Angewandte Chemie International Edition

DOI: 10.1002/anie.201002992

Photocatalysis

Metal-Free, Cooperative Asymmetric Organophotoredox Catalysis with Visible Light**

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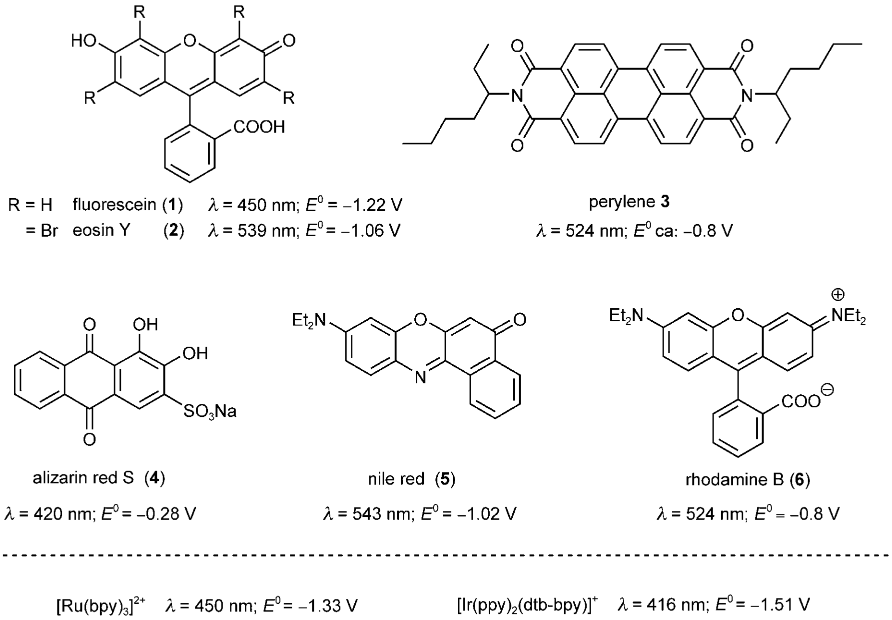
In the last decade organocatalysis has developed into an essential third branch of asymmetric catalysis that now complements the fields of metal and enzyme catalysis and provides widely applicable methods for efficient organic synthesis.[1,2] Especially the combination and integration in cooperative catalysis such as domino reactions[3] and the recent efforts in combining organocatalysis with metal activation[4] demonstrate that the potential of organocatalysis for the development of new activation modes in selective organic synthesis is still not fully uncovered. Moreover, photocatalysis with visible light[5] is undoubtedly one of the emerging strategies to meet the increasing demand for more sustainable chemical processes. Building on seminal results employing photoinduced electron-transfer processes,[6] which often required UV light, a number of powerful methods have been developed recently applying organometallic complexes such as $[Ru(bpy)_3]^{2+}$ and $[Ir(ppy)_2(dtb\text{-}bpy)]^+$ (bpy = bipyridine, ppy = 2-phenylpyridine, dtb-bpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine).[5,7] Of particular note is the cooperative combination of photocatalysis with an organocatalytic cycle[8] offering one of the rare catalytic methods for the enantioselective α-alkylation of aldehydes.[9,10]

However, the high cost and potential toxicity of the ruthenium and iridium salts as well as their limited availability in the future are disadvantages of these metal-based methods. Stimulated by the attractiveness of using green light, the most abundant part of solar light, we speculated that a number of red to orange dyes could also be used successfully in photoredox catalysis, and the choice of appropriate reaction conditions would additionally allow for the cooperative merging with asymmetric organocatalysis.

Herein, we present a versatile metal-free, purely organic photoredox catalysis with visible light. As a first example of our strategy we demonstrate the successful application of simple, inexpensive organic dyes as effective photocatalysts for the cooperative organocatalytic asymmetric intermolecular α-alkylation of aldehydes.[11]

Initial studies began with the screening of a number of red and orange dyes (Scheme 1) for the photocatalytic reductive dehalogenation of α-bromoacetophenone ($E^0 = -0.49$ V vs. SCE)[12] as a test reaction (Table 1).[6c,13] Following the observation that classic organic dyes show striking similarities to the widely employed organometallic ruthenium- and iridium-containing photosensitizers, we chose our test candidates based on their λ_{max}, their redox potential E^0, and their precedented use as photosensitizers for semiconductor-based photocatalysis or dye solar cells.[14,15]



Scheme 1. Absorption and redox properties of red and orange organic dyes used as photoredox catalysts (λ_{max} (CH_3CN) in nm; **3** in CH_2Cl_2; E^0 (dye/dye$^{\bullet-}$) in V vs. SCE)[16] in comparison with common organometallic photocatalysts. SCE: saturated calomel electrode.

To achieve this desired transformation we investigated the conditions reported by Stephenson and co-workers for the photocatalytic dehalogenation of activated benzylic halides in the presence of $[Ru(bpy)_3]^{2+}$. In accordance with their results

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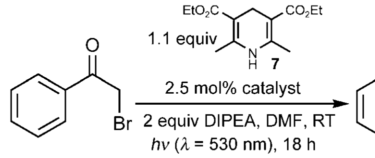
[**] This work was supported by the GRK 1626 ("Chemical Photocatalysis") of the DFG. S.F. gratefully acknowledges a fellowship of the Bayerische Eliteförderung.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201002992.

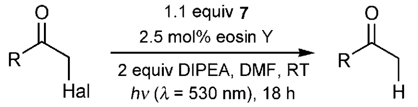
Table 1: Dehalogenation of α-bromoacetophenone.

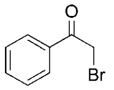
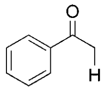
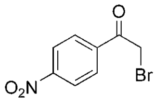
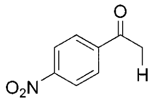
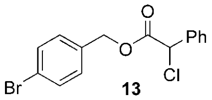
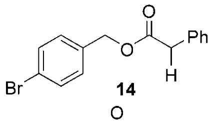
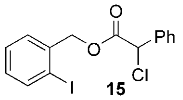
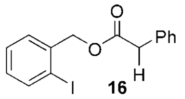


Entry[a]	Dye catalyst	Yield [%][b]
1	none	40
2	$[Ru(bpy)_3^{2+}]$ (**8**)[c]	100
3	alizarin red S (**4**)	36
4	perylene **3**	100
5	nile red (**5**)	100
6	fluorescein (**1**)	100
7	eosin Y (**2**)	100
8	eosin Y (**2**)	3[d]
9	eosin Y (**2**)	80[e]
10	rhodamine B (**6**)	80

[a] Standard conditions as described above. [b] GC yield determined using a calibrated internal standard. [c] A blue high-power LED (λ≈455 nm) was used instead. [d] Reaction was performed in the dark. [e] Reaction was conducted in sunlight; full conversion was reached after 1 h of irradiation.

Table 2: Photocatalytic reductive dehalogenation with eosin Y using Hantzsch ester **7** as a reduction equivalent.



Entry	Substrate	Product	Yield [%][a]
1	 **9**	 **10**	100[b]
2	 **11**	 **12**	83
3	 **13**	 **14**	78 (78)[c]
4	 **15**	 **16**	89 (88)[c]

[a] Yield of isolated products. [b] Yield determined by GC and NMR using appropriate calibrated internal standards. [c] Yields in brackets as reported in Ref. [13].

we noticed that also for our α-carbonyl bromide substrate the use of 1.1 equiv of Hantzsch ester **7** as a hydride source was beneficial to avoid potential side reactions.

While under these conditions a slow background reaction also leads to detectable amounts of the debrominated product (Table 1, entry 1), most of the simple organic dyes were effective for this transformation under optimized conditions, albeit with different yields. Whereas light proved essential for this transformation (Table 1, entry 8), the reaction can be conducted using different light sources. Fast conversion is observed in ambient sunlight (Table 1, entry 9), however with a slight decrease in product yield, potentially because of side reactions that may occur at the higher reaction temperature and at the UV portion of the solar spectrum.

Upon irradiation with green light[17] from high-power LEDs with an emission of $\lambda \approx 530$ nm, bleaching of the dyes was minimized but still observable for alizarin **4**, nile red (**5**), and rhodamine B (**6**) indicating the slow degradation of the photosensitizer. However, perylene **3** and the xanthene-based dyes **1** and especially eosin Y (**2**) proved to be sufficiently stable under the reaction conditions. Using eosin **2** as the photocatalyst affords the defunctionalized product in a very clean, high-yielding reaction as determined by both GC and NMR studies using appropriate internal standards.[18] Owing to its simplicity and favorable redox and photochemical properties eosin Y (**2**) was selected as the photocatalyst for our subsequent studies.[19]

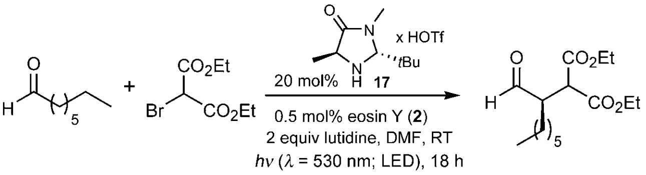
A number of dehalogenations (Table 2) under our optimized conditions showed that the reaction is also tolerant to aromatic residues with electron-withdrawing substituents (Table 2, entry 2). Polar functional groups such as esters are tolerated and exclusive chemoselectivity for α-activated substrates over aryl halides was observed for the defunctionalization (Table 2, entries 3 and 4). In all cases the obtained yields of the isolated products are equal or better than those for the reported transition-metal-catalyzed counterpart[13] proving the effectiveness of our operationally simple, inexpensive conditions.[20] It also should be noted that the irradiation power of the employed LEDs and therefore the applied energy to the reaction system is drastically less than that of sunlight or typically applied fluorescent lightbulbs.[17]

Next we turned our attention to the application of organic dyes as photoredox catalysts in the asymmetric organocatalytic C–C bond formations developed by MacMillan et al.[8] As highlighted in Table 3 the transformations were found to be both high-yielding and enantioselective when a combination of eosin Y (**2**) and MacMillan's imidazolidinone catalyst **17** were applied. Even though our organic-dye-sensitized conditions require somewhat longer reaction times,[21] we did not observe product racemization, which further illustrates the previously elucidated strict differentiation of the *trans*-substituted catalyst between α-methylene aldehydes and α-substituted products.[22] The enantioselectivity depends on the reaction temperature (Table 3, entries 1, 4, and 5) and −5 °C was found to be optimal. Performing the reaction under direct sunlight led to faster conversion, albeit with a slight erosion in enantioselectivity presumably because of the increased reaction temperature (roughly 30 °C).

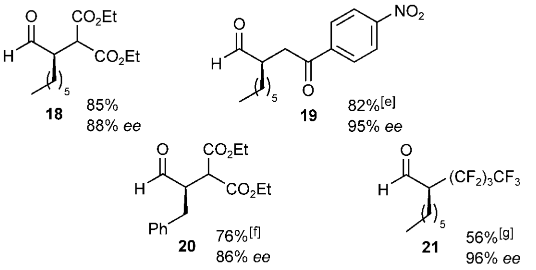
Our methodology is also compatible with the stereospecific incorporation of polyfluorinated alkyl substituents (Table 3, compound **21**), which are important elements in drug design to modulate specific properties.[23]

At present, the mechanistic picture of this reaction is not complete. It is evident, however, that eosin Y acts as a photoredox catalyst after its excitation with visible light and population of its more stable triplet state finally enabling single-electron transfer (SET; Scheme 2).[24] Similar to the chemistry of Ru^{2+*} both reductive and oxidative quenching are known for excited eosin Y ^{3}**EY***.[25] Because our results are comparable to those of MacMillan et al. we presume that

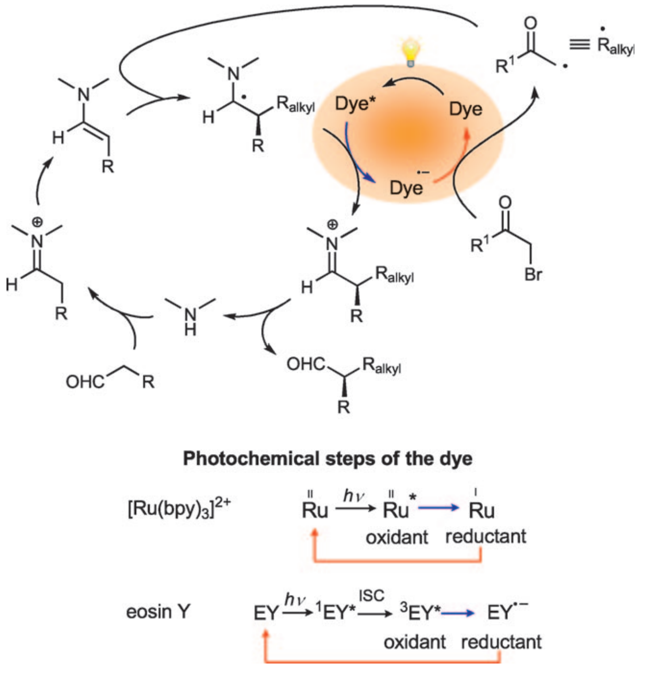
Table 3: Purely organocatalytic enantioselective α-alkylation/perfluoroalkylation of aliphatic aldehydes.



Entry	Variation from the standard conditions[a]	Yield [%][b]	*ee* [%][c]
1	none	63	77
2	23 W fluorescent bulb instead of LED	78	80
3	23 W fluorescent bulb instead of LED **and** $[Ru(bpy)_3]Cl_2$ (**8**)	75	76
4	$T = 0\,°C$	70	81
5	$T = -5\,°C$	85	88
6	sunlight ($T \approx 30\,°C$)[d]	77	76



[a] Standard conditions as described above. [b] Yield of isolated products. [c] Enantiomeric excess was determined as reported in Ref. [8a]. [d] Full conversion was reached after approximately 4 h. [e] Reaction was performed at +5 °C; *p*-NO_2-phenacyl bromide was used. [f] Phenylpropionaldehyde was used instead of octanal. [g] Reaction was performed at −15 °C; 1-iodoperfluorobutane was used instead of diethyl bromomalonate.



Scheme 2. Proposed mechanism and comparison of the photoredox cycles of Ru^{II} and eosin Y.

eosin Y acts a reductant—relying on the sacrificial oxidation of a catalytic amount of the enamine as the initial electron reservoir[26]—to furnish the electron-deficient alkyl radical by means of SET with an alkyl halide. Addition of this radical to the electron-rich olefin of the enamine that is simultaneously generated within the organocatalytic cycle merges both activation pathways. In the catalytic cycle the subsequent oxidation of the amino radical to the iminium species provides the electron for the reductive quenching of the dye's excited state ^{3}**EY***.[27]

Having successfully demonstrated the versatility of simple organic dyes for photoredox catalysis we directed our efforts to the determination of the quantum yield of the reaction to gain further information on its efficiency.[28] We reproducibly found values in the range of 6 to 9% indicating a more complex reaction course than the proposed simplified mechanistic platform. To further prove this assumption we conducted an additional GC-based yield determination after keeping the initially irradiated sample in the dark for 3 h and 6 h. Here we found a significant increase of the yield which might stem from the involvement of an amplifying "dark reaction".

In summary, we have developed a metal-free method using inexpensive eosin Y as a powerful photocatalyst for various photoredox transformations with a performance comparable to that of noble-metal catalysts. The discovery of a purely organic asymmetric cooperative photoredox organocatalysis will facilitate applications of these useful reactions in organic synthesis significantly as xanthene dyes are readily accessible, cheap, and less toxic than transition-metal complexes. This extension of highly versatile photoredox catalysis to classic organic dyes is expected to find broadly useful across many applications.

Received: May 17, 2010
Revised: June 10, 2010

Keywords: asymmetric alkylation · cooperative catalysis · organocatalysis · photocatalysis · xanthene dyes

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[18] See the Supporting Information for details.

[19] In a number of comparative studies using xanthene dyes as photoinitiators eosin Y has been shown to counterbalance high reactivity with sufficient stability. For selected examples, see: a) T. Lazarides, T. McCormick, P. Du, G. Luo, B. Lindley, R. Eisenberg, *J. Am. Chem. Soc.* **2009**, *131*, 9192–9194; b) M. V. Encinas, A. M. Rufs, S. G. Bertolotti, C. M. Previtali, *Polymer* **2009**, *50*, 2762–2767; c) S. H. Lee, D. H. Nam, C. B. Park, *Adv. Synth. Catal.* **2009**, *351*, 2589–2594.

[20] Price per mmol and molecular weight of different photocatalysts: $[\mathrm{Ru(bpy)_3}]\mathrm{Cl_2} \times 6\,\mathrm{H_2O}$ (MW = 748.62 gm mol^{-1}): $62.50; $[\mathrm{Ir(ppy)_2(dtb\text{-}bpy)}]\mathrm{PF_6}$ (MW = 1072.09 gm mol^{-1}): ca. $630 (single-step synthesis from commercial $[\{\mathrm{Ir(ppy)_2Cl}\}_2]$ with 2 equiv dtb-bpy); eosin Y (MW = 647.89 gm mol^{-1}): $2.66 (based on Sigma–Aldrich and Acros prices for 2010).

[21] In our hands using household fluorescent bulbs available in Germany (e.g. OSRAM, 23 W, 6500 K, 1470 lm) we also could not reach full conversion in the time span reported by MacMillan and co-workers[8a] with their optimized $[\mathrm{Ru(bpy)_3}]^{2+}$ conditions (see Table 3, entry 3).

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[27] Remarkably, in contrast to most photocatalytic processes MacMillan's system does not require any sacrificial oxidant or reductant by its design; both oxidation and reduction steps are productive and lead to the formation of the desired product.

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