

# Photoredox Catalysis with Visible Light\*\*

Kirsten Zeitler\*

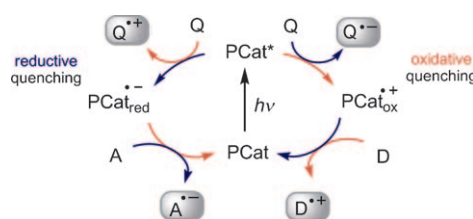
cycloaddition · organocatalysis · photocatalysis ·  
redox chemistry · ruthenium

The increasing need for more efficient synthetic methods and sustainable processes can be seen as a major driving force for new inventions; it also stimulates the creative rethinking of known concepts, which, in turn, will lead to the development of innovative chemistry.<sup>[1]</sup> For example, starting from the challenge to mimic and understand enzymatic transformations, organocatalysis has now become an important tool in modern organic synthesis with new reactivity that complements that of enzyme and metal catalysis.<sup>[2]</sup> As early as the beginning of the 20th century, photochemistry had already attracted the attention of (organic) chemists.<sup>[3]</sup> But recent years have seen broader interest in photochemical transformations because of the generally mild conditions required for substrate activation—ideally light alone—and their suitability for “green reactions”. While classical photochemical steps have found notable applications in synthesis<sup>[4]</sup> and the direct transformation of light into electric energy (photovoltaics) can already be considered a highly developed research field,<sup>[5]</sup> efforts in photocatalysis have mainly targeted the development of artificial photosynthesis systems for the conversion of solar energy into storable chemical fuels.<sup>[6]</sup> However, despite the obvious, practical advantages of visible light as an “infinitely available” promoter for chemical synthesis, the simple inability of most organic molecules to absorb light in the visible range of the spectrum has greatly limited the potential applications of photochemical reactions.

One major strategy to address this drawback and to develop new efficient processes using visible light is the use of photosensitizers and photocatalysts.<sup>[7]</sup> Upon irradiation, molecules are converted into their photoexcited states, which are chemically more reactive because of the significantly altered electronic distribution. Apart from following various common physical decay pathways, these photoexcited states can undergo chemical “deactivation” processes, which are either unimolecular and correspond to classical photochemical transformations (isomerizations, rearrangements, etc.) or proceed in a bimolecular manner. The interactions with other species range from bimolecular reactions such as photocycloadditions to quenching processes.<sup>[8]</sup> Here, the most

important pathways are energy-transfer reactions<sup>[9]</sup> and electron-transfer reactions; both play a crucial role as indirect initiators for all types of photocatalytic reactions.<sup>[10]</sup>

Photoredox catalysis relies on the general property of excited states to be both more easily reduced as well as more easily oxidized than their corresponding ground states, and so the photocatalyst can serve either as an electron donor or an electron acceptor to be regenerated in the catalytic cycle (Scheme 1). The photocatalyst undergoes two distinct electron-transfer steps; both the “quenching” and the “regenerative” electron transfer can be productive with respect to a desired chemical transformation. Ideally, the two electron-transfer processes are connected by the substrates or intermediates of the catalyzed reaction and therefore do not require any sacrificial electron donor or acceptor.



**Scheme 1.** Photoredox catalysis by reductive or oxidative pathways. Oxidation steps are depicted in red; reduction steps are in blue. PCat = photocatalyst, Q = quencher, D = donor, A = acceptor.

Recent research has focused on the use of the widely applicable and extensively studied organometallic ruthenium(II) polypyridine complexes (e.g.  $[\text{Ru}(\text{bpy})_3]^{2+}$ ), which are superior photoredox catalysts not only because of their absorbance in the visible range ( $\lambda_{\text{max}} \approx 450 \text{ nm}$ ), but also because of their unique properties in terms of chemical stability, excited-state lifetimes (originating from metal-to-ligand charge-transfer (MLCT)), and the favorable redox potentials in the excited state that can be fine-tuned by the adjacent ligands.<sup>[11]</sup>

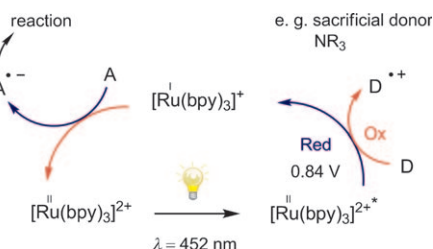
As photoredox catalysts,  $[\text{Ru}(\text{bpy})_3]^{2+}$  complexes serve as visible-light-activated single-electron-transfer (SET) agents; they mediate rapid, low-barrier one-electron steps to induce alternative reaction pathways<sup>[12]</sup> and have set new standards for effecting challenging transformations under mild and environmentally benign conditions.<sup>[4a,10]</sup> Some initial examples for this highly promising strategy have been published

[\*] Dr. K. Zeitler  
Institut für Organische Chemie, Universität Regensburg  
Universitätsstrasse 31, 93053 Regensburg (Germany)  
Fax: (+49) 941-943-4121  
E-mail: kirsten.zeitler@chemie.uni-regensburg.de

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only recently, but they already provide first insights into the versatility of such processes.

In photocatalyzed synthesis, so far mainly the reductive properties of photoexcited  $[\text{Ru}(\text{bpy})_3]^{2+*}$  have been used; in other words, following the reduction of excited  $\text{Ru}^{2+*}$  to a ruthenium(I) species in the presence of sacrificial electron donors such as tertiary amines, the photocatalyst serves as electron donor for different kinds of substrates. A corresponding catalytic cycle is depicted in Scheme 2.



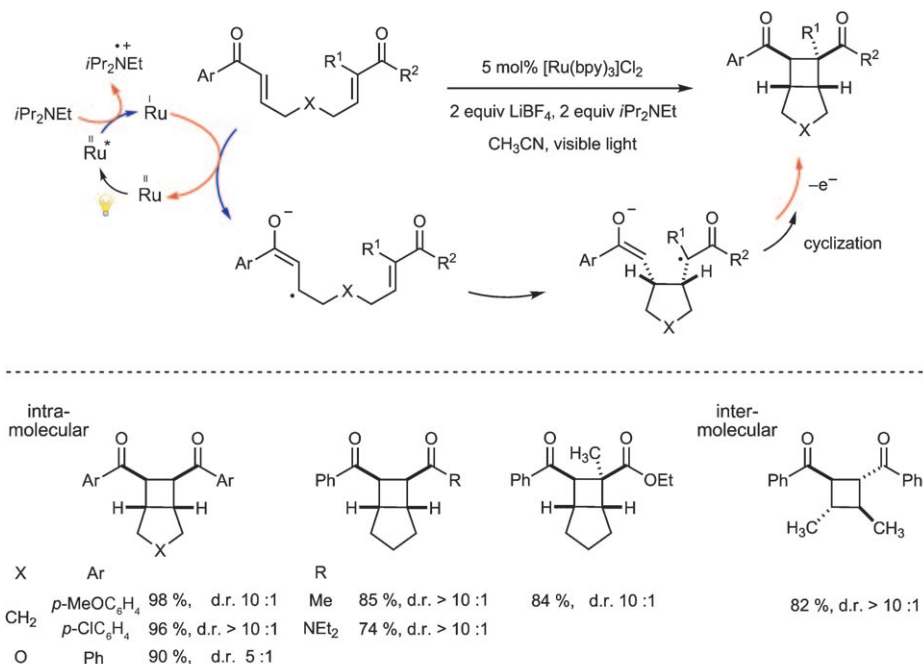
**Scheme 2.** Photomediated generation of electron-donating  $\text{Ru}^{\text{I}}$  species and subsequent activation of the substrate by reduction.

Inspired by the seminal work of Krische et al. on the initiation of the formal [2+2] cycloadditions of bis(enones) by the metal-mediated SET reduction of enones,<sup>[13]</sup> Yoon and co-workers applied Ru-based photoredox catalysis with visible light to generate the required radical anion intermediate from the corresponding aryl enones.<sup>[14]</sup> The electron donor ethyl-diisopropylamine was used to generate the reductive  $\text{Ru}^{\text{I}}$  species.<sup>[15]</sup> Upon irradiation with simple visible-light sources or sunlight, symmetrical and unsymmetrical substrates that possess at least one aryl enone moiety undergo efficient cyclization with high to excellent diastereoselectivity

(Scheme 3). Aryl enones with either electron-donating or electron-withdrawing substituents are suitable reaction partners, while a variety of  $\alpha,\beta$ -unsaturated carbonyl compounds can serve as Michael-type acceptors; even quaternary centers can be formed in the case of  $\alpha$ -substituted derivatives ( $\text{R}^1 \neq \text{H}$  in Scheme 3). In contrast to the intramolecular reaction, where the *cis* (*meso*) isomer is formed preferentially, the intermolecular dimerization affords the all-*trans* (*rac*) cyclobutane moieties. Importantly, the authors note that the presence of excess  $\text{LiBF}_4$  is an additional requirement for the successful reaction. Playing a dual role, the Li salt not only improves the solubility of the reactants in the  $\text{CH}_3\text{CN}$  mixture, but possibly also serves as a Lewis acid to facilitate the SET activation of the enone.

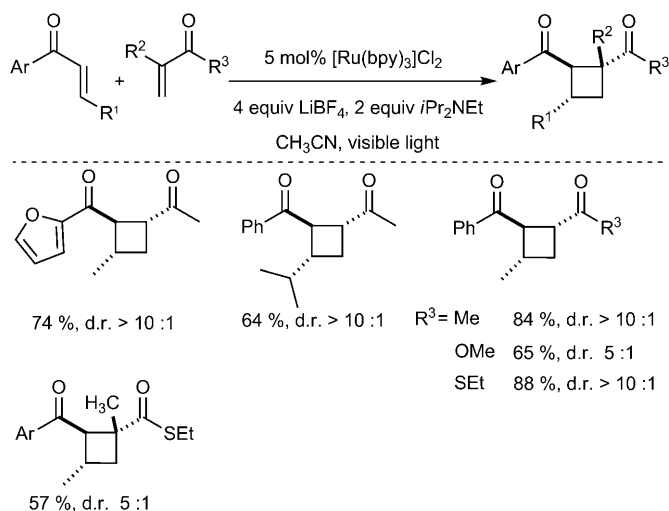
Based on this success for the homodimerization of aryl enone substrates,<sup>[14]</sup> Yoon and co-workers only very recently reported on a highly diastereoselective crossed intermolecular [2+2] cycloaddition of acyclic enones under comparable reaction conditions.<sup>[16]</sup> While higher-energy UV light can be directly absorbed by acyclic enones, it causes predominately photochemical *E/Z* isomerization of the substrates.<sup>[17]</sup> In contrast, the photocatalyzed reaction proceeds considerably differently. Electron transfer from the Ru sensitizer leads to the formation of the key radical anion intermediate, without intermediate access of the enones' electronically excited states, and the desired crossed cycloadduct is obtained as a single diastereomer in high yields.

For effective heterocoupling, active Michael acceptors are required as suitable electrophilic reaction partners in order to suppress the undesired homodimerization of the aryl enone. Again, electron-rich and electron-poor aryl and heteroaryl enones have proven to be active electrophores, and a variety of  $\alpha,\beta$ -unsaturated carbonyl compounds showed good to excellent acceptor properties as a function of their electro-



**Scheme 3.** Visible-light photocatalysis of formal [2+2] cycloadditions of enones.

philic character; thioesters, for example, provided high yields of cross-coupled products (Scheme 4). While the reaction is sensitive to steric bulk at the  $\beta$  position ( $R^1$ ) of the enones and



**Scheme 4.** Crossed intermolecular formal [2+2] cycloadditions of acyclic enones.

thus requires a greater excess of the acceptor to minimize homocoupling, the use of  $\alpha$ -substituted Michael acceptors ( $R^2 \neq H$ ) allows for the formation of quaternary centers. The potential role of  $Li^+$  as a Lewis acidic promoter of the reaction might lead to the development of asymmetric variants of this reaction. Until now, the difference in the redox potentials of aryl-substituted vs. alkyl-substituted and analogous enones has resulted in the high chemoselectivity of this process. An extension of this method to other enone-type substrates as “electrophores” may be possible by fine-tuning the photocatalyst’s redox properties through the choice of different ligands.

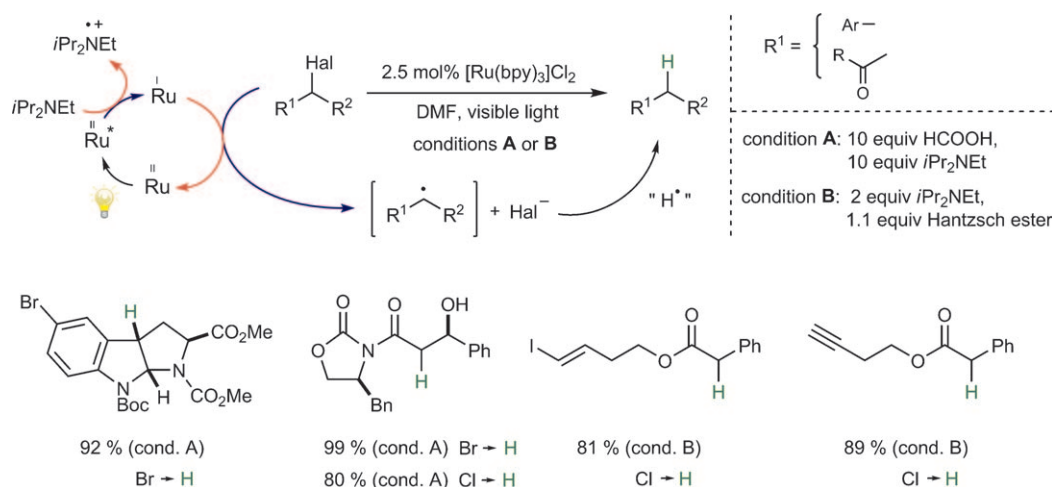
Another example of a highly chemoselective, photoredox-catalyzed reaction with visible light is the tin-free dehalogenation reaction of  $\alpha$ -carbonyl and  $\alpha$ -aryl halogen derivatives

recently disclosed by Stephenson and co-workers (Scheme 5).<sup>[18]</sup> The mild reductive dehalogenation can also be applied to highly functionalized molecules and might therefore prove to be an interesting alternative tool for late-stage removal of halogen atoms in total syntheses. So far, the method tolerates not only silyl ethers and free OH groups, but also esters, amides, carbamates, and alkynes; even in the presence of a vinyl iodide moiety no side reaction, such as the formation of cyclized products, was observed.

The photomediated reductive cleavage of  $\alpha$ -activated carbon–halogen bonds proceeds under mild conditions by a radical mechanism and tolerates a number of different hydrogen sources. When a tenfold excess of  $iPr_2NEt$  is used, the tertiary amine plays a dual role sacrificially donating an electron to form the Ru reductant and allowing hydrogen-atom transfer from the amine radical cation.<sup>[19]</sup> However, if the amine-based formation of a radical is less probable (e.g. when  $NEt_3$  is used), formic acid can serve as a hydrogen source, as was shown by isotope labeling experiments. Alternatively, Hantzsch ester derivatives can serve as highly efficient hydrogen sources, providing high yields of products in comparable reaction times—even with the less reactive chloro substrates (Scheme 5). Here Hantzsch esters are required in order to avoid the competitive  $S_N2$ -type side reactions of the formate ion.

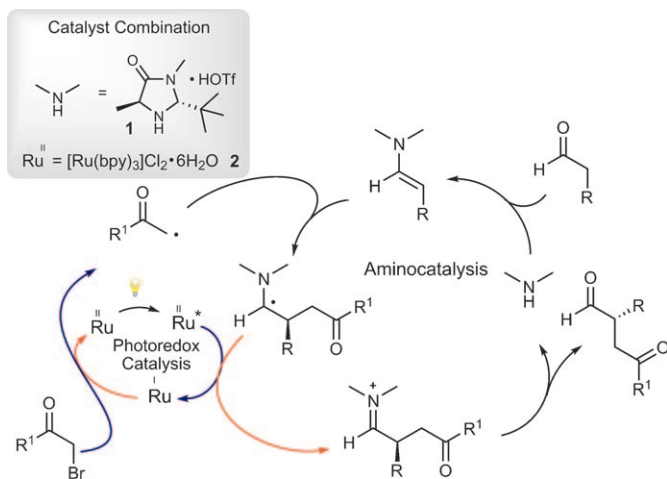
The current restriction to the removal of activated halogen atoms might be also overcome by tuning the photocatalyst’s redox potential. But apart from such reductive dehalogenation reactions, i.e. the quenching of the radical intermediate with a hydrogen source, this method might become a general tool for the initiation of radical reactions.

The combination of Ru-mediated photoredox catalysis with a SOMO-type aminocatalysis<sup>[20,21]</sup> (SOMO: singly occupied molecular orbital) as published by MacMillan and Nicewicz in 2008<sup>[22]</sup> provides a catalytic recycling system for the photocatalyst where both its oxidation and reduction steps are productive. Not only does the cooperative interaction of the two catalytic cycles (photoredox and organocatalytic) yield  $\alpha$ -alkylated aldehydes with high enantioselectivities in a previously elusive reaction, but also a sacrificial electron



**Scheme 5.** Tin-free photoredox catalytic reductive dehalogenation.

donor is not needed.<sup>[23]</sup> In fact, following an approach conceptually related to that described in the section above,<sup>[24]</sup> the alkyl radicals, which are photocatalytically derived from the corresponding activated halides,<sup>[25]</sup> are directly trapped by the electron-rich enamine species (Scheme 6). The resulting  $\alpha$ -amino radical is in turn oxidized by the photoexcited  $[\text{Ru}(\text{bpy})_3]^{2+*}$  providing the reductive  $\text{Ru}^+$  species for the dehalogenation.

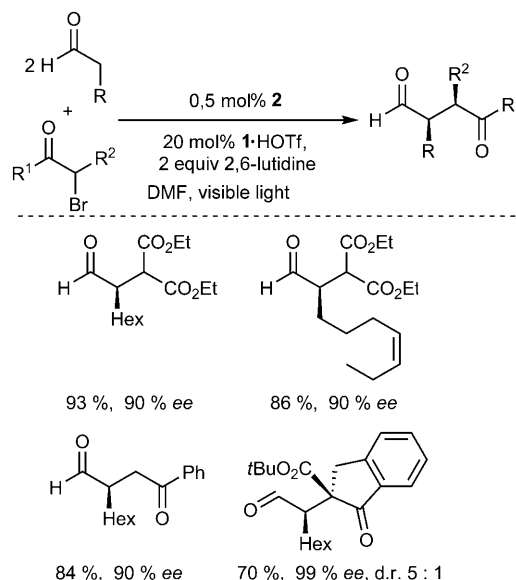


**Scheme 6.** Mechanism of combined photoredox catalysis/organocatalysis.

Unlike previous examples of SOMO-type catalytic cycles,<sup>[20]</sup> where the key  $3\pi$ -electron radical cation is only for the first initiation of the photolytic cycle formed upon enamine oxidation, the mechanism here is complementary. The authors claim such a sacrificial oxidation of a small amount of enamine intermediate.<sup>[26]</sup>

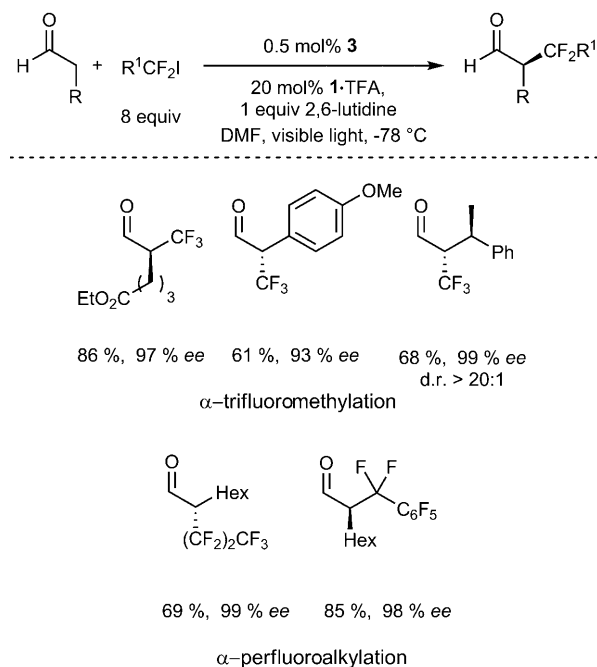
The  $\alpha$ -alkylation method proceeds under mild conditions and also requires only a standard energy-saving light bulb for as a light source (Scheme 7). The chiral imidazolidinone catalyst allows for the effective enantiofacial differentiation for the radical attack of the enamine, but will not react with the sterically more hindered  $\alpha$ -substituted products, and potential product racemization by enamine formation is avoided. A broad range of  $\alpha$ -alkylation products are accessible from aliphatic aldehydes in good to excellent yields and with high enantioselectivities (Scheme 7).

In a very recent extension of this merger of enamine and organometallic photoredox catalysis, MacMillan and co-workers have reported a visible-light-mediated, conceptually new approach to enantioselective  $\alpha$ -fluoroalkylation of “enolate equivalents”.<sup>[27]</sup> Irradiation of the catalytic system promotes the reductive generation of electrophilic fluoroalkyl radicals and their subsequent addition to the electron-rich enamine, which in is formed by a cooperative aminocatalytic cycle. While good results were obtained with the standard  $[\text{Ru}(\text{bpy})_3]^{2+}$  catalyst, an Ir-based catalyst ( $[\text{Ir}(\text{ppy})_2(\text{dtb-bpy})]^+$ ) proved to be superior in terms of yield and enantioselectivity (Ru cat: 67%, 87% ee vs. Ir cat: 79%, 99% ee). The asymmetric formation of the pharmaceutically interesting  $\alpha$ -fluoroalkyl compounds proceeds at low temper-



**Scheme 7.** Asymmetric intermolecular  $\alpha$ -alkylation of aldehydes.

atures and allows the construction of both trifluoromethyl and perfluoroalkyl-substituted derivatives (Scheme 8). As the reaction can be combined with various subsequent in situ transformations of the (unstable) aldehyde products without loss of enantioselectivity, this method provides easy access to a great variety of versatile fluorine-containing synthons such as  $\beta$ -trifluoromethyl alcohols and amines as well as to  $\alpha$ -trifluoromethyl acids and  $\alpha$ -trifluoromethyl amines by means of sequential oxidation and Curtius rearrangement. MacMillan's approach not only demonstrates the power of



**Scheme 8.** Enantioselective  $\alpha$ -trifluoromethylation/ $\alpha$ -perfluoroalkylation of aldehydes. Photocatalyst **3**:  $[\text{Ir}(\text{ppy})_2(\text{dtb-bpy})]\text{PF}_6$ ; ppy = 2-phenylpyridine, dtb-bpy = di-*tert*-butylbipyridine.

photoredox chemistry, but also illustrates the tremendous possibilities that arise from the combination of different concepts.

The Ru-photosensitized transformations discussed herein give only a first impression of the versatility of visible-light-mediated photoredox catalysis—the substrates can be generally activated by reduction as well as by oxidation—and show how stereocontrol can be achieved in this context. These examples might also pave the way for further potential applications and new developments as special equipment is no longer required to make use of visible light as a reagent, and the complications associated with the interaction of excess energy are avoided.

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