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Mechanistic Insights and Kinetic Analysis for the Oxidative Hydroxylation of Arylboronic Acids by Visible Light Photoredox Catalysis: A Metal-Free Alternative

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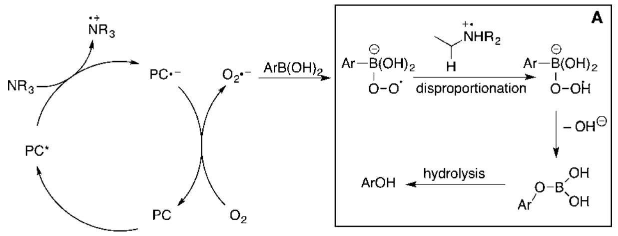
Supporting Information

ABSTRACT: The photocatalytic hydroxylation of boronic acids with methylene blue as photosensitizer proceeds with high efficiency. Detailed time-resolved studies of the relevant rate constants provide a clear mechanistic understanding of excited-state processes and guided the selection of the photocatalyst and the optimization of experimental conditions.

In the past decade, photoredox catalysis has attracted increasing attention,[1] as new light-initiated catalytic reactions continue to emerge. Remarkably, this new chemistry is usually obtained in the absence of any new understanding of the excited-state kinetics and mechanisms that underlie the new discoveries. In this contribution, we examine the excited-state kinetics relevant to the recently reported oxidative hydroxylation of arylboronic acids to yield the corresponding phenols, Scheme 1.[2] We compare the use of $Ru(bpy)_3Cl_2$ with methylene blue (MB) as a photocatalyst. Through determination of all the relevant rate constants using laser flash photolysis techniques, we have discovered a better, less expensive, and more environmentally benign catalytic system that also leads to improved reaction yields.

Scheme 1. Photocatalytic Conversion of Arylboronic Acids to Phenols[a]

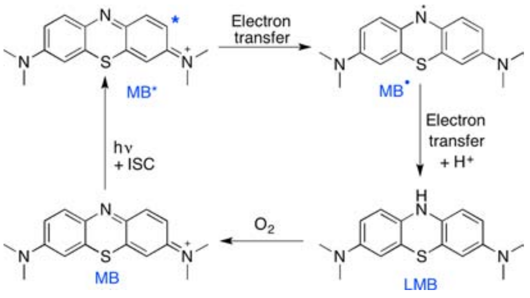


[a]As proposed by Xiao and co-workers.[2] PC represents the photocatalyst, $Ru(bpy)_3Cl_2$ or MB, the former being used in Xiao's report, along with Et_3N as the donor.

In the vast majority of cases, photocatalysis is performed with either a ruthenium or iridium photocatalyst using an amine, typically diisopropylethylamine ($i$$Pr_2NEt$), as a sacrificial electron donor to complete the catalytic cycle. Recently, we investigated the role of the amines and the corresponding α-aminoalkyl radicals produced in the photoredox catalytic cycle.[3] We demonstrated, using two different sources of α-aminoalkyl radicals, that the reductive cyclization of an aryl enone, demonstrated originally by Yoon and co-workers,[4] can be readily achieved in good yield simply by using organic sources of strongly reducing amine-derived radicals. We wondered if it would be possible to create a novel catalytic system that would utilize the excellent reducing capabilities of α-aminoalkyl radicals and be a viable replacement for traditional transition-metal catalysts. Herein, we report the use of MB, a member of the thiazine dye family, for the catalytic formation of α-aminoalkyl radicals for use in photoredox processes. Importantly, our selection of this system is based on a detailed understanding of the excited-state kinetics that govern the dynamics and efficiency of the photocatalytic process.

MB is an organic photosensitizer that is widely used in both biology and chemistry, most notably for its ability to generate singlet oxygen.[5] These sensitized reactions almost ubiquitously occur by way of the triplet state, where the triplet sensitizer and the substrate interact to form radicals or, in the case of oxygen, to generate singlet oxygen.[6] The two-electron photoreduction of MB is known to result in the colorless form, leuco-methylene blue (LMB in Scheme 2), which can be readily oxidized by oxygen to return to its original form.[7] Flash photolysis studies have indicated that the photoreduction occurs by electron- or hydrogen-transfer steps, producing a semireduced form of the methylene blue ($MB^\bullet$) as an intermediate (Scheme 2). This species can also act as a reducing agent.[8,9]

Scheme 2. Photoinduced Redox Cycling of Methylene Blue under Aerobic Conditions[a,9]



[a]Note that $MB^\bullet$ can also be trapped by oxygen (*vide infra*).

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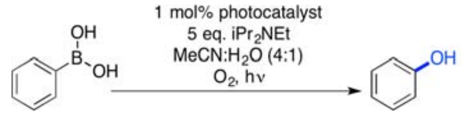
In 1976, Kayser and Young investigated the photoreduction of MB by both alkyl- and arylamines.[8,10] The authors showed that the reactive state of the dye, the triplet state, can be quenched by an amine to form a charge-transfer intermediate that leads to the semireduced form of the dye and an amine radical cation. It is well known that this amine radical cation deprotonates to form the corresponding α-aminoalkyl radical; therefore, MB can be used as a catalytic source of these radicals for use in photoredox processes. The semireduced form ($MB^{\bullet}$) has a modest reactivity toward oxygen ($k_{ox} = 5 \times 10^5\ M^{-1}\ s^{-1}$) but is known to be responsible for dye regeneration in other catalytic processes.[9]

There has been interest in replacing ruthenium and iridium with organic dye sensitizers to serve as organo-photocatalysts. Several recent reports[11,12] have employed Eosin Y for direct C−H arylation of heteroarenes with aryl diazonium salts and for C−C and C−P bond formation, while Rose Bengal[13] has led to oxyamination, coupling, and acylnitroso ene reactions. Eosin Y was also compared with other organic dyes.[11] A recent paper by Xiao et al. (*vide infra*) also mentioned briefly the potential use of Eosin Y for the hydroxylation of boronic acids.[2]

We decided to use Xiao's oxidative hydroxylation of arylboronic acids to phenols as a simple example to test MB as the basis for a metal-free photocatalytic system; the system is ideal as a mechanistic and kinetic tool. Quantitative conversion of the parent phenylboronic acid to its corresponding phenol was observed within 7 h using visible light irradiation (see reaction 1 and Figure 1). Also, MB showed higher catalytic activity when directly compared to $Ru(bpy)_3Cl_2$, and also provides the advantages of having lower cost and being completely transition-metal-free. Beyond establishing high conversions for a series of representative reactions, we have studied the kinetics of the key processes using laser flash photolysis techniques. While this Communication centers on MB, we have also carried out comparative measurements using $Ru(bpy)_3Cl_2$, so as to determine the origin of differences in reactivity.



(1)

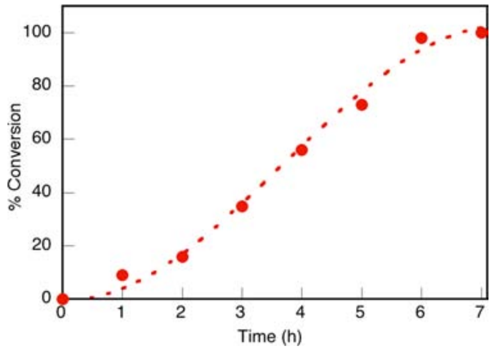


Figure 1. Conversion vs time plot for reaction 1 using methylene blue as the photocatalyst.

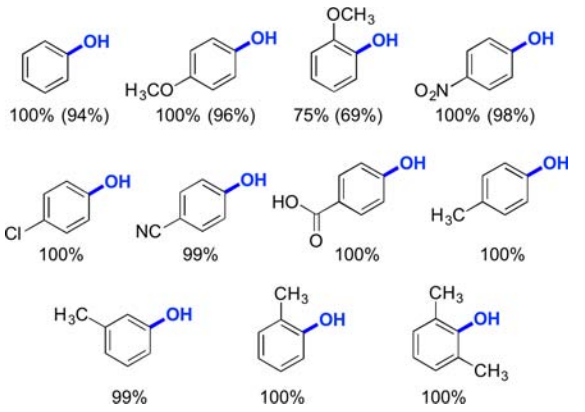
The system of reaction 1 was used as a test system in order to compare the performance of MB with $Ru(bpy)_3Cl_2$; the term "photocatalyst" refers to 1 mol% of one of these molecules. See the upper section in Table 1.

Table 1. Direct Comparison of Methylene Blue vs $Ru(bpy)_3Cl_2$ for the Oxidative Hydroxylation of Phenylboronic Acid in 4:1 Acetonitrile:Water (v/v; 7 h Reaction) and Rate Constants Derived from Laser Flash Photolysis Studies

	photocatalyst	
	methylene blue	$Ru(bpy)_3Cl_2$
conversion	100%	63%
isolated yield	94%	58%
	triplet quenching: k_q ($M^{-1}\ s^{-1}$)	
O_2	2.46×10^9	2.97×10^9
phenylboronic acid	1.34×10^8	see Figure S5[b]
phenol	5.81×10^5	see Figure S5[b]
iPr_2NEt	2.44×10^8	6.21×10^6
Et_3N[a]	4.68×10^7	3.9×10^6

[a]MB value in methanol from the literature.[8] [b]Supporting Information.

Chart 1. Percent Conversions and Isolated Yields (in Parentheses) for Various Phenols Derived from Boronic Acids[a]



[a]Conditions: *hν* for 7 h, 1 mol% MB, 5 equiv of iPr_2NEt in $MeCN:H_2O$ (4:1 v/v) and under O_2.

Intrigued by the high reaction efficiency shown in Table 1, we explored a number of related boronic acids using MB as photocatalyst. The striking results are shown in Chart 1. The reactions were performed in 4:1 acetonitrile:water (v/v), which proved to be an excellent solvent for the reaction mixture. Preliminary experiments with DMF as a solvent (used in literature reports[2]) gave as much as 40% yield of phenol even when no amine was added, probably due to the presence of amines as common impurities.[14,15]

In order to explore the reasons for the consistent high efficiency in the case of MB photocatalysis, we determined relevant rate constants using laser flash photolysis techniques with 308, 355, and 650 nm laser excitation (see Table 1 and Supporting Information). The pseudo-first-order rate constant for excited-state decay was monitored using transient absorbance or luminescence for MB and $Ru(bpy)_3Cl_2$, respectively; the second-order rate constant is obtained from the slope of a plot of this decay against the concentration of quencher. A key rate constant involves the reaction of the triplet state with the sacrificial electron donor, iPr_2NEt in this case. The corresponding plot shows that MB is quenched 40 times faster than $Ru(bpy)_3Cl_2$ (see Table 1, lower section), most likely one of the main reasons for the system's remarkable efficiency, Figure 2.

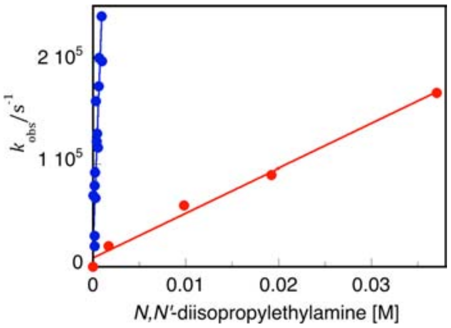


Figure 2. Rate of triplet quenching as a function of [iPr$_2$NEt] for Ru(bpy)$_3$Cl$_2$ (red) and for methylene blue (blue). See Table 1 for bimolecular rate constants and SI for a more detailed look at Ru(bpy)$_3$Cl$_2$.

Both MB and Ru(bpy)$_3$Cl$_2$ are readily quenched by oxygen to yield singlet oxygen; however, at the concentrations used in this work, the dominant pathway will be quenching by the amine. In any event, we examined the quenching of singlet oxygen by phenylboronic acid and iPr$_2$NEt (see SI) and obtained rate constants of 1.2×10^4 and 2.3×10^7 M^{-1} s^{-1}, respectively, indicating that singlet oxygen is 5000 times more likely to be quenched by iPr$_2$NEt over phenylboronic acid, and thus that singlet oxygen does not play a significant role in product formation. Singlet oxygen generation from MB or Ru(bpy)$_3$Cl$_2$ was examined and gave consistent data, as expected.

The fraction of triplets quenched by the amine can be readily calculated using eq 2; note that while reagents are typically specified in terms of "equivalents" in synthetic organic chemistry, these calculations require actual concentrations.

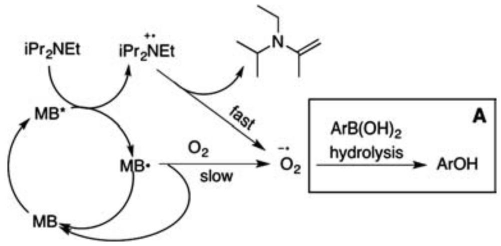
$$(\%\ \text{amine quenching}) = \frac{100 \times k_q^{\text{amine}}[\text{amine}]}{(\tau_0^{-1} + k_q^{\text{amine}}[\text{amine}] + k_q^{\text{boronic}}[\text{boronic}] + k_q^{O_2}[O_2] + k_q^{\text{phenol}}[\text{phenol}])} \tag{2a}$$

$$(\%\ \text{amine quenching}) \approx \frac{100 \times k_q^{\text{amine}}[\text{amine}]}{(\tau_0^{-1} + k_q^{\text{amine}}[\text{amine}] + k_q^{\text{boronic}}[\text{boronic}] + k_q^{O_2}[O_2])} \tag{2b}$$

where the various k_q terms refer to the rate constants of Table 1. Equation 2b refers to the initial condition in which phenol is absent. From the conditions of reaction 1, we calculate that 71% of the MB triplets are quenched by the amine. For comparison, for Ru(bpy)$_3$Cl$_2$ only 6% of the triplets will be quenched by the amine. The latter calculation requires an approximation for the boronic acid term, as the quenching process is not linear (*vide infra*); the necessary data are included in the Supporting Information. In fact, it is well known that while aromatic amines are very good quenchers of excited Ru(bpy)$_3$Cl$_2$,[16] their aliphatic counterparts are rather poor quenchers.[16,17] In contrast, aliphatic amines are excellent quenchers of the MB triplet.[8] Final yields (as in Table 1 and Chart 1) will also be influenced by the dynamics of all steps in Scheme 3, such as the generation of superoxide and the catalyst cycling; the spectral distribution of lamps and their overlap with the photocatalyst absorption are also important and, while not optimized in this work, deserve further examination.

Phenylboronic acids are excellent quenchers of excited states, but it would appear that only the monomeric form is a good quencher, and typical quenching plots (similar to those in Figure 2) are curved, reaching a plateau by the time the concentration is ~0.1 M (see Supporting Information). The well-known monomer−dimer equilibrium[18] is most likely responsible for this kinetic anomaly.

Scheme 3. Mechanism of Methylene Blue Photocatalysis, with Box A Adopted from Scheme 1 and the Reported Mechanism[2]



We now return to Figure 1, which at low to moderate conversions shows upward curvature; this observation puzzled us initially, as normally reactions show negative curvature as the reagents are consumed. However, data in Figure 1 and eq 2a provide a clear explanation. Since $k^{\text{boronic}} \gg k^{\text{phenol}}$, fewer triplets are quenched by the product relative to the boronic acid reagent, and thus more MB triplets survive to be quenched by the amine as the reaction proceeds, due to the lowering of the boronic acid concentration as it is converted to the corresponding phenol, causing a slight positive curvature early on. This is yet another example where kinetic data allowed for detailed mechanistic interpretation.

The reported mechanism involves oxidative attack by superoxide or HOO$^\bullet$ formed as part of the catalytic cycle, typically assigned to electron transfer from Ru(bpy)$_3^+$, which was in turn formed by electron transfer from the sacrificial electron donor. In our case, both the amine-derived α-amino radical and the semireduced methylene blue (MB$^\bullet$) are capable of transferring an electron to oxygen, with the rest of the reaction with the boronic acid following a previously proposed mechanism.[2] In principle, both radicals, MB$^\bullet$ and iPr$_2$NEt$^{+\bullet}$, are capable (although unlikely under oxygen) of participating in disproportionation reactions.[2] We have adopted box "A" from the literature,[2] even if the proposed disproportionation of amine-derived radicals in the presence of oxygen seems unusual.[19] In any event, it is clear that entry into box A in Schemes 1 and 3 leads exclusively to phenols.

In conclusion, our study demonstrates that in some cases the use of organic dyes as sensitizers for photocatalysis can lead to remarkably high yields using low-cost materials that are ultimately environmentally benign in comparison to their transition-metal counterparts. Understanding the increased efficiency and the optimal reaction conditions can frequently be done best on the basis of a detailed understanding of the reaction kinetics, which in many cases can be readily determined using laser flash photolysis techniques.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details on reaction conditions, product spectral data, conversion vs time plots, laser flash photolysis data, quenching plots, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Prier, C. K.; Rankic, D. A.; Macmillan, D. W. *Chem. Rev.* **2013**, *113*, 5322.

(2) Zou, Y. Q.; Chen, J. R.; Liu, X. P.; Lu, L. Q.; Davis, R. L.; Jorgensen, K. A.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 784.

(3) Ismaili, H.; Pitre, S. P.; Scaiano, J. C. *Catal. Sci. Tech.* **2013**, *3*, 935.

(4) Yoon, T. P.; Ischay, M. A.; Du, J. *Nature Chem.* **2010**, *2*, 527.

(5) Wilkinson, F.; Helman, W. P.; Ross, A. B. *J. Phys. Chem. Ref. Data* **1995**, *24*, 663. Tanielian, C.; Wolff, C. *J. Phys. Chem.* **1995**, *99*, 9831.

(6) Turro, N. J.; Ramamurthy, V.; Scaiano, J. C. *Modern Molecular Photochemistry of Organic Molecules*; University Science Publishers: New York, 2010.

(7) Obata, H.; Kogasaka, K.; Koizumi, M. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 125.

(8) Kayser, R. H.; Young, R. H. *Photochem. Photobiol.* **1976**, *24*, 395.

(9) Klimov, A. D.; Lebedkin, S. F.; Emokhonov, V. N. *J. Photochem. Photobiol.: A* **1992**, *68*, 191.

(10) Kayser, R. H.; Young, R. H. *Photochem. Photobiol.* **1976**, *24*, 403.

(11) Neumann, M.; Fuldner, S.; Konig, B.; Zeitler, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 951.

(12) Hari, D. P.; Schroll, P.; Konig, B. *J. Am. Chem. Soc.* **2012**, *134*, 2958.

(13) Liu, H.; Feng, W.; Kee, C. W.; Zhao, Y.; Leow, D.; Pan, Y.; Tan, C.-H. *Green Chem.* **2010**, *12*, 953. Pan, Y.; Kee, C. W.; Chen, L.; Tan, C.-H. *Green Chem.* **2011**, *13*, 2682. Teo, Y. C.; Pan, Y.; Tan, C. H. *ChemCatChem* **2013**, *5*, 235.

(14) Juillard, J. *Pure Appl. Chem.* **1977**, *49*, 885.

(15) Considerable formation of semireduced methylene blue was also observed in its laser flash photolysis in DMF. Interestingly, it was the time-resolved work that alerted us about possible problems with the solvent.

(16) Sandrini, D.; Maestri, M.; Belser, P.; Von Zelewsky, A.; Balzani, V. *J. Phys. Chem.* **1985**, *89*, 3675.

(17) Ballardini, R.; Varani, G.; Indelli, M. T.; Scandola, F.; Balzani, V. *J. Am .Chem. Soc.* **1978**, *100*, 7219. Rivarola, C. R.; Bertolotti, S. G.; Previtali, C. M. *Photochem. Photobiol.* **2006**, *82*, 213.

(18) Larkin, J. D.; Bhat, K. L.; Markham, G. D.; Brooks, B. R.; Schaefer, H. F.; Bock, C. W. *J. Phys. Chem. A* **2006**, *110*, 10633.

(19) Most participating radicals will be rapidly scavenged by oxygen, and thus unlikely to participate in radical−radical reactions. The exceptions are superoxide and the hydroxyperoxyl radical, which are unreactive toward oxygen.