Synthesis of Sterically Hindered Polychlorinated Biphenyl Derivatives

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Abstract: A series of sterically hindered (methoxylated) polychlorinated biphenyl derivatives were synthesized using the Suzuki and the Ullmann coupling reactions. The Suzuki coupling with $Pd(dba)_2$/2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (DPDB) gave better yields (65–98%) compared to the classic Ullmann coupling reaction (20–38%). Despite the reactive catalyst system, no significant coupling with aromatic chlorine substituents was observed. Crystal structure analysis of four PCB derivatives revealed solid state dihedral angles ranging from 69.7° to 81.0°, which indicates that these highly *ortho*-substituted PCB derivatives have some conformational flexibility.

Key words: biaryls, palladium, Suzuki cross-coupling, Ullmann cross-coupling, dihedral angle

Polychlorinated biphenyls (PCBs) are a group of ubiquitous environmental contaminants that were manufactured until the 1970s in the United States and are still in use in enclosed applications, such as transformers and capacitors.[1,2] Recent studies demonstrate that many PCB congeners are also formed inadvertently as by-products of industrial processes and can be found as by-products in paints.[3] Laboratory and epidemiologic studies have implicated PCBs in adverse human health effects such as cardiovascular disease, obesity, and cancer. One particular health concern are cognitive deficits in laboratory animals and children that have been linked to in utero exposure to PCB congeners with multiple *ortho*-chlorine substituents[4,5] and may be mediated by the Ryanodine receptor.[6–9] Structure-activity relationship studies demonstrate that sterically hindered PCB congeners with three or four *ortho*-chlorine substituents, specifically congeners with a 2,3,6-trichloro substitution pattern in one phenyl ring, are potent sensitizers of the Ryanodine receptor.[9]

One major obstacle towards investigating the developmental neurotoxicity of PCBs is the unavailability of pure PCB congeners and their respective metabolites, both as analytical standards for studies on disposition and in vitro and in vivo toxicity. Unsymmetrical PCB derivatives with multiple *ortho*-chlorine substituents can be synthesized using the Ullmann[10,11] or the Cadogan diaryl coupling reaction.[12] These approaches have significant drawbacks, including poor selectivity, low yields, and the formation of toxic by-products.[12–15] Lower chlorinated PCB derivatives with up to two *ortho*-chlorine substituents can be synthesized with good selectivity and in high yields using the Suzuki coupling of chlorinated iodo- or bromobenzenes with arylboronic acids.[11,16–19] Although sterically hindered Suzuki coupling reactions are well established for the preparation of biaryls with multiple *ortho*-methyl groups,[20–23] the available coupling procedures have not been applied to the synthesis of PCB derivatives with three or four *ortho*-chlorine substituents, partly because the catalyst systems employed in these studies will also catalyze the coupling with chloro substituents.

Here we explore strategies for the synthesis of suitable chlorinated precursors of methoxylated and hydroxylated PCB congeners containing a 2,3,6-trichloro substitution pattern in one phenyl ring and their coupling with chlorinated arylboronic acids using $Pd(dba)_2$/dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (DPDB) as an improved approach to multi- *ortho*-substituted PCB congeners, such as PCB 91 (2,2′,3,4′,6-pentachlorobiphenyl), PCB 95 (2,2′,3,5′,6-pentachlorobiphenyl), PCB 132 (2,2′,3,3′,4′,6-hexachlorobiphenyl) and PCB 149 (2,2′,3,4′,5′,6-hexachlorobiphenyl) derivatives. In addition, the molecular structures of selected PCB derivatives in the solid state were determined in order to aid in our understanding of their three-dimensional structure and, ultimately, their toxicity.

Iodinated chloroanisoles for the preparation of derivatives of environmentally relevant, neurotoxic PCB congeners are not readily available. Multistep syntheses of several suitable precursors, including 2,3,5-trichloro-4-iodoanisole (**1**), 2,4,5-trichloro-3-iodoanisole (**2**) and 3,5,6-trichloro-4-iodoveratrole (**3**) (Figure 1), have been reported previously.[10] In particular, the synthesis of **1** in large scale is challenging because key synthesis steps have poor regioselectivity and/or low yields. The following section briefly describes the strategies employed in this study for the synthesis of **1** and the corresponding bromide **4**.

4-Amino-3,5-dichloroanisole (**5a**) is a key intermediate for the synthesis of **1** (Scheme 1) and has been used by Waller et al. for the synthesis of PCB 136 (2,2′,3,3′,6,6′-hexachlorobiphenyl) metabolites.[10] Because of the poor yield of the approach employed by Waller et al., we initially investigated the following two approaches for the synthesis of **5a**: The first approach is based on the work of Kenny and co-workers, who synthesized **5a** in two steps

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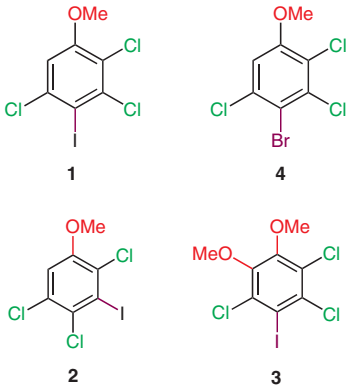
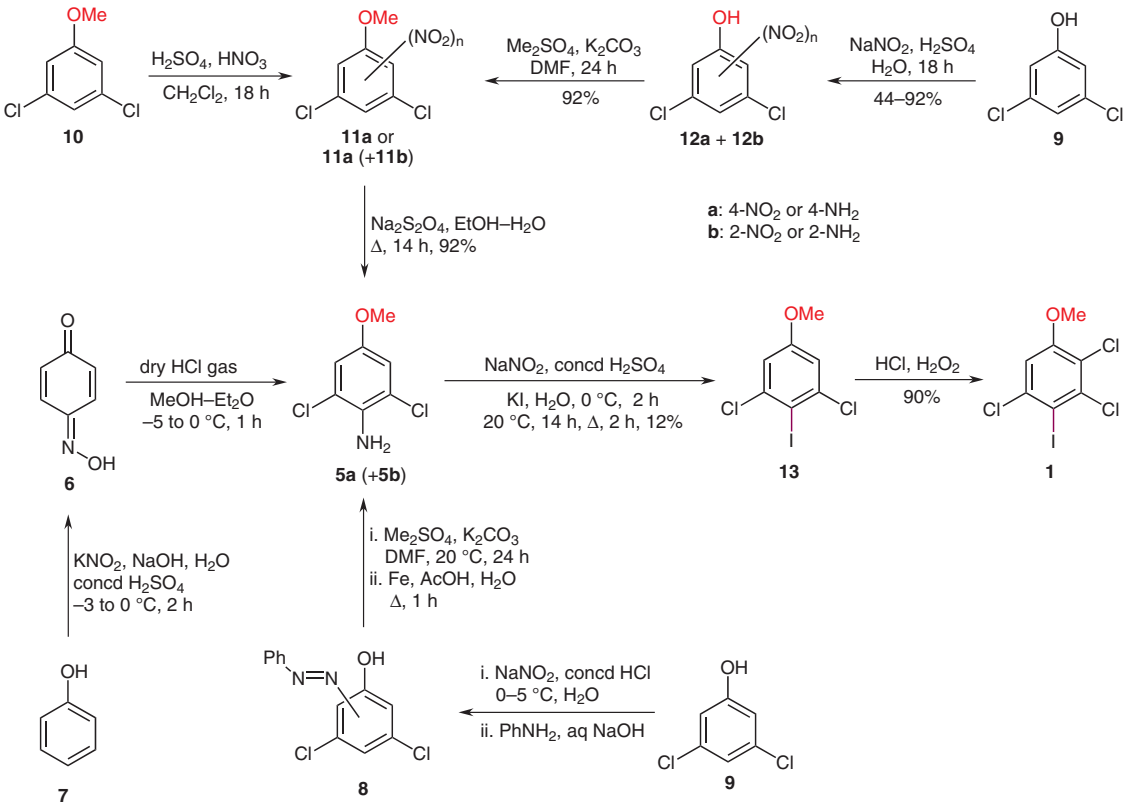


Figure 1 Structure of target intermediates 2,3,5-trichloro-4-iodoanisole (**1**), 2,4,5-trichloro-3-iodoanisole (**2**), 3,5,6-trichloro-4-iodoveratrole (**3**), and 4-bromo-2,3,5-trichloroanisole (**4**)

via benzoquinone monoxime (**6**) from phenol (**7**).[24] In our hands, the reaction of benzoquinone monoxime (**6**) with anhydrous HCl–MeOH–Et_2O yielded **5a** and 6-amino-5-chloro-1,3-dimethoxybenzene in a 1:19 ratio, as determined by ^1H NMR spectroscopy. Similarly, **5a** was only a minor product when benzoquinone monoxime **6** was reacted with trimethylsilyl chloride–MeOH instead of anhydrous HCl. The second approach investigated the synthesis of **5a** via the regioselective formation of an azo compound, such as **8**, from the corresponding halogenated phenol.[25,26] In contrast to the literature report, the formation of **8** from 3,5-dichlorophenol (**9**) was not regioselective and, based on TLC analysis, yielded approximately a 1:1 mixture of both possible regioisomers. Consequently, the methylation of this mixture with dimethyl sulfate followed by reduction with Fe/AcOH–H_2O yielded a mixture of 2- (**5b**) and 4-amino-3,5-dichloroanisole (**5a**). Overall, neither approach offers a more straightforward access to **5a** compared to published procedures.[10]

In subsequent attempts we employed strategies similar to the approach described by Waller et al. to synthesize **5a** (Scheme 1).[10] In their approach, the nitration of 3,5-dichloroanisole (**10**) resulted in a mixture of 3,5-dichloro-4- and 3,5-dichloro-2-nitroanisole (**11a** + **11b**), with the undesired 3,5-dichloro-2-nitroanisole (**11b**) being the major isomer.[10] Since the separation of **11a** from **11b** is difficult, Waller et al. reduced the mixture with $Na_2S_2O_4$ to 4- and 2-amino-3,5-dichloroanisole (**5a** and **5b**) and separated **5a** from the undesired by-product **5b** by column chromatography. In our hands, the nitration of anisole **10** to **11** was typically incomplete. Furthermore, we were unable to separate **5a** from **5b** on a preparative scale. Since Hartz and co-workers have successfully used the direct nitration of 3,5-dichlorophenol (**9**) followed by fractional crystallization to prepare **12a**,[27] we ultimately synthesized **5a** via the nitration of 3,5-dichlorophenol (**9**) (Scheme 1). Although we were unable to separate **12a** from **12b** by fractional crystallization, we successfully separated the two regioisomers by column chromatography in a 1:1.6 ratio of **12a**/**12b**. The structure of the desired 3,5-dichloro-4-nitrophenol (**12a**) was verified by X-ray crystal structure



Scheme 1 Syntheses of 4-amino-3,5-dichloroanisole (**5a**), a possible key intermediate for the preparation of 2,3,5-trichloro-4-iodoanisole (**1**). Pure **11a** and **5a** were synthesized from **12a**, which was synthesized from **9**, followed by separation of **12a** and **12b** by column chromatography (see text for details).

analysis (Figure 2). Subsequent methylation of **12a** followed by reduction of **11a** with $Na_2S_2O_4$ provided access to **5a**. 2,3,5-Trichloro-4-iodoanisole (**1**) was synthesized from **5a** as outlined by Waller et al. using a Sandmeyer reaction and chlorination with HCl–H_2O_2.

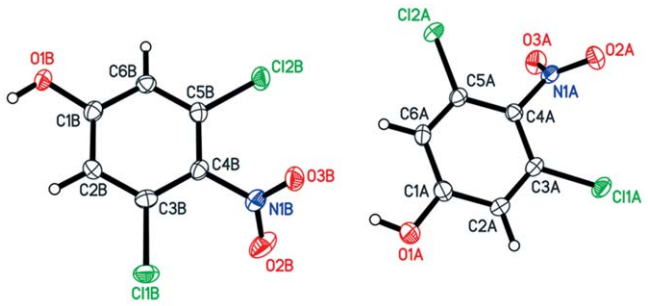
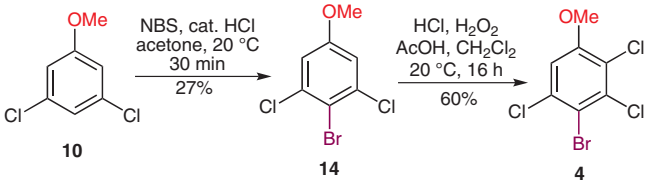


Figure 2 Molecular structure of 3,5-dichloro-4-nitrophenol (**12a**). Displacement ellipsoids are drawn at the 50% probability level.

The halogenation of 3,5-dichloroanisole (**10**) in the 4-position offers a direct approach to benzene derivatives with a 3,5-dichloro-4-methoxy substitution pattern, such as **14**. We were able to synthesize 4-bromo-3,5-dichloroanisole (**14**) from **10** by bromination with NBS/HCl (Scheme 2).[28] Although this reaction results in the formation of small quantities of the *ortho*-bromination product (as determined by GC-MS analysis), pure **14** could be obtained in 27% yield by recrystallization from methanol. Subsequent chlorination with H_2O_2–HCl yielded **4**, the brominated analogue of **1**. Although the iodination of 2,5-dichlorophenol with $AgSO_4/I_2$ in dichloromethane appears to occur preferentially in the 4-position,[29] iodination of **9** or **10** using the same conditions yielded a mixture of the corresponding 2-iodo-, 4-iodo-, and 2,4-diiodo products. Similar to the corresponding nitrophenols or anisoles, the separation of the iodinated products was challenging.



Scheme 2 Synthesis of 4-bromo-2,3,5-trichloroanisole (**4**) by bromination of 3,5-dichloroanisole (**10**) with NBS/HCl[28] followed by chlorination of **14** with HCl–H_2O_2.[10]

Since bromides are known to be less reactive in Suzuki coupling reactions compared to iodides,[30] initial experiments to utilize **4** for the synthesis of PCB derivatives focused on its conversion into the corresponding boronic acids or pinacolboronate esters. Attempts to convert **4** into the corresponding boronic acid, using *n*-BuLi at –78 °C followed by quenching with triisopropyl borate, or the pinacolboronate ester, using bispinacolatodiboron/PdOAc/KOAc in DMSO at 100 °C, were not successful. Synthesis of **1** from **4** via the corresponding aniline, followed by Sandmeyer reaction looked like a promising approach; however, conversion of **4** into the corresponding aniline using LHMDS as ammonia equivalent under palladium-catalyzed Buchwald amination conditions (LHMDS, DPDB, anhyd THF, 65 °C, 15–18 h) was also not successful. This was not entirely surprising because a similar amination reaction with **14** also did not give the expected aniline.[31]

A variety of catalysts and ligands have been employed for the synthesis of sterically hindered biaryls.[20–23] We investigated the preparation of PCB derivatives using $Pd(dba)_2$ and the commercially available ligand DPDB as a well-established catalyst system. Table 1 shows a comparison of the yields of PCB derivatives synthesized from **1**, **2**, **3**, or **4** using either the Suzuki [$Pd(dba)_2$, DPDB, K_3PO_4, toluene, 100 °C, 24 h] or Ullmann coupling reaction (230 °C, 7 d, Cu bronze). The yields of the Suzuki coupling reaction (65–98%) with iodides **1**, **2**, and **3** were superior to the yields of the corresponding Ullmann coupling reaction (20–38%). Better yields were typically obtained when fresh arylboronic acids were used as starting materials in the Suzuki coupling reaction. Although the $Pd(dba)_2$/DPDB catalyst system allows the Suzuki coupling of chlorinated benzenes,[22] the difference in the reactivity of the iodo versus chloro groups allowed the selective formation of the desired coupling products **15**–**18**. The lower yields of the Ullmann coupling reaction were, in part, due to homo-coupling of the respective iodo starting materials.

Bromide **4**, which is less reactive compared to the corresponding iodide **1**,[30] reacted in the Suzuki coupling according to GC-MS analysis. However, the reaction was not clean and it was impossible to obtain the coupled product (e.g., **16b**) in pure form, even after repeated chromatographic purification followed by crystallization. The yields of the Ullmann coupling reactions with bromide **4** were also inferior to its iodo counterpart **1** (Table 1). Overall, Suzuki coupling with iodides **1**, **2**, and **3** offers a comparatively straightforward approach to many parent PCBs and PCB derivatives with multiple *ortho*-chlorine substituents. However, the synthesis of some PCB derivatives, such as 2,2′,3,4′,5′,6-hexachloro-5-methoxybiphenyl (**17d**), via the Ullmann coupling reaction may be preferable due to the unavailability of the corresponding boronic acids from commercial sources (Scheme 3).

Since PCB congeners with multiple *ortho*-chlorine substituents can be neurotoxic in vitro[9] and in vivo,[32] milligram quantities of the hydroxylated metabolites of these PCB congeners are needed to assess their role in the developmental neurotoxicity of PCBs. While the demethylation of lower chlorinated methoxylated PCBs with BBr_3 is typically straightforward,[16,33] this approach was cumbersome in the cases of **16a–c** and **17a–d** and required a large excess of BBr_3 and long reaction times (Scheme 3). Although we were able to obtain the hydroxylated PCBs **19a–c** and **20a–d** in a quantity and purity sufficient for future biological studies, further work is needed to optimize

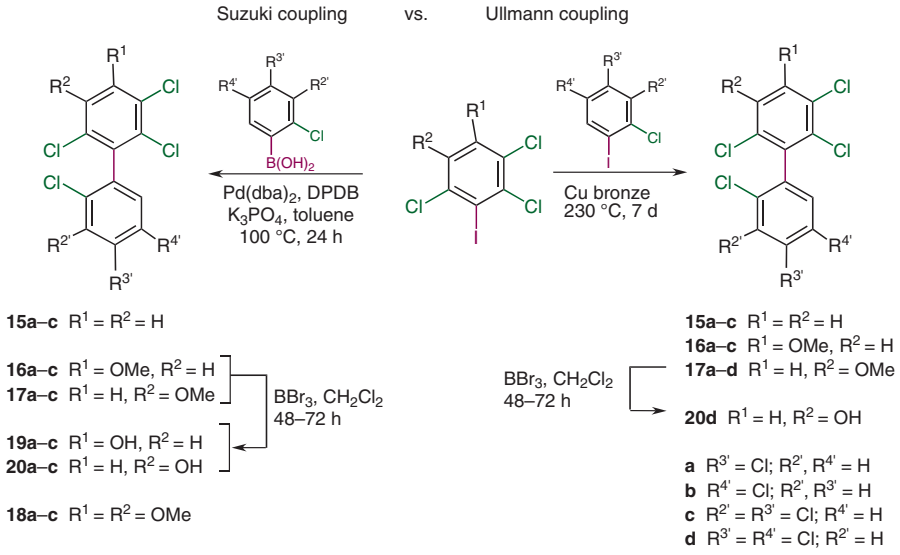
Table 1 Yields (%) of PCB Derivatives Synthesized Using the Suzuki and Ullmann Coupling Reactions[a]

PCB Derivative	**15** (R^1 = R^2 = H)		**16** (R^1 = OMe, R^2 = H)		**17** (R^1 = H, R^2 = OMe)		**18** (R^1 = R^2 = OMe)	
	Suzuki	Ullmann[b]	Suzuki	Ullmann[b]	Suzuki	Ullmann[b]	Suzuki	Ullmann[c]
a	76	27	93	28 (14)	69	38	71	–
b	75	29	98	20 (10)	65	38	71	–
c	78	26	91	27 (5)	50	34	66	–

[a] Values in parentheses are the yields obtained with the corresponding bromide **4**.
[b] Gas chromatographic yields.
[c] The Ullmann coupling reaction yielded a black material and no traces of the starting material were observed by gas chromatographic analysis.

this demethylation reaction, for example, by using demethylation reagents such as HBr.[10]

The three-dimensional structure of a PCB is largely determined by the number of *ortho* chlorine substituents and, thus, the dihedral angle between the phenyl rings of the biphenyl moiety.[34] The dihedral angle is an important factor in the interaction of individual PCB congeners or their metabolites with cellular target molecules. For example, PCBs and their hydroxylated metabolites with three or



Scheme 3 Synthesis of PCBs 91, 95, and 132 (**15a–c**) and the corresponding methoxylated PCB derivatives **16a–c**, **17a–d**, and **18a–c** using the Suzuki and the Ullmann coupling reactions. The monomethoxylated PCBs **16a–c** and **17a–d** were demethylated using an excess of BBr_3 to yield the corresponding hydroxylated PCB derivatives **19a–c** and **20a–d**. DPDB = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

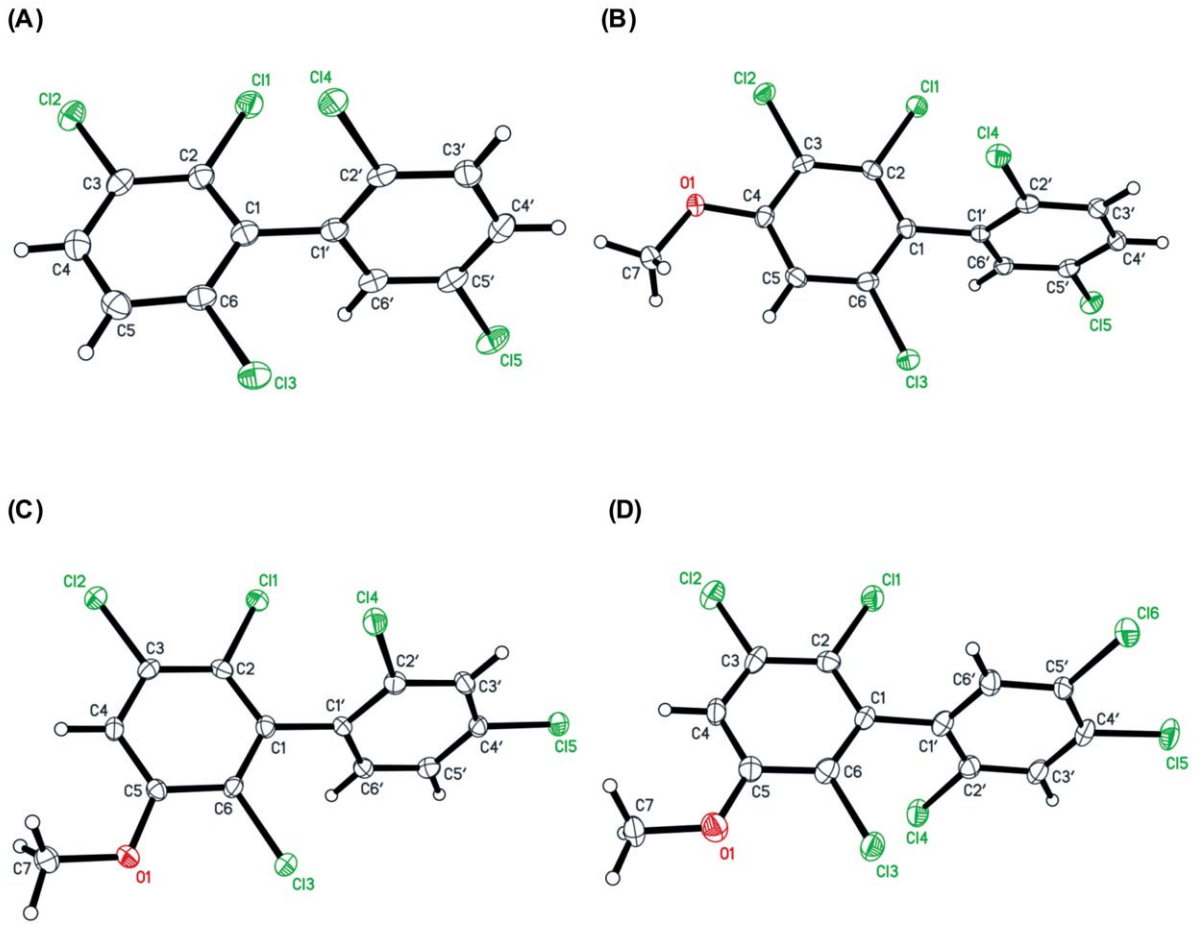


Figure 3 Molecular structure of (**A**) 2,2′,3,5′,6-pentachlorobiphenyl (**15b**), (**B**) 2,2′,3,5′,6-pentachloro-4-methoxybiphenyl (**16b**), (**C**) 2,2′,3,4′,6-pentachloro-5-methoxybiphenyl (**17a**), and (**D**) 2,2′,3,4′,5′,6-hexachloro-5-methoxybiphenyl (**17d**) showing the atom labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

four *ortho*-chlorine substituents are potent sensitizers of the Ryanodine receptor,[9] which is thought to play an important role in the developmental toxicity of PCBs. Here we report the crystal structure of PCB 95 (**15b**) and several structurally related methoxylated PCBs with three *ortho*-chlorine substituents **16b**, **17a**, and **17d** to unambiguously establish the substitution pattern and add to the number of crystal structures available for application in studies on quantitative structure-activity relationships (Figure 3).

PCB 95 (**15b**) crystallized in the monoclinic space group C2/c, with $a = 13.7060(3)$, $b = 11.4687(2)$, $c = 17.2180(3)$ Å, and $\beta = 113.313(1)°$. The two methoxylated pentachlorobiphenyls **16b** and **17a** were also monoclinic ($P2_1/n$ and $P2_1/c$, respectively). Similarly, two structurally related biphenyls with three *ortho* chlorine substituents, 2,2′,3,3′,6-pentachlorobiphenyl (PCB 84) and 2,2′,4,4′,5′,6-hexachloro-3-methoxybiphenyl, also crystallized in the monoclinic space group $P2_1/c$.[35,36] The dimensions of the unit cell were $a = 9.0848(2)$, $b = 12.6058(2)$, $c = 12.3064(3)$ Å, and $\beta = 92.0452(9)°$ for **16b** and $a = 7.1653(2)$, $b = 13.4435(3)$, $c = 14.4816(4)$ Å, and $\beta = 100.8733(9)°$ for **17a**. In both structures, the MeO containing rings of inversion related molecules make π-stacked pairs, with interplanar separations of 3.564(3) Å for **16b** and 3.529(3) Å for **17a**. In contrast to the pentachlorobiphenyl derivatives, the methoxylated hexachlorobiphenyl **17d** crystallized in the orthorhombic space group Pbca, with $a = 6.7926(1)$, $b = 17.6314(4)$, $c = 24.7070(6)$ Å.

The solid state dihedral angle of the four PCB derivatives shown in Figure 3 ranged from 69.65(9)° for **17a** to 80.96(7)° for **16b**. The other two PCB derivatives showed intermediate dihedral angles of 75.30(7)° and 78.38(12)° for **15b** and **17d**, respectively. The published dihedral angle of PCB 84 and 2,2′,4,4′,5′,6-hexachloro-3-methoxybiphenyl are 81.5° and 82.7°, respectively,[35,36] which is slightly larger than the dihedral angle of the PCB derivatives shown in Figure 3. In contrast, the calculated dihedral angle of PCBs with three *ortho*-chlorine substituents in aqueous solution is 90°.[35]

In comparison to PCBs with three *ortho*-chlorine substituents, the dihedral angles of PCB derivatives with two *ortho*-chlorine substituents are typically smaller and range from 58.3° to 75.3°,[37–40] whereas the dihedral angles of PCB derivatives with four *ortho*-substituents are larger and range from 83.92° to 87.3°.[41–43] Overall, the fairly large range of solid state dihedral angles is a result of crys-

tal packing effects that allows even PCB derivatives with three or four *ortho*-chlorine substituents to adopt an energetically less favorable conformation to minimize the lattice energy. As a consequence, PCB derivatives with multiple *ortho*-substituents have some conformational flexibility that can be important in their interactions with cellular target molecules, such as the Ryanodine receptor.

In summary, the Suzuki coupling reaction of chlorinated iodobenzenes and iodoanisoles with chlorinated arylboronic acids using $Pd(dba)_2$/DPDB allows straightforward access to individual PCB congeners and their methoxylated analogues, especially when compared to the classic Ullmann coupling reaction. The resulting methoxylated PCB derivatives can be converted into the corresponding hydroxylated compounds, thus providing access to putative hydroxylated PCB metabolites for toxicological studies. However, the synthesis of some key intermediates, such as **5a** or **13**, still remains a challenge due to the poor selectivity of the nitration and iodination reactions used in their synthesis. Compared to the calculated solution dihedral angle of 90°, the broad range of solid state dihedral angles of 69.7° to 81.0° suggests that even PCB derivatives with multiple *ortho*-substituents have considerable conformational flexibility.

Silica gel for flash chromatography (40–64 μm) was purchased from Sorbent Technologies (Atlanta, GA, USA). The NMR spectra were recorded on a Bruker Avance-300 or a Bruker Avance DRX-400 spectrometer in the University of Iowa Central NMR Research Facility (Iowa City, IA, USA). TMS was used as an internal standard. Combustion analyses were performed by Atlantic Microlab Inc. (Atlanta, GA, USA). HRMS were recorded by the High Resolution Mass Spectrometry Facility of the University of California Riverside (Riverside, CA, USA). Melting points were measured on a Mel-Temp melting point apparatus and are uncorrected. If no solvent is mentioned, melting points of the product after column chromatographic purification are reported. The purity of all PCB congeners and PCB derivatives was determined with an Agilent 6859 Gas Chromatograph (Agilent Technologies, CA, USA) equipped with flame ionization detector (FID) and a HP-1 (Methyl Silicone Gum) column (Hewlett Packard, PA, USA) and calculated based on the relative peak area. The following conditions were used for the gas chromatographic analysis: injector: 250 °C, detector (FID): 300 °C, starting temperature: 50 °C, final temperature: 250 °C, heating rate: 10 °C/min. In addition, GC-MS analysis of all compounds was performed in the electron impact (EI) mode on an Agilent 6890N Gas Chromatograph coupled with an Agilent 5975 Mass spectrometer (Agilent Technologies, CA, USA) using the same GC column and temperature program. Only the isotopic ion with the lowest mass is reported for all fragments observed in the MS spectra. The spectral data of all intermediates reported in Schemes 1–3 were in agreement with literature data.[10]

Nitration of 3,5-Dichlorophenol (9)

A solution of **9** (2.5 g, 15.3 mmol) and $NaNO_2$ (1.45 g, 27.6 mmol) in H_2O (25 mL) was cooled to 0 °C and H_2SO_4 (1.2 mL diluted with 6 mL H_2O) was added over a 15 min period.[27] The reaction mixture was heated under reflux for 6 h with the incremental addition of additional $NaNO_2$ (6.33 g, 119.4 mmol). The mixture was allowed to cool to 20 °C, stirred for 17 h, and extracted with EtOAc (2 × 80 mL). The combined organic extracts were washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), and filtered to yield a crude mixture of **12a** and **12b** in 44–92% yield. The 2-nitro and 4-nitro derivatives were separated by repeated column chromatography on silica gel with a gradient of hexane to $CHCl_3$ to MeOH–$CHCl_3$ (5:95, v/v).

3,5-Dichloro-4-nitrophenol (12a)

Brown-yellow solid; yield: 12%; mp 141–144 °C (hexane–$CHCl_3$; Lit.[44] mp 150 °C); R_f = 0.85 ($CHCl_3$–MeOH, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.9, 127.1, 159.2.

MS (EI, 70 eV): *m*/*z* (%) = 207 (31, $[M]^+$), 177 (100), 149 (37), 133 (29), 97 (24), 85 (16), 73 (19), 62 (36).

HRMS: *m*/*z* $[M]^+$ calcd for $C_6H_3Cl_2NO_3$: 206.9485; found: 206.9481.

3,5-Dichloro-2-nitrophenol (12b)

Yellow solid; yield: 22%; mp 44–48 °C (Lit.[44] mp 51 °C); R_f = 0.84 ($CHCl_3$–MeOH, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (m, 2 H), 9.88 (s, OH, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 118.3, 123.9, 130.4, 140.8, 155.3.

MS (EI, 70 eV): *m*/*z* (%) = 207 (100, $[M]^+$), 177 (89), 162 (12), 149 (68), 133 (34), 110 (20), 97 (71), 85 (15), 73 (25), 62 (45).

HRMS: *m*/*z* $[M]^+$ calcd for $C_6H_3Cl_2NO_3$: 206.9485; found: 206.9485.

Methylation of 3,5-Dichloro-4-nitrophenol (12a) and 3,5-Dichloro-2-nitrophenol (12b)

The respective nitro compound **12** (0.31 g, 1.5 mmol) was methylated with Me_2SO_4 (0.2 mL, 2.25 mmol) and K_2CO_3 (0.42 g, 3 mmol) in DMF (1 mL) at 60 °C for approximately 1 h.[45] The reaction mixture was poured into ice-cold H_2O and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with H_2O (15 mL), aq 2 N HCl (3 mL), brine (5 mL), and dried (Na_2SO_4). The product was purified by column chromatography on silica gel using a hexane–EtOAc gradient.

3,5-Dichloro-4-nitroanisole (11a)

Yellow solid; yield: 92%; mp 56 °C (Lit.[44] mp 70 °C); R_f = 0.18 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, OCH_3, 3 H), 6.92 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.3, 103.5, 114.4, 127.5, 160.3.

MS (EI, 70 eV): *m*/*z* (%) = 221 (33, $[M]^+$), 191 (100), 160 (20), 132 (10), 111 (11), 97 (40), 62 (23).

HRMS: *m*/*z* $[M]^+$ calcd for $C_7H_5Cl_2NO_3$: 220.9641; found: 220.9648.

3,5-Dichloro-2-nitroanisole (11b)

Yellow solid; yield: 65%; mp 65–66 °C (Lit.[44] mp 75 °C); R_f = 0.20 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, OCH_3, 3 H), 6.96 (d, *J* = 2.0 Hz, 1 H), 7.08 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.0, 111.9, 121.6, 137.0, 152.2.

MS (EI, 70 eV): *m*/*z* (%) = 221 (100, $[M]^+$), 191 (56), 174 (64), 160 (68), 148 (40), 128 (51), 109 (59), 97 (90), 74 (44), 62 (36).

HRMS: *m*/*z* $[M]^+$ calcd for $C_7H_5Cl_2NO_3$: 220.9641; found: 220.9636.

Bromination of 3,5-Dichloroanisole (10); 4-Bromo-3,5-dichloroanisole (14)

N-Bromosuccinimide (5.3 g, 29.8 mmol) and aq HCl (10% v/v, 1 mL) were added to a solution of **10** (5.0 g, 29.8 mmol) in acetone (50 mL) and stirred at 20 °C for 30 min.[28] The solvent was removed

under reduced pressure and the residue was washed with hexane (25 mL). Recrystallization from MeOH yielded the desired product **14** in 25% yield; mp 59–60 °C; R_f = 0.24 (hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 (s, OCH_3, 3 H), 6.93 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.9, 114.0, 114.8, 136.5, 158.8.

MS (EI, 70 eV): *m*/*z* (%) = 254 (58, $[M]^+$), 239 (8), 224 (8), 211 (20), 97 (21), 62 (15).

HRMS: *m*/*z* $[M]^+$ calcd for $C_7H_5BrCl_2O$: 253.8901; found: 253.8896.

Chlorination of 4-Bromo-3,5-dichloroanisole (14); 4-Bromo-2,3,5-trichloroanisole (4)

H_2O_2 (30%, 2.6 mL) and concd HCl (6.7 mL) was added to **14** (5.2 g, 20.3 mmol) in AcOH (50 mL).[10] CH_2Cl_2 (6 mL) was added to redissolve **14** and the heterogenous mixture was stirred for 16 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Recrystallization of the crude product from MeOH gave **4** in 60% yield as a white solid; mp 107–108 °C; R_f = 0.17 (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, OCH_3, 3 H), 6.98 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.0, 111.6, 115.0, 121.6, 134.1, 135.5, 155.1.

MS (EI, 70 eV): *m*/*z* (%) = 288 (49, $[M]^+$), 273 (18), 245 (24), 131 (21), 96 (14), 61 (11).

HRMS: *m*/*z* $[M]^+$ calcd for $C_7H_4BrCl_3O$: 287.8511; found: 287.8509.

Ullmann Coupling Reaction; General Procedure

A mixture of aryl iodide (3 mmol) or methoxyaryl iodide (1.5 mmol) and activated Cu bronze (3 g) in a sealed glass ampoule flushed with N_2 was heated in a sand bath at 230 °C for 7 d.[10] The ampoule was allowed to cool to r.t., opened, and the contents were extracted with boiling CH_2Cl_2 (3 × 100 mL). The combined extracts were dried (Na_2SO_4), filtered, and the solvent was evaporated under reduced pressure to give a dark brown, viscous oil. Repeated column chromatography on silica gel eluted with hexane, followed by recrystallization gave the corresponding biphenyl derivative **15**, **16**, or **17** in moderate yields (Table 1).

Suzuki Coupling Reaction; General Procedure

Suzuki reactions were carried out in 60 mL sample collection vials (I-Chem, New Castle, DE, USA) with a Teflon rubber septum. The dried glass vial was charged with the aryl iodide or methoxyaryl iodide (2 mmol), chlorinated arylboronic acid (2 mmol), followed by DPDB (45 mg), $Pd(dba)_2$ (26 mg), $K_3PO_4 \cdot H_2O$ (1.2 g), and toluene (2 mL), evacuated and backfilled with N_2. The reaction mixture was stirred at 110 °C for 24 h, diluted with CH_2Cl_2 (5 mL), filtered through Celite, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using hexane as eluent to provide the desired compound **15**, **16**, **17**, or **18** (Table 1).

2,2′,3,4′,6-Pentachlorobiphenyl (PCB 91, 15a)

Viscous oil (Lit.[46] mp 62–63 °C); >85% purity by GC-MS; R_f = 0.59 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.4 Hz, 1 H), 7.36–7.39 (m, 2 H), 7.47 (d, *J* = 8.8 Hz, 1 H), 7.47 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.5, 128.3, 129.6, 130.6, 131.5, 131.9, 133.3, 133.7, 134.3, 134.6, 135.3, 137.8.

MS (EI, 70 eV): *m*/*z* (%) = 324 (70, $[M]^+$), 289 (23), 254 (62), 184 (19).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{12}H_5Cl_5$: 323.8828; found: 323.8837.

2,2′,3,5′,6-Pentachlorobiphenyl (PCB 95, 15b)

Colorless crystalline solid; mp 91–92 °C ($CHCl_3$–MeOH) (Lit.[46] mp 93–94 °C); R_f = 0.59 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 2.0 Hz, 1 H), 7.35–7.38 (m, 2 H), 7.46 (pseudo t, *J* = 8.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.4, 130.1, 130.5, 130.7, 130.8, 131.8, 132.0, 132.8, 133.2, 133.5, 137.4, 137.7.

MS (EI, 70 eV): *m*/*z* (%) = 324 (88, $[M]^+$), 289 (42), 254 (86), 184 (38), 127 (26), 109 (19).

Anal. Calcd for $C_{12}H_5Cl_5$: C, 44.17; H, 1.53. Found: C, 43.97; H, 1.31.

2,2′,3,3′,4′,6-Hexachlorobiphenyl (PCB 132, 15c)

Colorless crystalline solid; mp 112–114 °C ($CHCl_3$–MeOH) (Lit.[46] mp 116–118 °C); R_f = 0.53 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 8.3 Hz, 1 H), 7.37 (d, *J* = 8.7 Hz, 1 H), 7.48 (d, *J* = 8.7 Hz, 1 H), 7.51 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 128.4, 128.6 (2 C), 130.8, 132.0, 132.5, 133.1, 133.5, 133.7, 134.6, 136.3, 138.2.

MS (EI, 70 eV): *m*/*z* (%) = 358 (56, $[M]^+$), 322 (24), 289 (44), 218 (22), 145 (19).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{12}H_4Cl_6$: 357.8439; found: 357.8445.

2,2′,3,4′,6-Pentachloro-4-methoxybiphenyl (16a)

Colorless crystalline solid; mp 127–128 °C ($CHCl_3$–MeOH); R_f = 0.38 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, OCH_3), 7.01 (s, 1 H), 7.12 (d, *J* = 8.2 Hz, 1 H), 7.34 (dd, *J* = 2.1, 8.2 Hz, 1 H), 7.52 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.7, 111.2, 121.0, 127.4, 129.46, 129.49, 132.1, 133.0, 134.46, 134.55, 134.9, 135.1, 156.0.

MS (EI, 70 eV): *m*/*z* (%) = 354 (62, $[M]^+$), 311 (14), 240 (26), 171 (12).

Anal. Calcd for $C_{13}H_7Cl_5O$: C, 43.75; H, 1.96. Found: C, 44.04; H, 1.98.

2,2′,3,5′,6-Pentachloro-4-methoxybiphenyl (16b)

Colorless crystalline solid; mp 129–130 °C ($CHCl_3$–MeOH); R_f = 0.39 (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 3 H, OCH_3), 7.01 (s, 1 H), 7.20 (d, *J* = 2.5 Hz, 1 H), 7.35 (dd, *J* = 2.5, 8.6 Hz, 1 H), 7.45 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.8, 111.1, 121.0, 129.3, 129.9, 130.6, 131.2, 132.5, 132.6, 132.9, 134.3, 137.4, 156.0.

MS (EI, 70 eV): *m*/*z* (%) = 354 (73, $[M]^+$), 311 (34), 286 (16), 241 (44), 207 (27), 171 (20).

Anal. Calcd for $C_{13}H_7Cl_5O$: C, 43.75; H, 1.96. Found: C, 43.91; H, 1.78.

2,2′,3,3′,4′,6-Hexachloro-4-methoxybiphenyl (16c)

Colorless crystalline solid; mp 168–169 °C ($CHCl_3$–MeOH); R_f = 0.34 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.97 (s, 3 H, OCH_3), 7.01 (s, 1 H), 7.05 (d, *J* = 8.3 Hz, 1 H), 7.48 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.8, 111.2, 121.2, 128.5, 129.4, 129.7, 132.3, 132.9, 134.3, 134.4, 136.3, 156.2.

MS (EI, 70 eV): *m*/*z* (%) = 388 (50, $[M]^+$), 345 (17), 275 (18), 205 (10).

Anal. Calcd for $C_{13}H_6Cl_6O$: C, 39.94; H, 1.55. Found: C, 39.68; H, 1.47.

2,2′,3,4′,6-Pentachloro-5-methoxybiphenyl (17a)
Colorless solid; mp 118–120 °C ($CHCl_3$–MeOH); R_f = 0.39 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, OCH_3), 7.11 (d, *J* = 8.2 Hz, 1 H), 7.11 (s, 1 H), 7.36 (dd, *J* = 2.1, 8.2 Hz, 1 H), 7.54 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.7, 113.3, 122.2, 124.5, 127.4, 129.6, 131.4, 131.7, 134.1, 134.7, 135.1, 138.3, 154.1.

MS (EI, 70 eV): *m*/*z* (%) = 354 (58, $[M]^+$), 339 (2), 311 (16), 241 (21), 171 (9).

Anal. Calcd for $C_{13}H_7Cl_5O$: C, 43.75; H, 1.96. Found: C, 43.77; H, 1.76.

2,2′,3,5′,6-Pentachloro-5-methoxybiphenyl (17b)
Colorless solid; mp 40–42 °C ($CHCl_3$–MeOH); R_f = 0.38 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, OCH_3), 7.12 (s, 1 H), 7.18 (d, *J* = 2.4 Hz, 1 H), 7.35 (dd, *J* = 2.5, 8.6 Hz, 1 H), 7.44 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.7, 113.3, 122.0, 124.3, 129.9, 130.4, 130.7, 131.67, 131.74 131.8, 132.7, 137.5, 138.1, 154.1.

MS (EI, 70 eV): *m*/*z* (%) = 354 (91, $[M]^+$), 339 (5), 311 (25), 241 (28), 171 (29).

Anal. Calcd for $C_{13}H_7Cl_5O$: C, 43.75; H, 1.96. Found: C, 43.80; H, 1.91.

2,2′,3,3′,4′,6-Hexachloro-5-methoxybiphenyl (17c)
Colorless crystalline solid; mp 134–135 °C ($CHCl_3$–MeOH); R_f = 0.34 (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, OCH_3), 7.03 (d, *J* = 8.3 Hz, 1 H), 7.12 (s, 1 H), 7.50 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.7, 113.4, 122.0, 124.2, 128.6, 131.9, 132.4, 133.6, 134.4, 136.4, 138.4, 154.2.

MS (EI, 70 eV): *m*/*z* (%) = 388 (44, $[M]^+$), 345 (14), 275 (8), 205 (8).

Anal. Calcd for $C_{13}H_6Cl_6O$: C, 39.94; H, 1.55. Found: C, 40.20; H, 1.44.

2,2′,3,4′,5′,6-Hexachloro-5-methoxybiphenyl (17d)
Colorless solid; yield: 43%; mp 91–92 °C ($CHCl_3$–MeOH); R_f = 0.39 (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, OCH_3), 7.13 (s, 1 H), 7.29 (s, 1 H), 7.64 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.7, 113.6, 122.1, 124.3, 131.0, 131.4, 131.8, 131.9, 132.3, 133.6, 135.8, 137.2, 154.3.

MS (EI, 70 eV): *m*/*z* (%) = 388 (47, $[M]^+$), 345 (16), 338 (12), 275 (23), 205 (12).

Anal. Calcd for $C_{13}H_6Cl_6O$: C, 39.92; H, 1.55. Found: C, 40.09; H, 1.27.

2,2′,3,4′,6-Pentachloro-4,5-dimethoxybiphenyl (18a)
Colorless solid; mp 70–72 °C ($CHCl_3$–MeOH); R_f = 0.42 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 7.12 (d, *J* = 8.3 Hz, 1 H), 7.35 (dd, *J* = 8.3, 2.1 Hz, 1 H), 7.54 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.22, 61.24, 127.0, 127.4, 127.8, 128.6, 129.6, 131.7, 133.2, 134.5, 135.2, 149.4, 151.2.

MS (EI, 70 eV): *m*/*z* (%) = 384 (64, $[M]^+$), 369 (24), 341 (18), 326 (20), 228 (20).

Anal. Calcd for $C_{14}H_9Cl_5O_2$: C, 43.51; H, 2.35. Found: C, 43.74; H, 2.26.

2,2′,3,5′,6-Pentachloro-4,5-dimethoxybiphenyl (18b)
Colorless oil; R_f = 0.44 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 7.19 (d, *J* = 2.4 Hz, 1 H), 7.35 (dd, *J* = 2.4, 8.3 Hz, 1 H), 7.44 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.22, 61.24, 127.0, 127.7, 128.5, 130.0, 130.7, 130.8, 132.1, 132.7, 133.0, 137.3, 149.4, 151.2.

MS (EI, 70 eV): *m*/*z* (%) = 384 (60, $[M]^+$), 369 (26), 341 (18), 326 (15), 228 (22).

Anal. Calcd for $C_{14}H_9Cl_5O_2$: C, 43.51; H, 2.35. Found: C, 43.91; H, 2.24.

2,2′,3,3′,4′,6-Hexachloro-4,5-dimethoxybiphenyl (18c)
Colorless solid; mp 93–95 °C ($CHCl_3$–MeOH); R_f = 0.41 (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, OCH_3), 4.00 (s, 1 H, OCH_3), 7.05 (d, *J* = 8.3 Hz, 1 H), 7.49 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 61.19, 61.22, 127.1, 127.6, 128.4, 128.6, 128.9, 132.4, 133.2, 134.0, 134.5, 136.3, 149.4, 151.3.

MS (EI, 70 eV): *m*/*z* (%) = 418 (56, $[M]^+$), 403 (20), 375 (9), 360 (20), 262 (20).

Anal. Calcd for $C_{14}H_8Cl_6O$: C, 39.95; H, 1.92. Found: C, 40.00; H, 1.79.

Demethylation Reaction; General Procedure
BBr_3 (1 M in hexane, 5 equiv) was added to a solution of the methoxylated biphenyl **16**, **17** (0.3 mmol) in anhyd CH_2Cl_2 (5 mL) under N_2.[33] The reaction mixture was stirred at r.t. for 14 h, cooled with ice/salt, and hydrolyzed with an equal volume of ice-cold H_2O. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with H_2O (3 × 25 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel with hexane–EtOAc (1:1, v/v) as eluent, followed by recrystallization from MeOH–$CHCl_3$ (3:1, v/v), to give the corresponding hydroxy compounds as white solids or colorless oils in 50–55% yield.

2,2′,3,4′,6-Pentachlorobiphenyl-4-ol (19a)
Colorless oil; yield: 62%; R_f = 0.21 (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85 (br s, 3 H, OH), 7.12 (d, *J* = 8.2 Hz, 1 H), 7.16 (s, 1 H), 7.35 (dd, *J* = 2.5, 8.6 Hz, 1 H), 7.53 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.4, 118.5, 127.4, 129.6, 129.8, 132.2, 133.4, 133.8, 134.4, 135.0, 135.2, 152.4.

MS (EI, 70 eV): *m*/*z* (%) = 340 (60, $[M]^+$), 270 (31), 241 (11), 171 (20).

HRMS: *m*/*z* $[M - H]^+$ calcd for $C_{12}H_4Cl_5O$: 338.8705; found: 338.8705.

2,2′,3,5′,6-Pentachlorobiphenyl-4-ol (19b)
Colorless oil; yield: 47%; R_f = 0.18 (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90 (br s, 3 H, OH), 7.16 (s, 1 H), 7.20 (d, *J* = 2.5 Hz, 1 H), 7.36 (dd, *J* = 2.5, 8.6 Hz, 1 H), 7.45 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.4, 118.5, 129.6, 130.0, 130.6, 131.2, 132.5, 132.6, 133.2, 133.6, 137.2, 152.4.

MS (EI, 70 eV): *m*/*z* (%) = 340 (68, $[M]^+$), 270 (345), 241 (11), 171 (20).

HRMS: *m/z* [M – H]$^+$ calcd for $C_{12}H_4OCl_5$: 338.8705; found: 338.8702.

2,2′,3,3′,4′,6-Hexachlorobiphenyl-4-ol (19c)
Colorless crystalline solid; yield: 49%; mp 94–95 °C ($CHCl_3$–MeOH); R_f = 0.19 (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.86 (br s, 3 H, OH), 7.05 (d, *J* = 8.3 Hz, 1 H), 7.16 (s, 1 H) 7.48 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.5, 118.6, 128.5, 129.4, 129.9, 132.4, 133.2, 133.6, 134.4, 134.5, 136.2, 152.6.

MS (EI, 70 eV): *m/z* (%) = 374 (50, [M]$^+$), 304 (32), 275 (10), 205 (17).

HRMS: *m/z* [M – H]$^+$ calcd for $C_{12}H_3Cl_6O$: 372.8315; found: 372.8316.

2,2′,3,4′,6-Pentachlorobiphenyl-5-ol (20a)
Colorless oil; yield: 50%; R_f = 0.19 (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.79 (br s, 1 H, OH), 7.13 (d, *J* = 8.3 Hz, 1 H), 7.26 (s, 1 H), 7.38 (dd, *J* = 2.1, 8.3 Hz, 1 H), 7.55 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.5, 119.5, 124.6, 127.5, 129.7, 131.4, 132.5, 134.2, 134.3, 135.5, 137.4, 150.5.

MS (EI, 70 eV): *m/z* (%) = 340 (63, [M]$^+$), 305 (10), 270 (27), 242 (14), 207 (12), 171 (19).

HRMS: *m/z* [M]$^+$ calcd for $C_{12}H_5Cl_5O$: 339.8778; found: 338.8791.

2,2′,3,5′,6-Pentachlorobiphenyl-5-ol (20b)
Colorless oil; yield: 50%; R_f = 0.19 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.15 (br s, 1 H, OH), 7.19 (d, *J* = 2.5 Hz, 1 H), 7.26 (s, 1 H), 7.37 (dd, *J* = 2.5, 8.6 Hz, 1 H), 7.43 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.6, 119.3, 124.5, 130.2, 130.4, 130.8, 131.8, 132.6, 132.9, 137.1, 137.2, 150.6.

MS (EI, 70 eV): *m/z* (%) = 340 (82, [M]$^+$), 305 (16), 270 (37), 241 (18), 207 (13), 171 (40).

HRMS: *m/z* [M – H]$^+$ calcd for $C_{12}H_4Cl_5O$: 338.8705; found: 338.8707.

2,2′,3,3′,4′,6-Hexachlorobiphenyl-5-ol (20c)
White crystalline solid; yield: 50%; mp 126–128 °C; R_f = 0.17 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (br s, 1 H, OH), 7.05 (d, *J* = 8.4 Hz, 1 H), 7.28 (s, 1 H), 7.51 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.7, 119.4, 124.4, 128.6, 128.8, 132.6, 132.7, 133.7, 134.7, 136.0, 137.5, 150.6.

MS (EI, 70 eV): *m/z* (%) = 374 (50, [M]$^+$), 339 (10), 305 (15), 275 (10), 205 (15).

HRMS: *m/z* [M]$^+$ calcd for $C_{12}H_4Cl_6O$: 373.8388; found: 373.8394.

2,2′,3,4′,5′,6-Hexachlorobiphenyl-5-ol (20d)
Colorless oil; yield: 50%; R_f = 0.18 (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.72 (br s, 1 H, OH), 7.28 (s, 1 H), 7.30 (s, 1 H), 7.65 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.8, 119.3, 124.5, 131.2, 131.6, 131.7, 132.4, 132.8, 133.9, 135.4, 136.3, 150.5.

MS (EI, 70 eV): *m/z* (%) = 374 (48, [M]$^+$), 303 (18).

HRMS: *m/z* [M – H]$^+$ calcd for $C_{12}H_3Cl_6O$: 372.8315; found: 372.8319.

X-ray Crystal Structure Analysis[47]
X-ray diffraction data of compounds **12a**, **15b**, **16b**, **17a**, and **17d** were collected at 90.0(2) K on a Nonius KappaCCD diffractometer as described previously.[34]

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(47) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 797054–797058. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk.