Advances in Photocatalytic Organic Synthetic Transformations in Water and Aqueous Media

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ABSTRACT: Advances in visible light-photocatalyzed preparative synthetic organic transformations in water or aqueous media are studied. Both the convenience of visible light photocatalytic strategies to achieve synthetic organic transformations and the employment of water or aqueous mixtures make this approach a very resourceful methodology. Mechanistic aspects for such photocatalyzed processes are discussed. The effects of water in the stereoselectivity of some reactions and considerations regarding the improved enantioselectivity in chiral catalytic photoredox reactions are manifested with the use of water. The use of water as a result of a protocol improvement or environmentally friendlier methodology as compared to the same reaction performed in organic solvents are also considered. All these combined effects of water as a reaction medium or its very presence in photocatalytic reactions have an ultimate goal which is to diminish the environmental impact of synthetic and photocatalytic processes. This perspective highlights the progress and state of the art organic transformations realized by photocatalytic techniques in water or aqueous systems as well as water as a reactant. In this regard, aromatic substitution reactions, radical additions to carbon–carbon double bonds, photooxidation reactions, decarboxylation processes, and miscellaneous reactions are presented.

KEYWORDS: Photocatalysis in water, Enantioselective photocatalysis, Diastereoselective photocatalysis, Photocatalyzed arylations, Decarboxylative reactions, Photocatalyzed deoxygenations, Photocatalyzed photooxidations, Photocatalyzed cyclizations, Photocatalyzed ATRA

INTRODUCTION

Visible light photoredox reactions have recently found many applications, occurring under mild conditions and not requiring radical chemical initiators nor stoichiometric amounts of chemical reductants or oxidants for redox neutral reactions. As an irradiation source, visible light reduces waste and curtails reaction expenses significantly. Photoredox catalysis is also tolerant of many functional groups present in organic scaffolds.¹ On the other hand, water or water mixtures with organic solvents is another facet of green chemistry that has been endorsed by organic chemists and industry alike. In this sense, the association of light and water could offer new perspectives and increase the chemists' armamentarium for functionalization reactions triggered by visible light photoredox catalysis, as both water and visible light are safe, inexpensive, and clean.^{2,3}

The majority of photocatalytic transformations conducted in water promote the removal of contaminants, either organic or organometallic.⁴ This is often done by the notorious redox properties of photocatalysts in their excited states, which convert them into highly oxidizing or reducing species, thus producing reactive intermediates that enable degradation of

contaminants without the need of chemical strong oxidants or reductants.⁵

However, preparative organic photoredox catalysis in water or aqueous media is not well developed on account of the poor solubility of most organic substrates and catalysts in water or aqueous solvents and difficulties in carrying out photoreactions in heterogeneous media. In this perspective, we describe organic synthetic transformations brought about by visible light photoredox catalysis in water or aqueous media.

Examples where water plays very significant roles in the reaction outcomes are provided. There are occasions where, in its absence, the desired product is not formed at all, or water itself also intervenes as a proton donor or oxygen donor or is necessary in stoichiometric amounts as a coreactant. Even more intriguing effects can be observed when water plays

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important roles in the stereoselectivity of the reaction, influencing and driving the formation of products with high diastereoselectivity as opposed to the same reactions performed in organic media. The effect of water for improving enantioselectivity in chiral catalytic photoredox reactions also are studied and explored with representative examples.

In other examples, water is used to solubilize some of the reactants or photocatalysts or employed as a result of a protocol improvement or environmentally friendlier methodology as compared to the same reaction performed in organic solvents. All these combined effects of water as a reaction medium or its very presence in photocatalytic reactions have an ultimate goal which is to diminish the environmental impact of the synthetic and photocatalytic process. There is a recent review article⁶ on visible light-mediated organic transformations in water with special emphasis on the type of photocatalyst (transition metal complexes, organic dyes, solid-supported photocatalysts, semiconductors, and those without photocatalysts).

In this perspective, we describe and emphasize the organic synthetic advantage of carrying out visible light-photocatalyzed reactions in water or aqueous media and classify the perspective into sections according to the synthetic transformation or synthetic goal accomplished. Among the organic transformations enabled by photocatalysis in water or aqueous mixtures, radical additions to carbon–carbon double bonds, aromatic substitution reactions and arylations, decarboxylative reactions, photooxidation and cyclization processes, and miscellaneous reactions are herein described. The mechanisms of the photocatalytic reactions are also given in order to cast some light onto the role of the aqueous medium in the photoreaction. Although this account does not pretend to be an exhaustive review of the literature, representative examples of the above photocatalyzed transformations in water or aqueous media are discussed.

■ PHOTOCATALYZED SUBSTITUTIONS OF ARENES IN AQUEOUS MEDIA

Homolytic Aromatic Substitutions with Ulterior Cyclizations. Homolytic aromatic substitution (HAS) is a convenient synthetic strategy to replace aromatic hydrogen atoms by suitable substituents in order to form new C–C or C–heteroatom bonds. Even more interesting are HASs ensuing cyclization reactions that form new cyclic scaffolds.

Strategies for the photocatalytic syntheses of phenanthridines in organic media contemplate tandem radical addition–cyclization of 2-isocyanobiphenyls and 2-(1-azidovinyl)-1,1'-biaryls with diverse radical precursors or the N–O bond homolysis cyclization reactions of oxime ethers and oxime esters.^{7–19}

A protocol for the preparation of phenanthridine-6-carboxylates from *N*-biaryl glycine esters in water was achieved by Natarajan and colleagues.²⁰

The authors²⁰ found the optimized reaction conditions were 2-([1,1'-biphenyl]-2-ylamino)acetate (0.3 mmol) as a substrate and 5 mol % of Rose Bengal as a photocatalyst in water under 34 W blue LED ($\lambda = 425$ nm) irradiation for 30 h in the presence of air. In order to explore the substrate scope, the authors²⁰ investigated a series of *N*-biaryl glycine esters (substituent effects on the aromatic ring with glycine ester group), as illustrated in Scheme 1.

Scheme 1. Scope of Reaction with Substituted Biaryls

As observed from Scheme 1, both electron-withdrawing and -donating substituents on the biaryl moiety produce high yields of substituted phenanthridines.

The authors²⁰ proposed a reaction mechanism such as that depicted in Scheme 2.

Scheme 2. Proposed Reaction Mechanism

Independent experiments conducted with dihydrophenanthridine 4 (Scheme 2) under irradiation with Rose Bengal as the photocatalyst under the optimized reaction conditions afforded phenanthridine 6 in quantitative yield, purporting that oxidation can occur within the photocatalytic cycle. To start with, excited photocatalyst Rose Bengal (RB^*) is able to oxidize 2-([1,1'-biphenyl]-2-ylamino)acetate to radical cation 1 yielding the radical anion of RB^* which reduces the oxygen present to an anion superoxide. This anion superoxide is, in turn, able to reduce intermediate radical cation 1 to radical 2, which upon homolytic aromatic substitution renders cyclohexadienyl radical intermediate 3. Peroxyl radical abstracts a H atom from intermediate 3 rendering dihydrophenanthridine 4. In a second catalytic cycle, oxidation of 4 takes place to afford phenanthridine 6.²⁰

The construction of other cyclic organic frameworks through photocatalysis has also been reported in water, such as the synthesis of CF₃-substituted dihydroisoquinolinones via the photoinduced radical cascade cyclization of *N*-allylbenzamides with CF₃SO₂Na^{6,21} (Scheme 3A), the methylsulfonyl-

Scheme 3. Photocatalytic Syntheses of Dihydroisoquinolinones (A), Sulfone-Containing Benzo[*a*]Fluoren-5-ones (B), Sulfonated 1-Alkylindolin-2-one (C), and Synthesis of Phenanthrols (D)

tion/bicyclization of 1,7-enynes with dimethyl sulfoxide for the synthesis of sulfone-containing benzo[*a*]fluoren-5-ones in the presence of iridium polypyridyl complexes in water^{6,22} (Scheme 3B), the direct preparation of sulfonated oxindoles through the metal-free photocatalytic reactions of *N*-arylacrylamides and sulfinic acids^{6,23} (Scheme 3C), or the synthesis of phenanthrols via the intramolecular cyclization and aromatization reaction of alkyl 1,1'-biaryl-2-ones under Eosin photocatalysis^{6,24} (Scheme 3D). All these reactions have been previously reviewed and are succinctly compiled in Scheme 3.⁶

Arylation Reactions. Radical arylation reactions are synthetic strategies that allow the formation of new C_{Ar}–C_{Ar} bonds or C_{aliph}–C_{Ar} bonds from aryl radicals.²⁵ There are extensive studies on photocatalyzed arylation reactions.^{26,27} Metal-free photocatalytic arylations²⁸ have been reported with numerous photocatalysts, such as carbon nitride-based catalysts.³⁰

A few examples of photocatalytic arylations in aqueous media have been informed.³¹

Xue and colleagues³² have developed a photocatalytic arylation reaction of electron-deficient heteroarenes in water starting from aryldiazonium salts. The authors³² optimized the reaction conditions using tetrafluoroborate 4-methoxybenzenediazonium salt (0.3 mmol), Ru(bpy)₃Cl₂ as the photocatalyst (2.5 mol %), 4-trifluoromethylpyridinium hydrochloride, and an electron-poor heteroaromatic compound (1.5 mmol) as the radical acceptor in water as the solvent (1 mL) irradiating with a 40 W fluorescent bulb for 40 h. Under these conditions, a 76% yield of 4-(trifluoromethyl-2-(4-methoxyphenyl) pyridine was obtained. The authors³² proceeded to investigate the reaction scope employing a broad range of heteroarene hydrochlorides and 4-methoxybenzenediazonium salt as the aryl radical precursor, according to Scheme 4.

Scheme 4. Selected Examples for 4-Methoxyphenylation (Ar) of Pyridine Hydrochloride Derivatives

As observed from Scheme 4, pyridines bearing electron-withdrawing groups (CF₃, CN, COOEt, Br) or electron donors (CH₃) afforded reasonably good yields of arylated products.

The authors³² next evaluated the substrate scope in terms of aryl diazonium salts, substituted with functional groups such as cyano, carboxyethyl, chlorine, bromine, and fluorine employing 4-trifluoromethylpyridine hydrochloride in water under photocatalysis as the radical acceptor. These transformations and yields are summarized in Scheme 5.

Scheme 5. Selected Examples of Photocatalytic Arylation of 4-Trifluoromethylpyridine Hydrochloride

As observed from Scheme 5, the reactivity of different substituted diazonium salts toward the production of the respective aryl radicals is somewhat similar, as contemplated from the arylated product yields.

More complex heterocyclic nuclei, such as caffeine and derivatives, were tested for the arylation scope. However, the reactions under the usual conditions proceeded in very low yields. Upon addition of formic acid, a yield enhancement was observed for these substrates (Scheme 6).

The authors³² also attempted a one-pot reaction synthesizing aryldiazonium salt and performing *in situ* the arylation of the heteroaromatic compound in water, obtaining reasonable yields of the coupling products.

A study of the mechanism through various probe experiments was undertaken. The addition of radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) suppressed the arylation process. On the basis of these latter experiments and literature precedent, the authors postulated a mechanism such as that illustrated in Scheme 7.

To commence, photocatalyst 7 (Scheme 7) is excited through visible light to afford 8, which through a reductive electron transfer with aryldiazonium salt produces an aryl

Scheme 6. Selected Examples for Photocatalytic 4-Methoxyphenylation of Caffeine Derivatives in Water

Scheme 7. Proposed Reaction Mechanism

radical, Ar•. Homolytic aromatic substitution with a pyridinium chloride gives radical intermediate 10, which is oxidized by more aryl diazonium salt to intermediate 11 and aryl radicals which enter the chain cycle. Deprotonation of intermediate 11 affords an arylated pyridine.³² Although this reaction is quite simple, and has been carried out in several organic solvents under different radical conditions, the improved methodology presented by the authors in water as the reaction medium and under photocatalysis represents a notorious advantage. As a final remark, the use of water has allowed an improved reactivity of pyridine nuclei as pyridinium salts toward arylation reactions, with the advantages of regioselectivity (substitution of pyridine rings at the 2-position), aryl precursors from soluble benzenediazonium salts, and arylation product yields. This methodology employs a standard metal–organic photocatalyst commonly available in laboratories. On the contrary, conventional photocatalyzed arylations of pyridine nuclei afford nonregioselectively substituted pyridine-arylated products in organic solvents.³³ This is most likely due to different spin densities at the 2-positions of pyridines and pyridinium hydrochloride salts.

Wang and collaborators³⁴ have disclosed the arylation reactions of heteroarenes, enol acetates, or benzoquinones employing aryl diazonium tetrafluoroborate salts under visible

light in an aqueous medium or pure water, a (polyaniline)-g-C₃N₄-TiO₂^{35–37} composite as the photocatalyst, and irradiation with a 14 W commercial fluorescent lamp (CFL). The scope of the transformation regarding heteroarenes is depicted in Scheme 8 and that of aliphatic substrates in Scheme 9.

Scheme 8. Scope of Arylation Reaction of Heteroarenes Employing (Polyaniline)-g-C₃N₄-TiO₂ Photocatalyst

The authors³⁴ investigated the reaction mechanism (Scheme 10).

The homolytic decomposition of diazonium salt 12 via an electron transfer (ET) process affords aryl radical 13 (Scheme 10). The addition of radical 13 to a heteroarene gives radical

Scheme 9. Scope of Arylation Reaction of Enol Acetates and Benzoquinones Employing (Polyaniline)-g-C₃N₄-TiO₂ Photocatalyst

Scheme 10. Proposed Reaction Mechanism

14, which is further oxidized by the photogenerated holes (h^+) to form carbocation intermediate 15. Finally, intermediate 15 is deprotonated to deliver the desired product. In the catalytic mode, the potentials of PANI (π^* -orbital, -2.14 eV; π -orbital, $+0.62$ eV) are more negative than the valence band (VB) and conduction band (CB) potentials of $g\text{-C}_3\text{N}_4$ (-1.13 and $+1.57$ eV, respectively) as well as those of TiO_2 (-0.29 and $+2.91$ eV, respectively). Consequently, the excited electrons migrate to the CB of TiO_2 , while the holes are gathered by the π -orbital of PANI. In this manner, the electron and hole are well separated, preventing the recombination process.³⁴

Next, a comparison between different photocatalyzed protocols for the arylation reactions of small heterocycles is shown in Table 1.

As observed from Table 1, yields of products under photocatalysis in water are slightly higher than those obtained in organic solvents, with the regioselectivity as good in water as in organic solvents.

■ RADICAL ADDITIONS TO CARBON–CARBON MULTIPLE BONDS IN AQUEOUS MEDIA

Alkylation of Alkenes. Addition of a saturated hydrocarbon (R-H or R-X) to an olefin to yield a saturated hydrocarbon of higher molecular weight is known as alkylation. Such reactions are employed to produce medium molecular-weight scaffolds from smaller molecules.³⁸ These processes can be performed through the intervention of metals,^{39,40} photocatalysts,^{41–43} or electrocatalysis.^{44,45} In general, radical 1,2-difunctionalization reactions of alkenes are quite general, and several photocatalytic methods have been employed.⁴⁶

Tetrabutylammonium decatungstate (TBADT)⁴⁷ is considered a competent and functional photocatalyst for hydrogen atom transfer (HAT) reactions that make possible the scission of both activated and unactivated aliphatic C–H bonds.^{48,49}

Bonassi and colleagues⁵⁰ have found a decatungstate-photocatalyzed alkylation of electron-deficient alkenes under continuous flow conditions. The optimized reaction conditions consist of the use of tetrabutylammonium decatungstate (TBADT, 0.4–2 mol %) as the photocatalyst, substrate of alkylbenzene (0.5 M), 1,2-dicyanoethylene (0.1 M) as the radical acceptor, LiClO_4 (0.5 M) in $\text{MeCN}:\text{water}$ (50 mL, 5:1) as the solvent mixture in a photochemical flow apparatus, and irradiation with a 500 W Hg vapor lamp. The scope of the reaction is illustrated in Scheme 11.

Scheme 11. Selected Examples of Alkylation of Electron-Deficient Alkenes

The use of a continuous flow approach enables a decrease of the residence time and an increase of the productivity with respect to batch processes. The concentrations of the

Table 1. Comparison between Photocatalyzed Protocols for Arylation of Small Heterocycles in Water (Column 2, This Perspective) and Organic Solvent (Column 3, Other Authors)

PRODUCT	Product % from photocatalysis in water (Scheme 8)	Product % from photocatalysis in organic solvents
	79	74, ^a 71 ^b
	87	85, ^a 78, ^b
	83	72 ^a
	81	70, ^a 79 ^b
	75	52, ^a 63 ^b
	82	55, ^a 63 ^b
	86	61, ^a 34 ^b

^aReference 28. In DMSO as the solvent, with Eosin Y as the photocatalyst. ^bReference 29. In DMSO as the solvent, with cercosporin as the photocatalyst.

substrates can be increased under flow conditions, leading to an improvement of the sustainability of the process.⁵⁰

Chen and collaborators⁵¹ developed a photocatalyzed radical methodology using water as the cosolvent for achieving the hydroxytrifluoroethylation of styrenes. In a typical reaction, *fac*-Ir(ppy)₃ is employed as the photoredox catalyst, with the reaction medium being a mixture of acetonitrile:water (8:1) in the presence of *N,N*-diisopropylethylamine as the reductive quencher under an oxygen atmosphere. Water plays a very significant role in the reaction outcome because in its absence the desired product is not formed. The authors⁵¹ investigated the scope of different styrene derivatives including styrenes in the presence of electron-donating or halogen substituents; in all cases, the reaction is well tolerated as shown in Scheme 12.

Scheme 12. Selected Examples for Hydroxytrifluoroethylation of Styrenes by Photoredox Catalysis Employing a Mixture of MeCN:H₂O (8:1) as Reaction Media

On the basis of different probe experiments, the authors proposed a reaction mechanism⁵¹ (Scheme 13) where initially the photocatalyst *fac*-Ir^{III}(ppy)₃ is promoted to an excited state which shows a metal-to-ligand charge transfer character affording *fac*-Ir^{IV}(ppy)₂(ppy)^{•−} which is further reduced by *N,N*-diisopropylethylamine generating *fac*-Ir^{III}(ppy)₂(ppy)^{•−}. A CF₃CH₂I molecule is reduced by *fac*-Ir^{III}(ppy)₂(ppy)^{•−} regenerating the photocatalyst into its active photoredox state and affording [CF₃CH₂I]^{•−} which rapidly yields I[−] and a trifluoroethyl radical (CF₃CH₂•) which is trapped by the styrene derivative affording intermediate 16 (Scheme 13). Under the presence of oxygen and water, radical intermediate 16 (Scheme 13) reacts with molecular oxygen and yields a hydroxytrifluoroethylation reaction product (Scheme 13).⁵¹

Although water participates in the reaction outcome providing the hydroxyl functionality in the β -trifluoromethylated alcohol, its absence, as stated before, does not form any reaction product, not even the atom transfer radical addition (ATRA, *vide infra*) iodinated product is observed.

Scheme 13. Proposed Reaction Mechanism for Hydroxytrifluoroethylation of Styrenes by Photoredox Catalysis Employing a Mixture of MeCN:H₂O (8:1) as Reaction Media

Enantioselective radical conjugate additions have been carried out with chiral inducers such as Al-Salen in DCM as the solvent⁵² or other chiral inducers in organic media.⁵³

Meggers and collaborators⁵⁴ developed a photocatalytic addition of alkyl radicals to alkenes with high enantioselectivity using mixtures of acetone and water as reaction media. In a typical reaction setup, the authors employed organotrifluoroborates as alkyl radical precursors, α,β -unsaturated acyl imidazoles (or pyrazoles) as substrates, *bis*-cyclometalated rhodium as the chiral Lewis acid catalyst, and 9-mesityl-10-methyl-acridinium perchlorate (Mes-AcrClO₄) as the photosensitizer under blue LED irradiation.⁵⁴ Regarding the organotrifluoroborate radical precursor, the reaction worked well with benzyltrifluoroborates with electron-donating and -withdrawing substituents, many alkoxyethyltrifluoroborates, and secondary and tertiary alkyltrifluoroborates. Regarding the α,β -unsaturated acyl imidazoles alkene substrates, the scope of the reaction was extended to aliphatic substituents, either electron-rich or electron-deficient aromatic moieties; some selected examples are shown in Scheme 14.⁵⁴

The authors⁵⁴ proposed the reaction mechanism shown in Scheme 15 based on several experiments including Stern–Volmer plots, radical trapping experiments, and reactions carried out in the presence of D₂O as the cosolvent. The alkyl radical source is potassium benzyltrifluoroborate. The reaction is initiated upon illumination of mesityl acridinium photocatalyst (path a), followed by a SET process with potassium benzyltrifluoroborate (path b) to yield a benzyl radical that adds to the *N,O*-rhodium-coordinated α,β -unsaturated 2-acyl imidazole (intermediate 17, Scheme 15, path c) substrate generating a secondary radical 18 (Scheme 15). Radical intermediate 18 (Scheme 15) is reduced by a single electron

Scheme 14. Selected Examples for Catalytic Enantioselective Addition of Alkyl Radicals to Alkenes by Visible Light-Activated Photocatalysis Using Mixtures of Acetone and Water as Reaction Media

transfer process from the reduced form of the photocatalyst (path d), affording a rhodium enolate (intermediate **19**, Scheme 15) and regenerating the photocatalyst. Finally, a water molecule protonates intermediate **19** (Scheme 15) yielding a rhodium-bound product (intermediate **20**, Scheme 15). In fact, the role of water is to form rhodium-bound intermediate **20** which, by protonation from water, weakens the Rh–O bond and collapses to product-regenerating intermediate **17** that re-enters the cycle (i.e., protonation of the C–enol bond). It must be outlined that the coordination of rhodium with the substrate enhances the rate of radical addition by a factor of 3×10^4 ; this means that the radical addition to a rhodium-coordinated substrate is much faster than the addition to the free substrate, allowing for the high enantioselectivity observed for the reaction.⁵⁴

Atom Transfer Radical Addition (ATRA) to Olefins. Photocatalyzed atom transfer radical additions (PhATRA) to

olefins have been found with metal photocatalysts, such as the polypyridyl complexes of Ir-^{55,56} and Ru-based photocatalysts,^{56–58} Bi₂O₃,^{59,60} Cu-derived complexes activated by light,^{61–63} TiO₂,⁶⁴ and Au complexes⁶⁵ in organic solvents. Nonmetal–organic photocatalysts, such as 4-methoxybenzaldehyde,^{66,67} and light-activated halogen-bonding complexes^{68,69} have also been reported to perform ATRA reactions. Pyrene-based metal organic frameworks have been found to achieve ATRA products.⁷⁰ Copper-mediated thermal reactions have also been studied for ATRA processes.^{71,72}

A seminal paper on photocatalyzed ATRA reactions in aqueous media has been advanced by Stephenson and colleagues.⁵⁶ The report by Stephenson and collaborators⁷³ can be considered the first found intermolecular ATRA reaction of haloalkanes and α -halocarbonyls with olefins by photoredox catalysis activated by visible light in aqueous media.⁷⁴ The authors⁷³ found optimal reaction conditions when employing Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ as a photocatalyst, 1 mmol of olefin, 2 equiv of the atom transfer agent, LiBr as the additive, a mixture of DMF:H₂O (1:4) as the reaction medium under Ar atmosphere, and irradiation with blue LEDs (Scheme 16). The reaction scope is extended to several olefins with different functional groups including alcohols, benzyl esters, alkyl bromides, silyloxy esters, esters, enones, carbamates, and aromatic rings (Scheme 16). Regarding the atom transfer agent, the reaction worked well with various haloalkanes and α -halocarbonyls, including CF₃I.⁷³

On the basis of several studies, the authors⁷³ proposed a reaction mechanism (Scheme 17) starting with the photoexcitation of the [Ir(III)] photocatalyst to afford *Ir[dF(CF₃)ppy]₂(dtbbpy)⁺ [Ir(III)*] that undergoes a single electron transfer process with the haloalkane (or α -halocarbonyl) generating Ir[dF(CF₃)ppy]₂(dtbbpy)²⁺[Ir(IV)] (bearing a halide as a counterion) and the electrophilic alkyl radical **21** (Scheme 17). Alkyl radical **21** (Scheme 17) adds to the olefin

Scheme 15. Proposed Reaction Mechanism for Catalytic Enantioselective Addition of Alkyl Radicals to Alkenes by Visible Light-Activated Photocatalysis Using Mixtures of Acetone and Water as Reaction Media

Scheme 16. Selected Examples for Intermolecular Atom Transfer Radical Addition (ATRA) to Olefins by Photoredox Catalysis in Aqueous Media Proposed by Stephenson and Collaborators⁷³

Scheme 17. Proposed Reaction Mechanism for Intermolecular Atom Transfer Radical Addition (ATRA) to Olefins by Photoredox Catalysis in Aqueous Media Proposed by Stephenson and Collaborators⁷³

forming radical adduct **22** (Scheme 17). The formation of the ATRA reaction product is possible by two different pathways. One possibility contemplates the oxidation of radical adduct **22** (Scheme 17) by [Ir(IV)] preassociated with the halide counterion, giving carbocation **23** (Scheme 17) that rapidly combines with the halide anion to yield the reaction product. It must be noted that external nucleophiles, including water (major cosolvent), do not react with proposed carbocation intermediate **23** (Scheme 17) as observed in the mechanistic experiments⁷³ performed by the authors. The second possibility for obtaining the ATRA reaction product involves a radical chain transfer mechanism where radical intermediate **22** (Scheme 17) abstracts a halide atom from a haloalkane (or

a-halocarbonyl) molecule giving the reaction product and alkyl radical **21** (Scheme 17) that can propagate the reaction.⁷³ The absence of oxygen or any other external oxidant probably prevents oxidation of intermediate **21** to a secondary carbocation, precluding the formation of the hydroxylic product, as observed from Scheme 12 (*vide supra*).

In another report,⁵⁶ the authors further exploited ATRA reactions in aqueous media with [Ru(bpy)₃]Cl₂ as the photocatalyst in DMF:water as the solvent mixture, affording products in reasonable yields.

A metal-free iodoperfluoroalkylation of alkenes employing Eosin Y as the photocatalyst (1 mol %) and aqueous Na₂S₂O₃ as the electron donor in the presence of perfluoroalkyl iodides has been found by Yajima and Ikegami.⁷⁵ Selected examples of the transformation are depicted in Scheme 18.

Scheme 18. Selected Examples for Iodoperfluoroalkylation of Alkenes in Aqueous Media

Through a series of experiments (use of TEMPO and luminescence quenching experiments), the authors,⁷⁵ proposed the following reaction mechanism in Scheme 19.

Scheme 19. Proposed Mechanism

In the proposed mechanism (Scheme 19), visible light-excited Eosin Y reduces the perfluoroalkyl iodide R_F-I to R_F radicals. The resulting oxidized Eosin Y (radical cation of Eosin Y) is reconverted to a photoactive catalyst in the presence of **24** (affording Na₂S₄O₆, **25**) or iodide (giving iodine radical). The reaction of R_F radicals with olefin renders intermediate radical **26**, which is converted to product by either one of the three routes available, that is, (i) abstraction of iodine from R_F-I, (ii) oxidation of intermediate radical **26** to carbocation **27** and ulterior iodide nucleophilic attack, or (iii) recombination of radical intermediate **26** with radical iodine, to afford the iodoperfluoroalkylated product. The nucleophilic route was

ruled out, as no product derived from a nucleophilic water attack on carbocation **25** was encountered. The authors,⁷⁵ however, discarded the radical chain possibility (i.e., **26** abstracted an iodine radical from R_F-I to propagate the chain, path (i)) on the basis of a light on/off experiment, where product formation is interrupted when irradiation is off (purporting that no radical chain is maintained). However, typical radical chain processes normally take place on the second or subsecond time scale, and so, the observation that product conversion is discontinued in the absence of light could also be in agreement with chain processes that cease faster than the time scale employed in the analytical measurement.⁷⁶

Prato and colleagues⁷⁷ have also reported on the photocatalyzed perfluoroalkylation of terminal olefins in MeCN/water mixtures employing perylene diimides as the photocatalyst and sodium ascorbate as the sacrificial donor, with perfluoroalkyl iodides as the source of perfluoroalkyl radicals, giving affordable yields of iodoperfluoroalkanes.

The addition of radicals to silyl ketenes has been studied in the past through thermal radical methods.⁷⁸ Acyl radicals, in turn, have been generated from α -ketoacids, aldehydes, anhydrides, acyl thioesters, carboxylic acids,⁷⁹ acyl silanes, or acyl chlorides by photocatalysis in organic solvents.⁸⁰

Zhang and colleagues⁸¹ have reported a sequential protocol in which a photoredox catalytic reaction is placed in sequence with asymmetric transfer hydrogenations of aryl ketones to provide different chiral alcohols with high enantioselectivity in aqueous mixtures of organic solvents. Although these reactions make use of water, water itself is not involved in the photocatalysis.

Sulfonation of Vinylcyclopropanes. Radical 1,3-functionalizations leading to 1,2,3-trisubstituted alkanes have been reported.⁸² In turn, 1,4-difunctionalizations have been achieved with alkyl diacyl peroxides or *N*-fluorobenzenesulfonylimide.⁸³ These processes have been carried out in organic solvents.

1,5-Difunctionalizations involving both the introduction of a fluoroalkylthio and a sulfone group are rare. One such example was provided by Liu and collaborators⁸⁴ who developed an environmentally friendly 1,5-trifluomethylthio-sulfonation of vinylcyclopropanes catalyzed by Eosin Y under visible light in a water phase. The optimum reaction conditions were obtained when α -cyclopropyl styrene suspended in water was subjected to the Eosin Y-photocatalyzed reaction in the presence of SDS and *S*-(trifluoromethyl)-4-chlorobenzenesulfonylthioate (**28**, Scheme 20) under white LED irradiation, obtaining a 76% yield of product (**29**, Scheme 20) and 7:1 stereoselectivity (Z:E) (Scheme 20).⁸⁴

The authors⁸⁴ were intrigued by the high Z stereoselectivity obtained in water (i.e., 7:1), as opposed to the reaction

Scheme 20. Optimized Reaction Conditions for 1,5-Trifluomethylthio-sulfonation of Vinylcyclopropanes Catalyzed by Eosin Y under Visible Light in Water Phase

performed in DMSO or DMF organic solvents. The stereoselectivity was found to improve with temperature, obtaining best results at 50 °C. They inspected the electronic effects and steric hindrance in the trifluoromethylthiosulfonylating reagent. When *S*-(trifluoromethyl) 4-(*tert*-butyl) benzenesulfonylthioate **30** (Scheme 21) was employed as difunctionalization

Scheme 21. Selected Examples for 1,5-Trifluomethylthio-sulfonation of Vinylcyclopropanes

reagent, an improved 13:1 stereoselectivity ratio was achieved in favor of the Z stereoisomer. The reasons for this preference are not given in the original publication but probably are related to a stabilized six-membered ring transition state structure for the incipient Z-isomer in water as compared to organic solvents. Having established the best reaction conditions, the authors⁸⁴ explored the scope of the reaction, as summarized in Scheme 21.

Para-substituted substrates achieved good isolated yields of products with very high Z/E ratios (Scheme 21).⁸⁴ The authors performed some control experiments. When TEMPO was used, the reaction was completely inhibited, and reagent **30** disappeared. Also, substrate cyclopropyl styrene remained. These results indicated that **30** is initiated first, and the arylsulfonyl radical thus regenerated adds to the styryl double bond ensuing a terminal carbon radical which is terminated with the trifluoromethylthio radical. The authors postulated a reaction mechanism such as that shown in Scheme 22.⁸⁴

Initially, upon visible light excitation of Eosin Y, a photoactive triplet state of the photocatalyst is generated (Scheme 22), which by ET to *S*-(trifluoromethyl)-arylsulfonylthioate reagent **31** generates arylsulfonyl radical **32**, which adds to styrylcyclopropane **33** to give radical intermediate **34**, which upon reaction with complex [Eosin Y/SCF₃] affords product **35** (Scheme 22).⁸⁴ The role of the MeCN/water (SDS) mixture is only an alternative to a classic all-organic solvent medium, such as that reported in the protocol for the photocatalyzed reaction carried out in 1,4-dioxane.⁸⁵

Arylation of Alkenes. Direct arylation of alkenes has been achieved by the Ru(IV) catalyst^{86,87} and by copper catalysis.⁸⁸

In 2014, König and colleagues⁸⁹ found the photocatalyzed arylation of styrene derivatives with tetrafluoroborate aryldiazonium salts, employing [Ru(bpy)₂]Cl₂ as the photocatalyst and irradiation with a 440 nm light source in CH₃CN/water.

Scheme 22. Proposed Reaction Mechanism for 1,5-Trifluomethylthio-sulfonylation of Vinylcyclopropanes

The scope of the transformation regarding the aryl diazonium salt is depicted in Scheme 23.

Scheme 23. Selected Examples for Arylation of Styrene in MeCN/Water

The reaction in terms of the scope of the alkene is illustrated in Scheme 24.

The authors⁸⁹ proposed a mechanism based on trapping experiments and literature precedent, according to Scheme 25.

An aryl radical is formed by an ET from the excited state of the photocatalyst $[Ru(bpy)_3]^{2+*}$ to diazonium salt and

Scheme 24. Selected Examples for 4-Methoxyphenylation of Alkenes

Scheme 25. Proposed Mechanism

Ru(III). The addition of an aryl radical to olefin affords radical intermediate **36**, which is then further oxidized to afford carbocation **37**. Finally, intermediate **37** is attacked by the solvent (a nitrile) (intermediate **38**), followed by hydrolysis to give an amino-arylated product. The participation of water in the reaction is to provide the H and O atoms in the water attack of intermediate **38**.

In a more recent report Wang and colleagues⁹⁰ have found an effective and benign visible light-induced Meerwein hydration reaction of alkenes in water.

The reaction employs diazonium salts bearing various electron-poor substituents on the aryl ring as aryl radical sources, an alkene as the radical acceptor, and mpg-C₃N₄ as the photocatalyst in water as the solvent under Xe light irradiation.

As shown in Scheme 26, a wide array of aryl diazonium salts and alkenes were tested. The reaction had good tolerance with several groups, such as nitro, acyl, cyanide, ester, methyl, and halogen groups giving the corresponding products in good yields.⁹⁰

Scheme 26. Aryldiazonium Salts and Alkene Scope: Photocatalytic Meerwein Hydration Reaction

Remarkably, the reaction could be driven by sunlight with good results compared with the model with Xe light irradiation (Scheme 27). These results indicated the suitability of the protocol for large-scale applications.⁹⁰

Scheme 27. Photocatalytic Meerwein Hydration Reaction Promoted by Sunlight

In the mechanistic proposal shown in Scheme 28, initially mp_g-C₃N₄ is excited upon irradiation; the excited mp_g-C₃N₄

Scheme 28. Proposed Mechanism of Photocatalytic Meerwein Hydration Reaction

reacts with the aryl diazonium salt in a single electron transfer (SET) to generate the corresponding aryl radical. The aryl radical adds to the alkene to produce benzyl radical 39 (Scheme 28), which is oxidized by the valence band of mp_g-C₃N₄ to form carbocation 40 (Scheme 28). Finally, H₂O acts as the nucleophile and reacts with 40 followed by deprotonation to yield the final product. Although the role of water as the nucleophile is obvious in this process, the feasibility of the reaction in the water heterogeneous system as opposed to in an organic homogeneous mixture is interesting as a protocol alternative.

Chilamari and colleagues⁹¹ have accomplished the arylation of alkenes starting from arylboronic acids in a mixture of water:methyl acetate (pH 7.8) utilizing lumiflavin, a bio-inspired flavin photocatalyst, under a nitrogen atmosphere. The scope of the transformation is illustrated in Scheme 29.

During the investigation of the reaction mechanism, the authors⁹¹ performed a series of experiments, such as quenching of fluorescence of lumiflavin with aryl boronic acid, computational experiments, radical trapping experiments with TEMPO, and deuterium-labeling studies with D₂O. In the mechanism proposed, excited lumiflavin reduces the aryl boronic acid to aryl radicals, which in turn add to the alkene double bond to render an alkyl radical that through a HAT generates the product.

Asymmetric Radical Conjugate Addition to α,β -Unsaturated Systems. Asymmetric acyl radical conjugate additions toward the synthesis of 1,4-dicarbonyl compounds have very recently been achieved through visible light photocatalysis.^{92,93}

Kuang and colleagues⁹⁴ have reported the combination of neutral Eosin Y with a chiral-at-metal *bis*-cyclometalated rhodium(III) complex (Λ -RhS or Δ -RhS). In this manner, aldehydes can be employed as acyl radical precursors to undergo catalytic enantioselective addition to α,β -unsaturated *N*-acyl-3,5-dimethylpyrazoles with high enantioselectivity.

The authors⁹⁴ found the optimum reaction conditions for the enantioselective reaction consist of neutral Eosin Y (1 mol %), a chiral-at-metal *bis*-cyclometalated rhodium(III) complex (4 mol %), *tert*-butyl methyl ether (TBME) (0.1 mL), and water (20 equiv) at 10 °C for 3 days under 18 W blue LED irradiation. The scope of the reaction is shown in Scheme 30.

As observed from Scheme 30, propionaldehyde, acetaldehyde, 3,3-dimethylbutanal, and benzaldehyde have been used successfully as substrates affording good yields of the asymmetric acyl radical conjugate addition products with high stereoselectivities.

Scheme 29. Representative Examples of Scope of Transformation Regarding Aryl Boronic Acid and Alkene

Scheme 30. Aldehyde Scope: Selected Examples of Enantioselective Addition to α,β -Unsaturated *N*-Acyl-3,5-dimethylpyrazoles

The authors also inspected the reaction in terms of the scope of the unsaturated *N*-acyl-3,5-dimethylpyrazoles, according to Scheme 31.⁹⁴

Scheme 31. Unsaturated *N*-Acyl-3,5-dimethylpyrazoles Scope: Selected Examples of Enantioselective Addition to α,β -Unsaturated *N*-Acyl-3,5-dimethylpyrazoles

As observed from Scheme 31, α,β -unsaturated *N*-acyl-3,5-dimethylpyrazoles substituted with cyclopentyl, methyl, ethyl-phenyl, and isopropyl groups afforded high yields and diastereoselectivities of the radical conjugate addition products, employing formaldehyde as the aldehyde source.

The authors⁹⁴ performed a series of control experiments in order to uncover the reaction mechanism. On the basis of redox potentials, excited Eosin Y ($E(S^*/S^{1-}) = +0.83$ V vs

SCE in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$)⁹⁵ is unable to oxidize an aldehyde to an acyl radical. The reaction is suppressed when TEMPO (a radical scavenger) is used. A plausible reaction mechanism is depicted in Scheme 32.

Acyl radical **41** (Scheme 32) is generated by a HAT reaction between Eosin Y* and an aldehyde. Radical **41** in turn adds to *N*-O–rhodium-coordinated *N*-acyl pyrazole substrate **42** to produce radical intermediate **43** that suffers reverse HAT with Eosin Y–H. Ligand exchange between intermediate **44** and the starting unsaturated amide delivers the chiral product and regenerates the active complex (Scheme 32).⁹⁴

■ DECARBOXYLATIVE AND DEOXYGENATIVE REACTIONS IN AQUEOUS MEDIA

Photoinduced decarboxylative functionalization has been employed to build an impressive array of functional molecules,^{96–99} such as decarboxylative conjugate addition,^{100,101} fluorination,^{102,103} and borylation.^{104,105} Photocatalysis has recently played a relevant role in decarboxylative reactions. There are recent review articles on single electron activation of arylcarboxylic acids^{106–108} where carboxylate groups can be transformed into reactive aryl carboxylic radicals, aryl radicals, and acyl radicals by electrocatalysis, photocatalysis, or in the presence of some SET oxidants.¹⁰⁶ Also, the deoxygenative functionalization of alcohols and carboxylic acids is an appealing approach for the conversion of these feedstocks into high-value products.¹⁰⁹ However, the direct deoxygenative transformation under mild conditions is cumbersome due to the lack of proper methods for the activation of the strong C–O bonds (102 kcal mol^{−1}). More recently, the strategy of visible light photocatalytic phosphoranyl radical fragmentation affords a novel entry for C–O, N–O, and S=O bond activation.¹¹⁰ Photocatalytic strategies for deoxygenation of alcohols and carboxylic acids through phosphoranyl radical fragmentation have recently been reviewed.^{109,111}

Wu and collaborators¹¹² developed a one-pot cascade process combining a photocatalyst with ketoreductase

Scheme 32. Proposed Reaction Mechanism

(KRED) to convert carboxylic acids into chiral alcohols in water (Scheme 33).

Scheme 33. Combining Photocatalysis and Biocatalysis: Summary of Reaction Pathway

For the formation of the keto product, the authors¹¹² found optimized reaction conditions involving 2-phenylpropionic acid (0.06 mmol) as the substrate, 2-sodium anthraquinone sulfonate, SAS (5 mol %) as the photocatalyst, and water as the solvent (2 mL) under blue LED irradiation. Under these reaction conditions, a 95% yield of acetophenone is obtained.

The authors¹¹² investigated the scope of the reaction under the optimized conditions considering different arylcarboxylic acids, according to Scheme 34.

Scheme 34. Selected Examples for Decarboxylation, Followed by Capturing O₂ and Then Conversion into Corresponding Ketones

A scale-up of the reaction (6.7 mmol of phenylpropionic acid) was carried out, and product acetophenone was obtained in a satisfactory yield (92%) after 30 h of irradiation.¹¹² The authors continued with the improvement of the one-pot protocol, thus employing a ketone reductase (KRED) for catalyzing the asymmetric reduction of the ketones. The selected enzyme was a carbonyl reductase from *Kluyveromyces thermotolerans* (KtCR) as a model enzyme, obtaining high enantioselectivities for the reduced alcohols, as shown in Scheme 35.¹¹²

For the S-selective KRED, the authors employed YueD from *Bacillus* sp. ECU0013^{113,114} which provided mainly (S)-alcohols through the above one-pot cascade reaction in very good enantiomeric excess and yields.

Although the authors did not discuss the mechanism involved,¹⁰⁰ a likely reaction pathway would entail excitation of an anthraquinone-2-sulfonic acid photocatalyst, whose triplet excited state would oxidize the carboxylic acid to its radical cation. The radical cation of the carboxylic acid would readily deprotonate affording the carboxylate radical which would undergo decarboxylation to yield a secondary benzyl radical.

Scheme 35. Substrate Scope of (R)-Selective One-Pot Decarboxylative Hydroxylation

This secondary benzyl radical would probably react with oxygen¹¹⁵ to afford to a ketone product; however, this last step of the reaction is conjectural and needs to be explored by further experimental evidence.

Zhang and colleagues¹¹⁶ have recently reported a visible light-mediated photocatalytic deoxygenation of aryl carboxylic acids through the employment of PPh₃ which triggers the deoxygenative carbon–carbon coupling of aryl-carboxylic acids with olefins in an aqueous phase leading to aromatic ketones. The authors¹¹⁶ found that the best reaction conditions employ aryl carboxylic acid (0.2 mmol, 1 equiv), alkene (1.5 equiv), photocatalyst Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (1 mol %), K₂HPO₄ (20 mol %), and PPh₃ (1.2 equiv). The authors investigated the scope of the reaction in terms of the arylcarboxylic acid and the alkene. A summary of the scope achieved for both aryl carboxylic acid and alkene is shown in Scheme 36.

The authors further applied the strategy with the aromatic moieties of known drugs such as telmisartan (specific antagonist of angiotensin II receptor), hiestrone (antineoplastic agent), and adapalene (for the treatment of acne), which readily suffered deoxygenative ketone synthesis.

In order to explore the mechanism, the authors¹¹⁶ carried out some control experiments, such as the reaction with 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and 2,6-di-*tert*-butyl-*p*-cresol. These additives inhibited the reaction completely. In the case of TEMPO, the adduct between the acyl radical and TEMPO was found, which purports to the presence of an acyl radical intermediate. When the authors¹¹⁶ employed 2-allylbenzoic acid as the substrate, the cyclization product 2-methyl-2,3-dihydro-1H-inden-1-one was obtained (Figure 1a), indicating the presence of acyl radicals. Deuterium-labeling experiments in D₂O showed that water was the source of the proton. When H₂¹⁸O was used as the solvent, the aromatic acid labeled with ¹⁸O (Figure 1b) indicated that the oxygen atom in Ph₃P=O arrives from the carboxylic acid and not from water. When the potassium salt of benzoic acid was used instead of free benzoic acid, a deoxygenative coupling product was obtained in moderate yield, which implied that the Ph₃P^{•+} radical cation reacts with benzoate (Figure 1c). Stern Volmer experiments revealed that the excited state of the photocatalyst (i.e., Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆^{•+}) is suppressed by Ph₃P.

A possible reaction mechanism is depicted in Scheme 37. Visible light excitation of the photocatalyst (i.e., Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆) leads to a triplet charge transfer state (metal-to-ligand) which oxidizes Ph₃P to its radical cation and the photocatalyst resulting in its reduced redox manifold. Ph₃P^{•+} species combines with the aryl carboxylate ion to form a P-centered radical, provoking the scission of the O–C=O bond, resulting in an acyl radical and Ph₃P=O. Acyl radical

Scheme 36. Scope of Deoxygenative Carbon–Carbon Coupling of Aryl-Carboxylic Acids with Olefins in Aqueous Phase Leading to Aromatic Ketones

Figure 1. Mechanistic probe experiments.

Scheme 37. Proposed Reaction Mechanism

attacks the double bond from the olefin giving a radical adduct which is further reduced by the lower oxidation state of the photocatalyst (i.e., Ir(II)) to yield a carbanion, which upon protonation from water affords the final product (Schgem 35c).

He and collaborators¹¹⁷ presented a visible light-induced deoxygenative C2-sulfonation of quinoline *N*-oxides in aqueous media. Optimized reaction conditions were achieved

employing quinoline *N*-oxide as the model substrate, $\text{Na}_2\text{Eosin Y}$ as the photocatalyst, and 4-methylbenzenesulfonic acid as the sulfonating reagent in acetone: H_2O (1.5:1) as the reaction medium with irradiation with blue LEDs under an air atmosphere (Scheme 38).¹¹⁷ The reaction is successfully

Scheme 38. Selected Examples for Visible Light-Induced Deoxygenative C2-Sulfonation of Quinoline *N*-Oxides with Sulfonic Acids in Aqueous Media

applied to different substituted quinoline *N*-oxide substrates with electron-withdrawing and electron-donating groups including halogen atoms. Regarding the sulfinic acid reagent, different benzenesulfonic acids bearing electron-rich and electron-poor substituents, such as ester, halides, trifluoromethyl, phenyl, and methoxy, all underwent the reaction and afforded their respective products in very good yields (Scheme 38).¹¹⁷

The authors performed a series of experiments including radical trapping with TEMPO, electron paramagnetic resonance studies, redox potential measurements, and kinetic isotope effect experiments in order to clarify the reaction mechanism. On the basis of all the evidence collected, the authors proposed a reaction mechanism (Scheme 39) where

Scheme 39. Proposed Reaction Mechanism for Visible Light-Induced Deoxygenative C2-Sulfonation of Quinoline *N*-Oxides with Sulfinic Acids in Aqueous Media

Na₂Eosin Y upon excitation with visible light performs a single electron oxidation of the sulfinic acid reagent, yielding sulfonyl radical cation **46** (Scheme 39) and the Na₂Eosin Y^{•-} radical anion which is further oxidized by O₂ present in air to afford Na₂Eosin Y in the ground state and anion superoxide O₂^{•-}. Radical cation **46** (Scheme 39) undergoes deprotonation by O₂^{•-} providing HO₂[•] and radical intermediate **47** (Scheme 39) which is in resonance with sulfur-centered radical intermediate **48** (Scheme 39). The quinoline *N*-oxide substrate reacts with radical intermediate **48** (Scheme 39) producing radical intermediate **49** (Scheme 39), which further combines with a second sulfur-centered radical intermediate **48** (Scheme 39) to yield intermediate **50** (Scheme 39), which undergoes a dehydro-aromatization process delivering the 2-sulfonylquinoline reaction product and releasing a sulfonic acid molecule.¹¹⁷

A transition metal-free photocatalytic methodology for the decarboxylative fluorination of aliphatic carboxylic acids employing a mixture of acetonitrile and water (1:1) as the reaction medium was reported by Ye and collaborators.¹⁰³ The most effective conditions for this transformation are met when employing 9-mesityl-10-methyl-acridinium perchlorate (Mes-AcrClO₄) or riboflavin as photocatalysts, Cs₂CO₃ as the base, Selectfluor as the fluorine source, and irradiation with a commercial fluorescent lamp (CFL) at room temperature and under a N₂ atmosphere (Scheme 40).¹⁰³ The reaction worked successfully with primary, secondary, and tertiary carboxylic acids, including *N*-protected amino acids with phthaloyl or succinyl groups (Scheme 40).¹⁰³

Scheme 40. Selected Examples for Decarboxylative Fluorination of Aliphatic Carboxylic Acids by Photoredox Catalysis Employing a Mixture of MeCN: H₂O (1:1) as Reaction Media

The authors¹⁰³ proposed a reaction mechanism based on experimental evidence, including luminescence suppression experiments, (Scheme 41) where the excited state of the

Scheme 41. Proposed Reaction Mechanism for Decarboxylative Fluorination of Aliphatic Carboxylic Acids by Photoredox Catalysis Employing a Mixture of MeCN: H₂O (1:1) as Reaction Media

photocatalyst performs a single electron oxidation of the alkyl carboxylate yielding an alkyl radical, CO₂, and the radical anion of the photocatalyst. Then, a fluorine atom is transferred from Selectfluor to the alkyl radical yielding the reaction product and radical dication **51** (Scheme 41). The authors proposed the closing of the photoredox cycle by a single electron transfer process from the photocatalyst radical anion to radical dication **51**, regenerating the photocatalyst (Scheme 41).¹⁰³

Macmillan and collaborators¹⁰² presented a protocol for the photocatalyzed decarboxylative fluorination of aliphatic acids in aqueous media. The optimized reaction conditions consist of the reactions of carboxylic acids with Selectfluor in the presence of the heteroleptic Ir(III) photocatalyst Ir[dF(CF₃)-

ppy]₂(dtbbpy)PF₆ with of Na₂HPO₄ as the base in CH₃CN:water (1:1) as the reaction medium and irradiation with blue LEDs under an Ar atmosphere. The scope of the reaction is extended to a broad family of alkyl carboxylic acids including primary, secondary, tertiary, benzylic, and homobenzylic carboxylic acids. Substrates bearing heteroatoms in the α or β position of the carboxylic group also gave the corresponding reaction products in high yields (Scheme 42).¹⁰²

Scheme 42. Selected Examples for Photocatalyzed Decarboxylative Fluorination of Aliphatic Acids Employing Selectfluor in the Presence of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ with of Na₂HPO₄ as Base in CH₃CN:water (1:1) as Reaction Media

The authors¹⁰² proposed a reaction mechanism (Scheme 43) starting with the photoexcitation of the photocatalyst

Scheme 43. Proposed Reaction Mechanism for Photocatalyzed Decarboxylative Fluorination of Aliphatic Acids Employing Selectfluor in the Presence of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ with of Na₂HPO₄ as Base in CH₃CN:water (1:1) as Reaction Media

Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆[Ir(III)] to afford *Ir[dF(CF₃)ppy]₂(dtbbpy)⁺ [Ir(III)*]. It is important to note that the authors' proposal¹⁰² includes an initial reduction of a sacrificial quantity of Selectfluor for obtaining Ir[dF(CF₃)ppy]₂(dtbbpy)²⁺[Ir(IV)], and this reaction is not included in Scheme 43. The carboxylic acid is deprotonated by HPO₄²⁻ and affords the alkyl carboxylate that performs a single electron

transfer process with Ir[dF(CF₃)ppy]₂(dtbbpy)²⁺[Ir(IV)] regenerating the Ir(III) photocatalyst and yielding an alkyl radical and CO₂. The alkyl radical abstracts a fluorine atom from Selectfluor giving the reaction product and radical cation intermediate **51** (Scheme 43) that replaces the initial Selectfluor by accepting an electron from Ir(III)* to yield the strongly oxidizing Ir(IV) that further reacts with another alkyl carboxylate anion propagating the reaction (Scheme 43).¹⁰²

Another example of photoredox catalysis based on a decarboxylative fluorination process was developed Paquin and collaborators, starting from aryloxyacetic acids.¹¹⁸ Optimal yields were obtained when employing Ru(bpy)₃Cl₂ as the photocatalyst, Selectfluor as the fluorine atom source, and NaOH as the base in either H₂O or CH₃CN:H₂O mixtures as reaction media (depending on carboxylic acid substrate solubility) upon visible light irradiation under a N₂ atmosphere (Scheme 44). The reaction scope includes a range of

Scheme 44. Selected Examples for Direct C–F Bond Formation by Means of Photoredox Catalysis Based on a Decarboxylative Fluorination Process Developed by Paquin and Collaborators¹¹⁸

aryloxyacetic acid derivatives with the aryloxy ring substituted with alkyl, phenyl, fluorine, or bromine substituents; a pyridyl derivative also afforded the fluorinated product in good yield (Scheme 44).¹¹⁸

Regarding some mechanistic aspects, the authors¹¹⁸ proved, by transient absorption (TA) spectroscopy experiments, that the reaction proceeds through a photoredox pathway involving a single electron transfer process from the triple metal-to-ligand charge transfer state (³MLCT) of the Ru(bpy)₃²⁺ catalyst to Selectfluor forming Ru(bpy)₃³⁺; the last being the key oxidant of the reaction that enables ulterior decarboxylative fluorination.¹¹⁸ In this sense, TA spectroscopy of Ru(bpy)₃(PF₆)₂ matches previous reports,¹¹⁹ with a depletion of the band at 450 nm corresponding to Ru(bpy)₃²⁺ and an increase of the band at 375 nm, which is assigned to ³*[Ru(bpy)₂(bpy•⁺)]²⁺. The spectra difference suggests that there is no interaction between the catalyst and phenoxyacetic acid. However, the excited state difference the spectrum of Ru(bpy)₃(PF₆)₂ in the presence of an excess of Selectfluor demonstrates the growth of a new absorption band centered at 450 nm. These findings are consistent with an ET pathway between (³MLCT) and Selectfluor, affording oxidized Selectfluor (radical cation) and Ru(bpy)₃³⁺, which oxidizes aryloxyacetic acid (Figure 2).

Figure 2. Oxidation and decarboxylation of aryloxyacetic acids.

A photocatalytic decarboxylative/defluorinative [4 + 3] annulation of *o*-hydroxyphenylacetic acids and trifluoromethyl alkenes was reported by Chen and collaborators.¹²⁰ The reaction affords fluorinated dihydrobenzoxepines via two consecutive C–F substitutions in a CF₃ group. This latter reaction was carried out in DMSO:water as the solvent mixture and employs 1,3,4,5-*tetrakis*(diphenylamine)-2,6-dicyanobenzene as the photocatalyst.

Zhu and collaborators¹²¹ achieved a decarboxylative cross-coupling reaction of α -oxocarboxylic acids with styrenes enabled by a domino-fluorination–protodefluorination reaction via photoredox catalysis in aqueous media. Optimized reaction conditions were obtained when benzoylformic acid and 4-methylstyrene were allowed to react in the presence of Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ as the photocatalyst, Selectfluor as the fluorine atom source, and sodium acetate as the base in CH₃CN:H₂O (1:1) as the reaction medium, with irradiation with blue LEDs under an Ar atmosphere (Scheme 45). The scope of the α -oxocarboxylic acid substrate embraces benzoylformic acid-bearing electron-rich and electron-withdrawing groups including heterocyclic 2-furanyl-, 2-thienyl-, and 2-naphthyl-substituted α -oxo acids (Scheme 45). The substrate scope regarding the alkene substrate includes a series of styrenes having substituents such as fluoro, chloro, bromo, methyl, or phenyl groups on the aromatic ring (Scheme 45).¹²¹

To gain mechanistic insights into the reaction pathway, the authors performed a series of experiments including radical trapping with TEMPO, reaction in the absence of a base, and

Stern–Volmer quenching studies.¹²¹ On the basis of the experiments performed and on the information available in the literature, the authors proposed a reaction mechanism initiated by photoexcitation of the Ir(III) photocatalyst to the excited state Ir(III)* followed by a reductive quenching process oxidizing the α -oxocarboxylic acid affording the reduced Ir(II) species, acyl radical **52** (Scheme 46) and CO₂. Acyl radical **52**

Scheme 46. Proposed Reaction Mechanism for Decarboxylative Cross-Coupling of α -Oxocarboxylic Acids with Styrenes Enabled by Domino-Fluorination–Protodefluorination Reaction via Photoredox Catalysis in Aqueous Media

(Scheme 46) adds to the double bond of styrene delivering benzylic radical **53** (Scheme 46) that abstracts a fluorine atom from Selectfluor yielding the acylfluorinated compound **54** (Scheme 46) and Selectfluor radical cation **51** (Scheme 46) that oxidizes the Ir(II) catalyst to the ground state Ir(III) species, thus generating reduced **55** (Scheme 46). The acylfluorinated compound **54** (Scheme 46) is unstable and

Scheme 45. Selected Examples for Decarboxylative Cross-Coupling of α -Oxocarboxylic Acids with Styrenes Enabled by Domino-Fluorination–Protodefluorination Reaction via Photoredox Catalysis in Aqueous Media

eliminates HF in the presence of a base affording the final α,β -unsaturated ketone product.¹²¹

Ramirez and Gonzalez-Gomez¹²² developed a decarboxylative Giese-type reaction of carboxylic acids induced by visible light. The proposed protocol employs 9-mesityl-10-methyl-acridinium perchlorate (Mes-AcrClO₄) as the photocatalyst, Na₂CO₃ as the base, and a mixture of acetonitrile:water (2:1) as the reaction media, with irradiation under blue LEDs without deoxygenation nor an inert atmosphere (Scheme 47).¹²² The suitable acceptors studied for this

Scheme 47. Selected Examples for Decarboxylative Giese-Type Reaction of Carboxylic Acids by Photoredox Catalysis Employing Diethyl 2-Ethylidene Malonate as Acceptor and Mixture of MeCN:H₂O (2:1) as Reaction Media

reaction are alkylidene malonates and malonitriles, α -substituted acrylates, conjugated ketones and aldehydes, and conjugated sulfones. On the other hand, the scope of carboxylic acids capable of smoothly reacting under these reaction conditions comprises various secondary and tertiary substrates, α -amino acids, α -keto acids, and α -oxy acids. Scheme 47 shows the scope of the reaction when employing a series of suitable carboxylic acids and diethyl 2-ethylidene malonate as the acceptor.¹²²

Scheme 48. Scope: Decarboxylative 1,4-Addition of α -Oxocarboxylic Acids with Michael Acceptors

Regarding some mechanistic aspects, the authors, by employing radical scavenger TEMPO, completely inhibited product formation. By performing the reaction using perdeuterated solvents, the authors excluded the probability of H abstraction of the α -acyl radical from the solvent as no deuterated product was observed employing CD₃CN:H₂O (2:1). On the other hand, the single-electron reduction of the α -acyl radical formed was verified as a final deuteration product was observed when employing CH₃CN:D₂O (2:1).¹²²

In 2015, Fu and co-workers¹²³ found the decarboxylative 1,4-addition of α -oxocarboxylic acids with Michael acceptors by photoredox catalysis. The protocol developed employs an iridium catalyst, Ir[dF(CF₃)ppy]₂(phen)PF₆, various 2-(hetero)aryl-2-oxocarboxylic acids as acyl radical sources, and different Michael acceptors, K₂HPO₄ as the base in a solvent mixture of DCM:H₂O (1:1) under 36 W blue LED irradiation.

Under these reaction conditions, several 2-oxo-2-(hetero)arylacetic acids and a wide range of Michael acceptors, such as α,β -unsaturated ester, ketone, amide, nitrile, and sulfone, reacted to afford the desired products in good yields (Scheme 48).¹²³

When the reaction of a 2-oxo-2-phenylacetic acid with a Michael acceptor was conducted in the presence of 2.0 equiv of TEMPO, no additional product was observed, and the adduct TEMPO-acyl radical was isolated in high yield as shown in Scheme 49.¹²³

Scheme 49. Radical Trapping Experiment with TEMPO

In the hypothesized mechanism (Scheme 50), the photo-excited photocatalyst (*Mⁿ) can be reductively quenched by α -oxocarboxylate to generate an acyl radical, CO₂, and the reduced Mⁿ⁻¹. The acyl radical adds to the Michael acceptor to produce radical adduct 56 (Scheme 50) that accepts one electron from Mⁿ⁻¹ to generate Mⁿ and intermediate 57 (Scheme 50). The 1,4-addition product is formed after protonation of 57 (Scheme 50).¹²³

Scheme 50. Proposed Mechanism: Photoredox-Catalyzed Decarboxylative 1,4-Addition of α -Oxocarboxylic Acid

A combination of photocatalysis with hypervalent iodine(III) reagents (HIRs)¹²⁴ represents an important tool in the field of iodine chemistry, and numerous organic transformations were achieved in a mild and environmentally benign system, included the aqueous media.

Huang and colleagues¹²⁵ found the deboronative/decarboxylative alkenylation triggered by visible light photoredox catalysis. The optimal reaction conditions (Scheme 51)

Scheme 51. Optimal Reaction Conditions and Scope: Deboronative/Decarboxylative Alkenylation by Photoredox Catalysis

consisted of a mixture of the corresponding alkyl trifluoroborate and vinyl carboxylic acid, $[\text{Ru}(\text{bpy})_3](\text{PF}_6)_2$ as the photocatalyst, an iodine(III) cyclic reagent acethoxybenziodoxole (BI-OAc) as the oxidant in $\text{DCE}:\text{H}_2\text{O}$ as the solvent mixture under blue LED ($\lambda_{\text{max}} = 468 \text{ nm}$) irradiation.

As shown in Scheme 51, the system was tested on several substrates, as primary, secondary, and tertiary alkyl trifluoroborates in combination with vinyl carboxylic acids substituted with aryl and acyl groups are rendered in good yields.¹²⁵

To cast some light onto the reaction mechanism, the authors¹²⁵ performed several control experiments. When the reaction was carried out in the presence of TEMPO, neither the desired product nor the alkene-TEMPO adduct were observed; only the alkyl-TEMPO adduct was isolated,

confirming the presence of alkyl radicals from the corresponding alkyl trifluoroborate compounds.

When the mixture of (*E*)-3-(*p*-tolyl)acrylic acid and BI-OAc (Scheme 52) was monitored by NMR experiments, the formation of a new vinyl carboxylic acid complex was observed. This complex was isolated and characterized by X-ray crystallography.¹²⁵

Scheme 52. Characterization of Benziodoxole Vinyl Carboxylic Acid Complex

With these results in hand, the authors proposed the reaction mechanism that is illustrated in Scheme 53. The vinyl

Scheme 53. Proposed Mechanism: Photocatalytic Alkenylation Reaction

carboxylic acid reacts with BI-OAc to afford benziodoxole vinyl carboxylic acid complex 58 (Scheme 53), which is oxidized in the initiation step. The trifluoroborate (or boronic acid) reacts with $[\text{Ru}(\text{bpy})_3]^{2+}$ to generate alkyl radical R and $[\text{Ru}(\text{bpy})_3]^{3+}$. The R radical adds to the double bond of complex 58 (Scheme 53) with formation of radical adduct 59 (Scheme 53), which undergoes decarboxylation to release the benziodoxole radical and the alkene product.¹²⁵

The authors¹²⁵ also reported the alkenylation of a water-soluble vinyl carboxylic acid (Scheme 54) at pH 7.4 in a phosphate saline buffer to afford the corresponding alkene with

Scheme 54. Photocatalytic Alkenylation of Trifluoroborate in Aqueous Media

a good yield which probes the potential application in the functionalization of biomolecules in neutral aqueous media.

In another report, Zhang and colleagues¹²⁶ developed a transition metal-free methodology consisting of the consecutive oxidative and decarboxylative acylation/ring expansion of vinylcyclobutanols with α -keto acids employing visible light photoredox catalysis.

The reaction mixture consists of α -keto acid and vinylcyclobutanol, with Rhodamine B as the photocatalyst, hydroxybenzodioxole (BI-OH) as the oxidant in a two-phase system of $\text{CH}_2\text{Cl}_2:\text{H}_2\text{O}$ (1:1) under visible light irradiation with a 23 W CFL lamp. With these conditions in hand, a variety of α -keto acids bearing electron-rich or electron-poor groups and several substituted vinylcyclobutanols (Scheme 55) reacted successfully in moderate to good yields.¹²⁶

Scheme 55. α -Keto Acid and Vinylcyclobutanols Scope: Metal-Free Oxidative Decarboxylative Acylation/Ring Expansion

In the proposed mechanism (Scheme 56), hypervalent complex reagent **60** (Scheme 56) generated *in situ* is oxidized by an excited photocatalyst (PC^*) to produce an acyl radical, CO_2 , and $\text{PC}^{\bullet-}$. The acyl radical adds to vinylcyclobutanol to generate radical adduct **61** (Scheme 56), which reacts with BI^+ to afford carbocation **62** and a BI radical. Intermediate **57**

Scheme 56. Proposed Mechanism: Metal-Free Oxidative Decarboxylative Acylation/Ring Expansion

(Scheme 56) undergoes 1,2-alkyl migration to produce the desired product with proton loss. Finally, the BI radical accepts the electron from $\text{PC}^{\bullet-}$ to regenerate the catalyst.¹²⁶

In control experiments, the acyl radical was evidenced by adding a trapping reagent (TEMPO) to the reaction mixture. Under these conditions, only trace amounts of the desired product was observed, and the acyl-TEMPO adduct was isolated.¹²⁶

■ PHOTOOXIDATION AND CYCLIZATION REACTIONS IN AQUEOUS MEDIA

Visible light photocatalysis has shown great potential to initiate oxidation reactions.¹²⁷

Solid polymeric graphitic carbon nitride ($\text{g-C}_3\text{N}_4$)^{128,129} is an organic semiconductor with a set of properties such as easy and economic preparation, a band gap less than 2.7 eV, absorption of light in the visible region (<450–460 nm),¹³⁰ and the capacity to activate molecular oxygen.^{128,131–134} All these properties make this a suitable option to mediate photoredox catalytic transformations under visible light irradiation conditions.¹³⁵

Hu and co-workers¹³⁵ have reported a metal-free heterogeneous photocatalytic system for aerobic oxidation of benzylic C–H bonds. The reaction was conducted in the presence of the organic substrate, $\text{g-C}_3\text{N}_4$ as the photocatalyst, oxygen as the oxidizing species, and water as the solvent and under blue light irradiation at room temperature.

As shown in Scheme 57, the optimal reaction conditions were applied to the oxidation of isochromans and phthalans to afford the corresponding 2-isochromanones and phthalides with good yields, respectively.¹³⁵

Scheme 58 summarizes the results of the oxidation of different alkylarenes to ketones. The authors¹³⁵ also reported the oxidation of isoindolines and tetrahydroisoquinolines in DMSO as the reaction solvent.

To demonstrate the practical application of the heterogeneous catalysis, a recycling procedure was established. The photocatalyst was recovered after a reaction with isochromans and subsequently reused. In these cases, the photocatalyst maintains a high photocatalytic activity.¹³⁵

Alcohols can be oxidized to aldehydes and ketones in water under visible light irradiation through the assistance of a 3-mercaptopropionic acid (MPA)-capped CdSe quantum dot (MPA-CdSe QD) and NiCl_2 without any external oxidant.¹³⁶ The scope of the reaction is briefly depicted in Scheme 59.

Although photocatalyzed cyclization reactions in water or aqueous media were discussed in the Homolytic Aromatic Substitutions with Ulterior Cyclizations section through the homolytic aromatic substitution mechanisms, we, in this section, discuss cyclization reactions involving π systems other than aromatics (double and triple bonds).

Tertiary amines can be oxidized to reactive iminium ions or azomethine ylides in the presence of water. On the other hand, secondary amines can be oxidized to imine intermediates leading to reactive electrophiles.^{137–139}

Hue and collaborators¹⁴⁰ attempted to oxidize *N*-alkylsubstituted arylhydroxylamines to nitrones by photocatalysis in water and single electron oxidation, with the aim to realize an ulterior [3 + 2] cycloaddition reaction of these nitron intermediates with alkenes, according to a proposed Scheme 60.

After a series of optimization attempts, including solvents, additives, reaction times and stoichiometry, the authors¹⁴⁰

Scheme 57. Photocatalyzed Aerobic Oxidation of Isochromans and Phthalans

Scheme 58. Photocatalyzed Aerobic Oxidation of Isochromans and Phthalans

Scheme 59. Oxidation of Alcohols to Aldehydes and Ketones

Scheme 60. Synthesis Design

achieved proper conditions for the [3 + 2] cycloaddition of these nitron intermediates with alkenes consisting of an aryl-alkyl hydroxylamine (0.1 mmol) substrate, alkene (0.3–0.4 mmol), [Ir(ppy)₂bpy]PF₆ as the photocatalyst (1 mol %), the presence of water (2.5 equiv) in ethyl acetate as the solvent, and irradiation with an 11 W fluorescent bulb for 24 h at room temperature. The scope of the transformation is illustrated in Scheme 61.

Different ester groups such as –CO₂Me, –CO₂Et, –CO₂ⁱPr, and –CO₂^tBu were included in the starting *N*-alkylsubstituted arylhydroxylamines under the current reaction conditions. In all cases, high yields and diastereoselectivities were encountered for the respective *N*-phenylisoxazolidines.¹⁴⁰

The authors¹⁴⁰ also inspected the scope of the reaction in relation to the aryl ring attached to the N atom, according to Scheme 62.

Scheme 61. Selected Examples for Evaluation of Different Ester Groups and Dipolarophiles in Photoredox Oxidative Cyclization Reaction of Nitrones and Alkenes

Scheme 62. Selected Examples for Evaluation of Different Aryl Groups and Dipolarophiles in Photoredox Oxidative Cyclization Reaction of Nitrones and Alkenes

As observed from Scheme 62, hydroxylamines substituted with aryl rings bearing Me, F, and Cl groups resulted in good yields and diastereoselectivities.

The authors¹⁴⁰ proposed a reaction mechanism such as that depicted in Scheme 63. Upon irradiation, the photocatalyst is converted to Ir³⁺ and quenched through a reductive ET by hydroxylamine 63 to produce Ir²⁺ and ammonium radical cation 64. The Ir³⁺ photocatalyst is regenerated through oxidative ET from oxygen to yield O₂^{•−}. Also, photoredox catalysis can provoke the generation of active species such as HO[•], HO[−], and H₂O₂ from water.^{141,142} In the case of the reactions above, the authors claimed that the presence of oxygen is the main source of the reactive oxygenated species.

Upon deprotonation, radical cation 64 can form either radical 65 or 66 (a carbon-centered radical or oxygen-centered radical, respectively). Electron transfer from 65 affords intermediate 67, which can be deprotonated by HOO[−] to nitron 68. A reaction of nitron 68 with alkene 69 affords [3 + 2] cycloaddition product 70 (Scheme 63).

Kumar and colleagues¹⁴³ have developed a visible light-induced dehydrogenative trifluoromethylation and oxidation of

Scheme 63. Proposed Reaction Mechanism

1,6-enynes with water, starting from a 1-(phenylethynyl)-2-(vinyl)benzene substrate toward the synthesis of trifluoromethylated C3-aryloylated benzofurans, benzothiophenes, and indoles. The authors found optimum reaction conditions consisting of the use of 1-(phenylethynyl)-2-(vinyl)benzene (0.1 mmol) as the substrate, 1,10-phenanthroline-5,6-dione as the photocatalyst (0.01 mmol), and a Langlois reagent $\text{CF}_3\text{SO}_2\text{Na}$ (0.3 mmol) in acetonitrile:water (9:1) as the solvent mixture in the presence of visible light.

The scope of the reaction¹⁴³ is illustrated in Scheme 64.

Scheme 64. Selected Examples for Construction of Trifluoromethylated C3-Aryloylated Benzofurans and Benzothiophenes

From Scheme 64, it is observed that both 2-iodophenols and 2-iodothiophenols can be used as substrates to yield 2-benzoyl-substituted benzofurans and benzo[*b*]thiophenes in good yields. Also, starting from 2-iodoanilines, trifluoromethylated C3-aryloylated indoles are synthesized in reasonably good yields (Scheme 65). The reaction employs the Langlois reagent and 4-methyl-*N*-(2-(arylethynyl)phenyl)-*N*-vinylbenzenesulfo-

Scheme 65. Selected Examples for Construction of Trifluoromethylated C3-Aryloylated Indoles

namide under a phenanthridinedione photocatalyst in $\text{MeCN}:\text{H}_2\text{O}$ as the solvent mixture.¹⁴³

As observed from Scheme 65, aryl groups with 4-methyl, H, 4-Br, and 4- OCH_3 were tested, providing good yields of the indole products.

The authors¹⁴³ performed a series of experiments in order to provide light to the reaction mechanism. When the reaction was undertaken in H_2^{18}O , the formation of O^{18} -labeled trifluoromethylated C3-aryloyl benzofuran was found, indicating that oxygen in product arises from water. Also, the reaction in D_2O showed a NMR signal at $\delta = 4.55$ ppm and $J = 42.8$ Hz, consistent with H_2 evolution according to Scheme 66.

Scheme 66. Labeling Experiments

The authors¹⁴³ also investigated the reaction pathway employing ESR experiments. In the presence of 2-methyl-2-nitrosopropane (MNP), a dimer resulted in the trapping of CF_3 radicals, observing the *tert*-butyl-trifluoromethyl nitroxide radical. Also, in the presence of TEMPO, a radical scavenger, the product was not found, and the adduct TEMPO- CF_3 was encountered. From redox parameters, the excited state redox potential of the photocatalyst 1,10-phenanthroline-5,6-dione (PQ) $E_{\text{red}}^{1/2*} (^3\text{PQ}^*/\text{PQ}^{\bullet-})$ is $+1.6$ V¹ and that of the Langlois reagent is $+1.05$ V (vs SCE),¹⁴⁴ which warrants the electron transfer process (meaning that PQ is strong enough to oxidize the Langlois reagent by electron transfer).

With the mechanistic probe experiments in hand, the authors¹⁴³ postulated the following reaction mechanism, according to Scheme 67.

Upon excitation of the photocatalyst PQ, its excited triplet excited state is able to oxidize the Langlois reagent to CF_3 radicals, which add in turn to substrate 71 to produce radical intermediate 73, which is oxidized by radical PQH to yield cation intermediate 73. Upon internal cationic cyclization of 73, vinylic intermediate 74 is generated, which upon water nucleophilic addition renders intermediate 76. Ulterior deprotonation and hydrogen evolution gives final product 78. An alternative radical pathway intermediate can be conceived through 75.¹⁴³

MISCELLANEOUS PHOTOREDOX REACTIONS IN AQUEOUS MEDIA

Condensation Reactions. Hossein and colleagues¹⁴⁵ established a protocol for the synthesis of substituted pyrazines

Scheme 67. Proposed Reaction Mechanism

from vinyl azides made possible by a dual-energy and electron-transfer strategy by visible light photocatalysis in aqueous medium.

The best reaction conditions include the use of vinyl azide (0.5 mmol), photocatalyst $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (1 mol %), and irradiation with a 455 nm LED in a $\text{CH}_3\text{CN}:\text{water}$ 4:1 mixture in open air. The scope of the transformation is shown in Scheme 68. Further optimization studies revealed that the addition of another oxidant such as $\text{K}_2\text{S}_2\text{O}_8$ did not provide any product indicating the importance of oxygen.¹⁴⁵

Scheme 68. Scope of Synthesis of Substituted Pyrazines

As observed from Scheme 68, aryl vinyl azides substituted with both electron-donating groups (MeO , CH_3) or electron-neutral groups (H , F) afforded good yields of substituted pyrazines

The authors¹⁴⁵ investigated the reaction mechanism, as suggested in Scheme 69. The mechanism starts with an energy

Scheme 69. Proposed Reaction Mechanism

transfer process from the excited $\text{Ru}(\text{II})^*$ photocatalyst to vinyl azide. Vinyl azide is converted into its triplet manifold **79**, which upon loss of nitrogen forms a reactive nitrene intermediate **80** that rearranges to the azirine **81**. This azirine **81** may undergo ring opening by water, leading to the formation of α -amino ketone **82**. The condensation of **82** to form dihydropyrazine species. This dihydro species is aromatized by an electron transfer process from $\text{Ru}(\text{II})^*$, yielding radical cation **83** and $\text{Ru}(\text{I})$. Species **83**, upon reaction with an anion superoxide, affords a pyrazine compound and concludes the reaction mechanism.¹⁴⁵

Synthesis of Boronates and Borylation Reactions. Li and collaborators¹⁴⁶ presented a photocatalytic strategy for the preparation of alkyl boronates from aliphatic esters in an aqueous reaction media. This transformation is very innovative because borylation reactions usually require anhydrous conditions. In a typical experiment, a primary carboxylic acid-derived *N*-acyloxyphthalimide, *bis*(pinacolato)diboron (B_2pin_2), and catalyst $[\text{Ir}(\text{ppy})_2\text{dtbpy}]\text{PF}_6$ are irradiated under visible light in a mixture of $\text{DMF}:\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (1:1:1) as the reaction medium (Scheme 70). The authors found this transformation to be useful for efficiently converting several primary *N*-acyloxyphthalimides with various electron-withdrawing, electron-donating, and electron-neutral groups; alkenes with (*Z*)-configuration as well as terminal alkynes, aryl bromides, and alkyl chlorides were all well tolerated (Scheme 70).¹⁴⁶

The authors¹⁴⁶ proved the radical nature of the reaction by performing radical cascade experiments and proposed a conceivable reaction pathway (Scheme 71). Upon light excitation, the $\text{Ir}(\text{III})$ photocatalyst performs a single electron transfer to *N*-acyloxyphthalimide affording the $\text{Ir}(\text{IV})$ photocatalyst and the *N*-acyloxyphthalimide radical anion which suffers homolytic cleavage yielding a carboxyl radical and a phthalimide anion (Scheme 71). The carboxyl radical

Scheme 70. Selected Examples for Decarboxylative Borylation of Primary Carboxylic Acid-Derived *N*-Acyloxypthalimide under Visible Light Photoredox Conditions Employing a Mixture of DMF:CH₃CN:H₂O (1:1:1) as Reaction Media

Scheme 71. Proposed Reaction Mechanism for Decarboxylative Borylation of Primary Carboxylic Acid-Derived *N*-Acyloxypthalimide under Visible Light Photoredox Conditions Employing a Mixture of DMF:CH₃CN:H₂O (1:1:1) as Reaction Media

undergoes decarboxylation generating CO₂ and an alkyl radical (Scheme 71). The phthalimide anion in the presence of water undergoes protonation generating a hydroxide ion that reacts with B₂pin₂ affording sp³–sp² diboron anion **84** (Scheme 71). The alkyl radical reacts with anion **84** yielding the desired reaction product and a boryl radical anion that performs a single electron transfer with the Ir(IV) photocatalyst regenerating the Ir(III) photocatalyst and closing the catalytic cycle (Scheme 71).¹⁴⁶

The borylation of diazonium salts with diboronate esters employing nontoxic carbon dots (CDs) as photocatalysts was recently carried out in water by Wu and colleagues.¹⁴⁷ The blue CDs were synthesized through reaction of 2,6-diaminopyridine with acrylic acid in the presence of ZnCl₂ in tetraethylene glycol as the solvent.¹⁴⁷ A general reaction is illustrated in Scheme 72. This result (Scheme 72) has been discussed in a review article.⁶

C–P Bond Formation. The formation of C–P bonds is relevant as organophosphorus compounds have many applications in pharmaceutical chemistry or are employed as ligands or intermediates in synthetic organic chemistry.¹⁴⁸

Scheme 72. Borylation of Diazonium Salts

In 2011, Rueping and colleagues¹⁴⁹ developed the first photoredox catalytic protocol for the oxidative carbon–phosphorus bond formation. The reaction has even more relevance from the perspective of the aqueous reaction medium employed, which brings useful implications in biological aqueous systems. The protocol employs *N*-aryl-tetrahydroisoquinolines and dialkyl (or aryl) phosphites as substrates and [Ir(ppy)₂(bpy)][PF₆] as the catalyst in a mixture of toluene and water as the reaction medium under visible light irradiation with a 5 W fluorescent lamp.

The scope of the reaction is shown in Scheme 73. The authors¹⁴⁹ also investigated several phosphite esters, with

Scheme 73. Visible Light-Mediated Oxidative Phosphonylation

different alkyl groups. The phosphite with the bulky groups (as –O^{*i*}Pr) reacted with the isoquinolinium ion intermediate generated photochemically under more prolonged reaction times and with poor yields. The dimethyl phosphite did not provide the product, probably due to the fast hydrolysis reaction of the dimethyl phosphite in the presence of water.

The resulting α-amino phosphonates are interesting compounds in medicinal chemistry with a myriad of applications, such as α-amino acids analogues, enzyme inhibitors, and present antibacterial and antifungal activity.¹⁵⁰

Other interesting examples for the construction of C–P bonds by photocatalysis in water followed. The direct synthesis of *Z*-alkenylphosphine oxides occurred through the addition of phosphoryl radicals to alkynes^{6,151} (Scheme 74A); also by this method, the syntheses of 3-phosphorylated thioflavones^{6,152} (Scheme 74B) and 3-phosphorylated benzothiophenes^{6,153} (Scheme 74C) have been attempted. All these methods have been recently reviewed and are succinctly summarized in Scheme 74.⁶

Debromination and Bromination Reactions. Willner and co-workers¹⁵⁴ have reported the photochemical debromination of 1,2-dibromoarylethanes to afford the corresponding 1,2-diarylethylenes using a heterogeneous system. For that purpose, they employed an alkylviologen, *N,N'*-dioctyl-4,4'-bipyridiniumdibromide (C₈V⁺) as an electron carrier, due its solubilization properties (which depend on its oxidation state).

The two-phase system is composed of an organic solution of a dihalogenated substrate in ethyl acetate and an aqueous solution of ruthenium *tris*(bipyridine) dichloride (Ru(bpy)₃²⁺), (NH₄)₃EDTA, and C₈V⁺. The reaction mixture was irradiated

Scheme 74. Photocatalyzed Syntheses of Phosphorylated Z-Alkenylphosphine oxides (A), 3-Phosphorylated Thioflavones (B), and 3-Phosphorylated Benzothiophenes (C)

with a 1000 W halogen-quartz lamp employing a filter ($\lambda > 400$ nm).

Upon irradiation of the biphasic system (Scheme 75), excited $\text{Ru}(\text{bpy})_3^{2+}$ is quenched by C_8V^+ (soluble only in

Scheme 75. Photocatalytic Reduction of 1,2-Dibromostilbene in a Two-Phase System Mediated by C_8V^{2+}

aqueous media) affording $\text{Ru}(\text{bpy})_3^{3+}$ and $\text{C}_8\text{V}^{\bullet+}$. This reduced form ($\text{C}_8\text{V}^{\bullet+}$), with lipophilic properties, is extracted into the organic phase. The active two-electron reducing agent C_8V is formed in a disproportionation reaction (eq 1).

The disproportionation reaction of $\text{C}_8\text{V}^{+\bullet}$ affords C_8V^{2+} (which is re-extracted into the aqueous phase) and C_8V , which is capable of reducing the dibromide. Finally, the debromination reaction recycles the mediating electron acceptor, and $\text{Ru}(\text{bpy})_3^{2+}$ is regenerated by oxidation of $(\text{NH}_4)_3\text{EDTA}$.

Using this system, the authors¹⁵⁴ achieved the conversion of several 1,2-dibromoarylethanes into the corresponding *trans*-stilbenes, as shown in [Scheme 76](#). No reduction of dibromides occurs when C_8V^{2+} is excluded from the reaction mixture.

Because the reducing species C_8V^{2+} is extracted into the aqueous phase after formation, the disproportionation reaction balance is shifted toward products. In fact, such a debromination reaction should be unfavorable in a homogeneous solution due to a low disproportionation constant ($K_d = 5 \times 10^{-8}$). Indeed, the irradiation of an acetonitrile mixture of $Ru(bpy)_3^{2+}$ as the sensitizer, C_8V^+ as the electron carrier, triethanolamine as the electron donor, and 1,2-dibromostilbene does not result in the formation of a debromination

Scheme 76. Product Yields: Debromination of 1,2-Dibromoarylethanes Mediated by C_8V^{2+} in a Two-Phase System

product, which emphasizes the relevance of water in this photocatalytic reaction.

The authors also reported¹⁵⁵ a remarkably similar cyclic chemical debromination of *meso*-1,2-dibromostilbene in a two-phase system. In that case, the chemical initiation is accomplished with the addition of sodium dithionite in the aqueous phase.

Formyloxylation Reactions. Zou and colleagues¹⁵⁶ achieved the formyloxylation reaction of 3-bromooxindoles in a mixture of water and *N,N*-dimethylformamide (DMF) in the presence of *fac*-Ir(ppy)₃ as the photoredox catalyst under visible light irradiation at ambient temperature, yielding 3-formyloxyoxindoles in high yields. The use of DMF provides the “H, C, O” source, and H₂O is the extra “O” source. The authors optimized the reaction conditions arriving at the following stoichiometry: 3,5-dibromo-1,3-dimethylindolin-2-one as the initial substrate (0.2 mmol), DMF (2 mL), H₂O (10 equiv), and *fac*-Ir(ppy)₃ (2 mol %) for 2.5 h. The scope of the transformation is illustrated in [Scheme 77](#).

Scheme 77. Selected Examples for Formyloxylation Reaction of 3-Bromooxindoles with Water and *N,N*-Dimethylformamide

As observed from [Scheme 77](#), 3-bromooxindoles bearing halogen substituents (Br, Cl) and cycloalkyl substituents (cyclopentyl) afforded good product yields of the respective formylation products.

The authors¹⁵⁶ also investigated the reaction mechanism. A proposal is depicted in [Scheme 78](#).

In the proposed mechanism (Scheme 78), the photocatalyst is excited into a triplet state (metal-to-ligand charge transfer complex, MLCT) capable to reduce by electron transfer substrate **85** to radical **86**. Radical **86** then reacts with DMF to yield radical **87**, which is oxidized by ET by substrate **85** to iminium species **88**, which upon reaction with water affords product **90** and dimethylamine amine **89** (Scheme 78).¹⁵⁶

Scheme 78. Proposed Reaction Mechanism

Allylation of Aldehydes. Allylation reactions have been described under Barbier conditions, with the involvement of various metals such as nickel,^{157,158} chromium,^{159–161} titanium,^{162,163} and cobalt.¹⁶⁴ Bismuth has also been used in allylation reactions under various conditions.^{165–171}

Potenti and colleagues¹⁷² have recently found the photocatalyzed allylation reaction of aldehydes mediated by Bi(OTf)₃ (10 mol %), employing 2,4,6-tri(9*H*-carbazol-9-yl)-5-chloroisophthalonitrile (3CzClIPN, 5 mol %) as the photocatalyst in EtOH:H₂O (1:1) as the mixture of solvents, and Hantzsch ester (HE, 2 equiv) as the electron source under blue LED irradiation. The authors¹⁷² avoided the use of Ir or Ru photocatalysts. The scope of the reaction was studied, according to Scheme 79.

Scheme 79. Selected Examples for Allylation of Aromatic and Aliphatic Acids

In this way, aromatic aldehydes bearing 4-fluoro, 4- CF_3 , 2-chloro, and 4-cyano substituents were rehearsed, affording good results of the respective benzylic alcohols. Aliphatic aldehydes such as valeraldehyde, 2-phenylacetaldehyde, 3-phenylpropanal, cyclohexanecarbaldehyde, and cinnamaldehyde also provide good product yields.¹⁷²

The authors investigated the mechanism of the reaction performing luminescence quenching experiments of the photocatalyst (i.e., 3CzClIPN). In the presence of increasing amounts of Bi(OTf)₃ or allyl bromide, no decrease in the emission intensity of 3CzClIPN* was observed. On the contrary, the addition of 4-chlorobenzaldehyde hardly decreased the intensity of fluorescence, explaining the pinacol

coupling in absence of Bi(OTf)₃. A similar behavior is observed when the HE is introduced in the presence of 3CzClIPN. Considering all the probe experiments performed, the authors¹⁷² proposed the following reaction mechanism (Scheme 80).

Scheme 80. Proposed Reaction Mechanism

The reductive quenching of 3CzClIPN by Hantzsch ester (HE) produces the radical cation of HE (according to redox potentials, $E_{1/2}$ 3CzClIPN*/3CzClIPN^{•-} = +1.56 V vs SCE and the oxidation potential of the Hantzsch's ester $E_{1/2}$ HE^{•+}/HE = +1.0 vs SCE,¹⁷³ purporting that oxidation of HE is feasible by 3CzClIPN*). The reducing 3CzClIPN^{•-} species is thus formed, which is able to reduce the Bi salt to Bi(0), which in turn complexes with allyl bromide. The insensitive reactions to oxygen and TEMPO rule out a free radical mechanism and formation of allylic radicals. The formation of Bi(0) should be considered to take place in the reaction mechanism. The insertion of bismuth to the C–Br bond could form allylbismuth(III), diallylbismuth(III), and triallylbismuth(III) species as the organometallic intermediates that react with aldehydes to give the corresponding homoallylic alkoxides. The protonated aromatized HE in the aqueous media allows the facile protonation of a Bi alkoxide intermediate, permitting the recycling of Bi salts.¹⁷²

CONCLUSIONS

The array of organic photocatalyzed reactions presented herein in water or aqueous media is encouraging the organic synthetic chemistry community to further explore the potential and advantages inherent in diminishing the environmental impact of the synthetic and photocatalytic processes performed in conventional organic solvents. Many ordinary reaction types have been discussed, such as radical additions to alkenes, ATRA reactions, arylation processes, homolytic aromatic substitutions, and several other standard organic transformations commonly employed for the synthesis of organic scaffolds that are made possible in water or water mixtures by photocatalysis.

One of the problems that chemists face when choosing reaction solvents is the solubility of reactants, as the vast majority of ordinary organic substrates are organic solvent soluble. Even a more critical situation emerges when employing light as a reactant (such as in photocatalysis), as heterogeneous media can interfere with proper photon absorption due to sample or photocatalyst heterogeneous distribution. However, all examples depicted in heterogeneous media or with nonwater-soluble reactants seem to proceed without difficulties, as illustrated in this perspective.

There is no barrier as to the use of any typical photocatalyst employed in organic synthesis when performing a photo-reaction in water or aqueous mixtures. Ir- and Ru-polypyridyl complexes have been found to give promising results when

reactions are carried out in water, as well as with organic dyes such as Rose Bengal, Eosin Y, 1,10-phenanthroline-5,6-dione, or graphitic carbon nitride ($g\text{-C}_3\text{N}_4$); quantum dots and carbon dots; or semiconductors such as TiO_2 and CdSe. Parallel studies on the photocatalyst efficiency in organic media and water should be addressed in those photocatalyzed reactions that can be carried out in both media in order to establish the capability of the methodology.

Also, the peculiar effects of water in some photocatalytic reactions have been uncovered, which further emphasizes the unique role of water as a solvent, particularly in photocatalytic systems, for example where, in its absence, the desired product is not formed at all, or water itself also intervenes as a proton donor or oxygen donor or is necessary in stoichiometric amounts as a coreactant. Even more intriguing effects can be observed when water plays a part in the stereoselectivity of the reaction, influencing and driving the formation of products with high diastereoselectivity as opposed to the same reactions performed in organic media. The effects of water for improving enantioselectivity in chiral catalytic photoredox reactions were also exposed and explored with representative examples.

Attention should be paid to those photocatalyzed reactions that do not work in organic solvents but do work in water or aqueous media with high product yields, as these should be considered an entry into new protocols and reaction types. Finally, there are myriads of photocatalyzed transformations in organic solvents that await to be revisited or attempted in water or aqueous media, demonstrating the potential of the methodology, the possibility of bringing to light unexpected selectivity and product yield enhancement, and ultimately diminishing the environmental impact of these organic synthetic procedures.

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