, Duffel MW, Parkin S, Lehmler H-J (2011a) Synthesis of sterically hindered polychlorinated biphenyl derivatives. Synthesis-Stuttgart 7:1045–1054. https://doi.org/10.1055/s-0030-1258454

Joshi SN, Vyas SM, Wu H, Duffel MW, Parkin S, Lehmler HJ (2011b) Regioselective iodination of chlorinated aromatic compounds using silver salts. Tetrahedron 67:7461–7469. https://doi.org/10.1016/j.tet.2011.07.064

Kania-Korwel I, Lehmler H-J (2016) Chiral polychlorinated biphenyls: absorption, metabolism and excretion—a review. Environ Sci Pollut Res 23:2042–2057. https://doi.org/10.1007/s11356-015-4150-2

Kania-Korwel I, Parkin S, Robertson LW, Lehmler H-J (2004) Synthesis of polychlorinated biphenyls and their metabolites with a modified Suzuki-coupling. Chemosphere 56:735–744. https://doi.org/10.1016/j.chemosphere.2004.04.035

Kania-Korwel I, Lukasiewicz T, Barnhart CD, Stamou M, Chung H, Kelly KM, Bandiera S, Lein PJ, Lehmler H-J (2017) Congener-specific disposition of chiral polychlorinated biphenyls in lactating mice and their offspring: implications for PCB developmental neurotoxicity. Toxicol Sci 158:101–115. https://doi.org/10.1093/toxsci/kfx071

Keegstra MA, Peters THA, Brandsma L (1992) Copper(I) halide catalysed synthesis of alkyl aryl and alkyl heteroaryl ethers. Tetrahedron 49:3633–3652. https://doi.org/10.1016/S0040-4020(01)88501-X

Leas DA, Dong Y, Vennerstrom JL, Stack DE (2017) One-pot, metal-free conversion of anilines to aryl bromides and iodides. Org Lett 19:2518–2521. https://doi.org/10.1021/acs.orglett.7b00771

Lehmler H-J, Robertson LW (2001a) Synthesis of hydroxylated PCB metabolites with the Suzuki-coupling. Chemsphere 45:1119–1127. https://doi.org/10.1016/S0045-6535(01)00052-2

Lehmler H-J, Robertson LW (2001b) Synthesis of polychlorinated biphenyls (PCBs) using the Suzuki-coupling. Chemosphere 45:137–143. https://doi.org/10.1016/S0045-6535(00)00546-4

Lehmler H-J, Parkin S, Robertson LW (2002) The three-dimensional structure of 3,3′,5′-trichloro-4-methoxybiphenyl, a "coplanar" polychlorinated biphenyl (PCB) derivative. Chemosphere 46:485–488. https://doi.org/10.1016/S0045-6535(01)00177-1

Lehmler H-J, Wu H, Parkin S (2013) 5,5′-Dichloro-2,2′-dimethoxybiphenyl. Acta Cryst E69:o650. https://doi.org/10.1107/S160053681300826X

Li X, Parkin S, Lehmler H-J (2014) 2,4-Di-chloro-1-iodo-6-nitro-benzene. Acta Cryst E70:o607. https://doi.org/10.1107/S1600536814008733

Li X, Holland EB, Feng W, Zheng J, Dong Y, Pessah IN, Duffel MW, Robertson LW, Lehmler H-J (2018) Authentication of synthetic environmental contaminants and their (bio)transformation products in toxicology: polychlorinated biphenyls as an example. Environ Sci Pollut Res 25:16508–16521. https://doi.org/10.1007/s11356-017-1162-0

Liu A-H, He L-N, Hua F, Yang Z-Z, Huang C-B, Yu B, Li B (2011) In situ acidic carbon dioxide/ethanol system for selective oxybromination of aromatic ethers catalyzed by copper chloride. Adv Synth Catal 353:3187–3195. https://doi.org/10.1002/adsc.201100467

Lu Z, Kania-Korwel I, Lehmler H-J, Wong CS (2013) Stereoselective formation of mono- and dihydroxylated polychlorinated biphenyls by rat cytochrome P450 2B1. Environ Sci Technol 47:12184–12192. https://doi.org/10.1021/es402838f

Maraš N, Polanc S, Kočevar M (2008) Microwave-assisted methylation of phenols with tetramethylammonium chloride in the presence of K_2CO_3 or Cs_2CO_3. Tetrahedron 64:11618–11624. https://doi.org/10.1016/j.tet.2008.10.024

McLean MR, Bauer U, Amaro AR, Robertson LW (1996) Identification of catechol and hydroquinone metabolites of 4-monochlorobiphenyl. Chem Res Toxicol 9:158–164. https://doi.org/10.1021/tx950083a

Miyaji R, Asano K, Matsubara S (2017) Induction of axial chirality in 8-arylquinolines through halogenation reactions using bifunctional organocatalysts. Chem Eur J 23:9996–10000. https://doi.org/10.1002/chem.201701707

Mostafa MAB, Bowley RM, Racys DT, Henry MC, Sutherland A (2017) Iron(III)-catalyzed chlorination of activated arenes. J Organomet Chem 82:7529–7537. https://doi.org/10.1021/acs.joc.7b01225

Murphy JM, Liao X, Hartwig JF (2007) Meta halogenation of 1,3-disubstituted arenes via iridium-catalyzed arene borylation. J Am Chem Soc 129:15434–15435

Narender N, Naresh M, Arun Kumar M, Mahender Reddy M, Swamy P, Nanubolu J (2013) Fast and efficient bromination of aromatic compounds with ammonium bromide and oxone. Synthesis 45:1497–1504. https://doi.org/10.1055/s-0033-1338431

Podgorsek A, Iskra J (2010) Conversion of aryl iodides into aryliodine(III) dichlorides by an oxidative halogenation strategy using 30% aqueous hydrogen peroxide in fluorinated alcohol. Molecules 15:2857–2871. https://doi.org/10.3390/molecules15042857

Pramanick PK, Hou Z-L, Yao B (2017) Mechanistic study on iodine-catalyzed aromatic bromination of aryl ethers by *N*-bromosuccinimide. Tetrahedron 73:7105–7114. https://doi.org/10.1016/j.tet.2017.10.073

Quibell JM, Perry GJP, Cannas DM, Larrosa I (2018) Transition-metal-free decarboxylative bromination of aromatic carboxylic acids. Chem Sci 9:3860–3865. https://doi.org/10.1039/c8sc01016a

Ren Y-L, Wang B, Tian X-Z, Zhao S, Wang J (2015) Aerobic oxidative bromination of arenes using an ionic liquid as both the catalyst and the solvent. Tetrahedron Lett 56:6452–6455. https://doi.org/10.1016/j.tetlet.2015.09.150

Saktrakulkla P, Dhakal RC, Lehmler HJ, Hornbuckle KC (2019) A semi-target analytical method for quantification of OH-PCBs in environmental samples. Environ Sci Pollut Res:1–13. https://doi.org/10.1007/s11356-019-05775-x

Shaikh NS, Parkin S, Lehmler H-J (2006) The Ullmann coupling reaction: a new approach to tetraarylstannanes. Organometallics 25:4207–4214. https://doi.org/10.1021/om060456a

Shaikh NS, Parkin S, Luthe G, Lehmler H-J (2008) The three-dimensional structure of 3,3′,4,4′-tetrachlorobiphenyl, a dioxin-like polychlorinated biphenyl (PCB). Chemosphere 70:1694–1698. https://doi.org/10.1016/j.chemosphere.2007.07.017

Singh VP, Yan J, Poon JF, Gates PJ, Butcher RJ, Engman L (2017) Chain-breaking phenolic 2,3-dihydrobenzo[*b*]selenophene antioxidants: proximity effects and regeneration studies. Chem Eur J 23:15080–15088. https://doi.org/10.1002/chem.201702350

Song Y, Parkin S, Lehmler H-J (2007) 4-Bromo-2-chloro-1-methoxybenzene. Acta Cryst E63:o2091–o2092. https://doi.org/10.1107/s1600536807013372

Song Y, Buettner GR, Parkin S, Wagner BA, Robertson L, Lehmler H-J (2008) Chlorination increases the persistence of semiquinone free radicals derived from polychlorinated biphenyl hydroquinones and quinones. J Organomet Chem 73:8296–8304. https://doi.org/10.1021/jo801397g

Song Y, Parkin S, Lehmler H-J (2010) 1-Bromo-2-chloro-4,5-dimethoxybenzene. Acta Cryst E66:o813. https://doi.org/10.1107/S1600536810008445

Song Y, Ambati J, Parkin S, Rankin SE, Robertson LW, Lehmler H-J (2011) Crystal structure and density functional theory studies of toxic quinone metabolites of polychlorinated biphenyls. Chemosphere 85:386–392. https://doi.org/10.1016/j.chemosphere.2011.07.004

Srinivasan A, Lehmler H-J, Robertson LW, Ludewig G (2001) Production of DNA strand breaks in vitro and reactive oxygen species in vitro and in HL-60 cells by PCB metabolites. Toxicol Sci 60:92–102. https://doi.org/10.1093/toxsci/60.1.92

Su J, Chen Q, Lu L, Ma Y, Auyoung GHL, Hua R (2018) Base-promoted nucleophilic fluoroarenes substitution of C-F bonds. Tetrahedron 74:303–307. https://doi.org/10.1016/j.tet.2017.11.067

Tajik H, Mohammadpoor-Baltork I, Albadi J (2007) Bromination of some aromatic compounds with potassium bromide in the presence of benzyltriphenylphosphonium peroxodisulfate. Synth Commun 37:323–328. https://doi.org/10.1080/00397910601033906

Tan T-F, Zhang J-X, Meng J-B (2005) An asymmetric biphenyl compound: 3-chloro-4,4′-dimethoxybiphenyl. Acta Cryst E61:o1210–o1211. https://doi.org/10.1107/s1600536805009323

Tang RJ, Milcent T, Crousse B (2018) Regioselective halogenation of arenes and heterocycles in hexafluoroisopropanol. J Organomet Chem 83:930–938. https://doi.org/10.1021/acs.joc.7b02920

Tay NES, Nicewicz DA (2017) Cation radical accelerated nucleophilic aromatic substitution via organic photoredox catalysis. J Am Chem Soc 139:16100–16104. https://doi.org/10.1021/jacs.7b10076

Tehrani R, Lyv MM, Van Aken B (2014) Transformation of hydroxylated derivatives of 2,5-dichlorobiphenyl and 2,4,6-trichlorobiphenyl by *Burkholderia xenovorans* LB400. Environ Sci Pollut Res 21:6346–6353. https://doi.org/10.1007/s11356-013-1629-6

Telu S, Parkin S, Robertson LW, Lehmler H-J (2010) Improved syntheses of non-dioxin-like polychlorinated biphenyls (PCBs) and some of their sulfur-containing metabolites. Environ Int 36:828–834. https://doi.org/10.1016/j.envint.2009.01.013

Thongsornkleeb C, Maibunkaew T, Tummatorn J, Bunrit A, Ruchirawat S (2014) Practical and metal-free electrophilic aromatic halogenation by interhalogen compounds generated in situ from N-halosuccinimide and catalytic TMSCl. Synlett 25:1769–1775. https://doi.org/10.1055/s-0034-1378225

Tilve RD, Kanetkar VR (2005) Regioselective iodination of activated arenes using phenyl trimethylammonium dichloroiodate in ionic liquid under microwave irradiation. Synth Commun 35:1313–1318. https://doi.org/10.1081/scc-200057244

Vajpayee V, Moon ME, Lee S, Ravikumar S, Kim H, Ahn B, Choi S, Hong SH, Chi K-W (2013) Halogenation and DNA cleavage via thermally stable arenediazonium camphorsulfonate salts. Tetrahedron 69:3511–3517. https://doi.org/10.1016/j.tet.2013.02.016

Vyas SM, Parkin S, Robertson LW, Lehmler H-J (2006a) 4-Chloro-2′,3′-dimethoxybiphenyl. Acta Cryst E62:o3639–o3640. https://doi.org/10.1107/s1600536806028923

Vyas SM, Parkin S, Robertson LW, Lehmler H-J (2006b) 2,5-Dichloro-4′-methoxybiphenyl. Acta Cryst E62:o4162–o4163. https://doi.org/10.1107/s1600536806033319

Waller SC, He YA, Harlow GR, He YQ, Mash EA, Halpert JR (1999) 2,2′,3,3′,6,6′-Hexachlorobiphenyl hydroxylation by active site mutants of cytochrome P450 2B1 and 2B11. Chem Res Toxicol 12:690–699. https://doi.org/10.1021/tx990030j

Wang T, Rabe P, Citron CA, Dickschat JS (2013) Halogenated volatiles from the fungus *Geniculosporium* and the actinomycete *Streptomyces chartreusis*. Beilstein J Org Chem 9:2767–2777. https://doi.org/10.3762/bjoc.9.311

Wang DY, Yang ZK, Wang C, Zhang A, Uchiyama M (2018) From anilines to aryl ethers: a facile, efficient, and versatile synthetic method employing mild conditions. Angew Chem Int Ed 57:3641–3645. https://doi.org/10.1002/anie.201712618

Wu H, Hynes J (2010) Copper-catalyzed chlorination of functionalized arylboronic acids. Org Lett 12:1192–1195. https://doi.org/10.1021/ol9029337

Xin H, Yang S, An B, An Z (2017) Selective water-based oxychlorination of phenol with hydrogen peroxide catalyzed by manganous sulfate. RSC Adv 7:13467–13472. https://doi.org/10.1039/c7ra00319f

Xiong X, Tan F, Yeung YY (2017) Zwitterionic-salt-catalyzed site-selective monobromination of arenes. Org Lett 19:4243–4246. https://doi.org/10.1021/acs.orglett.7b01899

Zhai G, Lehmler H-J, Schnoor JL (2011) New hydroxylated metabolites of 4-monochlorobiphenyl in whole poplar plants. Chem Cent J 55: 87. https://doi.org/10.1186/1752-153X-5-87

Zhang L, Hu X (2017) Room temperature C(sp^2)-H oxidative chlorination via photoredox catalysis. Chem Sci 8:7009–7013. https://doi.org/10.1039/c7sc03010j

Zhu Y, Mapuskar KA, Marek RF, Xu W, Lehmler HJ, Robertson LW, Hornbuckle KC, Spitz DR, Aykin-Burns N (2013) A new player in environmentally induced oxidative stress: polychlorinated biphenyl congener, 3,3′-dichlorobiphenyl (PCB11). Toxicol Sci 136:39–50. https://doi.org/10.1093/toxsci/kft186

Zilberman J (2003) One-step preparation of some 3-substituted anisoles. Org Process Res Dev 7:303–305. https://doi.org/10.1021/op020058t