Photocatalysis Hot Paper

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Chromoselective Photocatalysis: Controlled Bond Activation through Light-Color Regulation of Redox Potentials

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Abstract: *Catalysts that can be regulated in terms of activity and selectivity by external stimuli may allow the efficient multistep synthesis of complex molecules and pharmaceuticals. Herein, we report the light-color regulation of the redox potential of a photocatalyst to control the activation of chemical bonds. Light-color control of the redox power of a photocatalyst introduces a new selectivity parameter to photoredox catalysis: Instead of changing the catalyst or ligand, alteration of the color of the visible-light irradiation adjusts the selectivity in catalytic transformations. By using this principle, the selective activation of aryl–halide bonds for C–H arylation and the sequential conversion of functional groups with different reduction potentials is possible by simply applying different colors of light for excitation of the photocatalyst.*

Selective activation of chemical bonds in catalytic transformations is of key importance for the efficient production of fine chemicals and pharmaceuticals.[1] In enzyme catalysis, such selectivity is achieved by the confined molecular environment of active site of the enzyme, whereas in homogeneous transition-metal-based catalysis, the nature of the metal, and the electronic and steric features of the coordinating ligands, provide such selectivity.[1,2] However, sequential activation of chemical bonds requires either the use of different catalysts possessing different reactivity (and thus selectivity),[3] or a multifunctional catalyst, the reactivity of which can be altered by changing the reaction conditions, for example, through the use of additives or by changing the temperature or pH. In recent years, external-stimuli-responsive structural alterations (e.g., photoinduced ligand isomerizations)[4–10] that allow partial modification of the catalyst reactivity have been shown to tune catalyst function, but this approach is limited by the need for specific ligand design.

Instead of altering the molecular structure of the catalyst, we envisioned that stimuli-induced alteration of its redox potential could be an effective approach to control the reactivity. Among different external stimuli, for example, temperature or magnetic fields, visible light is of particular interest since it is easily available and applied. Herein, we report a strategy to control the reactivity of a redox-active photocatalyst by regulating its redox potential using different colors of light. The use of different redox states generated by different colors of visible light for photocatalyst excitation enables selective and sequential catalytic transformations of aryl–halide bonds in synthetically important C–H arylation reactions.

Rhodamine 6G (Rh-6G), a widely applied fluorescent xanthene dye,[11] yields the stable radical anion[12,13] Rh-6G$^{\bullet-}$ upon photoirradiation under nitrogen with visible light in the presence of *N*,*N*-diisopropylethylamine (DIPEA, an electron donor; Figure 1). The absorption spectra of Rh-6G and Rh-6G$^{\bullet-}$ differ significantly (Figure 2):[12,13] Rh-6G absorbs both

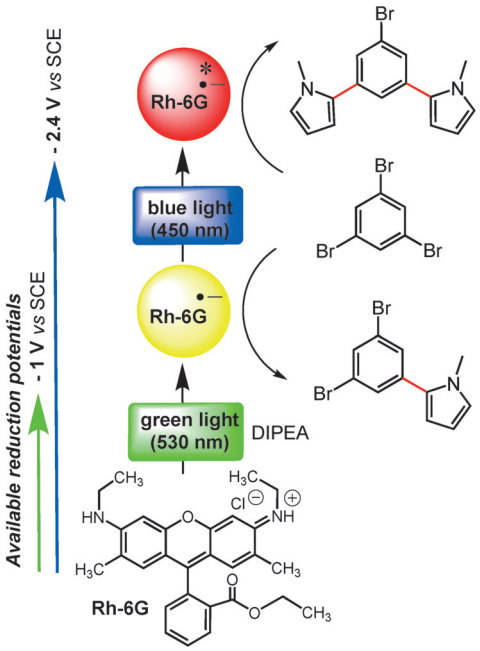

Figure 1. Light-color-selective generation of the redox active species Rh-6G$^{\bullet-}$ and Rh-6G$^{\bullet-}$*, which provide drastically different reduction potentials for photocatalysis.

in the green and blue regions of the visible-light spectrum, whereas Rh-6G$^{\bullet-}$ absorbs significantly only in the blue region (Figure 2 and Figure S2 in the Supporting Information).[12,13] This provides access to different redox states of Rh-6G through external control:

1) The excited state of Rh-6G (Rh-6G*) has a reduction potential of ca. −0.8 V vs. SCE (see the Supporting Information) in the absence of any electron donor molecule under visible-light irradiation, irrespective of the excitation wavelength.
2) The ground-state reduction potential of the Rh-6G$^{\bullet-}$ radical anion, formed upon photoirradiation in the presence of an electron donor (e.g., DIPEA) under

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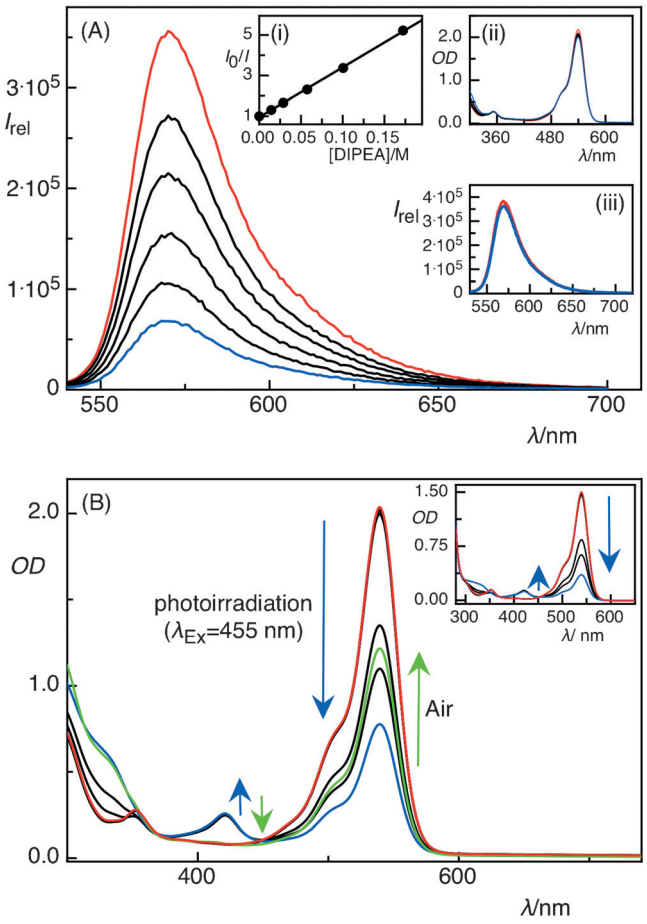


Figure 2. Spectroscopic investigation: A) Changes in the fluorescence spectra (in this case intensity, $\lambda_{Ex}=455$ nm) of Rh-6G upon the addition of DIPEA in DMSO. Insets: Stern–Volmer quenching plot of Rh-6G in the presence of DIPEA (i), and changes in the absorption (ii) and fluorescence (iii) spectra of Rh-6G in the presence of DIPEA and 4-bromobenzonitrile (as the test substrate). Unchanged absorption and fluorescence spectra of Rh-6G in the presence of DIPEA and 4-bromobenzonitrile, respectively, demonstrate that Rh-6G$^{\bullet-}$ accumulates in the reaction mixture only in the presence of DIPEA upon photoirradiation. B) Formation of the Rh-6G radical anion upon photoirradiation ($\lambda_{Ex}=455\pm15$ nm) in the presence of DIPEA in DMSO under nitrogen. Inset: generation of the Rh-6G radical anion with $\lambda=530$-(±15) nm irradiation. See the Supporting Information for further spectroscopic investigation and larger versions of the inset graphics.

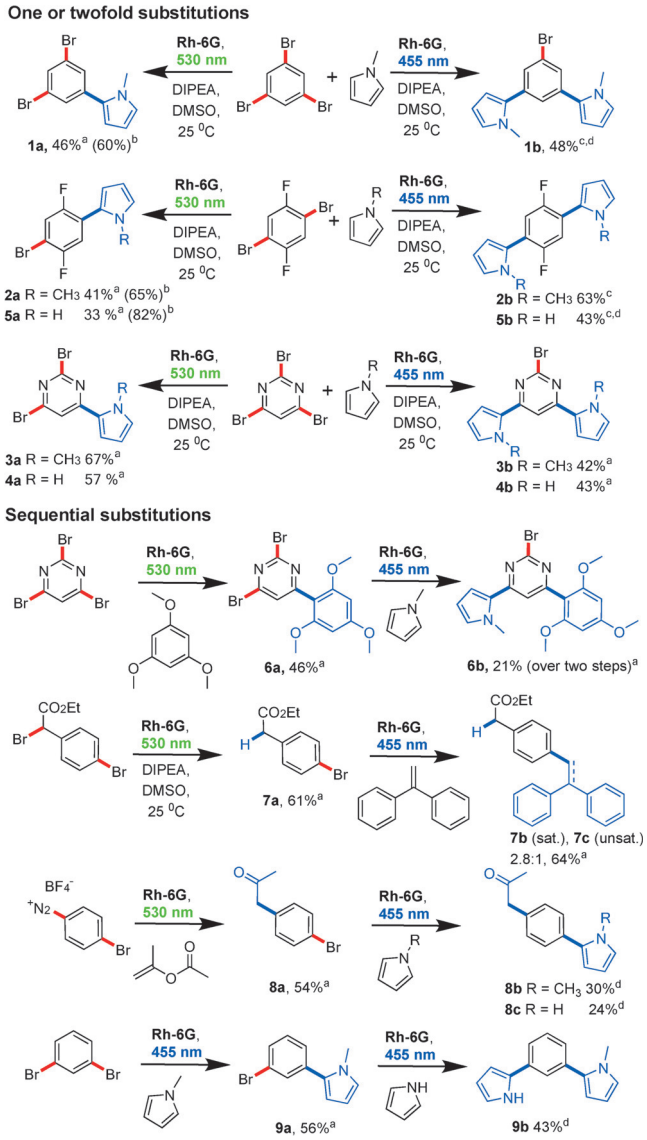
green-light irradiation, corresponds to ca. −1.0 V vs. SCE.[14]

3) The excited-state reduction potential of the radical anion Rh-6G$^{\bullet-}$* under blue-light irradiation[12,13] reaches more than −2.4 V vs. SCE.

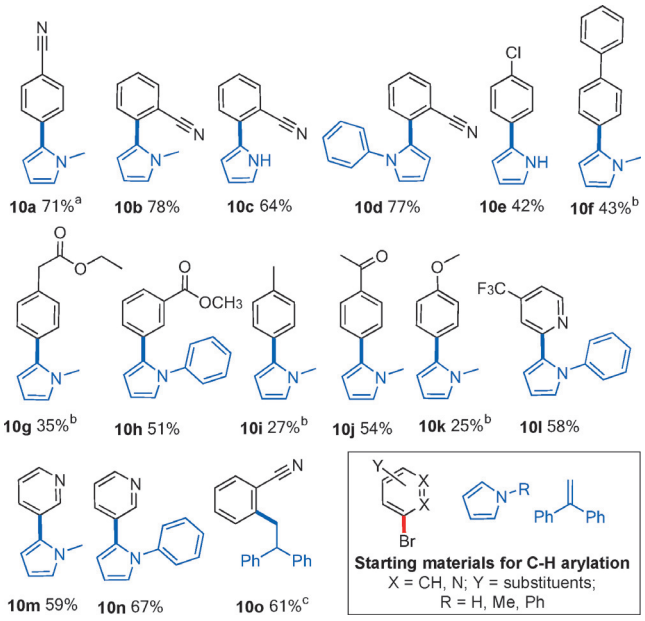
Such wavelength-dependent excitation of different redox states of dye molecules, particularly for xanthene dyes, have gained enormous importance in biological applications, for example to control the non-fluorescent "dark-state" and fluorescent "on-state" of a dye molecule in biomolecular imaging.[12,13,15–17] However, to the best of our knowledge, it has not been applied to control the selective activation of chemical bonds in synthetic catalytic photoredox transformations[18–20] using visible light.

An application of this photocatalytic system is the sequential activation of carbon–bromine bonds (see Figure 1) in aromatic and heteroaromatic compounds for C–H arylation reactions. Irradiation of 1,3,5-tribromobenzene or 1,4-dibromo-2,5-difluorobenzene, aryl bromide substrates with three or two bromine atoms, respectively, in DMSO in the presence of Rh-6G and DIPEA (2.2 equiv) as an electron donor, with green light ($\lambda=530$ nm) yields the corresponding radical anions, which fragment with loss of a bromide anion to generate aryl radicals.[21,22] Trapping of the reactive intermediates with *N*-methylpyrrole and subsequent rearomatization gives the monosubstitution products **1a** and **2a** in good yields. The reduction potential of Rh-6G (ca. −1.0 V vs. SCE) is not sufficient under these reaction conditions for subsequent activation of the remaining bromide substituents, even with higher catalyst loading. However, if the reactions are performed under blue-light irradiation ($\lambda=455$ nm), which increases the available reduction power of the photoredox catalyst to ca. −2.4 V vs. SCE, the reactions proceed to the two-fold-substituted products **1b** and **2b**. The two-fold-substituted products are obtained directly by irradiating the reaction mixtures with $\lambda=455$ nm light from the beginning. Representative examples of such sequential C–H arylation reactions with commercially available aryl bromide substrates with different trapping reagents are depicted in Scheme 1. Most importantly, if a new reaction partner for trapping of the aryl radical is added before the irradiation wavelength is switched, two different substituents are introduced sequentially in a controlled manner in one pot (Scheme 1, sequential substitutions). 2,4,6-Tribromopyrimidine, a commercially available substrate with a core structure found in many biologically active compounds and drug molecules,[23] was selectively functionalized depending on the light color. Control experiments confirmed that Rh-6G, DIPEA, and light irradiation are necessary for the catalytic photoredox C–H arylation reactions to proceed (see Tables S1, S2 in the Supporting Information).

Functional groups with different reduction potentials are selectively activated with Rh-6G in the presence of DIPEA when using different light colors as an external control. The reaction of ethyl 2-bromo-(4-bromophenyl)acetate,[24] which requires the reduction potential of Rh-6G$^{\bullet-}$[14] to form the radical in benzylic position, proceeds under green-light irradiation, whereas the subsequent activation of the aryl–bromide bond requires blue-light irradiation (see Table S3). Similarly, aryl radicals are generated selectively by activating the diazonium group (reduction potential ca. −0 V vs. SCE)[25] of 4-bromobenzene diazonium tetrafluoroborate in DMSO using photoexcited Rh-6G* in the absence of a base, which leaves the aryl–bromide bond intact. Reaction of the 4-bromoaryl radical with isopropenyl acetate gives 1-(4-bromophenyl)-propan-2-one.[26] Blue-light irradiation of Rh-6G in the presence of DIPEA leads to activation of the remaining bromine substituent. The resulting aryl radical reacts with pyrrole derivatives with sp^2–sp^2 carbon bond formation to yield **8b** and **8c**. The excited-state redox potential of Rh-6G (see Supporting Information for the estimated excited-state reduction potential of Rh-6G)[14] is sufficient for the reduction of diazonium salts[27] but not for the aryl bromide[21] (see



Scheme 1. Chromoselective one- and two-fold or sequential substitution reactions. [a] Yield of isolated product. [b] Yields in parenthesis are based on the conversion of starting materials calculated by taking the recovered isolated and quantified staring material into account. [c] Yield of isolated product over two steps in one pot; starting material is completely consumed, but monosubstituted products were isolated (27% for **1b** and 33% for **5b**). [d] Incomplete conversion of the monosubstituted intermediates. In the synthesis of compounds **7b**, **8b**,**c** and **9b**, the intermediates **7a**, **8a** and **9a** were isolated. All other reactions were performed in one pot by changing only the light source.



Scheme 2. Photocatalytic C–H arylation reactions. Reaction conditions: starting material (in all cases the corresponding aryl bromide; 0.1–0.6 mmol), Rh6G (10–15 mol%), DIPEA, DMSO, 25 °C, $\lambda_{Ex} = 455$ nm; reaction time 20–96 h; 5–25 equiv of the aryl radical trapping reagent. The amount depends on the reactivity of the reagent; 1,1-diphenylethylene was found to be more reactive than pyrroles. For detailed reaction conditions for all compounds, see the Supporting Information. [a] Yield for 0.6 mmol scale (76%). [b] Incomplete conversion of the starting material. [c] Addition product; the unsaturated substitution product was obtained in only 7%.

Table S3 for control reactions). The conversion of 1,3-dibromobenzene into the corresponding aryl radical requires the reduction power of the excited Rh-6G$^{\bullet-}$, but since the activation of the second bromide of the resulting compound (**9a**) is kinetically slower owing to the increased reduction potential,[21] a stepwise sequential substitution with *N*-methylpyrrole and pyrrole is possible.

Additional examples of C–H arylation reactions with Rh-6G photocatalysis under visible-light irradiation with benchstable aryl halides are shown in Scheme 2. Biologically important pyrrole derivatives and styrenes are suitable reaction partners for substituted aryl bromides possessing electron-withdrawing (e.g., -CN, -CO_2Et, -COMe, -CF_3, -Cl) as well as electron-donating (e.g., -Me, -Ph, -OMe) groups. The reduction potentials of aryl bromide substrates with several electron-donating groups are too high to be reduced[21] and define the limit of the method. However, the C–H arylation of *N*-methylpyrrole with 4-bromoanisole does proceed, although with a low yield of isolated product. Alkaloids such as β-nicotyrine and its derivatives (entry **10m**,**n** in Scheme 2) are obtained in good yields by simply mixing commercially available 3-bromopyridine, trapping reagents, Rh-6G, and DIPEA, followed by photoirradiation with visible light under nitrogen.

Based on spectroscopic and experimental results and recent reports, we propose mechanisms for the photocatalytic cycles involving Rh-6G$^{\bullet-}$ and Rh-6G$^{\bullet-}$* as the active redox species (Figure 3). For aryl bromides, a radical mechanism is supported by the formation of products **7b**,**c** and **10o** in the presence of the radical trap 1,1-diphenylethylene.[28] The Rh-6G$^{\bullet-}$ radical anion is not stable in the presence of oxygen (Figure 2),[12,13] which leads to the inhibition of C–H arylation (entry 6 in Tables S1,S2). Upon photoexcitation with green or blue light, Rh-6G takes an electron from DIPEA to give a radical anion/radical cation pair: Rh-6G$^{\bullet-}$ and DIPEA$^{\bullet+}$. The ground-state radical anion Rh-6G$^{\bullet-}$ can activate aryl bromide substrates with relatively low reduction potentials. However, if the irradiation wavelength is set to $\lambda = 455$ nm, Rh-6G$^{\bullet-}$ is excited again[12,13] and is able to activate aryl

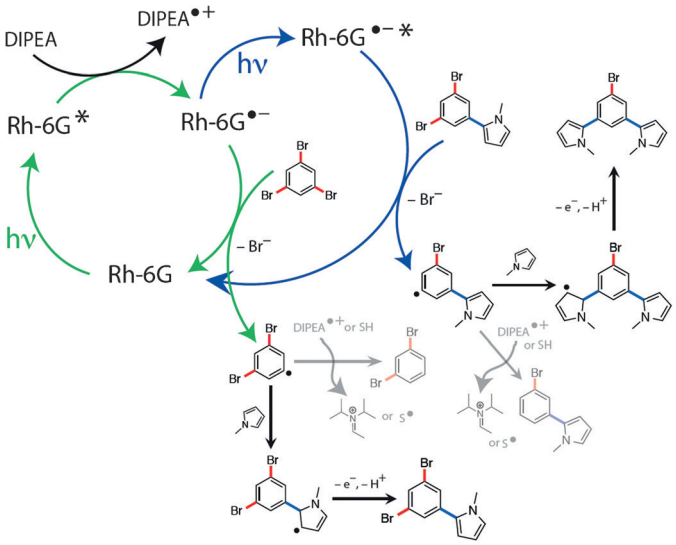


Figure 3. Proposed mechanism for the photocatalytic activation of aryl bromides involving the ground- and excited-state radical anions of Rh-6G under green- or blue-light irradiation, respectively.

bromide substrates with rather high reduction potentials[21] (e.g., bromo-substituted biaryls, 4-bromoanisole) to yield the aryl radical precursors (i.e., $Ar{-}Br^{\bullet-}$), thereby regenerating the neutral Rh-6G to complete the catalytic cycle. Fragmentation of $Ar{-}Br^{\bullet-}$ gives the aryl radical, which reacts with unsaturated compounds to yield C–C coupling products after reoxidation and loss of a proton. In a competing pathway, the aryl radical abstracts a hydrogen atom either from $DIPEA^{\bullet+}$ (see Section 6 in the Supporting Information) or from the solvent DMSO to give the reduction products and diisopropylamine, which were detected by gas chromatography mass spectrometry (GC-MS) analysis of the crude reaction mixtures (Figure S28 in the Supporting Information).[22,29]

In conclusion, the reduction potential of the xanthene dye Rh-6G can be tuned over a range of approximately 2.4 V by changing the irradiation wavelength for excitation. This light-color-guided formation of different redox states of Rh-6G enables chromoselective C–H arylations to yield functionalized arenes and heteroarenes from commercially available and bench-stable starting materials. The reaction conditions are exceptionally mild and operationally simple, and the functional-group tolerance is large. Rh-6G is commercially available in kilogram amounts and enables economic photoredox catalytic reactions for the synthesis of complex molecules, as well as late-stage functionalization of drugs and pharmaceuticals under metal-free conditions.

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