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Combined Directed *ortho* Metalation/Suzuki−Miyaura Cross-Coupling Strategies. Regiospecific Synthesis of Chlorodihydroxybiphenyls and Polychlorinated Biphenyls⊗

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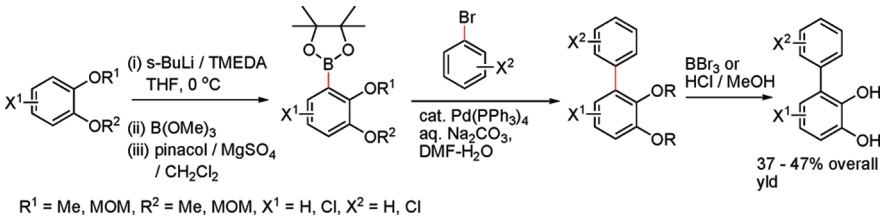

The Directed *ortho* Metalation (DoM)/Suzuki−Miyaura cross-coupling strategy is applied for the regiospecific construction of all isomeric monochloro and selected dichloro and trichloro 2,3-dihydroxybiphenyls (DHBs). The combined methodology highlights iterative DoM processes, hindered Suzuki−Miyaura couplings, and advantages in diversity in approaches from commercial starting materials leading to provision of chloro-DHBs as single isomers in high purity and on a gram scale. The syntheis of several PCBs are also reported.

Introduction

Microorganisms utilize an astonishing array of catabolic pathways to degrade a vast range of organic compounds of natural and xenobiotic origin. Detailed understanding of these microbial pathways is critical to the maintenance of the global carbon cycle as well as for developing effective bioremediation strategies.[1] Polychlorinated biphenyls (PCBs) constitute one of the most widely distributed classes of chlorinated environmental pollutants whose commercial mixtures typically contain over 60 of the possible 209 isomers differing in the number and position of the chloro substitutents.[2] Although the production

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⊗ This paper is dedicated to Dieter Seebach, with respect and in friendship, for inspirational chemistry of carbanions, and now beyond, and for clarity in lecture and didacticism in publication, prepared always ohne Hast.
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§ Queen's University.
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|| DSM Pharma Chem Regensburg GmbH.
Albany Molecular Research, Inc.
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(1) (a) Dagley, S. In *The Bacteria*; Sokatch, J. R., Ornston, L. N., Eds.; Academic Press: New York, 1986; pp 527−555. (b) Timmis, K. N.; Steffan, R. J.; Unterman, R. *Annu. Rev. Microbiol.* **1994**, *48*, 525.
(2) (a) Ayres, D.; Hellier, D. *Dictionary of Environmentally Important Chemicals*; Blackie: New York, 1998; p 245. (b) Tiedje, J. M.; Quensen, J. F., III; Chee-Sanford, J.; Schimel, J. P.; Boyd, S. A. *Biodegradation* **1993**, *4*, 231−240. (c) Erickson, M. D. *Analytical Chemistry of PCBs*; Lewis: Boca Raton, FL, 1992. (d) Abramowicz, D. A. *Crit. Rev. Biotechnol.* **1990**, *10*, 241.

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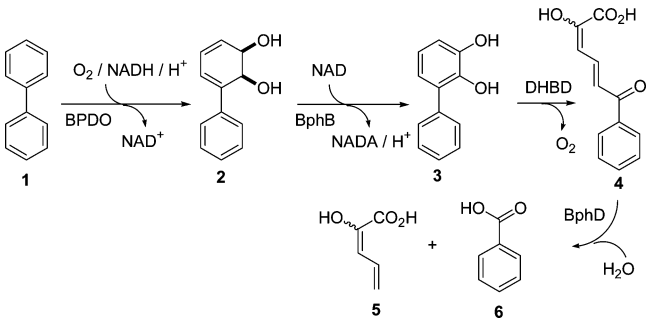
SCHEME 1. Enzymes Involved in the Aerobic Microbial Degradation of Biphenyl and PCBs[a]



[a] BPDO = biphenyl dioxygenase; BphB = 2,3-dihydro-2,3-dihydroxybiphenyl dehydrogenase; DHBD = 2,3-dihyroxybiphenyl dioxygenase; BphD = 2-hydroxy-6-oxo-6-phenylhexa-2,4-dienoate hydrolase.

and wide scale usage of PCBs has been banned in the industrial world for over 20 years, their persistence in soil and sediment, impact on delicate ecosystems such as the Arctic, and potential effect on human health purport the destruction of PCBs of continuing relevance.[3] The discovery of PCB degradation by a variety of microorganisms has sparked interest to exploit microbial catabolic pathways for the remediation of contaminated sites.[4−6]

A wide variety of bacteria can at least partially degrade PCBs by using the bph pathway (Scheme 1).[7] This pathway is responsible for the aerobic assimilation of biphenyl (**1**) by dihydroxylation (**2**) and formation of the catechol (**3**) followed by oxidative cleavage (**4**) and a fascinating vinylogous retro-aldol-type fragmentation to give 2-hydroxypenta-2,3-dienoate (**5**) and benzoate (**6**).[8a] Individual bacterial strains vary widely in their ability to degrade PCBs: only a few can completely degrade even lightly chlorinated congeners, and none can degrade the more highly chlorinated ones. To obtain insights into the nature of catabolic blocks, to engineer enzymes to overcome such blocks, as well as to probe the catalytic mechanisms of the *bph* enzymes, chlorinated dihydroxybiphenyls (DHBs) are required as single-isomer substrates. As part of continuing efforts in this area,[8] a synthetic program has evolved, and is ongoing, which has delivered chloro-DHBs as single isomers, in high purity, and in gram quantities by a combined directed *ortho* Metalation (DoM)/Suzuki−Miyaura cross-coupling tactic.[9] Herein we report the details of the regioselective synthesis of all isomeric monochloro-DHBs[10] and amplification of these studies to the preparation of some polyhalogenated DHBs and PCBs (Figure 1).

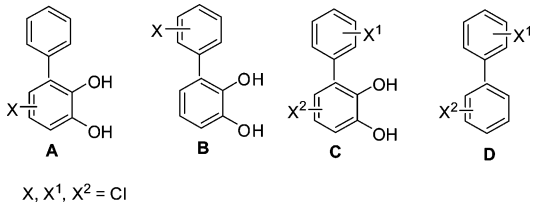
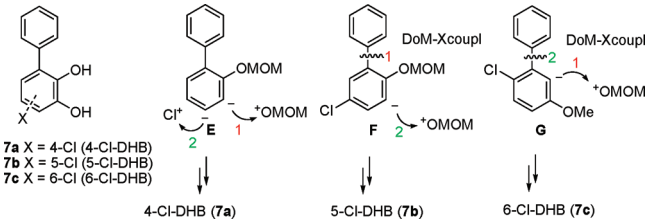


FIGURE 1. Classes of dihdyroxybiphenyls and PCBs prepared and projected by the directed *ortho* metalation/cross-coupling strategy.

SCHEME 2. Retrosynthetic DoM/Cross-Coupling Analysis for Chloro-DHBs 7a−c



Results and Discussion

Although the Suzuki−Miyaura cross-coupling technology has been previously applied to the synthesis of DHBs and PCBs and their metabolites,[11,12] combined directed *ortho* metalation (DoM)/Suzuki strategies[9] have, to the best of our knowledge, not been tested for the preparation of chlorinated biphenyls. The conceptual frameworks in which we placed the construction of the targeted DHBs may be illustrated by schematics **E**, **F**, and **G** (Scheme 2). Thus, according to schematic **E**, using a substrate readily available in two steps from commercial 2-hydroxybiphenyl, walk-around-the-ring functionalization may be achieved by introduction of an OH^+ synthetic equivalent (boronation and hydrogen peroxide treatment (step 1) and a Cl^+ electrophile (step 2) to achieve, after hydrolysis, the preparation of 4-Cl-DHB (**7a**). The synthesis of the isomeric 5-Cl-DHB (**7b**) is initiated from the MOM derivative of 4-chlorophenol (schematic **F**), which upon a DoM/cross-coupling sequence (step 1) followed by a second DoM and an OH^+ equivalent introduction (step 2) and hydrolysis leads to **7b**. The success of this simple synthesis

(3) McFarland, V. A.; Clarke, J. U. *Environ. Health Perspect.* **1989**, *81*, 225. Que, L.; Ho, R. Y. N. *Chem. Rev.* **1996**, *96*, 2607. Bugg T. D. H.; Winfield, C. J. *Nat. Prod. Rep.* **1998**, 513. Timmis, K. N.; Steffan, R. J.; Unterman, R. *Annu. Rev. Microbiol.* **1994**, *48*, 525.

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(6) Furukawa, K. *Trends Biotechnol.* **2003**, *21*, 187−190.

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(8) (a) Dai, S.; Vaillancourt, F. H.; Maaroufi, H.; Drouin, N. M.; Neau, D. B.; Snieckus, V.; Bolin, J. T.; Eltis, L. D. *Nature Struct. Biol.* **2002**, *9*, 934. (b) Seah, S. Y. K.; Labbé, G.; Nerdinger, S.; Johnson, M. R.; Snieckus, V.; Eltis, L. D. *J. Biol. Chem.* **2000**, *275*, 15701. (c) Vaillancourt, F. H.; Han, S.; Fortin, P. D.; Bolin, J. T.; Eltis, L. D. *J. Biol. Chem.* **1998**, *273*, 34887. (d) Seah, S. Y. K.; Terracina, G.; Bolin, J. T.; Riebel, P.; Snieckus, V.; Eltis, L. D. *J. Biol. Chem.* **1998**, *273*, 22943.

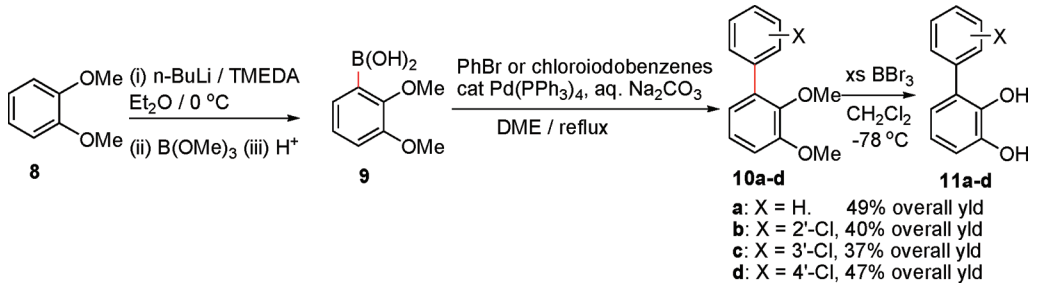
(9) For a review that encompasses other named cross-coupling reactions initiated by DoM, see: (a) Anctil, E.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150−160. (b) Anctil, E. J.-G.; Snieckus, V. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Diederich, F.,de Meijere, A., Eds.; Wiley-VC: New York, 2004; pp 761−814. For a specialized treatise, see: Cepanec, I. *Synthesis of Biaryls*: Elevier: Amsterdam, The Netherlands, 2004.

(10) (a) For a preliminary communication, see: Nerdinger, S.; Kendall, C.; Marchhart, R.; Riebel, P.; Johnson, M. R.; Yin, C.-F.; Eltis, L. D.; Snieckus, V. *J. Chem. Soc., Chem. Commun.* **1999**, 2259. More recently, Robertson has reported on the preparation of mono- and dihydroxylated PCB metabolites by a Suzuki−Miyaura cross-coupling protocol, see: (b) Lehmler, H.-J.; Robertson, L. W. *Chemosphere* **2001**, *45*, 137 and Gold has described a nonregioselective route via aryldiazonium salt coupling and its use to provide $^2H_3$-isotopomer chloro-DHBs, see: (c) Lin, P.-H.; Sangaiah, R.; Ranasinghe, A.; Ball, L. M.; Swenberg, J. A.; Gold, A. *Org. Biomol. Chem.* **2004**, *2*, 2624.

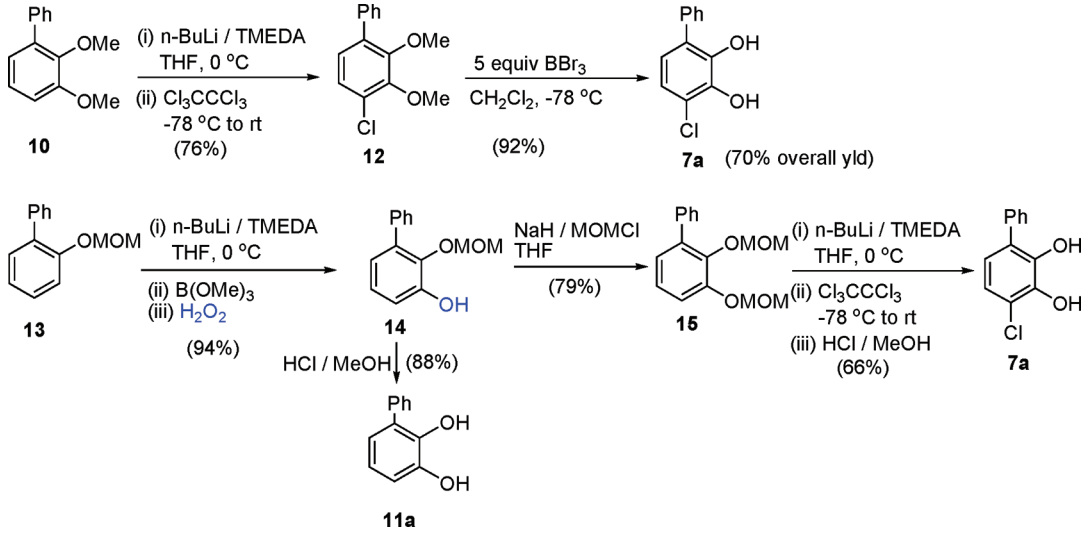
(11) Bauer, U.; Amaro, A. R.; Robertson, L. W. *Chem. Res. Toxicol.* **1995**, *8*, 92.

(12) Lehmler, H.-J.; Robertson, L. W. *Chemosphere* **2001**, *45*, 137.

SCHEME 3. The Synthesis of Chloro-DHBs 11a−d



SCHEME 4. Synthesis of Chloro-DHBs 7a and an Alternative Synthesis of 11a



rests on the symmetry of the starting material and the order of the directed metalation group (DMG) power, OMOM > Cl.[13] Similar dependency is evident in the construction of 6-Cl-DHB (**7c**) (schematic **G**) as the symmetrical starting 4-Cl anisole follows, in step 1, DMG = OMe > Cl metalation preference. The resulting anion upon subjection to OH^+ equivalent introduction by the two-step sequence and conversion of the resulting phenol into its MOM derivative (step 1) is primed to take advantage of regioselective DoM, controlled by the synergy of the Cl and OMOM DMGs.[13] Consequent DoM and cross coupling followed by hydrolysis leads to the target **7c**. These principles, of potential more general value for chlorinated hydrocarbon synthesis, pervade the preparation of DHBs presented below.

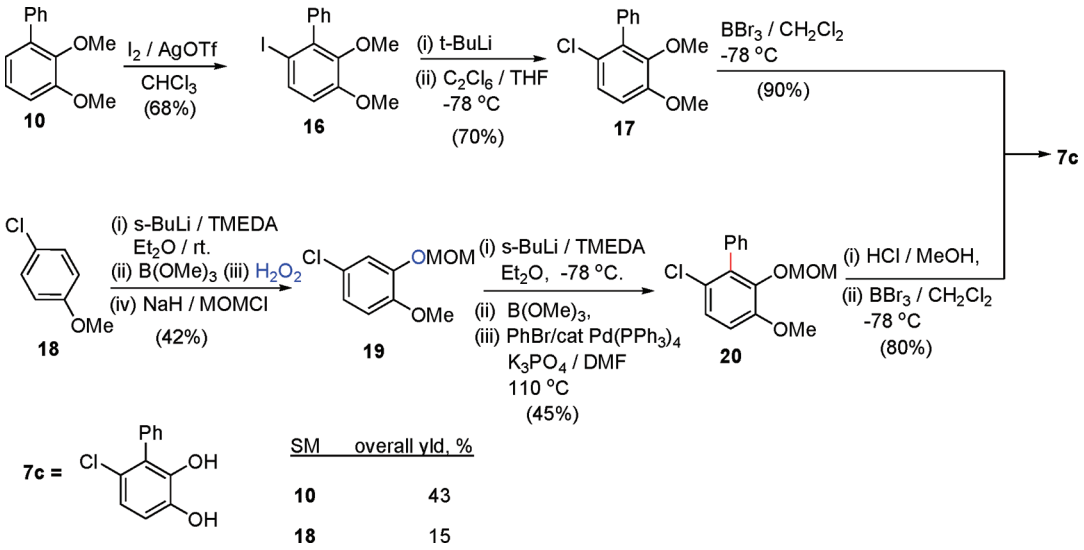
The synthesis of the isomeric monochloro DHBs **11a−d** (Scheme 3) begins conveniently from the same starting material, 1,2-dimethoxybenzene (**8**). Thus metalation−trimethyl borate quench afforded the boronic acid **9**, which, in crude form, was subjected to standard[14] Suzuki−Miyaura cross-coupling with bromobenzene or commercially available isomeric chloroiodobenzenes followed by BBr_3 deprotection to furnish, via intermediate dimethyl ethers **10a−d**, the biaryls **11a−d** in modest overall yields. These reactions were easily scaled to 10−20 mmol batches providing gram quantities of chloro-DHB products. Compounds **10** and **11a** have been previously prepared by a number of routes[10c] while compound **11c** was prepared by the identical Suzuki−Miyaura coupling in comparable yield.[11]

2,3-Dimethoxybiphenyl (**10**) also served as a common intermediate for two concise syntheses of the alternate ring chlorinated DHB **7a** (Scheme 4) and **7c** (Scheme 5). In the first route, metalation of **10** followed by chlorination with C_2Cl_6 gave **12**, which upon BBr_3 deprotection afforded **7a** in 70% overall yield (Scheme 4), while, in the alternate route, using the concept of OMOM DMG-initiated walk-around-the-ring functionalization (Scheme 2, **E**), compound **13** was subjected to an OH^+ synthetic equivalent introduction via sequential boronation and oxidation to give **14**. Conversion to the di-MOM derivative **15** allowed a subsequent second DoM process which, after C_2Cl_6 quench and HCl hydrolysis, afforded **7a** in 49% overall yield. Compound **14** also served as an intermediate for an alternative route to the parent DHB **11a** in 88% yield (see the Experimental Section).

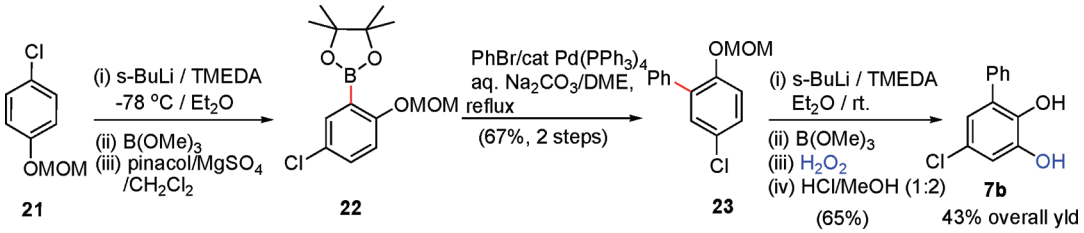
As a demonstration of the advantage of multiple-tree retrosynthetic analysis even in simple constructs, two distinct regiospecific syntheses were also devised for 6-chloro-DHB (**7c**) utilizing the common intermediate **10** (Scheme 5). In the first approach, treatment of **10** with iodine and silver trifluoroacetate led to the unanticipated exclusive formation of the 6-iodobiphenyl **16**. Metal−halogen exchange with *tert*-butyllithium and C_2Cl_6 quench afforded **17**, which, upon deprotection with BBr_3, furnished **7c** in 43% overall yield. As an alternative synthesis of **7c**, a walk-around-the-ring DoM/Suzuki−Miyaura cross-coupling sequence was adopted. Thus a metalation−boronation−oxidation sequence on *p*-chloroanisole (**18**) followed by

(13) For a qualitative ranking of DMG hierarchy, see: Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.
(14) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Josephy, P. D.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763.

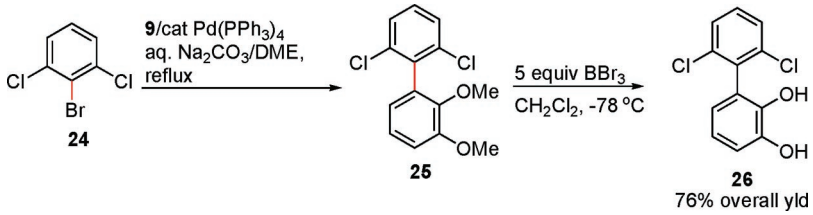
SCHEME 5. Two Routes to 6-Chloro-DHB (7c)



SCHEME 6. Synthesis of 5-Chloro-DHB (7b)



SCHEME 7. Synthesis of 2′,6′-Dichloro-DHB (26)



standard MOM derivatization furnished **19**. In the next step, the greater power of the MOM DMG compared to OMe, possibly with assistance from the weak Cl group,[15] manifests in regiospecific in-between metalation which, following boronation and cross coupling with bromobenzene, furnished **20** in modest yield. Simple sequential acid-mediated deprotection of both ethers afforded 6-chloro-DHB (**7c**) in 15% overall yield. In the latter route, a simple starting material **18** serves for an expeditious assembly of a contiguously tetrasubstituted aromatic in reasonable overall yield.

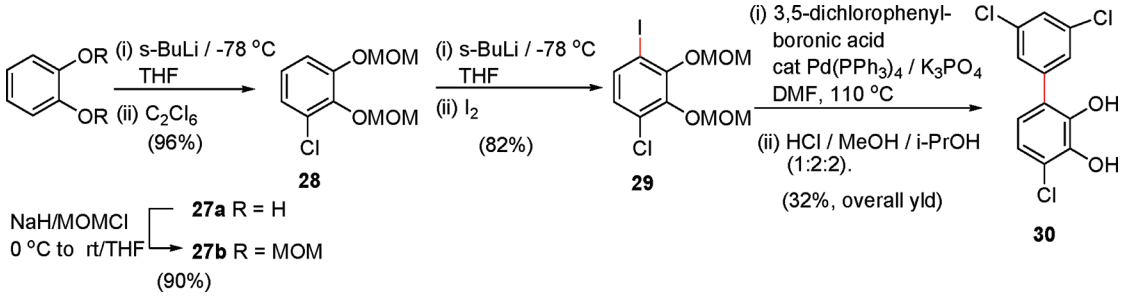
The regioselective construction of 5-chloro-DHB (**7b**, Scheme 6) commenced with the *ortho* metalation−boronation of **21** to afford **22** which, either as crude material or its corresponding pinacolate (see the Supporting Information), underwent Suzuki−Miyaura cross coupling to give the biphenyl **23**. The Cl functionality, now not meta-related to the OMOM DMG as in the case of **19**, has no DoM consequence[16] and hence the metalation−boronation−oxidation sequence leads, after deprotection, to the expected **7b** in 43% overall yield.

The requirement for more highly chlorinated DHBs for microbial degradation studies[8] was also met by regioselective DoM/Suzuki−Miyaura coupling strategies (Schemes 7 and 8). Thus, for the synthesis of 2′,6′-dichloro-DHB (**26**) (Scheme 7), commercially available **24** underwent smooth Suzuki−Miyaura coupling with arylboronic acid **9** (Scheme 3) to afford **25** (quantative yield) which, without purification, was subjected to standard demethylation to give **26** in good yield. This route, while representing a single case, suggests that Suzuki−Miyaura cross-coupling reactions of hindered diortho-halogenated partners may not be difficult to achieve.[10c] For the synthesis of 4,3′,5′-trichloro-DHB (**30**) (Scheme 8), catechol (**27a**) was converted into its di-MOM-diether (**27b**) which, upon metalation−chlorination, smoothly afforded **28** in high overall yield. As expected, a second metalation but followed by iodination led to the dihalogenated biphenyl **29**. The observed selectivities for the Suzuki reaction are well-known.[27] Differential reactivity for the subsequent cross coupling reaction having two different halogens having thus been established, treatment of **29** with commercial but expensive 3,5-dichlorobenzeneboronic acid

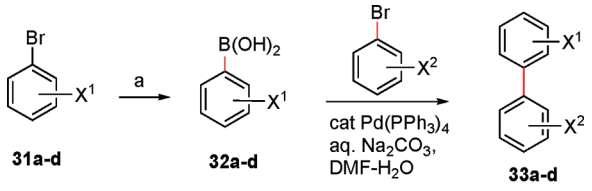
(15) For comparable cases, see: (a) Harvey, R. G.; Cortez, C.; Ananthanarayan, T. P.; Schmolka, S. *J. Org. Chem.* **1988**, *53*, 3936. (b) Weeratunga, G.; Jaworska-Sobiesiak, A.; Horne, S; Rodrigo, R. *Can. J. Chem.* **1987**, *65*, 2019.

(16) Fitt, J. J.; Gschwend, H. W.; Hamdan, A.; Boyer, S. K.; Haider, H. M. *J. Org. Chem.* **1982**, *47*, 3658.

SCHEME 8. Synthesis of 4,3′,5′-trichloro-DHB (30)



SCHEME 9. Synthesis of Selected PCBs (33a−d)



31, 32, 33	X^1	X^2	Overall yld, %
a	H	2,6-diCl	90
b	4-Cl	3,5-diCl	78
c	3,5-diCl	3,5-diCl	44
d	3,4-diCl	3,4-diCl	51

under anhydrous conditions[17] followed by HCl hydrolysis furnished the expected trichloro-DHB **30** in 32% overall yield. The advantage of DoM chemistry for the synthesis of differentially halogenated, electron-rich aromatics is exemplified by the convenient preparation of **29**.

Having provided the above chloro-DHB substrates for DHBD-catalyzed extradiol cleavage studies, attention turned to the synthesis of chlorinated biphenyls (PCBs) required for studies of the biphenyl 2,3-dioxygenase (BPDO)-catalyzed asymmetric dihydroxylation reaction.[8] In a brief study that parallels the work of Lehmer and Robertson but on different systems,[12] the regioselective synthesis of four PCB congeners, **33a−d** (Scheme 9), was achieved in short and convenient fashion by taking advantage of the commercial availability of chloro- and dichlorobromobenzene **31a−d** starting materials. Suzuki−Miyaura coupling with the boronic acids **32a−d**, prepared, excluding commercial **32a**, by metal−halogen exchange−boronation of the haloaroamatics **31a−d** under aqueous DMF conditions, afforded the PCBs **33a−d** in excellent to acceptable yields. The advantages of this strategy in higher yields over conventional (e.g., Cadogan[10c]) routes and in the handling of less toxic starting materials has already been emphasized.[12]

Conclusions

Convenient, short, and reasonably efficient syntheses of mono- (Schemes 3−6), di- (Scheme 7), and tri- (Scheme 8) chlorinated dihydroxybiphenyls (DHBs) via combined directed *ortho* metalation (DoM)/Suzuki−Miyaura cross-coupling strategies have been demonstrated. Furthermore, the rapid preparation of several regioisomerically pure PCBs from commercial halogenated aromatics has been achieved (Scheme 9). The rapidity and simplicity gained by the use of the DoM/Suzuki−Miyaura tactic is clearly illustrated by the regioselective synthesis of alternate-ring monochloro-DHBs **11a−d** (Scheme 3). Placing these modern synthetic methods into cooperative modes with proper consideration of the relative power of DMGs as schematized by conceptual features (Scheme 2, **E**, **F**, and **G**) leads to enhancement in the range of possible routes and in the selection of commercial starting materials. Illustrative of this potential are the syntheses of selected monochloro-DHBs **7a−c** (Schemes 4−6) which proceed in completely regioselective fashion to give single isomers which, by single recrystallization, give ultrapure samples for enzymatic or environmental monitoring (GC/HRMS)[10c] studies. Further advantage is achieved by alternative DoM/cross-coupling retrosynthetic analysis as evidenced by provision of two efficient routes to both 4-chloro-DHB (**7a**, Scheme 4) and 6-chloro-DHB (**7c**, Scheme 5). Concerning the widely appreciated and compellingly addressed detrimental steric hindrance effects in the Suzuki−Miyaura and related cross-coupling reactions,[18] the successful and efficient coupling to ultimately give **25** (Scheme 7), a triortho-substituted biaryl, although a single case, encourages the evaluation of other such cases. Finally, the value of iterative DoM pathways (Schemes 4 and 5), one with differential halogenation in service of regioselective cross coupling (Scheme 8), offers potential for further advancement of this chemistry.

Thus, in this work, the key attributes of DoM, its regioselectivity and its link to the Suzuki−Miyaura cross-coupling reaction, have been imparted singularly and iteratively to derive mono-, di-, and trichloro-DHBs. The purpose of the work is to provide these compounds as pure single isomers for the characterization of enzymatic pathways essential to understanding the degradation of PCBs and development of potential bioremediation strategies for these environmental pollutants.[8] While this goal constituted the continuing focus of the current work, the utility of the derived simple DoM concepts for the regioselective construction of polysubstituted, and perhaps particularly chlorinated (viz., Figure 1, **A−D**), aromatics may be appreciated.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on Bruker AC-200, AM-250, Avance-300, or Avance-400 instruments with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in parts per million (ppm) relative to TMS. ^{13}C NMR spectra were proton decoupled and recorded on Bruker Avance-200, Avance-300, or Avance-400 instrument spectrometers, using the carbon signal of deuterated solvent as the internal standard.

(17) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

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Melting points were determined on a Fisher Scientific hot stage melting point apparatus and are uncorrected. IR spectra were recorded on a BOMEM MB-100, MB-120, or MB-Series FT-infrared spectrophotometer as liquid films on NaCl plates or as KBr discs. Electron impact mass spectra (EIMS) were performed on Kratos MS890 (4 kV, 35 eV, 220 °C), Hewlett-Packard 5890 Series II/5971A MSD, or Varian Saturn 2000 spectrometers. The purity of the compounds was determined by a HP 6890 gas chromatograph (20% permethylated β-cyclodextrin column). All reported yields are isolated yields. THF and Et_2O were freshly distilled from sodium benzophenone ketyl under argon prior to use. Toluene was distilled from sodium. CH_2Cl_2 and DMF were distilled from CaH_2 (under reduced pressure for DMF). *n*-BuLi and *s*-BuLi were obtained from FMC Corporation or Sigma-Aldrich, as solutions in hexanes or cyclohexane, respectively, and were titrated periodically against *s*-butanol.[19] Starting chlorobenzene derivatives were purchased from Sigma-Aldrich and used without further purification. All reactions were performed in flame- or oven-dried glassware under argon, using syringe-septum cap techniques. Flash chromatography was carried out with Merck silica gel (0.040−0.063 mm).

2,3-Dimethoxyphenylboronic Acid (9).[19] A solution of TMEDA (26.8 mL, 179 mmol) and *n*-BuLi (70.8 mL, 2.53 M solution in hexanes, 179 mmol) in dry Et_2O (200 mL) was stirred for 15 min at 0 °C under an atmosphere of argon. 1,2-Dimethoxybenzene (**8**) (19.5 mL, 1.053 g/mL, 149 mmol) in dry Et_2O (20 mL) was added dropwise and the reaction mixture was stirred for 1 h at 0 °C. $B(OMe)_3$ (34.5 mL, 0.915 g/mL, 298 mmol) was then added and the pale yellow reaction mixture was stirred until it became clear, stirred another 10 min, warmed to rt, and adjusted to pH 6 with 1 N aq HCl. The mixture was diluted with CH_2Cl_2 (150 mL), and the aqueous layer was separated and extracted twice with CH_2Cl_2 (50 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated in vacuo. Recrystallization gave **9** (23.8 g, 88%) as colorless crystals: mp 66−68 °C (EtOAc/hexanes) (lit.[20] mp 72−73 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J_1 = 1.67 Hz, J_2 = 7.35 Hz, 1H, ArH), 7.14 (dd, J_1= 8.04 Hz, J_2 = 7.39 Hz, 1H, ArH), 7.05 (dd, J_1 = 1.65 Hz, J_2 = 8.08 Hz, 1H, ArH), 6.84 (br s, 2H, $B(OH)_2$), 3.95 (s, 3H, OCH_3), 3.88(s, 3H, OCH_3). The ^{1}H NMR spectrum was shown to be identical with that reported.[20]

2,3-Dimethoxybiphenyl (10a).[10c,21,22]To a 1000 mL 2-necked flask equipped with a condenser was added bromobenzene (3.8 mL, 1.491 g/mL, 36.5 mmol), $Pd(PPh_3)_4$ (2.11 g, 1.82 mmol), and THF (300 mL). The clear yellow solution was stirred for 15 min under an atmosphere of argon. 2,3-Dimethoxyphenylboronic acid (**9**) (9.95 g, 54.7 mmol) in THF (50 mL) was added dropwise followed by 2 M aq Na_2CO_3 (45.6 mL, 91.2 mmol) and the mixture was then heated at reflux for 13 h. The THF was removed and the residue was extracted twice with diethyl ether. The separated organic layer was washed with water, 2 N aq NaOH, and brine and dried ($MgSO_4$). Evaporation in vacuo and purification by flash -chromatography (EtOAc/*n*-hexane 1.5:8.5) afforded **10a** (5.94 g, 76%) as a pale yellow solid: mp 45−46 °C (EtOAc/hexanes) (lit.[21] mp 45 °C (light petroleum)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.56 (m, 2H, ArH), 7.46−7.36 (m, 3H, ArH), 7.14 (t, 1H, J = 7.9 Hz, ArH), 6.96 (dd, 2H, J = 8.1 Hz, J = 1.6 Hz, ArH), 3.94 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3). The ^{1}H NMR spectrum was shown to be identical with that reported.[21]

2,3-Dihydroxybiphenyl (11a). [10c,22] To a stirred solution of 2,3-dimethoxybiphenyl (**10a**) (4.13 g, 19.3 mmol) in dry CH_2Cl_2 (40 mL) at −78 °C under an atmosphere of argon was added boron tribromide (19.3 mL, 96.5 mmol) in CH_2Cl_2. The mixture was stirred for 2 h, allowed to warm to rt, and stirred overnight. Water (100 mL) was added dropwise at 0 °C and the mixture was warmed to rt. The aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. Purification by flash-chromatography (EtOAc/*n*-hexane 30:70) afforded **11a** (2.29 g, 64%, >99% purity by GC analysis) as an off-white solid: mp 112−113 °C (hexanes/EtOAc) (lit.[22] mp 114 °C (light petroleum)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.30 (m, 5H, ArH), 6.92−6.73 (m, 3H, ArH), 5.51 (br s, 1H), 5.33 (br s, 1H); HRMS calcd for $C_{12}H_{10}O_2$ 186.0681, found 186.0683. The ^{1}H NMR spectrum was consistent with that reported.[10c]

2′-Chloro-2,3-dimethoxybiphenyl (10b). To a solution of 1-chloro-2-iodobenzene (5.00 g, 21.0 mmol) in DME (100 mL) was added $Pd(PPh_3)_4$ (2.43 g, 2.10 mmol) and the solution was stirred for 15 min under argon. 2,3-Dimethoxyphenylboronic acid (**9**) (4.95 g, 31.4 mmol) in DME (50 mL) was added dropwise followed by the addition of 2 M aq Na_2CO_3 (80 mL, 160 mmol) and the mixture was then heated at reflux for 16 h. The solvent was removed in vacuo and the residue was extracted twice with diethyl ether. The combined organic layers were washed with water, 2 N NaOH, and brine, dried ($MgSO_4$), subjected to filtration, and concentrated in vacuo. Purification by flash chromatography (EtOAc/*n*-hexane 1:6) afforded **10b** (2.71 g, 52%) as pale yellow crystals: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47−7.22 (m, 7H, ArH), 7.09 (t, 1H, J = 7.9 Hz, ArH), 6.95 (dd, 2H, J = 8.1 Hz, J = 1.4 Hz, ArH), 6.82 (dd, 2H, J = 8.1 Hz, J = 1.3 Hz, ArH), 3.88 (s, 3H, OCH_3) 3.60 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 146.7, 137.4, 133.8, 133.5, 131.6, 129.3, 128.6, 126.3, 123.5, 122.9, 112.1, 60.6, 55.8; LRMS *m*/*z* (rel intensity) 250 (M + 2, 33), 248 (M^+, 100), 235 (7), 233 (22), 198 (84), 183 (12), 169 (7), 155 (20), 136 (18), 127 (24), 115 (9), 101 (8), 87 (6), 77 (9); HRMS calcd for $C_{14}H_{13}O_2Cl$ 248.0606, found 248.0604.

2′-Chloro-2,3-Dihydroxybiphenyl (11b). To a stirred solution of 2′-chloro-2,3-dimethoxybiphenyl (**10b**) (2.65 g, 10.7 mmol) in dry CH_2Cl_2 (40 mL) at −78 °C under an atmosphere of argon was added boron tribromide (5.07 mL, 53.7 mmol) in CH_2Cl_2. The mixture was stirred for 2 h, warmed to rt, and stirred overnight. Water (100 mL) was added dropwise at 0 °C and the mixture was warmed to rt. The aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were washed with water and brine, dried ($MgSO_4$), subjected to filtration, and concentrated. Purification by flash chromatography (EtOAc/*n*-hexane 25:75) afforded **11b** (2.29 g, 64%, >99% purity by GC analysis) as colorless crystals: mp 98 − 99 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45−7.21 (m, 4H, ArH), 6.92−6.78 (m, 3H, ArH), 5.37 (br, 2H, Ar-OH, H/D-exchange); MS *m*/*z* (rel intensity) 221 (M + 1, 2), 220 (15), 185 (20), 167 (2), 157 (6), 139 (5), 128 (8), 102 (2), 84 (100), 70 (2); HRMS calcd for $C_{12}H_9O_2Cl$ 220.0291, found 220.0293.

4-Chloro-2,3-dimethoxybiphenyl (12). A solution of TMEDA (13.0 mL, 83.0 mmol) and *n*-BuLi (32.8 mL, 2.56 M, 84.0 mmol) in dry THF (100 mL) was stirred for 15 min at 0 °C under argon. 2,3-Dimethoxybiphenyl (**10**) (5.13 g, 24.0 mmol) in dry THF (15 mL) was added dropwise and the mixture was stirred for 1 h at 0 °C. Hexachloroethane (14.2 g, 59.9 mmol) in THF (20 mL) was added and the reaction mixture was stirred for 45 min and then allowed to warm to rt. The reaction mixture was quenched with saturated NH_4Cl and the aqueous layer was separated and extracted with diethyl ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$, subjected to filtration, and concentrated. Purification by flash chromatography (9:1 hexanes/EtOAc) afforded **12** (4.54 g, 76%) as a pale yellow oil: IR (film) ν_{max} 3060, 2998, 2937, 2854, 1602, 1581, 1562, 1464, 1399, 1229, 1099, 1007, 866, 814, 788, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.36 (m, 5H, ArH), 7.20 (d, J = 8.4 Hz, 1H, ArH), 7.05 (d, J = 8.4 Hz, 1H, ArH), 3.98 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 150.4, 137.8, 135.7, 129.5, 128.7, 128.0, 127.9, 126.3, 125.5, 61.34, 61.32;

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LRMS *m*/*z* (rel intensity) 250 (M + 2, 28), 248.0 (M^+, 83), 232.9 (20), 198.0 (100), 182.9 (25), 154.9 (26), 138.7 (31), 127.0 (31), 125.4 (26), 101.5 (40); HRMS calcd for $C_{14}H_{13}O_2Cl$ 248.0604, found 248.0600.

2-Methoxymethoxy-3-hydroxybiphenyl (14). A solution of NaOH (15 mL, 40 wt %) was added dropwise to a solution of 2-hydroxybiphenyl (5.00 g, 29.3 mmol) in CH_2Cl_2 (70 mL) at 0 °C under dry argon and then stirred at 0 °C for 30 min. Chloromethyl methyl ether (11.8 g, 146 mmol) was added and the mixture was warmed to rt and stirred for 4 h. The reaction was diluted with water and the organic layer was separated and washed with water and brine, dried over $MgSO_4$, subjected to filtration, and concentrated to afford crude **13** (6.09 g, 97%), which was used without further purification. *n*-BuLi (20.0 mL, 1.70 M solution in hexanes, 34.1 mmol) was added dropwise to a stirred solution of **13** (6.09 g, 28.4 mmol) and TMEDA (4.08 g, 35.1 mmol) in Et_2O (100 mL) under argon at −30 °C and the reaction mixture was stirred for 2.5 h. $B(OMe)_3$ (13 mL, 4.0 equiv) was added and the reaction mixture was warmed to rt and stirred for a further 3.5 h. Water (50 mL) was added, followed by the addition of H_2O_2 (25 mL, 30% aq solution), and the solution was stirred for 2 h. The aqueous layer was separated and extracted once with diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$), subjected to filtration, and concentrated. Purification by flash chromatography (8:2 hexanes/EtOAc) afforded **14** (4.45 g, 68%) as a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50−7.33 (m, 5H, ArH), 7.11−6.84 (m, 4H, and Ar-OH, H/D-exchange), 4.73 (s, 2H, OCH_2O), 3.42 (s, 3H, OCH_3), which was used without purification in the synthesis of 2,3-dihydroxybiphenyl (**11a**).

2,3-Dihydroxybiphenyl (11a) from 14. A mixture of 2-methoxymethoxy-3-hydroxybiphenyl (**14**) (4.40 g, 32.7 mmol) in MeOH (20 mL) and HCl (10 mL, 3N) was stirred for 16 h at rt. The solution was diluted with CH_2Cl_2 (100 mL) and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), subjected to filtration, and concentrated. Purification of the residue via flash column chromatography (75:25 hexanes/EtOAc) afforded **11a** (3.18 g, 88%, >98% purity by GC-analysis) as an off-white solid, mp 105 − 108 °C (lit.[22] mp 118−119.5 °C), which showed an ^{1}H NMR spectrum identical with that reported.

4-Chloro-2,3-dihydroxybiphenyl (7a) from 15. *n*-BuLi (13.7 mL, 1.60 M solution in hexanes, 21.9 mmol) was added dropwise to a stirred solution of 2,3-bis(methoxymethoxy)biphenyl (**15**) (5.00 g, 18.2 mmol) and TMEDA (3.17 mL, 1.2 equiv) in Et_2O (100 mL) under argon at 0 °C and the reaction mixture was stirred 2.5 h then cooled to −78 °C. C_2Cl_6 (8.61 g, 36.4 mmol) was added and the reaction mixture was warmed to rt and stirred for 1 h. The reaction was quenched with saturated NH_4Cl (50 mL) and the aqueous layer was separated and extracted once with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), subjected to filtration, and concentrated. Purification by flash chromatography (6:1 hexanes/EtOAc) afforded 2,3-bis-(methoxymethoxy)-4-chlorobiphenyl (4.90 g, 89%) as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.51−7.32 (m, 5H, ArH), 7.21 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 5.24 (s 2H, OCH_2O), 4.82 (s, 2H, OCH_2O), 3.68 (s, 3H, OCH_3), 2.99 (s, 3H, OCH_3), which was used without purification. The 2,3-bis(methoxymethoxy)-4-chlorobiphenyl was dissolved in a mixture of aqueous HCl (15 mL, 3 N) and MeOH (30 mL) was and the whole was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and the aqueous layer was separated and extracted once with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), subjected to filtration, and concentrated. Purification by flash chromatography (7:3 hexane/EtOAc) afforded **7a** (2.30 g, 81%, >98% purity by GC analysis) as an off-white solid, which showed an ^{1}H NMR spectrum identical with that of **7a** prepared from **12** as described above.

6-Iodo-2,3-dimethoxybiphenyl (16). To a stirred solution of 2,3-dimethoxybiphenyl (**10a**) (1.86 g, 8.08 mmol) and AgOTf (1.79 g, 8.08 mmol) in $CHCl_3$ (50 mL) at rt was added dropwise a solution of I_2 (2.47 g, 9.70 mmol) in $CHCl_3$ (50 mL). The reaction mixture was stirred for 0.5 h, then passed through a pad of celite, and the pad of celite was washed with $CHCl_3$. The solvent was removed in vacuo, water (100 mL) and EtOAc (100 mL) were added, the layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), subjected to filtration, and concentrated. Purification of the residue by flash column chromatography (9:1 hexane:EtOAc) afforded **16** (1.95 g, 68%) as a pale yellow solid: mp 81−83 °C (EtOAc/hexanes); GC ret time = 12.81; IR (KBr) ν_{max} 3065, 3021, 2961, 2930, 2834, 1563, 1459, 1407, 1293, 1249, 1216, 1118, 998, 805 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, 1H, ArH, J = 8.9 Hz), 7.49−7.26 (m, 3H, ArH), 7.07−7.24 (m, 2H, ArH), 6.63 (d, 1H, ArH, J = 8.4 Hz), 3.80 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3); ^{13}C NMR (75 MHz) δ 153.4, 147.2, 141.1, 140.7, 134.0, 129.6, 127.9, 127.6, 113.6, 89.1, 60.7, 56.0; LRMS *m*/*z* (rel intensity) 340.1 (M^+, 63), 197.9 (100), 182.9 (37), 169.1 (22), 154.9 (50), 151.9 (22), 148.9 (26), 140.8 (33), 138.9 (39), 127.1 (54), 125.9 (58), 114.8 (24.47), 112.9 (29), 110.8 (48), 108.9 (28), 104.9 (55); HRMS calcd for $C_{14}H_{13}O_2I$ 339.9960, found 339.9953.

6-Chloro-2,3-dimethoxybiphenyl (17). A solution of *t*-BuLi (8.61 mL, 1.35 M solution in hexanes, 11.6 mmol) was added dropwise to a stirred solution of 6-iodo-2,3-dimethoxybiphenyl (**16**) (1.66 g, 4.65 mmol) in THF (70 mL) at −78 °C and the reaction mixture was stirred for 15 min. A solution of hexachloroethane (2.78 g, 99.8%, 9.70 mmol) in THF (20 mL) was added dropwise by cannula and the whole was stirred for 45 min at −78 °C. The reaction mixture was quenched with satd NH_4Cl and the whole was evaporated in vacuo. The residue was disolved in EtOAc (100 mL) and the solution was washed with water (25 mL) and brine (25 mL), dried (Na_2SO_4), subjected to filtration, and concentrated. Purification by flash column chromatography (9:1 hexane:EtOAc) afforded **17** (0.91 g, 70%) as an off-white solid: mp 90−91 °C (EtOAc/hexanes) (lit.[21] mp 90.5−91 °C (MeOH)); GC ret time = 11.83; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.36 (m, 5H, ArH), 7.02 (d, J = 8.7 Hz, 1H, ArH), 6.68 (d, J = 8.7 Hz, 1H, ArH), 3.73 (s, 3H, OCH_3), 3.43(s, 3H, OCH_3). The ^{1}H NMR spectral data were shown to be identical with that reported.[21]

2′,6′-Dichloro-2,3-dihydroxybiphenyl (26). A flask containing 1-bromo-2,6-dichlorobenzene (**24**) (0.17 g, 0.75 mmol), 2,3-dimethoxyphenylboronic acid (**9**) (0.14 g, 0.77 mmol), and Pd-$(PPh_3)_4$ (20 mg, 0.017 mmol) was flushed with argon and DME (10 mL) was added. After 10 min of stirring, aq Na_2CO_3 (2 M, 6 mL) was added and the whole was heated at reflux for 12 h. The reaction mixture was cooled then evaporated in vacuo and the residue was extracted with Et_2O (2×). The combined organic layer was washed with water and brine, dried (Na_2SO_4), then subjected to filtration, and the filtrate was concentrated. Purification by flash chromatography (EtOAc/hexane 1:5) afforded 2′,6′-dichloro-2,3-dimethoxybiphenyl (**25**) (0.19 g, 90%) as a colorless oil that was used without further purification in the reaction described below.

To a stirred solution of 2′,6′-dichloro-2,3-dimethoxybiphenyl (**25**) (0.19 g, 0.67 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C under an atmosphere of argon was added BBr_3 (1 M in hexane, 3 mL). The mixture was stirred for 2 h, allowed to warm to rt, and stirred for 12 h. Water (10 mL) was added dropwise at 0 °C and the mixture was warmed to rt. The aqueous layer was separated and extracted with CH_2Cl_2 (2×). The combined organic extract was washed with water and brine, dried (Na_2SO_4), then subjected to filtration, and the filtrate was concentrated. Purification by flash chromatography (EtOAc/hexane 1:3) afforded **26** (0.13 g, 76%) as colorless crystals: mp 138−140 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 8.3 Hz, 2H, ArH), 7.31 (dd, J = 8.6, 7.5 Hz, 1H, ArH), 7.00 (dd, 8.0, 1.6 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.70 (dd, J = 7.5, 1.7 Hz, 1H), 5.30 (s, 1H, Ar-OH), 4.84 (s, 1H, Ar-OH); ^{13}C NMR (100 MHz, DMSO) δ 145.7, 143.4, 137.2, 135.2, 130.1, 128.4, 124.7, 120.8, 119.2, 115.8; MS EI *m*/*z* (rel intensity) 254

(M^+, 89), 218 (26), 184 (100); HRMS calcd for $C_{12}H_8Cl_2O_2$ 253.9901, found 253.9906.

3,5,3′,5′-Tetrachlorobiphenyl (33c). A solution of 1-bromo-3,5-dichlorobenzene (**31c**) (300 mg, 1.33 mmol) in THF (30 mL) at −78 °C was treated dropwise with *n*-BuLi (0.60 mL, 2.40 M solution in hexanes, 1.44 mmol) and the resulting solution was stirred for 1 h. $B(OMe)_3$ (0.17 mL, 1.44 mmol) was added dropwise and the reaction mixture was stirred for 45 min, warmed to rt, then quenched with satd NH_4Cl and the aqueous layer was separated and extracted with diethyl ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), then subjected to filtration, and the filtrate was concentrated to afford crude 3,5-dichlorophenylboronic acid (**32b**) (200 mg, 79%) as a colorless solid that was used in the following cross-coupling reaction without further purification.

To a flask equipped with a condenser was added $Pd(PPh_3)_4$ (48 mg, 0.04 mmol), 3,5-dichlorophenylboronic acid (**32b**) (200 mg, 1.05 mmol), Na_2CO_3 (125 mg, 1.18 mmol), and 3,5-dichloro-1-bromobenzene (**31c**) (260 mg, 1.15 mmol) in a mixture of DMF−water (50−12 mL) and the mixture was stirred at rt for 15 min under dry argon atmosphere and then heated to reflux for 2 d. The solvent was removed in vacuo and the residue was partitioned between EtOAc (100 mL) and water (50 mL). The organic layer was separated, washed with water (50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), then subjected to filtration, and the filtrate was concentrated. Purification by flash column chromatography (9:1, hexane:EtOAc) afforded **33c** (135 mg, 44%) as a colorless solid: mp 165−167 °C (hexanes) (lit.[26] mp 171−173 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 1.6 Hz, 4H, ArH), 7.68 (t, J = 1.6 Hz, 2H, ArH); LRMS *m*/*z* (rel intensity) 296 (M + 6, 11), 294 (M + 4, 53), 294 (M + 2, 100), 290 (M^+, 80), 222 (21), 220 (33).

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Supporting Information Available: Experimental procedure and characterization data for the synthesis of compounds **10c**, **11c**, **10d**, **11d**, **7a** from **12**, **15**, **7c** from **17**, **19**, **7c** from **19**, **22**, **23**, **7b**, **27b**, **28**, **29**, **30**, **33a**, and **33d** and ^{1}H NMR and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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