Photochemistry

DOI: 10.1002/ange.201107028

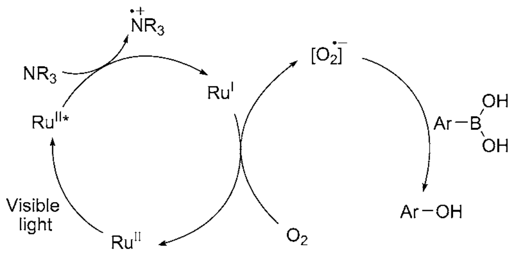
# Highly Efficient Aerobic Oxidative Hydroxylation of Arylboronic Acids: Photoredox Catalysis Using Visible Light**

*You-Quan Zou, Jia-Rong Chen, Xiao-Peng Liu, Liang-Qiu Lu, Rebecca L. Davis, Karl Anker Jørgensen,* and Wen-Jing Xiao**

The development of green and sustainable methods for effective synthesis of fine chemicals is an important goal in our society. During the last decade, visible-light photoredox catalysis has shown great promise as a method to advance these goals. As a result of its high natural abundance, benign environmental impact, cleanliness, and sustainability,[1] photocatalysis using visible light is a reliable and powerful tool.[2] In this context, there are several examples of its usefulness, including asymmetric alkylation of aldehydes,[3] [2+2] cycloaddition of enones,[4] [3+2] cycloaddition of aryl cyclopropyl ketones,[5] reductive dehalogenation,[3d,6] radical addition to unsaturated bonds,[7] and coupling reactions.[8,9] Despite these advances, oxidative reactions initiated by visible light are largely unexplored. In 2003, Zen et al. reported a visible-light photocatalytic reaction for the oxidation of sulfides into sulfoxides.[10] Later, Zhao et al. oxidized alcohols to aldehydes using visible light and dye-sensitized $TiO_2$.[11] Recently, the groups of Blechert and Wang[12] developed a metal-free photooxidative system to achieve the oxidation of amines and alcohols, and Jiao et al. described the use of a $Ru^{II}$ polypyridine complex and 4-methoxypyridine to promote the conversion of α-aryl halogen derivatives into α-aryl carbonyl compounds.[13]

The molecular oxygen in air has been widely used as a green oxidant in synthesis.[14] Consequently, the development of visible-light photooxidative reactions using air as the oxidant is highly desirable. We recently developed a visible-light-induced oxidation/[3+2] cycloaddition/oxidative aromatization sequence for dihydroisoquinoline esters and electron-deficient alkenes or alkynes to construct pyrrolo[2,1-*a*] isoquinolines.[15,16] In this sequence, a superoxide radical anion, which was generated from molecular oxygen, plays a key role throughout the process. Based on the investigation of the mechanism, we envisioned that this kind of highly active species might have Lewis basicity and therefore react with the appropriate acidic components. We report herein the realization of this strategy for the direct aerobic oxidative hydroxylation of arylboronic acids to aryl alcohols using visible-light irradiation and air as the source of the terminal oxidant.

In this reaction, we envisioned that the superoxide radical anion generated from the photoredox cycle could react with arylboronic acids because of its Lewis acidity, which arises from the vacant p orbital on the boron atom, followed by a series of rearrangements to provide aryl alcohols (Scheme 1).



**Scheme 1.** Concept of the visible-light-induced aerobic oxidative hydroxylation of arylboronic acids.

It is well known that phenols serve as versatile intermediates and building blocks in the chemical and pharmaceutical industries, and many efficient and straightforward methods have been established to successfully convert arylboronic acids into phenols.[17] To the best of our knowledge, this is the first example of oxidative hydroxylation of arylboronic acids using a visible-light photocatalytic strategy.

The reaction of 4-methoxyphenylboronic acid (**1a**) with $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ (2 mol%; bpy = bipyridine) in the presence of $Et_3N$ (2.0 equiv) and air (open to air, without bubbling air) in DMF under irradiation with visible light was used for the screening process. To our delight, the reaction occurred to give the desired 4-methoxyphenol (**2a**) in 90% yield after 48 hours (Table 1, entry 1). Encouraged by these results, a series of control experiments was performed. In the absence of any one of the reaction parameters/reagents, little or no conversion was observed (Table 1, entries 2–8). These results show that the photocatalyst, amine, air, and visible light are all essential for the reaction and support the photocatalytic model for this reaction.

Next, we focused our attention on optimization of the reaction conditions. A survey of solvents showed that the

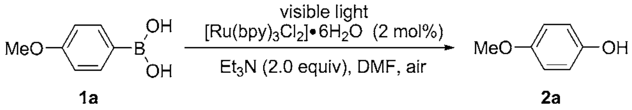
---

[*] Y.-Q. Zou, Dr. J.-R. Chen, X.-P. Liu, Dr. L.-Q. Lu, Prof. Dr. W.-J. Xiao
Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University
152 Luoyu Road, Wuhan, Hubei 430079 (China)
E-mail: wxiao@mail.ccnu.edu.cn
Prof. Dr. W.-J. Xiao
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
Shanghai 200032 (China)
Dr. R. L. Davis, Prof. Dr. K. A. Jørgensen
Center for Catalysis, Department of Chemistry, Aarhus University
8000 Aarhus C (Denmark)
E-mail: kaj@chem.au.dk

[**] We are grateful to the National Science Foundation of China (NO. 21072069 and 21002036) and the National Basic Research Program of China (2011CB808600) for support of this research.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201107028.

***Table 1:*** Screening and control experiments.[a]

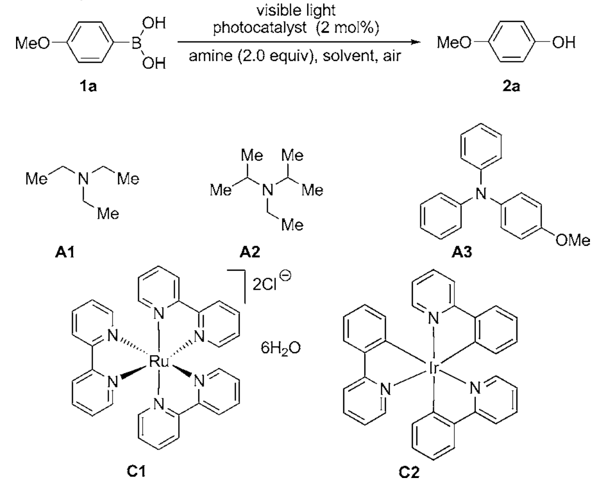


| Entry | Visible light | Photo-catalyst | Air | $Et_3N$ | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | + | + | + | + | 90 |
| 2 | − | − | + | + | n.r. |
| 3 | + | − | + | − | n.r. |
| 4 | − | + | + | + | n.r. |
| 5 | + | − | + | + | trace |
| 6 | + | + | − | + | trace |
| 7 | + | + | + | − | trace |

[a] Reaction conditions: **1a** (0.50 mmol), $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ (2 mol%), $Et_3N$ (2.0 equiv), DMF (5 mL), 36 W fluorescence lamp irradiation, and air for 48 h. [b] Yield of isolated product. DMF = *N*,*N′*-dimethylformamide, n.r. = no reaction.

transformation was not very sensitive to the reaction media; DMSO, DMF, $CH_3CN$, MeOH, and EtOH were all suitable for this reaction, and **2a** was obtained in good to excellent yield (Table 2, entries 1–5). DMF was found to be the most efficient solvent, thus providing the highest yields in the shortest time, whereas with $H_2O$ the yield of **2a** decreased to 60% (Table 2, entry 6). The quenching reagents of amines were also examined in DMF. Notably, it was found that the redox reagents had a significant effect on this reaction. When *N*,*N*-diisopropylethylamine was used, the reaction was completed within 28 hours and gave **2a** in 93% yield (Table 2, entry 7). In sharp contrast, the 4-methoxy-*N*,*N*-diphenylaniline, which is often used in photoredox catalysis, proved ineffective in this system (Table 2, entry 8). Finally, the effect of different photocatalysts was explored; tris[2-phenylpyridinato-C$^2$,*N*]iridium(III) was shown to require longer reaction times than $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ (Table 2, entries 9 and 10 versus entries 2 and 7).

***Table 2:*** Optimization of reaction conditions.[a]

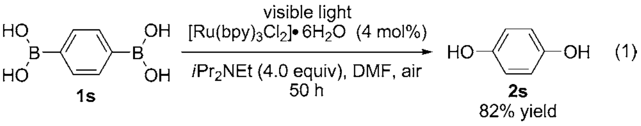


| Entry | Photo-catalyst | Solvent | Amine | *t* [h] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | **C1** | DMSO | **A1** | 60 | 86 |
| 2 | **C1** | DMF | **A1** | 48 | 90 |
| 3 | **C1** | $CH_3CN$ | **A1** | 96 | 77 |
| 4 | **C1** | MeOH | **A1** | 72 | 90 |
| 5 | **C1** | EtOH | **A1** | 72 | 89 |
| 6 | **C1** | $H_2O$ | **A1** | 96 | 60 |
| 7 | **C1** | DMF | **A2** | 28 | 93 |
| 8 | **C1** | DMF | **A3** | 96 | trace |
| 9 | **C2** | DMF | **A1** | 96 | 89 |
| 10 | **C2** | DMF | **A2** | 84 | 90 |

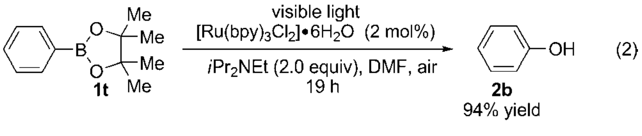
[a] Reaction conditions: **1a** (0.50 mmol), photocatalyst (2 mol%), amine (2.0 equiv), DMF (5 mL), 36 W fluorescence lamp irradiation, and air. [b] Yield of isolated product. DMSO = dimethylsulfoxide.

The scope of the light-induced photoredox catalytic aerobic oxidative hydroxylation of arylboronic acids is summarized in Table 3. Under the optimized reaction conditions, a wide range of arylboronic acids were smoothly oxidized to the corresponding aryl alcohols in good to excellent yields. As shown in Table 3, arylboronic acids **1a–r** bearing electron-neutral, electron-donating, and electron-withdrawing substituents were effectively converted into the desired phenols and analogues. We found that the electron-deficeint arylboronic acids reacted slightly faster than the electron-rich ones (Table 3, entries 10–15 versus 3–9). More importantly, the electron-rich phenols, which are difficult to obtain from the traditional nucleophilic substitution of arylhalides, can be easily generated using this photocatalytic method (Table 3, entries 1, and 3–9).

Perhaps more significantly, 1,4-phenylenediboronic acid (**1s**) also proved to be a good substrate, thus generating hydroquinone (**2s**) without loss in reaction efficiency. Using photocatalytic reaction conditions similar to those described above, **2s** was obtained in 82% yield after 50 hours when using an increased catalyst loading (4 mol%) and redox reagent loading (4.0 equiv) [Eq. (1)].



The substrate scope of this methodology has been extended to the use of phenylboronic pinacol ester **1t**, which is a derivative of phenylboronic acid. To our delight, the desired product **2b** was isolated in 94% yield after 19 hours [Eq. (2)].



To develop the metal-free version of this reaction, we started to examined the feasibility of using organic dyes.[3d,8d,11] Application of Acid Red 87 in the reaction of **1a** under irradiation by visible light provided the hydroxylated product **2a** in 90% yield after 96 hours [Eq. (3)].

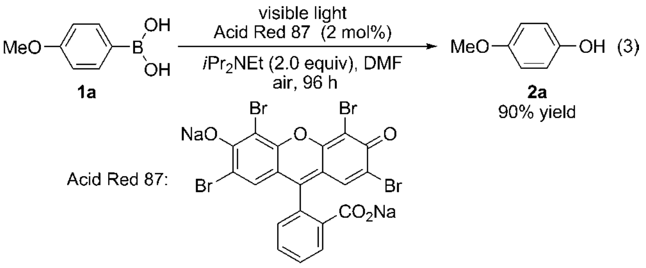
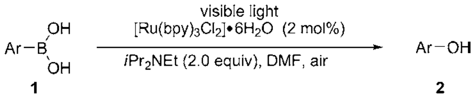
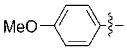
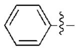
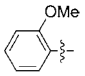
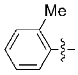
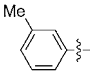
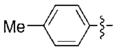
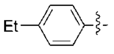
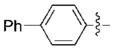
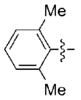
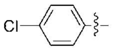
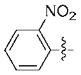
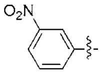
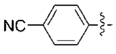
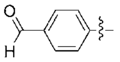
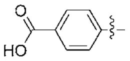
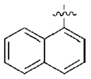
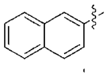
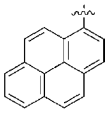


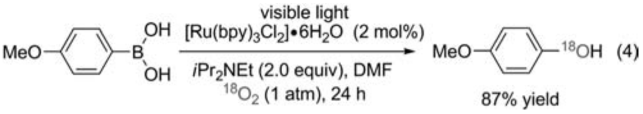
*Table 3:* Visible-light-induced aerobic oxidative hydroxylation of aryl boronic acids.[a]

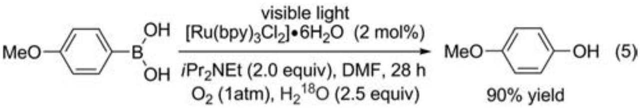


| Entry | Ar | *t* [h] | Yield [%][b] |
|---|---|---|---|
| 1 |  | 28 | 93 (**2a**) |
| 2 |  | 28 | 81 (**2b**) |
| 3 |  | 28 | 72 (**2c**) |
| 4 |  | 32 | 72 (**2d**) |
| 5 |  | 24 | 91 (**2e**) |
| 6 |  | 24 | 94 (**2f**) |
| 7 |  | 28 | 77 (**2g**) |
| 8 |  | 24 | 94 (**2h**) |
| 9 |  | 48 | 69 (**2i**) |
| 10 |  | 16 | 95 (**2j**) |
| 11 |  | 24 | 71 (**2k**) |
| 12 |  | 24 | 92 (**2l**) |
| 13 |  | 16 | 95 (**2m**) |
| 14 |  | 24 | 96 (**2n**) |
| 15 |  | 24 | 94 (**2o**) |
| 16 |  | 72 | 83 (**2p**) |
| 17 |  | 72 | 87 (**2q**) |
| 18 |  | 72 | 86 (**2r**) |

[a] Reaction conditions: **1** (0.50 mmol), $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ (2 mol%), $iPr_2NEt$ (2.0 equiv), DMF (5 mL), 36 W fluorescence lamp irradiation, and air. [b] Yield of isolated product.

To obtain some insight into the mechanism of this reaction, we carried out two $^{18}$O-labeling experiments [Eqs. (4) and (5)] and some computational studies. The HRMS analysis of the product shows that the hydroxy oxygen atom of the product originates from molecular oxygen rather than from water.[18,19]





While a precise reaction mechanism awaits further study, a plausible catalytic cycle is depicted in Scheme 2.[20] It is proposed that molecular oxygen is first reduced to the superoxide radical anion by the Ru$^{I}$/tripyridine complex. The radical anion then reacts with boronic acid to generate the intermediate **A**. The radical anion **A** then abstracts a hydrogen atom from the triethyl ammonium radial cation to form intermediate **B**.[21,8a] The formation of the hydroxylated product occurs by rearrangement of **B** into **C** with subsequent hydrolysis. However, the oxidative quenching cycle cannot be excluded in this reaction system.[18,23]

To shed some light on the mechanism, a computational study was undertaken. Quantum chemical computations were applied to examine the mechanism of the conversion of the intermediate **B** into **C** (Figure 1).[24] The rearrangement of **B** to **C** was found to be a concerted process with a barrier of 17.5 kcal mol$^{-1}$ for phenyl boronic acid (**1b**). Substituent effects were also examined computationally using models containing *p*-nitrile (**1m**) or *p*-methoxy (**1a**) groups. In both models, the substituent was shown to have only a small effect on the barrier for rearrangement, as the transition-state energies for **1m** and **1a** were calculated to be 16.7 and 18.9 kcal mol$^{-1}$, respectively.

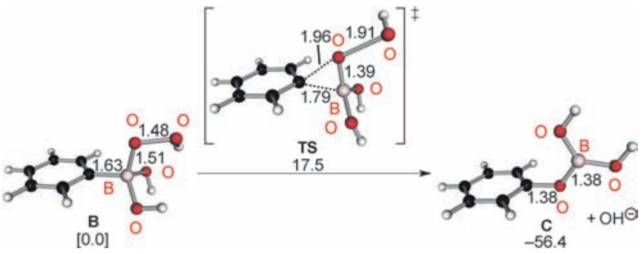
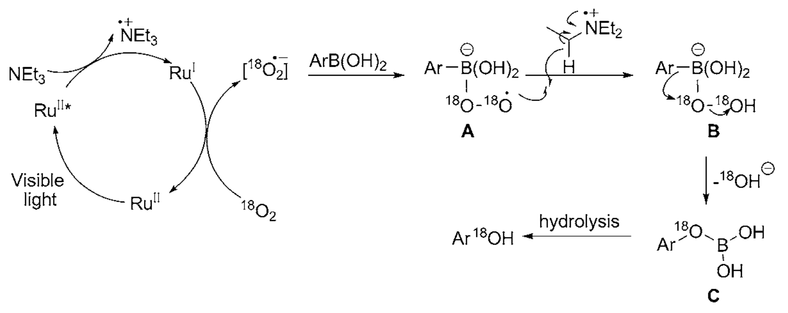


***Figure 1.*** Species involved in the conversion of **B** into **C**. All energies are zero-point corrected electronic energies in kcal mol$^{-1}$ and are relative to **B**. Bond distances reported in Ångstroms.

To better understand the reactivity of the intermediate **B** and explain why the reaction occurs through this tetrahedral boron intermediate, we examined the molecular orbitals involved in the transformation. In studying the HOMO-1 and



*Scheme 2.* Proposed mechanism for the oxidative dehydroxylation of arylboronic acids.

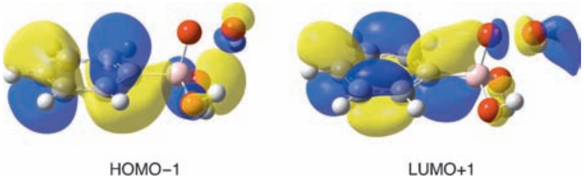


*Figure 2.* Calculated HOMO-1 and LUMO + 1 of the intermediate **B**.

LUMO + 1 of **B**[26] (Figure 2), we see that the π system of the benzene ring in the HOMO-1 is correctly aligned with the antibonding orbital of the peroxide in the LUMO + 1. This suggests that it is the π system of the benzene ring that attacks the peroxygen atom and not the carbon–boron σ bond. On the basis of orbital interactions in **B**, it is clear that boron must have a tetrahedral geometry for the rearrangement to occur.

In conclusion, we have developed a visible-light initiated aerobic oxidative hydroxylation of arylboronic acids using air as the oxidant. This new reaction protocol combines visible light with air in a single reaction system and shows great substrate tolerance providing rapid and efficient access to a variety of functionalized phenols and analogues in a highly concise fashion. Computational and experimental investigations indicate that the active intermediate is a boron peroxo complex and that the aromatic fragment is transferred in a concerted manner to one of the peroxygen atoms.

Received: October 5, 2011

**Keywords:** boron · oxidation · photooxidation · ruthenium · synthetic methods

---

[1] G. Ciamician, *Science* **1912**, *36*, 385.
[2] For selected reviews, see: a) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102; b) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527; c) K. Zeitler, *Angew. Chem.* **2009**, *121*, 9969; *Angew. Chem. Int. Ed.* **2009**, *48*, 9785; d) D. Ravelli, D. Dondi, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2009**, *38*, 1999; e) D. Gust, T. A. Moore, *Acc. Chem. Res.* **1993**, *26*, 198.
[3] a) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77; b) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875; c) H.-W. Shih, M. N. Vander Wal, R. L. Grange, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 13600; d) M. Neumann, S. Fuldner, B. Konig, K. Zeitler, *Angew. Chem.* **2011**, *123*, 981; *Angew. Chem. Int. Ed.* **2011**, *50*, 951.
[4] a) M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2008**, *130*, 12886; b) J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2009**, *131*, 14604; c) M. A. Ischay, Z. Lu, T. P. Yoon, *J. Am. Chem. Soc.* **2010**, *132*, 8572.
[5] Z. Lu, M. Shen, T. P. Yoon, *J. Am. Chem. Soc.* **2011**, *133*, 1162.
[6] a) J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756; b) L. Furst, J. M. R. Narayanam, C. R. J. Stephenson, *Angew. Chem.* **2011**, *123*, 9829; *Angew. Chem. Int. Ed.* **2011**, *50*, 9655.
[7] a) J. D. Nguyen, J. W. Tucker, M. D. Konieczynska, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2011**, *133*, 4160; b) J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 368; c) J. W. Tucker, J. D. Nguyen, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Chem. Commun.* **2010**, *46*, 4985; d) L. Furst, B. S. Matsuura, J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 3104; e) R. S. Andrews, J. J. Becker, M. R. Gagné, *Angew. Chem.* **2010**, *122*, 7432; *Angew. Chem. Int. Ed.* **2010**, *49*, 7274.
[8] a) A. G. Condie, J. C. González-Gómez, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464; b) M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny, D. C. Fabry, *Chem. Commun.* **2011**, *47*, 2360; c) M. Rueping, S. Zhu, R. M. Koenigs, *Chem. Commun.* **2011**, *47*, 8679; d) D. P. Hari, B. König, *Org. Lett.* **2011**, *13*, 3852.
[9] For other examples, see: a) P. V. Pham, D. A. Nagib, D. W. C. MacMillan, *Angew. Chem.* **2011**, *123*, 6243; *Angew. Chem. Int. Ed.* **2011**, *50*, 6119; b) A. E. Hurtley, M. A. Cismesia, M. A. Ischay, T. P. Yoon, *Tetrahedron* **2011**, *67*, 4442; c) J. W. Tucker, J. M. R. Narayanam, P. S. Shah, C. R. J. Stephenson, *Chem. Commun.* **2011**, *47*, 5040; d) C. Dai, J. M. R. Narayanam, C. R. J. Stephenson, *Nat. Chem.* **2011**, *3*, 140; e) R. S. Andrews, J. J. Becker, M. R. Gagné, *Org. Lett.* **2011**, *13*, 2406; f) M. Zhu, N. Zheng, *Synthesis* **2011**, 2223.
[10] J.-M. Zen, S.-L. Liou, A. S. Kumar, M.-S. Hsia, *Angew. Chem.* **2003**, *115*, 597; *Angew. Chem. Int. Ed.* **2003**, *42*, 577.
[11] M. Zhang, C.-C. Chen, W.-H. Ma, J.-C. Zhao, *Angew. Chem.* **2008**, *120*, 9876; *Angew. Chem. Int. Ed.* **2008**, *47*, 9730.
[12] a) F. Su, S. C. Mathew, G. Lipner, X. Fu, M. Antonietti, S. Blechert, X. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 16299; b) F. Su, S. C. Mathew, L. Möhlmann, M. Antonietti, X. Wang, S. Blechert, *Angew. Chem.* **2011**, *123*, 683; *Angew. Chem. Int. Ed.* **2011**, *50*, 657.
[13] Y. Su, L. Zhang, N. Jiao, *Org. Lett.* **2011**, *13*, 2168.
[14] For selected reviews on oxidative reactions with molecular oxygen, see: a) S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400; b) T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.* **2005**, *105*, 2329.
[15] Y.-Q. Zou, L.-Q. Lu, L. Fu, N.-J. Chang, J. Rong, J.-R. Chen, W.-J. Xiao, *Angew. Chem.* **2011**, *123*, 7309; *Angew. Chem. Int. Ed.* **2011**, *50*, 7171.
[16] See also: J. Xuan, Y. Cheng, J. An, L.-Q. Lu, X.-X. Zhang, W.-J. Xiao, *Chem. Commun.* **2011**, *47*, 8337.
[17] For recent examples about converting arylboronic acids into aromatic alcohols, see: a) K. Inamoto, K. Nozawa, M. Yonemoto, T. Kondo, *Chem. Commun.* **2011**, *47*, 11775; b) J. Xu, X. Wang, C. Shao, D. Su, G. Cheng, Y. Hu, *Org. Lett.* **2010**, *12*, 1964; c) K. Hosoi, Y. Kuriyama, S. Inagi, T. Fuchigami, *Chem. Commun.* **2010**, *46*, 1284; d) G. K. S. Prakash, S. Chacko, C. Panja, T. E. Thomas, L. Gurung, G. Rasul, T. Mathew, G. A. Olaha, *Adv. Synth. Catal.* **2009**, *351*, 1567; e) E. Kianmehr, M. Yahyaee, K. Tabatabai, *Tetrahedron Lett.* **2007**, *48*, 2713; f) R. E. Maleczka, F. Shi, D. Holmes, M. R. Smith III, *J. Am. Chem. Soc.*

**2003**, *125*, 7792; g) R. Benjamin, B. R. Travis, B. P. Ciaramitaro, B. Borhan, *Eur. J. Org. Chem.* **2002**, 3429; h) J. Simon, S. Salzbrunn, G. K. S. Prakash, N. A. Petasis, G. A. Olah, *J. Org. Chem.* **2001**, *66*, 633; i) K. S. Webb, D. Levy, *Tetrahedron Lett.* **1995**, *36*, 5117.

[18] Please see the Supporting Information for details.

[19] During the preparation of this manuscript, Fukuzumi et al. reported elegant work on the photooxygenation of benzene to phenol. In their reaction system, the oxygen of the hydroxy group in phenol was derived from $H_2O$. See: K. Ohkubo, T. Kobayashi, S. Fukuzumi, *Angew. Chem.* **2011**, *123*, 8811; *Angew. Chem. Int. Ed.* **2011**, *50*, 8652.

[20] Another mechanism involving the formation and rearrangement of an anionic bridged peroxy boron species was also explored computationally. However, the barriers for rearrangement of this intermediate proved to be too large ($>40$ kcal mol$^{-1}$) to be considered reasonable for a reaction occurring at room temperature. (See the Supporting Information for details.).

[21] Oxidation of amines and ammonium radical cations by singlet $O_2$ has previously been reported: G. Jiang, J. Chen, J.-S. Huang, C.-M. Che, *Org. Lett.* **2009**, *11*, 4568.

[22] The concerted rearrangment of organic peroxyboranes has previously been proposed: A. G. Davies, *J. Chem. Res.* **2008**, *7*, 361, and references therein.

[23] a) D. Kotkar, V. Joshi, P. K. Ghosh, *Chem. Commun.* **1987**, 4; b) A. Das, V. Joshi, D. Kotkar, V. S. Pathak, V. Swayambunathan, P. V. Kamat, P. K. Ghosh, *J. Phys. Chem. A* **2001**, *105*, 6945.

[24] Calculations were performed with *GAUSSIAN09*. Geometries were optimized without symmetry constraints at the B3LYP/6-311G + (d,p)[25] level of theory in a solvent cavity (PCM) using solvent parameters for DMF. See the Supporting Information for the complete references on theoretical methods.

[25] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372; c) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; d) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623.

[26] HOMO-1 and LUMO + 1 are generated from optimized geometry of **B** in the gas phase.