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Communication

Non-innocent Radical Ion Intermediates in Photoredox Catalysis: Parallel Reduction Modes Enable Coupling of Diverse Aryl Chlorides

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ABSTRACT: We describe a photocatalytic system that elicits potent photoreductant activity from conventional photocatalysts by leveraging radical anion intermediates generated *in situ*. The combination of an isophthalonitrile photocatalyst and sodium formate promotes diverse aryl radical coupling reactions from abundant but difficult to reduce aryl chloride substrates. Mechanistic studies reveal two parallel pathways for substrate reduction both enabled by a key terminal reductant byproduct, carbon dioxide radical anion.

Reductive activation of organic molecules via single electron transfer (SET) is a fundamental elementary step that underpins diverse and powerful synthetic transformations.[1−4] Photoredox catalysis promotes SET through conversion of energy from visible light into chemical redox potential and has enabled a suite of carbon−carbon and carbon-heteroatom bond-forming reactions.[5−9] When considering whether a substrate will be suitable for photoredox reduction, two primary catalyst parameters are initially considered: (1) $E_{1/2}(\mathrm{PC}^{\bullet+}/\mathrm{PC}^{*})$ and (2) $E_{1/2}(\mathrm{PC}/\mathrm{PC}^{\bullet-})$.[7,10,11] These values reflect redox potentials bounded by the energy of photons in the visible region, a limitation compounded by energy losses to intersystem crossing.[12] As a result, many abundant but challenging to reduce substrates are excluded from photoredox activation based on these guidelines (Figure 1A).[13−15]

Aryl radicals are reactive intermediates that engage in a myriad of synthetically valuable transformations.[16−18] Classically, aryl radical intermediates are generated from aryl diazonium salts, iodides, or bromides.[19−29] Aryl chlorides are rarely used as radical precursors despite the fact they comprise over two-thirds[30] of commercially available aryl halides (Figure 1B).[31−35] This is a consequence of their resistance to reductive activation,[13] and high $\mathrm{C(sp^2)}{-}\mathrm{Cl}$ BDE.[36,37] König recently pioneered an elegant strategy, termed consecutive photoinduced electron transfer (conPET), wherein a photochemically generated radical anion is subsequently excited.[38,39] This approach primes the photocatalyst with an electron prior to excitation and, in principle, can generate much deeper reduction potentials through $E_{1/2}(\mathrm{PC}/\mathrm{PC}^{\bullet-*})$. Indeed, later implementations of this conPET strategy unlocked exceptionally challenging reductions.[40,41] However, all recent advances in visible light photoredox methods that reduce electronically diverse chloroarenes have been limited to proteodefunctionalization and borylation reactions.[40,42−45] Recent electrophotocatalytic[46−49] approaches have directly generated these electron-primed photocatalysts cathodically.[50,51] While this strategy has begun to expand the range of radical coupling

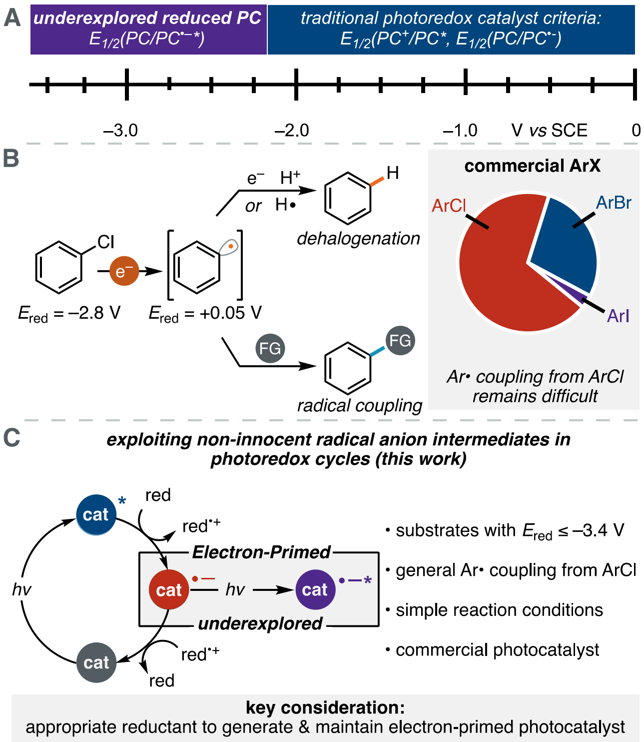

Figure 1. (A) Energy limitations for photoredox catalysis and electron-primed photoredox catalysis. (B) Aryl chloride abundance and reactivity as aryl radical precursors. (C) Strategy employing chemical reductants to exploit electron-primed photoredox catalysis. All V vs SCE.

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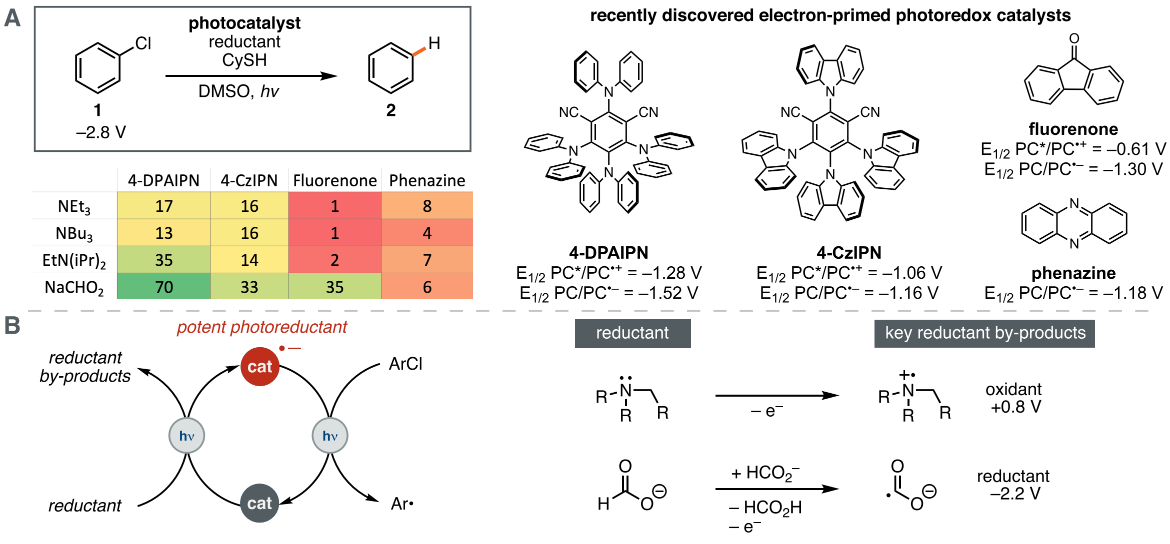


	4-DPAIPN	4-CzIPN	Fluorenone	Phenazine
NEt_3	17	16	1	8
NBu_3	13	16	1	4
$EtN(iPr)_2$	35	14	2	7
$NaCHO_2$	70	33	35	6

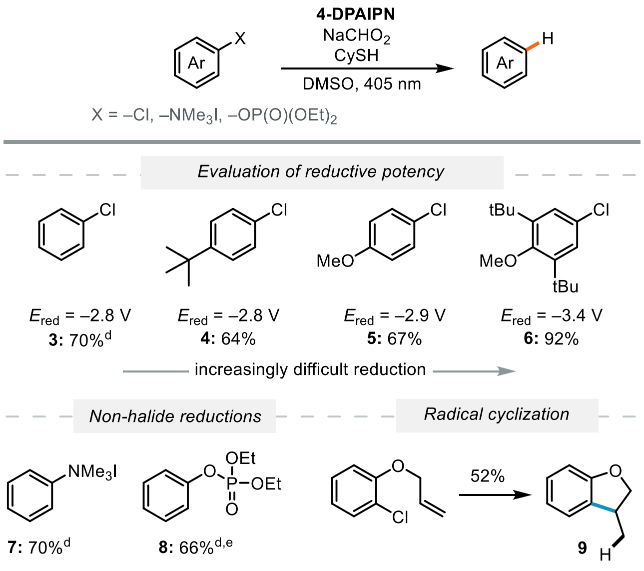
Figure 2. (A) Unlocking radical anion photocatalyst reactivity by evaluation of reductant for catalyst activation. Reactions were conducted on 0.1 mmol scale with 10 mol % **4-DPAIPN** and 3 equiv of $NaCHO_2$. Reactions were analyzed via gas chromatography. (B) Overview of key considerations for chemical reducants as catalyst activators. All V vs SCE.

reactions that engage aryl chlorides, a general approach to leverage the expansive pool of aryl chloride substrates in radical couplings has remained elusive and the need for electrochemical equipment remains a barrier in some settings.[52,53] In particular, net-reductive radical coupling processes, such as alkene hydroarylation,[54−56] have remained elusive for aryl chloride substrates for all modern methods. We suspect that the paucity of net-reductive processes is a consequence of the intrinsic challenges of circumventing premature reduction of the aryl radical intermediate ($E_{\mathrm{red}}(\mathrm{Ph}^{\bullet}/\mathrm{Ph}^{-}) = +0.05$ V vs SCE)[57] in the presence of a stoichiometric reductant.

Our group recently used electrochemistry to examine a diverse set of organic radical anions for photocatalytic activity in the reductive cleavage of strong $C(sp^2)$−O and $C(sp^2)$−N bonds.[58] These experiments revealed that numerous radical anions, including those derived from commonly employed photoredox catalysts, can serve as potent photocatalytic reductants upon cathodic reduction. These data fit into a growing body of literature from our group[59] and others[40,60] that suggest photocatalyst-based redox events can engender more potent activity from conventional photocatalysts. Taken together, these data led us to consider whether we could redesign a photocatalytic system to favor formation of photoactive radical anion intermediates to elicit deeply reducing potentials and expand the repertoire of coupling reactions available from aryl chlorides under operationally simple conditions (Figure 1C). Herein, we disclose that selection of an appropriate reductant to generate and maintain an active electron-primed photoredox catalyst *in situ* enables reduction potentials far beyond those expected from conventional catalyst selection criteria. These new reduction conditions promote a diverse array of intermolecular coupling reactions, including net-reductive coupling processes, from readily available aryl chloride substrates.

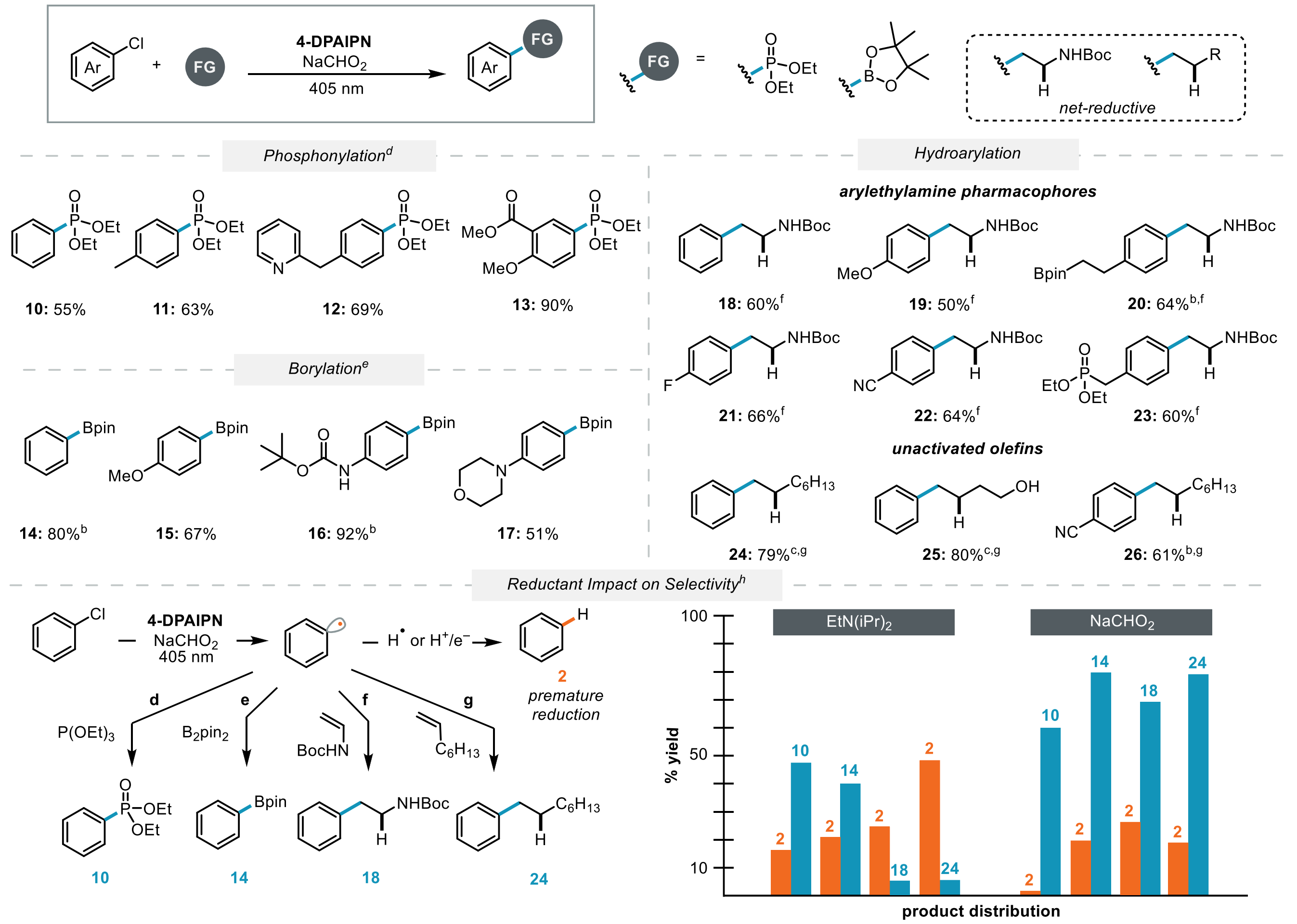
We first evaluated a suite of organic compounds recently found to possess photocatalytically active radical anion congeners[58] for activity in the dehalogenation of PhCl ($E_{\mathrm{red}} = -2.8$ V vs SCE). Considering only conventional photoredox catalyst selection parameters ($PC/PC^{\bullet-}$ and $PC^*/PC^{\bullet+}$), this reduction would be exceedingly endothermic (>1 V) for the photocatalysts under investigation. Therefore, activity in this assay would implicate *in situ* formation of a distinct and potent reductant. Initially, we examined a range of trialkylamine reductants because these are common reductants in photoredox catalysis, including in conPET strategies (Figure 2A).[38,40,61] We found that each catalyst modestly promoted this energetically demanding dehalogenation reaction. The isophthalonitrile catalysts, which are both excellent neutral chromophores[62] as well as electron-primed photoredox catalysts,[58] promoted the reaction most efficiently albeit still in poor yield. To exclude halogen atom transfer (XAT) aryl radical generation,[63−65] we examined the reductive defunctionalization of anilinium and aryl phosphate salts (Table 1). These are each challenging reductive cleavage reactions[66,67] of

Table 1. Evaluation of Catalytic System[a,b,c]



[a] Reactions were run on 0.1 mmol scale with 10 mol % **4-DPAIPN**, 3 equiv of $NaCHO_2$, and 5 mol % CySH. [b] All V vs SCE. [c] NMR yield. [d] GC yield. [e] 15 mol % 4-DPAIPN.

Table 2. Intermolecular Couplings from Challenging Aryl Chloride Precursors[a]



[a]Reactions were run on 0.4 mmol scale. Isolated yield unless otherwise noted. [b]NMR yield. [c]GC yield. [d]Reactions were run with **4-DPAIPN** (12–15 mol %), $NaCHO_2$ (3 equiv), and $P(OEt)_3$ (5 equiv). [e]Reactions were run with **4-DPAIPN** (5 mol %), $NaCHO_2$ (3 equiv), B_2pin_2 (3 equiv), and Cs_2CO_3 (3 equiv). [f]Reactions were run with **4-DPAIPN** (6 mol %), $NaCHO_2$ (3 equiv), *N*-vinyl carbamate (2.5 equiv), and CySH (5 mol %). [g]Reactions were run with **4-DPAIPN** (6 mol %), $NaCHO_2$ (3 equiv), alkene (5 equiv), and CySH (5 mol %). [h]Reactions were run with conditions *d*–*g*, using either $EtN(iPr)_2$ or $NaCHO_2$ as the reductant. See the Supporting Information for details.

nonpolarizable leaving groups unlikely to undergo XAT processes. We found both substrates underwent productive defunctionalization, albeit in diminished yield (Figure S13).

A broader survey of reductants less commonly employed in photoredox catalysis (Figure S14) revealed that sodium formate substantially enhanced the photoreductant activity of **4-DPAIPN** (Figure 2A). We suspect this improvement occurs because formate salts undergo a second-order hydrogen atom transfer (HAT) process upon oxidation[68] that results in formic acid and carbon dioxide radical anion.[69−72] As a consequence, a second reducing equivalent is liberated from formate after initial oxidation. We suspect that the carbon dioxide radical anion can either reduce another equivalent of photocatalyst or promote the reaction by direct reduction of substrate ($E_{1/2}(CO_2/CO_2^{\bullet-})$ = −2.2 V vs SCE).[73] In each mechanistic manifold, the SET is rendered irreversible by the release of CO_2 gas. This scenario contrasts starkly with the trialkylamine reductants, which result in oxidizing amine radical cation intermediates ($E_{1/2}(NR_3^{\bullet+}/NR_3)$ = <1 V vs SCE) that could deactivate the radical anion photocatalyst via back electron transfer (Figure 2B).[61,74,75]

We next evaluated the potency of this new catalytic system. Having established that chlorobenzene could be reduced (−2.8 V vs SCE), we probed dehalogenation of increasingly electron-rich aryl chlorides. These experiments revealed that substrates with reduction potentials as low as −3.4 V vs SCE are efficiently reduced. Additionally, these conditions promoted the challenging reductive cleavage of both an anilinium and aryl phosphate substrate. Taken together, these data clearly implicate processes beyond a conventional photoredox manifold. For example, the reduction of **6** would be predicted to be endothermic by nearly 2 V (>40 kcal/mol at room temperature) based on the most reducing conventional redox couple of **4-DPAIPN** ($E_{1/2}(PC/PC^{\bullet-})$ = −1.5 V vs SCE).[76] We next attempted to validate the intermediacy of an aryl radical in this formate driven system. As anticipated, these conditions furnished the five-membered ring product **9** in high selectivity for radical cyclization. Despite its exceptionally reducing potentials, we suspected that this operationally simple procedure would be amenable to high-throughput techniques widely employed in medicinal chemistry. To this end, we rapidly evaluated the tolerance of complex drug-like scaffolds using a commercially available informer plate designed to

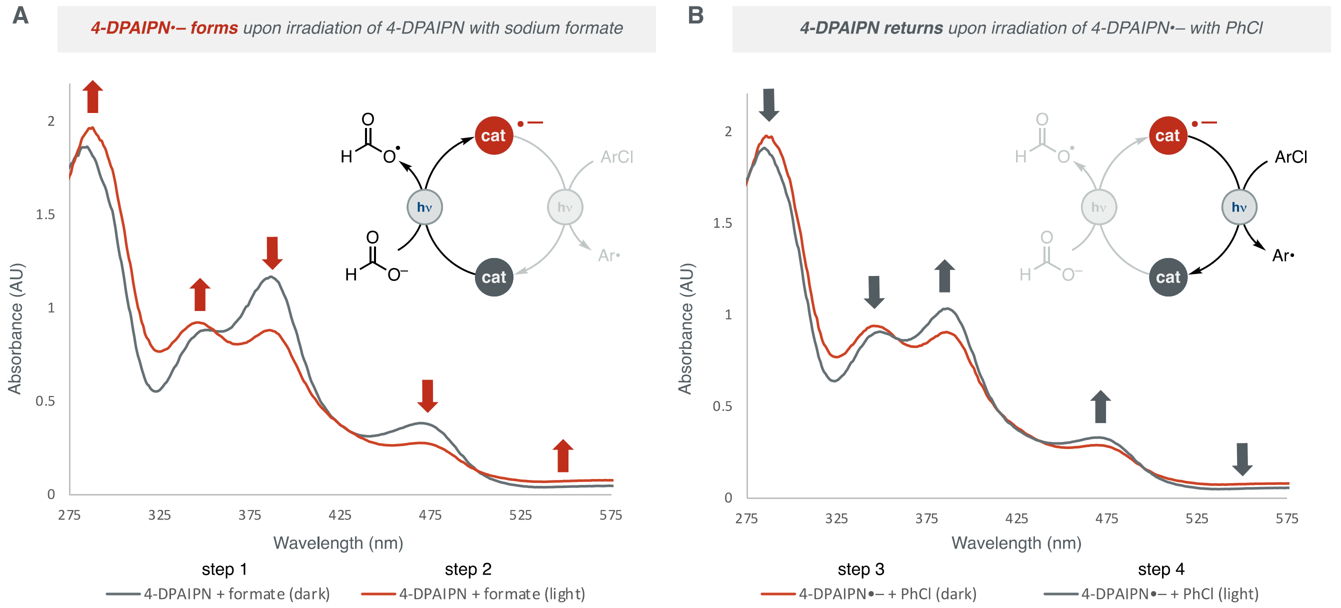


Figure 3. (A) UV–vis absorption spectrum demonstrating 4-DPAIPN$^{•-}$ generation in the presence of sodium formate and light. (B) UV–vis absorption spectrum demonstrating that 4-DPAIPN$^{•-}$ reverts to 4-DPAIPN upon exposure to PhCl and subsequent irradiation.

challenge modern cross-coupling technology. We found that not only was photocatalytic activity retained in the well-plate format but that several of these functional group rich molecules were effectively transformed (Figure S16).

Although, in principle, aryl radicals are highly versatile synthetic intermediates, premature reduction precludes radical coupling reactions in many cases. This is particularly problematic when potent reductants are required. To evaluate selectivity for radical coupling, we targeted redox-neutral photo-Arbuzov and radical borylation processes. These established aryl radical transformations produce biologically relevant aryl phosphonates[77] and versatile organoboron products.[78] In both cases, we found that chloroarene substrates readily underwent the desired radical coupling process.[79] We found that both difficult to reduce electron-rich aryl chlorides and substrates bearing potentially reducible functional groups such as esters and amides were well-tolerated (Table 2). Furthermore, the catalytic system tolerated medicinally relevant heterocycles.

Next, we evaluated the reductive hydroarylation of alkenes. This challenging aryl radical reaction requires precise control over the relative rates of radical coupling versus proteodehalogenation. HAT is mechanistically required to furnish product and cannot be simply suppressed. Initially, we targeted the synthesis of arylethylamines via hydroarylation. Recently, Jui and co-workers reported that aryl radical intermediates productively couple with vinyl carbamates to produce the arylethylamine pharmacophore.[56] Although one of the most reducing conventional photocatalysts was employed, the majority of the reaction scope was composed of aryl iodide substrates and only aryl chloride substrates bearing withdrawing groups were viable. Intriguingly, we found that although the vinylcarbamate substrate is thermodynamically easier to reduce than most chloroarenes ($E_{\mathrm{red}} = -2.2$ V vs SCE), these potent reductive conditions selectively transformed chlorobenzene into *N*-Boc phenethylamine in high yield. Even as the gap between the chloroarene and vinyl carbamate coupling partner widens, synthetically useful arylethylamine yields are still observed. Similar to the other radical couplings, we found aryl chlorides bearing reductively sensitive functional groups were tolerated. We also found these conditions promoted the coupling of aryl chlorides and unactivated alkenes despite the fact that such a hydroarylation remains challenging with any aryl radical precursor.[80] Finally, we questioned whether formate was uniquely effective for each of these radical coupling reactions or whether alkylamines were suitable terminal reductants. While EtN(i-Pr)$_2$ and **4-DPAIPN** promote photoreduction of chlorobenzene, both reactivity and radical selectivity were diminished in each coupling reaction. Of note, competitive proteodehalogenation nearly precluded net-reductive hydroarylation when alkylamines were used.[81]

Having established a generally applicable catalytic system to engage aryl chloride substrates in radical coupling reactions, we next conducted a preliminary mechanistic investigation into the process. First, we probed whether an electron-primed photoredox mechanism—wherein the **4-DPAIPN** radical anion is generated and subsequently excited—was feasible under these conditions. We irradiated a mixture of **4-DPAIPN** and sodium formate while monitoring speciation by absorption spectroscopy (Figure 3A). This resulted in a decrease in **4-DPAIPN** features and growth of new features consistent with electrochemically reduced **4-DPAIPN** (Figure S20). Next, we probed the photoreduction of aryl chlorides. Chlorobenzene was added to the reaction mixture and, upon irradiation, the absorption features of **4-DPAIPN** were restored (Figure 3B). As expected based on the >1 V underpotential, no return of **4-DPAIPN** was observed upon addition of chlorobenzene to **4-DPAIPN** radical anion in the absence of light. Consistent with this mechanistic picture, Stern–Volmer analysis resulted in no measurable quenching of excited **4-DPAIPN** by chlorobenzene. In contrast, formate salts did quench the excited state. Cyclohexanethiol, which was added to the net-reductive transformations as an HAT cocatalyst, also quenches the excited state and likely mediates the electron-transfer events in these systems by an analogous mechanism (Figure S18). Taken together, these experiments are consistent with our working hypothesis that photooxidation of formate results in

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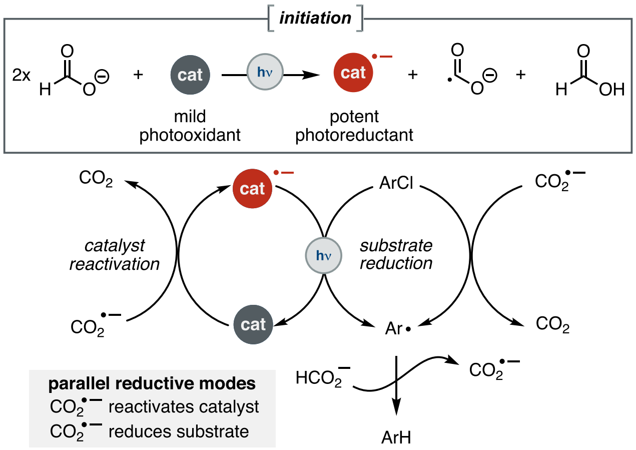
the **4-DPAIPN** radical anion, which can be subsequently excited to photoreduce chlorobenzene and return **4-DPAIPN**.

While the UV−vis experiments indicate that an electron-primed photoredox mechanism is feasible, we recognized that carbon dioxide radical anion is sufficiently reducing ($E_{red}(CO_2/CO_2^{\bullet-}) = -2.2$ V vs SCE)[73] to promote reductive fragmentation of some of the aryl chloride substrates studied without the intervention of an electron-primed photoredox manifold. To evaluate the relative contribution of direct substrate reduction by $CO_2^{\bullet-}$, we attempted to generate this radical anion directly by homolysis of $(PhS)_2$ under 370 nm light in the absence of **4-DPAIPN**.[82] We envisioned thiyl radical could abstract a hydrogen atom from formate to directly generate $CO_2^{\bullet-}$ *in situ* (Figure S23).[71,83,84] These conditions resulted in quantitative conversion of 4-chlorobenzonitrile ($E_{red} = -2.1$ V vs SCE). However, only 9% conversion of chlorobenzene ($E_{red} = -2.8$ V vs SCE) and <5% conversion of chloroanisole ($E_{red} = -2.9$ V vs SCE) were observed under these photocatalyst-free conditions. In contrast, all three of these substrates are dehalogenated in comparable efficiency through use of the **4-DPAIPN** conditions. We suspect both mechanisms operate in parallel for substrates within the bound of the potency of $CO_2^{\bullet-}$ (−2.2 V vs SCE) but that an electron-primed photoredox manifold supports more thermodynamically demanding reductions. In both cases, the $CO_2^{\bullet-}$ reductant byproduct plays an active role either (a) reducing the substrate directly or (b) reducing the photocatalyst to reactivate it without requiring persistent multiphoton excitation (Scheme 1).

Scheme 1. Plausible Mechanism for Aryl Chloride Reduction and the Roles of Formate and Its Byproducts



Overall, we have illustrated that use of a formate-based terminal reductant in combination with an isophthalonitrile photocatalyst can engage aryl chlorides in diverse synthetically useful coupling reactions. We anticipate that these operationally simple reaction conditions comprise a broadly useful approach to photochemically induce difficult reductive processes. Beyond the immediate synthetic utility, these results are important because they challenge the notion that the terminal reductant can be viewed as merely an electron-source to turn over the photocatalyst. These data fit within a growing body of literature that suggests terminal reductant byproducts can play a non-innocent role in photoredox catalysis.[64,65,74] We suspect that these results could also offer an alternative explanation for recent examples wherein isophthalonitrile catalysts have appeared to reduce substrates beyond their expected redox potentials[65,85] and, more broadly, illustrate the importance of radical ion intermediates in photoredox catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c05988.

Experimental procedures, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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