

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

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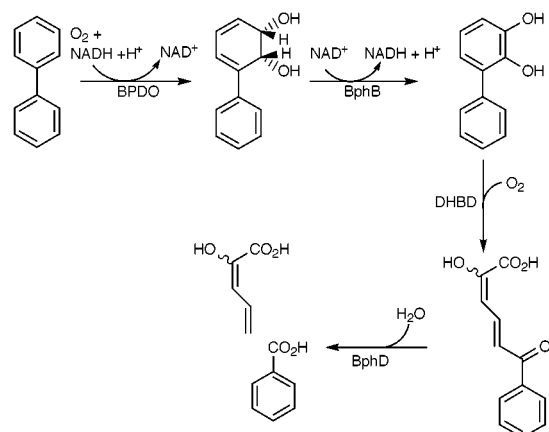
Monochloro DHBs **1a–d** and **2a–c** have been regioselectively synthesised in good overall yields by a combination of directed *ortho* metalation and Suzuki–Miyaura cross-coupling.

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.<sup>1</sup> For biphenyl, fundamental interest in understanding the respective proposed mechanisms of the extradiol cleavage of catechol by 2,3-dihydroxybiphenyl-1,2-dioxygenases (DHBDOs)<sup>2,3</sup> and the subsequent hydrolysis of the ring cleaved product catalysed by 2-hydroxy-6-oxo-6-phenylhexa-2,4-dienoate hydrolase (BphD)<sup>3</sup> (Scheme 1) is intensified by the prospect of exploiting these enzymes in the degradation of environmental pollutants such as polychlorinated biphenyls (PCBs).<sup>4,5</sup> In connection with ongoing studies in this area,<sup>6</sup> 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 (DoM)<sup>7</sup> and Pd-catalyzed Suzuki–Miyaura cross-coupling<sup>8</sup> reactions, a methodological theme currently evolving in our laboratories.<sup>9</sup> 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**).

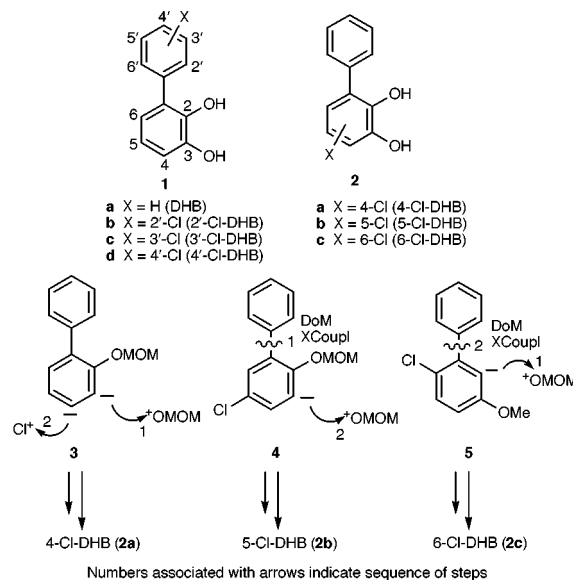
Metalation<sup>7</sup> and a trimethyl borate quench of **6** (Scheme 3) afforded the boronic acid **7** which, in crude form, was subjected to Suzuki–Miyaura cross-coupling with bromobenzene or commercially available isomeric chloriodobenzenes followed by standard BBr<sub>3</sub> deprotection to furnish 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<sup>10</sup> to introduce an OH<sup>+</sup> 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 DoM reaction,

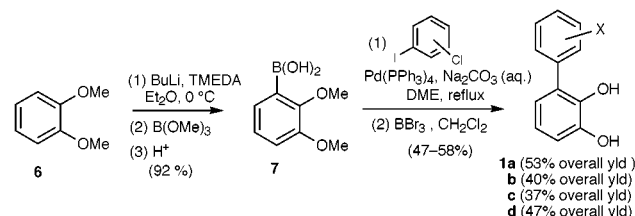


**Scheme 1** Enzymes involved in the aerobic microbial degradation of biphenyl and PCBs: BPDO = biphenyl dioxygenase; BphB = 2,3-dihydroxybiphenyl dehydrogenase; DHBD = 2,3-dihydroxybiphenyl dioxygenase; BphD = 2-hydroxy-6-oxo-6-phenylhexa-2,4-dienoate hydrolase.

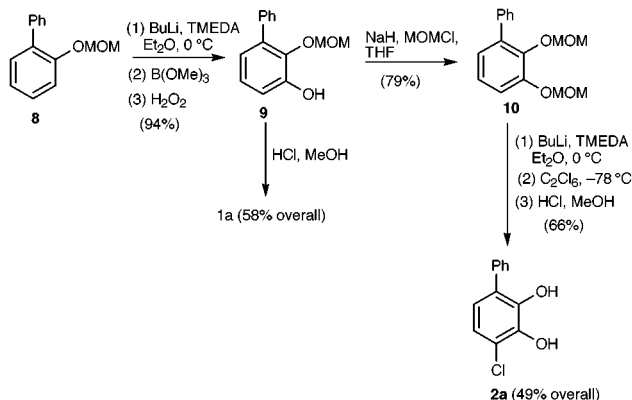
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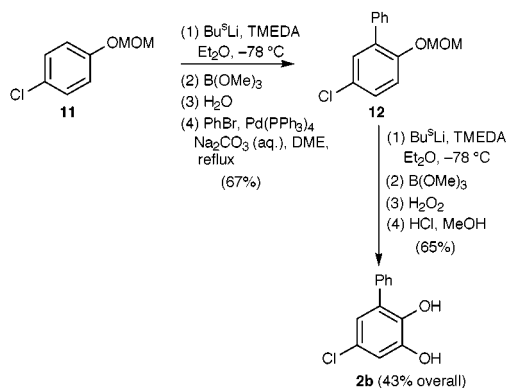
**Scheme 2**



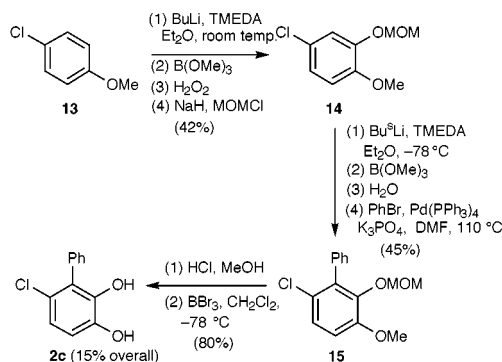
**Scheme 3**



Scheme 4



Scheme 5



Scheme 6

chlorination with  $\text{C}_2\text{Cl}_6$ , and HCl-mediated deprotection completed the walk-around-the-ring sequence to afford **2a** in good overall yield (49%). The regioselective 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  $\text{OH}^+$  synthon introduction as for **8**, followed by hydrolysis, led to **2b** in an acceptable overall yield (43%). The synthesis of 6-chloro-DHB<sup>11</sup> **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  $\text{BBr}_3$  deprotection to afford **2c** (15%). The regioselectivity 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.<sup>6</sup>

This work demonstrates the expedient synthesis of all monochloro 2,3-DHBs by the directed *ortho* metalation–Suzuki–Miyaura cross-coupling sequence.<sup>7</sup> 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<sup>12</sup> to gain further understanding of the respective catalytic mechanisms of DHBD and BphD.<sup>2,3†</sup>

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## Notes and references

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

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- 6-Cl-DHB (**2c**) was also prepared as follows: iodination ( $\text{I}_2$ ,  $\text{AgO-COCF}_3$ ,  $\text{CHCl}_3$ ) of 2,3-dimethoxybiphenyl gave exclusively the 6-iodo isomer which, upon metal–halogen exchange and chlorination ( $\text{Bu}^t\text{Li}$ , THF,  $-78^\circ\text{C}$  then  $\text{C}_2\text{Cl}_6$ ) followed by deprotection ( $\text{BBr}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ) furnished **2c** in an overall yield of 29%.
- 3-Et (23% overall), 3-Pr<sup>i</sup> (11% overall), 3-Bu<sup>t</sup> (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)].

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