Visible light-mediated photoredox catalysis has emerged as one of the fastest growing fields in organic synthesis. Typically, a photoactive catalyst absorbs light in the visible region and participates in single electron transfer processes with organic substrates. This is a mild, economical and environmentally friendly approach to promote radical-based organic transformations and potentially unlock unique reaction pathways.

The most well studied photoredox catalysts are complexes of ruthenium and iridium. Typical examples include tris(2,2'-bipyridine)ruthenium(II) and tris[2-phenylpyridinato-C^2,N]iridium(III). These complexes are unique in that the ligand-centered π* orbital is lower in energy than the metal-centered e_g orbital.

Upon irradiation with visible light, an electron is transferred from the t_2g orbital (metal) to the π* orbital (ligand) which (after rapid intersystem crossing) results in an excited triplet state. The long lifetime of the triplet state (1100 ns) allows the photocatalyst to engage in single electron transfer (SET) reactions with organic molecules.

Excited photocatalysts will initially act as either oxidants (reductive quenching cycle) or reducing agents (oxidative quenching cycle) depending on the substrate of the reaction. The resulting metal species will then undergo a second single electron oxidation/reduction, returning the catalyst to its original oxidation state. Substrates of photocatalyzed reactions may participate in either redox step in the catalytic cycle and will often participate in both. Redox potentials can be readily tuned for a given reaction by altering the metal used or changing the ligands (see above for examples).
Early examples

Chemical reactions that are promoted by light absorption (photochemistry) have been studied since the early 20th century. The application of photocatalysts as a means of harvesting light energy in fields such as artificial photosynthesis and the production of chemical fuels has also been extensively studied. In contrast, up until recently, the application of photocatalysis for organic synthesis using visible light was relatively rare. Some key early examples, which paved the way for the recent explosion in this field, are outlined below.

One of the earliest examples of visible light photoredox catalysis was the reduction of electron-poor alkenes using Ru(bpy)$_2$Cl$_2$ as the catalyst and BNAH as a stoichiometric reducing agent.

\[
\text{CO}_2\text{Me} + \text{NHN}_{\text{Ar}} \xrightarrow{\text{Ru(bpy)}_2\text{Cl}_2 (2 \text{ mol})} \text{MeOH, pyridine \text{ visible light}} \rightarrow \text{CO}_2\text{Me}
\]

Pac, *JACS*, 1981, 103, 6495

Fukuzumi and co-workers provided an early example of reductive dehalogenation of α-bromocarbonyl compounds using Ru(bpy)$_2$Cl$_2$ as a photocatalysis.

\[
\text{Ph} - \text{Me} \xrightarrow{\text{Ru(bpy)}_2\text{Cl}_2 (2 \text{ mol})} \text{MeCN \text{ visible light}} \rightarrow \text{Ph} \text{Me}
\]


One of the first examples of photocatalytic oxidation was reported by Cano-Yelo and Deronzier in 1984. A ruthenium photocatalyst along with a stoichiometric aryldiazonium salt could be employed for the oxidation of benzylic alcohols to aldehydes.

\[
\text{OH} + \text{PhN}_{2} \xrightarrow{\text{Ru(L)}_2\text{Cl}_2 (2 \text{ mol})} \text{MeCN \text{ visible light}} \rightarrow \text{H} + \text{Ph}
\]


Fukuzumi also reported the use of the 9-mesityl-10-methylacridinium ion as an effective photoredox catalyst. The first reaction reported using this catalyst was the cycloaddition of dioxygen with anthracene derivatives. This catalyst has since been applied to a range of other transformations (see section 3).

\[
\text{Acridinium cat.} \xrightarrow{\text{MeCN, O}_2 \text{ visible light}} \text{Me}
\]

Fukuzumi, *JACS*, 2004, 126, 15999
Seminal reports

While the examples of published during the 1980s and 1990s provided some early precedent for the concept of visible light-mediated photoredox catalysis, the dramatic increase of interest in this field is often attributed to 3 key papers from 2008-2009.

In 2008, MacMillan et al. demonstrated that it is possible to merge SOMO organocatalysis and photoredox catalysis. This dual-catalysis system expanded the scope of enamine catalysis to include alkyl halides as electrophiles.

MacMillan, Science, 2008, 322, 77

Concurrently, Yoon and co-workers demonstrated that the intramolecular [2+2] cycloaddition of dienones can be promoted by photoredox catalysis. This report demonstrated how photoredox catalysis allows known, redox-mediated processes to proceed under relatively mild conditions.

Yoon, JACS, 2008, 130, 12886

In 2009, Stephenson employed photoredox catalysis for the reductive cleavage of aliphatic halides. A broad range of functional groups were tolerated and this transformation provided an alternative to the use of toxic tin reagents (commonly employed for reductive dehalogenation).

Stephenson, JACS, 2009, 131, 8756
1. Photoredox reactions catalyzed by ruthenium or iridium complexes

Photoredox-catalyzed reactions can be classified according to whether the substrates undergo a net oxidative, reductive or redox neutral transformation. For net oxidative or net reductive reactions a stoichiometric oxidant or reducing agent is required, whilst in redox neutral processes substrates will undergo both single electron reduction and oxidation as part of the reaction mechanism.

1.1 Net oxidative reactions

1.1.1 Formation of iminium ions via photoredox catalysis

Iminium ions can be generated by two-electron oxidation of tertiary amine substrates. Tertiary amines are good electron donors, which can readily form aminium radical cations by single-electron oxidation. The C-H bond dissociation energy of the α-protons of an aminium radical cation is low, allowing a reducing agent to abstract a hydrogen atom to form an iminium ion. Alternatively, the aminium radical cation can undergo α-deprotonation to form an α-amino radical, which then undergoes a second single electron oxidation to give the iminium ion.

Iminium ions generated by photoredox catalysis can react with nucleophiles to form new carbon-carbon bonds. An early example is the photoredox-catalysed aza-Henry reaction via an iminium ion intermediate. Oxygen acts as the terminal oxidant for this net oxidative process.

Subsequent studies have shown that the iminium ions generated from tetrahydroisoquinoline scaffolds can be trapped with a broad range of nucleophiles.

Stephenson, JACS 2010, 132, 1464; Wang, ACIE, 2012, 51, 8050
1.1.2 Oxidative cyclizations

Photocatalysis has also been used for the synthesis of benzothiazoles and indoles by oxidative cyclization, with oxygen as a terminal oxidant.

1.2 Net Reductive reactions

Net reductive reactions are those in which the substrate is reduced using photoredox catalysis in the presence of a stoichiometric reducing agent.

1.2.1 Alkene reduction

Photoredox catalysis has been used for the reduction of electron-poor alkenes, with 1-benzyl-1,4-dihydronicotinamide (BNAH) used as the stoichiometric reductant. BNAH reduces the excited ruthenium catalyst and the resultant Ru(I) complex then reduces the electron deficient alkene.
1.2.2 Ring opening/allylation

An iridium photocatalyst in combination with stoichiometric Hantzsch ester has been used for the tandem epoxide-opening/allylation of ketoepoxides.


1.2.3 Reductive dehalogenation

Reductive dehalogenation can be effected under mild conditions using photoredox catalysis. The reaction proceeds via a reductive quenching cycle, with DIPEA acting as the terminal reducing agent. Labeling studies showed that the DIPEA is the predominant hydrogen source for the radical intermediate.

Stephenson, *JACS*, 2009, 131, 8756
Radical intermediates formed by reductive dehalogenation can be used for the construction of C-C bonds. One example is the functionalization of indoles, pyrroles and furans with activated halides.


Photoredox-catalyzed reductive dehalogenation/indole alkylation was later employed as the key coupling step for the synthesis of gliocladin C.

Stephenson, *ACIE*, **2012**, *41*, 9655

A major limitation of ruthenium-catalyzed reductive dehalogenation is that it is only effective for activated halides (adjacent to an acyl or aryl group). To expand the scope of this reaction an iridium photocatalyst can be employed. The greater reduction potential of Ir-complexes enables the reduction of unactivated alkyl, vinyl and aryl halides.

Redox neutral reactions

In redox neutral reactions the substrates participate in both the reductive and oxidative steps of the photocatalytic cycle, with no change to the overall oxidation state from starting materials to product. The ability to have both oxidation and reduction processes occurring simultaneously for one overall reaction can enable reaction pathways that would otherwise not be possible.

1.3.1 [2+2] Cycloadditions

Thermally-forbidden [2+2] cycloadditions can be promoted using photoredox catalysis. An example of this is the intramolecular [2+2] cycloaddition of dienones to form cyclobutane derivatives.

Intermolecular [2+2] cycloadditions are also possible and proceed with good diastereoselectivity. To favour formation of non-dimeric products, it is important that one of the starting materials is an aryl enone. This reaction has been carried out enantioselectively by using Eu(OTf)₃ as a Lewis acid with an amino acid-derived chiral ligand.

1.3.2 [4+2] Cycloadditions – Diels-Alder Reaction

While many Diels-Alder reactions proceed readily either under ambient conditions or when heated, [4+2] cycloaddition of an electron-rich diene with an electron-rich dieneophile is generally not possible, even at high temperature. Photoredox catalysis can be used to promote the [4+2] cycloaddition of two electron-rich starting materials.

Yoon, *JACS*, 2011, 133, 19350

1.3.3 C–H arylation of amines

The direct C–H arylation of amines with cyano-bearing aromatics can be catalyzed by an Ir-photocatalyst. This reaction was discovered by “accelerated serendipity”, an automated system where many combinations of catalysts and random organic substrates are rapidly screened to find novel and unexpected chemical reactions.

1.3.4 Late-stage methylation and cyclopropanation of bioactive heterocycles

Merck have applied photoredox catalysis for late-stage C–H methylation and cyclopropanation of drugs and drug-like compounds. The mild reaction conditions provide an excellent means to alter complex molecules in the presence of a range of functional groups.

![Diagram](image)

1.3.5 Trifluoromethylation

Direct C–H trifluoromethylation of aromatic and heteroaromatic compounds can be carried out using photoredox catalysis, with triflic chloride acting as the CF$_3$ source. This reaction can be used for late-stage functionalization of complex molecules.

![Diagram](image)

A more mild and scalable photocatalytic trifluoromethylation method has also been developed, with trifluoroacetic anhydride as a readily available CF$_3$ source that is easier to handle than triflic chloride. For this reaction pyridine N-oxide acts as a redox auxiliary, which forms a TFA-ester adduct with a significantly lower oxidation potential than TFAA.
1.3.6 Decarboxylative couplings

Radical decarboxylation is an attractive method for organic synthesis. The major advantages are that carboxylic acids are abundant and inexpensive, the radical intermediates produced can be converted into many chemical products and that CO$_2$ is produced as a traceless byproduct. While there are many known methods for radical decarboxylation, these tend to require harsh conditions, prefunctionalization of the acid or high energy UV light. Photoredox catalysis offers a mild alternative for generating radical intermediates from carboxylic acids.

Photoredox catalysis can be employed for the radical decarboxylation of α-amino acids and α-oxo acids. The radical intermediates generated can be coupled to cyano-substituted aromatic compounds.

Photoredox-mediated decarboxylation has been employed for the conjugate addition of a range of carboxylic acids to Michael acceptors, providing a convenient alternative to the generation of organometallic nucleophiles. Methods have also been developed for C-F bond formation via radical decarboxylation. While examples were limited to aryloxyacetic acids, conditions were later developed to allow the decarboxylative fluoronation of a broad range of carboxylic acids.

\[ \text{R} \text{COOH} + \text{R} \text{CON} \rightarrow \text{R}_1 \text{COCH} \text{R}_2 \]  
\[ \text{X=CN} \]


Photoredox-promoted decarboxylative fragmentation of an acyloxyphthalimide followed by radical conjugate addition was employed as the key step in the synthesis of aplyvioline. This reaction generates an all-carbon quaternary centre with high stereoselectivity.

Overman, ACIE, 2012, 51, 9576
2 - Dual catalysis

Photoredox catalysis can also be incorporated into a “dual catalysis” system, whereby the photocatalytic cycle is coupled to a second catalytic cycle. This can allow organic transformations that would not be possible by applying either catalyst independently.

2.1 - Enamine catalysis

Since their first report in 2008, MacMillan and co-workers have significantly expanded the scope of the enamine/photoredox dual catalysis system. \( \alpha \)- and \( \beta \)-alkylation of aldehydes and ketones using a range of electrophiles is now possible.

2.1.1 \( \alpha \)-Alkylation

Aldehydes and ketones can be coupled with alkyl halides by employing a chiral secondary amine catalyst along with a Ru- or Ir-photocatalyst. This approach generally provides products with good enantioselectivity. The catalytic cycle involves reduction of the alkyl halide to generate a radical species, which then adds to an enamine intermediate formed from the amine catalyst and the aldehyde substrate. The resulting \( \alpha \)-amino radical is oxidized to an iminium ion, which is then hydrolysed to provide the alkylated product and regenerate the amine catalyst.

2.1.2 β-Functionalization

Direct β-functionalization of saturated carbonyl compounds is a particularly challenging transformation, which can now be carried out using photoredox/enamine dual catalysis.

These reactions all proceed via the same catalytic cycle. In the case of substituted benzonitriles, the benzonitrile is first reduced by the excited photocatalyst. The photocatalyst then oxidizes an enamine intermediate, providing an enaminyl radical cation that is subsequently deprotonated to generate a β-centered radical. Combination of the radical intermediates followed by elimination of cyanide gives the β-arylated product.


2.2 – Nickel catalysis

Recently, photoredox catalysis in combination with nickel catalysis has been used to unlock novel reaction pathways. Nickel/photoredox dual catalysis was first used for the coupling of α-amino carboxylic acids or benzyl trifluoroborates with vinyl or aryl halides.

In either case the catalytic cycle is the same, with the photocatalyst required for generation of a radical species from the carboxylic acid or trifluoroborate starting materials and for reducing Ni(I) to Ni(0) to restart the nickel catalytic cycle.

It was later shown the oxygen is essential for this reaction; no reaction was observed when the solvent was rigorously degassed. The order of the oxidative addition and radical addition in the nickel catalytic cycle has also been debated.
Other reactions that can be carried out using nickel/photoredox dual catalysis include: 1) cross-coupling of dimethylaniline with aryl halides, 2) cross-coupling of secondary trifluoroborates with aryl halides and 3) ether synthesis via coupling of alcohols with aryl bromides.


2.3 – Hydrogen atom transfer (HAT) catalysis

The variety of radical species generated using photoredox catalysis can be expanded by incorporation of a hydrogen atom transfer (HAT) catalyst. The HAT catalyst (generally a thiol or amine) is oxidized by the photocatalyst, and the resulting radical intermediate removes a hydrogen atom from the starting material to generate the desired radical.

Photoredox/HAT dual catalysis has been employed for the alkylation of heteroarenes, with alcohols used as benign and readily available alkylation agents. Under these conditions methanol can be used as methylating agent for a range of heteroarenes. A similar catalytic system can be used for the formation of lactones from alcohols and methyl acrylate. These reactions both proceed by the formation of an $\alpha$-oxo radical species via hydrogen atom transfer.

Other examples of HAT/photoredox catalysis include: 1) the coupling of benzonitriles or imines with benzyl alcohols and 2) direct C-H allylic arylation with benzonitrile species.
2.4 – Palladium catalysis

Pd/photoredox catalysis has been employed for the C-H arylation of arenes using aryl diazonium salts. This transformation can be catalyzed by palladium in the absence of a photoredox catalyst; however, high temperatures are required. Incorporation of a photocatalytic cycle allows the reaction to proceed under mild conditions.

The combination of a photocatalyst and a palladium catalyst can be used for the decarboxylative allylation of benzyl and α-amino allyl esters under mild conditions. These substrates cannot undergo decarboxylative allylation via an anionic pathway (i.e., in the absence of a photocatalyst).
In the proposed catalytic cycle the photocatalyst plays a role in both oxidizing the aniline species (which leads to decarboxylation) and in reducing the palladium π-allyl species to give an allyl radical.


2.5 – Copper catalysis

A dual copper/photocatalyst system has been employed for the fluoroalkylation of boronic acids. In comparison to other trifluoromethylation reactions, this transformation proceeds under relatively mild conditions and can tolerate halide-substituted boronic acids.

Sanford, JACS, 2012, 134, 9034

2.6 – Gold catalysis

A gold/photocatalyst system can be used for the oxy- and aminoarylation of alkenyl alcohols and amines with aryl diazonium salts.

Glorius, JACS, 2013, 135, 5505
2.7 – NHC catalysis

A combination of photoredox catalysis and NHC catalysis can be utilized for the oxidative coupling of tetrahydroquinolines and aldehydes. The reaction proceeds via attack of the highly nucleophilic Breslow intermediate on a photo-generated iminium ion, which provides acylated products with moderate to good enantioselectivity.

![reaction diagram]

Rovis, *JACS*, 2012, 134, 8094

3. Organic photoredox catalysts

Iridium and ruthenium complexes exhibit excellent photochemical properties making them extremely useful as photocatalysts; however, they do have some inherent disadvantages. These metal complexes can be expensive and relatively toxic, which can limit scale-up of photocatalyzed reactions. A number of organic dyes also exhibit the desirable photochemical properties required for photoredox catalysis, providing an attractive alternative to Ru- and Ir-complexes. These organic compounds tend to be cheaper, less toxic, easy to handle and, in some synthetic transformations, outperform inorganic catalysts. The main disadvantage of organic photocatalysts is the reduced flexibility for fine-tuning redox potential.

Eosin Y has been employed as a photoredox catalyst for the direct C–H arylation of heteroaromatic compounds. This provides a mild alternative to metal-catalyzed or base-promoted conditions which have been previously used for this transformation, and allows a range of functional groups to be tolerated.
Eosin Y can be used as an alternative photocatalyst for the $\alpha$-alkylation of aldehydes using the enamine catalysis system originally described by MacMillan.

Mesityl acridinium salts are also useful photocatalysts, exhibiting excellent oxidizing ability upon excitation with visible light (higher reduction potential than Ir-catalysts). A recent application of these catalysts is the anti-Markovnikov cyclisation of alkenols. These conditions provide the opposite regioselectivity to conventional catalytic methods for such cyclization reactions.

Similar conditions can be employed for the intermolecular anti-Markovnikov addition of a range of inorganic and organic species to alkenes.
In a recent report, a mesityl acridinium photocatalyst was employed for the site-selective C–H amination of arenes bearing an electron-donating group. This mild coupling can be performed in the presence of a range of functional groups allowing the generation of a range of simple and complex aminated aromatic compounds from readily accessible starting materials.

A chiral xanthone-based catalyst has been developed which can catalyze both inter- and intramolecular [2+2] cycloadditions in moderate to good enantiomeric excess.