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Dichromatic Photocatalytic Substitutions of Aryl Halides with a Small Organic Dye

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Abstract: Photocatalytic bond activations are generally limited by the photon energy and the efficiency of energy and electron transfer processes. Direct two-photon processes provide sufficient energy but the ultra-short lifetimes of the excited states prohibit chemical reactions. The commercial dye 9,10-dicyanoanthracene enabled photocatalytic aromatic substitutions of non-activated aryl halides. This reaction operates under VIS irradiation via sequential photonic, electronic, and photonic activation of the simple organic dye. The resultant highly reducing excited photocatalyst anion readily effected C-H, C-C, C-P, C-S, and C-B bond formations. Detailed synthetic, spectroscopic, and theoretical studies support a biphotonic catalytic mechanism.

The efficient utilization of visible light for the activation of organic molecules has been developed to great maturity over the past decade.^[1] However, many of the photocatalytic processes require activated substrates that facilitate the generation of radical intermediates in the vicinity of heteroatomic functional groups (amines, carbonyls)^[2] or by irreversible reaction steps^[3]. Consequently, photocatalytic activations of unbiased or non-activated substrates have received very little attention. Generally, the scope of photocatalytic bond activations is limited by the energy of the visible photon (which is sufficient for the cleavage of weak C-I, C_{sp3}-Br and π -bonds) and the energetic losses during the involved energy and electron transfers.^[4] The reductive cleavage of non-activated aryl bromides/chlorides by photocatalytic energy transfer or single electron transfer (SET) is beyond the range of the visible spectrum which constitutes a severe limitation of arene functionalizations. Apart from direct UV processes,^[5] recent examples of successful activations of non-activated aryl halides with visible light include the use of strongly reducing excited iridium photocatalysts (with transition metal co-catalysts)^[6] and indirect two-photon processes (Scheme 1).^[7] The latter approach holds great potential due to its high modularity by combining different photocatalysts with photonic activation, energy transfer, and electronic activation steps. While the physical properties of such biphotonic processes are fairly

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well understood with simple model systems,^[8] their applications to more complex organic synthesis settings are scarce. Recent examples of biphotonic activations of aryl halides toward aromatic substitutions include consecutive photo-induced SET cascades^[7a-d] and triplet-triplet annihilation^[7e-f] (Scheme 1, bottom). These approaches constitute new modes of reductive bond activation by the accumulation of two visible photons which significantly expand the "energy window" of photo-catalytic aromatic substitutions. However, the overall photocatalytic efficiency is still rather low, the reaction scope barely explored, the reaction conditions mostly complex, and the mechanistic minutiae of the multicomponent reactions not fully understood. Therefore, we have initiated a program that aimed at the extension of the concept of sequential photonic and electronic activations in order to populate a highly reducing excited radical anion state of the photocatalyst which engages in facile reductive bond activation of various aryl-Br/Cl electrophiles. We believed that a powerful photocatalyst would be a single small weight organic dye that combines the benefits of commercial availability, low price, high solubility, high absorbance of the ground state and the radical anion in the visible region, long lifetime of the excited states, and facile access to the radical anion.



Scheme 1. Methods of photocatalytic aryl halide activation.

With these framework conditions, we investigated 9,10-dicyanoanthracene (DCA), a simple molecule that fulfills all aforementioned criteria. The photophysical data of DCA and its radical anion were reported (Figure 1).^[9] While DCA itself is a moderate photo-oxidant,^[10] the oxidation potential (-2.5 eV)^[11] and lifetime $(\sim 5 \text{ ns})^{[9a]}$ of the excited radical anion DCA^{--*} are prime qualifications for its use as a strongly reducing photocatalyst. Applications of DCA^{•-*} to reductive activations of non-activated aryl halides were so far not reported. Herein, we demonstrate the competence of DCA to act as a simple yet powerful photo-reductant in the presence of low-power visible light. This combination exhibits tangible advances over the current state of photocatalytic reductive activation of aryl halides in terms of catalyst and reagents loading, reaction conditions, and applicability to various aromatic functionalization reactions. Further, a detailed mechanistic picture of the underlying photophysical and chemical events was drawn from laser flash photolysis, steady-state fluorescence, and DFT calculations.



Figure 1. Normalized spectra of white, blue, green LED emission (dashed lines) and DCA (blue line), transient DCA^{•-} absorption (green line).

λ [nm]

The small organic dye DCA has three distinct absorption bands in the visible near-UV-to-blue region while the radical anion DCA. absorbs green light.^[9] The need of simultaneous irradiation with green and blue light was circumvented by an operationally simpler setup with a single cold-white LED that exhibits very similar emission and no tailing into the UV (Figure 1). We studied the reaction of 4-bromobenzonitrile (1) and the electron-rich N-methyl pyrrole (Table 1).^[11] Initially, we adopted literature conditions^[7a] in the presence of a high excess of N-methyl pyrrole and diisopropylethylamine (DIPEA) which afforded with 10 mol% photocatalyst very good yields of 2a (entry 1). The high catalytic efficiency of DCA even allowed a significant optimization of the reaction conditions under irradiation with a single cold-white LED for 5 h at 20 °C (higher substrate concentration, lower excess of N-methyl pyrrole, no excess of amine, entry 2). In the absence of either component (catalyst, pyrrole, base, light), no cross-coupling was observed (entries 3-5). The poor reactivity with either blue (455 nm) or green light (525 nm) irradiation supports the notion of a dual photo-activation by excitation of DCA and its radical anion (entry 6). It is important to note that the photocatalyst exhibited good solubility in acetonitrile and good stability toward bleaching and decomposition. Quantitative analysis of a standard reaction documented a loss of less than 1/4 of the catalyst concentration at total conversion of **1**.^[11]

Table 1. Optimization of reaction conditions.^[a]



^[a] **1** (0.2 M), DCA (5 mol%), DIPEA (1.2 equiv.), *N*-methyl pyrrole (20 equiv.) in MeCN (1 mL); irradiation (cold-white LED, >410 nm), 20 °C, 5 h. ^[b] GC yields of **2**; conversion in parentheses if not >95%. ^[c] 82% isolated yield. ^[d] 45% benzonitrile as single product.



Scheme 2. Substrate scope of the 2-aryl pyrrole synthesis. Conversions in parentheses if not >90%. ^[a] 40 equiv. *N*-methyl pyrrole.

We postulate a reaction mechanism that commences with the selective excitation of DCA with blue light to the excited singlet state ¹DCA* (Scheme 3). From fluorescence quenching studies in the presence of DIPEA (Figure 2, top), a quenching rate constant of $k_q(S_1) = 2.3 \cdot 10^{10} M^{-1} s^{-1}$ was calculated^[11] which indicates that the radical ion pair formation (DIPEA^{•+} DCA^{•-}) in the first catalytic turnover occurs at diffusion rates. Fluorescence studies documented that the quenching with DIPEA is the major deactivation pathway of ¹DCA* (99%) which proves the high efficiency of catalytic reaction initiation.^[11] Excitation of DCA^{•-} with green light results in the formation of DCA^{•-*}. This highly reducing species effects mesolysis of aryl bromides and chlorides to give Ar• which was confirmed by TEMPO trapping.^[11] Reaction of Ar[•] with N-methyl pyrrole gives a cyclic vinylogous amino radical which undergoes thermodynamically favoured oxidation by DCA* ($\Delta G = -2.7 \text{ eV}$). Experimental support for this process rather than the SET from DIPEA comes from the high synthetic efficiency of reactions in the presence of only 1.1 equiv. DIPEA despite the consumption of 1 equiv. base in the terminal acid-base reaction with HBr (entry 2, Table 1 and Scheme 2). SET between the cyclic α -enamine radical intermediate with ground state DCA is 4.55 kcal mol⁻¹ (0.2 eV) uphill. The quasi co-catalytic role of amine for the initiation of photocatalysis is also evident from the fact that little to no hydrodehalogenation was observed under standard conditions as, unlike literature protocols,^[7a] no excess of DIPEA was employed and the majority of amine resides as HBr salt. Reaction of 1a in d3acetonitrile gave no deutero-benzonitrile.



Scheme 3. Key experimental and theoretical data in support of a reaction mechanism that involves sequential photonic, electronic, and photonic activation of DCA.



Figure 2. Top: Fluorescence quenching of DCA (0.01 mM) with DIPEA (0, 4, 8, 11, 15, 19, 28, 39 mM) in MeCN/air. DCA absorption: 0.5 (λ_{exc} 400 nm). *Inset:* Stern-Volmer plot for k_q(S₁). *Bottom:* DCA^{•-} decay monitored at 520 nm after laser flash photolysis (355 nm; 10 mJ/pulse): DCA (10⁻⁴ M), Et₃N (6·10⁻² M), MeCN, Ar: without 1 (black), with 10⁻³ M 1 (red).^[11]

An alternative radical chain mechanism via SET from the 2-aryl-2*H*-pyrrol-3-yl radical to ArX is thermodynamically prohibited ($\Delta G > 30$ kcal mol⁻¹).^[11] Likewise, the halogen atom transfer from ArHal to the same intermediate is an uphill process. We believed that the SET from the excited radical anion DCA^{•-*} (-2.5 eV vs. SCE) to the aryl halide would constitute the rate-limiting step in reactions with deactivated electrophiles. A detailed thermodynamic and kinetic analysis was derived from DFT calculations (CAM- $B3LYP/6-31++G^{**}$).^[11] The 1e-reductions of 1a and the other reactive electrophiles by DCA^{•-*} are thermodynamically feasible $(\Delta G_2 \leq 0)$. The kinetic barriers toward the radical anion ArX^{•-} are generally small ($\Delta G_2^{\neq} = 0.03 \text{ eV}$). The trend of substrate reactivity is very accurately mirrored by the thermodynamic and kinetic data which predict unfavourable Gibbs energies and higher activation barriers only for the reactions of electron-rich aryl halides.^[11] However, low reactivity can be a direct consequence of reversibility of the electron transfer and subsequent mesolysis. The insufficient reducing power of ground-state-DCA^{•-} (-0.6 to -0.89 V vs. SCE) for the reductive activation of aryl bromides (DFT: $\Delta G_1 > 0$) was demonstrated by laser flash photolysis experiments which showed identical decay traces of DCA^{•-} in the absence and in the presence of 1a, respectively (at 520 nm, see Figure 2, bottom). This observation is in full agreement with the thermodynamics of this hypothetical SET event.^[11]

The scope of dichromatic photocatalytic aromatic substitutions could also be extended to other C-heteroatom functionalizations (Scheme 4). The DCA-catalyzed reaction enabled phosphorylation at low catalyst loading and catalytic (10 mol%!) amine concentration,^[13] sulfide formation from disulfide,^[14] and the metal-free borylation from diborane^[15].



Scheme 4. Method extensions to C-Het couplings. [a] 10 mol% DIPEA.

In conclusion, we have developed an operationally simple photocatalytic reductive activation of aryl halides under mild conditions. Synthetic, spectroscopic, and theoretical studies support the notion of a *dichromatic* photocatalysis mechanism which does not require a sacrificial reductant. Sequential photonic, electronic, and photonic activation of 9,10-dicyanoanthracene, a simple, low-molecular weight, soluble, and photostable organic dye, resulted in the formation of the strongly reducing excited radical anion DCA^{•-*} that is capable of cleaving unactivated C-halide bonds. Photocatalytic applications to aromatic C-H, C-C, C-S, C-P, and C-B bond formations were demonstrated. Further endeavours toward the development of effective biphotonic activations with simple organic dyes are currently being investigated.

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Conflict of interest

The authors declare no conflict of interest.

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Dichromatic Photocatalytic Substitutions of Aryl Halides with a Small Organic Dye



Two photons to tango: A highly reducing photocatalytic system was developed that involves the sequential combination of photonic, electronic, and photonic activation of 9,10-dicyanoanthracene, a simple commercial and soluble organic dye. The ultimately formed excited radical anion DCA^{--*} enables the reductive activation of various aryl bromides and chlorides under mild conditions and the application to hetero-biaryl cross-coupling and heteroatom functionalizations. Detailed spectroscopic and theoretical studies support the postulated dichromatic photocatalytic mechanism.

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