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# Potent Reductants via Electron-Primed Photoredox Catalysis: Unlocking Aryl Chlorides for Radical Coupling

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**ABSTRACT:** We describe a new catalytic strategy to transcend the energetic limitations of visible light by electrochemically priming a photocatalyst prior to excitation. This new catalytic system is able to productively engage aryl chlorides with reduction potentials hundreds of millivolts beyond the potential of  $Na^0$  in productive radical coupling reactions. The aryl radicals produced via this strategy can be leveraged for both carbon–carbon and carbon–heteroatom bond-forming reactions. Through direct comparison, we illustrate the reactivity and selectivity advantages of this approach relative to electrolysis and photoredox catalysis.

ctivation of organic molecules through single electron A transfer (SET) is a pillar of preparative chemistry. New strategies to induce redox events have the potential to significantly impact organic synthesis.<sup>1</sup> In the past decade, visible-light photoredox catalysis has enabled a tremendous array of carbon-carbon and carbon-heteroatom bondforming reactions.<sup>2,3</sup> Unfortunately, blue light (440 nm) possesses sufficient energy for a maximum driving force of only 2.8 eV, and the available energy is further diminished by nonradiative pathways and intersystem crossing.<sup>4</sup> Thus, despite catalyst design improvements,<sup>5,6</sup> many desirable substrates remain inert to visible-light photoredox catalysis.<sup>7</sup> As a result of this limitation, dissolving metal conditions,<sup>8</sup> which employ reactive alkali metals in condensed ammonia, remain uniquely potent reductants in the synthetic arsenal<sup>9</sup> and are still commonly used despite significant hazards and poor chemo-selectivity.<sup>10,11</sup> Aiming to provide safer and more scalable conditions for challenging reductions, recent efforts have exploited overcharge protection to unlock deeply reducing cathodic potentials for electroorganic synthesis.<sup>12</sup> However, the requisite electrode overpotentials intrinsically limit the functional group tolerance. Furthermore, radical intermediates generated at a cathode are prone to reduction to anions.<sup>13</sup> Overall, a new catalytic paradigm to access extremely reducing potentials under mild conditions and without reduction of radical intermediates would address a long-standing challenge in organic synthesis (Figure 1).

To overcome the energetic limitations of blue photons, König and co-workers recently introduced an appealing approach designed to drive challenging SET events using the energy of two photons rather than one.<sup>14,15</sup> This strategy relies on the light-mediated generation and subsequent photochemical excitation of catalytic radical anion intermediates. Although these systems push the limits of photoredox catalysis, they remain many orders of magnitude less reducing than alkali metals. Inspired by photophysical studies suggesting that other organic radical ions can serve as potent photoreductants,<sup>16,17</sup> we questioned whether an alternative means of priming a photoredox catalyst with an electron prior to excitation could provide a general catalyst design platform to transcend the energetic limitations of visible light.

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We hypothesized that electrochemistry<sup>18,19</sup> could offer a more flexible approach than photoreduction to generate electron-primed photoredox catalysts. In addition to providing access to new catalysts, this approach eliminates the complications<sup>20</sup> that can arise from the terminal reductants commonly used in photoredox catalysis, such as Et<sub>3</sub>N. This



**Figure 1.** Strategies to induce SET reduction. All potentials shown are relative to SCE. PTH = 10-phenylphenothiazine.

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strategy builds on both long-standing<sup>21</sup> and recent<sup>22</sup> pioneering efforts combining electrochemistry with photochemistry.<sup>23</sup> The majority of these examples take advantage of the desirable features of electrochemistry to generate known photochemically active intermediates or catalysts. However, electrochemical generation of new families of photocatalysts for organic synthesis remains largely unexplored. Recently, Lambert and co-workers reported a new and highly oxidizing photocatalyst (with a calculated potential of +3.3 V vs SCE) that is electrochemically accessible under a mildly oxidizing potential.<sup>22d</sup> Concurrently, we were exploring the use of electrochemistry to access new, electronically destabilized photocatalysts for challenging reductions.<sup>24</sup> Herein we demonstrate that electrochemistry is a viable strategy to generate highly reducing electron-primed photoredox catalysts. We exploit this approach to identify an aryl imide photocatalyst capable of engaging substrates with reduction potentials on par with alkali metals in SET-initiated radical coupling reactions under otherwise mild conditions.

To explore this idea, we targeted the reductive generation of aryl radicals from unactivated precursors. These reactive intermediates are known to participate in a range of synthetically useful carbon–carbon and carbon–heteroatom bond-forming reactions; however, they are typically generated from diazonium salts or aryl iodides using modern photoredox catalysts.<sup>25</sup> With the most reducing visible-light photoredox catalysts, aryl bromides are suitable radical precursors.<sup>26,27</sup> Unfortunately, aryl chlorides comprise over half of the commercially available aryl halides<sup>28</sup> yet are inert under conventional visible-light photoredox catalysis unless they bear electron-withdrawing groups.<sup>29–31</sup> This limitation is a result of the combination of thermodynamically challenging SET and the low fragmentation rate due to the relatively strong  $C(sp^2)$ – Cl bond.<sup>32</sup>

To assess the viability of the proposed electrophotocatalytic approach, we investigated the dehalogenation of 4-bromobiphenyl (1) because of its reduction potential beyond the standard range of photoredox catalysts (-2.4 V vs SCE) and rapid fragmentation after reduction, as this provides a highfidelity readout for successful SET.<sup>32</sup> Using this model reaction, we assessed a series of aryl imides for activity under visible-light irradiation and an appropriate electrochemical potential to reductively activate the imide (Table 1). The radical anion derived from perylene diimide (PDI) can act as an electron-primed photoredox catalyst under two-photon conditions<sup>14a</sup> and is also well-behaved electrochemically.<sup>33</sup> Unfortunately, PDI proved ineffective in the dehalogenation of 1 under these conditions. Photophysical studies have indicated that naphthlene-based analogues (NpDI and NpMI) are more potent photoreductants after they are primed with an electron,<sup>17c</sup> but they have yet to be leveraged in synthesis. Excitingly, under electrophotocatalytic conditions both NpDI and NpMI promoted the dehalogenation of 1, despite significant electrochemical underpotentials in each case (1.6 and 1.1 V vs SCE respectively). While both NpMI and NpDI are sufficiently potent photoreductants to reduce 1, NpMI promoted dehalogenation significantly more efficiently. However, further stripping down the aromatic core to a phthalimide derivative, PhMI, resulted in a less effective photocatalyst than NpMI. On the basis of these data, we selected NpMI for further study after verifying that no significant conversion was observed in the absence of an applied voltage, light, or the catalyst.

Table 1. Electrochemical Access to Electron-Primed Photocatalysts  $^{a,b,c}$ 

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<sup>*a*</sup>All redox potentials given relative to SCE. <sup>*b*</sup>Ar = 2,6-diisopropylphenyl. <sup>*c*</sup>Reactions were conducted on a 0.4 mmol scale in DMF (0.1 M Bu<sub>4</sub>NPF<sub>6</sub>) in the presence of 2,4,6-tri-*tert*-butylphenol (10 mol %) and isopropyl alcohol (1 equiv). See the Supporting Information (SI) for further details.

Having identified a promising electrochemically accessible photocatalyst, we explored whether this system could engage abundant but much more challenging aryl chlorides in radical coupling reactions. We first probed the viability of a photo-Arbuzov process,<sup>34</sup> a classic carbon–heteroatom bond-forming reaction that proceeds through an aryl radical intermediate (Table 2). For these studies, we employed more convenient constant-current conditions.35 We found that under simultaneous electrolysis and irradiation, NpMI induced the high-yielding coupling of aryl chlorides with reduction potentials at and beyond the limits of conventional visible-light photoredox catalysis (2-3). To identify the limits of this catalytic system, we next evaluated increasingly electron-rich aryl chloride substrates. Excitingly, aryl chloride substrates bearing electron-donating groups still underwent efficient SETinduced phosphorylation (4-7) even though they possess reduction potentials comparable to that of  $Na^0$  (-2.9 V vs SCE). Notably, an exceptionally electron-rich aryl chloride  $(-3.4 \text{ V vs SCE})^{36}$  was successfully reduced to produce 7. This result indicates that these conditions provide potency comparable to that of  $Li^0$  (-3.3 V vs SCE). To our delight, despite the presence of such a potent reductant, aryl chloride substrates bearing potentially sensitive functional groups<sup>7,3</sup> such as esters (8), nitriles (9), carbamates (10), organoboron reagents (11), and heterocycles (12 and 13) all underwent productive SET-induced radical phosphorylation, and the



#### Table 2. Scope of Aryl Chloride Phosphorylation<sup>a</sup>

<sup>*a*</sup>Reactions were conducted on a 0.4 mmol scale and run for 8 h. Et<sub>3</sub>N (2 equiv) was employed in the anode as the counter reaction. See the SI for further experimental details. <sup>*b*</sup>The reaction was run for 14 h. <sup>*c*</sup> $E_{\rm red}$  was determined by differential pulse voltammetry <sup>*d*</sup>0.4 mA current.

corresponding products were isolated in good to excellent yields.

Having established the viability of carbon-heteroatom bond-forming reactions from diverse aryl chlorides, we next aimed to intercept the aryl radical intermediate with a heterocycle to form a new carbon-carbon bond (Table 3). We found that the aryl radical intermediates generated under these conditions from neutral to electron-rich aryl chlorides (14–18) could be effectively coupled to *N*-methylpyrrole, a classic radical trap.<sup>38</sup> Again, reductively sensitive functional groups were well-tolerated despite the potency of the photoreductant employed (19–21).

With a new catalytic strategy in hand, we next compared its efficacy to those of traditional photochemical and electrochemical approaches for the reductive activation of aryl chlorides (Figure 2). To this end, we investigated the relative yields of *N*-methylpyrrole coupling and dehalogenation within a subset of aryl chloride substrates ranging from electrondeficient to electron-rich. When the electron-primed photo-



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"Reactions were conducted on a 0.4 mmol scale and run for 27 h.  $Et_3N$  (2 equiv) was employed in the anode as the counter reaction. See the SI for further experimental details.

redox system was used, each substrate delivered the desired product with excellent selectivity for radical coupling over dehalogenation. In contrast, 10-phenylphenothiazine (PTH), an exceptionally reducing photoredox catalyst (-2.1 V vs SCE),<sup>26a</sup> could only induce the coupling of the electron-deficient aryl chloride. The neutral and electron-rich substrates were unconverted by PTH, consistent with the energetic limitations of visible-light photoredox. Direct electrolysis, on the other hand, provided significantly diminished selectivity for coupling of the electron-deficient substrate (2:1) and the other two substrates yielded in exclusively dehalogenation. These results are consistent with over-reduction at the electrode surface that precludes radical coupling reactions at the requisite potentials for aryl chloride reduction.

We next subjected radical clock **22** to both electron-primed photoredox and direct electrolysis conditions to probe the presence of an aryl radical intermediate and benchmark the rate of its over-reduction (Scheme 1). The aryl radical derived from **22** undergoes radical cyclization with a rate of  $8 \times 10^9$ s<sup>-1</sup>.<sup>39</sup> As anticipated, **NpMI** under blue-light irradiation and constant-current electrolysis delivered selective cyclization (54% yield,  $\geq$ 20:1 selectivity for cyclization over dehalogenation and aryl anion-derived<sup>40</sup> isomerization products). This result is fully consistent with the proposed intermediacy of an aryl radical intermediate and high selectivity for radical chemistry instead of over-reduction. Direct electrolysis,



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**Figure 2.** Comparison of reactivities and selectivities observed with various methods of generating aryl radical intermediates using *N*-methylpyrrole as a radical trap. Yields of coupling and dehalogenation were measured relative to an internal standard. The electron-primed photoredox conditions were the same as in Table 3. The photoredox conditions followed pyrrole coupling procedures from the literature employing PTH as a photocatalyst. Several direct electrolysis conditions were attempted. The reported conditions provided the highest yield of A and were standard reaction conditions from Table 3 without catalyst. For further details, see the SI.



<sup>a</sup>The reaction was conducted on a 0.4 mmol scale for 20 h.

however, provided no observable cyclization and generated only dehalogenation and isomerization products consistent with anionic intermediates. This indicates that under the direct electrolysis conditions investigated, any radical reactions with rate constants lower than  $10^9 \text{ s}^{-1}$  will not be viable because of competitive electrochemical reduction of the radical. This is consistent with the facile reduction of aryl radical intermediates at electrode surfaces (phenyl radical  $E_{\text{red}} = +0.05 \text{ V vs SCE}$ ).<sup>41</sup>

Finally, we aimed to gain preliminary insight into the promising chemoselectivity observed with this potent catalytic reductant. Notably, classic photoredox approaches are sensitive to not only the reduction potential of the substrate but also the fragmentation rate of the radical anion formed via SET.<sup>25a</sup> This is likely due to competition between back electron transfer and the productive fragmentation and coupling. Although back electron transfer can be a hindrance,<sup>42</sup> we suspect that this feature also contributes to the excellent chemoselectivity profiles observed in photoredox catalysis. Thus, we wanted to ascertain whether the exceptionally potent photoreductant explored herein exhibited analogous reactivity or whether SET was irreversible.

To this end, we conducted a series of one-pot intermolecular competition experiments between bromo- and chlorobiphenyl (Figure 3). These halogen congeners possess the same



**Figure 3.** Comparison of one-pot competition experiments.  $k_{\rm rel}$  is given as  $k_{\rm Br}/k_{\rm CI}$  and was measured by gas chromatography based on reactions run to low conversion (<20%). The electron-primed photoredox conditions followed from Table 1. The direct electrolysis conditions were those reported in ref 44. Previously reported photoredox conditions were employed 26a. See the SI for details.

reduction potential (-2.4 V vs SCE), but their radical anions exhibit significantly different fragmentation rates.<sup>32,43</sup> We subjected a 1:1 mixture of the two aryl halides to **NpMI** under simultaneous irradiation and a working potential of -1.3 V vs SCE. We found that the initial rate of  $C(sp^2)$ -Br cleavage was significantly higher than that of  $C(sp^2)$ -Cl cleavage ( $k_{rel} =$ 8) despite the fact the two aryl halides possess identical reduction potentials. This observation excludes that conversion is based exclusively on the reduction potential. In stark contrast, the two substrates are converted at similar rates under direct electrolysis conditions ( $k_{rel} = 2$ ).<sup>44</sup> Consistent with prior work in photoredox catalysis, PTH promoted the dehalogena-

tion of bromobiphenyl more rapidly than that of the chloride  $(k_{rel} = 15)$ . Taken together, these data indicate that productive conversion is not governed exclusively by the reduction potential under either electron-primed or conventional photoredox catalysis. This observation provides a plausible rationale

for the promising chemoselectivity observed under the conditions reported herein relative to deeply reducing direct electrolysis, which predominantly commits to product formation on the basis of the substrate reduction potential.

Overall, we have demonstrated that electrochemical stimulation is a viable strategy to generate catalytic photoreductants capable of transcending the limits of modern photoredox catalysis. We report effective radical couplings of substrates hundreds of millivolts more challenging to reduce than previous photoredox strategies, including substrates with reduction potentials well beyond that of Na<sup>0</sup> and more negative than that of Li<sup>0</sup>. Crucially, despite accessing such negative potentials, the reactions possess functional group tolerance profiles more consistent with traditional photoredox catalysis than direct electrolysis and result in high selectivity for radical coupling over dehalogenation. Beyond unlocking electronically diverse aryl chlorides as aryl radical precursors, these data lay the foundation for a new catalyst design paradigm. We anticipate that electrochemically priming photocatalysts prior to excitation will allow much more challenging reductions than are feasible with blue light alone and will result in a myriad of transformations inspired by what is feasible under dissolving metal conditions and beyond.

# ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b12328.

Experimental procedures, electrochemical characterization, radical clock and competition experiments, comparison of reductive activation methods, constantcurrent control experiments, product isolation and characterization, and NMR spectra (PDF)

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#### Notes

The authors declare no competing financial interest.

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