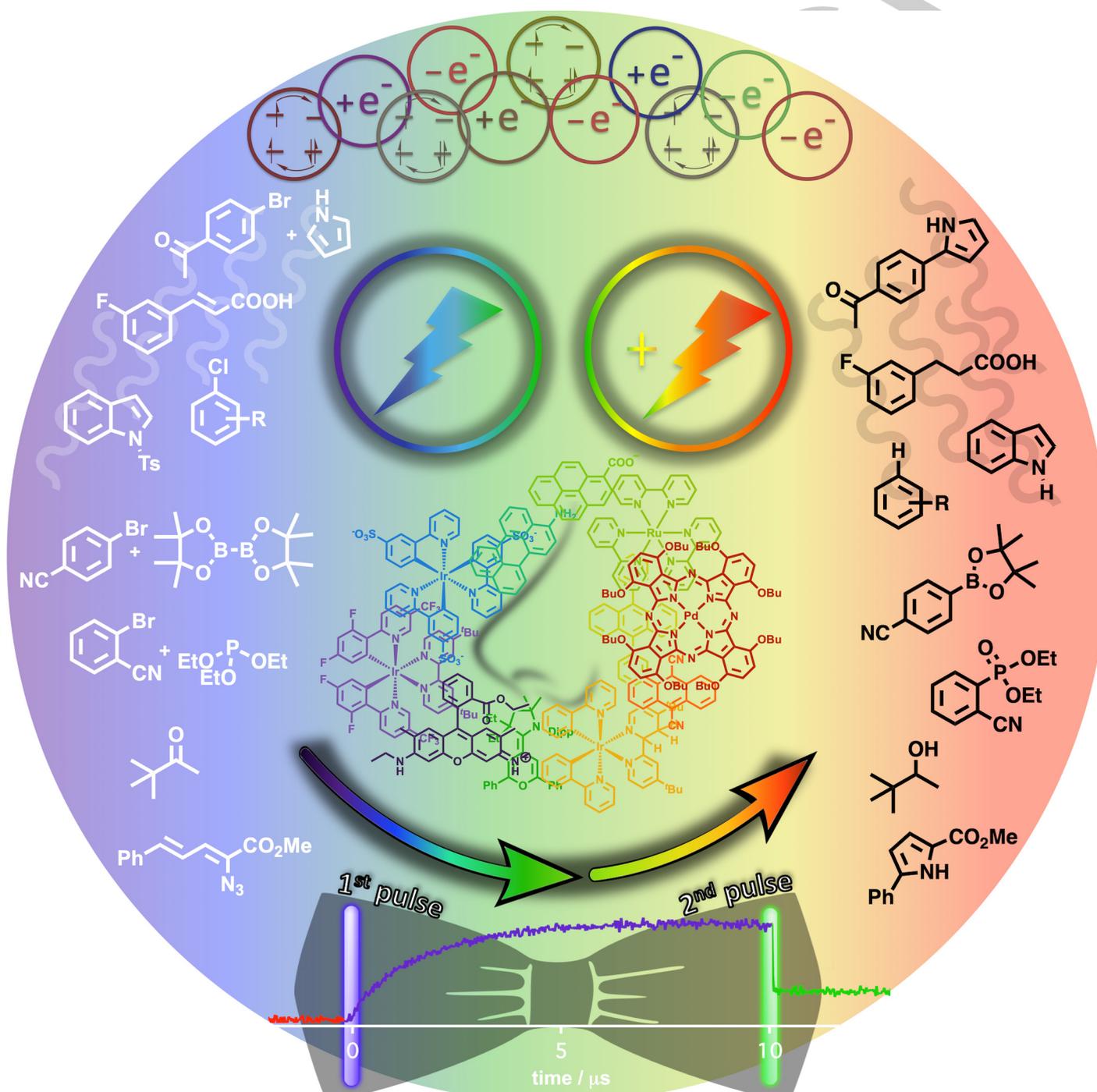


Multi-Photon Excitation in Photoredox Catalysis: Concepts, Applications, Methods

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Abstract: The energy of visible photons and the accessible redox potentials of common photocatalysts set thermodynamic limits to photochemical reactions that can be driven by traditional visible-light irradiation. UV excitation can be damaging and induce side reactions, hence visible or even near-IR light is usually preferable. Thus, photochemistry currently faces two divergent challenges, namely the desire to perform ever more thermodynamically demanding reactions with increasingly lower photon energies. The pooling of two low-energy photons can address both challenges simultaneously, and whilst multi-photon spectroscopy is well established, synthetic photoredox chemistry has only recently started to exploit multi-photon processes on the preparative scale. Herein, we have a critical look at currently developed reactions and mechanistic concepts, discuss pertinent experimental methods, and provide an outlook into possible future developments of this rapidly emerging area.

1. Introduction

Photoredox catalysis is an old concept that has been developed to a remarkable level of sophistication over the past decade.^[1] Now, some inherent thermodynamic limitations of traditional visible-light irradiation strategies are becoming increasingly evident. Two key factors govern these thermodynamic restrictions, namely the limited energy of visible photons (up to 300 kJ/mol), and the excitation energy loss on the way from light absorption by the photosensitizer till substrate activation by the reacting catalyst species. As a rule of thumb, that energy loss amounts to at least 25 % (more typically about 50%) compared to the initial photon energy, which is due to the accumulated energy losses caused by internal conversion, intersystem crossing, and oxidation or reduction of the catalyst itself. Hence, the range of redox potentials in which robust visible-light absorbing photocatalysts are operational is rather narrow. Increasing the photon energy is often not an option because many organic substrates directly absorb UV light, which can cause photo-damage and undesired side reactions. A more viable alternative is the development of tailor-made photoredox catalysts with aggressive redox properties, but this requires significant efforts and can jeopardize the stability of the photocatalysts.^[2] To drive thermodynamically increasingly challenging reactions with visible light and well-established photocatalysts, the synthetically oriented photoredox community therefore recently started to exploit multi-photon excitation. By this strategy, the thermodynamic hurdles are overcome by combining the energy of two (or more) photons per catalytic turnover.

Spectroscopists have explored multi-photon processes in considerable depth, often with pulsed lasers that provided very high excitation densities, and short-lived photoproducts were

usually formed in micro-molar concentrations.^[3] The demonstration and popularization of triplet-triplet annihilation upconversion (TTA UC) in solution using continuous-wave (cw) lasers represented an important advance because multi-photon processes became more widely amenable,^[4] requiring neither pulsed lasers nor time-resolved spectrometers. Technological advances leading to the availability of high-power LEDs with outputs covering the entire visible spectral range further contributed to making multi-photon chemistry applicable in the synthetic laboratory. The fact that such processes are now exploitable for preparative-scale conversions is remarkable and represents a breakthrough in photochemistry.

The field of multi-photon excitation-based photoredox catalysis is still very young, with studies reporting preparative-scale reactions only since 2014. Whilst the synthetic utility for thermodynamically challenging reactions seems undisputable, mechanistic aspects have led to several controversial discussions. The field would likely benefit from stronger interaction between synthetically oriented organic chemists on the one hand and spectroscopists as well as physical-inorganic chemists on the other hand to tackle synthetic as well as mechanistic challenges for new photochemical systems. In this spirit and working near the interface of these sub-disciplines, we prepared this article. We provide an overview of the different relevant concepts of multi-photon excitation and consider their thermodynamic and kinetic particularities based on spectroscopic studies performed with laser techniques. Furthermore, we discuss their synthetic applications and important mechanistic aspects, which seem crucial for allowing further rational progress in this field. High-end as well as more straightforward techniques for obtaining fundamental insight are outlined, and finally we contemplate possible future directions for research on multi-photon excitation-based photoredox catalysis. We hope that this article will provide some useful guidance in identifying challenges, pitfalls, and opportunities in this emerging field.

2. Consecutive photo-excitation in the simplest case

All currently known preparative-scale photoredox reactions relying on multi-photon excitation operate based on the consecutive (rather than simultaneous) absorption of photons. An overview of the photon densities required for *consecutive* (stepwise) two-photon absorption processes in the context of photochromic reactions has been given recently,^[5] and these light power considerations hold also true for the processes discussed herein. However, much higher excitation densities than provided by laboratory-fit LEDs and cw-lasers would be required for *simultaneous* two-photon absorption to be efficient.^[6] The sequence of ground-state absorption followed by

excited state absorption events (upper and right part of Fig. 1) therefore represents the conceptually most straightforward way to access highly energetic species. Such sequences have been explored extensively in the field of photon upconversion with lanthanide doped oxide or halide materials.^[7] Trivalent lanthanides in these materials often exhibit multiple very long-lived f-f excited states, and therefore sizeable excited-state populations can build up even at moderate excitation powers, and this can be exploited for the conversion of near-infrared into visible or UV light. However, in molecular compounds in fluid solution, the lifetimes of electronically excited states are typically much shorter, and consequently the deceptively simple concept in Fig. 1 becomes tricky to realize for efficient preparative-scale chemical conversions.

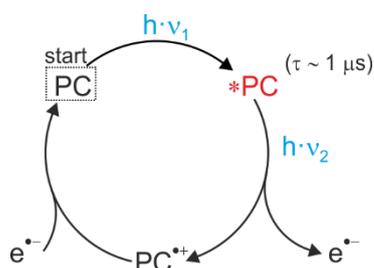


Figure 1. Simplified reaction via higher excited (triplet) states. PC = photoactive compound; the asterisk denotes an electronically excited state.

Photoionization studies with pulsed lasers provide quantitative insight into the sequential photon absorption implied in the mechanism of Fig. 1. For instance with xanthone as photoactive compound (PC), a first UV photon almost quantitatively produces the lowest triplet (T_1) state (*PC) with a lifetime (τ) of ca. 20 μ s in a methanol/water mixture, which can be further excited to a higher triplet (T_n) by a secondary UV photon.^[8] Ionization from the T_n state occurs with a quantum yield (ϕ) of only 0.008 due to very rapid relaxation of that T_n state, yet the formation of hydrated electrons (e_{aq}^-) and oxidized xanthone ($PC^{+\bullet}$) was clearly detectable. However, photoredox catalysis was not performed with this system; the need for UV excitation and the low ionization quantum yield would represent significant disadvantages.

The full catalytic cycle of Fig. 1 was completed in a system comprised of 3-aminoperylene (PerNH₂) as photocatalyst and ascorbate monoanion (HAsc⁻) as sacrificial electron donor, enabling the green-light induced decomposition of chloroacetate (Table 1, entry 1) with turnover numbers of ca. 170.^[9] This has become a common test reaction to corroborate the spectroscopic detection of hydrated electrons, and it exploits the superpower of e_{aq}^- with its reduction potential of -2.9 V vs. NHE. Successful chloroacetate degradation indicates that other environmentally harmful and persistent halo-organic substances can potentially be decomposed, which is relevant for detoxifying wastewater.^[10] The creation of micellar nano-reactors with SDS (sodium dodecylsulfate) in water was crucially important, because it shields the photocatalyst (PerNH₂ and its oxidized form, PerNH₂^{•+}) in the lipophilic inside from the hydrated electrons and other aggressive radicals on the outside of the micelles; catalyst regeneration with HAsc⁻ remained efficient at the micelle-water interface.^[11] However, owing to the short lifetime of the excited singlet intermediate produced with the first photon (about 5 ns), this reaction had to be performed with a

pulsed Nd:YAG laser that provided high excitation densities in short periods of time.

Table 1. Reactions following the mechanism in Fig. 1 along with employed photocatalysts.

entry	photocatalyst	exemplary reactions
1 ^a		
2 ^b		
3 ^c		

^a ref. [9], ^b ref. [12], ^c ref. [13].

Aiming to exploit the mechanism of Fig. 1 under continuous-wave (non-pulsed) irradiation conditions, we discovered that the [Ir(sppy)₃] complex (Table 1, entry 2) catalyzes the formation of hydrated electrons in the presence of triethanolamine (TEAO) or ascorbate.^[12] A diode laser (447 nm) sufficed for the 50 mg scale photoreduction of 4-(trifluoromethyl)benzoate to the corresponding difluoromethyl compound, as well as for the decomposition of a benzylammonium cation. Despite the importance for pharma industry, only few good methods for the selective activation of CF₃ groups seem to be known yet,^[14] and the structural motif of the benzylammonium cation is present in many widely-used quaternary ammonium compounds,^[15] which need to be degraded in wastewater. Two-pulse two-color laser flash photolysis provided unambiguous evidence for the mechanism in Fig. 1: An initial 430-nm pulse populates the ³MLCT excited state of [Ir(sppy)₃] with a lifetime of 1.6 μ s, exhibiting strong excited-state absorption between 460 and 570 nm. In this wavelength range, the ground state does not absorb hence a 532-nm secondary laser pulse selectively promotes ³MLCT-excited [Ir(sppy)₃] to a higher triplet excited state, from which photoionization then occurs with a quantum yield of 1.3%. The hydrated electron exhibited a lifetime of 1.4 μ s in this system, hence there is ample time for bimolecular reactions (see section 9). In the continuous-wave NMR-scale experiments described above, the 447-nm diode laser was able to induce both ground- and excited-state excitation.

The excitation density is a key parameter in all two-photon reactions, and we exploited this to control the outcome of a photochemical reaction by changing the light intensity.^[13] The simple introduction or omission of an optical lens in the excitation beam path allowed switching between one- and two-photon induced preparative-scale conversions. As two-photon reactions, the hydrodehalogenation of a benzoate substrate and the reduction of a cinnamic acid derivative were explored (Table 1, entry 3). Dechlorination and olefin hydrogenation is possible only in presence of the lens, whilst in its absence e_{aq}^- is not formed and merely debromination of the benzoate and triplet-

triplet energy transfer from $[\text{Ir}(\text{sppy})_3]$ to the cinnamic acid are observable.

Under continuous irradiation, preparative-scale chemical conversions according to the mechanism in Fig. 1 almost unavoidably imply many unproductive excitations of the photoactive compound. Consequently, the photostability of PC is a key factor that requires careful attention. $[\text{Ir}(\text{sppy})_3]$ is remarkably robust even under long-term intense irradiation,^[12] and this is part of the reason why the reactions in Table 1 (entries 2 & 3) were possible. However, this is not always the case for PCs, as discussed in detail below (sections 3, 4 and 8). The temporary storage of energy in *PC relies on long excited state lifetimes, and therefore triplet excited states are inherently better suited for the mechanism in Fig. 1 than short-lived singlet excited states. However, excited singlet states as intermediates, which can be re-excited with pulsed lasers,^[9] are more attractive from the thermodynamic point of view as they store a larger fraction of the initial photon energy than a triplet could do. Natural lifetimes (τ_0) of ca. 1 μs for T_1 or longer are advantageous; the higher excited T_n states typically have lifetimes in the picosecond regime and can only react when very high concentrations of possible reaction partners are present.^[16] Micellar environments can help suppress undesirable side reactions and improve PC stability,^[17] as discussed in further detail in the next section.

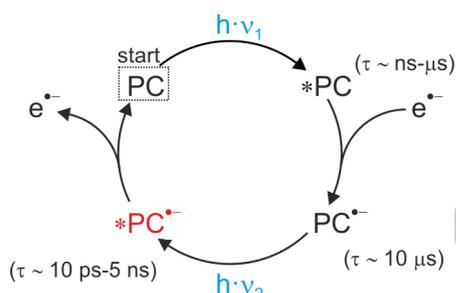


Figure 2. Reaction via electronically excited one-electron reduced species. PC = photoactive compound.

3. The next level: Reductive excited-state quenching followed by excitation of one-electron reduced species

In the mechanism of Fig. 1, secondary excitation produces PC^{*+} , which is subsequently reduced back to PC by sacrificial reagents. When reversing the sequence of secondary excitation and electron transfer from the sacrificial donor, the overall reaction follows the sequence of elementary steps illustrated in Fig. 2. An important advantage in this case is that the photoexcited species *PC no longer needs to be particularly long-lived, and singlet excited states with nanosecond lifetimes can be suitable. The key condition is then that sufficiently strong sacrificial electron donors are present at high enough concentrations, in order to ensure rapid reductive quenching of *PC and efficient formation of PC^{*-} . Typically, stronger electron donors are needed for this purpose than in the case of the mechanism in Fig. 1, because *PC is usually a weaker oxidant than PC^{*+} . Another important advantage of the mechanism in Fig. 2 is the longevity of PC^{*-} compared to *PC in Fig. 1: The one-electron reduced species PC^{*-} can readily exhibit lifetimes of several tens of microseconds or even longer,^[18] which compares

favorably to the *PC lifetime of $[\text{Ir}(\text{sppy})_3]$ in the preceding section (1.6 μs). This increases the achievable steady-state concentration of species that can undergo further photoexcitation in the overall two-photon process.

Table 2. Reactions (along with photocatalysts) for which one-electron reduced species according to the mechanism in Fig. 2 were invoked as intermediates.

entry	photocatalyst	exemplary reactions
1 ^a	Rh-6G	
2 ^b	PDI	
3 ^c	DCA	
4 ^d	Aq-OH	
5 ^e	$[\text{Ru}(\text{bpy})_3]^{2+}$, $[\text{Ru}(\text{dmb})_3]^{2+}$, $[\text{Ru}(\text{dcoB})_3]^{2+}$	
6 ^f	$[\text{Ir}(\text{ppy})_2(\text{dtbpy})]^+$	

^a ref. [19], ^b ref. [20], ^c ref. [21], ^d ref. [22], ^e ref. [23], ^f ref. [24].

On the other hand, the lifetime of $^*PC^{*-}$ becomes a crucial factor. Organic radical anions typically have excited-state lifetimes in the range of 10 ps to 5 ns.^{[3], [25]} For instance, the photoexcited 9,10-dicyanoanthracene radical anion (DCA^{*-}) exhibits τ_0 of ca. 5 ns,^[25b] but naphthalene or perylene diimide radical anions (PDI^{*-}) only have lifetimes on the order of 100 ps.^[25a] This can severely limit the likelihood for bimolecular reactions, because diffusion competes poorly with such rapid excited-state deactivation at synthetically relevant substrate concentrations (section 9). Thus, the actual reducing species in Fig. 2, $^*PC^{*-}$, is orders of magnitude shorter-lived than the reductant in Fig. 1, the hydrated electron (1.4 μs , see above). In several cases, $^*PC^{*-}$ has been reported to photo-ionize, yielding long-lived e_{aq}^{*-} ,^[26] but this will be discussed further below, and we will now first focus on cases in which $^*PC^{*-}$ was considered as reductant of organic substrates on preparative scales.

Using Rhodamine 6G (Rh-6G) as photocatalyst, preparative-scale reactions of the type in Table 2, entry 1, become possible under continuous blue light irradiation,^[19] and a spectroscopic study supports the view that the mechanism in Fig. 2 can lead to such reactions, particularly under conditions in which photocatalysts and substrates are pre-associated.^[27] In presence

of excess DIPEA (*N,N*-diisopropylethylamine), the fluorescent excited state of Rh-6G is quenched reductively, and the resulting one-electron reduced species (PC^*) is formed. Secondary excitation is then thought to form $^*PC^*$ with a reduction potential of ca. -2.4 V vs. SCE,^[19] sufficient for reductive debromination of aryl bromides and thereby leading to short-lived aryl radicals that can be intercepted by *N*-methylpyrrole. Under blue light irradiation C-H arylations are possible for a fairly broad range of substrates and a few different radical interceptors, and twofold (sequential) reactions on a given substrate can be performed in good yields. 1,3,5-Tribromobenzene (Table 2, entry 1) requires a potential of -1.6 V vs. SCE for reduction^[28] hence PC^* is not a sufficiently strong donor ($E^0 = -1.0$ V vs. SCE),^[19] and further excitation is necessary. PC^* absorbs much more strongly at 455 nm than at 530 nm, and indeed only blue excitation provides the doubly pyrrole-substituted product, whereas green light yields exclusively the singly substituted product after 96 hours with high catalyst loadings and a turnover number of 3.

The second reaction in Table 2, entry 1, is chromoselective: The ethyl 2-bromo-2-(4-bromophenyl)acetate substrate can be reduced efficiently to ethyl 2-bromo-2-phenylacetate with green light because that reaction requires a potential of ca. -0.8 V vs. SCE^[29] and PC^* is oxidized at -1.0 V vs. SCE. However, onward reaction with 1,1-diphenylethylene requires debromination of the aryl ring, which occurs only at substantially more negative potentials (-1.7 to -2.0 V vs. SCE for related compounds)^[28, 30] hence further excitation with blue light is necessary.

The light-driven reduction of aryl halides using PDI (perylene diimide) as catalyst and TEA (triethylamine) as reductant (Table 2, entry 2) was interpreted in the same mechanistic framework of Fig. 2,^[20, 31] but spectroscopic and photochemical studies cast doubt on the initial mechanistic interpretation.^[32] The lowest excited state of PDI^* has a lifetime of only 145 ps,^[25a] the extinction coefficient of PDI^* at the employed irradiation wavelength of 455 nm is comparatively low, and C-Cl bond cleavage is typically the rate-determining step in the reductive dehalogenation of aryl chlorides (Ar-Cl),^[33] making reverse electron transfer from $[Ar-Cl]^*$ to PDI very competitive. Using the reduction of 4'-bromoacetophenone as model reaction, the mechanistic study found that the onset of acetophenone formation correlated with PDI^* degradation, and the conclusion was that this reaction takes place through an unidentified photodecomposition product of PDI .^[32] Using the less challenging substrate 4-bromobenzaldehyde instead of 4'-bromoacetophenone as substrate, a combined NMR and UV-Vis study with in situ photo-irradiation found no clear correlation between PDI^* degradation and product formation, and the mechanism of Fig. 2 seems to operate.^[34]

In a subsequent study of photochemical ATRA (atom transfer radical addition) reactions between olefins and perfluoroalkyl iodides, 0.05 mol% of PDI was added to the reaction mixture and photo-irradiated in presence of ascorbate in acetonitrile-water solvent mixtures.^[35] The authors speculated that photochemically generated PDI^* forms electron donor-acceptor-type (EDA) complexes with the perfluoroalkyl iodide substrates, and that further excitation of these EDA complexes enables the ATRA reaction. After a typical photoreaction, 28% of PDI were recoverable, and this was interpreted as evidence for the possibility that PDI is indeed the photocatalyst, rather than a degradation product. Nevertheless, the authors observed that there is significant photo-degradation.^[35] In yet another related study, PDI was covalently anchored to nanosilica, and

photochemical reductive dehalogenations were investigated. The authors noted that PDI is "quite stable under the photocatalytic conditions".^[36] Incorporation of PDI into a metal-organic polymer was claimed to facilitate catalyst-substrate interaction,^[37] which is in line with the view that such pre-association can be important for the photoreaction of short-lived radical anion excited states.^[27]

A very recent picosecond transient absorption study provides direct evidence for bimolecular electron transfer between photoexcited PDI^* and a range of substrates with reduction potentials more positive than -1.7 V vs. SCE.^[38] However, for substrates with more negative potentials (and this is likely the case for several of the initially investigated aryl chlorides),^[20a, 30, 33] a different mechanism, possibly a thermally activated pathway, seems to be operative.^[38]

The system in Table 2, entry 3,^[21] does not suffer from the problem of exceedingly short $^*PC^*$ lifetime, because $^*DCA^*$ is fluorescent and has a comparatively long excited-state lifetime of ca. 5 - 10 ns depending on solvent.^[25b, 39] Electrolysis at a constant cell voltage permits essentially quantitative conversion of DCA to DCA^* ,^[40] making selective PC^* photoexcitation straightforward and leading to an overall monophotonic process. The observation of electrophotocatalytic turnover of a variety of substrates therefore lends additional credibility to the view that DCA indeed allows for biphotonic reactions along the mechanism of Fig. 2.^[40b] With an estimated potential of -3.2 V vs. SCE the reducing power of $^*DCA^*$ is particularly high; as noted above, the relevant expectable $^*PC^*$ potential in the case of Rh-6G is -2.4 V vs. SCE.^[19] As there is almost no spectral overlap between the absorption of the neutral and reduced forms of DCA, two different wavelengths or white light are required to excite both species.

Early spectroscopic studies demonstrated that some quinone-based radical anions have excited states with lifetimes in the nanosecond regime,^[41] and application-oriented studies of quinones as photoredox catalysts were reported recently.^[22, 42] It was speculated that the reaction in Table 2, entry 4, might proceed (at least partly) along the mechanism of Fig. 2,^[22] but the complexity of the coupled acid/base and oxidation/reduction chemistry of quinones makes a thorough mechanistic analysis particularly challenging for this class of compounds. For the 9,10-anthraquinone radical anion an excited-state lifetime of 71 ps in 2-methyl-THF at 77 K was reported,^[43] and hence bimolecular reactions would have to rely largely on photocatalyst-substrate pre-association.

As noted above, excitation of PC^* in Fig. 2 can induce photo-ionization in selected cases, leading to solvated electrons that can have much longer lifetimes than photoexcited organic radical ion species. Visible-light induced electron detachment has been explored in a series of studies employing $[Ru(bpy)_3]^{2+}$ and some of its derivatives as photoactive compounds in aqueous solution (Table 2, entry 5). Using the ascorbate dianion (Asc^{2-}) as reductant, $[Ru(bpy)_3]^+$ (corresponding to PC^* in Fig. 2) is generated with a quantum efficiency of 0.38 - 0.48 after excitation at 532 nm.^[23a, 26a] Secondary excitation with a temporally delayed 532-nm laser flash induces photo-ionization with a quantum yield of 0.013 in a two-pulse experiment in de-aerated water,^[26a] and the resulting hydrated electrons exhibit a lifetime of 165 ns.^[23a] At very high concentrations of the reductive quencher Asc^{2-} , the whole absorption-photoreduction-absorption sequence (compare, Fig. 2) operates within a single 5-ns laser pulse. Using the simplified setup with just one frequency-doubled Nd:YAG laser providing 5-ns pulses at a

repetition rate of 10 Hz, e_{aq}^- concentrations on the order of 10 μM were generated per laser flash (600 mJ/cm^2), and this is similar to what is typically achievable by pulse radiolysis. Laser flashing over 30 minutes allowed reactions on a 10 mM scale, for instance the reduction of *tert*-butylmethylketone (Table 2, entry 5) or the dechlorination of chloroacetate.^[23a]

Similar turnover numbers (ca. 1400) for chloroacetate degradation became later achievable with a green LED (3.6 W/cm^2),^[44] and since then the visible-light driven generation of synthetically relevant e_{aq}^- concentrations no longer has to rely on pulsed lasers (typically providing 100 MW/cm^2). This important advance initially required the use of SDS micelles to decelerate undesired recombination of $[\text{Ru}(\text{bpy})_3]^+$ with the quasi-stable ascorbyl radical Asc^\cdot . That anion is restricted to the outside of the micelles whilst $[\text{Ru}(\text{bpy})_3]^{2+}$ and $[\text{Ru}(\text{bpy})_3]^+$ are inside but near the interface. An undesirable side effect of this compartmentalization strategy is a decreased rate constant for reductive $^3\text{MLCT}$ quenching by Asc^{2-} , but this can be counteracted by increasing the ascorbate concentration.

This micelle strategy can be used for example for the hydrogenation of cinnamates and fumarates (Table 2, entry 5), or for reductive dehalogenations of benzoates in water.^[23b] With urate dianion (HUr^{2-}) instead of Asc^{2-} as electron source, cross coupling reactions become more efficient (Table 2, entry 5), because HUr^{2-} cannot act as efficient H-atom donor, causing less hydrodehalogenation.^[23c] When Asc^{2-} is employed as reductant, the ascorbate monoanion HAsc^\cdot is always present in noticeable concentrations, and the latter can act as an efficient H-atom donor.^[45]

Further conceptual progress was made by using an anionic Ru^{II} photocatalyst with six carboxylate groups ($[\text{Ru}(\text{dcob})_3]^{4-}$) and urate dianion as electron source (Table 2, entry 5, bottom). When HUr^{2-} is oxidized by the excited Ru^{II} complex, it deprotonates and remains dianionic. Since the metal complex in this case is also anionic, Coulombic repulsion limits undesirable reverse electron transfer between oxidized donor and reduced photocatalyst, and consequently the $[\text{Ru}(\text{dcob})_3]^{4-}/\text{HUr}^{2-}$ system enabled the micelle-free production of synthetically useable amounts of hydrated electrons with an LED for the first time.^[23d] Blue rather than green light was used to optimize the excitation process.

The micelle strategy was recently adapted to accommodate water insoluble substrates such as lipophilic alkyl chlorides (Table 2, entry 6), which were activated to carbon-centered radicals using visible-light irradiation of an Ir^{III} complex.^[24] Micelles were formed from SLES (sodium lauryl oligoethylene glycol sulfate) and 1-pentanol helped to solubilize hydrophobic substrates. It was speculated that there might be favorable pre-aggregation in the sense that the chlorine atoms of the substrates point towards the outside of the micelle, thereby facilitating photocatalytic reactions with the Ir complex. The one-electron reduced form of $[\text{Ir}(\text{ppy})_2(\text{dtbpy})]^+$ was observable by UV-Vis spectroscopy following irradiation in presence of Asc^{2-} , and further excitation of this PC^\cdot species was thought to yield $^*\text{PC}^\cdot$ with a reduction potential of ca. -2.8 V vs. SCE. No further information regarding $^*\text{PC}^\cdot$ seems to be available; in particular its lifetime seems to be unknown. This situation is different from the abovementioned case of $[\text{Ir}(\text{sppy})_3]$ (Table 1, entries 2 & 3), in which $^*\text{PC}^\cdot$ was observed to photoionize and in which there was unambiguous evidence for the formation of long-lived hydrated electrons as reactive intermediates, and their reactions with several challenging substrates were monitored in a direct manner.^[12-13] However, studying the substrate activation step in

isolation for mechanisms as in Fig. 2 usually requires two-pulse laser flash photolysis – an experimental technique that is not widely available (section 9).

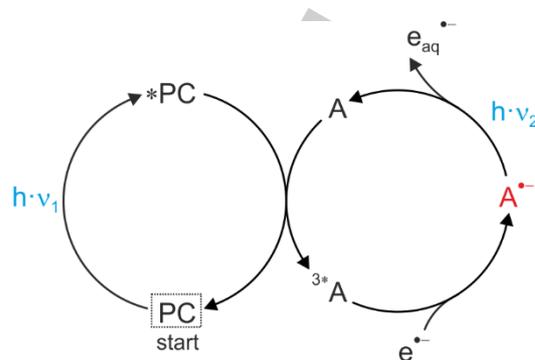


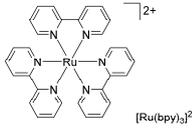
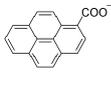
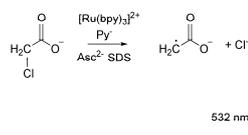
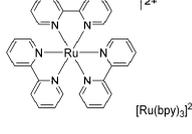
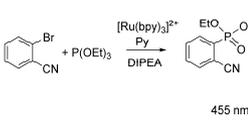
Figure 3. Photoionization of triplet-triplet energy acceptors. PC = photoactive compound, A = acceptor, e_{aq}^- is the hydrated electron.

4. The 3rd level: Separating primary and secondary absorber

The mechanisms of Fig. 1 and Fig. 2 both rely on a single photoactive compound, but some advantages can emerge from a reaction sequence in which the first and the second photon of the overall biphotonic reaction are absorbed by different substances. Fig. 3 illustrates this concept. When using a metal complex as photoactive compound, a long-lived triplet excited state can form efficiently via rapid intersystem crossing and triplet-triplet energy transfer (TTET) to suitable acceptors (A) can occur. Many polycyclic aromatic hydrocarbon (PAH) compounds have triplets near the lowest $^3\text{MLCT}$ state of common d^6 metal emitters such as Ru^{II} polypyridines or cyclometalated Ir^{III} complexes, and TTET in such cases often results in the rapid formation of ^3A exhibiting very long lifetimes.^[46] When ^3A is quenched reductively with sacrificial electron donors, A^\cdot forms, and this highly reducing PAH radical anion can potentially be used directly for photoredox chemistry,^[47] or A^\cdot can be excited further to produce even more strongly reducing hydrated electrons (Fig. 3).^[48]

The concept in Fig. 3 was first exploited for photoredox catalysis with $[\text{Ru}(\text{bpy})_3]^{2+}$ and a carboxylate-substituted pyrene (Py) in a micellar environment (Table 3, entry 1).^[48] Both TTET from the $^3\text{MLCT}$ -excited Ru^{II} complex to Py as well as reductive quenching of $^3\text{Py}^\cdot$ by Asc^{2-} occur with rate constants exceeding $2 \cdot 10^8 \text{ M}^{-1} \text{ s}^{-1}$. The natural lifetime of the resulting $\text{Py}^{\cdot 2-}$ species (corresponding to A^\cdot in Fig. 3) is 67 μs , and such a long lifetime could in principle negatively affect long-term stability of the overall catalytic system. Gratifyingly, ionization of $\text{Py}^{\cdot 2-}$ occurs with a quantum yield of 0.054 upon excitation at 532 nm, which compares favorably to the UV-C (254 nm) induced formation of e_{aq}^- in the so-called sulfite process.^[10] These combined properties allowed the photo-degradation of chloroacetate with green light (Table 3), as two-pulse laser experiments revealed.^[48] Currently, the decomposition of chlorinated and fluorinated organic waste relies largely on UV-C light produced by mercury lamps,^[10-11, 49] but such short-wavelength radiation tends to have limited penetration depth in wastewater because many compounds absorb strongly in the UV-C. The ability to perform this reaction (Table 3, entry 1) with visible light therefore provides an important proof-of-concept.

Table 3. Sensitizer / acceptor combinations and photoreactions related to the mechanism of Fig. 3 (see text for details).

entry	sensitizer	acceptor	exemplary reaction
1 ^a			 532 nm ^b
2 ^c			 455 nm

^a ref. [48], ^b reaction not performed on preparative scale, ^c ref. [47a].

Later studies claimed to make direct usage of the A^{•-} species from Fig. 3 without further excitation, for example for photo-Arbusov reactions with aryl halides (Table 3, entry 2),^[47a] but currently it seems that the initial mechanistic interpretation was too simplistic. Alternative processes such as sensitized triplet-triplet annihilation upconversion or other mechanisms (see also section 5) that consume two photons might be operative.^[47b, 47c] Clearly, PAH radical anions have strong reducing power already in their electronic ground state, and hence the idea of exploiting A^{•-} as reductant is attractive.^[50]

A special case for the combined energy and electron transfer reactivity with PAHs has been used for a trifluoromethylation reaction using a cobalt photocatalyst (not shown).^[51] In contrast to the abovementioned mechanisms, where the long-lived triplet state of pyrene is reductively quenched, an oxidative quenching pathway (leading to a A^{•+} instead of A^{•-} as in Fig. 3), produces trifluoromethyl radicals from trifluoromethanesulfonyl chloride. In this special case the acceptor also serves as the substrate to yield selective trifluoromethylation at its most electron-rich position. A quadratic dependence (see also section 9) on the irradiation density has been found for the product formation to support the stated mechanism.^[51]

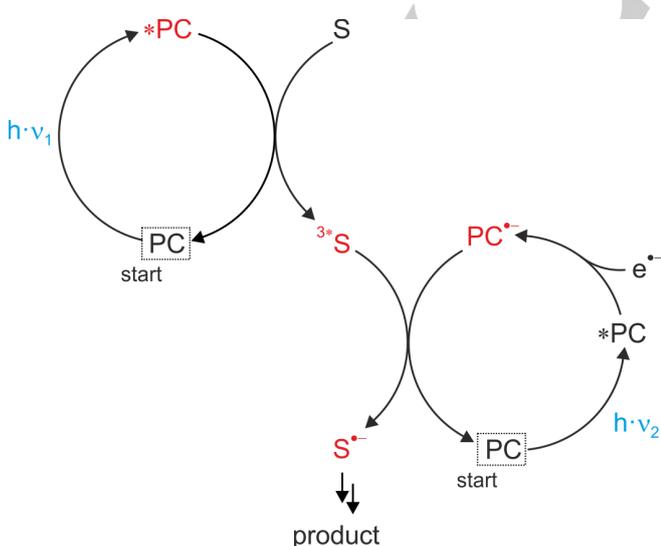


Figure 4. Photo-reduction of triplet-excited substrates. PC = photoactive compound, S = substrate.

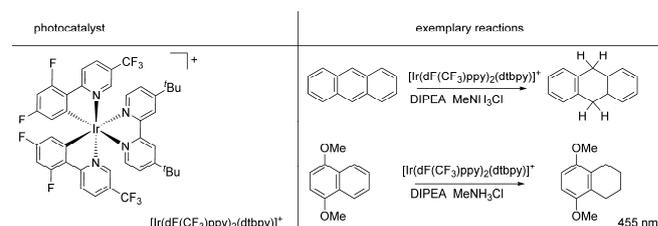
5. A hidden level: Photoreduction of triplet-excited substrates

When the triplet acceptor A in the reductive mechanism of Fig. 3 is no longer a co-catalyst but the substrate, then the mechanism in Fig. 4 can become operative. This concept relies on a split reactivity of the primary photoactive compound: Part of it undergoes TTET after excitation (upper left part of Fig. 4), whereas another fraction of the same *PC is reductively quenched by a sacrificial reagent to form PC^{•-} (lower right), which can then transfer an electron to the triplet-excited substrate. This concept permits unusually challenging reductions because the triplet-excited substrate is a good acceptor (at least when compared to its electronic ground state) and PC^{•-} is a strong donor. Both ^{3*}substrate as well as PC^{•-} can have lifetimes in the range of 10-100 μs,^[18] and this ensures a relatively high probability for bimolecular encounters, comparable to the sensitized triplet-triplet annihilation mechanism (see next section). For optimal performance, the mechanism in Fig. 4 requires a careful balance between TTET and reductive quenching of *PC, and the relative concentrations of substrate and sacrificial reagent are expected to be crucially important.

The concept in Fig. 4 was put forward for Birch-type reductions of aromatic systems such as those in Table 4, relying on an Ir^{III} photocatalyst and DIPEA as sacrificial reagent.^[52] The scope of these photoreductions is defined by the triplet energy and the aromatic stabilization energy of the substrates. Consequently, anthracenes work best; benzene does not react at all, whereas phenanthrenes as well as naphthalenes show good reactivity, some of the latter even converting to tetrahydronaphthalenes (Table 4). PCs with triplet energies much higher than those currently available for d⁶ metal complexes^[53] would be required for activation of benzene via this mechanism.

After formation of the one-electron reduced substrate via the mechanism in Fig. 4, DIPEA^{•+} was thought to act as an H-atom donor to give a carbanion species which is subsequently protonated either by MeNH₂Cl or by iminium ions resulting from DIPEA decomposition. A photochemical E1cB reaction indeed provided evidence for a carbanion intermediate.^[52] Curiously, a change of the DIPEA concentration by a factor of 10 had essentially no influence on the product yield, which is unexpected in the framework of the mechanism of Fig. 4, because of the abovementioned balance between energy and electron transfer quenching of *PC. Under comparable experimental conditions with a closely related tertiary amine reductant, a similar Ir^{III} complex undergoes photo-driven ligand reduction, yielding a highly reducing new Ir species that was the actual photocatalyst in thermodynamically challenging reactions (section 8).^[54]

Table 4. Birch-type photoreductions of aromatic substrates presumed to follow the mechanism of Fig. 4.^[52]



6. A completely different game: Exploitation of sensitized triplet-triplet annihilation upconversion

Triplet-triplet annihilation upconversion (TTA UC) is a mature field [55] that has received considerable attention from photo-physicists and physical-inorganic chemists over the past 15 years,[4, 56] but synthetic applications are yet relatively scarce. An early example is the anthracene dimerization sensitized by visible-light irradiation of $[\text{Ru}(\text{dmb})_3]^{2+}$, whereby singlet-excited (upconverted) anthracene undergoes [4+4] cycloaddition with ground-state anthracene (Table 5, entry 1).[57] That reaction exploits the upconversion product (*i.e.*, the singlet-excited annihilator) directly, whilst several recent studies rely on additional electron transfer steps for photoredox catalysis.

Fig. 5 illustrates one of the key concepts, where PS represents the sensitizer and A the annihilator. Singlet excited states (^1A) formed after bimolecular reaction between two triplet-excited annihilators (^3A) can act as electron donors towards substrates, and A can subsequently be regenerated from A^{*+} by sacrificial electron donors or by reaction intermediates. In comparison to the concept in Fig. 3, weaker electron donors can be used (for example DIPEA in Table 5, entry 5 as opposed to Asc^{2-} in Table 3, entry 1), because the populated singlet state of the annihilator has a higher energy compared to the triplet states. This general concept has been applied for reductive activation of aryl bromides using butane-2,3-dione (BD) as sensitizer and 2,5-diphenyloxazole (PPO) as annihilator (Table 5, entry 2).[58] Excitation of BD with blue light and subsequent TTET yields ^3PPO with a lifetime of 2.3 μs in DMF under N_2 , and triplet-triplet annihilation forms ^1PPO . The latter stores an excitation energy of ca. 3.60 eV and is sufficiently reducing for aryl bromides. After the reductive dehalogenation step, the resulting aryl radical abstracts an H-atom from DMF to result in overall hydrodehalogenation.

Table 5. Sensitizer / annihilator couples and reactions proceeding via sensitized triplet-triplet annihilation upconversion.

entry	sensitizer	annihilator	exemplary reactions
1 ^a			
2 ^b			
3 ^c			
4 ^d			
5 ^e			
6 ^e			
7 ^f			

^a With a cw-laser, incident power 13 mW, ref. [57]; ^b with a pulsed laser (10 Hz, 15 mJ/pulse), ref. [58]; ^c with a 2 W laser, ref. [59]; ^d with a cw-laser, optical output 500 mW, ref. [60]; ^e with laser diodes and LEDs, ref. [61]; ^f with pulsed laser, ref. [62].

A closely related concept was exploited for C-C coupling between aryl halides and *N*-methylpyrrole (Table 5, entry 3), using an organoboron dye (DBP) as sensitizer and 9,10-diphenylanthracene (DPA) as annihilator.[59] In this case, the singlet excited (upconverted) annihilator acts directly as electron donor vis-à-vis the substrate. This is possible because ^1DPA has an oxidation potential of ca. -1.85 V vs. SCE and 4-bromoacetophenone is reduced at -1.81 V vs. SCE.[59] DPA is then regenerated from DPA^{*+} by electron donation from radical intermediates formed in the course of the trapping of aryl radicals with *N*-methylpyrrole, and consequently there is no need for sacrificial reagents. In combination with a Pt^{II} octaethyl porphyrin sensitizer, the DPA annihilator furthermore proved useful for reduction of aryl halides in organic gel matrices (not shown).[63] Following excitation with blue light, the reaction follows a very similar pathway as for the DBP/DPA combo, with DMF serving as H-atom source.

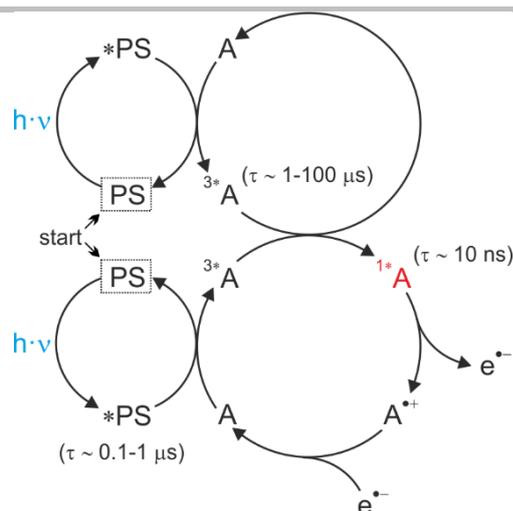


Figure 5. Photoredox catalysis via sensitized triplet-triplet annihilation upconversion. PS = photosensitizer, A = annihilator.

TTA UC is very common in organic solvents but extremely rare in aqueous solution. Recently, we reported the first lab-scale photoreduction based on TTA UC in neat water.^[60] Using $[\text{Ru}(\text{bpy})_3]^{2+}$ in combination with anthracene-9-propionate (APA) and a green cw-laser as excitation source, trichloroacetate degradation was possible under aerobic conditions (Table 5, entry 4). The solubility of O_2 in water is much lower than in typical organic solvents, and hence only a comparatively small fraction of the anthracene annihilator undergoes endoperoxide formation with photogenerated $^1\text{O}_2$. ^1APA has a reduction potential of ca. -2.0 V vs. NHE and reacts with trichloroacetate by a factor of 2.5 faster than $\text{CO}_2^{\cdot-}$.^[64] Conversions up to 43% with turnover numbers reaching 15 were achievable.

Near-infrared (NIR) light penetrates much deeper through many media (including biological tissue) than visible radiation, and this makes NIR-to-visible upconversion particularly attractive. Sensitizers with energetically low-lying yet sufficiently long-lived triplet excited states are required for this purpose, a combination of properties that limits the possible choices rather drastically. A Pd^{II} octabutoxy-phthalocyanine (PdPc) sensitizer (Table 5, entry 5) absorbs red light at 730 nm, and in combination with a furanyldiketopyrrolopyrrole (FDPP) TTA UC to the green spectral range is possible.^[61] In the presence of Eosin Y as photoredox catalyst, several types of photoredox reactions including hydrodehalogenation (Table 5, entry 5) and amine oxidation, can thus be driven with red photons. A power output of the red light source 1000 times weaker than that of a blue irradiation source was sufficient to obtain comparable yields for hydrodebromination, and this was attributed to the increased penetration depth into the reaction vessel, making the effectively illuminated volume greater for red light.^[61]

Using the combination of a Pt^{II} tetraphenyltetranaphthoporphyrin (PtTPTNP) and a *tert*-butylated perylene (TTBP), photoredox reactions without additional catalyst become possible (Table 5, entry 6).^[61] In this case, the singlet excited annihilator directly promotes the cyclization of a dienyli azide to a pyrrole. Furthermore, the polymerization of methyl methacrylate can be initiated via C-Br bond reduction using this system.

Performing photoisomerization reactions by TTA UC represents an uncommon approach to reactions that normally require UV or blue light. The PdPh_4TBP complex (Table 5, entry 7) sensitizes

triplet excitation of the Pery-RPIC moiety, which is integrated into a photochromic phenoxy-imidazolyl unit, and TTA UC with red light triggers the formation of a colored biradical.^[62] Concepts like this should in principle be usable to activate catalysts.

Pd^{II} and Pt^{II} complexes such as those included in Table 5 (entries 5-7) are typical red-light absorbers which are frequently used for TTA UC.^[4] Os^{II} polypyridines represent another attractive option which allow direct excitation into $^3\text{MLCT}$ states,^[65] and this can minimize the energy loss associated with TTA UC and maximize achievable anti-Stokes shifts. Applications of such Os, Pd, or Pt sensitizers in hydrogels are of significant interest in the context of biological applications.^[65-66] Near-infrared excitation of lanthanide doped fluoride or oxide nanoparticles represents another potentially interesting avenue. This concept has been applied for example to the NIR-driven release of caged compounds^[67] and could become interesting for photoredox catalysis.^[68]

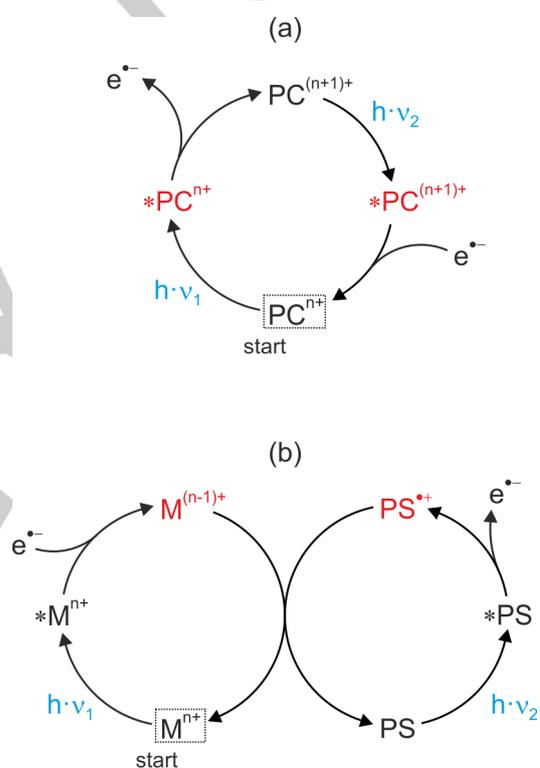


Figure 6. (a) Photocatalyst regeneration via (a) secondary excitation and (b) with an auxiliary photosensitizer. PC = photoactive compound, M^{n+} = metal-based photocatalyst, PS = auxiliary photosensitizer.

7. Restart again: Photocatalyst regeneration via secondary excitation

In most photoredox processes, the resting state of the photocatalyst is reestablished in a thermal manner, requiring no further light input after the photoreaction. For instance, in the mechanism of Fig. 1, PC is regenerated from PC^{2+} with a sacrificial electron donor in a spontaneous reaction. However, this is not always possible, and there exist cases in which a photoreaction produces a form of the catalyst that requires a secondary light-driven step to regenerate the initial PC species. This concept is illustrated by Fig. 6a, in which the initially excited catalyst ($^*\text{PC}^{n+}$) acts as photoreductant, leading to the formation of $\text{PC}^{(n+1)+}$. Excitation of the later forms the photooxidant

*PC⁽ⁿ⁺¹⁾⁺, which is then reduced back to PCⁿ⁺. Such reactivity is mostly relevant for d- and f-metal complexes in which different oxidation states are readily accessible, and which can react via inner-sphere electron transfer processes with ligated substrates. The need for catalytic species with photoactive excited states in two different oxidation states is a key limitation in this concept. By contrast to the mechanism of Fig. 2, where the photoactive compound (PC) is reductively quenched followed by subsequent re-excitation to form a powerful photoreductant, in the case of Fig. 6a an oxidative cycle is operative. An organic catalyst for which this mechanism was reported had to rely on anionic SDS micelles to stabilize the radical cation of the catalyst (not shown).^[69] Interestingly, SDS had a dual function in this example, because it served as electron donor as well.

Spectroscopic investigations show that the mechanism of Fig. 6a is applicable to the photoionization of [Ru(bpy)₃]²⁺ coupled to photochemically induced water oxidation.^[70] Near-UV excitation at 308 and 355 nm induces electron detachment from ³MLCT-excited [Ru(bpy)₃]²⁺ in water, forming hydrated electrons and [Ru(bpy)₃]³⁺. Two-pulse experiments demonstrate that the latter converts back to [Ru(bpy)₃]²⁺ (either in its ³MLCT or its ground state) under UV excitation. That photoreduction of [Ru(bpy)₃]³⁺ occurs with a quantum yield of 0.023 at 355 nm and liberates hydroxyl radicals as confirmed by scavenging experiments.^[70b]

Table 6. Photocatalysts and reactions for which the mechanisms in Fig. 6a (entries 1 & 2)^[71] and in Fig. 6b (entry 3) are relevant.^[72]

entry	photocatalyst	auxiliary photosensitizer	exemplary reactions
1 ^a		N/A	
2 ^b		N/A	
3 ^c	$Cl_n-Ce^{IV}-O_R$		

^a ref. ^[71a], ^b ref. ^[71b], ^c ref. ^[72].

In preparative-scale photoredox catalysis, a variant of the mechanism in Fig. 6a was discussed to account for the UV-A-driven Miyaura Borylation of haloarenes by [CeCl₆]³⁻ (Table 6, entry 1).^[71a] In its lowest 4f-5d excited state, the hexachlorocerate(III) anion has an oxidation potential of ca. -3.0 V vs. SCE which is sufficient for reductive dehalogenation of many aryl chlorides,^[73] and the resulting aryl radicals react with bis(pinacolato)diboron (B₂pin₂). Reaction quantum yield studies point to a radical chain mechanism, but no product was formed in the dark periods of an experiment in which photo-irradiation occurred only intermittently. Consequently, a light-dependent process converting [CeCl₆]²⁻ back to [CeCl₆]³⁻ was discussed. LMCT excitation of the cerium(IV) complex seems plausible, and release of Cl[•] from that excited state followed by coordination of Cl⁻ (present in excess in the reaction mixture) is thought to regenerate [CeCl₆]³⁻.^[71a]

Recent work showed that perylenes (Pyr) have multiple stable redox states, and the concept in Fig. 6a was invoked to explain thermodynamically challenging photoreductions such as the

reductive cleavage of *N*-tosyl groups (Table 6, entry 2).^[71b] The neutral Pyr compound was thought to act as excited-state reductant, and its one-electron oxidized form (which has a similar extinction coefficient as neutral Pyr at the excitation wavelength of 394 nm) was considered as excited state oxidant. Detailed mechanistic studies were relegated to later investigations, but thermodynamic analysis of the mechanism suggested in ref. ^[71b] substantiates its feasibility. Evidently, thermodynamics always need to be considered before a mechanism is proposed.^[47] On the other hand, observable peak potentials for irreversible redox events should only be used with caution. Moreover, redox potentials are sensitive to the actual experimental conditions, and the latter can be very different in electrochemical and photoredox experiments.^[47c]

In the mechanism of Fig. 6a, a single compound is photoactive in two different excited states, but this is a comparatively rare occurrence. An alternative light-driven pathway to restoring the photocatalyst involves the use of an auxiliary photosensitizer, which provides the necessary driving-force when spontaneous photocatalyst regeneration is not possible. In the concept of Fig. 6b, the photocatalyst is a metal complex that acts as oxidant upon excitation, and in a parallel process a photosensitizer (PS) acts as excited-state reductant. Thermal electron transfer from the reduced metal complex (M⁽ⁿ⁻¹⁾⁺) to the oxidized photosensitizer (PS^{•+}) subsequently regenerates the resting state of the overall system. This concept resembles the Z-scheme of natural photosynthesis more closely than most of the abovementioned two-photon excitation strategies,^[32] because it relies on two distinct chromophores, not just on the same chromophore in different redox states.^[74]

In organic photoredox catalysis, the mechanism of Fig. 6b was put forward to account for the cerium and DPA co-catalyzed reaction between cycloalkanols and alkenes to form bridged lactones (Table 6, entry 3).^[72] The cerium source is CeCl₃ and excess chloride was used, presumably because this favors the formation of [CeCl₆]³⁻ (M⁽ⁿ⁻¹⁾⁺ in Fig. 6b) instead of [Ce₂Cl₉]³⁻.^[73] DPA^{•+} (corresponding to PS^{•+} in Fig. 6b), generated via photo-oxidation of DPA, is able to oxidize the Ce^{III} to Ce^{IV}, and cycloalkanols can ligate to the latter under deprotonation.^[72] Excitation into the LMCT absorption band of the resulting Ce^{IV} alkoxide complex (Mⁿ⁺ in Fig. 6b) reinstates the Ce^{III} oxidation state and liberates an alkoxy radical. The latter reacts onwards via β-scission, radical cross coupling with an electron deficient alkene, and ultimately leads to the bridged lactone product (Table 6, entry 3, bottom). Of key importance is the fact that DPA^{•+} is thermodynamically competent for the oxidation of Ce^{III} to Ce^{IV}. The electron released from DPA after photoexcitation reduces a radical intermediate into an anionic species that is subsequently protonated, and addition of an exogenous oxidant is not necessary.

8. Unexpected boost: Photochemical photocatalyst to photocatalyst conversion

Long-term irradiation of reaction mixtures in photochemistry can lead to catalyst degradation or its conversion into a new species with drastically altered properties. The photo-degradation of molecular Pd^{II} complexes, sometimes considered active for photochemical H₂ production, into colloidal palladium is an example illustrating this aspect.^[75] Organic photoredox chemistry faces similar challenges,^[76] and the question regarding the identity of the catalytically active species is often not trivial.

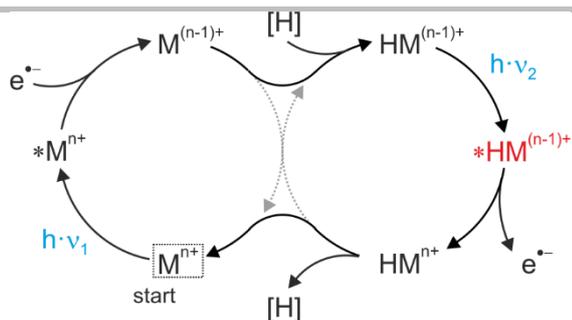
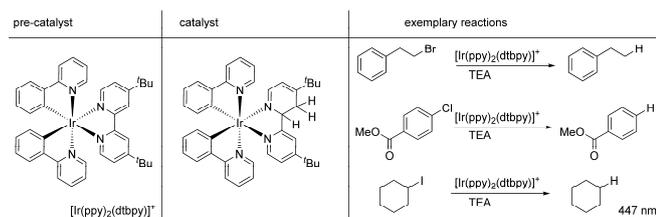


Figure 7. Photochemical pre-catalyst to photocatalyst conversion.

The concept in Fig. 7 illustrates a possible scenario under reducing conditions, particularly in presence of tertiary amine reductants that can furthermore act as H-atom donors. In this case, initial reductive excited-state quenching (generating $M^{(n-1)+}$ from $*M^{n+}$) may be followed by spontaneous H-atom transfer from an amine radical cation. Photo-irradiation of the resulting two-electron reduced species yields a more potent excited-state donor ($*HM^{(n-1)+}$) than excitation of the initially present M^{n+} .

Table 7. A case of photochemical conversion of a pre-catalyst to a photocatalyst according to the mechanism in Fig. 7.^[54]



The mechanism in Fig. 7 is relevant for the hydrodehalogenation of aryl and alkyl halides (Table 7).^[54] Irradiation of $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]^+$ (Table 7, left) in the presence of TEA leads to the formation of a new green emitting Ir species. Based on MS and NMR experiments the latter was identified as a complex in which the dtbbpy ancillary ligand is partially dearomatized with a saturated C-C bond on one of the pyridine units (Table 7, middle). The excited-state oxidation potential of this reduced species (-1.7 V vs. SCE), corresponding to $\text{HM}^{(n-1)+}$ in Fig. 7, is significantly more negative than that of the initially present (photoexcited) $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]^+$ complex (-1.15 V vs. SCE). Thus, in the presence of reductive quenchers that are also H-atom donors,^[77] the partially dearomatized complex was considered the catalytically active species for the thermodynamically challenging substrate activations. A related concept had been discussed earlier for photochemical CO_2 reduction with an Ir photocatalyst.^[78]

9. Kinetic aspects and pertinent methods in multi-photon excitation

Photoredox catalysis commonly relies on short-lived excited states and radical intermediates, but multi-photon excitation processes can get kinetically particularly delicate. For instance, the mechanism in Fig. 2 involves one-electron reduced species (PC^*) that can be stable for minutes in their electronic ground state,^[79] but this situation drastically changes upon further

photoexcitation producing $*\text{PC}^*$, and if these are organic radical ions, then very short excited-state lifetimes are expected.^[25] Similarly short lifetimes may be associated with $*\text{PC}^{(n+1)+}$ in the mechanism of Fig. 6a. Furthermore, the mechanisms in Fig. 4 and Fig. 5 rely on the encounter between two unstable species, and the former even involves a delicate balance between energy and electron transfer reactivity of $*\text{PC}$. Thus, kinetic aspects play a key role in multi-photon excitation processes, and these depend of course on the individual characteristics of a given photochemical system. Nevertheless, some general considerations can be made.

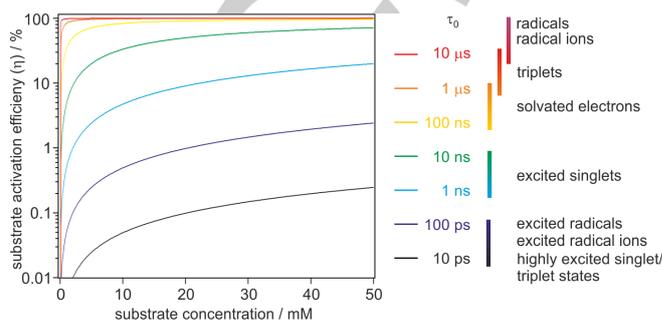


Figure 8. Competition between a diffusion-controlled photochemical reaction and inherent deactivation for species with different natural lifetimes according to eq. 1.

For any given electronically excited or radical species, its deactivation by a combination of radiative and nonradiative relaxation processes (or radical recombinations) competes with possible substrate-activation reactions. In the simplest bimolecular case, the rate of the latter is the multiplication product of the rate constant for the reaction (k_Q in units of $\text{M}^{-1} \text{s}^{-1}$) times the concentration of the substrate $[\text{Q}]$. The rate of inherent excited-state decay by luminescence and nonradiative processes simply corresponds to the inverse of the natural lifetime ($k_0 = \tau_0^{-1}$).^[18] The ratio η between the natural decay rate (assuming first-order kinetics as approximation) and the total decay rate in the presence of a substrate as quencher (eq. 1) is a measure for the probability of a reactive species to undergo a chemical reaction.

$$\eta = \frac{k_Q \cdot [\text{Q}]}{k_0 + k_Q \cdot [\text{Q}]} = \frac{\tau_0 - \tau}{\tau_0} \quad (\text{eq. 1})$$

Experimentally, η can be determined by comparing the lifetime τ of the reacting species in presence of a given substrate concentration with its natural lifetime τ_0 . Fig. 8 contains a semi-logarithmic plot of η versus substrate concentration for excited states and radicals with natural lifetimes ranging from 10 ps to 10 μs and diffusion-controlled reaction rates ($k_Q = 5 \cdot 10^9 \text{ M}^{-1} \text{ s}^{-1}$). As is evident from the purple line in Fig. 8, even in the favorable case of diffusion-controlled photochemical reaction in a typical organic solvent, an excited state with a natural lifetime τ_0 of 100 ps has merely a 2 in 100 probability to undergo photochemistry when the substrate is present at 50 mM concentration. This implies long reaction times even if we optimistically assume both a high formation quantum yield of the precursor of that excited state (e.g., a T_1 state or a radical anion as in sections 2 and 3) and a very long lifetime for this precursor. Natural lifetimes of the reacting species on the order of 1 ns or longer are needed

for decent substrate activation efficiencies, and only lifetimes in the range of 0.1 μs or longer permit the use of low substrate concentrations to maintain high photochemical reaction efficiencies. As noted above, the discussion here is valid for diffusion-controlled reactions. In instances in which there is pre-association between the photocatalyst and the substrate, photochemical reactions can potentially be very efficient despite very short excited-state lifetimes.^[27, 35]

It is tempting to argue that photons are cheap and low η values can be counteracted by increasing the intensity and/or the duration of the photo-irradiation, but this is delicate in view of possible (catalyst) photo-degradation. As noted in the sections above, in selected cases there was clear evidence for the conversion of catalysts into other catalytically active species,^[32, 54, 75a, 78] and this may be a more frequent phenomenon than one might commonly think.

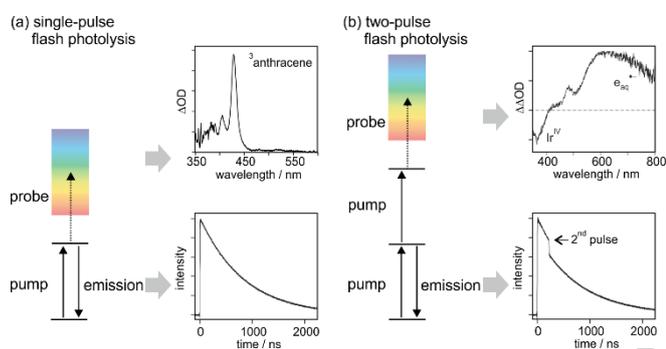


Figure 9. One- and two-pulse laser flash photolysis for direct observation of reaction intermediates.

General methods for mechanistic studies in photocatalysis have been reviewed recently,^[80] and therefore we focus here exclusively on techniques that are particularly relevant for photoredox catalysis involving multi-photon excitation. The most direct and informative way of elucidating a photochemical mechanism is to detect reaction intermediates by time-resolved methods such as transient absorption spectroscopy, and to identify the species causing the observable spectroscopic signatures by a complementary technique such as spectro-electrochemistry. Ordinary single-pulse flash photolysis (Fig. 9a) is ideally suited for investigation of photophysical and photochemical processes that typically occur after the absorption of single photons. Key observables are the UV-Vis spectral changes occurring after photoexcitation, resulting in transient difference spectra that essentially represent a subtraction of absorption spectra recorded before and after the excitation laser pulses (upper right of Fig. 9a). The temporal evolution of transient absorption signals or the luminescence decay of the initiating species (lower right of Fig. 9a) provide direct kinetic and mechanistic information. For investigation of photochemical processes involving the consecutive absorption of two photons, two-pulse flash photolysis is the most insightful technique (Fig. 9b). In this case, one obtains a difference of difference spectra (upper right of Fig. 9b), which isolates the influence of the second laser pulse on the transient spectrum. For this purpose, the instrument measures the UV-Vis spectra before the first pulse, after the first pulse and after the second pulse. The inter-pulse delay becomes an important experimental parameter, which needs to be adapted to the lifetime of the primary excited state and to the kinetics of eventual

photochemical onward reactions that need to be completed before secondary excitation. Different excitation wavelengths may be required for selective excitation of individual species. For instance, it is advantageous when the secondary laser pulse exclusively excites the photoproduct formed with the first laser pulse.^[12] Monitoring the quasi-instantaneous depletion of luminescence produced by the secondary excitation pulse (lower right of Fig. 9b) can be helpful to gain quantitative insight into the efficiency of the secondary excitation process. However, the main point is to identify the spectral signatures of the species whose formation requires both excitation pulses.

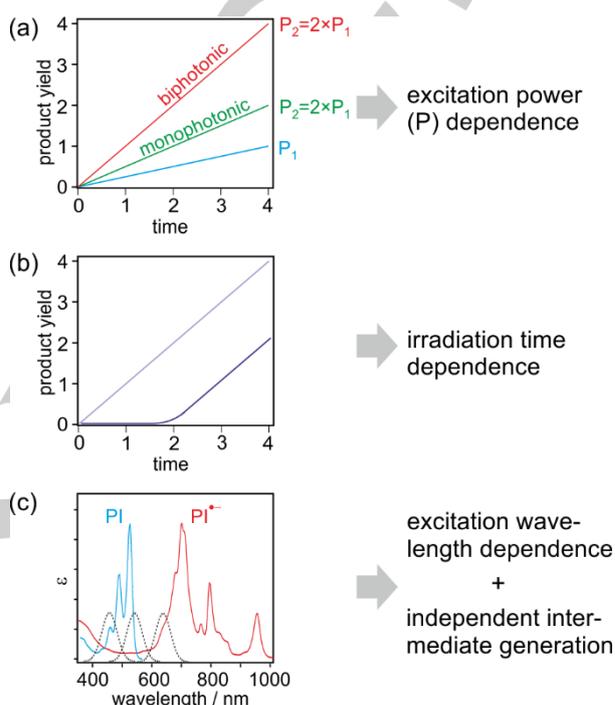


Figure 10. Simpler methods for mechanistic studies not requiring spectroscopic equipment with high temporal resolution. The dotted lines in (c) mark typical outputs of blue, green and red LEDs.

To our knowledge, there are currently no commercial instruments available for two-pulse laser flash photolysis. We use a commercial transient absorption spectrometer, equipped with beam expanding optics ensuring optimal overlap between pump and probe pulses, and two nanosecond lasers along with a delay generator to control synchronization of the lasers and the detection system.^[12-13, 60] This setup permits quantitative two-pulse two-color experiments (one Nd:YAG laser is equipped with an OPO, the other is frequency-doubled).^[81] When radical ions and their electronically excited states are of interest, the first laser pulse might well be replaced by pulse radiolysis.^[3h, 82] In some cases, transient infrared spectroscopy can be much better suited than UV-Vis detection, because IR signatures can be more diagnostic, allowing better discrimination between photoproducts resulting from single and double excitation.^[83] Mechanistic insight into photoredox reactions that rely on multi-photon excitation can also be gained with simpler methods. For instance, the dependence of product yield on excitation power (P) is a relatively straightforward experiment (Fig. 10a). In the initial phase of a biphotonic reaction, the product yield is expected to show a quadratic dependence on P.^[12, 51-52, 84] Thus, doubling the excitation power from P_1 to $P_2 = 2 \cdot P_1$ will not simply

result in a doubled yield as for monophotonic reactions (green line in Fig. 10a), but instead one expects a four-fold increase of the yield for a biphotonic reaction (red line in Fig. 10a). Quantification of product accumulation as a function of continuous irradiation time (over seconds or minutes) can provide information about so-called induction phases, which are initial periods during which no photochemical product is yet accumulated (light purple trace in Fig. 10b). During this time, pre-catalysts can be converted to the real catalysts in a light-dependent process.^[32, 75a] Lastly, the efficiency of photoproduct formation is expected to be wavelength dependent (Fig. 10c).^[85] The photo-action spectrum monitoring the amount of product accumulation as a function of irradiation wavelength should reflect the absorption spectra of the individual species that absorb in a given catalytic cycle. For example, in the mechanism of Fig. 2, that photo-action spectrum should essentially reflect the multiplication product of the absorption spectra of PC and PC^{*}. However, since the first photon is usually much more productively used than the second, both absorption spectra need weighting factors that reflect the relative quantum yields, e.g., in ref. ^[26a] the quantum yield for PC^{*} generation with a first photon is about 40 times higher than that of the PC^{*} ionization with the second photon. Hence, in a consecutive mechanism, overlap between the emission spectrum of the light source (dotted lines in Fig. 10c) with the species absorption the second photon is always more important. Recording a photo-action spectrum is a somewhat laborious experiment, which might become easier in the future with wavelength tunable LEDs and on-line photoproduct detection.^[34]

Electrochemical generation of radical anions or cations and their subsequent photo-excitation can turn a biphotonic process into a monophotonic reaction, because the formation of these radicals no longer requires light input.^[25c, 86] Under suitable conditions, high concentrations of radical ions can be generated by electrolysis, and the photophysical and photochemical processes following their excitation can be explored directly. Such experiments can provide valuable complementary information to multi-photon excitation studies. Electrophotocatalytic studies for preparative-scale reactions under the combined action of an electrochemical potential and visible light are now gaining increased attention.^[40b, 87]

The benchtop methods in Fig. 10 are applicable under the conditions of the actual photoredox catalysis, whereas the laser techniques in Fig. 9 usually require more dilute solutions and monitor processes on much shorter timescales under pulsed irradiation with high peak powers. The observation time window in the continuous irradiation approaches in Fig. 10 is typically up to 10 orders of magnitude longer than the timescale of the laser experiments in Fig. 9, and the latter usually fail to provide information concerning changes of the photochemical system over long irradiation times.^[23c] This can be a concern for example when sacrificial reagents undergo secondary chemistry after initial photoreactions, or when photocatalysts decompose or convert into other catalytically active species. As noted recently, spectroscopic or electrochemical investigations on complex photochemical mechanisms should always be analyzed with caution, because they are frequently carried out under conditions differing significantly from those used for synthetic reactions.^[47c]

10. Concluding remarks and outlook

Multi-photon excitation processes were first brought into play for preparative-scale photoredox catalysis ca. 5 years ago, and our review illustrates how much progress has been made in this field since then. Many advances were possible through empirical studies but important mechanistic questions linger. The tools for exploration of mechanisms are available (section 9) but need to be used more systematically if the field is to make further rational advance.

A multitude of mechanistic concepts has been developed already, and some of them are understood much better than others. For instance, photoredox catalysis based on sensitized triplet-triplet annihilation upconversion (section 6) can build on the solid foundation laid by prior spectroscopic studies, and this should readily enable further applications in synthetic chemistry. On the other hand, concepts such as the parallel energy and electron transfer reactivity of photocatalysts in the same reaction system (section 5) are underexplored, but are likely to have significant synthetic potential. Yet other concepts, for example the more classical consecutive two-photon absorption processes of sections 2 & 3 were thoroughly explored by physical chemists, but currently there seems to be a disconnect between these earlier spectroscopic studies and new preparative-scale photoredox studies. This has led to several controversies, and the field would likely benefit from more collaborative efforts. Additional synergies could emerge from closer interaction between researchers exploring photoinduced multi-electron transfer and light-driven charge accumulation on the one hand,^[83a, 83b, 88] and investigators studying multi-photon excitation in photoredox catalysis on the other hand, because these fields share significant common ground. Ultimately, sustainable progress will depend on both the creativity of screening-like research and the thorough understanding of all elementary reaction steps leading from an electronically excited state to a stable product.^[89] The field of proton-coupled electron transfer (PCET) could serve as a role model, which illustrated how deep fundamental insight and the development of generally applicable concepts ^[90] can fertilize synthetic advances in organic photoredox chemistry.^[91]

Many synthetic applications of multi-photon excitation based photoredox catalysis have been developed for reductive transformations but comparatively little work has been reported for oxidations.^[92] Most of the concepts discussed above are readily adaptable to oxidative transformations, and a study discussing an oxidative equivalent of the concept from section 3 appeared recently.^[93] Possible issues with degradation of radical cation intermediates and their excited-state lifetimes similar to those discussed for radical anions in reductions (sections 3 & 9) as well as with photocatalyst stability (section 8) will have to be considered thoroughly under oxidizing conditions.

Multi-photon excitation processes provide access to thermodynamically very demanding photoredox reactions with low-energy photons, though they require higher photon fluxes (section 9) and comparatively long-lived intermediates for transient storage of energy. Despite recent breakthroughs in the LED technology, it is currently still challenging to generate LED emission below 300 nm,^[94] and UV-A LEDs are usually only very weakly emissive compared to their visible counterparts, which are far less accompanied by health and safety issues than UV light sources. Owing to additional disadvantages of UV light such as the above-mentioned filter effects and selectivity problems, multi-photon processes relying on visible light will likely remain attractive even in view of future UV LED developments.

The limits in terms optimizing the redox power and minimizing the photon energy are not reached yet. In solvents that are not readily reducible, visible-light generated solvated electrons are attractive reagents with lifetimes in the 100 ns to μ s range. Long explored by pulse radiolysis and later with pulsed laser methods, the hydrated electron only recently made the important step into the reaction flask for lab-scale photoredox catalysis under continuous irradiation.^[12, 44] In terms of minimizing the photon energy, the field might benefit from the development of new near-infrared absorbers with long-lived (triplet) excited states,^[95] complementing the well-known Pd^{II}, Pt^{II} and Os^{II} families of complexes which are currently popular.

Multi-photon excitation-based photoredox catalysis is not necessarily restricted to homogenous solutions, but can instead also occur with suspended nanoparticles, as the example of photocatalytic nitrobenzene to aniline reduction by six-fold consecutive PCET on CdS quantum dots illustrates.^[96] The idea of exploiting lanthanide based upconversion materials such as Er³⁺ and Yb³⁺ co-doped NaYF₄ and alike seems attractive,^[68] because this would permit near-infrared excitation, and multiple excited states with long lifetimes can be expected.^[97]

An emerging field in multi-photon chemistry is the use of a catalyst at different stages of a chemical transformation to perform two-photon driven cascade reactions. Substrates and intermediates are converted via triplet energy transfer sequences,^[98] two light-induced electron transfer steps,^[99] or a combination of both elementary photochemical steps.^[100] Consecutive two-photon excitation is potentially useful to control the outcome of reactions,^[98b, 100-101] using for example the excitation wavelength^[19] or the irradiation power^[13] as control parameters. Furthermore, combinations of some of the concepts discussed in sections 2 – 6 could eventually even permit triphotonic processes though this will require particularly careful design of the photochemical system. Clearly, multi-photon excitation in photoredox catalysis is an intellectually stimulating field at the interface of physical-inorganic chemistry, spectroscopy, and organic chemistry. There is a good chance that future major developments in photoredox catalysis will continue to follow the recent trend of relying on multi-photon excitation.

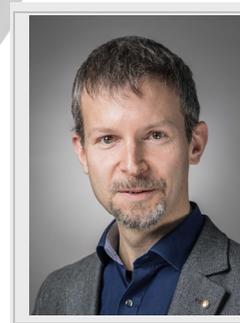
Felix Glaser, born in 1994, studied chemistry at the University of Basel (Switzerland). He received his MSc degree under the supervision of Oliver S. Wenger in 2018 working on light-driven reactions involving challenging reduction steps. In the same year he started his doctoral studies in the same group, where he is currently focusing on reactivity control for photochemical reactions as well as on dual photocatalysis.



Christoph Kerzig, born in 1987, studied chemistry at the University of Halle (Germany), where he obtained his PhD degree under the supervision of Martin Goez in 2017. He then joined the group of Oliver S. Wenger at the University of Basel (Switzerland) with a Leopoldina postdoc fellowship. During his research stay in Basel, he was also a visiting scientist in Gothenburg (Sweden) working on upconversion with Karl Börjesson. His research focuses on mechanistic photochemistry, optical spectroscopy and multi-photon chemistry.



Oliver S. Wenger received a Ph. D. degree from the University of Berne in 2002 after work with Hans U. Güdel. Postdoctoral stays at Caltech with Harry B. Gray (2002-2004) and at University of Strasbourg with Jean-Pierre Sauvage (2004-2006) were followed by an assistant professorship at University of Geneva. In 2009, the Wenger group moved to Georg-August-Universität Göttingen, and in 2012 returned to Switzerland to join the University of Basel.



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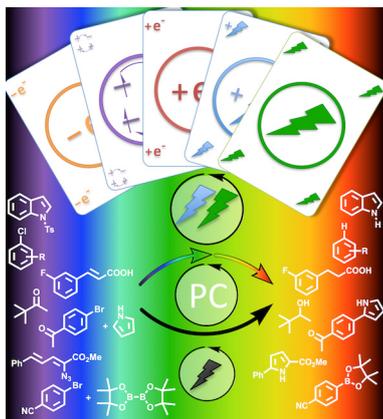
Keywords: photocatalysis • photochemistry • electron transfer • energy transfer • redox chemistry

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Two are better than one: By combining the input from two low energy photons, thermodynamically very challenging reactions can be driven. Empirical advances combined with insights from spectroscopy have made multi-photon excitation processes amenable to preparative-scale photoredox chemistry. A critical look at currently developed concepts and reactions identifies challenges, pitfalls and opportunities for future research in this emerging area at the interface of physical-inorganic chemistry, spectroscopy, and synthetic organic chemistry.

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