Reductive Electrophotocatalysis: Merging Electricity and Light To Achieve Extreme Reduction Potentials

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Abstract

We describe a new electrophotocatalytic strategy that harnesses the power of light and electricity to generate an excited radical anion with a reducing potential of –3.2 V vs SCE, which can be used to activate substrates with very high reduction potentials ($E_{red} \approx$ –1.9 to –2.9 V). The resultant aryl radicals can be engaged in various synthetically useful transformations to furnish arylboronate, arylstannane, and biaryl products.

Due to the unique reactivity of open-shell intermediates, the development of catalytic transformations driven by single-electron transfer (SET) has been an area of intense research in organic chemistry.[1] In particular, the employment of unconventional means of activation, including photoredox catalysis[2] and electrocatalysis,[3] has provided unique entry to single-electron reactivities and led to new solutions to challenging synthetic problems that are not readily addressed using existing tools. In the realm of redox organic reactions, both photoredox catalysis and electrochemistry have been successfully applied to a diverse suite of oxidative transformations. However, reductive transformations, particularly those that require highly reducing potentials, remain an underdeveloped area for both of these reaction strategies.[2b,3a] In principle, electrochemistry can grant access to extreme reducing potentials, and significant contributions in this regard have recently been made.[4] Nevertheless, the constant application of such highly biased potentials can lead to uncontrolled reactions due to accumulation of reactive intermediates near the electrode surface as well as compromised

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b10678.
Procedures and characterization data (PDF)

chemoselectivity in complex reaction systems. Thus, the development of catalytic strategies that are both highly reducing and also chemoselective remains a major challenge.

To this end, we envisioned a new electrophotocatalytic strategy that merged the power of electrical and photochemical energy[5] to realize extremely high reduction potentials under catalyst control. The Lambert group recently described an oxidative electrophotocatalytic system that achieved an extremely high oxidation potential (3.33 V vs SCE).[6] This high oxidizing power resulted from the photoexcitation of an open-shell, radical cation intermediate that was generated by electrochemical means. We reasoned that a similar potency should be achievable for reductive chemistry through the generation and photoexcitation of a radical anion intermediate. Indeed, the strongly reducing character of radical anions has long been known.[7] Recently, König described systems that undergo sequential photoinduced reduction to form radical anions followed by a second photoexcitation of the resulting radical anions.[8] Such a strategy, however, requires that the same catalyst must serve as both a photooxidant and, once reduced, a photoreductant. In addition, the photooxidation step can be problematic in that it necessitates the formation of oxidative byproducts (e.g., $Et_3N^{\bullet+}$), which limits the effective reducing power of the system due to back electron transfer or competing side reactions.[2b]

We propose a new electrophotocatalytic strategy to access extremely reducing intermediates via tandem cathodic reduction and photoexcitation. The use of electrochemistry circumvents the photooxidation step in the consecutive dual photoredox approach, because the catalyst radical anion can be generated from the neutral precursor without the need for a chemical reductant. For example, cathodic reduction of dicyanoanthracene (DCA; $E_{1/2} = -0.82$ V) results in the corresponding radical anion $DCA^{\bullet-}$, which absorbs visible light and exhibits a strong fluorescence emission (excitation energy $E_{0,0} = 2.38$ eV; see Scheme 1).[9] The photoexcited DCA ($DCA^{\bullet-}*$) is estimated to display an exceptionally high reducing potential of -3.2 V (vs SCE),[10] which TD-DFT calculations suggest arises from a SOMO-HOMO level inversion featuring a very unstable electronic structure with a half-filled bonding orbital (ψ_1) and a filled antibonding orbital (ψ_2) (see Figure S3 in Supporting Information). This value is on par with some of the most reducing elemental metals such as Li ($E = -3.3$ V). Moreover, $DCA^{\bullet-}*$ has been estimated to have a lifetime of 13.5 ns,[9] sufficiently long to engage in reductive activation of suitable substrates. Importantly, the tandem electrochemical activation and photoexcitation allows the formation of this highly reducing catalyst in a very low concentration in a controllable fashion, thus providing an avenue to circumvent the chemoselectivity issues frequently associated with strongly reducing conditions using chemical reductants or direct electrolysis. In this Communication, we apply this electrophotocatalytic strategy to the reductive functionalization of a wide range of aryl halides with reduction potentials (E_{red}) as low as -2.94 V.

As a proof of concept, we first confirmed that $DCA^{\bullet-}$ can be generated and is stable under preparative electrochemical conditions (Figure 1). Using a porous carbon cathode and a zinc plate sacrificial anode in an H-type divided cell, the application of a constant cell voltage of 3.2 V (corresponding to a cathodic potential of -1.0 V vs SCE) resulted in the formation of a deep orange solution in the cathodic compartment. The UV–vis absorption spectrum of this solution is identical to that of $DCA^{\bullet-}$ reported in the literature.[9]

We next set out to investigate our proposed electrophotocatalytic system in the context of the reductive functionalization of aryl halides. In recent years, the generation of aryl radicals from aryl halides has been shown to be a productive synthetic strategy.[11] However, current methods are largely limited to substrates with relatively labile carbon–halogen bonds or low reduction potentials.[8,11] For example, aryl chlorides often display high reduction potentials (> −2.0 V) and strong bond dissociation energies (>97 kcal/mol),[12] and thus can be difficult to engage in reductive reactions in the single-electron manifold. In addition, electron-rich aryl halides are often recalcitrant to single electron reductions. Here, we show that reductive electrophotocatalysis allows for the engagement of these challenging substrates.

We chose to study the borodechlorination of ethyl 4-chlorobenzoate (**1**, E_{red} = −2.04 V vs SCE)[12] using DCA as the catalyst and bis(pinacolato)diboron (B_2pin_2) as the radical acceptor (Table 1). To date, only a few examples are available for the borylation of aryl chlorides under metal-free conditions.[13] After optimization, we observed that the application of both blue light and current enabled efficient coupling of **1** and B_2pin_2 to furnish arylboronate **2** in 88% yield (entry 1). The optimal conditions employed pyridine (20 mol %) as an additive, $TBAPF_6$ as the electrolyte, carbon foam and zinc plate as cathode and anode, respectively, in MeCN with an applied cell voltage of 3.2 V under blue LED irradiation. A set of control experiments revealed that current, light, and DCA are all necessary for reactivity (entries 2–4). Pyridine, which is known to coordinate to B_2pin_2 and promote the formation of a B-centered persistent radical intermediate,[13a,14] was beneficial to reaction efficiency (entry 5).

We found that the use of white CFL was also productive (entry 6), albeit with slightly reduced efficiency relative to the blue LEDs. Changing the sacrificial anode from Zn to Al did not significantly affect the reaction yield (entry 7). The reaction, in principle, can be conducted in an undivided cell, which indeed provided the desired product in 37% yield. However, the reaction was prematurely terminated due to the formation of a zinc bridge between the cathode and anode that short-circuited the electrochemical setup (entry 8). Anthraquinone (AQ), which exhibits similar light-induced redox reactivities,[9] was also an effective catalyst, albeit with diminished yield (entry 9). Importantly, this reaction was also applicable to the reductive borylation of 4-chloroanisole (**3**), which has a highly negative reduction potential (E_{red} = −2.90 V vs SCE)[15] (entry 10). This result highlights the extreme reducing power that this catalytic system can provide. Notably, this substrate has not been successfully engaged in high yielding reductive functionalizations using photoredox catalysis.

We have found that this reaction is capable of borylating a wide range of aryl halides. A number of functional groups potentially sensitive to strongly reducing conditions, such as ester (**2** and **5**), ketone (**6**), amide and carbamate (**7** and **12**), thiophene (**14**), and *N*-Boc indole[16] (**15**) groups, were well tolerated (see Table 2). Notably, substrate **16** with an acidic C–H bond a to the ester group underwent desired transformation without epimerization of the stereogenic center. These results showcase that, although our catalytic strategy grants access to extremely reducing potentials, it does so under catalyst control with a high level of chemoselectivity that is typically uncommon in reactions promoted by potent reducing metals. In principle, the same types of products could be obtained using Pd-catalyzed

borylation. Nevertheless, this metal-catalyzed method[17] provided substantially lower yield for substrates bearing multiple Lewis basic coordinating groups (e.g., **16–18**).[18] When applied to the functionalization of indomethacin methyl ester, a pharmaceutical agent, 35% of the desired borylate was isolated (**18**).

We note that certain aryl chlorides were poorly reactive and returned the majority of the starting material, despite the fact that their reduction potentials suggest that they would be suitable substrates. We reason that in these cases, back electron transfer from intermediate [Ar–Cl$^{•-}$] to DCA is sufficiently fast to outcompete scission of the C–Cl bond. This hypothesis led us to investigate the corresponding aryl bromides. As expected, the reductive borylation activity was restored. An intramolecular competition experiment revealed that the mesolytic cleavage of a C–Br bond is indeed substantially faster than that of a C–Cl bond, as 1-chloro-4-bromobenzene (**19**) was selectively transformed to borodebrominated product **20.**

Notably, in addition to haloanisoles, several other electron-rich arenes and hetereoarenes (**11–15**) were found to be suitable substrates. Some of these aryl halides (e.g., **10, 11, 12, 15**) display very negative reduction potentials and represent highly challenging substrates for single electron reduction,[8] yet were productive under the optimal conditions.

The synthetic utility of this electrophotocatalytic protocol was further expanded to the formation of C–Sn and C–C bonds by employing different radical trapping agents (Table 3). For example, using hexamethylditin as a coupling partner, we developed metal-free stannylation of aryl halides (**22–26**). Using *N*-methylpyrrole or 1,4-difluorobenzene, C–H arylation products (**27–30**) were isolated in moderate to high yields.

A mechanistic rationale is shown in Figure 2A (pathway A). Thus, the DCA catalyst undergoes cathodic reduction to generate DCA$^{•-}$, which is then photoexcited to generate DCA$^{•-}$*.[8e] This highly reducing species can then donate an electron to the π-system of the aryl halide[9] to furnish intermediate **31** and to regenerate the DCA catalyst. Aryl halide radical anions **31** are known to undergo mesolytic cleavage to form aryl radicals **32**,[19] which can then proceed to the functionalized products.

We also recognized the possibility of a photoinduced reduction of DCA at the cathode to form DCA$^{•-}$ (Figure 2A, pathway B), in analogy to König's dual photocatalytic system. However, this pathway is unlikely because DCA ($\lambda_{max} < 420$ nm) is not efficiently excited by the blue LEDs used in our study. Furthermore, controlled potential electrolysis at different cathodic potentials from 0 to −1.2 V (Figure 2B) revealed that the onset potential for the reductive borodehalogenation is about −0.4 V (5% yield), whereas the optimal reactivity occurs above the thermodynamic reduction potential of DCA (−0.82 V). The low potential threshold for an outer sphere electron transfer event is typically ca. 500 mV below the thermodynamic potential of the reductant.[20] Meanwhile, because of the highly oxidizing nature of DCA* ($E \approx 2.0$ V),[2b] an applied potential of 0 V should have been more than sufficient to reduce DCA*. Thus, these data are fully consistent with the proposed mechanism involving direct electrochemical activation of DCA.

The second alternative pathway entails the formation of an electron-donor acceptor complex between DCA[•−] and the aryl halide substrate,[2b] followed by light-promoted inner sphere electron transfer from DCA[•−] to the substrate. However, mixing DCA[•−] with **3** produced no changes to the UV−vis spectrum (see Supporting Information for details), which argues against this proposal.[2c,21]

In summary, we report a new electrophotocatalytic strategy to access radical anion species with exceedingly high reducing power through tandem electrochemical activation and photoexcitation. This strategy made possible the chemoselective activation of inert substrates with very negative reduction potentials, which are challenging using existing redox modules that rely solely on photoredox activation. We anticipate that this conceptual advance will be broadly applicable in organic synthesis for reactions that require extreme redox power.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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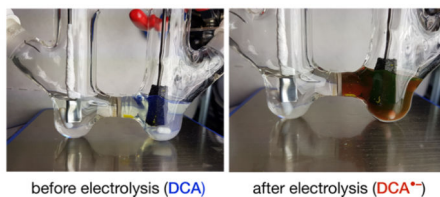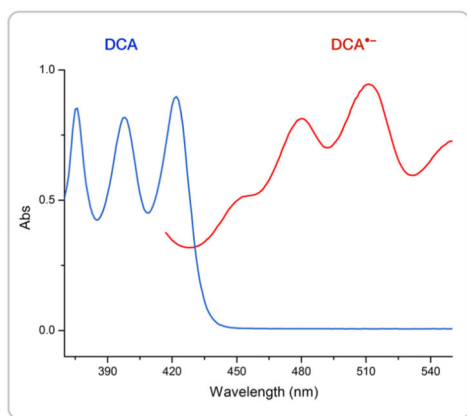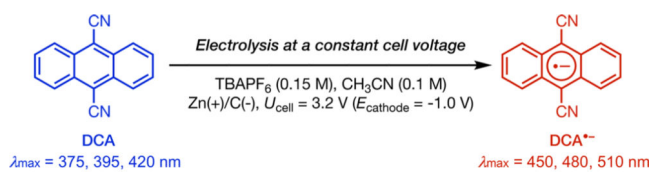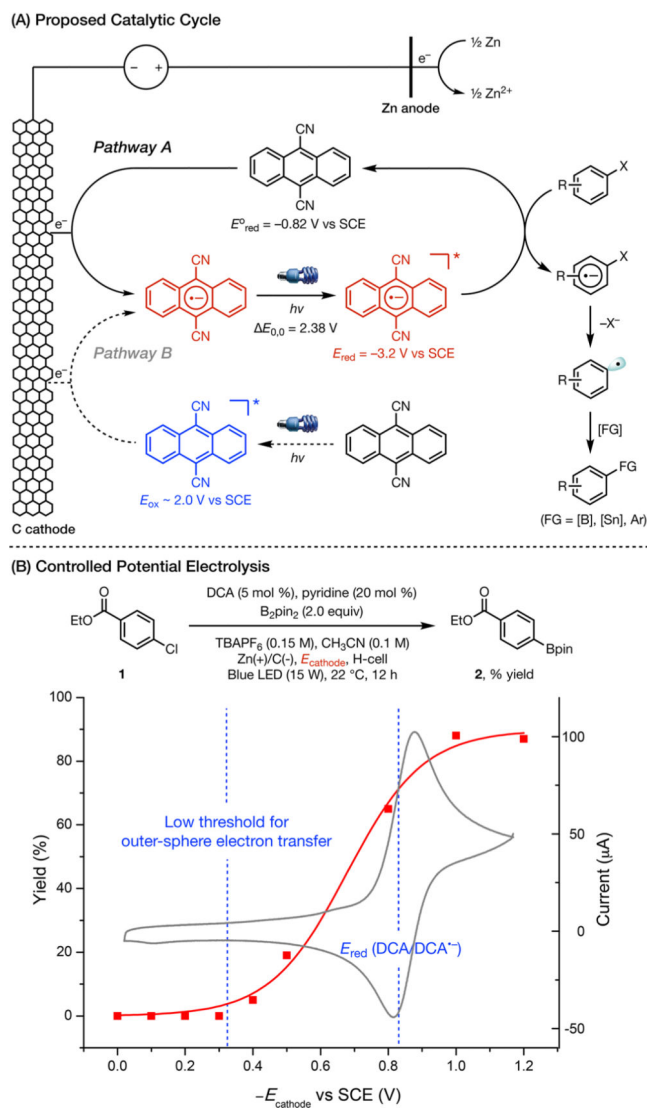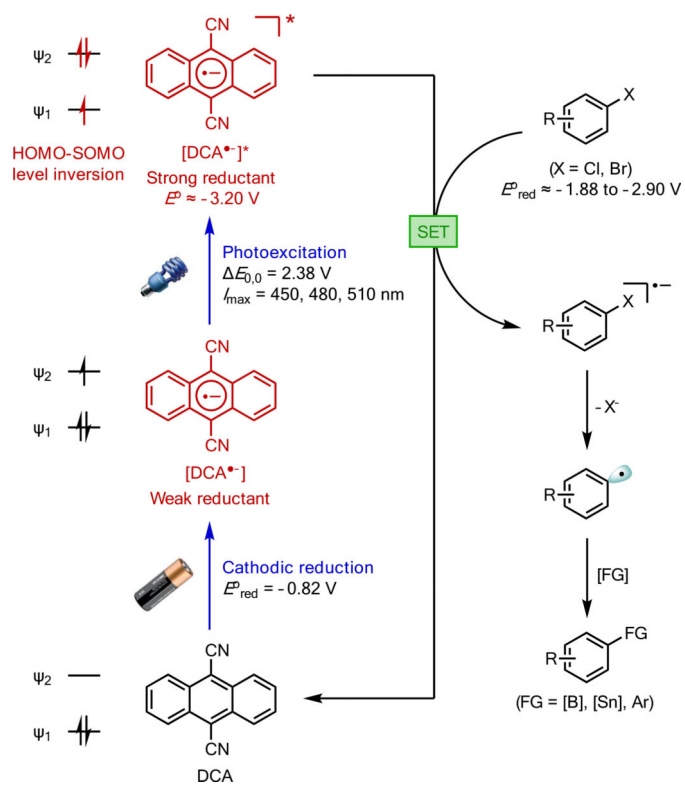
Figure 1.
Electrochemical generation of radical anion.

Figure 2.
Mechanistic experiments. In part B, red squares represent the reaction yield at a given applied cathodic potential, and the gray trace shows the cyclic voltammogram of DCA.

Scheme 1.
Reductive Electrophotocatalysis for the Functionalization of Aryl Halides

Table 1.

Reaction Optimization[a]

entry	variation from "standard conditions"	yield (%)
1	none	90 (88)
2	no applied voltage	<5
3	no light irradiation	<5
4	no DCA	<5
5	no pyridine	58
6	CFL (23 W) instead of blue LED	70
7	Al(+)/C(−) instead of Zn(+)/C(−)	65
8	undivided cell	37
9	AO as a catalyst instead of DCA	66
10	**3** as substrate	57 (53)

[a]Cathodic chamber: **1** (0.4 mmol, 1.0 equiv), DCA (5 mol%), B$_2$pin$_2$ (2.0 equiv), pyridine (20 mol%), TBAPF$_6$ (0.15 M), CH$_3$CN (0.1 M); anodic chamber: TBAPF$_6$ (0.15 M), CH$_3$CN (0.1 M); cell voltage (U_{cell}) = 3.2 V; yields determined by ^{1}H NMR (isolated yield in parentheses).
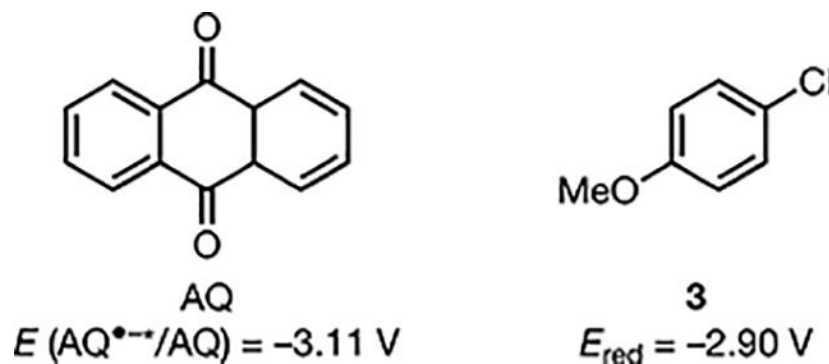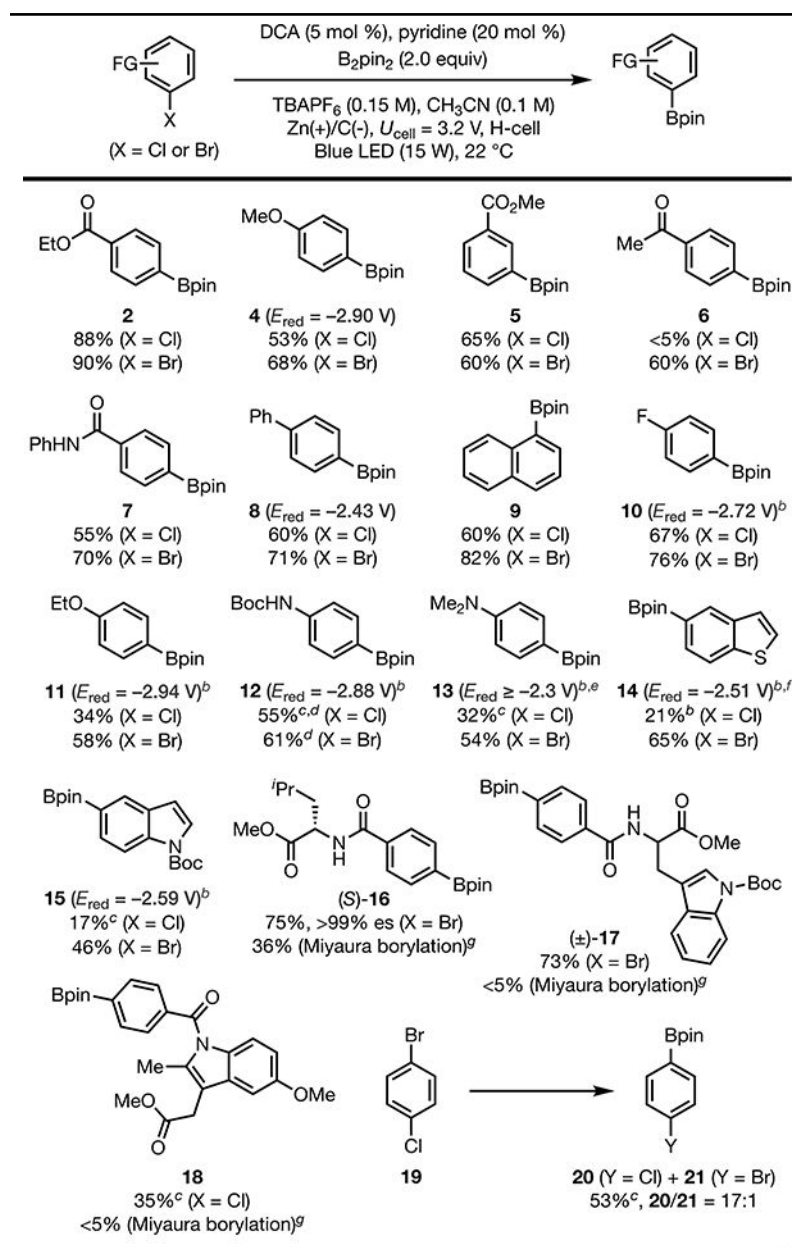

AQ
$E (AQ^{\bullet -*}/AQ) = -3.11$ V

3
$E_{red} = -2.90$ V

Table 2.

Scope of Electrophotocatalytic Borylation[a]

		CO₂Me	O
2	**4** (E_{red} = −2.90 V)	**5**	**6**
88% (X = Cl)	53% (X = Cl)	65% (X = Cl)	<5% (X = Cl)
90% (X = Br)	68% (X = Br)	60% (X = Br)	60% (X = Br)

7	**8** (E_{red} = −2.43 V)	**9**	**10** (E_{red} = −2.72 V)[b]
55% (X = Cl)	60% (X = Cl)	60% (X = Cl)	67% (X = Cl)
70% (X = Br)	71% (X = Br)	82% (X = Br)	76% (X = Br)

11 (E_{red} = −2.94 V)[b]	**12** (E_{red} = −2.88 V)[b]	**13** (E_{red} ≥ −2.3 V)[b,e]	**14** (E_{red} = −2.51 V)[b,f]
34% (X = Cl)	55%[c,d] (X = Cl)	32%[c] (X = Cl)	21%[b] (X = Cl)
58% (X = Br)	61%[d] (X = Br)	54% (X = Br)	65% (X = Br)

15 (E_{red} = −2.59 V)[b]	**(S)-16**	**(±)-17**
17%[c] (X = Cl)	75%, >99% es (X = Br)	73% (X = Br)
46% (X = Br)	36% (Miyaura borylation)[g]	<5% (Miyaura borylation)[g]

18	**19**	**20** (Y = Cl) + **21** (Y = Br)
35%[c] (X = Cl)		53%[c], **20**/**21** = 17:1
<5% (Miyaura borylation)[g]		

[a]Isolated yields are reported. Optimal conditions from Table 1 used.

[b]Calculated E_{red} values for aryl chlorides (see SI).

[c]10 mol% DCA.

[d]Yield determined by ¹H NMR.

^{e}E_{red} could not be accurately determined.

^{f}Aryl halide (0.25 mmol, 1 equiv), Pd(dppf)Cl$_2$ (5 mol %), KOAc (3.0 equiv), B$_2$pin$_2$ (1.2 equiv) in DMSO (0.85 mL) under 110 °C for 12 h.

Table 3.
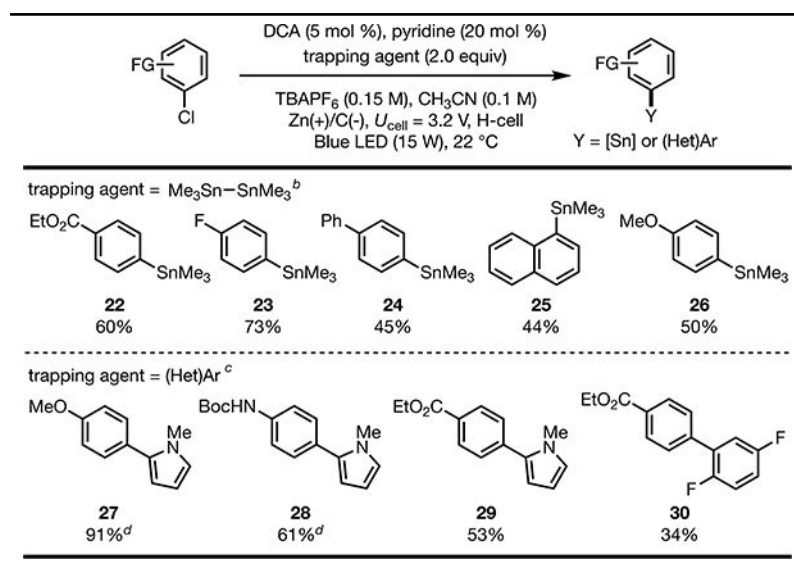
Diverse Functionalization of Electrophotocatalytically Generated Aryl Radicals[a]

[b]Yields determined by ^{1}H NMR.

[c]20 equiv of (hetero)arene was used as the trapping agent.

[d]10 mol% DCA.