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Authors: Javier Bardagi, Indrajit Ghosh, Matthias Schmalzbauer, Tamal Ghosh, and Burkhard König
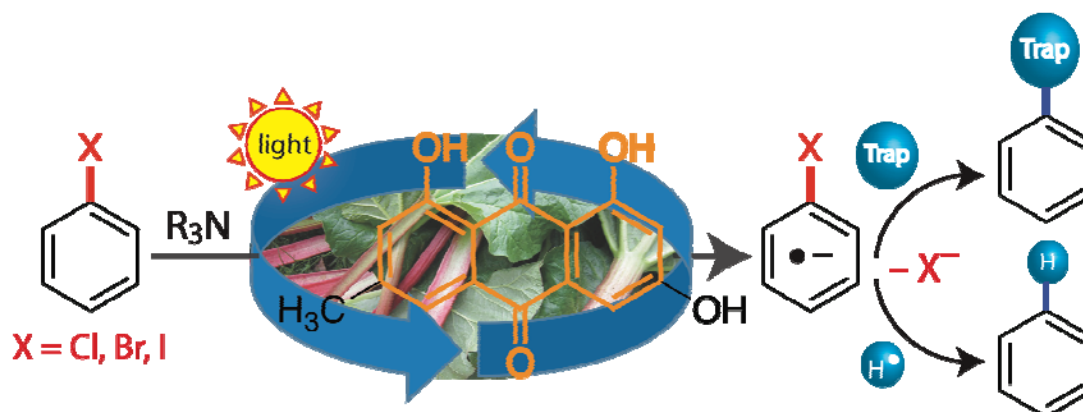
Anthraquinones as photoredox catalysts for the reductive activation of aryl halides

Javier I. Bardagi, Indrajit Ghosh, Matthias Schmalzbauer, Tamal Ghosh, and Burkhard König*

Institute of Organic Chemistry, University of Regensburg, D-93040 Regensburg, Germany

*Correspondence to: burkhard.koenig@ur.de

Graphical abstract

Abstract

Quinones are ubiquitous in nature, as structural motif of natural products or redox mediator in biological electron transfer processes. While their oxidation properties have already been widely used in chemical and photochemical reactions, applications of quinones in reductive photoredox catalysis are less explored. We report the visible light photoreduction of aryl halides (Ar–X; where, X = Cl, Br, I) by 1,8-dihydroxyanthraquinone. The resulting aryl radical anions fragment into halide anions and aryl radicals, which react in hydrogen abstraction or C–C bond forming reactions. The active photocatalyst is generated from 1,8-dihydroxyanthraquinone by photoinduced single electron reduction to the radical anion or subsequent protonation and further reduction (or *vice versa*) to the semiquinone anion. Subsequent visible light excitation of the anthraquinone radical anion or semiquinone anion converts them into very potent single electron donors. A plausible mechanism of the reaction is proposed based on control experiments and spectroscopic observations.

Keywords: Quinone, radical anion, electron transfer, C–H arylation, visible light

*T*he use of visible light for the generation of reactive intermediates in organic transformations has many advantages, and the growing interest over the last decade on visible light mediated photoredox catalytic synthetic transformations demonstrates the feasibility of the approach.[1-9] Ru- or Ir-based coordination complexes have gained enormous attention because of their excellent visible light harvesting properties, modest to extremely high oxidation and reduction potentials, relatively long excited state lifetimes, and reasonably good chemical and photo stability under synthetic oxidative and reductive conditions.[2] In addition, considerable efforts have been made in developing metal-free photoredox catalytic methods using organic dyes,[8, 10-14] such as eosin Y[10-11] or rhodamine derivatives,[13-14] or organic heterogeneous photocatalysts[15] for synthetic transformations.

Quinones[8, 16-17] occur in nature and are known for their excellent electron accepting and hydrogen-abstracting abilities.[16, 18] Not surprisingly, different quinone derivatives have been used for photooxidative transformations using visible light.[19-22] Fukuzumi reported the photoredox catalytic conversion of benzene to phenol using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) under visible light irradiation.[23] Itoh and subsequently Yuan reported trifluoromethylations of arenes and heteroarenes using anthraquinone-2-carboxylic acid[24] and DDQ[25], respectively. Itoh reported the synthesis of carboxylic acids from their respective methyl aromatics using 2-chloroanthraquinone.[26] Recently, Brasholz disclosed cascade

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dehydrogenation/6π-cyclization/oxidation reactions of 1-(nitromethyl)-2-aryltetrahydroisoquinolines in the presence of 1-aminoanthraquinone in order to obtain tetracyclic 12-nitroindolo[2,1-a]isoquinoline products.[19] Similarly, the same group also reported an intermolecular version using 1,5-diaminoanthraquinone as a photocatalyst for synthetic transformations of *N*-aryl-tetrahydroisoquinolines and nitromethane to prepare the same product.

Anthraquinone (**Aq**) and its derivatives (Figure 1A) form coloured radical anions upon single electron reduction (see Figure 1B for the absorption spectra of electrochemically generated radical anion of 1,8-dihydroxyanthraquinone (**Aq-OH**)). The radical anions of anthraquinones possess moderate reduction potentials in their ground state (*e.g.*, E^0(**Aq/Aq$^{•-}$**) and E^0(**Aq-OH/Aq-OH$^{•-}$**) are –0.82 V and –0.55 V *vs* SCE, respectively)[27], and can be accessed electrochemically, chemically, or *via* photoinduced single electron transfer processes in the presence of a suitable electron donor under inert atmosphere (see Figure 3A). Eggins[28] as well as Lund and Eriksen[29] showed that the excited states of coloured radical anions of anthraquinone (**Aq**) (or in general quinone derivatives, see ref. 28) are powerful reductants and are capable of transferring electrons to organic substrates that possess extremely negative reduction potentials (*e.g.*, 1,2-dibromobenzene, an aryl halide substrate with a reduction potential of –1.88 V *vs* SCE[28]). Although the radical anions of quinone derivatives are known as common intermediates in natural and synthetic photochemical energy storage,[16, 30] they have not been applied in photoredox catalytic reductive transformations so far. Knowing that the excited states of radical anions act as powerful reductants,[12-13, 28-29, 31] we envisioned employing anthraquinone derivatives for the photoredox catalytic reduction of aryl halide substrates, including aryl chlorides, to obtain aryl radicals either for metal-free dehalogenation reactions[12, 32-35] or for synthetically important carbon–carbon[12, 32, 36-38] bond formation reactions. Such photoredox catalytic methods[12-13, 32-39] are valuable alternatives to well-established transition metal based activation methods. Herein, we report the use of 1,8-dihydroxyanthraquinone as photocatalyst for synthetically important C–C bond formation reactions using aryl halides as bench–stable starting materials and visible light.

(A) Anthraquinone (Aq)   1,4-Diaminoanthraquinone (Aq-NH₂)   1,8-Dihydroxyanthraquinone (Aq-OH)

Unisol Blue   Frangulin B   Frangulin A

(B) Aq-OH   Aq-OH$^{•-}$
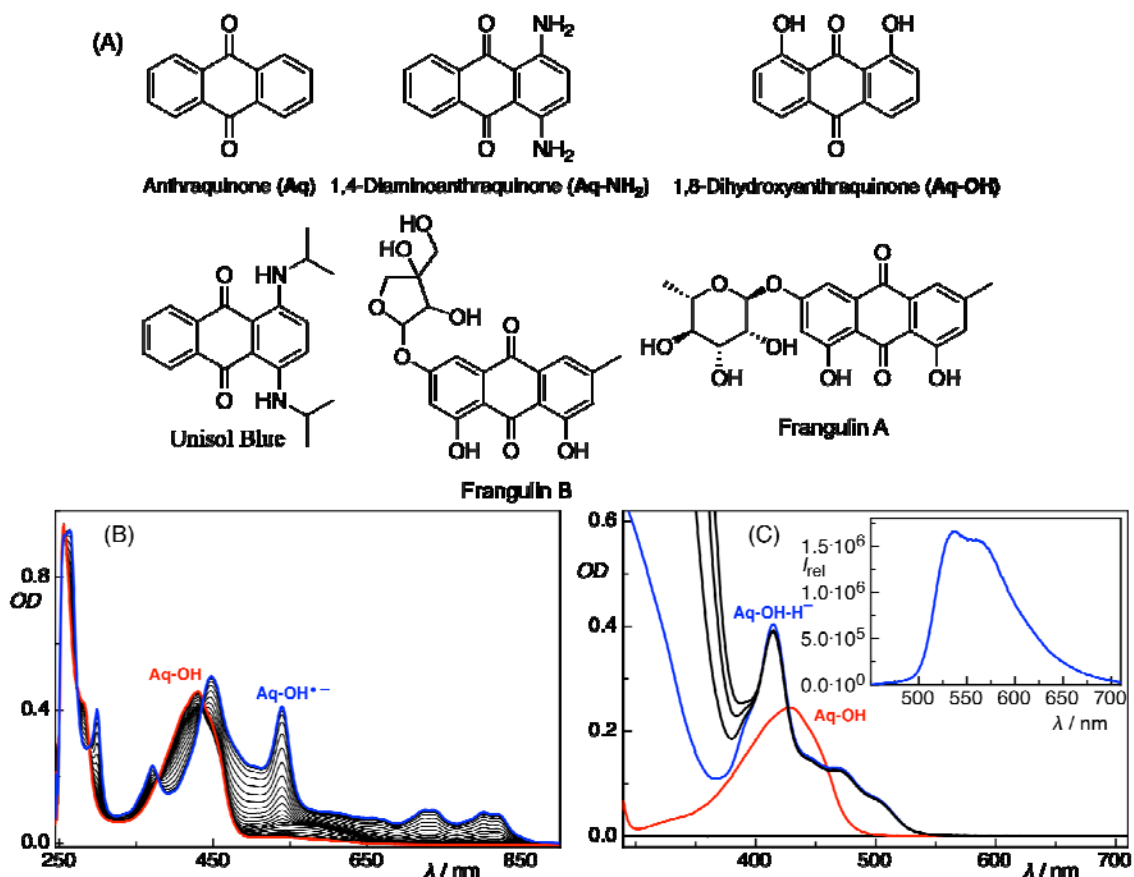
(C) Aq-OH-H$^-$ Aq-OH

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Figure 1. (A) Chemical structures of anthraquinone derivatives investigated herein. (B) Spectroelectrochemistry of **Aq-OH** in deaerated DMF. (C) Formation of 1,8-dihydroxyanthraquinone semiquinone anion (**Aq-OH-H⁻**) in the presence of $Na_2S_2O_4$.[40] In the inset, the luminescence spectrum (λ_{Ex} = 427 nm) of **Aq-OH-H⁻** is shown. For the formation of the radical anion and the semiquinone anion of **Aq-OH** upon photoirradiation in the presence of Et_3N see Figure 3.

We began our investigations with methyl 2-bromobenzoate (**1a**) as a test substrate and 1,8-dihydroxyanthraquinone as a photoredox catalyst. A mixture of **1a**, **Aq-OH** (10 mol%), and triethylamine (Et_3N, 1.0 equiv, as a sacrificial electron donor and hydrogen atom donor, see below) was irradiated in DMF with a blue LED (λ_{Ex} = 455 ± 15 nm) for 24h. Methyl benzoate **2a** was obtained in 61% yield (see entry 1 in Table 1).[41] Continuous irradiation of the same reaction mixture for 48h gave **2a** in 74% yield for *ca.* 90% substrate conversion. Control experiments, *i.e.*, omitting each of the individual catalytic components, confirmed that the photocatalyst, electron donor, and most importantly light irradiation are necessary for the photoredox catalytic dehalogenation reactions to take place (see entries 1–6 in Table 1). Among other derivatives of anthraquinone, including Unisol Blue, used for microscopy, **Aq-OH** was selected for further experiments due to the better chemical product yield (*c.f.*, entries 1 and 11–15 in Table 1). Natural occurring Frangulin A/B, derivatives of 1,8-dihydroxyanthraquinone, perform as good as **Aq-OH** (entry 16) indicating a superior catalytic performance of this core structure.

Having the optimized reaction conditions (see entries 1–2 and 8–10 in Table 1) in hand, which requires simple mixing of aryl halides, commercially available inexpensive **Aq-OH**, Et_3N, and photoirradiation with blue LEDs under nitrogen, the scope of the method was explored with different aryl halide substrates. Good to excellent photo-reduction yields (up to 87%) were obtained with aryl bromide substrates possessing different substituents, for example, –CN, $-CO_2Me$ (*–o*, *–m*, and *–p*), –CHO, –COMe, and $-CONH_2$ (see Figure 2), demonstrating the mild nature of the photoredox catalytic reaction condition. Bromobenzene gave a poor product yield due to its very high reduction potential. The yield increased with iodobenzene as substrate (25%); 4-iodotoluene was reduced in 27% yield and 4′-iodoacetophenone in 60% yield. Aryl chloride substrates with suitable reduction potentials (*e.g.*, 2-chlorobenzonitrile, see Figure 2 for reductive C–H arylation reactions using 2-chlorobenzonitrile) could also be activated using this catalytic method. However, aryl halide substrates with very high reduction potentials (*e.g.*, 4-bromoanisole), could not be activated effectively for synthetically useful transformations and describe the limit of the substrate scope of the reaction.

Table 1. Control reactions and optimization of the photoredox catalytic reduction condition using methyl 2-bromobenzoate (**1a**) as a test substrate under visible light irradiation.[a]

Entry	Donor (equiv)	Catalyst (mol%)	Conditions	Yield in % (% conv) [b]
Control reactions				
1	Et_3N (1.0)	**Aq-OH** (10)	455 nm, 24 h	61 (80)
2	Et_3N (1.0)	**Aq-OH** (10)	455 nm, 48 h	74 (90)
3	–	–	455 nm, 48 h	0 (1) [c]
4	Et_3N (1.0)	–	455 nm, 48 h	≥ 1 (2) [c]
5	–	**Aq-OH** (10)	455 nm, 48 h	13 (24)
6	Et_3N (1.0)	**Aq-OH** (10)	**Dark**, 48 h	0 (0) [c]
7	Et_3N (1.0)	**Aq-OH** (10)	455 nm, 48 h	9 (11) [d]
Optimization of the reaction condition				
8	Et_3N (1.0)	**Aq-OH** (2)	455 nm, 24 h	47 (58)
9	Et_3N (1.0)	**Aq-OH** (5)	455 nm, 24 h	44 (54)
10	Et_3N (0.7)	**Aq-OH** (10)	455 nm, 24 h	47 (64)

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Different anthraquinone derivatives (see Figure 1A for chemical structures)

11	Et$_3$N (1.0)	**Aq** (10)	455 nm, 24 h	35 (62)
12	Et$_3$N (1.0)	**2-EtAq** (10)	455 nm, 24 h	34 (62)
13	Et$_3$N (1.0)	**2-NH$_2$-Aq** (10)	455 nm, 24 h	48 (76)
14	Et$_3$N (1.0)	**Aq-NH$_2$** (10)	455 nm, 24 h	6 (18)
15	Et$_3$N (1.0)	**Unisol Blue** (10)	455 nm, 24 h	3 (16)
16	Et$_3$N (1.0)	**Frangulin** (10)	455 nm, 24 h	58 (74)

[a] Reactions were performed under nitrogen using 0.1 mmol methyl 2-bromobenzoate (**1a**) in 1.0 mL of DMF with a blue LED (λ_{Ex} = 455 ± 15 nm. See supporting information for the reaction setup). [b] Calculated from GC analysis (error *ca.* ± 5%) using the internal standard method (see supporting information for details). In the parenthesis, substrate conversion is shown. [c] The yield is below the GC quantification limit. [d] The reaction was performed with 4-bromoanisole as substrate.

The photoredox catalytic single electron transfer (SET) reduction reactions proceed *via* a radical mechanism as strongly supported by the experimental results and recent literature reports.[32, 42] Additionally, when a reaction mixture containing 4′-bromoacetophenone or 2-bromobenzonitrile was irradiated in the presence of 1,1-diphenylethylene, a radical scavenger,[43-44] the coupling products **3n** and **3o+3p** were obtained in 42% and 58% isolated yields (see Figure 2 and supporting information for further details), respectively, providing further evidence for the radical nature of the reaction.
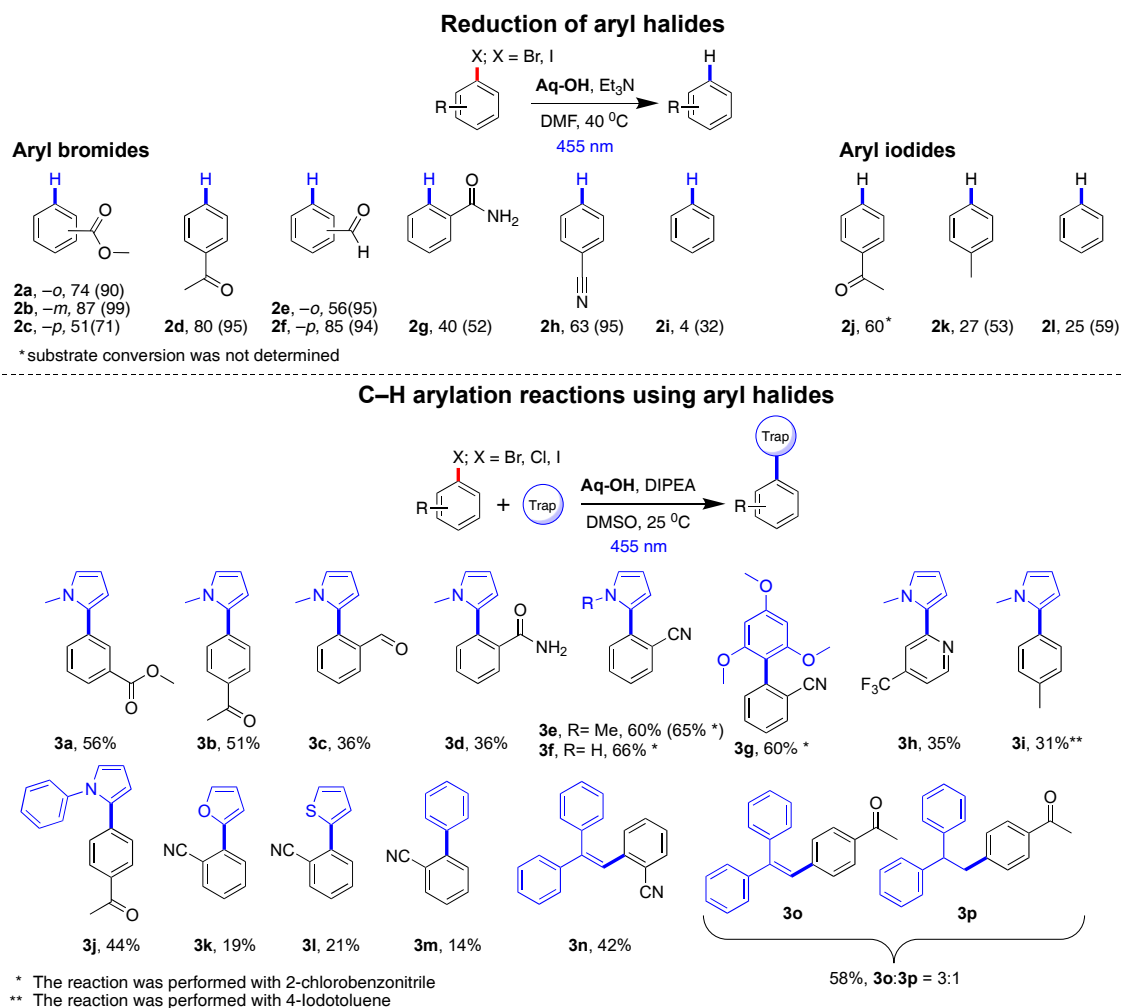

Figure 2. Photoredox catalytic reduction yields and the yields of C–C bond forming reactions using aryl halides as substrates (Ar–X; where, X = I, Br, Cl). For photoreduction reactions, substrate conversions after 48h are shown in the parenthesis (see also supporting information).

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With these results, we explored the photoredox catalytic generation of aryl radicals from their respective halides for C–C bond forming reactions using arenes, heteroarenes, and unsaturated double bonds. The main challenge in this case, which was also observed for other photoredox catalytic C–H arylation reactions using aryl halides,[12-13, 32, 36-38] is the competing hydrogen atom abstraction by the reactive aryl radicals either from the radical cation of the amine or from the solvent leading to the reduction product. However, when a reaction mixture containing 2-bromobenzonitrile, **Aq-OH**, DIPEA, and benzene was irradiated with blue LEDs, the desired product **3m** was obtained in 14% yields.[45] Similarly, when furan and thiophene were introduced as the radical trapping reagent, the desired products **3k** and **3l** were obtained in useful yields. Note that thiophene and furan efficiently trap aryl radicals under photoredox conditions in redox neutral reactions, in which the excited state of the photocatalyst transfers an electron to the aryl radical precursor and no sacrificial electron donor is necessary (*e.g.*, photoredox catalytic generation of aryl radicals from their respective diazonium salts[11, 32]). However, they consistently fail to trap aryl radicals generated from the respective aryl halides under other reported photoredox catalytic conditions. For instance, it has recently been reported that thiophene and furan fail to trap 2-benzothiazole radicals generated *via* single electron transfer from the respective bromides under photoredox catalytic conditions in the presence of *fac*-Ir(ppy)$_3$ and R$_3$N as an electron donor.[36] The reason for this is still unclear and needs further detailed investigations. The **Aq-OH**–based photoredox catalytic system allows the C–H arylations of thiophene and furan, although in low *ca.* 20% isolated yields. When 1,3,5-trimethoxybenzene, a substituted arene, was used as a trapping reagent for the 2-cyanophenyl radical, the expected product was obtained in 60% isolated yield. With pyrrole derivatives as trapping reagents, the C–H arylated products were isolated in moderate to good yields. Notably, unprotected pyrrole reacts cleanly with the aryl radicals. All investigated heterocycles (*i.e.*, furan, thiophene, and pyrrole derivatives) were selectively arylated at the 2-position (see Figure 2). C–H functionalization reaction of 1,1-diphenylethylene with 2-bromobenzonitrile gave **3n** in 42% yield. 4'-Bromoacetophenone gave a mixture of **3p** and **3q** in 58% isolated yield confirming that both hydrogen atom abstraction and the oxidation reaction take place subsequent to the aryl radical addition step (see Figure S3). The C–H arylation reactions are also effective when aryl chlorides were used as the precursors of aryl radicals. Using 2-chlorobenzonitrile as substrate compounds **3e–3g** were obtained in good isolated yield.
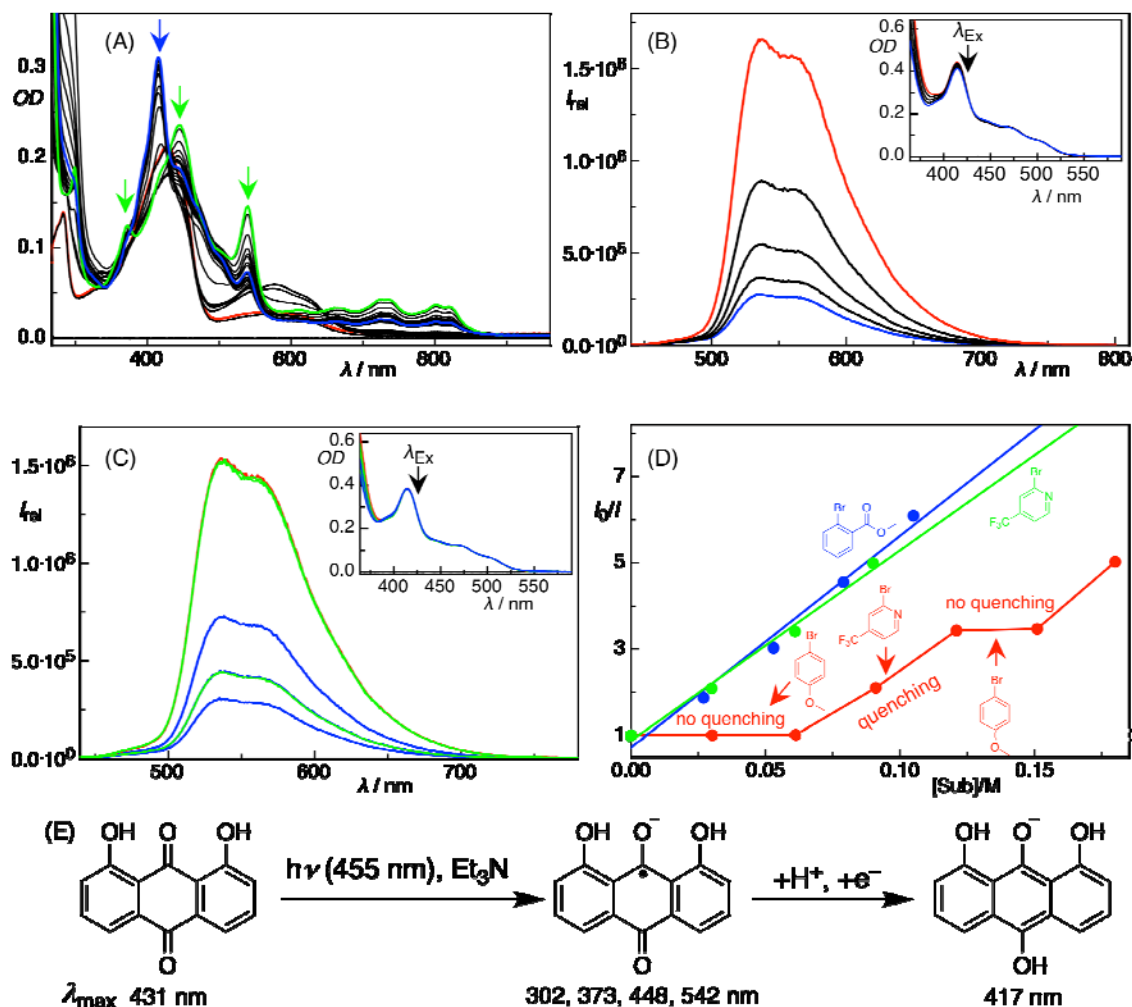
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Figure 3. (A) Changes in the absorption spectra of **Aq-OH** upon photoirradiation ($\lambda_{Ex} = 455 \pm$ 15 nm) in the presence of Et$_3$N under nitrogen in DMF. The green and blue arrows indicate the absorption maxima of **Aq-OH·−** and **Aq-OH-H−**, respectively. For the photoirradiation experiment in DMSO see Figure S2. (B) Changes in the fluorescence spectra of 1,8-dihydroxyanthraquinone semiquinone anion (**Aq-OH-H−**) upon successive addition of methyl 2-bromobenzoate (**1a**, test substrate). In the inset, changes in the absorption spectra of **Aq-OH-H−** upon successive addition of **1a** are shown. (C) Alternative luminescence quenching titration plot of **Aq-OH-H−** with 4-bromoanisole (green curves) and 2-bromo-4-(trifluoromethyl)pyridine (blue curves) is shown (see the Stern-Volmer quenching plot in Figure (D)). In the inset changes in the absorption spectra of **Aq-OH-H−** upon addition of 2-bromo-4-(trifluoromethyl)pyridine and 4-bromoanisole are shown. (D) Stern-Volmer quenching plot of **Aq-OH-H−** with methyl 2-bromobenzoate, 2-bromo-4-(trifluoromethyl)pyridine, and the fluorescence response (in this case, intensity) of **Aq-OH-H−** upon alternating addition of 2-bromo-4-(trifluoromethyl)pyridine and 4-bromoanisole are shown (see the mechanism section and supporting information for more details). (E) Chemical structures along with their respective reported absorption maxima[27] of photo- and redox-active species of **Aq-OH** are depicted.

The presence of different photo- and redox-active species (including all intermediates in the reaction mixture) under the synthetic reaction conditions, and the challenges of performing spectroscopic and electrochemical experiments under non-idealized reaction conditions do not allow us to report a complete mechanism. However, based on the literature reports[28-29, 32, 42] and spectroscopic investigations (see Figure 1 and 3 and supporting information) a proposed mechanism is depicted in Figure 4. The reaction did not yield any photoreduction product (see entry 6 in Table 1) or C–H arylated products in the dark. The absence of an effective

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luminescence quenching of **Aq-OH** in the presences of methyl 2-bromobenzoate demonstrates that the excited state of **Aq-OH** is not responsible for initiating the single electron transfer to aryl halides (Figure S1). Upon visible light photoexcitation, the excited state of **Aq-OH** is quenched by Et$_3$N generating the radical anion **Aq-OH**$^{\bullet-}$ (and the radical cation of Et$_3$N, *i.e.*, Et$_3$N $^{\bullet+}$) that upon protonation and successive reduction (or *vice versa via* a consecutive or a coupled step) forms the semiquinone anion, **Aq-OH-H**$^-$. The presence of both **Aq-OH**$^{\bullet-}$ and **Aq-OH-H**$^-$ species was confirmed by irradiating a mixture of **Aq-OH** and Et$_3$N under nitrogen in DMF and in DMSO (see Figure 3A and Figure S2). Notably, the electron transfer from the ground state radical anion of anthraquinone or the semiquinone anion to the aryl halide substrates is thermodynamically unlikely due to their intrinsic low ground state reduction potentials (*c.f.*, E^0(**Aq-OH/Aq-OH**$^{\bullet-}$ = *ca.* – 0.5 V *vs* SCE and ref. 46). The semiquinone anion **Aq-OH-H**$^-$ could be generated in the presence of Na$_2$S$_2$O$_4$ under nitrogen (see Figure 1) and is luminescent.[40, 47] The absorption spectra of **Aq-OH-H**$^-$ did not change in the presence of methyl 2-bromobenzoate, but the **Aq-OH-H**$^-$ luminescence was significantly quenched (Figure 3). The luminescence of **Aq-OH-H**$^-$ is also quenched in the presence of 2-bromo-4-(trifluoromethyl)pyridine (another investigated substrate), but was not effected significantly by the presence of 4-bromoanisole (a substrate that is difficult to activate under the photoredox catalytic condition (see Figure 3). The alternating quenching experiment (see Figure 3), in which 2-bromo-4-(trifluoromethyl)pyridine and 4-bromoanisole were added alternatively, gave the expected luminescence responses (*i.e.*, when 4-bromoanisole was added the luminescence was unaltered, but upon addition of 2-bromo-4-(trifluoromethyl)pyridine in the same solution the luminescence was quenched). Upon photoexcitation, the radical anion of **Aq-OH** is capable of transferring an electron to the investigated aryl halide substrate. Previous work[28-29] on the luminescence quenching of the excited state of **Aq**$^{\bullet-}$ by aryl halides supports this proposal.
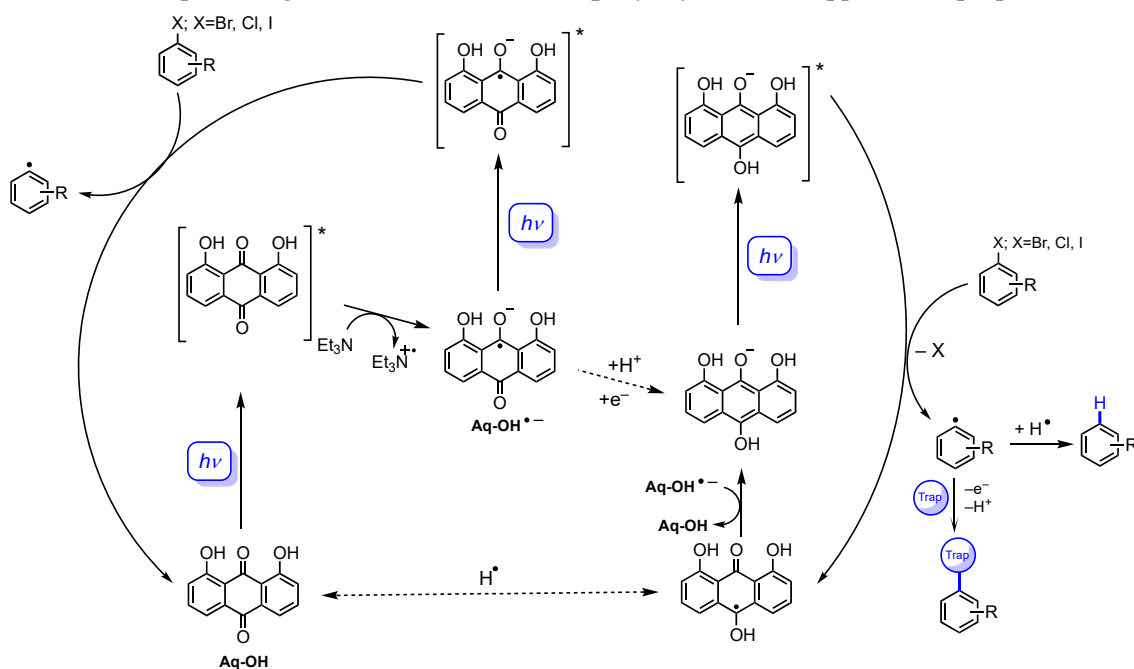

Figure 4. Proposed mechanism of the photoredox catalytic cycle for the photoreduction of aryl halides and C–C bond formation reactions using suitable trapping reagents.

Upon single electron transfer to aryl halides (Ar–X, where X = Cl, Br, and I), the generated Ar–X$^{\bullet-}$ subsequently fragments to yield aryl radicals that either abstract a hydrogen atom from the radical cation of R$_3$N (*i.e.*, Et$_3$N$^{\bullet+}$ or DIPEA$^{\bullet+}$) or from the solvent molecules (in this case, DMF or DMSO) to yield the reduction product, or reacts with (hetero)aryls or unsaturated double bonds yielding the corresponding C–C coupling products after oxidation and release of a proton (Figure 4). Gas chromatography–mass spectrometry (GC-MS) analysis of the crude product mixture confirmed the formation of diethylamine (see Figure S3 in SI). During the course of the photoreaction, **Aq-OH** degrades. Such bleaching is often observed in

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photoredox catalytic reactions using organic dyes[44] or transition metal photocatalysts.[48] In addition, the formation of substituted **Aq-OH** from a reaction with the aryl radicals was observed.[49] These photoproducts can continue to participate in the photoredox transformations.[50]

Radical anions and semiquinone anions of anthraquinones, a class of quinoid compounds, gain sufficient redox energy under the visible light irradiation to perform synthetically challenging reductive transformations. 1,8-Dihydroxyanthraquinone (**Aq-OH**) forms its coloured radical anion and semiquinone anion upon visible light irradiation in the presence of R_3N under nitrogen. The radical anion and the semiquinone anion are excited by visible light and transfer a single electron to aryl halides, which react in dehalogenation or C–C bond forming reactions. We believe that the described results will pave the way to a broader use of commercially available and inexpensive anthraquinone derivatives in synthetic photoredox catalytic reductive transformations.

Experimental Section

General procedure for the photoreduction of aryl halides (Method A): In a 5 mL snap vial, equipped with a magnetic stirring bar, the respective aryl halide (0.1 mmol, 1.0 equiv) and catalyst (0.01 mmol, 0.10 equiv) were dissolved in dry DMF (total volume of the solution 1.0 mL) and the resulting mixture was degassed (× 2) *via* a syringe needle. Triethylamine (Et$_3$N, 0.10 mmol, 1.0 equiv) was added under N$_2$, and the reaction mixture was irradiated through the plane bottom side of the snap vial at 40 °C using a 455 nm LED. The reaction progress was monitored by GC analysis. The yields of the reduction products were determined from GC measurements using appropriate internal standards.

General procedure for C–H arylation reactions (Method B): In a 5 mL snap vial, equipped with a magnetic stirring bar, the aryl halide (0.2 mmol, 1.0 equiv) and 1,8-dihydroxy-9,10-anthraquinone (**Aq-OH**, 0.02 mmol, 0.1 equiv) were dissolved in dry DMSO (total volume of the solution 1.0 mL), and the resulting mixture was degassed by syringe needle. *N,N*-diisopropylethylamine (DIPEA) (0.20–0.40 mmol, 1–2 equiv) and the corresponding trapping agent (4.0–6.0 mmol, 20–30 equiv) were added under N$_2$ and the reaction mixture was irradiated through the plane bottom side of the snap vial at 25 °C using a 455 nm LED for the time reported below. The reaction progress was monitored by GC analysis until full conversion was obtained or the reactions slow down significantly. For work-up, one of the two following procedures were used: (i) the reaction mixture was transferred into a separating funnel and 10 mL of distilled water and 2 mL of brine were added. The resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuum. Silica gel (*ca.* 1.0 g) was added to prepare the dry load for column chromatography. (ii) The reaction mixture was transferred into a flask and DMSO was partially evaporated (approx. 0.5 mL) under reduced pressure, ethyl acetate (10 mL) and silica gel (*ca.* 1.0 g) was added to prepare the dry load for column chromatography. In both methods, purification was achieved by flash column chromatography using petrol ether/ethyl acetate as eluents on silica gel.

For the additional spectroscopic investigations and characterization of C–H arylated products see supporting information.

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