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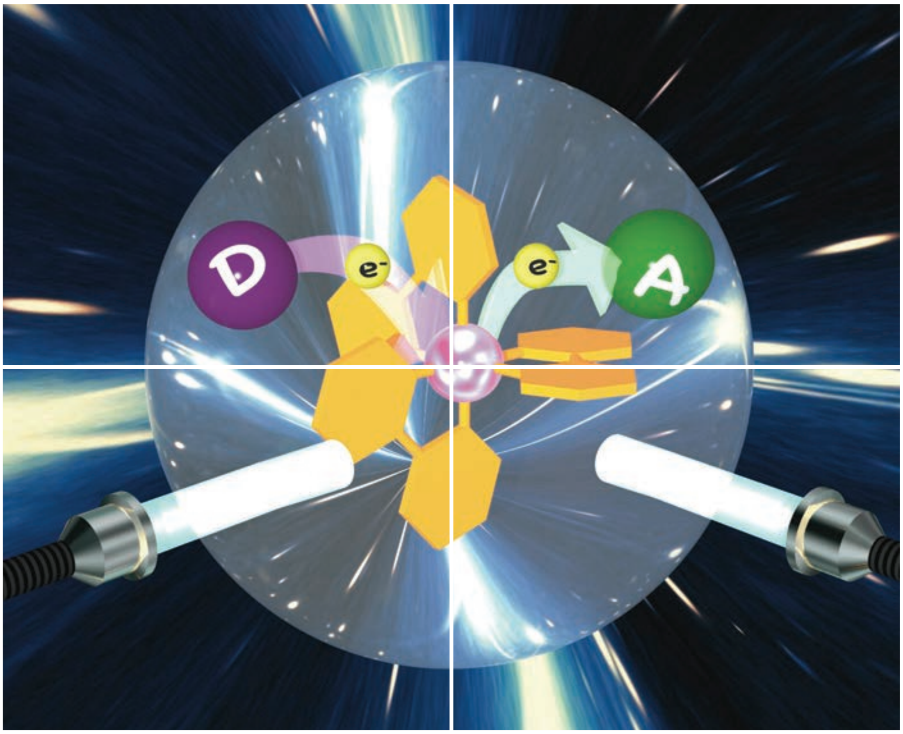

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REVIEW

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Visible-light radical reaction designed by Ru- and Ir-based photoredox catalysis

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Photoredox catalysis by well-known ruthenium(II) polypyridine complexes and the relevant Ir cyclometalated derivatives has become a powerful tool for redox reactions in synthetic organic chemistry, because they can effectively catalyze single-electron-transfer (SET) processes by irradiation with visible light. Remarkably, since 2008, this photocatalytic system has gained importance in radical reactions from the viewpoint of not only a useful and selective protocol but also green chemistry. In this review, we will describe recent developments of radical reactions involving various carbon-centered radicals through photoredox processes mediated by Ru- and Ir-based photocatalysts.

1. Introduction

For the past few years, the visible-light-induced photocatalytic strategy, *i.e.* photoredox catalysis, with well-defined ruthenium (II) polypyridine complexes and the relevant Ir cyclometalated derivatives has emerged as a powerful tool for redox reactions due to its ability to cause single-electron-transfer (SET) processes under mild conditions by irradiation of visible light (sunlight).[1,2] It is attracting the attention of many researchers from the viewpoint of the development of new transformation as well as green and sustainable chemistry. Since 2008, it has represented one of the new trends in organic chemistry (Fig. 1) and is still expanding.

Redox reactions are often associated with radical reactions.[3] Conventional strategies, such as the use of a stoichiometric amount of oxidant or reductant, electrolysis, and photolysis are accompanied by disadvantages: the formation of considerable amounts of waste derived from the oxidant or reductant or the need for special equipment for electrochemical or photochemical processes. In modern synthetic organic

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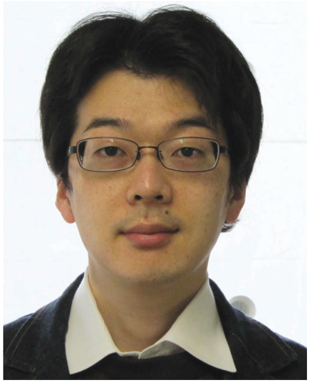


Takashi Koike

Takashi Koike was born in 1977 in Toyama, Japan. He received his doctoral degree from the Tokyo Institute of Technology in 2005 under the guidance of Prof. Takao Ikariya. After his graduate career, he joined the Professor Robert H. Grubbs' group in the California Institute of Technology, USA as a postdoctoral research scholar. In 2007 he returned to the Tokyo Institute of Technology as an assistant professor of Chemical Resources Laboratory. His research interests are in synthetic organic chemistry and organometallic chemistry. Recently, his efforts have been directed to the development of visible-light-driven photocatalysis.

Munetaka Akita

Munetaka Akita was born in Fukuoka, Japan, in 1957. He studied organometallic chemistry under the supervision of Professors Makoto Kumada and Kohei Tamao (Kyoto University) and Professors Akira Nakamura and Hajime Yasuda (Osaka University). Soon after receiving his Ph.D. degree in 1984, he joined Professor Yoshihiko Moro-oka's group at the Tokyo Institute of Technology as a research associate. He was appointed as a professor in 2002. The recent research efforts of his group have been devoted to application of carbon-rich organometallics to molecular devices (molecular wires and stimuli-responsive systems), visible-light-promoted catalysis, and supramolecular systems based on anthracene.

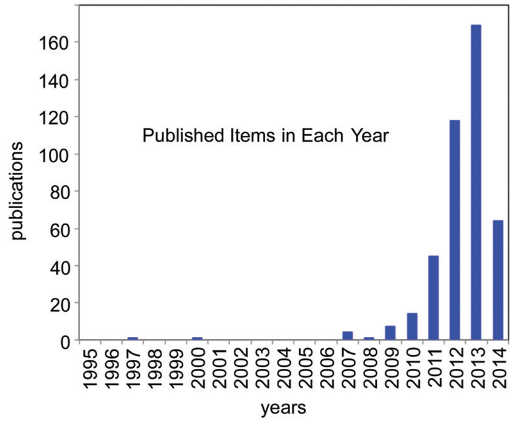
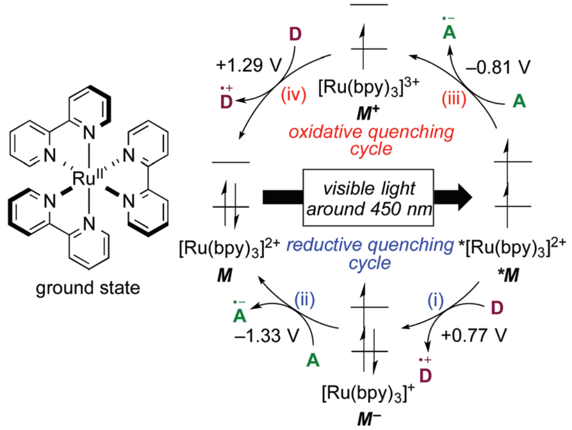


Fig. 1 Number of publications in the last 20 years concerned with the study on "photoredox catalysis" (from ISI web of Knowledge; as of 05/09/2014).



Scheme 1 Photoredox cycle of $[Ru(bpy)_3]^{2+}$.

chemistry, protocols need to be easy and safe to use, as well as having efficient and selective outcomes.

Photoredox processes with octahedral Ru and Ir polypyridine complexes are triggered by visible light (sunlight), which is regarded as a mild and abundant stimulus. In addition, normal glassware is allowed to be used. Thus, photoredox catalysis shows merits as a useful tool for generation of organic radicals. In this review, we will deal with the generation of carbon-centered radicals from a variety of precursors and their subsequent radical reactions promoted by metal complex-based photoredox catalysts, especially using octahedral Ru and Ir polypyridine complexes. Before discussing the main subject, we will review the basic photochemical properties of representative photoredox catalysts and strategies for photoredox catalysis.

1.1 Photochemical properties of $[Ru(bpy)_3]^{2+}$

The well-investigated tris(2,2′-bipyridine)ruthenium complex, $[Ru(bpy)_3]^{2+}$, is the most widely used photoredox catalyst because it exhibits outstanding photochemical properties.[4] In this section, photochemical properties of $[Ru(bpy)_3]^{2+}$ will be explained as a representative example. Firstly, its absorption maximum (around 450 nm) is in the visible-light region, indicating that it can be easily excited by visible light. Photoexcitation can be performed using a fluorescent light bulb, a LED lamp, a Xe lamp, or even natural sunlight. Secondly, the lifetime of the luminescent triplet excited state (τ = approximately 1 μs), $^*[Ru(bpy)_3]^{2+}$, resulting from electron transfer from the dπ orbital of the ruthenium center to the π^* orbital of the 2,2′-bipyridine ligand (MLCT) followed by intersystem crossing, is sufficiently long enough for chemical transformations to proceed. Thirdly, the triplet excited state, $^*[Ru(bpy)_3]^{2+}$, undergoes single-electron-transfer (SET) to/from external organic molecules, *i.e.* this triplet state can serve either as a single electron oxidant or reductant. Further successive redox reactions regenerate the initial ground state, $[Ru(bpy)_3]^{2+}$ (Scheme 1). In addition, the photoredox catalyst is air- and moisture-stable and commercially available. Therefore, photoredox catalysis using this Ru photoredox catalyst has become a popular tool for redox reactions of diverse organic compounds.

The cycle consisting of a sequence of (i) electron transfer from an electron donor **D** to $^*[Ru(bpy)_3]^{2+}$ ($^*\boldsymbol{M}$) associated with formation of reduced $[Ru(bpy)_3]^{+}$ ($\boldsymbol{M}^{-}$) and (ii) reduction of an electron acceptor **A** associated with regeneration of the ground state of the catalyst ($\boldsymbol{M}$) is called a *reductive quenching cycle*. On the other hand, the cycle consisting of a sequence of (iii) electron transfer from $^*[Ru(bpy)_3]^{2+}$ ($^*\boldsymbol{M}$) to an electron acceptor **A** associated with formation of the high-oxidation-state $[Ru(bpy)_3]^{3+}$ ($\boldsymbol{M}^{+}$) and (iv) oxidation of an electron donor **D** associated with regeneration of the ground state of the catalyst ($\boldsymbol{M}$) is called an *oxidative quenching cycle*. Both of these cycles produce $\mathbf{D}^{+\bullet}$ and $\mathbf{A}^{-\bullet}$ radicals in a single reactor through SET processes to make, overall, the transformation redox-neutral. The terms *reductive* and *oxidative* can be confusing and require explanation. *Reductive* refers to reduction of the photoexcited species $^*\boldsymbol{M}$, whereas the external electron donor **D** is oxidized in the same process. *Oxidative* means oxidation of the photoexcited species $^*\boldsymbol{M}$ concomitant with reduction of the external electron acceptor **A**.

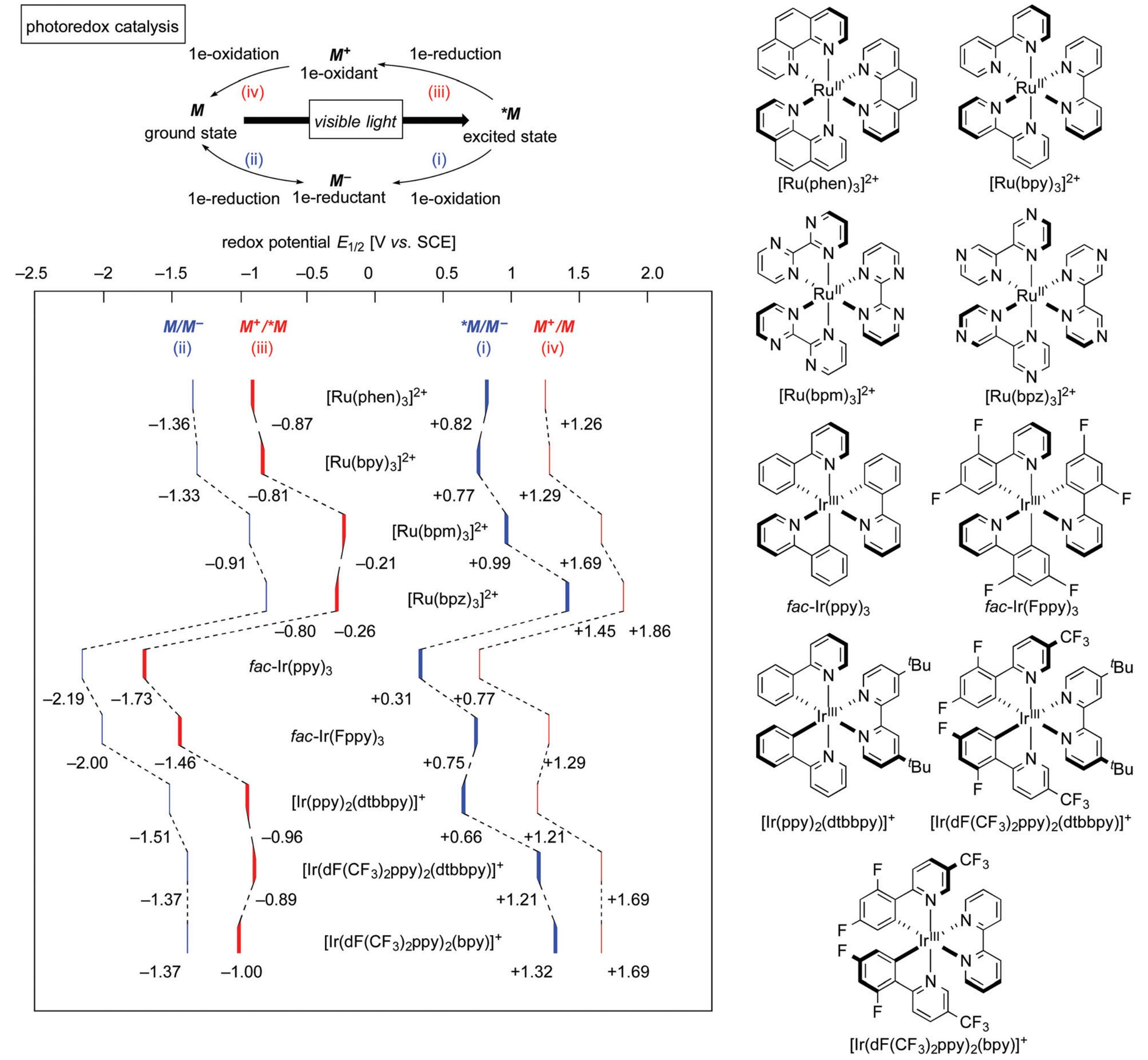
1.2 Basic strategies for photoredox catalysis

Redox potentials of catalytic species and organic reactants are the most important factors to be considered when photoredox reactions are designed. As shown in Scheme 1, the highly reduced species, $[Ru(bpy)_3]^{+}$ ($\boldsymbol{M}^{-}$), generated upon reductive quenching, serves as a 1e-reductant ($\boldsymbol{M}/\boldsymbol{M}^{-}$ = −1.33 V *vs.* SCE = Standard Calomel Electrode, in MeCN) and, to be noted, is a stronger reductant than the photoexcited species itself ($\boldsymbol{M}^{+}/^*\boldsymbol{M}$ = −0.81 V *vs.* SCE in MeCN). On the other hand, an oxidative quenching cycle produces the highly oxidized species $[Ru(bpy)_3]^{3+}$ ($\boldsymbol{M}^{+}$), which turns out to be a strong 1e-oxidant. In the field of photoredox chemistry using $[Ru(bpy)_3]^{2+}$, it is well-known that the combined use of the sacrificial electron donor **D** (*e.g.*, triethylamine) or acceptor **A** (*e.g.*, methyl viologen: *N*,*N*′-dimethyl-4,4′-bipyridinium) efficiently leads to redox reactions mediated by $[Ru(bpy)_3]^{+}$ ($\boldsymbol{M}^{-}$) and $[Ru(bpy)_3]^{3+}$ ($\boldsymbol{M}^{+}$), respectively. Thus, addition of a sacrificial reductant or oxidant has been the classical strategy to promote photoredox reactions.

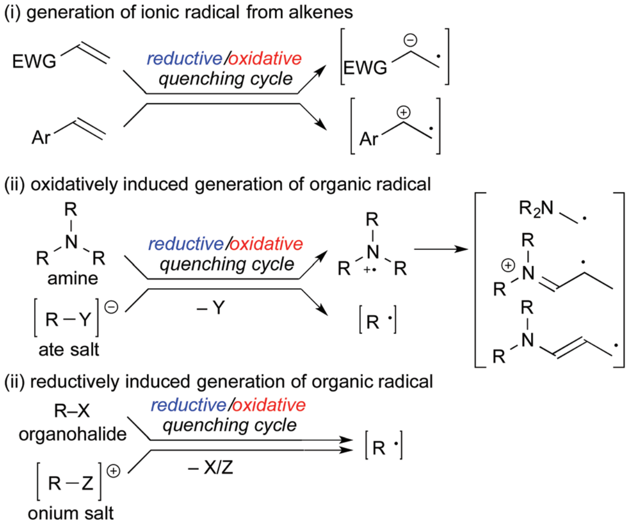
The relevant ruthenium polypyridine derivatives and isoelectronic cyclometalated iridium complexes also exhibit visible-light-induced photoredox catalysis, while the redox potentials of the catalytic species are dependent on the structure of the ligands and the central metal.[1h,4a,b,5] In addition, photocatalytic reactions with copper, platinum and gold complexes have been reported.[6] Moreover, organic photoredox catalysis, which is mediated by organophotocatalysts, is also an interesting topic;[7] however, a long lifetime of excited states of metal-based complexes, derived from the heavy atom effect, can promote chemical transformation more efficiently. Photoredox catalysts featured in this review are summarized in Scheme 2. The tuning of redox potentials by the ligands and the metal is regarded as another strategy for improving the efficiency of catalytic reactions.

Dual catalytic systems combining photoredox catalysis with another catalysis can achieve reactions, which cannot be achieved by just one of the catalytic systems.[1n] A catalytic system can activate organic molecules (**D** or **A**) or intermediates to convert the reactant into reactive species with permissible redox potentials, at which photocatalysts can undergo SET. In particular, this strategy may be applied to selective transformations, such as enantioselective and regioselective reactions.

In the subsequent sections, methods for generation of organic radicals by photoredox catalysis will be outlined as follows: (i) generation of ionic radicals from redox reaction of alkenes, (ii) oxidatively induced generation of organic radicals



Scheme 2 Photoredox catalysts featured in this review. The redox potentials for *[Ir(Fppy)$_3$] were calculated based on literature data.[5e,h]

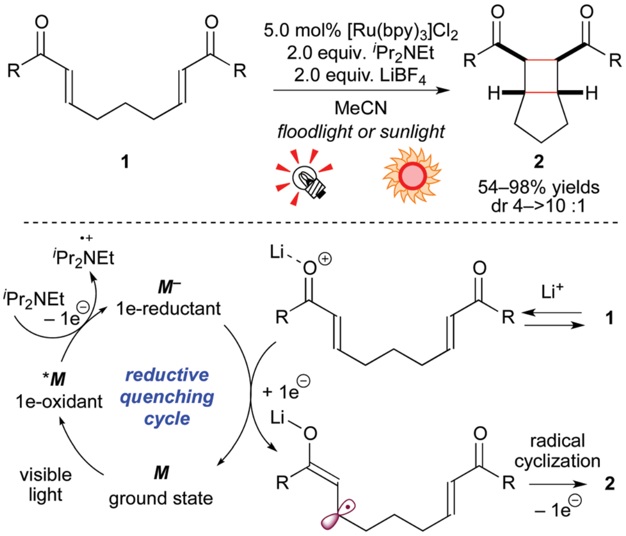


Scheme 3 Generation of various C-centered radicals highlighted in this review.

and (iii) reductively induced generation of organic radicals (Scheme 3). Judicial choice of appropriate radical precursors, substrates and photocatalysts is the key to construct a sophisticated photocatalytic radical reaction.

2. Generation of ionic radicals from redox reaction of alkenes

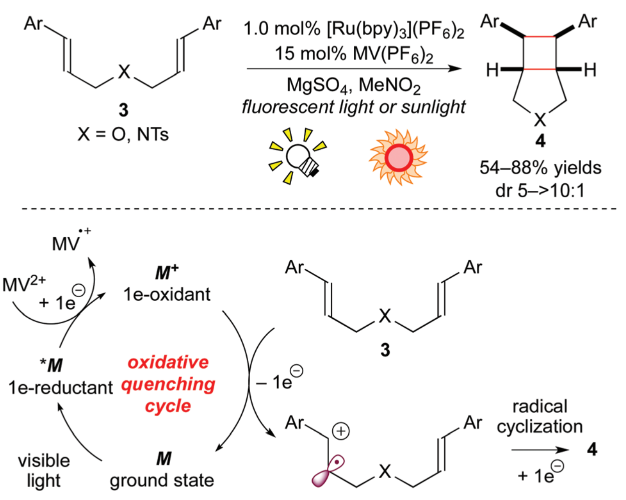
Neutral molecules undergo 1e-redox reaction, *i.e.* SET, to produce ionic radical species. The group of Yoon has been intensively developing cycloaddition reactions *via* ionic radicals generated from either 1e-reduction or 1e-oxidation of alkenes by photoredox catalysis. In 2008, they demonstrated that, in the presence of the Ru photocatalyst $[Ru(bpy)_3]Cl_2$ (5.0 mol%), a sacrificial electron donor ($^iPr_2NEt$), and a Lewis acid ($LiBF_4$), bis(enone) **1** is smoothly reduced to the corresponding radical anion, which is converted to the [2 + 2] intramolecular cycloadduct **2** (Scheme 4).[8a] In these reactions, addition of an electron donor and a Lewis acid is essential to produce a strongly reducing Ru species ***M***⁻ from the photoexcited species ****M*** and to lower the LUMO level of **1**, respectively. Analogous [2 + 2] cyclization by high-energy UV photolysis[9] and electrochemical methods[10] was reported, but these reaction systems required special reactors. In contrast, the present photocatalytic protocol allows one to conduct the reaction using usual glassware and a readily available light source, including natural sunlight. Furthermore, they extended the present reaction based on the reductive quenching cycle to *crossed intermolecular* [2 + 2] cycloadditions of enones[8b] and intramolecular [3 + 2] cycloadditions of aryl cyclopropyl ketones.[8c] The latter reaction is induced by the action of the Ru photocatalyst and the Lewis acid $La(OTf)_3$. Their report mentioned that the choice of Lewis acid was critical for the SET event from the strongly reducing $[Ru(bpy)_3]^+$ ($\boldsymbol{M}^-$) species to carbonyl groups. It should be noted that these systems are typical examples of dual catalysis, *i.e.* Lewis acid catalysis and photoredox catalysis.



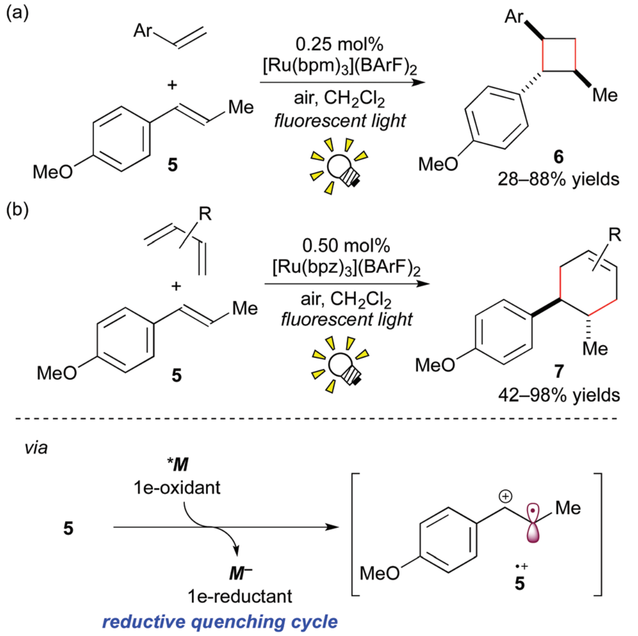
Scheme 4 [2 + 2] Cycloadditions of electron-deficient alkenes through the reductive quenching cycle.

As mentioned in the Introduction section, the photoexcited species of metal-based photoredox catalysts can serve both as 1e-oxidants and 1e-reductants. The combination of the Ru photocatalyst with a sacrificial electron acceptor has been proven to affect 1e-oxidation of electron-rich alkenes, leading to radical cations. Yoon and co-workers also described a process complementary to the above-mentioned cycloaddition reactions of electron-deficient enones. The cyclized product **4** was obtained from the reaction of the electron-rich bis(alkene) **3** through the oxidative quenching cycle using MV^{2+} (methyl viologen) as a sacrificial electron acceptor (Scheme 5).[8d]

More recently, it was reported that *direct* oxidation of the electron-rich styrene **5** through the reductive quenching



Scheme 5 Photo-oxidative [2 + 2] cycloadditions of electron-rich alkenes.



Scheme 6 (a) Crossed intermolecular [2 + 2] cycloaddition of styrenes. (b) Radical cation Diels–Alder cycloadditions.

cycle by $[Ru(bpm)_3](BArF)_2$ (bpm: 2,2′-bipyrimidine; BArF: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate), which forms an excited state ($*M/M^-$ = +0.99 V *vs.* SCE in MeCN), is stronger than that using $[Ru(bpy)_3]^{2+}$. The Ru photocatalyst, $[Ru(bpm)_3](BArF)_2$, effected crossed intermolecular [2 + 2] cycloaddition using oxygen as the terminal oxidant (Scheme 6a).[8e] It is notable that, in this reaction, the further stronger oxidizing photocatalyst $[Ru(bpz)_3]^{2+}$ (bpz: 2,2′-bipyrazine, $*M/M^-$ = +1.45 V *vs.* SCE in MeCN) turned out to be sluggish because cycloreversion of the product **6** was induced by the photoactivated $[Ru(bpz)_3]^{2+}$.

Furthermore, it was revealed that [4 + 2] cycloadditions of electron-rich alkenes can also be promoted through 1e-oxidation of alkenes by photoredox catalysis.[8f] The Ru photocatalyst, $[Ru(bpz)_3](BArF)_2$ (0.50 mol%), effected the Diels–Alder type cycloaddition reactions of styrene **5** with various dienes (Scheme 6b). But it should be noted that this photocatalytic protocol through the cation radical intermediate $\mathbf{5}^{+\bullet}$ provides the product **7**, which cannot be formed by thermal Diels–Alder cycloaddition.

As is shown, careful tuning of the redox properties of the photocatalysts leads to successful cycloaddition reactions of both electron-rich and -deficient alkenes through ionic radical intermediates.

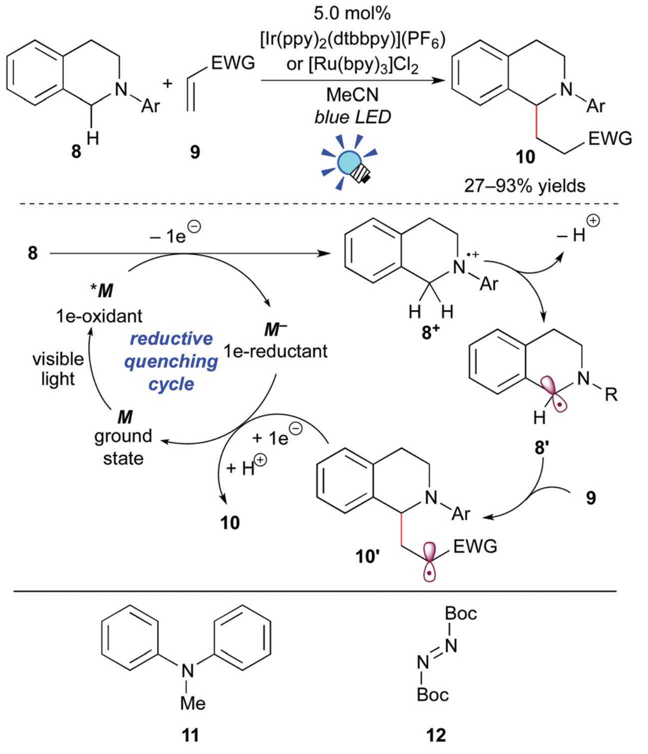
3. Oxidatively induced generation of organic radicals

As mentioned in the above sections, electron-rich tertiary amines are frequently used as sacrificial electron donors to enhance the reducing power of the excited photocatalyst. Recently, photoredox-catalyzed oxidation of electron-rich amines has become a powerful tool for the synthesis of nitrogen atom-containing compounds, including bioactive compounds. One trend involves transformations of iminium ions[11] and azomethine ylide intermediates[12] through two-electron oxidation of amines by combining a photoredox catalyst with an appropriate oxidant. Reactions of the generated ionic species with a variety of nucleophiles or dipolarophiles have been explored. This review, however, will focus on reactions involving carbon-centered radical species.

3.1 Photogeneration of the α-aminoalkyl radical

One-electron oxidation of tertiary amines provides amine radical cations. Subsequent deprotonation produces α-aminoalkyl radicals, which can serve as nucleophiles to react with a variety of electrophiles. Thus, this transformation can achieve elusive C–H functionalization of amines at the α-position.[13] In 2012, Pandey and Reiser *et al.* developed the photoredox reaction between the α-aminoalkyl radical generated from *N*-aryltetrahydroisoquinoline **8** and an electron-deficient alkene **9** (Scheme 7).[14]

The authors showed that both the Ru photocatalyst, $[Ru(bpy)_3]Cl_2$, and the Ir photocatalyst, $[Ir(ppy)_2(dtbbpy)](PF_6)$ (ppy: 2-phenylpyridine; dtbbpy: 4,4′-di-*tert*-butyl-2,2′-bipyridine), promote the reaction. In some examples, however, the Ir photocatalyst is more effective. A proposed reaction mechanism based on the reductive quenching cycle is illustrated in Scheme 7. The photoexcited species ***M*** undergoes SET from



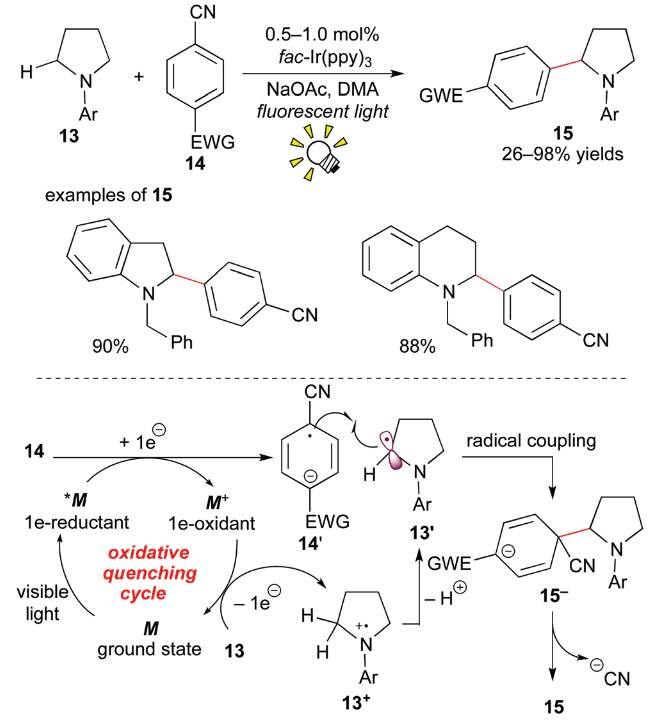
Scheme 7 Addition of the α-aminoalkyl radical to electron-deficient double bonds.

tetrahydroisoquinoline **8** to give the radical cation $\mathbf{8}^{+}$ and the strong reducing agent $\boldsymbol{M}^{-}$. Subsequent deprotonation converts $\mathbf{8}^{+}$ to the α-aminoalkyl radical **8′**. Conjugated addition of the nucleophilic radical **8′** to the electron-deficient alkene **9** yields the radical intermediate **10′**, which is reduced by the highly reduced species $\boldsymbol{M}^{-}$, with concomitant regeneration of ***M***. Subsequent protonation of the resulting anionic species produces the adduct **10**. It should be noted that this photocatalytic reaction does not require any sacrificial electron donor or acceptor, *i.e.* a redox neutral process.

Almost at the same time, the Nishibayashi group reported the analogous reaction of aniline **11** with electron-deficient alkenes in the presence of $[Ir(ppy)_2(dtbbpy)](BF_4)$.[15a] Moreover, they extended this reaction to C–H amination of amines at the α-position using di-*tert*-butyl azodicarboxylate **12** as an electrophile.[15b]

In 2011, MacMillan *et al.* showed a different pathway to access α-aminoalkyl radicals, *i.e. via* an oxidative quenching cycle, and achieved C–H arylation of amines at the α-position.[16]

The photocatalytic reaction of the cyclic or acyclic amine **13** with the cyanoarene derivative **14** in the presence of *fac*-$Ir(ppy)_3$ (0.5–1.0 mol%) under visible light irradiation afforded the corresponding α-arylated amine **15**. The nitrile group serves as a leaving group. A proposed reaction mechanism is depicted in Scheme 8. The photoactivated species ****M*** undergoes SET with the cyanoarene **14**, leading to the radical anion **14′** and the strongly oxidizing species $\boldsymbol{M}^{+}$. The amine **13** is oxidized by $\boldsymbol{M}^{+}$ to result in the formation of the α-aminoalkyl radical **13′** and the ground state ***M***. The radical coupling of **13′** with **14′** produces the C–C coupled intermediate $\mathbf{15}^{-}$. Finally, aromatization *via* elimination of the cyanide anion produces the α-arylated amine product **15**. In particular, protected indoline and tetrahydroquinoline architectures, which are prevailing cyclic amine structures in bioactive compounds, are applicable.



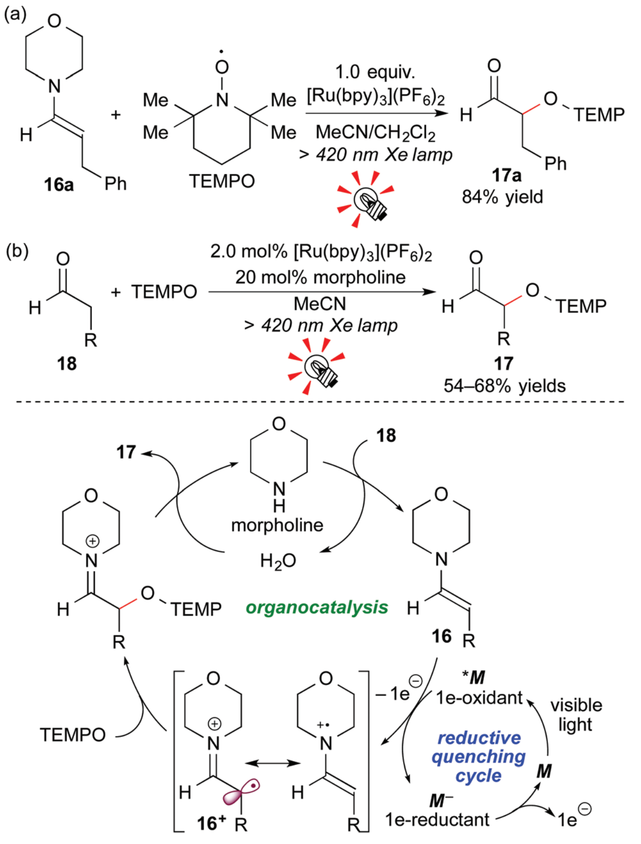
Scheme 8 α-C–H arylation of amines.

These reports were followed by related work involving generation of α-aminoalkyl radicals from various electron-rich amines.[15c,17]

3.2 Photo-oxidation of enamines

Enamines, which are accessible by reaction of carbonyl compounds and secondary amines, are a class of electron-rich tertiary amines, *i.e.* electron donors. In addition, 1e-oxidation of enamines is connected to "SOMO-activation" studies, leading to functionalization of carbonyl compounds at the α-position.[18]

In 2009, Koike and Akita reported that the Ru photocatalyst, $[Ru(bpy)_3](PF_6)_2$, effected stoichiometric oxidative coupling of the enamine **16a** with TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxy) under visible light irradiation to give the α-oxyaminated aldehyde **17a** after hydrolysis (Scheme 9a). Moreover, this system was extended to a photocatalytic system. Catalytic amounts of $[Ru(bpy)_3](PF_6)_2$ (2.0 mol%) and morpholine (20 mol%) effected direct α-oxyamination of the aldehyde **18**. A plausible reaction mechanism, involving a cooperative

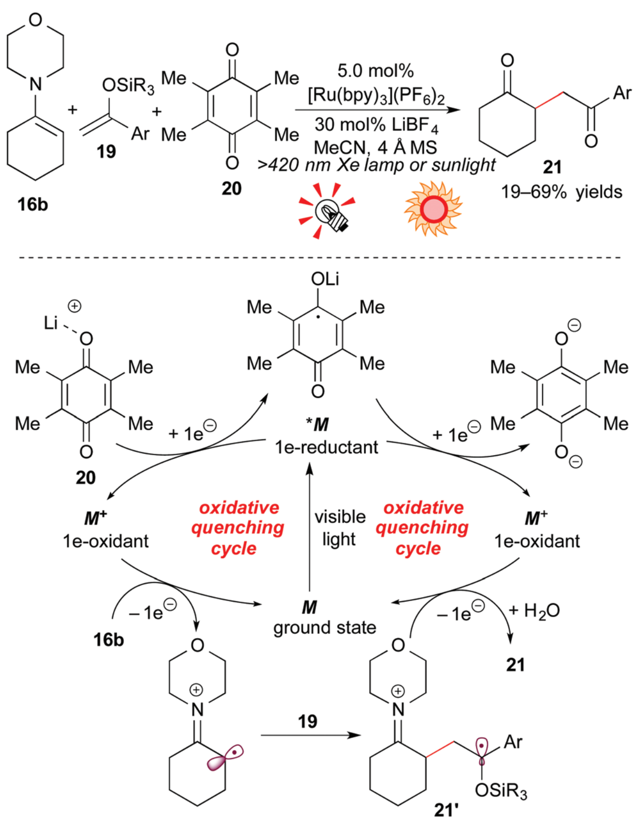


Scheme 9 Photocatalytic α-oxyamination of enamine (a) and aldehydes (b).

catalytic cycle consisting of photocatalysis (reductive quenching cycle) and organocatalysis, is shown in Scheme 9b. Morpholine first reacts with the aldehyde **18** to give the enamine **16**, which then undergoes 1e-oxidation by the excited species ***M***. Importantly, the aldehyde **18** cannot be directly oxidized by the photocatalyst because of its very high oxidation potential. Final radical coupling of the cationic radical intermediate **16**$^+$ with TEMPO, followed by hydrolysis, gives the product **17** and morpholine.[19a]

Furthermore, the group of Koike and Akita extended this reaction to C–C bond formation through the 2e-oxidation process: oxidative coupling of the enamine **16b** with silyl enol ether **19**. The choice of the electron-acceptor turned out to be crucial in the reaction. The combination of duroquinone **20**, an electron acceptor, and the Lewis acid $LiBF_4$ dramatically improved the yield of the γ-diketone product **21**. A possible reaction mechanism through the oxidative quenching cycle is illustrated in Scheme 10.

The excited species ****M*** undergoes SET with duroquinone **20**, activated by Li^+, to be converted into the strongly oxidizing species ***M***$^+$. Oxidation of the enamine **16b** by ***M***$^+$ followed by addition to silyl enol ether **19** gives the radical intermediate **21′**, and subsequent 1e-oxidation by ***M***$^+$ gives the corresponding coupling product. The resulting compound is converted into the γ-diketone **21** upon hydrolysis. In addition, natural sunlight can also be harnessed as the light source.[19b]

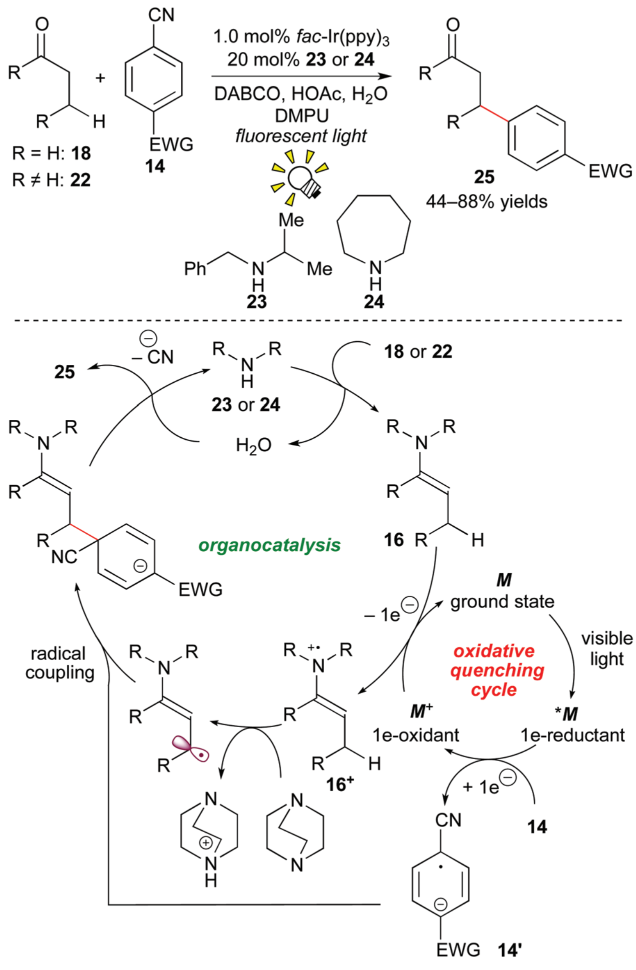


Scheme 10 Photocatalytic oxidative coupling of enamines with silyl enol ethers.

In 2013, MacMillan and co-workers developed a β-arylation of carbonyl compounds *via* photoredox-catalyzed generation of an enamine radical cation. The direct β-functionalization of carbonyl compounds has been regarded as a challenging transformation. A proposed mechanism merging photoredox catalysis and organocatalysis is depicted in Scheme 11.

First, photoactivated species ****M*** undergoes SET to the cyanoarene **14**, providing the aryl radical anion **14′** and the highly oxidized species ***M***$^+$. A subsequent SET event from the enamine **16**, which is generated from the reaction of the secondary amine catalyst with the aldehyde **18** *in situ* to the oxidant ***M***$^+$ provides the enamine radical cation **16**$^+$ and ***M*** of the ground state. Importantly, coupling of the enamine cation radical **16**$^+$ with the aryl anion radical **14′** does not proceed at the α-position of the carbonyl group. Instead, deprotonation by the base, DABCO (1,4-diazabicyclo[2.2.2]octane), at the β-position gives the β-enaminyl radical intermediate. At this stage, radical coupling produces the β-functionalized product **25** after elimination of the CN group and hydrolysis.[20a]

More recently, they extended this reaction to the β-hydroxyalkylation of the carbonyl compounds through 1e-reduction of ketones instead of cyanobenzene **14**.[20b]



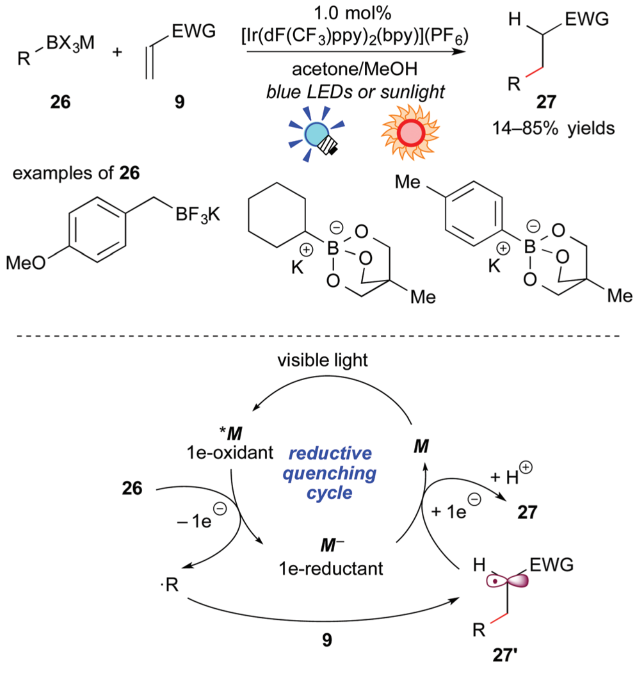
Scheme 11 β-Arylation of carbonyl compounds with cyanoarenes.

3.3 Generation of carbon-centered radicals from organoborates

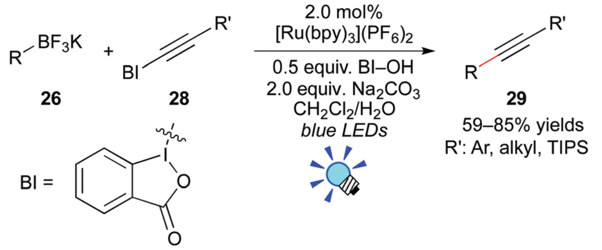
As described above, oxidative generation of nitrogen-containing organic radicals from electron-rich tertiary amines by photoredox catalysis is feasible and enables one to develop unique photocatalytic radical transformations. For the next stage, access to simple organic radicals, such as alkyl and aryl radicals, has remained an interesting topic. Recently, organoborates have attracted great interest as organic radical precursors because they are (i) air- and moisture-stable, (ii) harmless and (iii) tolerable with a variety of functionalities. It has been found that organic radicals can be generated from organoborate derivatives upon oxidation, but previously reported examples required *an excess amount* of oxidant or co-oxidant.[21]

Akita and co-workers developed photoredox-catalyzed generation of organic radicals from the corresponding organoborates.[22a] In addition, it was revealed that the reaction of organoborates with electron-deficient alkenes proceeds smoothly in the presence of *a catalytic amount* of the Ir photoredox catalyst, $[Ir(dF(CF_3)ppy)_2(bpy)](PF_6)$, which exhibits a strong oxidizing ability at the photoexcited state. A plausible reaction mechanism through a reductive quenching cycle is shown in Scheme 12.

First, the excited species $^*\boldsymbol{M}$ undergoes SET from the organoborate **26** to generate a carbon-centered radical ($^\bullet$R) and the highly reduced species $\boldsymbol{M}^-$, accompanied by elimination of the boron unit. The carbon-centered radical $^\bullet$R reacts with the electron-deficient alkene **9** to afford a C–C coupled radical intermediate **27′**. Finally, reduction of **27′** by the reductant $\boldsymbol{M}^-$ followed by protonation with methanol gives the product **27** together with ***M*** of the ground state. Alkyl- and aryl-borates can be applied to this reaction system. This catalytic system does not require any sacrificial oxidant and reductant, hence a redox neutral process. Furthermore, they showed the generation of an organic radical bearing a heteroatom at the α-position of the radical center, *i.e.* α-alkoxymethyl radical, from the corresponding organoborate[22b] and harnessed sunlight as the light source.



Scheme 12 Photocatalytic Giese reaction of organoborates with electron-deficient alkenes.



Scheme 13 Photocatalytic deboronative alkynylation.

More recently, Chen and co-workers reported photocatalytic deboronative alkynylation of primary, secondary, and tertiary alkylborates **26** with alkynylbenzoiodoxoles **28** in the presence of the Ru photocatalyst, $[Ru(bpy)_3](PF_6)_2$ (Scheme 13).[23] They proposed that organic radicals are generated from organoborates through the oxidative quenching mechanism, in which hydroxybenzoiodoxole serves as the electron acceptor. They showed that the reactions of boronic acids also give the corresponding coupling products **29**.

These results suggest that generation of organic radicals with a range of functional groups is accessible by oxidation of organoborates by photoredox catalysis, leading to promising radical initiating systems.

4. Reductively induced generation of organic radicals

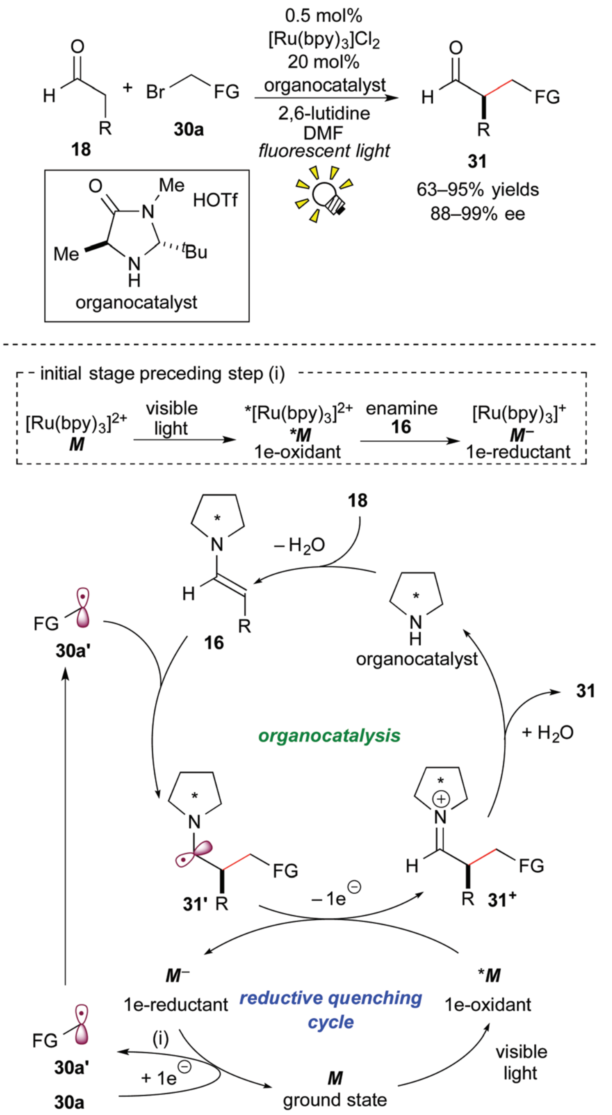
One of the most commonly used methods for generation of organic radicals is photolysis or thermolysis of organic halides in the presence of AIBN (azobisisobutyronitrile) and $HSnBu_3$. But the use of explosive AIBN and harmful tin-reagent is a drawback from the viewpoint of safety. It is well-known that 1e-reduction of organic halides and organic onium salts generates organic radicals. As mentioned in "Introduction", the excited photoredox catalyst can serve as a 1e-reductant under mild reaction conditions, *i.e.* visible light irradiation at room temperature. Thus, photoredox catalysis can provide a new and green protocol for the generation of organic radicals. In this section, representative photocatalytic radical reactions, which involve organic halides and onium salts as organic radical precursors, will be summarized.

4.1 Photo-reduction of organic halides

In 2008, Nicewicz and MacMillan reported an elusive asymmetric intermolecular α-alkylation of the aldehyde **18** with the *activated* alkyl bromide **30a** by elegantly merging

Ru photoredox catalysis with chiral amine organocatalysis.[24a] The reaction mechanism proposed for the synergistic catalysis is illustrated in Scheme 14.

At the initial stage, the excited species, $^*[\mathrm{Ru(bpy)_3}]^{2+}$ (****M***), is reduced by the enamine **16** derived from the reaction of the secondary chiral amine catalyst with the aldehyde **18**. The resulting strong reductant, $[\mathrm{Ru(bpy)_3}]^{+}$ (***M***$^-$), undergoes SET with the alkyl halide **30a**, leading to the formation of the alkyl radical **30a′** and regeneration of the ground state $[\mathrm{Ru(bpy)_3}]^{2+}$(***M***). The alkyl radical **30a′** reacts with the preformed enamine **16** to give the C–C coupled radical intermediate **31′**. 1e-oxidation of the radical intermediate **31′** by the photoactivated species ****M*** proceeds in the mainstream to afford the iminium intermediate **31**$^+$ and the reductant ***M***$^-$, which follows the above-mentioned SET event for generation of the alkyl radical **30a′**. Subsequent hydrolysis produces the α-alkylated aldehyde **31** together with the organocatalyst.

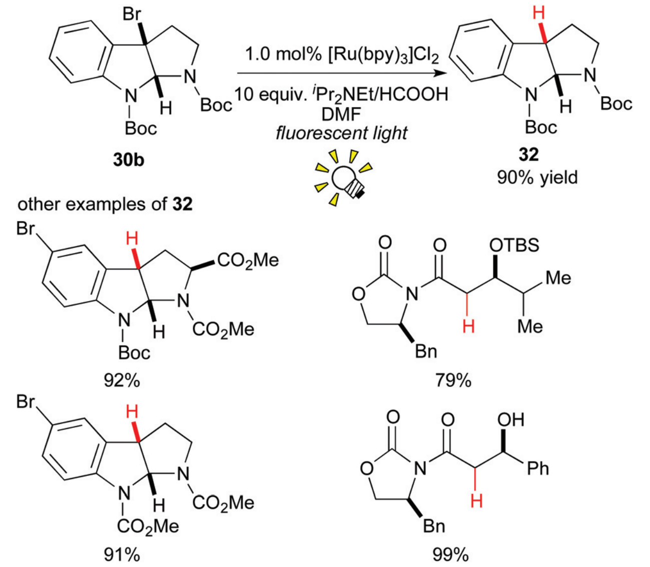


Scheme 14 Merger of catalysis for asymmetric α-alkylation of aldehydes.

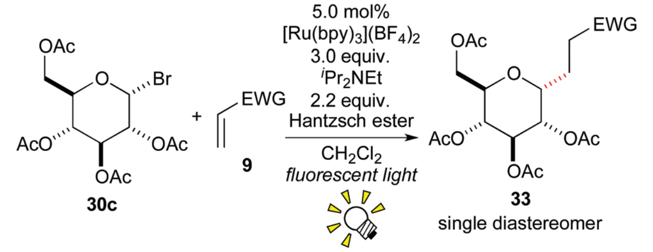
The mechanism proposed by the authors is based on the reaction of a SOMOphilic enamine **16** with an electron-deficient radical **30a′**, which is in contrast to those mentioned in section 3.2. It is noteworthy that the present catalytic system can provide an easy access to various optically active α-alkylated aldehydes **31** in high yields with excellent enantioselectivity.[24]

In 2009, Stephenson and co-workers reported an environmentally benign tin-free reductive dehalogenation of alkyl halides in the presence of $[\mathrm{Ru(bpy)_3}]\mathrm{Cl_2}$ and an amine as the hydrogen atom source under visible light irradiation (Scheme 15).[25a] It was proposed that the alkyl radical is formed *via* 1e-reduction of the alkyl halide **30b** by the action of the photoredox catalyst. Furthermore, they extended their tin-free generation method of organic radicals to radical C–C bond formation with alkenes[25b,c] and electron-rich heteroarenes.[25d]

In 2010, Gagné *et al.* described an intermolecular radical addition of the glycosyl halide **30c** to the electron-deficient alkene **9**, leading to the C-glycoside **33** in good yields with high diastereoselectivity (Scheme 16).[26]

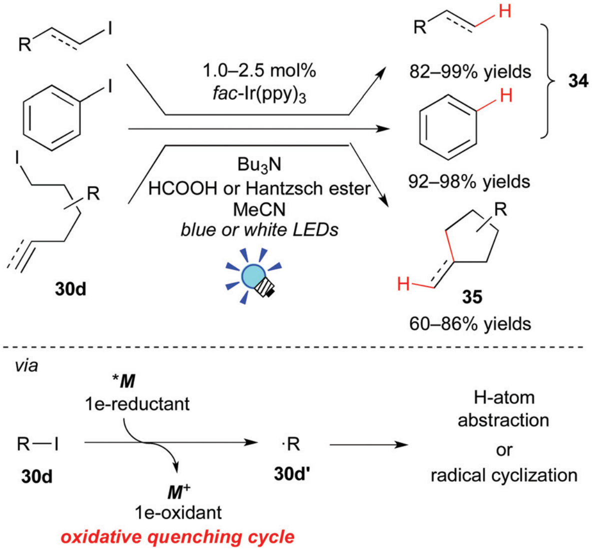


Scheme 15 Tin-free reductive dehalogenation.

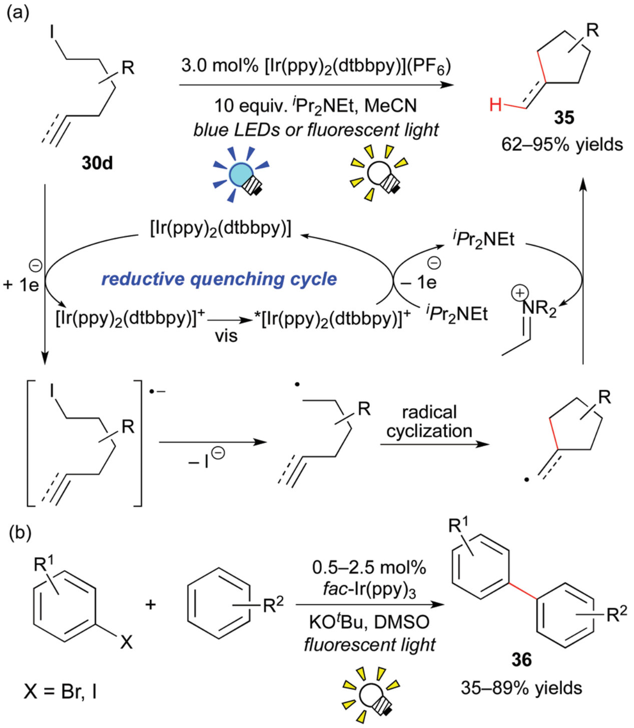


EWG = $\mathrm{CO_2Me}$: 94%, COMe, 86%, CN: 85%

Scheme 16 Tin-free Giese reaction.



Scheme 17 Photogeneration of organic radicals from unactivated organic iodides.



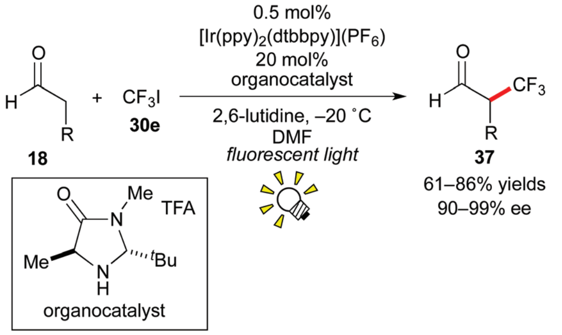
Scheme 18 (a) Photocatalytic radical cyclization. (b) Photocatalytic synthesis of biphenyls.

These reports were followed by many related studies on photocatalytic radical reaction using *activated* alkyl halides as the radical precursors.[27] Recently, the group of Hawker reported a unique radical polymerization system, whereby generation of organic radicals was controlled by photoredox catalysis.[27f]

In 2012, Stephenson *et al.* revealed that the Ir photocatalyst, *fac*-Ir(ppy)$_3$, affects the generation of organic radicals from *unactivated* alkyl, alkenyl and aryl iodides (Scheme 17).[28a] The photoexcited state, *[*fac*-Ir(ppy)$_3$], has a high reduction potential enough to reduce *unactivated* organic iodides. Therefore, ****M*** undergoes direct SET to the organic iodide **30d** to generate the organic radical **30d′** ($^\bullet$R). H-atom abstraction and radical cyclization of the resulting radical **30d′** afford the corresponding dehalogenated product **34** and the C–C coupled product **35**, respectively. The photocatalyst is regenerated with a reductant, being either ^{n}Bu$_3$N/HCOOH or Hantzsch ester (diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate).

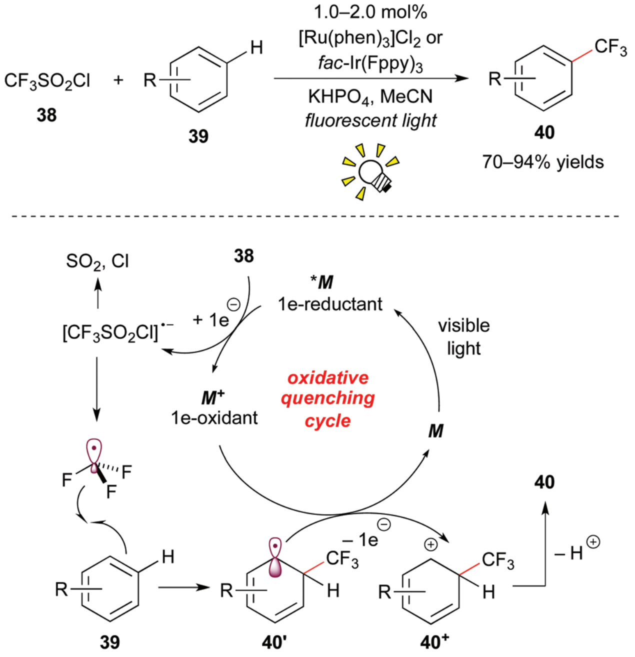
Almost at the same time, Lee and co-workers reported analogous work, *i.e.* the combination of the Ir photocatalyst, [Ir(ppy)$_2$(dtbbpy)](PF$_6$), and an electron donor, ^{i}Pr$_2$NEt, affecting the generation of the organic radical from the *unactivated* organic iodide **30d** (Scheme 18a).[28b] Their reaction proceeds *via* a reaction pathway different from Stephenson's report, *i.e.* the reductive quenching cycle. Moreover, the group of Li developed direct arylation of arenes with aryl halides by photoredox catalysis, leading to biaryl **36** (Scheme 18b).[28c]

In 2009, the group of MacMillan reported that photoredox catalysis is effective for the generation of a trifluoromethyl radical ($^\bullet$CF$_3$) from CF$_3$I **30e** (Scheme 19).[29] The above-mentioned dual catalytic system consisting of photocatalysis and organocatalysis (Scheme 14) also affected asymmetric trifluoromethylation of the aldehyde **18** using CF$_3$I **30e** as a CF$_3$ source, leading to the valuable enantioenriched α-trifluoromethylated aldehyde **37**, which is known as a useful building block for synthesis of chiral organofluorine compounds.[30] In this reaction, the Ru catalyst, [Ru(bpy)$_3$]$^{2+}$, also afforded the product but in a yield lower than that obtained by the Ir photocatalyst, [Ir(ppy)$_2$(dtbbpy)](PF$_6$). The Ir catalyst exhibits a reduction potential higher than that of the Ru catalyst and can generate the CF$_3$ radical from CF$_3$I more effectively.

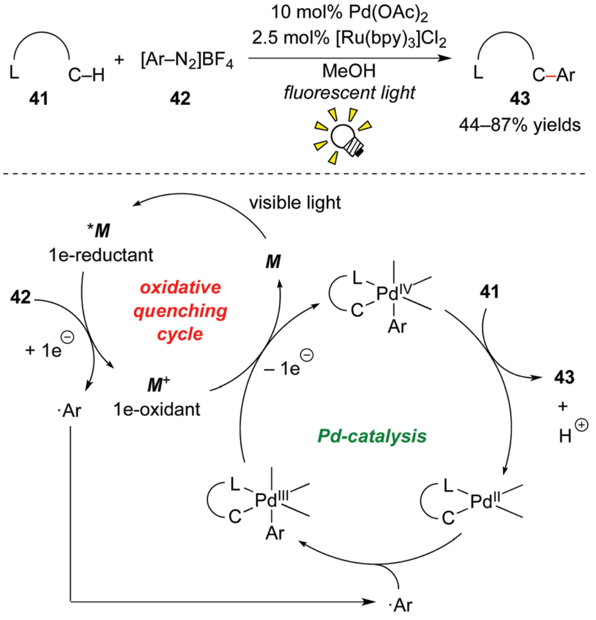


Scheme 19 Synthesis of α-CF$_3$-aldehydes by photoredox catalysis.

Furthermore, Nagib and MacMillan reported high-impact work on direct C–H trifluoromethylation of arenes by photoredox catalysis.[31a] The use of [Ru(phen)$_3$]Cl$_2$ (phen: phenanthroline) or *fac*-Ir(Fppy)$_3$ (Fppy = 2-(2,4-difluorophenyl)pyridine) as a photocatalyst and CF$_3$SO$_2$Cl **38** as a CF$_3$ source enables the reaction with the broad scope with respect to arene **39**, *i.e.* electron-rich/electron-deficient heteroarenes and unactivated



Scheme 20 Photocatalytic direct trifluoromethylation of aryl C–H bonds.



Scheme 21 C–H arylation based on dual catalysis.

arenes, in the absence of a *sacrificial* electron donor (Scheme 20).

The excited species ****M*** reacts with CF_3SO_2Cl **38** by the first SET process to give $^{\bullet}CF_3$ and the strong oxidant $\boldsymbol{M}^+$. The reaction of $^{\bullet}CF_3$ with arene **39** affords the corresponding cyclohexadienyl radical **40′**, which is oxidized by the oxidant $\boldsymbol{M}^+$ to give the cyclohexadienyl cation **40**$^+$ while regenerating ***M***. Deprotonation of the cation intermediate **40**$^+$ produces the trifluoromethylated arene **40**. It is noteworthy that they showed direct trifluoromethylation of bioactive compounds such as ibuprofen, Vitamin P, and Lipitor and proposed a new approach to the *late-stage trifluoromethylation*. As remarked in their report, the exploration of CF_3I **30e** as a CF_3 radical source turned out to limit the substrate scope to electron-rich arenes. This approach for trifluoromethylation of π-electron rich arenes such as indole, furan, pyrrole, and thiophene was reported by Cho and co-workers almost at the same time.[31b]

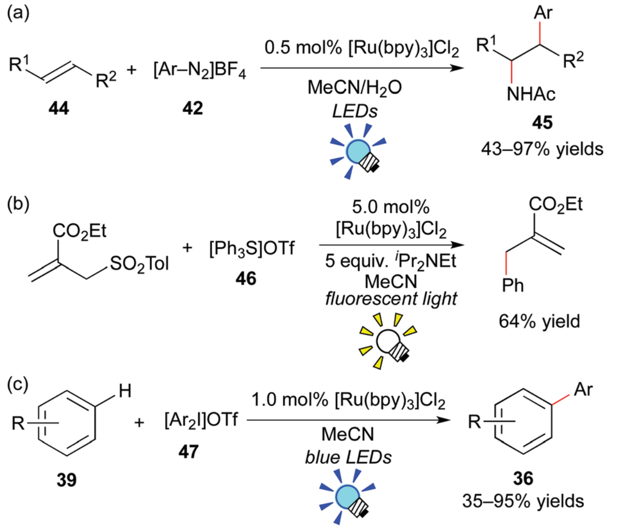
Recently, a great number of studies on radical trifluoromethylation using CF_3I and CF_3SO_2Cl by photoredox catalysis have appeared.[1o,32] Organofluorine compounds have their importance increasing in pharmaceutical and agrochemical fields.[33] Thus, photoredox-catalyzed trifluoromethylation can become one of the most promising methods for the synthesis of diverse organofluorine compounds.

4.2 Photo-reduction of organic onium salts

Much attention has been paid to aryl onium salts as radical precursors as an alternative to using aryl halides.[34] Additionally, in the photoredox chemistry of $[Ru(bpy)_3]^{2+}$, Kellogg *et al.* described the generation of aryl radicals by reduction of phenacylsulphonium salts in 1978.[35] Furthermore, Pschorr-type cyclization through reduction of aryl diazonium salt derivatives was reported by Cano-Yelo and Deronzier in 1984.[36] These reports, along with the recent advancements of organic onium reagents, have stimulated many researchers to develop new photoredox-catalyzed radical transformations using onium reagents.[1j]

In 2011, Sanford and co-workers reported direct C–H arylation of arene **41** bearing a directing group, such as pyridine, amide, pyrazole, pyrimidine and oxime ether groups, with aryl diazonium **42** by merging photoredox catalysis with Pd catalysis (Scheme 21).[37] The ligand-directed C–H arylation by palladium catalysis has been well studied in the past few decades.[38] However, the reaction required high temperatures to achieve high yields. The rate-determining step is considered to be formation of the key active Pd–Ar species. They showed that radical arylation of Pd species using aryl diazonium salt **42** by action of the photoredox catalyst, $[Ru(bpy)_3]Cl_2$, leads to a C–H arylation under mild reaction conditions. A plausible mechanism based on the dual catalysis process starts with SET from ****M*** to aryl diazonium salt **42**, accompanying formation of highly oxidized species $\boldsymbol{M}^+$ and $^{\bullet}Ar$. The reaction of $^{\bullet}Ar$ with the palladacycle generated by C–H activation of the substrate affords the Pd^{III} intermediate. The Ru oxidant induces the second SET event from the Pd^{III} intermediate to regenerate the photocatalyst and generate the Pd^{IV} intermediate. Finally, C–C bond-forming reductive elimination produces the arylated product **43** together with the original Pd^{II} catalyst. This dual catalysis by merging photoredox catalysis and transition-metal catalysis is also fascinating and provides new ways to develop catalytic transformations.[39,1n]

König *et al.* have intensively developed methods for arylation with aryl diazonium salts using the organic dye eosin Y and a metal-based photoredox catalyst. They reported photoredox-

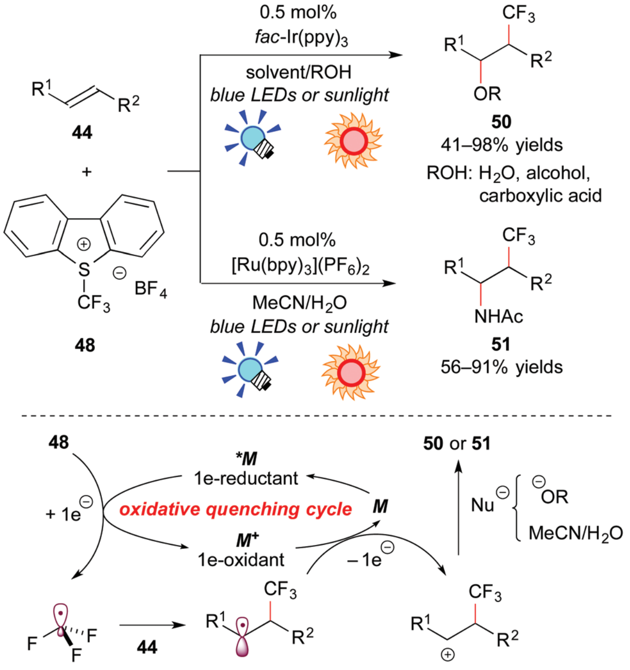


Scheme 22 Photogeneration of aryl radicals from aryl onium salts.

catalyzed arylation of heteroarenes, alkynes and alkenes with aryl diazonium salts.[40,41] For example, they recently showed intermolecular amino-arylation of the alkene **44** (Meerwein addition) in the presence of $[Ru(bpy)_3]Cl_2$.[41c] They examined other photocatalysts, including organic dyes such as eosin Y, and revealed that $[Ru(bpy)_3]Cl_2$ is the best photocatalyst among them (Scheme 22a).

In 2013, the group of Fensterbank, Goddard and Ollivier reported that triarylsulfonium salt **46** can serve as a source of aryl radicals by action of the Ru photocatalyst, $[Ru(bpy)_3]Cl_2$ (Scheme 22b).[42] Moreover, Xiao and co-workers described that diaryliodonium salt **47** can serve as another source of aryl radicals in the presence of $[Ru(bpy)_3]Cl_2$ (Scheme 22c).[43] Shortly after their reports, a great number of studies related to arylation through generation of aryl radicals from aryl onium salts by photoredox catalysis have been reported.[44]

On the other hand, the group of Koike and Akita paid attention to electrophilic trifluoromethylating reagents, such as Umemoto's reagent **48** (*S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate),[45] and Togni's reagent **49** (1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one),[46] which are easy to handle in terms of shelf-stable onium reagents at room temperature. They proved that electrophilic trifluoromethylating reagents can serve not only as precursors for the CF_3 radical, but also as direct electron acceptors from the photoexcited catalyst. They developed efficient and selective trifluoromethylative difunctionalization of alkenes by photoredox catalysis (Scheme 23). The photoreaction of the alkene **44** with Umemoto's reagent **48** in *O*-containing solvents, such as H_2O, alcohols, or carboxylic acids, in the presence of *fac*-$Ir(ppy)_3$ under visible light irradiation exclusively afforded the corresponding oxytrifluoromethylated product **50** in a regioselective manner. In addition, the photocatalytic reaction of the alkene **44** with Umemoto's reagent **48** in MeCN containing a small amount of water, which is known as an aminative carbocation-trapping agent, proceeded smoothly *via* Ritter-type reaction to give the corresponding aminotrifluoromethylated product **51** in good yields. The Ru photocatalyst, $[Ru(bpy_3)](PF_6)_2$, can promote the transformation in a manner similar to the Ir catalyst.

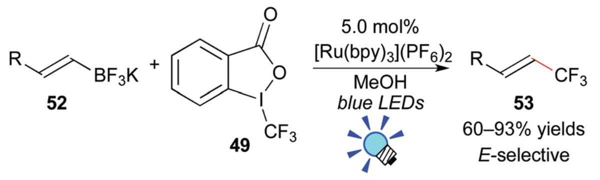


Scheme 23 Photoredox-catalyzed difunctionalization of alkenes through construction of a $C-CF_3$ bond.

A plausible reaction mechanism through the oxidative quenching cycle is shown in Scheme 23. First, Umemoto's reagent **48** is reduced by ****M*** to generate $^{\bullet}CF_3$. Addition of $^{\bullet}CF_3$ to the alkene **44** gives the radical intermediate, which is oxidized by $\boldsymbol{M}^+$ formed through the SET process. Finally, the β-trifluoromethylated carbocation intermediate undergoes solvolytic nucleophilic attack to afford the trifluoromethylated product **50** or **51**.[47a,c] More recently, they extended this photocatalytic reaction to intramolecular trifluoromethylative lactonization of alkenoic acids.[47e]

The authors also showed that Togni's reagent **49** can serve as a CF_3 radical source. Under similar reaction conditions, application of potassium vinyltrifluoroborate **52** to this photocatalytic system provided the trifluoromethylated alkene **53** *via* deboronation (Scheme 24). Their photoredox-catalyzed protocol for construction of $C_{alkenyl}-CF_3$ bonds exhibits a broad scope with excellent efficiency and stereoselectivity.[47b]

Shortly after their reports, other groups also reported radical trifluoromethylation using electrophilic CF_3 reagents in



Scheme 24 Photocatalytic synthesis of CF_3-alkenes *via* deboronation.

the presence of a photoredox catalyst.[1o,48] These onium salt-based CF_3 reagents can be handled easily compared to conventional CF_3 radical sources, such as gaseous CF_3I and hydrolyzable CF_3SO_2Cl. In addition, different outcomes of reactions have been obtained.

5. Conclusions and outlook

In conclusion, photoredox catalysis with Ru and Ir photoredox catalysts has emerged as a powerful tool for the generation of carbon-centered radicals from diverse organic compounds, including conventional radical precursors, such as organic halides and onium salts. More sophisticated photocatalytic systems will be designed by an appropriate choice of photocatalyst, radical precursor and substrate: a redox neutral transformation without addition of an excess amount of oxidant or reductant. We expect that the present photocatalytic protocol expands the research field of radical reactions and stimulates development of novel reactive but storable radical precursors. Furthermore, newly designed photoredox catalysts will be exploited to achieve novel transformations.

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