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Photocatalysis: A Green Tool for Redox Reactions

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Abstract

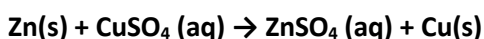
Reduction-and-oxidation (redox) reactions are one of the most utilized approaches for the synthesis of value-added compounds. With the growing awareness of green chemistry, researchers have searched for new and sustainable pathways for performing redox reactions. From this, a new field has gained tremendous attention, namely photoredox catalysis. Here, molecules can be easily oxidized or reduced with the use of one of Nature's biggest resources: visible light. This tutorial paper gives the basics of photoredox catalysis along with limited examples to encourage further research in this blooming research area.

1 Introduction

Due to climate change, energy shortage, and increased amounts of pollution, a new area in chemistry has risen to cope with these problems: green or sustainable chemistry.¹ The development of green chemistry has been linked to a new environmental problem-solving strategy, namely the prevention of pollution through innovative strategies and the design of new technologies that deal with post-reaction pollution. Nowadays, sustainable chemistry is a widely discussed field in chemical synthesis as the chemical industry favors environmentally friendly pathways to reduce pollution and energy consumption. Quantifying the greenness of chemical processes can be done by measuring such variables as the yield, prices of reactants, atom efficiency, catalytic or stoichiometric amounts used, and the energy profile.² Given these variables, photoredox catalysis is an interesting field in green chemistry because it combines the advantages of catalysis and the use of a renewable energy source. As this field is relatively new, this tutorial paper aims to provide basic knowledge on photoredox catalysis.

2 Redox Chemistry

A reduction–oxidation reaction (redox process) is a chemical reaction in which electrons are exchanged between chemical species. Characteristic of this type of reaction is a change in the oxidation state of the atoms. Usually, these reactions involve a reducing agent and an oxidizing agent. The reducing agent undergoes oxidation (is oxidized) and loses electrons, while the oxidizing agent undergoes reduction (is reduced) and gains electrons. In other words, the oxidation process is linked to the loss of electrons or an increase in the oxidation state, whereas the reduction process is linked to the gain of electrons or a decrease in the oxidation state. The oxidation number (also called oxidation state) gives an indication of the number of electrons surrounding the atom. When an atom is reduced in a redox reaction, the atom gains electrons causing its oxidation number to increase by one or more. A general example of a redox reaction is given in Equation 1.



Equation 1 Redox reaction of zinc with copper(II) sulphate, where zinc is oxidized, and copper is reduced.

The term 'oxidation' comes from the reaction with molecular oxygen (dioxygen, O₂) to form oxides because oxygen was the first known oxidizing agent.³ Besides oxygen, other chemicals can also act as oxidizing agents, so the term was expanded to include all chemicals that promote oxidations. In the case of reduction, the term originates from the mass lost upon heating metallic ores to extract the metal.³ Later, Antoine Lavoisier proved that the mass loss originates from the loss of oxygen as a gas.³ In the literature, the terms 'reduction' and 'hydrogenation' are frequently interchanged, because hydrogen is the reducing agent in many reduction reactions.

Chemists often split redox reactions into two half-reactions.⁴ These give an indication of what happens in the oxidation on the one hand, and what happens in the reduction on the other hand. If these two half-reactions are combined, the complete redox reaction is obtained.⁵ Half-reactions form a useful tool in tables of standard reduction potentials (e.g., Table 1).⁶ The standard reduction potential indicates how easily a reduction reaction proceeds (how easily electrons are taken up).⁷ The value zero was arbitrarily assigned to the reaction of two hydrogen ions with two electrons to form hydrogen gas. High values indicate an easy reduction (easy gain of electrons), whereas low values indicate an easy oxidation (easy loss of electrons).⁷ In general, a substance will reduce another substance if its standard reduction potential is more negative than the standard reduction potential of the other substance. Conversely, a substance will oxidize another substance if its standard reduction potential is more positive than the standard reduction potential of the other substance.

Table 1 Common standard reduction potentials.

Half reaction	Reduction potential (V)
$\text{F}_2(\text{g}) + 2\text{e}^- \rightarrow 2\text{F}^-(\text{aq})$	2.87
$\text{O}_2(\text{g}) + 4\text{H}^+ + 4\text{e}^- \rightarrow 2\text{H}_2\text{O}(\text{l})$	1.23
$\text{Cu}^+(\text{aq}) + \text{e}^- \rightarrow \text{Cu}(\text{s})$	0.52
$2\text{H}^+(\text{aq}) + 2\text{e}^- \rightarrow \text{H}_2(\text{g})$	0.00
$\text{Fe}^{2+}(\text{aq}) + 2\text{e}^- \rightarrow \text{Fe}(\text{s})$	-0.45
$2\text{H}_2\text{O}(\text{l}) + 2\text{e}^- \rightarrow \text{H}_2(\text{g}) + 2\text{OH}^-(\text{aq})$	-0.83
$\text{Li}^+(\text{aq}) + \text{e}^- \rightarrow \text{Li}(\text{s})$	-3.04

Redox reactions have multiple applications, for example in metallurgy,⁸ and even occur in nature, for example in photosynthesis.⁹ Moreover, in organic synthetic chemistry, many reactions involve oxidation and/or reduction, and these are all classed as organic redox reactions. However, these reactions are different from classical redox reactions, because many do not actually involve electron transfer.¹⁰ In fact, other criteria are used, such as the gain of oxygen and/or the loss of hydrogen in an organic oxidation reaction, or the reduction in electron density of a molecule when it is oxidized.¹¹ Nevertheless, some organic redox reactions include one-electron transfer mechanisms, such as the Birch reduction.¹²

When talking about organic redox reactions, a small group of functional-group transformations are frequently referred to.¹⁰ This is usually exemplified by the methane (CH₄, **1**) to carbon dioxide (CO₂, **2**) series. Ordering the functional groups from the most reduced state to the most oxidized state is possible by comparing the number of hydrogen atoms bound to the carbon atom. Because hydrogen is less electronegative than oxygen, the transformation from CH₄ to CO₂ is associated with a loss of electron density at the carbon atom, and a loss of electrons is associated with oxidation. Therefore,

CH₄ is the most reduced molecule in the series, whereas CO₂ is the most oxidized molecule in the series. However, other functional groups can be used to give indications of the oxidation state.¹⁰ Table 2 shows the most common simple functional groups for an explanation of the oxidation state of the carbon atom.

Table 2 Simple functional groups listed according to the oxidation state.

-IV	-II	0	+II	+IV
	$\begin{array}{c} \text{OH} \\ \\ \text{H}-\text{C}-\text{H} \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{H}-\text{C}-\text{H} \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{H}-\text{C}-\text{OH} \end{array}$	$\begin{array}{c} \text{O}=\text{C}=\text{O} \\ 2 \end{array}$
$\begin{array}{c} \text{H} \\ \\ \text{H}-\text{C}-\text{H} \\ \\ \text{H} \\ 1 \end{array}$	$\begin{array}{c} \text{Cl} \\ \\ \text{H}-\text{C}-\text{H} \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{Cl} \\ \\ \text{H}-\text{C}-\text{Cl} \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{Cl} \\ \\ \text{Cl}-\text{C}-\text{Cl} \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{Cl} \\ \\ \text{Cl}-\text{C}-\text{Cl} \\ \\ \text{Cl} \\ 3 \end{array}$
	$\begin{array}{c} \text{H} \\ \\ \text{H}-\text{C}-\text{NH}_2 \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{OH} \\ \\ \text{H}-\text{C}-\text{NH}_2 \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{H}-\text{C}-\text{NH}_2 \\ 4 \end{array}$	
$\begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ \text{H}-\text{C}-\text{C}-\text{H} \\ \quad \\ \text{H} \quad \text{H} \\ 5 \end{array}$	$\begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ \text{H}-\text{C}=\text{C} \\ \quad \\ \text{H} \quad \text{H} \end{array}$	$\text{H}-\text{C}\equiv\text{C}-\text{H} \\ 6 \end{array}$		

Organic redox reactions are often classified into other organic reaction classes. The most common include organic redox reactions involving a nucleophilic attack, which are usually classified as nucleophilic substitution reactions. Other examples include redox reactions in which a leaving group is eliminated and can therefore be considered as elimination reactions. In organic chemistry, many reagents are available for the reduction or oxidation of functional groups.¹⁰ However, it is necessary to ensure that the correct reagent is used that affects only the desired functional group in the organic molecule. Furthermore, different reagents will reduce or oxidize a functional group on an organic molecule to a different extent or to form different isomers.¹⁰

3 Photochemistry

Photochemistry concerns chemistry where light is involved.¹³ The term is generalized for chemical reactions caused by the absorption of ultraviolet (UV, 100–400 nm), visible (VIS, 400–750 nm), or infrared (IR, 750–2500 nm) light. A photochemical reaction requires a light source that emits wavelengths close to the wavelength of the electronic transition of the reactant. For this purpose, mercury-vapor lamps (mainly 254 nm), laser beams (wide variety of wavelengths), and LEDs (wide variety of wavelengths) are used in laboratories.¹⁴ The importance of photochemistry becomes clear, as it forms the basis of photosynthesis, the depletion of the stratospheric ozone layer, and the formation of vitamin D.¹⁵ Although the longest-practiced photochemical reaction is bleaching, the first mention of a photochemical reaction was the deterioration of β -santonin crystals, which discolored to yellow and cracked when exposed to sunlight.¹⁶ This photochemical phenomenon was first observed by Trommsdorff in 1834, but it was not until 2007 that the reaction was understood.¹⁷ Garcia-Girabay and coworkers found that the deterioration is caused by a sequential rearrangement, intermolecular Diels–Alder reaction, and intramolecular [2+2] cycloaddition. The dimerization changes the volume of the crystal, causing it to crack. In this respect, it is worth mentioning that the first person who made efforts to understand the effect of light on chemical reactions was Giacomo Ciamician, an Italian scientist. In fact, Giacomo Ciamician is considered the pioneer of photocatalysis.¹⁸

3.1 Laws of Photochemistry

There are two basic laws of photochemistry. The first law of photochemistry is called the Grotthuss-Draper law (also called the principle of photochemical activation).¹⁹ This law states that photochemical reactions can only occur when light is absorbed by a chemical substance. For this to happen, organic molecules, such as dyes, must absorb light at optical frequencies. The law was first proposed by Theodor Grotthuss in 1817 and later by John William Draper in 1842, and it forms the basis for understanding fluorescence, phosphorescence, photochemical reactions, and other photochemical phenomena. The second law of photochemistry, known as the Stark–Einstein law or the photoequivalence law, was named after Johannes Stark and Albert Einstein, who independently proposed the law in 1908 and 1913, respectively.¹⁹ This law states that each photon of light absorbed by a chemical system will activate no more than one molecule in a photochemical reaction. A photon is a unit of electromagnetic radiation with an energy equal to the product of Planck's constant (h) and the frequency of the incident radiation (ν). By considering Avogadro's number (N_A ; 6.02×10^{23} particles per mole), the law is adapted as follows. For each mole of a substance that reacts, 6.02×10^{23} photons are absorbed. In general, the absorption of a photon is followed by secondary photochemical processes (fluorescence, phosphorescence, nonradiative phenomena, etc.), so that not all the absorbed photons will contribute to the formation of the product.

3.2 Principles

The frontier molecular orbital theory, developed by Fukui et al., states that two molecules react when the highest occupied orbital (HOMO) of one molecule and the lowest unoccupied orbital (LUMO) of the other molecule interact with each other.²⁰ When a molecule absorbs energy, its HOMO and LUMO are changed, resulting in a different reactivity. As a result, some reactions that cannot occur thermally can occur photochemically.

Photochemical excitation is illustrated in a Jablonski diagram (Figure 1). A molecule absorbs energy, which promotes an electron to a higher electronic level to produce an electronically excited molecule. The spin is retained because of the spin-selection rule. Depending on the energy of the incident electromagnetic radiation, various singlet excited states with different vibrational energies can be accessed. Kasha's rule states that higher singlet states relax more quickly to S_1 (the first singlet excited energy level or LUMO) by internal conversion, so that the only relevant singlet excited state is S_1 .²¹ From the S_1 level, radiative and nonradiative pathways can occur. Radiative pathways are transitions to lower-energy states with emission of light, whereas the energy in nonradiative pathways is lost as heat. The electron can return to the S_0 level by fluorescence (radiative) or by internal conversion (nonradiative), but it can also undergo a spin-forbidden nonradiative intersystem crossing (spin conversion) to the first excited triplet state T_1 . Deexcitation from T_1 to S_0 is also spin-forbidden, making the T_1 level the longest-lived excited state (nanoseconds to milliseconds). Slow T_1 to S_0 transitions include phosphorescence (radiative) and nonradiative transitions. Due to the longer existence of the T_1 level, it can undergo energy transfer and electron transfer with a substrate to induce a bimolecular reaction. In general, the umbrella term 'photoinduced electron transfer' (PET) encompasses the whole process of excitation followed by electron transfer between the excited-state molecule and the ground-state molecule. Note that the singlet excited state can also serve as an energy level for PET.

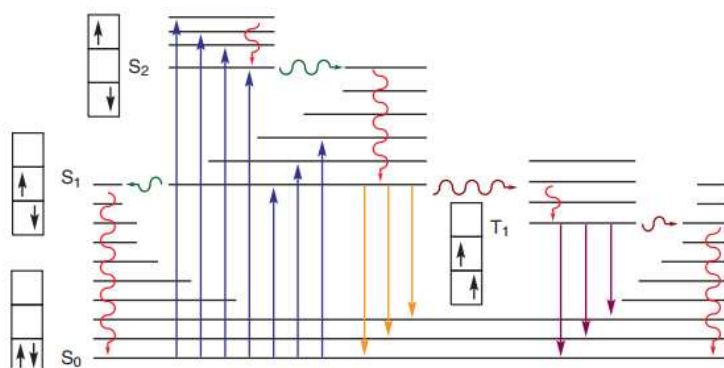


Figure 1 Simplified Jablonski diagram. Blue: Absorption; Orange: Fluorescence; Purple: Phosphorescence; Green: Internal conversion; Red: Vibrational relaxation; Brown: Intersystem crossing.

3.3 Examples

Excitation of olefins proceeds through a π -to- π^* transition. This eliminates the σ -bond, so that it is possible to rotate around the previous position of the bond. Rotation around this bond is not observed in thermal reactions. As a result, the alkene can undergo various reactions, including *cis-trans* isomerization and cycloadditions. Photochemically induced arrangements in the electronic states of molecules are used in such organic reactions as the pericyclic [2+2] cycloaddition reaction of two alkenes.²² These reactions are thermally disallowed because their HOMO and LUMO do not interact with each other. This can be solved by exciting one electron photochemically from the π -orbital to the π^* -orbital (now the excited HOMO orbital). The excited HOMO and the ground-state LUMO can now interact with each other, which means that a reaction takes place. A visual representation is given in Figure 2 for the synthesis of cyclobutane (7).

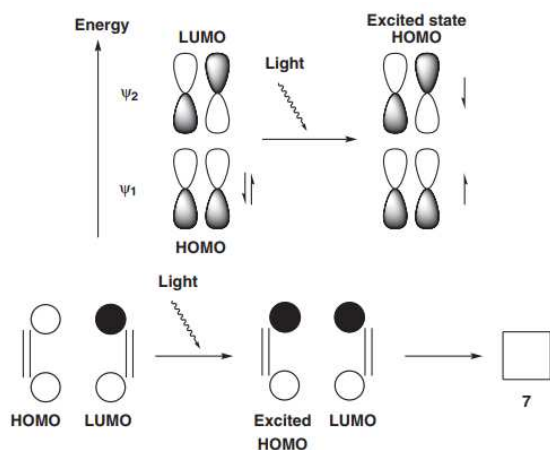
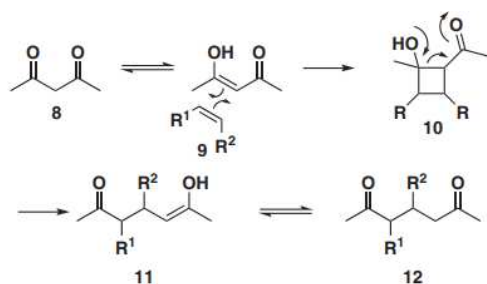


Figure 2 Photochemical [2+2] cycloaddition of two ethene molecules to form cyclobutane (7)

An extension of the [2+2] cycloaddition reaction is the De Mayo reaction (Scheme 1).^{22,23} Here, the enol of a 1,3-diketone **8** undergoes a [2+2] cycloaddition with an alkene **9** to form the corresponding cyclobutane ring **10**. This cyclobutane ring is relatively unstable and undergoes a retroaldol reaction to form **11**, which tautomerizes to yield the corresponding 1,5-diketone **12**. The final product is equivalent to the 1,3-diketone with two carbon atoms inserted in the C=C double bond.



Scheme 1 The De Mayo reaction

4 Photoredox Catalysis

Organic synthesis makes use of many different redox reactions, making the redox reaction one of the most important chemical modifications for the synthesis of valuable compounds and pharmaceuticals. In terms of ‘greenness’, these reactions perform poorly due to their use of toxic reagents in excess or stoichiometric quantities. In addition, standard organic redox reactions can produce large amounts of chemical waste, consume a lot of energy (high temperatures or pressures), involve reagents that are explosive, and so on. Therefore, new chemical routes are desirable for making redox reactions greener. One way is the use of photoredox catalysis, since this can make use of renewable resources, such as sunlight. Furthermore, the reactions are conducted at room temperature and generally produce small amounts of byproducts, depending on the reaction.

Photocatalysis refers to the synergism between photochemistry, catalysis, and energy transfer, which means that these reactions only proceed in the presence of light and a catalyst. However, photocatalysts differ from typical catalysts since they only catalyze when they are in an excited state. In such catalytic reactions, the energy of light is used to accelerate a chemical reaction through single-electron transfer (SET) events. In particular, the catalyst is a lightsensitive material that, when excited by light, allows the transfer of electrons between chemical compounds. The interaction of organic molecules with light is generally weak.²⁴ As a result, the excited state of organic molecules is only available by irradiating the molecules with UV light. UV light is very energetic, meaning that it can cause photodegradation of organic molecules. This is not the case for photocatalysts, because they absorb light with greater efficiency at longer wavelengths.²⁴ This makes photocatalysis more generally applicable than photochemistry in the synthetic laboratory. Furthermore, visible light is easier to use than UV light, because it can be used immediately, its energy cost is lower, and it can be used for a longer time. In addition, UV lamps generate a lot of heat, which can lead to undesired thermal reactions. Finally, LEDs have narrow emission bands, which permits the selective excitation of one reactant instead of generating excited states of multiple reactants.

In fact, many photochemical reactions exist in Nature. Inspired by this, chemists started mimicking this reaction strategy in the laboratory. However, most photochemical reactions performed in the laboratory require a catalyst and are, therefore, classified as photocatalytic reactions. Photocatalysis was first described by Eibner in his research on the bleaching of Prussian blue by ZnO.²⁵ At around the same period, Bruner and Kozak discussed the photocatalytic degradation of oxalic acid in the presence of uranyl salts and light.²⁶ After that, photocatalysis was little studied due to a lack of interest.²⁷ Nevertheless, the oil crisis of the 1970s led scientists to look for renewable energy sources such as solar energy. Nowadays, photoredox catalysis is frequently used in organic synthesis as an important tool for the selective activation of small molecules and for the formation of new chemical bonds.

4.1 General Principle

The general principle of photoredox catalysis can be explained by Figure 3. First, incident light excites the photocatalyst. As a result, an electron is promoted from the HOMO level to the LUMO level to generate the singlet excited photocatalyst. The spin of this electron is then reversed (intersystem crossing), which generates the triplet excited state of the photocatalyst. This triplet excited state has an electron at a higher energy level compared with the ground state of the photocatalyst. Therefore, it can more easily donate electrons to a substrate, which makes the triplet excited state of a photocatalyst an excellent reductant. Moreover, compared with the ground-state photocatalyst, the triplet excited state has a vacant position in an energetic lower-lying orbital. As a result, it can also easily accept electrons from a substrate, which makes the triplet excited state of a photocatalyst an excellent oxidant.

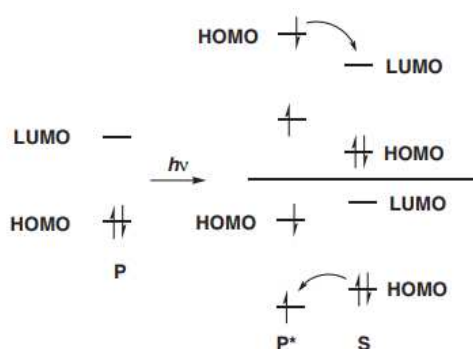
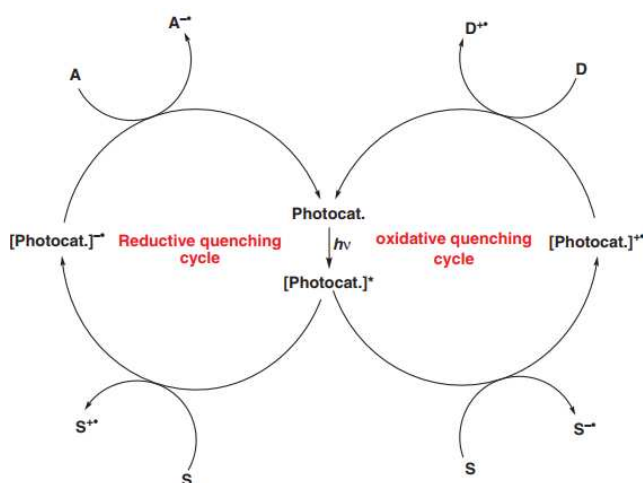


Figure 3 Photoexcitation of the catalyst to either a reductant (top) or an oxidant (bottom), depending on the energy levels of the substrate. P = photocatalyst, P^* = excited photocatalyst, S = substrate.

After the triplet-excited photocatalyst is formed, it can appear in an oxidative quenching cycle (participating as a reducing agent) or in a reductive quenching cycle (participating as an oxidizing agent). In both of these cases, the photocatalyst engages in a SET event with an organic substrate as shown in Figure 3 and Scheme 2. After this step, the catalyst is in the ground state of either its oxidized or reduced form. To return to the ground state, the catalyst must participate in a second SET event. In the oxidative quenching cycle, the catalyst is regenerated by reducing it back to its original oxidation state. Conversely, in the reductive quenching cycle, the catalyst is regenerated by the oxidation to its original oxidation state. In most of these cases, a stoichiometric amount of a reductant or an oxidant is added to regenerate the photocatalyst for subsequent cycles. However, in some cases, a second reactant takes care of this.

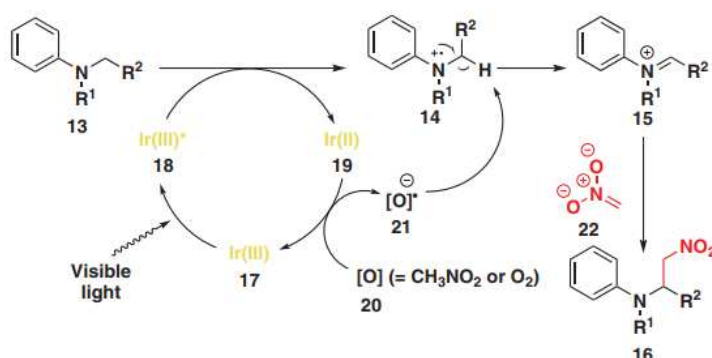


Scheme 2 Photocatalytic cycles. A = acceptor, D = Donor, S = Substrate.

4.2 Classification of Redox Processes

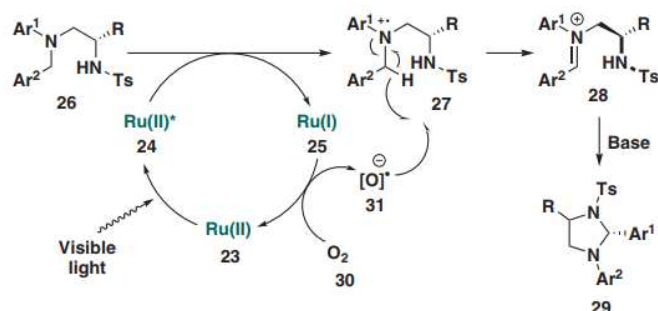
4.2.1 Net Oxidative

Photoredox catalytic reactions are divided into three classes, depending on the net redox transformation of the substrate: net oxidative, net reductive, or redox neutral. Net-oxidative reactions require a stoichiometric amount of a sacrificial oxidant to restore the catalyst to its original state. In most cases, the sacrificial oxidant is chosen to be oxygen gas (O_2), as it is one of the cheapest oxidants available. An example is the photoredox catalyzed aza-Henry C–H functionalization reaction reported by Stephenson and co-workers (Scheme 3), where an amine **13** is functionalized at the α -position to give a nitro compound **16**.²⁸ An iridium-based photocatalyst **17** is excited to **18**, which undergoes a SET with the amine **13** to form the Ir(II) complex **19** and an amine radical **14**. The iridium-based catalyst is regenerated by a second SET of **19** with an oxidant **20**, with the generation of an oxidant radical **21**. This oxidant radical abstracts a hydrogen atom from radical **14** to form iminium ion **15**. Lastly, nucleophile **22** attacks the iminium ion to form the final β -substituted product **16**. The ability to use other nucleophiles in this photocatalytic amine C–H bond oxidation gives this procedure synthetic value in the organic laboratory for performing, for example, Strecker, Sakurai, Mannich, or Friedel–Crafts-type reactions.²⁹



Scheme 3 Net-oxidative photoredox system of a catalytic aza-Henry C–H bond functionalization

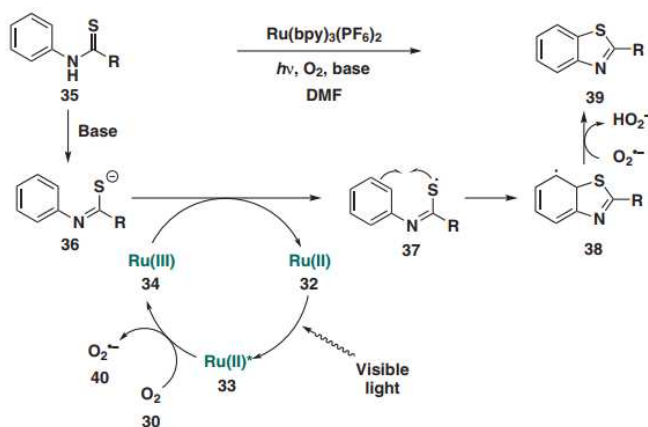
Moreover, various research groups have made use of an iminium-ion intermediate to synthesize a variety of organic molecules. In this manner, Xiao and co-workers were able to synthesize asymmetric tetrahydroimidazoles from diamines, which were cyclized by photoredox catalysis (Scheme 4).³⁰ Here, a Ru-based photocatalyst **23** is excited by light and quenched by the diamine **26** to produce the ruthenium(I) complex **25** and intermediate **27**. The catalytic circle is completed by a second SET with dioxygen (**30**) to produce a reactive oxygen species (ROS) **31**. The ROS then abstracts a hydrogen from intermediate **27** to form iminium ion **28**. A base-induced intramolecular attack of the amine on the iminium ion cyclizes the molecule to form the desired tetrahydroimidazole **29**.



Scheme 4 Net-oxidative synthesis of tetrahydroimidazoles from diamines

Another example where a sacrificial oxidant is needed is the photocatalyzed synthesis of 2-substituted

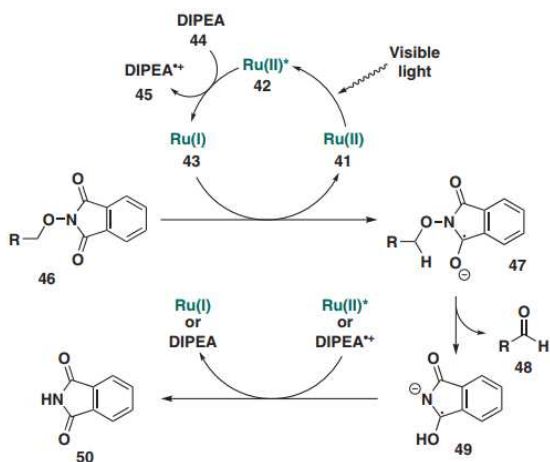
benzothiazoles, as reported by Li and co-workers³¹ The normal synthesis of these compounds relies on metal-catalyzed C–H bond functionalization. Li and co-workers were able to synthesize the compounds through radical cyclization of thioanilides by a visible-light photoredox approach (Scheme 5). Here, a Ru-based photocatalyst **32** is excited and oxidized by molecular oxygen **30** to produce a superoxide radical **40**. At the same time, the thioanilide **35** is deprotonated by a base to form anion **36**. Single-electron oxidation of **36** by the oxidized photocatalyst **34** generates a sulfur-centered radical **37**, with regeneration of the Ru-based photocatalyst. This sulfur-centered radical attacks the benzene ring to form intermediate **38**. Lastly, the generated superoxide radical abstracts a proton from this intermediate to provide benzothiazole **39**.



Scheme 5 Net-oxidative synthesis of 2-substituted benzothiazoles **39**

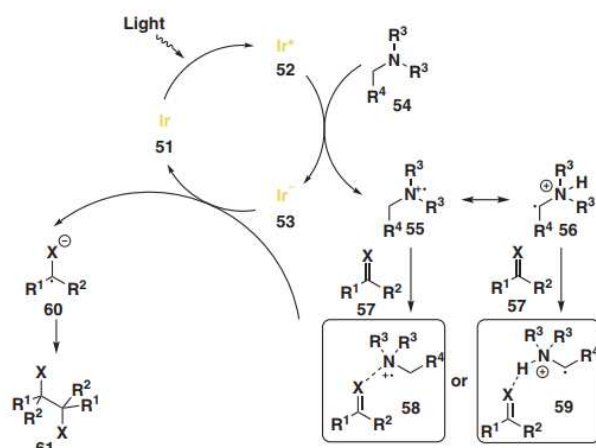
4.2.2 Net Reductive

For net-reductive reactions, a stoichiometric amount of a reducing agent is required to restore the catalyst to its original state. Reducing agents such as 1-benzyl-1,4-dihydronicotinamide (BNAH)³² and *N,N*-diisopropylethylamine (DIPEA)³³ are appropriate for this reaction. An example is given in a report by Zlotorzynska and Sammis that describes the fragmentation of *N*-alkoxyphthalimides for the synthesis of various aldehydes and ketones (Scheme 6).³⁴ They proposed a mechanism where a Ru-based catalyst (**41**) is excited by light and then immediately undergoes an SET with DIPEA (**44**) to generate DIPEA^{•+} (**45**) and a ruthenium(I) complex **43**. A second SET between **43** and the phthalimide **46** then results in intermediate **47**. After an intramolecular elimination, the desired aldehyde **48** is generated along with the phthalimide radical anion **49**. Finally, phthalimide **50** is formed after a third SET with either DIPEA^{•+} (**45**) or with **42** to form DIPEA (**44**) or **43**, respectively.



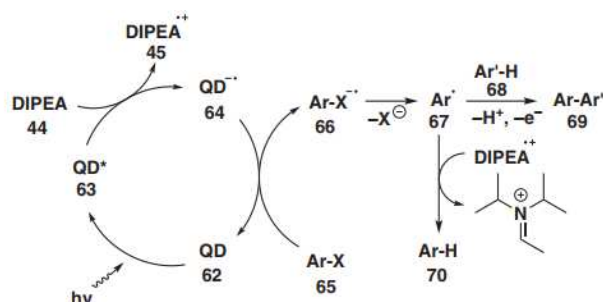
Scheme 6 Net-reductive synthesis of various aldehydes or ketones **48** from *N*-alkoxyphthalimides **46**

Another example involves the reductive coupling of aldehydes, ketones, or imines. The reductive dimerization of benzaldehyde has been known since 1990.^{35a} However, this method was only applicable to a few aldehydes, and ketones would not react at all. This is attributed to the very high reduction potential of ketones (acetophenone: $E_{1/2} = -2.2\text{V}$ vs. the ferrocene/ferrocenium).³⁶ In 2015, Rueping and co-workers were able to circumvent this problem by using tributylamine (TBA) as a sacrificial reducing agent.^{35b} This reagent was needed to activate the ketone by interacting with it. The mechanism is shown in Scheme 7. An Ir-based catalyst **51** is excited by light and quenched by TBA (**54**) to produce **53** and intermediate **55**. This intermediate interacts with an aldehyde, ketone, or imine **57** to form complex **58** through a two-center/three-electron interaction. Alternatively, the α -ammonium radical **56** is formed by a [1,2]-H shift, which can also activate the aldehyde, ketone, or imine through a hydrogen bond (**59**). A second SET occurs between **53** and complex **58** or **59** to generate intermediate **60**. Lastly, the two radicals combine to generate the desired product **61**.



Scheme 7 Net-reductive dimerization of aldehydes ($X = O$; $R_1 = \text{Ar}$; $R_2 = \text{H}$), ketones ($X = O$; $R_1, R_2 \neq \text{H}$), or imines ($X = \text{NHBn}$; $R_1 = \text{Ar}$; $R_2 = \text{H}$)

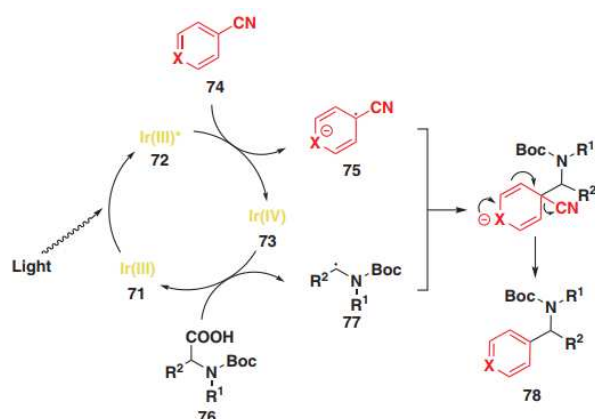
Another example of a net-reductive photocatalytic system is the use of quantum dots for the reductive dehalogenation followed by C–H arylation. One of the earliest contributions towards reductive dehalogenation reactions was reported by Fukuzumi et al. in 1990.³⁷ Here, the net reaction was the elimination of a halide. However, the use of the generated radical for a subsequent reaction was desirable. In 2017, König and co-workers were able to trap this radical to form a new C–C bond.³⁸ The proposed mechanism is given in Scheme 8. First, the quantum dot **62** is excited by light and reduced by DIPEA (**44**) to form **64** and DIPEA^{•+} (**45**). Then, **64** undergoes a second SET with an aryl halide **65**, generating **66**. Subsequently, the halide anion is released and an aryl radical **67** is formed and subsequently trapped by a pyrrole derivative **68**. Oxidation and release of a proton then yield the desired product **69**. The aryl radical can also abstract a proton from DIPEA^{•+} (**45**) to generate **70**.



Scheme 8 Net-reductive dehalogenation followed by C–C coupling ($\text{Ar}' = \text{pyrrole derivative}$)

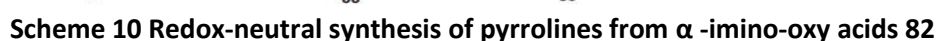
4.2.3 Redox Neutral

In redox-neutral reactions, substrates participate in both SET steps of the catalytic cycle, thereby acting as both reductants and oxidants. No sacrificial reductant or oxidant is required for this reaction to proceed, as the catalyst is brought back to its original state by the substrate itself. An example is the decarboxylative arylation by photoredox catalysis reported by Zuo and MacMillan (Scheme 9).³⁹ Here, light excites an iridium(III) complex **71** to **72**, which undergoes a SET with **74** to generate a cyano-substituted (het)aromatic radical **75** and an iridium(IV) complex **73**. The photocatalyst is regenerated by a second SET with **76** with formation of a decarboxylated radical **77**. Afterward, the generated radicals **75** and **77** couple to form the desired product **78** after the elimination of the cyano group.



Scheme 9 Redox-neutral decarboxylative coupling with a cyano-substituted (hetero)aromatic compound **74**

An example where the substrate participates in both an oxidative and a reductive SET is the alkene carboimination for the synthesis of pyrrolines reported by Jiang and Studer.⁴⁰ Here, an α -iminooxyacetic acid is used as the starting compound to generate an iminyl radical. After cyclization, the resulting radical is further reduced to generate an anion, which closes the catalytic system (Scheme 10). First, an Ir-based catalyst **79** is excited by light and reduced by carboxylate **83**, formed by deprotonation of the α -imino oxy acetic acid **82**. As a result, carboxyl radical **84** is formed along with **81**. The carboxyl radical is unstable and fragments into an iminyl radical **85**, CO₂, and acetaldehyde. Then, 5-*exo*-cyclization generates the carbon-centered radical **86**, which attacks an alkene **87** to generate **88**. A second SET between **88** and **81** regenerates the Ir-based catalyst and produces carbanion **89**. Lastly, the desired product **90** is formed after protonation.

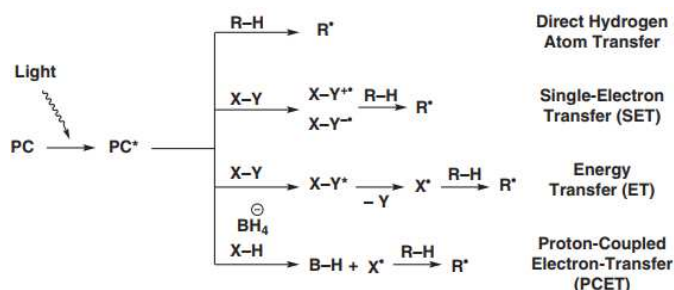


In reality, the mechanism of photoredox catalysis is much more complicated. In other words, the mechanism depicted in Scheme 2 is a simplified representation because it shows only PET phenomena where one photon results in one product. This model reaction is unrealistic due to the radiative and nonradiative transitions of excited electrons. For this purpose, the term ‘quantum yield’ has been introduced, which indicates the number of product entities formed per absorbed photon.⁴¹ A quantum yield close to unity is desirable, since this indicates that the effectiveness of such a photoredox catalysis reaction is at its maximum. However, some photoredox catalytic reactions have a quantum yield greater than unity because they possess intermediates that are capable of releasing or capturing electrons and thereby introducing new catalytic chains.⁴²

Often, control experiments without a catalyst provide the desired product of a photocatalytic redox reaction, even when the reactants do not absorb the incident wavelengths of the chosen illumination. This phenomenon is explained by the formation of a charge-transfer complex upon mixing the reactants.⁴³ Charge-transfer complexes are capable of absorbing photons at lower energies than the reactants, making the redox reaction possible without the addition of a catalyst. Taking these complexes into account, the mechanism for the formation of the desired product can take place via different routes and can provide additional byproducts. The above section describes the electron-transfer mechanism, which is the most common mechanism. However, four other mechanisms are also known: (a) The excited state of the photocatalyst abstracts a hydrogen atom from the substrate, generating a substrate radical (HAT),⁴¹ (b) the excited photocatalyst activates the substrate through energy transfer,⁴⁴ (c) a radical is split and attacks an olefin (ATRA),⁴⁵ and (d) proton-coupled electron transfer.⁴⁶

The use of a hydrogen-atom transfer (HAT) reagent in photoredox catalysis offers a distinctive approach to substrate activation for the activation of C–H bonds. It involves the movement of a proton and an electron between two species, generating a reactive radical species. In photoredox catalysis, several distinctive pathways for HAT exist. The first involves direct HAT, where the excited photocatalyst abstracts a hydrogen atom from a C–H bond. Secondly, the excited photocatalyst can convert a co-catalyst into its radical ion by a SET phenomenon; the radical ion can then abstract a hydrogen atom from the substrate. Alternatively, energy is transferred from the excited photocatalyst

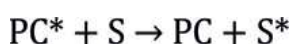
to the co-catalyst, which then undergoes homolytic cleavage to generate a radical species. This radical, in turn, can abstract a hydrogen atom from the substrate. Finally, in the presence of a base, the excited photocatalyst can undergo a protoncoupled electron transfer with the co-catalyst to generate a radical that can, in turn, abstract a hydrogen atom from the substrate.⁴⁷ In fact, the last example is an illustration of a proton-coupled electron transfer (PCET) and is, therefore, not considered a HAT phenomenon. All pathways are given in Scheme 11.



Scheme 11 HAT-mediated pathways in photoredox catalysis

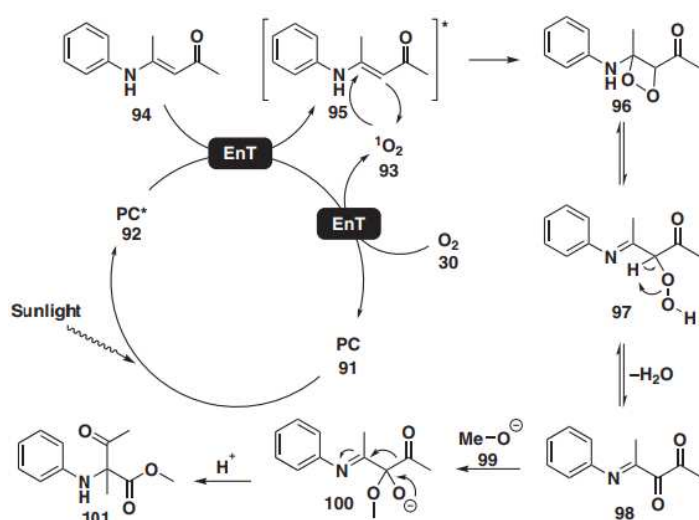
4.3.2 Energy-Transfer Reactions

Energy transfer (ET) from an excited photocatalyst to organic compounds can give rise to various distinctive reaction modes that differ considerably from the corresponding ground-state modes. Excited states of organic compounds have been used in a variety of organic synthetic protocols, including pericyclic reactions, isomerization reactions, and others. Because most organic molecules do not absorb visible light, more energetic UV light has to be used to excite them to their triplet excited states. This entails many disadvantages, including narrow functional-group tolerance and poor selectivity toward the desired products. Visible-light-mediated photocatalysis with ET is a solution to these problems. This phenomenon can be simply described as the transfer of energy from the excited photocatalyst to the substrate, where the photocatalyst (PC) is deactivated to its ground state and the substrate (S) is activated to its excited state (Equation 2).⁴⁸



Equation 2 Simplification of ET in photoredox catalysis

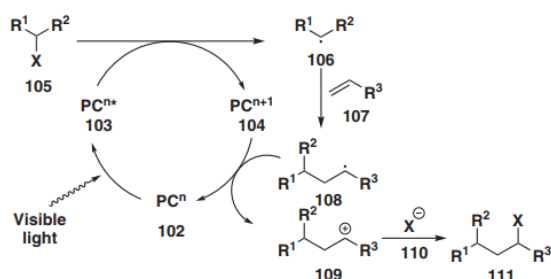
The energy-transfer mechanism is illustrated in Scheme 12 for the case in which oxygen is used as the sacrificial oxidant. Using this principle, we were able to synthesize α -amino carbonyl compounds directly from enaminones with a Nature-inspired catalyst.⁴⁴ Using chlorophyll, which possesses abundant Mg centers, we were able to generate singlet oxygen to provide easier access to α -amino carbonyl compounds with a high turnover number (Scheme 12). First, chlorophyll (**91**) is excited by light to form chlorophyll* (**92**), which undergoes an energy-transfer phenomenon with molecular oxygen (**30**) to produce singlet oxygen (**93**). Simultaneously, another excited-state chlorophyll molecule can undergo an energy-transfer phenomenon with the enaminone **94** to generate **95**, which undergoes a [2+2] cycloaddition with the in-situ-generated singlet oxygen (**93**) to form **96**. This dioxetane intermediate is quickly transformed into the hydroperoxide intermediate **97** by a ring-opening pathway. Water is then eliminated to form the dicarbonyl imine intermediate **98**, which is attacked by a methoxide anion **99** to generate **100**. Finally, the desired product **101** is obtained after an acid-catalyzed intramolecular 1,2-acyl migration.



Scheme 12 Use of the energy-transfer principle for the synthesis of α -amino carbonyl compounds **101**

4.3.3 Atom-Transfer Radical Addition

In organic synthesis, the mono- and difunctionalization of olefins are among the most valuable procedures for generating value-added products such as pharmaceuticals. One synthetic procedure is the atom-transfer radical addition (ATRA), where an atom-transfer agent splits a C-X bond to form a radical that attacks a C=C bond of an olefin. As a result, two new C-X bonds are formed.⁴⁹ The ATRA principle is explained by Scheme 13. First, the photocatalyst **102** is excited by light and quenched by substrate **105** to generate radicals **106** and **104**. Radical **106** attacks an olefin **107** to form radical **108**, which undergoes a second SET to generate cation **109**, with the regeneration of the photocatalyst. Cation **109** is trapped by a nucleophile **110** to form the desired product **111**.



Scheme 13 ATRA principle for the difunctionalization of olefins **107**

4.3.4 Proton-Coupled Electron Transfer

The net result of a proton-coupled electron transfer does not differ from that of a HAT. However, in the case of HAT, a hydrogen radical is transferred, where the proton and electron travel concurrently from a single donor to a single acceptor. In PCET, however, a hydrogen radical is also transferred, but the proton and electron can originate from two separate donors, or can travel to two distinct acceptors. Generally, for PCET phenomena, a base accepts a proton from the substrate and the electron is transferred to a photocatalyst through a SET phenomenon (Scheme 11).⁵⁰

4.4 Stern–Volmer Plots

One of the most frequently used methods for determining a mechanism is through quenching experiments. A photocatalyst excited by light returns to its ground state by emitting light

(intramolecular deactivation). However, in the presence of an appropriate organic molecule (quencher), an SET occurs (intramolecular deactivation). As a result, the fluorescence of the catalyst is reduced. Increasing the concentration of the quencher results in a lower emission from the photocatalyst that can be observed, as illustrated in Figure 4. The main goal of such experiments is to gain information on which molecules can interact with an excited-state photocatalyst to form highly reactive radicals.⁵¹

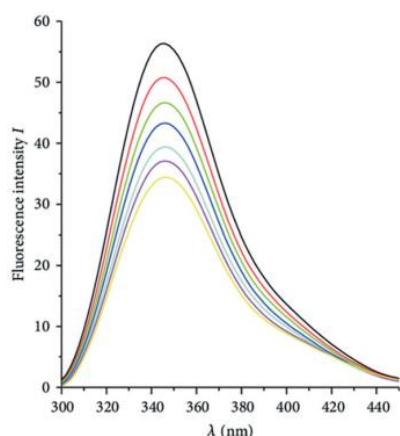


Figure 4 Fluorescence quenching of an excited-state photocatalyst by an appropriate quencher⁵¹

Another way to plot the results of these experiments is the Stern–Volmer plot (Figure 5). Here the concentration of the quencher [Q] is plotted against the intensity of fluorescence when no quencher is present divided by the intensity of fluorescence when the quencher is present (I_f^0/I_f).

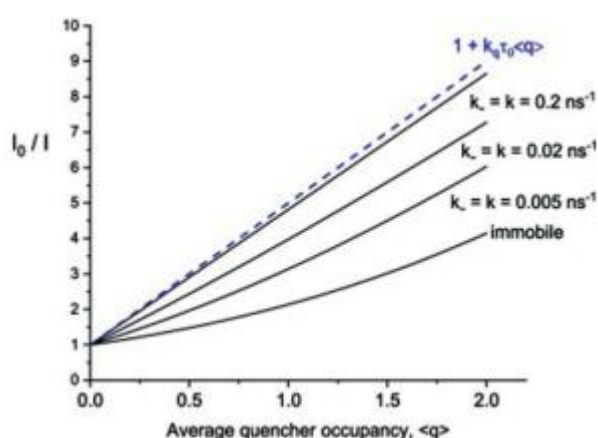


Figure 5 A Stern–Volmer plot⁵²

The kinetics of this quenching experiment follow the Stern–Volmer relationship (Equation 3). Here I_f^0 is the intensity of the fluorescence without a quencher, I_f is the intensity of fluorescence with a quencher, k_q is the quencher rate coefficient, τ_0 is the lifetime of the emissive excited state of the photocatalyst without a quencher, and [Q] is the concentration of the quencher. Note that this equation is only applicable in cases where diffusion is not the rate-determining step.

$$\frac{I_f^0}{I_f} = 1 + k_q \tau_0 [Q]$$

Equation 3 The Stern–Volmer equation⁵²

When the quencher is consumed by the excited photocatalyst, a new quencher molecule has to diffuse through the solution to the newly excited photocatalyst. When diffusion is slow, the quencher rate

coefficient is no longer a constant, and is given by Equation 4. Here, R is the ideal gas constant, T is the temperature in kelvin, η is the viscosity of the solution, r_a and r_b are the radii of the two molecules, and d_{cc} is the distance at which the quenching is expected to occur. In this case, a curve is observed in the Stern–Volmer plot.

$$k_q = \frac{2RT}{3\eta} \left[\frac{r_b + r_a}{r_b r_a} \right] d_{cc}$$

Equation 4 Stern–Volmer equation where diffusion is limited in the solution

4.5 Photophysical Properties

One of the most important properties is the local absorbance maximum for the lowest energy absorption, $\lambda_{\max}^{\text{abs}}$.⁴¹ This value is the wavelength at which maximum absorbance occurs from the ground state S_0 to the first excited state S_1 . Although Kasha's rule says that higher excited states quickly relax to S_1 , it is desirable to irradiate the molecule at the lowest possible energy to minimize the excitation of other molecules.²¹ When other molecules are excited, competitive photochemical reactions might occur. An application of this value is the determination of the light source for a particular organic-dye photoredox catalyst.

Another important property is the lifetime of fluorescence τ_f , as it gives an indication of the lifetime of the S_1 level (τ_{S1}) for participation in photochemical reactions.⁴¹ Assuming that the nonradiative pathways are much slower than radiative pathways permits the use of the approximation $\tau_f \approx \tau_{S1}$. As a rule of thumb, organic dyes with $\tau_f < 1$ ns will not readily participate in PET, because the rate of deexcitation will exceed the rates of diffusion processes. In general, the longer is τ_f , the greater the likelihood of encountering a substrate to induce a reaction.

The quantum yield of intersystem crossing (ϕ_{isc}) indicates the number of times intersystem crossing occurs per photon. In other words, it is an indication of how easily the T_1 state is formed. Because the transition from T_1 to S_0 is spin-forbidden, the lifetime of T_1 (τ_{T1}) is several magnitudes larger. Therefore, the likelihood for PET with a substrate is increased, which results in a higher reactivity.⁴¹

4.6 Redox Potentials

The redox potential is a measure of the tendency of a chemical species to gain electrons from an electrode and thereby, be reduced. The redox potential is measured in units of volts (V) or millivolts (mV). Each chemical has its own redox potential that can be measured by using cyclic voltammetry. A more positive value of the redox potential indicates a greater affinity for electrons to be gained and thus a higher tendency to be reduced. The redox potential of the photocatalyst must be matched to the reagents for the reaction. Cyclic voltammetry (or other electrochemical methods) may provide data on the ground-state potential, but the potential of an excited state is impossible to measure with these methods because of the short lifetime of the excited species.⁵³ The potential of an excited state can be estimated by two methods. The first method uses a comparison between the rate of excited-electron transfer to a series of stable reactants with a known ground-state potential. A second and more common method estimates the excited state potential by using the excited-state energy $E_{0,0}$ to correct the ground-state redox potentials, as given by Equation 5.⁴¹

$$E_{\text{red}}^* = E_{\text{red}} + E_{0,0} + w_r$$

$$E_{\text{ox}}^* = E_{\text{ox}} - E_{0,0} + w_r$$

Equation 5 Calculation of the excited-state reduction or oxidation potential

Here E^* is the excited state reduction or oxidation potential, E is the potential of the ground-state redox couple, $E_{0,0}$ is the energy difference between the zeroth vibrational level of the ground and the excited state, and w_r is an electrostatic work term describing charge generation and separation within the electron-transfer complex. Values for w_r depend on the solvent, reactant, and product but can, in most cases, be neglected for a simpler calculation of the excited redox potential of the photocatalyst. Additionally, when the excited-state redox potential is found, the Gibbs free energy of PET (ΔG_{PET}) can be calculated.⁴¹ When an excited-state catalyst (cat^*) is reduced and the ground-state substrate (sub) is oxidized, ΔG_{PET} can be calculated by using Equation 6.

$$\Delta G_{\text{PET}} = -F(E_{\text{red}}^*(\text{cat}^*/\text{cat}^{\bullet-}) - E_{\text{ox}}(\text{sub}^{\bullet+}/\text{sub}))$$

Equation 6 Gibbs free energy of photoinduced electron transfer when the substrate is oxidized

Alternatively, when an excited-state catalyst is oxidized and a ground-state substrate is reduced, ΔG_{PET} can be calculated from Equation 7.

$$\Delta G_{\text{PET}} = -F(E_{\text{red}}^*(\text{sub}/\text{sub}^{\bullet-}) - E_{\text{ox}}(\text{cat}^{\bullet+}/\text{cat}^*))$$

Equation 7 Gibbs free energy of photoinduced electron transfer when the substrate is reduced

PET occurs only when ΔG_{PET} is negative. Keeping this in mind, oxidation of the substrate occurs only when the E_{red}^* of the catalyst is more positive than the E_{ox} of the substrate. Likewise, reduction of the substrate occurs when E_{ox}^* of the catalyst is more negative than E_{red} of the substrate.

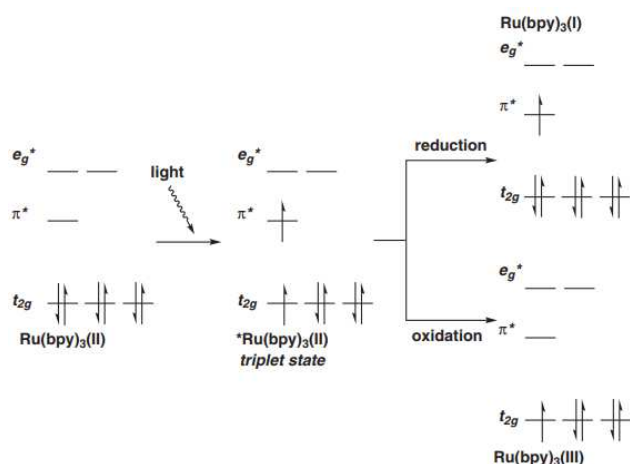
5 Photocatalysts

Photoredox catalyst structures are dominated by highly conjugated systems, as they need to absorb energy from the incoming light. Nevertheless, they have little in common, as shown by the diversity of their structures (Figures 6 to 14 and Scheme 15). The most common photoredox catalysts can be divided into three classes: transition-metal-based catalysts, organic dyes, and semiconductors (such as titanium, tungsten, or cadmium compounds).²⁴

5.1 Metal-Based Photocatalysts

Metal-based photocatalysts are the most studied photocatalysts.⁵⁴ As a result, they have a wide variety of applications in organic chemistry.⁵⁵ In general, excitation of the photocatalyst is the result of a metal-to-ligand charge transfer, where an electron is transferred from the metal (usually from a d-orbital) to a ligand orbital (usually a π^* -orbital). The resulting excited photocatalyst relaxes to the lowest singlet excited state (S_1) without emitting electromagnetic radiation. At this level, further relaxation to the ground state is possible through the emission of a photon (fluorescence) or through spin conversion into the triplet excited state (T_1).

The photoredox properties of metal-based photocatalysts are exemplified by $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (Scheme 14; $\text{bpy} = 2,2'$ -bipyridine). First, the complex is excited by transfer of an electron from the t_{2g} level (metal) to the π^* -orbital (ligand). The resulting singlet excited photocatalyst is converted into the triplet excited state by spin conversion. From this triplet excited state, the photocatalyst can act as a reducing agent (giving an electron from its newly occupied π^* -orbital to the substrate) or an oxidizing agent (accepting an electron from the substrate in the newly generated vacant position in the t_{2g} orbital), depending on the substrate used. The triplet excited state is relatively stable because relaxation to the ground state (phosphorescence) is slow, as it requires emission of a photon the spin of which must be inverted, which is a spin-forbidden pathway.



Scheme 14 Orbital diagram for Ru(bpy)₃Cl₂ photocatalyst

The properties of a transition-metal-based photocatalyst can be modified by changing the metal center and/or the ligands. More electronegative metals and ligands stabilize electrons better. Therefore, the more electronegative are the ligands in transition-metal complexes, the more oxidizing the photocatalyst is (itself being reduced, gaining an electron). An example is the comparison between [Ru(bpy)₃]²⁺ and [Ru(ppy)₂(bpy)]⁺ (ppy = 2-phenylpyridine) in which a less electronegative ppy ligand replaces one bpy ligand. Therefore, on replacing both bpy ligands with ppy ligands, the photocatalyst becomes even more reducing, since ppy retains electrons less well than bpy. The most familiar and widely used transition-metal-based photoredox catalysts contain an iridium or ruthenium central metal with ppy, bpy, and/or phenanthroline ligands. Figure 6 shows two examples, namely [Ru(bpy)₃]²⁺ (112) and [Ir(ppy)₂(dtbbpy)]⁺ (113; dtbbpy = 5,5'-di-*tert*-butyl-2,2'-bipyridine).

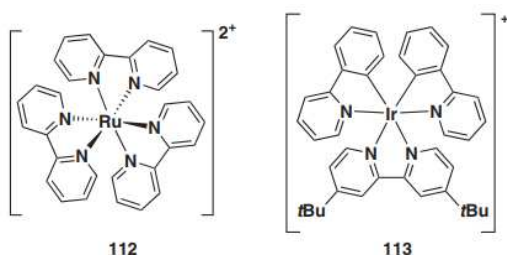


Figure 6 Common transition-metal-based photocatalysts

5.2 Organic Dyes

A group of photocatalysts that are more interesting are the organic dyes.⁴¹ One of their main advantages is the elimination of expensive, scarce, or toxic metals, which increases the sustainability of these photoredox systems even more.⁵⁶ In fact, the utilization of organic dyes also enhances the metal-free catalysis domain, which is becoming very popular in organic synthesis.^{57–60} Furthermore, these metal-free (photo)catalysts are highly desirable in the pharmaceutical industry, since they do not leach any metal into the final product.

The mechanism of photocatalysis is the same as for metal-based photocatalysts. Light excites the organic dye and this is followed by internal conversion into the S₁ excited level. From here, spin conversion takes place into the T₁ excited state, which acts as an oxidant or reductant depending on the substrate added to the mixture. Organic dyes are environmentally friendly and cost-effective alternative photocatalysts because they do not contain any toxic or expensive transition metals. Furthermore, most of them are readily available. Moreover, organic dyes, such as acridinium salts are easy to synthesize in the laboratory.⁵⁸ The most commonly known and used organic photoredox

catalysts include cyanoarenes, benzophenones, quinones, triaryl(thia)pyrylium salts, quinolinium salts, acridinium salts, xanthenes, and rhodamines.

5.2.1 Cyanoarenes

Photoredox catalysis using cyanoarenes as photocatalysts generally uses the singlet excited state for PET.⁴¹ The most common cyanoarenes for photocatalysis are *p*-dicyanobenzene (*p*-DCB; **114**), naphthalene-1,4-dicarbonitrile (1,4-DCN; **115**), and anthracene-9,10-dicarbonitrile (DCA; **116**) (Figure 7), each of which has a high singlet-excited-state energy, e.g. 2.89 eV for DCA, making them useable for the oxidation of substrates with an oxidation potential greater than 2.0 V.⁵⁹ In addition, this class of organic dyes has a long lifetime of fluorescence ($\tau_f \approx 13$ ns for DCA), resulting in a high probability of singlet-excited-state PET.⁶⁰ After a PET phenomenon, good reductants are formed. Recovery of the initial form of the photocatalyst is easily achieved with dioxygen to form the superoxide radical ($O_2^{\cdot -}$) for oxygenation reactions. Cyanoarenes with multiple benzene rings (1,4-DCN and DCA) are more useful, as they absorb light in the visible region of the spectrum and have longer singlet-excited lifetimes than cyanobenzenes (e.g., *p*-DCB has a τ_f of 9.7 ns).⁶¹

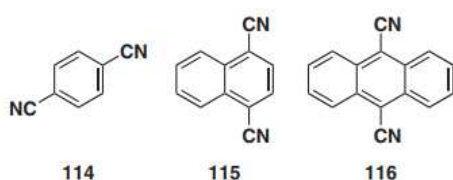


Figure 7 Common cyanoarene organic-dye photoredox catalysts

5.2.2 Benzophenones

Compared with cyanoarenes, benzophenones have a superior quantum yield of intersystem crossing close to unity (e.g., 9*H*-fluoren-9-one has a ϕ_{ISC} of 0.97).⁶² This can be explained by the presence of the carbonyl group, because the S_1 and T_1 of benzophenones are close in energy. For this reason, benzophenones use their triplet excited state for PET. The most common benzophenones are 9*H*-fluoren-9-one (**117**), xanthone (**118**), thioxanthone (**119**), and Michler's ketone (**120**) (Figure 8). In general, benzophenones act through photoinduced HAT to form a ketyl radical.⁶³ Dimerization of the ketyl radicals can be problematic when using benzophenones as photocatalysts, since reverse HAT for the regeneration of the catalyst is slow.⁶⁴ However, benzophenones can also readily reduce oxygen to form superoxide radicals for oxygenation reactions.⁶⁵

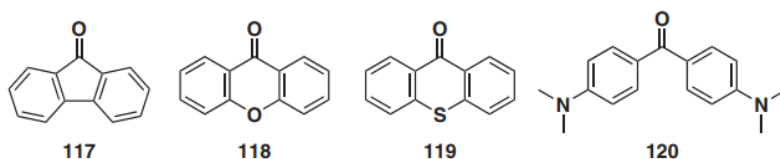


Figure 8 Common benzophenone organic-dye photoredox catalysts

5.2.3 Quinones

Most (benzannulated)quinones show similarities to benzophenones, namely an efficient intersystem crossing to form triplet excited states (e.g., anthraquinone has a ϕ_{ISC} of 0.90).⁶⁶ In addition, their mode of operation also involves PET.⁴¹ Quinones, however, have the ability to abstract a second hydrogen atom to form the corresponding quinols because they possess a second ketone functionality. By using a sacrificial oxidant such as molecular oxygen, the quinol can be transformed back into the quinone photocatalyst. The most common quinones are anthraquinone (**121**) and 1,4-benzoquinone (**122**) (Figure 9).

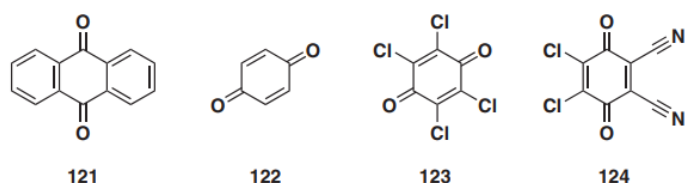


Figure 9 Common quinone organic dyes used as photoredox catalysts

Two extreme examples exist, namely p-chloranil (**123**) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; **124**) (Figure 9), as they can act efficiently as oxidants in their ground states. Therefore, in their excited triplet state, they are marvelous oxidants. However, the conversion of the quinol back into the quinone is challenging due to its very high reduction potential.⁴¹

5.2.4 Triarylpyrylium Salts

Another class of organic-dye photocatalysts are the triarylpyrylium salts, which absorb in the visible range ($\lambda_{\text{max}}^{\text{abs}} \approx 425 \text{ nm}$). However, the singlet lifetime of triarylpyryliums tends to be short (e.g., $\sim 4 \text{ ns}$ for 2,4,6-triphenylpyrylium derivatives), making PET from the singlet excited state somewhat inefficient.⁶⁰ 2,4,6-Triphenylpyrylium tetrafluoroborate (**125**) is the most common photocatalyst of this class of organic dyes, and substitution of its aryl rings to, for example, 2,4,6-tri(*p*-methoxyphenyl)pyrylium tetrafluoroborate (**126**) is a relatively easy method to extend the photophysical properties (Figure 10).⁶⁰ Salt **126** has a quantum yield of intersystem crossing of about 0.569, making both its singlet and triplet excited states important for PET.

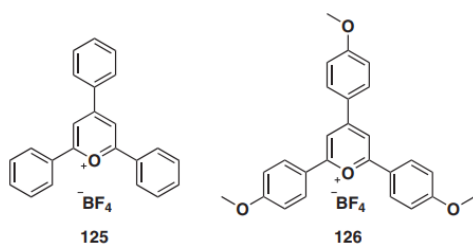


Figure 10 Common triarylpyrylium salt organic dyes used as photoredox catalysts

An interesting feature of pyrylium salts is the reduction potential of the resulting pyranyl radicals, which is not negative enough for the oxidation of oxygen to generate superoxide radicals.⁶⁷ Therefore, pyrylium salts are used where aerobic reactions are undesirable. In some cases, however, the pyrylium salt reacts with oxygen to generate a peroxy radical, which can act as an intermediate in aerobic oxidation reactions.⁶⁷ Despite their photocatalytic activity, these organic dyes have two main problems: (a) they readily dimerizes with consequent changes in their photophysical properties,⁶⁸ and (b) nucleophiles readily attack the pyrylium core, which also changes the photophysical properties of the dye.⁶⁹

5.2.5 Triarylthiapyrylium Salts

This class of organic dyes can be compared with triarylpyrylium salts. However, their intersystem crossing quantum yield is close to unity (e.g., 2,4,6-triphenylthiapyrylium has a ϕ_{ISC} of 0.94), making the triplet excited state a much more important state for photocatalysis.⁷⁰ Like pyryliums, thiapyryliums do not undergo PET with oxygen to generate the superoxide radical, but can form peroxy radicals.⁴¹ The most commonly known and used organic dyes of this class are the 2,4,6-triphenylthiapyrylium salts analogous to the triarylpyrylium salts shown in Figure 10, but with the central oxygen atom replaced by a sulfur atom.

5.2.6 Quinolinium Salts

N-Alkylquinolinium salts are widely used as photocatalysts due to their high-energy singlet excited states (e.g., the *N*-methylquinolinium ion has an $E_{0,0}^{S1}$ of 3.50 eV).⁶¹ In addition, the lifetimes of their singlet excited states are quite long [e.g., the *N*-methylquinolinium ion (**127**) has a τ_f of 23.37].⁷¹ This makes this class of organic dyes highly oxidizing in the singlet excited state. However, the ground-state cation is prone to undergo nucleophilic addition reactions.⁷² Furthermore, the singlet excited radical is prone to undergo radical reactions.⁷³ As a result, the quinolinium salt is partially dearomatized, leading to less-efficient absorption of photons in the near-UV to visible-light region of the spectrum. The most useful quinolinium salts, which do not readily dearomatize through nucleophilic addition or radical reactions, are the 3-cyano-1-methylquinolinium salts such as **128** (Figure 11).

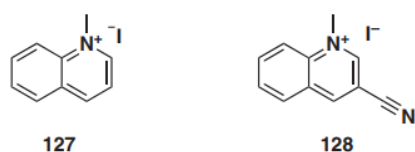


Figure 11 Common quinolinium salt organic dyes used as photoredox catalysts

5.2.7 Acridinium Salts

This class of organic dyes are often seen as enhanced analogues of quinolinium salts, because nucleophilic attacks and radical reactions are eliminated through obstruction by the additional aromatic ring.⁴¹ Furthermore, the additional aromatic ring expands the conjugated π -system, leading to absorption of photons from the visible-light region of the spectrum. In general, acridinium salts are powerful singlet excited-state oxidants, whereas the resulting acridinyl radicals are unable to reduce oxygen to generate the corresponding superoxide radicals. Among the simplest acridinium salts are the *N*-methylacridinium salts such as **129** (Figure 12), which has a long singlet-excited lifetime ($\tau_f = 37$ ns).⁷⁴ However, nucleophilic addition and radical reactions at the 9-position are still observed, which limits its use as a catalyst.⁷² Therefore, 9-substituted acridinium salts, such as 9-mesityl-10-methylacridinium tetrafluoroborate (**130**), are more frequently used in photoredox catalytic reactions in organic synthesis.

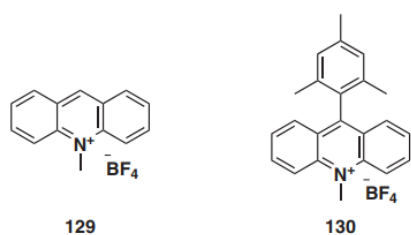
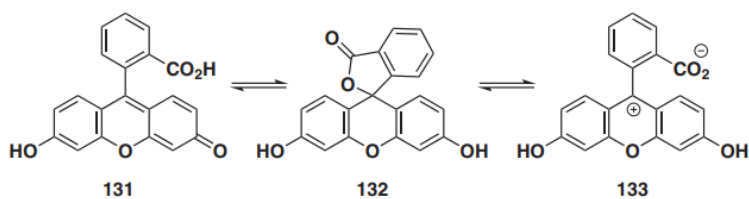


Figure 12 Common acridinium salt organic dyes used as photoredox catalysts

5.2.8 Xanthenes

Xanthenes have been intensively investigated due to their photocatalytic properties. Interestingly, neutral fluorescein exists in three forms: the quinonoid **131**, lactone **132**, and zwitterionic **133** forms (Scheme 15).⁴¹ Due to the presence of acidic protons, the absorption wavelength depends on the pH, and the dianion (basic conditions) has the absorption maximum with the longest wavelength.⁷⁵



Scheme 15 Neutral forms of fluorescein

Halogenated analogues of fluorescein are also subject to these equilibria (form and pH). Therefore, the photocatalytic activity can change drastically depending on the solvent and the form used. The most widely used fluorescein-based organic dyes include rose bengal (**134**), eosin Y (**135**), and erythrosine (**136**) (Figure 13). The more halogenated the analogue of fluorescein, the greater is its intersystem crossing quantum yield (0.03 for fluorescein, 0.32 for eosin Y, and 0.77 for rose bengal).⁷⁶ As a result, the halogenated analogues use their triplet excited states in photocatalytic reactions. Studies have shown that eosin Y can quench itself to recover the initial photocatalyst.⁷⁷ Later, it was shown that rose bengal is also capable of doing this.⁷⁸ However, in most cases, the photocatalyst radical undergoes an electron transfer with oxygen to generate a superoxide radical for oxygenation reactions.⁷⁹

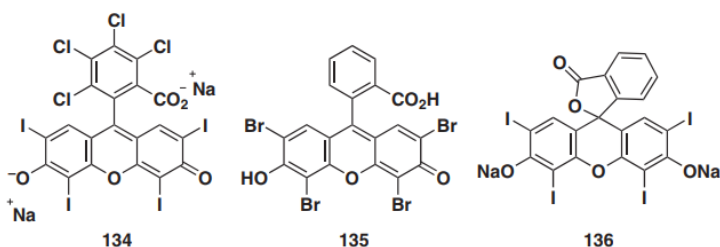


Figure 13 Common fluorescein-based organic dyes used as photoredox catalysts

5.2.9 Rhodamines

Rhodamines are analogues of fluorescein-based organic dyes in which the ketone and alcohol functionalities are modified to imines and amines, respectively. Like fluorescein-based derivatives, rhodamines exist in multiple forms depending on the pH. The intersystem crossing quantum yield is very low (0.002 for rhodamine 6G), which permits the triplet excited state to be neglected as a source for PET.⁸⁰ The most commonly used rhodamines are rhodamine B (**137**) and rhodamine 6G (**138**) (Figure 14).

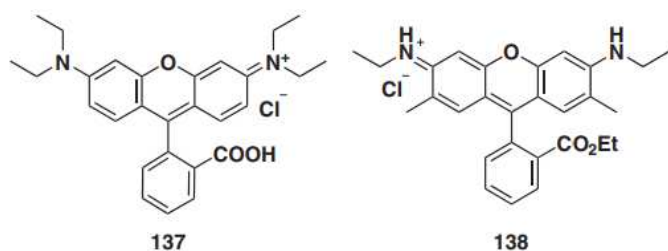
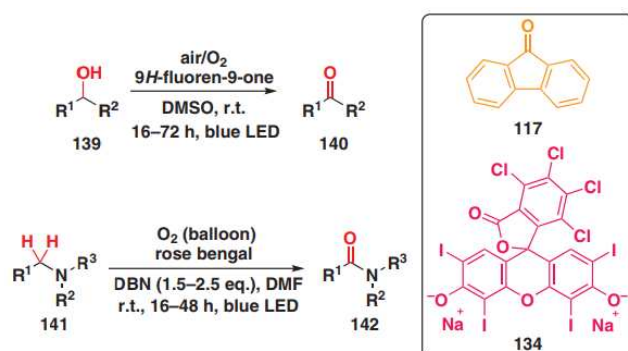


Figure 14 Common rhodamine organic dyes used as photoredox catalysts

5.2.10 Examples of Organic-Dye-Catalyzed Photoredox Reactions

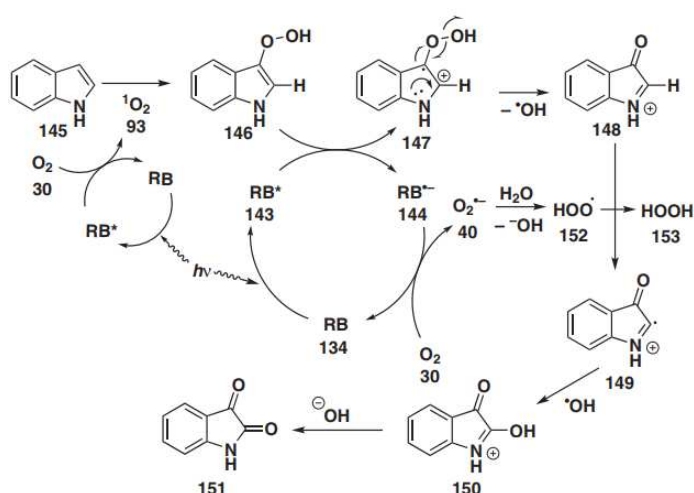
The oxygenation of alcohols and amines is an illustrative example of a photoredox reaction in which an organic dye is used as a photocatalyst. Our group has developed protocols for the oxidation of nonactivated alcohols **139** and for the oxygenation of tertiary amines **141** by using 9H-fluoren-9-one (**117**) or rose bengal (**134**), respectively, in the presence of air or oxygen and a blue light-emitting

diode (LED) to give corresponding ketones **140** or amides **142**, respectively (Scheme 16).⁵⁶ The normal synthesis of carbonyl compounds or amides requires the use of a stoichiometric amount of an oxidant such as iodosobenzene or a peroxide compound. This results in the formation of stoichiometric amounts of byproducts that are potentially toxic and harmful. By switching to oxygen as the oxidant, the formation of byproducts from the organic oxidants is eliminated, thereby increasing the greenness of the oxidation reaction.⁸¹ In the oxidation of amines to amides, a catalytic quantity of the base 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) is added for hydrogen abstraction.⁸²



Scheme 16 Oxidation of alcohols and amines by using a benzophenone (**117**) or a xanthene (**134**) as the photocatalyst

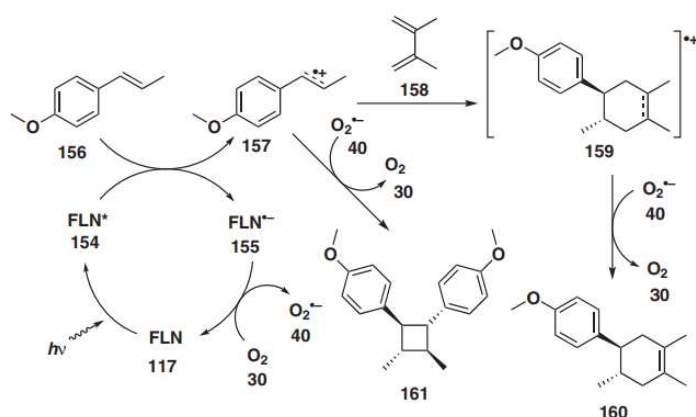
The synthetic variety of organophotocatalysis is illustrated by another application of rose bengal. In 2020, our group reported the use of rose bengal for the dearomatization of indoles and pyrroles to value-added scaffolds for the synthesis of various pharmaceuticals with anticancer, antitumor, antiviral, and antiinflammatory properties.⁷⁹ Rose bengal (**134**) is excited by light and quenched by oxygen (**30**) to form singlet oxygen (**93**), which attacks indole (**145**) to form the corresponding peroxy species **146** (Scheme 17). This is further oxidized to generate the rose bengal radical anion (**144**) together with **147**, which eliminates a hydroxyl radical to form cation **148**. A second SET occurs between **22** and **144** and oxygen (**30**) to produce a superoxide radical (**40**), which reacts with water to form a peroxide radical (**152**). This radical abstracts a hydrogen atom from cation **148** to generate **149** and hydrogen peroxide (**153**). Recombination of **149** and a hydroxyl radical forms hydroxy ketone **150**, which is transformed into the desired product **151** by deprotonation by OH⁻.



Scheme 17 The use of rose bengal (**134**) to dearomatize indoles to value-added scaffolds

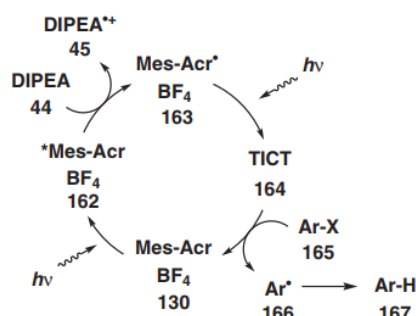
Simple ketones such as 9H-fluoren-9-one (**117**) can act as a photocatalyst for various organic transformations and its use in (aza)Diels–Alder reactions has been reported by our group (Scheme 18).⁶⁵ Various cyclohexene derivatives, as well as dihydropyridinone derivatives, were obtained in high

to excellent yields by using this strategy. Furthermore, in the absence of a diene, a [2+2] cycloaddition was observed. Some cyclobutane derivatives show promising properties as anticancer, antiviral, or antifungal pharmaceuticals. Hence, we synthesized two bioactive cyclobutanes in high yields by using 9H-fluoren-9-one (FLN; **117**) as the organophotocatalyst. The mechanism is shown in Scheme 18. First, 9H-fluoren-9-one (FLN; **117**) is excited by light and quenched by *trans*-anethole (**156**), which is converted into its radical cation **157**. The catalytic cycle is closed by a second SET of FLN^{•−} (**155**) with oxygen (**30**) to form a superoxide radical (**40**). Radical cation **157** undergoes a [4+2] cycloaddition with diene **158** to form radical cation **159**. Lastly, a second SET with the superoxide radical (**40**) occurs to form the desired cyclohexane derivative **160**. In the absence of a diene, radical cation **157** undergoes a [2+2] cycloaddition with itself through a second SET with a superoxide radical (**40**) to form the cyclobutane derivative **161**.



Scheme 18 The use of 9H-fluoren-9-one (**117**) for light-promoted Diels–Alder reactions

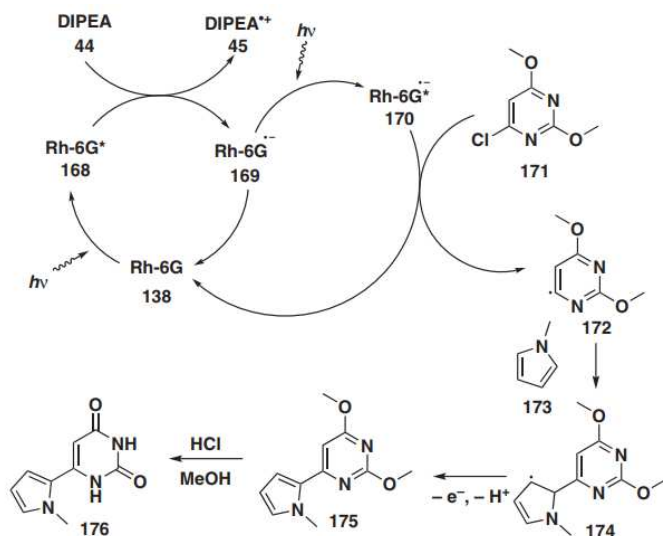
Another example is the reductive dehalogenation of aryl halides reported by Nicewicz and co-workers (Scheme 19).⁸³ They made use of an acridinium salt as the organophotocatalyst. First, the organic dye **130** is excited by light to generate Mes-Acr^{•+} (**162**). Subsequently, this undergoes an SET with DIPEA (**44**), generating Mes-Acr^{•+} (**163**) and the corresponding amine radical cation **45**. Mes-Acr^{•+} is again excited by light, generating a highly reducing twisted intramolecular charge-transfer state (TICT; **164**), which undergoes an SET with an aryl halide **165**, generating an arene radical anion and restoring the photocatalyst. Finally, the arene radical anion fragments to yield an aryl radical **166**, which abstracts a hydrogen atom from the amine radical cation to form the desired product **167**.



Scheme 19 Dehalogenation of aryl halides by using an acridinium salt as the photocatalyst

The use of a rhodamine-based organophotocatalyst is illustrated by a reaction developed by König and co-workers,⁸⁴ who synthesized arylated nucleobases from substituted pyrimidine compounds (Scheme 20). They proposed a mechanism in which rhodamine 6G (Rh-6G; **138**) is excited by light and quenched by DIPEA (**44**) to form Rh-6G^{•−} (**169**) and **45**. The radical anion **169** undergoes a second photoexcitation to form **170**, which reduces the substituted pyrimidine **171** to radical **172**. After that, this radical is trapped by a heteroarene, a double bond, or a substituted arene **173** to provide radical **174**.

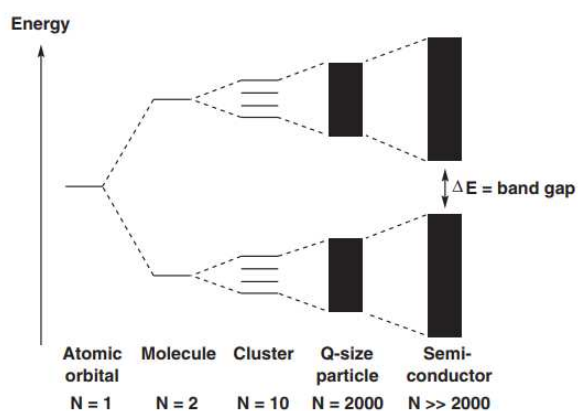
After oxidation and rearomatization, product **175** is formed. The product reacts further with HCl to give the desired product **176**.



Scheme 20 Synthesis of an arylated nucleobase by using a rhodamine 6G as the photocatalyst

5.3 Semiconductors

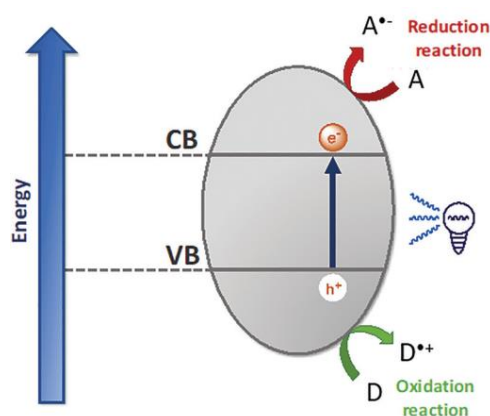
Isolated atoms contain electrons that occupy atomic orbitals, each of which has a discrete energy level. When atoms form a molecule, their atomic orbitals overlap. Moreover, the Pauli principle states that two or more identical electrons cannot occupy the same quantum state within a molecule. Thus, when two identical atoms combine, their atomic orbitals split into two degenerate molecular orbitals with different energies. If a large number N of identical atoms form a solid (such as a crystal), each atomic orbital splits into N degenerate molecular orbitals, each with its own energy level. Because there are many atoms in a solid, the energy levels are very closely spaced in energy and can be considered as a continuous energy band. In some cases, however, a band gap is formed between ranges of energy not covered by any band. Such solids are called semiconductors and can act as photocatalysts (Scheme 21). The most commonly used semiconducting photocatalyst is titanium dioxide.⁸⁵ More recently, other metal centers, such as cadmium in cadmium sulfide (CdS), have been used.⁸⁶ Furthermore, metal-free semiconductors such as graphitic carbon nitride (g-C₃N₄) have been also used for improved sustainability.⁸⁷



Scheme 21 Electron band structure of a semiconductor

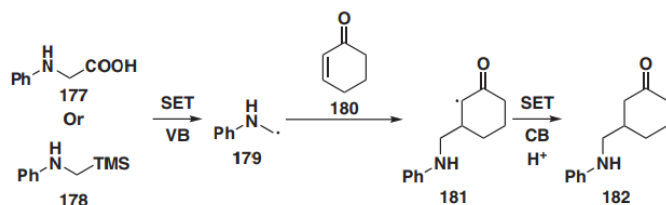
Semiconductor photocatalysts are activated by the absorption of light (photons) of energies that exceed the band-gap energy. From here on, an electron is promoted from the valence band (VB) to

the conduction band (CB), leaving a positive hole in the valence band. Each band can now function as a photoredox catalyst.^{85a} Positive holes in the valence band want to gain electrons and, therefore, catalyze oxidation processes. Excess electrons in the conduction band catalyze reduction processes. The size of the band gap determines the optical properties and the color. Semiconductors with a band gap of between 1.5 and 3.0 eV absorb visible light and have red to violet colors. Recombination, the process in which excited electrons fall back to the VB, is however possible if the band gap is very small. The principle of semiconductor photocatalysis is illustrated in Scheme 22.



Scheme 22 Principle of semiconductor photocatalysis. A = Acceptor; D = Donor.

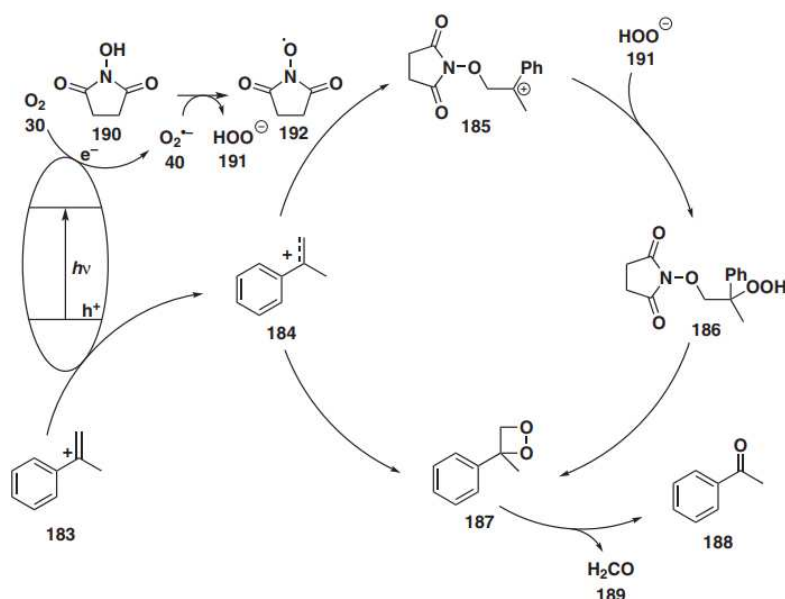
An example of a semiconductor-catalyzed photoredox reaction is the addition of α -aminoalkyl radicals to various substrates such as α,β -unsaturated ketones or alkenes by using g-C₃N₄. This concept was reported by Rueping and coworkers^{85b} and is illustrated in Schemes 22 and 23. First, an electron from g-C₃N₄ is excited from the VB to the CB. At the VB, substrate **177** or **178** is oxidized to form the radical **179**, with the elimination of CO₂ or TMS, respectively. Radical **179** attacks the double bond of cyclohex-2-en-1-one (**180**) to form the radical **181**. At the CB, this radical is reduced to form the carbanion, which is immediately protonated to form the desired product **182**.



Scheme 23 Semiconductor-mediated photoredox reaction for α -aminoalkyl radical addition to alkenes

The use of a photoredox system for the oxidative cleavage of C=C double bonds as an alternative to the ozonolysis reaction was first introduced by Inoue and co-workers.⁸⁸ It was not until 2020 that our group reported a metal-free heterogeneous photocatalyst for this transformation.⁸⁹ We used polymeric carbon nitride as the photocatalyst in the presence of hydroxysuccinimide (NHS) as a hydrogen donor (Scheme 24). Interestingly, this photoredox system was also efficient when natural sunlight was used. First, incident light on g-C₃N₄ excites an electron from the VB to the CB. The positive hole in the VB oxidizes the styrene derivative **183** to the corresponding radical cation **184**, and the excess electrons in the CB reduce oxygen (**30**) to a superoxide radical anion (**40**). Then, a [2+2] cycloaddition between the superoxide radical and the radical cation generates **187**, which cleaves to form the desired ketone **188** and formaldehyde (**189**). However, another pathway was also found that involved NHS (**190**). The superoxide anion (**40**) abstracts a hydrogen atom from NHS to produce **192** and a hydroperoxide anion (**191**). Then, **192** attacks the radical cation **184** to form **185**, which reacts

further with the hydroperoxide radical to form **186**. Finally, intermediate **187** forms and is cleaved to afford the desired ketone **188** and formaldehyde (**189**).



Scheme 24 Semiconductor-mediated photoredox reaction for the oxidative cleavage of C=C bonds

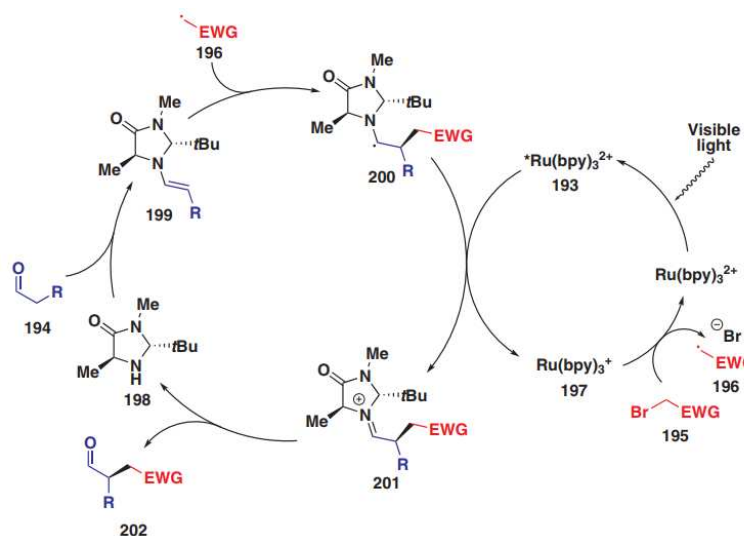
6 Dual Catalysis

A simplistic representation of traditional catalysis involves a lowering of the activation energy of a single substrate. Afterward, this substrate reacts with an inactivated substrate to form the product. However, substrates that require additional activation will not react by using traditional catalysis. One way to solve this problem is by using multistep processes, such as one-pot reactions.⁹⁰ However, multistep processes are often avoided due to their need for stoichiometric quantities of multiple reactants. Another solution is to use a dual-catalysis system that makes use of two or more catalysts in one step to activate two or more substrates. Generally, dual catalysis relies on narrowing the HOMO–LUMO gap for better interaction of the substrates by lowering the LUMO of Substrate 1 and raising the HOMO of Substrate 2. Due to the activation of two or more substrates, organic transformations can occur that would not be possible by using only one catalytic cycle.⁹¹

Dual catalysis can be subdivided into three classes: cooperative, synergistic, and multifunctional catalysis. In synergistic catalysis, both substrates are activated simultaneously, each by a unique catalytic cycle that is interconnected with other catalytic cycles. On the other hand, both cooperative and multifunctional catalysis involve only one catalytic cycle, with cooperative catalysis making use of two catalysts and multifunctional catalysis using one catalyst only.⁹¹

Photoredox catalysts can be used synergistically with other catalysts. In such dual-catalyst systems, the photocatalyst is used to absorb light, which is followed by activation of an organic molecule.²⁴ The other catalyst is used to further convert the generated intermediates.⁹²

One of the first reported dual-catalyst systems for photoredox catalysis and organocatalysis was reported by MacMillan and co-workers in 2008.⁹³ Their work involved the α -alkylation of aldehydes **194** by using electrophiles such as alkyl halides **195** (Scheme 25). The alkyl halide is reduced to a radical species **196** by using a Ru or Ir photocatalyst **197**. This radical then adds to an enamine intermediate **199**, formed from the aldehyde **194** and an amine catalyst **198**. The resulting radical **200** is oxidized to an iminium ion **201**, which can be hydrolyzed to provide the α -alkylated aldehyde **202**. By using a chiral organocatalyst, chirality is obtained in the product.



Scheme 25 Trifluoromethylation of aldehydes through synergism between photoredox catalysis and organocatalysis

7 Conclusions

In conclusion, photoredox catalysis has been explained in this tutorial account. It is clear that photoredox chemistry forms a greener and more sustainable approach than classical thermal redox reactions for the synthesis of various compounds.⁹⁴ Over recent decades, many photoredox systems have been reported, ranging from CO₂-reduction reactions to more advanced enantioselective radical-addition reactions.^{95,96} The main reason for this is the ease of photoredox reactions, their ability to generate highly reactive radicals, and the possibility of generating compounds that cannot be synthesized through classical thermal organic chemistry.

Recent advances in photoredox chemistry indicate the numerous possibilities of this sustainable approach. In fact, many new directions are found within photoredox catalysis. Much attention has been paid to methods for enhancing the efficiencies of photocatalysts. One of them involves a combination of two semiconductors to form a Z-scheme, since these systems are effective for separating electron-hole pairs. In this way, undesired recombination phenomena can be reduced or completely eliminated to enhance photocatalytic efficiency. Another involves metal loading of semiconductors. In fact, single-atom photocatalysis is one of the most active research topics within photoredox catalysis, because these catalysts possess intriguing reactivity and selectivity due to their unsaturated coordination sites, excellent charge-transfer dynamics, and captivating abilities to harvest light for photocatalytic reactions. Moreover, they are excellent catalysts for understanding structure-property relationships ascribed to their atomic-scale structure.⁹⁷ However, these catalysts have almost solely been used for the photocatalytic reduction of CO₂, photocatalytic H₂ generation, photocatalytic water splitting, and for photocatalytic nitrogen reduction.⁹⁸

Another new direction in photoredox catalysis is the use of dopants in heterogeneous photocatalysts. In this way, the bandgap can be tuned to increase the photosensitizing ability in the visible range. Moreover, dopants can have positive effects on the catalyst, giving it a better efficiency, stability, conductivity, etc.⁹⁹

Although photoredox catalysis has many advantages and a wide range of applications, it is still a field in organic chemistry that is not very clearly understood. As a result, photoredox chemistry provides several opportunities for the development of excellent chemistry.¹⁰⁰ In fact, in recent decades a lot of research has been devoted to photoredox catalysis and has yielded excellent outcomes, for example,

in Z-scheme heterojunctions, single-atom photocatalysis, and others. Moreover, with the discovery of dual catalysis, which can activate two or more substrates for a transformation that would not be possible by using only one catalytic cycle, new avenues have been found for synthesizing challenging compounds in a sustainable way. In particular, the combination of a photocatalyst with a chiral catalyst gives the opportunity to synthesize various compounds enantioselectively.¹⁰¹ We expect that many more advances will appear in the near future.

Conflict of Interest

The authors declare no conflict of interest.

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