Directed *ortho* Metalation and Suzuki–Miyaura cross-coupling connections: regiospecific synthesis of all isomeric chlorodihydroxybiphenyls for microbial degradation studies of PCBs

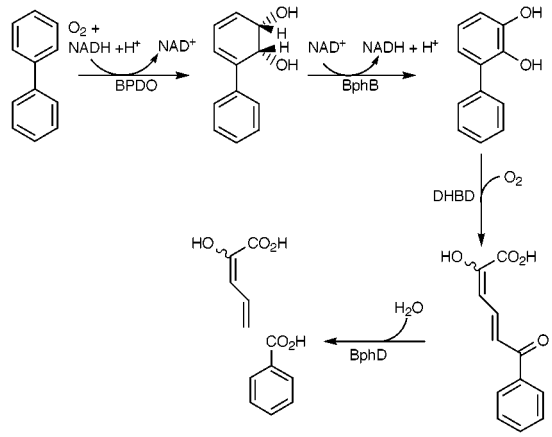
S. Nerdinger,[a] C. Kendall,[b] R. Marchhart,[a] P. Riebel,[a] M. R. Johnson,[b] C.-F. Yin,[b] L. D. Eltis[c]† and V. Snieckus*[b]

[a] *Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo, Waterloo, ON, Canada N2L 3G1*
[b] *Department of Chemistry, Queen's University, Kingston, ON, Canada K7L 3N6. E-mail: snieckus@chem.queensu.ca*
[c] *Department of Biochemistry, Université Laval, Québec City, Québec, Canada G1K 7P4*

Received (in Corvallis, OR, USA) 7th September 1999, Accepted 28th September 1999

Monochloro DHBs 1a–d and 2a–c have been regioselectively synthesised in good overall yields by a combination of directed *ortho* metalation and Suzuki–Miyaura cross-coupling.

The aerobic microbial degradation of aromatic compounds such as toluene, naphthalene and biphenyl is an essential link in the global carbon cycle and generally proceeds *via* catechol intermediates involving cleavage by either intradiol or extradiol dioxygenases.[1] For biphenyl, fundamental interest in understanding the respective proposed mechanisms of the extradiol cleavage of catechol by 2,3-dihydroxybiphenyl-1,2-dioxygenases (DHBDs)[2,3] and the subsequent hydrolysis of the ring cleaved product catalysed by 2-hydroxy-6-oxo-6-phenylhexa-2,4-dienoate hydrolase (BphD)[3] (Scheme 1) is intensified by the prospect of exploiting these enzymes in the degradation of environmental pollutants such as polychlorinated biphenyls (PCBs).[4,5] In connection with ongoing studies in this area,[6] we describe the regiospecific synthesis of all six isomeric monochloro-2,3-dihydroxybiphenyls (DHBs) **1b–d** and **2a–c**. The synthetic route takes advantage of combined Directed *ortho* Metalation (D*o*M)[7] and Pd-catalyzed Suzuki–Miyaura cross-coupling[8] reactions, a methodological theme currently evolving in our laboratories.[9] The key conceptual features, depicted for **3–5** (Scheme 2), include new strategies of oxygen-directed metalation group (DMG) use in walk-around-the-ring functionalization (**2a**, **2c**).

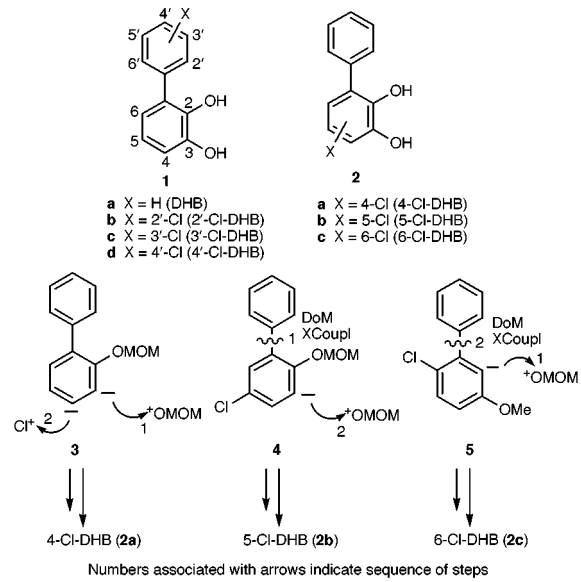


Scheme 1 Enzymes involved in the aerobic microbial degradation of biphenyl and PCBs: BPDO = biphenyl dioxygenase; BphB = 2,3-dihydro-2,3-dihydroxybiphenyl dehydrogenase; DHBD = 2,3-dihyroxybiphenyl dioxygenase; BphD = 2-hydroxy-6-oxo-6-phenylhexa-2,4-dienoate hydrolase.

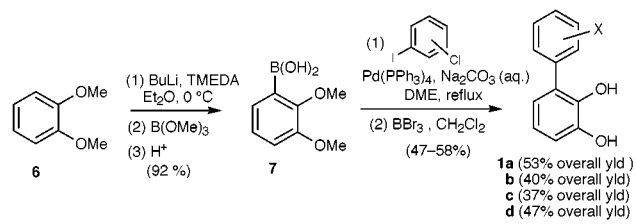
† Current address: Department of Microbiology and Immunology, University of British Columbia, Vancouver, B.C., Canada V6T 1Z3.

Metalation[7] and a trimethyl borate quench of **6** (Scheme 3) afforded the boronic acid **7** which, in crude form, was subjected to Suzuki–Miyaura cross-coupling with bromobenzene or commercially available isomeric chloroiodobenzenes followed by standard BBr_3 deprotection to furnish biaryls **1a–d** in modest overall yields on a gram scale. A comparable yielding (58%) alternate synthesis (Scheme 4) of parent compound **1a** from 2-MOM biphenyl **8**, prepared (NaH, MOMCl, THF, room temperature) from inexpensive 2-hydroxybiphenyl, proceeded by metalation–boronation–oxidation[10] to introduce an OH^+ synthon to afford **9** followed by hydrolysis.

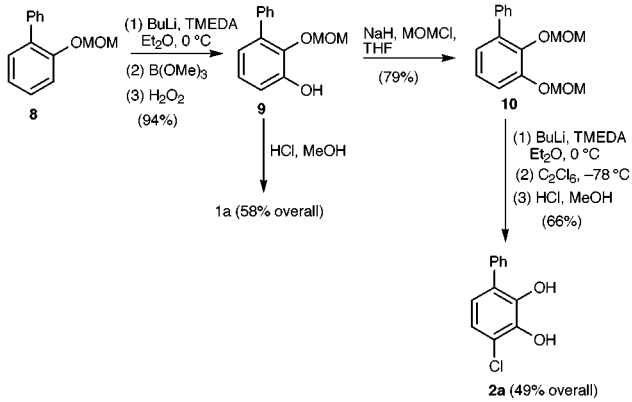
Intermediate **9** also served for a concise synthesis of 4-chloro-DHB **2a** (Scheme 4). Thus, conversion to the MOM derivative **10** as before followed by a second D*o*M reaction,



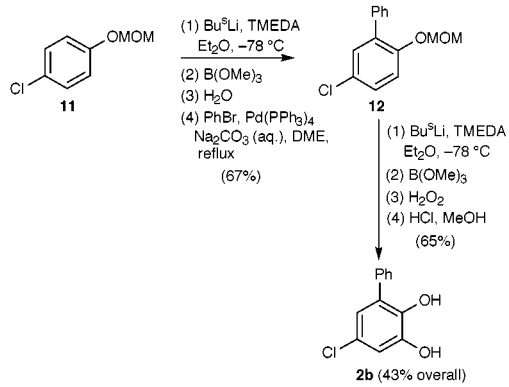
Scheme 2



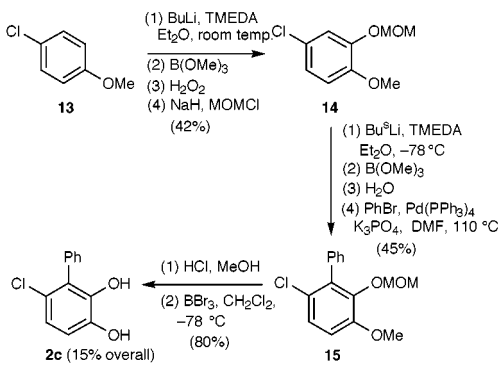
Scheme 3



Scheme 4



Scheme 5



Scheme 6

chlorination with C_2Cl_6, and HCl-mediated deprotection completed the walk-around-the-ring sequence to afford **2a** in good overall yield (49%). The regiospecific construction of 5-chloro-DHB **2b** (Scheme 5) began from the 4-chlorophenol-derived **11** which, upon metalation–boronation-cross-coupling, gave the biphenyl **12**. Adapting the OH^+ synthon introduction as for **8**, followed by hydrolysis, led to **2b** in an acceptable overall yield (43%). The synthesis of 6-chloro-DHB[11] **2c** (Scheme 6) was achieved in a similar fashion, again exploiting the walk-around-the ring sequence. Thus, metalation of **13** followed by boronation–oxidation afforded the intermediate phenol which was converted to the MOM derivative **14**. Subsequent metalation–trimethyl borate quench afforded the 2-boronic acid, which, in crude form, was subjected to Suzuki–Miyaura cross-coupling with bromobenzene to give **15**, followed by hydrolysis and BBr_3 deprotection to afford **2c** (15%). The regiospecificity of all DoM reactions was established by 1D- and 2D-NMR. Final products were obtained in purities > 99% as required for the substrate specificity and inhibition studies of DHBD and BphD.[6]

This work demonstrates the expedient synthesis of all monochloro 2,3-DHBs by the directed *ortho* metalation–Suzuki–Miyaura cross-coupling sequence.[7] The key attribute of DoM, its regioselectivity, is imparted singularly and in an iterative manner (**3**), and leads to single isomer chloro-DHBs in high purity and in gram quantities. The method is being used for the provision of other diverse chloro-DHBs as well as catechols[12] to gain further understanding of the respective catalytic mechanisms of DHBD and BphD.[2,3]‡

We are grateful to NSERC (Strategic grant STP0193182) for generous support of this interdisciplinary study.

Notes and references

‡ All new compounds show analytical and spectral (^1H, ^{13}C NMR, HRMS) data fully consistent with their structures.

1 S. Dagley, in *The Bacteria*, ed. J. R. Sokatch and L. N. Ornston, Academic Press, New York, 1986, pp. 527–555.
2 L. Que and R. Y. N. Ho, *Chem. Rev.*, 1996, **96**, 2607.
3 T. D. H. Bugg and C. J. Winfield, *Nat. Prod. Rep.*, 1998, 513.
4 K. N. Timmis, R. J. Steffan and R. Unterman, *Annu. Rev. Microbiol.*, 1994, **48**, 525.
5 D. D. Focht, *Curr. Opin. Biotechnol.*, 1995, **6**, 341.
6 (*a*) S. Y. K. Seah, G. Terracina, J. T. Bolin, P. Riebel, V. Snieckus and L. D. Eltis, *J. Biol. Chem.*, 1998, **273**, 22943; (*b*) F. H. Vaillancourt, S. Han, P. D. Fortin, J. T. Bolin and L. D. Eltis, *J. Biol. Chem.*, 1998, **273**, 34 887; (*c*) S. Y. K. Seah, G. Labbe, S. Nerdinger, M. R. Johnson, V. Snieckus and L. D. Eltis, submitted for publication.
7 V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.
8 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*b*) A. Suzuki, in *Metal Catalyzed Cross-Coupling Reactions*, ed. F. Diedrich and P. J. Stang, Wiley-VCH, Weinheim, 1998.
9 C. A. Quesnelle, O. B. Familoni and V. Snieckus, *Synlett*, 1994, 349 and references cited therein; V. Snieckus, in *Chemical Synthesis: Gnosis to Prognosis*, ed. C. Chatgilialoglu and V. Snieckus, NATO ASI Series E, 1996, vol. 320, Kluwer, Dordrecht, The Netherlands, p. 191; G. Queguiner, F. Marsais, V. Snieckus and J. Epsztajn, *Adv. Heterocycl. Chem.*, 1991, **52**, 187.
10 A. D. Ainley and F. Challenger, *J. Chem. Soc.*, 1930, 2171.
11 6-Cl-DHB (**2c**) was also prepared as follows: iodination (I_2, $AgOCOCF_3$, $CHCl_3$) of 2,3-dimethoxybiphenyl gave exclusively the 6-iodo isomer which, upon metal–halogen exchange and chlorination (Bu^tLi, THF, −78 °C then C_2Cl_6) followed by deprotection (BBr_3, CH_2Cl_2, −78 °C) furnished **2c** in an overall yield of 29%.
12 3-Et (23% overall), 3-Pr^i (11% overall), 3-Bu^t (28% overall), and 3-Cl species (77% overall) have been prepared by this method (P. Riebel and V. Snieckus, unpublished results and utilized as described elsewhere). [ref. 6(*a*), (*b*)].

Communication 9/07279I