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Unexpected Phenol Production from Arylboronic Acids under Palladium-Free Conditions; Organocatalyzed Air Oxidation

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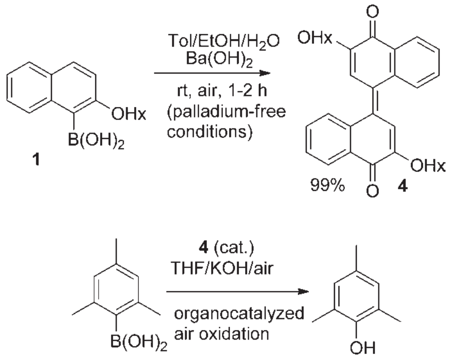
ABSTRACT



An intriguing class of quinones that efficiently catalyze the air oxidation (overall hydroxylation) of arylboronic acids to the corresponding phenol is reported. Autocatalysis in the parent system is particularly efficient and leads to rapid, quantitative synthesis of quinones such as 4 from boronic acid 1 at room temperature using air as stoichiometric oxidant. The efficiency results from a balance between two-stage conjugate addition and migration with each step driven by aromatization of a naphthalene fragment.

Suzuki–Miyaura cross-couplings employing boronic acids as the organometallic component are widely encountered.[1] Indeed it is reasonable to state that the reaction is among the most important to be developed over recent decades. The scope of the reaction is now broad. Part of the reason for the wide use of the reaction derives from the use of boronic acids. They are typically relatively easy to synthesize and have long-term shelf stability. Reactions generally do not require dry or inert conditions. To promote transmetalation and rapid catalytic turnover, boronic acids (or their boronate esters) need to be activated by reaction with an appropriate nucleophile to form the boronate complex. Preisolation of these species is often convenient.[2] The conversion of carbon–boron bonds into carbon–oxygen bonds via intramolecular migration are similarly very important reactions. They are exemplified by the anti-Markovnikov synthesis of alcohols from alkenes but extend to many other multistep processes that first involve other C–B to C–C migrations.[3] The final C–B to C–O conversion is invariably achieved using hydrogen peroxide that, under basic conditions, generates HOO^- that adds to boron to form the boronate salt. C–B to C–O migration then proceeds with displacement of hydroxide as leaving group.

As part of a separate program we sought to couple simple bromobenzenes with alkoxynaphthylboronic acids **1** and **5**. The coupling reaction was expected to be relatively

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(1) Reviews on the Suzuki–Miyaura reaction include (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (c) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419.

(2) Cammidge, A. N.; Goddard, V. H. M.; Gopee, H.; Harrison, N. L.; Hughes, D. L.; Schubert, C. J.; Sutton, B. M.; Watts, G. L.; Whitehead, A. J. *Org. Lett.* **2006**, *8*, 4071.

(3) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, 1988.

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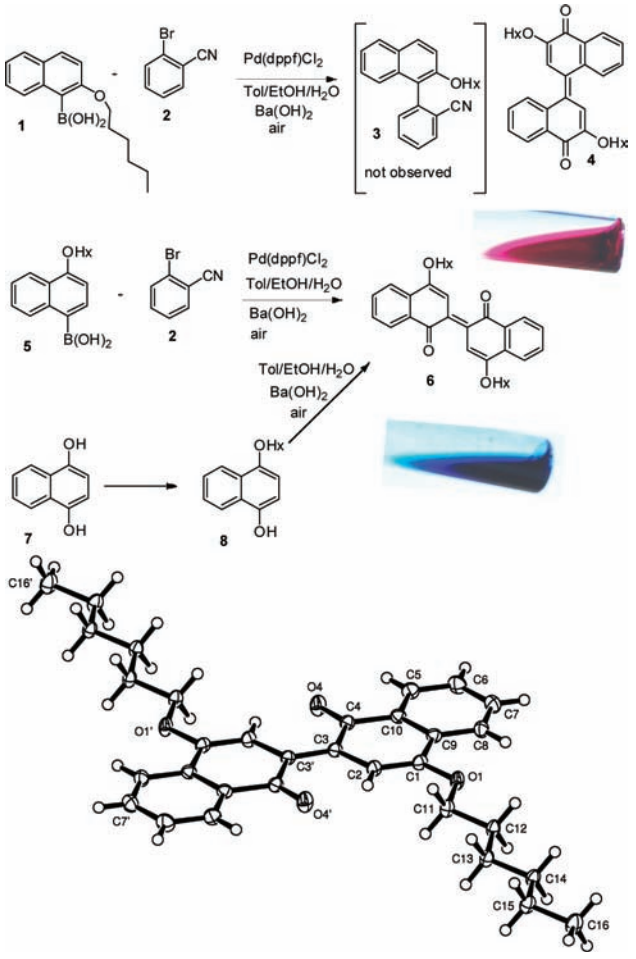
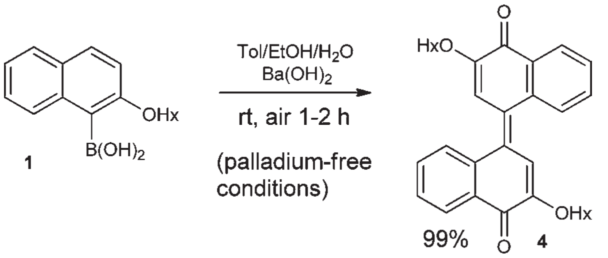
Scheme 1. Exclusive Formation of Quinones **4** and **6** during Suzuki–Miyaura Couplings Employing Alkoxynaphthylboronic Acids **1** and **5** via their Corresponding Naphthols and the Crystal Structure of **6**[9]



straightforward, although it was recognized that the boronic acid component had significant steric demand. In fact, Suzuki–Miyaura coupling under standard conditions[4] (Pd, toluene/ethanol/water) gave none of the desired product. Rather, the highly colored quinones **4** (dark pink) and **6** (blue) were isolated in high yields (Scheme 1). At first sight production of **4** and **6** can be easily rationalized. It is known that metals such as palladium can catalyze the oxidation of boronic acids to alcohols using molecular oxygen, and phenolic side products are often observed in such reactions.[5] Efficient catalysis of the process by copper has also been recently reported.[6] Oxidative coupling was easy to verify through independent synthesis of alkoxynaphthol **8**. Subjecting **8** to the reaction conditions (base, air) rapidly yielded quinone **6**, and no other reagents were needed. Such oxidative couplings often employ metal salts as reagents or catalysts,[7] although aerobic oxidation is also reported.[8]

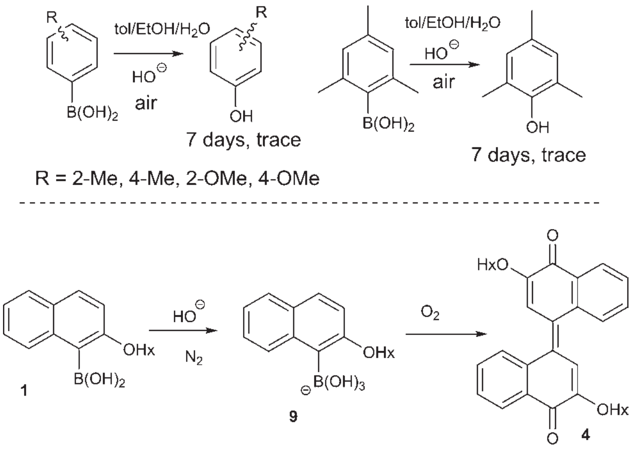
The key step therefore appears to be the production of phenol from boronic acid, and the most surprising observation occurred during model reaction studies. In one model, designed as a control experiment, the palladium catalyst was omitted from the reaction. Remarkably, an identical outcome was observed, and the reaction produced **4** in essentially quantitative yield in about 1 h at room temperature (Scheme 2).

Scheme 2. Palladium-Free Conversion of Alkoxynaphthylboronic Acid **1** to Quinone **4**



Oxidative hydroxylation of certain alkylboronates is known to occur via a radical mechanism,[10] but this observation is unexpected for the arylboronic acids under this study and therefore a separate, unique mechanism must operate. The generality of the palladium-free phenol production was therefore investigated further. Simple, electron-rich, and sterically encumbered arylboronic acids were subjected to the aerobic, basic reaction conditions, but in all cases the reactions failed to yield any more than a trace of the corresponding phenols (Scheme 3). The oxidation reaction therefore appeared to be unique to specific alkoxynaphthylboronic acids. A careful control experiment was performed whereby oxygen was rigorously excluded from a reaction carried out in an NMR tube. In the absence of oxygen the reaction of **1** unambiguously rests at the trihydroxyboronate salt[2] state, **9**. Production of the quinone **4** (via the naphthol) occurs rapidly when air is allowed into the reaction (Scheme 3).

Scheme 3. Model Reactions Showing Only Trace Phenol Formation from Typical Arylboronic Acids and Demonstration That Oxygen Drives Naphthol and Quinone Formation for **1**



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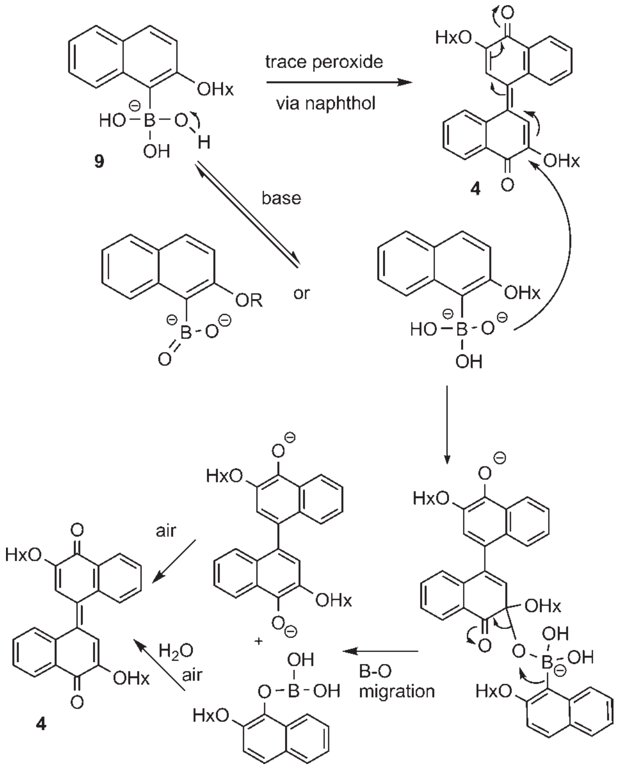
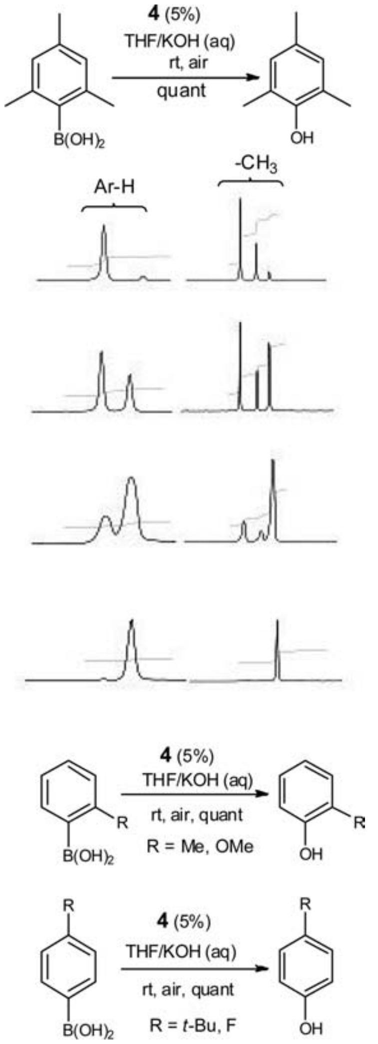
(4) (a) Bahl, A.; Grahn, W.; Stadler, S.; Feiner, F.; Bourhill, G.; Brauchle, C.; Reisner, A.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1485. (b) Andersen, N. G.; Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 9556.

Scheme 4. Mechanism for the Autocatalytic Production of Quinone **4**



Two further observations then led to the final unmasking of the process taking place in these transformations.

Scheme 5. Use of **4** as a General and Versatile Organocatalyst for Oxidative Hydroxylation of Arylboronic Acids by Air[a]



[a] Inset: conversion of mesitylboronic acid to mesityl alcohol monitored by ^{1}H NMR spectroscopy (Ar-H, left, and Me, right); time = 0 (top), time = 7 days (bottom).

Closer monitoring of the reaction revealed that there is an induction period (ca. 5–20 min) after which time the reaction proceeds rapidly to completion. Further screening of conditions revealed that at least 2 equiv of strong base (barium hydroxide, sodium hydroxide, etc.) was required for reaction. These observations allowed the mechanism of the overall reaction to be unraveled, and it was found to proceed via an autocatalytic pathway, accounting for both the observed kinetics (induction period) and the substrate specificity. Scheme 4 describes the mechanism operating. Trace peroxide produces a low concentration of naphthol in the mixture. Oxidative phenolic coupling (slow due to high dilution) gives quinone **4** after further air oxidation. In the presence of strong base, trihydroxyboronate salt **9** undergoes further deprotonation, and the resulting nucleophile attacks quinone **4** in a conjugate addition driven by aromatization of one naphthalene fragment. Migration of the naphthalene unit from boron to oxygen is facile and

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(5) (a) Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829. (b) Chaicharoenwimolkul, L.; Munmai, A.; Chairam, S.; Tewasekson., U.; Sapudom, S.; Lakliang, Y.; Somosook, E. *Tetrahedron Lett.* **2008**, *49*, 7299. (c) Sakurai, H.; Tsunoyama, H.; Tsukuda, T. *J. Organomet. Chem.* **2007**, *692*, 368. (d) Yoo, K. S.; Yoon, C. H.; Jung, K. W. *J. Am. Chem. Soc.* **2006**, *128*, 16384. (e) Tsunoyama, H.; Sakurai, H.; Ichikuni, N.; Negishi, Y.; Tsukuda, T. *Langmuir* **2004**, *20*, 11293. (f) Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231. (g) Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G.; Combs, A. P. *Tetrahedron Lett.* **2003**, *44*, 1691. (h) Crawford, C. L.; Barnes, M. J.; Peterson, R. A.; Wilmarth, W. R.; Hyder, M. L. *J. Organomet. Chem.* **1999**, *581*, 194. (i) Smith, K. A.; Campi, E. M.; Jackson, W. R.; Marcuccio, S.; Naeslund, C. G. M.; Deacon, G. B. *Synlett* **1997**, 131.

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(7) (a) Kral, A.; Laatsch, H. *Z. Naturforsch. B* **1993**, *48*, 1401. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (c) Hon, S.-W.; Li, C.-H.; Kuo, J.-H.; Barhate, N. B.; Liu, Y.-H.; Wang, Y.; Chen, C.-T. *Org. Lett.* **2001**, *3*, 869. (d) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S. *J. Org. Chem.* **1999**, *64*, 2264. (e) Toda, F.; Tanaka, K.; Iwata, S. *J. Org. Chem.* **1989**, *54*, 3007. (f) Corma, A.; Garcia, H. *Chem. Rev.* **2002**, *102*, 3837. (g) Sakamoto, T.; Yonehara, H.; Pac, C. *J. Org. Chem.* **1997**, *62*, 3194. (h) Otsuka, T.; Okamoto, I.; Kotani, E.; Takeya, T. *Tetrahedron Lett.* **2004**, *45*, 2643.

(8) Bao, J. B.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S. M.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392.

(9) Crystal structure data is deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 838471.

(10) Cadot, C.; Dalko, P. I.; Cossy, J.; Ollivier, C.; Chuard, R.; Renaud, P. *J. Org. Chem.* **2002**, *67*, 7193.

favored by aromatization of the second naphthalene fragment of the catalyst. Hydrolysis of the boronate produced and air oxidation of both products produce more quinone **4** to mediate further boronic acid oxidation.

The final verification of the catalytic activity of quinones such as **4** was achieved by returning to the original model reactions. For example, mesitylboronic acid produces no more than a trace of the corresponding phenol product when treated with concentrated KOH in THF for 7 days at room temperature (Scheme 3). However, addition of a catalytic quantity (ca. 5%) of **4** leads to smooth air oxidation. This and the other reactions were most conveniently monitored by NMR spectroscopy (using deuterated THF and KOH in D_2O) and gave complete conversion of the arylboronic acid to the corresponding phenol in 3–7 days. The reactions stalled after consumption of all available air in the tube and restarted when it was opened periodically. The catalyst remained at the end of the reaction, suggesting robustness and reusability.

In summary we have discovered a class of organic quinones that catalyze the air oxidation (overall hydroxylation) of arylboronic acids to the corresponding phenols. Autocatalysis in the parent system is particularly efficient and leads to rapid, quantitative synthesis of quinones **4** and **6**. The quinones show wide potential for mediating air oxidations resulting from a balance between two-stage conjugate addition and migration (each driven by aromatization of a naphthalene fragment) and efficient air oxidation under basic conditions to return the quinone from the resulting bisnaphtholate. Ease of production of quinones such as **4** and consequent low cost, combined with potential for straightforward immobilization on solid supports, make them a potentially important new class of oganocatalyst for mediating clean air oxidations.

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Supporting Information Available. Experimental methods for **4** and **6** and details of the X-ray structure of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.